PATHOLOGY

MD

PATHOLOGY

Cellular Injury and Adaptation

Cellular Injury and Adaptation

Learning Objectives

- ❑ Explain causes of cellular injury
- ❑ Demonstrate understanding of cellular changes during injury and cell death
- ❑ Answer questions about cellular adaptive responses to injury
- ❑ Describe cellular alterations during injury

Cellular Injury and Adaptation

CAUSES OF CELLULAR INJURY

Hypoxia

Infection

Trauma Physical injuries, chemical Injuries

Congenital defects

Immunological disease

Neoplastic changes

Cellular Injury and Adaptation

Hypoxia is the most common cause of injury; it occurs when lack of oxygen prevents the cell from synthesizing enough ATP by aerobic oxidation. Major mechanisms leading to hypoxia are ischemia, cardiopulmonary failure, and decreased oxygen carrying capacity of the blood (e.g., anaemia). **Ischemia**, due to a loss of blood supply, is the most common cause of hypoxia and is typically related to decreased arterial flow or decreased venous outflow (e.g., atherosclerosis, thrombus, thromboembolism).

Cellular Injury and Adaptation

Pathogens (viruses, bacteria, parasites, fungi, and prions) can injure the body by direct infection of cells, production of toxins, or host inflammatory response.

Viruses:

Bacteria:

Parasites:

Fungi:

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Immunologic dysfunction

Includes hypersensitivity reactions and autoimmune diseases.

How many type of hypersensitivity are there?

What is myasthenia gravis?

Cellular Injury and Adaptation

Congenital disorders are inherited genetic mutations (e.g., inborn errors of metabolism).

Cellular Injury and Adaptation

Chemical Injury can occur with drugs, poisons (cyanide, arsenic, mercury, etc.), pollution, occupational expsure (CCl_4, asbestos, carbon monoxide, etc.), and social/lifestyle choices (alcohol, smoking, IV drug abuse, etc.)

Cellular Injury and Adaptation

Physical forms of injury include trauma (blunt/penetrating/crush injuries, gunshot wounds, etc.), burns, frostbite, radiation, and pressure changes.

Cellular Injury and Adaptation

Nutritional or vitamin imbalance

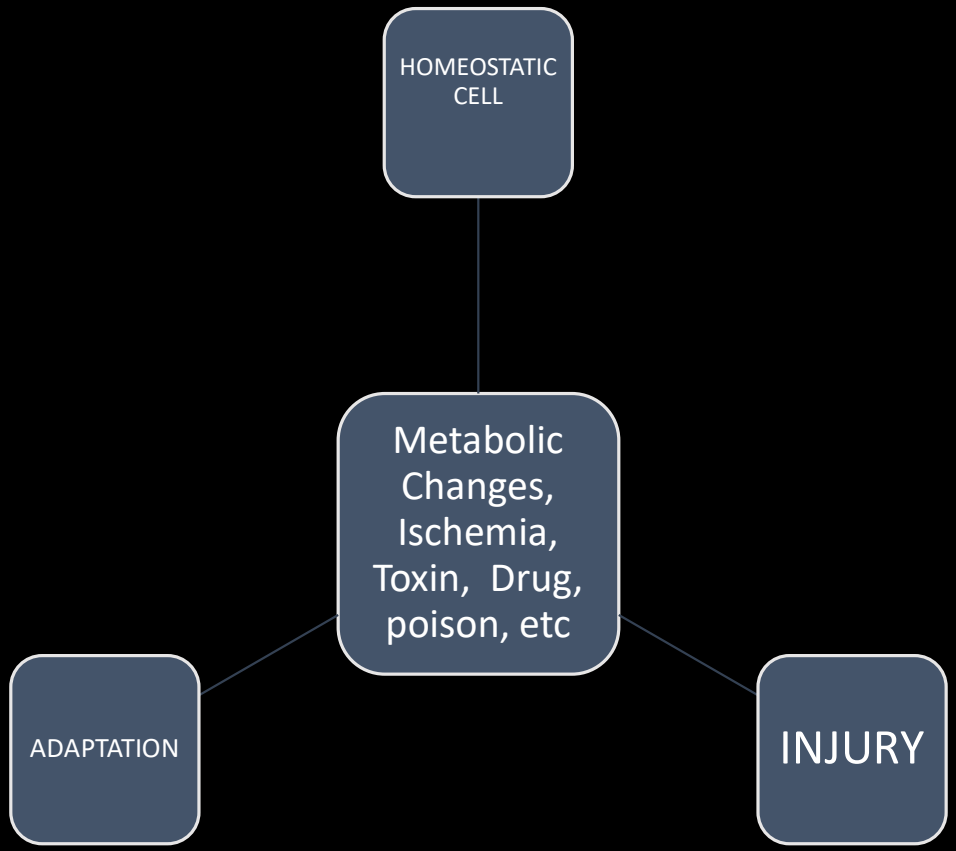
- **Inadequate calorie/protein intake** can cause marasmus (decrease in total caloric intake), and kwashiorkor (decrease in total protein intake).
- **Excess caloric intake** can cause obesity (second leading cause of premature preventable death in the United States) and atherosclerosis.
- **Vitamin deficiencies** can be seen with vitamin A (night blindness, squamous metaplasia, immune deficiency), vitamin C (scurvy), vitamin D (rickets and osteomalacia), vitamin K (bleeding diathesis), vitamin B12 (megaloblastic anemia, neuropathy, and spinal cord degeneration), folate (megaloblastic anemia and neural tube defects), and niacin (pellagra [diarrhea, dermatitis, and dementia]).

Cellular Injury and Adaptation

CELLULAR CHANGES DURING INJURY

Cellular responses to injury include adaptation (hypertrophy or atrophy, hyperplasia or metaplasia), reversible injury, and irreversible injury and cell death (necrosis, apoptosis, or necroptosis).

Cellular Injury and Adaptation



Cellular Injury and Adaptation

The **cellular response to injury depends on several important factors**, including the type of injury, duration (including pattern) of injury, severity and intensity of injury, type of cell injured, the cell's metabolic state, and the cell's ability to adapt.

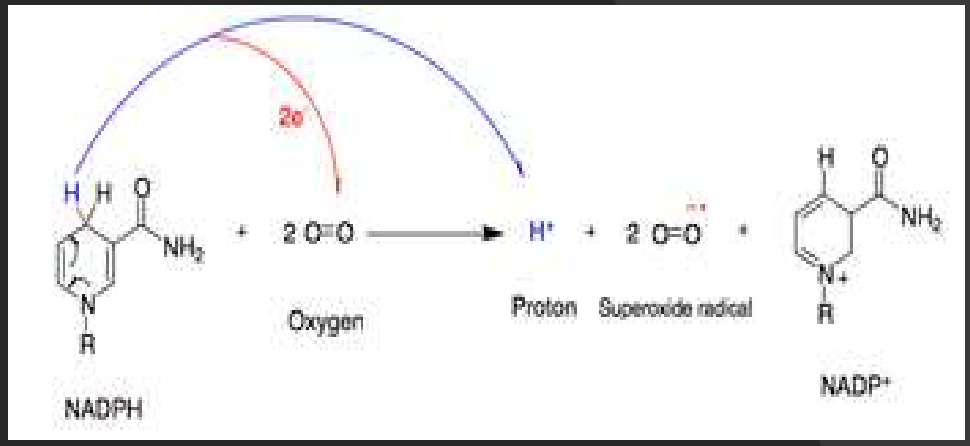
Cellular Injury and Adaptation

- The **cellular response to injury depends on several important factors**, including the type of injury, duration (including pattern) of injury, severity and intensity of injury, type of cell injured, the cell's metabolic state, and the cell's ability to adapt.
- The **critical intracellular targets that are susceptible to injury** are DNA, production of ATP via aerobic respiration, cell membranes, and protein synthesis.

Cellular Injury and Adaptation

Important mechanisms of cell injury are as follows:

• Damage to DNA, proteins, lipid membranes, and circulating lipids (LDL) can be caused by oxygen-derived free radicals, including superoxide anion (O2• –), hydroxyl radical (OH•), and hydrogen peroxide (H2O2).



Note

Reversible and irreversible changes represent a spectrum. Keep in mind that any of the reversible changes can become irreversible.

Cellular Injury and Adaptation

Important mechanisms of cell injury are as follows:

• ATP depletion: Several key biochemical pathways are dependent on ATP. Disruption of Na+/K+ or Ca++ pumps cause imbalances in solute concentrations. Additionally, ATP depletion increases anaerobic glycolysis that leads to a decrease in cellular pH. Chronic ATP depletion causes morphological and functional changes to the ER and ribosomes.

Note

Reversible and irreversible changes represent a spectrum. Keep in mind that any of the reversible changes can become irreversible.

Cellular Injury and Adaptation

Important mechanisms of cell injury are as follows:

• Increased cell membrane permeability: Several defects can lead to movement of fluids into the cell, including formation of the membrane attack complex via complement, breakdown of Na+/K+ gradients (i.e., causing sodium to enter or potassium to leave the cell), etc.

Note

Reversible and irreversible changes represent a spectrum. Keep in mind that any of the reversible changes can become irreversible.

Cellular Injury and Adaptation

Important mechanisms of cell injury are as follows:

- Influx of calcium can cause problems because calcium is a second messenger, which can activate a wide spectrum of enzymes. These enzymes include proteases (protein breakdown), ATPases (contributes to ATP depletion), phospholipases (cell membrane injury), and endonucleases (DNA damage).

Note

Reversible and irreversible changes represent a spectrum. Keep in mind that any of the reversible changes can become irreversible.

	cAMP System
First Messenger: Neurotransmitters (Receptor)	Epinephrine (α2, β1, β2) Acetylcholine (M2)
First Messenger: Hormones	ACTH, ANP, CRH, CT, FSH, Glucagon, hCG, LH, MSH, PTH, TSH
Signal Transducer	GPCR/G_s (β1, β2), G_i (α2, M2)
Primary effector	Adenylyl cyclase
Second messenger	cAMP (cyclic adenosine monophosphate)
Secondary effector	protein kinase A

Cellular Injury and Adaptation

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Phosphoinositol system
Epinephrine (α1) Acetylcholine (M1, M3)
AGT, GnRH, GHRH, Oxytocin, TRH
GPCR/G_q
Phospholipase C
IP3; DAG; Ca2+
PKC; CaM

Cellular Injury and Adaptation

Important mechanisms of cell injury are as follows:

- Mitochondrial dysfunction causes decreased oxidative phosphorylation and ATP production, formation of mitochondrial permeability transition (MPT) channels, and release of cytochrome c (a trigger for apoptosis).

Note

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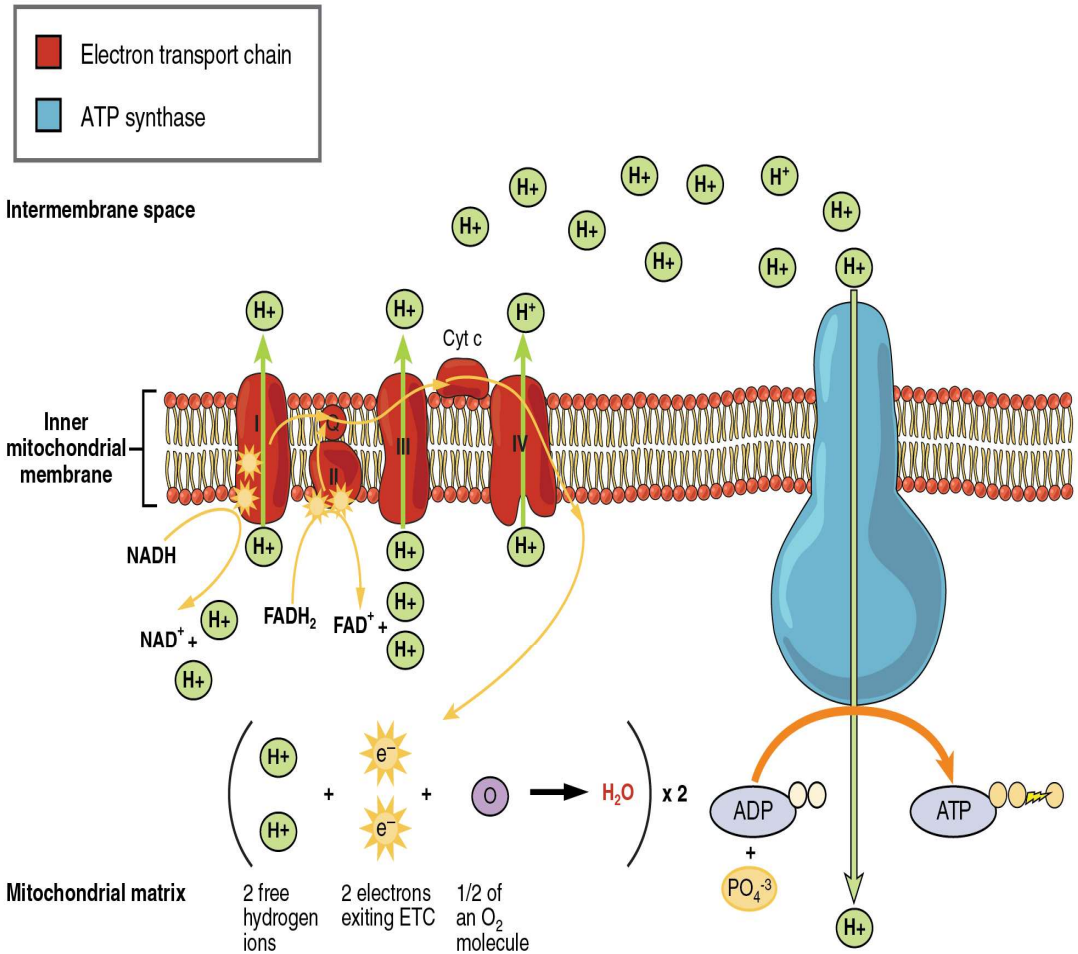


Cellular Injury and Adaptation

Reversible cell injury:

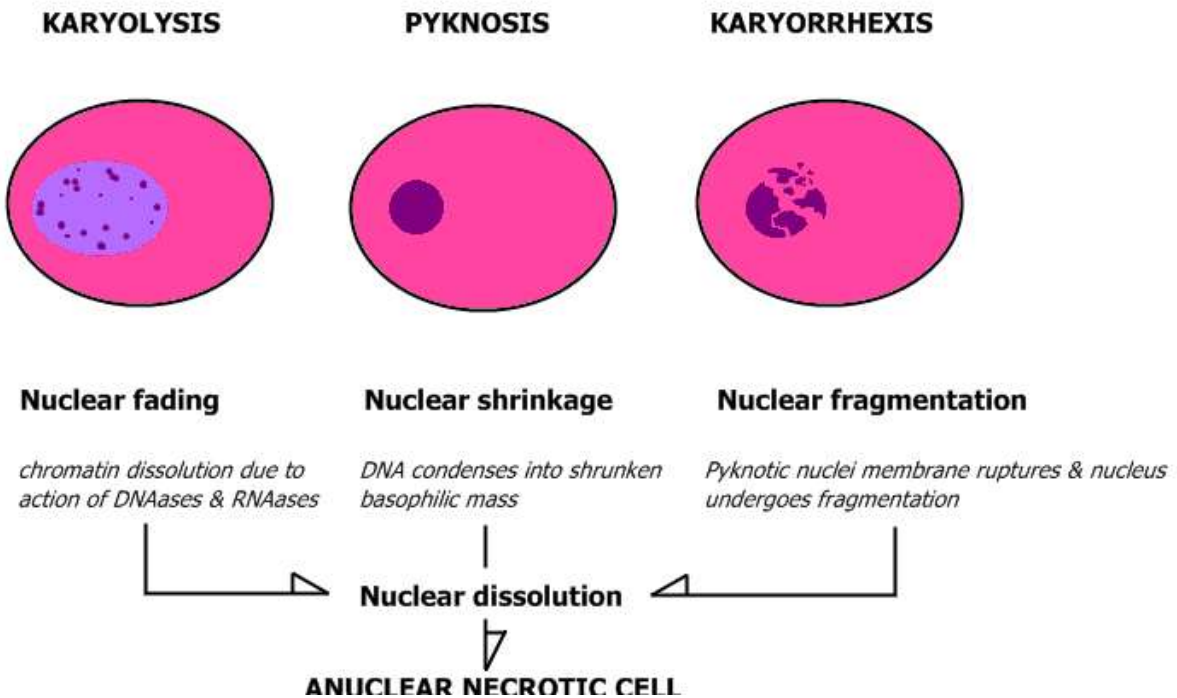
- **Decreased synthesis of ATP** by oxidative phosphorylation.
- **Decreased function of Na+K+ ATPase membrane pumps**, which in turn causes influx of Na+ and water, efflux of K+, cellular swelling (hydropic swelling), and swelling of the endoplasmic reticulum.
- The **switch to anaerobic glycolysis** results in depletion of cytoplasmic glycogen, increased lactic acid production, and decreased intracellular pH.
- **Decreased protein synthesis** leads to detachment of ribosomes from the rough endoplasmic reticulum.
- **Plasma-membrane blebs and myelin figures** may be seen.

Cellular Injury and Adaptation

Irreversible cell injury:

- **Severe membrane damage** plays a critical role in irreversible injury, allows a massive influx of calcium into the cell, and allows efflux of intracellular enzymes and proteins into the circulation.
- **Marked mitochondrial dysfunction** produces mitochondrial swelling, large densities seen within the mitochondrial matrix, irreparable damage of the oxidative phosphorylation pathway, and an inability to produce ATP.
- **Rupture of the lysosomes** causes release of lysosomal digestive enzymes into the cytosol and activation of acid hydrolases followed by autolysis.
- **Nuclear changes** can include pyknosis (degeneration and condensation of nuclear chromatin), karyorrhexis (nuclear fragmentation), and karyolysis (dissolution of the nucleus).

Cellular Injury and Adaptation



Irreversible cellular injury

Cellular Injury and Adaptation

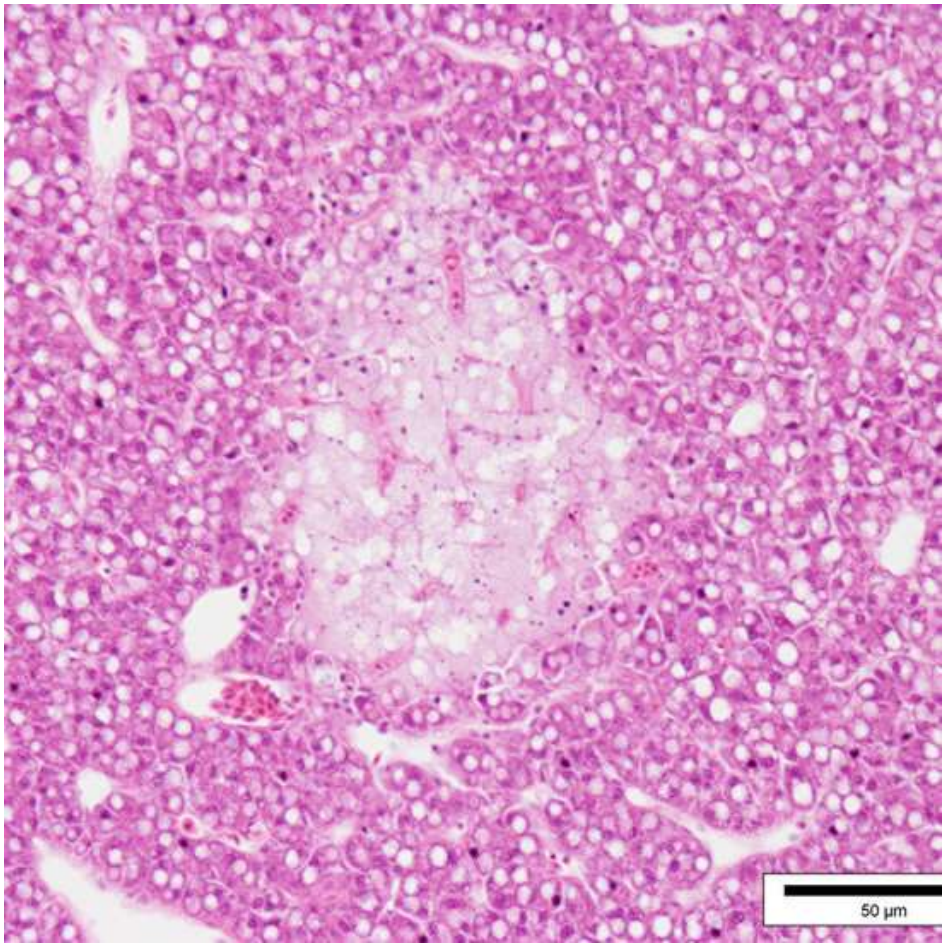
CELL DEATH

Morphologic types of necrosis (cell death in living tissue, often with an inflammatory response) are as follows:

- **Coagulative necrosis**
- **Liquefaction necrosis**.
- **Caseous necrosis**

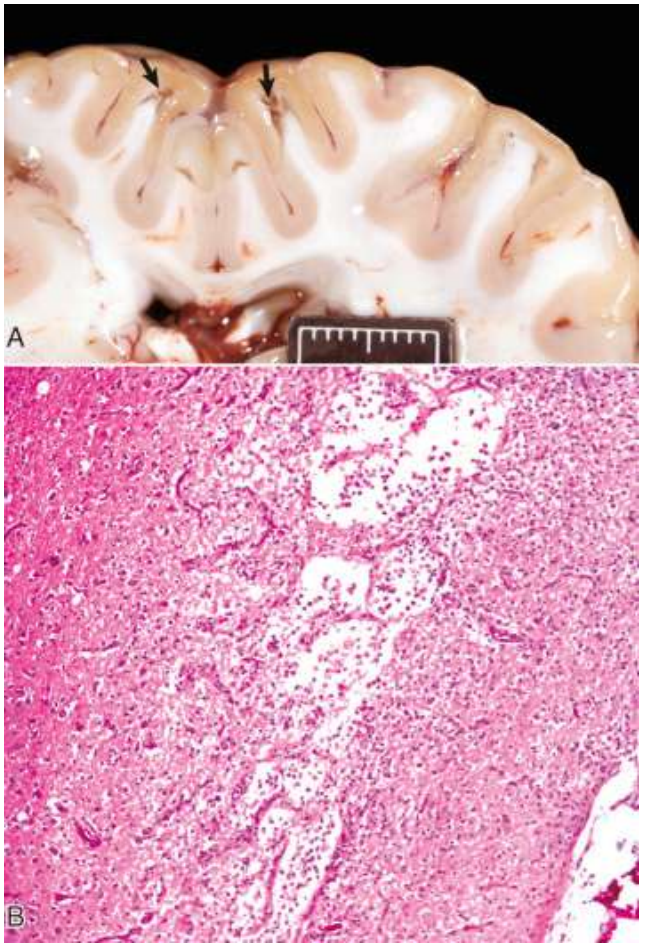
Cellular injury and adaptation

Coagulative necrosis, the most common form of necrosis, is most often due to ischemic injury (infarct). It is caused by the denaturing of proteins within the cytoplasm. Microscopic examination shows loss of the nucleus but preservation of cellular shape. Coagulative necrosis is common in most organs, including the heart, liver, and kidney, but not the brain.



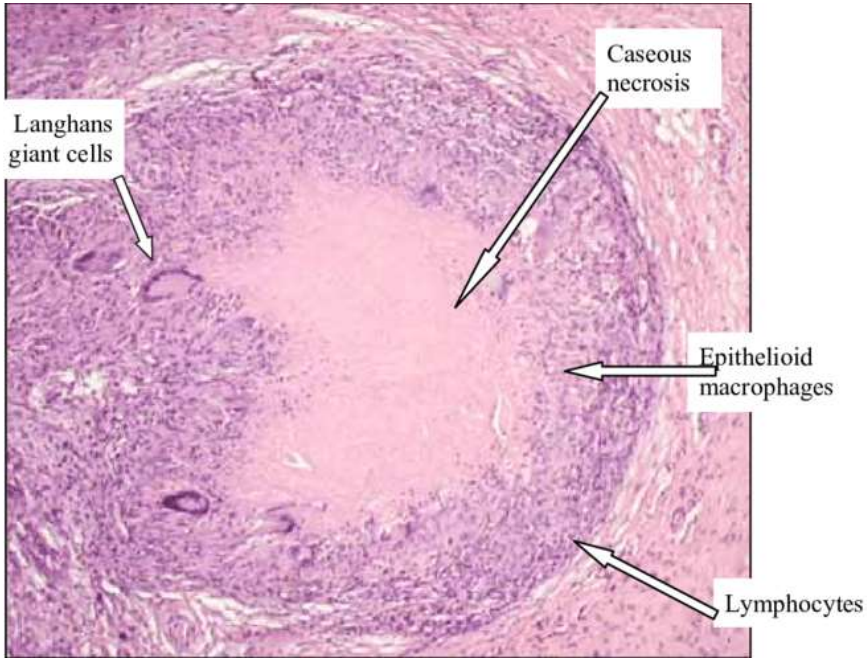
Cellular injury and adaptation

• **Liquefaction necrosis** results from cellular destruction by hydrolytic enzymes, leading to autolysis (release of proteolytic enzymes from injured cells) and heterolysis (release of proteolytic enzymes from inflammatory cells). Liquefaction necrosis occurs in abscesses, brain infarcts, and pancreatic necrosis.



Cellular Injury and Adaptation

Caseous necrosis is a combination of coagulation and liquefaction necrosis. The gross appearance is soft, friable, and “cheese-like.” Caseous necrosis is characteristic of granulomatous diseases, including tuberculosis.



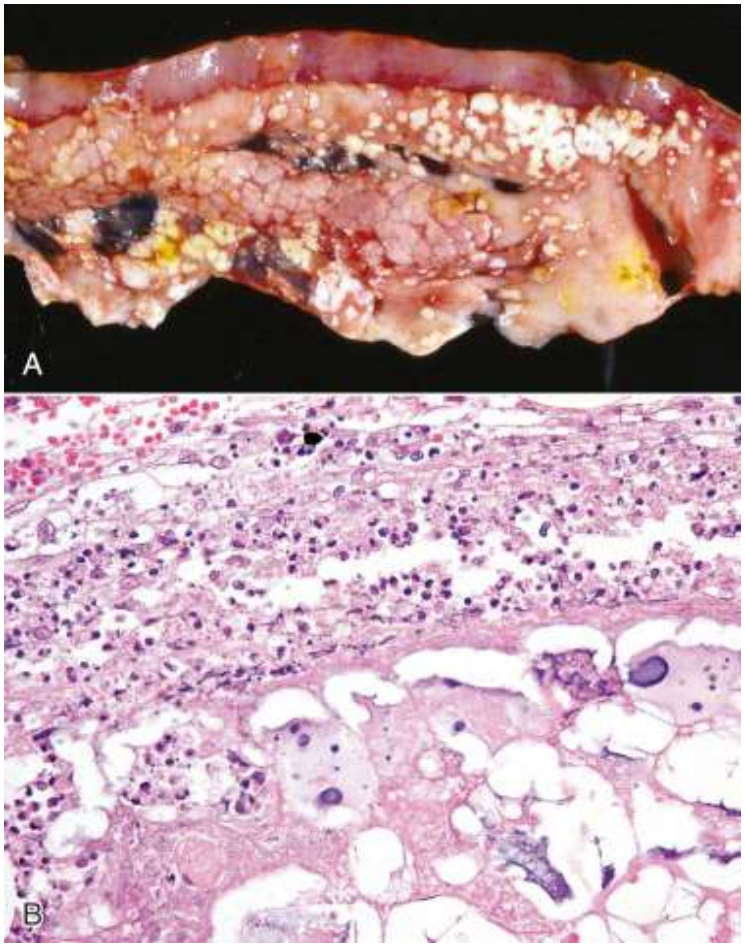
Cellular injury and adaptation

Fat necrosis is caused by the action of lipases on adipocytes and is characteristic of acute pancreatitis. On gross examination fat necrosis has a chalky white appearance. In fat necrosis the enzyme lipase releases fatty acids from triglycerides. The fatty acids then complex with calcium to form soaps. These soaps appear as white chalky deposits.

It is usually associated with trauma of the pancreas or acute pancreatitis.[2][3] It can also occur in the breast,[4] the salivary glands[5] and neonates after a traumatic delivery

Cellular injury and adaptation

Fat necrosis



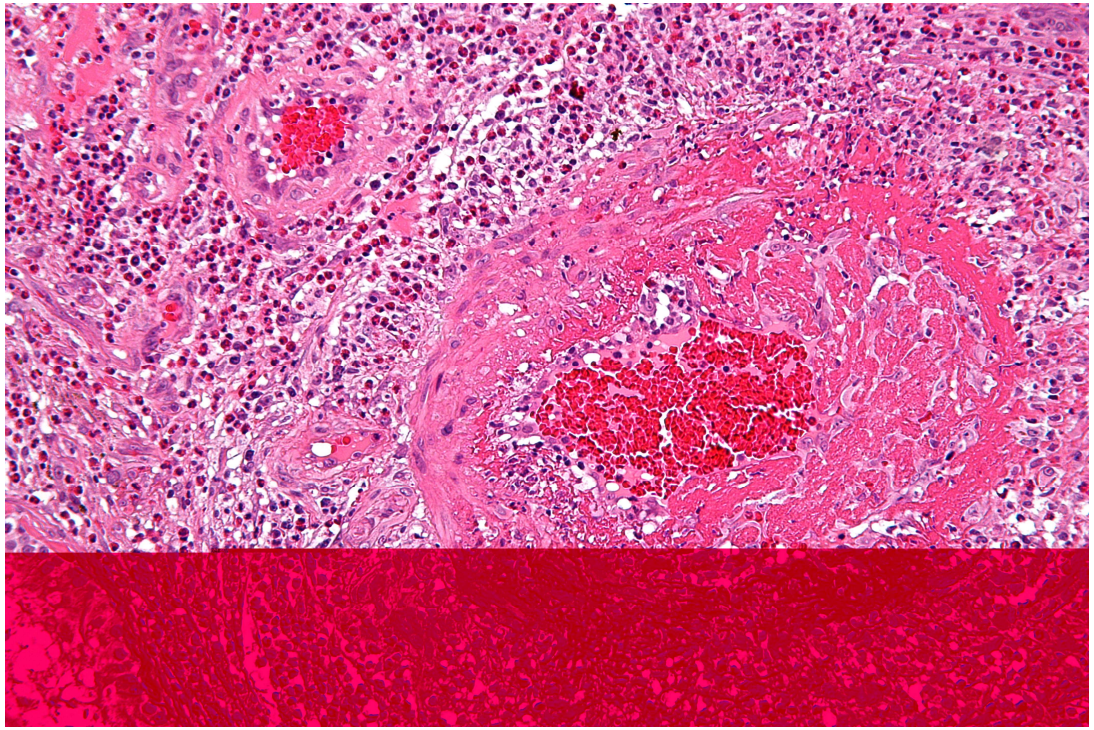
Cellular Injury and Adaptation

Fibrinoid necrosis is a form of necrotic connective tissue that histologically resembles fibrin. On microscopic examination fibrinoid necrosis has an eosinophilic (pink) homogeneous appearance. It is often due to acute immunologic injury (e.g., hypersensitivity type reactions II and III) and vascular hypertensive damage.

Fibrinoid necrosis is a specific pattern of irreversible, uncontrolled cell death that occurs when antigen-antibody complexes are deposited in the walls of blood vessels along with fibrin.

Cellular injury and adaptation

Fibrinoid necrosis



Cellular injury and adaptations

Gangrenous necrosis

Is a gross term used to describe dead tissue. Common sites of involvement include lower limbs, gallbladder, GI tract, and testes. Dry gangrene has coagulative necrosis for the microscopic pattern, while wet gangrene has liquefactive necrosis.

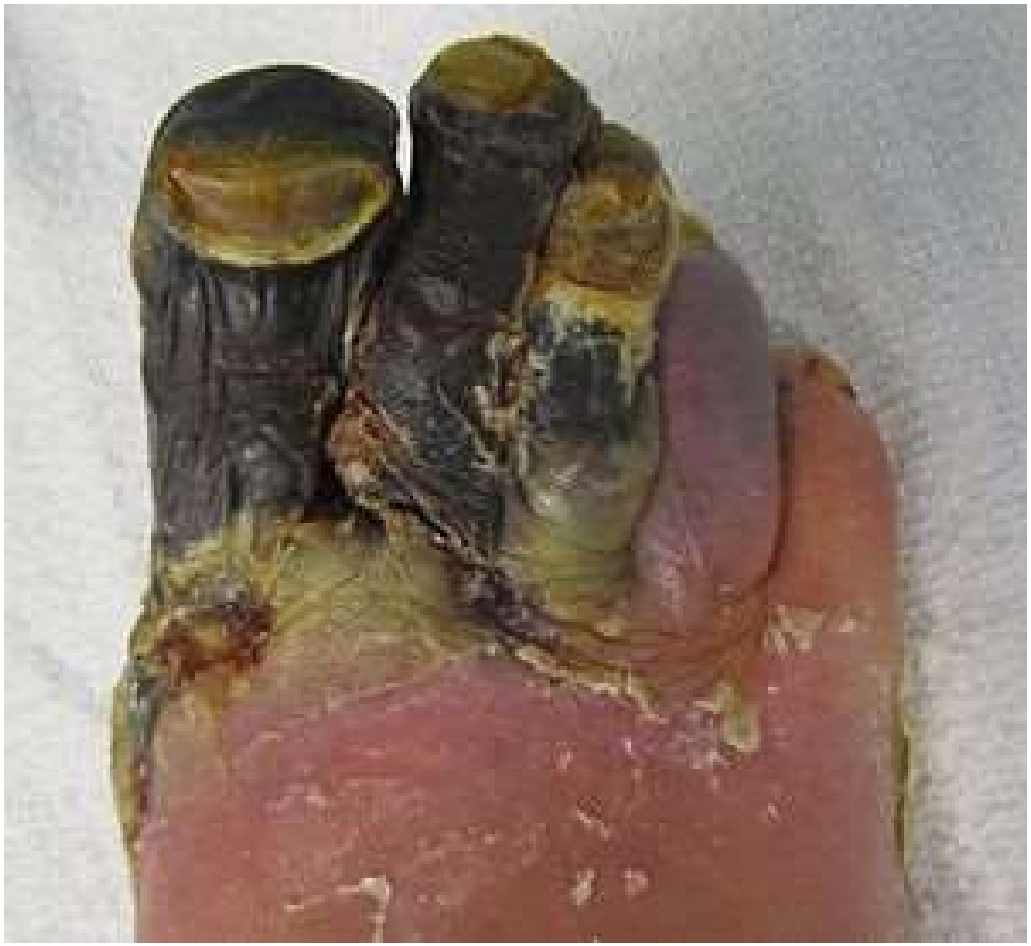
Dry gangrene

Wet gangrene

Gas gangrene

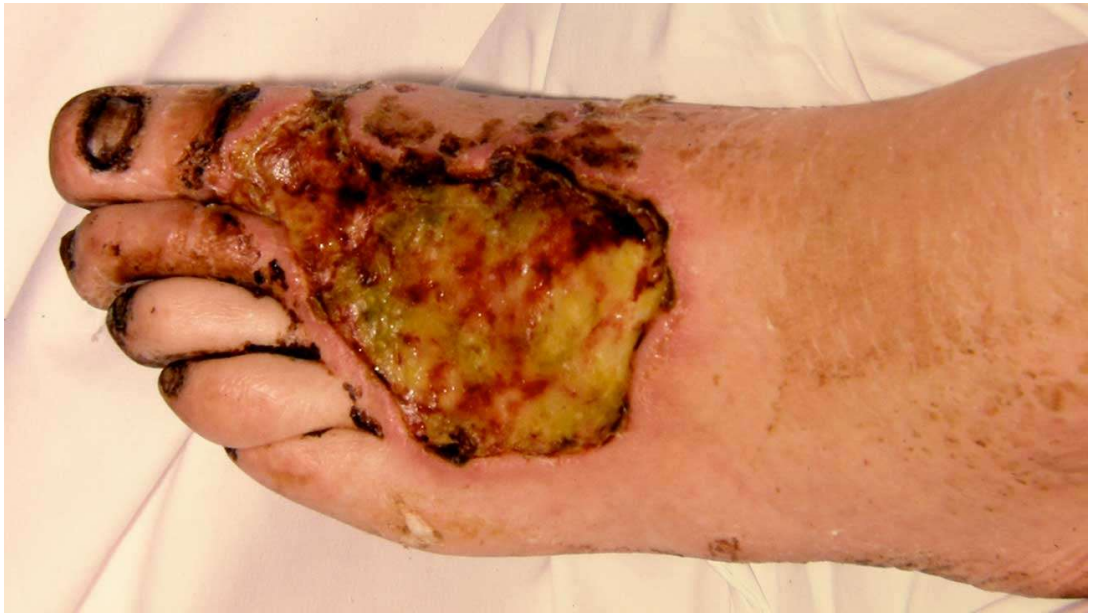
Cellular Injury and Adaptation

Dry gangrene is a form of coagulative necrosis that develops in ischemic tissue, where the blood supply is inadequate to keep tissue viable. It is not a disease itself, but a symptom of other diseases. Dry gangrene is often due to peripheral artery disease,but can be due to acute limb ischemia.



Cellular injury and Adatation

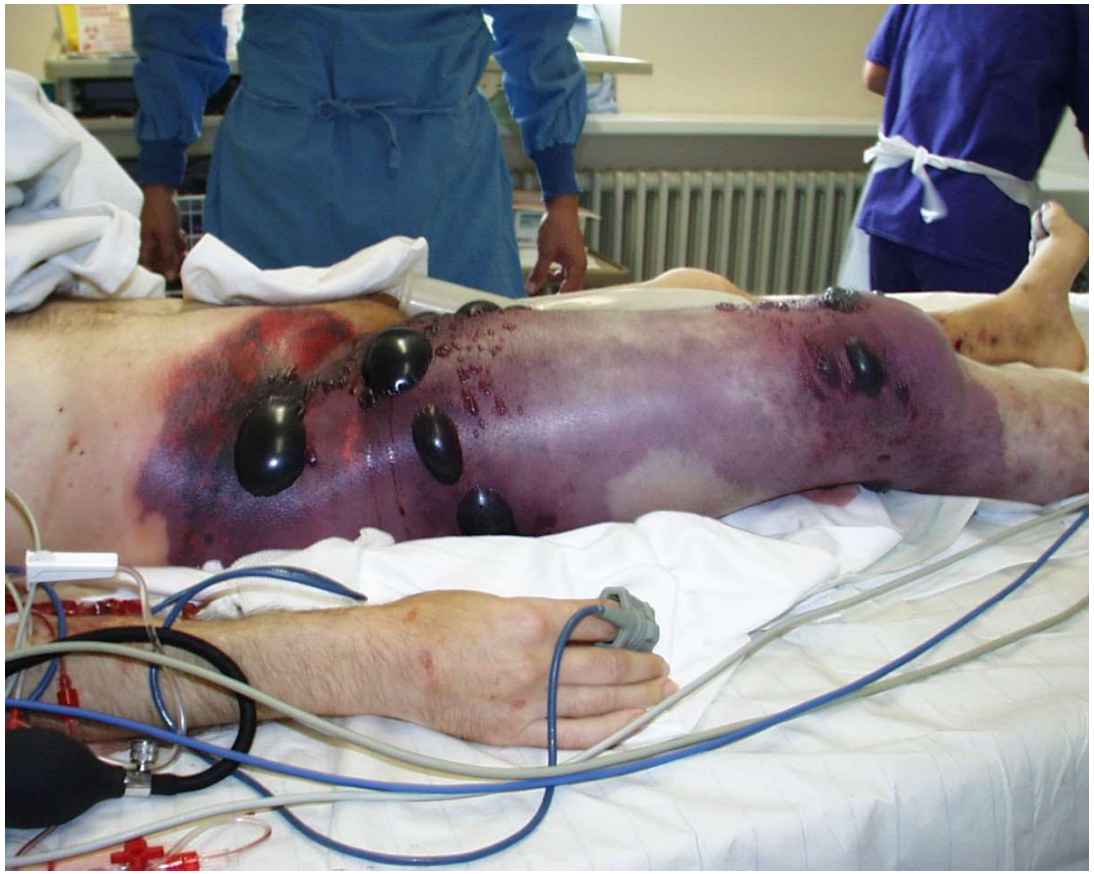
Wet, or infected, gangrene is characterized by thriving bacteria and has a poor prognosis (compared to dry gangrene) due to sepsis resulting from the free communication between infected fluid and circulatory fluid. In wet gangrene, the tissue is infected
by saprogenic microorganisms (*Clostridium perfringens* for example), which cause tissue to swell and emit a bad smell. Wet gangrene usually develops rapidly due to blockage of venous (mainly) or arterial blood flow.



Cellular injury and adaptations

Gas Gangrene

Gas gangrene is a bacterial infection that produces gas within tissues. It can be caused by *Clostridium*, most commonly alpha toxin-producing *C. perfringens*, or various non clostridial species. Infection spreads rapidly as the gases produced by the bacteria expand and infiltrate healthy tissue in the vicinity. Because of its ability to quickly spread to surrounding tissues, gas gangrene should be treated as a medical emergency.



Cellular Injury and Adaptation

Apoptosis is a specialized form of programmed cell death without an inflammatory response. It is an active process regulated by proteins that often affects only single cells or small groups of cells.

• In **morphologic appearance,** the cell shrinks in size and has dense eosinophilic cytoplasm. Next, nuclear chromatin condensation (pyknosis) is seen that is followed by fragmentation of the nucleus (karyorrhexis). Cytoplasmic membrane blebs form next, leading eventually to a breakdown of the cell into fragments (apoptotic bodies). Phagocytosis of apoptotic bodies is by adjacent cells or macrophages.

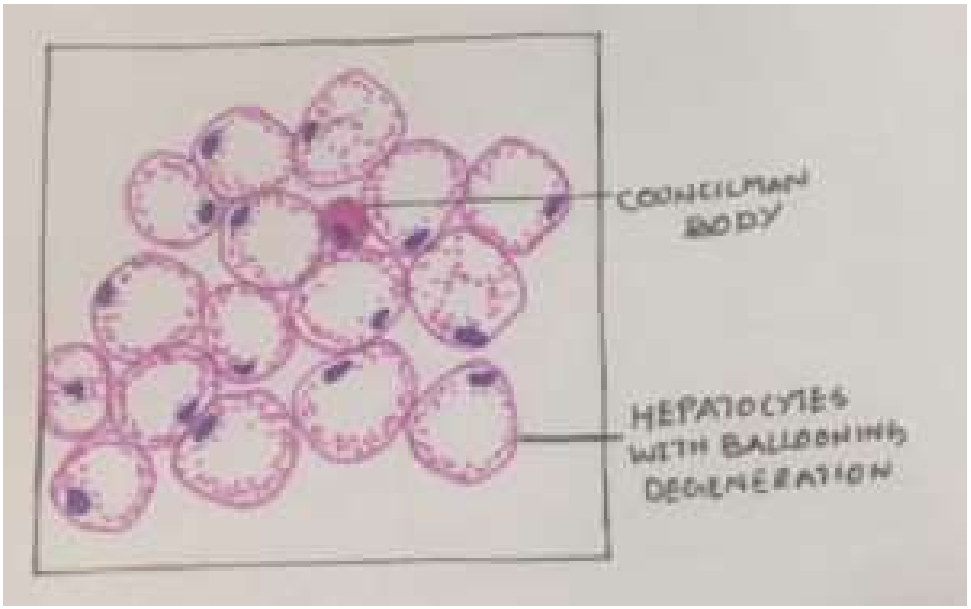
• **Stimuli for apoptosis** include cell injury and DNA damage, lack of hormones, cytokines, or growth factors, and receptor-ligand signals such as Fas binding to the Fas ligand and Tumor necrosis factor (TNF) binding to TNF receptor 1 (TNFR1).

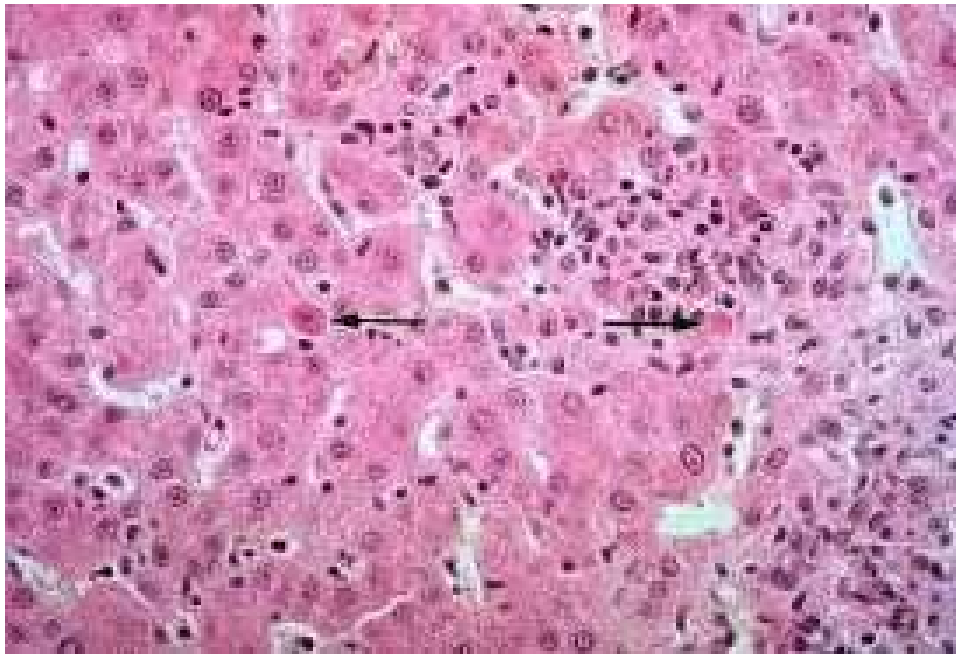
FasR: The Fas receptor (FasR), or CD95, is the most intensely studied member of the death receptor family.

• **Apoptosis is regulated by proteins.** The protein bcl-2 (which inhibits apoptosis) prevents release of cytochrome c from mitochondria and binds pro-apoptotic protease activating factor (Apaf-1). The protein p53 (which stimulates apoptosis) is elevated by DNA injury and arrests the cell cycle. If DNA repair is impossible, p53 stimulates apoptosis.

Cellular Injury and Adaptation

- **Execution of apoptosis** is mediated by a cascade of caspases (cysteine aspartic acid proteases). The caspases digest nuclear and cytoskeletal proteins and also activate endonucleases.
- **Physiologic examples of apoptosis** include embryogenesis (organogenesis and development), hormone-dependent apoptosis (menstrual cycle), thymus (selective death of lymphocytes).
- **Pathologic examples of apoptosis** include viral diseases (viral hepatitis [Councilman body]), graft-versus-host disease, and cystic fibrosis (duct obstruction and pancreatic atrophy).
- **Serum enzyme markers of cell damage** include Aspartate aminotransferase (AST) (liver injury), Alanine aminotransferase (ALT) (liver injury), Creatine kinase (CKMB) (heart injury), and Amylase and Lipase (pancreatic injury; amylase also rises with salivary gland injury).





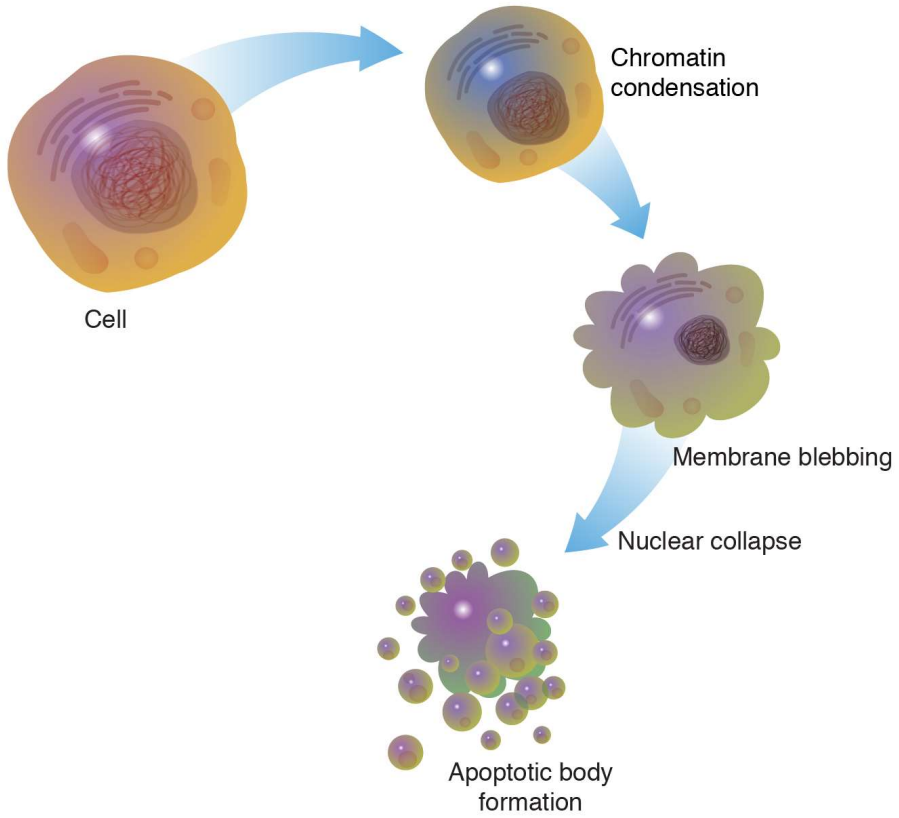
Cellular injuries and adaptations

Viral hepatitis

Councilman bodies

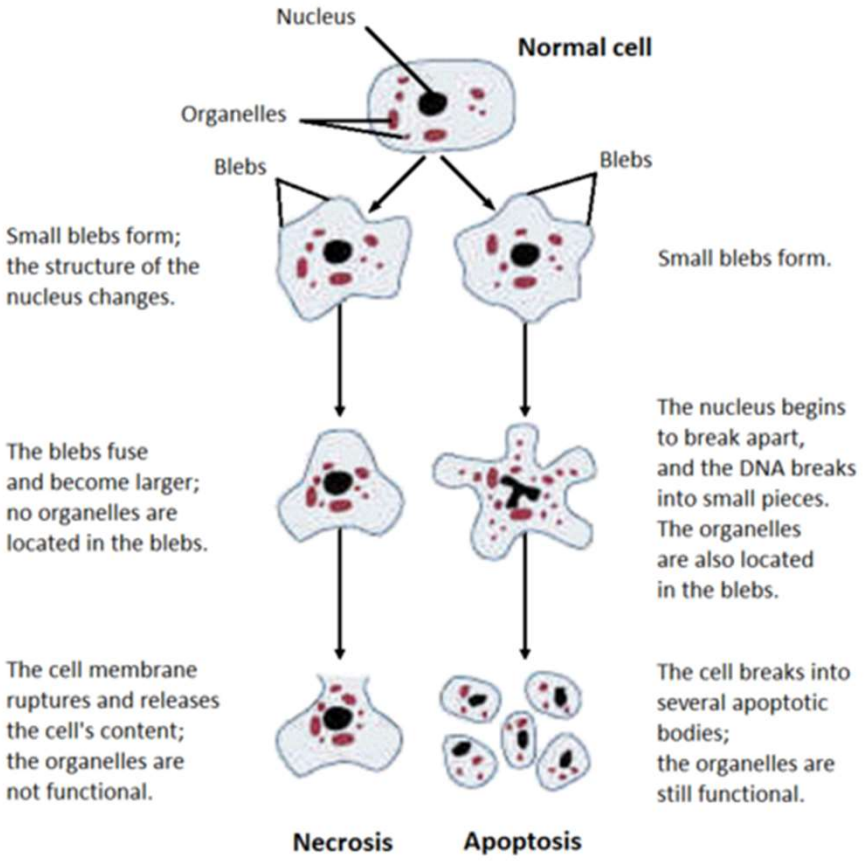
Cellular injury and adaptation

Apoptosis



Cellular injury and adaptation

Apotosis



Cellular Injury and Adaptation

CELLULAR ADAPTIVE RESPONSES TO INJURY

In general, cellular adaptation is a potentially reversible change in response to the environment.

Atrophy is a decrease in cell/organ size and functional ability. Causes of atrophy include decreased workload/disuse (immobilization); ischemia (atherosclerosis); lack of hormonal or neural stimulation, malnutrition, and aging.

Light microscopic examination shows small shrunken cells with lipofuscin granules. Electron microscopy shows decreased intracellular components and autophagosomes.

Cellular Injury and Adaptation

Hyperplasia is an increase in the number of cells in a tissue or organ. Some cell types are unable to exhibit hyperplasia (e.g., nerve, cardiac, skeletal muscle cells).

- Physiologic causes of hyperplasia include compensatory mechanisms (e.g., after partial hepatectomy), hormonal stimulation (e.g., breast development at puberty), and antigenic stimulation (e.g., lymphoid hyperplasia).
- Pathologic causes of hyperplasia include endometrial hyperplasia and prostatic hyperplasia of aging. Hyperplasia is mediated by growth factors, cytokines, and other trophic stimuli; Increased expression of growth-promoting genes (proto-oncogenes); and increased DNA synthesis and cell division.

Cellular Injury and Adaptation

Metaplasia is a reversible change of one fully differentiated cell type to another, usually in response to irritation. It has been suggested that the replacement cell is better able to tolerate the environmental stresses. For example, bronchial epithelium undergoes squamous metaplasia in response to the chronic irritation of tobacco smoke.

- The proposed mechanism is that the reserve cells (or stem cells) of the irritated tissue differentiate into a more protective cell type due to the influence of growth factors, cytokines, and matrix components.

Cellular Injury and Adaptation

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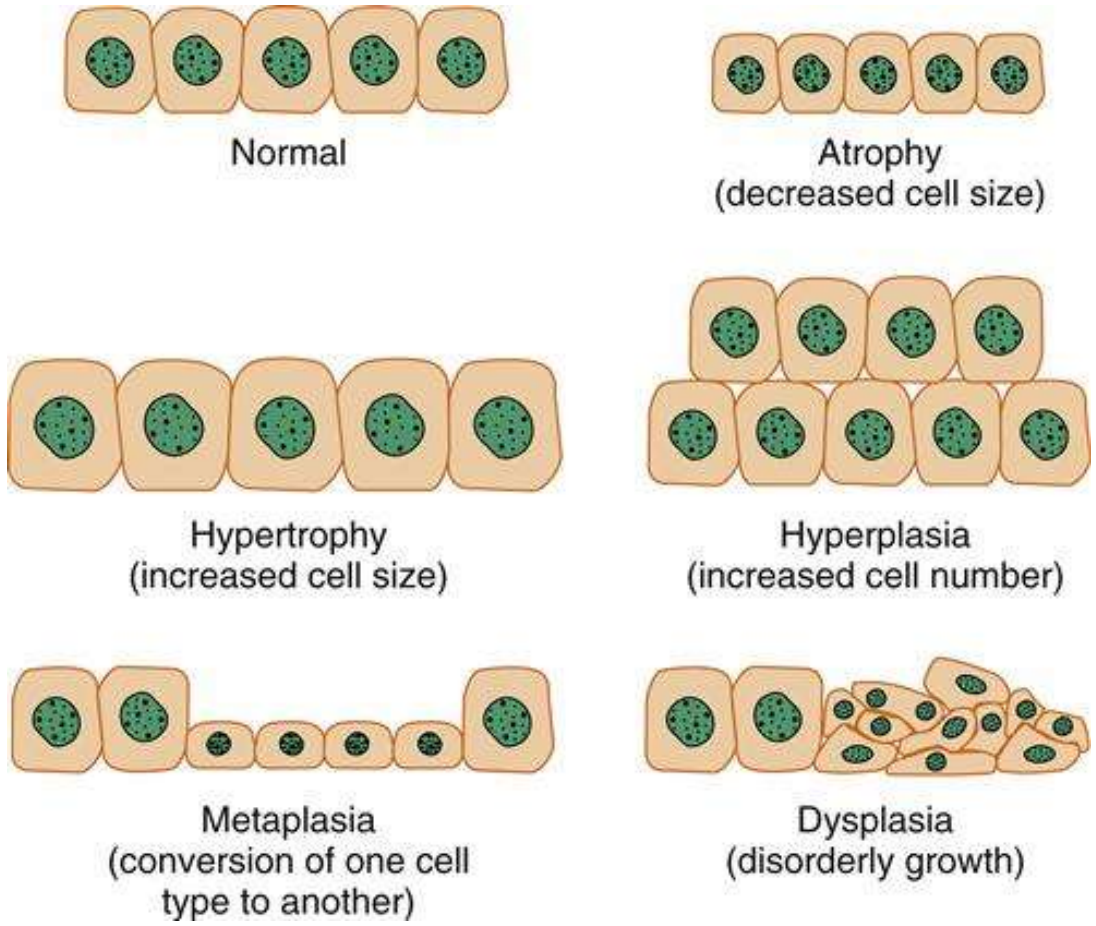
Clinical Correlate

- Barrett oesophagus is a classic example of metaplasia. The esophageal epithelium is normally squamous, but it undergoes a change to intestinal epithelium (columnar) when it is under constant contact with gastric acid.

Cellular injury and adaptation

Cellular changes



Cellular Injury and Adaptation

OTHER CELLULAR ALTERATIONS DURING INJURY

Pathologic accumulations

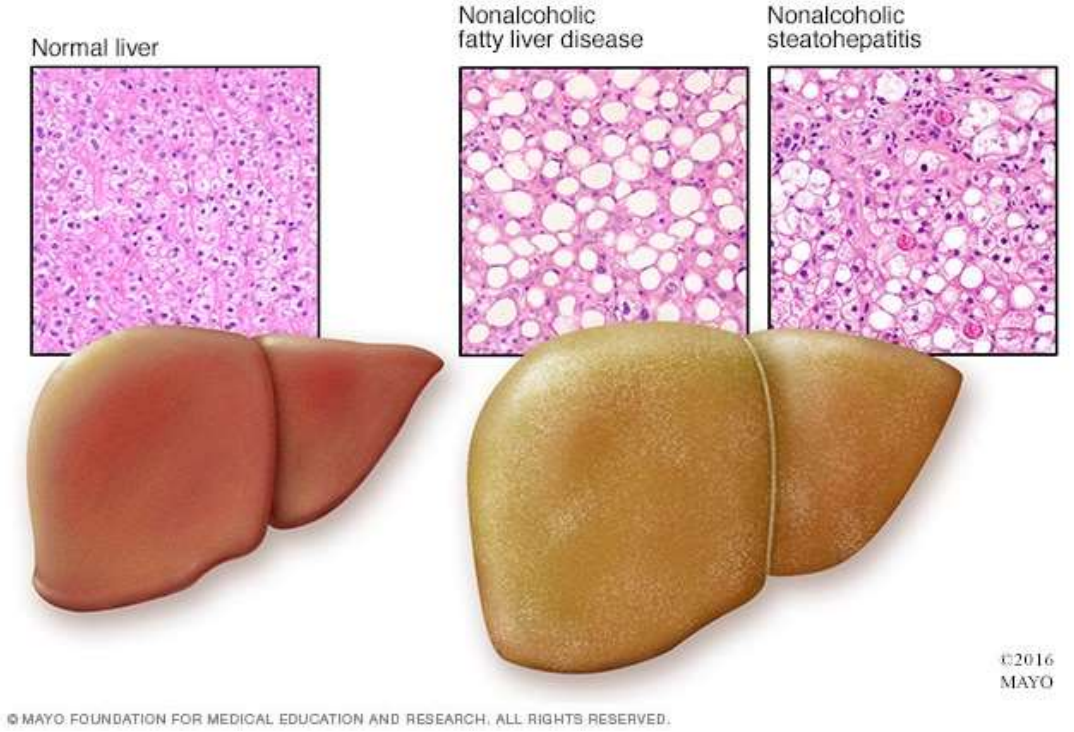
- **Lipids** that can accumulate intracellularly include triglycerides (e.g., fatty change in liver cells), cholesterol (e.g., atherosclerosis, xanthomas), and complex lipids (e.g., sphingolipid accumulation).
- **Proteins** can accumulate in proximal renal tubules in proteinuria and can form Russell bodies (intracytoplasmic accumulation of immunoglobulins) in plasma cells.
- **Glycogen storage diseases** (*See* Genetic Disorders chapter.)
- **Exogenous pigments** include anthracitic pigmentation of the lung (secondary to the inhalation of carbon dust), tattoos, and lead that has been ingested (e.g., gingival lead line, renal tubular lead deposits).

Cellular injury and adaptation

Fat accumulation

Stains for lipids

Oil Red-O

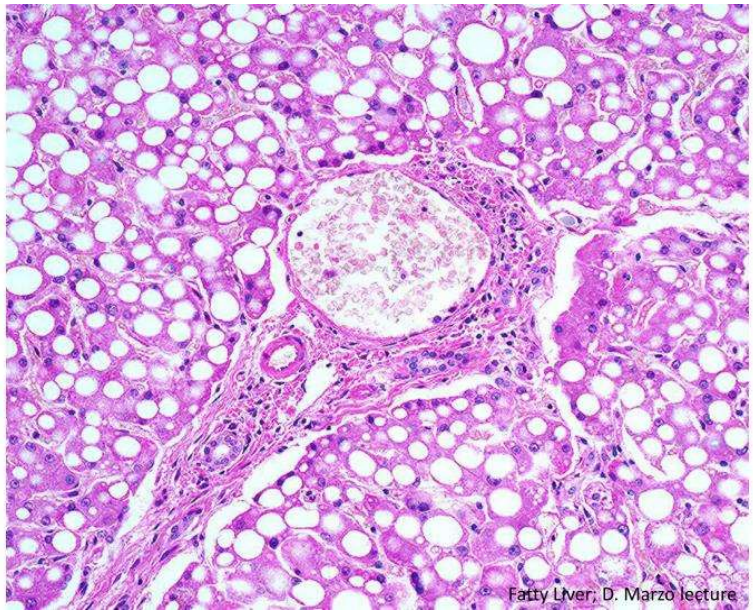


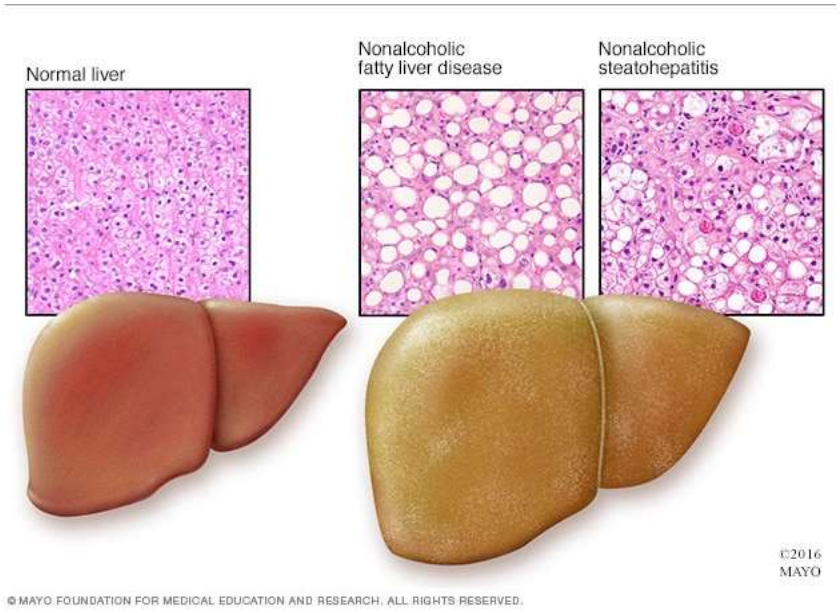
Cellular injury and adaptation

Fat accumulation

Stains for lipids

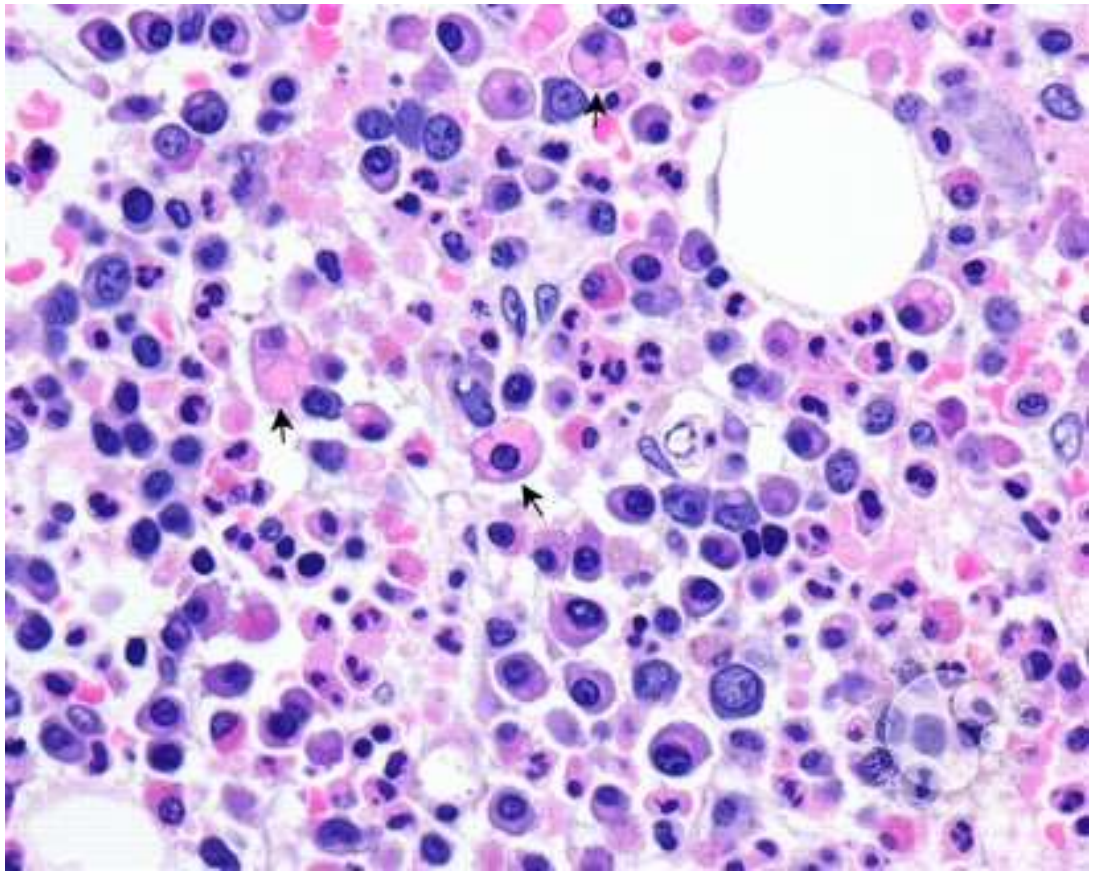
Oil Red-O





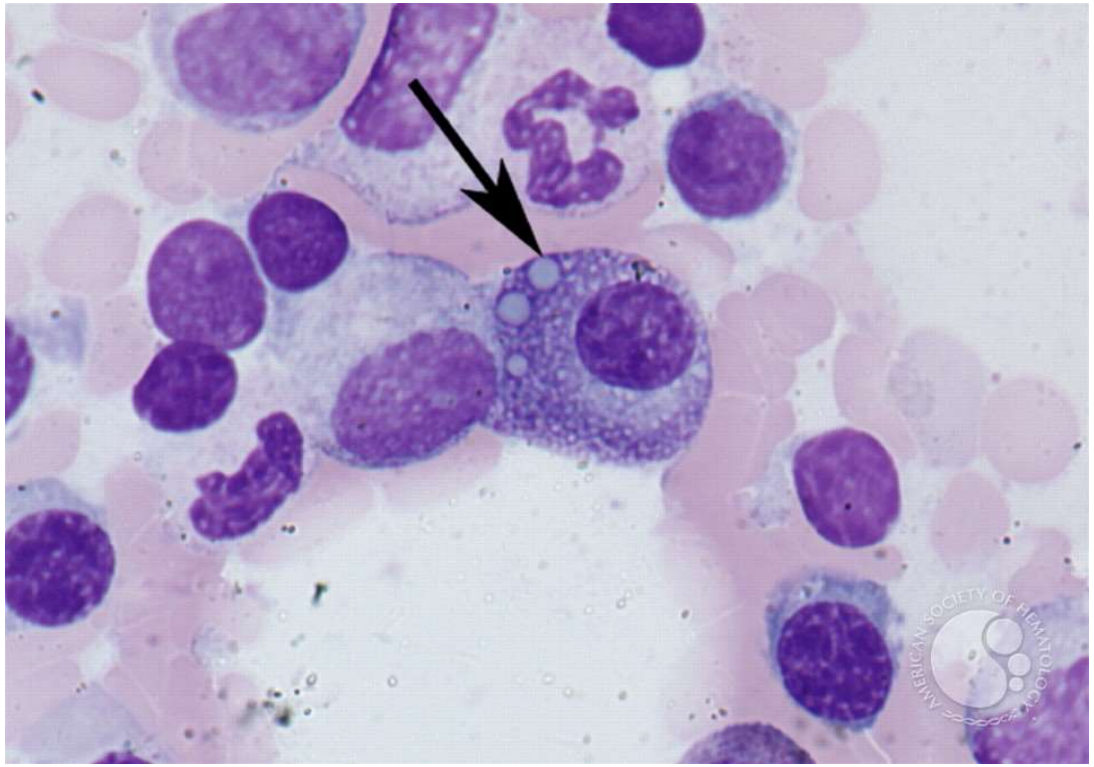
Cellular injury and adaptation

Protein Accumulation



Cellular injury and adaptation

Russel Bodies



Cellular injury and adaptation

Glycogen storage disorder

PAS Stain

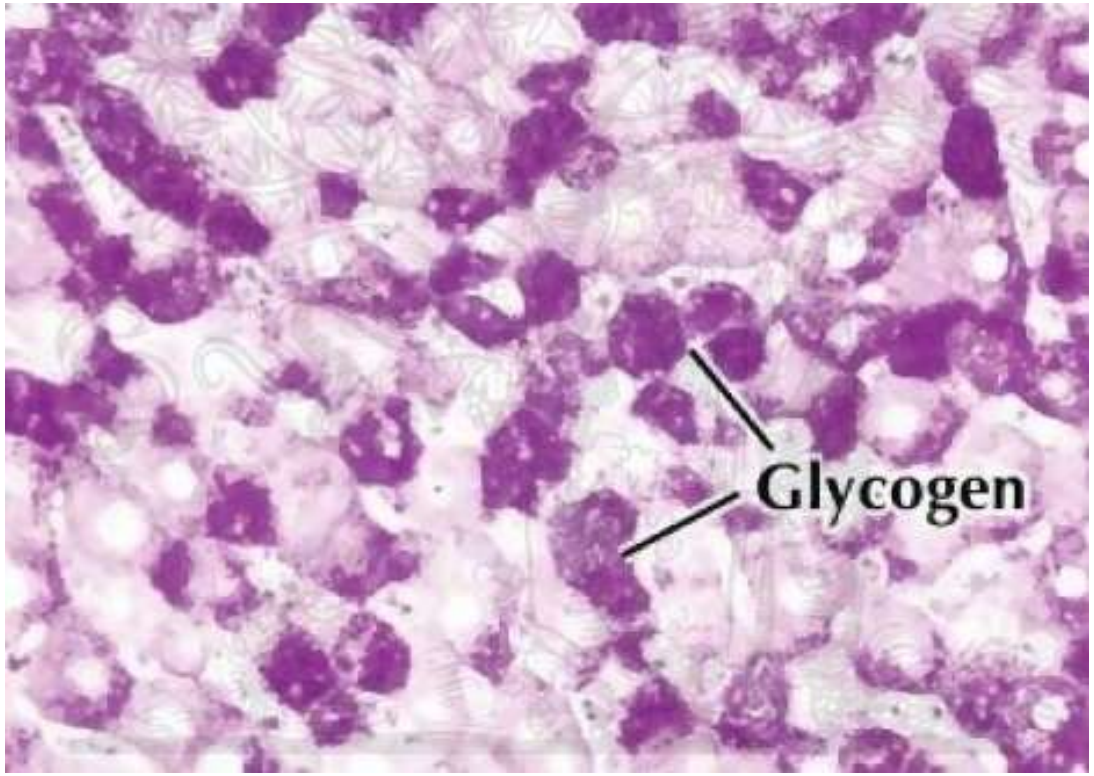
Von Gierkes

Pompe's

Cori

Anderson

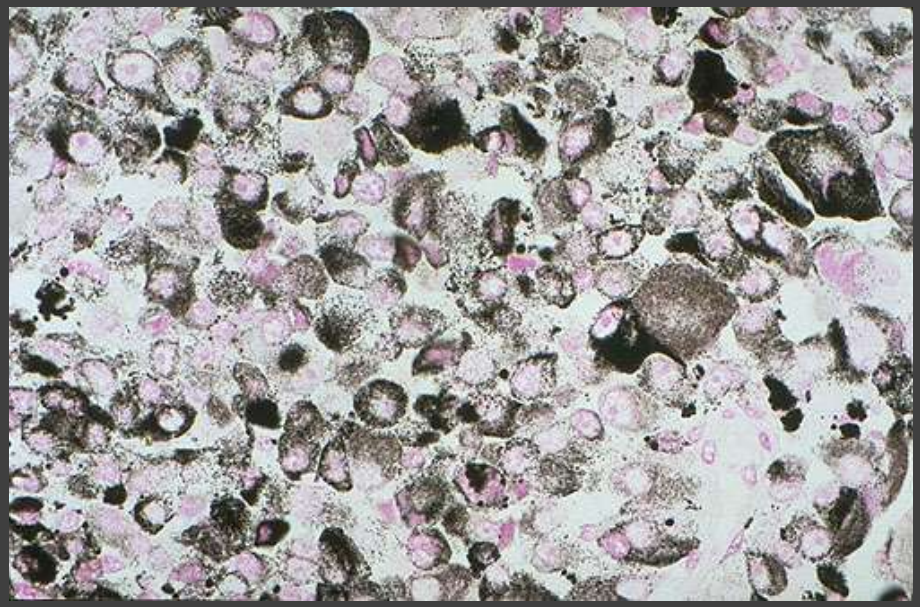
Mc Alders



Cellular Injury and Adaptation

Endogenous pigments

- **Lipofuscin** is a wear-and-tear pigment that is seen as perinuclear yellow brown pigment. It is due to indigestible material within lysosomes and is common in the liver and heart.
- **Melanin** is a black-brown pigment derived from tyrosine found in melanocytes and substantia nigra.
- **Hemosiderin** is a golden yellow-brown granular pigment found in areas of haemorrhage or bruises. Systemic iron overload can lead to hemosiderosis (increase in total body iron stores without tissue injury) or hemochromatosis (increase in total body iron stores with tissue injury). Prussian blue stain can identify the iron in the hemosiderin.
- **Bilirubin** accumulates in new-borns in the basal ganglia, causing permanent damage (kernicterus).



Cellular injury and adaptation

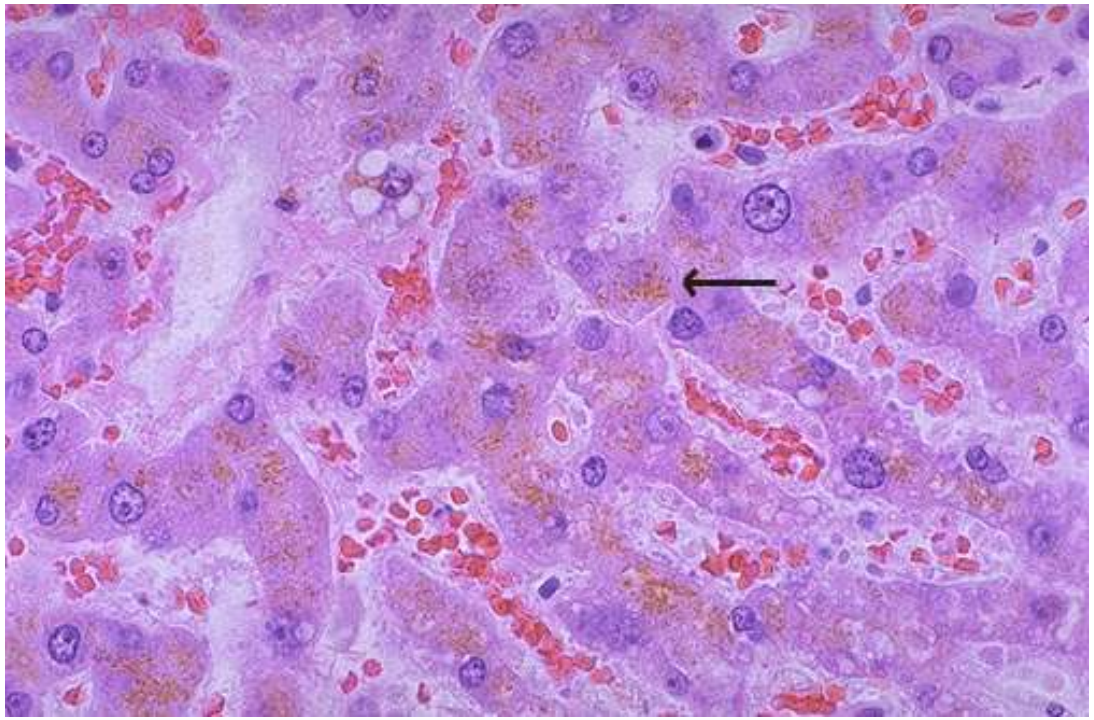
Melanin

Melanin stains are Fontana-Masson (stains melanin black)

Cellular injury and adaptation

Lipofuscin Endogenous pigment

Lipofuscin is **stained** by several lipid-**staining** methods: Sudan III and oil red. It gives acid-fast coloration with Carbol fuchsin. It **stains** with ferric ferricyanide (Schmorl method I), methyl green, and the periodic acid-Schiff (PAS) reaction.



Cellular Injury and Adaptation

Hyaline change is a nonspecific term used to describe any intracellular or extracellular alteration that has a pink homogenous appearance (proteins) on H&E stains.

- Examples of **intracellular hyaline** include renal proximal tubule protein reabsorption droplets, Russell bodies, and alcoholic hyaline.
- Examples of **extracellular hyaline** include hyaline arteriolosclerosis, amyloid, and hyaline membrane disease of the new-born.

Cellular Injury and Adaptation

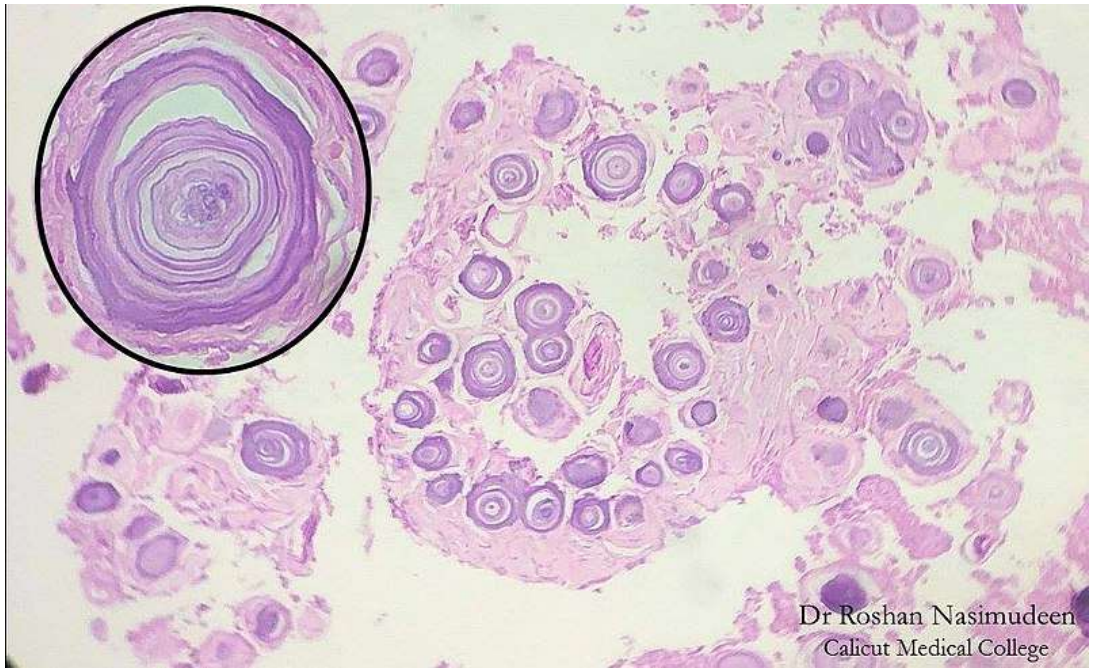
Pathologic forms of calcification

- **Dystrophic calcification** is the precipitation of calcium phosphate in dying or necrotic tissues. Examples include fat necrosis (saponification), psammoma bodies (laminated calcifications that occur in meningiomas and papillary carcinomas of the thyroid and ovary), Mönckeberg medial calcific sclerosis in arterial walls, and atherosclerotic plaques.

- **Metastatic calcification** is the precipitation of calcium phosphate in normal tissue due to hypercalcemia (supersaturated solution). The many causes include hyperparathyroidism, parathyroid adenomas, renal failure, paraneoplastic syndrome, vitamin D intoxication, milk-alkali syndrome, sarcoidosis, Paget disease, multiple myeloma, metastatic cancer to the bone. The calcifications are in the interstitial tissues of the stomach, kidneys, lungs, and blood vessels.

Cellular Injury and Adaptation

Psammoma bodies



Cellular Injury and Adaptation

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