كلية : التربية للعلوم الصرفة

القسم او الفرع : علوم الحياة

المرحلة: دكتوراه

أستاذ المادة : ا.م. د.لؤي حاتم علي

اسم المادة باللغة العربية : علم النسج المرضية

اسم المادة باللغة الإنكليزية : histopathology

اسم المحاضرة الأولى باللغة العربية: مقدمة عن علم الامراض والتكيفات الخلوية

اسم المحاضرة الأولى باللغة الإنكليزية : INTRODUCTION TO PATHOLOGY

INTRODUCTION TO PATHOLOGY

Pathology is the study of disease by scientific methods. The word pathology came from the Latin words “patho” & “logy”. ‘Patho’ means disease and ‘logy’ means study, therefore pathology is a scientific study of disease. Diseases may, in turn, be defined as an abnormal variation in structure or function of any part of the body. Pathology gives explanations of a disease by studying the following four aspects of the disease.

1. Etiology,
2. Pathogenesis,
3. Morphologic changes and
4. Functional derangements and clinical significance.

1. Etiology

Etiology of a disease means the cause of the disease. If the cause of a disease is known, it is called primary etiology. If the cause of the disease is unknown, it is called idiopathic. Knowledge or discovery of the primary cause remains the backbone on which a diagnosis can be made, a disease understood, & a treatment developed. There are two major classes of etiologic factors: genetic and acquired (infectious, nutritional, chemical, physical, etc). Detailed discussion will be given in subsequent topics. The etiology is followed by pathogenesis.

2. Pathogenesis

Pathogenesis means the mechanism through which the cause operates to produce the pathological and clinical manifestations. The pathogenetic mechanisms could take place in the latent or incubation period. Pathogenesis leads to morphologic changes.

3. Morphologic changes

The morphologic changes refer to the structural alterations in cells or tissues that occur following the pathogenetic mechanisms. The structural changes in the organ can be seen with the naked eye or they may only be seen under the microscope. Those changes that can be seen with the naked eye are called gross morphologic changes & those that are seen under the microscope are called microscopic changes. Both the gross & the microscopic morphologic changes may only be seen in that disease, i.e. they may be specific to that disease. Therefore, such morphologic changes can be used by the pathologist to identify (i.e. to diagnose) the disease. In addition, the morphologic changes will lead to functional alteration & to the clinical signs & symptoms of the disease.

4. Functional derangements and clinical significance

The morphologic changes in the organ influence the normal function of the organ. By doing so, they determine the clinical features (symptoms and signs), course, and prognosis of the disease.

In summary, pathology studies: -

Etiology Pathogenesis Morphologic changes Clinical features & Prognosis of all diseases.

Understanding of the above core aspects of disease (i.e. understanding pathology) will help one to understand how the clinical features of different diseases occur & how their treatments work. This understanding will, in turn, enable health care workers to handle & help their patients in a better & scientific way. It is for these reasons that the health science

student should study pathology. In addition, the pathologist can use the morphologic changes seen in diseases to diagnose different diseases. There are different diagnostic modalities used in pathology. Most of these diagnostic techniques are based on morphologic changes

III. Diagnostic techniques used in pathology

The pathologist uses the following techniques to the diagnose diseases:

a. Histopathology

b. Cytopathology

c. Hematopathology

d. Immunohistochemistry

e. Microbiological examination

f. Biochemical examination

g. Cytogenetics

h. Molecular techniques

i. Autopsy

A. Histopathological techniques

Histopathological examination studies tissues under the microscope. During this study, the pathologist looks for abnormal structures in the tissue.

Tissues for histopathological examination are obtained by biopsy. Biopsy is a tissue sample from a living person to identify the disease. Biopsy can be either incisional or excisional.

Once the tissue is removed from the patient, it has to be immediately fixed by putting it into adequate amount of 10% Formaldehyde (10% formalin) before sending it to the pathologist. The purpose of fixation is:

1. to prevent autolysis and bacterial decomposition and putrefaction

2. to coagulate the tissue to prevent loss of easily diffusible substances

3. to fortify the tissue against the deleterious effects of the various stages in the preparation of sections and tissue processing.

4. to leave the tissues in a condition which facilitates differential staining with dyes and other reagents.

Once the tissue arrives at the pathology department, the pathologist will exam it macroscopically (i.e. naked-eye examination of tissues).

Then the tissue is processed to make it ready for microscopic examination. The whole purpose of the tissue processing is to prepare a very thin tissue (i.e. five to seven μm or one cell thick tissue) which can be clearly seen under the microscope. The tissue is processed by putting it into different chemicals. It is then impregnated (embedded) in paraffin, sectioned (cut) into thin slices, & is finally stained. The stains can be Hematoxylin/Eosin stain or special stains such as PAS, Immunohistochemistry, etc... The Hematoxylin/Eosin stain is usually abbreviated as H&E stain. The H&E stain is routinely used. It gives the nucleus a blue color & the cytoplasm & the extracellular matrix a pinkish color. Then the pathologist will look for abnormal structures in the tissue. And based on this abnormal morphology he/she will make the diagnosis. Histopathology is usually the gold standard for pathologic diagnosis.

B. Cytopathologic techniques

Cytopathology is the study of cells from various body sites to determine the cause or nature of disease.

IV. The causes of disease

Diseases can be caused by either environmental factors, genetic factors or a combination of the two.

A. Environmental factors

Environmental causes of disease are many and are classified into:

1. Physical agents

2. Chemicals

3. Nutritional deficiencies & excesses

4. Infections & infestations

5. Immunological factors

6. Psychogenic factors

1. Physical agents

These include trauma, radiation, extremes of temperature, and electric power. These agents apply excess physical energy, in any form, to the body.

2. Chemicals

With the use of an ever-increasing number of chemical agents such as drugs, in industrial processes, and at home, chemically induced injury has become very common. Their effects vary:

• Some act in a general manner, for example cyanide is toxic to all cells.

• Others act locally at the site of application, for example strong acids and caustics.

• Another group exhibit a predilection for certain organs, for example – the effect of paracetamol and alcohol on liver. Many toxic chemicals are metabolized in liver and excreted in kidney, as a result, these organs are susceptible to chemical injury.

3. Nutritional deficiencies and excesses

Nutritional deficiencies may arise as a result of poor supply, interference with absorption, inefficient transport within the body, or defective utilization. It may take the form of deficiency either of major classes of food, usually protein and energy, or vitamins or elements essential for specific metabolic processes, e.g. iron for haemoglobin production. Often, the deficiencies are multiple and complex.

On the other hand, dietary excess plays an important role in diseases in Western countries. Obesity has become increasingly common, with its attendant dangers of type 2 diabetes, high blood pressure and heart disease.

4. Infections and infestations

Viruses, bacteria, fungi, protozoa, and metazoa all cause diseases. They may do so by causing cell destruction directly as in virus infections (for example poliomyelitis) or protozoal infections (for example malaria). However, in others the damage is done by toxins elaborated by the infecting agent as in diphtheria and tetanus. Like chemicals, they may have a general effect or they may show a predilection for certain tissues.

5. Immunological factors

The immune process is essential for protection against micro-organisms and parasites. However, the immune system can be abnormal which can lead to diseases. The abnormalities of the immune system include:

A. Hypersensitivity reaction

This is exaggerated immune response to an antigen. For example, bronchial asthma can occur due to exaggerated immune response to the harmless pollen.

B. Immunodeficiency

This is due to deficiency of a component of the immune system which leads to increased susceptibility to different diseases. An example is AIDS.

C. Autoimmunity

This is an abnormal (exaggerated) immune reaction against the self antigens of the host. Therefore, autoimmunity is a hypersensitivity reaction against the self antigens. For example, type 1 diabetes mellitus is caused by autoimmune destruction of the beta cells of the islets of Langerhans of the pancreas.

6. Psychogenic factors

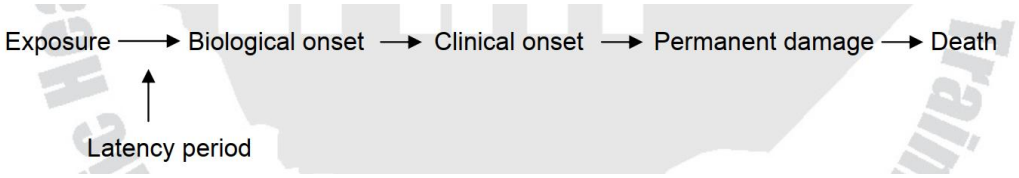
The mental stresses imposed by conditions of life, particularly in technologically advanced communities, are probably contributory factors in some groups of diseases.

B. Genetic Factors

These are hereditary factors that are inherited genetically from parents. Detailed discussion will be done on this topic in a subsequent chapter.

V. Course of disease

The course of disease is shown with a simplified diagram as follows.



The course of a disease in the absence of any intervention is called the natural history of the disease. The different stages in the natural history of disease include:

a) Exposure to various risk factors (causative agents)

b) Latency, period between exposure and biological onset of disease

c) Biological onset of disease; this marks the initiation of the disease process, however, without any sign or symptom. Following biological onset of disease, it may remain asymptomatic or subclinical (i.e. without any clinical manifestations), or may lead to overt clinical disease.

d) Incubation (induction) period refers to variable period of time without any obvious signs or symptoms from the time of exposure.

e) The clinical onset of the disease, when the signs and symptoms of the disease become apparent. The expression of the disease may be variable in severity or in terms of range of manifestations.

f) The onset of permanent damage, and

g) Death

Natural recovery, i.e. recovery without any intervention, can occur at any stage in the progression of the disease.

VI. Outcome and consequences of disease

Following clinical onset, disease may follow any of the following trends:

a) Resolution can occur leaving no sequelae,

b) The disease can settle down, but sequelae are left, or

c) It may result in death.

VII. Clinical & biologic death

Clinical death

Clinical death is the reversible transmission between life and biologic death. Clinical death is defined as the period of respiratory, circulatory and brain arrest during which initiation of resuscitation can lead to recovery.

Clinical death begins with either the last agonal inhalation or the last cardiac contraction. Signs indicating clinical death are

• The patient is without pulse or blood pressure and is completely unresponsive to the most painful stimulus.

• The pupils are widely dilated

• Some reflex reactions to external stimulation are preserved. For example, during intubations, respiration may be restored in response to stimulation of the receptors of the superior laryngeal nerve, the nucleus of which is located in the medulla oblongata near the respiratory center.

• Recovery can occur with resuscitation.

Biological Death

Biological death (sure sign of death), which sets in after clinical death, is an irreversible state of cellular destruction. It manifests with irreversible cessation of circulatory and respiratory functions, or irreversible cessation of all functions of the entire brain, including brain stem.

However, one should notice that there are internationally accepted criteria to diagnose biological death.

CELLULAR REACTIONS TO INJURY

II. Introduction

Cell injury underlies all diseases. So to understand diseases one, has to start by knowing what cell injury is. When a cell is exposed to an injurious agent (i.e. the causes of diseases discussed in chapter one), the possible outcomes are:

1. The cell may adapt to the situation or

2. They cell may acquire a reversible injury or

3. The cell may obtain an irreversible injury & may die. The cell may die via one of two ways: either by necrosis or by apoptosis.

Which of these outcomes occur depends on both the injurious agent & on cellular factors. In other words, the result depends on the type, severity, & duration of the injury & on the type of the cell.

This chapter covers the types of cellular adaptation, reversible cell injury, & cell death in that order.

III. Types of cellular adaptation

The types of cellular adaptation include hypertrophy, atrophy, hyperplasia, Dysplasia & metaplasia.

A. Hypertrophy

Hypertrophy is increase in the size of cells. Increased workload leads to increased protein synthesis & increased size & number of intracellular organelles which, in turn, leads to increased cell size. The increased cell size leads to increased size of the organ. Hypertrophy is caused either by increased functional demand or by specific endocrine stimulations. With increasing demand, hypertrophy can reach a limit beyond which degenerative changes and organ failure can occur.

Examples: the enlargement of the left ventricle in hypertensive heart disease & the increase in skeletal muscle during sternous exercise.

B. Hyperplasia

Hyperplasia is an increase in the number of cells from an increased rate of cell division. It can lead to an increase in the size of the organ. It is usually caused by hormonal stimulation. It can be physiological as in enlargement of the breast during pregnancy or it can pathological as in endometrial hyperplasia. If cells have mitotic ability and can synthesize DNA, both hyperplasia and hypertrophy can occur. Hyperplasia may be a predisposing condition to neoplasia .ex: Female breast in puberty & lactation, Compensatory hyperplasia in the liver

C. Atrophy

Atrophy is a decrease in the size of a cell due to loss of cell substance (protein degradation & lysosomal proteases digest extracellular endocytosed molecules). This can lead to decreased size of the organ and Often hormone dependent (insulin, TSH, etc…). The

atrophic cell shows autophagic vacuoles which contain cellular debris from degraded organelles. Atrophy can be caused by:

1. Disuse (Decreased workload)

2. Undernutrition

3. Decreased endocrine stimulation

4. Denervation (Loss of innervation)

5. Old age.(Ageing)

D. Metaplasia

Metaplasia is the replacement of one differentiated tissue by another differentiated tissue, Metaplasia is a “reversible” change (adaptation). There are different types of metaplasia. Examples include:

1. Squamous metaplasia

This is replacement of another type of epithelium by squamous epithelium. For example, the columnar epithelium of the bronchus can be replaced by squamous epithelium in cigarette smokers

2. Osseous metaplasia

This replacement of a connective tissue by bone, for example at sites of injury.

Persistence of signals that result in metaplasia often lead to progression from metaplasia to dysplasia and possibly to adenocarcinoma.

E. Dysplasia:

Abnormal changes in size, shape, appearance, and organizational structure of the cells, sometimes atypical hyperplasia can progress to neoplasia, Caused by persistent injury or irritation, Cervix, oral cavity, gallbladder, and respiratory tract

IV. Reversible cellular changes & accumulations

Even though there are many different kinds of reversible cellular changes & accumulations, here we will only mention fatty change & accumulation of pigments.

1. Fatty change

This is accumulation of triglycerides inside parenchymal cells. It is caused by an imbalance between the uptake, utilization, & secretion of fat. Fatty change is usually seen in the liver, heart, or kidney. Fatty liver may be caused by alcohol, diabetes mellitus, malnutrition, obesity, & poisonings. These etiologies cause accumulation of fat in the hepatocytes by the following mechanisms:

a. Increased uptake of triglycerides into the parenchymal cells.

b. Decreased use of fat by cells.

c. Overproduction of fat in cells.

d. Decreased secretion of fat from the cells.

2. The accumulations of pigments

Pigments can be exogenous or endogenous. Endogenous pigments include melanin, bilirubin, hemosiderin, & lipofuscin. Exogenous pigments include carbon. These pigments can accumulate inside cells in different situations.

a. Melanin

Melanin is a brownish-black pigment produced by the melanocytes found in the skin. Increased melanin pigmentation is caused by sun tanning & certain diseases e.g. nevus, or malignant melanoma. Decreased melanin pigmentation is seen in albinism & vitiligo.

b. Bilirubin

Bilirubin is a yellowish pigment, mainly produced during the degradation of hemoglobin. Excess accumulation of bilirubin causes yellowish discoloration of the sclerae, mucosae, & internal organs. Such a yellowish discoloration is called jaundice.

Jaundice is most often caused by

1. Hemolytic anemia

Hemolytic anemia is characterized by increased destruction of red blood cells.

2. Biliary obstruction

This is obstruction of intrahepatic or extrahepatic bile ducts. It can be caused by gallstones.

3. Hepatocellular disease

This is associated with failure of conjugation of bilirubin.

c. Hemosiderin

Hemosiderin is an iron-containing pigment derived from ferritin. It appears in tissues as golden brown amorphous aggregates & is identified by its staining reaction (bluecolor) with the Prussian blue dye. Hemosiderin exists normally in small amounts within tissue macrophages of the bone marrow, liver, & spleen as physiologic iron stores. It accumulates in tissues in excess amounts in certain diseases. This excess accumulation is divided into 2 types:

1. Hemosiderosis

When accumulation of hemosiderin is primarily within tissue macrophages & is not associated with tissue damage, it is called hemosiderosis.

2. Hemochromatosis

When there is more extensive accumulation of hemosiderin, often within parenchymal cells, which leads to tissue damage, scarring & organ dysfunction, it is called hemochromatosis.

d. Lipofuscin/end product:

&. This yellowish, fat-soluble pigment is an end product of membrane lipid peroxidation.
b. It is sometimes referred to as "wear-and-tear" pigment.

&. It commonly accumulates in elderly patients, in whom the pigment is found most often within hepatocytes and at the poles of nuclei of myocardial cells. The combination of lipofuscin accumulation and atrophy of organs is referred to as brown atrophy.

V. Cell death

Cells can die via one of the following two ways:

1. Necrosis

2. Apoptosis

1. Necrosis

In necrosis (Irreversible), excess fluid enters the cell, swells it, & ruptures its membrane which kills it. After the cell has died, intracellular degradative reactions occur within a living organism. Necrosis does not occur in dead organisms. In dead organisms, autolysis & heterolysis take place**.**

Morphologic changes: 1- Increased eosinophilia of cells 2-Pyknosis of nuclei 3-Karyorrhexis 4- Karyolysis: dissolution of the nucleus from hydrolytic enzymes 5-Release of catalytic enzymes from lysosomes cause either autolysis or heterolysis.

Morphologic appearance of necrosis is due to: * Enzymic digestion of the cell * Denaturation of proteins.

Necrosis occurs by the following mechanisms:

A. Hypoxia

B. Free radical-induced cell injury

C. Cell membrane damage

D. Increased intracellular calcium level

A. Hypoxia

Hypoxia is decreased oxygen supply to tissues. It can be caused by:

1. Ischemia

Ischemia is decreased blood flow to or from an organ. Ischemia can be caused by obstruction of arterial blood flow – the most common cause, or by decreased perfusion of tissues by oxygen-carrying blood as occurs in cardiac failure, hypotension, & shock.

2. Anemia

Anemia is a reduction in the number of oxygen-carrying red blood cells.

3. Carbon monoxide poisoning

CO decreases the oxygen-capacity of red blood cells by chemical alteration of hemoglobin.

4. Poor oxygenation of blood due to pulmonary disease.

The cell injury that results following hypoxia can be divided into early & late stages:

1. Early (reversible) stages of hypoxic cell injury

At this stage, hypoxia results in decreased oxidative phosphorylation & ATP synthesis. Decreased ATP leads to:

a. Failure of the cell membrane Na – K pump, which leads to increased

intracellular Na & water, which cause cellular & organelle swelling. Cellular swelling (hydropic change) is characterized by the presence of large vacuoles in the cytoplasm. The endoplasmic reticulum also swells. The mitochondria show a low amplitude swelling. All of the above changes are reversible if the hypoxia is corrected.

b. Disaggregation of ribosomes & failure of protein synthesis.

2. Late (irreversible) stages of hypoxic cell injury.

This is caused by severe or prolonged injury. It is caused by massive calcium influx & very low pH, which lead to activation of enzymes, which damage the cell membrane& organelle membranes. Irreversible damage to the mitochondria, cell membranes, & the nucleus mark the point of no return for the cell, that is after this stage, the cell is destined to die.

Release of aspartate aminotransferase (AST), creatine phosphokinase(CPK), & lactate dehydrogenase (LDH) into the blood is an important indicator of irreversible injury to heart muscle following myocardial infarction.

B. Free radical-induced injury

Free radical is any molecule with a single unpaired electron in the outer orbital. Examples include superoxide & the hydroxyl radicals. Free radicals are formed by normal metabolism, oxygen toxicity, ionizing radiation, & drugs & chemicals, & reperfusion injury. They are degraded by spontaneous decay, intracellular enzymes such as glutathione peroxidase, catalase, or superoxide dismutase, & endogenous substances such as ceruloplasmin or transferrin. When the production of free radicals exceeds their degradation, the excess free radicals cause membrane pump damage, ATP depletion, & DNA damage. These can cause cell injury & cell death.

a. Cell membrane damage

Direct cell membrane damage as in extremes of temprature, toxins, or viruses, or indirect cell membrane damage as in the case of hypoxia can lead to cell death by disrupting the homeostasis of the cell.

b. Increased intracellular calcium level

Increased intracellular calcium level is a common pathway via which different causes of cell injury operate. For example, the cell membrane damage leads to increased intracellular calcium level. The increased cytosolic calcium, in turn, activates enzymes in the presence of low pH. The activated enzymes will degrade the cellular organelles.

Types of necrosis

The types of necrosis include:

1. Coagulative necrosis
2. Liquefactive necrosis
3. Fat necrosis
4. Caseous necrosis
5. Gangrenous necrosis.

1. Coagulative necrosis

Cogulative necrosis most often results from sudden interruption of blood supply to an organ, especially to the heart. It is, in early stages, characterized by general preservation of tissue architecture. It is marked by the following nuclear changes: Pyknosis (which is chromatin clumping & shrinking with increased basophilia), karyorrhexis (fragmentation of chromatin), & karyolysis (fading of the chromatin material). Increased cytoplasmic eosinophilia occurs because of protein denaturation and loss of cytoplasmic RNA

2. Liquefactive necrosis

Liquefactive necrosis is characterized by digestion of tissue. It shows softening & liquefaction of tissue. It characteristically results from ischemic injury to the CNS. It also occurs in suppurative infections characterized by formation of pus.

3. Fat necrosis

Fat necrosis can be caused by trauma to tissue with high fat content, such as the breast or it can also be caused by acute hemorrhagic pancreatitis in which pancreatic enzymes diffuse into the inflamed pancreatic tissue & digest it. The fatty acids released from the digestion form calcium salts (soap formation or dystrophic calcification). In addition, the elastase enzyme digests the blood vessels & cause the hemorrhage inside the pancreas, hence the name hemorrhagic pancreatitis**.**

4. Caseous necrosis

Caseous necrosis has a cheese-like (caseous, white) appearance to the naked eye. And it appears as an amorphous eosinophilic material on microscopic examination reflecting the crumbly, white, and soft texture of the necrotic material with no recognizable cellular structures. It is typically associated with certain chronic infections, most notably tuberculosis. The necrotic material is surrounded by a ring of epithelioid macrophages, Langhans giant cells, and lymphocytes.

5. Gangrenous necrosis

refers to a type of tissue death (necrosis) that results from a lack of blood supply, often combined with bacterial infection. It is not a specific pattern of necrosis itself but rather a clinical term describing the gross appearance of necrotic tissue. Gangrene can affect any part of the body but is most commonly seen in the extremities, such as the fingers, toes, or limbs, and sometimes in internal organs like the intestines.

Types of Gangrenous Necrosis:

1. **Dry Gangrene**:
    - **Cause**: Ischemia (lack of blood supply) without significant bacterial infection.
    - **Appearance**: Tissue is dry, shriveled, and dark (black or brown) due to coagulative necrosis.
    - **Common Locations**: Peripheral limbs in conditions like atherosclerosis or diabetes.
    - **Progression**: Slow and less associated with systemic symptoms.
2. **Wet Gangrene**:
    - **Cause**: Ischemia combined with bacterial infection.
    - **Appearance**: Tissue is swollen, soft, and may have a foul smell due to bacterial overgrowth and liquefactive necrosis.
    - **Common Locations**: Internal organs or wounds.
    - **Progression**: Rapid, with severe systemic effects like sepsis, which can be life-threatening.
3. **Gas Gangrene**:
    - **Cause**: Infection with gas-producing bacteria, typically *Clostridium* species.
    - **Appearance**: Tissue may be pale or reddish-purple with gas bubbles under the skin (crepitus).
    - **Common Locations**: Deep wounds or muscle tissue.
    - **Progression**: Extremely rapid and often fatal without prompt treatment.

Necrosis can be followed by release of intracellular enzymes into the blood, inflammation or dystrophic calcification. Inflammation will be discussed in the next chapter**.**

2. Apoptosis

Apoptosis is the death of single cells within clusters of other cells. (Note that necrosis causes the death of clusters of cells.) In apoptosis, the cell shows shrinkage & increased acidophilic staining of the cell. This is followed by fragmentation of the cells. These fragments are called apoptotic bodies. Apoptosis usually occurs as a physiologic process for removal of cells during embryogenesis, menstruation, etc… It can also be seen in pathological conditions caused by mild injurious agents.

Apoptosis is not followed by inflammation or calcification. The above mentioned features distinguish apoptosis from necrosis.

Two main pathways:

1- Intrinsic 'mitochondrial' pathway: Increased permeability of mitochondrial membrane results in release of pro-apoptotic factors (cytochrome c and AIF) that activate downstream caspases □ death.

2- Extrinsic 'death receptor pathway': FAS and TNF1 receptor families with death domain.

Steps & Cellular targets in Injury:

1- Mitochondria: Interruption of oxidative metabolism , Loss of energy due to formation of mitochondrial permeability transition pore (MPT) → loss of membrane potential → prevents ATP generation (ATP depletion) , Cytochrome c released into cytosol → activates apoptosis. , O2 depletion → ROS

2- Cell Membranes ν Important sites of damage : Mitochondrial membrane→↓ ATP ν Plasma membrane→ failure of Na pump leads to ↑cellular amounts of water , Lysosomal membrane → enzyme release, activation & digestion of cell components

3- Influx of Calcium: ν Ca stability is maintained by ATP ν Loss of Ca homeostasis → ↑cytosolic Ca+ → activation of: ν phospholipases ν proteases ν ATPases ν Endonucleases

4-Protein synthesis: High fluid levels cause ribosomes to separate from the swollen endoplasmic reticulum → ↓protein synthesis, ↑glycolysis Metabolic acidosis 5- Genetic apparatus DNA defects & mutations

After death

Cellular constituents are digested by lysosomal hydrolases → enzymes & proteins leak into extracellular space → useful in diagnosis , Myocardial Infarction (creatine kinase & troponins) , Liver injury (biliary obstruction): Alkaline phosphatase ν Dead cells converted to phospholipid masses (Myelin Figures) → Phagocytosis or degraded to fatty acids → calcification.

Comparison of apoptosis with necrosis…….

VI. Pathologic calcification

Pathologic calcification is divided into 2 types:

1. **Metastatic calcification**

   This is caused by hypercalcemia, resulting from hyperparathyroidism, milk-alkali syndrome, sarcoidosis etc…

2. **Dystrophic calcification**

   This occurs in previously damaged tissue, such as areas of old trauma, tuberculous lesions, scarred heart valves, & atherosclerotic lesions.

   Unlike metastatic calcification, it is not caused by hypercalcemia. Typically, the serum calcium level is normal**.**

Degeneration:

Degeneration of cells refers to the process in which cells lose their normal structure, function, or vitality due to injury, disease, or aging. This deterioration can result in impaired tissue or organ function and is often associated with various pathological conditions.

Causes of Cell Degeneration:

1. **Aging**: Natural wear and tear over time can lead to cellular dysfunction.
2. **Oxygen Deficiency (Hypoxia)**: Caused by reduced blood supply or blocked oxygen delivery.
3. **Infections**: Bacterial, viral, or fungal infections can damage cells.
4. **Toxins**: Exposure to harmful chemicals, drugs, or environmental toxins.
5. **Chronic Inflammation**: Prolonged immune responses can destroy healthy cells.
6. **Nutritional Deficiencies**: Lack of essential nutrients like vitamins and minerals.
7. **Oxidative Stress**: Accumulation of free radicals that damage cell components.
8. **Genetic Disorders**: Mutations or inherited conditions that disrupt normal cellular processes.

Degenerative Changes

One of the basic & fundamental results of injury is a series of changes in cells or intercellular tissue that long have been designated as degeneration & infiltration In the degenerations there is an alteration in the cellular elements usually in the nature of a metabolic or enzymatic disturbance in the injured cells, While in infiltration there is a substance accumulation in the cells in the cells or adjacent tissues in abnormal amounts or which are not normally observed such as Ca or pigments, or fats Some changes are reversible but if there is prolonged or sever , irreversible changes resulting in cell death or tissue necrosis.

Consequences of Cell Degeneration:

- Loss of tissue or organ function.
- Increased susceptibility to infections or further damage.
- Chronic inflammation or scarring.
- Potential progression to cell death (apoptosis or necrosis).

There are several types of degeneration, classified based on the underlying changes occurring within cells or tissues. These types can be categorized by the substance accumulating in the cells, the structural changes, or the pathological processes. Here are the most common types:

1. Fatty Degeneration (Steatosis)

- **Definition**: Accumulation of fat droplets within the cytoplasm of cells, especially in organs like the liver, heart, and kidneys.
- **Causes**: Alcohol abuse, obesity, diabetes, malnutrition, or toxins.
- **Example**: Fatty liver disease.

---

2. Hydropic Degeneration

- **Definition**: Accumulation of water within the cytoplasm, leading to cell swelling.
- **Causes**: Hypoxia, infections, or exposure to toxins.
- **Example**: Cellular swelling seen in liver damage.

---

3. Hyaline Degeneration

- **Definition**: Deposition of a glassy, homogenous, proteinaceous material in tissues or cells.
- **Causes**: Long-term inflammation, aging, or metabolic disorders.
- **Example**: Hyaline deposits in blood vessels during arteriosclerosis.

---

4. Mucoid Degeneration

- **Definition**: Abnormal accumulation of mucin or mucopolysaccharides within cells or extracellular spaces.
- **Causes**: Connective tissue disorders.
- **Example**: Myxedema in hypothyroidism.

---

5. Amyloid Degeneration (Amyloidosis)

- **Definition**: Deposition of amyloid protein in tissues, causing dysfunction.
- **Causes**: Chronic infections, autoimmune diseases, or genetic mutations.
- **Example**: Amyloidosis in Alzheimer's disease.

---

6. Fibrous Degeneration

- **Definition**: Replacement of normal tissue with fibrous (scar-like) tissue, leading to stiffness and loss of function.
- **Causes**: Chronic inflammation or injury.
- **Example**: Pulmonary fibrosis.

---

7. Caseous Degeneration

- **Definition**: Tissue death resulting in a soft, cheese-like appearance, often associated with granulomas.
- **Causes**: Tuberculosis or fungal infections.
- **Example**: Caseous necrosis in lymph nodes affected by TB.

---

8. Calcific Degeneration

- **Definition**: Deposition of calcium salts in tissues, often as a result of chronic injury or necrosis.
- **Causes**: Chronic inflammation, necrosis, or metabolic imbalances.
- **Example**: Calcification in atherosclerotic plaques.

---

9. Necrotic Degeneration

- **Definition**: Irreversible cell death due to severe damage, resulting in tissue breakdown.
- **Causes**: Ischemia (lack of blood flow), toxins, or trauma.
- **Example**: Myocardial infarction (heart attack).

---

10. Lipoid Degeneration

- **Definition**: Accumulation of lipids in cells where they are not typically present.
- **Causes**: Metabolic disorders or infections.
- **Example**: Niemann-Pick disease.

---

11. Glycogen Degeneration

- **Definition**: Abnormal accumulation of glycogen in cells due to metabolic disorders.
- **Causes**: Enzyme deficiencies in glycogen storage diseases.
- **Example**: Pompe disease.

---

12. Reticular Degeneration

- **Definition**: Degeneration characterized by the destruction of reticular (network-like) fibers within tissues.
- **Causes**: Necrosis or severe inflammation.
- **Example**: Seen in certain liver diseases.

---

13. Fibrinoid Degeneration

- **Definition**: Deposition of fibrin-like material in tissues, often associated with immune reactions.
- **Causes**: Autoimmune diseases or severe hypertension.
- **Example**: Fibrinoid necrosis in blood vessels.

Aging and Cellular Death

*** Theories**

Aging is caused by accumulations of injurious events , Aging is the result of a genetically controlled developmental program.

Mechanisms :

Genetic, environmental, and behavioral, Changes in regulatory mechanisms

Degenerative alterations.

Cellular aging:

Genetic e.g. failure of repair mechanisms, Clock genes overexpression of antioxidative enzymes

Telomerase activity …….etc Telomerase activity stops in somatic cells, but continues in stem cells & germ cells

Environmental: generation of FR, diet

Accumulation of multiple defects→ Aging ν Aged cells show Lipofuscin pigment , abnormally folded proteins & advanced glycosylation end products (AGES's)