Intracellular accumulations

some times , cells may accumulate abnormal amounts of various substances, which may be harmless or may cause injury .

The substance may be located in the cytoplasm, within organelles (typically lysosomes),or in the nucleus, and it may be synthesized by the affected cells or it may be produced elsewhere.

The main mechanisms of abnormal intracellular accumulations are:-

(1) Abnormal metabolism, A normal substance is produced at a normal but the metabolism is inadequate to remove it as in fatty change in the liver.

(2) Mutations causing alterations in protein so that its accumulate intracellularly because of genetic (mutation) .

(3) A deficiency of critical enzymes responsible for breaking down certain compounds lead to accumulate it in lysosomes .

(4) An inability to degrade phagocytosed particles, as in carbon pigment accumulation in the lung .

Fatty change (steatosis)

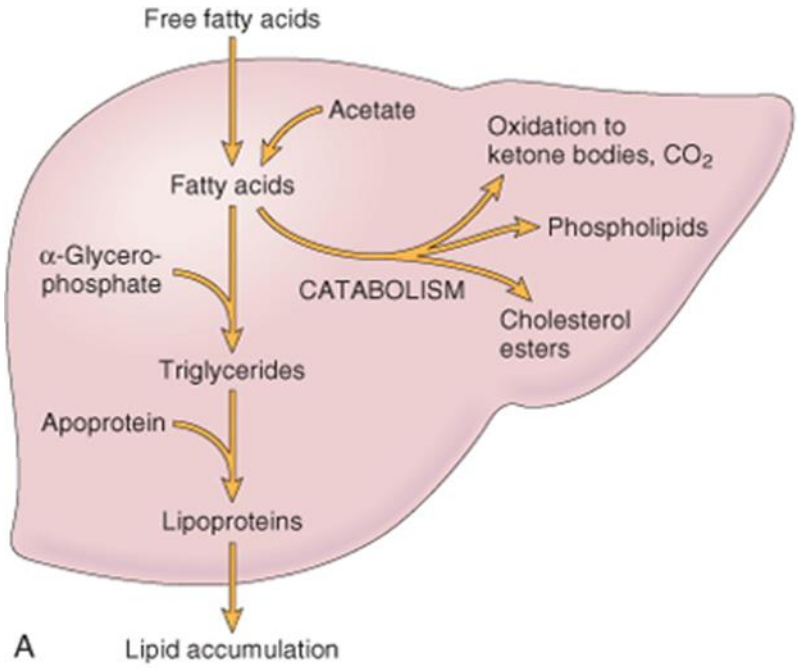
Alcohol abuse and diabetes associated with obesity are the most common cause of fatty change in the liver in industrialized nations

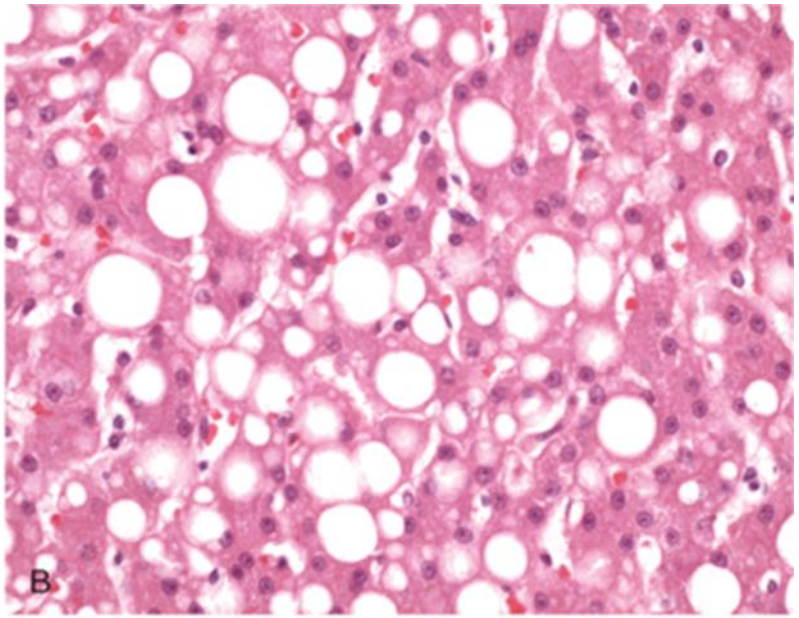
Free fatty acids from adipose tissue or ingested food are normally transported into hepatocytes, where they are esterified to triglycerides converted into cholesterol or phospholipids or oxidized to ketone bodies. Triglycerides from the hepatocytes required the formation of complexes with apoprotiens to form lipoproteins which are able to enter the circulation.

Excess accumulation of triglycerides may result from defect at any step from fatty acid entry to lipoprotein exit.

- ✓ Hepatotoxins e.g.(alcohol) alter mitochondrial and SER function and thus inhibit fatty acid oxidation;
- ✓ protein malnutrition decreases the synthesis of apoprotiens
- ✓ anoxia inhibits fatty acid oxidation
- ✓ starvation increase fatty acid mobilization from peripheral stores.

The significance of fatty change depends on the cause and severity of the accumulation. When mild it may have no effect. severe fatty change may impair cellular function, but the change is reversible. In the more severe form, fatty change may cause cell death.





- Cholesterol and Cholesteryl Esters

Cellular cholesterol metabolism is tightly regulated to synthesis of normal cell membrane without significant intracellular accumulation. phagocytic cells (macrophages) may become overloaded with lipid (cholesterol, and cholesteryl esters) in several different pathologic processes ,mostly characterized by increased intake or decreased catabolism of lipids.

Atherosclerosis is the most important example for this change.

- Proteins protein accumulations are less common than lipid accumulations; they may occur when excesses are presented to the cells or if the cells synthesize excessive amounts .

-In the kidney ,trace amounts of protein(albumin) filtered through the glomerulus are normally reabsorbed in the proximal convoluted tubules.

In kidney disease like **nephrotic syndrome**, there is heavy protein leakage across the glomerular filter so there is much more protein is reabsorbed resulting in the histologic appearance of pink, hyaline droplets in the cytoplasm .

- Another example is the marked accumulation of newly synthesized

Proteins (immunoglobulins) that may occur in plasma cells, forming rounded, eosinophilic **Russell bodies**.

- Glycogen

Excessive intracellular deposits of glycogen are associated with abnormalities in the metabolism of either glucose or glycogen.

Diabetes mellitus, is the prime example of abnormal glucose metabolism. glycogen accumulates in renal tubular epithelium ,cardiac myocytes , and β cells of the islets of Langerhans.

Glycogen also accumulates within cells in a group of genetic related disorders collectively referred to as **glycogen storage diseases , or glycogenoses** .

- Pigments

are colored substances that are either

-**Exogenous**,coming from outside the body. The most common exogenous pigment is carbon (coal dust) , a ubiquitous air pollutant . When inhaled, it is phagocytosed by alveolar macrophages and transported through lymphatic channels to the regional **tracheobronchial lymph nodes**. Aggregates of the pigment blacken the draining lymph nodes and pulmonary parenchyma called **Anthracosis .**

The most common exogenous pigment is

1- inhaled pigments :-

A- Pneumoconiosis:- asbestos fibers and silica dusts.

B- Anthracosis deposition of coal dust .

2- injected pigments (tattooing):-

Indian ink and carbon deposit in dermis.

- Endogenous, synthesized within the body itself .

Endogenous pigments include :-

1-Lipofuscin, or "wear-and-tear pigment," is an insoluble brownish-yellow granular intracellular material that accumulates in a variety of tissues (particularly the heart, liver, and brain) as a result of aging or atrophy .

Lipofuscin represents complexes of the lipid and protein that derived from lipids peroxidation of subcellular membranes . It is not injurious to the cell but is a marker of past free radical injury .

The brown pigment, when present in large amounts, imparts an appearance to the tissue that is called **brown atrophy**

2-Melanin is, brown-black pigment that is synthesized by melanocytes located in the epidermis and acts as a screen against harmful ultraviolet radiation.

Although melanocytes are the only source of melanin, adjacent basal keratinocytes in the skin can accumulate the pigment (e.g., in freckles).

3- Hemosiderin is a hemoglobin-derived granular pigment that is golden yellow to brown and accumulates in tissues when there is a local or systemic excess of iron . Although hemosiderin accumulation is usually pathologic , small amounts of this pigment are normal in the macrophage of the bone marrow, spleen, and liver, where aging red cells are normally degraded .

Excessive deposition of hemosiderin called **hemosiderosis** , and more extensive accumulations of iron seen in **hereditary hemochromatosis**

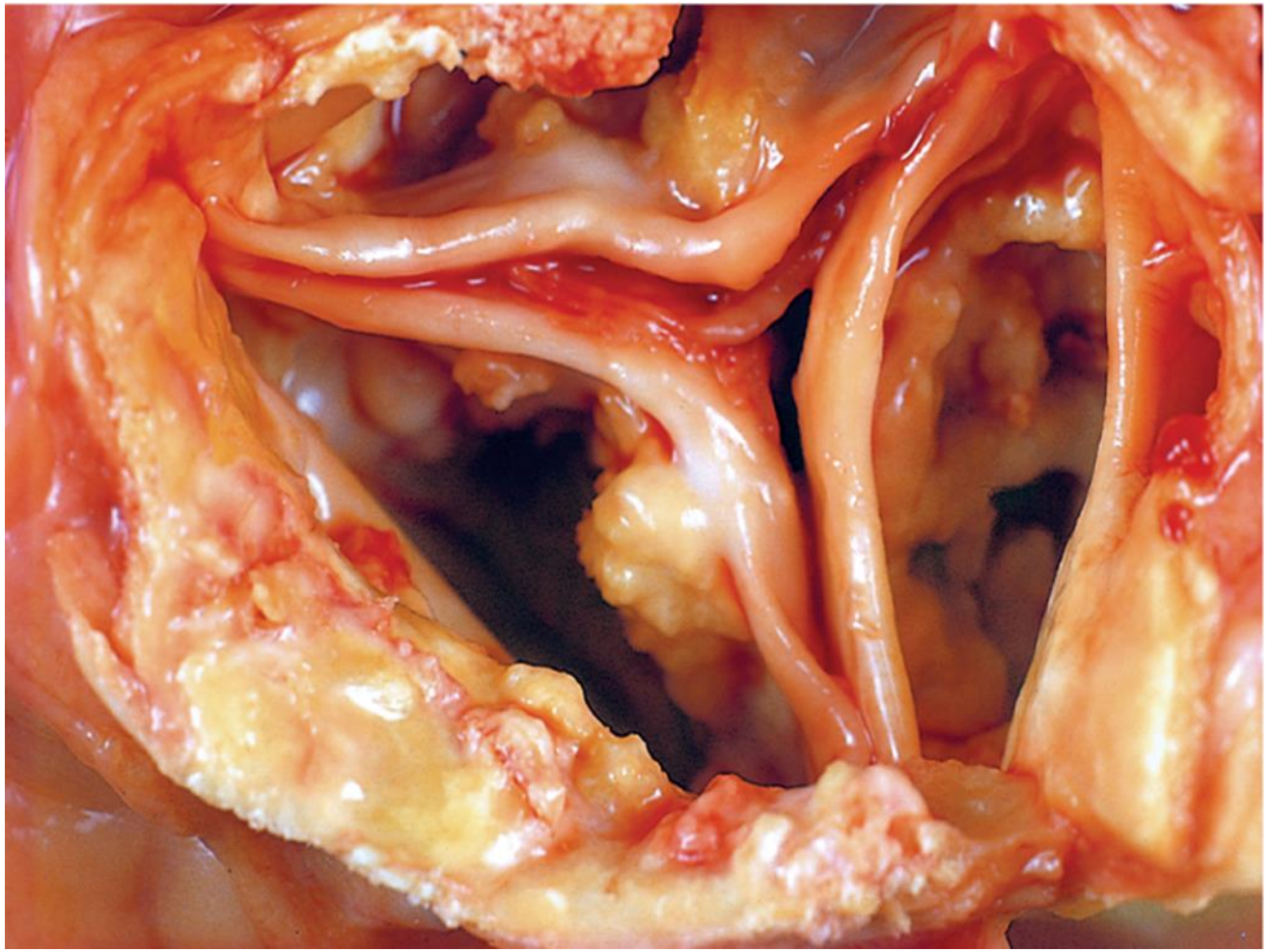
Pathologic Calcification

A common process in a wide variety of disease states . It is abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium, and other minerals in all tissues other than bones and teeth .

There are two distinct types of Pathological calcification:-

1- Dystrophic calcification

In this form , calcium metabolism is normal but it deposits in injured or dead tissue , such as areas of necrosis of any type . It is virtually ubiquitous in the arterial lesions of advanced atherosclerosis . Although dystrophic calcification may be an incidental finding indicating 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 persons .



Calcification of the aortic valve. 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

Pathogenesis of dystrophic calcification

The pathogenesis of dystrophic calcification involves **initiation** and **propagation**, both of which may be either intracellular or extracellular . The end product is the formation of **crystalline calcium phosphate** which formed by reaction of phosphate ions with calcium ions.

2- Metastatic calcification

In this form there is defect in calcium metabolism (hypercalcemia) and can occur in normal tissues.

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).

(3) Vitamin D-related disorders including vitamin D intoxication and sarcoidosis .

(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 vessels, kidneys, lungs and gastric mucosa .

Irreversible cell injury

1- Necrosis

is irreversible cell death characterized by loss of membrane integrity and leakage of cellular contents culminating in dissolution of cells.

- necrosis resulting from the degradative action of **enzymes** liberated from injured cells.

-The leaked cellular contents elicit a local host reaction, called **inflammation**, that attempts to eliminate the dead cells and start the subsequent repair process.

-**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 .

Causes

1-Poisons

A- Chemical poisons such as insecticides , fungicides.

B- Bacterial toxins.

C- Plant poisons.

D-Enterotoxins.

2- loss of blood supply.

3- physical agents as trauma ,burn ,radiation , UV.

4- Immunologic reaction as AG-AB reactions

Morphology

Necrosis is characterized by changes in the **cytoplasm** and **nuclei** of the injured cells

-Cytoplasmic changes

1-The necrotic cells show increased eosinophilia (i.e., red staining from the eosin dye, the "E" in "H&E"). Due to increased binding of eosin to denatured cytoplasmic proteins and due to loss of the basophilia that is normally imparted by the ribonucleic acid (RNA) in the cytoplasm (basophilia is the blue staining from the hematoxylin dye, the "H" in "H&E").

2- The cell may have a more glassy homogeneous appearance than viable cells because of the loss of lighter staining glycogen particles.

3- When enzymes have digested the cytoplasmic organelles, the cytoplasm becomes vacuolated and appears **moth eaten**

Nuclear changes

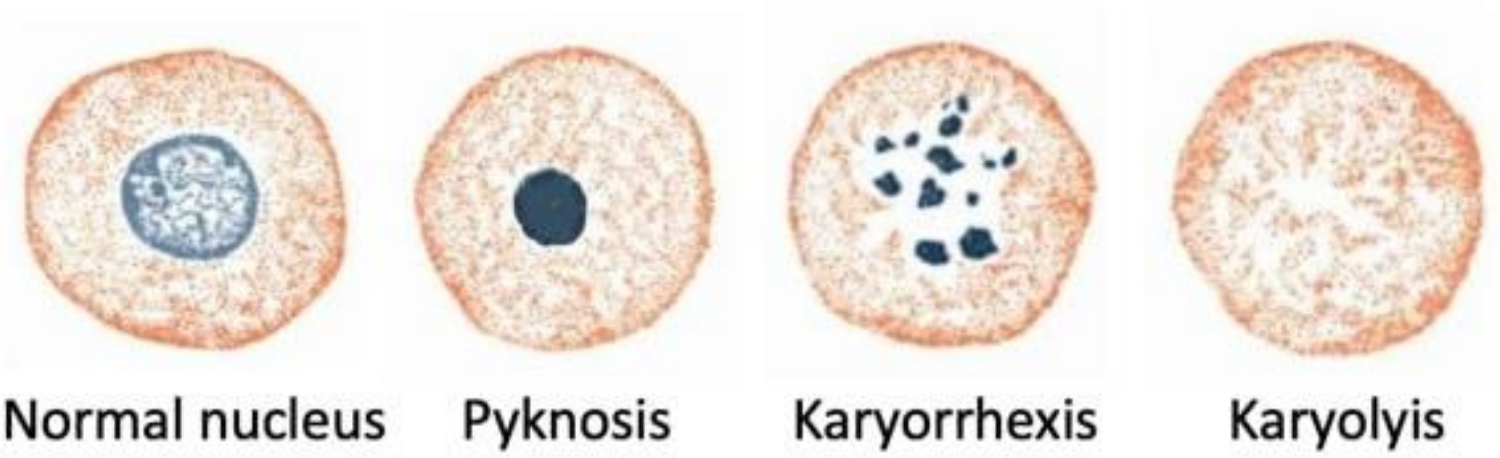
resulting from a breakdown of DNA and chromatin which include :-

A- pyknosis , characterized by nuclear shrinkage and increased basophilia ; the DNA condenses into dark shrunken mass.

B- karyorrhexis , the pyknotic nucleus undergoes fragmentation.

C- karyolysis:- The basophilia of the chromatin may fade, presumably secondary to deoxyribonuclease (DNase) activity .

In 1 to 2 days, the nucleus in a dead cell may completely disappear.



Fates of necrotic cells.

1-Necrotic cells may persist for some time or may be digested by enzymes and disappear.

2-Dead cells may be replaced by myelin figures, which are either phagocytosed by other cells or further degraded into fatty acids. These fatty acids bind calcium salts, which may result in the dead cells becoming calcified.

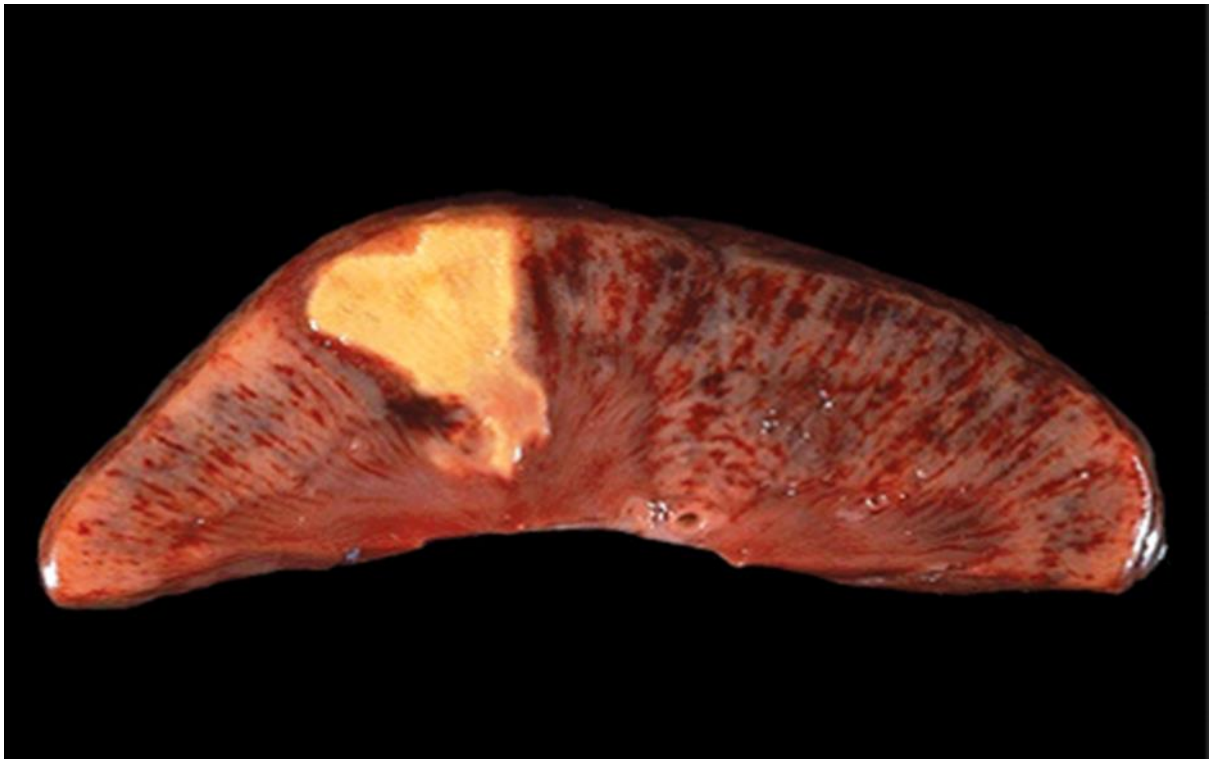
Patterns of Tissue Necrosis

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 after death of cells in the tissue .

The affected tissues take on a firm texture . the injury denatures not only structural proteins but also enzymes there by blocking the proteolysis of the dead cells; as a result, eosinophilic , anucleate cells may persist for days or weeks.

Leukocytes are recruited to the site of necrosis, and the dead cells are digested by the action of lysosomal enzymes of the these leukocytes. The cellular debris is removed by phagocytosis of neutrophils and macrophages.

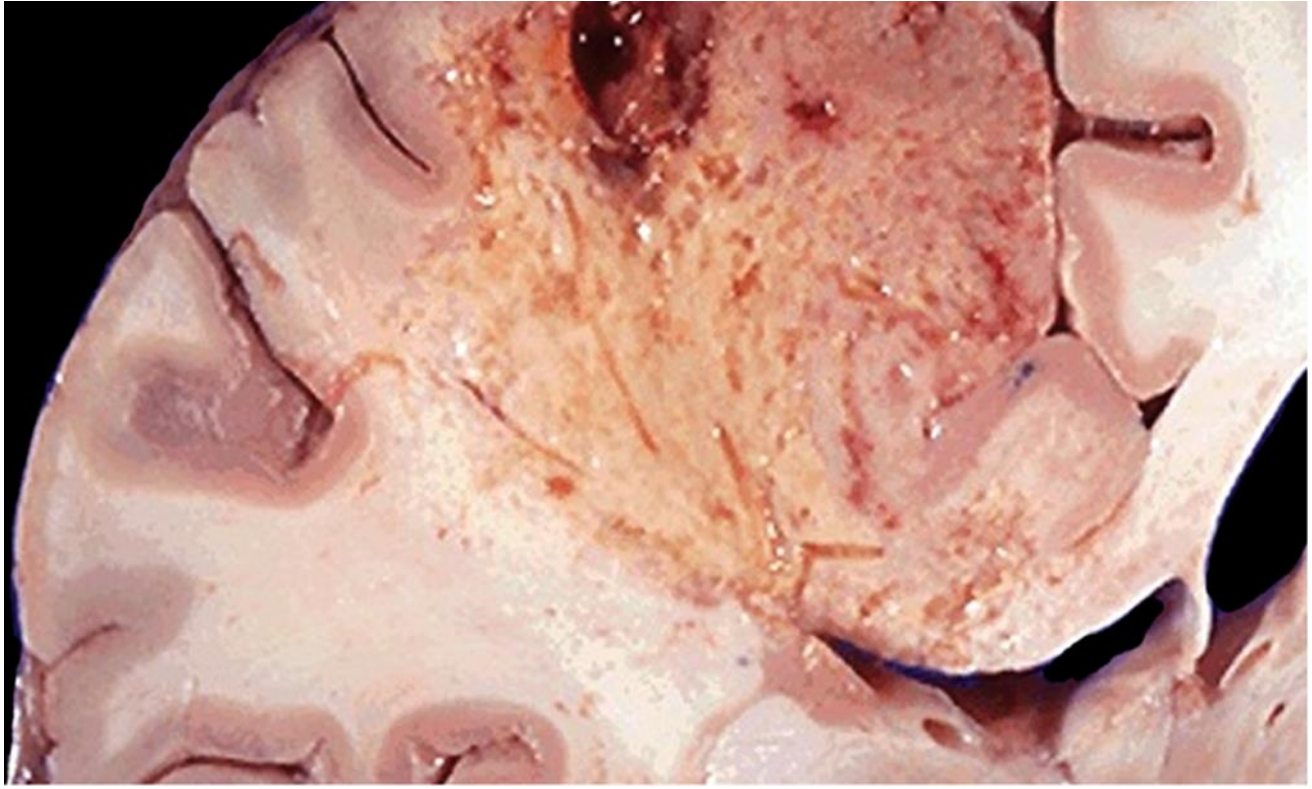
Coagulative necrosis is characteristic of **infarcts** (areas of ischemic necrosis) in all solid organs except the brain.



Coagulative necrosis. Show kidney infarct (yellow)

2- Liquefactive necrosis is seen in bacterial or, occasionally, fungal infections, 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. The dead cells are completely digested , transforming the tissue into a viscous liquid . Eventually, removed by phagocytes . If the process was initiated by acute inflammation, the material is **creamy yellow** and is called **pus.**



Liquefactive necrosis of the brain

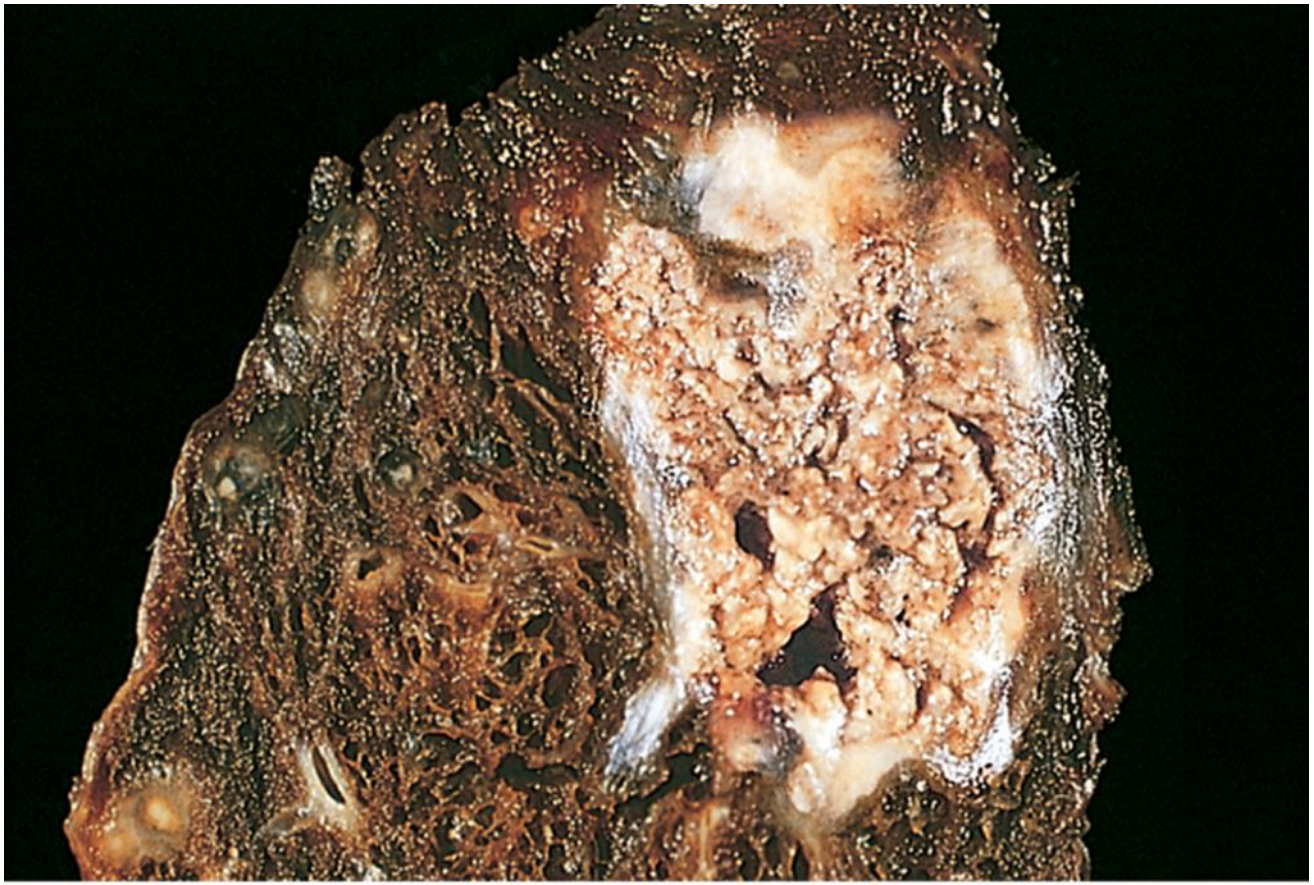
3- Gangrenous necrosis the term is still commonly used in clinical practice .It usually refers to the condition of a limbs (generally the lower leg) that has lost its blood supply and has undergone coagulative necrosis in multiple tissue layers.

When bacterial infection is superimposed, the coagulative necrosis changes to liquefactive necrosis because of the destructive contents of the bacteria and the attracted leukocytes (resulting in so-called "**wet gangrene**").

4- **Caseous necrosis** is most often encountered in foci of tuberculous infection. Caseous means **“cheeselike,”** referring to the friable yellow-white appearance of the area of necrosis on gross examination .On microscopic examination, the necrotic focus appears as a collection of fragmented or lysed cells with an amorphous granular pink appearance .

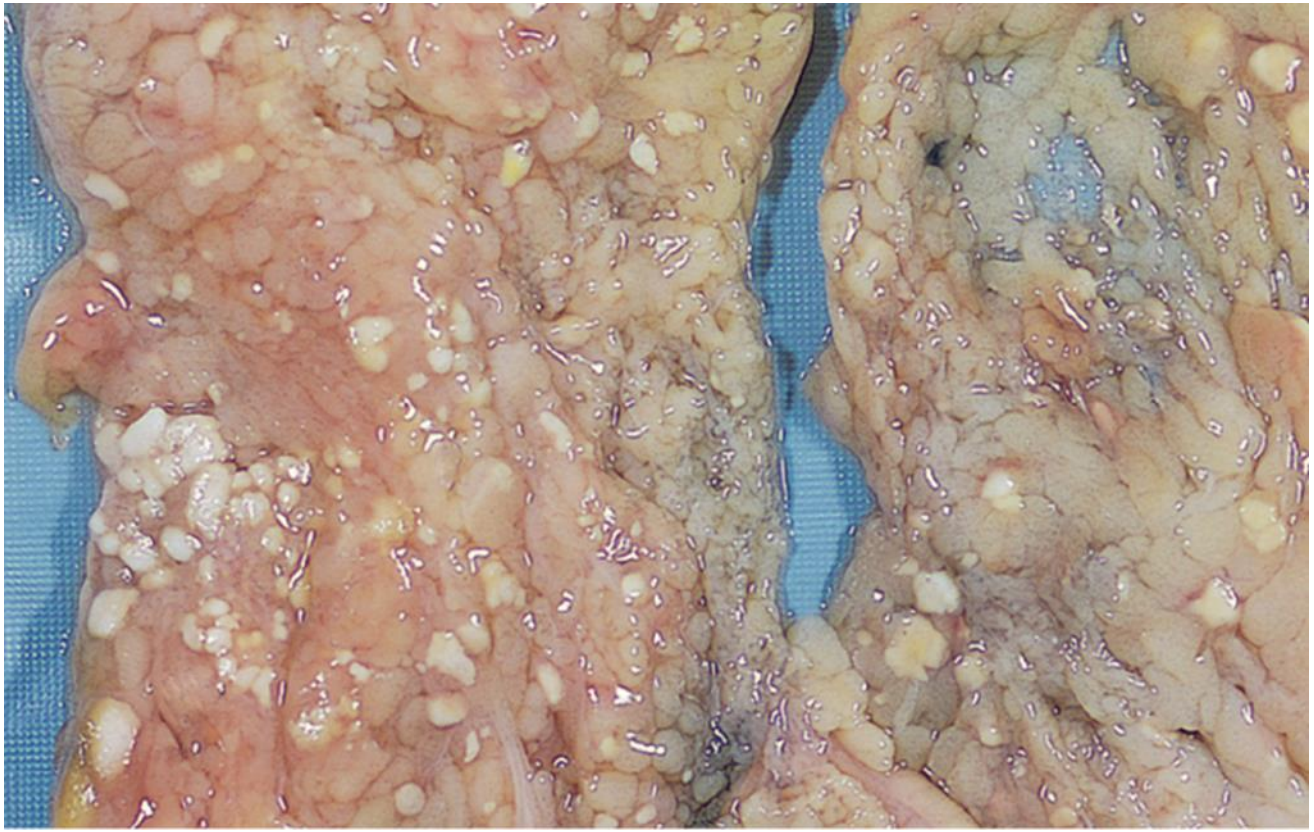
Unlike **coagulative necrosis**, the tissue architecture is completely obliterated and cellular outlines cannot be discerned. Caseous necrosis is often surrounded by

a collection of inflammatory cells; this appearance is characteristic of a nodular inflammatory lesion called a **granuloma**.



Caseous necrosis. A tuberculous lung with a large area of caseous necrosis containing yellow-white and cheesy debris.

5- **Fat necrosis**, focal areas of fat destruction, resulting from release of pancreatic lipases to the pancreas and the peritoneal cavity . This occurs in **acute pancreatitis** .In this disorder , pancreatic enzymes (lipases) that have leaked out of acinar cells and ducts liquefy the membranes of fat cells in the peritoneum, and lipases split the triglyceride esters contained within fat cells. The released fatty acids combine with calcium to produce grossly visible chalky white areas (fat saponification) , which enable the surgeon and the pathologist to identify the lesions . On histologic examination, the foci of necrosis contain necrotic fat cells surrounded by calcium deposits and an inflammatory reaction .



The areas of white chalky deposits represent foci of fat necrosis with calcium soap formation (saponification) in the mesentery.

6- **Fibrinoid necrosis** is a special form of necrosis usually seen in immune reactions in which of antigens and antibodies complexes are deposited in the walls of arteries . Deposits of these "immune complexes," together with plasma protein (fibrin) that has leaked out of vessels, produce a bright pink, amorphous appearance on H&E stains, called **"fibrinoid" (fibrin-like).**

this type of necrosis is found in the immunologically mediated diseases (e.g., polyarteritis nodosa) .

2- Apoptosis (Programmed cell death)

- *Apoptosis is a pathway of cell death in which cells activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins* .

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

- The plasma membrane of the apoptotic cell remains intact, but the membrane is altered in such a way that the cell and its fragments become avid targets for phagocytes. The dead cell is rapidly removed before its contents have leaked out , for this reason the apoptotic cell death does not elicit an inflammatory reaction in the host. Thus, 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.

CAUSE OF APOPTOSIS

1- Apoptosis in Physiologic Situations

Apoptosis occurs normally in many situations, and serves to eliminate potentially harmful cells and cells that have outlived their usefulness.

1-*The programmed destruction of cells during embryogenesis,* Normal development is associated with the death of some cells and the appearance of new cells and tissues.

2-*Involution of hormone-dependent tissues upon hormone deprivation,* such as endometrial cell breakdown during the menstrual cycle , and regression of the lactating breast after weaning.

3-*Cell loss in proliferating cell populations,* such as intestinal crypt epithelia, so as to maintain a constant number.

4-Death of cells that served their useful purpose, such as neutrophils in an acute inflammatory response, and lymphocytes at the end 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.

6-*Cell death induced by cytotoxic T lymphocytes,* a defense mechanism against viruses and tumors these cell s kill and eliminate virus-infected and neoplastic cells.

2-Apoptosis in Pathologic Conditions

When cells are damaged beyond repair, especially when the damage affects the cell's DNA or proteins; in these situations, the irreparably damaged cell is eliminated

1-DNA damage*.* Radiation, cytotoxic anticancer drugs, extremes of temperature, and even hypoxia can damage DNA, either directly or via production of free radicals. If repair mechanisms cannot cope with the injury, the cell triggers intrinsic mechanisms that induce apoptosis.

2-Accumulation of misfolded proteins lead to apoptotic cell death .

3-Cell injury in certain infections*,* particularly viral infections,in which infected cells is died due to the virus is induce apoptotic death **.**

4-Pathologic atrophy in parenchymal organs after duct obstruction*,* such as occurs in the pancreas, parotid gland, and kidney**.**

Mechanisms of Apoptosis

There are two pathways for Apoptosis

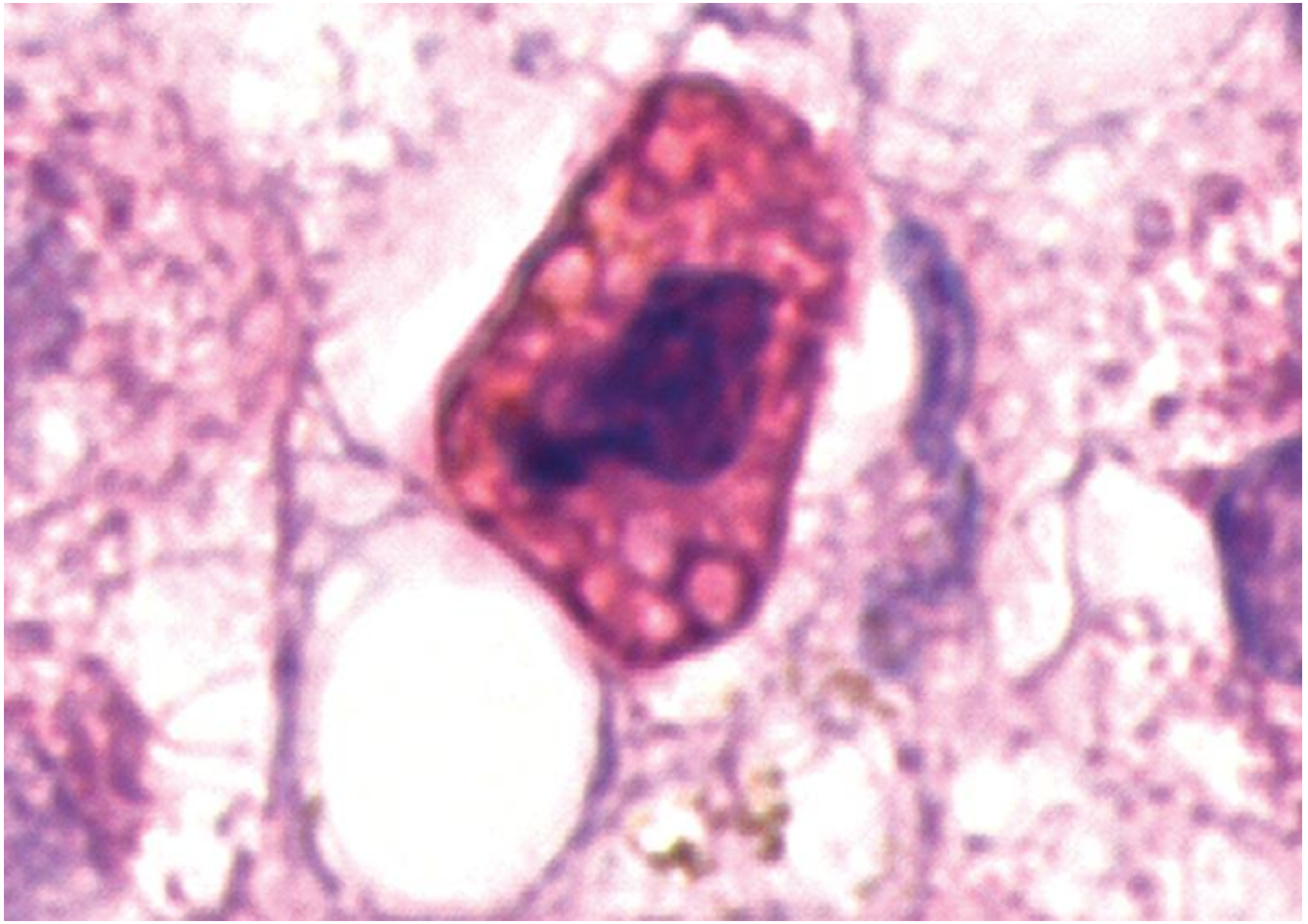
1- Mitochondrial pathway: (intrinsic pathway).

2-Death receptor pathway: (extrinsic pathway) .

Both results in activation of **caspase** which lead to nuclear fragmentation and formation of apoptotic bodies.

Morphology of apoptosis

In H&E-stained tissue sections, apoptotic cells may appear as round or oval masses with intensely eosinophilic cytoplasm . Nuclei show various stages of chromatin condensation and aggregation and, ultimately, karyorrhexis.



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 cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage.