Cell Injury

Girl's Slides Only Important
Doctor's notes Extra information

Twitter :
@Pathology438

Objectives

- Understand the concept of cells and tissue adaptation to environmental stress including the meaning of hypertrophy, hyperplasia, aplasia, atrophy, hypoplasia and metaplasia with their clinical manifestations.
- Is aware of the concept of hypoxic cell injury and its major causes.
- Understand the definitions and mechanisms of free radical injury.
- Knows the definition of apoptosis, tissue necrosis and its various types with clinical examples.
- Able to differentiate between necrosis and apoptosis.
- Understand the causes of and pathologic changes occurring in fatty change (steatosis), accumulations of exogenous and endogenous pigments (carbon,silica,iron, melanin, bilirubin and lipofuscin).
- Understand the causes of and differences between dystrophic and metastatic calcifications.

Introduction to Adaptation to environmental stress

Cells sometimes need to adjust their structure and function to fit **changing demands**; within their physiological capabilities.

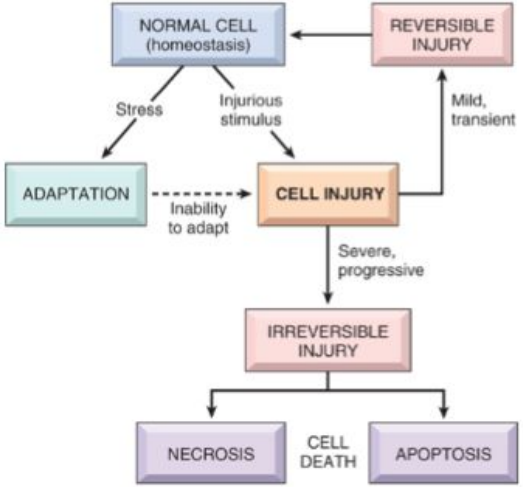
changing demand = physiological stress or pathological stimulus.

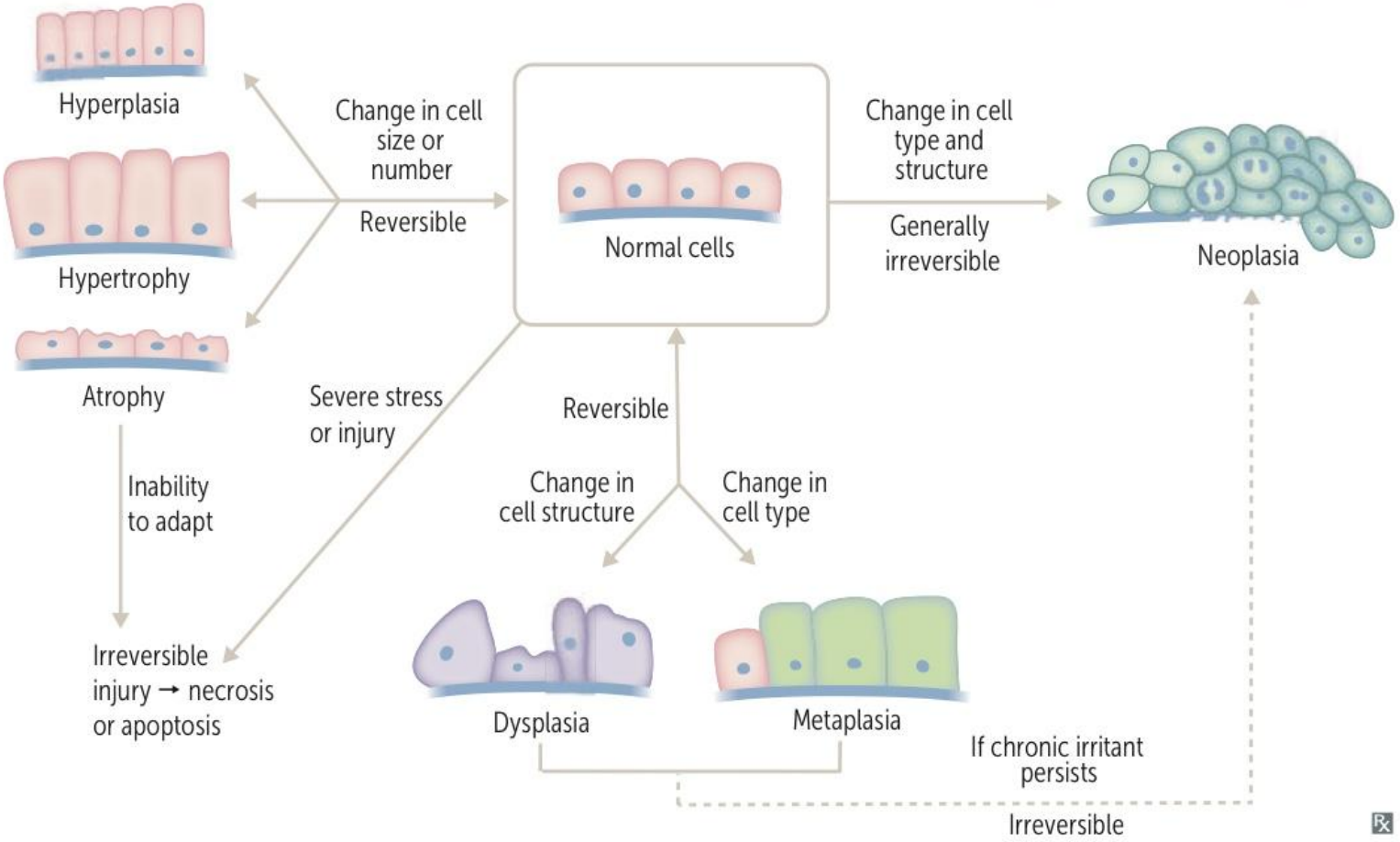
Adaptations: reversible changes in the number, size, phenotype, metabolic activity, or functions of cells in response to changes in their environment.

The principal adaptive responses are:

1. hypertrophy
2. hyperplasia
3. atrophy
4. metaplasia.

Within certain limits injury is **reversible**, and cells return to normal but severe or persistent stress results in **irreversible injury** and death of the affected cells.)




Hyperplasia
Hypertrophy
Atrophy
Change in cell size or number
Reversible
Normal cells
Change in cell type and structure
Generally irreversible
Neoplasia
Inability to adapt
Severe stress or injury
Irreversible injury → necrosis or apoptosis
Reversible
Change in cell structure
Change in cell type
Dysplasia
Metaplasia
If chronic irritant persists
Irreversible

Hypertrophy

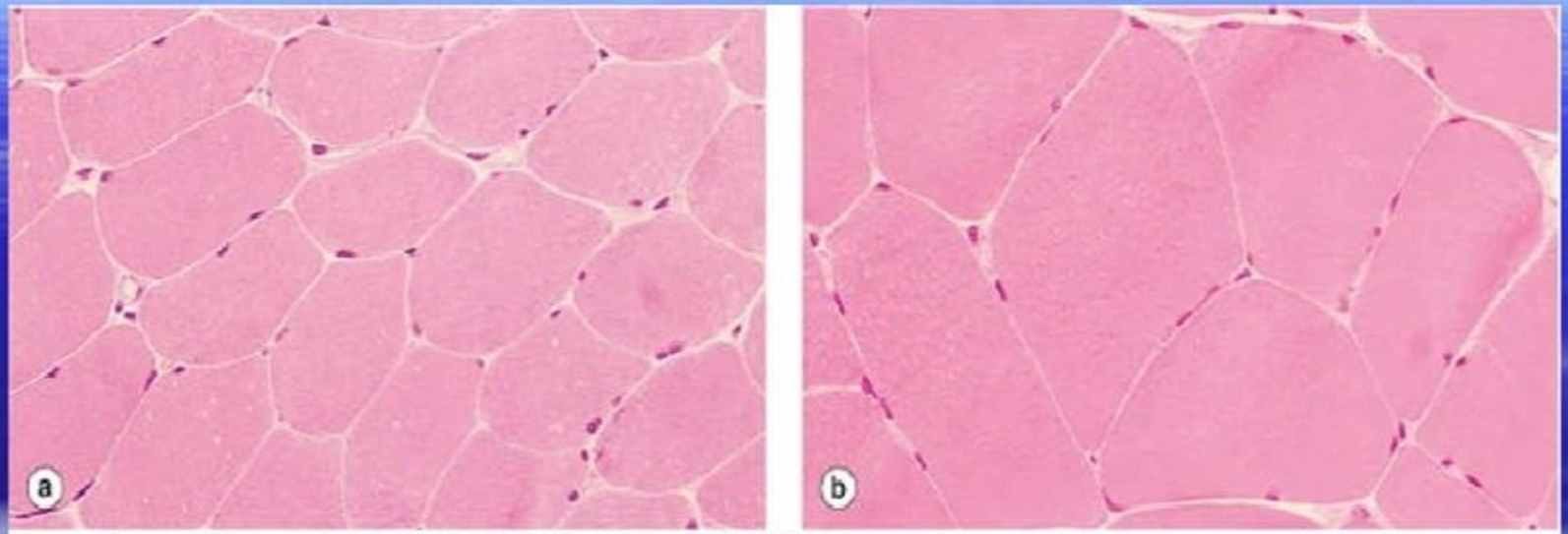
- Increased cell and organ size.
- In pure hypertrophy there are no new cells, just bigger cells containing increased amount of structural proteins and organelles.
- Increased demands lead to hypertrophy. when the cell need to do more work.
- Hypertrophy: it is normal if 1 or 2 cells increased in size but hypertrophy is due to increase in a lot of cells like (200 cell).
- Hypertrophy takes place in cells that are not capable of dividing e.g. striated muscles.
- Hypertrophy can be physiologic or pathologic.

Physiological Hypertrophy

1-Breast during lactation.
2-the skeletal muscles undergo only hypertrophy in response to increased demand by exercise
3-Pregnant uterus

Pathologic Hypertrophy

1-Cardiomyocytes of the myocardium in heart failure.
2-people who remove one kidney experience hypertrophy in the other.

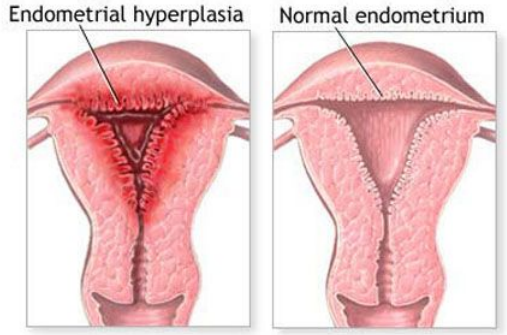


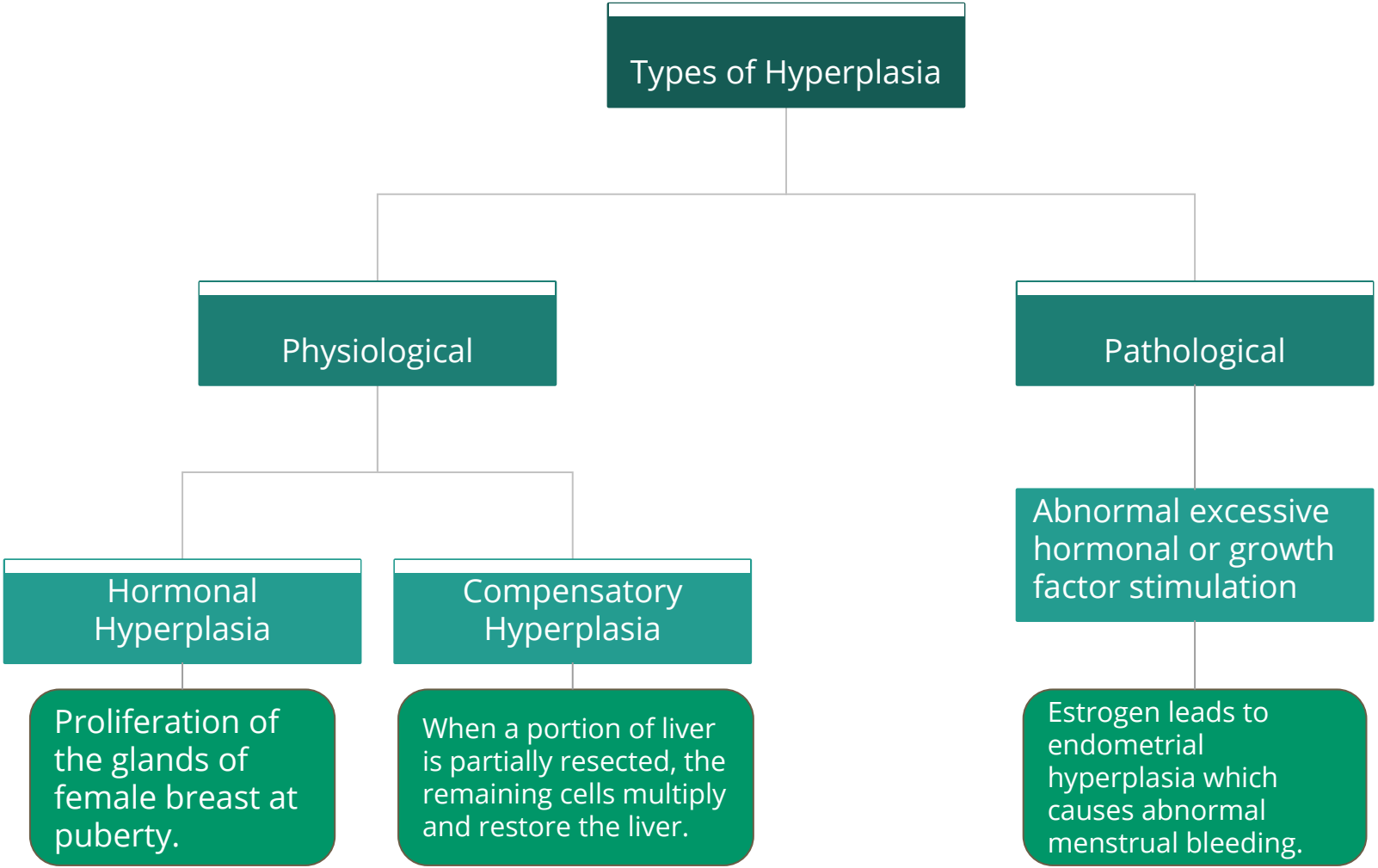
Hypertrophy of skeletal muscle in response to exercise. Hypertrophy in the absence of hyperplasia is typically seen in muscle where the stimulus is an increased demand for work. Taken at the same magnification, (a) shows muscle fibers in transverse section from the soleus muscle of a normal 50-year-old man, and (b) shows fibers from the same muscle in a veteran marathon runner. Note the dramatic increase in the size of the fibers in response to the demands of marathon running.

Adaptation	Opposite adaptation
Hypertrophy	Atrophy
Hyperplasia	Involution

Hyperplasia

- **Hyperplasia:** Increase in the size of an organ or tissue, caused by an increase in the number of cells.
- Occur in response to increase in demand.
- Occur by;
  - Growth Factor
  - Hormonal Stimulus
  - Irritation
- Only in cells that can replicate or contain abundant tissue stem cells: hepatocytes ✓.....nerve, muscle, cardiac ✗
- hypertrophy can be induced by hormone such as estrogen.
- usually occurs together with hypertrophy. for example During pregnancy, uterine enlargement is caused by both hypertrophy and hyperplasia of the smooth muscle cells in the uterus. also prostatic hyperplasia is another example




Types of Hyperplasia
Physiological
Pathological
Hormonal Hyperplasia
Compensatory Hyperplasia
Abnormal excessive hormonal or growth factor stimulation
Proliferation of the glands of female breast at puberty.
When a portion of liver is partially resected, the remaining cells multiply and restore the liver.
Estrogen leads to endometrial hyperplasia which causes abnormal menstrual bleeding.

Hypoplasia and Aplasia(not adaptive responses)

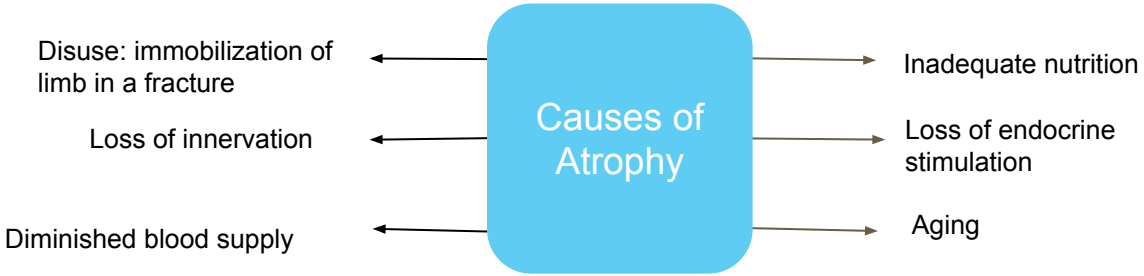
- **Hypoplasia:** refers to an organ that does not reach full size.
- -hypoplasia> ex: babies who are born with incomplete developed hands or legs.

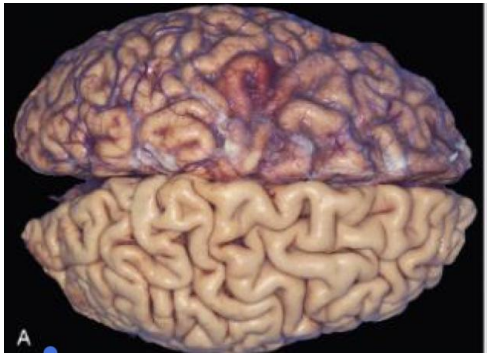
- **Aplasia**: failure of cell production.
- aplasia > ex: loss or absence of organs;like babies who are born without tibia or remus.

- both are developmental disorders
- one refers to incomplete development(hypoplasia), the other refers to complete loss or absence.

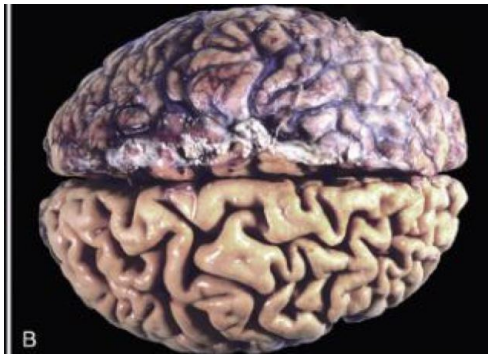
ATROPHY

- It is the **shrinkage in the size** of the cell.
- They have diminished function but cells are not dead.
- Hyperplasia can occur;
- Physiologically: loss of hormone due to menopause due to age.
- Pathological: denervation, atherosclerosis in the brain.
- Protein synthesis decreases due to low metabolic activity, this occurs by ubiquitin-proteasome pathway, and increase in protein degradation.
- Autophagy is increased in atrophic cells in attempt to survive.





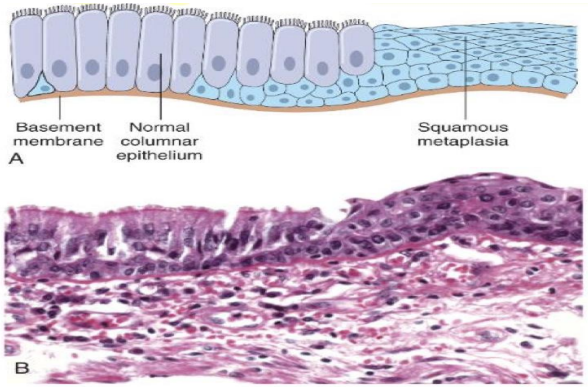
A. Normal brain of a young adult.



B. Atrophy of the brain in an 82-year-old man with atherosclerotic disease.

METAPLASIA

- **Metaplasia:** a change in which the cell changes from one type to the other.
- Reversible if causative agent is removed.
- Only occurs in epithelial and mesenchymal cells.
- Cells sensitive to a causative/toxic agent are replaced by another cell types better able to tolerate the environment.
- Tissue lose their functionality due to metaplasia.
- If stress persists it will lead to dysplasia and then neoplasia.
- Examples:-
  a. Squamous metaplasia
  b. Columnar metaplasia
  c. Osseous metaplasia
  d. Myeloid metaplasia



Metaplasia of normal columnar (left) to squamous epithelium (right) in a bronchus.

Squamous & Columnar cell metaplasia

1-Squamous metaplasia

- Columnar are replaced by squamous

  In Cervix: replacement is at the squamocolumnar junction

  In respiratory tract: Chronic injury caused by chronic smokers

  in the bronchus columnar epithelium $\xrightarrow[\text{to}]{\text{changes}}$ squamous cell
- Although the squamous will survive better, the protective function of the columnar epithelium is lost, such as mucus secretion and ciliary action.
- If the causative agent persists, it may cause malignant transformation.
- Smoking initially causes squamous metaplasia, and then squamous cell cancers.

2-columnar cell metaplasia

- Squamous replaced by columnar

  In esophagus: *barrett's oesophagus,* the normal stratified squamous epithelium changes to columnar epithelium.

This change can be precancerous and lead to development of adenocarcinoma of esophagus

Osseous and Myeloid metaplasia

This is only found in the Female slides

3-osseous metaplasia

Is the formation of new bone at site of tissue injury. cartilaginous metaplasia may also occur.

4-Myeloid metaplasia

Is the Production of hematopoietic tissue in sites other than the bone marrow, such as the liver or spleen.

Involution

This is only found in the Female slides

Involution : It is the reduction in cell number.

Hypoplasia:

- Hypoplasia refers to an organ that does not reach its full size. It is a developmental disorders and not an adaptive response.

Aplasia:

- The failure of cell production and it is also a developmental disorders e.g. during fetal growth aplasia can lead to agenesis of organs.

Cell Injury

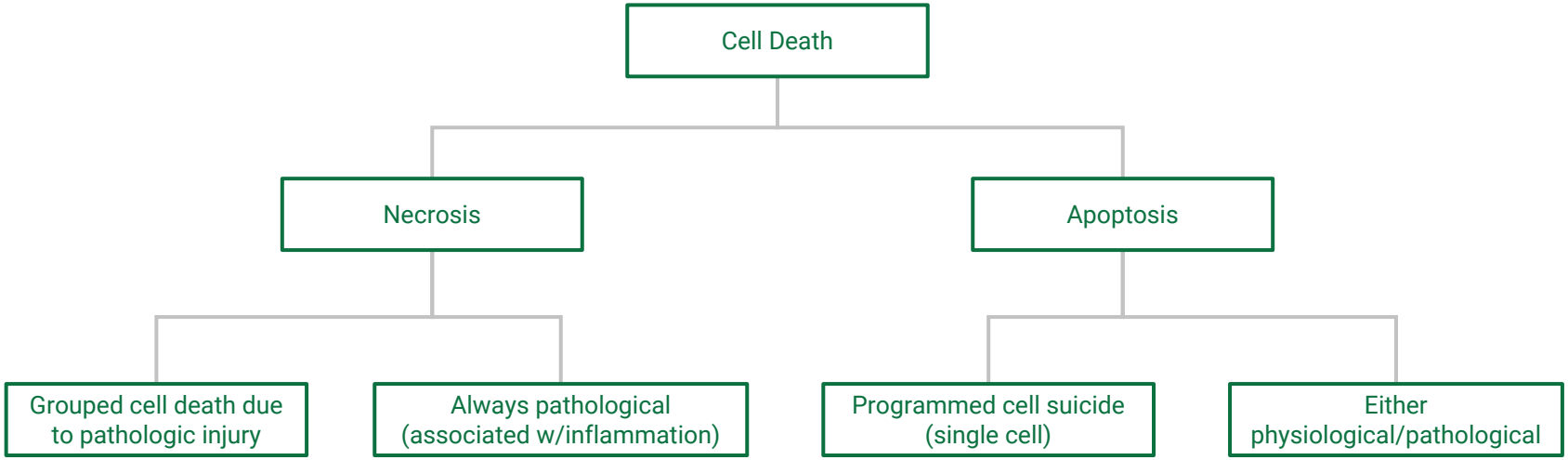
- Cell death
- Necrosis
- Apoptosis

Cell Injury:

When a cell fails to adapt to stress or external changes, it develops cell injury (can either be reversible or irreversible).

Cell Death:

When a cell injury is too severe and cannot be reversed, the ultimate result is cell death, which can be divided into two forms.



Causes of Cell Injury

01	**Oxygen Deprivation (Hypoxic)**	• Common cause of cell injury/death • Could be caused by myocardial infarction (ischemia), or anemia (low O2 carrying capacity) • Susceptibility order: Neurons-->Cardiac-->Hepatocytes-->Skeletal
02	**Physical Agents**	• Mechanical Trauma • Sudden atmospheric pressure changes • Radiation
03	**Chemical Agents**	• High O2 concentration • Poisons • Alcohol and Drugs
04	**Infectious Agents**	• Bacteria/Viruses
05	**Immunological Agents**	• Thyroid damage by autoantibodies
06	**Genetic Derangements**	• Sickle Cell Anemia
07	**Nutritional Imbalances**	• Hypernutrition • Malnutrition

Mechanisms of Cell Injury

1- Mitochondrial damage

- Low O2 supply (caused by ischemia) to cell will lead to mitochondria shutting down and no ATP production. Instead it produces Free radicals.

2-ATP depletion

ATP depletion means that redox reactions do not take place.

- Caused by mitochondrial failure and some toxins.
- Having no ATP will result in reduction of membrane pump activity, causing imbalance in the cell.
- Disturbing the solutes concentration causes the cell to swell and ER to dilate.
- Anaerobic glycolysis → glycogen (cell cannot make ATP, uses stored glycogen for energy.)

3-Influx of Ca into cell

- Calcium enters cell because of membrane pump damage→ activates enzymes that will trigger apoptosis

4- accumulation of free radicals (next slide)

5- permeability of membrane

Membrane damage caused by:

- 1- decreased phospholipid synthesis. (No ATP)
- 2- Increased phospholipid breakdown. (Ca high, phospholipase enzyme activate, break down membranes)
- 3- Free radicals.
- 4- Cytoskeletal abnormalities. (Ca high, Protease enzyme activate, damage cytoskeleton.)

Affected membranes:

- mitochondrial
- Plasma
- lysosomal

→ 1- Leakage of enzymes
2- digestion of cellular components
3- necrosis

6- accumulation of damaged DNA: Triggers apoptosis to prevent mutations.

Mechanisms of Cell Injury

- Reactive Oxygen Species (Free radicals) are atoms that have lost 1 or more electrons.. They are unstable, harmful, and hyper reactive.
- They enter reactions to stabilize themselves, but damage the cell in return.
- They attack nucleic acids/ proteins/ lipids.
- Free radicals increase under these circumstances:
  - Radiation.
  - Oxygen therapy and reperfusion injury.
  - Toxins.
  - Leukocyte response to inflammation.

Reperfusion: Tissue damage caused by blood supply returning after a period of ischemia

Common Free radicals:

1- Superoxide anion: O_2-

2- Hydrogen peroxide: H_2O_2

3- hydroxyl group: OH

Nitrogen Oxide: NO

Can be removed by:

- Antioxidants: e.g Vitamins A,C,E.
- Enzymes:

  1- Superoxide Dismutase(turns O2 to Hydrogen peroxide).

  2- Glutathione peroxidase (In cytoplasm) + Caspase (in peroxisomes) (turns hydrogen peroxide to water).

Mechanism of cell injury (pictures)

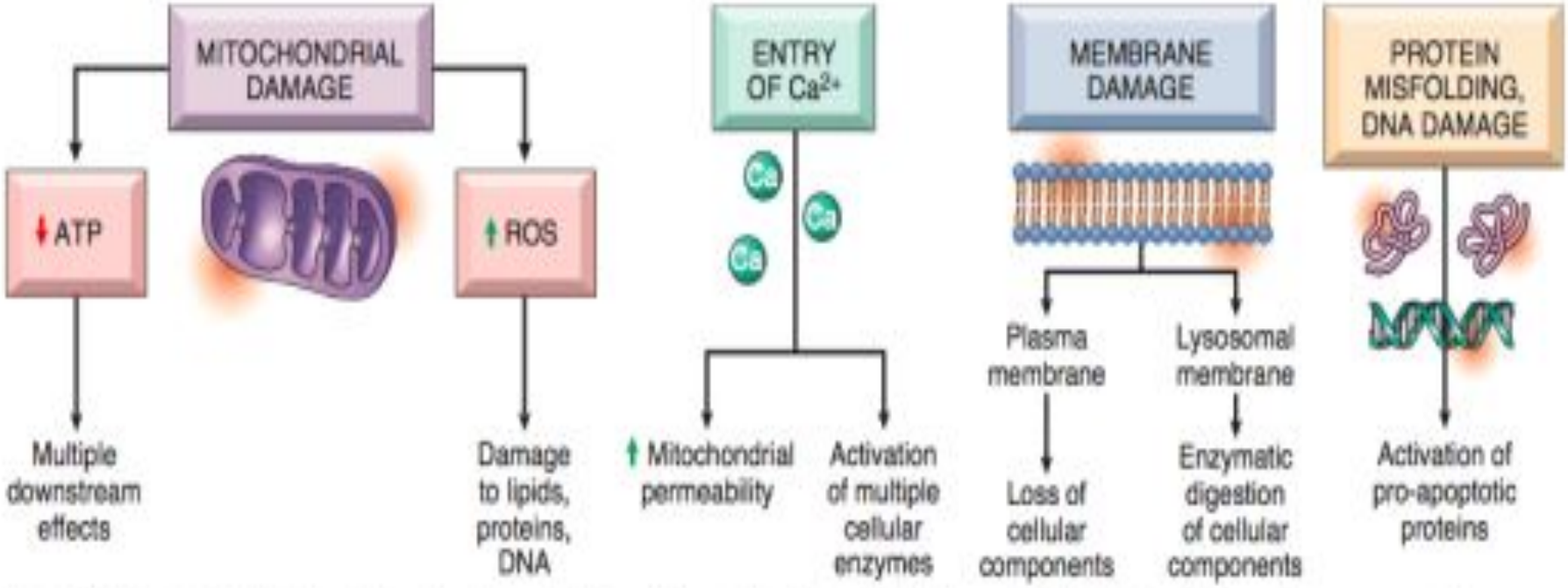
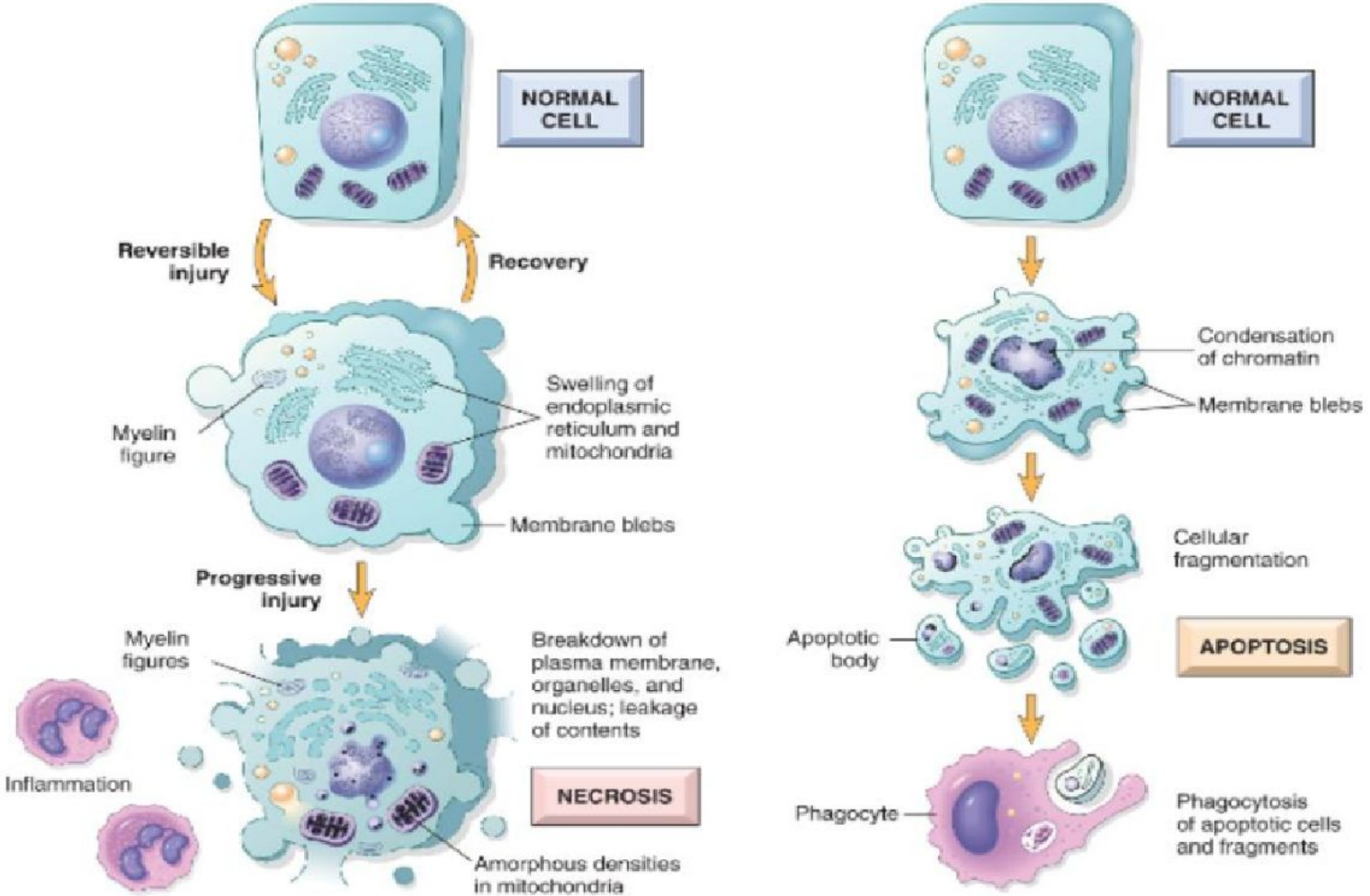
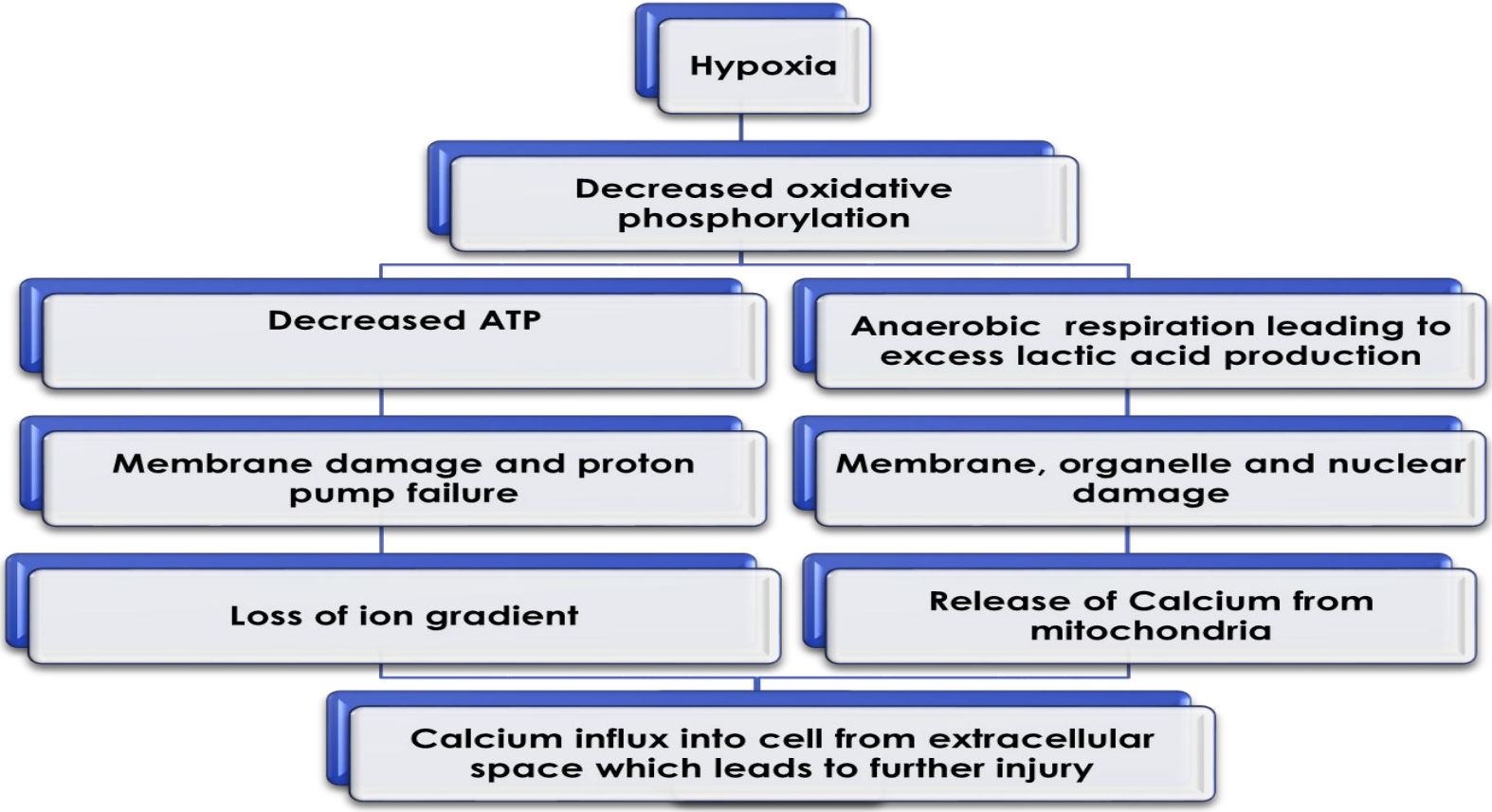


Figure 2-16 The principal biochemical mechanisms and sites of damage in cell injury. ATP, Adenosine triphosphate; ROS, reactive oxygen species.


NORMAL CELL
Reversible injury
Recovery
Myelin figure
Swelling of endoplasmic reticulum and mitochondria
Membrane blebs
Progressive injury
Myelin figures
Breakdown of plasma membrane, organelles, and nucleus; leakage of contents
Inflammation
NECROSIS
Amorphous densities in mitochondria
NORMAL CELL
Condensation of chromatin
Membrane blebs
Cellular fragmentation
Apoptotic body
APOPTOSIS
Phagocyte
Phagocytosis of apoptotic cells and fragments

MECHANISM IN HYPOXIC CELL INJURY



REVERSIBLE CELL INJURY

- The type of injury, the time duration of injury and the severity of injury will determine the extent of cell damage i.e. whether the injury is reversible or irreversible.
- **Earliest changes** associated with cell injury are **reversible**.

They are:

1. Swelling & vacuolization of cytoplasm called hydropic/ vacuolar degeneration.
2. Defect in protein synthesis. (Due to loss of ribosomes).
3. Swelling of cell organelles.
4. Disturbance in membrane permeability (imbalance of substances).
5. Myelin figures (less than irreversible).

The cell can cope with these changes up to a certain point,

and if the stimulus was stopped,

it will revert back to its normal state.

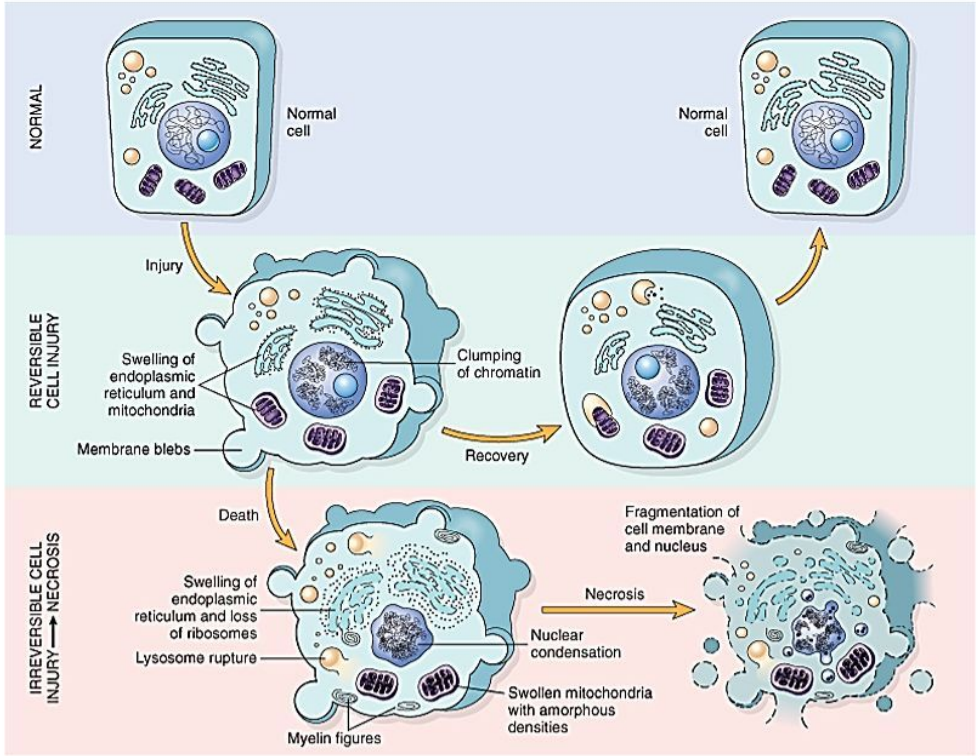
IRREVERSIBLE CELL INJURY

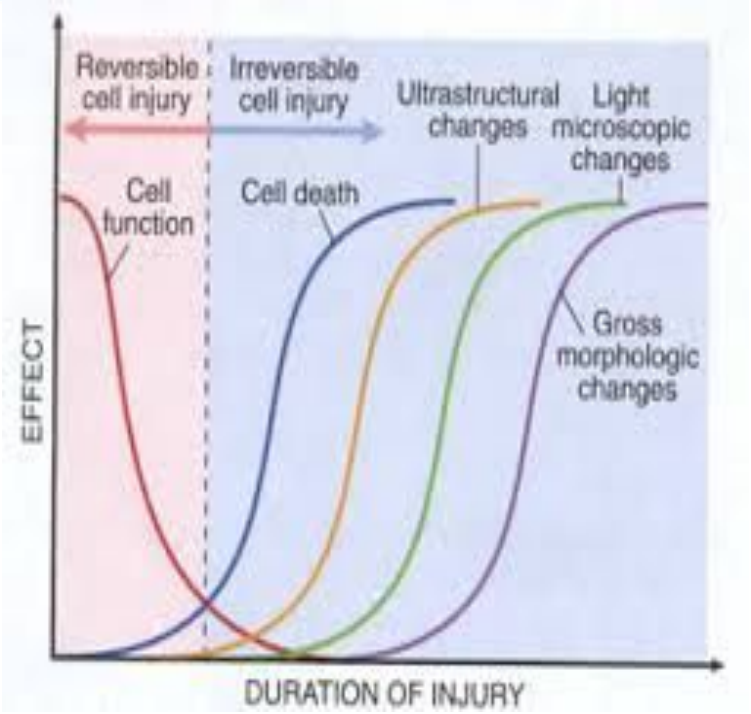
Persistent or excessive injury, however, causes cells to pass the threshold into **irreversible injury.**

Irreversible injury is marked by:

1. severe mitochondrial damage with the appearance of large, amorphous densities in mitochondria.
2. Severe plasma/cell membrane damage
3. Increased eosinophilia (Damaged DNA -> cannot form RNA -> less RNA in cytoplasm)
4. Numerous myelin figures
5. Rupture of lysosomes -> leakage -> digestion of cellular contents
6. Nuclear damage:
   - Pyknosis: DNA condenses into a solid mass and the nucleus shrinks ⇧ (Basophilia)
   - Karyolysis: Chromatin is lost, ⇩ (Basophilia)
   - Karyorrhexis: nucleus fragments (happens after pyknosis)

Reversible and Irreversible Cell Injury





Necrosis

Necrosis : is a type of cell death, due to enzymatic digestion and denaturation of intracellular proteins in the injured cell.

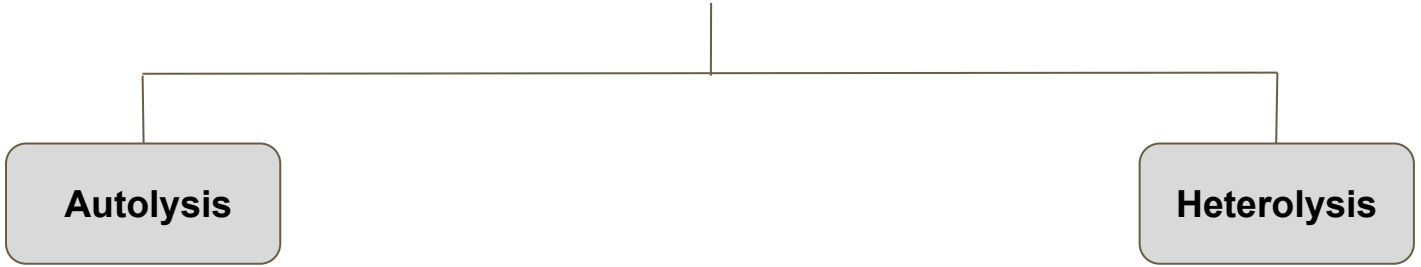
- It occurs in irreversible injury.
- It is usually associated with inflammation in the surrounding tissue.
- It involves the death of a group of cells in one area.
- Necrosis is always pathological

Necrosis can result in:

- Cessation/ loss of function of the involved tissue/organ.
- Release of enzymes and protein due to the complete rupture of the cellular cytoplasmic membrane, we can measure them in the blood (so we can diagnose the diseases by measuring the necrotic product) and also can help determine the time and the extent of injury e.g. Cardiac enzymes in myocardial infarction (heart attack).
- An inflammatory response

This is only found in the Female slides

Types of lysis

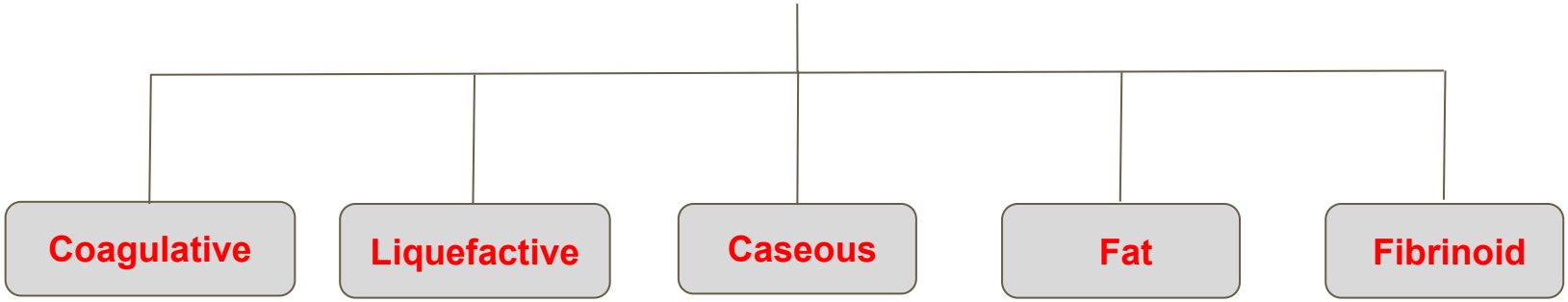


It is the death (disintegration) of cells or tissues by its own enzymes.

Seen in cells after death (post mortem).
Also seen in some pathologic conditions in living organisms.

It is the death (disintegration) of cells or tissues by enzymes from lysosomes of neighboring cell (usually leukocytes).

Types of necrosis



Coagulative necrosis

Characteristically seen when blood flow to an organ is affected leading to **ischemic** (hypoxic) death of cells in that organ.

Occurs in all solid organs except the brain.

It is infarction of the affected organ. It can be seen in:

- Heart (called as **myocardial infarction**)
- kidney (called as **renal cortical necrosis/infarct**)
- Spleen, liver (**splenic or hepatic infarct**) etc.

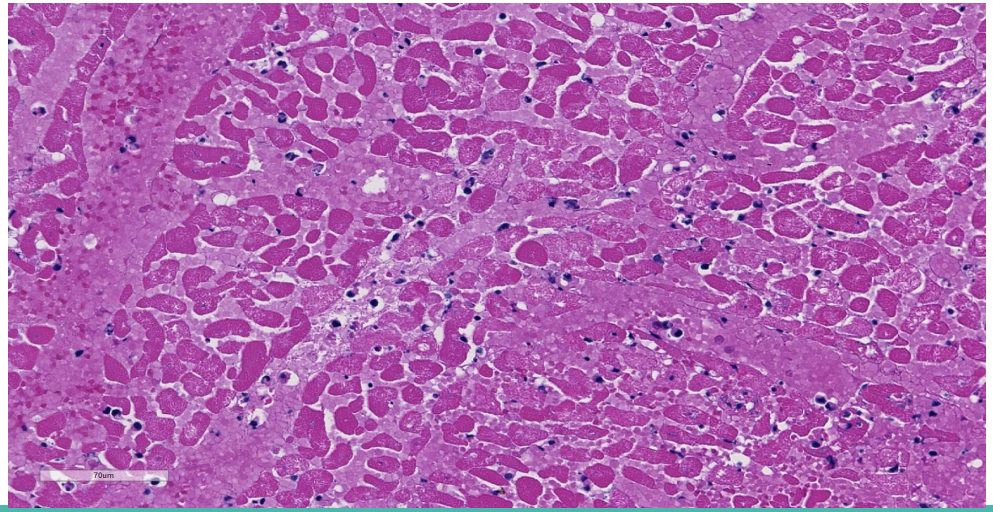
Grossly: The affected organ looks pale and firm (solid). It looks like cooked meat or boiled egg.

Microscopy: there is preservation of the general tissue architecture and always characterized by all the features of necrosis (well be explained next slide). Ultimately, the necrotic cells are removed by phagocytosis by the macrophages (they act like vacuum cleaners).

For more information about ischemia and hypoxia https://www.cvphysiology.com/CAD/CAD005

Microscopic features of coagulative necrosis

- Absence of nucleus (dissolution, disappear, fragmented, karyolysis, shrinkage, pyknotic).
- Complete rupture of the basement membrane.
- Swelling of the organelles.
- Increases eosinophilia.
- The architecture of the organ still preserved.

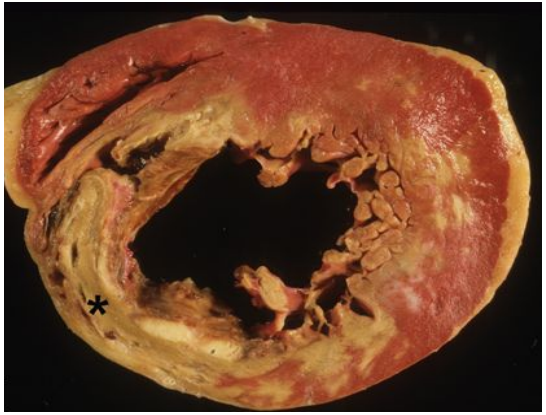


Myocardial infarction

Also known as heart attack, Necrosis of heart muscles resulting from **ischemia**.

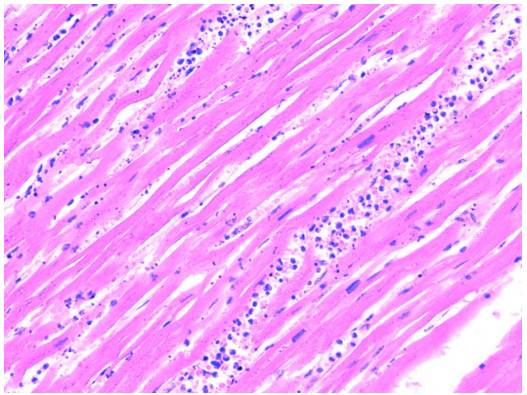
The major cause of this disease is **atherosclerosis** (accumulation of cholesterol on the blood vessels).

Symptoms: retrosternal chest pain.



Grossly: Myocardial infarct of the left ventricle is acquired by partly pale yellowish and partly hemorrhagic area, this area is most likely necrosis.

Microscope: Cytoplasmic membrane ruptured + increased eosinophilia + some nuclei become small and shrinkage (pyknosis) + some myocardial muscle fibers + disappear of some nucleus (kyrolysis).



In myocardium it takes 1-2 hours of ischemia > hypoxemia > hypoxia > necrosis **(in the brain about 3-5 minutes)**

The pathogenesis: Old man has diabetes, hyperlipidemia, high cholesterol and high triglyceride > Accumulate in coronary artery (which supply the myocardium with blood) > Atherosclerosis > Obstruction of coronary arteries (especially when he has thrombosis) > Occlusion the coronary artery > No oxygen come to the coronary artery (ischemia) > Cell injury > Coagulative necrosis.

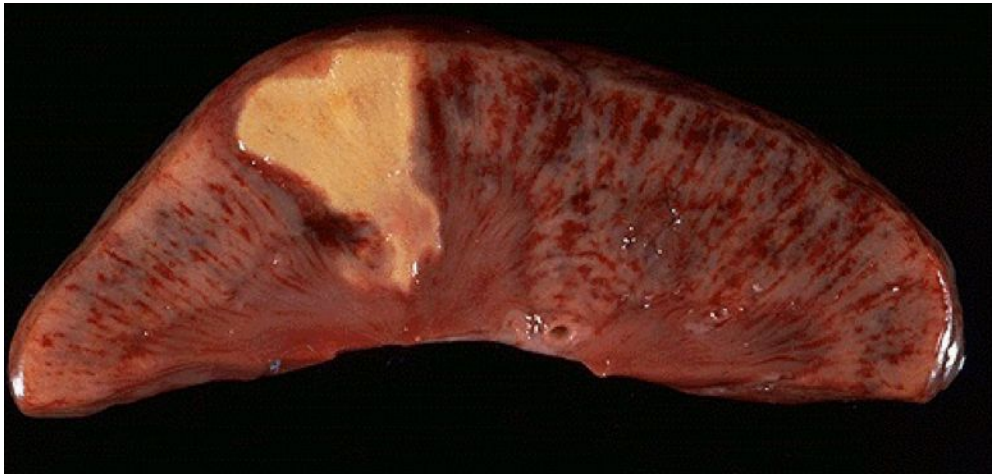
Kidney coagulative necrosis

The kidney undergone an infarction + coagulative necrosis because of ischemia of a particular blood supply.

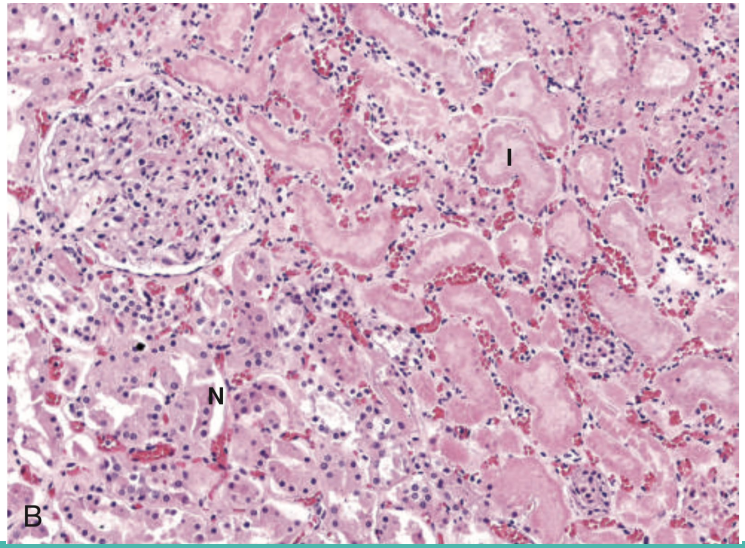
Grossly : We can see a wedge-shaped kidney infarct (yellow).

Microscopic : Cell outlines are preserved (cells look ghostly), and everything looks red.

Grossly



Microscopic



Liquefactive

- It is a type of necrosis which results in transformation of the tissue into a liquid viscous mass, usually occurs in organs that are rich in fluids, e.g. **Brain**, CNS.

This type of necrosis leads to a complete loss of architecture.

characteristically seen in:

- **Hypoxic** cell death in the central nervous system/brain.
- **Suppurative** (pus or abscess producing) infections especially bacterial infection.

Pus= صديد
Abscess= خراج

The affected tissue is softened/liquefied by the action of hydrolytic enzymes which are:

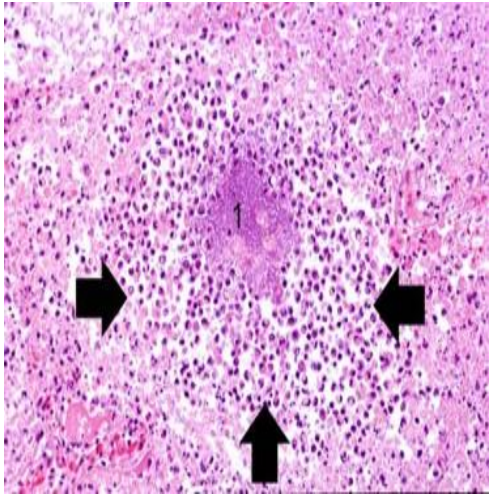
-- Released from the **lysosomes** in the brain cells.

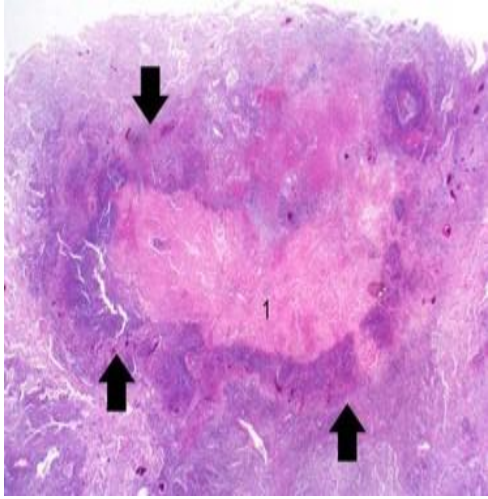
-- Released from the **neutrophils** in the pus/abscess.

The affected area is soft with liquefied creamy yellow center containing necrotic cells, and neutrophils and is called pus/abscess.

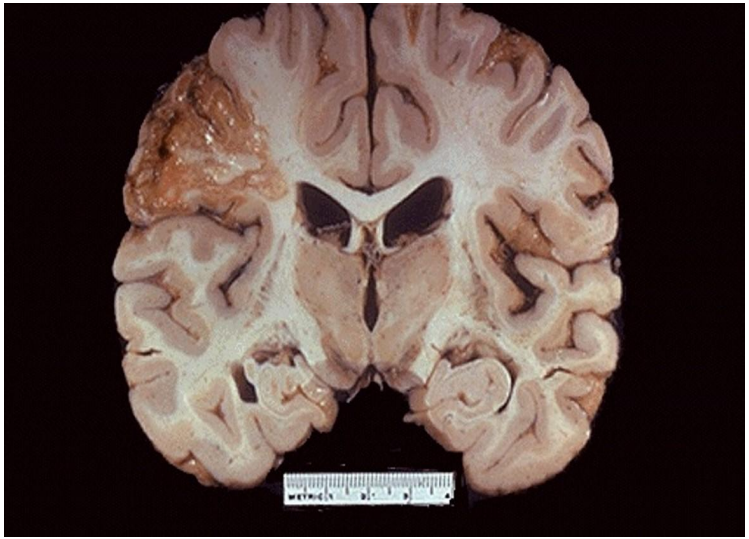
Ultimately, most necrotic cells are **phagocytosed**.

Liquefactive necrosis (center labeled one is necrosis) and surrounding is neutrophils.





An area in this brain tissues showing yellowish discoloration with hemorrhagic region.



Symptoms when liquefactive necrosis takes part on the brain include:

- Can’t move his right or left arm and leg.
- Can’t speak.
- Can’t swallow.
- Can’t breath.

This depends on the affected area of the brain.

Caseous

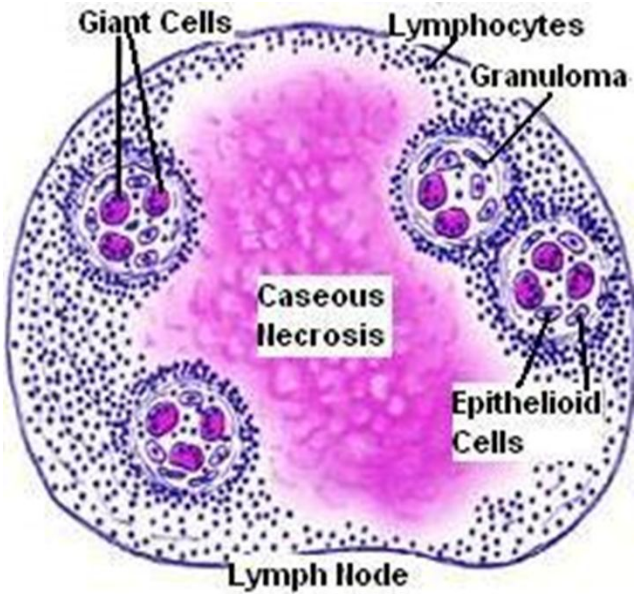
*Whenever you hear Caseous necrosis .. Always think of TB (Tuberculosis).Teamwork 437

It is a type of **coagulative necrosis** classically seen in **tuberculosis** (infection by mycobacterium tuberculi).

Tuberculosis is a very common disease which mostly affects the lungs.

Grossly : It is white, soft, curdy, **cheesy-looking "caseous" material.**

Microscopic : Examination, the necrotic area appears as amorphous pink granular debris surrounded by a collar of **epitheloid cells (they are modified macrophages)**, **lymphocytes and giant cells.**

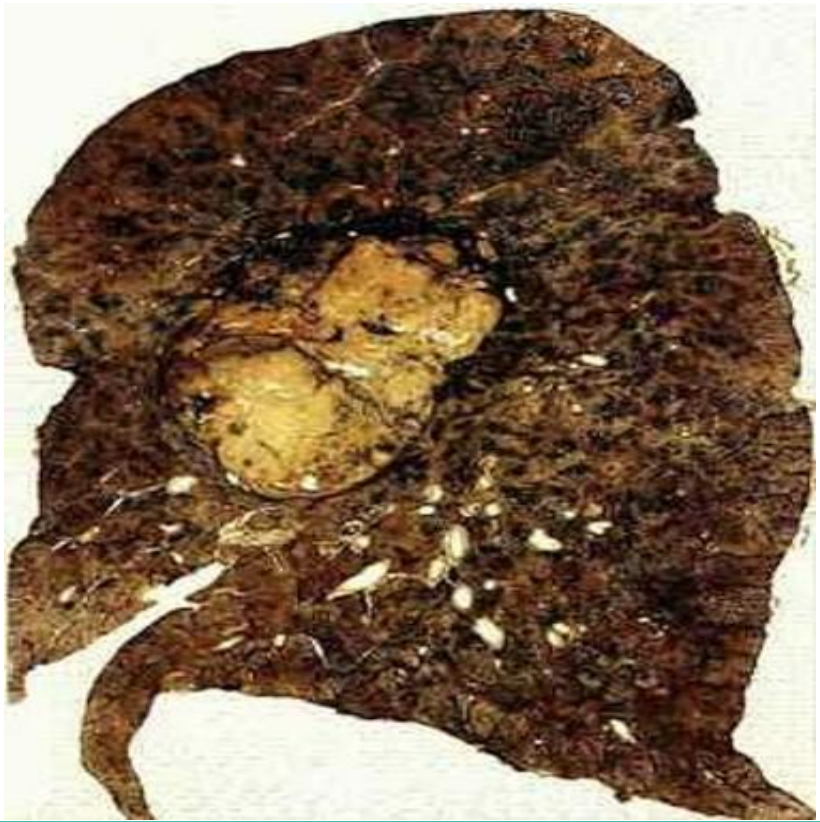


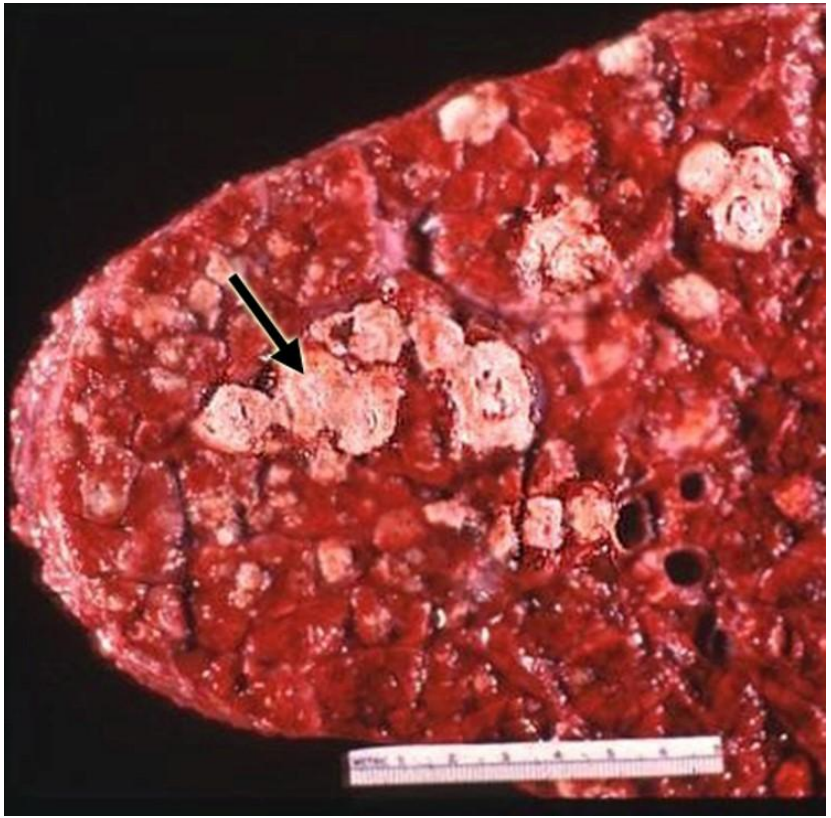
This is known as **granuloma**.

Here the tissue architecture is completely obliterated (lost).

(Unlike the coagulative necrosis where the general tissue architecture is preserved).Teamwork 437

Tuberculous lung with a large area of caseous necrosis. The caseous debris is yellow-white and cheesy.





Fat

It is necrosis of fat cells, occurs in any organ contains **fats**.

- Typically, it is seen in acute pancreatitis in which the injured pancreatic cells release the **lipase** and amylase enzymes into the fat in the abdominal cavity and cause enzymatic digestion of fat cells.

- The released **lipase** breaks down the fat cells into glycerol and free fatty acids.

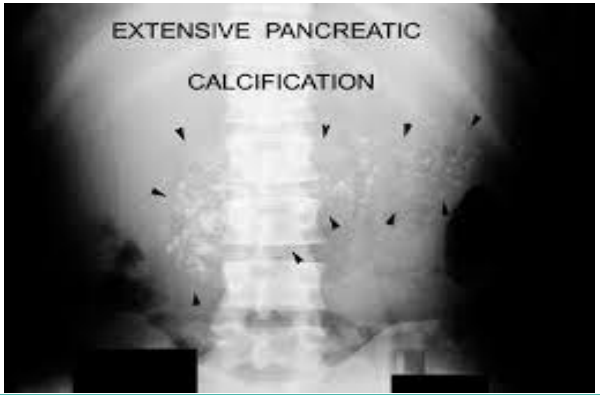
- The produced fatty acids combine with **calcium** circulating in the blood to produce calcium soaps which looks like chalky white spots in the necrotic fat. This process is called as fat saponification.

- The outlines of necrotic/dead fat cells can be seen. (Inflammation is minimal)

- Fat necrosis can also be seen in breast fat and other fatty areas due to traumatic injury.

- When you look under the microscope we find dead adipocyte (because there's no nuclei + the cytoplasmic membrane in many areas ruptured) .

so the patient will have calcifications.

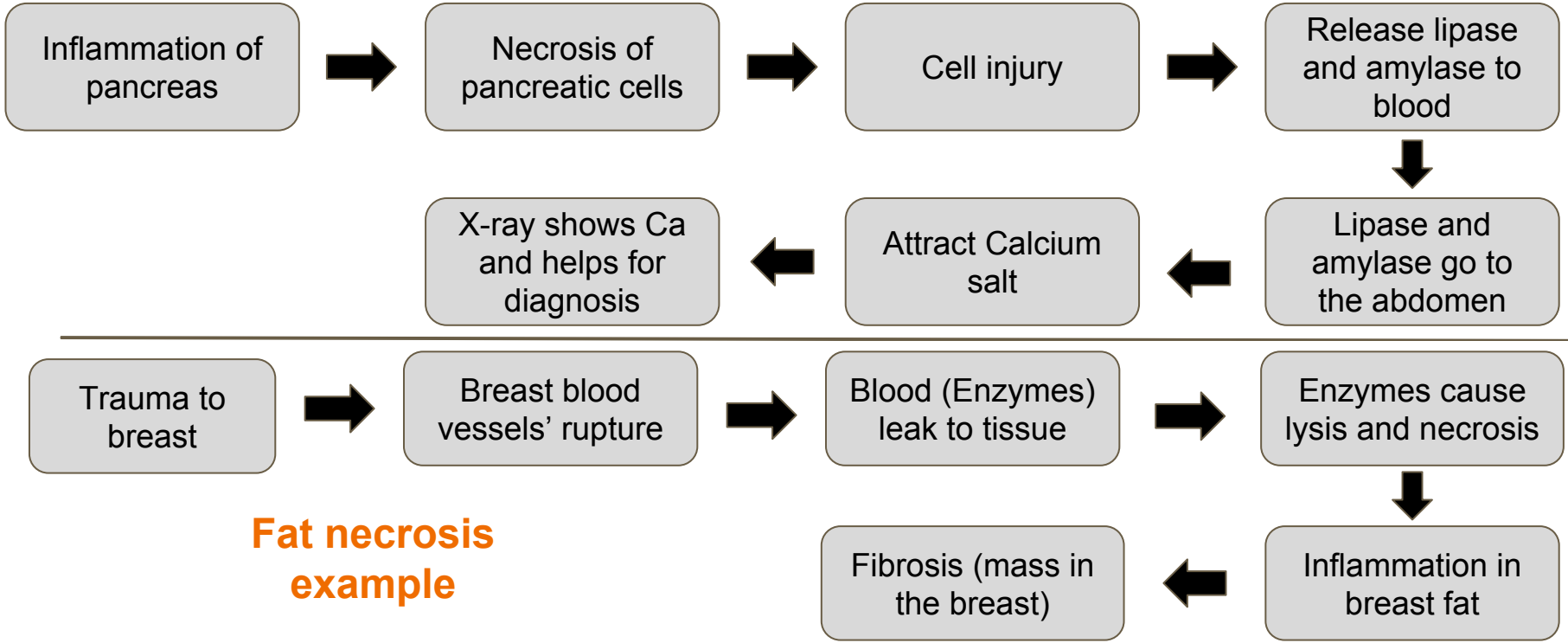


Fat Cont’

When you have a patient with a chronic abdominal pain and you do a chest X-ray you can find the calcification (because the calcium is very dense).

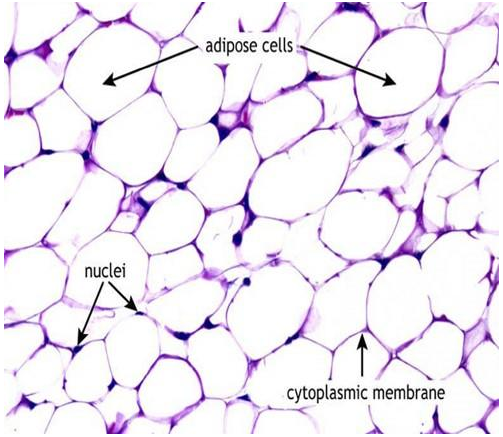
Pancreatitis does NOT necessarily cause **hypercalcemia** (will be explained in this chapter). Pancreatitis may be present with normal calcium levels in the blood.

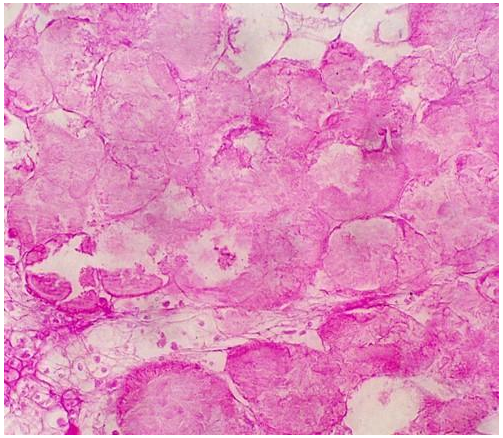
Pathogenesis:



Fat necrosis example

Normal adipose tissue





Fat necrosis

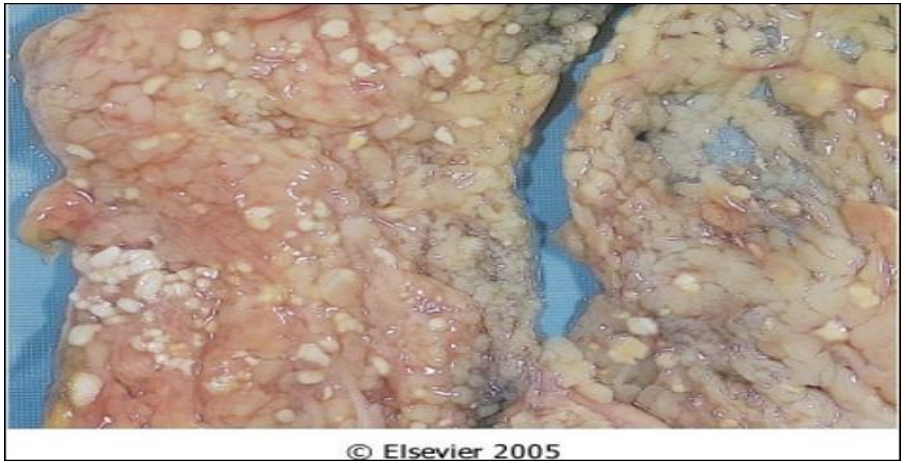


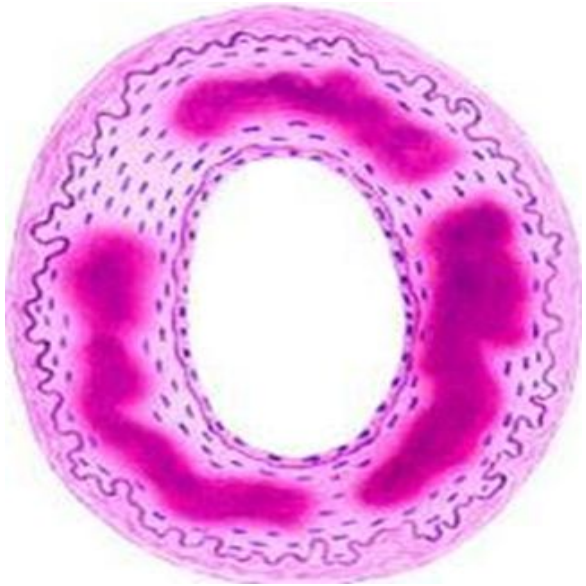
Figure 1-21 Foci of fat necrosis with saponification in the mesentery. The areas of white chalky deposits represent calcium soap formation at sites of lipid breakdown.

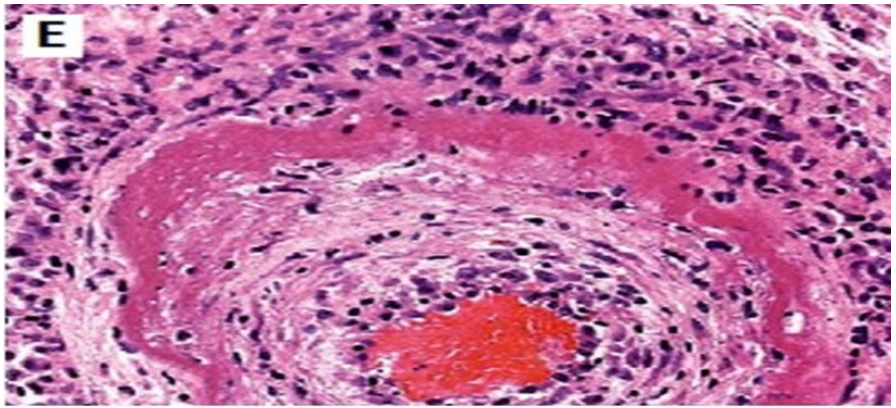
Fibrinoid

It’s a type of necrosis, which occurs in **blood vessels** usually as result of immune mediated diseases (autoimmune diseases) or severe hypertension.

There is deposition of fibrin material in the arterial walls, which appears smudgy and acidophilic/eosinophilic.

- An autoimmune disorder occurs when the body's immune system attacks and destroys healthy body tissue.





Fibrinoid necrosis in an artery. The wall of the artery is bright pink with dark neutrophils

التهاب كبيبات الكلى

Glomerulonephritis

This’s a blood vessel taking from the **kidney**

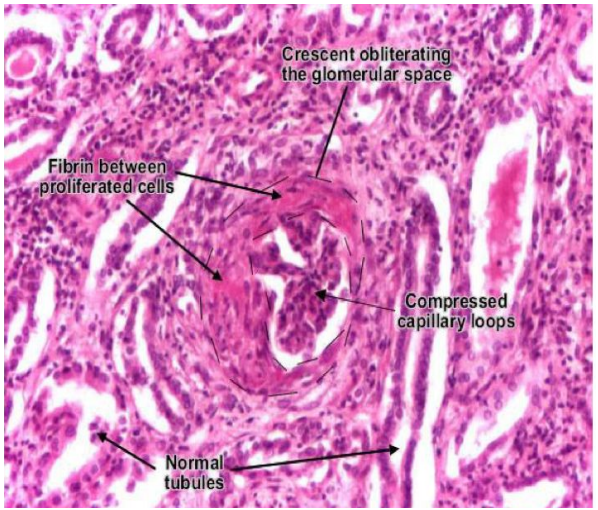
This person has got an **autoimmune disease** so this patient has and immune complex inside his blood (a large molecule consisting of antigens + antibodies bound together) this molecule goes into the circulation

But because it has got a very large molecular weight

It gets entrapped in the walls of the blood vessels

Then it creates an inflammatory reaction and this reaction will lead to cell injury

The injury will lead to **Fibrinoid necrosis**.



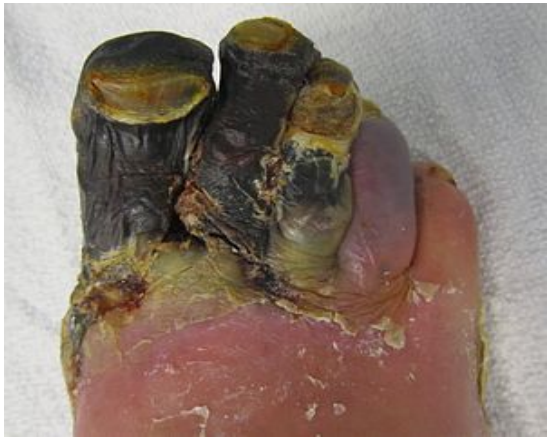
Gangrenous

It's **not** a main type of necrosis.

Gangrenous has two types :

1. Dry gangrene (mummification): it is a form of coagulative necrosis that develops in ischemic tissue.

- Is non-infected ischemic coagulative necrosis of tissue, It is without superadded infection.
- The affected part is dry, shrunken and dark reddish-black.
- Very common in patients who have **diabetes mellitus**, diabetes increases the incidence of atherosclerosis.
- An incident of atherosclerosis > obstruction of the blood vessels > ischemia > hypoxia > low O_2 coming to the tissues > cell injury **(irreversible)** > the patient comes to you with black fingers or toes and loss of sensation > the area infected has to be amputated as a **treatment**.



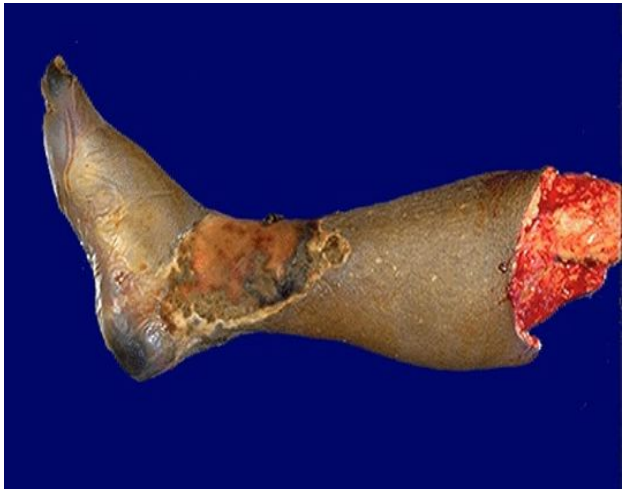
Gangrenous Cont’

2. Wet gangrene (infected) :

It is dry gangrene with superadded bacterial infection (putrefactive).

- Develops rapidly due to blockage of venous (mainly) and/or arterial blood flow.
- Rare and it occurs in certain circumstances (like war) when an open wound comes in contact with **soil**.
  .
- Gram-positive (saprogenic) Clostridia species is anaerobe (does not require oxygen for growth) so it needs to produce gas forming bubbles and a very bad smell.
- It has a **poor prognosis** compared to dry gangrene. **WHY** ?

  Because the infection can spread to the rest of the body (septicemia) and be life threatening (death).
- The affected part becomes foul smelling and black and starts decomposing.
- Treatment : Amputation.
- Diabetes can be a risk factor for wet gangrene



How do I use the information that I got about necrosis to make the diagnosis?

Damage in the organ	Enzymes elevated
Cardiac muscle (myocardium)	Troponin I & Troponin T**, Creatine Kinase Mb isoform**
Liver (Hepatocytes)	Alanine transaminase (ALT), Aspartate transaminase (AST)
Striated (skeletal) muscles	Creatine Kinase (CK-MM4)
Pancreas	Lipase, Amylase

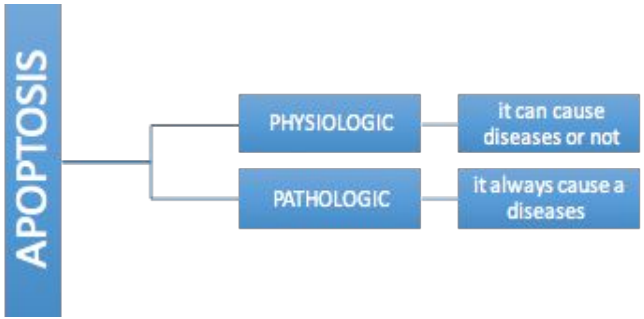
Apoptosis

APOPTOSIS: is programmed cell death.(or single cell death)
Apoptosis means "falling off". It is a type of cell suicide

•Is results from activation of 'death pathway genes

•It is a pathway of cell death in which cells destined to die activate their own enzymes to degrade their own nuclear DNA and proteins. *(mentioned in robbins)*

•Usually, there is just a single cell undergoing apoptosis; NOT a group of cells or a whole tissue.
•no inflammatory reaction is found during apoptosis.



Note: Apoptosis and necrosis can sometimes coexist

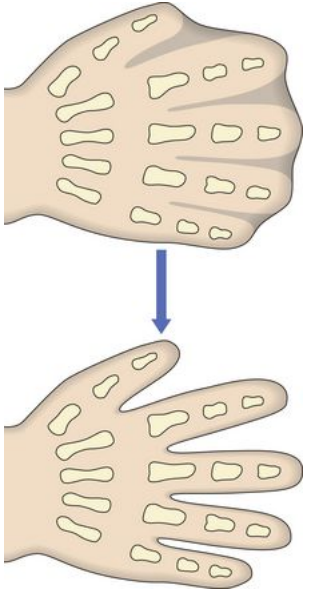
Apoptosis in Physiologic Situations

Examples:

- **Embryogenesis** (death of embryonic cells in the limb buds, (fingers of your hand) **leading to the formation of finger** and toes.

If apoptosis doesn't happen then he has a congenital malformation and some of his fingers are stuck together.

- **Hormone-dependent**: e.g. endometrial cell breakdown during the menstrual cycle, the regression of the lactating breast after weaning, and prostatic atrophy after castration (adaptive atrophy).
- **Apoptosis in proliferating cells** (Predetermined death)**:** e.g. intestinal epithelial lining is always being replaced. (cells that are always being changed).
- Cells that after performing their function undergo apoptosis e.g. neutrophils and lymphocytes in inflammation.
- Sometimes body produced harmful lymphocytes and they are also destroyed by apoptosis



Embryogenesis

Apoptosis in Pathologic Conditions

- **Hepatitis virus:** induced liver cells apoptosis (Acidophilic bodies)
- **Immune injury:** related skin keratinocytes (Civatte bodies) seen in certain skin diseases
- **Corticosteroid:** induced atrophy of the neonatal thymus. (Thymus of infants)
- **Pathologic atrophy in organs** e.g. pancreas, parotid gland, and kidney
- **Cell death in tumors** (usually accompanied by necrosis).
- **Cell death produced by injury e.g. radiation.**

Note : Some time apoptosis can be precancers

Mechanism

- The death pathway genes are activated which trigger apoptosis.

Cell shrinkage.

- **Chromatin condensation in the nucleus:** This is the most characteristic feature of apoptosis. The nucleus may break up into fragments.

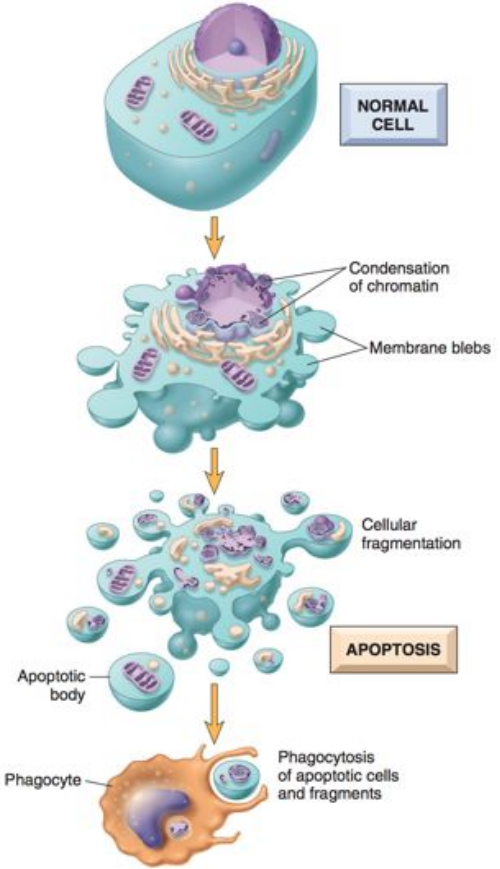
- **Formation of cytoplasmic blebs and apoptotic bodies:** The apoptotic cell first shows surface blebbing, then fragments into membrane bound apoptotic bodies. The apoptotic bodies contain cytoplasmic content with or without nuclear material.

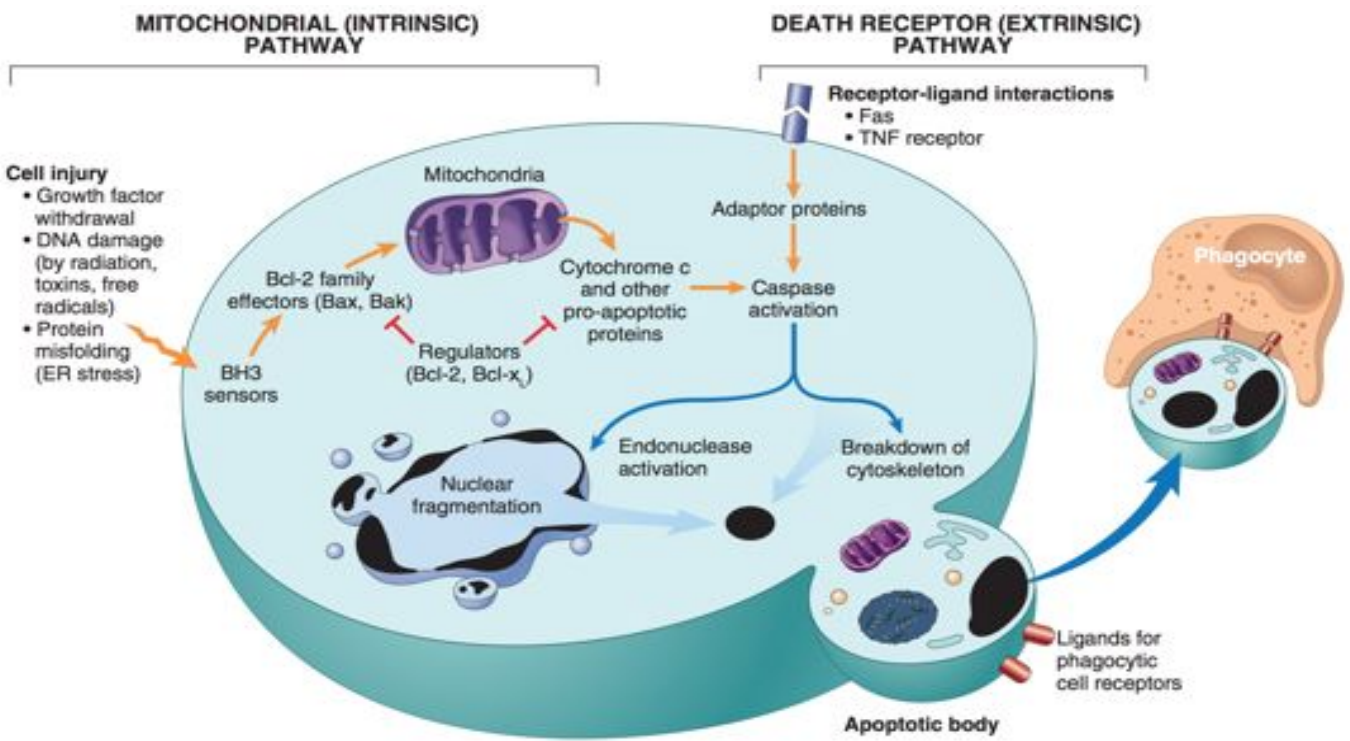
- **The cell's plasma membrane remains intact.** The plasma membrane of the apoptotic cell sends signal to macrophages, inviting the macrophages to phagocytose it.

- **Phagocytosis of apoptotic bodies by the macrophages.** Because, during the entire process, the apoptotic body is bound by plasma membrane, there is no release of the cytoplasmic content into the surrounding tissue and therefore there is no inflammation.

Apoptosis is very important if apoptosis doesn't happen then unwanted cell won't die and this can cause or lead to cancer

Unwanted mean: that they are no longer useful for the body or they are expired so the body needs to replace them to make new ones



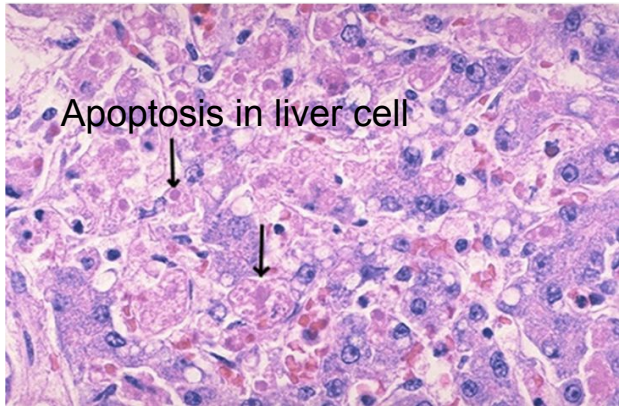


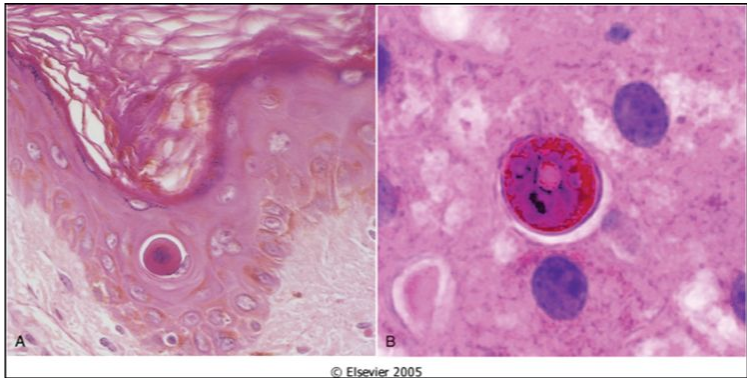
Trigger > bh3 receptor > activation of caspases >folding of proteins > damage in the intranuclear inclusion > fragmentation of the nucleus > apoptotic bodies >cell dies > phagocytosis ether by macrophages or adjacent cell

Morphology of Apoptosis

Histological appearance:

- Apoptotic cell appear Round or Oval mass.
- The apoptotic cell is intensely Eosinophilic.
- Dense nucleus.
- No Inflammation.





Note: Usually, there is just a single cell undergoing apoptosis.

Comparison Between Apoptosis and Necrosis:

	Feature	Necrosis	Apoptosis
1	Cell Size	Enlarged (swelling, Bigger)	Reduced (shrink, smaller)
2	Nucleus	nuclear changes: karyolysis,pyknosis, and karyorrhexis	Fragmentation (break down) into nucleosome sized fragments.
3	Plasma membrane	Disrupted (braked)	Intact (held together), with altered structure, especially the orientation of lipids.
4	Cellular contents	Digested by enzymes and may leak out of the cell	Intact and may be released in apoptotic bodies.
5	Adjacent inflammation	Inflammation is usually present	No inflammation
6	Physiologic or pathologic role	ALWAYS pathologic.	Physiologic most of the time. It may be pathologic in some times especially if there is DNA damage.

Intracellular accumulations

Some substances can accumulate inside the cell in large amounts and cause problems in the cell and the organ. The substance may accumulate in either the cytoplasm or the nucleus.

The accumulating substance can be:

- Substance that is present in the cell **normally** but has accumulated in excess.
- An **abnormal** substance that is not present in the cell normally. It can be either: **Exogenous** (from outside the body) **Endogenous** (from inside the body)
- **Pigments:** They can be endogenous or exogenous.

Substance that is present in the cell normally:

A) Water :

Abnormal accumulation of water in cells is called hydropic change (cellular swelling).
It is an early signs of cellular degeneration in response to injury.
It is due to the failure of energy-dependent ion pumps present on the plasma membrane and this leads to loss of normal ionic and fluid homeostasis.

B) Glycogen :

accumulates in the liver, muscles or kidneys in patients with inborn **errors of glycogen metabolism** or **diabetes mellitus.**

***Glycogen storage diseases: it is a group of genetic diseases in which there is abnormal glycogen metabolism.**

C) Protein :

accumulates in the proximal renal tubules in patients with **proteinuria.**

Substance that is present in the cell normally:

D) Lipids :

All major classes of lipids can accumulate in cells :

- **Triglycerides (fatty change):**
  Accumulates in the liver in patients with chronic alcoholism, and who are extremely obese.
  Also called **steatosis**. **Caused by : ALcohol, diabetes, Starvation, Severe Anemia, etc**

- **Cholesterol/cholesterol esters :**
  (Can be seen in atherosclerosis in which there is accumulation of cholesterol in the smooth muscle cells and macrophages in the wall of arteries).

  ***Atherosclerosis leads to heart disorders.**
  ***Lipids > triglycerides > most likely found in the liver.**

- **Phospholipids**

E) Pigments:

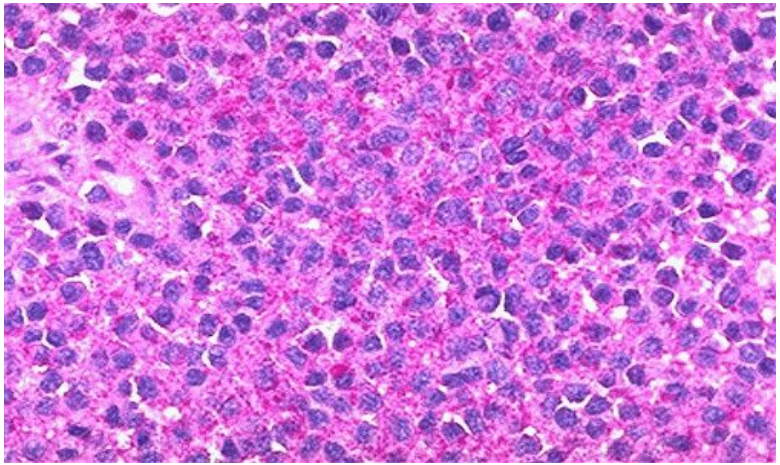
- **Exogenous.**
- **Endogenous.**

Accumulation of Glycogen:

Glycogen stains pinkish/violet with mucicarmine stain or the periodic acid schiff (PAS) stain. And they appear as clear vacuoles within the cytoplasm.

- **Glycogen accumulation is seen in:**

- **Diabetes mellitus: Glycogen is found in the proximal convoluted tubules of kidney, liver, the β cells of the islets of Langerhans and heart muscle cells etc.**
- **Glycogen storage diseases: (previously mentioned).**



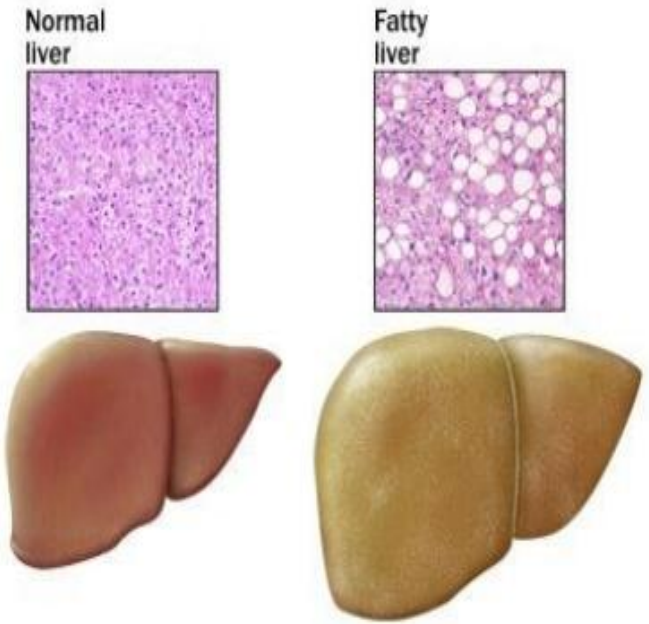
Steatosis (Fatty Change):

This is only found in the Female slides

Morphology of Steatosis in liver :

- **Gross :** In mild cases liver looks normal. In severe cases liver is enlarged, yellow and greasy.
- **Light microscopy:** clear vacuoles in the cytoplasm, cells rupture, and the fat globules merge, producing a so-called fatty cysts.

The lipid stains orange-red with Sudan IV or Oil Red-O stains



An abnormal substance that is not present in the cell normally:

This is only found in the Female slides

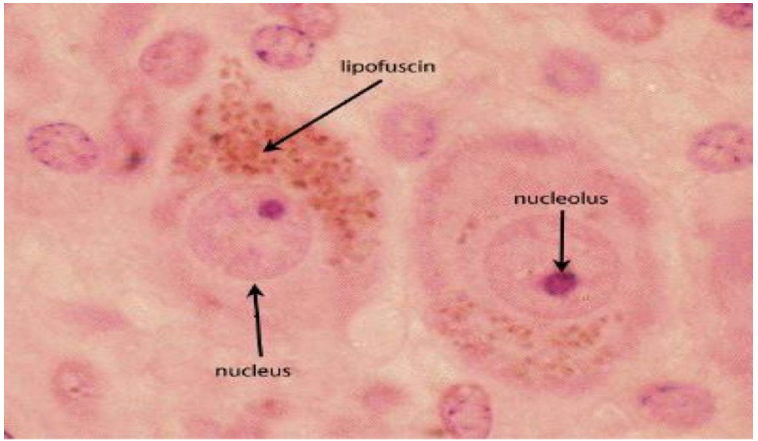
- **Exogenous** (from outside the body) e.g. a mineral or component of bacteria etc.

- **Endogenous** (from inside the body) e.g. a product of abnormal synthesis or metabolism.

Types of pigments

a. **<u>Lipofuscin</u>** (aging pigment) (tear and wear pigment) : It looks brown yellowish found in the lysosomes of older people. It is mostly found in the **liver & the heart**. It is a sign of aging & it is **<u>NOT</u>** pathologic.

- If it is not pathological why should we know it ?? To not mix it with other pigments and make wrong diagnosis .
- Indicate history of free radical injury and lipid peroxidation.



Types of pigments cont’

b. **Hemosiderin** (Iron accumulation)

The iron-rich brown pigment derived from hemolyzed red blood cells .

- Hemochromatosis (primary rare genetic disorder)
- increase in iron absorption in the intestine caused by gene alteration
- Accumulate in the liver , pancreas and skin
- Appears gray in the skin (pigmentation)
- causes bronze diabetes

- Hemosiderosis (secondary)
- needs blood transfusion because of anemia
- iron accumulation in liver, spleen and bone marrow .

Cont’

c. **Melanin** is the brown pigment found in the melanocytes and melanomas that gives the dark color to the skin .

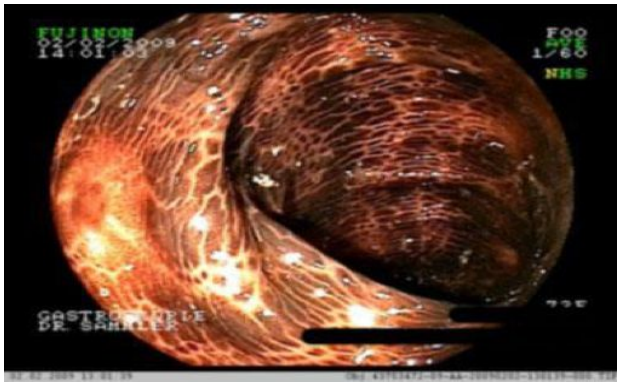
Melanosis coli : it **isn’t pathological** . It is found in people who have chronic constipation (إمساك مزمن) , especially if **laxatives** (مسهلات) or purgatives were used . The cells of the colon become black and (**melanin like**) chemicals are accumulated in the cells of the colon .

- **DO NOT MIX between** melanin pigment and melanosis coli . They are not the same thing . In melanosis coli a pigment which looks very much like melanin is found in the intestines .

hyper-pigmentation (just remember having a

in your face for one week when it is gone

your left with a mark)



Cont’

d. Tattoo (Indian ink) : Indian ink may be used by tattoo parlors to make a tattoo. This ink is antigen and forms an allergic reaction. It is a foreign chemical. Macrophages engulf the ink but can’t . Macrophages stay in the dermis of the skin (2nd layer of the layer) . When taking a biopsy , we find macrophages containing blue granules of pigments .

e. Bilirubin : Yellowish substance produced during the breakdown of RBCs . Accumulation of bilirubin can cause severe cholestasis jaundice.

Exogenous pigment

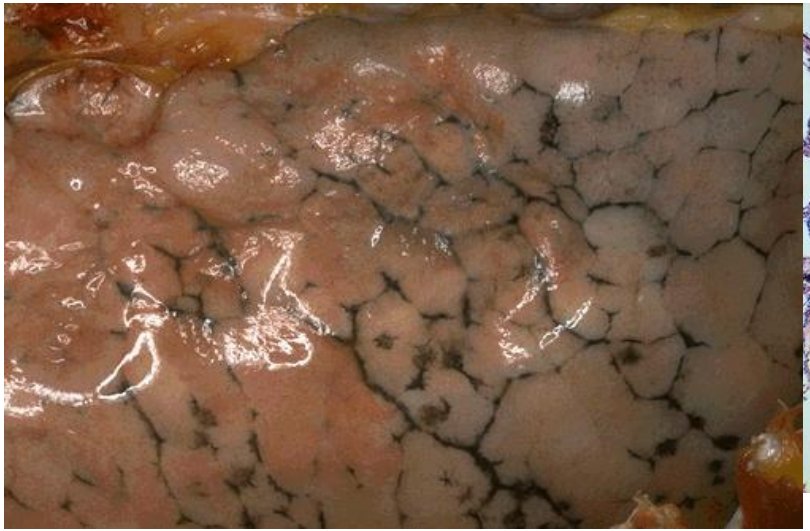
- **Anthracosis**: the most common exogenous pigment is carbon pigment or coal dust
- which is an air pollutant. when breathing dirty polluted air, it is picked up by macrophages in the lung alveoli and also transported to the neighboring lymph nodes.
- In the coal mining industry, there is too much carbon dust in the lung of coal miners which leads to lung disease known as **coal workers' pneumoconiosis**

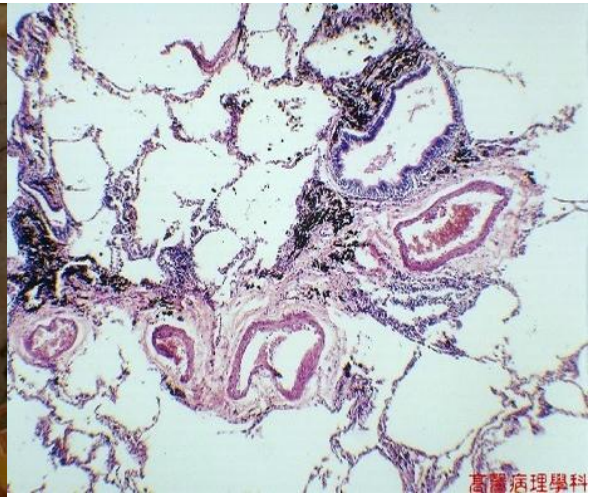
other exogenous pigments that can be harmful are : silica,lead,iron dust and silver

Tattooing: is a form of localized, exogenous pigmentation of the skin.

macrophages stays in the dermis of the skin(2nd layer of the skin)

Exogenous pigment



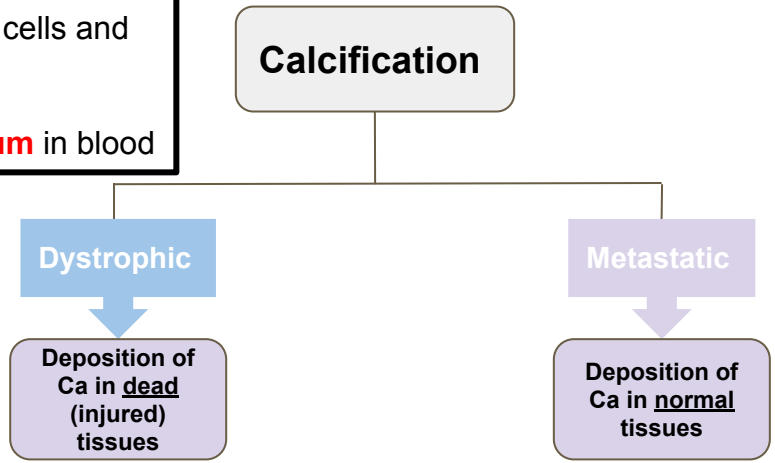


Anthracosis lung

Abnormal Pathologic calcification

Calcification：Deposition of **Ca** in the cells and extracellular matrix.

Hypercalcemia : An increase of **calcium** in blood



Dystrophic calcification: Accumulation of calcium in diseased cells caused by extracellular circulation or interstitial fluid.This process is **not** associated with **Hypercalcemia**.

Unhealthy cells could be injured or dead.

Any trauma can has dystrophic calcification.

Dystrophic calcification may happen with normal calcium in the blood.

Metastatic calcification: It is secondary to Hypercalcemia (associated with elevated calcium levels in the blood).
It can causes calcification in such inappropriate locations as pulmonary alveolar septa, renal tubules and blood vessels.

Continued

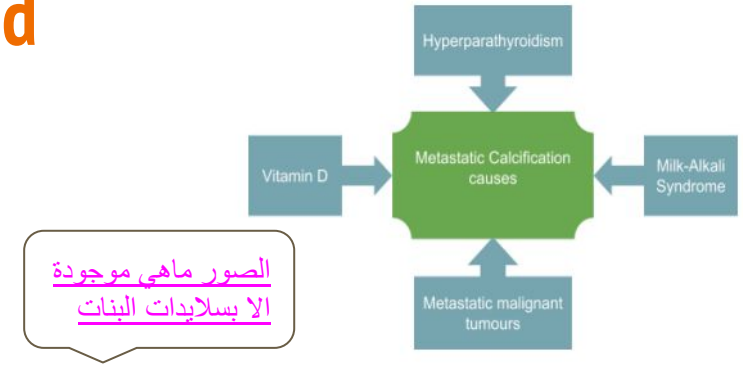
Dystrophic Calcification	Metastatic Calcification
Occurs in necrotic tissue.	Occurs in normal tissue.
Doesn't cause Hypercalcemia.	Causes Hypercalcemia.

To identify which type of calcification, we should do blood test to see the calcium level in blood.
If **normal** > **dystrophic**
If **high** > **metastatic**

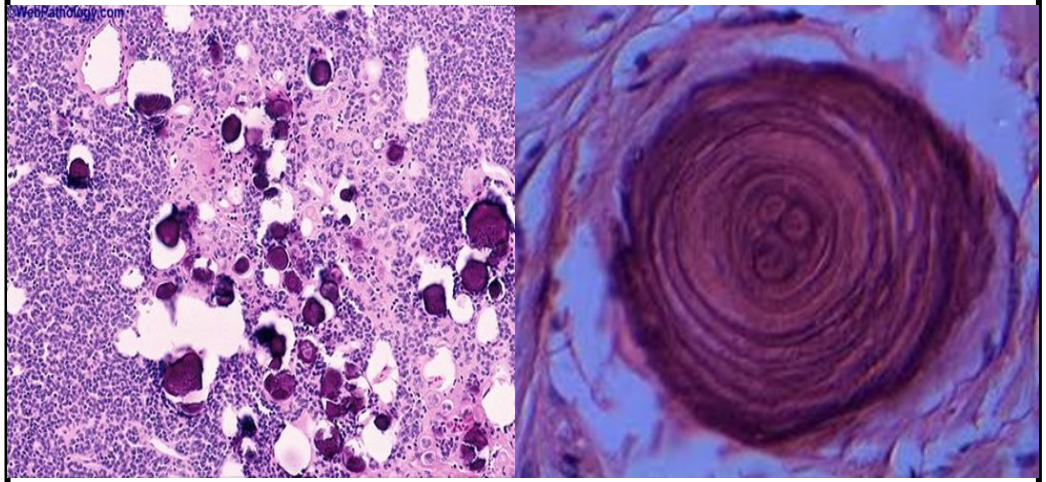
Psammoma body is a special type of **dystrophic** calcification made up of concentric lamellated calcified structures. They are seen in papillary cancers in the body (e.g. thyroid, ovary, kidney) and in the meningioma of the brain.

Whatever the site of deposition, the calcium salts appear **macroscopically** as fine, white granules or clumps, often felt as gritty deposits.

Histologically, calcium salts are **basophilic**, amorphous granular. They can be intracellular, extracellular, or both.



Psammoma bodies



كل الكلام الازرق مو موجود بسلايدات البنات ، ولكن ذكره الركابي في المحاضرة ، اما التعداد نفسه مهم.

Hypercalcemic disorders that causes Metastatic Calcification :

- **Hyperparathyroidism** :
  Parathyroid hormone is secreted by parathyroid glands. It increases the absorption of calcium from the intestines. In hyperparathyroidism, the hormone levels are elevated; which leads to higher levels of calcium in the blood.

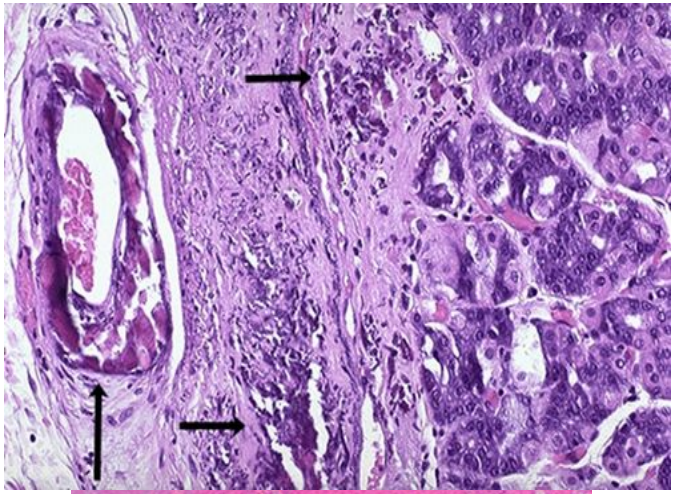
  What are the causes of hyperparathyroidism?

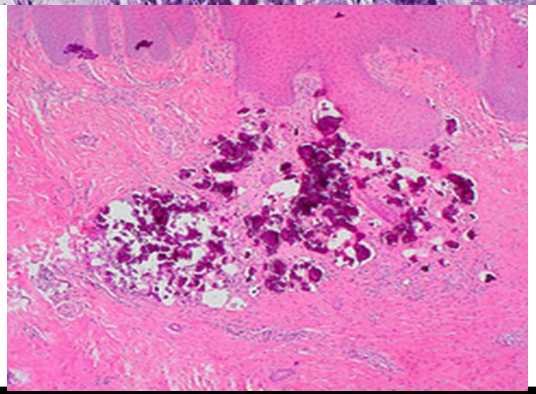
  - A disease in the gland (parathyroid hormone): due to a tumor in the gland, or hyperplasia.
  - Secondary parathyroidism: a chronic renal failure makes the body loses lots of calcium with urine, the parathyroid gland is excited to produce more parathyroid hormone.

- **Metastatic malignant tumor** :
  A part of a primary tumor has moved (metastasis) to another organ (extension of a tumor). If this organ is the bone, the bone is lysed (broken down) and the blood calcium levels are elevated.
- **Vitamin D intoxication (hypervitaminosis D)** :
  Vitamin D helps the body to absorb calcium, however, if it is consumed in large quantities it could lead to this condition & the blood calcium levels rise.

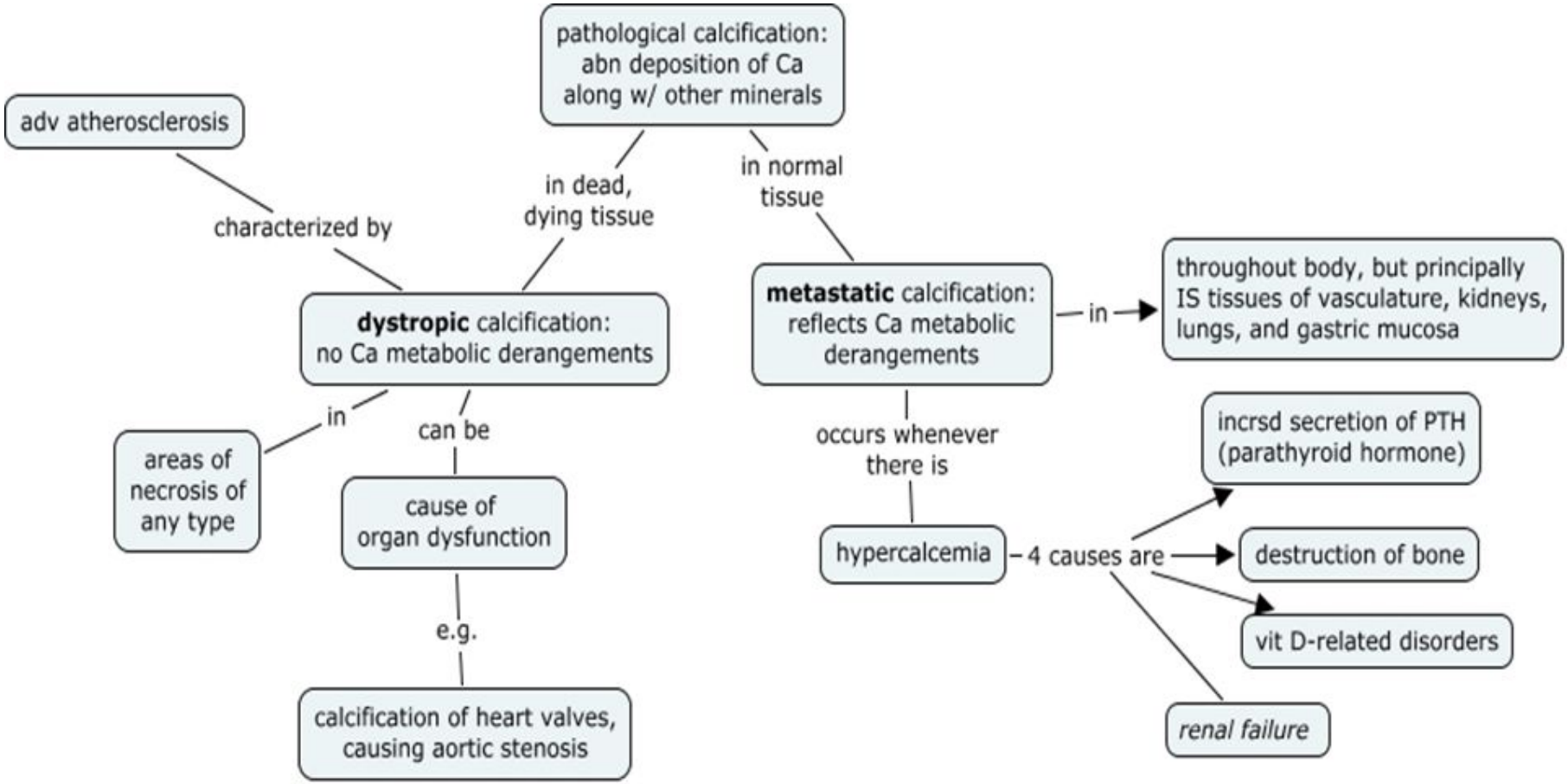
- **Milk Alkali Syndrome** :
  Note: Mild (little) hypercalcemia can normally occur in older people. But if seen in youngsters, we must know the cause.

Pathologic Calcification





صورة للشرح


pathological calcification: abn deposition of Ca along w/ other minerals
adv atherosclerosis
characterized by
in dead, dying tissue
in normal tissue
dystropic calcification: no Ca metabolic derangements
metastatic calcification: reflects Ca metabolic derangements
in
throughout body, but principally IS tissues of vasculature, kidneys, lungs, and gastric mucosa
in
areas of necrosis of any type
can be
cause of organ dysfunction
e.g.
calcification of heart valves, causing aortic stenosis
occurs whenever there is
hypercalcemia
4 causes are
incrsd secretion of PTH (parathyroid hormone)
destruction of bone
vit D-related disorders
renal failure

NOTE : In girls note : (most likely we will not be asked about this topic) ALrikabi said self study for this topic.

Amyloid deposition

Definition: It is an extracellular deposition of fibrillar amyloid protein in various organs (kidney, liver blood vessels,heart,etc) leading to organ damage.

- It happens between the cells of various tissues.
- It leads to group of clinical conditions collectively known as amyloidosis.

Types of amyloidosis

	primary amyloidosis	secondary amyloidosis
Definition	it is associated with plasma cell abnormality.	it is secondary to chronic inflammatory or autoimmune diseases.
characterized by deposits of	AL amyloid	AA amyloid
source of amyloid	AL amyloid derived from the immunoglobulin light chain	AA amyloid derived from serum amyloid-associated protein.
site of amyloid deposits	AL amyloid deposits are found in (kidney,blood vessels and heart),	AA amyloid deposits are found in (kidney, liver and spleen)

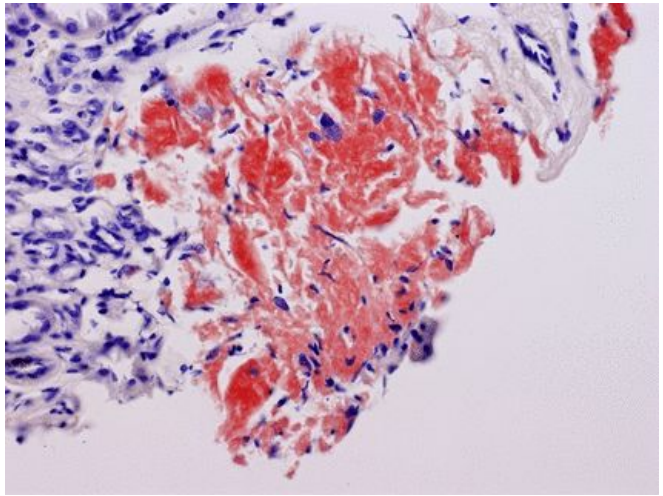
NOTE : serum amyloid-associated protein is produced by the liver in chronic inflammatory or autoimmune diseases like :

- Rheumatoid arthritis.
- Chronic osteomyelitis
- Tuberculosis

Morphology of amyloid

This is only found in the Female slides

- Light microscopy : It is pink eosinophilic material with congo red stain it appears bright orange.
- Electron microscopy : Amyloid deposits are composed of non-branching fibrils, 7.5 to 10 nano micron in diameter.
- Diagnosis : Can only be made with biopsy of organs like the kidney , rectum gingiva and skin



MCQs

1- pregnant uterus is an example of:

a)Physiologic Hypertrophy
b) Physiologic & pathologic Hypertrophy
c) Pathologic Hypertrophy
d) none of the above.

2- It is the shrinking in the size of the cell:

a) Hypertrophy
b) Hyperplasia
c) Atrophy
d) metaplasia.

3- when cell too severe and cannot be reversed the result is:

a) Necrosis
b) cell injury
c) cell death
d) Atrophy.

4- which of the following is occurs in any organ that contain fat?:

a) Fat necrosis
b) caseous necrosis
c) Fibrinoid necrosis
d) coagulative necrosis.

5- Low O_2 supply to cell will lead first to :

a) ATP depletion
b) cell death
c) Hypoplasia
d) accumulation of damage DNA

6- Change in size, number, phenotype, or function in the cell is :

a) cell injury
b) Adaptation
c) cell death
d) non of the above.

1-a
2-c
3-c
4-a
5-a
6-b

MCQs

7- An autoimmune disorder occurs when the body's immune system attacks and destroys healthy body tissue :

a) gangrenous
b) Fibrinoid
c) Liquefactive
d) caseous.

8- usually occurs in organs that are rich in fluids :

a) Fibrinoid necrosis
b) Fat necrosis
c) Liquefactive necrosis
d) gangrenous.

9- rare gangrenous :

a) wet gangrene
b) dry gangrene
c) gangrenous
d) non of the above.

10- which of the following is a main type of necrosis:

a) Fibrinoid, coagulative, caseous.
b) Liquefactive, gangrenous, fat.
c) fat, Liquefactive.
d) a&b.
e) a&c.

7- b
8- c
9- a
10- e

Team members

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- عبدالله الحوامدة
- طارق العقيل
- عبدالرحمن الحواس
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- فيصل القبلان
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- أميرة الزهراني
- دينا عورتاني
- رهام يوسف
- طيبة الزيد
- ريما السرحاني
- ريما المطوع
- ريما القحطاني
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