Pathophysiology

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Lecture 3

Irreversible Cell Injury

Reversible cell injury. In early stages or mild forms of injury the functional and morphologic changes are reversible, if the damaging stimulus is removed. At this stage, although there may be significant structural and functional abnormalities, the injury has typically not progressed to severe membrane damage and nuclear dissolution.

Cell death. With continuing damage, the injury becomes irreversible, at which time the cell cannot recover and it dies. There are two types of cell death—**necrosis** and **apoptosis**—which differ in their morphology, mechanisms, and roles in disease and physiology

Necrosis: The term necrosis was first used by morphologists to refer *to a series of changes that accompany cell death, largely resulting from the degradative action of enzymes on lethally injured cells.* Necrotic cells are unable to maintain membrane integrity, and their contents often leak out. The enzymes responsible for digestion of the cell are derived either from the lysosomes of the dying cells themselves or from the lysosomes of leukocytes that are recruited as part of the inflammatory reaction to the dead cells.

General microscopical findings of Necrosis:

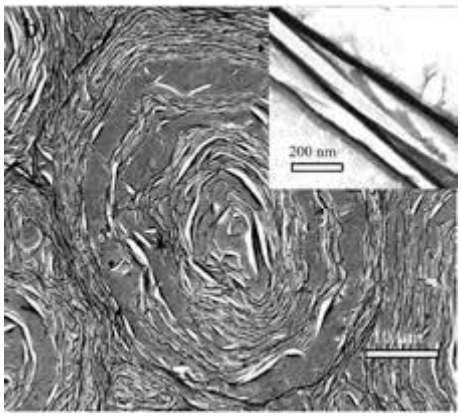
1- Increased eosinophilia.

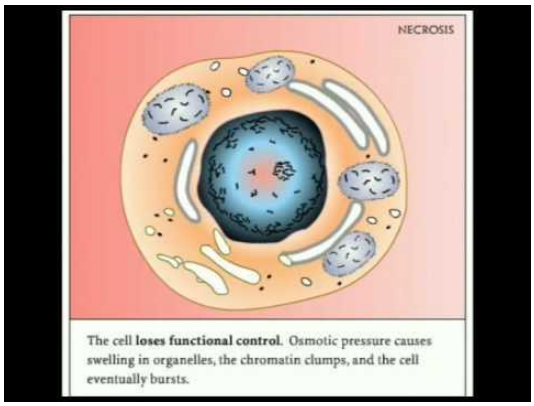
2- Nuclear shrinkage, fragmentation, and dissolution.

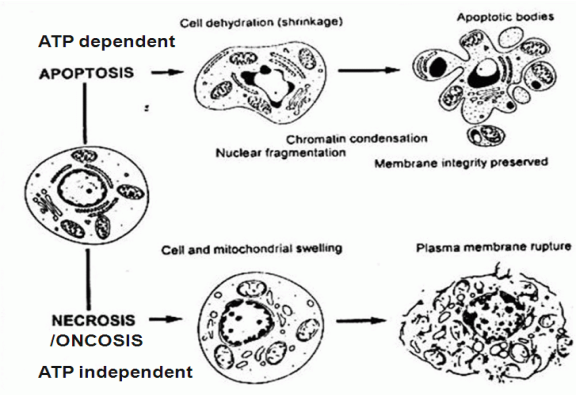
3- Breakdown of plasma membrane and organelles membranes.

4- Myelin figures; leakage and enzymatic digestion of cellular contents.

Myelin figures : *A rolled-up or scroll-like arrangement of a lipid bilayer within a cell, superficially resembling the myelin sheath of nerves; myelin figures are observed with the electron microscope in the cytoplasm or as inclusion in mitochondria and autophagic vacuoles where they may represent artifacts of lipid fixation.*







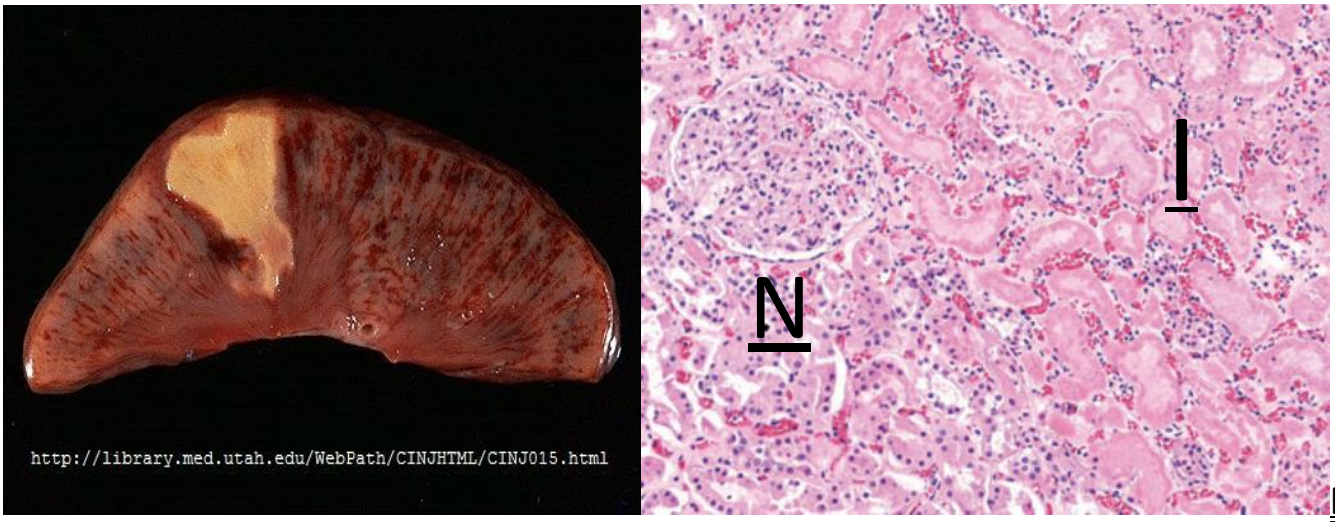
Necrosis

Happens in a collection of cells in a tissue or an organ, e.g. in *the ischemic myocardium*, results in death of the entire tissue and sometimes an entire organ.

Morphologic distinct patterns of tissue necrosis:

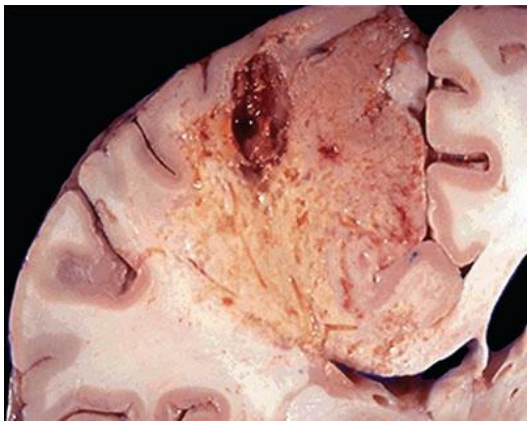
1- Coagulative necrosis: *Is a form of tissue necrosis in which the component cells are dead but the basic tissue architecture is preserved for at least several days.*
The affected tissues take on a **firm texture**.
Pathophysiologically : The injury denatures not only effects structural proteins but also the enzymes and so blocks the proteolysis of the dead cells; as a result, eosinophilic, anucleate cells may persist for days or weeks.

The necrotic cells are removed by phagocytosis of the cellular debris by infiltrating leukocytes and by digestion of the dead cells by the action of lysosomal enzymes of the leukocytes. Coagulative necrosis is characteristic of infarcts (areas of ischemic necrosis) in all solid organs **except** the brain.



Coagulative necrosis. A, A wedge-shaped kidney infarct (yellow) with preservation of the outlines. B, Microscopic view of the edge of the infarct, with normal kidney (N) and necrotic cells in the infarct (I). The necrotic cells show preserved outlines with loss of nuclei, and an inflammatory infiltrate is present (difficult to discern at this magnification).

2- Liquefactive necrosis: Is seen in focal bacterial or, occasionally, fungal infections, not ischemia because microbes stimulate the accumulation of inflammatory cells and the enzymes of leukocytes digest ("liquefy") the tissue. For obscure reasons, hypoxic death of cells within the central nervous system often evokes liquefactive necrosis.



Pathophysiologically

Whatever the pathogenesis:

A- The vascular supply to the tissue is still preserved.

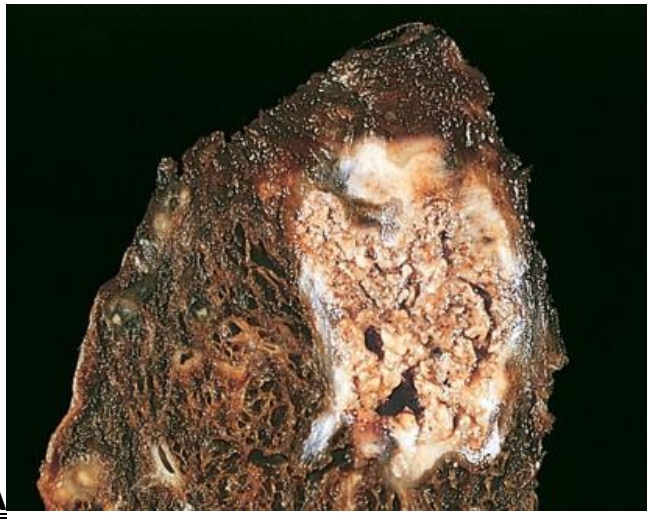
B- Liquefaction completely digests the dead cells.

C- A transformation of the tissue into a liquid viscous mass.

D- If the process was initiated by **acute inflammation**, the material is frequently creamy yellow and is called **pus**.
E- For some chronic inflammations **Caseous necrosis** is encountered most often in foci of tuberculosis infection. 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
- An amorphous granular appearance.
- The tissue architecture is completely obliterated.
- Cellular outlines cannot be discerned.
- Caseous necrosis is often enclosed within a distinctive inflammatory border; this appearance is characteristic of a focus of inflammation known as a **granuloma.**



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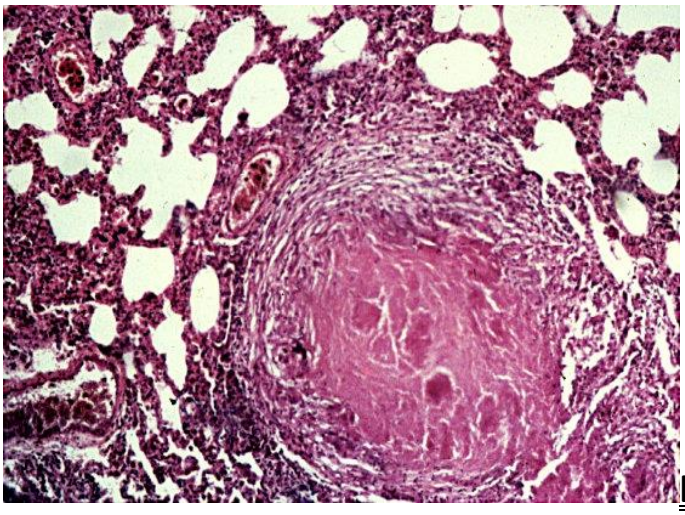

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A: Caseous necrosis. A tuberculous lung with a large area of caseous necrosis containing yellow-white and cheesy debris. B: On microscopic examination with H&E staining, it is characterized by acellular pink areas of necrosis surrounded by a granulomatous inflammatory process.

3- Fat necrosis, *Is a focal areas of fat destruction, typically resulting from release of activated pancreatic lipases into the substance of the pancreas and the peritoneal cavity. This occurs in the calamitous abdominal emergency known as acute pancreatitis.*

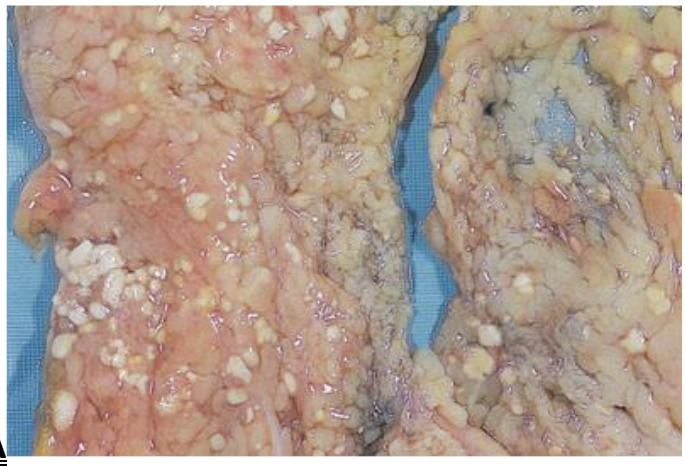
Pathophysiology

In this disorder:

A. Pancreatic enzymes that have leaked out of acinar cells and ducts.
B. Liquefying the membranes of fat cells in the peritoneum.
C. The lipases split the triglyceride esters contained within fat cells.
D. The released fatty acids combine with calcium
E. The result is a grossly visible chalky white area (**fat saponification**), which enable the surgeon and the pathologist to identify the lesions.

On microscopic examination:

- The foci of necrosis contain shadowy outlines of necrotic fat cells.
- With basophilic calcium deposits.
- Surrounded by an inflammatory reaction.



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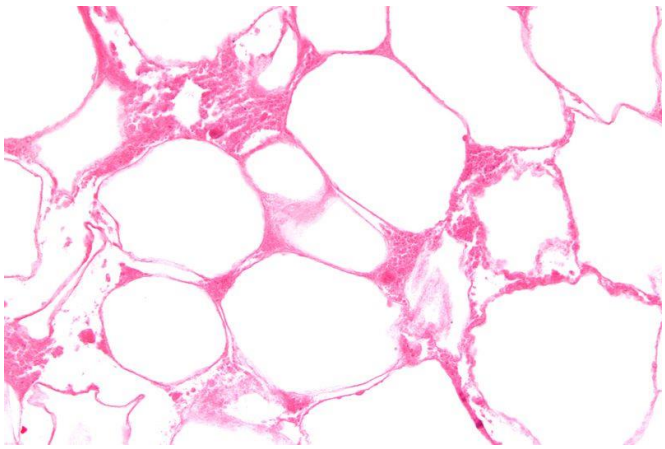


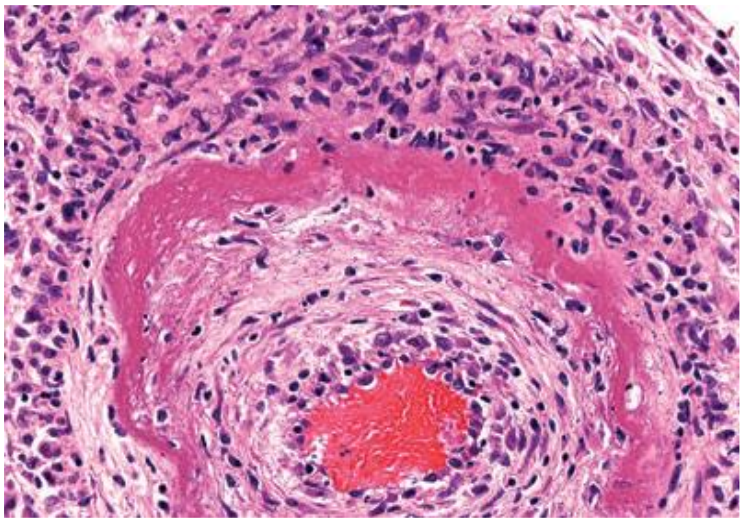
B

A. Fat necrosis in acute pancreatitis. The areas of white chalky deposits represent foci of fat necrosis with calcium soap formation (saponification) at sites of lipid breakdown in the mesentery. B. The cytoplasm has been pushed to the periphery with a crescent ghostly nucleus and the hall space is filled with fatty acid.

4- Fibrinoid necrosis *is a special form of necrosis usually seen in immune reactions involving blood vessels.*

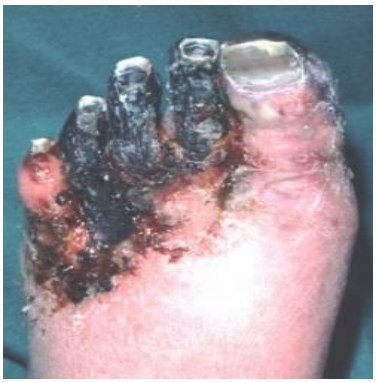
Pathophysiology

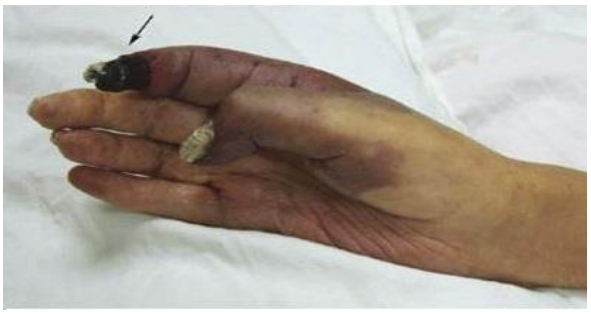
A. This pattern of necrosis is prominent when complexes of antigens and antibodies are deposited in the walls of arteries.
B. Deposits of these "immune complexes," together with fibrin that has leaked out of vessels.
C. A bright pink and amorphous appearance in H&E stains, called "fibrinoid" (fibrin-like).
D. Immunologically mediated diseases (e.g., polyarteritis nodosa) in which this type of necrosis is seen.



Fibrinoid necrosis in an artery in a patient with polyarteritis nodosa. The wall of the artery shows a circumferential bright pink area of necrosis with protein deposition and inflammation (dark nuclei of neutrophils).

Although **Gangrenous necrosis** is not a distinctive pattern of cell death, the term is still commonly used in clinical practice. It is usually applied to a limb, generally the lower leg, that has lost its blood supply and has undergone coagulative necrosis involving multiple tissue layers (so called ***dry gangrene***). When bacterial infection is superimposed, coagulative necrosis is modified by the liquefactive action of the bacteria and the attracted leukocytes (so called ***wet gangrene***).





Apoptosis

Is a pathway of cell death that is induced by a 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.

Fragments of the apoptotic cells then break off, giving the appearance that is responsible for the name (apoptosis, "falling off").

Characteristics

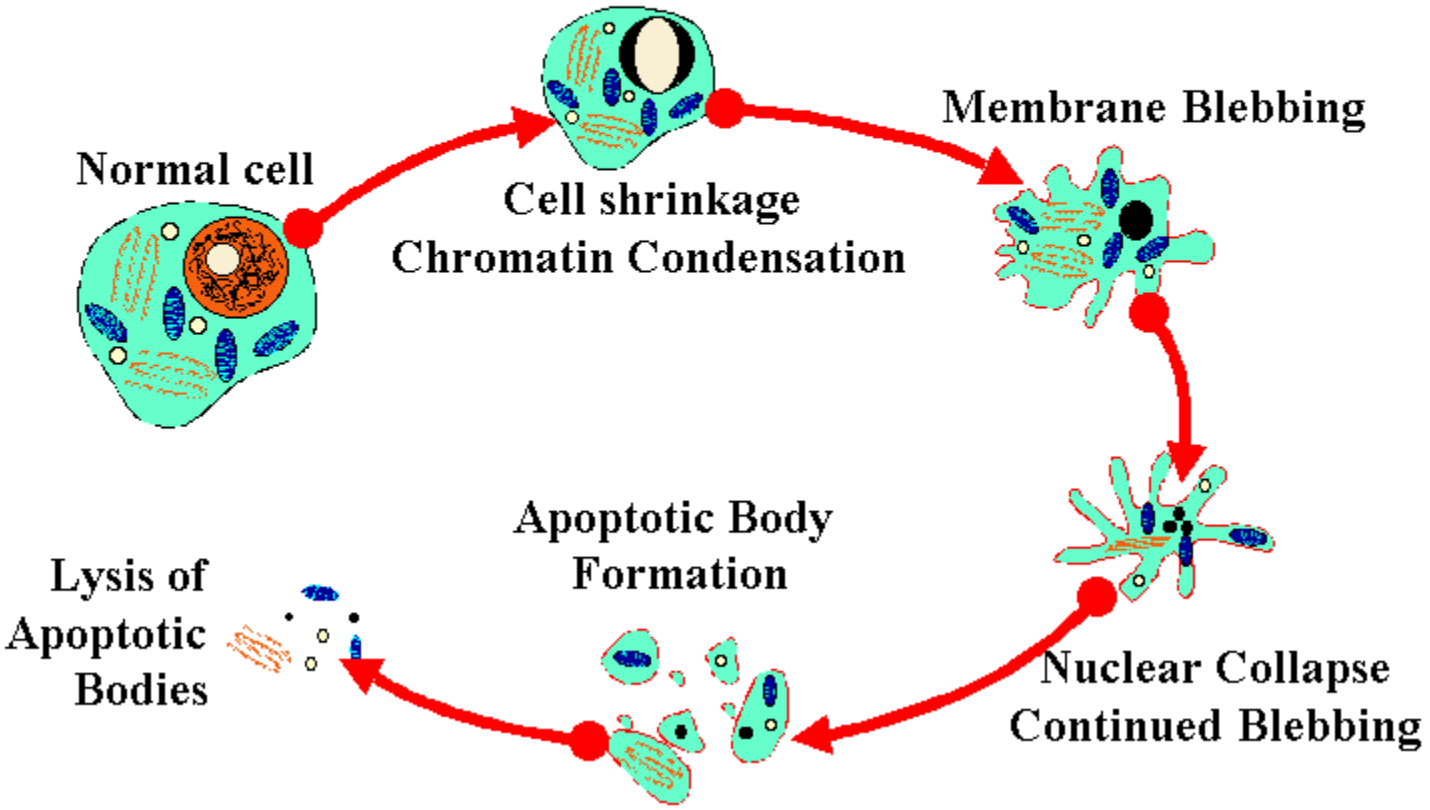
- The plasma membrane of the apoptotic cell remains intact.
- The membrane is altered surrounding the remaining of the cell fragments.
- The cell and its fragments become avid targets for phagocytes.
- The dead cell is rapidly cleared before its contents have leaked out.
- Cell death by this pathway does not elicit an inflammatory reaction.

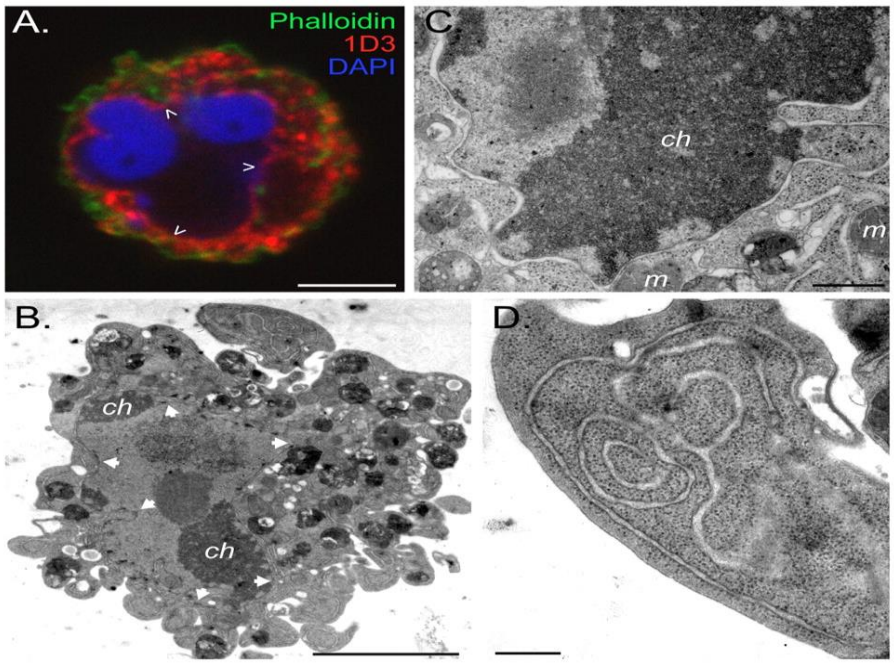
Apoptosis differs from necrosis, which is characterized by loss of membrane integrity, enzymatic digestion of cells, leakage of cellular contents, and frequently a host reaction.

Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-size fragments
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	Invariably pathologic (culmination of irreversible.	Often physiologic, means of eliminating unwanted cell injury) cells; may be pathologic after some forms of cell injury, especially DNA damage.

Apoptosis
(Programmed Cell Death)





Pathophysiology

Initiation of Apoptosis:

1- **Mitochondrial (intrinsic) pathway** is triggered by:

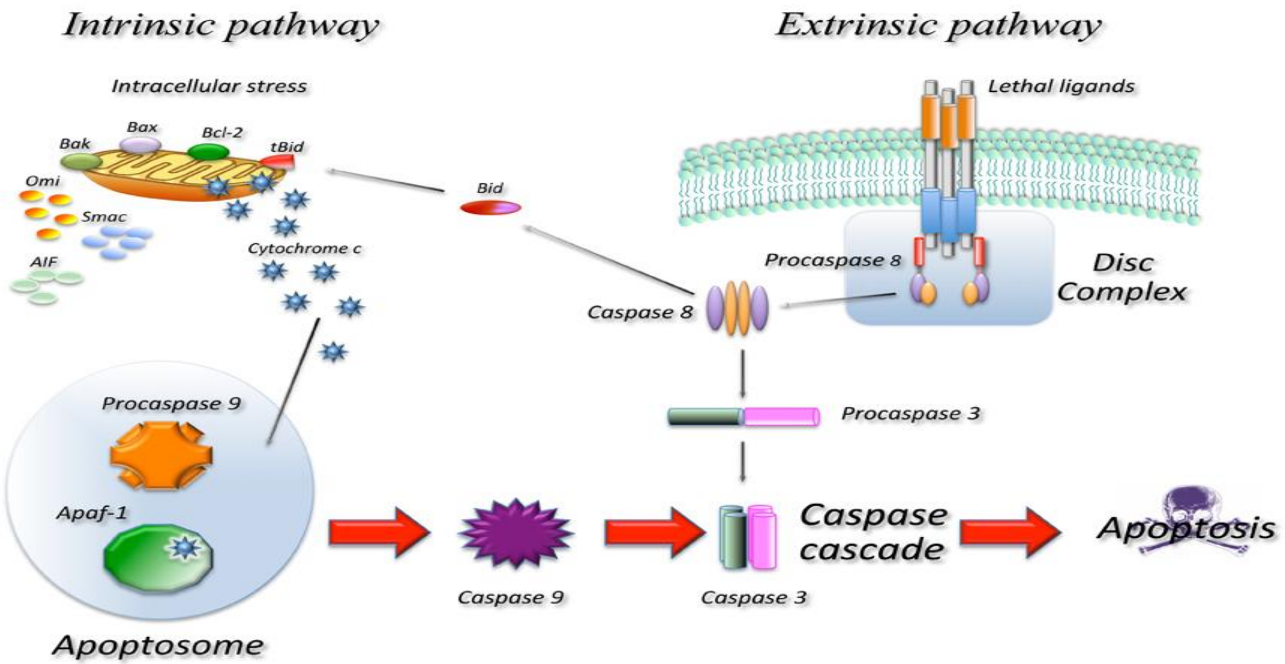
A. Loss of survival signals.
B. DNA damage beyond repair.
C. Accumulation of misfolded proteins (ER stress). E.g Aging, cystic fibrosis and Neurodegenerative Diseases.

All these will lead to:

i. Leakage of pro-apoptotic proteins from mitochondrial membrane.
ii. Into the cytoplasm.
iii. Trigger Caspase activation *which is normally inhibited by anti-apoptotic members of the Bcl family, which are induced by survival signals including growth factors.*

2**- Death receptor (extrinsic) pathway** *is responsible for elimination of self-reactive lymphocytes and damage by cytotoxic T lymphocytes*.

It is initiated by engagement of death receptors(members of the Tumor necrotizing factor (TNF) receptor family by ligands on adjacent cells.

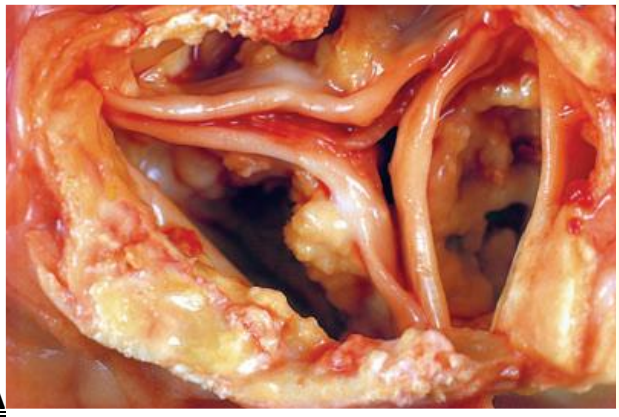


PATHOLOGIC CALCIFICATION

The abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium, and other minerals in the tissue.

Types of pathological calcification:

1- **Dystrophic calcification** is encountered in areas of necrosis of any type. It mostly **indicates insignificant past cell injury**, it may also be a cause of organ dysfunction. For example, calcification can develop in aging or damaged heart valves, resulting in severely compromised valve motion. Dystrophic calcification of the aortic valves is an important cause of aortic stenosis in the elderly.



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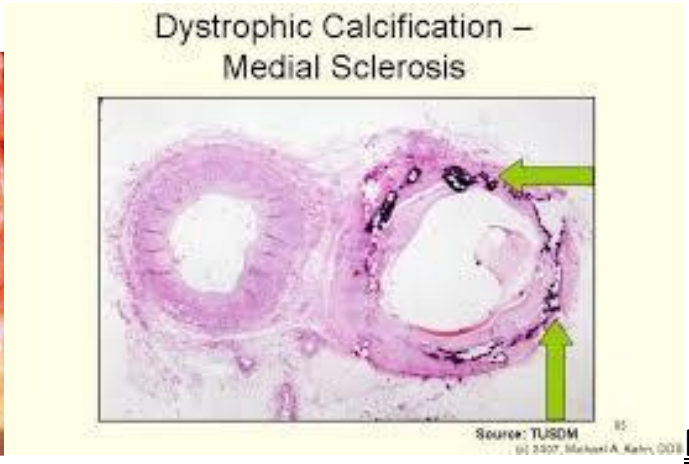


B

A. Calcification of the aortic valve. A view looking down onto the unopened aortic valve in a heart with calcific aortic stenosis. The semilunar cusps are thickened and fibrotic. Behind each cusp are large, irregular masses of dystrophic calcification that will prevent normal opening of the cusps. B. calcification appears as intracellular and/or extracellular basophilic deposits. In H.& E.

2- **Metastatic calcification** *can occur in normal tissues whenever there is hypercalcemia.*

The four major causes of hypercalcemia are:-

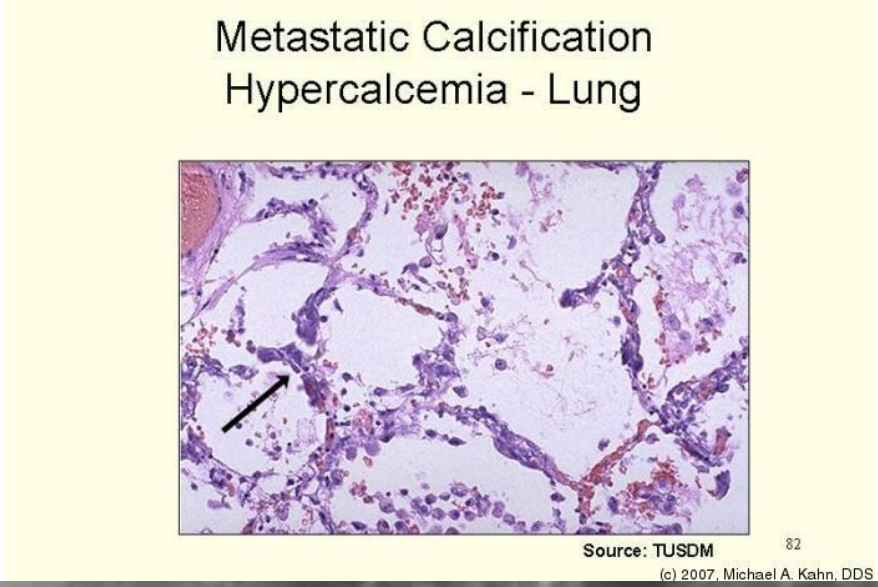
(1) Increased secretion of parathyroid hormone, due to either primary parathyroid tumors or production of parathyroid hormone-related protein by other malignant tumors.

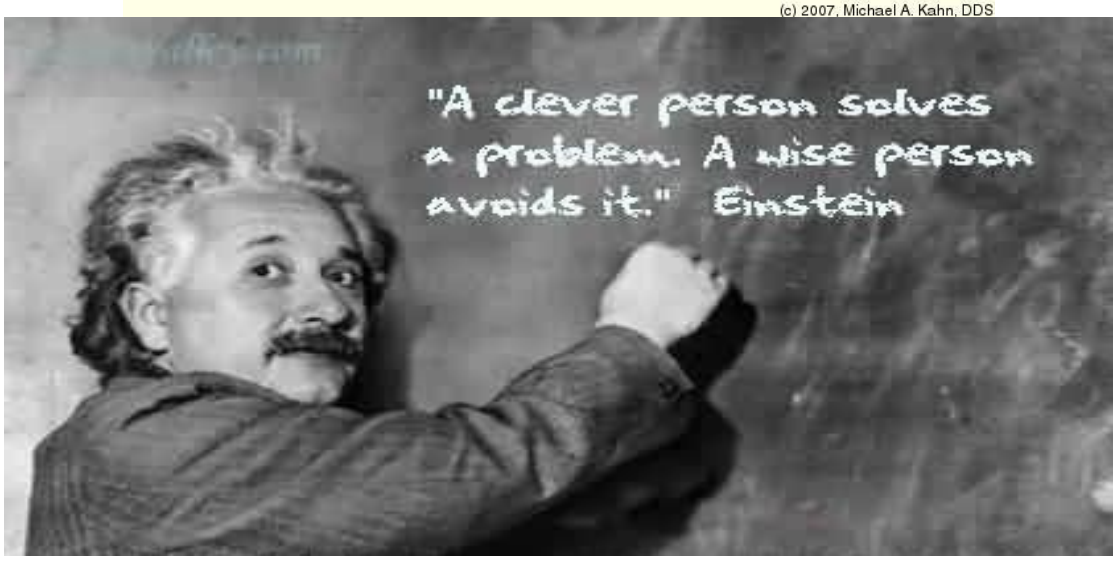
(2) Destruction of bone due to the effects of accelerated turnover (e.g., Paget disease), immobilization, or tumors(increased bone catabolism associated with multiple myeloma, leukemia, or diffuse skeletal metastases).

(3) Vitamin D–related disorders including vitamin D intoxication and sarcoidosis (in which macrophages activate a vitamin D precursor).

(4) Renal failure, in which phosphate retention leads to secondary hyperparathyroidism.

Metastatic calcification can occur widely throughout the body but principally affects the interstitial tissues of the vasculature, kidneys, lungs, and gastric mucosa. The calcium deposits morphologically resemble those described in dystrophic calcification. Although they do not generally cause clinical dysfunction, extensive calcifications in the lungs may produce remarkable radiographs and respiratory deficits, and massive deposits in the kidney (nephrocalcinosis) can cause renal damage.





Thank you