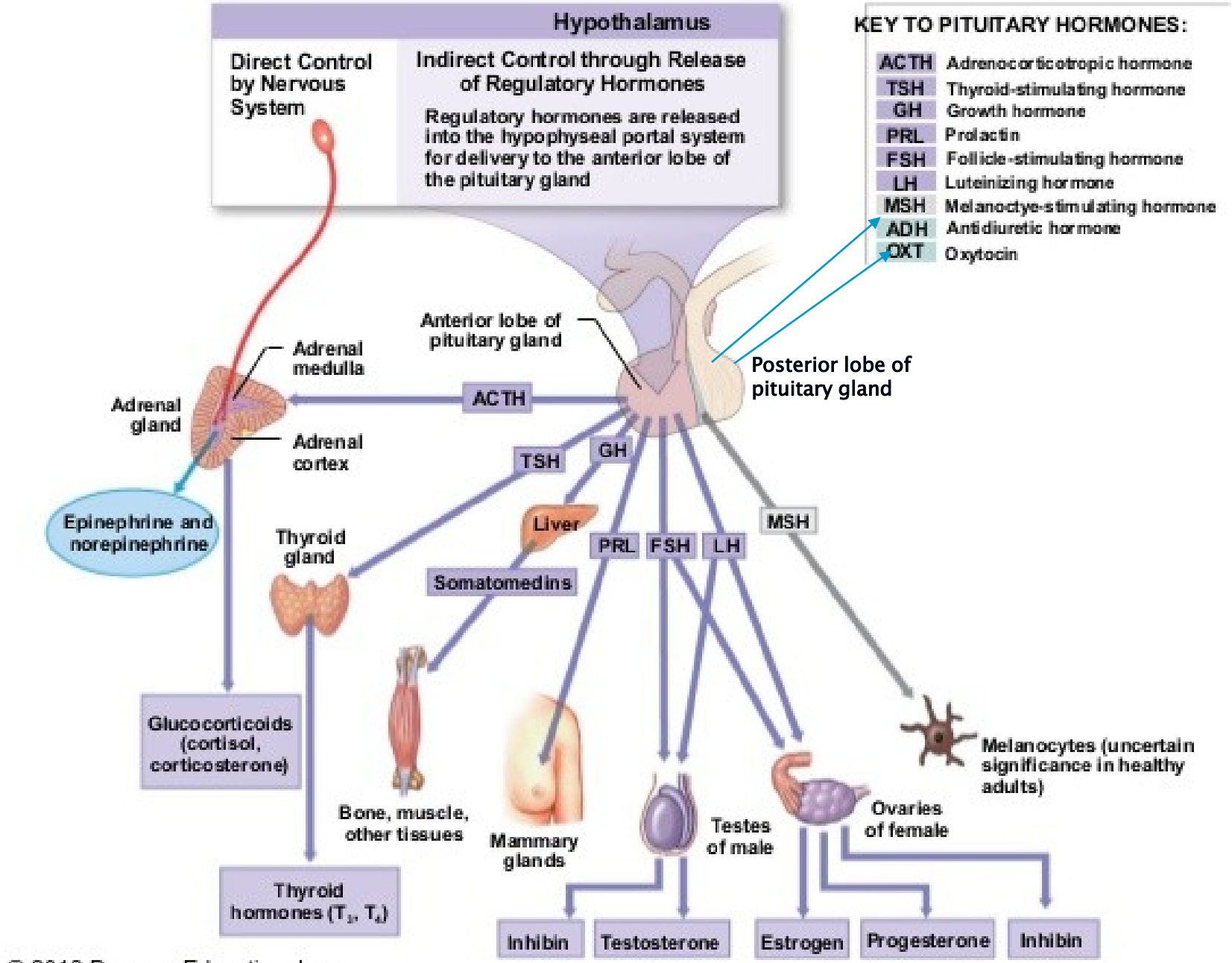
Pathology of the endocrine system.

Markéta Hermanová

Masaryk University, Medical Faculty

- Pituitary gland
- Thyroid
- Parathyrois
- Adrenal gland
- Endocrine pancreas



Pathological basis of endocrine signs and symptoms	
Sign or symptom	**Pathological basis**
Hormone excess (hyperfunction)	Endocrine gland hyperplasia cause by increased trophic stimulus to secretion Functioning neoplasm of endocrine gland
Hormone deficiency (hypofunction)	Endocrine gland atrophy due to loss of trophic stimulus to secretion Destruction of endocrine gland by inflammation, ischamia or non-functioing tumor
Diffuse enlargement of gland	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,…)

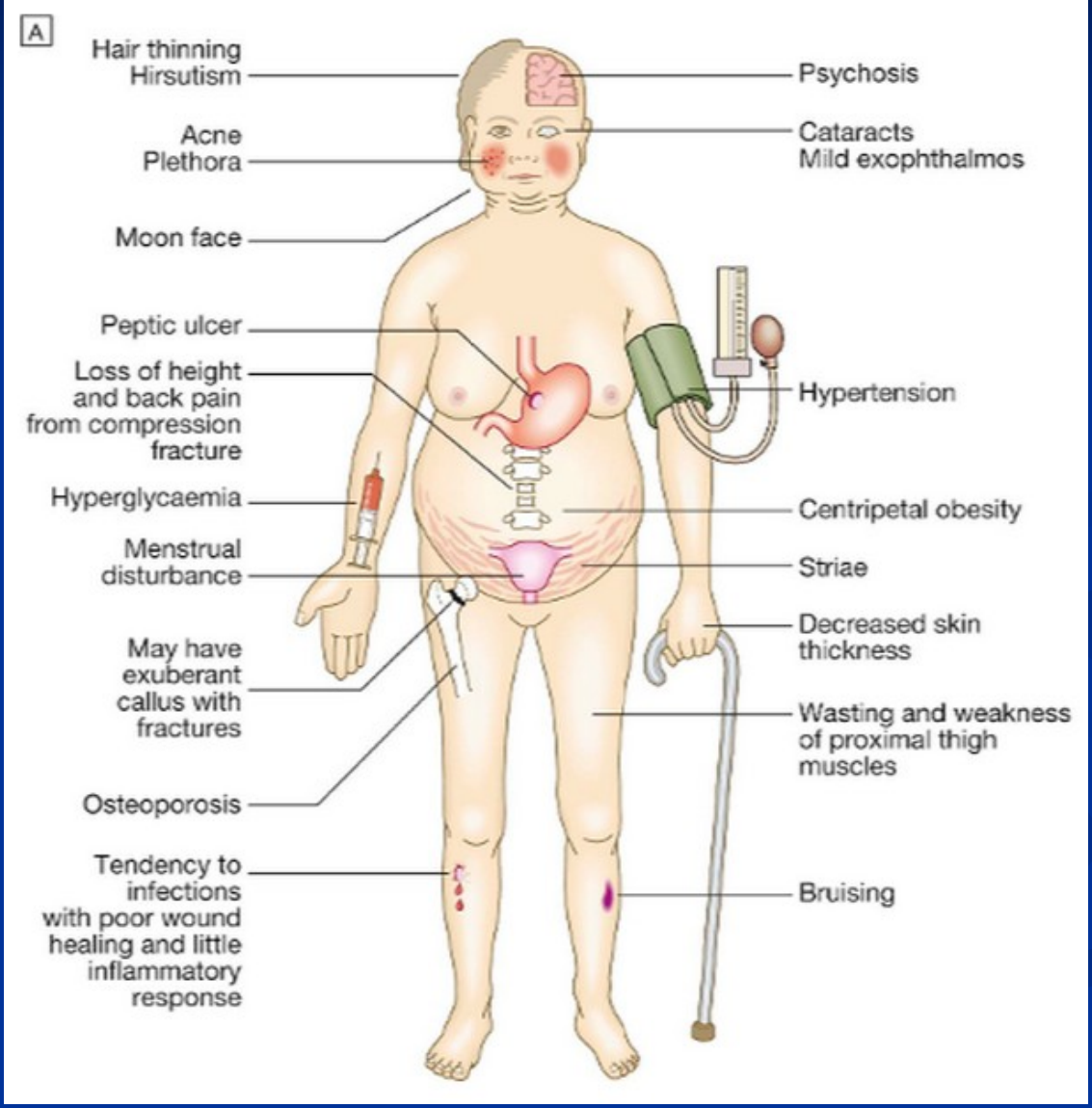
- **Hyperfunction/hyperpituitarism**
  - in adenomas, carcinomas, hyperplasias, due to hypothalamic reasons

Adenomas of the adenohypophysis

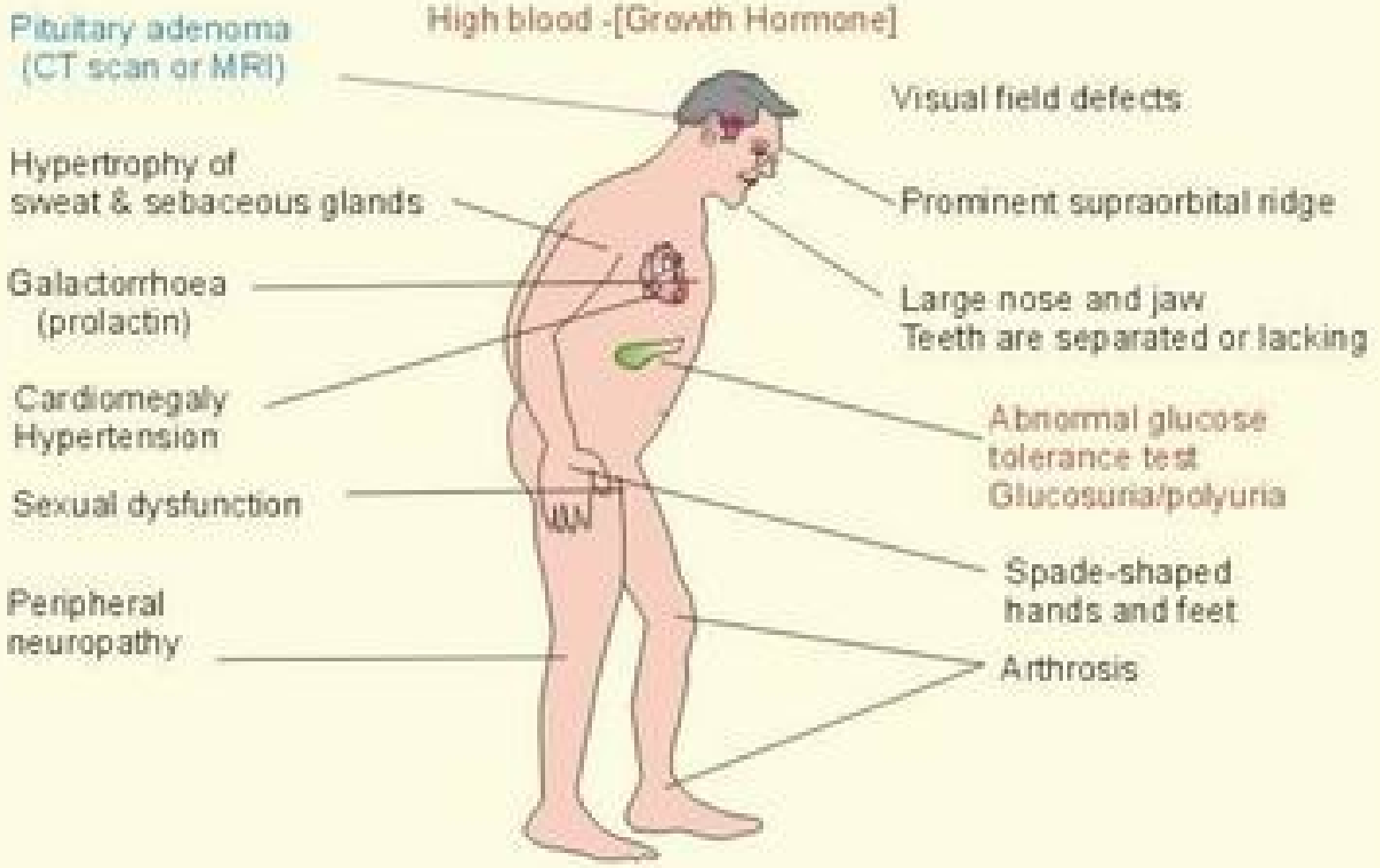
Adenoma type	Clinical picture
Prolactinoma	Commonest type, produces galactorrhoea and menstrual disturbances
GH-secreting	Produces gigantism in children and acromegaly in adults
ACTH-secreting	Produces Cushing syndrome
Others	Exceptionally rare (TSH-, FSH-, LH- secreting)
	Plurihormonal
	Hormonally non-functioning

Association with MEN-1 syndrome!

Cushing syndrome



Acromegaly


High blood -[Growth Hormone]
Pituitary adenoma
(CT scan or MRI)
Visual field defects
Hypertrophy of
sweat & sebaceous glands
Prominent supraorbital ridge
Galactorrhoea
(prolactin)
Large nose and jaw
Teeth are separated or lacking
Cardiomegaly
Hypertension
Abnormal glucose
tolerance test
Glucosuria/polyuria
Sexual dysfunction
Spade-shaped
hands and feet
Peripheral
neuropathy
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 decase
- solid, cystic or multilocular

Adrenals

- **Medulla**

- Production of catecholamins (adrenalin, noradrenalin)

- **Tumors:**

- Pheochromocytoma

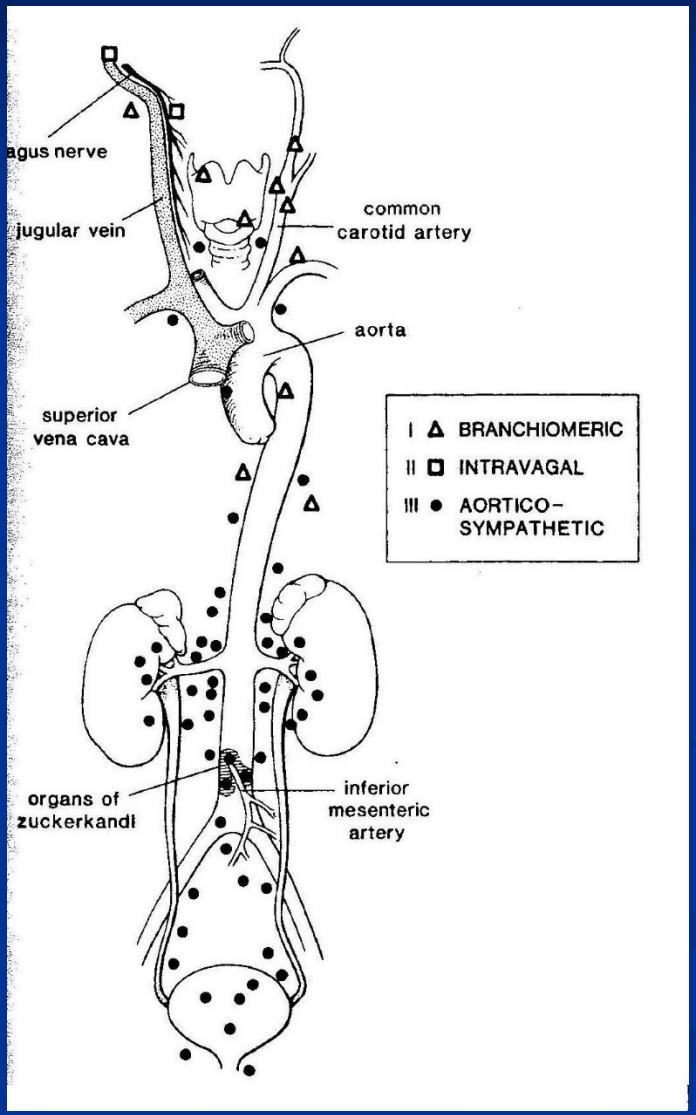
- symptoms due to excess catecholamine secretion (secondary hypertension with ↑risk of cerebral bleeding), sweating)
- Adrenal or extraadrenal, uni or bilateral, assoc. with MEN 2A and 2B (10 %)
- 10 % with malignant biological behavior

- Neuroblastoma

(tumor of children, malignant)

- Ganglioneuroblastoma, ganglioneuroma

Extraadrenal 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) nodulat goiter
  - Hyperfunctional (toxic) adenoma
  - Hyperfunctional thyreoidal carcinoma
  - Iodine induced hyperthyreoidismus
  - Neonatal thyreotoxicosis (of mothers with m. G-B)

- **Secondary associated with hypertyreoidismem**
  - TSH producing pituitary adenoma
  - TRH overproduction

- **Without association with hyperthyreoidism**
  - Subacute granulomatous thyreoiditis
  - Chronic lymphocytic thyreoiditis
  - Struma ovarii (mature ovarial teratoma)

Hypothyreoidismus:

A) congenital - cretenismus

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

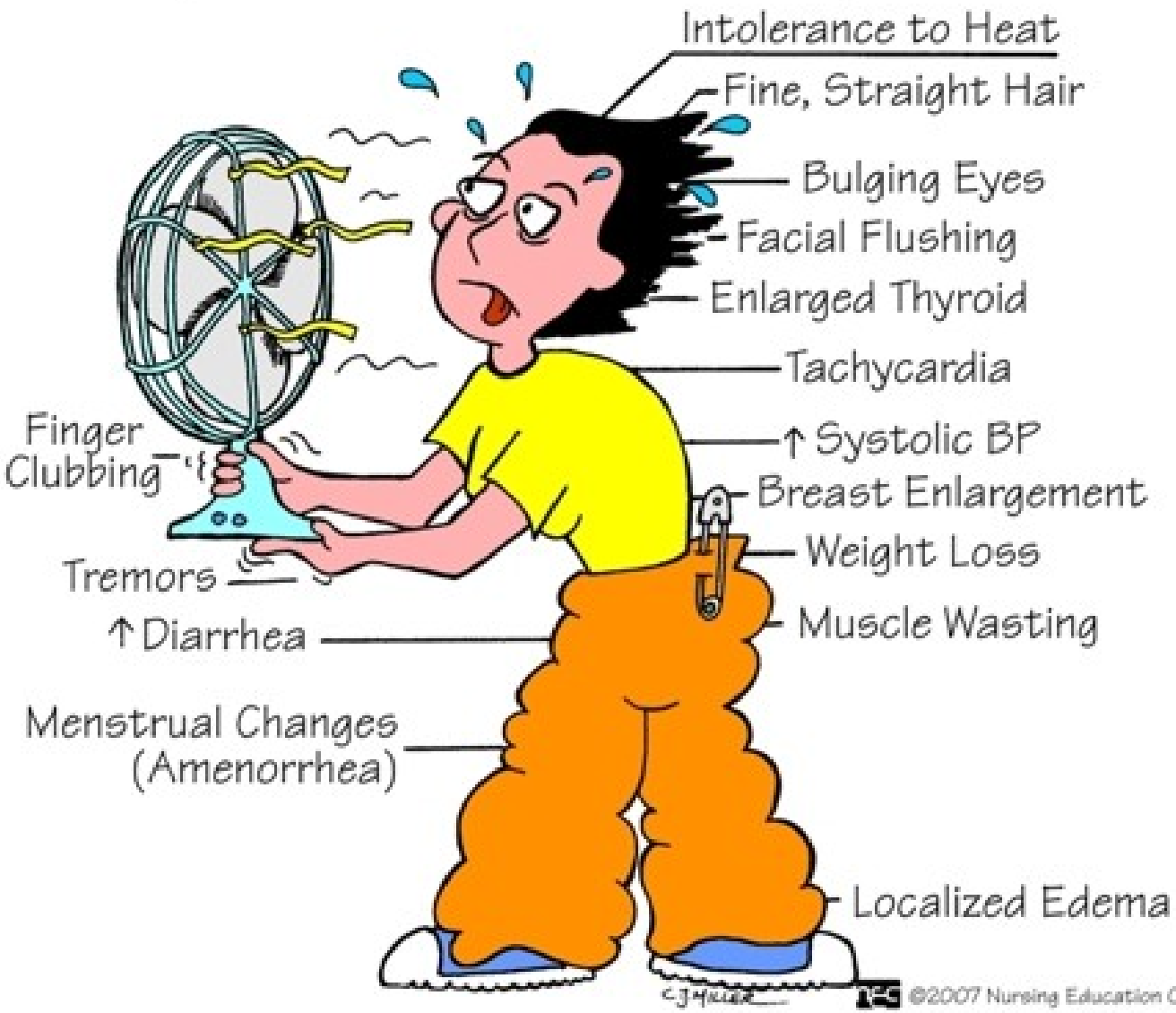
B) aquiered – myxoedema

- **Clinical signs of cretenism:**
  - Impaired physical growth and mental development, hypomimic face, tongue protrusion, umbilical hernia

- **Clinical signs of myxoedema**
  - Accumulation of mucosubstances in corium (and viscerally)
  - Hypercholesteroĺaemia, accelerated AS
  - Dry cold skin, gruff voice, muscle weakness, prone to hypotermia, dry hair, brittle nails, oligo –amenorea, obesity, psychic disorders - depression,….
  - Coma with hypothermia, circulaton failure

- **Causes**
  - **Primary**
  - Developmental (dysgenesis: mutation in genes for TSH-receptor, TTF)
  - Genetically caused resistence to thyreoidal hormones
  - Surgical ablation, radiation
  - Autoimmunne thyreoiditis
  - Iodine deficiency
  - Congenital biosynthetical defect (dyshormonogenetic goiter)
  - Drugs – thyreostatic
  - **Secundary and tertiary** (hypothalamic anf hypophyseal reasons)

HYPERTHYROIDISM



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 ophtalmopathy-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, thyreoglobulin, peroxidase – antibody-dependent cell-mediated cytotoxicity (ADCC)
- Enlarged thyroid, lymphoplasmocytic infiltrate, lymphatic follicles, oncocytic transformation of thyreocytes, fibrotisation
- Often assoc. with other autoimmune diseases
- Increased risk of malignant lymphoma (MALToma) and carcinom of the thyroid

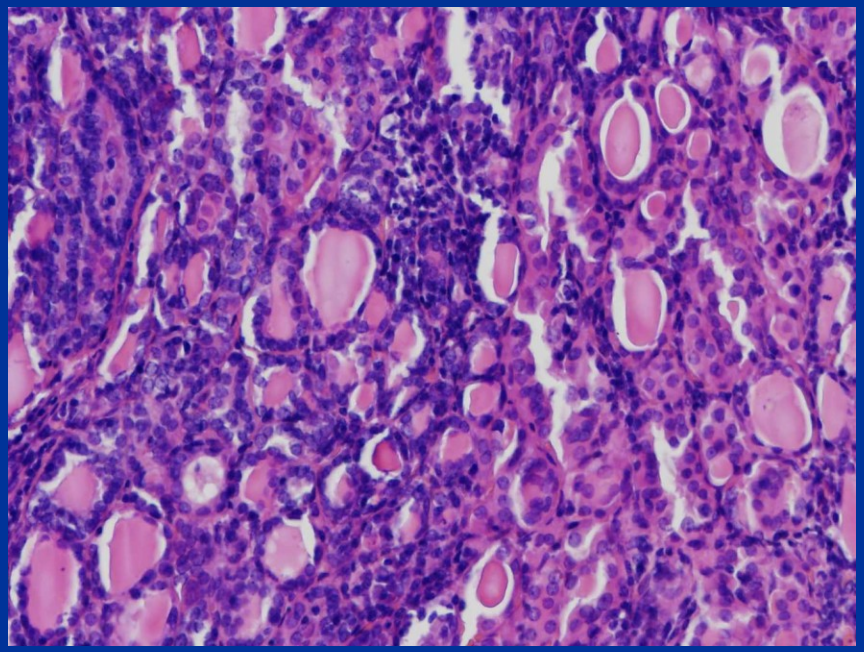
Thyroiditis

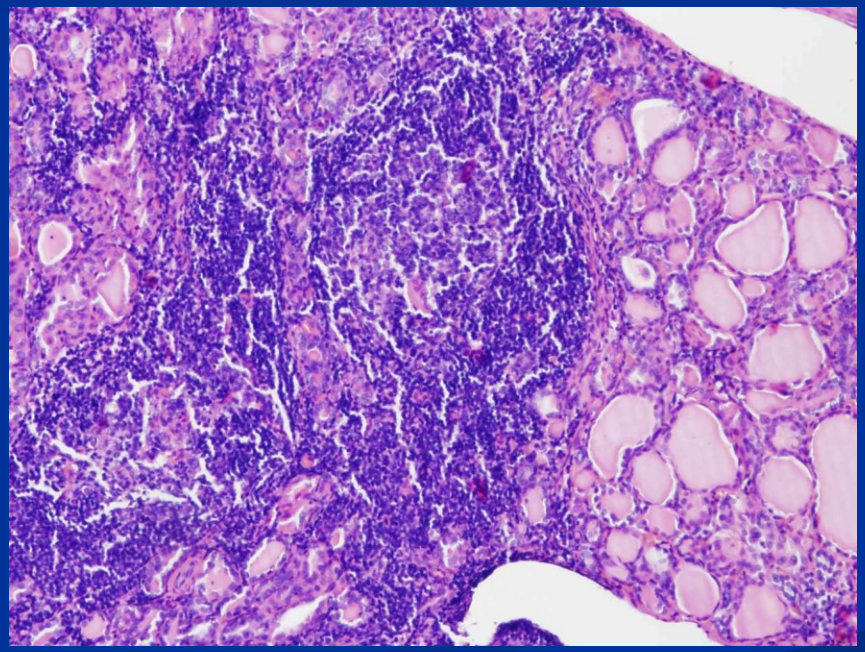
- **Subacute granulomatous thyroiditis (de Quervainova)**
- F:M = 3-5:1
- virus-induced host tisuue damage? cytotoxic T lymphocytes
- Painfully enlarged thyroid, fever, fairly abrupt onset
- Focal disruptions nad necroses of follicules, granulocytic and granulomatous reactions, fibrotisation)

- **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)





Sclerosing lesions associated with IgG4

- Autoimmune pancreatitia
- 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 thyreoiditis**

- 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

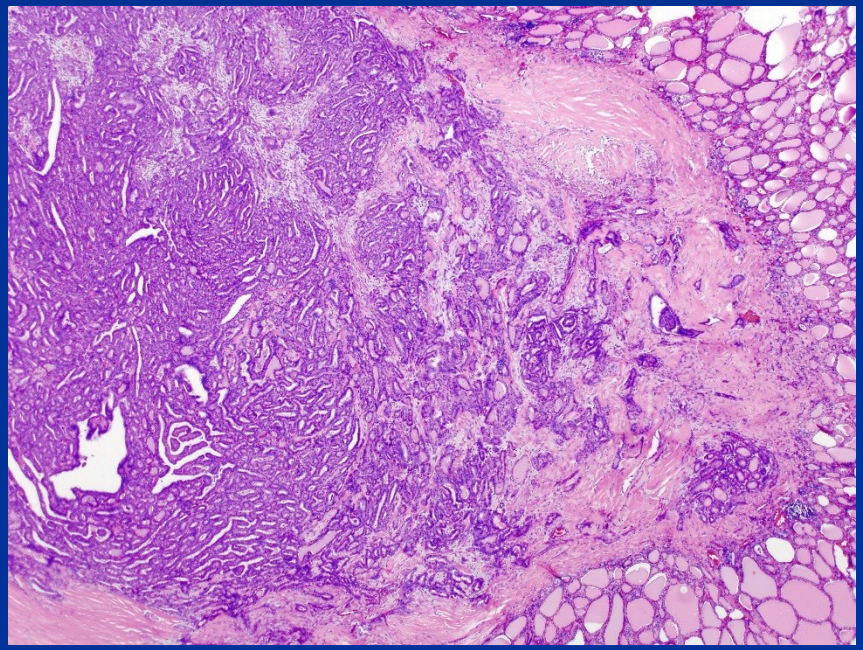
- **Benign**
  - **Follicular adenoma**

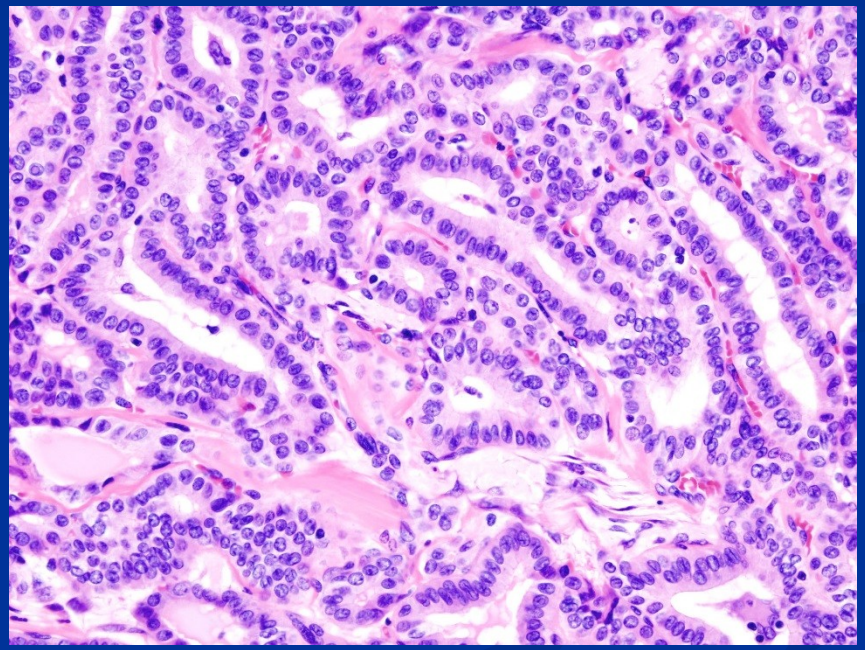
- **Malignant**
  - **Carcinoma**
  - **Lymphoma**

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

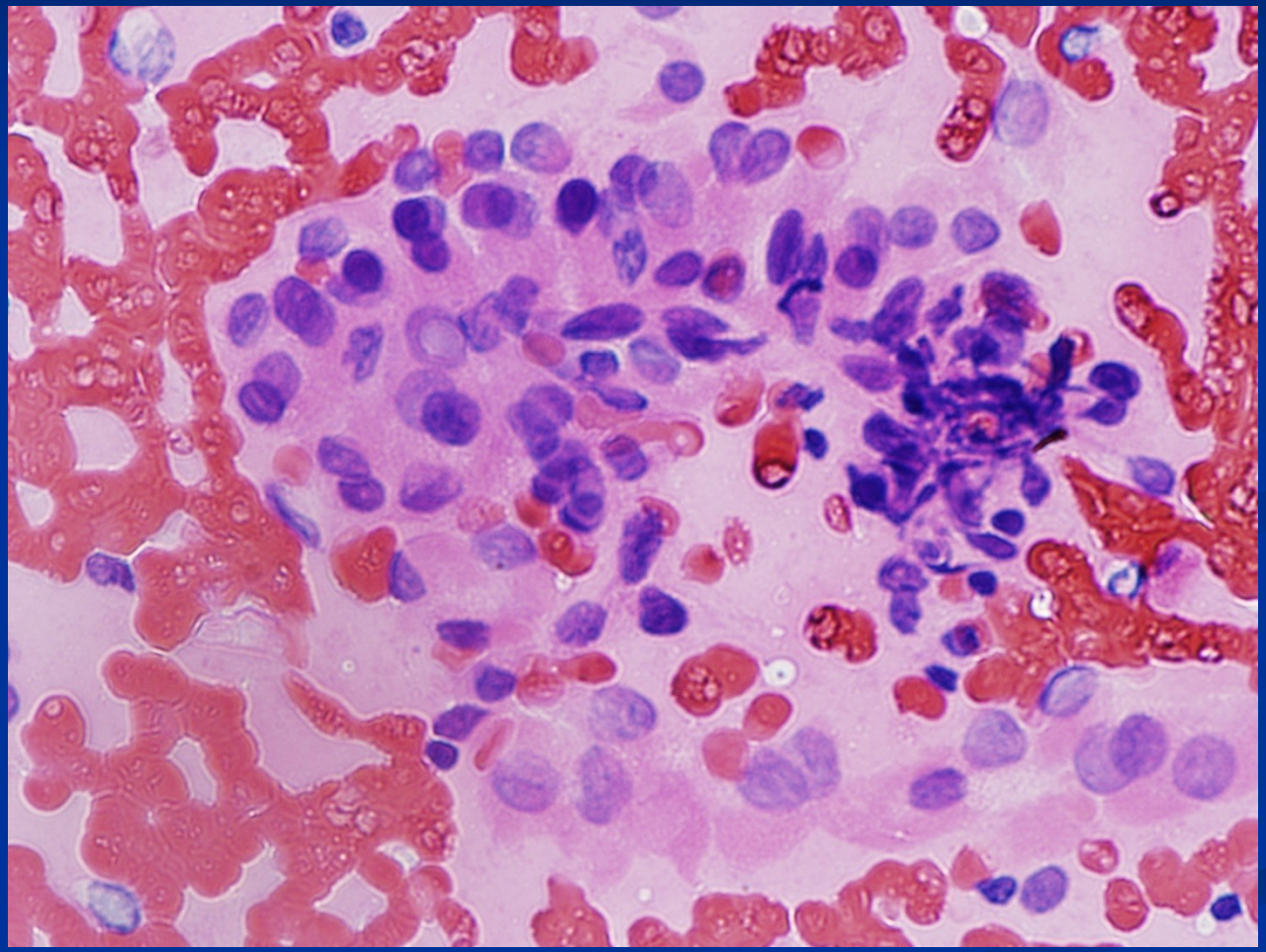
Carcinoma of the thyroid				
Type	**Proportion of all cases (%)**	**Typical age range**	**Mode of spread**	**Prognosis**
Papillary	60-70	Children, young adults	Lymphatic, to lymph nodes	Excellent
Follicular	20-25	Young-middle age	Haematogenous, to bones	Good
Anaplastic	10-15	Elderly	Aggressive local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

Papillary carcinoma of the thyroid



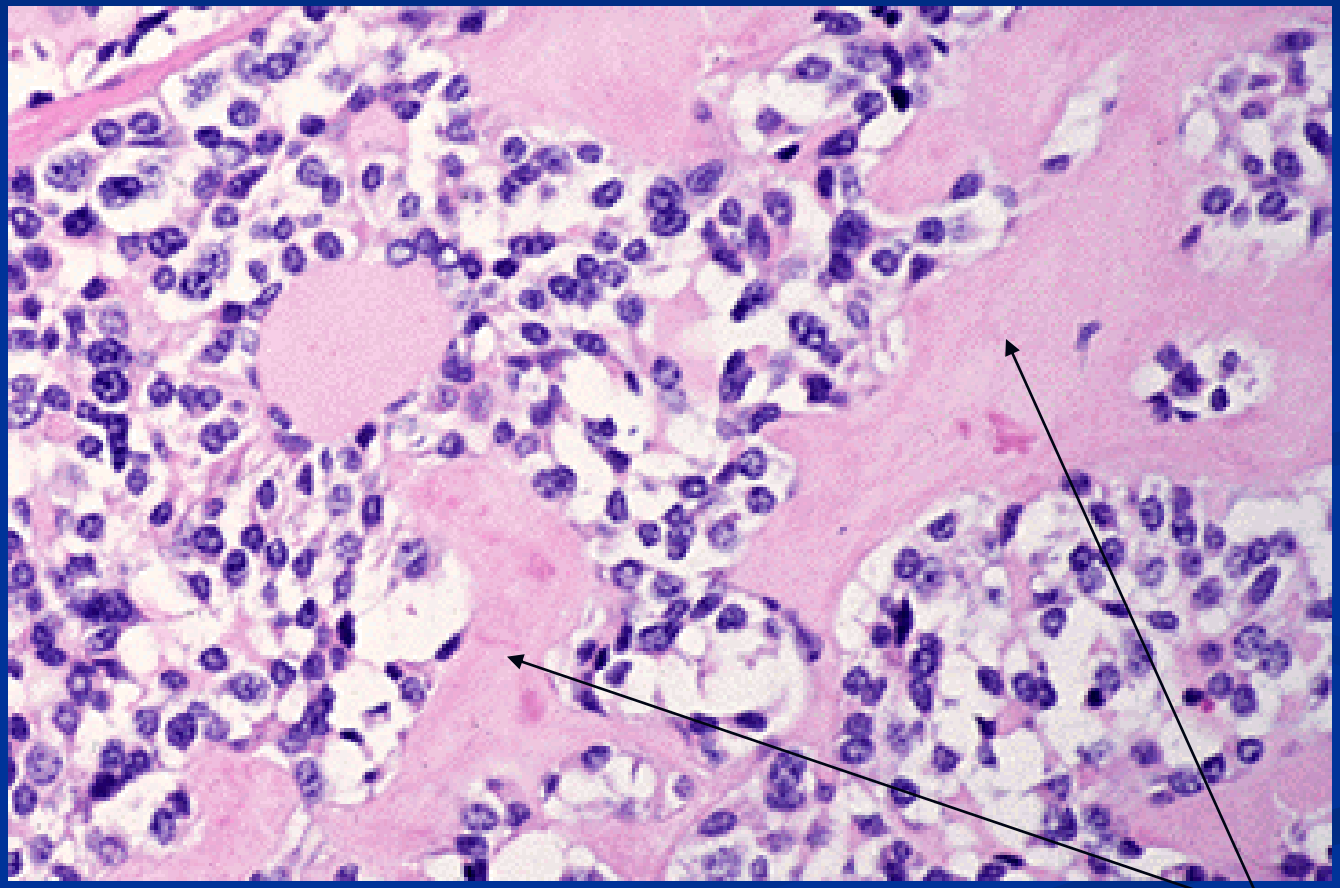


Papillary carcinoma of the thyroid

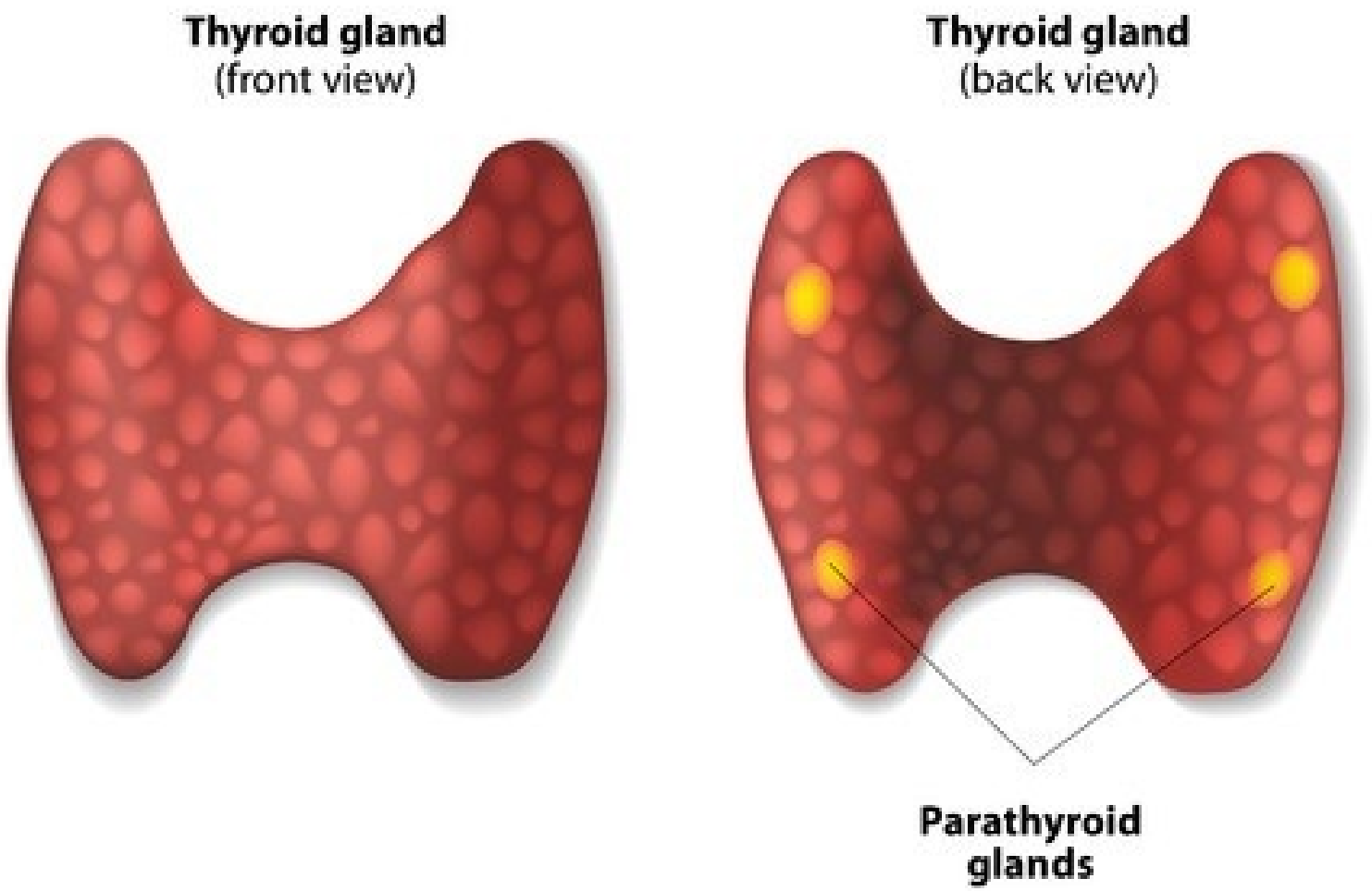


FNAB

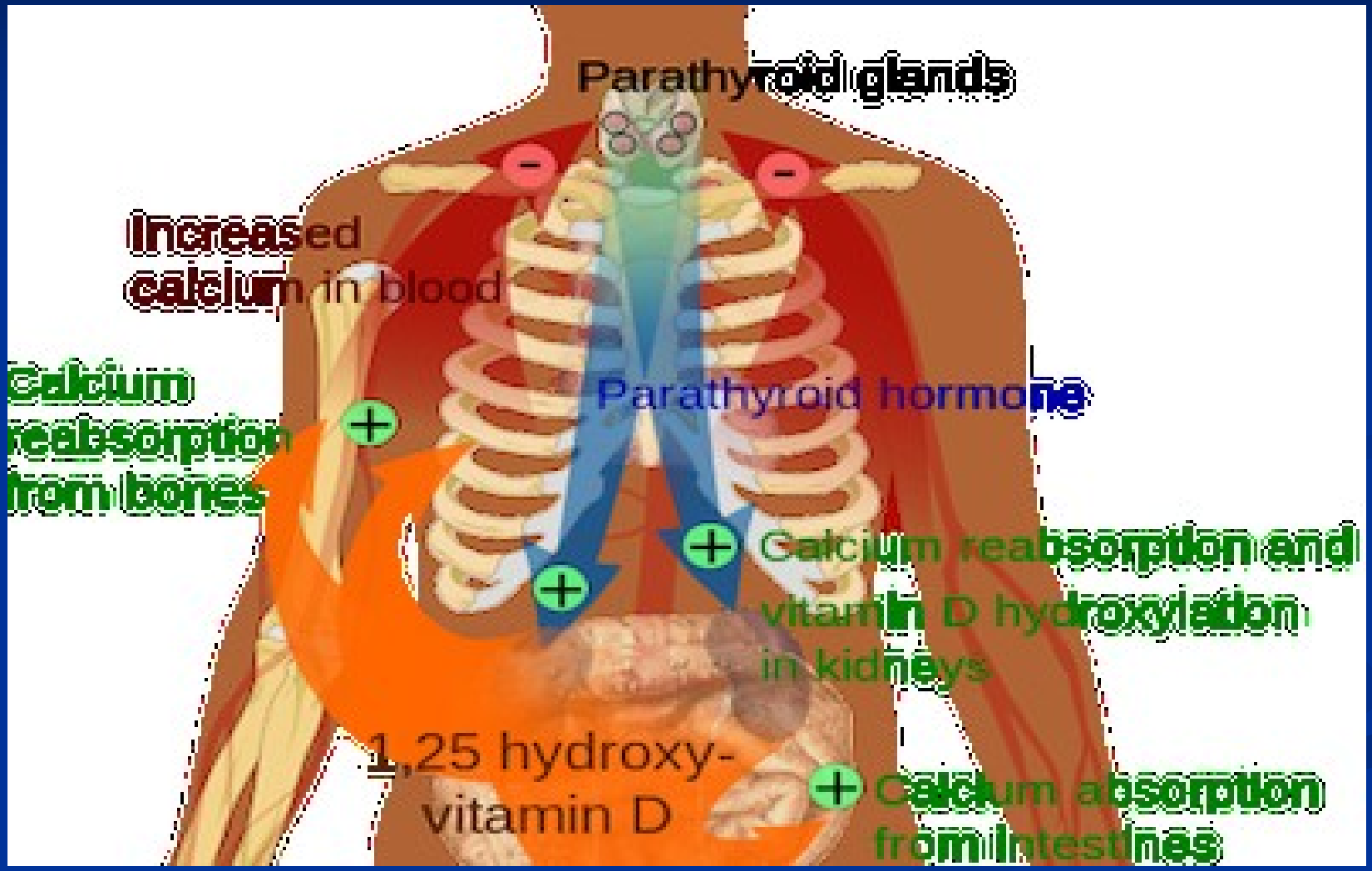
Medullary carcinoma of the thyroid



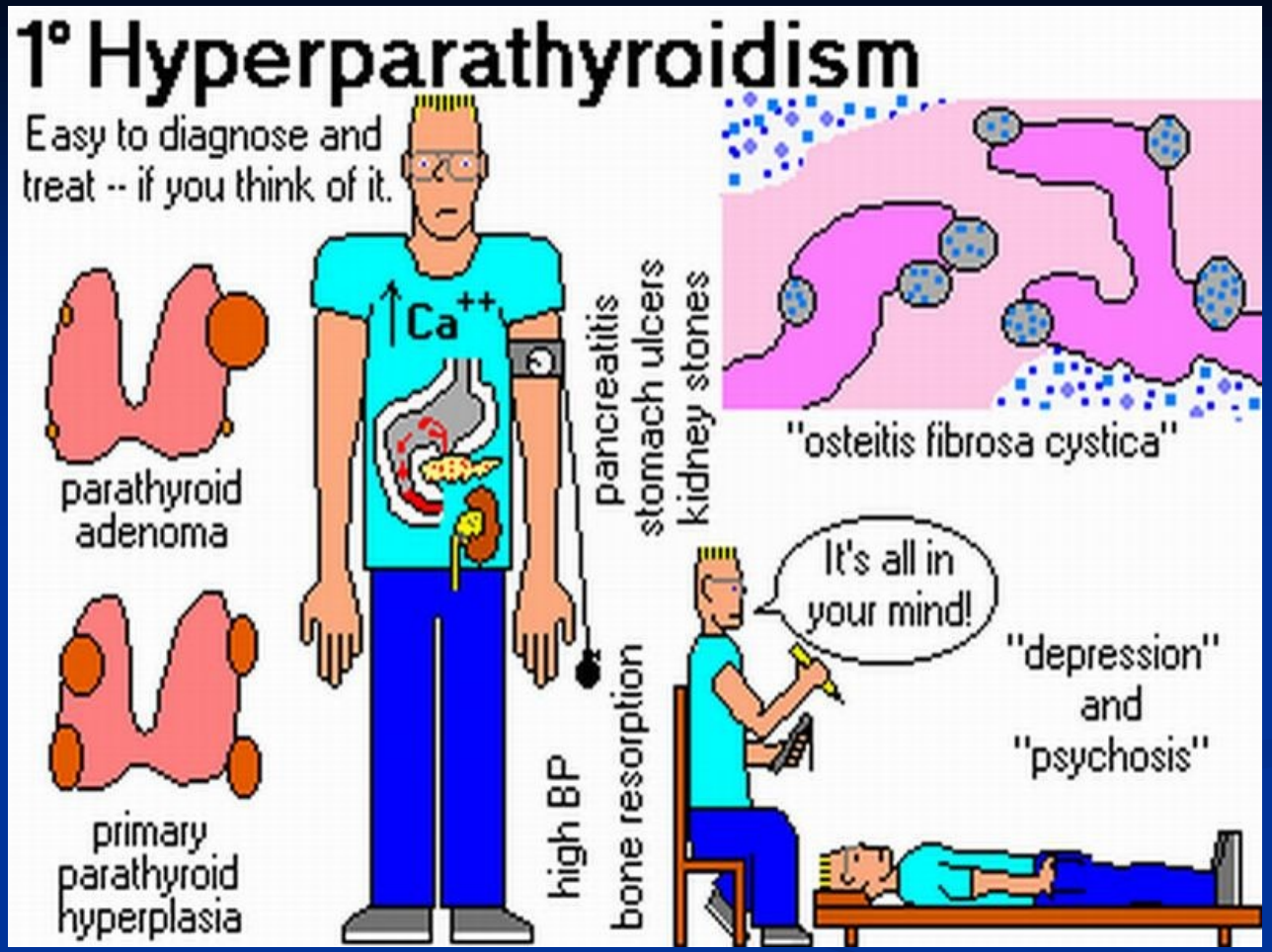
THYROID AND PARATHYROID



Parathyroid



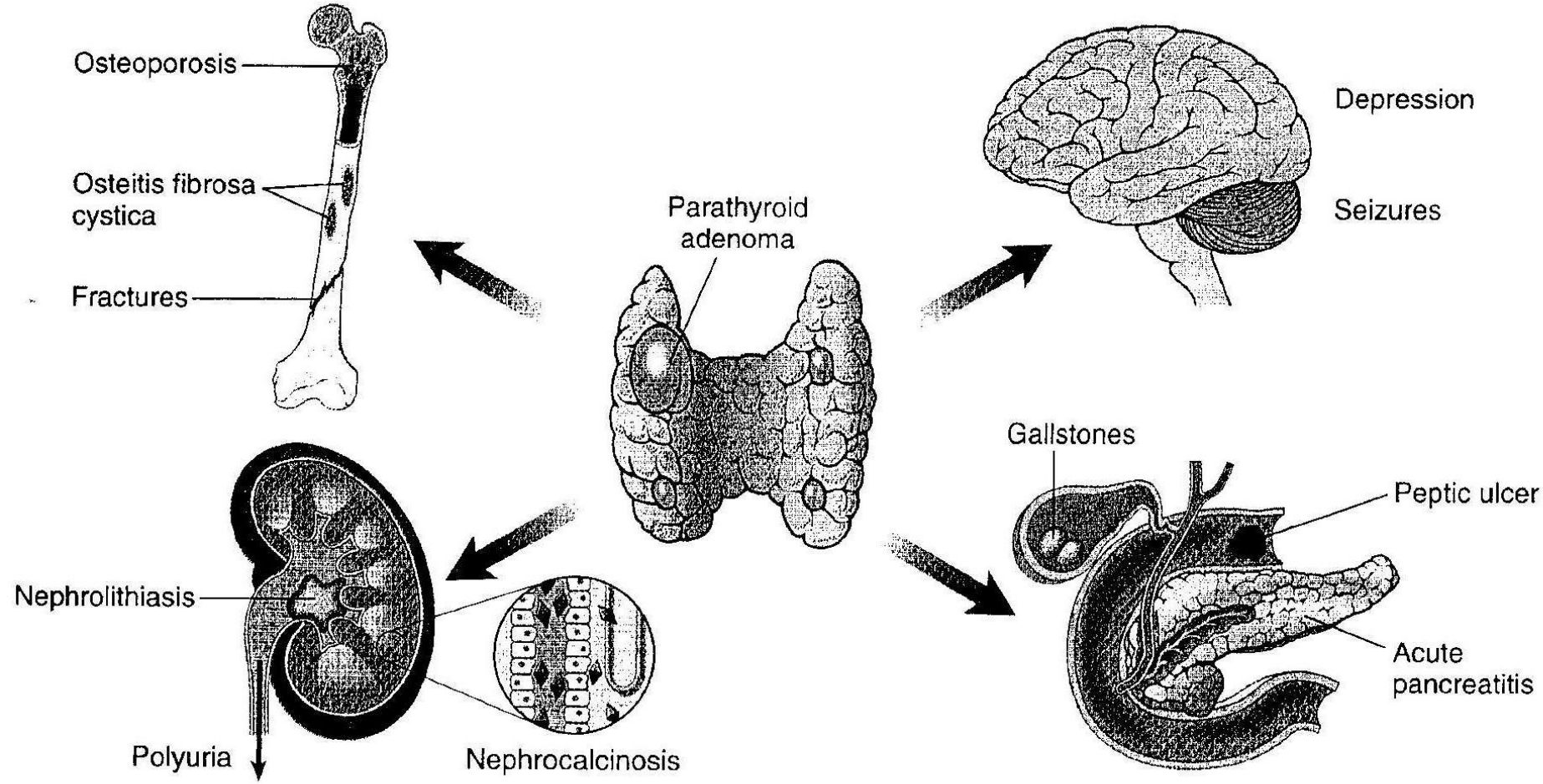
Primary



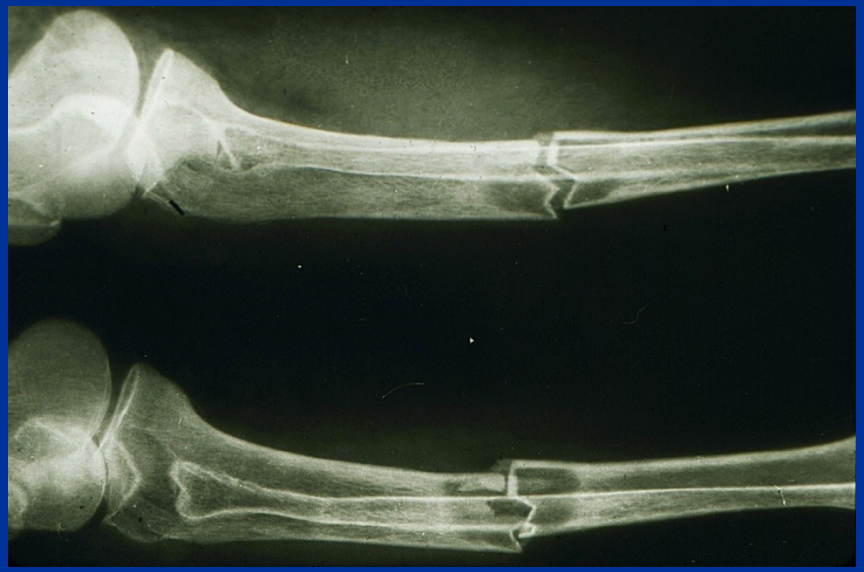
Secondary hyperparathyreoidsm: a physiological response to hypocalcaemia (e.g. in malabsorption, renal failure)

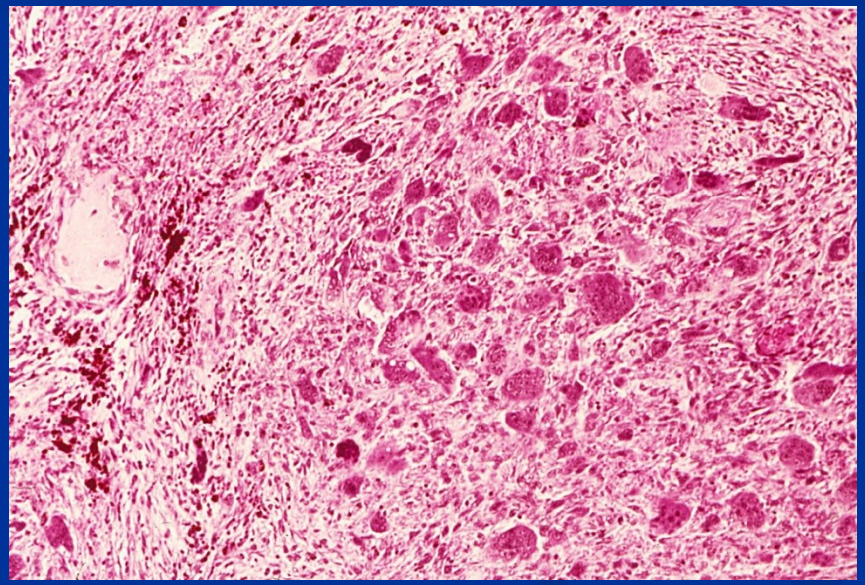
MEN 1, MEN 2

Clinical signs of hyperparathyreoidismu



Pathological fracture and brown pseudotumor





Hypoparathyreoidism

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

Pseudohypoparathyreoidism
- Insensitivity of peripheral tissues to PTH
- Usually genetically caused

- **Caused by:**
- Removal of or damage of the glands during thyreoidectomy
- Idiopathic, autoimmune (also as a part of polyendocrine syndrome)
- Congenital hypoplasia or aplasia (Di George syndroma)
- 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)

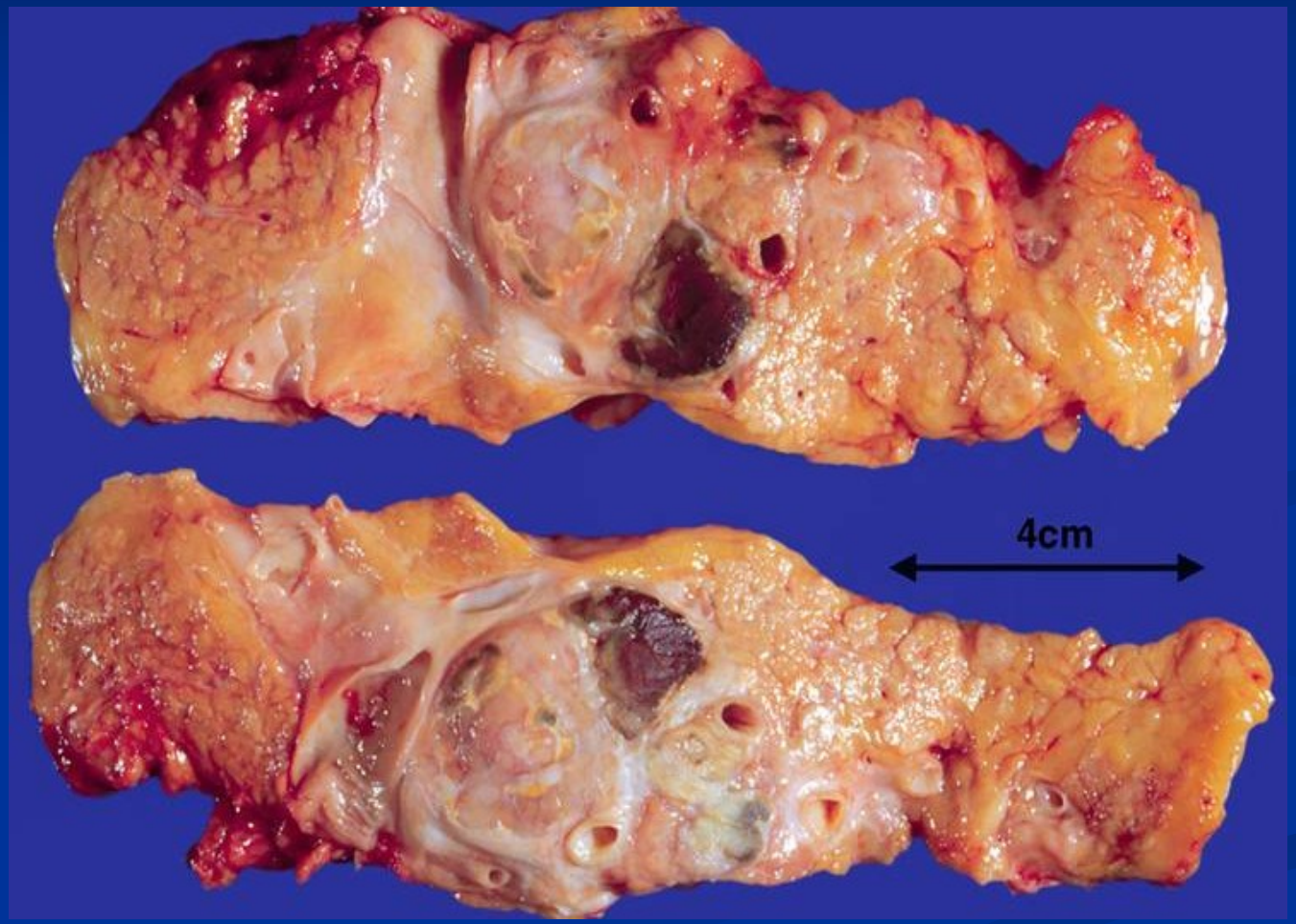
Islet cell tumor and gastrinomas may occur as a part of inherited MEN (multiple endocrine neoplasia) syndrome.

Neuroendocrine neoplasias – tumors of the endocrine pancreas

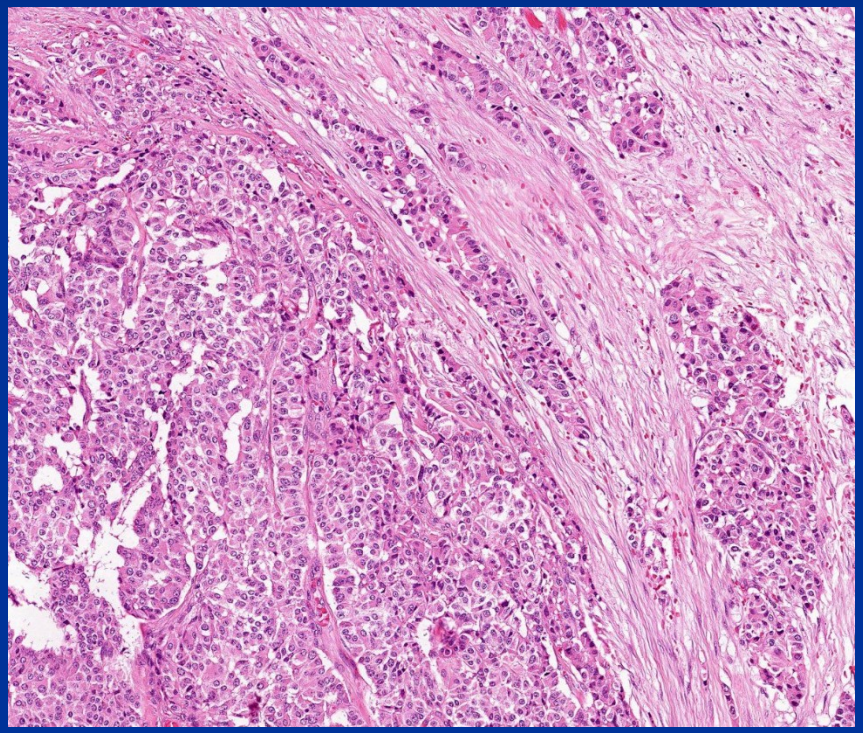
- Neuroendocrine tumor (NET)
  - Non-functional pancreatic NET (NET G1, G2)
  - NET G1
  - NET G2
  - NET G3 (from WHO 2019)

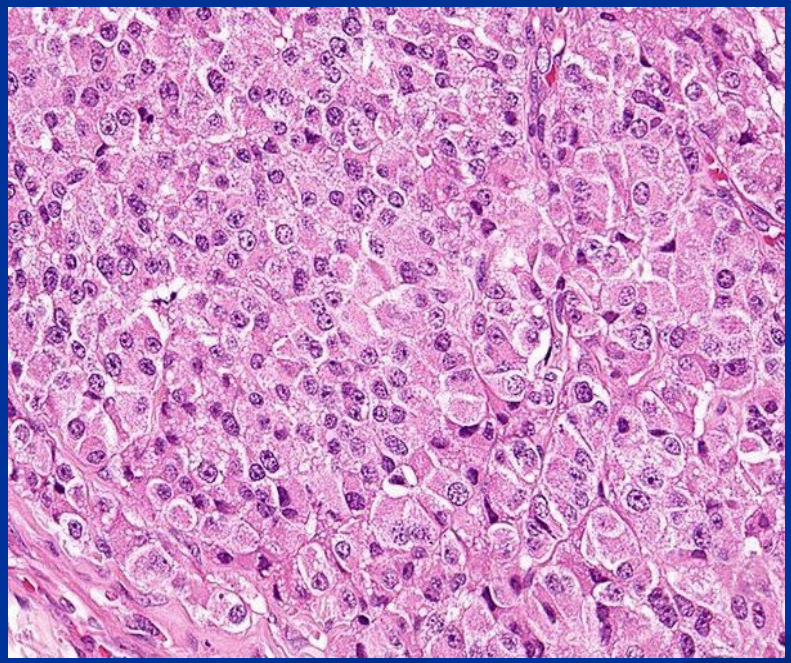
- Neuroendocrine carcinoma (NEC)
  - Large cell type NEC
  - Small cell type NEC

Neuroendocrine neoplasia of the pancreas.

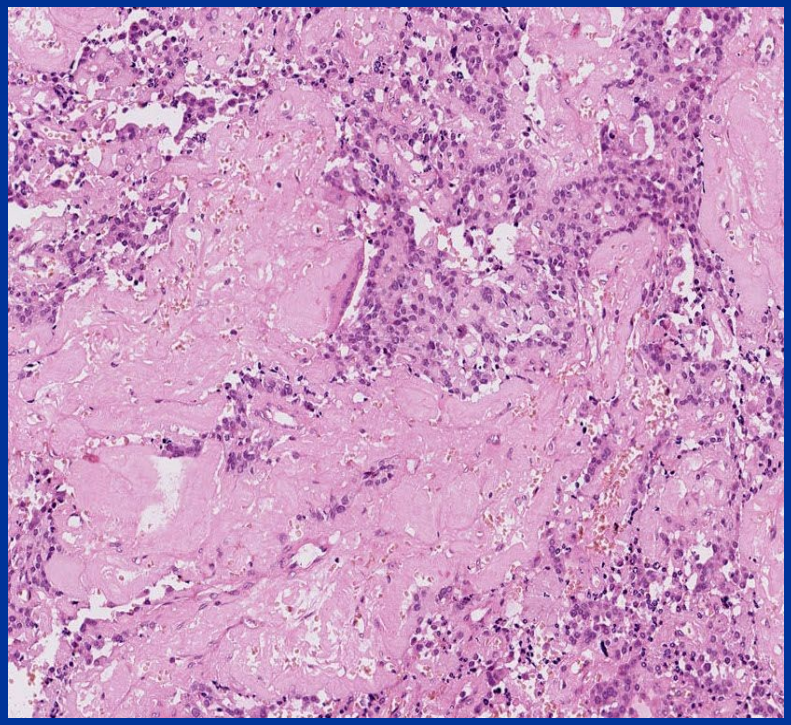


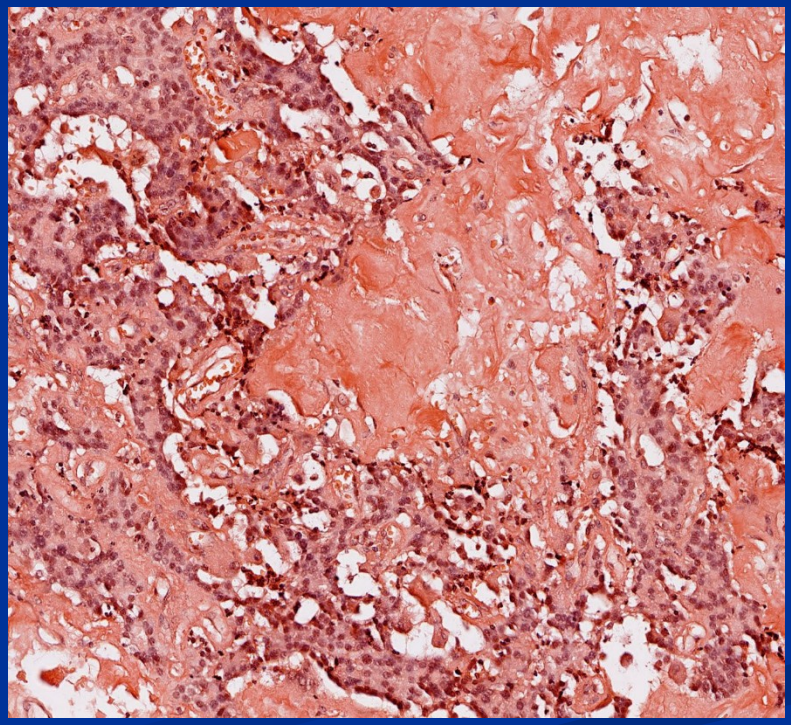
Neuroendocrine neoplasia of the pancreas.





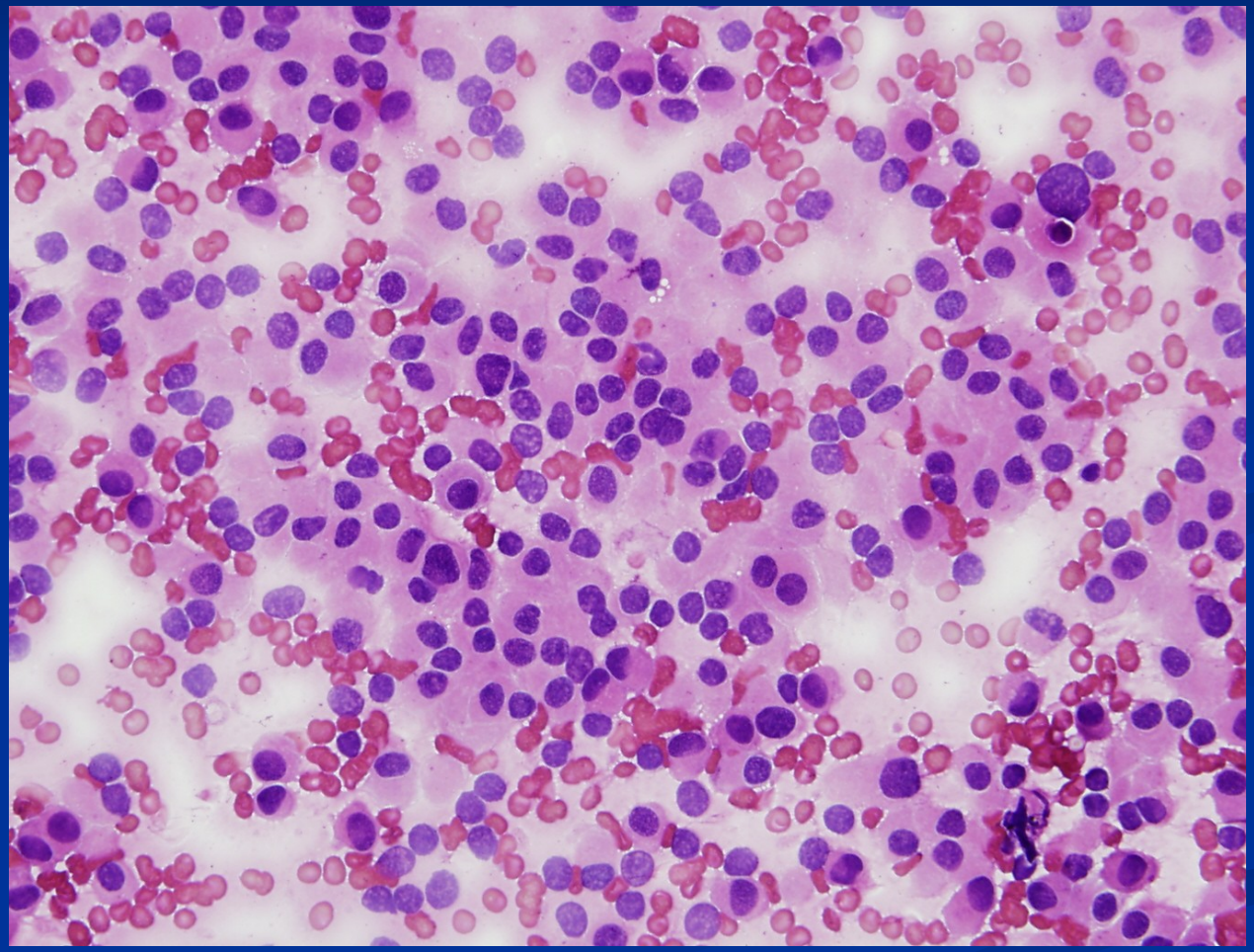
Amyloid deposits in insulinoma



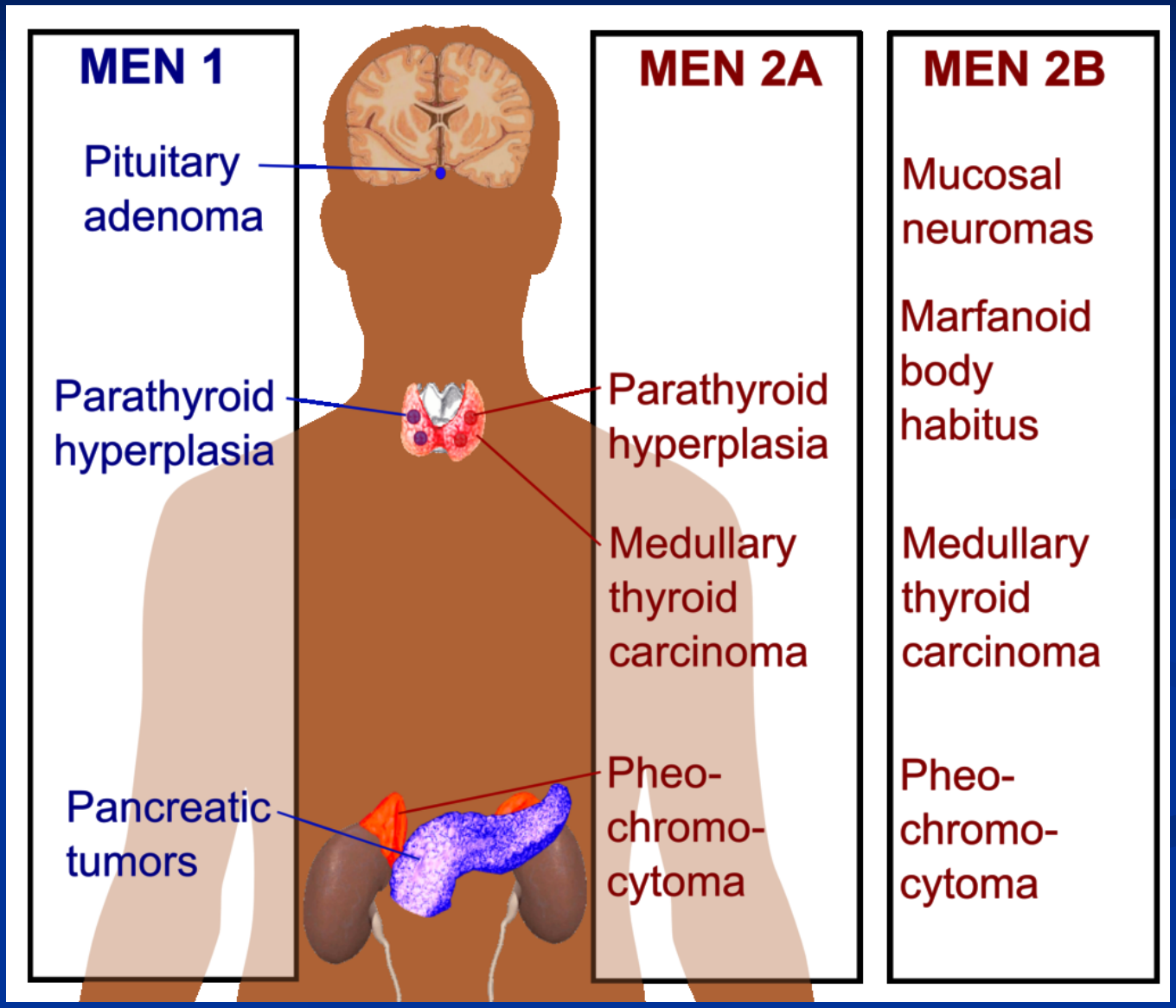


FNAB

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
  - Autoimunne 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 syndroma
  - Hyperthyreoidismus
  - Glucagonoma, feochromocytoma
- **Infections**
  - CMV
  - Coxackie virus B
- **Drugs**
  - Glucocorticoids, hormones of thyroid, alpha interferon, proteases inhibitors, thiazids, phenytoin, …
- **Genetic syndromas assoc. with DM**
  - Down syndroma
  - Klienefelter syndroma
  - Turner syndroma
- **Gestational DM**

Differences between types of diabetes mellitus (DM: abnormal metabolic state characterised by glucose intolerance due to inadequate insulin action)		
Features	**Type 1 (ketosis-prone, juvenile onset, insulin-dependent)**	**Type 2 (not ketosis-prone, maturity onset, non-insulin-dependent)**
Age of onset	Usually <20y	Usually >40y
Proportion of all cases	<10 %	>90%
Type of onset	Abrupt (acute or subacute)	Gradual
Etiological factors	Possible viral/autoimmune, resulting in destruction of islet cells	Obesity associated insulin resistence
HLA asocciation	Yes (=genetic predisposition in DM)	No
Insulin antibodies	Yes	No
Body weight at onset	Normal or thin, obesity uncommon	Majority are obese (80%)
Endogenous insulin production	Decreased (little or none)	Variable (above or below normal)
Ketoacidosis	May occur	Rare
Treatment	Insulin, diet, exercise	Diet, oral hypoglycemic agents, exercise, insulin, and weight control

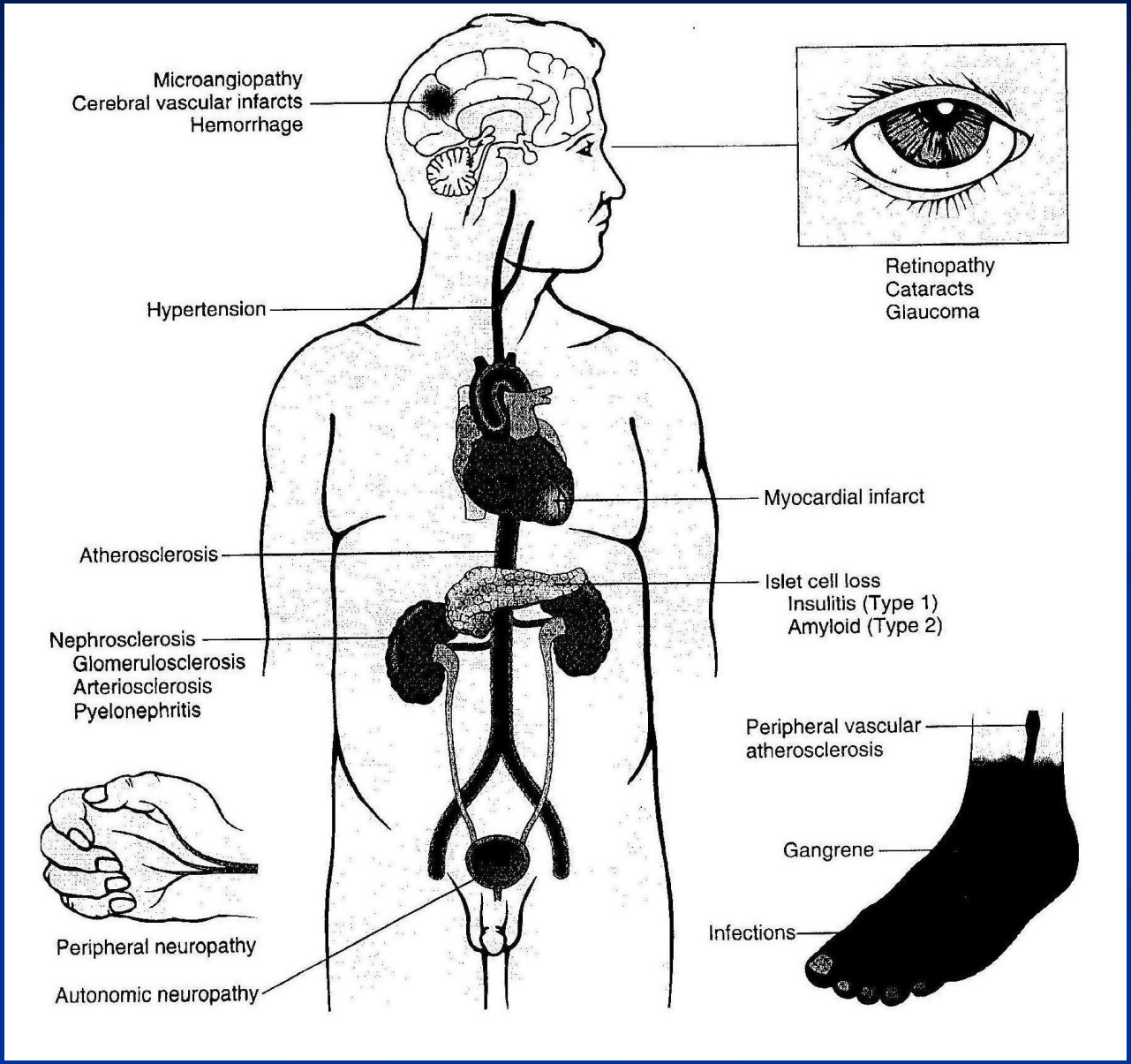
Risk factors for type 1 and type 2 diabetes mellitus
Type 1 DM risk factors
Type 1 DM in a first-degree relative (sibling or parents)
Type 2 DM risk factors
Positive family history
Ethnic origin (black, native americans, hispanic, asian american, pacific islanders)
Obesity
Increasing age
Habitual physical inactivity, sedentary lifestyle
History of gestational DM
Other clinical conditions assoc. with insulin resistence (e.g. polycystic ovary syndrome)
History of vasular diseases
Previously identified impaired fasting glucose or impaired glucose tolerance
Hypertension
HDL cholesterol level <35mg/dL and/or triglyceride level ≥250mg/dL
Cigarette smoking

Cardinal clinical signs of DM at diagnosis

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

Complications of diabetes	
Situation	**Complication**
Large blood vessels	Accelerated arteriosclerosis leading to: - Myocardial infarction - Cerebrovascular diseases - Ischaemic limbs - Responsible for 80 % of adult diabetic death
Small blood vessels	Endothelial cells and basal lamina damage. Retinopathy (major cause of blindness), nephropathy
Peripheral nerve	Diabetic neuropathy (v.s. due to disease of small vessels supplying the nerves)
Neutrophils	Susceptibility to infection
Pregnancy	Pre-eclamptic toxaemia Large babies Neonatal hypoglycamia
Skin	Gangrene of extremities Soft tissue lesions (Granuloma annulare, necrobiosis lipoidica)

Complications of diabetes.



Thank you for your attention…