



Pathology : INT-108

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MediQ team



SCAN OR CLICK!



1. Introduction

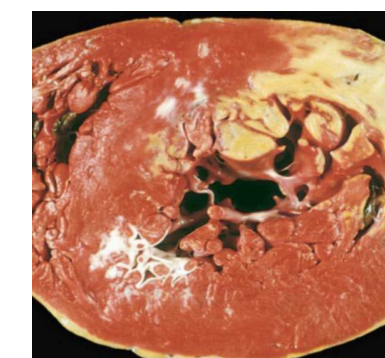
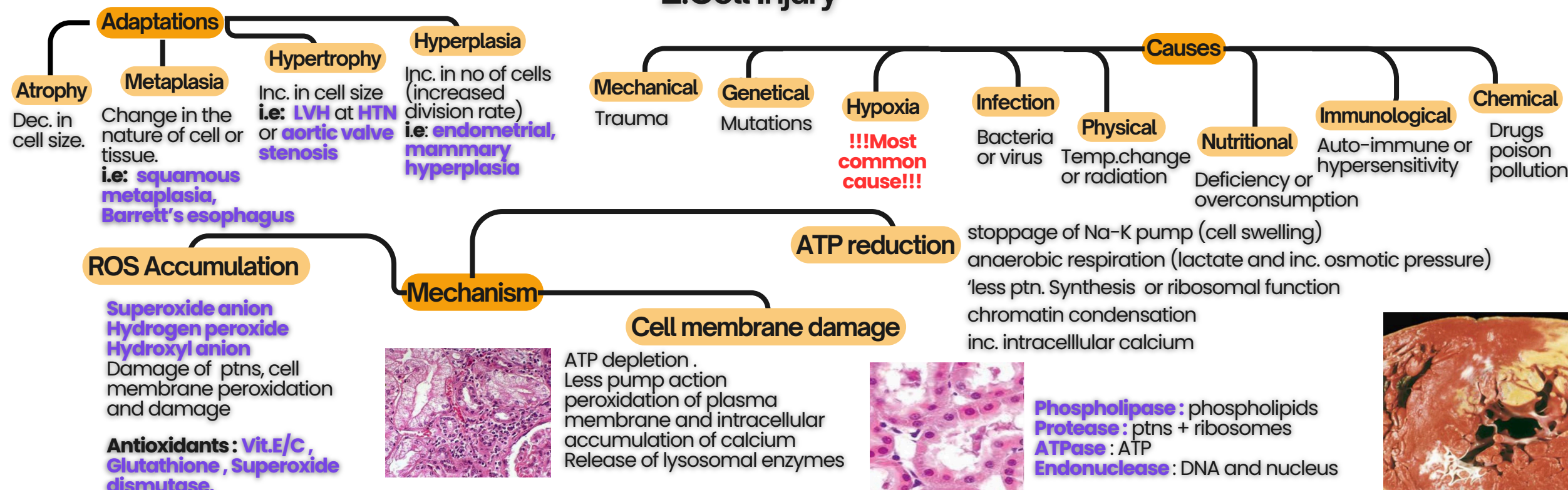
- Epidemiology** (**incidence**): distribution and determinants of disease in different populations.
- Etiology** **causes of disease**
Primary, cryptogenic or idiopathic: unknown cause, iatrogenic, Genetic, Environmental (**infective, chemical, radiation, mechanical**)
Combination: multifactorial etiology
- Pathogenesis** mechanism by which etiology produce disease
- Morphology**
structural changes
Gross: surgical removal or postmortem (**autopsy**)
Microscopic: light or electron microscopy
Lesion: structural abnormality seen in organ (**mass, ulcer**)
- Complications** (**squeal**): secondary effects of disease (**tumor leading to intestinal obstruction**)
- Prognosis** (**outcome**): the course of the disease – the fate can be changed by **surgical** or **medical** intervention
- Classification**
- **congenital** (genetic or not)
- **acquired**: inflammatory, hemodynamic, growth changes, disorders of immunity, metabolic disease, degenerative disease)

3. Reversible Cell Injury (Degeneration)

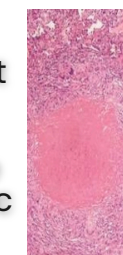
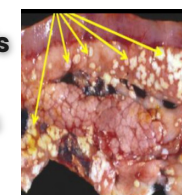
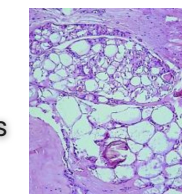
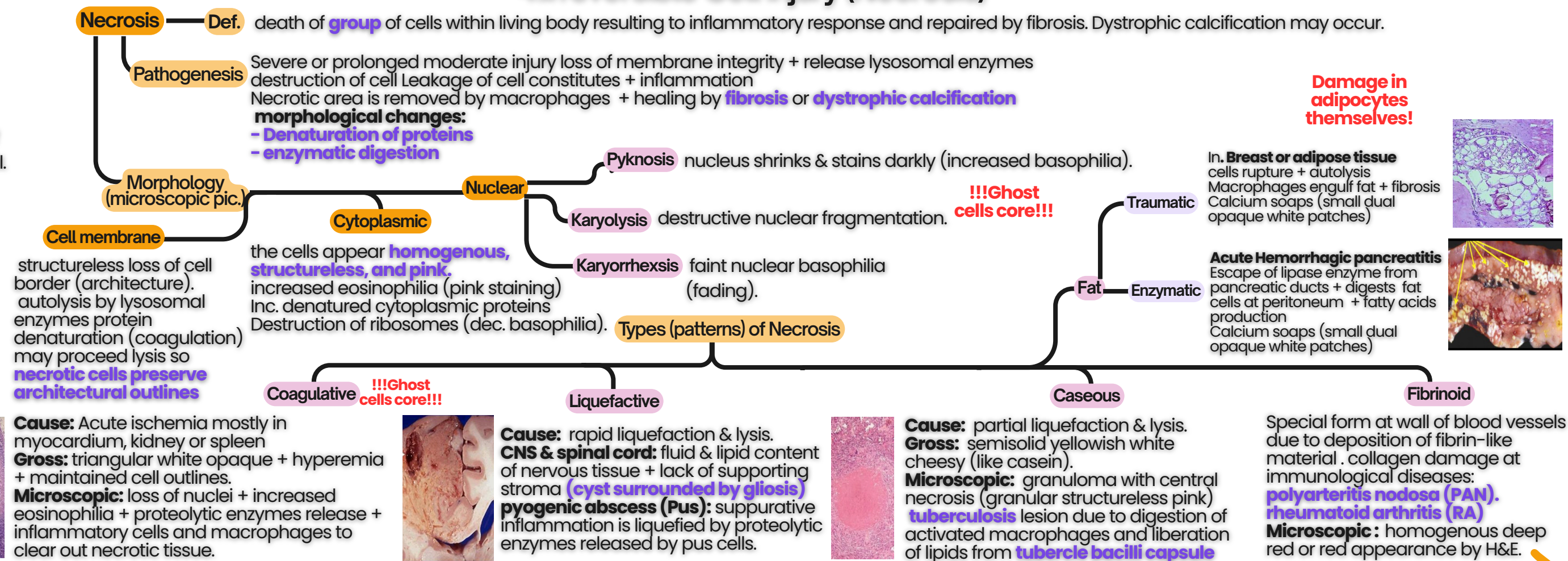
- Cloud Swelling (early)**
Due to water accumulation. **At liver, kidney tubular cells or myocardium cells.**
Low ATP leads to stoppage of Na-K pump and water accumulation
anaerobic respiration leads to accumulation of lactate leading to high osmotic pressure as well.
- Hydropic degeneration (advanced)**
Vacuolar degeneration (**cell ballooning**)
Microscopic: excess water accumulation in cells leading to **pale vacuoles** in cytoplasm.
- Fatty Change**
with hypoxic and toxic injury lipid appears as empty vacuoles in cells involved or dependent on fat metabolism (**hepatocytes and myocardial cells**)
at myocardium **spotty at ischemia or diffuse at diphtheria**



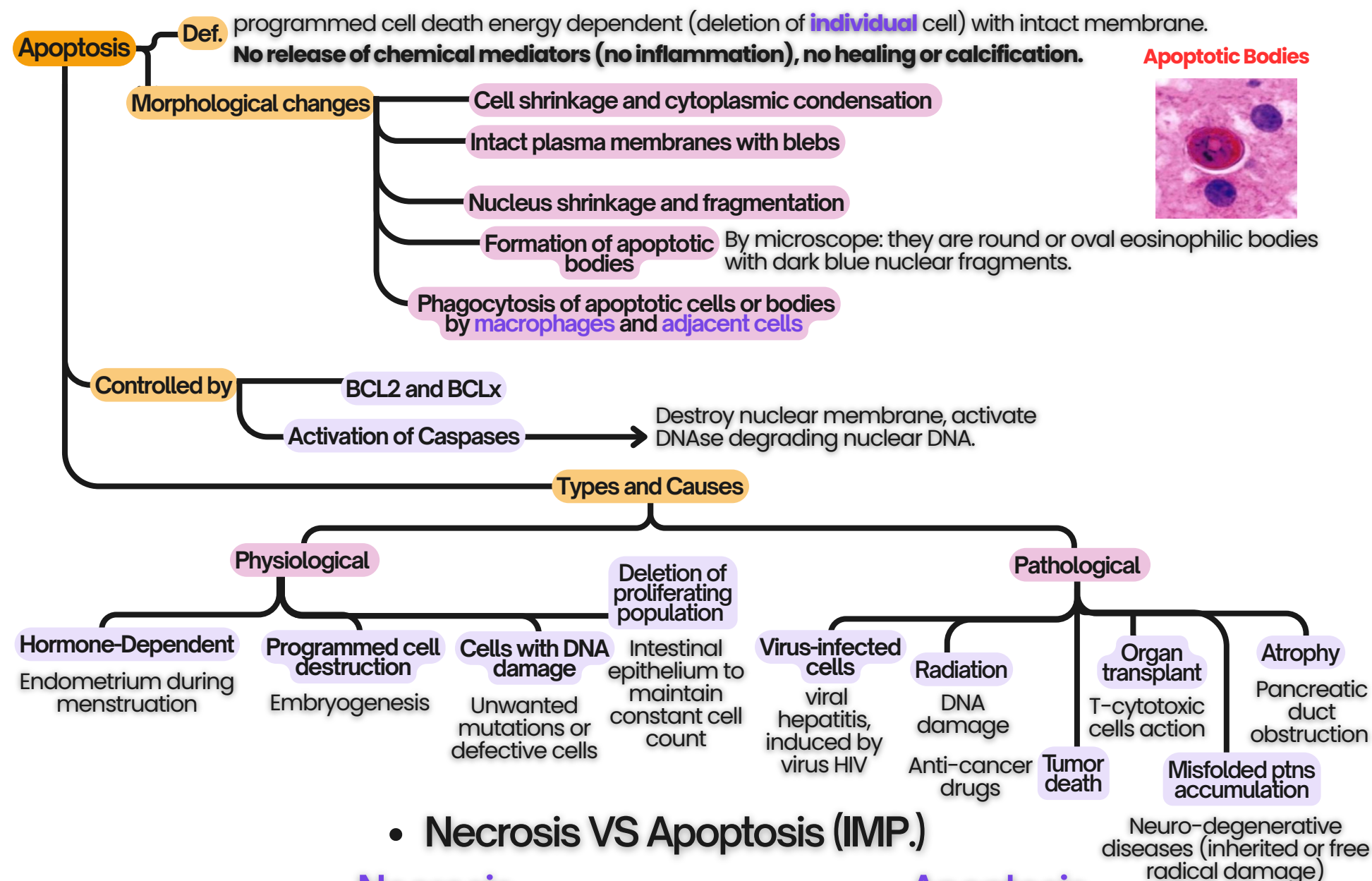
2. Cell Injury



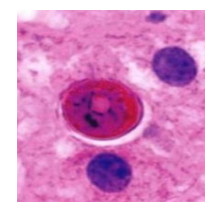
4. Irreversible Cell injury (Necrosis)



5. Irreversible Cell injury (Apoptosis)



Apoptotic Bodies



• Necrosis VS Apoptosis (IMP.)

Necrosis

Cause	Pathological
Cell size	Enlarges
Nucleus	Pyknosis, karyorrhexis, karyolysis and dissolved
Membrane	Disrupted
Inflammation	Yes
Energy	Passive
Cells	Multiple

Apoptosis

Cause	Physiological and pathological
Cell size	Shrinks
Nucleus	Fragmented (nucleosomes)
Membrane	Intact with blebs
Inflammation	No
Energy	Active
Cells	Individual

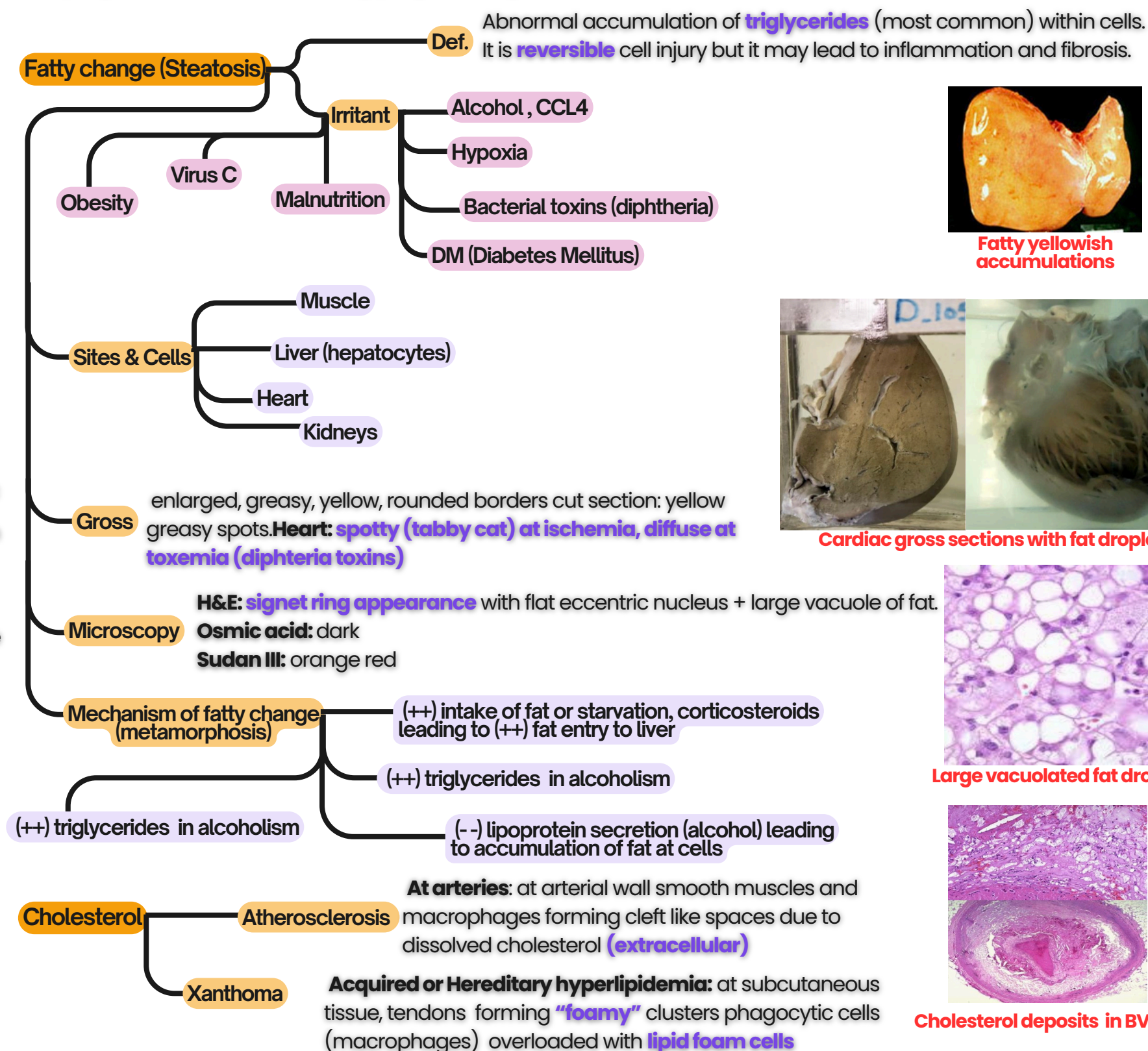
6. Intracellular Accumulations

Normal endogenous: water, protein, carbohydrates, lipid inadequate removal (**fatty liver**) or genetic or enzymatic defect (**as lysosomal storage diseases**).

Abnormal endogenous: α 1 antitrypsin mutated gene so defective folding or transport.

Abnormal exogenous: macrophages with abnormal carbon.

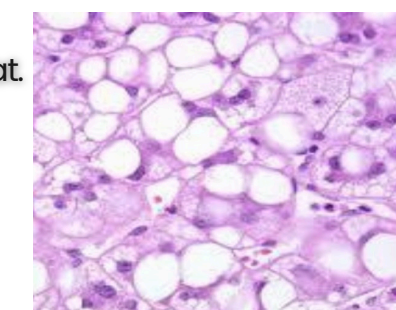
Glycogenosis: clear vacuoles at **glycogen storage disease & DM**



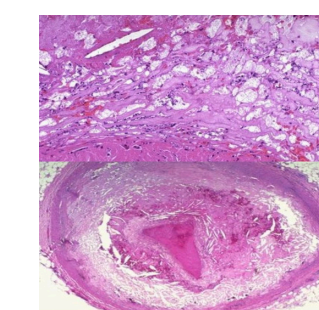
Fatty yellowish accumulations



Cardiac gross sections with fat droplets



Large vacuolated fat droplets



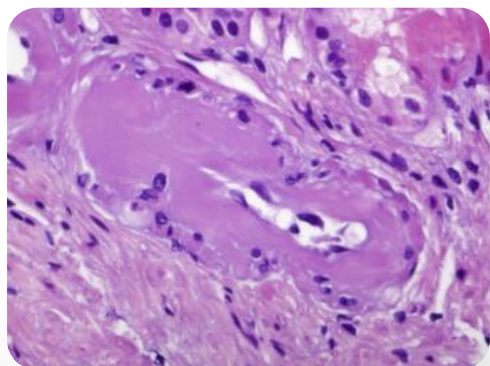
Cholesterol deposits in BVs

Hyaline change

Accumulation of hyaline protein material: **homogenous, glassy pink** appearance is stained with H&E
Descriptive histological term rather than specific cell injury marker

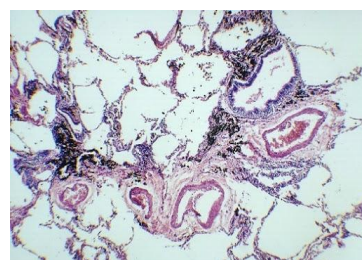
Intracellular:
Mallory bodies: hepatocytes (chronic alcohol)
Russell bodies: at plasma cells (IGs) at chronic inflammation

Extracellular:
leiomyoma: smooth muscle tumor
old scar (collagenous fibrous tissue) (not clear basis)
prolonged hypertension and DM: extravasates plasma proteins accumulate at kidney basement membrane: arteriosclerosis and atherosclerosis



Exogenous pigmentation

Inhalation: black pig. of lung and LNs due to carbon inhalation "**anthracosis**"
Coal worker pneumoconiosis: fibroblastic reaction around carbon dusts serious lung disease
Inoculation: tattooing: injection in dermis phagocytosed by macrophages permanent



3 Hemosiderin

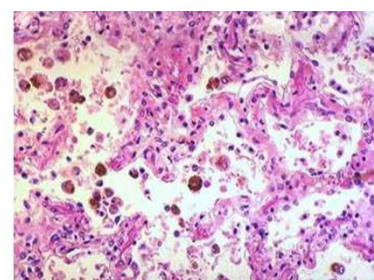
(-- apoferritin, transferrin)

Hemoglobin derived **golden yellow** granular pigment (ferritin micelles)
→ **Hemosiderosis:** accumulation of hemosiderin within macrophages without tissue damage
→ **Hemochromatosis:** accumulation of hemosiderin within parenchymal cells (liver) with tissue damage, scarring and organ dysfunction

Localized:
→ Ex. Chronic venous congestion of the lung, varicose veins
→ Formed by phagocytosed extravasated RBC's (break down Hb → iron from heme → ferritin deposition)

Generalized: SYSTEMIC: systemic overload of iron
Causes:
→ (++) absorption of iron
→ Hemolytic anemia
→ Repeated blood transfusion (exogenous)

Pathology:
→ At first in mononuclear phagocytes of liver, bone marrow, spleen, LN + scattered Macrophages at skin, pancreas, kidney
→ Progressive accumulation → pigmented liver, pancreas, heart, endocrine glands
→ **Microscopic:** coarse golden granular pigment seen by Prussian blue (stains non heme ferric ion)



Pigments

Endogenous pigmentation

1 Lipofuscin

→ "wear-and-tear pigment"
→ Insoluble not injurious **brownish-yellow** intracellular **perinuclear** material (due to **lipid peroxidation** of cell membranes and action of ROS) with age or atrophy.
→ Not injurious to the cell
→ At liver or heart cells of aging patients or severe malnutrition and cancer

Brown Atrophy of the heart (senile atrophy)
Gross:
Heart: is (--) at size, brown in color
Coronaries: are tortuous with normal length
Pericardial fat: is replaced by jelly like tissue (serous atrophy of fat)
Microscopic:
Muscle fibers: thin and atrophic
Around nucleus: **yellow brown** fine granular lipofuscin pigment stained by H&E



2 Melanin

Tyrosine by tyrosinase enzyme → dihydroxyphenylalanine

Endogenous non hemoglobin derived, **brown black** pigment in melanocytes

- 1. Prolonged exposure** to sun light
- 2. Pigmented skin tumor** nevi or melanomas
- 3. Chloasma:** brown patches at face, nipple, genitalia of pregnant women due to hormonal changes
- 4. Addison disease:** adrenal disease → (++) POMC → (++) MSH at sun exposure areas and pressure areas (neck, elbow, knee, knuckles)
- 5. Café au lait patches:** neurofibromatosis

Decreased melanin pigmentation albinism and vitiligo



Primary hemochromatosis

→ **The most common** form of iron overload
→ Congenital gene defect (homozygote) at **chromosome 6** (heterozygote (++) iron absorption)
→ Increase absorption of iron
→ Transferrin is overloaded
Sites: liver, heart, pancreas, skin, endocrinal glands
Gross:
- Liver: large, dense, **chocolate brown**
- at the cytoplasm of the periportal hepatocytes
- Fibrous micronodular (**liver cirrhosis**)
- heart (**heart failure**)
- It involve skin, adrenal gland, pancreas, pituitary gland (++) melanotropin secretion + hemosiderin deposition in skin (**bronzed diabetes**)

Extra cellular deposition

1 CALCIUM

Dystrophic calcification

Of **injured or necrotic dead** tissue deposition of **normal serum calcium**

Examples:

- congenital bicuspid aortic valve
- atheromatous plaques
- old thrombus
- caseous necrosis (T.B)
- fat necrosis
- dead fetus (lithopedion)



Metastatic Calcification

Of normal living tissue (viable) but (++) calcium (hypercalcemia)

1. (++) **calcium absorption**: hypervitaminosis D
2. (++) **parathyroid hormone**:
 - 1ry: Parathyroid tumor, parathyroid hormone secreted by other neoplasm
 - 2ry: renal failure
3. **Milk alkali syndrome**: milk + calcium carbonate
4. **Bone destruction**:
 - Prolonged immobilization,
 - Cancer at bone, multiple myeloma, metastasis (cancer breast)
 - Increased bone turn over (Paget's disease)

At sites relative alkaline

- o mucosa of stomach
- o Renal tubule
- o Lung alveoli
- o Wall of arteries, pulmonary veins

Usually no clinical dysfunction but at kidney (**nephronocalcinosis**)

→ renal failure

Morphology: (both dystrophic and metastatic):

Gross: **chalky white** granular material

Microscopic: **basophilic** amorphous granular depositions

Continue Primary hemochromatosis

Microscopic:

Yellow golden brown Coarse granular pigments at the cytoplasm visualized by Prussian blue reaction

Involvement of the rest of lobule and bile epithelium with kupffer cells pigmentation

Hemozoin:

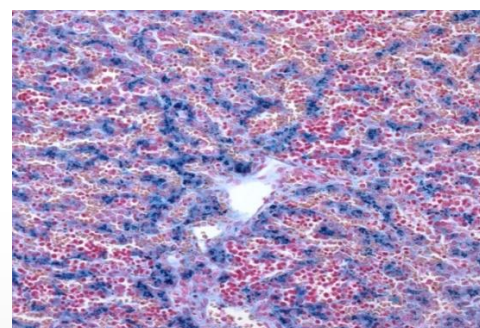
is a brown iron containing pigment (insoluble crystalline form of heme) produced by blood

feeding parasites (bilharzia, malaria)

taken by macrophages of liver spleen and other organs

not reactive to **Prussian blue**

N.B: hemoglobin derived: hemosiderin, hemozoin



2 AMYLOIDOSIS

Extracellular deposition of abnormal protein (90% fibril protein **β pleated configuration** & 10% glycoprotein" amyloid P protein")

At basement membranes, reticulin fibers and wall of BL VS

The affected tissue appears **waxy and hard**

Pathogenesis:

- Abnormal folding of the proteins → become insoluble → aggregate and deposited at extracellular tissue
- Normally misfolded proteins → degraded by proteasomes intracellular or by macrophages extra cellular
- Failure of quality control mechanisms → accumulation of misfolded proteins outside cells
- These proteins are:
 - **Normal proteins**: inherent tendency to fold improperly when produced by high amounts
 - **Mutant proteins**: that misfold and aggregate

Types of amyloid proteins: >20 types

1. (**AL**): amyloid light chain: Ig immunoglobulin derived from plasma cells

2. (**AA**): amyloid associated proteins: non Ig derived from serum amyloid associated

protein (SAA) that is produced by liver as acute phase response

N.B:

- **Transthyretin**: normal serum protein binds and transports thyroxine and retinol
- **β 2 microglobulin**: normal serum protein, component of class I HLA molecules
- **Amyloid (Ab)**: peptide forms core of cerebral plaques and deposits within cerebral vessel walls in Alzheimer disease

Systemic amyloidosis: Primary amyloidosis

• AL

• With multiple myeloma (B cell dyscrasia): plasma cell tumor from bone marrow leading to extensive bone erosion

• (++) single type of Ig (**IgG**) single light chain (**Kappa**) (**light chain forms amyloid**)

• At kidney, heart, spleen,

N.B: monoclonal gammopathy: (++) light chain without clinically appeared myeloma

Secondary amyloidosis (reactive)

mostly at liver, kidney, and spleen

• **SAA**: acute phase reactant protein secreted by liver when stimulated by cytokines it

will produced by inflammatory cells

- In long standing **chronic** inflammation
- T.B
- Bronchiectasis
- Chronic osteomyelitis
- Rheumatoid disease
- Ulcerative colitis, Crohn's disease



Senile amyloidosis



minute depositions, **transthyretin** (mainly at heart and blood vessels) – few cases with significant clinical importance – (Excess normal transthyretin)

Dialysis associated amyloidosis

-β 2 microglobulins

- With long-term hemodialysis, decreased With new dialysis filters
- at synovial membranes → arthropathy, carpal tunnel syndrome

Heredofamilial amyloidosis

- Rare
 - Familial Mediterranean fever (**AA protein**).
 - Familial amyloid polyneuropathies.
- N.B: systemic amyloidosis will lead to organomegaly (**macroglossia**, hepatomegaly, splenomegaly, cardiomegaly)
Will lead to systemic dysfunction: heart failure, kidney: proteinuria, hyperproteinemia, generalized edema

Localized amyloidosis

- At medullary carcinoma: pro **calcitonin** precursor from C cells in thyroid gland (no clinical significance but help identification of tumor)
- **Alzheimer**: cerebral amyloidosis at wall of vessels and neuritic plaques (**A β 2 protein**)
- **Pancreas**: islets of Langerhans with type 2 DM (proinsulin)
- **Skin, laryngeal wall, lung** (rarely seen, without obvious cause)

Amyloidosis of Kidney

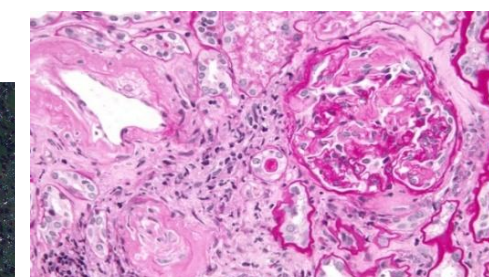
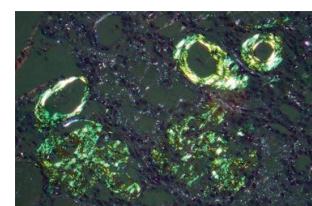
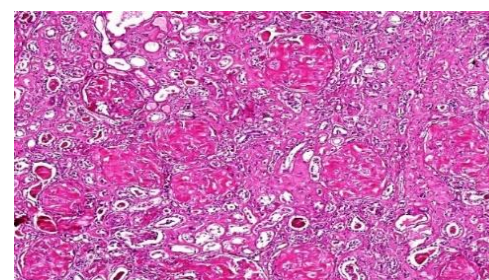
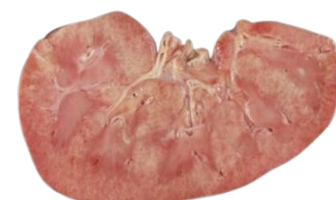
Gross:

- Enlarged
- **Brown waxy amyloid (dots)** depositions at glomeruli.
- Cut surface: pale **yellow**
- Late: contracted kidney due to **ischemic necrosis**

Microscopic:

- Amyloid depositions at **basement membrane** of glomerular capillaries and **mesangium**
- Capillaries: obliterated by thick **homogenous pink amyloid** depositions
- Thick wall of arterioles by amyloid → ischemia → atrophy of tubules → fibrosis
- Late fibrosis due to ischemic atrophy
- Amyloid deposition at basement membrane of tubules
- Tubular **hyaline cast (proteinuria)**
- N.B: apple green with congo red with polarized light

Clinical: proteinuria then renal failure



Staining characteristics of amyloid:

Gross:

- **Lugol's iodine**: healthy tissue will be yellow, amyloid stains dark **brown** (amyloid = starch like)
- Iodine + 1% sulfuric acid: amyloid stains blue

Microscopic:

- **H&E**: amyloid stains pink
 - **Congo red**: amyloid stains orange red
 - With **polarized light**: **apple green** light on dark back ground (apple green birefringence) (using two filters one fixed and one rotating in the path of light)
 - **Metachromatic stains** (methyle violet and crystal violet): amyloid stains rose red, rest of tissue stains violet
- N.B: the most common site is kidney biopsy if renal manifestations, or rectal, gingival (biopsy) if systemic **Macroglossia** is the most common oral manifestation

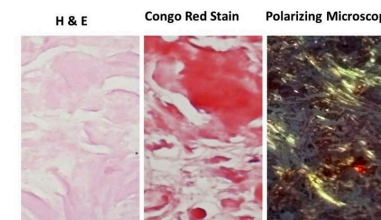
At GIT:

- At tongue → **macroglossia**
- At intestine → affect blood vessels early then extend to submucosa, musculosa, subserosa → mucosal atrophy
- **Malabsorption** and protein loss

At heart: at small BLVS and interstitium replacing muscle fibers
- Enlarged with thick firm myocardium → **arrhythmia** and heart failure

At kidney:

- Proteinuria, hypoproteinemia, **generalized edema**
- At other organs: adrenals, thyroid, pituitary



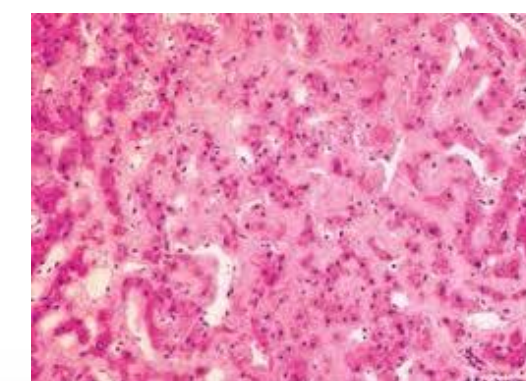
Amyloidosis of Liver

Gross:

- Enlarged, heavy, firm, **rubbery**
- Borders: sharp
- Cut surface: **waxy light brown** streaks on background of yellow liver (fatty change)

Microscopic:

- Amyloid deposition at wall of sinusoids → pink streaks
- Pressure and anoxia of Liver → atrophy
- Wall of hepatic arterioles and venules → thick by amyloid deposition



Amyloidosis of Spleen

Sago Spleen

- Enlarged rubbery firm spleen
- Cut sec.: **brown**, glassy **dots** (follicles with amyloid depositions) on red background
- Amyloid deposition on wall of central arterioles in lymph follicles at **white pulp**
- Thick pink wall of arteries and narrow lumen

Diffuse amyloid spleen (Lardaceous spleen)

- Less common
- Enlarged spleen
- Cut section: brown **streaks** of amyloid deposition
- Amyloid deposition in **sinusoids of red pulp** and **atrophy** of white pulp

