Cell Death(Either by Necrosis or Apoptosis)

1-Necrosis

-By **enzymatic digestion** of cells after irreversible injury.

-When damage to membrane is severe ,enzymes leak out of **Lysosomes** ,enter the cytoplasm & **digest the cell** .

-Cellular contents also leak out through the damaged plasma membrane &start a host reaction (**Inflammation)** .

-**Necrosis is the major pathway of cell death in injuries resulting from :**

a)Ischemia b)Exposure to toxins.

c)Infections. D)Trauma

→*Necrosis is always pathologic process.*

→Types of Necrosis:

1-Coagulative Necrosis	**- Is a form of tissue necrosis in which:-** -The component cells are **dead** but the basic **tissue architecture** is **preserved** for at least several days. -The affected tissue has a **firm texture** . -The injury denatures both **structural enzymes** and **Lysosoma**l enzymes so, blocks the **proteolysis** of dead cells. - **The necrotic cells are removed by phagocytosis of the cellular debris by:** a) Infiltrating leukocytes. b) Digestion of dead cells by the action of **lysosomal enzymes of the leukocytes.** -**Coagulative necrosis is characteristic of infarcts "area of ischemic necrosis" in all solid organs except the brain.**
2-Liquifative necrosis	- **Liquification completely** digests the dead cells, resulting in transformation of the tissue into **a liquid viscous mass**. - If the process was initiated by acute inflammation the material is frequently **creamy yellow** and is called pus. "mainly dead neutrophils". - Seen in **focal bacterial** or occasionally **fungal infection** because microbes stimulate the accumulation of **inflammatory cells** and the enzyme of the **leukocytes digest "liquefy**" the tissue. - For unknown reason, **hypoxic death** of cells with the central nervous system often causes liquefactive necrosis. e.g Cerebral infarction & lung abscesses.
3-Caseous Necrosis	-Encountered most often in foci of **tuberculosis infection** (Acid fast bacteria). -The term "**caseous" (Cheese like"** is derived from the friable **yellow-white appearance** of the area of necrosis. -On microscopic examination, the necrotic focus appears as a collection of **fragmented or lysed cells** with an **amorphous granular appearance.** -Unlike coagulative necrosis, the **tissue architecture is completely obliterated "destroyed**" and cellular **outlines cannot be distinguished.** - Caseous necrosis is often enclosed within a **distinctive inflammatory border.** -Always surrounded by a border of **lymphocytes & macrophages** resulting in the formation of **granuloma.**

4-Gangarenous Necrosis	- Initially there is a **Coagulative necrosis** from the **loss of blood** supply (The stage is called **dry gangrene**) ,if **bacterial infection** is **superimpose**d ,mainly **Clostridia spp**. ,there is **liquefactive necrosis** this stage is called **Wet gangrene**. - Usually applied to a limb generally **lower leg** that has lost its blood supply and has undergone **coagulative necrosis** "dry gangrene" involving multiple tissue layers, the limb should be **amputated**, When **bacterial infection is superimposed**. -**Gangrenous tissue** is foul smelling & black ,the bacteria produces **collagenase enzyme** which **destroy Collagen** & **enable infection** to spread rapidly reaches blood stream ,if fermentation occurs **Dry gangrene**.
5-Fat Necrosis	-It refers to focal areas of **fat destruction**. - This occurs, in acute **pancreatitis** in this disorder, pancreatic **lipases** split the **triglycerides esters** contained within fat cells. - The released fatty acids combined **with calcium** to produce grossly **visible chalky white areas "fat saponification"** which enable the surgeon and the pathologic to identify the lesion.
6-Fibrinoid Necrosis	-Seen in **immunological reactions** involving blood vessels. -Deposition of immune complex **(Ag-Ab)leaking Fibirin deposits=Fibrinoid arterial walls.**

→Laboratory diagnosis of Necrosis:

-Leakage of **intracellular proteins** through the damaged cell membrane & ultimately into the circulation provides a means of detecting **tissue specific necrosis using blood or serum samples:**

a)**Cardiac muscles** contains unique isoform of the enzyme **Creatine Kinase & the contractile protein Troponine.**

b)Hepatocytes contain **Transaminase enzyme.**

→Outcomes of Necrosis:

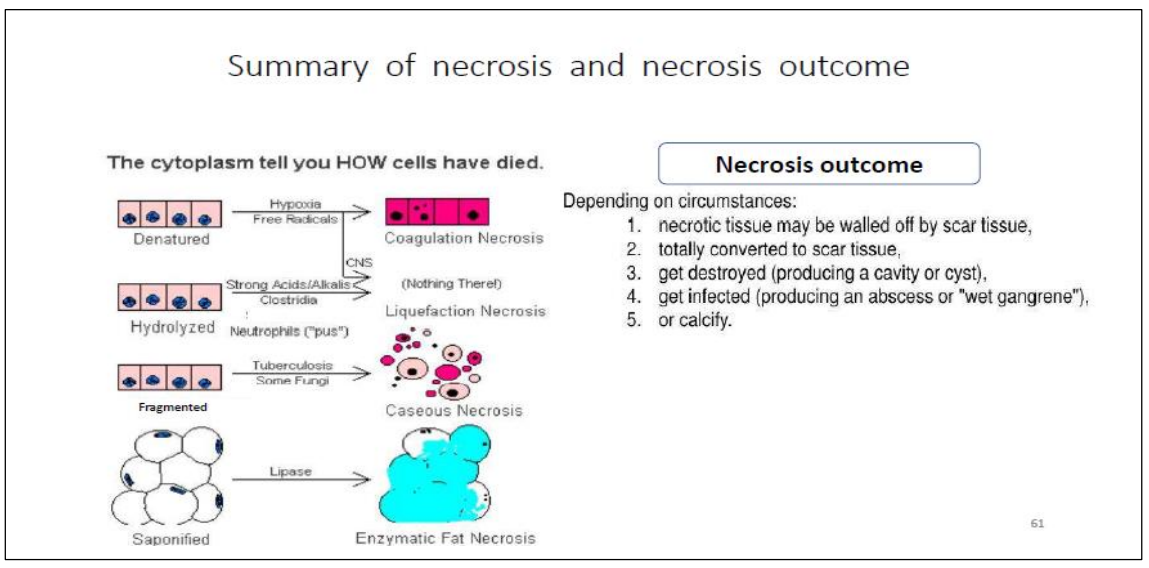
1-Necrotic tissues may be **walled off by scar tissue**.

2-Totally converted to **scar tissue.**

3-Get destroyed producing a **cavity or cyst**.

4-Get infected producing an **absses or gangarene.**

5-**Calcification.**

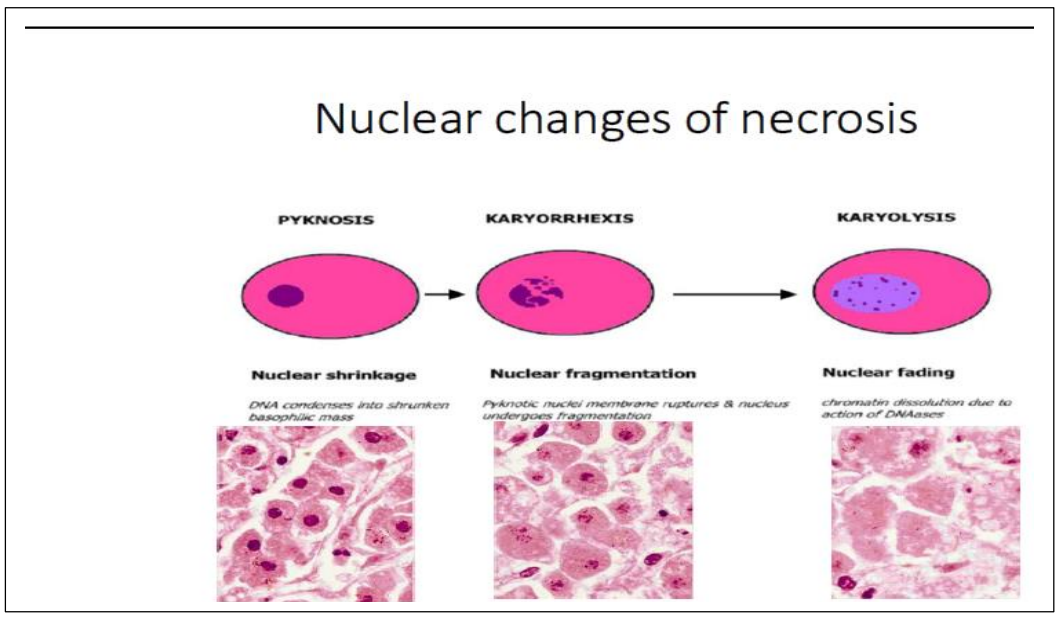


→Nuclear changes of Necrosis:

a)Pyknosis: Shrinkage of nucleus

b)Karyorrhexis: Fragmentation of nucleus

c)Karyolysis; Nuclear lysis.



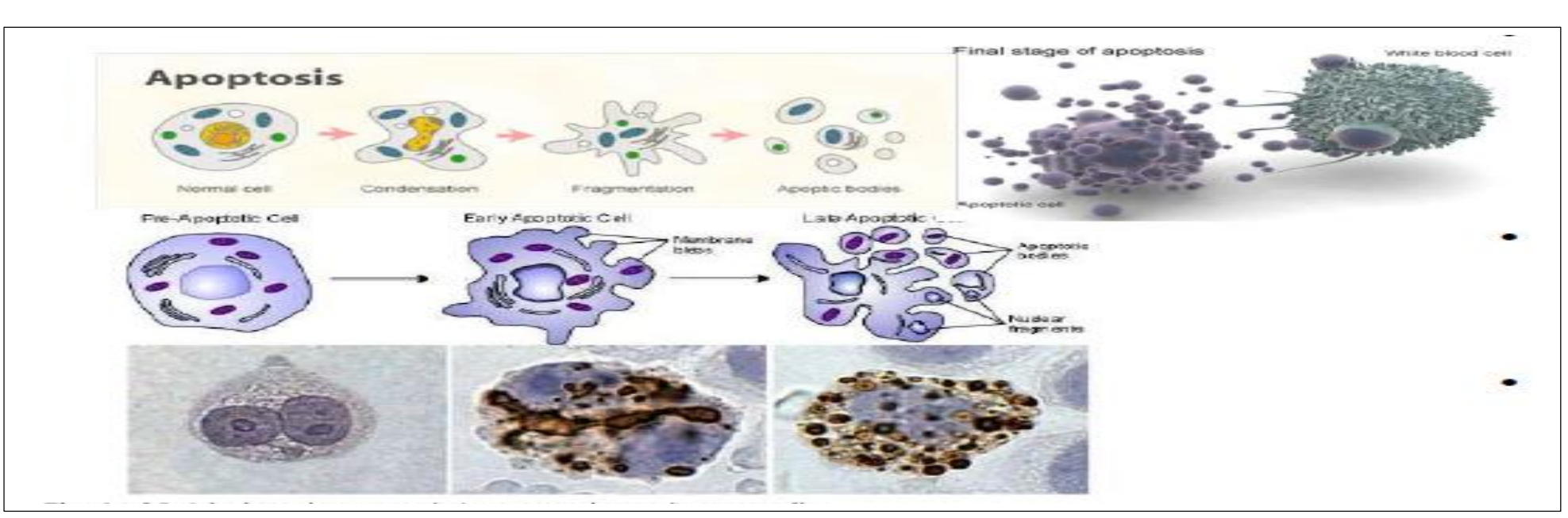
2-Apoptosis

-When a cell is deprived of growth factors or cell's DNA or proteins are **damaged beyond repair ,the cell kills itself by Apoptosis .**

-It is **energy dependent ,active ,strictly regulated type of cell death seen in specific situations.**

-Apoptosis serves many normal functions (i.e. Physiologic),&is not necessarily associated with pathological injury.

-Tightly regulated **suicide program** in which cells destined to die activate enzymes capable of degrading the cells, own nuclear DNA and nuclear and cytoplasmic proteins.
-The plasma membrane of the apoptotic cell **remains intact**.
- The cells and its fragments become **targets for phagocytes**.
-The dead cell is rapidly cleared before its contents have **leak out.**
-Therefore, cell death by this pathway doesn't elicit an **inflammatory reaction in the host.**



-May be physiologic or Pathologic:

A- Apoptosis in Physiologic Situations:

- Death by apoptosis is a normal phenomenon that serves to eliminate cells that are no longer needed and to **maintain a steady number of various cell populations** in tissues:-

-It's important in the following physiologic situations:

1- The programmed destruction of cells **during embryogenesis** e.g digits & cavity e.g. Frog's tail.
2-Shrinkage of **hormone - dependent** tissue upon **hormone deprivation**, such as endometrial cell breaks down during menstrual cycle and regression of the lactating breast after weaning.

3- Cell loss in **proliferating cell population**, so as to maintain a constant number.

4- Death of cells that have **served their useful purpose**, such as neutrophils in an acute inflammation and lymphocytes at the of an immune response.

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

- In order to prevent reactions against one's own tissues.

B- Apoptosis in pathologic conditions

- Apoptosis eliminates cell that are genetically altered or injured beyond repair without eliciting a severe host reaction, thus keeping the damage as contained as possible, death by apoptosis is responsible **for loss of cells in a variety of pathologic states**:-

1- DNA damage:

- By **Radiation, Cytotoxic anticancer drugs, extremes of temperature** and even **hypoxia** can damage DNA either directly or indirect by production of free radicals.
-If the repair mechanisms cannot cope with the injury, the cell triggers **intrinsic mechanisms that induce apoptosis.**
-In this situation, elimination of the cell may be a better alternative than risking mutations in the damaged DNA which may develop to **malignant transformation**.
-If the stimulus exaggerated, it'll progress to **necrotic cell death.**
-**Chemotherapeutic agents**, induce apoptosis of cancer cells which work by damaging DNA.

2-Accumulation of Misfolded Proteins:

-**Mutation in genes** encoding proteins leads to **improperly folded** protein or because of extrinsic factors, such as damage caused **by free radicals**.

- Excessive accumulation of these proteins the ER leads to a condition called **ER stress, which culminates in apoptotic death of cells.**

3-Cell injury in certain infections:

- Viral infections, in which loss of infected cells is largely due to apoptotic death that may be induced by the **virus "As in adenovirus and HIV"** or by the **host immune** response "as in **viral hepatitis".**

Mechanism of Apoptosis

-By activation of enzyme called **Caspase** (Cysteine Protease that cleave proteins after aspartic residues), leads to Cascade of activated Caspases which will **activate two enzymes:**

a)Nucleases : which will degrade the DNA .

b) Proteases : which will damage the Cytoskeleton.

-Activation of Caspase depends on balance between Pre & Anti-Apoptotic proteins.

-The activation (Caspases activation) includes Two main mechanism :

a)Intrinsic (Mitochondrial pathway):

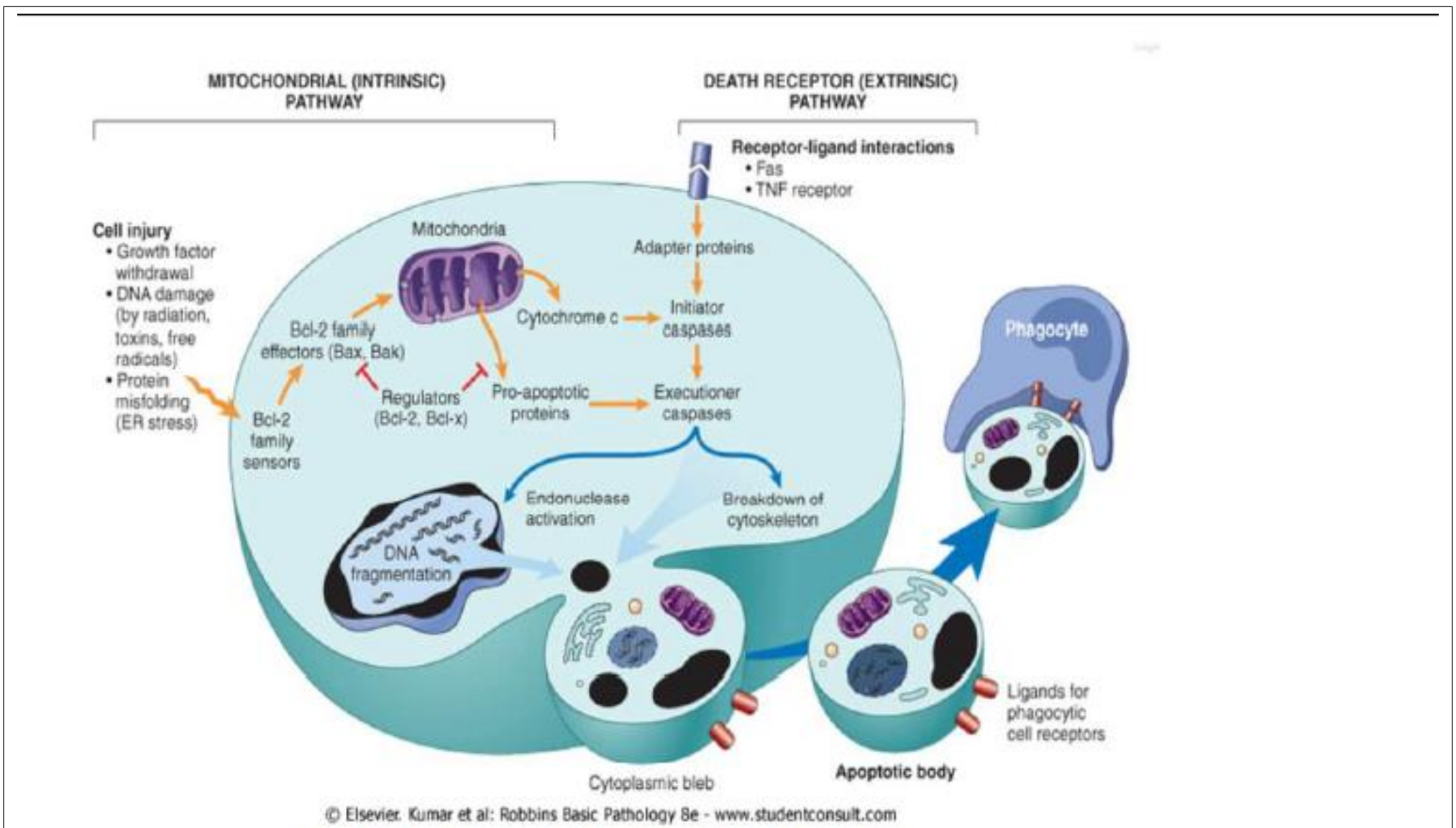
-It requires the blockage of anti-apoptic proteins (Bcl2 & BCK) & activation of pro-apoptic bodies (Bak & Bax) to expose cytoplasmic Caspase receptors,it may involve an enzyme called Cytochrome C which activates Caspase.

b)Extrinsic (Death receptor pathway) :

-Fas & TNF receptors on the T-lymphocytes from outside the cell which triggers Apoptosis.

→These pathways induced under different conditions & involve different molecules.

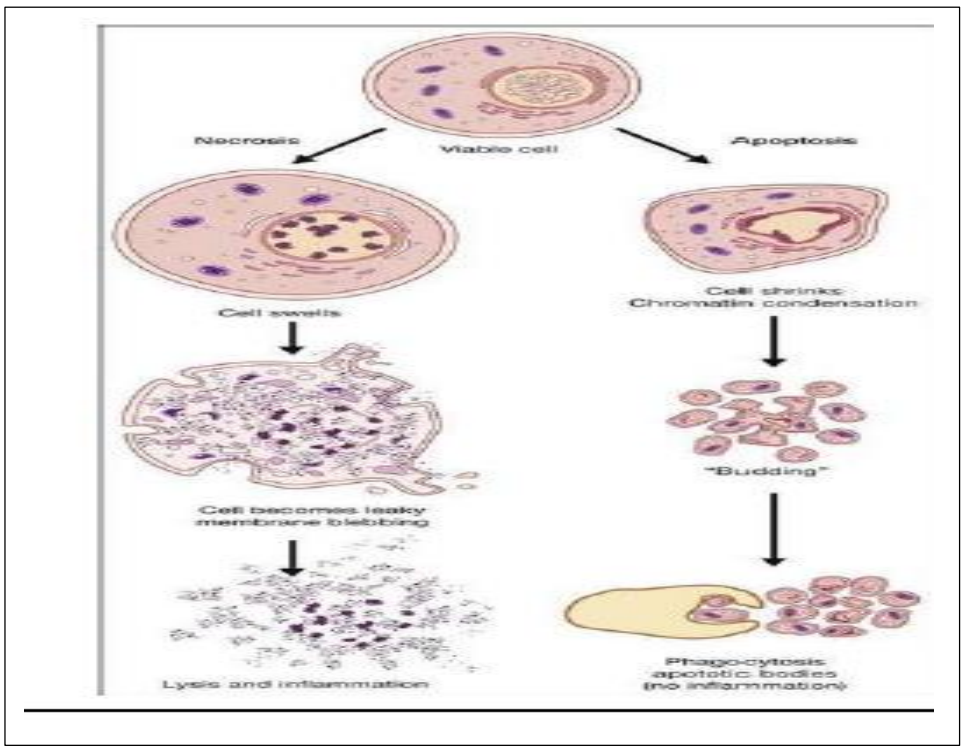
-Activation of Caspase initiate activation of **Nuclease enzyme that degrade DNA & other enzymes that degrade Cytoskeleton.**



What is Apoptosis The Apoptotic Pathways and the Caspase Cascade.mp4

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Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → Karyorrhexis → Karyolysis	Fragmentation into nucleosome-size fragment
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	pathologic (due to irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage.



Subcellular responses in cell injury

Autophagy & heterophagy

→Autophagy: (self-eating).

-Stressed cells **digest internal organelles** to provide source of energy under **starved conditions**, It involves **lysosomal digestion** of the cell's own components.

-It is a survival mechanism when there is nutrients deprivation .

→ Heterophagy:

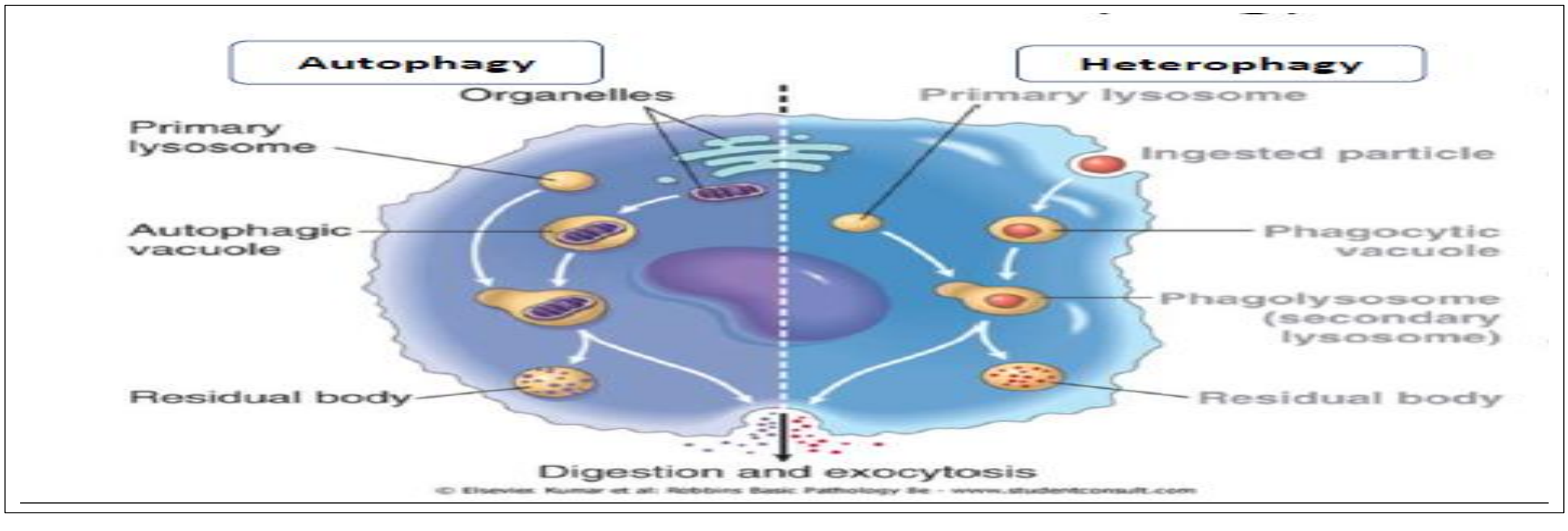
-A macrophage ingests extracellular substances by the process of phagocytosis.

-The enzymes in **Lysosomes** can break down most proteins and carbohydrates, but some **lipids may remain undigested**.

-**Lysosomes** with **undigested debris** may persist within *cells* as ***residual bodies*** or may be **extruded**.

a)***Lipofuscin pigment*** granules represent indigestible material resulting from lipid peroxidation.

b) **Carbon particles inhaled** from the atmosphere or inoculated pigment in tattoos, can persist in phagolysosomes for decades.



Pathological science:
Pharmacy department; third stage, second lecture.
Types of necrosis in **Pathophysiology. Cell necrosis: Irreversible injury to cells as a result of noxious stimuli invariably leads to cell death. Such noxious stimuli include:**
infectious agents (bacteria, viruses, fungi, parasites).
oxygen deprivation or hypoxia.
extreme environmental conditions such as heat, radiation, or exposure to ultraviolet irradiation.
(Necrosis as a form of cell death is almost always associated with a pathological process).
cells die by necrosis; they exhibit two major types of microscopes or macro -scopic appearance.

pyknosis in a bile infarction. **cytoplasmic hyper eosinophilia seen in left side.** pseudopalisading glioblastoma

The nucleus changes in necrosis and characteristics of this change are determined by the manner in which its DNA breaks down:
Karyolysis: the chromatin of the nucleus fades due to the loss of the DNA by degradation.
Karyorrhexis: the shrunken nucleus fragments to complete dispersal.
Pyknosis: the nucleus shrinks, and the chromatin condenses.

Liquefactive Necrosis.

coagulative Necrosis
Caseous Necrosis.
Fibrinoid necrosis.
Fat Necrosis.
The liquefactive necrosis, **also known as colliquative necrosis, is characterized by partial or complete dissolution of dead tissue and transformation into a liquid, viscous mass. The loss of tissue and cellular profile occurs within hours in liquefactive necrosis. in part to the activities of hydrolytic enzymes which causes dissolution of cellular organelles in a cell undergoing necrosis. The enzymes responsible for liquefaction are derived from either bacterial hydrolytic enzymes or lysosomal hydrolytic enzymes. Also, the pattern is seen following ischemic injury in the brain. While the reason for liquefactive necrosis following ischemic injury in the brain.**
Gross Appearance: The tissue is in a liquid form and sometimes creamy yellow because of pus formation.
Microscopic: Inflammatory cells with numerous neutrophils.

coagulative necrosis, the other major pattern, is characterized by the maintenance of normal architecture of necrotic tissue for several days after cell death.
Gross Appearance: tissue is firm and architecture is maintained for days after cell death.
Microscopic: Preserved cell outlines without nuclei.

Caseous:
A unique type of cell death seen with tuberculosis.

Gross Appearance: White, soft, cheesy-looking (caseating) material
Microscopic: A uniformly eosinophilic center (necrosis) surrounded by a collar of lymphocytes and activated macrophages (giant cells, epithelioid cells). The entire structure formed in response to tuberculosis is known as a granuloma.

Caseous material like cheesy.

Fat Necrosis:
Fat necrosis occurs from acute inflammation affecting tissues with numerous adipocytes such as pancreas and breast tissue. Damaged cells release digestive enzymes which break down lipids to generate free fatty acids.
Gross Appearance: Whitish deposits as a result of the formation of calcium soaps.
Microscopic: A nucleated adipocytes with deposits of calcium (Seen on H&E as areas of bluish stains).

Fat necrosis in intestine white patches. Fat necrosis in pancreas.

Fibrinoid Necrosis:
This is a pattern associated with vascular damage (autoimmunity, immune-complex deposition, infections (**viruses**, **spirochetes (motile helical Gram negative eubacteria)**,(several important diseases, Lyme disease " annular rash, arthritis, carditis and may cause at end stage encephalopathy, leptospirosis, swine dysentery, periodontal disease and some form relapsing fever. Treatment by doxycycline and ceftriaxone. **rickettsia "obligate intracellular bacteria" gram negative found in tick** . lice transmitted by blood. cause self-limiting fever. Q fever, typhus, spotting fever, treatment doxycycline.
Gross Appearance: Usually not grossly discernible.
Microscopic: Deposition of fibrin within blood vessels.
Fibrinoid necrosis is usually visible only microscopically.
Deposition of fibrin like material in hypertension, peptic ulcer and atherosclerosis.
(Buildup of fats, cholesterol and other substances in and on the artery walls).

Gangrenous Necrosis:
Ischemic necrosis of the lower limbs. (Sometimes upper limbs or digits).
Gross Appearance: Black skin with varying degree of putrefaction.
Microscopic: Combination of coagulative necrosis, due to ischemia (dry gangrene); and liquefactive necrosis (wet gangrene) if a bacterial infection is superimposed.

Inflammation: natural response of the body's immune system to injury, infection, or stress.
Causes: infection, or stress.
Results: complex process that involves the release of chemicals from immune cells, blood vessels, and other tissues that help to fight off harmful substances and repair damaged tissues. So, when tissues are damaged or infected, immune cells release chemical signals such as cytokines, chemokines, and prostaglandins that trigger inflammation. These chemicals cause blood vessels to dilate and become leaky, allowing immune cells and other substances to enter the affected tissues.
Immune cells that contribute to inflammation include:

Neutrophils: common type of white blood cells and are often the first cells to arrive at the site of injury or infection. They are responsible for engulfing and destroying invading pathogens.

Neutrophils are often seen in areas of acute inflammation.
Macrophages: white blood cell's role in the immune system's response to infection and inflammation. They are involved in phagocytosis, the process of engulfing and destroying invading pathogens. Macrophages inside tissue are called histiocytes.
Mast cells: mast cells release a range of potent mediators, including histamine, proteases, cytokines, and chemokines, into the surrounding tissues.
While inflammation is typically a protective response, long-standing or chronic inflammation can be harmful and has been linked to a variety of diseases, including arthritis, diabetes, heart disease, and cancer.