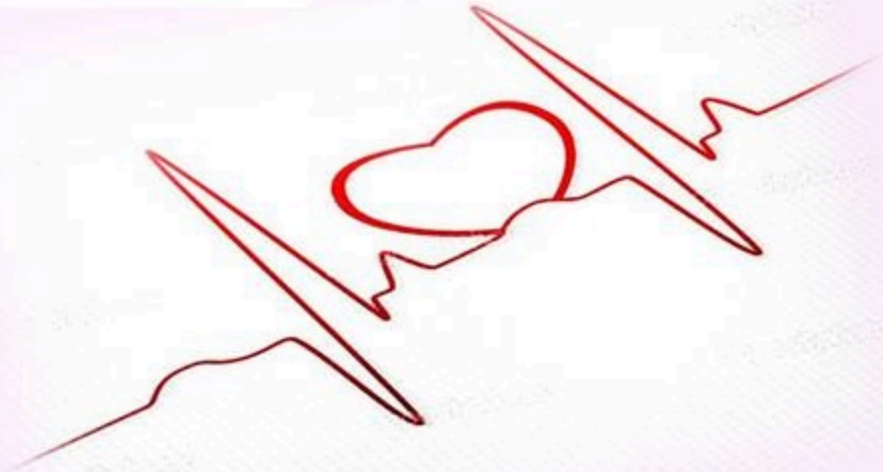
PATHOLOGY

Medical Committee
The University of Jordan

SHEET

SlIDE



Lecture Number: 2

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Cell Death, Cell Injury & Adaptations

Note: This topic will take four lectures, so this sheet just contains what the doctor said, and the book has a different arrangement.

OVERVIEW OF CELLULAR RESPONSES TO STRESS

- Basic concepts:

What is homeostasis?

- A steady state that cells normally maintain in which the intracellular milieu is kept within a fairly narrow range of physiologic parameters among all levels of organization in the body.

- Cells are active participants in their environment, constantly adjusting their structure and function to accommodate changing demands and extracellular stresses.

- As cells encounter physiologic stresses or pathologic stimuli, they can undergo adaptation, achieving a new steady state and preserving viability and function (within a new physiological range) such as coffee which causes certain types of addiction, through increases in metabolic rates, so if you didn`t drink coffee on a certain day you will face complications.

- Example on adaptation:

- If your body feels cold then the thermal receptors on your skin will send a message to the temperature center in your brain and this center will respond to this change by sending effectors to skeletal muscles to start shivering releasing heat and thus raising the temperature, while in the opposite case the effectors will be on your sweat glands to start sweating and reduce body temperature. By doing this the body can reestablish its balance.

- Note the above mentioned bodily response is the physiological response. There are also higher motor function responses; for example if you feel cold, the first thing you're going to do is put more clothes on, turn on the heating. If you feel too hot, you will do the opposite.

- However what we are interested in, in pathology, is looking at the cellular level and how the cells respond to these changes which in turn create imbalances in your homeostasis. Homeostasis at the level of the cell depends on both the forces or stresses which it exerts on its surroundings, and on the forces or stresses exerted by its surroundings on itself.

- If the adaptive capability is exceeded or if the external stress is inherently harmful, cell injury develops.

- Within certain limits, injury is *reversible*, and cells return to a stable baseline; however, if the stress is severe, persistent and rapid in onset, it results in *irreversible injury* and death of the affected cell through either necrosis or apoptosis. However keep in mind that death of a cell is not always a bad thing; sometimes death of a cell can be beneficial as a means of renewal or regeneration of a more effective cell in place of the old one.

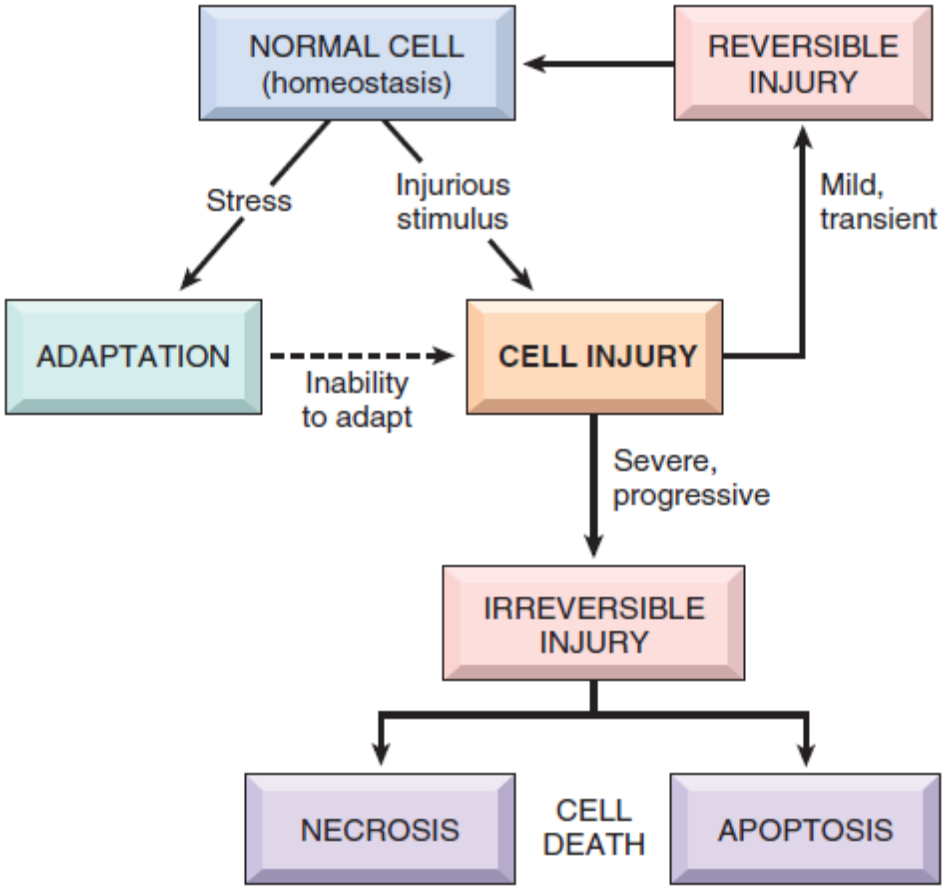


Figure 1–1 Stages in the cellular response to stress and injurious stimuli.

Cellular adaptations:

- Adaptations are divided into physiologic and pathologic

1. Physiologic adaptations

- Usually represent responses of cells to normal stimulation by hormones or endogenous chemical mediators.
- Example: The hormone-induced enlargement of the breast and uterus during pregnancy.

2. *Pathologic adaptations* :

- They are responses to stress that allow cells to modulate their structure and function and thus escape injury.

- There are reversible changes in the number, size, metabolic activity, or function of the cells in response to changes in their environment, which include:

1. Hypertrophy
2. Hyperplasia
3. Atrophy
4. Metaplasia

- All stresses exert their effects first at the molecular or biochemical level.

- Cellular function may be lost long before cell death occurs, and the morphologic changes of cell injury (or death) lag far behind both.

Example: Myocardial ischemia:
- Myocardial cells become non-contractile in 1-2 minutes
- They die after 20-30 minutes
- In this case, the iron pumps will no longer work in the cell, and water will start to accumulate inside the cell, leading to observable changes.
- They appear dead by EM (electron microscope) after 2-3 hours and by light microscopy after 6-12 hours and by gross examination after about 24 hours

Types of adaptations*:*

1. Hypertrophy
- Is an increase in the **size of cells** resulting in increase in the size of the organ.
- **In contrast**, hyperplasia is characterized by an increase in cell number because of proliferation of differentiated cells and replacement by tissue stem cells.
- In pure hypertrophy there are no new cells, just bigger cells containing increased amounts of structural proteins and organelles.
- Hyperplasia is an adaptive response in cells capable of replication, whereas hypertrophy occurs when cells have a limited capacity to divide.
- Hypertrophy and hyperplasia can occur together (**mixed**), and obviously both result in an enlarged organ.

Example of combined hypertrophy and hyperplasia
- The massive physiologic enlargement of the uterus during pregnancy occurs as a consequence of estrogen-stimulated smooth muscle hypertrophy and smooth muscle hyperplasia.

- Hypertrophy can be: physiologic or pathologic.

- Hypertrophy is caused either by increased functional demand or by growth factor or hormonal stimulation.

- Pure hypertrophy occurs in the striated muscle cells in both the skeletal muscle and the heart in response to increased demands, these types of cells can undergo only hypertrophy because adult striated muscle cells have a limited capacity to divide.

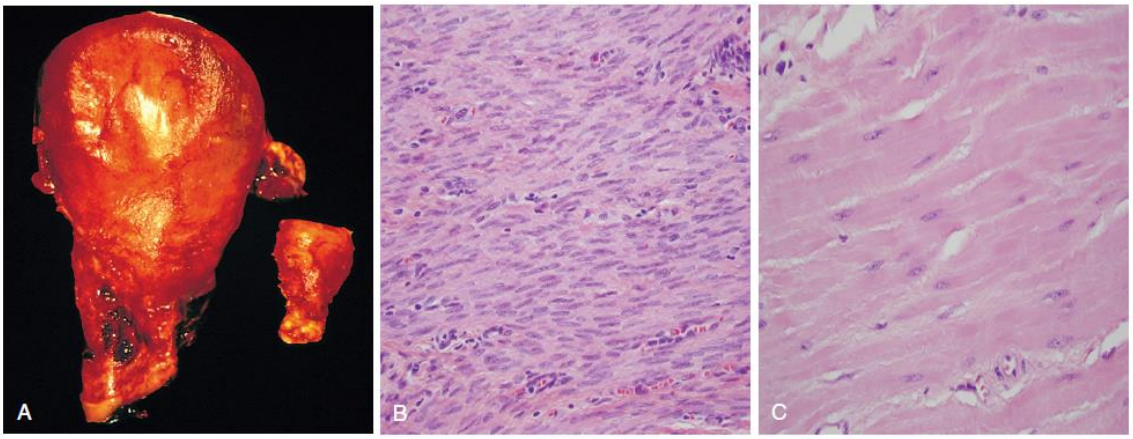
- Remember you must be able to differentiate between Pure and Mixed hypertrophy. Pure hypertrophy is only an increase in the size of the cells. Mixed hypertrophy is increase in size and number as well. When looking at the cellular level we are always

talking about pure hypertrophy (because of the very minimal proliferation), while when considering the organ in question, we may refer to either pure or mixed hypertrophy.

Example of physiologic hypertrophy:

- The strong physique of the weightlifter stems from the hypertrophy of individual skeletal muscles.

- The increasing of the uterus size during pregnancy. (mixed)



Example of pathologic hypertrophy

- Cardiac enlargement that occurs with hypertension or aortic valve disease.
- The mechanisms driving cardiac hypertrophy involve at least two types of signals:

a. Mechanical triggers, such as stretching
b. Trophic triggers, which are soluble mediators that stimulate cell growth, such as growth factors and adrenergic hormones.

Mechanism :

These stimuli :
a. Turn on signal transduction pathways
b. That lead to the induction of a number of genes,
c. Which in turn stimulate synthesis of many cellular proteins, including growth factors and structural proteins.
d. The result is the synthesis of more proteins and myofilaments per cell, which increases the force generated with each contraction, enabling the cell to meet increased work demands.
e. There may also be a switch of contractile proteins from adult to fetal or neonatal forms.

- For example, during muscle hypertrophy, the α-myosin heavy chain is replaced by the β form of the myosin heavy chain, which produces slower, more energetically economical contractions

NOTE:

- Whatever the exact mechanisms of hypertrophy, a limit is reached beyond which the enlargement of muscle mass can no longer compensate for the increased burden

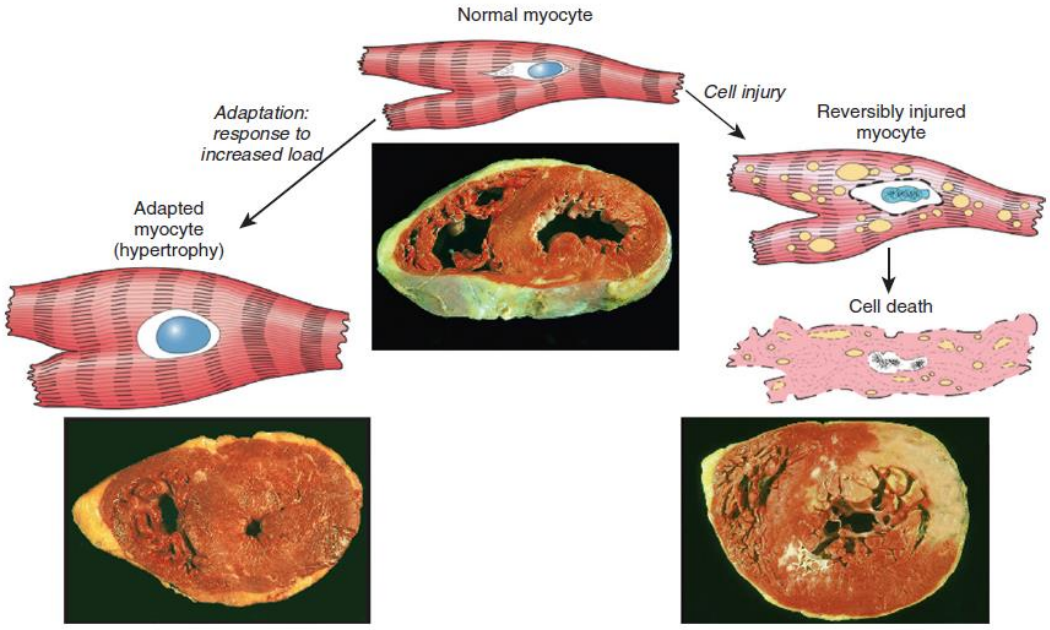
- When this happens in the heart, several "degenerative" changes occur in the myocardial fibers, the most important are fragmentation and loss of myofibrillar contractile elements.

- The variables that limit continued hypertrophy and cause the regressive changes are incompletely understood.

- There may be finite limits of:

A. The vasculature to adequately supply the enlarged fibers
B. The mitochondria to supply adenosine triphosphate (ATP),
C. The biosynthetic machinery to provide the contractile proteins or other cytoskeletal elements.

- The net result of these changes is ventricular dilation and ultimately cardiac failure, a sequence of events that illustrates how an adaptation to stress can progress to functionally significant cell injury if the stress is not relieved.



2. Hyperplasia

- It occurs if the tissue contains cell populations capable of replication.
- It may occur concurrently with hypertrophy and often in response to the same stimuli.
- Hyperplasia can be physiologic or pathologic and in both situations cellular proliferation is stimulated by hormones or growth factors.

Physiologic hyperplasia types:

1. Hormonal hyperplasia:
- Such as the proliferation of the glandular epithelium of the female breast at puberty and during pregnancy
2. Compensatory hyperplasia,
- In which residual tissue grows after removal or loss of part of an organ
- For example, in cases of **liver transplantation** when part of a liver is resected from the donor, mitotic activity in the remaining cells begins as early as 12 hours later, eventually restoring the liver to its normal weight.
- The stimuli for hyperplasia in this setting are polypeptide growth factors produced by uninjured hepatocytes.
- After restoration of the liver mass, cell proliferation is "turned off" **by various growth inhibitors.**

Pathologic hyperplasia

- Most cases are caused by excessive hormonal or growth factor stimulation.

Examples:

- Endometrial Hyperplasia

- After a normal menstrual period there is a burst of uterine epithelial proliferation that is normally tightly regulated by stimulation through pituitary hormones and ovarian estrogen and by inhibition through progesterone.
- However, a disturbed balance between estrogen and progesterone causes endometrial hyperplasia, which is a common cause of abnormal menstrual bleeding.
- If there is an imbalance in the secretion of estrogen in comparison to progesterone (estrogen a lot more than progesterone), then the uterine endometrium will experience profound changes due to hyperplasia, which is a fertile ground for cancer development. And if the pathologic hyperplasia is converted into cancer, then the cancer cells will no longer be responsive to simply cutting the production of the hormone estrogen, allowing the situation to exacerbate further.

Physiologic hyperplasia

- Wound healing

- Hyperplasia also is an important response of connective tissue cells that are stimulated by growth factors in wound healing, in which proliferating fibroblasts and blood vessels (mainly endothelial cells) aid in repair and fill up the back.
- Physiologic hyperplasia can also be seen during puberty and/or pregnancy in the mammary glands in females.

NOTES:

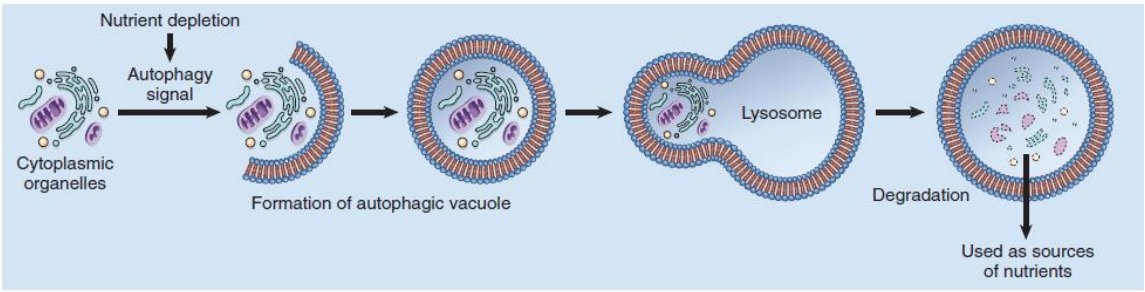
- In all of these situations, *the hyperplastic process remains controlled; if the signals that initiate it come to a stop, the hyperplasia disappears*
- It is this responsiveness to normal regulatory control mechanisms that distinguishes pathologic hyperplasia from cancer, in which the growth control mechanisms become deregulated (dysplasia)
- Some viruses like the HPV (human pipilloma virus) have the ability to encode growth-factor-like proteins. Upon entering the body and releasing these proteins inside the cells, the cells will be tricked into thinking this invasive, foreign protein is the normal internally secreted growth hormone, and begin proliferating indefinitely. The HPV can lead to warts on the skin.

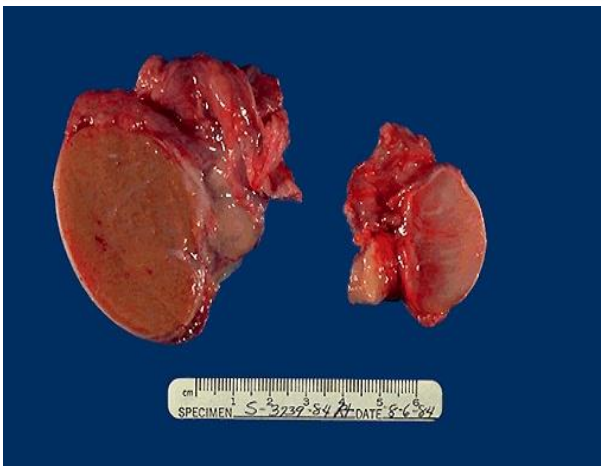
3. Atrophy

- Shrinkage in the size of the cell by the loss of cell substance .
- When a sufficient number of cells are involved, the entire tissue or organ diminishes in size, becoming atrophic
- Although atrophic cells may have diminished function, they are not dead.
- Causes of atrophy include :

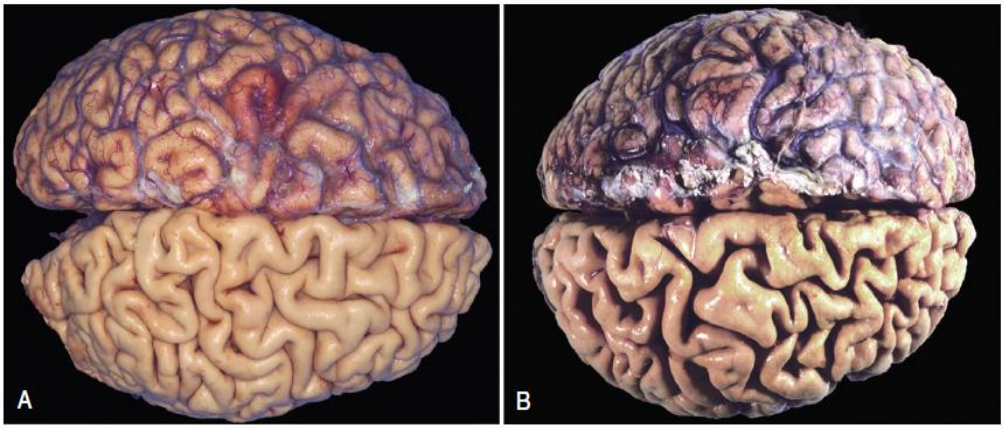
a. A decreased workload (e.g., immobilization of a limb to permit healing of a fracture),
b. Loss of innervation,
c. Diminished blood supply,
d. Inadequate nutrition,
e. Loss of endocrine stimulation like atrophy of endometrium in menopause)
f. Aging (senile atrophy)

- Although some of these stimuli are physiologic (e.g., the loss of hormone stimulation in menopause) and others pathologic (e.g., denervation), the fundamental cellular changes are identical
- The cellular changes represent a retreat by the cell to a smaller size at which survival is still possible; a new equilibrium is achieved between cell size and diminished blood supply, nutrition, or trophic stimulation (for example by hormones → menopause).
- The mechanisms of atrophy consist of a combination of ***decreased protein synthesis*** and ***increased protein degradation*** in cells.
- Protein synthesis decreases because of reduced metabolic activity.
- The degradation of cellular proteins occurs mainly by the ***ubiquitin-proteosome pathway.***
- Nutrient deficiency and disuse may activate **ubiquitin ligases**, which attach multiple copies of the small peptide ubiquitin to cellular proteins and target them for degradation in **proteosomes**.
- In many situations, atrophy is also accompanied by increased *autophagy,* with resulting increases in the number of *autophagic vacuoles, which are fused with lysosomes, and digested.*





Testicular atrophy



Brain atropy due to Alzheimer`s disease.

4. Metaplasia

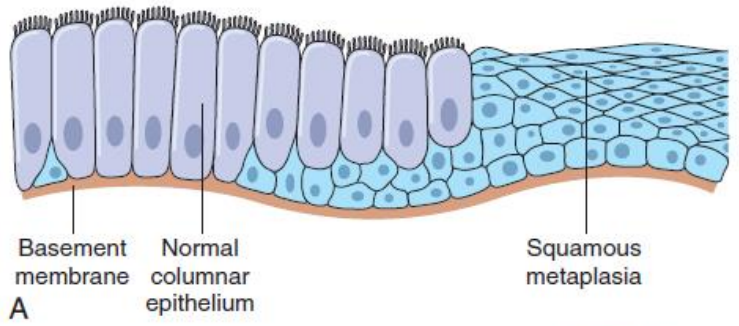
- Is a reversible change in which one adult cell type (epithelial or msenchymal) is replaced by another adult cell type
  - Stem cell by differentiation will give one type of cells, and by transformation it will give another new type.
- In this type of cellular adaptation, a cell type sensitive to a particular stress is replaced by another cell type better able to withstand the adverse environment.
- Is thought to arise by reprogramming of stem cells to differentiate along a new pathway rather than a phenotypic change (trans-differentiation) of already differentiated cells.

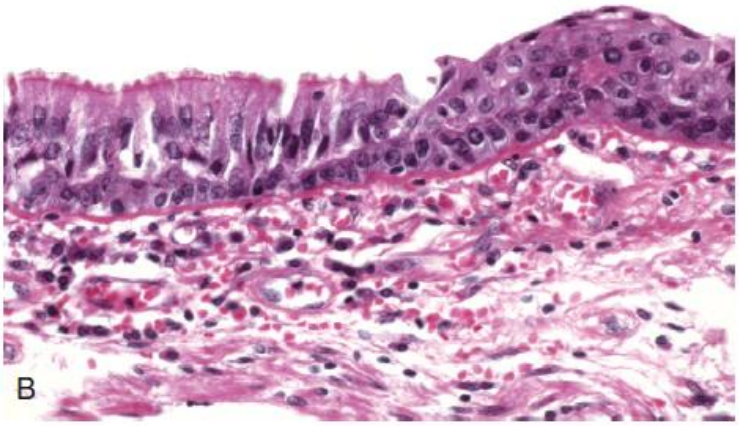
1. Epithelial metaplasia

A. Cigarette smoking:

Causes metaplasia of the respiratory epithelium (columnar)to squamous epithelium

- The rugged stratified squamous epithelium may be able to survive the noxious chemicals in cigarette smoke that the more fragile specialized columar epithelium would not tolerate.
- Although the metaplastic squamous epithelium has survival advantages, important protective mechanisms are lost, such as mucus secretion and ciliary clearance of particulate matter
- Epithelial metaplasia is therefore a double-edged sword.
- Moreover, *the influences that induce metaplastic change, if persistent, may predispose to malignant transformation of the epithelium*
- In fact, squamous metaplasia of the respiratory epithelium often coexists with lung cancers composed of malignant squamous cells.
- It is thought that cigarette smoking initially causes squamous metaplasia, and cancers arise later in some of these metaplastic regions.





B. Vitamin A deficiency

- Vitamin A is essential for normal epithelial differentiation, its deficiency may also induce squamous metaplasia in the respiratory epithelium

C. Cervical infection:

- Endocervix → The columnar epithelium is replaced by stratified squamous epithelium

D. Barrett Esophagus:

- Metaplasia need not always occur in the direction of columnar to squamous epithelium;

- In chronic gastric reflux, the normal stratified squamous epithelium of the lower esophagus may undergo metaplastic transformation to gastric or intestinal-type columnar epithelium.

2. Connective tissue Metaplasia may also occur in mesenchymal cells but in these situations it is generally a reaction to some pathologic alteration and not an adaptive response to stress.
- For example, bone is occasionally formed in soft tissues, particularly in foci of injury

OVERVIEW OF CELL INJURY AND CELL DEATH

- Cell injury results when cells are stressed so severely that they are no longer able to adapt or when cells are exposed to inherently damaging agents or suffer from intrinsic abnormalities (e.g., in DNA or proteins).

- Injury may progress through a reversible stage and culminate in cell death

1. *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.

2. 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 mechanisms, morphology, and roles in disease and physiology*

NOTES:
- The cellular derangements of reversible injury can be corrected, and if the injurious stimulus abates, the cell can return to normalcy.
- Persistent or excessive injury, however, causes cells to pass "point of no return" into *irreversible injury* and *cell death.*
- The events that determine when reversible injury becomes irreversible and progresses to cell death remain poorly understood
- Although there are no definitive morphologic or biochemical correlates of irreversibility, *two phenomena consistently characterize irreversibility:*
a. The inability to correct mitochondrial dysfunction (lack of oxidative phosphorylation and ATP generation) even after resolution of the original injury,
b. Profound disturbances in membrane function.
- Injury to lysosomal membranes results in the enzymatic dissolution of the injured cell, which is the culmination of injury progressing to necrosis.

1. Morphology of Reversible Injury

- The two main morphologic correlates of reversible cell injury are cellular swelling and fatty change :

A. Cellular swelling :

- Is the first manifestation of almost all forms of injury to cells
- Is a reversible alteration that may be difficult to appreciate with the light microscope,
- It may be more apparent at the level of the whole organ.
- When it affects many cells in an organ, it causes :

a. Some pallor (as a result of compression of capillaries),
b. Increased turgor (abases),
c. Increase in weight of the organ.

Microscopic examination

- Small, clear vacuoles within the cytoplasm; these represent distended and pinched-off segments of the endoplasmic reticulum (ER).
- This pattern of nonlethal injury is sometimes called **vacuolar degeneration .**

B. Fatty change:

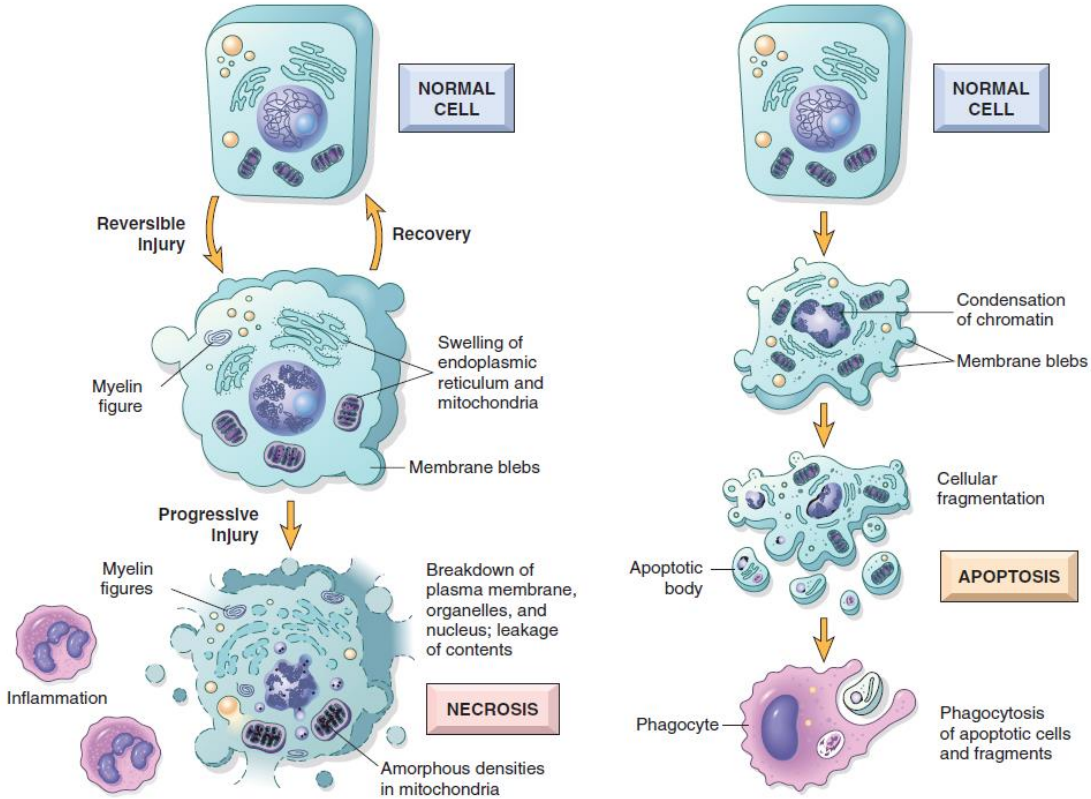
- Is manifested by the appearance of lipid vacuoles in the cytoplasm.
- It is principally encountered in cells participating in fat metabolism (e.g., hepatocytes, myocardial cells) and is also reversible.

The ultrastructural changes associated with reversible injury include:

1. Plasma membrane alterations such as
a. Blebbing, blunting, or distortion of microvilli,
b. Loosening of intercellular attachments
2. Mitochondrial changes such as swelling and the appearance of phospholipid-rich amorphous densities
3. Dilation of the ER with detachment of ribosomes and dissociation of polysomes; and
4. Nuclear alterations, with clumping of chromatin.
5. The cytoplasm may contain phospholipid masses, called myelin figures, which are derived from damaged cellular membranes.

2. Morphology of irreversible cell injury:

Has two patterns, Necrosis and Apoptosis



A. Necrosis:

- Necrosis is the type of cell death that is associated with loss of membrane integrity and leakage of cellular contents culminating in dissolution of cells, largely resulting from the degradative action of enzymes on lethally injured cells.
- The leaked cellular contents often elicit a local host reaction, called *inflammation,* that attempts to eliminate the dead cells
- The enzymes responsible for digestion of the cell may be derived from the lysosomes of the dying cells themselves and from the lysosomes of leukocytes that are recruited as part of the inflammatory reaction to the dead cells.

Morphology of necrosis

I. Cytoplasmic changes

a. Necrotic cells show **increased eosinophilia** (i.e., pink staining from the eosin dye-the E in the hematoxylin and eosin [H&E] stain
- This change is attributable:

1. In part to increased binding of eosin to denatured cytoplasmic proteins
2. And in part 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").

b. Compared with viable cells, the cell may have a more glassy, homogeneous appearance, mostly because of the loss of glycogen particles.

c. Myelin figures are more prominent in necrotic cells than during reversible injury.
d. When enzymes have digested cytoplasmic organelles, the cytoplasm becomes vacuolated and appears "moth-eaten

- By electron microscopy

a. Discontinuities in plasma and organelle membranes,
b. Marked dilation of mitochondria
c. Appearance of large amorphous densities,
d. Disruption of lysosomes, and Intracytoplasmic myelin figures

II. Nuclear changes.

- Nuclear changes assume one of three patterns, all due to breakdown of DNA and chromatin.

a. karyolysis

- The basophilia of the chromatin may fade**),** presumably secondary to deoxyribonuclease (DNase) activity

b. **Pyknosis,**

Characterized by nuclear shrinkage and increased basophilia; the DNA condenses into a solid shrunken mass.

c. In the third pattern, **karyorrhexis,**

- The pyknotic nucleus undergoes fragmentation. In 1 to 2 days, the nucleus in a dead cell may completely disappear.
- Electron microscopy reveals profound nuclear changes culminating in nuclear dissolution.

Nuclear changes of necrosis***Fates of necrotic cells.***

- Necrotic cells may persist for some time or may be digested by enzymes and disappear.
- 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 ultimately becoming **calcified.**

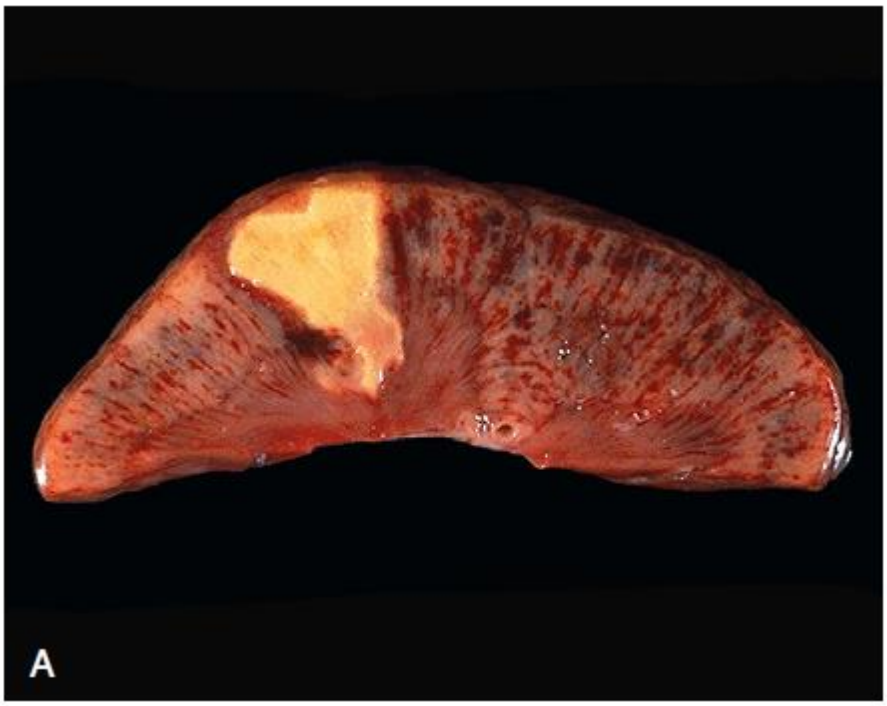
Patterns of Tissue Necrosis

- There are several morphologically distinct patterns of tissue necrosis, which may provide clues about the underlying cause.
- Although the terms reflect underlying mechanisms, such terms are in common use, and their implications are understood by both pathologists and clinicians.

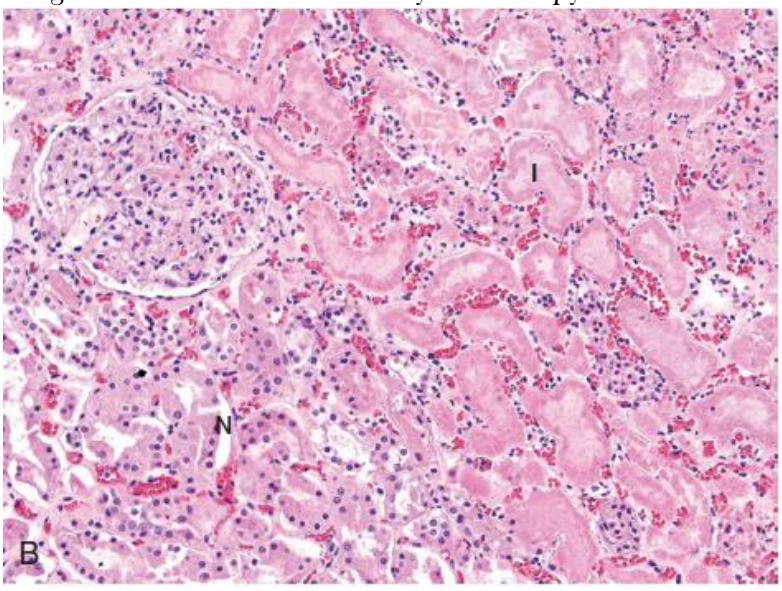
I. Coagulative necrosis

- Is a form of necrosis in which the underlying tissue architecture is preserved for at least several days.
- The affected tissues take on a firm texture.
- Presumably the injury denatures not only structural proteins but also enzymes, thereby 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 leukocytes.
- The cellular debris is then removed by phagocytosis.
- Coagulative necrosis is characteristic of **infarcts** (areas of ischemic necrosis) in all of the solid organs except the brain

Coagulative necrosis in the kidney:



Coagulative necrosis in the kidney-microscopy:



II. Liquefactive necrosis:

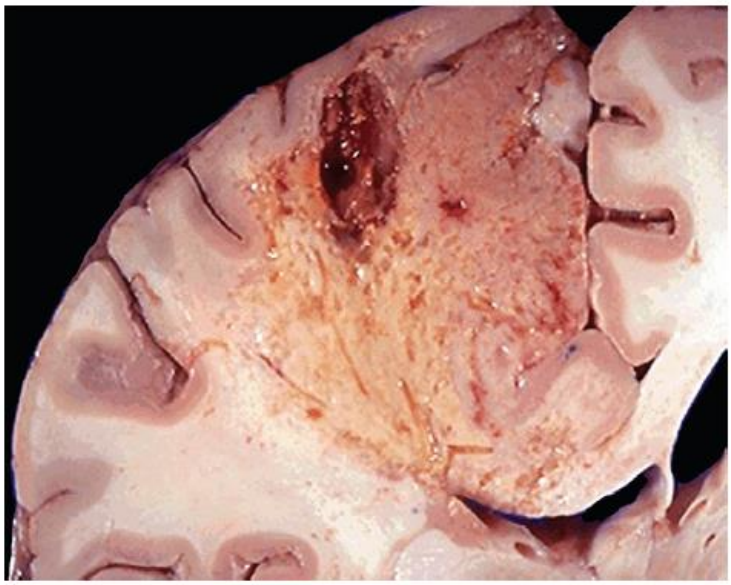
Causes:

a. Is seen in focal bacterial or, occasionally, fungal infections, because microbes stimulate the accumulation of inflammatory cells and the enzymes of leukocytes digest ("liquefy") the tissue.

b. For obscure reasons, hypoxic death of cells within the central nervous system often evokes liquefactive necrosis

- Whatever the pathogenesis, the dead cells are completely digested, transforming the tissue into a **liquid viscous mass.**
- Eventually, the digested tissue is removed by phagocytes.

- If the process was initiated by acute inflammation, as in a bacterial infection, the material is frequently creamy yellow and is called **pus**. Pus is the remains of phagocytic digestion.

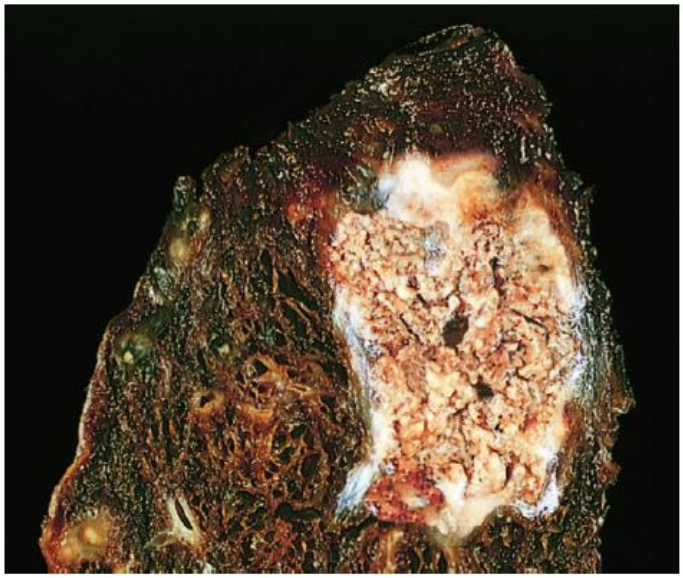


III. Gangrenous necrosis

- Is not a distinctive pattern of cell death, the term is still commonly used in clinical practice.
- It usually refers to the condition of a limb, generally the lower leg that has lost its blood supply and has undergone coagulative necrosis involving multiple tissue layers **(Dry gangrene – ex. frostbite).**
- When bacterial infection is superimposed, coagulative necrosis is modified by the liquefactive action of the bacteria and the attracted leukocytes (resulting in so-called **wet gangrene, which can also be seen in diabetic foot of a diabetes patient)**.

IV. Caseous necrosis :

- Is encountered most often in foci of tuberculosis infection.
- **Caseous** means "cheese-like," referring to the friable yellow-white appearance of the area of necrosis
- Microscopically: The necrotic focus appears as a collection of fragmented or lysed cells with an amorphous granular pink appearance in the usual H&E-stained tissue. Granuloma can be accomplished with caseous necrosis.
- Unlike with coagulative necrosis, the tissue architecture is completely obliterated and cellular outlines cannot be discerned.
- The area of caseous necrosis is often enclosed within a distinctive inflammatory border; this appearance is characteristic of a focus of inflammation known as a granuloma.



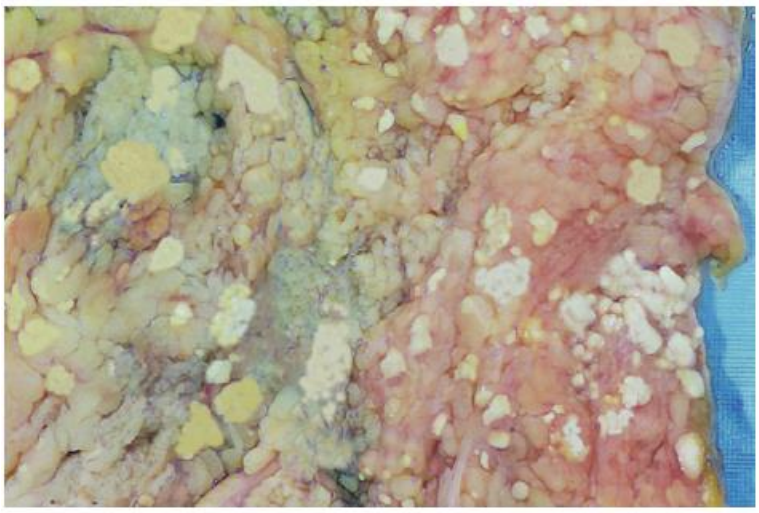
V. Fat necrosis

- Refers to focal areas of fat destruction
- Two forms

a. Enzymatic fat necrosis

- 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
- In this disorder, pancreatic enzymes 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 and histologically; the foci of necrosis contain shadowy outlines of necrotic fat

cells with basophilic calcium deposits, surrounded by an inflammatory reaction.



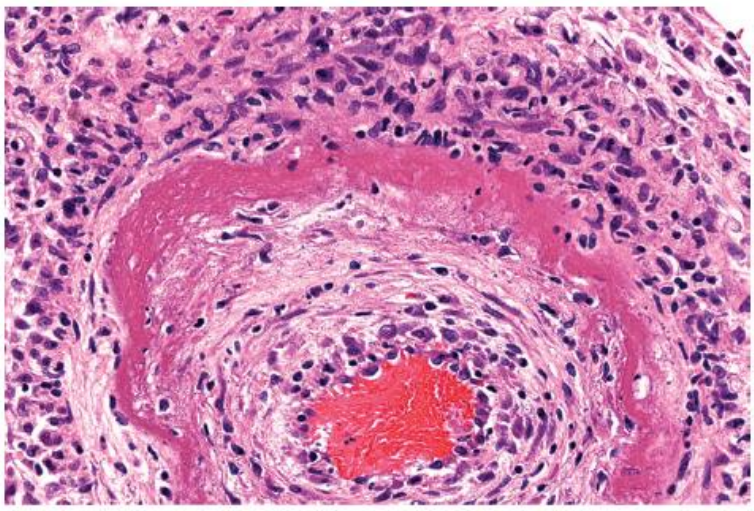
b. Traumatic fat necrosis like in breast trauma that might result in fat necrosis that can be calcified and misdiagnosed clinically as malignant tumor.
Because that it is highly important to take the patients history, if she faced such strong trauma or this is a true cancer.

- Fat necrosis

1-Enzymatic fat necrosis 2-Traumatic fat necrosis: Enzymatic fat necrosis in the pancreas

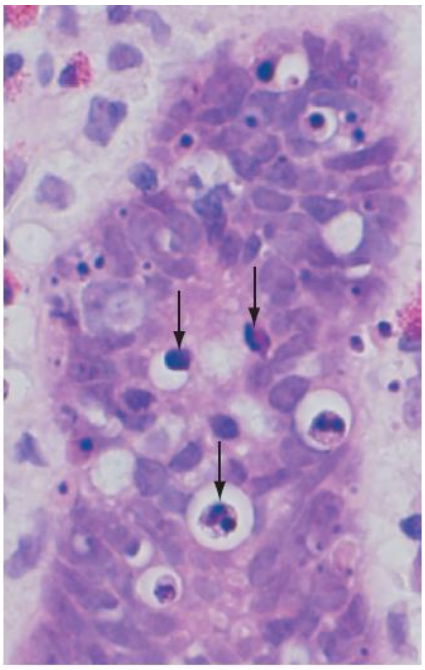
VI. Fibrinoid necrosis

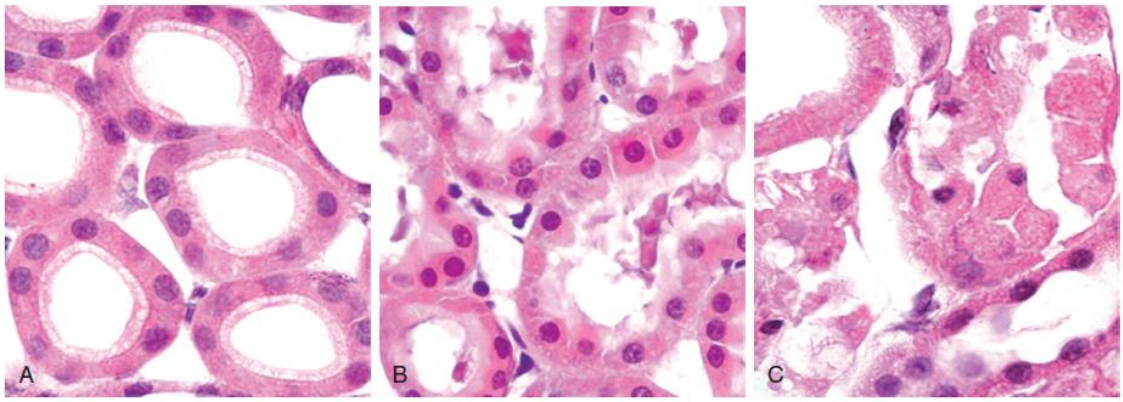
- Is a special form of necrosis, visible by light microscopy.
- Usually occurs in immune reactions in which complexes of antigens and antibodies are deposited in the walls of arteries.
- The deposited immune complexes (antibodies and antigens), together with fibrin that has leaked out of vessels, produce a bright pink and amorphous appearance on H&E preparations called **fibrinoid** (fibrin-like) by pathologists.



B. Apoptosis

- Is a pathway of cell death in which cells activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins.
- In this process fragments of 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 is altered in such a way that the cell and its fragments become avid targets for phagocytes.
- The dead cell and its fragments are rapidly cleared before cellular contents have leaked out, so *apoptotic cell death does not elicit an inflammatory reaction in the host.*
- Apoptosis differs in this respect from necrosis, which is characterized by loss of membrane integrity, enzymatic digestion of cells, leakage of cellular contents, and frequently a host reaction.
- However, apoptosis and necrosis sometimes coexist, and apoptosis induced by some pathologic stimuli may progress to necrosis.





- Summary

Apoptosis

Active process
Physiological & pathological
Occur in single cells
The cell size is small
The plasma membrane is intact but with altered structure
The cellular contents are intact but may be released in apoptotic bodies
No inflammatory reaction

Necrosis

Passive process
Always pathological
Affects mass of cells
The cell is enlarged (swelling)
The nucleus show pyknosis→karyorrhexis→karyolysis
The plasma membrane is disrupted
The cellular contents show enzymatic digestion and may leak out of the cell
Stimulates Inflammation

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