Pathology **Cell injury**

LEC. 3

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- **4- Gangrenous Necrosis**:
  - This is a type of coagulative necrosis that occurs due to ischemia (e.g. in bowel, limb etc.).
  - There is **necrosis** of tissue with superadded **putrefaction**.

Gangrene= Necrosis + infection + putrefaction (enzymatic decomposition).

- Gangrene is classified into 3 types -
  1. Dry gangrene
  2. Wet gangrene
  3. Gas gangrene

A. Dry Gangrene

- occurs in the distal part of the limb due to **ischemia**,
- Typical examples of a dry gangrene are on the **toes and feet** of an old patient due to **atherosclerosis.**
- Usually initiated at the toe region which is farthest from the blood region
- This gangrene **slowly grows** upwards and reaches a point where the blood supply is adequate enough to keep the whole tissue viable.
- The affected part is dry, shrunken and **dark black,** resembling mummified flesh. The dark coloration is due to liberation of hemoglobin from hemolyzed red blood cells which is converted by hydrogen sulfide (H_2S) produced by the bacteria, resulting in formation of **black iron sulfide** that remains in the tissues
- A "Line of separation" is well formed between the gangrenous part and the viable part.

B. Wet gangrene

- Usually occurs in the **moist tissues** and organs such as the **mouth**, **bowel**, l**ung**, **cervix**, and **vulva** etc.
- **Diabetic leg** & **Bedsores** are other examples with high sugar contents in the necrotic tissue which is favorable for the bacteria to grow.
- Wet gangrene usually develops rapidly due to **blockage of venous** and less commonly arterial blood flow from thrombosis or embolism.
- At the affected part, stuffed blood encourages the formation and growth of the invading bacteria. And the toxic products formed by the bacteria are absorbed causing the systemic manifestations of septicaemia, and then finally to death.

- There is no clear demarcation of any line of separation.

C. Gas gangrene

- is a special form of wet gangrene that is caused by a gas-forming **Clostridia(Clostridium perfringens which** is a gram positive anaerobic bacteria) which enters into the tissues through **open contaminated wounds.**
- Or this invasion can also occur as a complication of **operation on colon** which usually contains the bacteria Clostridia.
- The bacteria produces many toxins which can produce necrosis and edema locally and are absorbed producing systemic manifestations.

• Fat Necrosis.

There are two types of fat necrosis

1. **Traumatic** Fat Necrosis. 2. **Enzymatic** Fat Necrosis.

Traumatic Fat Necrosis

- Fat necrosis often occurs in women with very large breasts or in response to a **trauma or blow to the breast.**
- Is a condition in which painless, round, firm lumps caused by damaged and disintegrating fatty tissues form in the breast tissue.
- Fat necrosis can also see after surgery on the breast, post radiotherapy on breast cancer.
- These lumps are not malignant and there is no reason to believe that they increase a woman's risk of cancer.
- **Microscopically** characterized by foamy macrophages (even giant cells formation) infiltrating necrotic breast tissue.

Enzymatic Fat Necrosis

- It describes focal areas of fat destruction, typically occurring after pancreatic injury (mainly **acute pancreatitis**).
- There is release of pancreatic enzymes (mainly **lipase**) as a result of injury, into adjacent fatty tissue of greater omentum.
- These enzymes will liquefy fat cells membranes & hydrolyze triglycerides esters within these fat cells & result in the formation of fatty acids combine with calcium.
- These combined fatty acids will produce grossly chalky white areas (Fat Saponification).
- Microscopically, there are shadowy outlines of necrotic fat cells with basophilic calcium deposits & a surrounding inflammatory reaction.

Fibrinoid necrosis is a special form of necrosis usually seen in immune reactions involving blood vessels. This pattern of necrosis typically occurs when complexes of antigens and antibodies are deposited in the walls of arteries. Deposits of these "immune complexes," together with fibrin that has leaked out of vessels, result in a bright pink and amorphous appearance in H&E stains, called "fibrinoid" (fibrin-like) by pathologists. Usually seen in **vasculitis**.

For all types of necrosis, most necrotic cells & their debris are removed by extracellular digestion & leukocytes phagocytosis

Apoptosis(Programmed Cell Death):

- **Apoptosis** is a pathway of cell death that is induced by a tightly regulated intracellular suicide program, in which cells destined to die activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins.
- Apoptosis should be differentiated from Necrosis.
- Apoptosis is responsible for **programmed cell death** in several physiological & pathological conditions

Examples of Physiological conditions:

1. **The programmed destruction of cells during embryogenesis**, including implantation, organogenesis.

2. **Hormone-dependent involution in the adult,** such as endometrial cell breakdown during the menstrual cycle

3. **Death of host cells (inflammatory cells),** like neutrophils in an acute inflammatory response, and Lymphocytes at the end of an immune response.

4. **Elimination of potentially harmful self-reactive lymphocytes**, either before or after they have completed their maturation.

5. **Cell death induced by cytotoxic T cells**, a defense mechanism against viruses and tumors that serves to eliminate virus-infected and neoplastic cells.

Failure of cells to undergo physiologic apoptosis may result in:

1-aberrant development **2-** unimpeded tumor proliferation **3-** autoimmune diseases.

Examples of Pathological conditions:

1. **Cell death produced by a variety of injurious stimuli,** such as DNA damage due to radiation & anticancer drugs, this damage DNA may result in malignant transformation of the cells.
2. **Cell injury in certain viral diseases,** such as viral hepatitis.

3. **Cell death in tumors,** most frequently during regression but also in actively growing tumors.

Morphologic Features of Apoptosis:

1. **Cell shrinkage.**
2. **Chromatin condensation**. This is the most characteristic feature of apoptosis. The chromatin aggregate peripherally, under the nuclear membrane, into dense masses of various shapes and sizes (**Karyorrhexis**).

3**. Formation of cytoplasmic blebs and apoptotic bodies.** The apoptotic cell first shows extensive surface blebbing, then undergoes fragmentation into membrane-bound apoptotic bodies composed of cytoplasm and tightly packed organelles, with or without nuclear fragments.

4.Phagocytosis of apoptotic cells or cell bodies, usually by macrophages.
5.Apoptosis does not induce inflammation.
Plasma membranes are thought to remain intact during apoptosis, until the last stages, when they become permeable to normally retained solutes.

On **microscopical examination** of apoptotic areas in tissues stained with hematoxylin and eosin, apoptosis involves single cells or small clusters of cells. The apoptotic cell appears as a round or oval mass of intensely eosinophilic cytoplasm with dense nuclear chromatin fragments.

Mechanisms of apoptosis:

- Apoptosis is induced by a cascade of molecular events that result in activation of caspases, which are responsible for the features of apoptosis.
- The process of Apoptosis may be **divided into** 2 phases:
  - **initiation phase**, (CASPASES Activation)
  - **execution phase**, **(**Cell death by activated CASPASES)
- **Initiation of apoptosis** occurs principally **by signals from two pathways** :

1. **Extrinsic, or receptor-initiated, pathway**
2. **Intrinsic or mitochondrial pathway.**

Extrinsic (receptor initiated) pathway:

- This pathway is **initiated** by group of receptors (**death receptors**), that are present on a variety of cells.
- These death receptors are members of family (called **tumor necrosis factor(TNF**) which contain death domain, which is essential for delivering of apoptotic signals.
- The best-known death receptors are the **type 1 TNF receptor** (TNFR1) and a related protein called **Fas** (this Fas protein is responsible for initiation phase of apoptosis by **activation of caspases)**

- This pathway of apoptosis can be **inhibited** by a protein called **FLIP** (prevent the activation of caspases by Fas proteins),

The Intrinsic (Mitochondrial) Pathway.

- Apoptosis is occurred in this pathway as a result of **increased permeability mitochondrial membrane** releasing a protein called cytochrome **C** to the cytoplasm initiate the suicide program of apoptosis.
- This change in permeability of mitochondrial membrane is due to replace of normally present **anti- apoptotic proteins (Bcl-2)** by **pro- apoptotic proteins like BAX and BAK**.
- These pro- apoptotic proteins will induce apoptosis by activation of caspases.
- **Execution phase of apoptosis.**

This final pathway of apoptosis, which is characterized by group of distinctive biochemical events that result from synthesis & activation of **caspases enzymes.**

These caspases will result in **morphological changes of apoptosis** by induce the followings processes: 1-protein cleavage, 2-protein cross linkage,

3-DNA breakage 4-removal of dead cells by phagocytosis.

Comparison between Coagulative & Liquefactive necrosis

	Coagulative necrosis	Liquifactive necrosis
Cause of cell injury	Hypoxia / Ischemia	Infection / hypoxia
Examples	Myocardial infarction	Hypoxic death of brain cells
Pathogenesis	Protein Denaturation	Enzymatic digestion
Morphological features	Preserve general architecture of tissue with loss of cellular details	Loss of both tissue architecture & cellular details

Comparison between Coagulative Necrosis & Apoptosis

	Coagulative necrosis	Apoptosis
Stimuli	Hypoxia, Toxins	Physiological & Pathological facto
Histological appearance	Cellular swelling, disrupted membran pyknosis of Nucleus	Cellular shrinkage, chromatin condensation, formation of Apoptot bodies
Mechanisms	ATP depletion, membrane injury.	Gene activation, Caspases activation
Tissue reactions	Inflammation	NO inflammation

Necroptosis

As the name indicates, this form of cell death is a hybrid that shares aspects of both necrosis and apoptosis. The following features characterize necroptosis

is a form of programmed cell death that is controlled by death signals and displays a death pattern like that of necrosis.

Found in inflammation and ischemia-reperfusion injury.