Pathology of Endocrine Organs
Part 1.

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Overview

1. Pathology of endocrine organs
   - Pituitary gland
   - Pineal gland
   - *Thyroid gland (see next lecture!)*
   - Parathyroid glands
   - Adrenal glands
   - Endocrine pancreas
   - Sex-cord stroma
2. General aspects of neuroendocrine tumors of non-endocrine organs (DNES)
3. Syndromes associated with endocrine tumors

Pathology of endocrine organs

Endocrinological classification (pathophysiology)

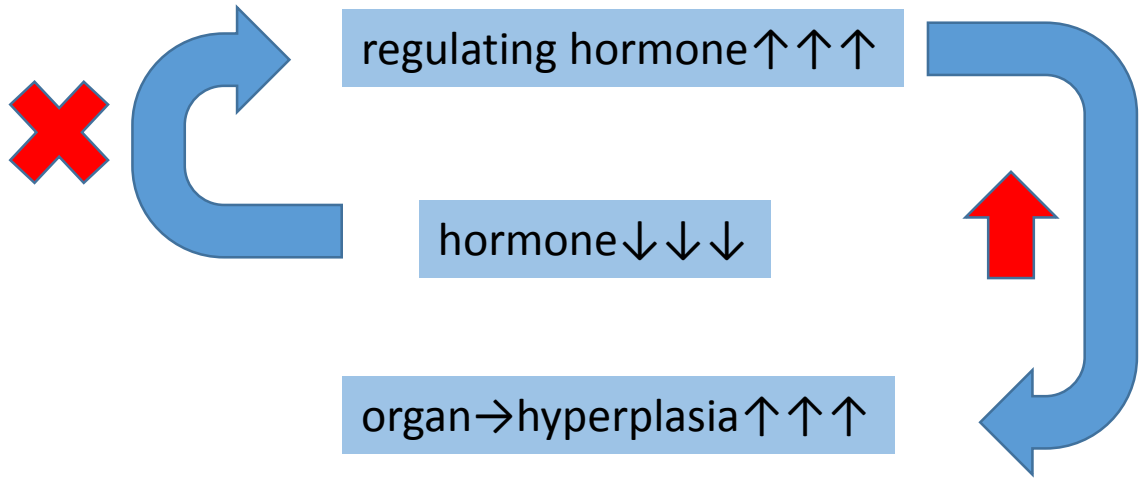
- Causes and consequences of decreased/no hormon function (=hypo…ism)
  - Underproduction
  - No effect
- Causes and consequences of increased hormon function (=hyper…ism)
  - Overproduction

Morphological classification (pathology)

- Congenital disorders
- Adaptive disorders
- Circulatory disorders
- Inflammatory disorders
- Neoplasia

Special issues in endocrine pathology

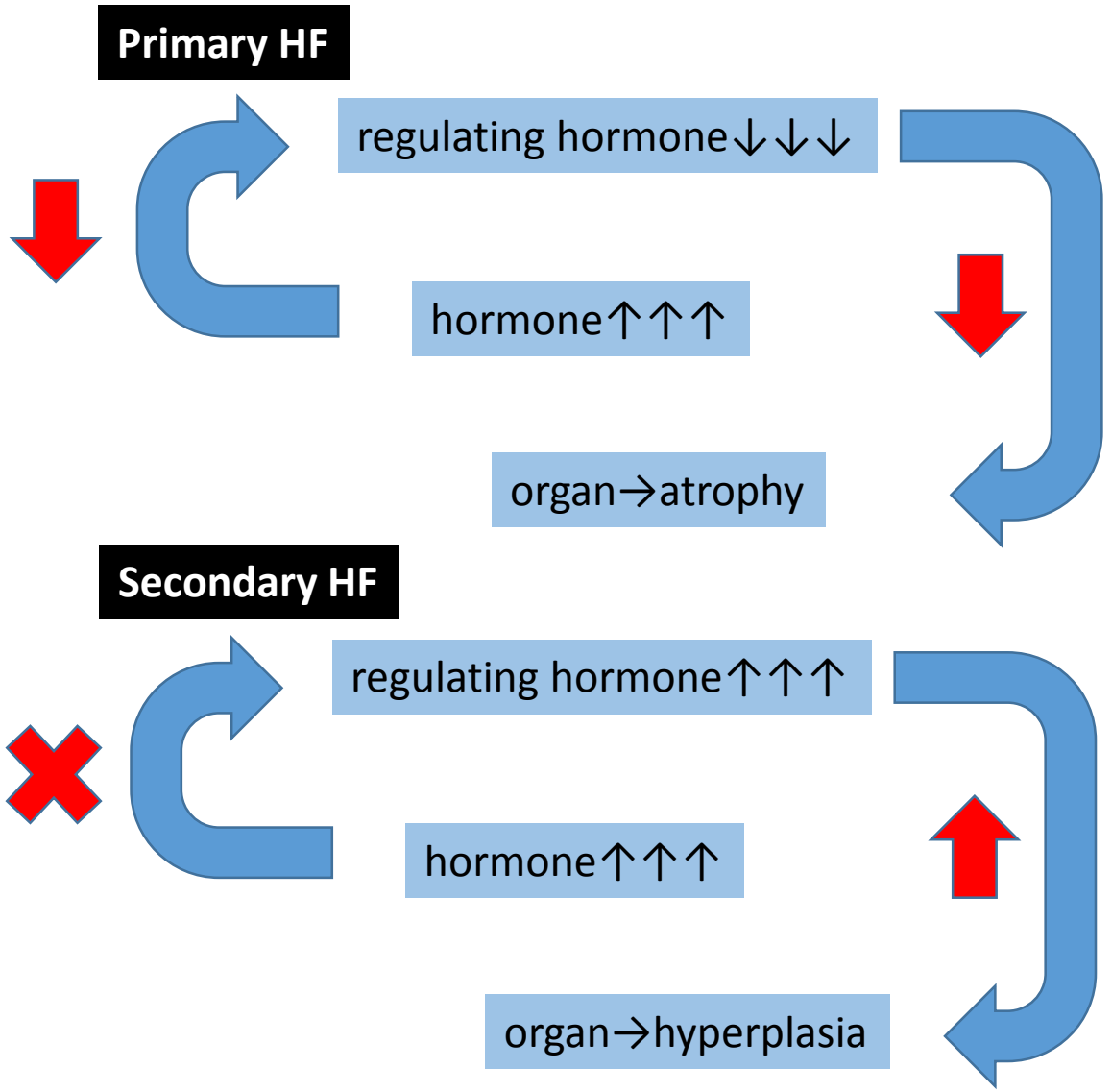
- **Congenital disorders=enzimopathies**
  - Inappropriate hormone production
  - No effective hormone function
  - No feedback



- Examples: dyshormonogenetic goiter, adrenogenital syndrome

Special issues in endocrine pathology

- **Adaptive disorders**
  - Primary hyperfunction = autonomous hormone production
  - Secondary hyperfunction = excessive release of regulating hormone/factor
    - Central
    - Ectopic (paraneoplasia)
  - Tertiary hyperfunction = secondary hyperfunction with an autonomous population



Special issues in endocrine pathology

- **Circulatory disorders**
  - Very rare= small organs with rich vascularisation
  - Ischemia can occur in the pituitary gland due to its limited space
- **Inlammations**
  - Almost always of autoimmune etiology
  - T-cell mediated (type IV) eg. diabetes mellitus type 1, autoimmune adrenalitis
  - Antibody mediated (type II) → acts as a regulating hormon eg. Graves disease
  - Infections affecting endocrine organs are very rare

Special issues in endocrine pathology

- **Neoplasias**

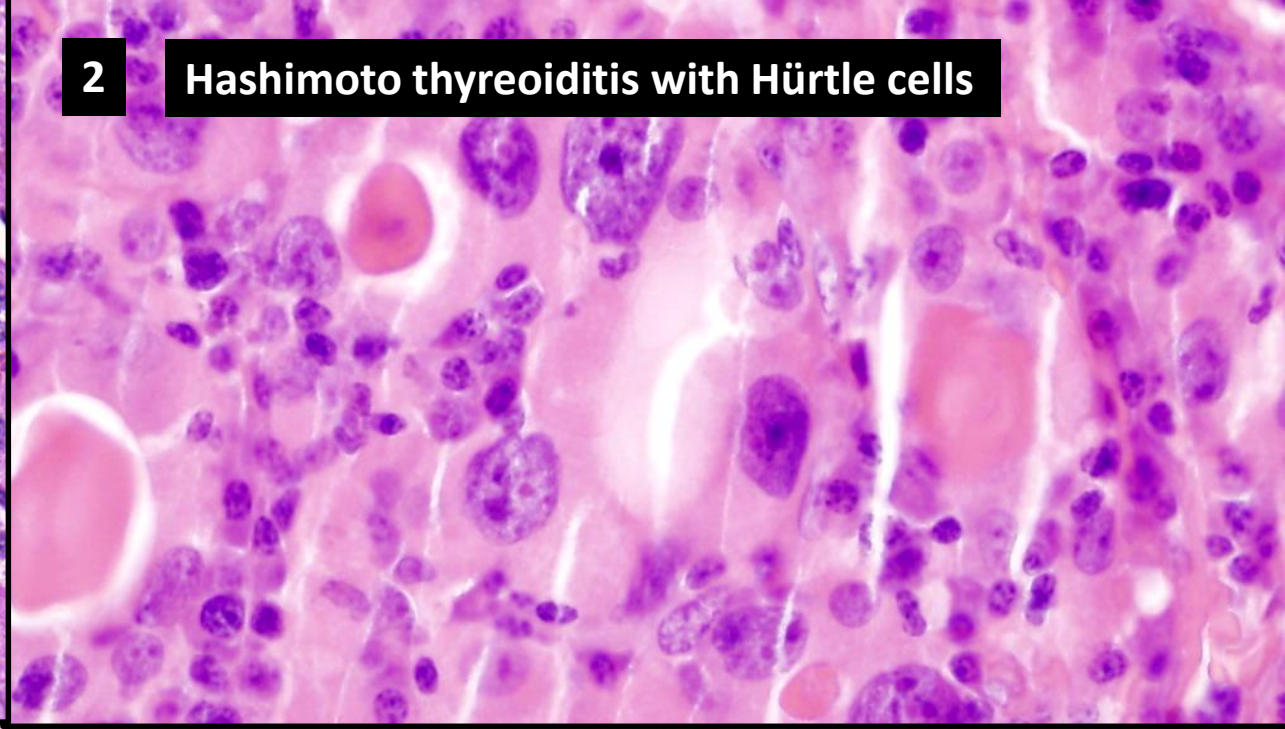
  Origin

  - Endocrine: thyroid follicles, adrenal cortex, sex-cord stroma
  - Neuroendocrine (tumors with neurosecretory features-see later): pituitary gland, thyroid C-cells, parathyroid glands, adrenal medulla, gastro-entero-pancreatic and other neuroendocrine cells of respiratory, urinary tract, skin etc. (GEP/DNES)

  Dignity

  - Classic cytomorphologic criteria of malignancy is NOT valid in endocrine organs!
  - Atypia, polymorphism, bizarre cells are more often found in hyperactivity than in malignancies!
  - *Exception: papillary thyroid carcinoma→diagnosis based on unique cytological features*
  - Criteria of endocrine malignancy in general: **local/vascular invasion and/or metastasis**
  - Neuroendocrine tumors are potentially malignant irrelevant to their microscopic morphology (see DNES tumor classification)


1
Adrenal cortical adenoma with bizarre cells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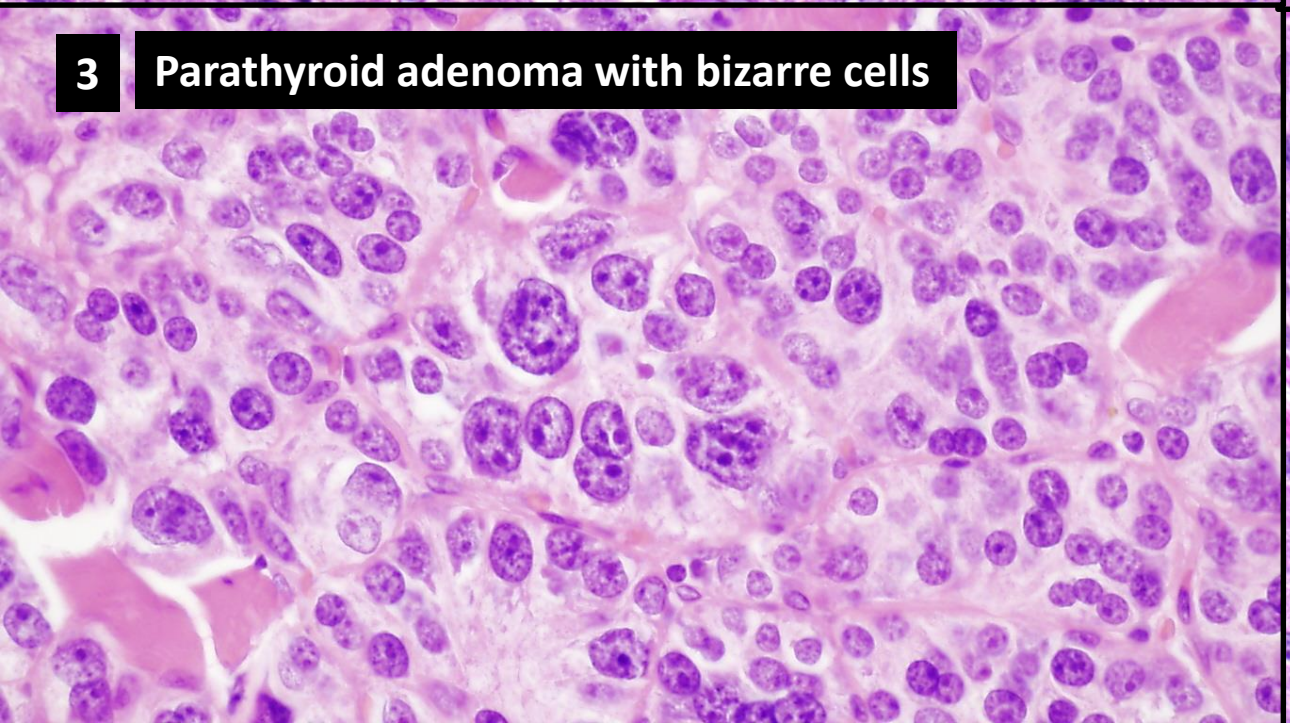
Hashimoto thyreoiditis with Hürtle cells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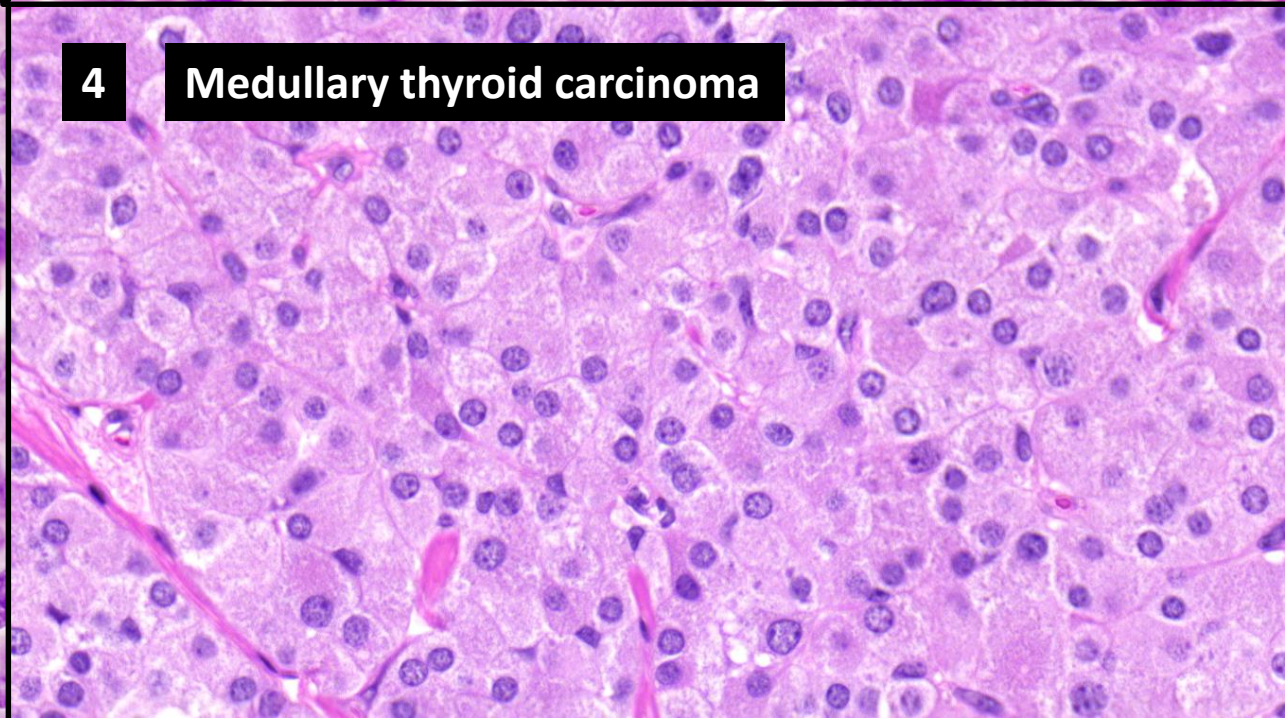
Parathyroid adenoma with bizarre cells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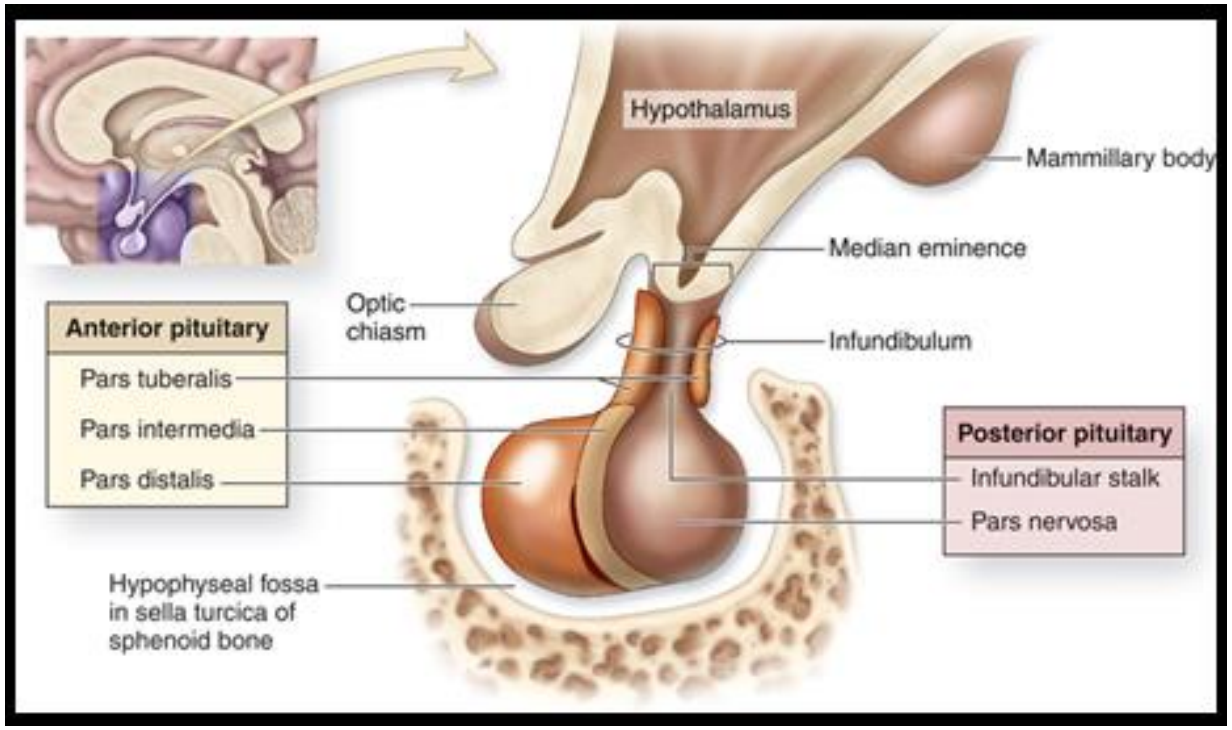
Medullary thyroid carcinoma

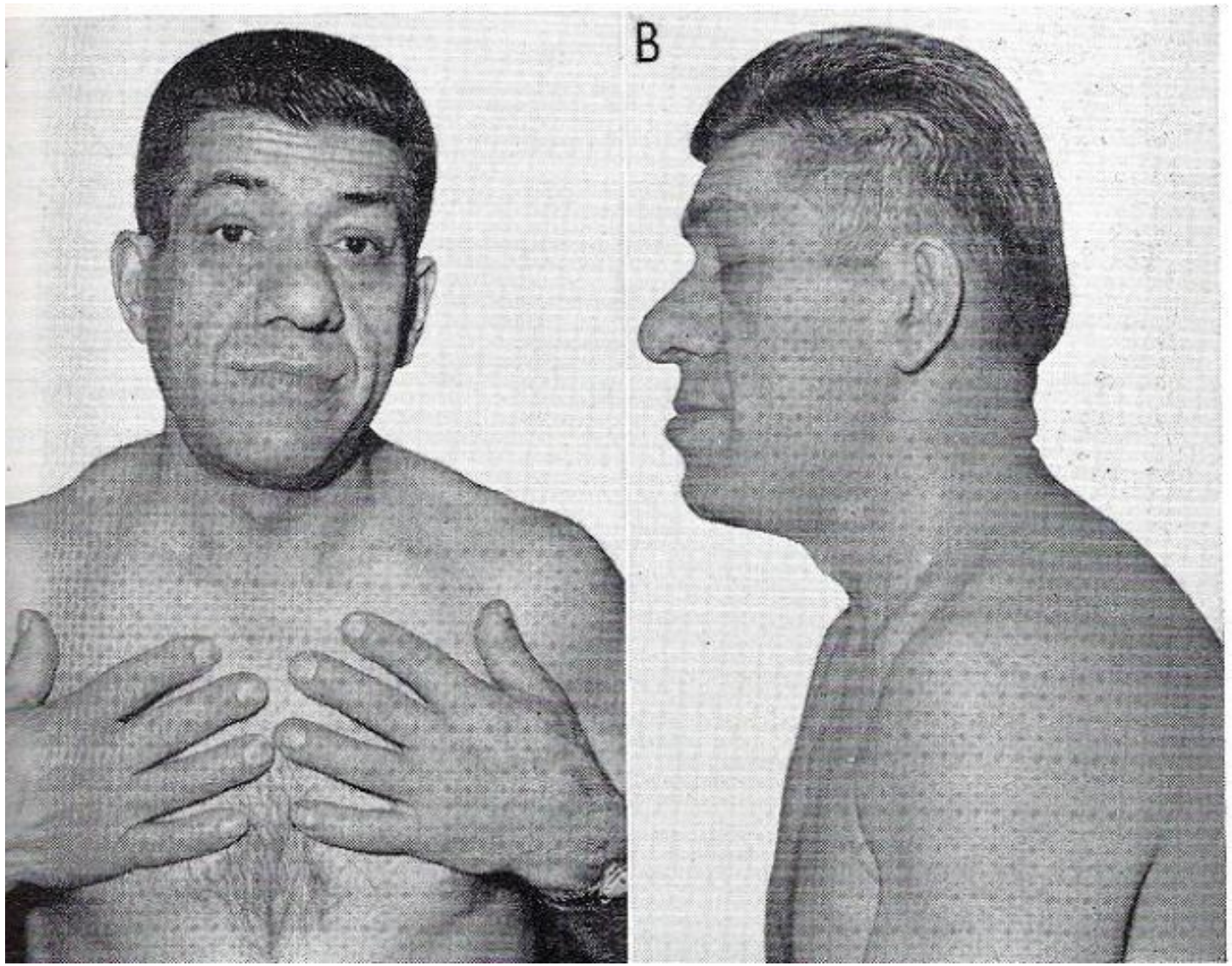
Pituitary gland *(p1098)*



- Anatomy
  - Anterior lobe (adenohypophysis)
  - Posterior lobe (neurohypophysis)
  - Note: local mass effect may cause visual field abnormalities
- Function:
  - Anterior lobe
    - Somatotroph cells: GH
    - Lactotroph cells: prolactin
    - Corticotroph cells: ACTH
    - Thyrotroph cells: TSH
    - Gonadotroph cells: FSH, LH
  - Posterior lobe: ADH, oxytocin

Hyperpituitarism

- >99% adenomas
  - Microadenoma: <1 cm, macroadenoma: >1cm
  - Classification based on hormone secretion
    - Most common: prolactinoma — galactorrhea
    - Somatotroph adenoma — gigantism, acromegaly
    - Corticotroph adenoma — central Cushing syndrome
    - Other rare variants (gonadotroph, thyrotroph, nonfunctioning)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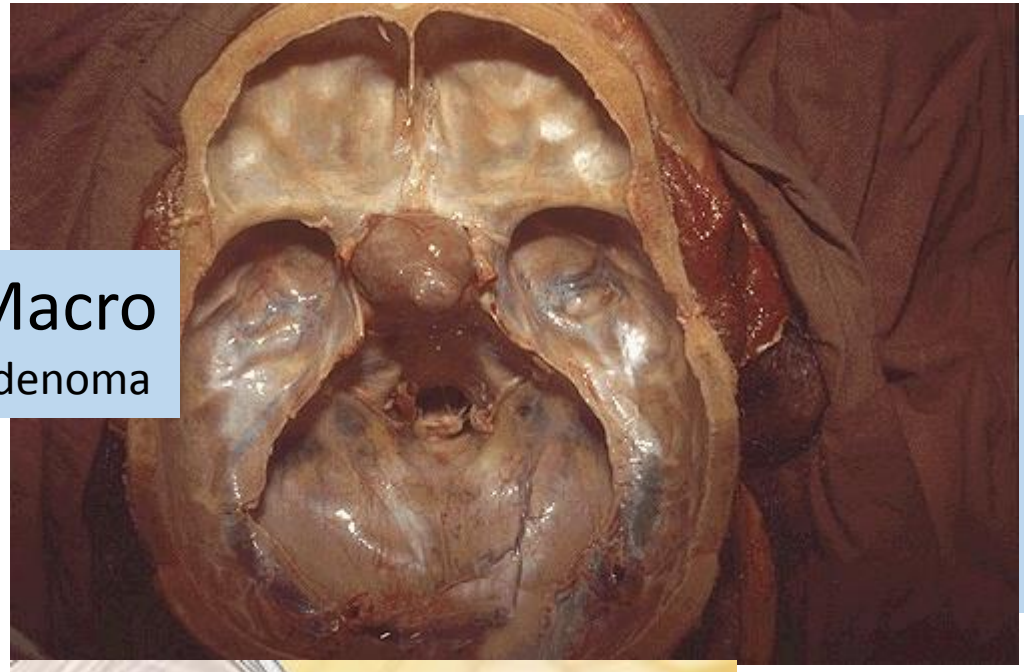
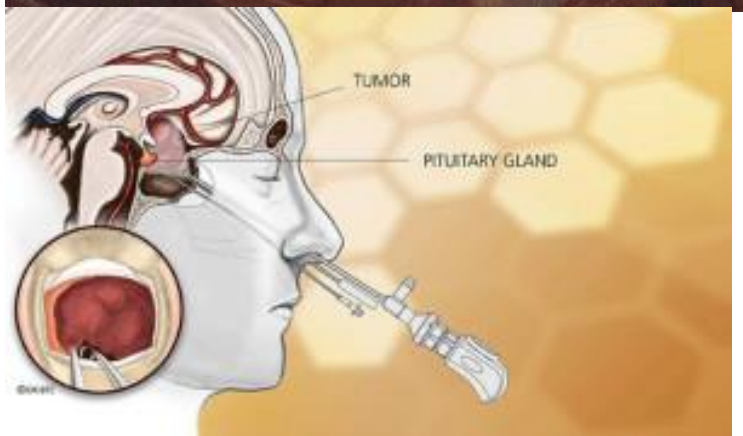
Morphology

Macro

Adenoma



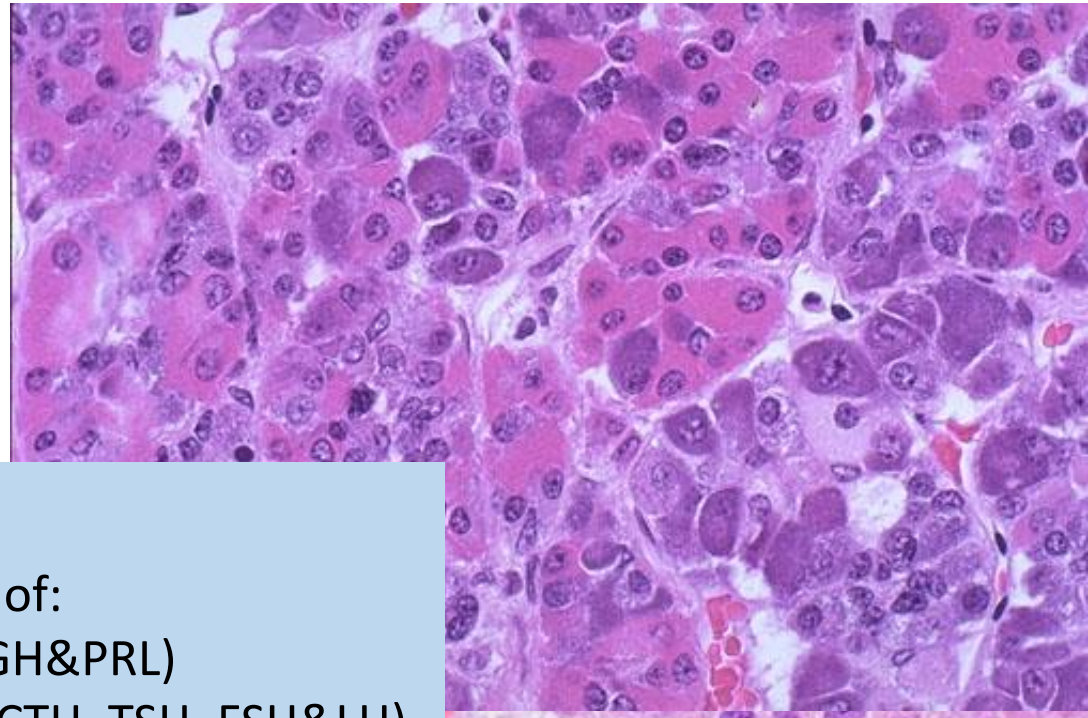


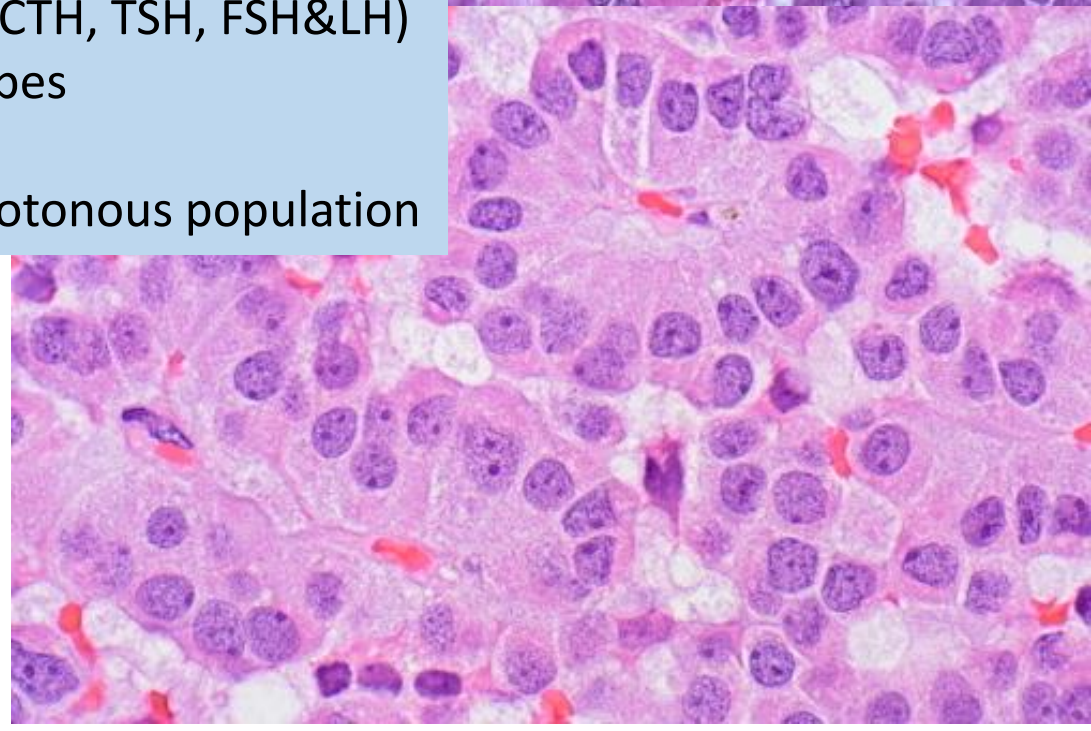
Micro

Normal: mixture of:

- acidophils (GH&PRL)
- basophils (ACTH, TSH, FSH&LH)
- Chromophobes

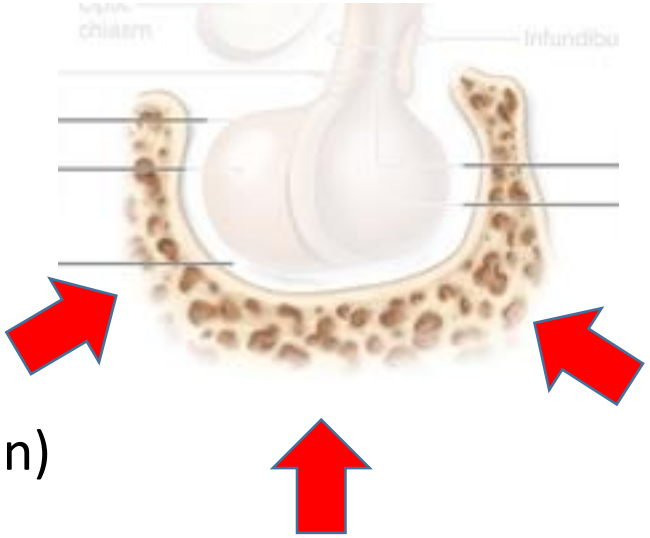
Adenomas: monotonous population





Hypopituitarism

All kind of pituitary damage may result in empty sella syndrome



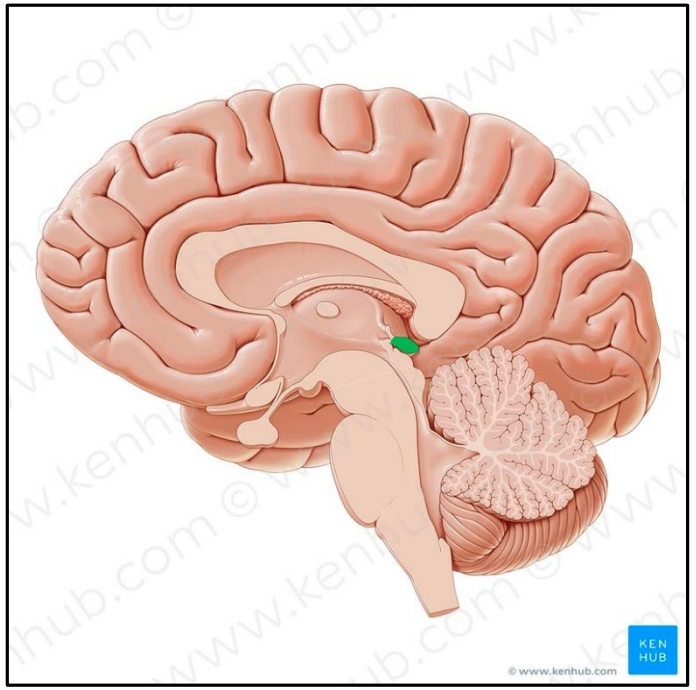
- Physical damage
  - Mass lesion: adenoma
  - Trauma
  - Surgery, irradiation
- Vascular disorders
  - Pituitary apoplexy (rare cause of sudden death)
  - Sheehan syndrome (ischemic necrosis in pregnant women)
- Genetic defects
- Hypothalamic hormone deficiency (eg. suprasellar tumors)
- Infections (rare, granulomatous, eg. TB, sarcoidosis)

Posterior pituitary syndromes

- Hyperfunction
  - Syndrome of inappropriate ADH (SIADH)
  - Generally ectopic ADH secretion=paraneoplasia (small cell lung carcinoma)

- Hypofunction
  - Diabetes insipidus
  - Trauma, tumor etc.

Pineal gland

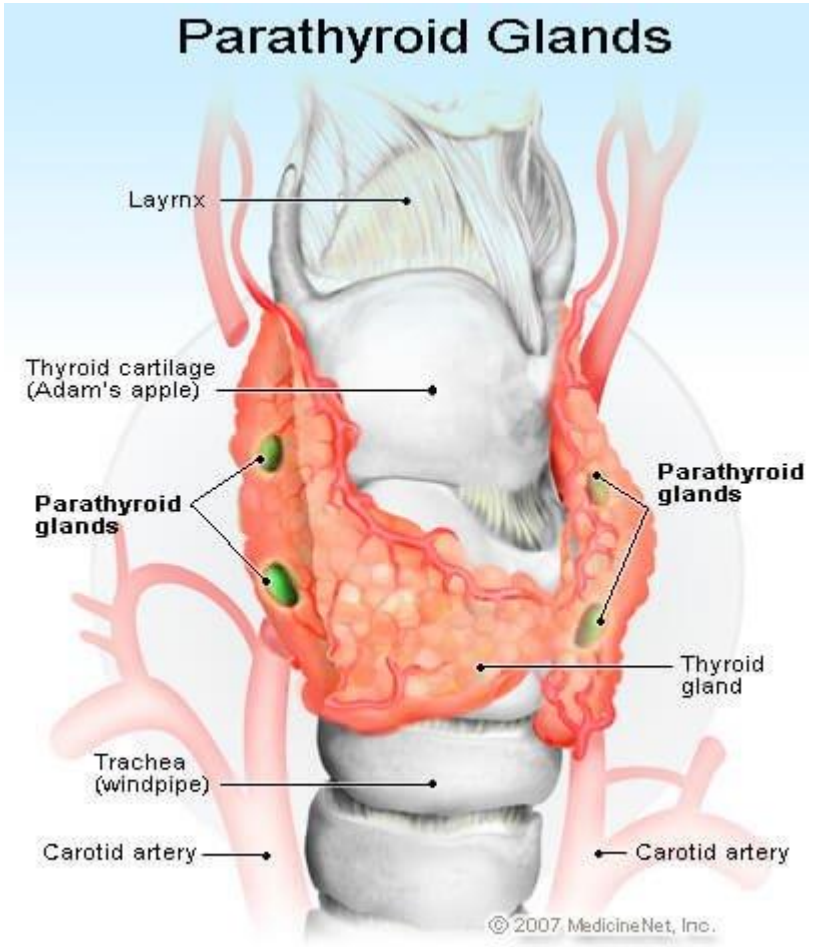


- Tumors
  - Pinealoma – deriving from pinealocytes, no special hormonal syndrome
  - Interestingly most of pineal gland tumors are of germ cell origin (eg. teratoma)

Parathyroid glands *(p1126)*

- Anatomy
  - 2 x paired organs
  - Rarely mediastinal location (intrathymic)
  - Histologically 3 different cell types (chief, water clear, oxyphil)

- Function
  - Parathormone release
  - Directly controlled by blood Ca 2+
  - Very short half life – Ca 2+ level is suitable to monitorize PTH release



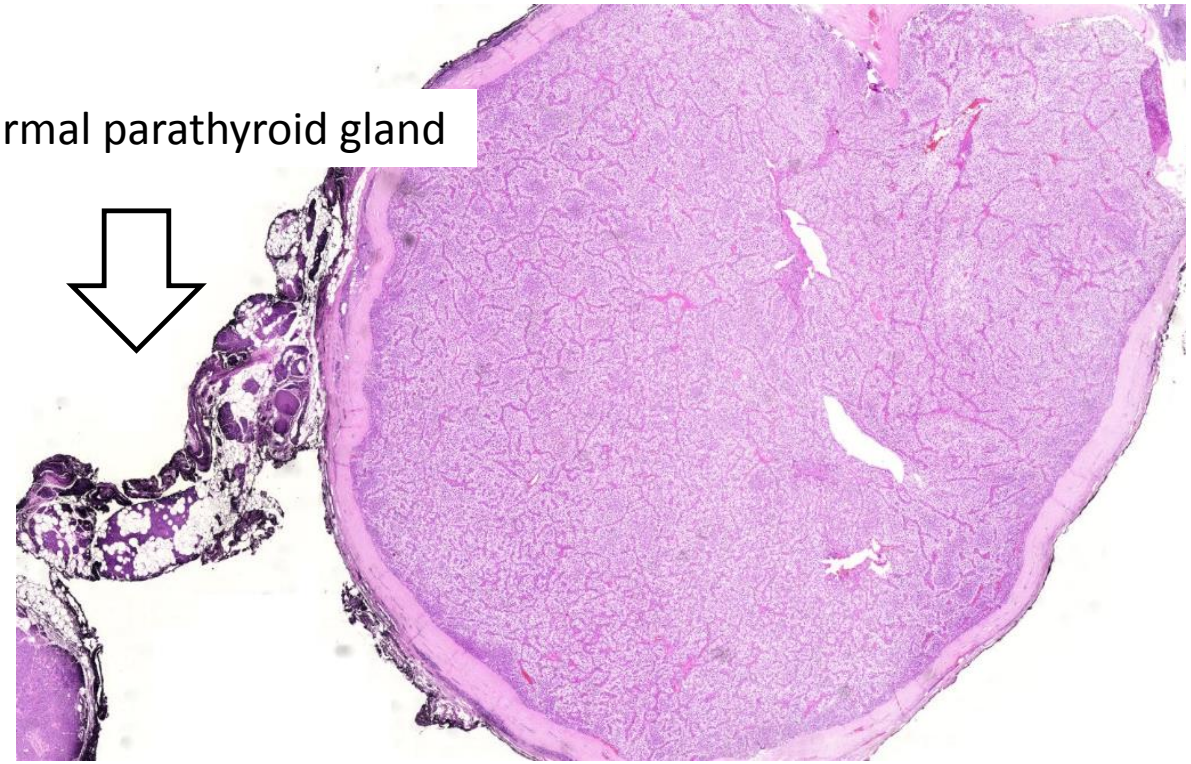
Hyperparathyreoidism, hypercalcemia

- Primary (PHPT)
  - 90% adenoma, 9% hyperplasia (MEN), 1% carcinoma
  - Usually solitary lesion
  - Preoperative diagnosis: Radionuclide scan/FNAB
  - Surgery: intraoperative Ca 2+ test!

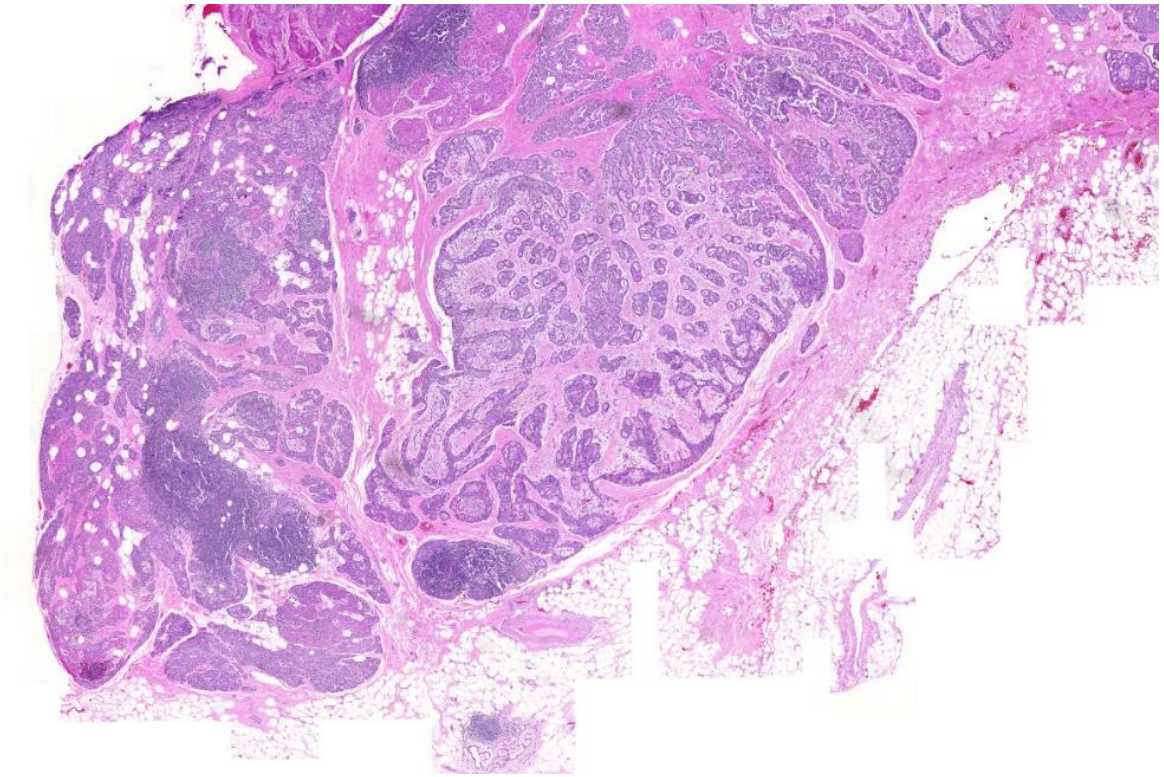
- Secondary
  - Cause: excessive Ca 2+ loss
  - Chronic renal failure
  - Hyperplastic change in all glands

- Malignancy associated hypercalcemia – PTH related protein (PTH-rP)
  - Common paraneoplasia with poor prognosis
  - Solid tumors: lung-head&neck squamous cell carcinoma, breast carcinoma, renal cell carcinoma
  - Hematologic malignancy: multiple myeloma

Morphology

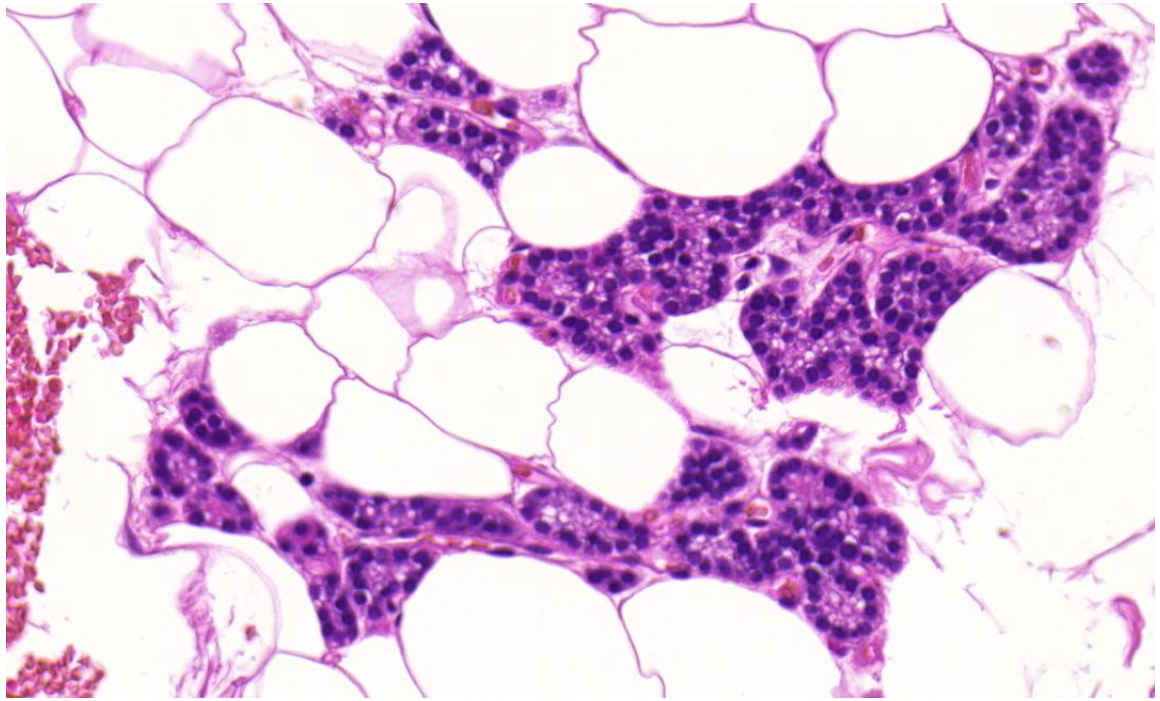


adenoma

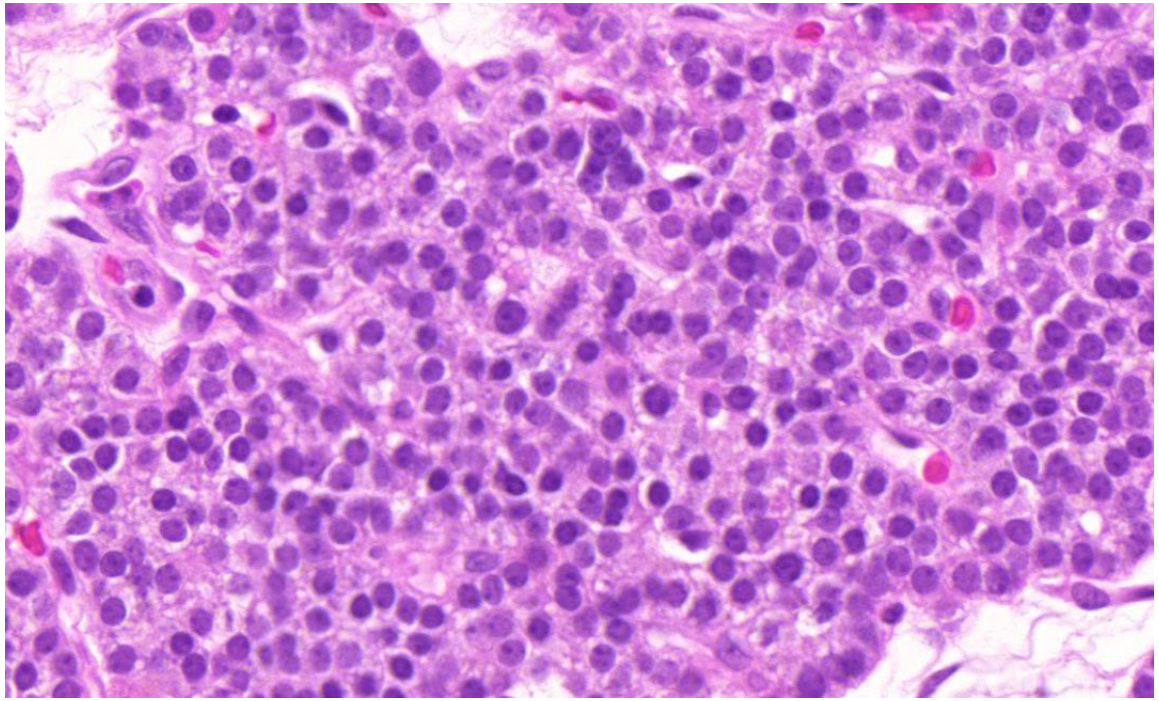


hyperplasia

Micro morphology



normal

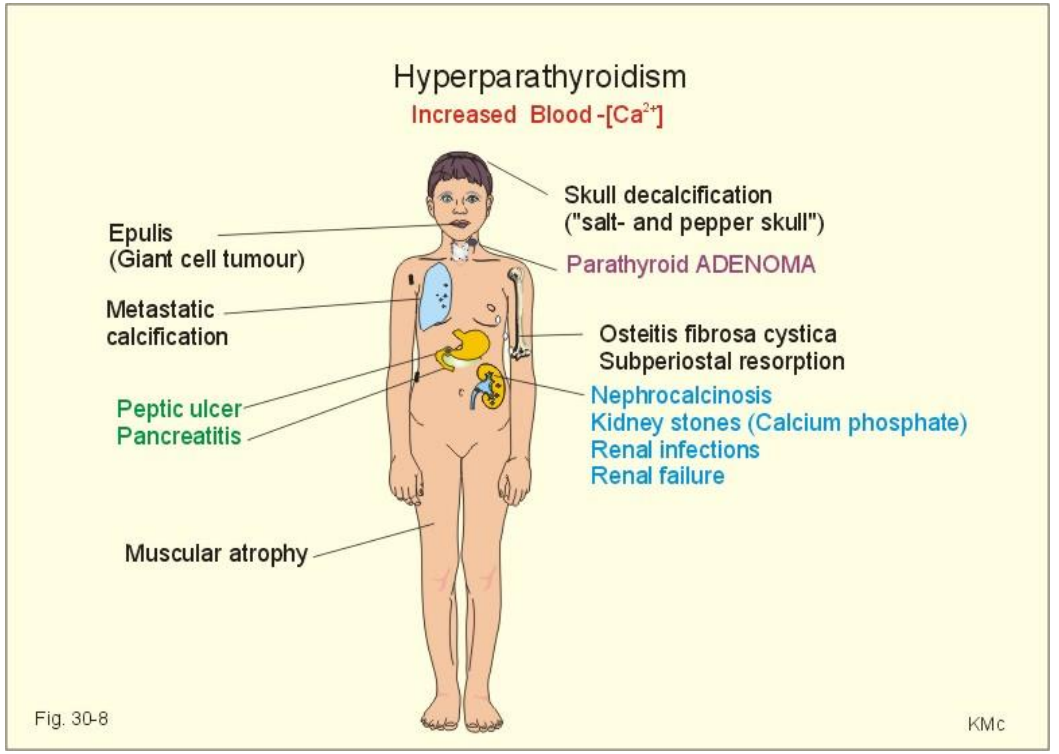


adenoma

Consequences of hyperparathyreoidism

- Increased osteoclast activity
  - Skeletal lesions: osteitis fibrosa cystica, „brown tumor”

- Elevated Ca 2+ level
  - Repeating nephrolithiasis
  - Gastrointestinal malfunction (constipation)
  - CNS: depression
  - Neuromuscular: weakness
  - Cardial disorders: valvular calcification



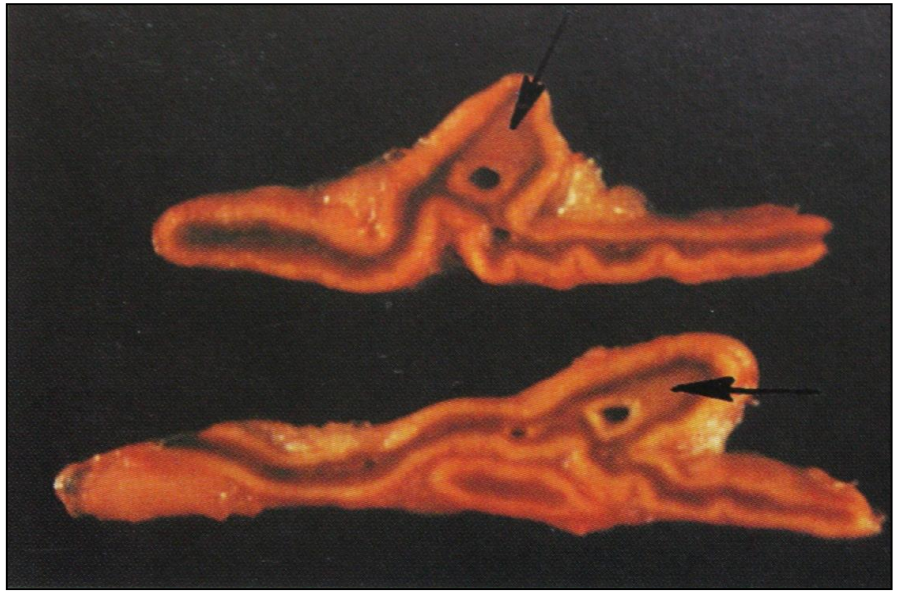
Hypoparathyreoidism

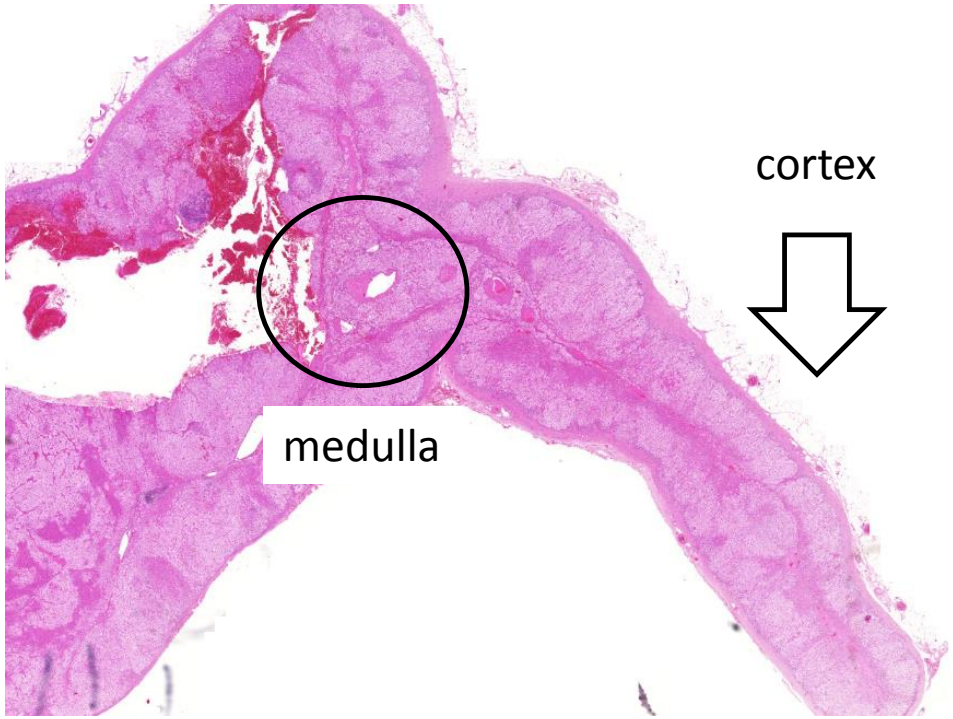
- Generally iatrogenic (total thyreoidectomy)
- Autoimmune parathyreoiditis
- Genetic disorders
- Aplasia

- Consequences: decreased Ca 2+ level
  - Tetany, anxiety-depression, ocular and dental disorders, heart conduction abnormalities etc.

Adrenal glands (p1148)

- Anatomy
  - Paired organs
  - Rarely ectopic=eg. funicular
  - Different development (mesodermic&neuroectodermic)
- Function
  - Cortex: steroid hormones
    - Glucocorticoids
    - Mineralocorticoids
    - Sex steroids
  - Medulla: catecholamines





Adrenocortical hyperfunction

Cushing syndrome = hypercortisolism

- Central (=Cushing disease)
  - Pituitary corticotroph adenoma
  - Secondary hypercortisolism (ACTH↑, cortisol↑)
  - Diffuse adrenal hyperplasia
- Peripherial Cushing syndrome
  - Primary adrenal nodular hyperplasia or adenoma, rarely carcinoma
  - Primary hypercortisolism (ACTH↓, cortisol↑)
  - Adrenal cortex atrophy
- Ectopic Cushing syndrome
  - Paraneoplasia, eg. SCLC
  - Secondary hypercortisolism (ACTH ↑ ↑ ↑, cortisol↑)
  - Diffuse adrenal hyperplasia
- Exogenous Cushing syndrome
  - Glucocorticoid medication generally for immunosupressive purpose

Conn syndrome = hyperaldosteronism

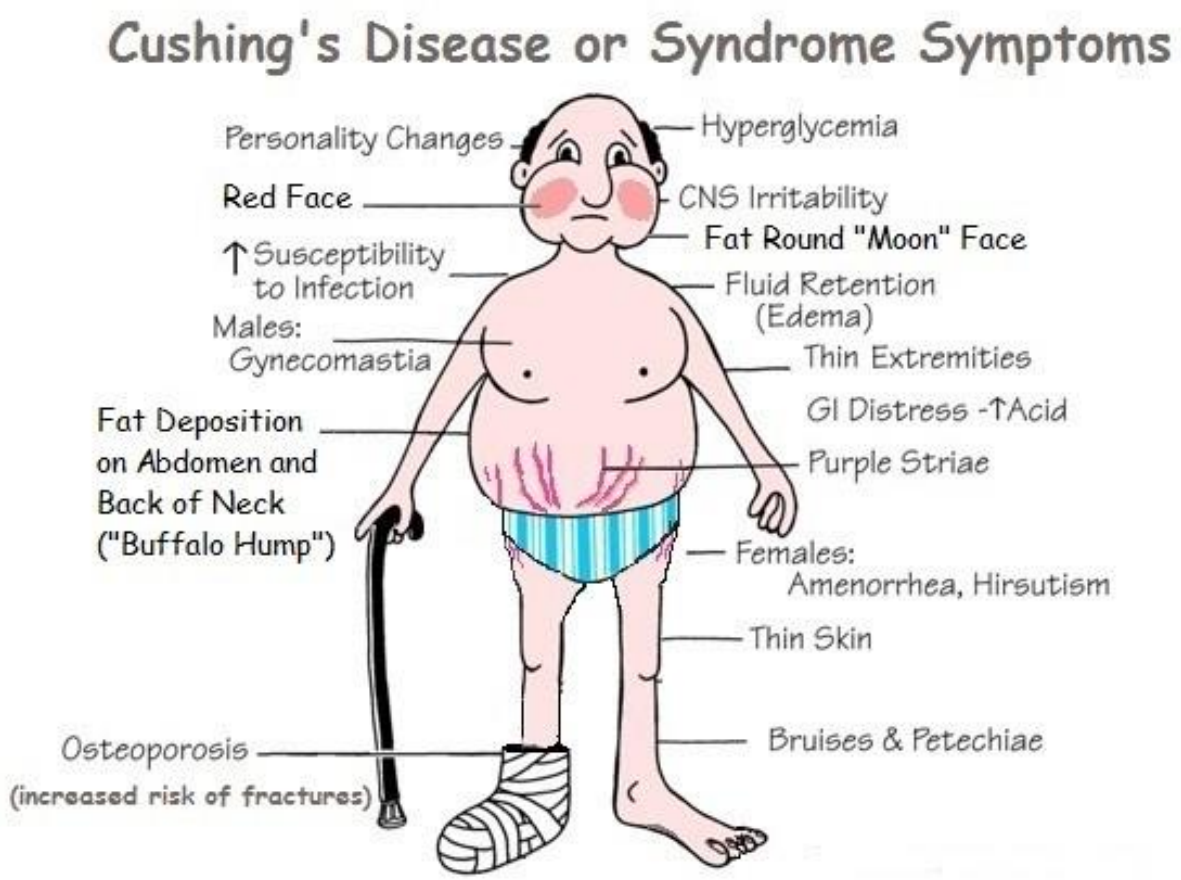
- primary adrenal adenoma
- rarely nodular hyperplasia
- Secondary hyperaldosteronism
  - Increased renin level: renal hypoperfusion, pregnancy
  - Renin producing tumors: very rare

Hyperfunction of sex hormones

- Malignant cortical neoplasia
- Adrenogenital syndrome

Adrenocortical hyperfunction - symptoms

Cushing syndrome =hypercortisolism

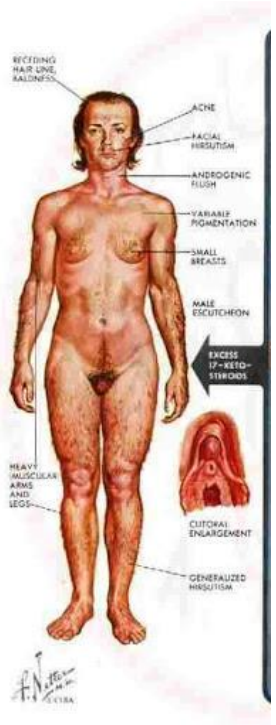


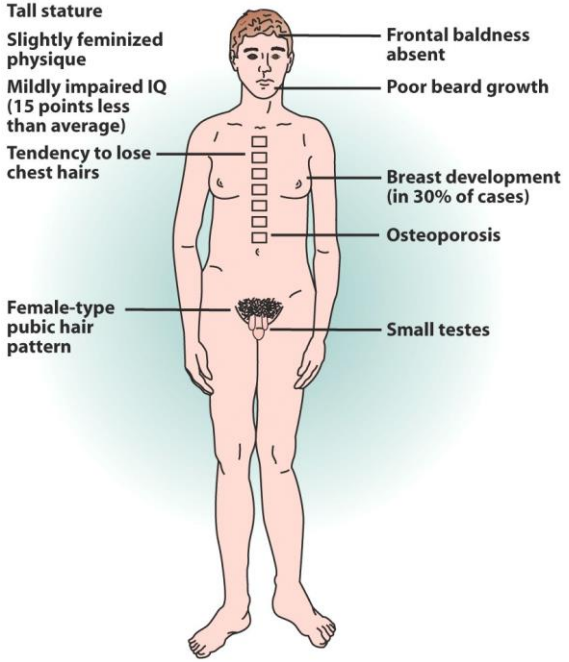
Conn syndrome = hyperaldosteronism

- No external signs

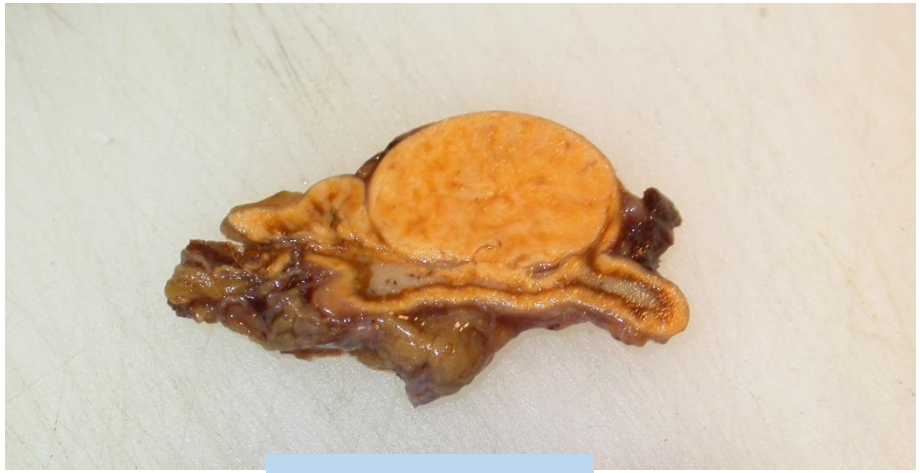
Hyperfunction of sex hormones

- Virilization, feminization



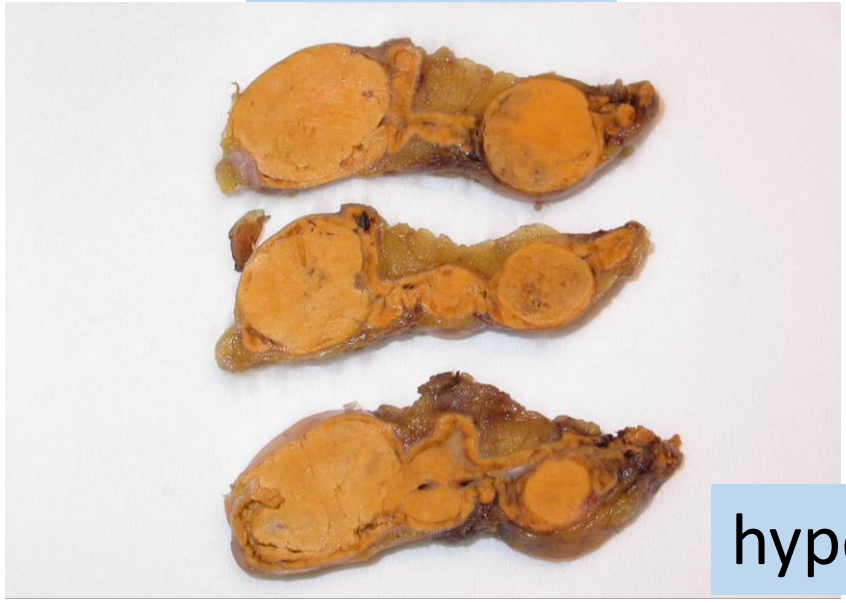


Morphology of adrenal cortical lesions



adenoma

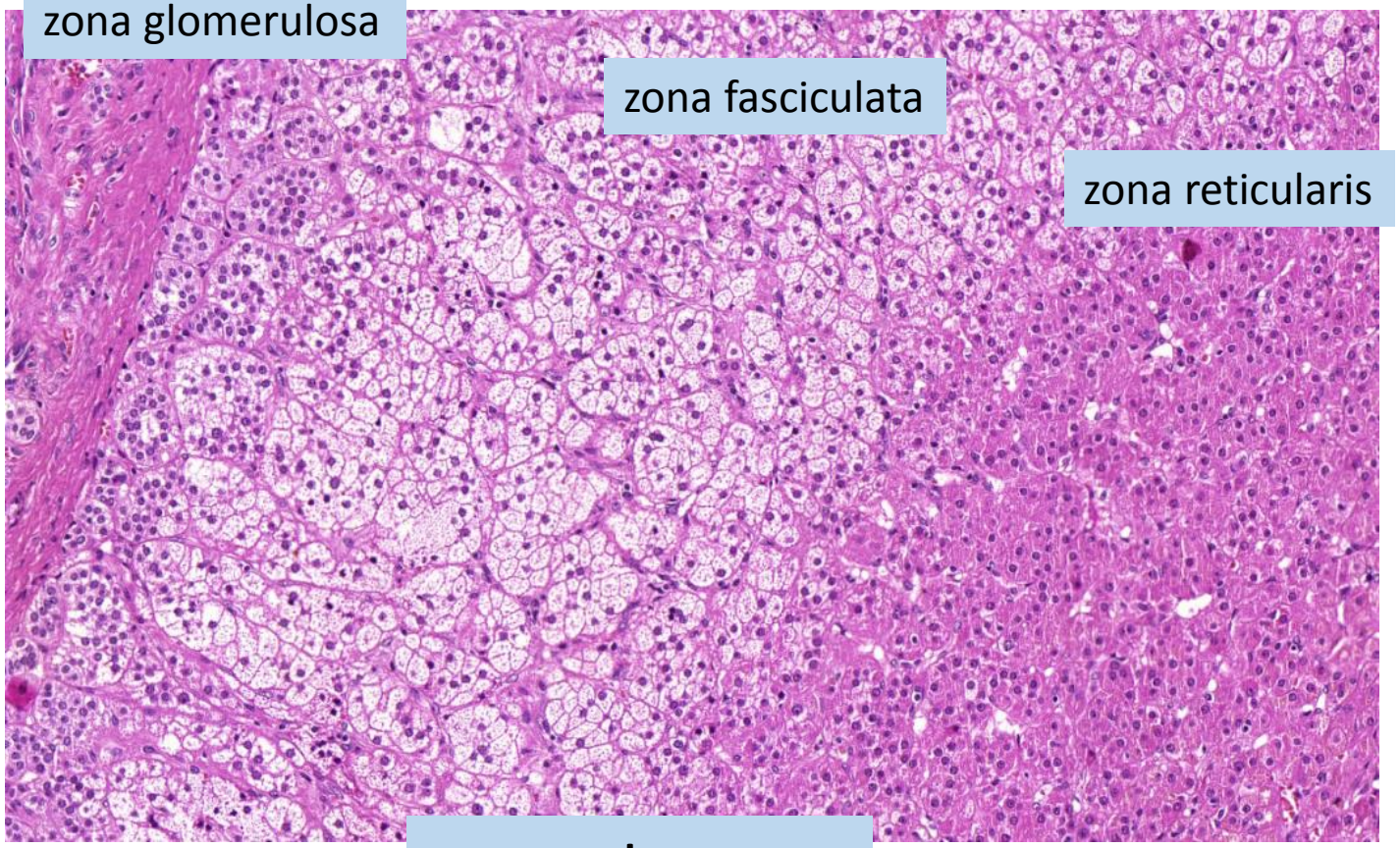
primary=nodular



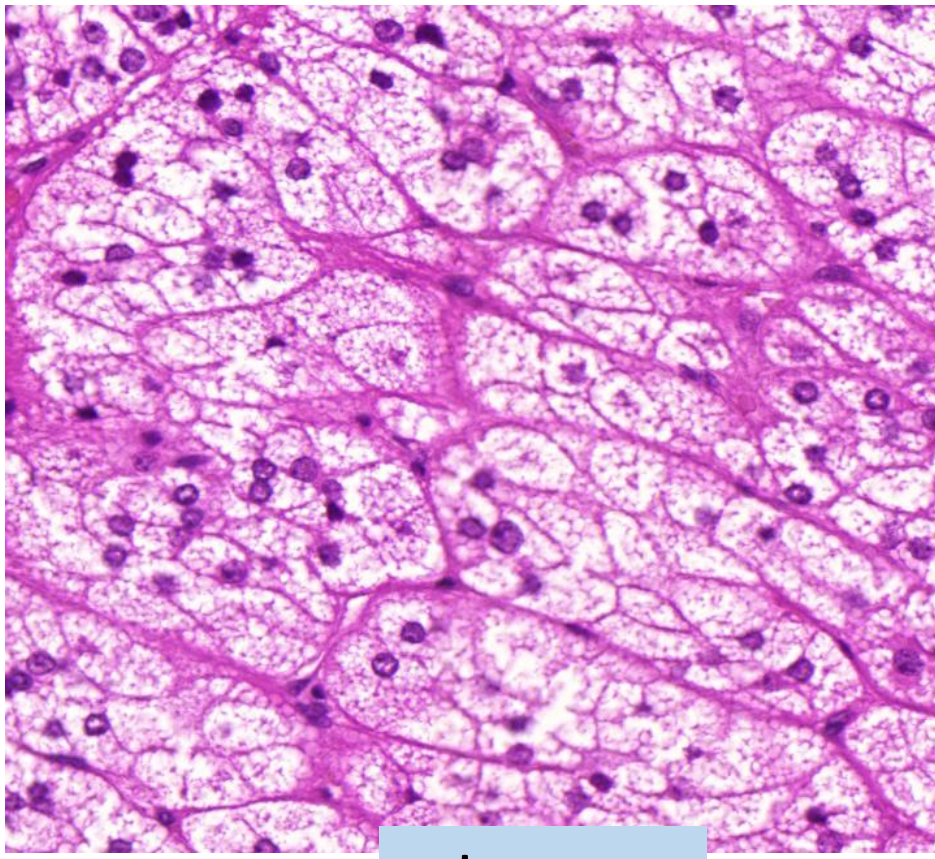
hyperplasia

secondary=diffuse

Microscopic morphology



normal cortex



adenoma

Adrenocortical insufficiency

Primary

- Genetic abnormality
  - adrenogenital syndrome=21 hydroxylase deficiency
  - mineralocorticoids↓, glucocorticoids ↓ , sex steroids↑
  - ACTH ↑ ↑ ↑
  - Super-sized adrenals
- Congenital hypoplasia
- Acute hemorrhagic necrosis

  =Waterhouse-Friderichsen sydrome (meningococcus sepsis)
- Primary chronic adrenocortical insufficiency= Addison disease

ACTH ↑ and POMC ↑ (=hyperpigmentation)

  - Autoimmune adrenalitis
  - Infections (fungal, TB)
  - Metastatic cancer, lymphoma

Secondary

- ACTH deficiency
  - Hypopituitarism
  - **Long term steroid administration=atrophy**

  → Addison symptoms without hyperpigmentation

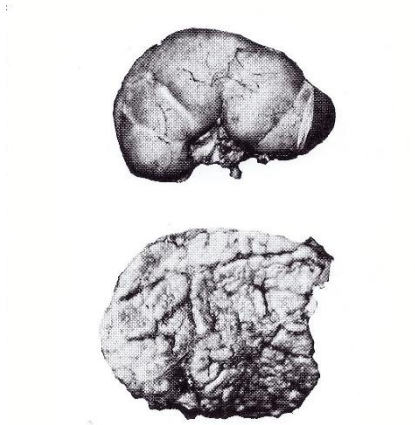
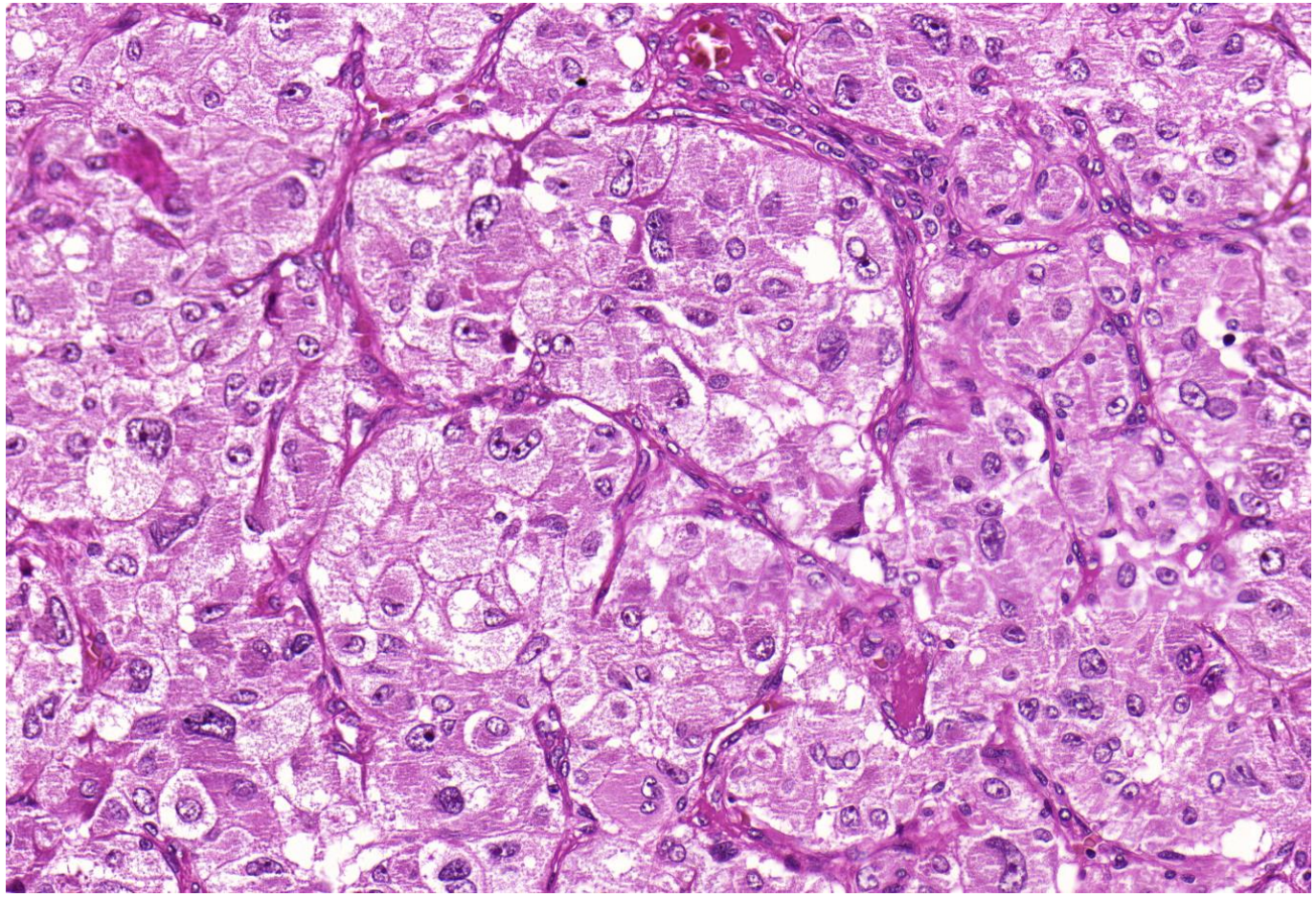


Figure 34
(Figures 34 and 35 from same patient)
CONGENITAL ADRENAL HYPERPLASIA
Gross photograph of kidney and adrenal from a patient with congenital adrenal hyperplasia who died at the age of 6 weeks. Combined adrenal weight was 22 g. 17-ketosteroid urinary excretion in 24 hours was increased to greater than 10 times normal. This is probably an example of severe 21-hydroxylase defect. Actual size. (Courtesy of the Department of Pathology, University of Leeds, Leeds, England.)

Adrenal medulla

- Pheochromocytoma
  - >90% hormonally active=secondary hypertension
  - >90% benign clinical course (no evident histological signs of malignancy)
  - Frequent germline genetic abnormalities: >10% (see later)

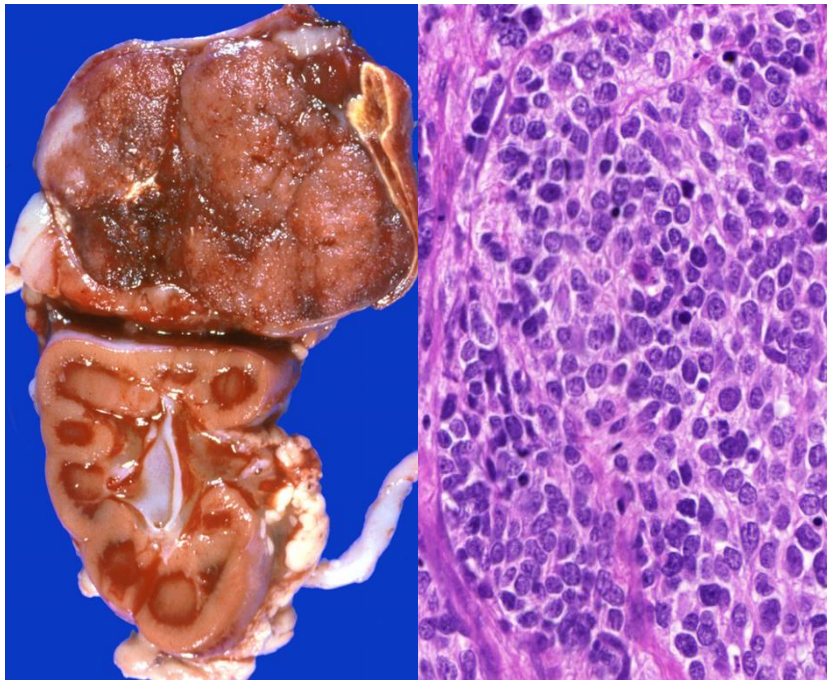
Morphology

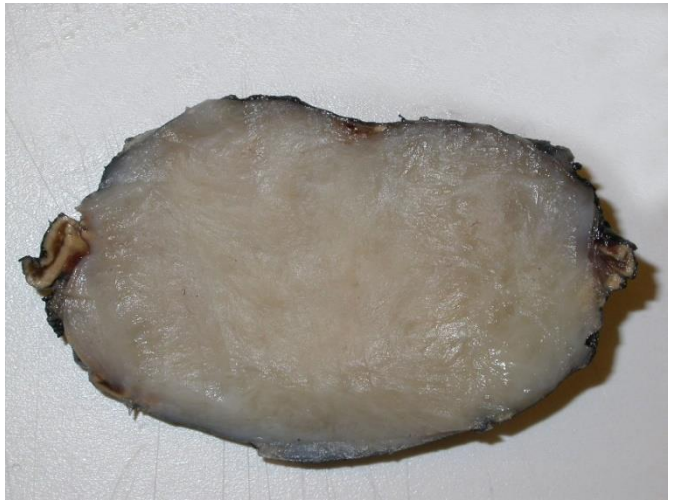


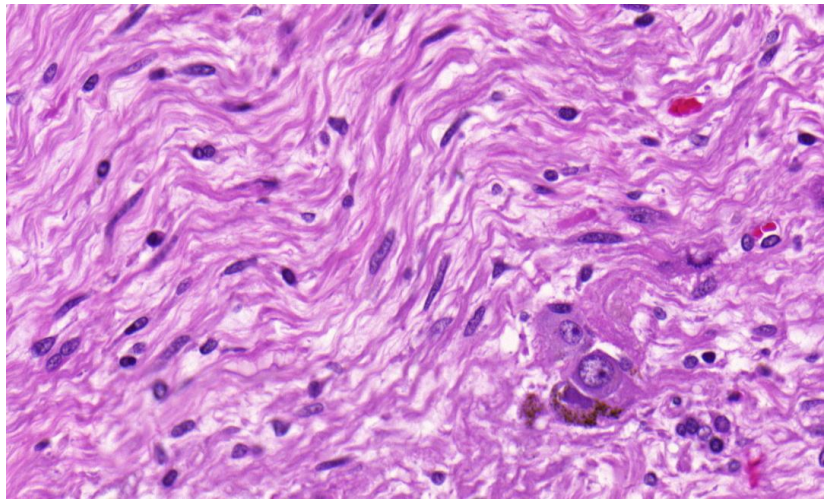
Ganglion-like chief cells and sustentacular cells form „zellballen”

Embryonal type medullary tumors

- Neuroblastoma (see childhood tumors)
- Mature form: ganglioneurinoma – incidendal, hormonally inactive tumor in adults



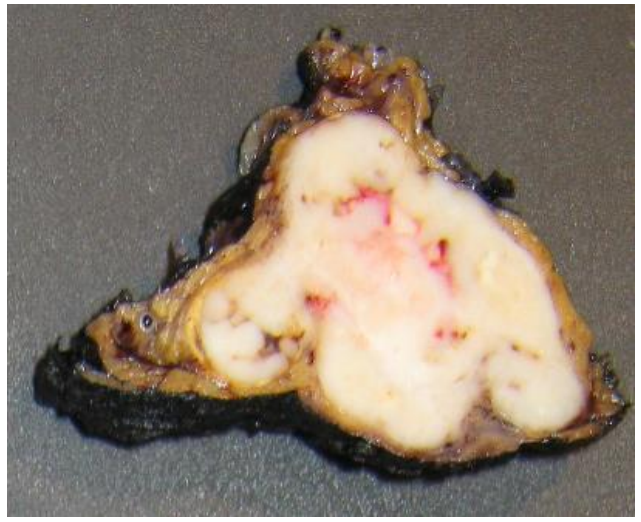


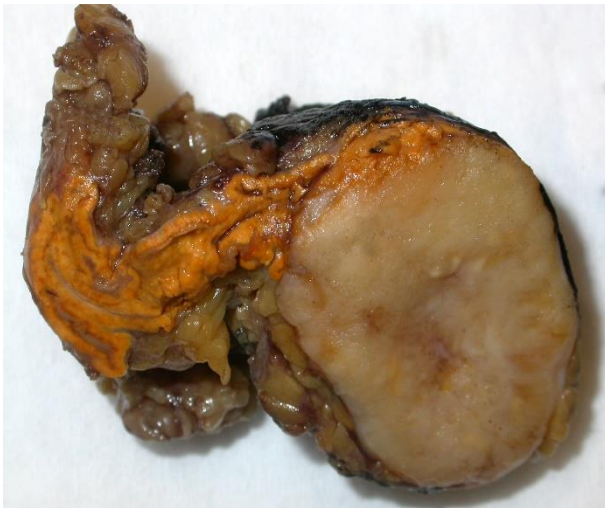


Hormonally inactive adrenal tumors

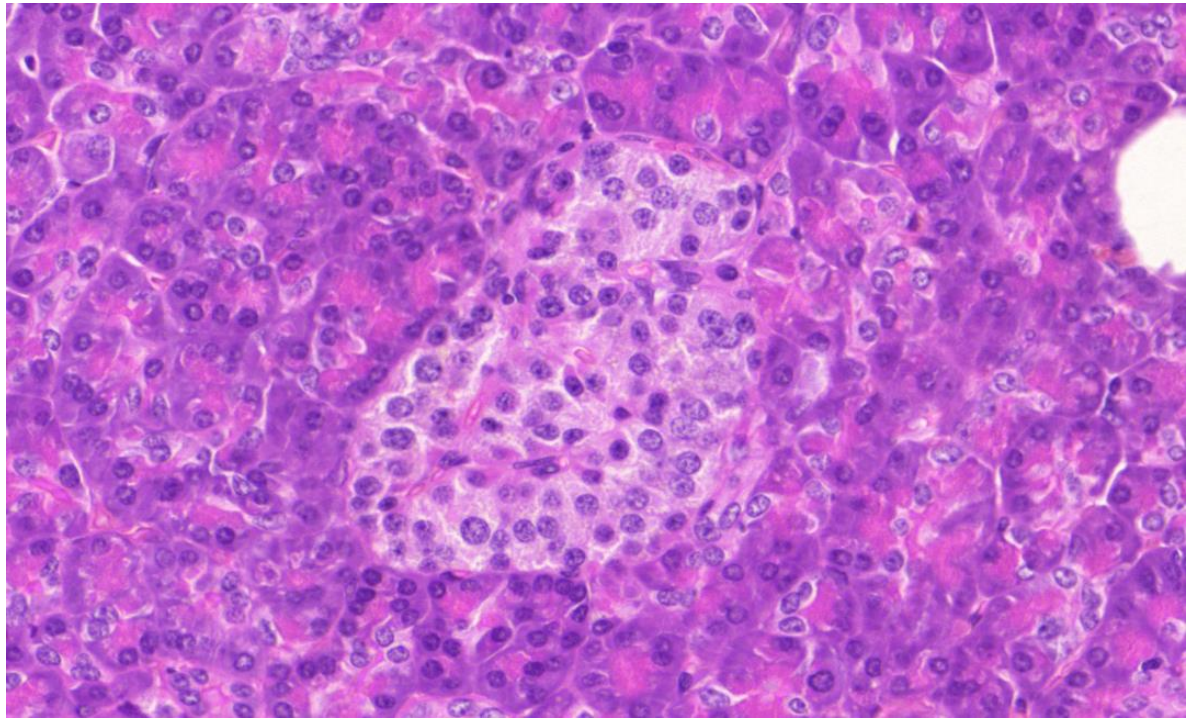
- Incidental cortical adenoma
  - Most frequent autopsy finding within the adrenals

- Metastatic malignancies
  - Lung-, kidney-, breast-, colorectal carcinoma, melanoma





Endocrine pancreas



- Anatomy
  - Islets of Langerhans are not visible macroscopically
- Function
  - ß-cells: insulin production
  - α-cells: glucagon production
  - δ-cells: somatostatin
  - Other hormone products: pancreatic polypeptide, vasoactive intestinal polypeptide, gastrin

Hyperfunction of endocrine pancreas

- Always primary – generally hormonally active neuroendocrine tumors
  - Hyperinsulinism: insulinoma (generally benign), rarely islet hyperplasia (nesidioblastosis)→hypoglycemia
  - Glucagonoma →diabetes, characteristic skin lesion (necrolytic migratory erythema)
  - Gastrinoma →Zollinger-Ellison syndrome
  - VIPoma →WDHA syndrome (=watery diarrhea, hypokalemia, achlorhydria)

  - General tumor features: see NET classification

Hypofunction of endocrine pancreas

- Diabetes mellitus (DM) is a group of metabolic disorders caused by hyperglycemia which is a result of defect in insulin secretion or insulin action or both
- Hyperglycemia is not a morphological disorder thus DM is a clinical diagnosis
- Classification of DM also based on clinical tests – morphology of endocrine pancreas is not examined routinely
- Pathology studies focus on the late morphological consequences of DM (generally faced them in the autopsy hall)

Classification of DM (p1132)

- Mixed insulin resistance and ß-cell dysfunction: type 2 DM
- Inflammatory
  - Autoimmune T-cell mediated (hypersensitivity type IV): DM type 1
  - Infective: very rare (CMV)
- Exocrine pancreas defect (pancreatogenic DM)
  - Chronic pancreatitis
  - Total pancreatectomy
- Gestational DM
- Endocrinopathies (eg. Cushing syndrome)
- Drugs
- Genetic causes

Pathogenesis of complications in DM (p1138)

Basic problems resulted from

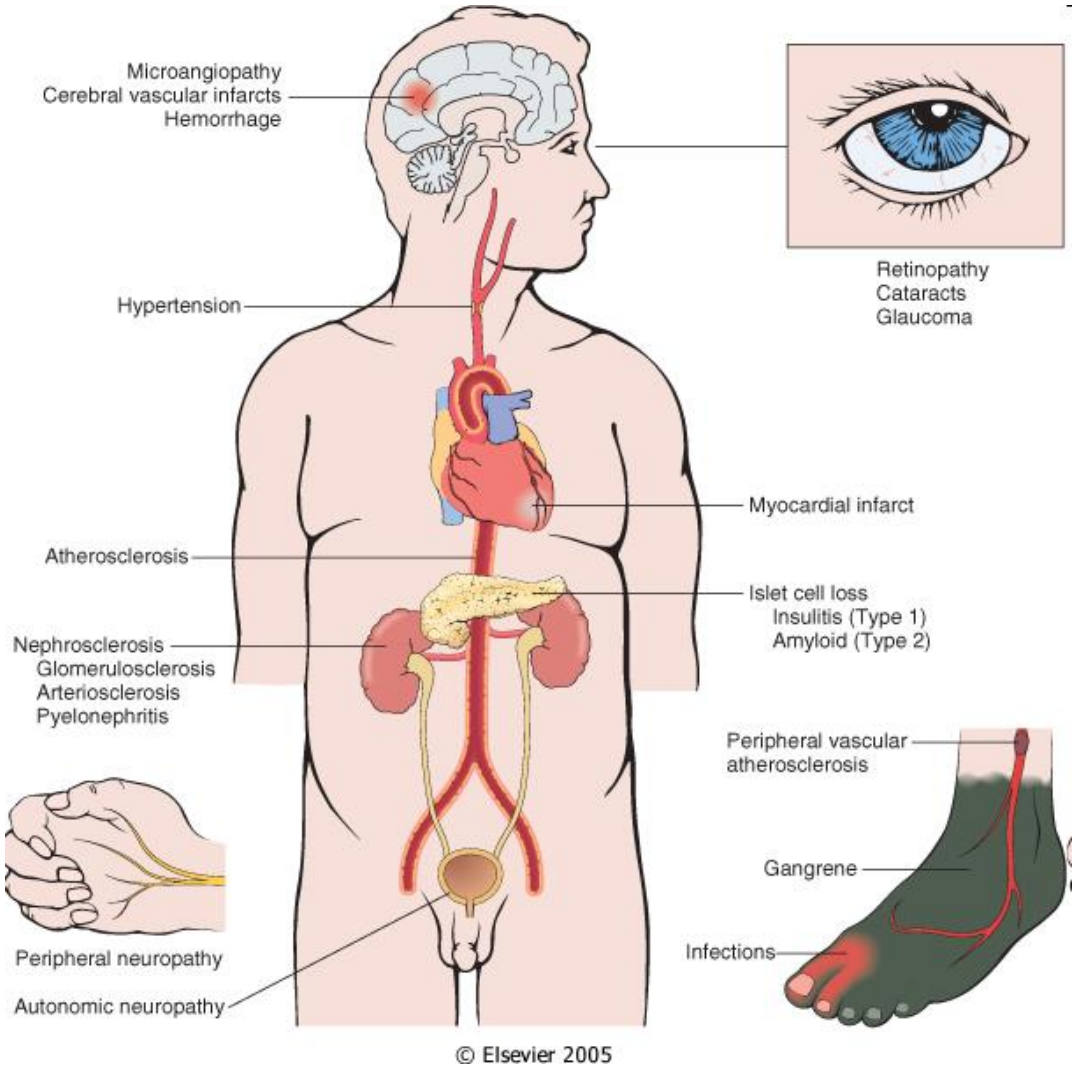
1. Glycation
2. PKC (protein kinase C) activation and
3. Intracellular hyperglycemia

These problems result in → degeneration of:

1. Arterial intima (endothelial injury)
2. Arterioles
3. Basement membrane
4. Retina, lenses
5. Nerves

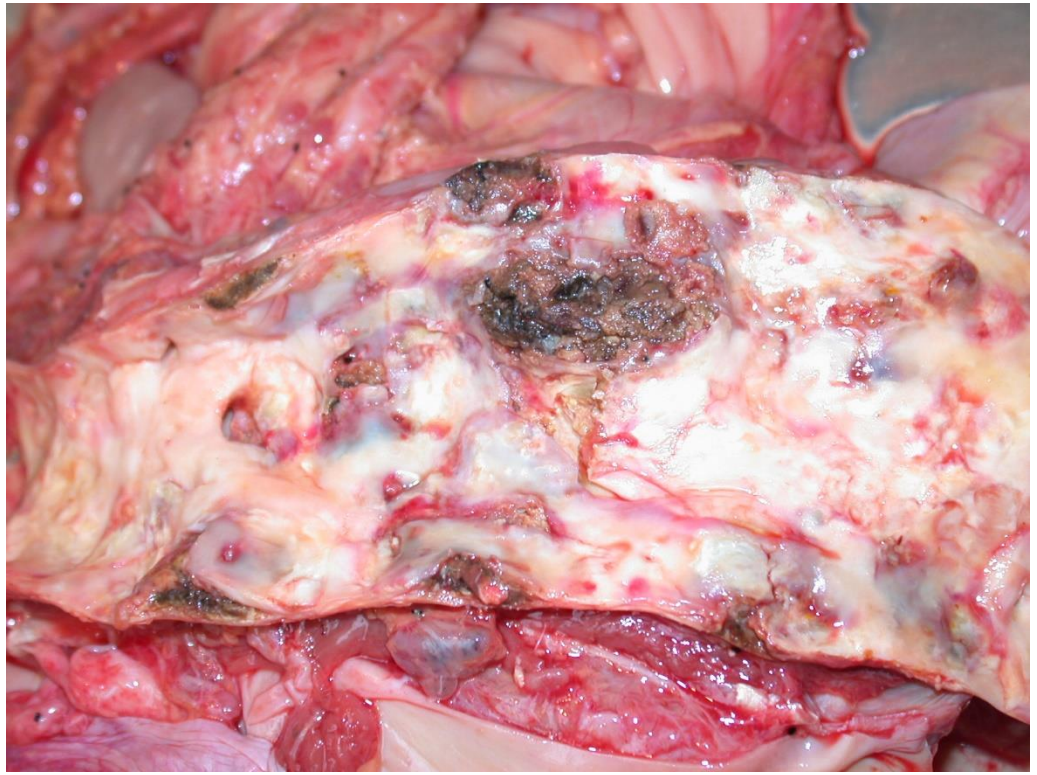
+ Increased risk of infections

Target organs affected by DM and its morphology (p1139-43)



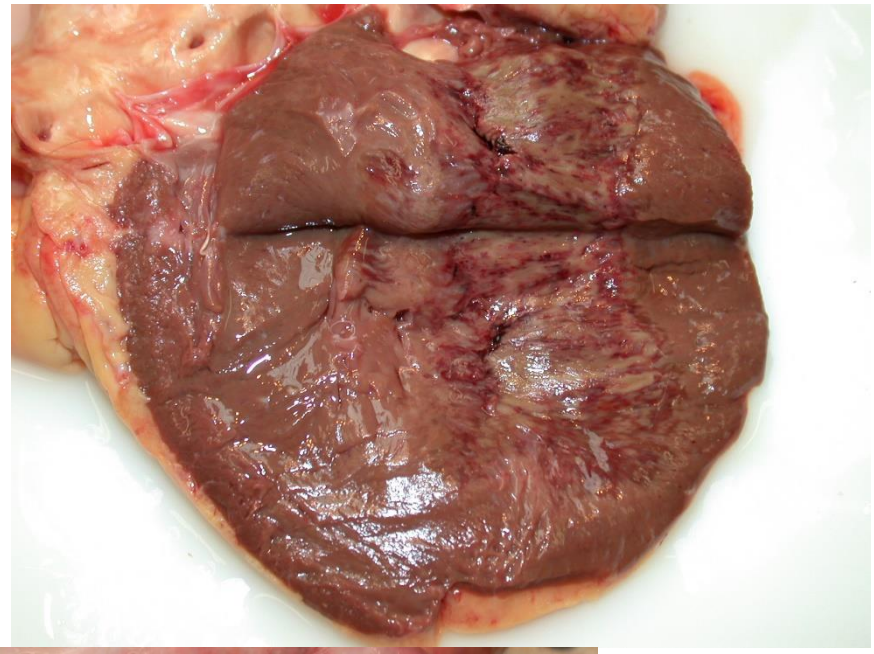
Macrovascular Disease

- Accelerated atherosclerosis
  - DM is one (but not the only!) of the most important risk factors of atherosclerosis
- PAD: Peripheral Artery Disease
  - Commonly affect legs

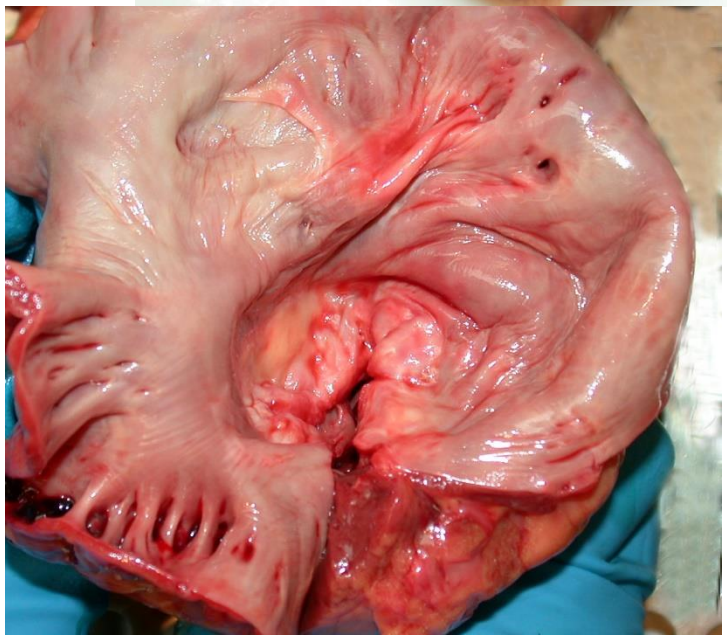


Cardiac complications

- AMI – accelerates coronary sclerosis

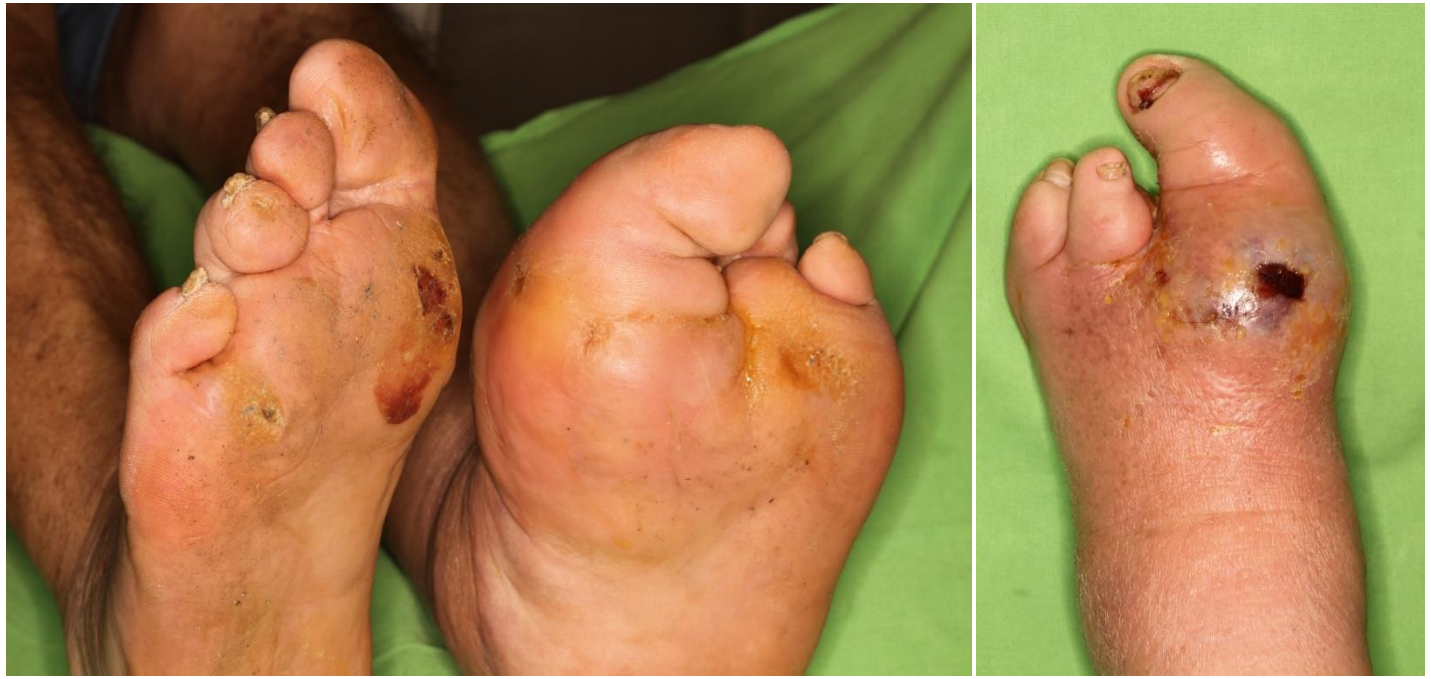


- Valvular and mitral annulus calcification



„Diabetic foot”

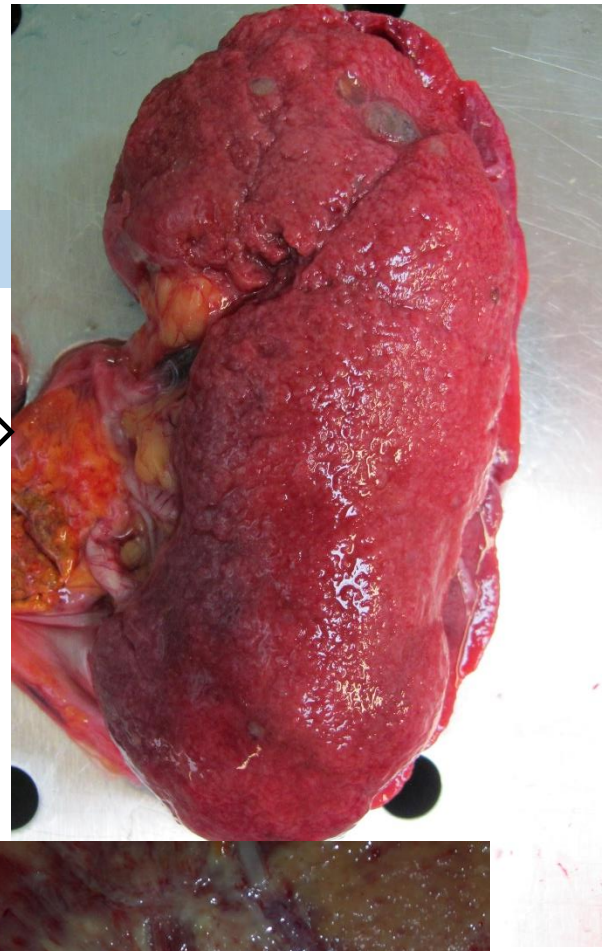
- Gangrene and skin ulcers from
  - PAD
  - Microangiopathy
  - Neuropathy
  - Infections



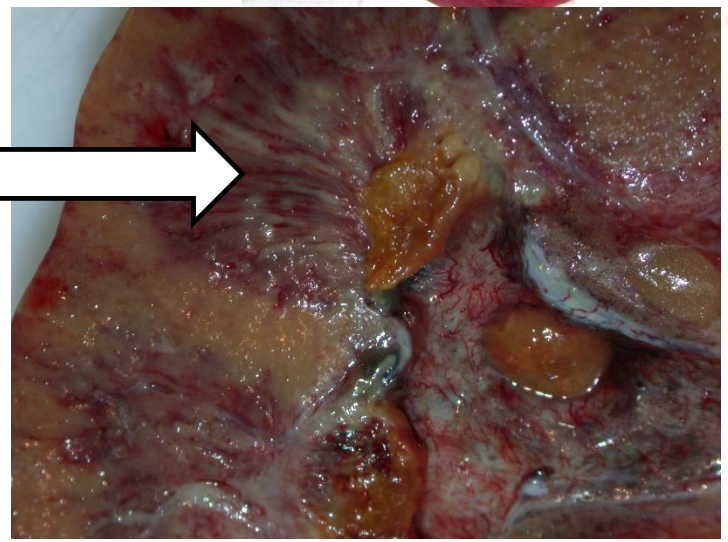
Renal complication

- Micro- and macroangiopathy
- Glomerular damage
  - Nodular glomerulosclerosis = Kimmelstiel-Wilson disease
  - Diffuse mesangial sclerosis

nephrosclerosis

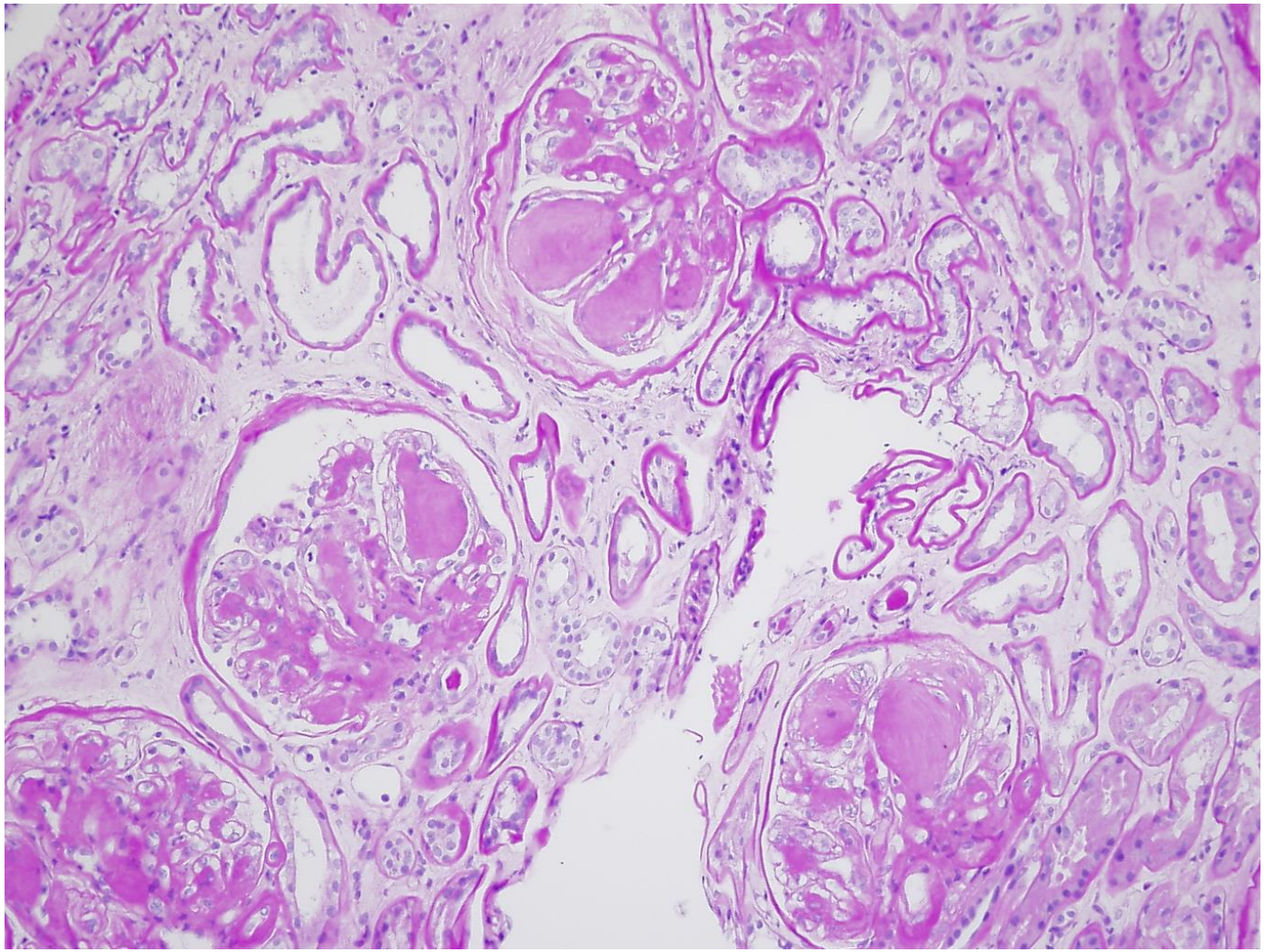


- Pyelonephritis
  - Acute PN with necrotizing papillitis
  - Chronic PN



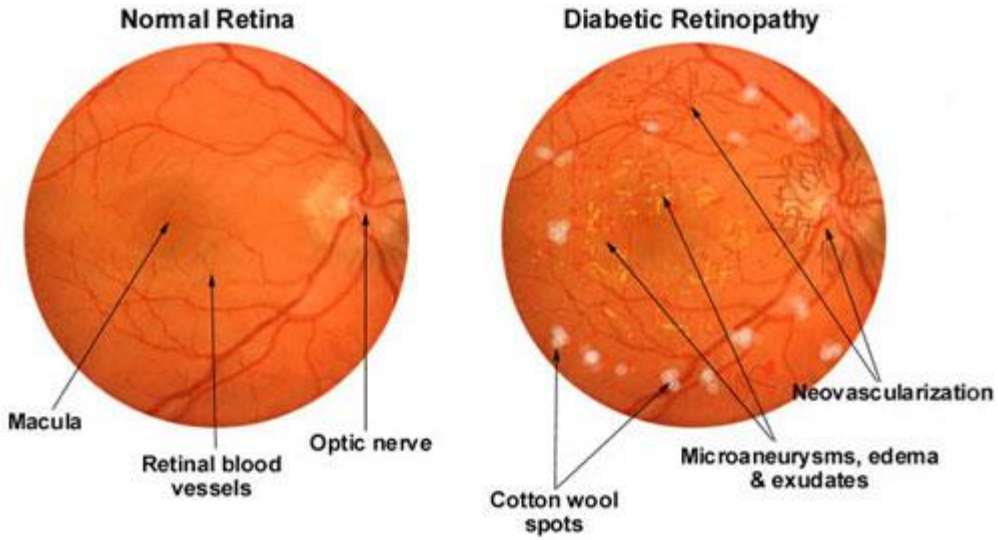
- End stage kindey

Kimmelstiel-Wilson disease (see nephropathology lecture)



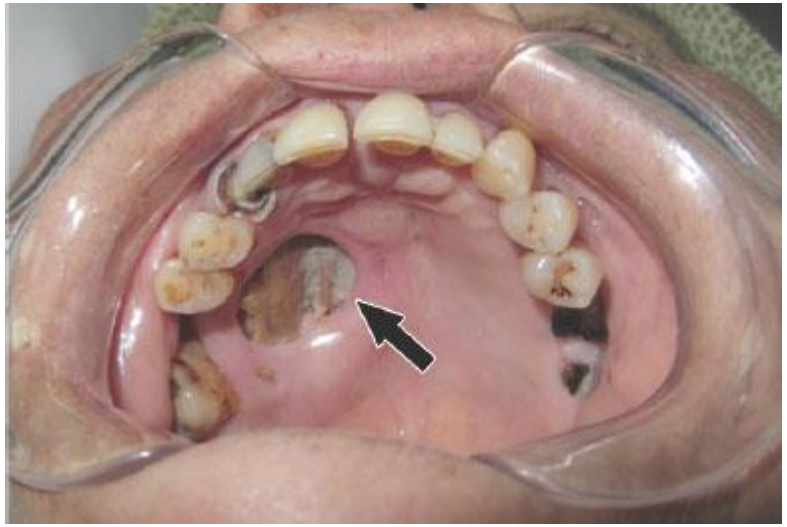
Eye disorders

- Diabetic retinopathy
  - Proliferative microangiopathy
  - Microhemorrhages
  - Fibrosis
- Cataract
- Glaucoma



Infections in DM

Rhinocerebral mucormycosis



www.smj.org.sa/index.php/smj/article/view/11859/7488

TABLE 1. CLINICAL FEATURES, DIAGNOSIS, AND CAUSATIVE ORGANISMS OF SELECTED INFECTIONS IN PATIENTS WITH DIABETES.

INFECTION	CLINICAL FEATURES	DIAGNOSTIC PROCEDURE*	ORGANISMS	COMMENTS
Respiratory tract				
Community-acquired pneumonia	Cough, fever	Chest radiography	*Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae,* other gram-negative bacilli, atypical pathogens	Pneumococcal infection carries a higher risk of death in diabetic than in nondiabetic patients
Urinary tract				
Acute bacterial cystitis	Increased urinary frequency, dysuria, suprapubic pain	Urine culture	*Escherichia coli,* proteus species	Bacteriuria more common in diabetic than in nondiabetic women
Acute pyelonephritis	Fever, flank pain	Urine culture	*E. coli,* proteus species	Emphysematous infection should be considered
Emphysematous pyelonephritis	Fever, flank pain, poor response to antibiotics	Radiography or CT scanning	*E. coli,* other gram-negative bacilli	Emergency nephrectomy often required
Perinephric abscess	Fever, flank pain, poor response to antibiotics	Ultrasonography or CT scanning	*E. coli,* other gram-negative bacilli	Surgical drainage usually required
Fungal cystitis	Same as for acute bacterial cystitis	Urine culture	Candida species	Difficult to distinguish colonization from infection
Soft tissue†				
Necrotizing fasciitis	Local pain, redness, crepitus, bullous skin lesions	Radiography or CT scanning	Gram-negative bacilli, anaerobes (type I), or group A streptococci (type II)	High mortality; emergency surgery required
Other				
Invasive otitis externa	Ear pain, otorrhea, hearing loss, cellulitis	Clinical examination, magnetic resonance imaging	*Pseudomonas aeruginosa*	Prompt otolaryngologic consultation recommended
Rhinocerebral mucormycosis	Facial or ocular pain, fever, lethargy, black nasal eschar	Clinical examination, magnetic resonance imaging, pathological findings	Mucor and rhizopus species	Strong association with ketoacidosis; emergency surgery required
Abdomen				
Emphysematous cholecystitis	Fever, right-upper-quadrant abdominal pain, systemic toxicity	Radiography	Gram-negative bacilli, anaerobes	High mortality; gallstones in 50%; emergency cholecystectomy required

*CT denotes computed tomography.

†Foot infections are described in detail in Table 3.

Sex cord stromal neoplasias *(p1050 and 992)*

Hyperfunction of sexual hormones: see adrenal cortical hyperfunction

- Ovarian tumors
  - Granulosa-Theca cell tumors
    - Hyperestrogenism may cause endomterial HP and carcinoma!
  - Fibroma/thecoma
    - Usually incidental, hormonally inactive
  - Sertoli-Leydig cell tumors
    - hyperandrogenism
- Testicular tumors
  - Leydig cell tumor
    - Precocitiy in childhood
  - Sertoli cell tumor

General aspects of neuroendocrine tumors of non-endocrine organs (DNES)

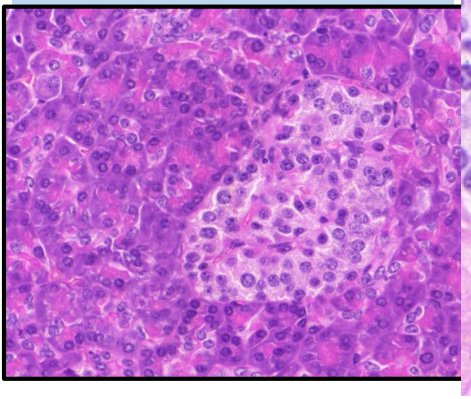
- Deriving from dispersed neuroendocrine cells of epithelial tissues (aka APUD cells)
- Diagnostic criterion: presence of at least 1 NE marker immunohistochemically

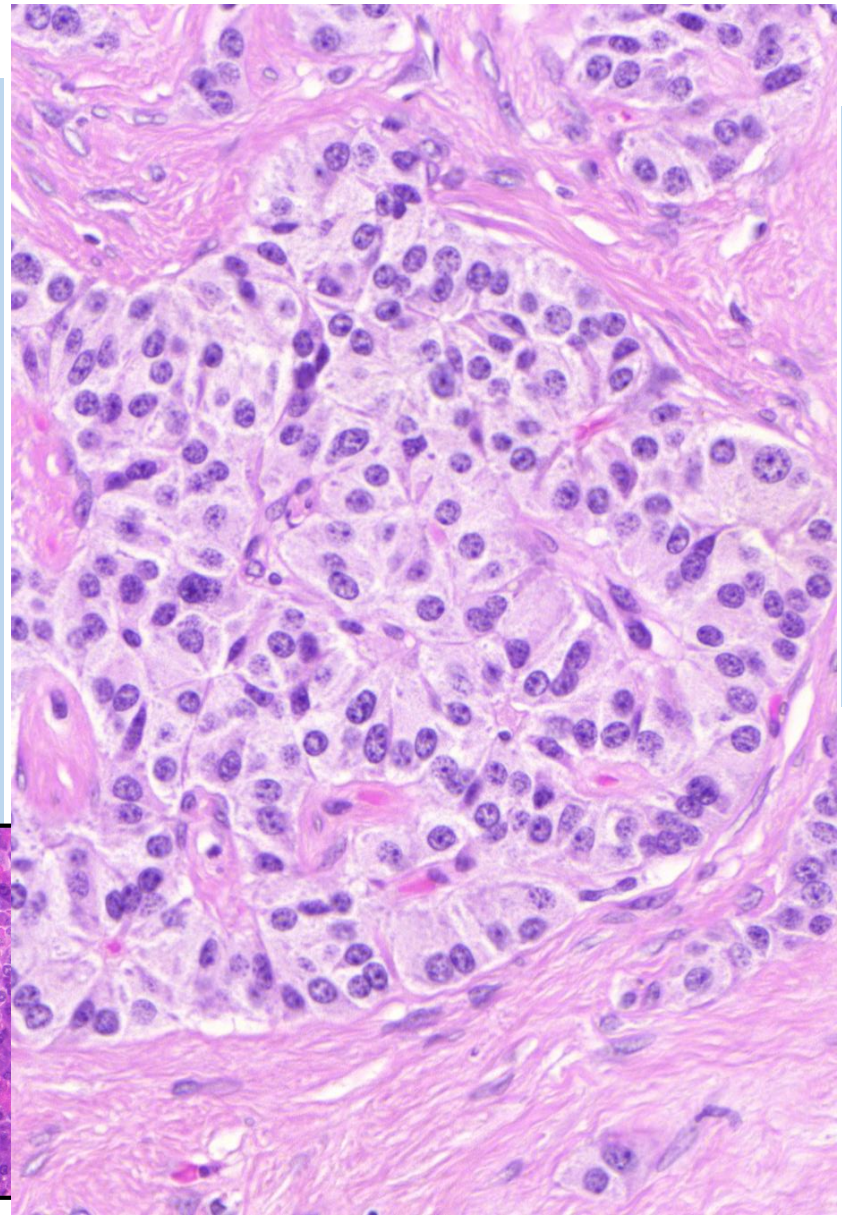
- Gastro-Entero-Pancreatic NeuroEndocrine Tumors (GEP-NET)
  - WHO classification of GEP-NET 2010
    - Neuroendocrine tumor, grade 1-3 (based on mitotic count/Ki67 index)
    - Neuroendocrine carcinoma grade 3 (based on morphology)
- Neuroendocrine tumors of the lung
  - WHO classification of lung tumors 2015
    - Typical/atypical carcinoid
    - Small cell lung carcinoma (SCLC)
    - Large cell neuroendocrine carcinoma
- Others
  - Urinary tract
  - Skin
  - Breast

Morphology of NE differentiation in tumors

NE differentiation present:

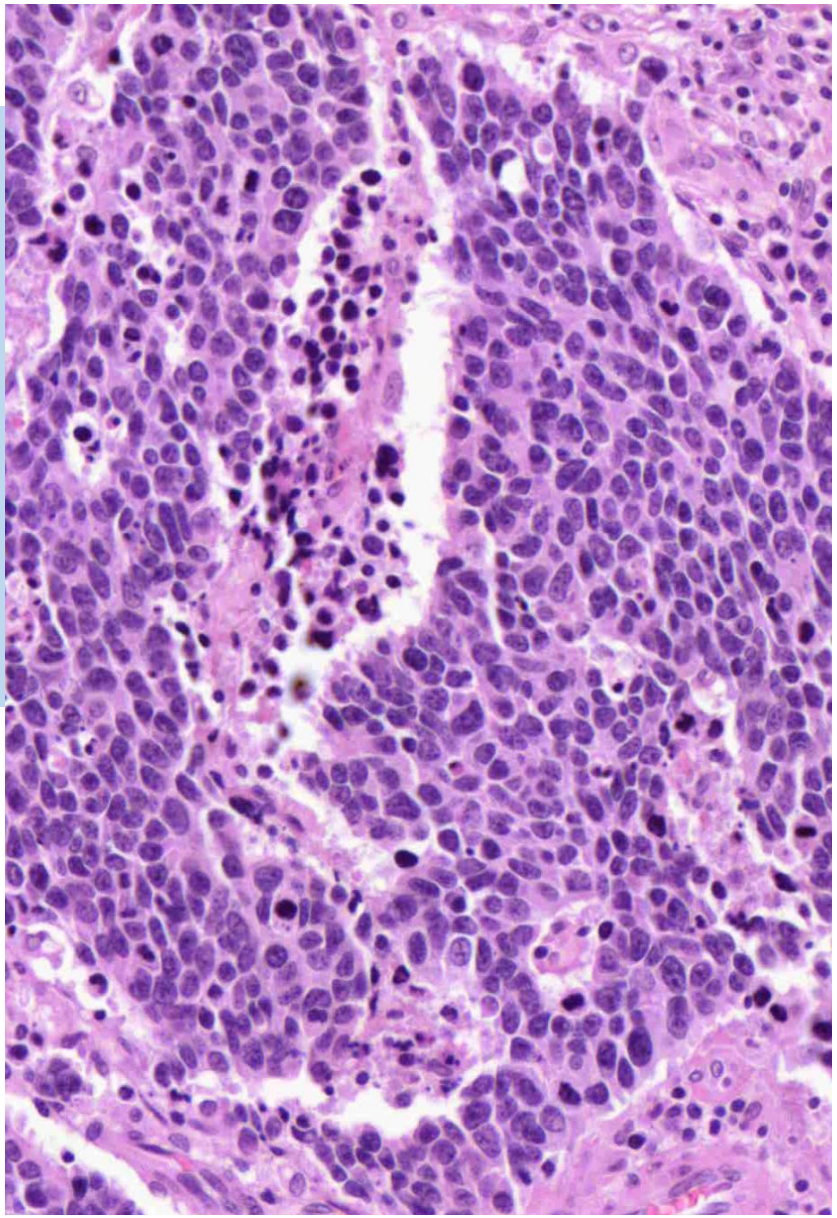
1. Insular structures common
2. Salt&pepper chromatin
3. Plasmocytoid appearance
4. Low mitotic count
5. No necrosis



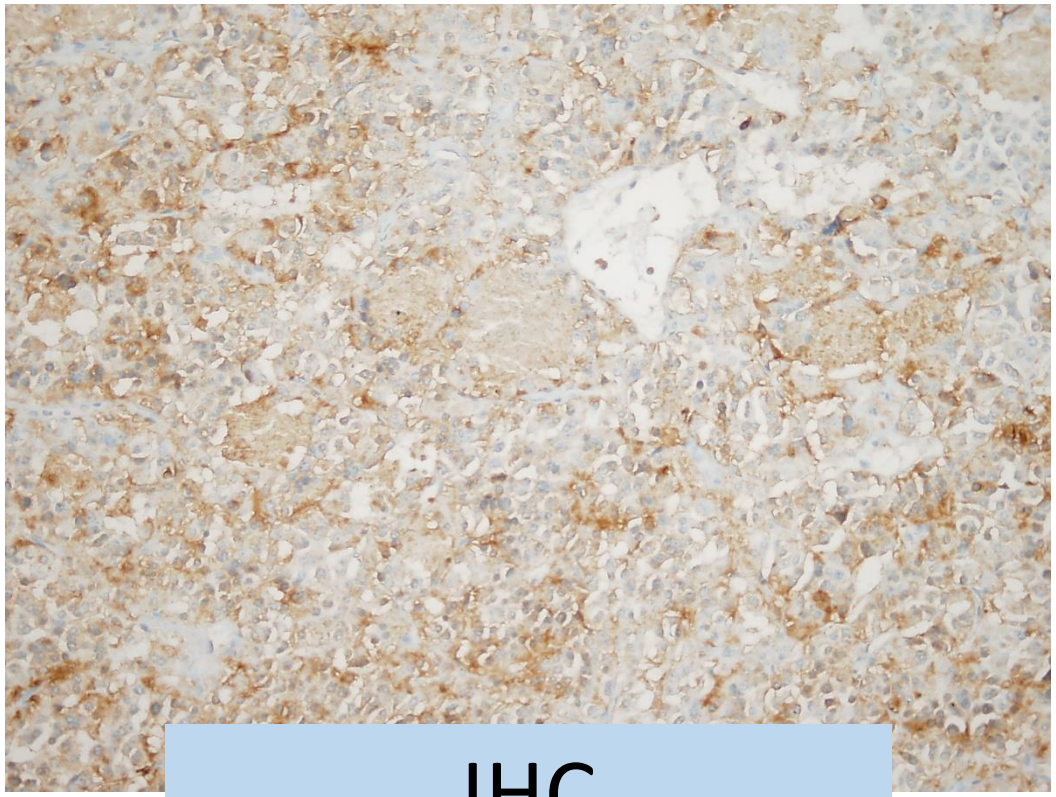


Poorly differentiated neuroendocrine carcinoma (small cell type)

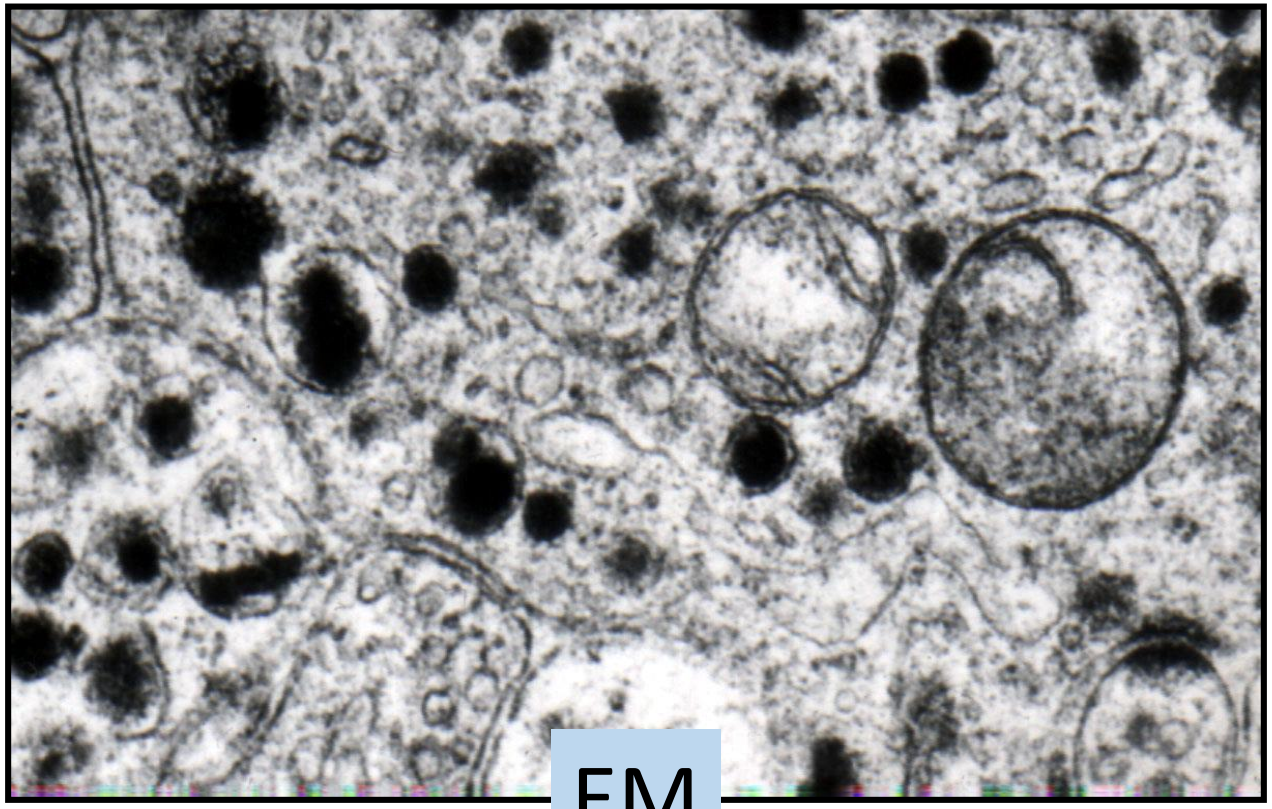
1. Hyperchromasia
2. Polymorphism
3. High mitotic count
4. Necrosis



Presence of neurosecretory granules



IHC
(chromogranin A)



EM

Grading of GEP-NETs

- Grade 1: Ki 67:<2%, mitoses: <2/10 HPF
- Grade 2: Ki 67: 2-10%, mitoses 2-10/10 HPF
- Grade 3: Ki 67: >20%, mitoses >10/10 HPF

Overview of NE neoplasias in different organs

Organ	NE differentiation present Clinical behaviour: slow progression even in metastatic stage	Poorly differentiated Clinical behaviour: poor prognosis, rapid progression
Pancreas	NET grade 1,2 Insulinoma: practically benign	NEC grade 3: poor prognosis
Stomach, duodenum	NET grade 1,2 • MEN 1 & atrophic gastritis associated: good prognosis • Sporadic: worse prognosis	
Small bowel	NET grade 1,2,3: high metastatic potential	
Colon	Rectum: grade 1,2: good prognosis	Proximal colon: NEC grade 3: poor prognosis
Appendix	NET grade 1: usually incidental finding in appendectomy: good prognosis	
Lung	Typical/atypical carcinoid: indolent clinical course	NEC (small/large cell): poor prognosis • Frequent paraneoplastic hormon secretion
Urinary tract		NEC: poor prognosis
Skin		Merkel cell carcinoma: highly aggressive
Breast	Generally ER positive Prognosis not differ from usual breast cancer	

Syndromes associated with endocrine tumors

(p1161)

Syndrome	Mutated gene	Tumor types	Prognosis
Multiple endocrine neoplasia (MEN) type 1	MEN1	Parathyroid (PHPT) Pancreas Pituitary Gastric and duodenal gastrinomas (multiple) „3Ps"	Poor if NEC occur (mainly of pancreas)
MEN type 2	RET	2A: Parathyroid hyperplasia, phaeochromocytoma, medullary thyroid carcinoma • Preventive thyreoidectomy needed in childhood • Pheochromocytomas are usually benign 2B: plus neuromas and marfanoid habitus Familial medullary thyroid cancer • Only MTC occur	Good if preventive thyreoidectomy performed
VHL	VHL	Phaeochromocytoma	Other cancer types (renal cell carcinoma)
Neurofibromatosis	NF1	Phaeochromocytoma	
Familial paraganglioma (more types)	SDH (succinil dehydrogenase)	Phaeochromocytoma	Frequently malignant phaeochromocytoma

References

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In memory of dr. Illyés György (Gyuri)
1955-2017