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Pathology

Doctor 2017 | Medicine | JU

Sheet Slides

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Last lecture we talked about two mechanisms of adaptation of cells under stress, in this lecture we will talk about other mechanisms of adaptation, as well as cell injury and death.

❖Mechanisms of adaptation:

1) Hypertrophy: increase in cell size.
2) Hyperplasia: increase in cell number.
3) Atrophy: decrease in cell size and function.

- **Mechanisms of atrophy:**
  - Decrease in protein synthesis (the opposite of hypertrophy).
  - Increase in protein degradation.
  - Autophagy (the cell starts to eat itself, in order to use the energy of its components to adapt and stay alive).

Note: atrophic cell can still function, but less than normal.

- **Causes of atrophy:**
  - **Decreased workload** (the opposite of increase demand in hypertrophy).

    Example: immobilization of limb after fracture, so that the movement of the limb is reduced, and the decreased demand for movement cause muscles to atrophy. This is why when the cast is removed, the fractured region appears thin.

    Note: this atrophy is reversible, so when the normal movement is restored and the load on the muscle increases, its size increases.

  - **Loss of innervations** (nerve stimulation is what causes muscles to contract). loss of innervation can happen due to trauma that causes cut of nerve (pathologic), or fracture that is accompanied with cut of nerve (pathologic), or

due to some illnesses such as diabetes which cause motor neuropathy or less functioning in nerves (This is why diabetics have atrophic muscles and skin).

- **Diminished blood supply** because of ischemia, or atherosclerosis that affect especially the lower limb (pathologic),so when the blood supply to lower limb is decreased this causes the muscles and skin to atrophy.

- **Inadequate nutrition**. cells need nutrition and oxygen in order to produce energy, so if there is inadequate nutrition to cells due to ischemia or malnutrition, cells will atrophy.

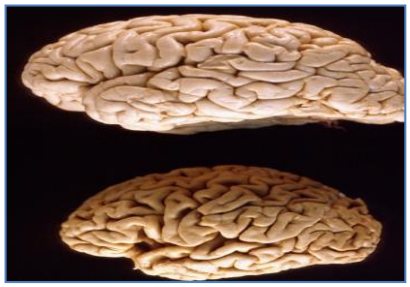
- **Loss of endocrine stimulation**.

  Example: endometrium after menopause. estrogen levels after menopause decrease, and estrogen is the stimulating and proliferating force of endometrium, So if biopsy is taken from endometrium after menopause, it appears atrophic, and this is physiologic (normal) because of the drop in estrogen.

- **Aging**

It affects the brain especially (senile atrophy).

Look at the figure aside which shows normal brain on the top, and atrophic brain on the bottom, notice the increased spaces between folds of the brain due to the atrophy.



4) Metaplasia: change from one cell type to another.

Important note: This change doesn't occur to terminally differentiated cells, it occurs to stem cells.

For example, squamous cells don't differentiate into another cell type, rather the stem cells that give us squamous cells switch into another type of differentiation. (stem cells: the cells that are responsible for differentiation to other cell types).

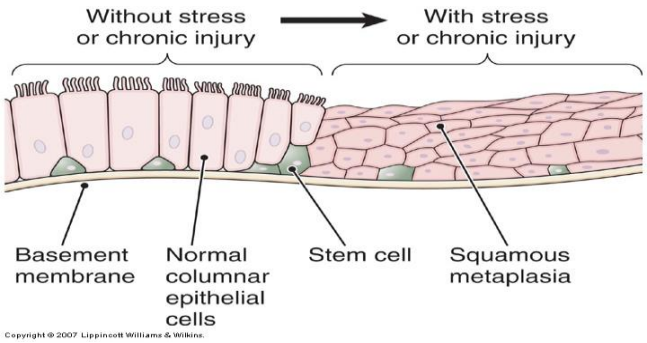
- **Examples of metaplasia:**
  - the change that occurs in the **respiratory epithelium** (in the bronchial tree) of smokers or when exposure to smoke or dust. the normal **pseudostratified ciliated epithelial** cells that line the bronchi are replaced by **stratified squamous epithelial** cells.

    Although the stratified squamous epithelium is able to adapt better with smoke and has high resistance to smoking, but the protective function of the bronchial tract is lost because cilia and goblet cells are not existing anymore, remember that cilia is important for clearance of particles, and goblet cells secrete mucous which is also very important for function.

    So metaplasia gives a more resistant tissue, but on the expense of the function (**higher resistance and less function**).

    Also, the problem with this squamous epithelium in the lung is that it might convert to cancer. The squamous cell carcinoma of the lung is mainly caused by metaplasia followed by dysplasia and then transform to cancer.

    Note: Metaplasia is reversible, but advanced stages, accumulation of mutations or conversion to dysplasia, cause it to become irreversible.



  - Another example of metaplasia is **gastroesophageal reflux disease (GERD)**. This disease causes reflux of acidic juices of the stomach to the lowest part of the esophagus. These acids cause the normal **stratified squamous epithelium** of the lower esophagus to be replaced by gastric or intestinal type **columnar epithelium.** This change happens in order to adapt with acids, because columnar epithelium is more resistant to acids since it secretes mucous. Although this change provides higher resistance to acidity, the protection mechanism of esophagus that is provided by squamous epithelium is lost. And the problem is increased risk of esophageal cancer.

- **Vitamin A deficiency** can also cause metaplasia. Vitamin A is needed for normal differentiation of cells. So deficiency in vitamin A cause stem cells in the bronchial tree (for example) to differentiate into squamous epithelium instead of pseudostratified ciliated columnar epithelium.

10:00

❖Cell injury and death

- **Causes of cell injury:**

1) **Oxygen deprivation (hypoxia).**

All cells need oxygen to perform oxidative phosphorylation and produce ATP which is necessary to all metabolic functions. Brain cells are the most cells sensitive to hypoxia because they don't perform anaerobic respiration, so brain cells can withstand ischemia for only two minutes. On the other hand, other tissues especially those that store glycogen such as liver and muscles can withstand hypoxia for longer time because they can undergo anaerobic glycolysis and produce ATP. For example, cardiac muscle can withstand hypoxia for 30 minutes, and skeletal muscle can withstand hypoxia for a longer time. This is why brain strokes are faster to happen than heart attacks or thrombosis to skeletal muscle.

The most common cause of hypoxia is **ischemia**, which is reduced blood supply caused by blockage of an artery. Sometimes hypoxia happens due to other reasons such as **carbon monoxide poisoning**, or **anemia** (reduction in the oxygen carrying capacity).

2) **Chemical agents, toxins.**
Some of them are innocent like sugar and salt but they can cause cell injury if taken in high amounts. For example, in people who have diabetes and hyperglycemia, high sugar levels can affect blood vessels, kidneys and every single organ. Also, other chemicals like insecticides, CO, cigarette smoke, ethanol and drugs -especially when used excessively or inappropriately- can cause cell injury.

3) **Infectious agents**, Such as viruses, bacteria, fungi, and protozoan.

4) **Immunologic reactions**, such as allergy or autoimmune diseases.

5) **Genetic factors.**

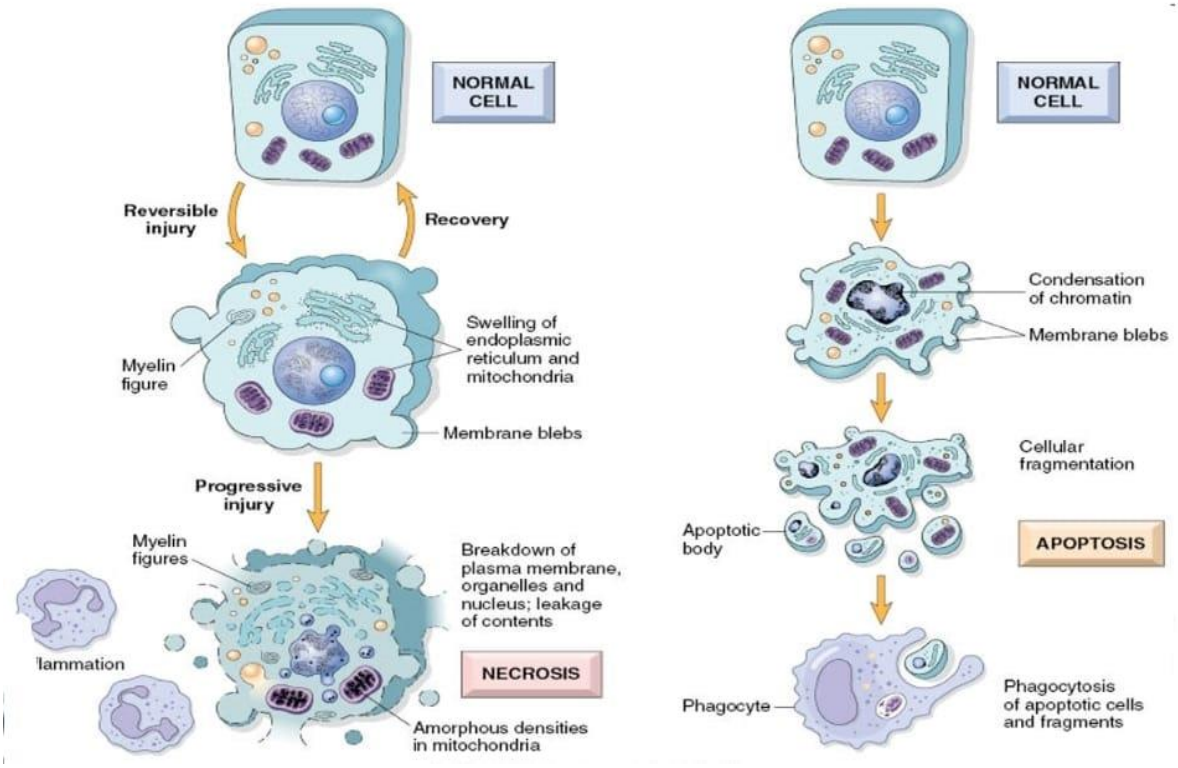
many diseases are caused by genetic factors, starting from chromosomal abnormalities such as trisomy 21 (down syndrome), ending with single gene mutations such as sickle cell anemia. (genetic factors are variable)

6) **Nutritional imbalances**. either over nutrition and resultant obesity, or under nutrition and resultant cachexia and malnutrition. Also vitamin deficiencies can cause cell injury.

7) **Physical agents**, like trauma, sudden changes in temperature (excessive heat, excessive cold), electric shocks and sudden changes in atmospheric pressure.

8) **Aging**

Cell injury:



Notice the normal cell has normal size and intact cell membrane and organelles. When it undergoes reversible cell injury, it increases in size (swells), cell membrane has blebs **but it remains intact**. When the cell undergoes irreversible cell injury, cell membrane is ruptured.

Note: the swelling of the cell after cell injury is NOT considered hypertrophy, because the cell swells due to the entrance of liquids and not due to synthesis of proteins or organelles.

So as we saw there are two types of cell injury, now let's talk about each one in details.

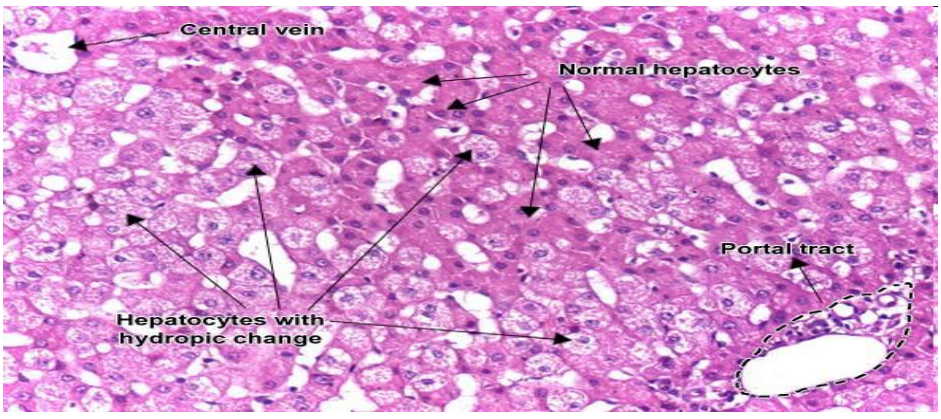
1) reversible cell injury

If the damaging stimulus is removed, injured cells can return to normal since the cell membrane is still intact.

- Most important **morphologic changes** that follows reversible cell injury:
  (A) cellular swelling
  Macroscopic appearance: the whole organ appears swollen.
  Microscopic appearance: cells are enlarged.

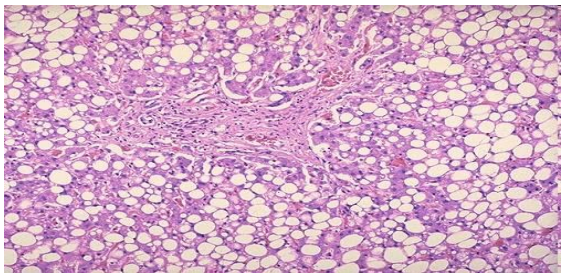
  (B) fatty change
  Macroscopic appearance: the color of the tissue is greasy.
  Microscopic appearance: fat droplets inside the cells.

Notice the figures below that show these morphologic changes after reversible cell injury:



In **cellular swelling**, at gross examination, the affected organ is enlarged, pale and soft. Microscopically, the cells are enlarged, with a clear cytoplasm (due to the presence of small clear or pale vacuoles, with indistinct shape and limits) and a normal nucleus in central position; blood capillaries are compressed, explaining the organ's pallor. White regions correspond to water.

Notice the two figures aside that represen t**fatty change** in injured liver. Macroscopically, it appears yellow in color due to the precense of fat droplets. Microscopically, fatty deposition (like adipose tissue).



Note: fatty change is observed only in organs that are involved in lipid metabolism such as liver, whereas cellular swelling is observed in all types of cells.

20:00

Other changes (on the level of organelles) + (ultrastructural – can't be seen under the light microscope):

- plasma membrane alterations (blebbing, blunting).
- mitochondrial change (swelling and densities).
- dilation of ER, with detachment of ribosomes attached to the ER and inability of cells to synthesize proteins.
- nuclear clumping (condensation) of chromatin, the nucleus decreases in size and appears very dark under the electron microscope.
- Cytoplasmic myelin figures (a fatty material that covers neurons). They result from the collection of phospholipids that are derived from damaged cellular membranes.

  Note: reversibly injured cell is still alive but it loses its function (unlike adaptation in which the cell remains functional).

2) Irreversible injury = cell death = necrosis

- Changes that follow irreversible cell injury:

  (A) Loss of plasma membrane and intracellular membranes (the cell and organelles burst and ruptured). Lysosomal enzymes and other enzymes inside organelles leak out to the cytoplasm, and then from cytoplasm to outside the cell, and may enter the blood stream.

  (B)irreversible mitochondrial dysfunction. because mitochondrial membrane is damaged, the cell is not able to produce energy (unlike reversible cell injury in which the cell can produce energy in small amounts by anaerobic respiration).

  (C)loss of DNA and chromatin structural integrity, the nucleus disappears or disintegrates.

  These three changes are accompanied by local inflammatory reactions, as type of response and emergency from the body to the injury calling for inflammatory cells to clean up the area, so keep in mind that necrosis is always accompanied by inflammation unlike apoptosis.

Other changes (ultrastructural):

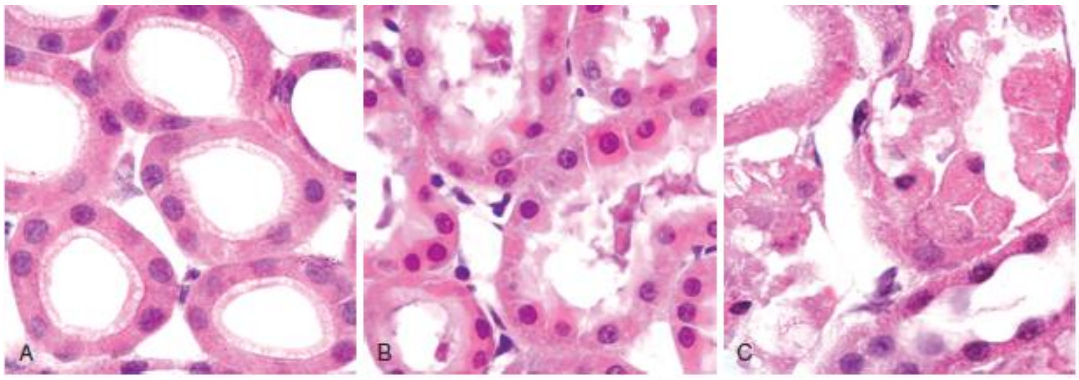
- Increased cytoplasmic eosinophilia (appears under the light microscope by H&E stain), because of denaturation of proteins, eosin stain binds to these proteins giving pinkish color. Also, DNA which gives basophilia (bluish color) is lost.
- Marked dilatation of the ER, mitochondria, and detachment of ribosomes.
- Mitochondrial densities.
- More myelin figures.

  These changes are more markedly shown in irreversible cell injury than reversible, but the main differences that distinguish the irreversible cell injury is the three points we mentioned above.

Nuclear changes in irreversible injury:

- **Pyknosis**: shrinkage and increased basophilia.
- **Karyorrhexis:** fragmentation.
- **Karyolysis**: nuclear material fades and disappears with time.

Normal, reversible and irreversible cell injury



The picture shown above is a section of T-tubules in the kidney. Morphologic changes in reversible and irreversible cell injury (necrosis).

(A) Normal kidney tubules: nucleus and cytoplasm are present, nucleus is basophilic, tubules intact.

(B)reversible injury: increased basophilia of condensed nuclei, and swelling of cells.

(C)irreversible injury: loss of nuclei, disappearance and fragmentation of cells.

30:00

- **Mechanisms of cell death**

1) Necrosis
- Cell death by irreversible cell injuries (always pathologic).
- Rapid and uncontrollable (the body can't deal with it).
- Accompanied by inflammation Severe disturbances, such as Ischemia, toxins, infections, and trauma.

2) Apoptosis (peaceful death)
- Highly regulated process and it is called committing suicide.
- Caused by less severe injury.
- Regulated by genes and signaling pathways.
- Controlled.

3) Necroptosis

Necrosis and apoptosis together. For example, when there is ischemia on heart, the main death type of heart cells is necrosis, but some cells die by apoptosis.

Note: the mechanism of cell death depends on the nature of **the injury**, magnitude and duration. It also depends on **the cell itself** and its adaptivity, for example, skeletal muscle cell withstands ischemia better than brain cell.

This table shows the differences between necrosis and apoptosis, and we will return to it later on.

Table 1–1 Features of Necrosis and Apoptosis

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

DNA, deoxyribonucleic acid.

▪ Clinical implications

1) Leakage of intracellular proteins through the damaged cell membrane and ultimately into the circulation provides means of detecting tissue-specific necrosis using blood or serum samples.

Examples:

- someone has chest pain and we want to detect if he has **myocardial infarction**, we take a blood sample and test the levels of cardiac enzymes, if heart cells undergo necrosis, their enzymes leak out to the blood and they will be detected in high levels.

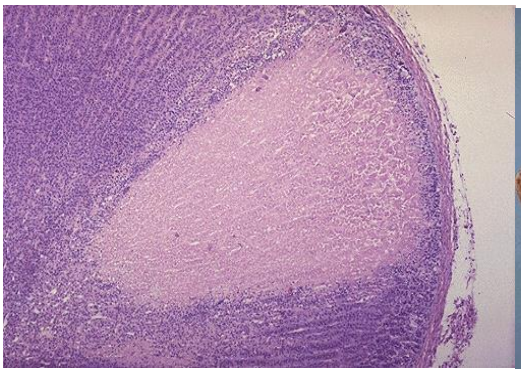
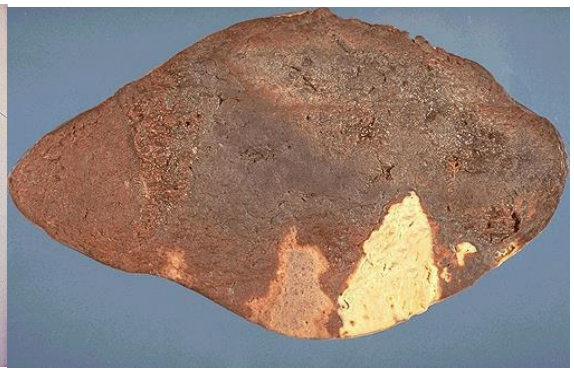
  Note: We should consider the time it takes for each enzyme to reach the peak since it's variable between different enzymes.
- Another example is **hepatitis**. If we suspect a patient to have hepatitis we test for liver enzymes. If detected in high levels, this indicates necrosis in liver cells.

2) Another clinical implication in addition to diagnosis is monitoring. For example, if we want to monitor the response to treatment of hepatitis, we detect the changes in enzymes levels whether they are decreasing or not.

3) Morphologic pattern of necrosis (the change we observe on macroscopic, microscopic, or ultrastructural level). It gives us clinical input to know the reason of necrosis.

- There are **different types of necrosis** according to its cause:

1) **Coagulative necrosis**
   - Caused by ischemia (ischemic necrosis), happens in all solid organs that are subjected to ischemia (heart, muscle, liver, spleen, kidney, or any other type of tissue except the brain, it commits another type of necrosis).
   - The region that undergoes coagulative necrosis appears pail macroscopically, usually wedge shaped (look at liver in the figures below).
   - Microscopically, Conserved tissue architecture initially (for one or two days after death of cells) before the inflammatory cells clear the area. So this type happens without inflammation initially.
   - Leukocyte lysosomes and phagocytosis required for clearance.
   - Anuclear eosinophilic on LM (dead cells).

2) **Liquefactive necrosis**

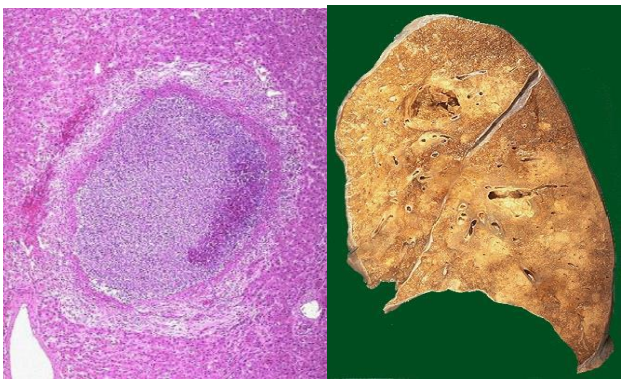
This type of necrosis happens in two situations:

(A) Focal (localized) infections such as abscess and cavitation.

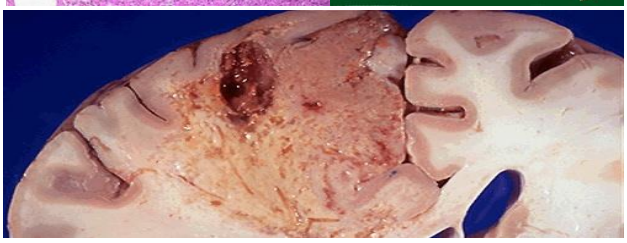
These infections may be bacterial, fungal, parasitic or any other type of infection.

(B) Ischemia to the brain.

Look at the figures to the top showing a cavity in lung. This cavity is filled with pus (sheets of neutrophils, cellular debris and infectious agents), and it appears like bluish area under the microscope.



And the figure to the bottom shows a section in brain with cavity that is caused by ischemia.



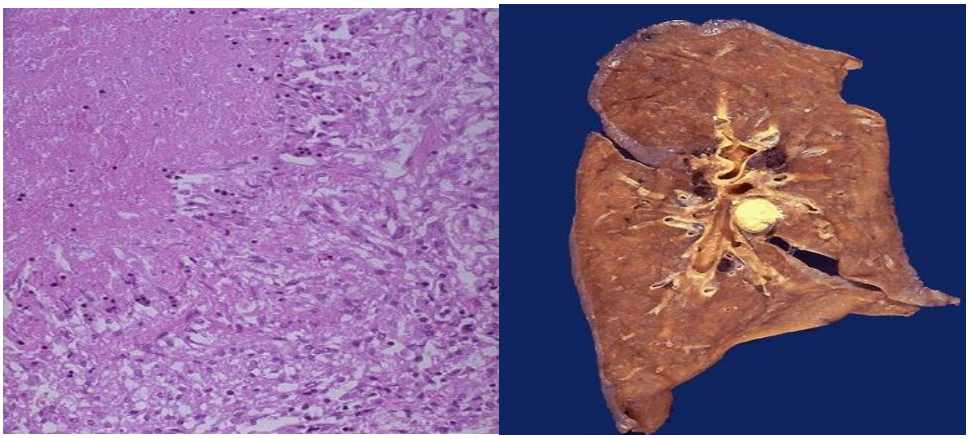
- Liquefactive necrosis occurs by the effect of lysosomal enzymes that are released from the dead cells and the inflammatory cells. So the tissue becomes digested. Center liquefies and digested tissue is removed by phagocytosis.
- The tissue appears liquefied (semifluid), thus it's named liquefactive necrosis.

3) Gangrenous necrosis

- Clinical term.
- It is basically a coagulative necrosis (caused by ischemia), but happens in many tissue types at the same time.
- Best example is diabetic foot or gangrene in the lower limb, which is ischemia to the skin, subcutaneous tissue, muscle and bone, all caused by the same ischemia.
- the tissue appears macroscopically black in color.
- There are two types of gangrene: dry (without infection), and wet (with infection).

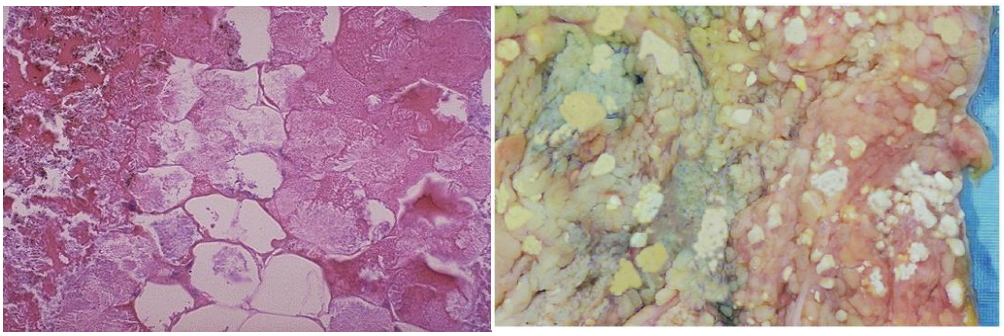
4) Caseous necrosis

- Caseous means “cheeselike”, referring to the yellow appearance of the area macroscopically (notice lung in the figure below). This yellow material contains debris (remained parts of the lysed cells).
- This type can be considered a combination of coagulative necrosis (caused by ischemia), and liquefactive necrosis (caused by infection).
- The best example is tuberculosis.
- The tissue architecture is not preserved.
- Microscopically, caseous acellular center is filled with cellular debris and surrounded by granuloma (collection of macrophages), notice the figure in the bottom.



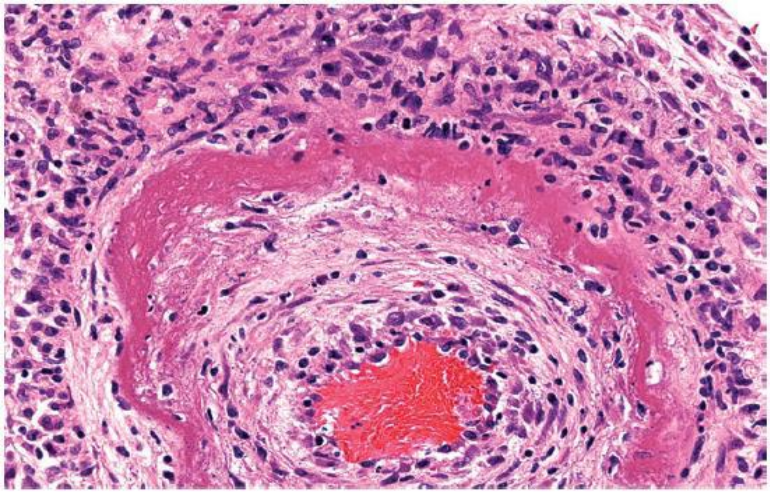
5) Fat necrosis

- The death of fatty tissue.
- Occurs in acute pancreatitis due to the release of pancreatic lipases. These enzymes digest surrounding omentum (fatty tissue that surrounds abdominal organs), result in lysed fatty cells. Then fats and triglycerides are released to the outside and degraded by the enzymes into fatty acids that have high affinity to calcium in the blood, and saponification reaction occurs to produce grossly visible whitish chalky areas.
- Cells are burst without nuclei and tissue architecture is lost.



6) **Fibrinoid necrosis**

- Associated with immune reactions in which complexes of antigens and antibodies are deposited in the wall of blood vessels, and deposition of fibrin material (autoimmune disease called vasculitis).
- Deposited fibrin material that leaks from the wall of damaged vessels show a bright pink appearance during H&E preparations.



GOOD LUCK♡^_^