Cell Injury, Cell Death
# Classification of morphologic forms of cell injury

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Changes of CELL

Adaptation

- Hyperplasia
- Metaplasia
- Atrophy
- Dysplasia

Injury

- Irreversible
- Reversible

Intracellular accumulations

- Protein
- Lipids
- Carbohydrates
- Ions
- Pigments

Cell swelling

- Necrosis
- Apoptosis
- Intermediate filaments (cytokeratin)
  - Mallory bodies

- Cell swelling

- Cytoplasm – fatty change

- Golgi – fatty change

- Mitochondria – injury

- Lysosome – storage diseases
Dystrophy

**Dystrophy** – is a pathological process resulting from cells and tissues metabolism disturbances and accompanying with the structural damage.

**Morphologically:** 1) the appearance of compounds that are normally not present or contained little, 2) the disappearance from cells and tissues their inherent compounds
Mechanisms of dystrophy development

1. **Infiltration** – superfluous entering of the metabolism products from the blood and lymph into cells and intercellular matter and accumulation in it.

   Ex.: atherosclerosis, protein dystrophy of renal tubular epithelium ← proteinuria

2. **Decomposition** – disintegration of cells structures and intercellular matter with accumulation of its products in the cell.

   Ex.: fatty dystrophy with diphtheria intoxication in cardiomyocytes

3. **Abnormal synthesis** – synthesis and accumulation in cells in ordinary substances, which don’t occur there in norm.

   Ex.: amyloidosis

4. **Transformation** – kind metabolism products from common products.

   Ex.: carbohydrates transform into fats
Classification of dystrophies

1. According to localization:
   Parenchymatous, mesenchymal, mixed

2. According to metabolism kind disturbances predominance:
   Protein, lipid, carbohydrate, mineral

3. According to genetic factor influence:
   Congenital, acquired

4. According to spreading:
   Local, general.
Dystrophies

- Intacellular accumulations (Parenchymatous dystrophies)
- Extracellular accumulations (Mesenchimal dystrophies)
- Inta- and extracellular accumulations (Mixed dystrophies)
Parenchymatous protein dystrophies

- granular
- hyaline-drop
- hydropic
- keratin
Granular dystrophy

Accumulation of small granules in the cytoplasm due to mitochondrial swelling.

Macro: “turbid swelling” of organ.

Fully reversible.
Hyaline-drop dystrophy

Accumulation of protein drops in the cytoplasm of tubular kidney epithelium in proteinuria due to infiltration
Hyaline-drop dystrophy

Mallory bodies (alcoholic hyaline) – perinuclear accumulation of hyaline bodies in hepatocytes in some liver diseases (alcoholic hepatitis, nonalcoholic steatohepatitis, etc.)

Mallory bodies consist of intermediate filaments
Hyaline-drop dystrophy

• Outcomes
  – It could be reversible
  – Proceed to coagulative (dry) necrosis
Hydropic dystrophy

- Cellular swelling
- Grossly, the affected organ such as kidney, liver or heart muscle is enlarged due to swelling.

Outcomes
- It could be reversible
- Proceed to colliquative (wet) necrosis
Keratin dystrophy

- Increased formation of keratin in keratinized epithelium
  - Hyperkeratosis in callus, congenital general ichthiosis
- Formation of keratin in nonkeratinized epithelium
  - Leukoplakia
  - Keratin in lung cancer
Ichthiosis

- Ichthio – fish
- Congenital general hyperkeratosis of skin
Keratin dystrophy

- Outcomes:
  - Leukoplakia is a precancerous lesion
  - Heavy ichtiosis is lethal in young age
Parenchymatous fatty (lipid) dystrophy

Fatty change or **steatosis** is the intracellular accumulation of neutral fat within parenchymal cells.

- Fatty liver (alcohol, diabetes, obesity, chronic hypoxia)
- Tiger heart (chronic hypoxia, diphtheria)
- Renal tubular epithelium ← lipiduria
- Storage diseases
Storage diseases (lipids)

Sphingolipidoses

*General definition:* Rare hereditary disorder of lysosomal sphingolipid catabolism.

Most importantly, sphingolipids are components of the myelin sheaths. Accordingly, sphingolipidoses manifest themselves as (a) neuronal disorders and (b) visceromegaly (enlargement of internal organs) due to storage in the reticuloendothelial system.

- Gaucher’s Disease
- Niemann-Pick’s disease.
- Tay-Sachs Disease
**Dietary liver steatosis** (HE) x 200

**Steatosis of the renal tubules** (oil-red stain) x 150 (G=glomerulus)
Accumulation of Gaucher cells: cytoplasm that resembles crumpled tissue paper.
Parenchymatous carbohydrate dystrophies

• Disturbance of glycogen metabolism
  – Diabetes (hepatocytes, renal tubular epithelium ← glycosuria)
  – Storage diseases

• Disturbance of glycoprotein metabolism
  – Accumulation of mucins and mucous like substances
    • Colloid goiter
    • Cystic fibrosis
Storage diseases (carbohydrates)

Glycogenoses – group of glycogen storage disorders due to a hereditary enzyme defect.

- Type I (von Gierke disease)
- Type II (Pompe disease)
- Type III (Forbes disease)
Type I glycogenosis (liver)
(HE) x 150

Type I glycogenosis (liver)
 x 150

Colloid goiter
Cystic fibrosis

Cystic fibrosis, also known as mucoviscidosis, is an autosomal recessive genetic disorder that affects most critically the lungs, and also the pancreas, liver, and intestine. It is characterized by abnormal transport of chloride and sodium across an epithelium, leading to thick, viscous secretions.

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Dystrophies

- Intacellular accumulations (Parenchymatous dystrophies)
- Extracellular accumulations (Mesenchimal dystrophies)
- Inta- and extracellular accumulations (Mixed dystrophies)
MESENCHIMAL DYSTROPHIES

It is pathological process which damages the stroma of organs and blood vessels walls.
MESENCHIMAL DYSTROPHIES

• Protein mesenchimal dystrophies
  – Mucoid swelling
  – Fibrinoid swelling
  – Hyalinosis
  – Amyloidosis

• Mesenchymal lipid (fatty) dystrophies
  – Simple lipids (obesity and lipomatosis)
  – Cholesterol (atherosclerosis)

• Mesenchymal carbohydrate dystrophies
Mucoid swelling

- reversible
- glucosaminoglycans are accumulated in stroma
- metachromasia is characteristic histological sign (unordinary color)
Fibrinoid swelling

• Follows *mucoid swelling* (next step)
• Irreversible damage of connective tissue, accompanying with the fibrinoid formation
• Could lead either to fibrinoid necrosis (acute) or hyalinosis (chronic)
Fibrinoid swelling

Fibrinoid necrosis

Hyalinosis

- Hyaline is a homogeneous deposit or structural change in tissue.
- Under histologic examination it appears eosinophilic.
- Macroscopically it appears as an area of whitish tissue.
- Types:
  - Vascular hyalinosis
  - Hyalinosis of proper connective tissue
Sugar-coated spleen
(collagen hyalinization)
Amyloidosis

- *Amyloid* is a hyaline-like material with a microfibril structure that stains positively by *Congo red* dye.
Structure of amyloid

These components are common to all types of amyloid:

- *Fibril protein* with a β-pleated structure (β-pleated fibrils). This protein varies with the underlying disease and its name is used to identify the respective type of amyloid.

- *Amyloid P component* arises from SAP (serum amyloid P component, which is physiologic serum protein, a component of the glomerular basement membrane).

- *Heparan sulfate proteoglycans* are proteoglycans of the basement membrane type.
Main Types of Amyloid

- **AL Amyloid** (*light-chain amyloid*) – systemic primary amyloidosis (*plasmacytic neoplasms*)
- **AA Amyloid** (*amyloid A*) – systemic secondary amyloidosis (*Chronic inflammation: infections – osteomyelitis and tuberculosis; autoimmune – rheumatoid arthritis*)
- **AF Amyloid** (*familial amyloid*) – single-point mutation of transthyretin (*familial amyloid polyneuropathies*).
C Amyloidosis of the liver (Congo red) x 150

D Amyloidosis of the liver (Congo red) x 150
Relations between different protein mesenchimal dystrophies

Mucoid swelling → Fibrinoid swelling

Fibrinoid swelling → Hyalinosis

Hyalinosis → Chronic insufficiency of an organ

Fibrinoid necrosis

Amyloidosis → Chronic insufficiency of an organ
MESENCHIMAL DYSTROPHIES

• Protein mesenchimal dystrophies
  – Mucoid swelling
  – Fibrinoid swelling
  – Hyalinosis
  – Amyloidosis

• Mesenchymal lipid (fatty) dystrophies
  – Simple lipids (obesity and lipomatosi
  – Cholesterol (atherosclerosis)

• Mesenchymal carbohydrate dystrophies
Mesenchymal carbohydrate dystrophies

• Acquired – mucous edema in hypothyreosis

• Congenital – Mucopolysaccharidoses (proteoglycan lysis deficiencies)
  – Hurler’s Syndrome
Hurler’s Syndrome

*Synonym:* mucopolysaccharidosis I.

*Definition:* Hereditary mucopolysaccharide storage disorder due to deficient α-L-iduronidase with mucopolysacchariduria.

*Morphologic characteristics:* In contrast to normal cells, storage cells are characterized by honeycombed cytoplasm (▶ B) with PAS-positive material in lysosomal vacuoles. These storage lysosomes (p. 30) are large vacuoles containing fine granular material (▶ A).

**Clinical presentation and morphology:**
Findings in Hurler’s syndrome include:
- Gargoyleism (see above; ▶ C, D) with short stature, dementia, arteriosclerosis, aortic insufficiency, hepatosplenomegaly, and corneal opacification.
- Mucopolysaccharides in the urine include dermatan and heparan sulphate.

Maximum life expectancy is 10 years.
C Face in Hurler’s syndrome

D Gothic gargoyle
Dystrophies

- Intacellular accumulations (Parenchymatous dystrophies)
- Extracellular accumulations (Mesenchimal dystrophies)
- Inta- and extracellular accumulations (Mixed dystrophies)
- Reversible cell injury (cell swelling)
Mixed dystrophies

It is pathological process effects stroma and parenchyma.

Metabolism disturbances of:

• nucleoproteins,

• mineral substances (inorganic compounds)
  – Ca, Fe, Cu

• chromoproteins (pigments).
  – Exogenous pigments
  – Endogenous pigments
    • Lipidogenic pigments
    • Hematogenous pigments
    • Proteinogenic pigments (melanin)
Hyperuricemia

General definition: Group of disorders with high serum uric acid levels due to impaired purine metabolism (gout).

Gouty tophus

Podagra
Mixed dystrophies

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• nucleoproteins,

• mineral substances (inorganic compounds)
  – Ca, Fe, Cu

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    • Lipidogenic pigments
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    • Proteinogenic pigments (melanin)
Iron Overload

• Hemochromatosis
  Definition: Hereditary iron storage disease with systemic organ lesions due to increased iron absorption.

• Secondary Siderosis (Hemosiderosis)
  Definition: Increased iron deposits in tissue in the form of hemosiderin.

Hemochromatosis is parenchymal siderosis; secondary siderosis is phagocytic siderosis.
Hemochromatosis

Morphologic characteristics:

Liver: Early iron overloading results in storage of iron in the hepatocytes and bile duct epithelia. This causes brown discoloration of the parenchyma and leads to chronic liver damage and portal cirrhosis in the form of “pigment cirrhosis”.

Myocardium: The iron deposits in the myocardial cells produce toxic myocardial fibrosis that reduces the strength of the heartbeat. This in turn results in reactive myocardial thickening, leading to secondary cardiomyopathy.

Pancreas: The iron deposits in the cells of the exocrine and endocrine glands cause toxic pluriglandular insufficiency. This results in progressive pancreatic fibrosis (pancreatic “cirrhosis”) with brown discoloration of the parenchyma (giving the pancreas a rusty appearance) and secondary diabetes mellitus. This disorder is referred to as “bronze diabetes” because of the accompanying bronze hyperpigmentation of the skin.
Hemosiderosis

Pathogenesis: The disorder is due to one of the following mechanisms:

- **Iron overload** due to increased breakdown of hemoglobin (transfusion siderosis);
- **Defective iron utilization** due to defective heme or globin synthesis;
- **Nutritional or toxic liver damage** resulting from (a) alcohol abuse, in which iron is deposited in the spleen and liver (due to the increased iron content of fermented fruit juices) and/or (b) malnutrition (Bantu siderosis).

Morphology: In contrast to hemochromatosis, iron in hemosiderosis is initially absorbed by the cells of the macrophage system (reticuloendothelial system) and only later stored in parenchymal cells, leading to brown discoloration of the organs.
Copper Overload

Wilson's Disease

Synonym: hepatolenticular degeneration.

Definition: Hereditary systemic copper toxicosis resulting from dysfunctional copper secretion in bile. This leads to damage of the liver and basal ganglia of the brain (degeneration of the lens nucleus).

Liver: Asymptomatic cases usually involve only minimal fatty degeneration. Symptomatic cases involve a feather-like pattern of vacuolar liver cell degeneration leading to chronic liver inflammation with progressive parenchymal destruction (chronic aggressive hepatitis). This later progresses to liver cirrhosis.

Cerebral nuclei (putamen, nucleus lentiformis, nucleus caudatus, substantia nigra): Ganglion cells accumulate copper. This causes degeneration in the form of spongiform dystrophy.

Cornea: Patients exhibit a Kayser-Fleischer ring, a brownish-green ring-shaped pattern of copper deposits in the periphery of the cornea.
Mixed dystrophies

It is pathological process effects stroma and parenchyma.

Metabolism disturbances of:

• nucleoproteins,
• mineral substances,
• chromoproteins (pigments).
  – Exogenous pigments
  – Endogenous pigments
    • Lipidogenic pigments
    • Hematogenous pigments
    • Proteinogenic pigments (melanin)
Lipidogenic pigments

• Lipofuscin (fuscus (Latin), yellow)
• Ceroid (cera (Latin), wax)
• Lipochrome (lipos (Greek) – fat, chromos – color)
**Lipofuscin:** Formation of lipid pigments increases with cell age. In older persons, hepatocytes in the central lobe and myocardial cells are characterized by abundant yellowish brown lipofuscin granules (▶D; see also p. 114). This gives the tissue of aging organs a dark brown color (age-related atrophy, p. 124). L. Aschoff referred to lipofuscin in 1910 as “wear-and-tear pigment” because of its indication of cell age and its presence in telolysosomes.

**Lipofuscin (hepatocytes)**

(HE) x 600
**Ceroid:**

Increased lipid turnover in macrophages leads to formation of a lipid pigment with a coarse homogeneous appearance known as ceroid (►E). Ceroid stains red like the wax coatings of mycobacteria under a Ziehl-Neelsen stain (►F). Ceroid is typically observed in the liver in the resorption phase of acute viral hepatitis (p. 240) or in resorptive granulation tissue. Where there is simultaneous breakdown of hemoglobin, ceroid may also be mixed in with the ferrous hemosiderin pigment (p. 106).

**Note:** Ceroid and lipofuscin:
- Ceroid ("clean-up pigment") occurs in macrophages as a result of heterophagy.
- Lipofuscin ("aging pigment" or "wear-and-tear pigment") occurs in organ cells as a result of autophagy.
Lipochrome (β-Karotin)

It gives natural color of fat, adrenal gland, Corpus luteum and serum. It is increased when the neutral fat is accumulated.
Mixed dystrophies

It is pathological process effects stroma and parenchyma.

Metabolism disturbances of:

• nucleoproteins,
• mineral substances,
• chromoproteins (pigments).
  – Exogenous pigments
  – Endogenous pigments
    • Lipidogenic pigments
    • Hematogenous pigments
    • Proteinogenic pigments (melanin)
Hematogenous pigments

• normal:
  – feritin
  – haemosyderin
  – bilirubin

• pathological:
  – haematoidin
  – haematin
  – hematozoidin
  – porphirin
Bilirubin

• **Bilirubin** is a normal haemoglobin-derived non-iron containing pigment which presents in the bile.

• Normal level of bilirubin in blood is less than 1mg/dl. Excess of bilirubin causes an important clinical condition called jaundice.
Hemosiderin

**Hemosiderin:**

*Definition:* Ferrous, yellowish brown pigment that is free of pyrrole (siderin).

*Pathogenesis:* Requiring 2 days to develop, the substance forms only in living cells that also store the phagocytized iron in this form, i.e., cells of the reticuloendothelial system. This produces brown discoloration in the storage tissue.
**Haematoidin**

**Hematoidin:**

*Definition:* Nonferrous, reddish brown pigment containing pyrrole (indirect bilirubin).

*Pathogenesis:* Macrophages are unable to approach erythrocytes in the center of a hemorrhage. The resulting disintegration of hemoglobin results in the release of iron and crystallization of residual material containing pyrrole rings (C). The disorder takes three weeks to develop.

**Note:** Where hemoglobin is broken down, green *biliverdin* and then yellow *bilirubin* are created. This color change may be observed in hematomas.
Hematin

**Hematin:**

**Definition:** Blackish-brown pigment.

**Pathogenesis:** The substance develops in an upper gastrointestinal hemorrhage when the hemoglobin comes into contact with hydrochloric acid (►F). Therefore vomited blood is black (hematemesis).
Hematozoidin

**Hematozoidin:**

*Definition:* Brownish-gray malarial pigment (partially crystallized hematin).

*Pathogenesis:* The substance is formed by the living malaria pathogen (Plasmodium; p. 278) in erythrocyte parasitism and is stored in cells of the reticuloendothelial system (▶ G).
Porphyria

General definition: This group of diseases involves atypical types of porphyria and alternating skin, liver, and blood damage due to defective porphyrin synthesis. Primary porphyria result from congenital enzyme defects, secondary porphyria from toxic enzyme blockages.

General pathogenesis: Atypical metabolites of heme synthesis (porphyrin) are created. Some of these are excreted in the stool and in urine. Symptoms depend on the type of porphyrin involved and may include red discoloration; there are intralysosomal porphyrin deposits erythroblasts, and in epidermal, cartilaginons and bone cells, and liver cells → brown discoloration.
Congenital Erythropoietic Porphyria

Clinical presentation: Symptoms presented by Count Dracula and the werewolf well illustrate congenital erythropoietic porphyria.

Note: The “Dracula syndrome” includes daytime sleep (photophobia), “bloody” teeth (erythrodontia), and deathly paleness (anemia). The “werewolf syndrome” includes facial hair (hypertrichosis), “bloody” teeth (erythrodontia), and missing nose and fingers (mutilation).
NORMAL

Enzymatic digestion and leakage of cellular contents

NECROSIS

Apoptotic body

Phagocytosis of apoptotic cells and fragments

APOPTOSIS

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# Features of Necrosis and Apoptosis

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<th>Feature</th>
<th>Necrosis</th>
<th>Apoptosis</th>
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<td>Cell size</td>
<td>Enlarged (swelling)</td>
<td>Reduced (shrinkage)</td>
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<tr>
<td>Nucleus</td>
<td>Pyknosis → karyorrhexis → karyolysis</td>
<td>Fragmentation into nucleosome-size fragments</td>
</tr>
<tr>
<td>Plasma membrane</td>
<td>Disrupted</td>
<td>Intact; altered structure, especially orientation of lipids</td>
</tr>
<tr>
<td>Cellular contents</td>
<td>Enzymatic digestion; may leak out of cell</td>
<td>Intact; may be released in apoptotic bodies</td>
</tr>
<tr>
<td>Adjacent inflammation</td>
<td>Frequent</td>
<td>No</td>
</tr>
<tr>
<td>Physiologic or pathologic role</td>
<td>Invariably pathologic (culmination of irreversible cell injury)</td>
<td>Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage</td>
</tr>
</tbody>
</table>
Necrosis

Normal Cell → Pyknosis → Karyorrhexis → Karyolysis

Nuclear Changes In Irreversible Cell Injury
Necrosis

- Coagulative necrosis
  - Caseous necrosis
  - Fibrinoid necrosis
  - Cencer’s necrosis
- Liquefaction (colliquative) necrosis
- Fat necrosis
- Gangrene
  - Dry Gangrene
  - Wet Gangrene
  - Gas Gangrene
- Infarction
- Sequestration
Coagulative necrosis
Colliquative necrosis
Infarction
Cavern formation

**Nekroseabräumprinzip**

3. Abszess-Selbstreinigungsprinzip:

Abszess $\rightarrow$ Fistelung $\rightarrow$ Entleerung an innere Oberfläche $\rightarrow$ Kollapsheilung Kaverne

**Nekroseabräumprinzip**

4. Abszess-Selbstreinigungsprinzip:

Abszess $\rightarrow$ Fistelung $\rightarrow$ Entleerung an äußere Oberfläche $\rightarrow$ Kollapsheilung Kaverne
Ulcer formation