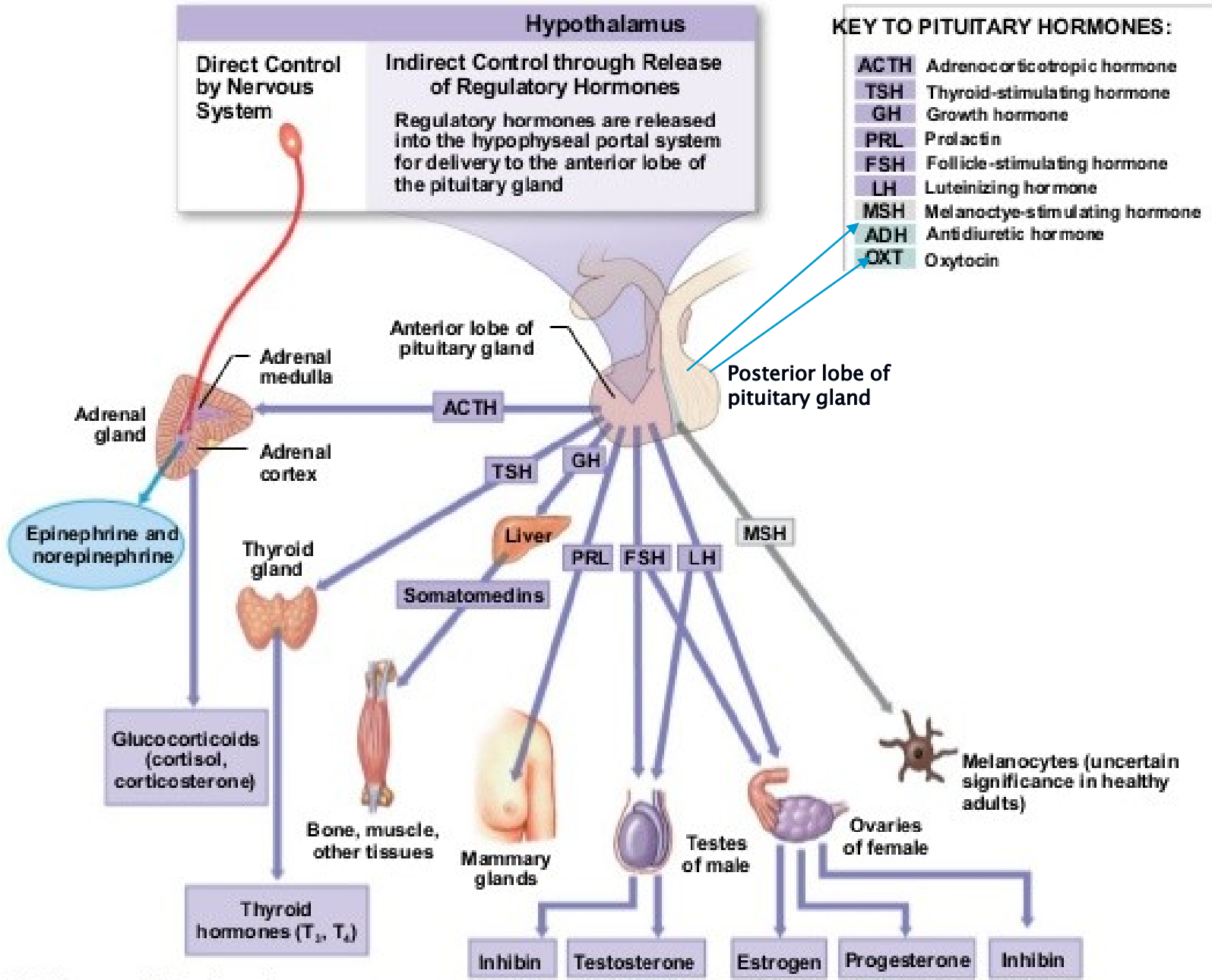


# Pathology of the endocrine system.

**Markéta Hermanová**

Masaryk University, Medical Faculty

- Pituitary gland
- Thyroid
- Parathyroids
- Adrenal gland
- Endocrine pancreas



## Pathological basis of endocrine signs and symptoms

Sign or symptom	Pathological basis
<b>Hormone excess (hyperfunction)</b>	Endocrine gland hyperplasia cause by increased trophic stimulus to secretion Functioning neoplasm of endocrine gland
<b>Hormone deficiency (hypofunction)</b>	Endocrine gland atrophy due to loss of trophic stimulus to secretion Destruction of endocrine gland by inflammation, ischemia or non-functioning tumor
<b>Diffuse enlargement of gland</b>	Inflammatory cell infiltration Hyperplasia

# Pituitary

## ■ Adenohypophysis

### ■ Hypofunction/partial or panhypopituitarism

- Due to destruction by tumor or compression, Rathke's cleft cyst; due to hypothalamic reasons
- Due to inflammation (autoimmune); due to genetic abnormalities of hormone synthesis
- Due to ischaemic necrosis, radiation damage or surgical ablation
- Leads to secondary hypofunction of adenohypophyseal dependent endocrine glands (atrophy of gonads, hypothyreosis, hypocorticalism,...)

### ■ Hyperfunction/hyperpituitarism

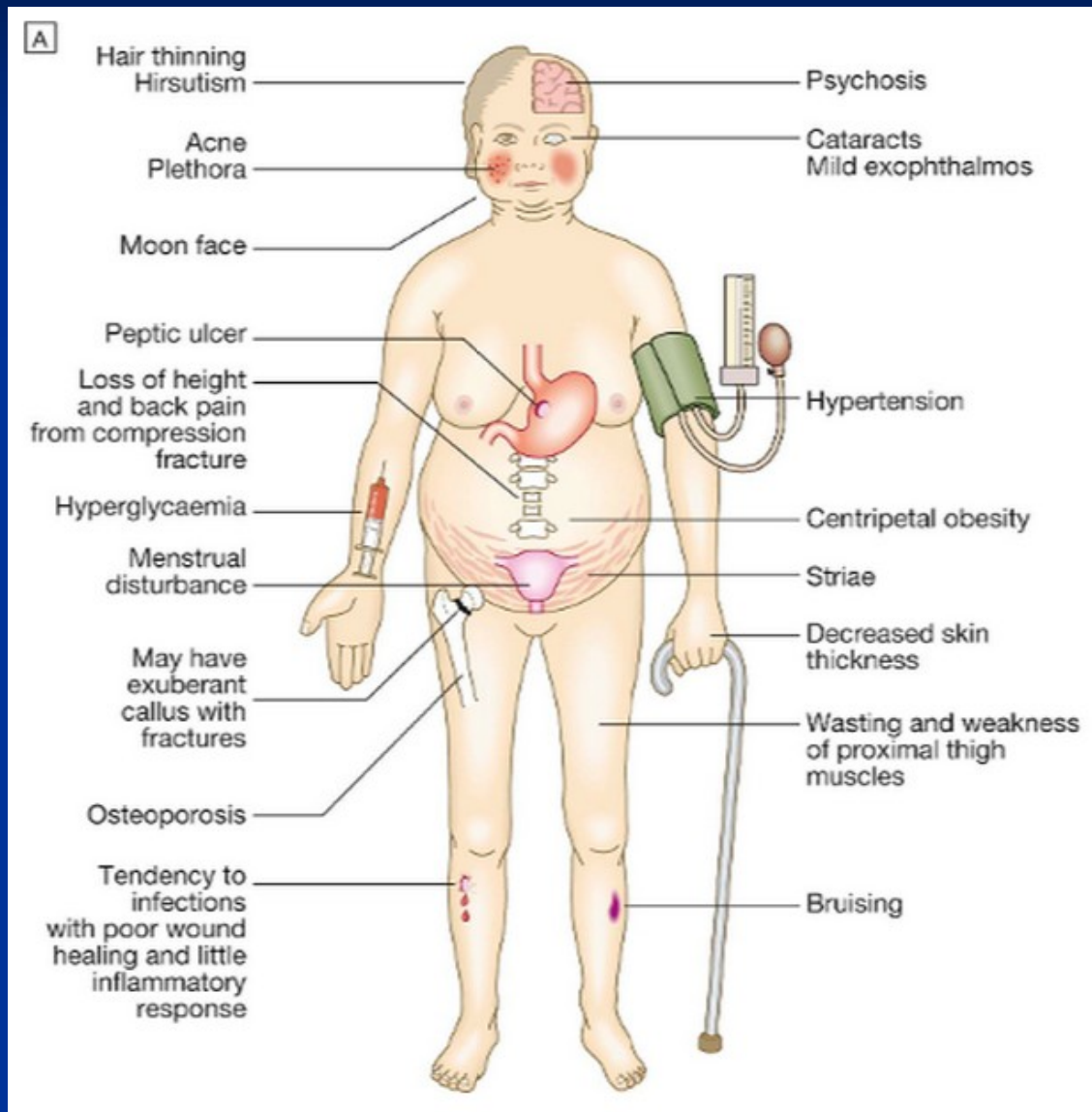
- in adenomas, carcinomas, hyperplasias, due to hypothalamic reasons

# Adenomas of the adenohypophysis

Adenoma type	Clinical picture
Prolactinoma	Commonest type, produces galactorrhoea and menstrual disturbances
GH-secreting	Produces gigantism in children and acromegaly in adults
ACTH-secreting	Produces Cushing syndrome
Others	Exceptionally rare (TSH-, FSH-, LH- secreting)
	Plurihormonal
	Hormonally non-functioning

Association with MEN-1 syndrome!

# Cushing syndrome



# Acromegaly

Pituitary adenoma  
(CT scan or MRI)

High blood - [Growth Hormone]

Hypertrophy of  
sweat & sebaceous glands

Galactorrhoea  
(prolactin)

Cardiomegaly  
Hypertension

Sexual dysfunction

Peripheral  
neuropathy

Visual field defects

Prominent supraorbital ridge

Large nose and jaw  
Teeth are separated or lacking

Abnormal glucose  
tolerance test  
Glucosuria/polyuria

Spade-shaped  
hands and feet

Arthrosis





# Neurohypophysis

## ■ Antidiuretic hormone (ADH)

### ■ ADH deficiency – diabetes insipidus (DI)

- Due to hypothalamus damage (trauma, tumor, inflammation.. due to hypothalamic reasons)
- Polyuria, polydipsia
- In peripheral forms of DI the renal tubules insensitive to ADH

### ■ Excess ADH

- Usually due to ectopic production by tumors (neuroendocrine carcinomas of the lung)

## ■ Oxytocin

# Hypothalamic suprasellar tumors

## ■ Gliomas

## ■ Craniopharyngeoma

- usually benign, malignisation rare; from the Rathke's cleft epithelial rests
- children (5-15 years; endocrinopathies) + 2nd peak in 6th decade
- solid, cystic or multilocular

# Adrenals

## ■ Medulla

- Production of catecholamins (adrenalin, noradrenalin)

## ■ Tumors:

### - Pheochromocytoma

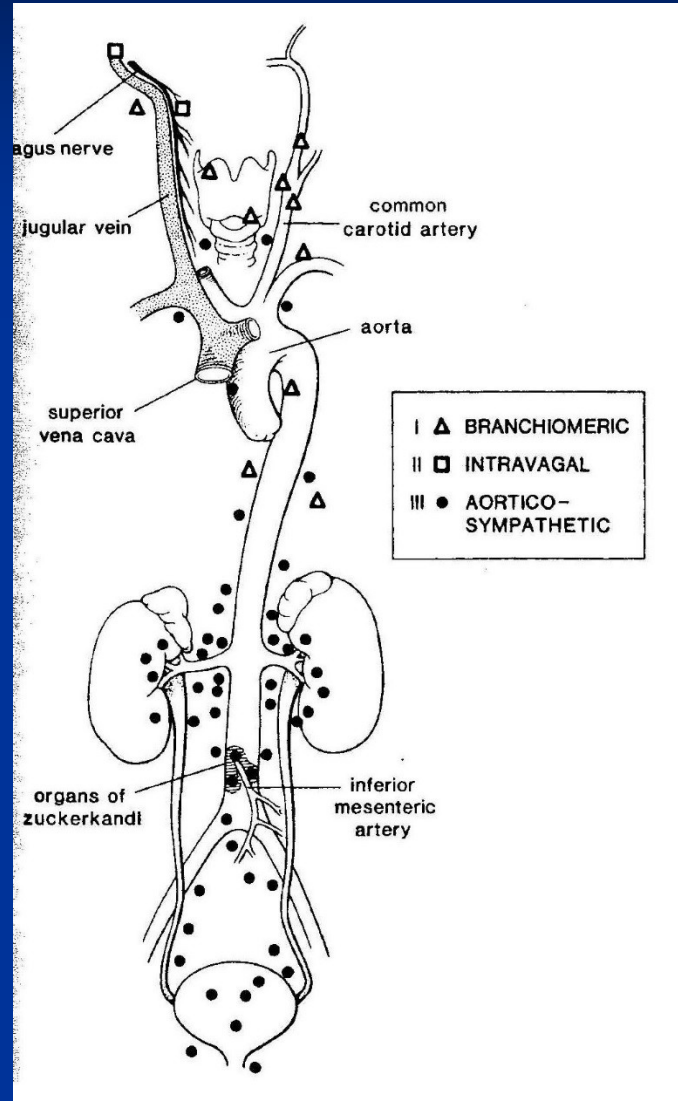
- symptoms due to excess catecholamine secretion (secondary hypertension with ↑risk of cerebral bleeding), sweating)
- Adrenal or extraadrenal, uni or bilateral, assoc. with MEB 2A and 2B (10 %)
- 10 % with malignant biological behavior

### - Neuroblastoma

(tumor of children, malignant)

### - Ganglioneuroblastoma, ganglioneuroma

# Extradrenal system of chromaffine paraganglia



# Adrenals

## ■ Cortex

- Production of glucocorticoids, mineralocorticoids, sex steroids

## ■ Hyperfunction:

- Cushing syndrome

(excess secretion of ACTH, tumors of adrenals, treatment by steroids)

- Conn's syndrome

(overproduction of mineralocorticoids: retention of water, hypertension, muscular weakness, arrhythmias)

## ■ Hypofunction

- Caused by autoimmune adrenalitis, tbc, necrosis of adrenals in sepsis, destruction by tumors,...

- Weight loss, lethargy, hypotension, pigmentation, hyponatraemia

# Thyroid

## ■ Hyperthyroidism

- Syndrome due to excess T3 and T4
- Very rarely due to excess TSH
- Caused by Grave´ disease/thyreoiditis, in which the thyroid stimulating autoantibodies are produced
- Rarely due to functioning adenoma or toxic nodular goiter

## ■ Hypothyroidism (myxoedema)

- Syndrome due to insufficient circulating T3 and T4
- If congenital , causes cretenism
- Commonest cause is Hashimoto´ s thyreoiditis (=autoimmune thyreoiditis)

# Causes of thyreotoxicosis

## ■ Primary associated with hyperthyreoidism

- Diffuse toxic hyperplasia (m. Graves-Basedow)
- Hyperfunctional (toxic) nodular goiter
- Hyperfunctional (toxic) adenoma
- Hyperfunctional thyroidal carcinoma
- Iodine induced hyperthyreoidism
- Neonatal thyreotoxicosis (of mothers with m. G-B)

## ■ Secondary associated with hyperthyreoidism

- TSH producing pituitary adenoma
- TRH overproduction

## ■ Without association with hyperthyreoidism

- Subacute granulomatous thyroiditis
- Chronic lymphocytic thyroiditis
- Struma ovarii (mature ovarian teratoma)

# Hypothyroidism:

## A) congenital - cretinism

(endemic (in iodine deficiency); sporadic (due to enzymatic defect))

## B) acquired – myxoedema

### ■ Clinical signs of cretinism:

- Impaired physical growth and mental development, hypomimic face, tongue protrusion, umbilical hernia

### ■ Clinical signs of myxoedema

- Accumulation of mucosubstances in corium (and viscera)
- Hypercholesterolaemia, accelerated AS
- Dry cold skin, gruff voice, muscle weakness, prone to hypothermia, dry hair, brittle nails, oligo –amenorea, obesity, psychic disorders - depression,....
- Coma with hypothermia, circulatory failure

### ■ Causes

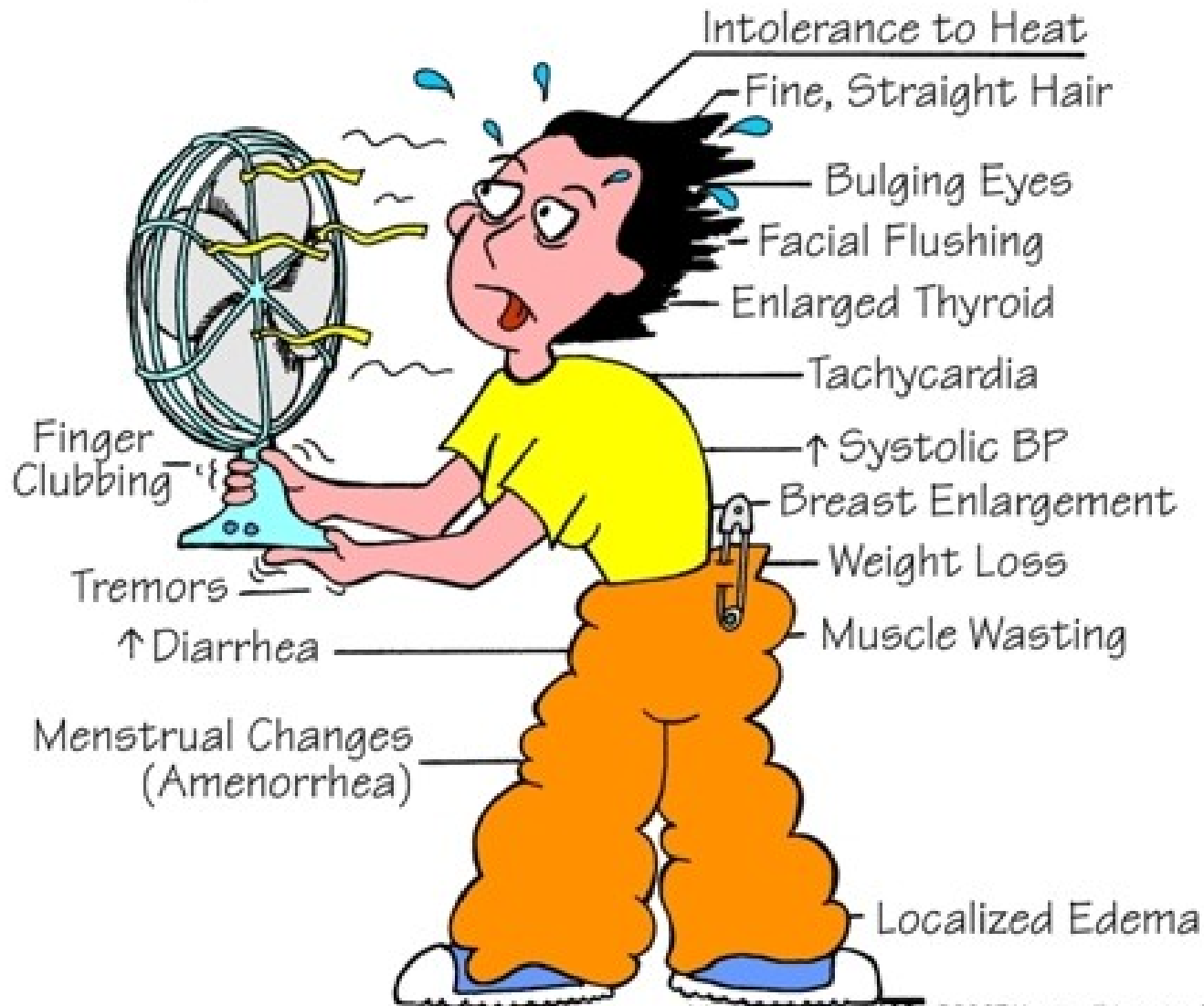
#### - Primary

- Developmental (dysgenesis: mutation in genes for TSH-receptor, TTF)
- Genetically caused resistance to thyroidal hormones
- Surgical ablation, radiation
- Autoimmune thyroiditis
- Iodine deficiency
- Congenital biosynthetic defect (dysmorphogenetic goiter)
- Drugs – thyreostatic

#### - Secondary and tertiary (hypothalamic and hypophyseal reasons)



# HYPERTHYROIDISM



cj4122



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# HYPOTHYROIDISM



# M. Graves-Basedow

(diffuse parenchymatous toxic (hyperfunctional) goitre)

- F>M, 2nd to 4th decade, genetically predisposed
- Autoimmune disease: stimulating autoantibodies against TSH receptor
- Hyperthyreoidism+infiltrative ophthalmopathy-exophthalmos (T cells, oedema, GAGs, adipocytes) +(pretibial myxoedema)
- Diffuse hypertrophy and hyperplasia
- „too many follicular cells and too little colloid“
- Surgical removal or radioiodine ablation

# Thyroiditis

## ■ Chronic autoimmune lymphocytic thyroiditis (Hashimoto's)

- F:M = 10:1
- Genetic predisposition
- CD8+ cytotoxic T cells mediated cell death; cytokines mediated cell death
- Autoantibodies against TSH receptor, thyroglobulin, peroxidase – antibody-dependent cell-mediated cytotoxicity (ADCC)
- Enlarged thyroid, lymphoplasmocytic infiltrate, lymphatic follicles, oncocytic transformation of thyrocytes, fibrotisation
- Often assoc. with other autoimmune diseases
- Increased risk of malignant lymphoma (MALToma) and carcinom of the thyroid

# Thyroiditis

## ■ Subacute granulomatous thyroiditis (de Quervainova)

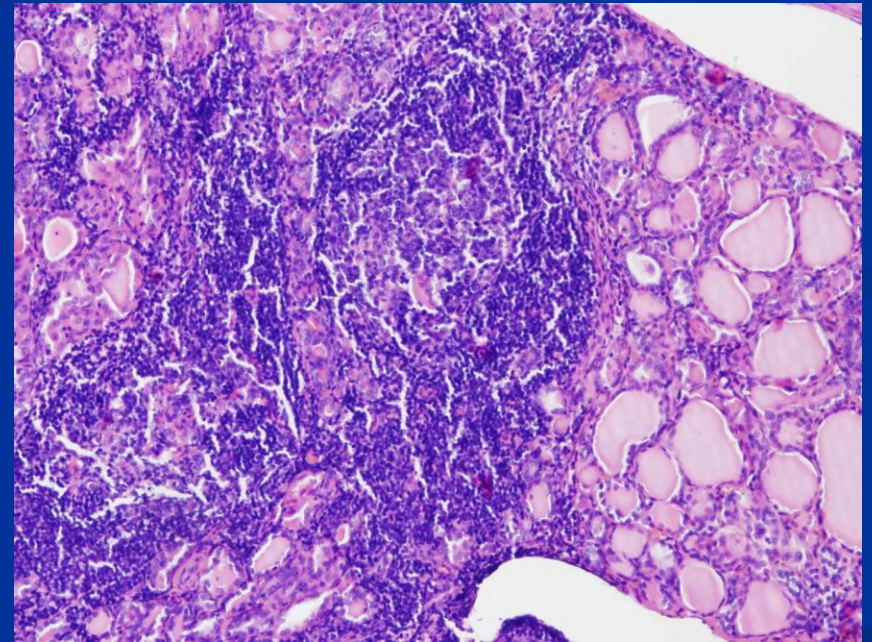
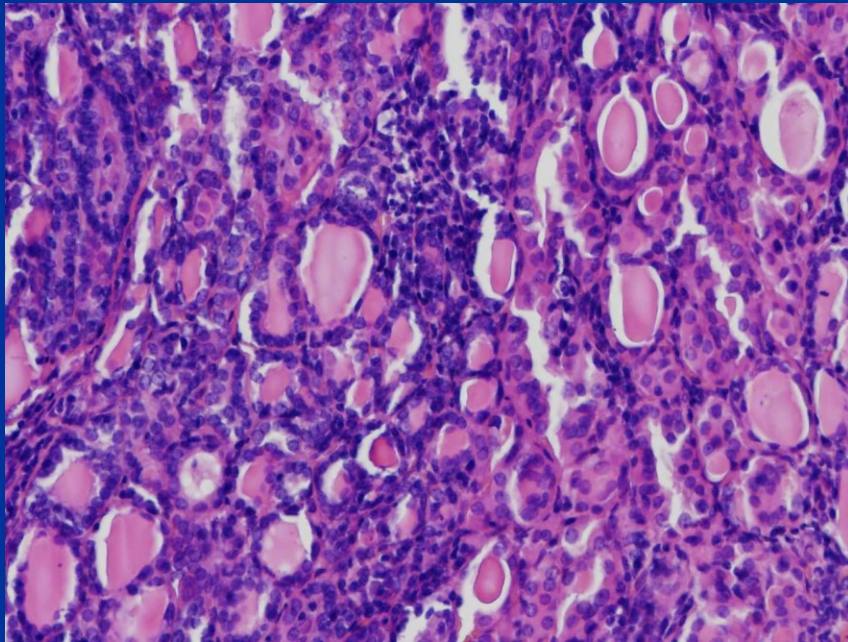
- F:M = 3-5:1
- virus-induced host tissue damage? cytotoxic T lymphocytes
- Painfully enlarged thyroid, fever, fairly abrupt onset
- Focal disruptions and necroses of follicles, granulocytic and granulomatous reactions, fibrotisation)

## - Chronic sclerosing thyroiditis (Riedl's)

- Fibrotising inflammation involving thyroid and also surrounding tissues and organs (stenosis of trachea, paresis of n. recurrens, hypothyroidism)
- Systemic connective tissue disease (IgG4 assoc.?), fibrotising Hashimoto's thyroiditis?, idiopathic fibrosis?

## ■ Subacute lymphocytic thyroiditis (often post partum thyroiditis)

# Chronic autoimmune lymphocytic thyroiditis (Hashimoto's thyroiditis)



# Sclectrosing lesions associated with IgG4

- Autoimmune pancreatitis
  - Sclerosing cholangitis
  - Lymphoplasmocytic sclerosing cholecystitis
  - Sclerosing sialoadenitis
  - Idiopathic retroperitoneal fibrosis (M. Ormond)
  - Inflammatory pseudotumor of the liver, lung, pituitary gland
  - Tubulointerstitial nephritis assoc. with IgG4
  - Interstitial pneumonia assoc. With IgG4
  - Sclerosing prostatitis
  - **Sclerosing thyroiditis**
- 
- M>F; immunosuppressive therapy response (steroids)
  - Imitation of neoplastic lesions
  - Sclerosing lesions with lymphoplasmocytic infiltrates, irregular fibrotisation, obliterative phlebitis, IgG4+ plasma cells.
  - Increased risk of malignant lymphoma

# Goitre

(enlargement of the whole gland)

- Parenchymatous goitre vs colloid goitre
- Diffuse vs nodular goitre
- Hypofunctional vs hyperfunctional vs eufunctional
  
- **Aetiology**
  - Iodine deficiency, due to endemic goitre or food faddism
  - Rare inherited enzyme defects in T3 and T4 synthesis
  - Drugs that induce hypothyroidism



# Thyroid tumors

## ■ Benign

- Follicular adenoma

## ■ Malignant

- Carcinoma

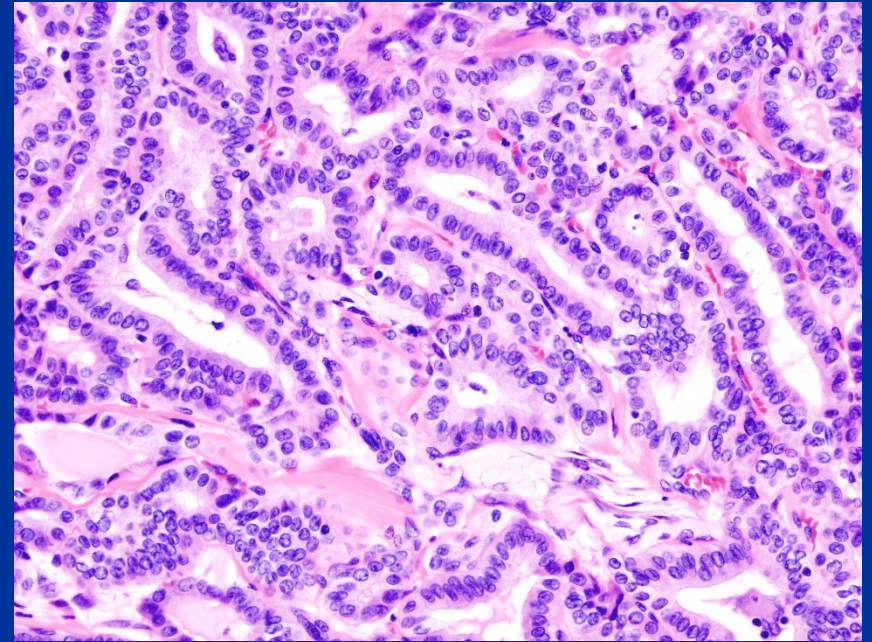
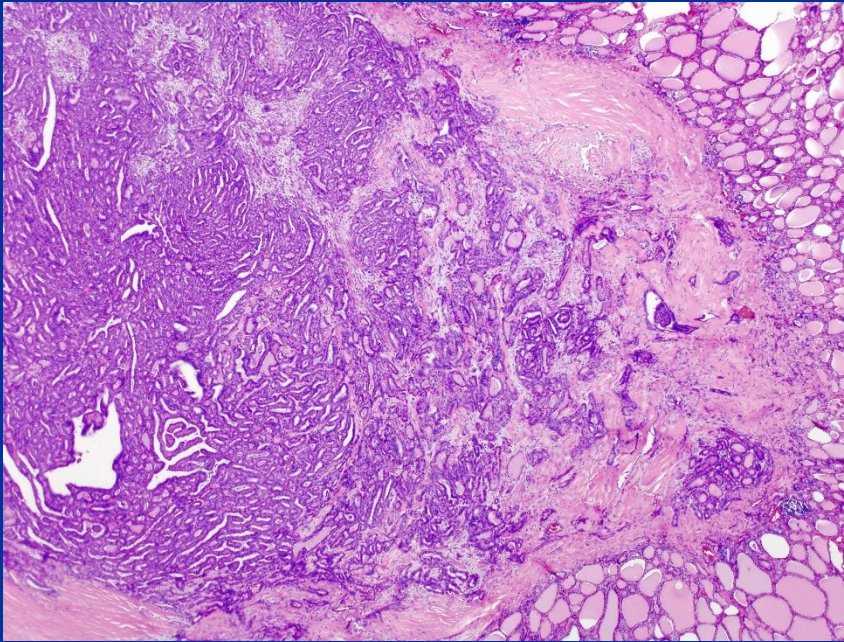
- Lymphoma

(lymphoma (usually non-Hodgkin's lymphomas of B-cell type, variable prognosis))

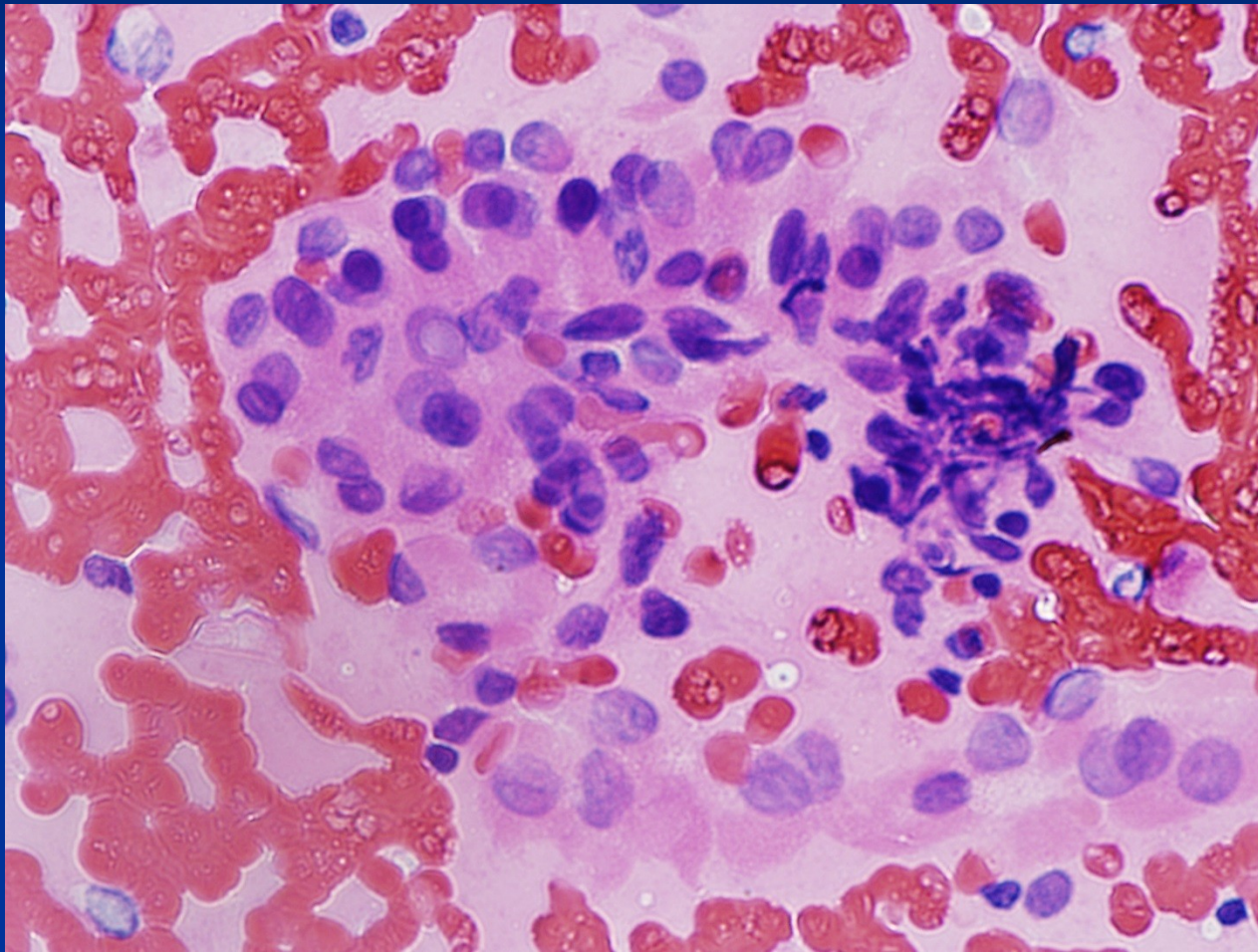
## Carcinoma of the thyroid

Type	Proportion of all cases (%)	Typical age range	Mode of spread	Prognosis
<b>Papillary</b>	60-70	Children, young adults	Lymphatic, to lymph nodes	Excellent
<b>Follicular</b>	20-25	Young-middle age	Haematogenous, to bones	Good
<b>Anaplastic</b>	10-15	Elderly	Aggressive local extension	Very poor
<b>Medullary</b>	5-10	Usually elderly, also familial case (MEN sy)	Local, lymphatic, haematogenous	Variable, more aggressive in familial cases

# Papillary carcinoma of the thyroid

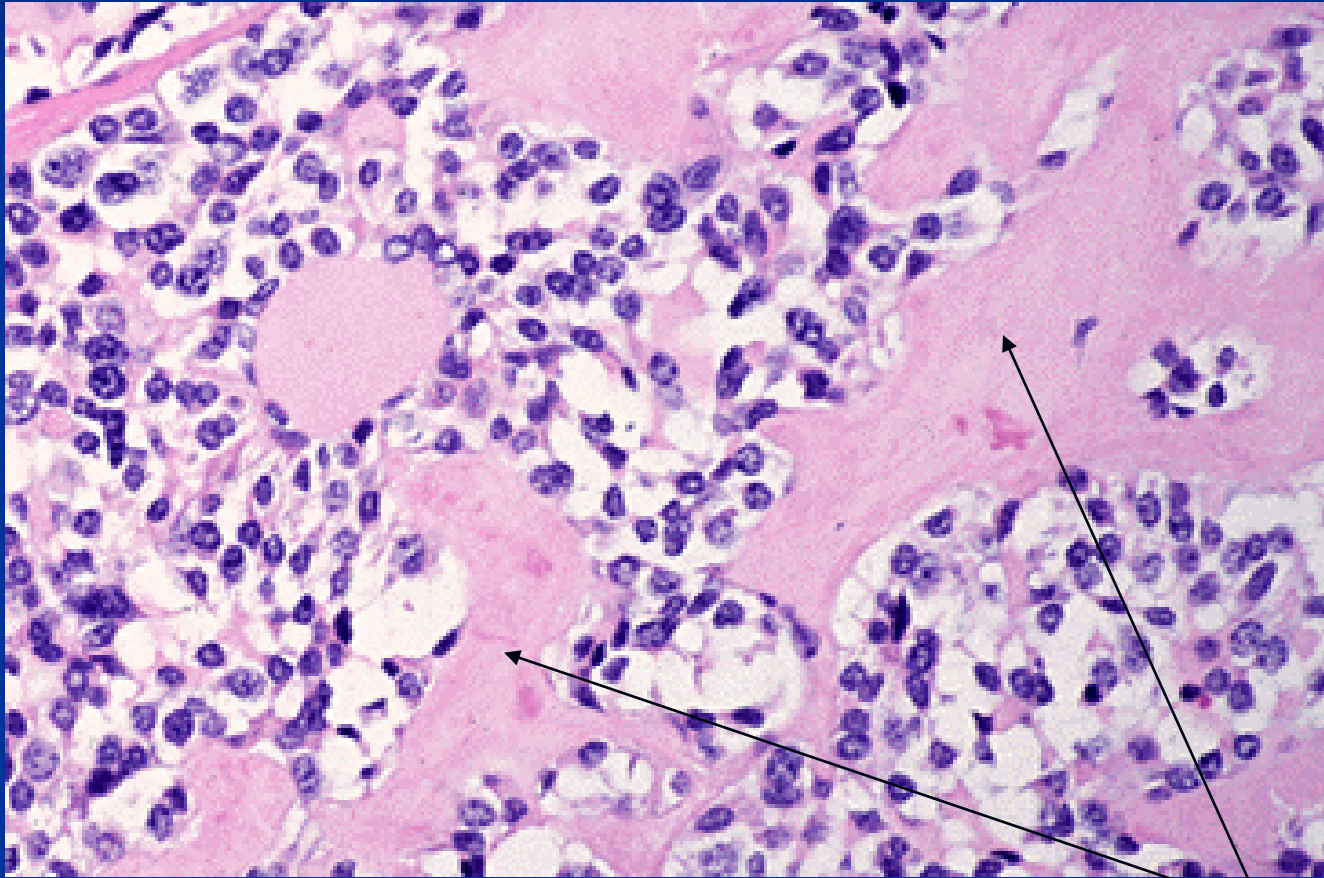


# Papillary carcinoma of the thyroid



FNAB

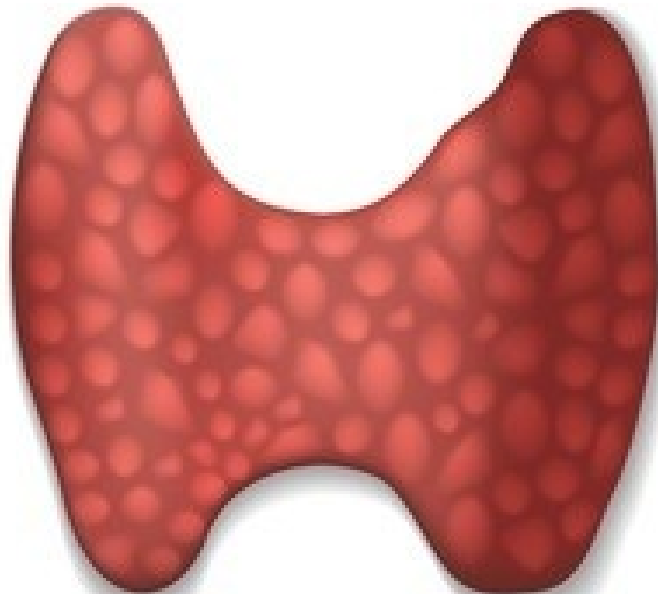
# Medullary carcinoma of the thyroid



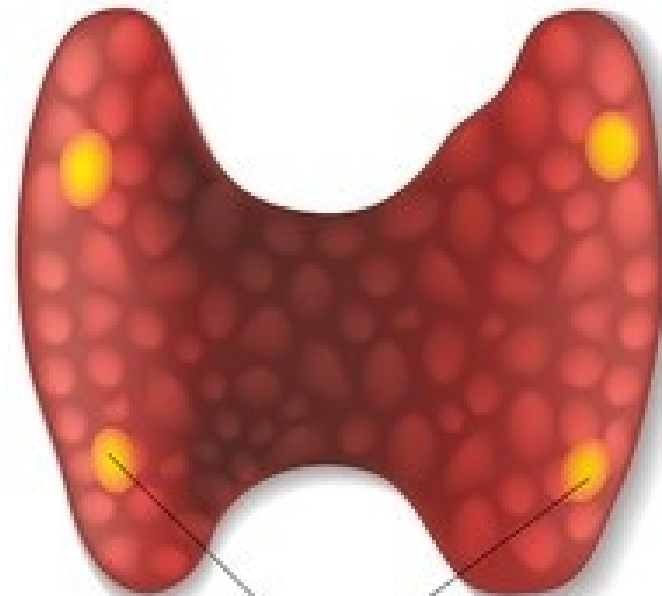
Amyloid deposits

# THYROID AND PARATHYROID

**Thyroid gland**  
(front view)

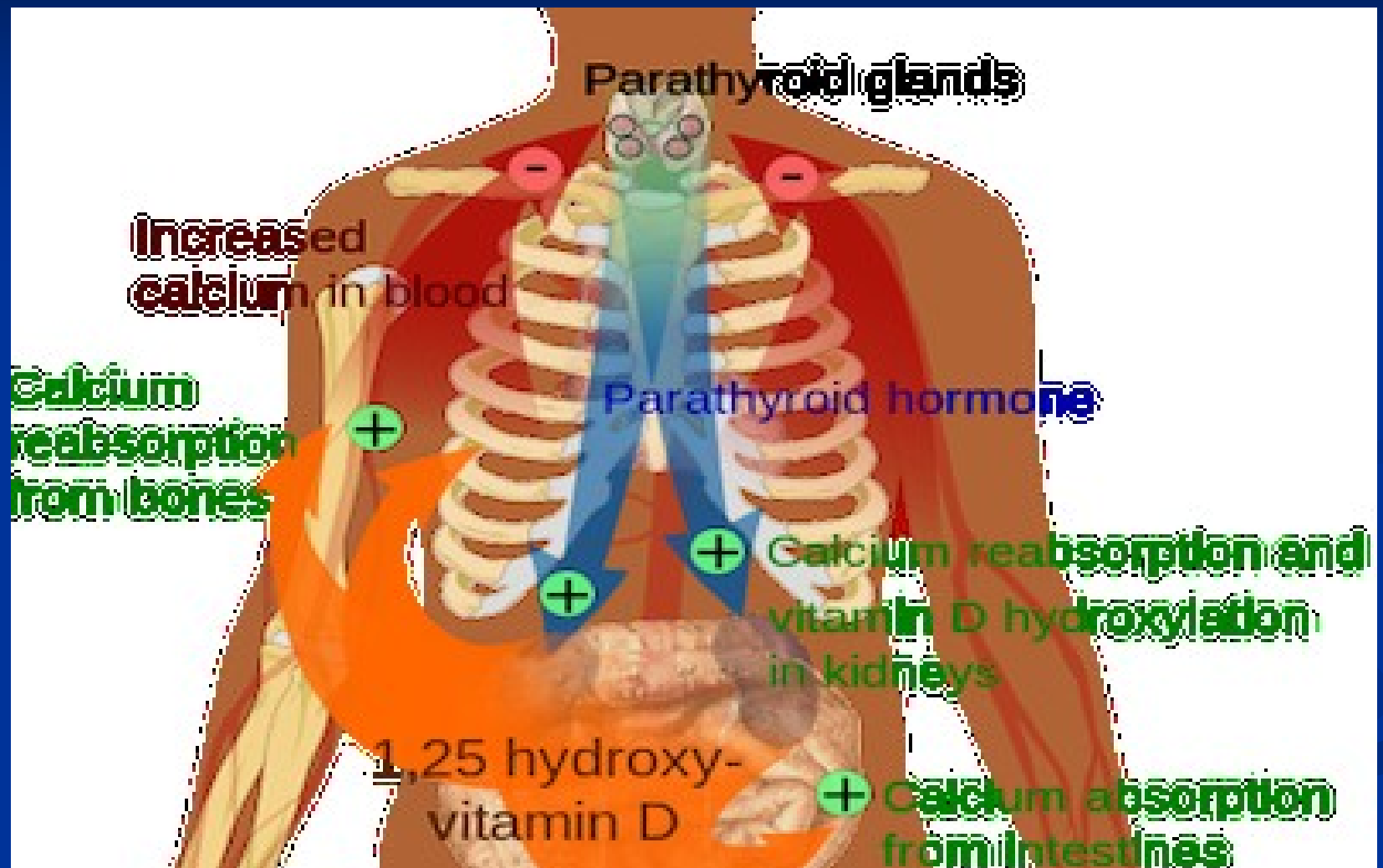


**Thyroid gland**  
(back view)



**Parathyroid  
glands**

# Parathyroid



# Primary

## 1° Hyperparathyroidism

Easy to diagnose and treat -- if you think of it.



parathyroid adenoma



primary parathyroid hyperplasia



↑Ca<sup>++</sup>  
pancreatitis  
stomach ulcers  
kidney stones

high BP  
bone resorption



"osteitis fibrosa cystica"

It's all in your mind!

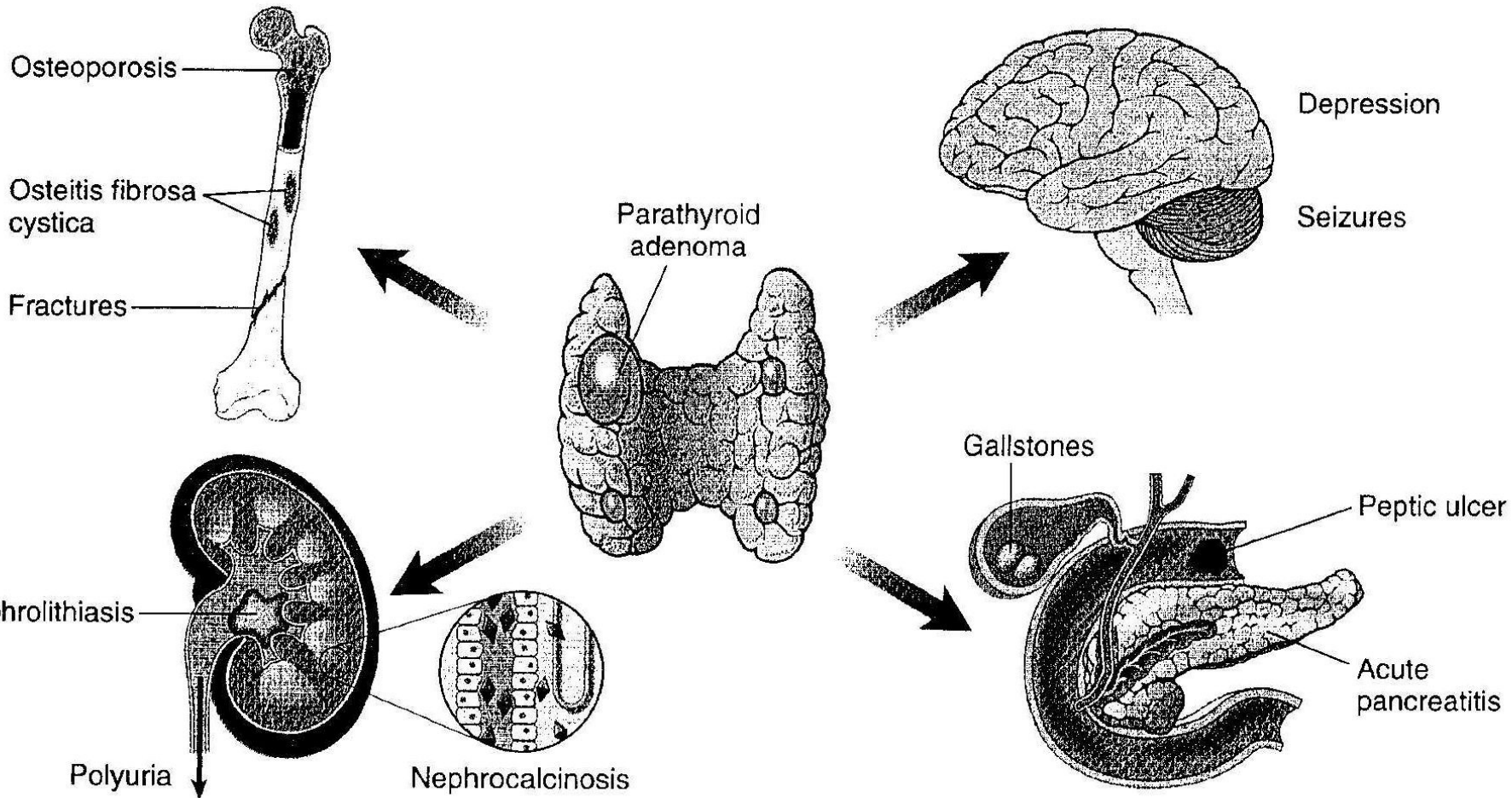
"depression" and "psychosis"

**Secondary hyperparathyroidism:** a physiological response to hypocalcaemia (e.g. in malabsorption, renal failure)

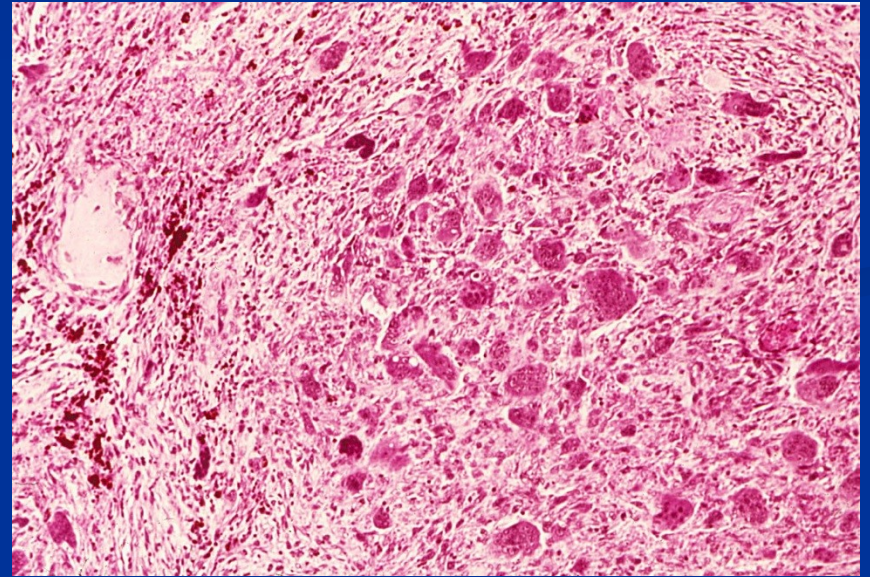
MEN 1, MEN 2



# Clinical signs of hyperparathyreoidismu



# Pathological fracture and brown pseudotumor



# Hypoparathyroidism

## ■ Causes hypocalcaemia

- Tetany (spasm of the skeletal muscle)
- Convulsions
- Paraesthesiae
- Psychiatric disturbances
- Rarely cataracts and brittle nails

### Pseudohyperthyroidism

- Insensitivity of peripheral tissues to PTH
- Usually genetically caused

## ■ Caused by:

- Removal of or damage of the glands during thyroidectomy
- Idiopathic, autoimmune (also as a part of polyendocrine syndrome)
- Congenital hypoplasia or aplasia (Di George syndrome)
- Congenital deficiencies

Other causes of hypocalcaemia: chronic renal failure, vitamin D deficiency, excess loss during lactation

# Endocrine pancreas: islet cell tumors – neuroendocrine neoplasias

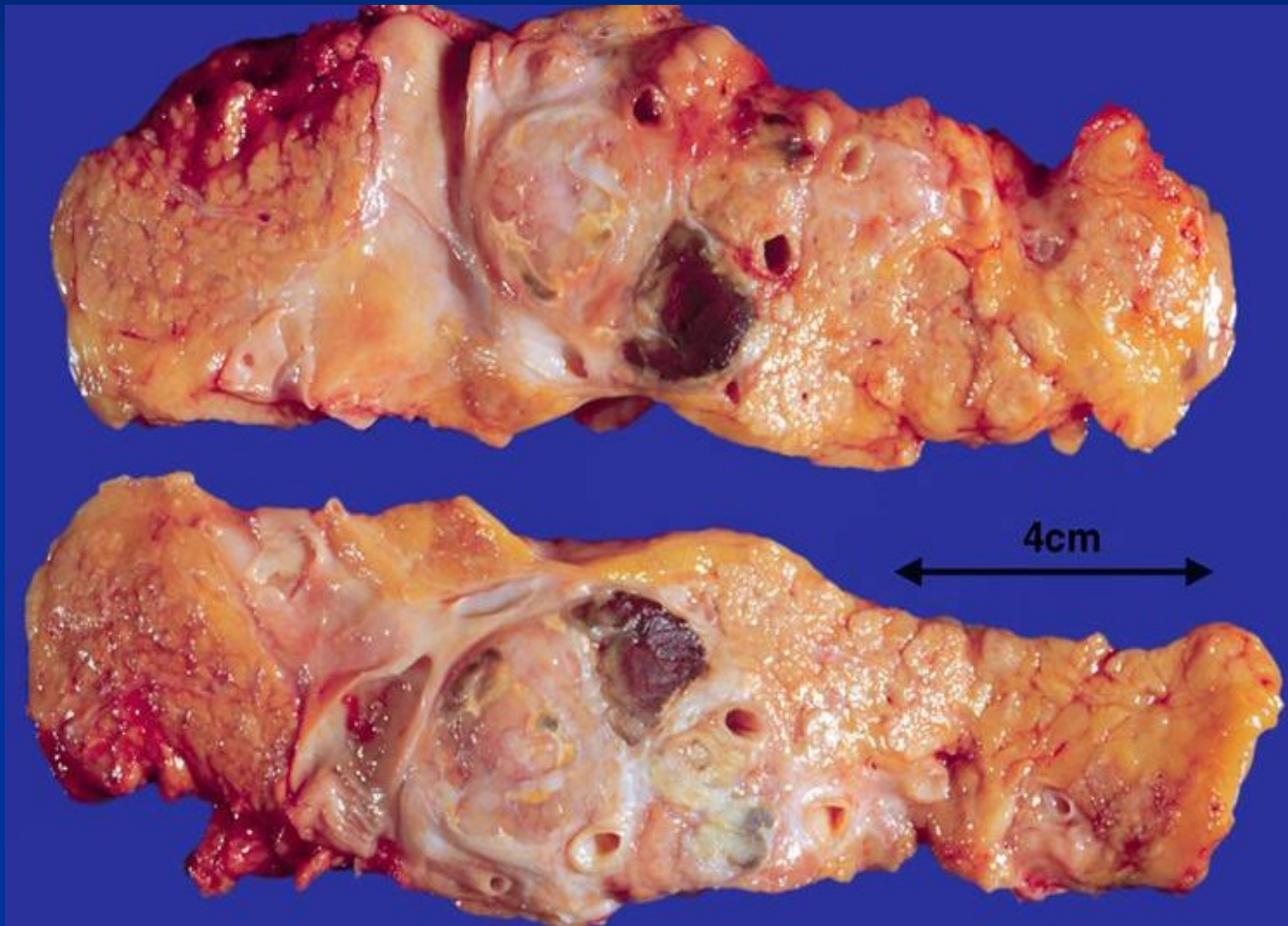
- Less common than pancreatic adenocarcinoma (1-2 % of pancreatic tumors)
- Present with endocrine effects and can be malignant:
  - **Insulinoma:** hypoglycaemia due to hypersecretion of insulin
  - **Glucagonoma:** secondary diabetes and skin rash
  - **Gastrinoma:** hypersecretion of gastric acid due to gastrin action resulting in severe peptic ulcerations
  - ....others (somatostatinoma, VIPoma, serotoninoma, with ectopic hormonal production (ACTH, calcitonin)
  - Non-functional
  - Microadenoma (<0,5 cm)

Islet cell tumor and gastrinomas may occur as a part of inherited MEN (multiple endocrine neoplasia) syndrome.

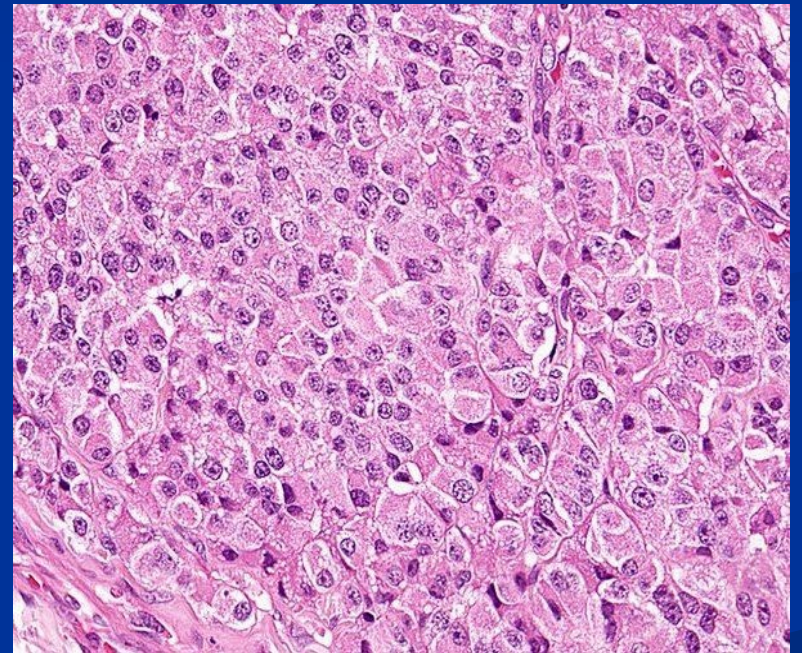
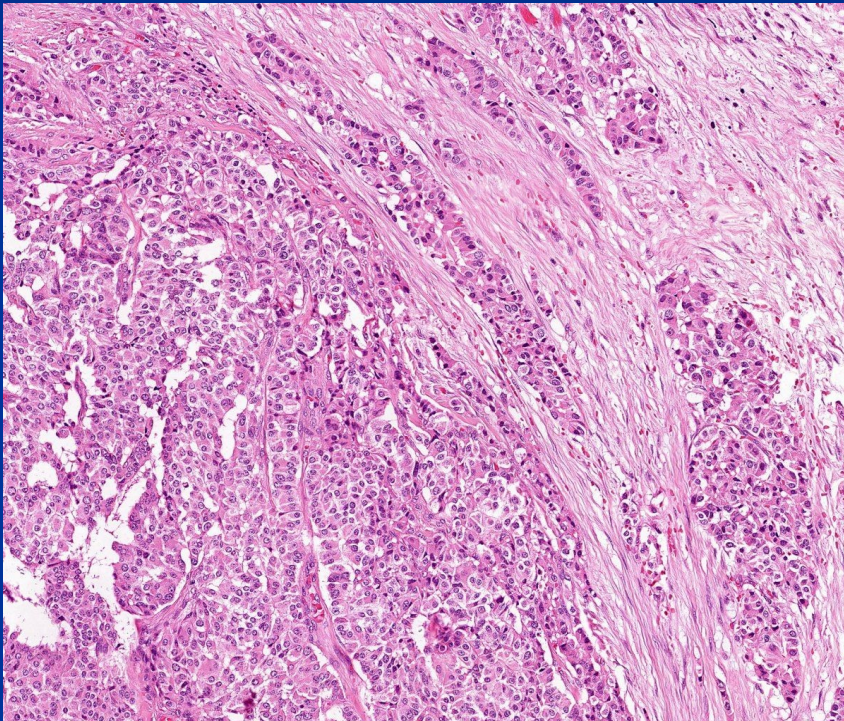
# Neuroendocrine neoplasias – tumors of the endocrine pancreas

- Neuroendocrine tumor (NET)
  - Non-functional pancreatic NET (NET G1, G2)
  - NET G1
  - NET G2
  - NET G3 (from WHO 2017)
- Neuroendocrine carcinoma (NEC)
  - Large cell type NEC
  - Small cell type NEC

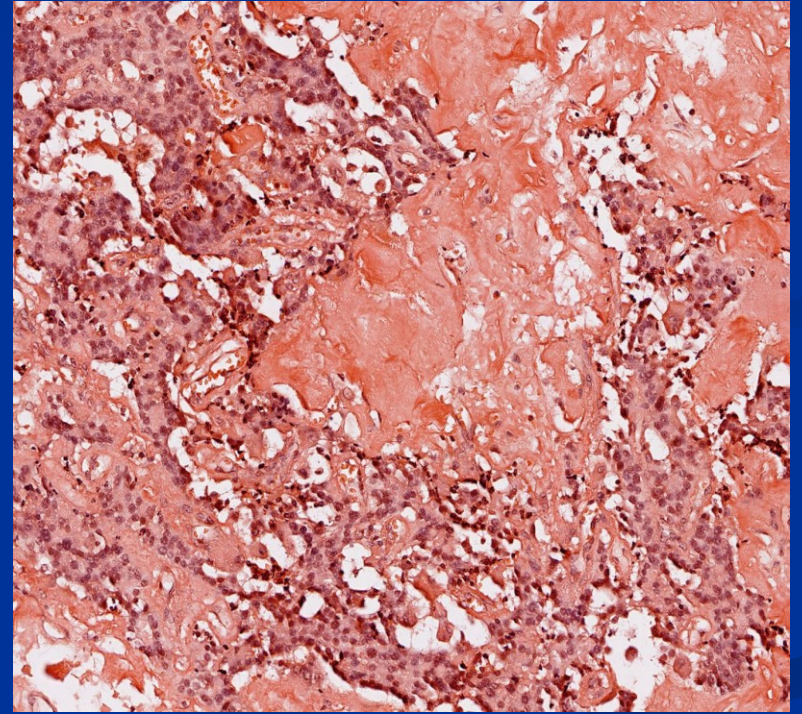
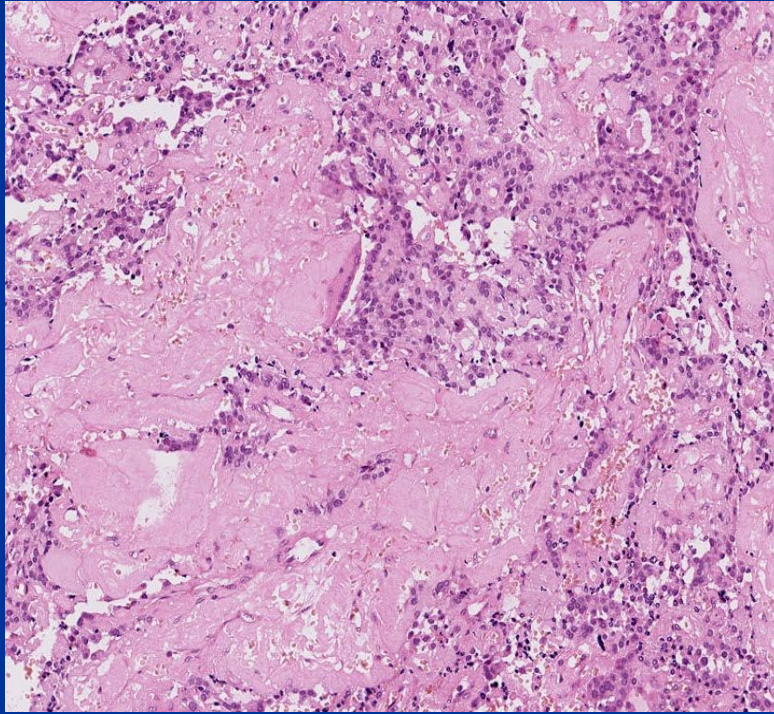
# Neuroendocrine neoplasia of the pancreas.



# Neuroendocrine neoplasia of the pancreas.



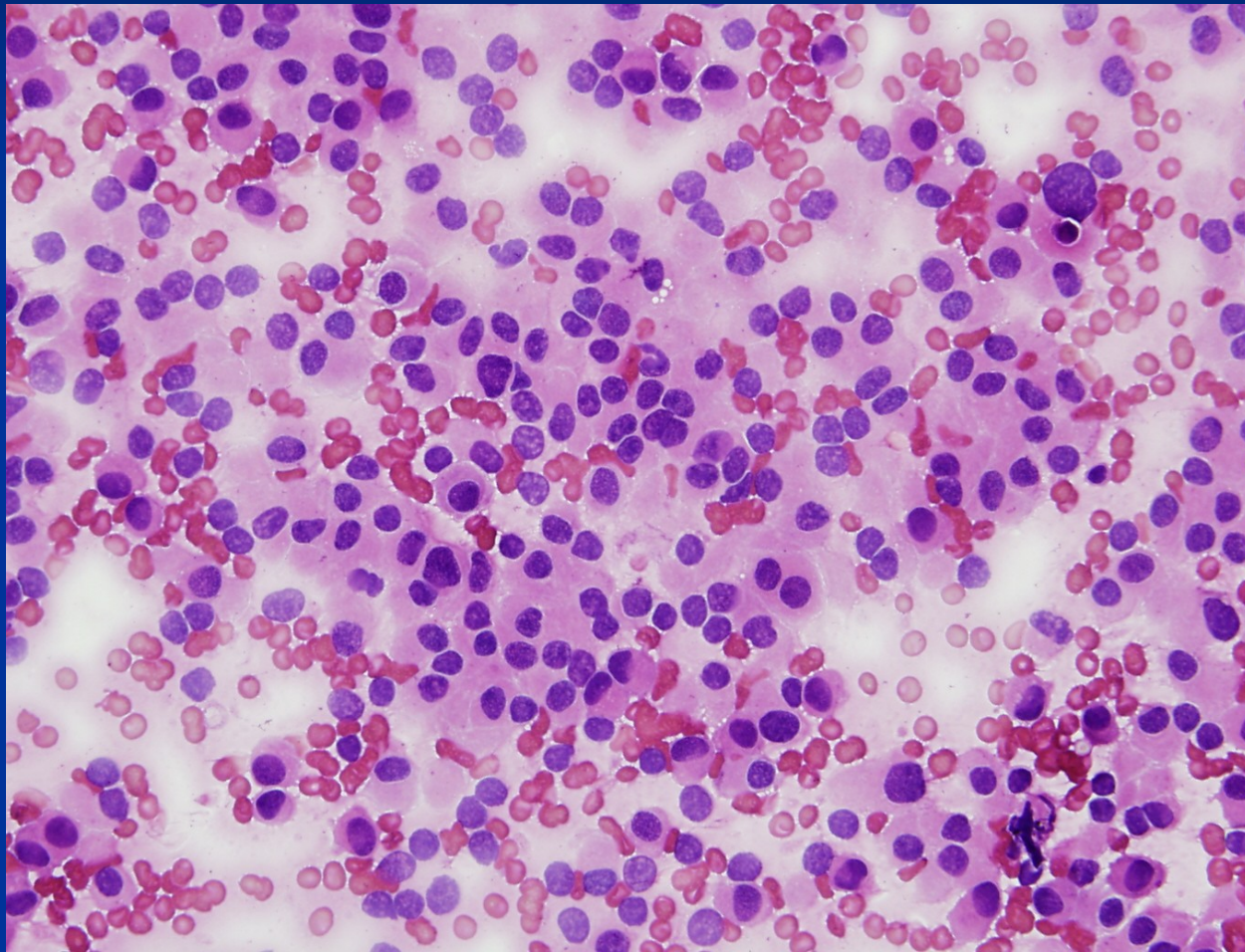
# Amyloid deposits in insulinoma



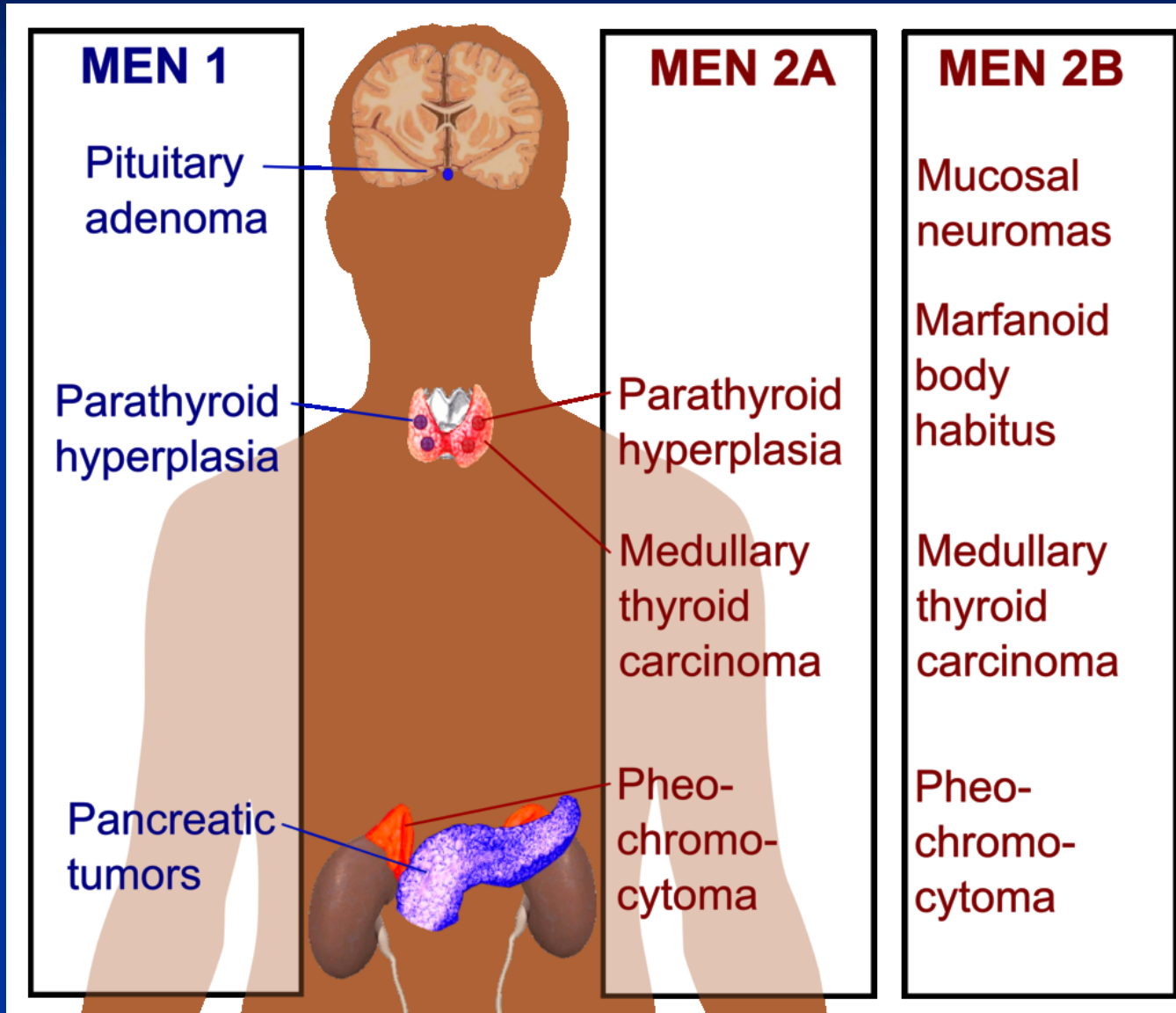


## FNAB

cytology of neuroendocrine neoplasia of the pancreas.



# Multiple endocrine neoplasia (MEN) syndromes



# Diabetes mellitus

(group of metabolic disorders sharing the common sign– hyperglycemia)

## ■ Type 1

- Immune mediated destruction of B cells
- Autoimmunne IDDM in genetically predisposed patients + environmental factors (viruses)

## ■ Type 2

- Insulin rezistent, with relative or absolute insulin deficiency
- Genetics; obesity, life style

## ■ Genetically caused defects of B cells functions

- „maturity-onset diabetes of the young“ (mutations in different genes)
- „mitochondrial diabetes“ (mutations in mtDNA; oxidative phosphorylation failures)

## ■ Genetically caused defects in insulin function

- Insulin gene, insulin receptor gene mutations, defects of proinsulin conversion

## ■ Disorders of exocrine pancreas

- Chronic pancreatitis
- Pancreatectomy
- Pancreatic neoplasia
- Cystic fibrosis
- Haemochromatosis

# Diabetes mellitus

(group of metabolic disorders sharing the common sign– hyperglycemia)

## ■ Endokrinopathies

- Acromegaly
- Cushing syndrome
- Hyperthyroidism
- Glucagonoma, pheochromocytoma

## ■ Infections

- CMV
- Coxsackie virus B

## ■ Drugs

- Glucocorticoids, hormones of thyroid, alpha interferon, protease inhibitors, thiazides, phenytoin, ...

## ■ Genetic syndromes assoc. with DM

- Down syndrome
- Klinefelter syndrome
- Turner syndrome

## ■ Gestational DM

**Differences between types of diabetes mellitus  
(DM: abnormal metabolic state characterised by glucose intolerance due to inadequate insulin action)**

<b>Features</b>	<b>Type 1 (ketosis-prone, juvenile onset, insulin-dependent)</b>	<b>Type 2 (not ketosis-prone, maturity onset, non-insulin-dependent)</b>
<b>Age of onset</b>	Usually <20y	Usually <40y
<b>Proportion of all cases</b>	<10 %	>90%
<b>Type of onset</b>	Abrupt (acute or subacute)	Gradual
<b>Etiological factors</b>	Possible viral/autoimmune, resulting in destruction of islet cells	Obesity associated insulin resistance
<b>HLA association</b>	Yes (=genetic predisposition in DM)	No
<b>Insulin antibodies</b>	Yes	No
<b>Body weight at onset</b>	Normal or thin, obesity uncommon	Majority are obese (80%)
<b>Endogenous insulin production</b>	Decreased (little or none)	Variable (above or below normal)
<b>Ketoacidosis</b>	May occur	Rare
<b>Treatment</b>	Insulin, diet, exercise	Diet, oral hypoglycemic agents, exercise, insulin, and weight control

## Risk factors for type 1 and type 2 diabetes mellitus

### Type 1 DM risk factors

Type 1 DM in a first-degree relative (sibling or parents)

### Type 2 DM risk factors

Positive family history

Ethnic origin (black, native americans, hispanic, asian american, pacific islanders)

Obesity

Increasing age

Habitual physical inactivity, sedentary lifestyle

History of gestational DM

Other clinical conditions assoc. with insulin resistance (e.g. polycystic ovary syndrome)

History of vascular diseases

Previously identified impaired fasting glucose or impaired glucose tolerance

Hypertension

HDL cholesterol level  $<35\text{mg/dL}$  and/or triglyceride level  $\geq 250\text{mg/dL}$

Cigarette smoking

# Cardinal clinical signs of DM at diagnosis

- Polyuria
- Polydipsia
- Polyphagia, excessive hunger (in type 1)
- Weight loss (in type 1)
- Recurrent blurred vision
- Ketonuria (in type 1)
- Weakness, fatigue, dizziness
- Often asymptomatic (type 2)

## Complications of diabetes

Situation	Complication
<b>Large blood vessels</b>	Accelerated arteriosclerosis leading to: <ul style="list-style-type: none"><li>- Myocardial infarction</li><li>- Cerebrovascular diseases</li><li>- Ischaemic limbs</li><li>- Responsible for 80 % of adult diabetic death</li></ul>
<b>Small blood vessels</b>	Endothelial cells and basal lamina damage. Retinopathy (major cause of blindness), nephropathy
<b>Peripheral nerve</b>	Diabetic neuropathy (v.s. due to disease of small vessels supplying the nerves)
<b>Neutrophils</b>	Susceptibility to infection
<b>Pregnancy</b>	Pre-eclamptic toxemia Large babies Neonatal hypoglycemia
<b>Skin</b>	Gangrene of extremities Soft tissue lesions (Granuloma annulare, necrobiosis lipoidica)



# Complications of diabetes.

