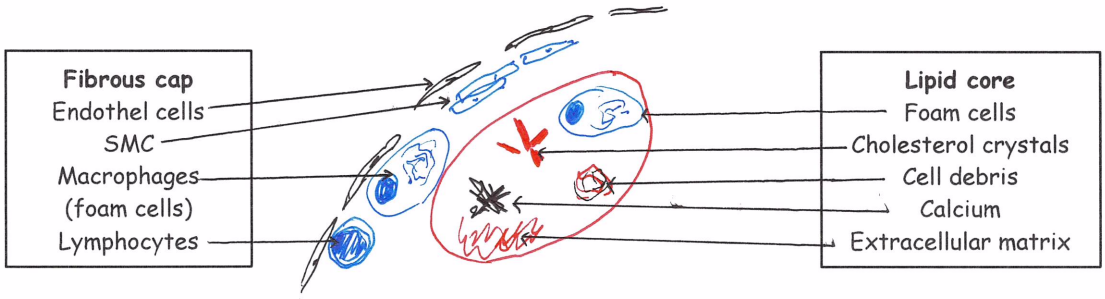
CHOLESTEROL ACCUMULATION

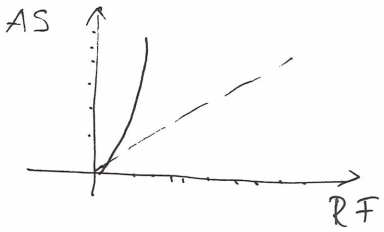
- Most of the cells use cholesterol for synthesis of membranes
- Cholesterol is accumulated in intracellular vacoules of phagocytic cells
- Pathologic condition – atherosclesosis (AS), cholesterolosis

1. Atherosclesosis

- Intimal plaque protude into vascular lumina
- Morphology: fibrous cap + lipid core



- Epidemiology:
  - Disease of developed nation
  - High mortality in US – 5X more than in Japan
  - Risk factors: 2 risk factors – 4 fold risk
    3 risk factors – 7 fold risk



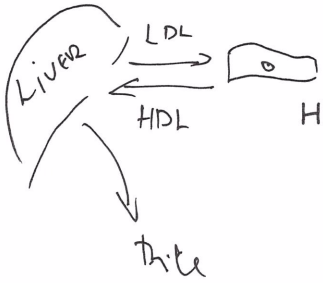
A/ Major constitutional factors

1. Age – 40-60 y - risk increase 5 times
2. Gender – premanopausal women protected
   – postmenopausal women and men equal risk
3. Genetics – familiar predisposition
   – familiar accumulation hypertension, diabetes, hypercholesterinaemia

B/ Major modifiable risk factors

1. Hypercholesterinaemia – one of the most important

LDL – „bad cholesterol"
- physiology: deliver cholesterol to peripherial tissue
- mainly in animal fats, butter, egg
- omega 3 fatty acids reduce LDL



HDL – „good cholesterol" – protective role
- mobilize cholesterol from plaque – transports to liver – delivers to bile
- obesity, smoking – reduce HDL level
- alcohol – increases HDL level

Lip(a) – modified from LDL
- contain apoprotein B-100
- independent from LDL or cholesterol
- high Lip(a) - high risk for IHD

2. Hypertension
- both systolic and diastolic increase risk

3. Cigarett smoking
- prolonged (years) smoking increase the risk
- measurement - pack/year

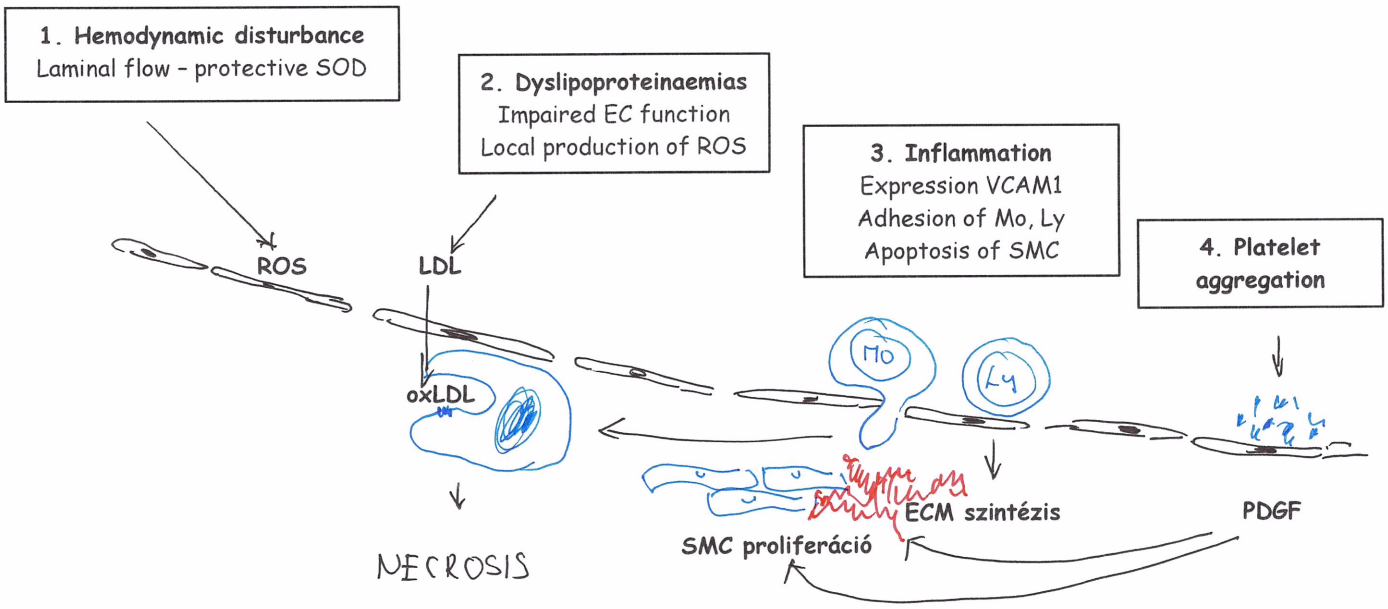
4. Diabetes mellitus
- main factor – increased hypercholesterinaemia

C/ Additional factors

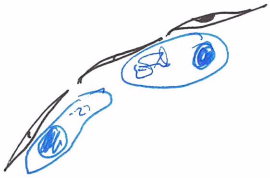
1. Inflammation
- inflammation is linked to AS development and rupture
- C-reactive protein – synthesis in liver and endothel
- C' ctivation, obsonisation
- increase local thrombosis

2. Obesity
3. Lack of excercise
4. Stressful life
5. Type A – competetive type of personality

- Pathogeneseis
- Response to injury
- Non-denuding endothelial dysfunction
- Increased permeability
- Enhanced leukocyte adhesion



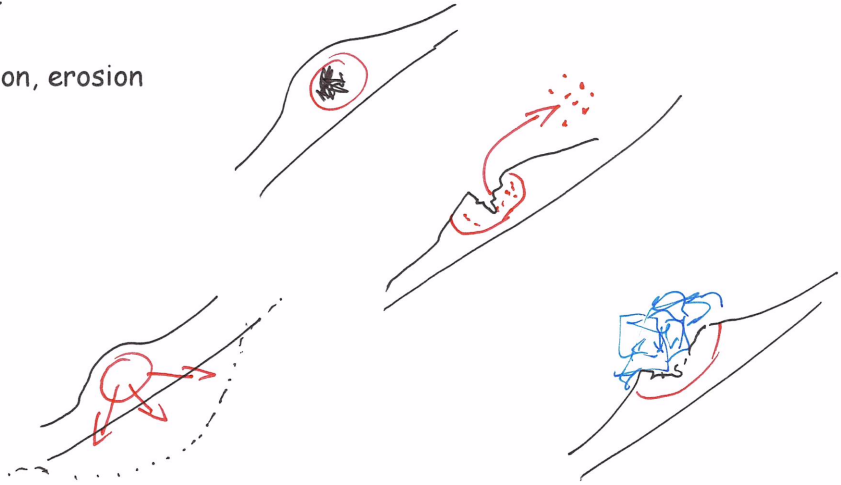
- Morphology



A/ Fatty streak
  - Lipid-filled foam cells in the intima
  - Cause no disturbance of blood flow
  - In infants (aorta), aldolescent (coronary)
  - Relation to AS is unknown – may regress or progress to AS

B/Atherosclerotic plaque
  - Cells – SMC, macrophages, T-cells, neovascularisation
  - ECM – collagene, elastic fiber, proteoglycans
  - Lipid – intracellular, extracellular, cholesterol cristals

C/ Complicated plaque
  - Calcification
  - Rupture, ulceration, erosion
  - Thrombosis
  - Haemorrahge
  - Atheroembolism
  - Aneurysma



- Prevention of AS

A/ Primer prevention
  - Program to prevent clinical manifestations and progression
  - Risk factor identification (hypertension, smoking, weight control, ect)
  - Education should be start at childhood

B/ Secondary prevention
  - Prevent reccurance of clinical symptoms
  - Surgical intervention
  - Anti-thrombotic threatment – aspirin
  - Blood pressure control
  - LDL controll – statins

PROTEIN ACCUMULATION

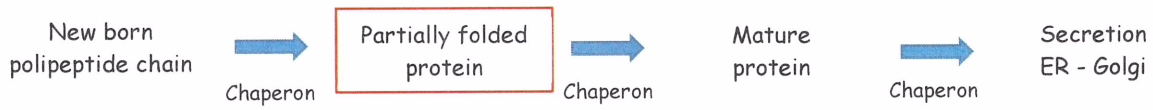
- Accumulation can be intracellular or extracellular
- The pathomechanisms are diverse

A/ Excess of protein presented to the cell
- Kidney tubular cells reabsorb proteins by pinocytosis
- Pinocytic vesicules fuse with lysosomes – pinkish droplets in the cell
- Nephrosis syndrome – massive proteinuria

B/ Excessive protein synthesis of the cell
- Russel bodies – dystended ER
- Daucher bodies

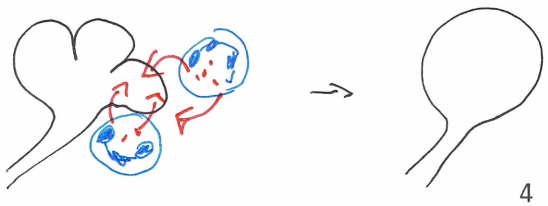
C/ Protein accumulation caused by cell injurry
- Mallory body – toxic effect of alcohol
  - aggregation of cytosceleton (keratin) and other proteins

D/ Defects in protein folding
- Protein can be α-helix or β-helix
- Protein configuration – critical to function
  - critical to transport across cell organs
- Intermediates are vulnerable for intracellular accumulation
- Chaperons – stabilize intermediers



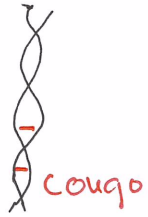
1. α1-antitripsin deficiency

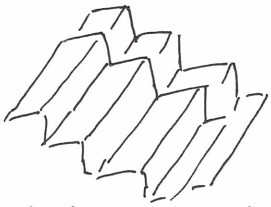
- Mutation in the protein – slow folding – partially folded intermediers
- Aggregate in the ER of the liver – no secretion
- α1 antitripsin – inhibitor of proteases (alestase)
  - in serum, tissue fluids, macrophages
  - neutralize protease activity of neutrophils
- Deficiency of enzyme – emphysema
- Disbalance of protease – anti-protease



2. Amyloidosis

- Diverse etiology: inherited, inflammatory, neoplastic diseases
- Extracellular deposition of fibrillar proteins
- Features of amyloid
  - aggregation of misfolded proteins
  - soluble in normal – nonsoluble of amyloid
  - binds a range of proteoglycans and plasma proteins (heparin sulphat)
- Name – looks like „starch" amylose – amyloid
- Pathogenesis
  - disease of protein misfolding
  - non-branching fibers 7.5-10 nm - β-sheet polypeptide chain
  - Congo-red bridge fibers – red-green dicroism
  - more than 20 biochemically distinct forms





Amyloid light chain (AL) – Immune dyschrasia (primary amyloidosis)

- Produced by neoplastic plasma cells – multiple myeloma
- Made up if Ig light chain or fragment of it
- Only certain types of light chains form amyloid (6-15%)

Amyloid associated (AA) – Reactive systemic amyloidosis (secondary amyloidosis)

- Derived from serum protein precursor SAA (serum amyloid-associated protein)
- SAA – synthesis in liver
  - increased in inflammatory states „acute phase protein"
  - associated with infectious (TB) and autimmun disorders (RA)

Amyloid beta (Aβ)

- In cerebral lesion of Alzheimer disease
- Originated from APP (amyloid precursor protein)
- Found in core of cerebral plaques

Transthyretin (TTR) – Amyloidosis of aging

- Normal serum protein – binds and transports thyroxine
- Senile systemic amyloidosis – senile cardiac amyloidosis

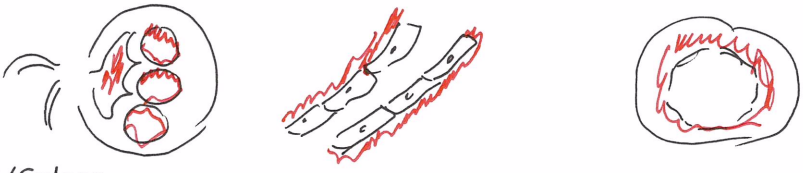
Morphgology:

- Macroscopically associated with organomegaly
- On cut surface using iodine + sulphuric acid – brown color
- Microscopically amorphus extracellular deposit

- Amyloid surrounds cells and destroys – pressure atrophy
- Detection with Congo red staining – apple-green birefringence

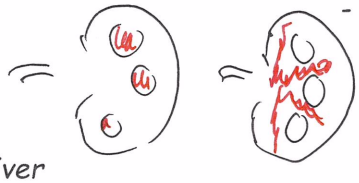
A/ Kidney

- Most common and most serios clinical consequences
- Deposit in glomeruli, mesangium, peritubular interstitium, walls of wessel



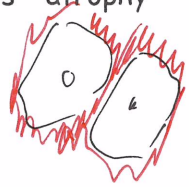
B/Spleen

- Two different patterns: - „sago spleen" localised to follicules
  - localised to sinuses and extend to pulp (sheet like deposit)



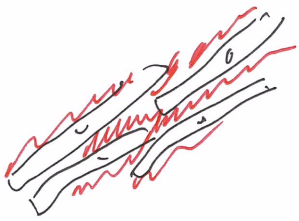
C/ Liver

- Massive enlargemet ~ 9000g
- On cut surface pale, waxy, grayish
- Microscopically amyloid is in the Dissl spaces, surrends parenchyma cells – atrophy
- Massive involvement may associated with good function



D/ Heart

- Dew-drop like subendocardial elevation
- Heart may be enlarged and firm
- Amyloid deposit between myofibers – pressure atrophy



E/Other organs

- GI – gingiva, intestine, rectum
- Endocrine organs – adrenals, thyroid, pituitary (no functional disturbance)

Clinical manifestation:

- Nonspecific – weakness, fatigue, weight loss
- Renal – proteinuria, renal failure
- Cardiac – restrictive cardiomyopathy
- Median survival 1-3 years

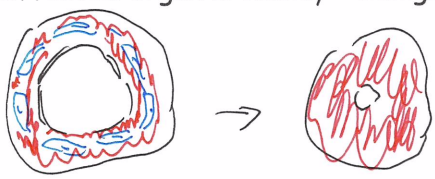
Diagnosis:

- Kidney, rectal, gingival biosy – Congo staining
- AL – urinary, serum electrophoresis, BM biopsy

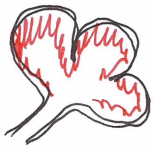
HYALINE ACCUMULATION

Hyaline
- Descriptive histological term – non-specific biochemical material
- May be within the cells or in extracellular spaces
- Homogenous, glassy pink in HE
- Diverse patomechanism generate „hyaline"

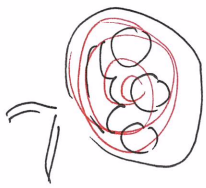
1. **Hyalinic arteriolosclerosis**
   - In diabetes mellitus and hypertension
   - Hyaline - leakage of plasma components across vascular endothelium
     - increasing extracellular matrix prodaction by SMC
   - Diabetes - chronic metabolic stress
   - Hypertension – chronic hemodynamic stress
   - Conseqence - narrowing of the lumen – reduced blood supply
   - Mostly affected organ is kidney – benign nephrosclerosis



2. **Hyaline membrane disease**
   - IRDS, ARDS
   - Leakage of plasma to alveolar spaces
   - Hyaline membrane: fibrinogene, fibrin, cell debris, plasma proteins



3. **Hyalinic glomeruli**
   - End stage of kidney diseases
   - Hyaline: plasma proteins, mesangial matrix, collagene
   - Most frequent in glomerulonephritis



4. **Mallory hyaline**
   - In alcoholic liver disease
   - Aggregated cytosceletal proteins (cytokeratin)
   - Derenerative procedure – response to injury