Cell injury and cellular adaptations (necrosis, atrophy, intracellular accumulations).
Circulation disorders.

Dentistry

Institute of Pathological Anatomy
Faculty of Medicine, Comenius University Bratislava
Pathologic agent

- **CELLULAR ADAPTATIONS**: cell has the capacity to adequately adapt
- **REVERSIBLE CELL INJURY**: adaptive mechanisms exceeded, but the cell survives
- **IRREVERSIBLE CELL INJURY**: cell dies (vulnerable cells/stress is excessive/long lasting)
Pathologic agent:
- Physical agents
- Chemical agents
- Microbial agents
- Hypoxia, ischaemia
- Immunologic agents
- Nutritional derangements
- Aging
- Drugs
- Psychogenic diseases
- Iatrogenic factors
- Idiopathic diseases

CELLULAR ADAPTATIONS
(atrophy, hypertrophy, hyperplasia, metaplasia, dysplasia)

REVERSIBLE CELL INJURY
(intracellular accumulations)

IRREVERSIBLE CELL INJURY
(cell death – necrosis, apoptosis)
Cellular adaptations

- reversible functional and/or structural responses to physiologic or pathologic stimuli
- the goal for the cell is to survive in an altered state and preserve the former function of the cell/tissue

1. **Physiologic adaptation** – to modified physiologic stimuli
2. **Pathologic adaptation** – to non-lethal pathologic injury
Cellular adaptations

1. **atrophy** — reduction of the number and/or size of cells
2. **hypertrophy** — increase in the size of cells
3. **hyperplasia** — increase in the number of cells
4. **metaplasia** — reversible change of one type of mature, differentiated cell to another type of mature, differentiated cell
5. **dysplasia** — disordered cellular development, can progress into neoplasia
Simple atrophy

- decrease of cellular size
Numeric atrophy

- decrease of cellular number, irreversible
Atrophy

- result of decreased protein synthesis and increased protein degradation in cells of normally developed tissues

**Physiologic** – observed in normal development and during aging

**Pathologic:** Starvation atrophy
Ischemic atrophy
Atrophy of inactivity
Neuropathic atrophy
Endocrine atrophy
Pressure atrophy
Idiopathic atrophy
Skeletal muscle, HE

Atrophied muscle fibers
Intracellular accumulations ("dystrophy")
Intracellular accumulations („dystrophy“)

1. **constituents of normal cell metabolism** produced in excess (lipids, proteins, carbohydrates, amyloid, urates)

2. **abnormal substances** due to lack of some enzymes (storage diseases, inborn errors of metabolism, DM)

3. **pigments**; endogenous (lipofuscin), exogenous (carbon dust)
Steatosis of liver

• Intracellular accumulation of fat substances

• **Etiology:**

  1. Conditions with **excess fat** (obesity, DM, congenital hyperlipidaemia)

  2. Liver cell **damage** (alcohol, starvation, hypoxia, chronic illnesses, hepatotoxins, drugs)

  - Microvesicular, macrovesicular, mixed forms
  - The predominantly affected zone of hepatic lobule (1-3) can vary based on the damaging stimulus
Liver steatosis
Fat droplets within hepatocytes

Liver steatosis, HE

Unaffected hepatocytes

Fat droplets within hepatocytes
Liver steatosis, oil red

Positively staining fat droplets
Lipomatosis - pancreas (78)

- **Etiology** – metabolic, functional
- Increase of fat cell number
- Replacement of the pancreatic cells with mature adipocytes for preservation of size and shape of the organ
Small area of preserved pancreatic tissue embedded in fat tissue
Normal pancreatic tissue

Mature adipocytes

Pancreas lipomatosis, HE
Necrosis

- irreversible cellular injury
- intravital cell death

Different causes, mechanism, appearance and outcome than apoptosis!

Autolysis = enzymatic self-digestion of cells (usually postmortal)

Types:
1. coagulative necrosis
2. liquefaction (colliquative) necrosis
3. caseous necrosis
4. fat necrosis
5. fibrinoid necrosis
Coagulative necrosis

- coagulation of proteins

- Macro: area looks firm (as if cooked), eventually softer (removal of cellular debris by leukocytes)
- Micro: outlines of the cells and basic structures are discernible, cells more eosinophilic, swollen, no visible nuclei

- most common form of necrosis, can occur in most organs due to different causes
Swollen necrotic hepatocytes without visible nuclei, basic liver structure is preserved
Liquefactive necrosis

- proteolysis – digestion of dead cells – the tissue liquifies due to the relative lack of supporting stroma and extracellular proteins (typical in brain tissue)

- Macro: tissue looks semi-liquid
- Micro: outlines of cells and structures are not preserved

- focal bacterial or fungal infections (abscess), infarction of the brain
Apoptosis

- programmed and tightly regulated cell death, also naturally occurring (cell suicide)

- triggered by pathologic stimuli which turn on EC or IC pathways

- regulates by TSGs and POGs
Necrosis

- **outcome of necrosis:**
  - resorption
  - reparation
  - pathologic calcification
  - **gangrene** (large ischemic coagulative necrosis – extremities, appendix,...)
    - **wet** gangrene (infected necrosis caused by anaerobic microorganisms)
    - **dry**
    - **gas** (C. perfringens)
Encephalomalacia (91)

- Colliquative necrosis of the brain tissue
- Cause – local ischemia of the cerebral tissue (thrombosis, embolism, hypotension)
- Without (ischemic) or with bleeding (hemorrhagic)
- Characteristic finding: proliferation of microglia - debris-laden macrophages (eliminatory reaction)
- Result - postmalatic pseudocyst or glial scar
Poorly demarcated area with subarachnoidal collection of blood
Semi-liquified area of brain tissue with focal hemorrhages
Perifocal brain edema

Vessels filled with erythrocytes

Disassembled neuropil with numerous leukocytes
Encephalomalacia, HE

Debris-laden macrophages
Anemic infarction - kidney (5)

- Coagulative necrosis of the kidney tissue
- Infarction = ischemic necrosis

- **Cause** – local ischemia

- Reactive inflammatory demarcation edge is composed of Leu and Ery (hyperemia)

- **Result** - scar
Area of acute anemic infarction
Hyperemic edge
Scars after old infarctions
Acute infarction with blurred appearance
Coagulative necrosis

Acute inflammatory infiltrate

Acute anemic infarction of kidney, HE
Acute anemic infarction of kidney, HE

Coagulative necrosis – „shadows“ of renal structures

Remnants of glomeruli

Remnants of tubules
Hemorrhagic lung infarction (6)

- **Coagulative** necrosis of the lung tissue

- **Cause** – ischemia due to lung embolism (most frequently embolus from deep vein thrombosis)

  - Develops only if lung circulation failure does not occur and the patient survives

  - If caused by thromboembolism, only affects the lung segment in which the artery is occluded
PREDISPOSING FACTORS FOR RED INFARCTION

1. loose tissue
2. tissues with dual circulation
3. previously congested tissues

!!! exception rather than the rule!!!

- lungs are oxygenated from b. and p. arteries but also directly from air

PREDISPOSING FACTORS FOR LUNG INFARCTION

1. compromise in bronchial circulation
2. region of the lung is underventilated (underlying pulmonary disease)
Sharply demarcated area of lung hemorrhage confined to a segment
A lung segment affected by hemorrhagic infarction, the base of the necrotic area is on the pleural side with apex pointing towards the hilus.
Hemorrhagic lung infarction, HE

Shadows of alveolar septa are discernible, with no vital cells

Alveoli filled with ery

Hemorrhagic lung infarction, HE
Focal necrosis – myocardial infarction (93)

• Local ischemia of the tissue – coagulative necrosis

• **Causes** - thrombosis, embolism, **atherosclerosis**, spasm of coronary artery, arteritis, changes of blood composition

• **Risk factors**: higher age, male gender, hypertension, smoking, DM, hyperlipidemia, ...

• Located predominantly in the left ventricle of the heart

• **Transmural (STEMI) / non-transmural (N-STEMI)**
Macro:

<12 h. – no changes

24 h. – cyanotic discoloration

48 – 72 h. – lightbrown, softer

3-7 days – pale yellow, soft, hyperaemic rim

Acute myocardial infarction: yellow-brown discoloration of the affected myocardium with softer consistency
Focal necrosis – myocardial infarction (93)

• Micro:
  • 6-12 hours – edema, haemorrhage, beginning of necrosis
  • 24-72 hours – necrosis (muscle hypereosinophilia, loss of nuclear staining), PMNL infiltration
  • 3-7 days – resorption of necrotic cells
  • from 5th day – formation of granulation tissue
  • later scar formation (2 months)
  • if the patient survives – formation of mature fibrous tissue (scar) replacing the necrotised cardiomyocytes
Cardiomyocytes without visible nuclei, with preserved cellular borders

Intracellular lipofuscin deposits

Acute inflammatory infiltrate

Acute myocardial infarction, HE
Acute myocardial infarction, HE

"Wavy" pattern of cardiomyocytes, without visible nuclei

Acute inflammatory infiltrate
Acute myocardial infarction, HE

Extensive acute inflammatory infiltrate among cardiomyocytes with preserved borders, without visible nuclei
Myocardial infarction healing – granulation tissue, HE

Fibrous tissue with capillaries with ery
Scar after myocardial infarction, HE

Mature fibrous tissue with adipocytes
Focal necrosis – myocardial infarction (93)

- **Complications** – sudden death, arrhythmia, rupture (of ventricular wall, septum, papillary muscle), cardiac tamponade, heart failure (acute/chronic), valve disease (prolapse, regurgitation), aneurysm of ventricle, Dressler’s syndrome, pericarditis episthenocardiaca, thromboembolism (cardiac dyskinesia), recurrence

- Result - myocardial scar or death
Disturbances of body fluids. Oedema

- excess of fluid in interstitial spaces, cavities

1. localised (inflammation, allergy, venous or lymphatic obstruction)
2. generalized (heart failure, renal, hepatal disease, ...)

• Causes
  – Increase of hydrostatic pressure (arterial, venous)
  – Decreased content of proteins in serum (oncotic)
  – Increased permeability of capillaries
  – Blockage of lymphatic drainage
  – Sodium and water retention
Arteriole

Capillary

Lymphatic vessel with node

Venule

AP 4.27 kPa

P 3.33 kPa

P 3.33 kPa

VP 1.6 kPa
Arteriole

Venule

Lymphatic vessel with node

Capillary

Norm (standard)

AP

VP

P

100%

10%

90%
**Inflammation**
(increased permeability of the capillary wall)
Lung oedema (265)

- **Causes:** left heart failure, inflammation, disorders of blood composition, disorders of lymphatic drainage, inhalation of toxic gases, combination

- **Macro:** lungs are heavier, more solid, frothy liquid pours out from the cut surface

- **Micro:** alveoli filled with homogenous eosinophilic substance (coagulated proteins from plasma), in heart failure also erythrocytes in capillaries and/or alveoli
Lung edema

Abundant clear, frothy fluid pouring out spontaneously from cut surface
Lung edema

Abundant clear, frothy fluid pouring out from cut surface on pressure
Lung edema, HE

Congested vessels with ery

Alveoli filled with pale eosinophilic fluid
Lung edema, HE

Congested capillaries with erythrocytes

Alveoli filled with pale eosinophilic fluid

Air bubbles
Disorders of blood circulation

Parameters needed for normal blood flow:
1. Normal anatomic features
2. Normal physiologic regulation of blood flow
3. Normal biochemical composition of the blood

Haemodynamic disturbances:
1. Disturbances in the volume of the circulating blood (hyperaemia, congestion, haemorrhage, shock)
2. Circulatory disturbances of obstructive nature (thrombosis, embolism, ischaemia, infarction)
Disturbances in the volume of circulating blood

**Hyperaemia (active hyperaemia)** – increased volume of blood from arterial and arteriolar dilatation (e.g. inflammation, high grade fever, blushing)
- **clinically** - redness, increased temperature

**Venous congestion (passive hyperaemia, venostasis)** – dilation of veins and capillaries due to impaired venous drainage (leads to chronic hypoxia)
- **clinically** – bluish colour (cyanosis)
- **acute / chronic**
  1. **local** – e.g. portal venous obstruction in cirrhosis of the liver
  2. **systemic (general)** – in left-sided heart failure (pulmonary congestion), in right-sided heart failure (chronic venous congestion of the liver, spleen, kidney)
Brown induration of lungs (157)

- Chronic left heart failure

- Macro: Lungs are brown, heavy and harder
- Micro:
  - Accumulation of fluid in alveoli
  - Accumulation of Ery in alveoli → phagocytosis of Ery by macrophages → metabolic change of hemoglobin to hemosiderin (brown color) → formation of siderophages („heart failure cells“)
  - Fibrosis of alveolar septae in longer duration
  - Pulmonary hypertension
Brown induration of lungs

Lungs are heavier, more firm, with red-brown color
Chronic venostasis of liver (10)

- chronic right heart failure, occlusion of inferior vena cava, hepatic vein
- Macro: yellowbrown liver tissue with darkred foci - nutmeg liver
- Micro: dilatation of central veins and sinusoids → pressure atrophy or hypoxic necrosis of centrolobular hepatocytes and hypoxic steatosis of peripheral hepatocytes
- Hemosiderin deposition in hepatocytes around central veins
- later-accumulation of connective tissue - fibrosis (cardiac)
Chronic liver venostasis, HE

Central vein

Dilated sinusoids filled with erythrocytes
Chronic liver venostasis, HE

Hemosiderin deposits in hepatocytes around central vein
Thrombus, thrombosis

Thrombus (intravital aggregate of coagulated blood within vascular lumen, adheres to endothelium)
- in the heart, arteries, veins, microcirculation
- Virchow triad – 1. endothelial injury
  2. altered blood flow
  3. hypercoagulability
Thrombus, thrombosis

Grossly:

1. **white** thrombus (arterial)
2. **red** thrombus (venous)
3. **mixed** thrombus
   - lysis / propagation / emolism / organisation / recanalisation

**Arterial thrombi**
   - ischaemia → infarction (ischemic necrosis)

**Cardiac, venous thrombi**
   - thromboembolism

**Microthrombi in microcirculation**
   - DIC
Embolus, Embolism

**Embolus** (insoluble material carried in the bloodstream that can lead to vessel obstruction)

1. **solid** (thrombus, tumour cells, parasites, bacterial clumps, foreign bodies)
2. **liquid** (amniotic fluid, fat, bone marrow)
3. **gaseous** (air)

- paradoxical embolism
Pulmonary artery embolism (7)

- Most often by blood thrombus (from deep veins of lower extremities)

- Other materials:
  - malignant cells
  - air
  - fat
  - amniotic fluid
  - bacteria
Pulmonary artery embolism (7)

• Result depends on size of the embolus:
  - asymptomatic / minor dyspnoea $\rightarrow$ pulmonary hypertension and right ventricular failure
  - pulmonary infarction
  - cardiovascular collapse with sudden death
Thrombus completely occluding pulmonary artery branch lumen
Venostasis and focal hemorrhage in adjacent lung tissue

Thrombus in pulmonary artery lumen

Pulmonary thromboembolus, HE
Questions

1. What are the chief differences between apoptosis and necrosis? What is the microscopic appearance of necrotic and apoptotic cell?
2. Can you think of a case of myocardial infarction in which no morphologic cause in coronary arteries can be found?
3. Can deep vein thrombosis of lower extremities cause thromboembolism into cerebral arteries?