CELL RESPONSE TO INJURY

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CAUSES OF CELL INJURY:

1. ***Hypoxia:*** the main cause of cell injury.

- Decrease oxygen supply is caused by:
  a. Ischemia e.g. arterial occlusion and atherosclerosis.
  b. Inadequate oxygenation e.g. cardiac and pulmonary diseases.
  c. Decreased oxygen carrying capacity of the RBCs e.g anemia and carbon monoxide poisoning.

2. ***Infectious agents:*** Bacteria, viruses, rickettsia, fungi and parasites.
3. ***Physical agents:*** Trauma, heat, cold, radiation and electric shock.
4. ***Chemical agents:*** Acids, alkalies, animal and plant poisons and some therapeutic drugs.
5. ***Immunologic reactions.***
6. ***Nutritional deficiencies.***
7. ***Genetic and enzymatic derangements.***

MECHANISMS OF CELL INJURY:

(1) ATP depletion mainly caused by hypoxia.
(2) Defects in membrane permeability.
(3) Formation of toxic oxygen-free radicals as superoxide and hydrogen peroxide caused by chemicals and radiation.
(4) Increase intracellular calcium (Ca influx from the plasma or release from mitochondria and endoplasmic reticulum).

- Calcium activates the following cellular enzymes:

a. Phospholipases which degrade membrane phospholipids.
b. Proteases which breakdown cellular proteins.
c. ATPases which deplete ATP.
d. Endonucleases which fragment chromatin.

- **Effects of Cell Injury:**
  The effects of cell injury depend upon:
  a. Type of injured cell
  b. Nature of injurious agents
  c. Severity of injurious agents

1. **Reversible cell injury (degeneration):**
2. Caused by mild injury or injury of short duration.

- Active parenchymatous cells with higher rate of metabolism suffer more than supporting stroma cells.
- Reversible cell injuries include:

a. Acute cellular swelling (cloudy swelling and hydropic swelling).

b. Fatty change.

2. **Irreversible cell injury:**

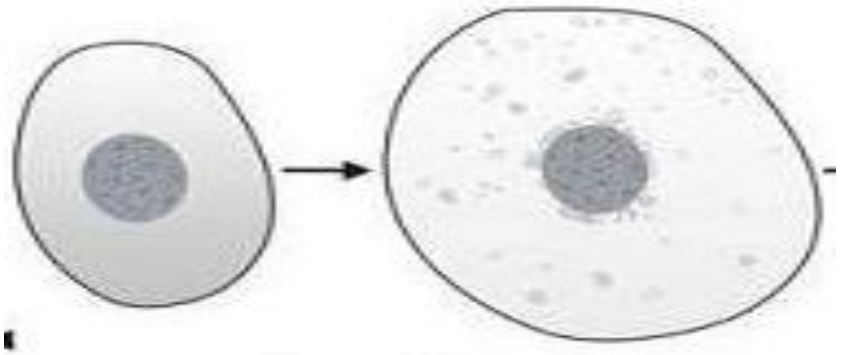
- Caused by severe injury or injury of long duration→ damage to the nucleus and cell death occur.
- The morphologic patterns of cell death:

  a. Necrosis.

  B. Apoptosis.

CLOUDY SWELLING:

- **Definition:**
- Reversible cell injury characterized morphologically by swelling of the cells and granularity of the cytoplasm.
- Cellular swelling is due to water accumulation.



- **Pathogenesis:**
- Injurious agents mainly hypoxia inhibit oxidative phosphorylation and ATP formation by the mitochondria.
- Loss of ATP which is the energy source causes:

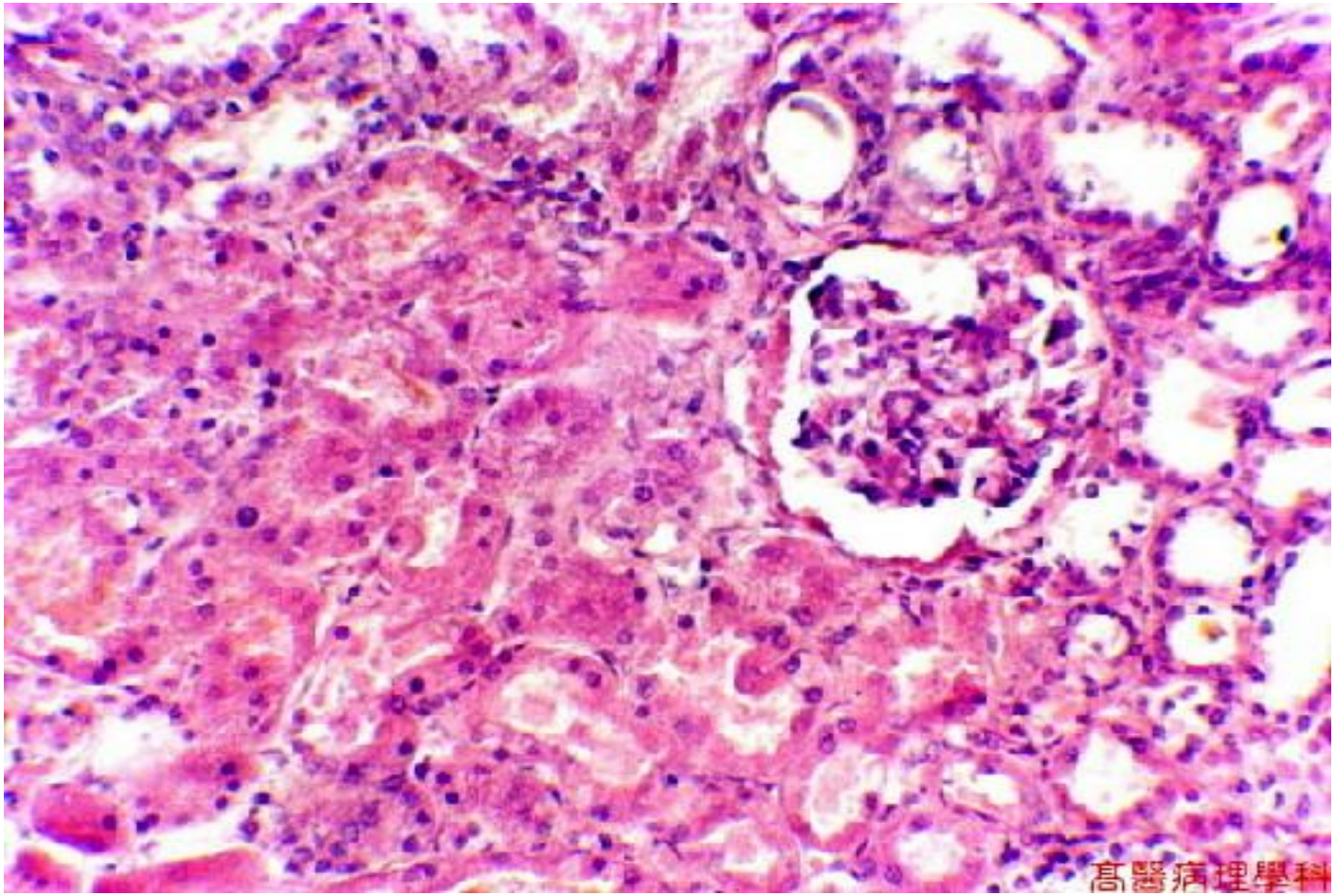
1. Failure of the active cell membrane transport (sodium pump).
   - Sodium enter the cell and potassium diffuse out of the cell.
   - Accumulation of sodium is followed by entry of water.
2. Anaerobic ATP synthesis starts, and catabolites as lactate and inorganic phosphates accumulate and increase the intracellular osmotic load.

PATHOLOGICAL FEATURES:

- ***Organs affected:*** Highly specialized parenchymatous cells e.g. liver cells, renal convoluted tubules and heart muscles.
- ***Gross picture:*** The affected organ appears swollen, soft, bloodless due to compression of the capillaries by the swollen cells.
- The borders are rounded.
- The cut surface appears cloudy (less glistening), opaque and bulges outwards.

- ***Microscopic picture:***
- The cells are swollen due to entry of water.
- The cytoplasm shows innumerable fine red granules.
- The nucleus is normal.
- The capillaries between the cells are compressed.

CLOUDY SWELLING OF THE KIDNEY:



- **Clinically:**

1. Kidney affection causes proteinuria due to incomplete reabsorption of the filtered proteins by the affected renal tubules.
2. Liver affection causes no significant functional changes.
3. Heart affection results in its dilatation and decreased efficiency.

- **Fate:**
- Cloudy swelling is reversible.
- If the injury stops the cell returns to normal, but if the injury continues cloudy swelling proceeds to hydropic swelling, or complete necrosis.

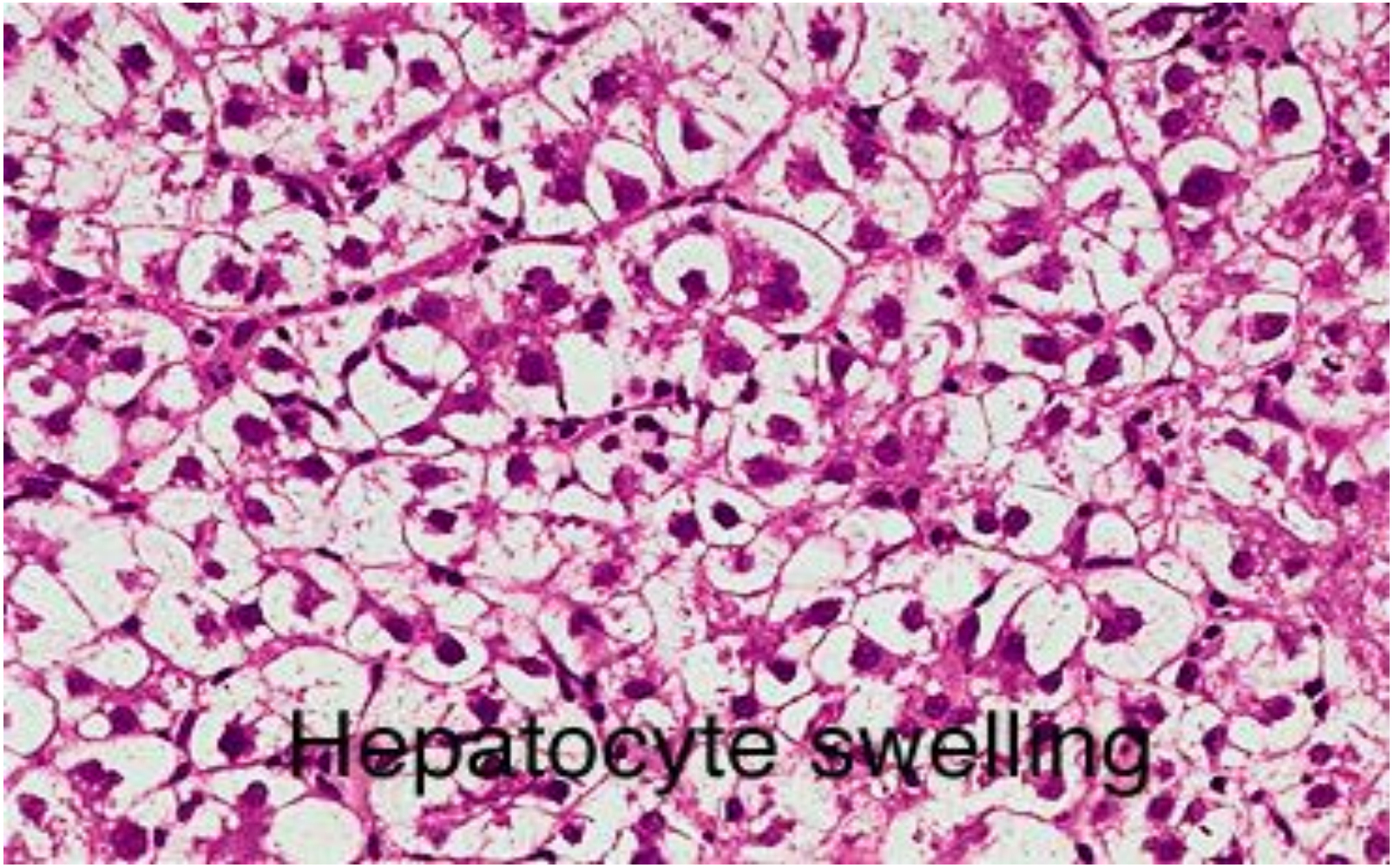
HYDROPIC SWELLING:

- **Definition:**
- Hydropic swelling (hydropic degeneration) is a reversible cell injury characterized by excess water accumulation inside the cells forming vacuoles in the cytoplasm.
- The lesion is more advanced than cloudy swelling.
- **Causes and Pathogenesis:** Similar to cloudy swelling.

- **Microscopic picture:**
- The cells are swollen due to excess water accumulation.
- The cytoplasm is pale & shows multiple vacuoles.
- The nucleus is normal.

- Examples of hydropic degeneration are:
- Epidermal cells in burns, urticaria & viral infections as small pox.
- Ballooning degeneration of liver cells in viral hepatitis and alcohol poisoning.
- Beta cells of islets of Langerhans early in diabetes mellitus.
- Renal tubules in potassium deficiency caused by severe diarrhea.

HYDROPIC DEGENERATION:



FATTY CHANGE:

- **Definition:**
- Pathological accumulation of excess neutral fat in parenchymatous cells.
- **Etiology & Pathogenesis:**
- Fat produced at/or carried to injured cells cannot be metabolized due to diminished enzyme activity, so it accumulates in the cytoplasm.

- **Causes:**

(1) Hypoxia.

(2) Bacterial toxins of acute and chronic infections.

(3) Chemical agents as alcohol, phosphorous and carbon tetrachloride.

- Because of the importance of the liver in fat metabolism, fatty changes in the liver cells are also caused by:

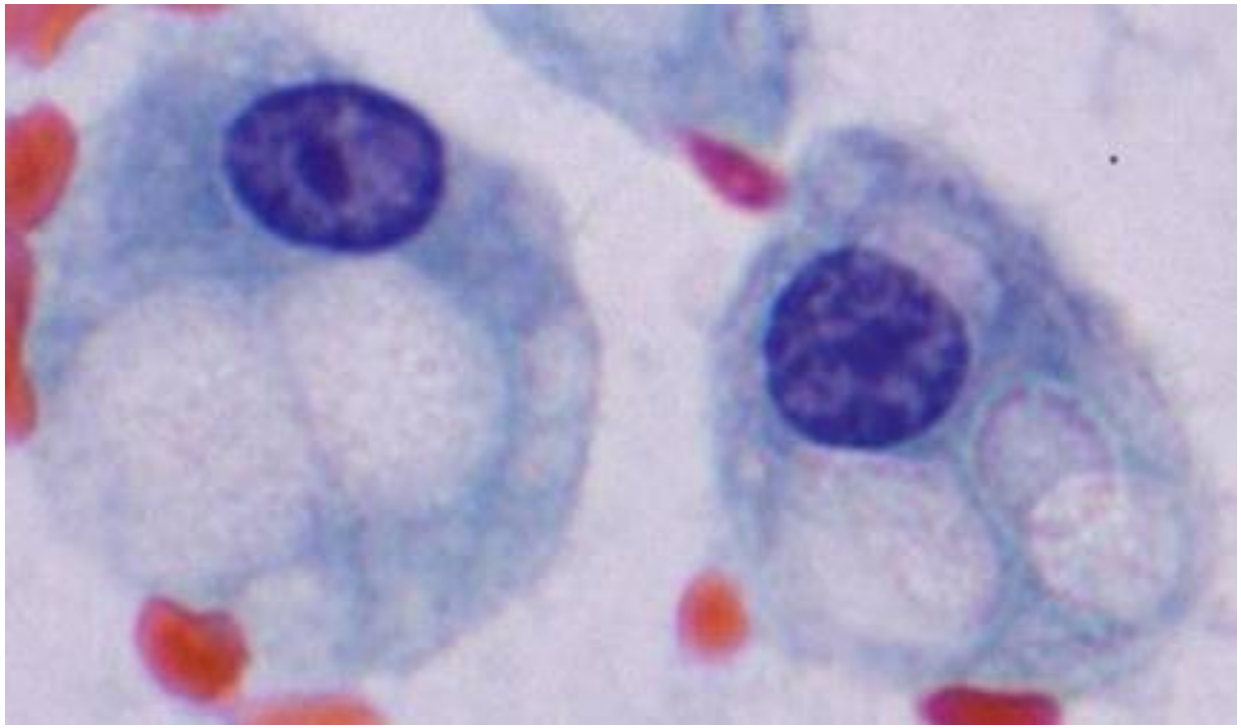
a. Excess fat brought to the liver cells as in:
   - Excess intake of fats and carbohydrates.
   - Starvation with excess mobilization of fat from fat stores.
b. Diseases of the liver cells as in viral hepatitis.
c. Deficiency of lipotropic factors as choline and methionine.

- The diseased cells cannot metabolize the normal amount of fat reaching it.
- Lipotropic factors are necessary for transformation of neutral fat to choline containing phospholipids e.g. lecithin in the liver.
- This is the form of fat which most of the body cells can utilize.
- So absence of lipotropic factors leads to accumulation of neutral fat inside the liver cells.

- **Gross Picture:**
- The affected organ is enlarged and soft in consistency.
- The capsule is tense.
- The color is pale yellow.
- The borders are rounded.
- The cut surface bulges and is greasy to touch.

- **Microscopic Picture:**
- The cells appear swollen and show multiple tiny fat globules in the cytoplasm around the nucleus.
- The fat appears as vacuoles in paraffin sections (fat dissolves in xylol).
- The fat globules fuse together forming a big globule that pushes and flattens the nucleus against the cell membrane giving the cell a signet ring appearance.

- The swollen cells compress the intercellular capillaries.
- In frozen sections fat can be stained by fat stains; orange with sudan III and black with osmic acid.

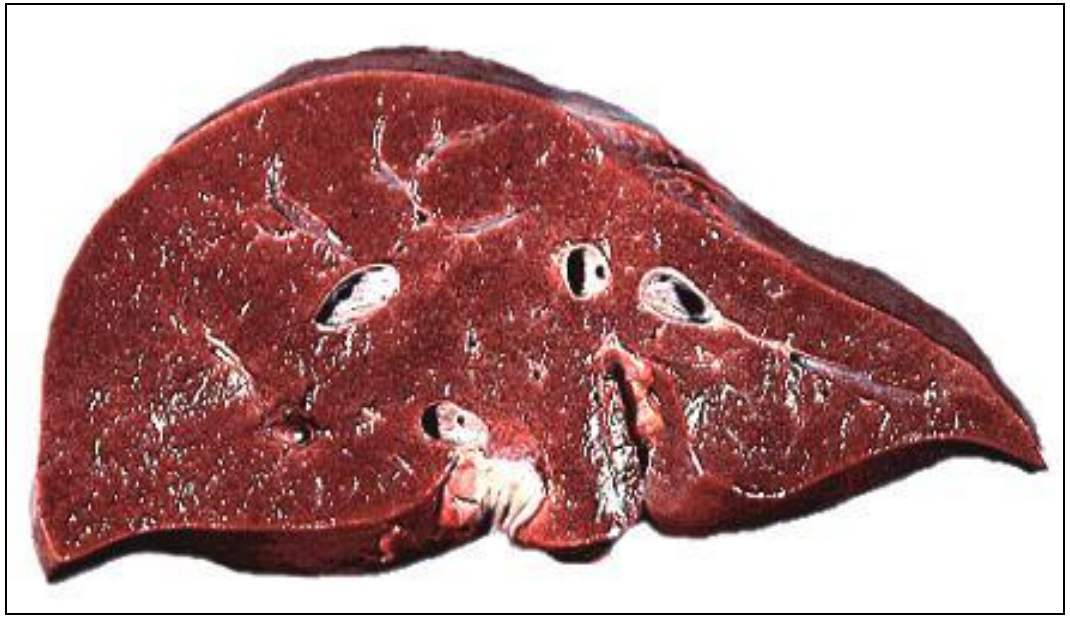


- **Organs Affected:**

1. **Liver:**

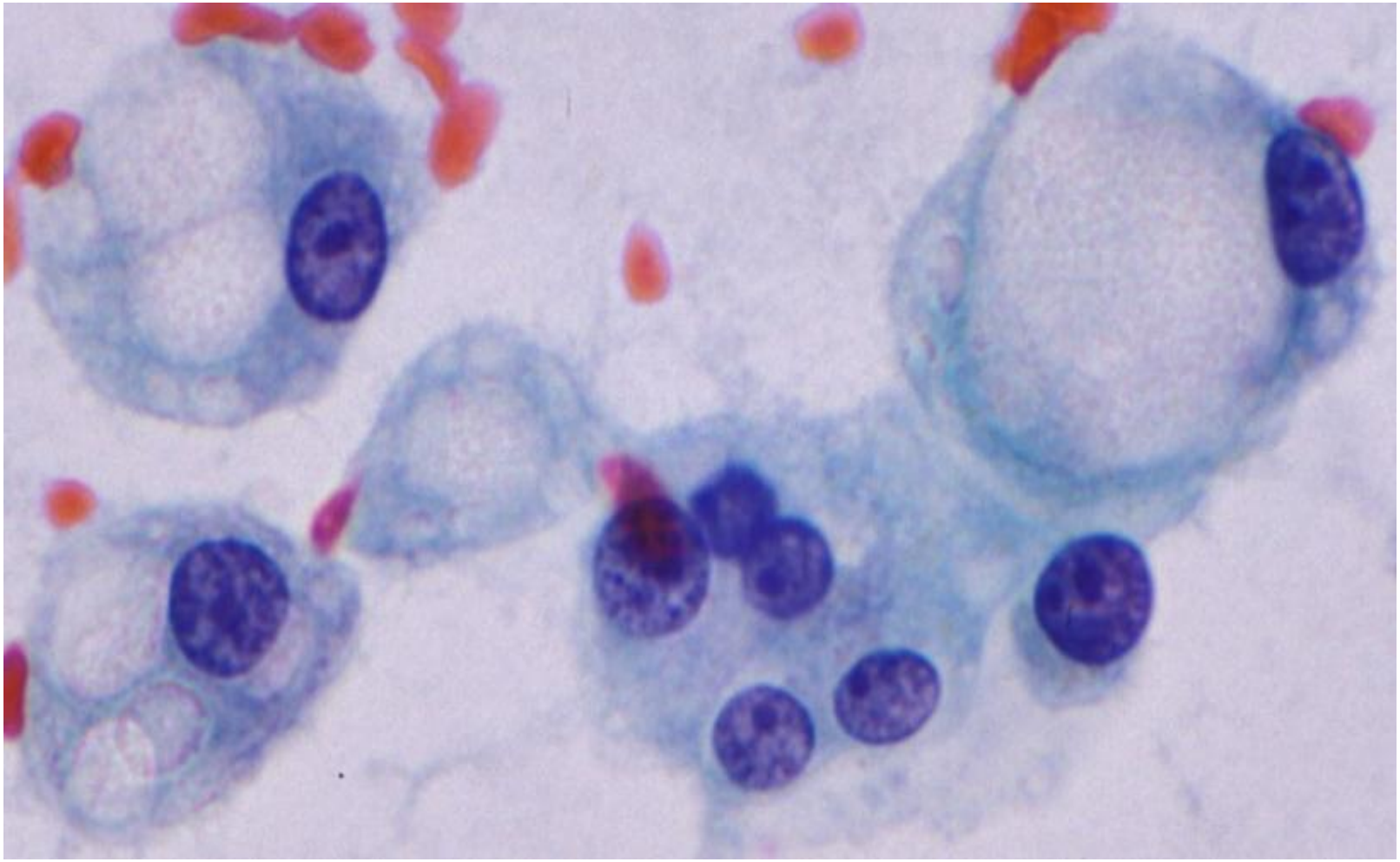
- Fatty change in the liver is either:
  a. ***Diffuse:*** As in severe toxemia, severe anemia and chemic poisons.
  b. ***Patchy:*** As in chronic venous congestion.

Normal Liver

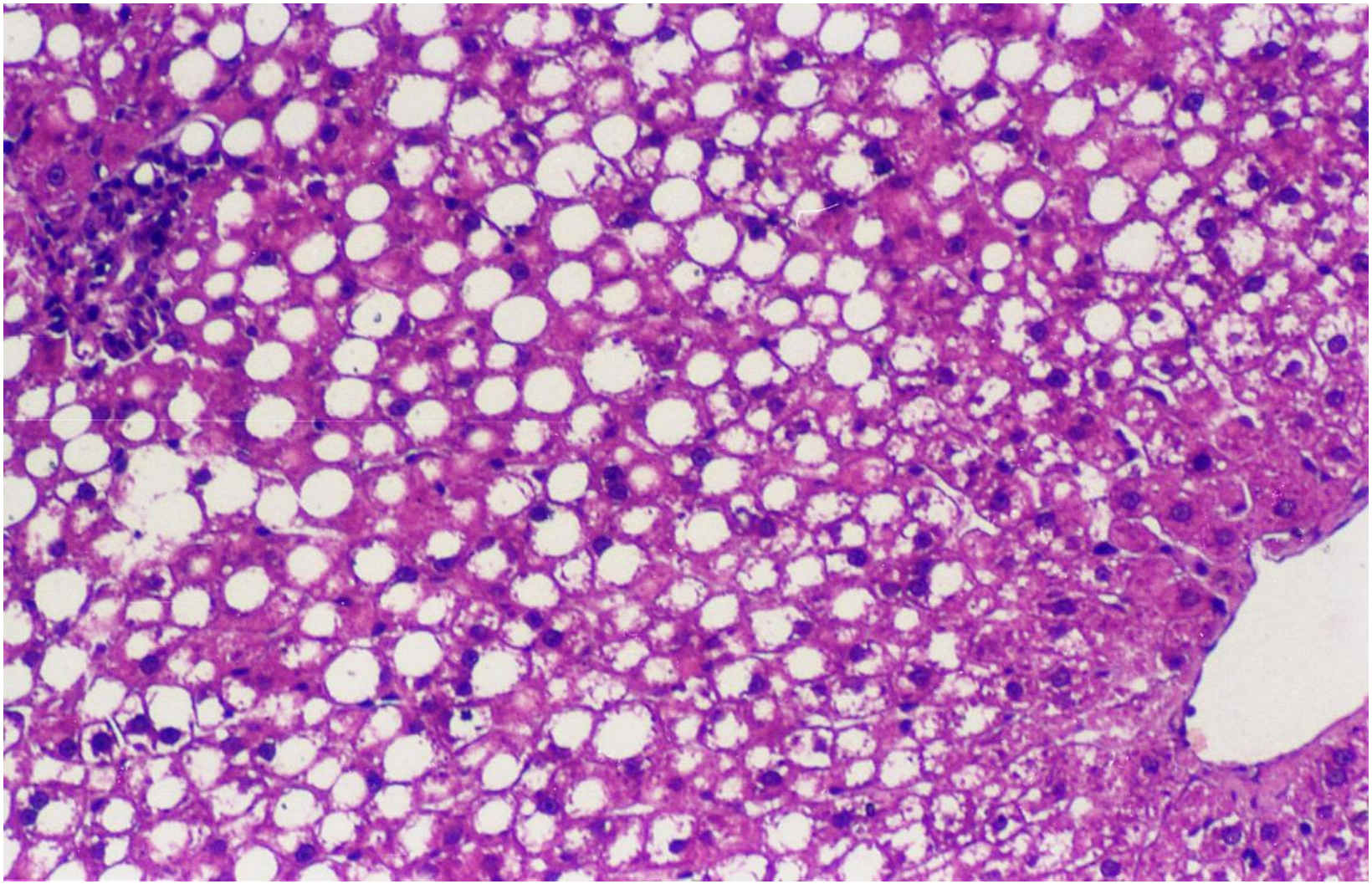


Fatty Liver

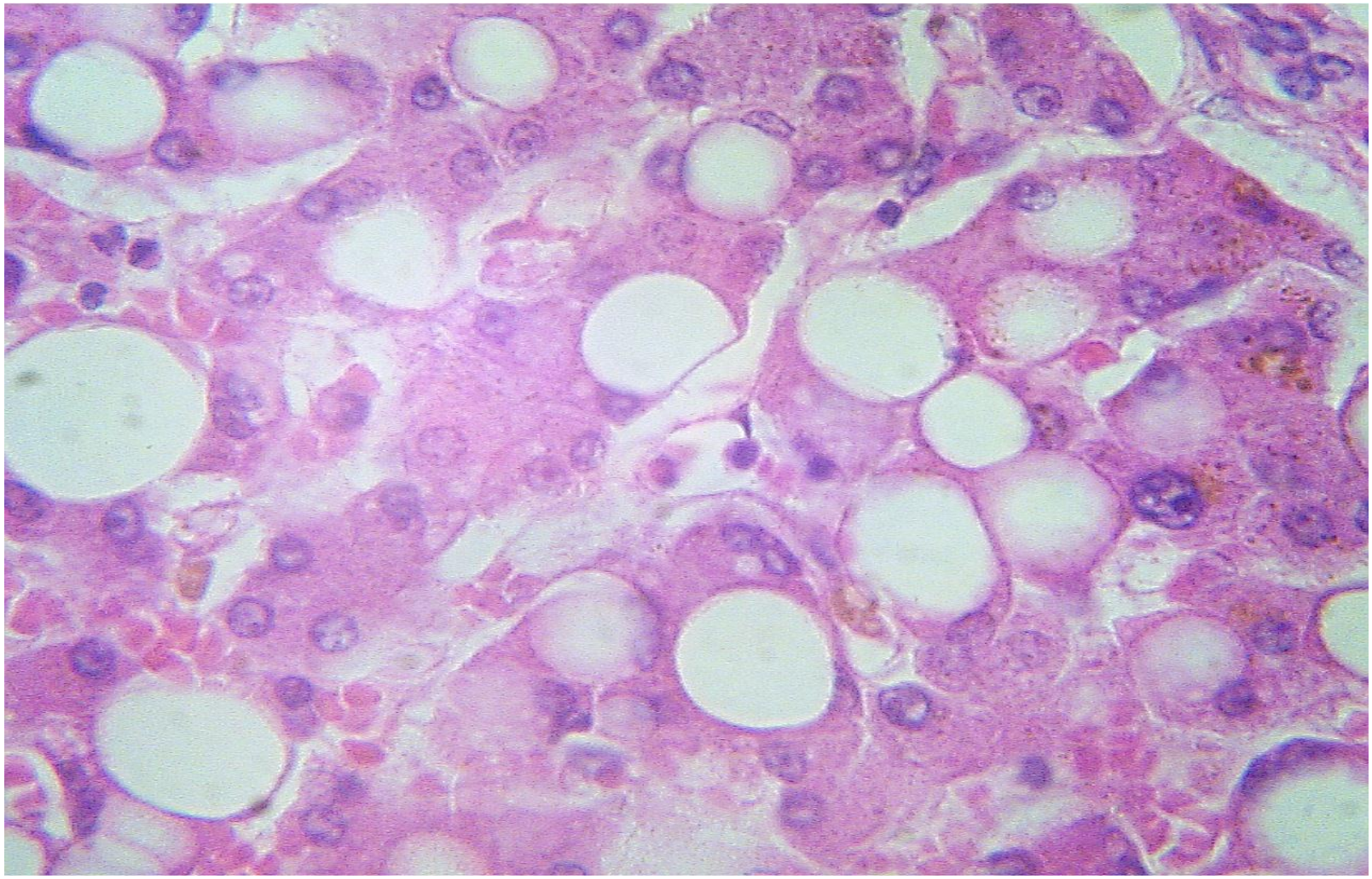
FATTY DEGENERATION



FATTY DEGENERATION OF THE LIVER



FATTY DEGENERATION OF THE LIVER



2. **Heart:**

- The heart appears soft, friable, flabby with dilated chambers and atrio-ventricular rings.
- Microscopically tiny fat globules (vacuoles in paraffin sections) are arranged in longitudinal rows in the muscle fiber
- Fatty changes in the heart are either:

a. ***Diffuse:***

- Occurs in acute infections with marked toxemia as in diphtheria (toxic myocarditis).
- The myocardium shows a diffuse pale yellow color.
- The condition may terminate in acute heart failure.

b. ***Patchy:***

- Occurs in severe and chronic anemia's.
- The myocardium shows yellow streaks alternating with brown streaks best seen on the endocardial surface, the appearance is called tabby cat or thrush breast striation.

3. **Kidney:**

- Fat globules are deposited in the cells of the convoluted tubule and ascending loop of Henle’s.
- The cortex becomes swollen and pale yellow.

NECROSIS:

- **Definition:**
- Local death of cells or tissues within the living body.
- Necrosis occurs either directly or follows reversible injury.

- **Causes and Pathogenesis:**
- **Macroscopic Picture:**
- Necrotic tissue appears opaque and whitish or yellowish in color.
- The surrounding tissue appears red due to inflammatory hyperemia.

- **Microscopic Picture:**
- Immediately after necrosis dead cells appear like living cells.
- Then a series of changes take place rapidly in the structure of the dead cells caused by the lytic catabolic action of the released lysosomal enzymes.
- The changes are nuclear and cytoplasmic.

1. **Nuclear Changes:**

a. ***Pyknosis:*** The nucleus shrinks, its chromatin becomes dense and it stains darkly.

b. ***Karyorrhxis:*** The nucleus breaks up into multiple small fragments.

- Commonly a pyknotic nucleus undergoes karyorrhexis.

c. ***Karyolysis:*** The nucleus appears to dissolve and fails to take the stain due to chromatin hydrolysis.

2. **Cytoplasmic Changes:**

a. The cells appear swollen (cytomegaly).

b. In hematoxylin and eosin stained sections there is cytoplasmic eosinophilia. This is due to loss of RNA with consequent loss of the normal cytoplasmic basophilia, plus increased binding of eosin to denatured cytoplasmic proteins.

c. The cells loose the cell membrane and become indistinct from each other.

d. Blue stained calcium deposit appear later on.

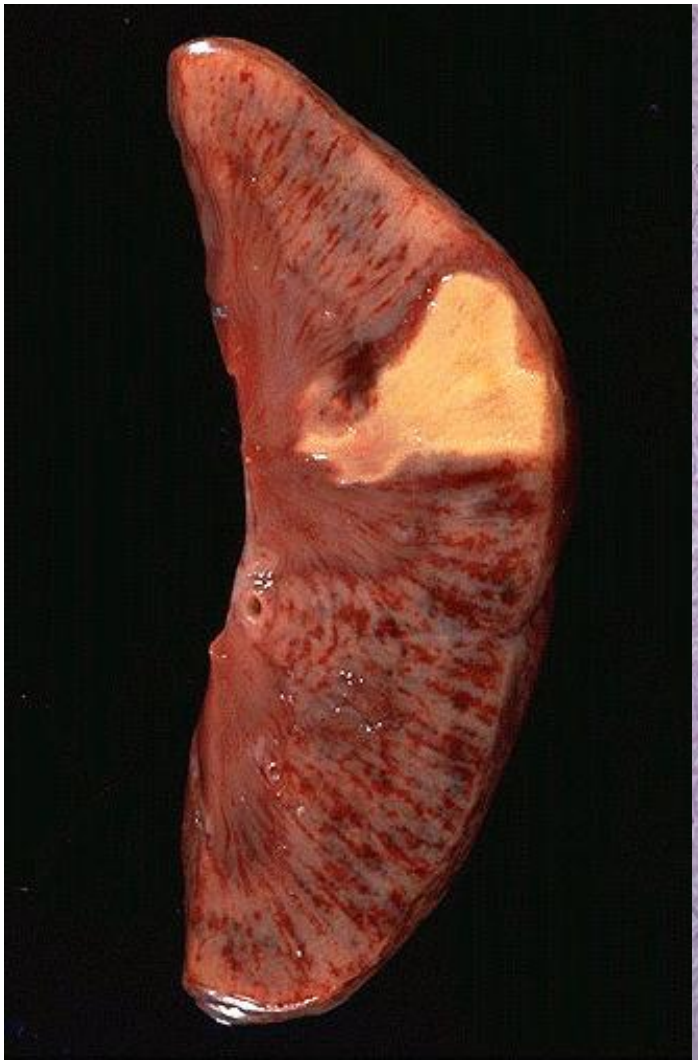
TYPES OF NECROSIS:

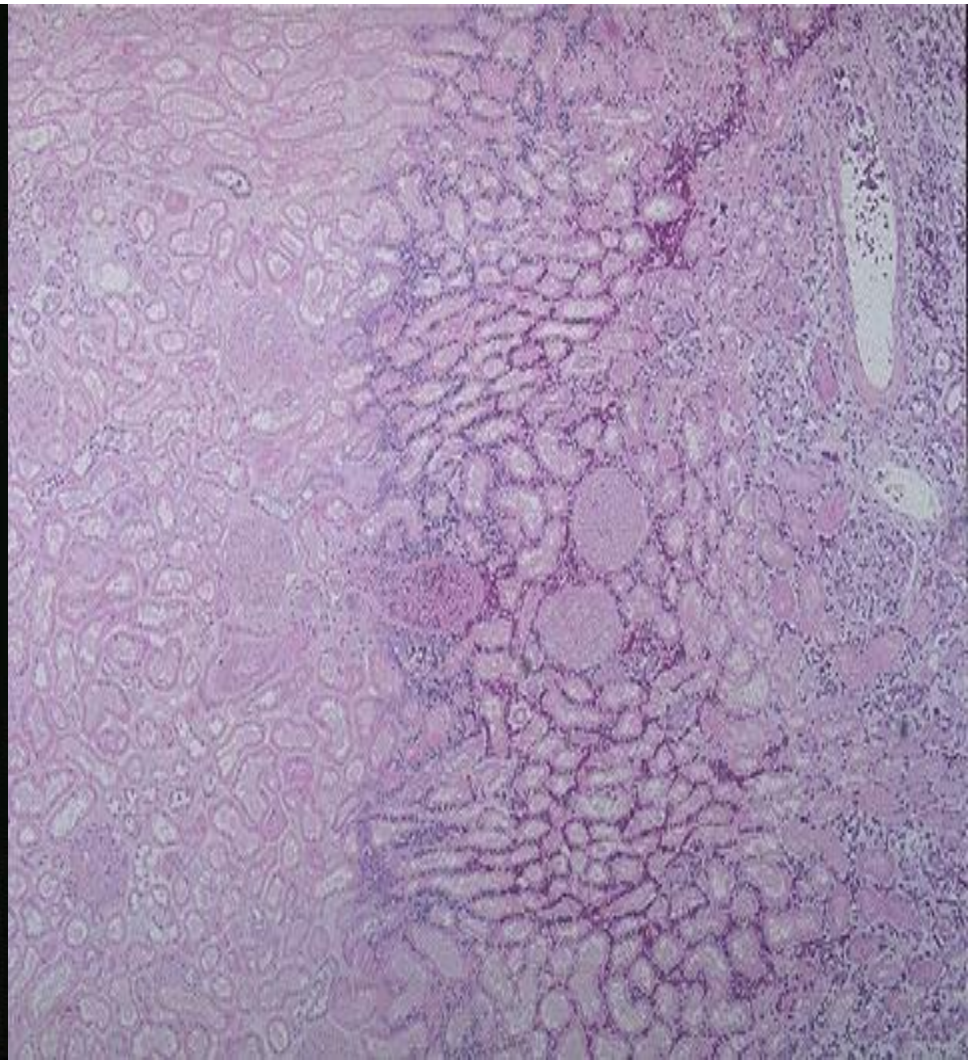
COAGULATIVE NECROSIS:

- Commonly caused by sudden cut of the supply as in infarcts.
- It seems likely that the cellular protein denatured causing the tissue to become firm and opaque white.

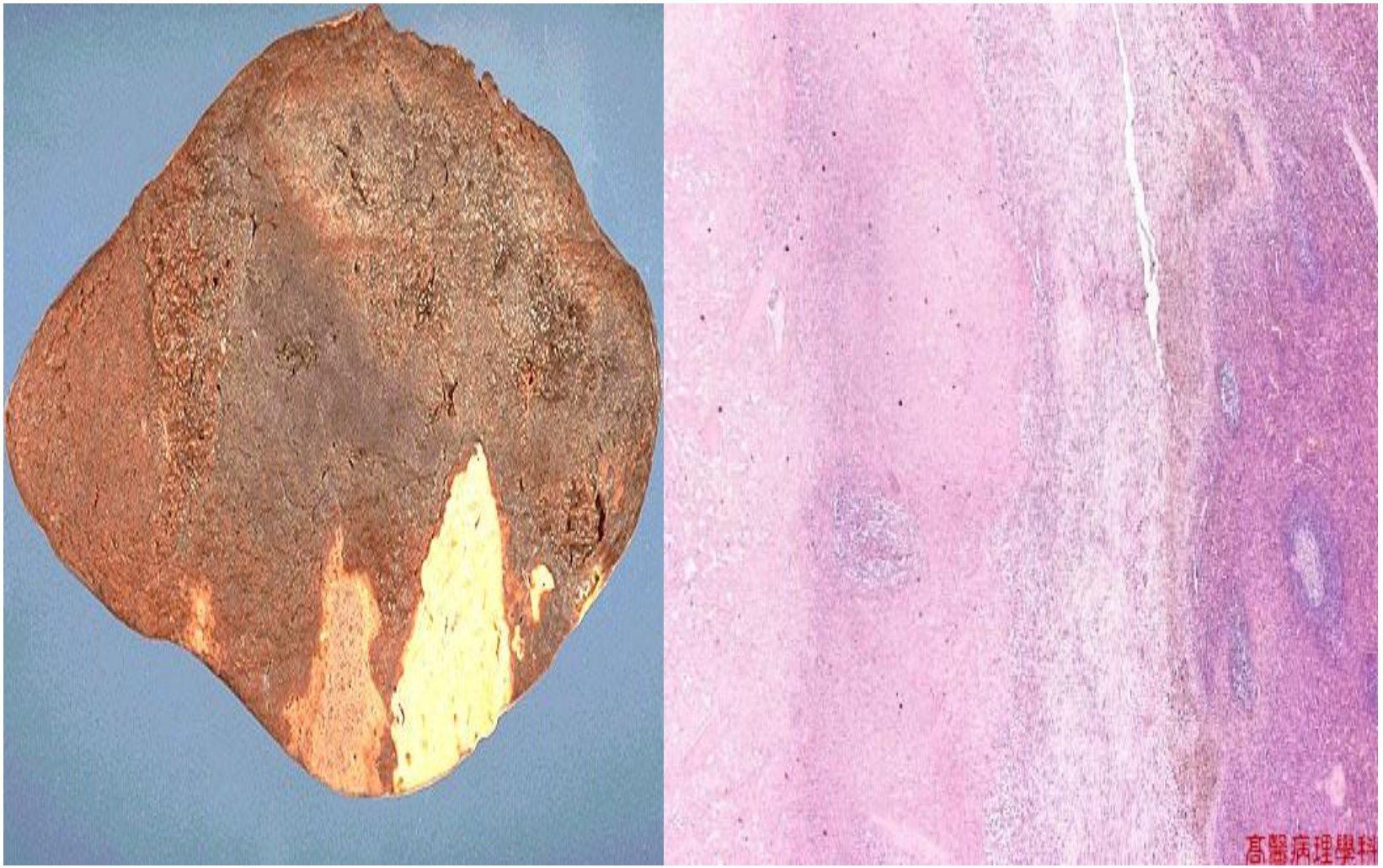
- ***Microscopically:***
- Early the general architecture of the tissue is set with no cellular details.
- Lately dead tissue appears homogenous structureless and pink stained.
- The blood vessels and fibrous stroma are more resistant to the process of necrosis and their outlines remain longer time.

INFARCTION OF THE KIDNEY

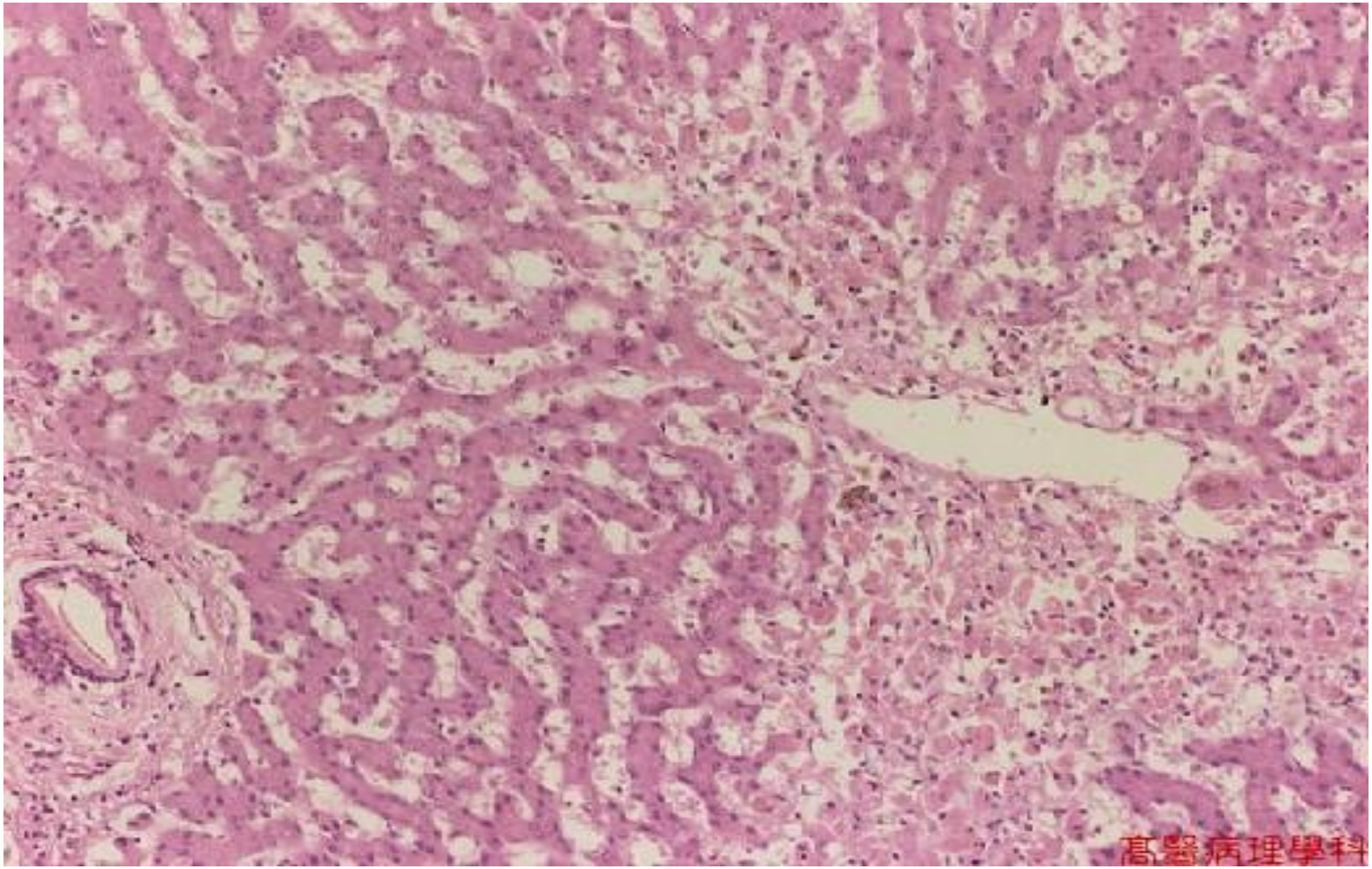




INFARCTION OF THE SPLEEN



INFARCTION OF THE KIDNEY



LIQUEFACTIVE NECROSIS:

- The necrotic tissue is rapidly liquefied.
- It occurs in:

a. ***Infarctions of the brain and spinal cord:***

- The softening and liquefaction is due to the high lipid and fluid content of the nervous tissue.

b. ***Pyogenic abscess:*** The central necrotic core is liquefied by the proteolytic enzymes released from the pus cells.

c. ***Amoebic abscess:*** The liquefaction is due to the action of liquefactive enzymes produced by the parasite.

CASEATION NECROSIS:

- Necrosis followed by slow partial liquefaction.
- Grossly the caseating material is dry, pale yellow and resembles creamy cheese or casein.
- Microscopically all cellular details are lost and the tissues appear structureless, granular or homogenous and pink stained.

- Caseation occurs in tuberculous lesions and in gumma of syphilis
- Caseation in gumma is slow and incomplete, so the outline of the tissue is preserved for a longer time.
- Caseation necrosis is caused by antigen-antibody reaction (allergic necrosis).

FAT NECROSIS:

- It is of two types:

1. ***Enzymatic fat necrosis:***

- It occurs in acute hemorrhagic pancreatitis.
- The enzyme lipase which escapes from the ruptured pancreatic ducts acts on the fat of the omentum, mesentery and abdominal organs.

- Lipase splits fat into glycerol and fatty acids.
- Glycerol is absorbed in the blood.
- Fatty acids deposit with calcium as small dull opaque white patches.
- Microscopically the affected fat cells appear cloudy and surrounded by foreign body giant cell reaction and fibrosis.

2. ***Traumatic fat necrosis:***

- It occurs as a result of trauma to the adipose tissue of the breast and subcutaneous fat.
- The fat cells rupture and self-digestion takes place.

- **Fate of Necrotic Tissue:**

1. ***Small area of necrosis:*** Part of the necrotic tissue is removed by the macrophages.

- The rest gets liquefied and drained by the lymphatics and veins.
- Healing occurs by regeneration or by granulation tissue formation followed by fibrosis.

2. ***Large area of necrosis:*** Gets surrounded by a fibrous capsule and may show dystrophic calcification later on.

APOPTOSIS:

- **Definition:**
- Distinctive morphologic pattern of cell death affecting cell or small group of cells.
- Apoptosis is an energy-dependent programmed cell death for removal of unwanted individual cells.
- Apoptosis literally in Greek means “dropping off’.

- **Morphological Changes:**

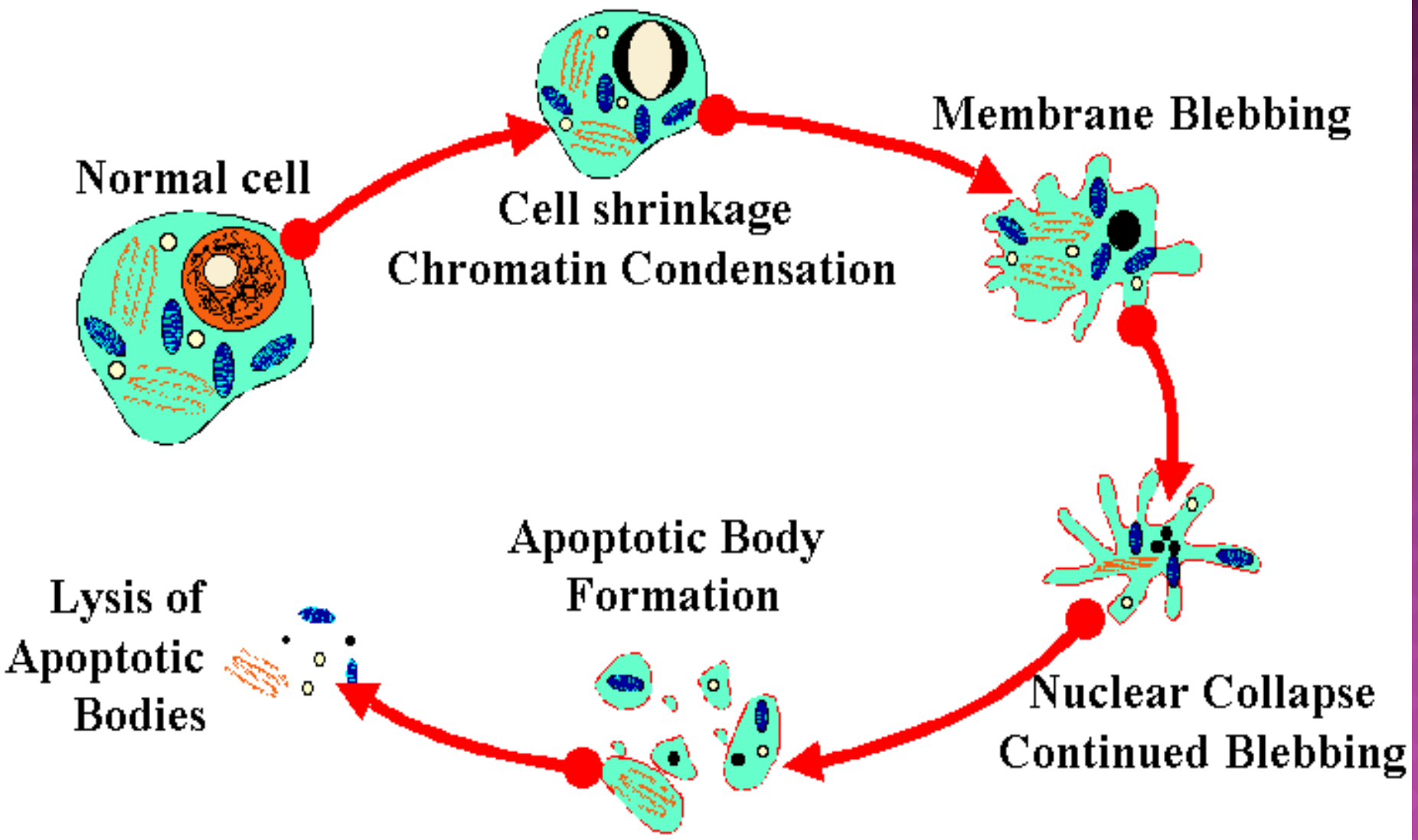
1. Shrinkage of the cell.
2. Condensation and fragmentation of chromatin.
3. Rapid break down of the cell to form apoptotic bodies.

- Apoptotic bodies have intense eosinophilic cytoplasm and dense chromatin fragmentation.

4. Apoptotic bodies are phagocytosed by neighboring cells or macrophages.

- Lack of inflammation in surrounding tissues.

Apoptosis
(Programmed Cell Death)



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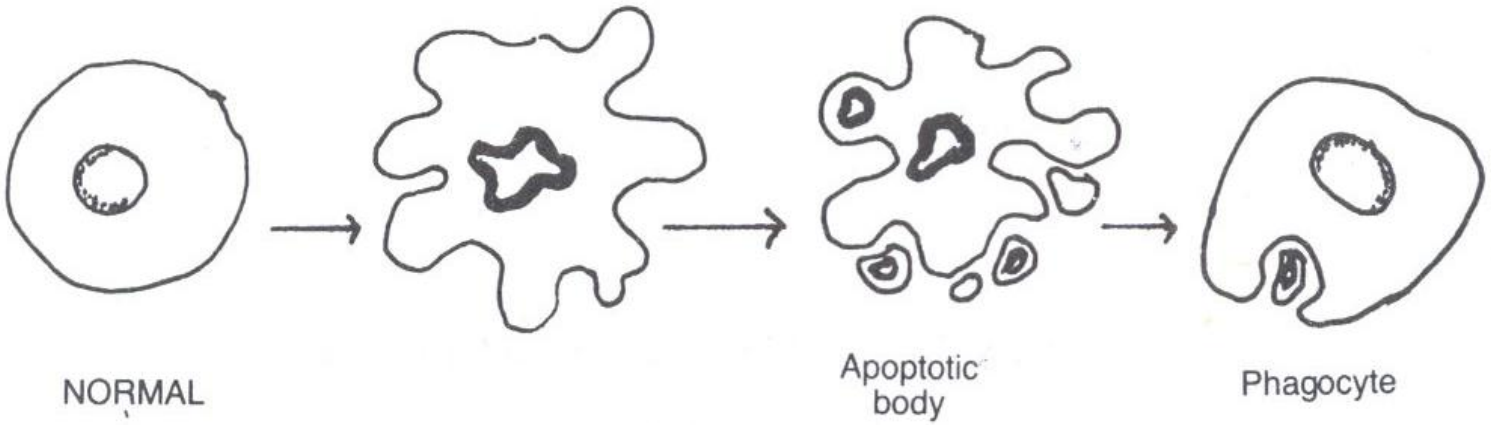

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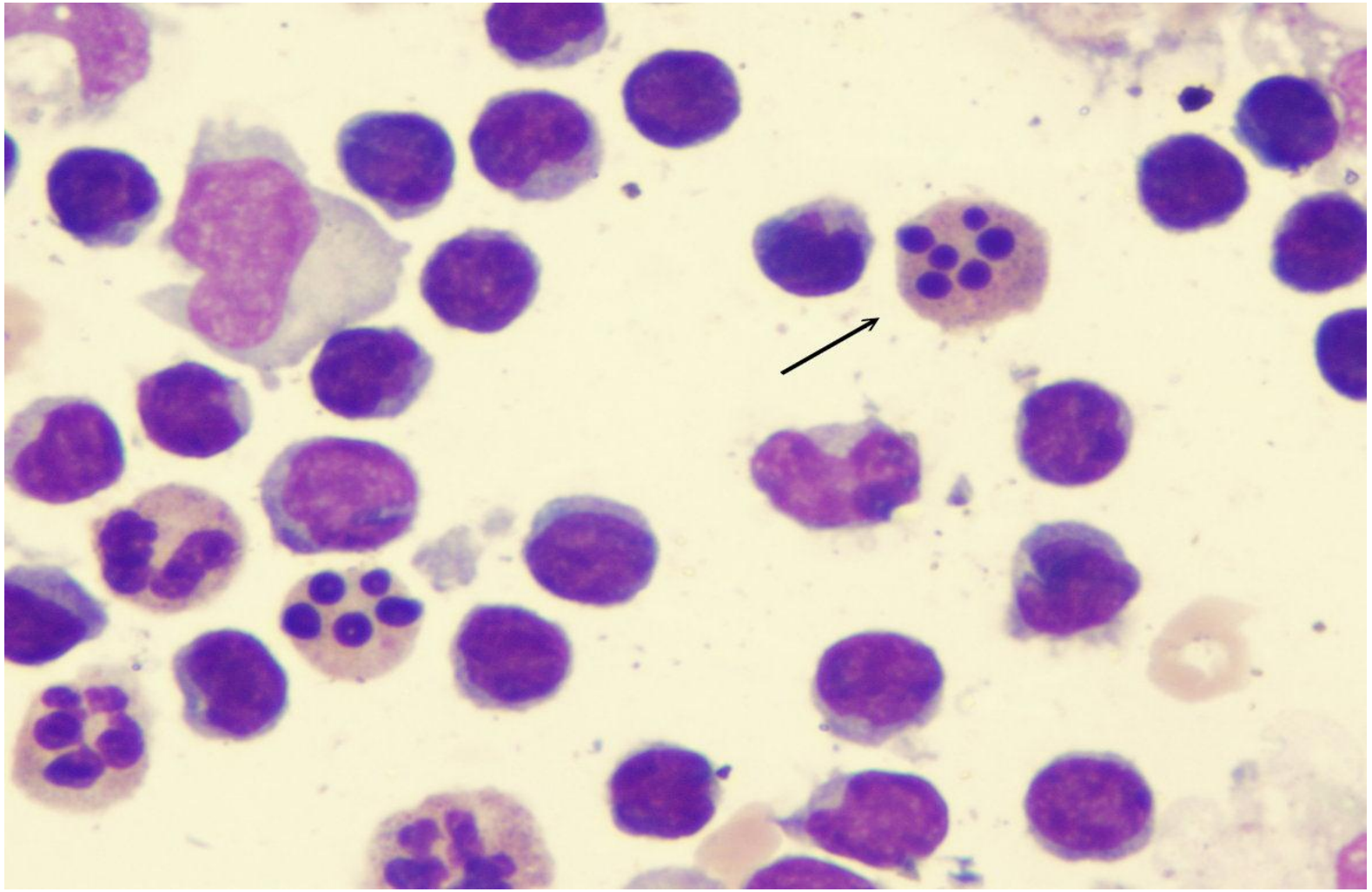

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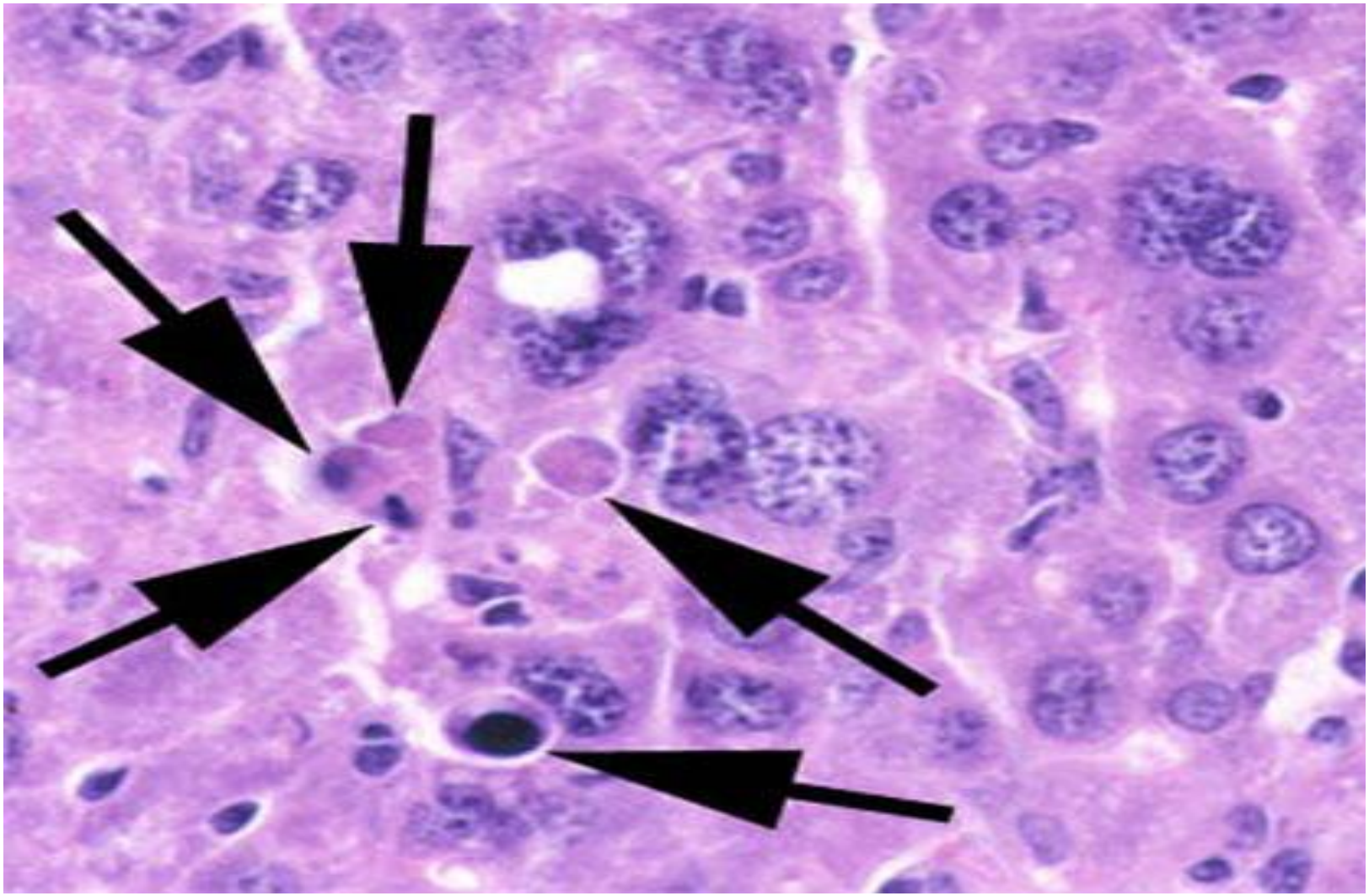
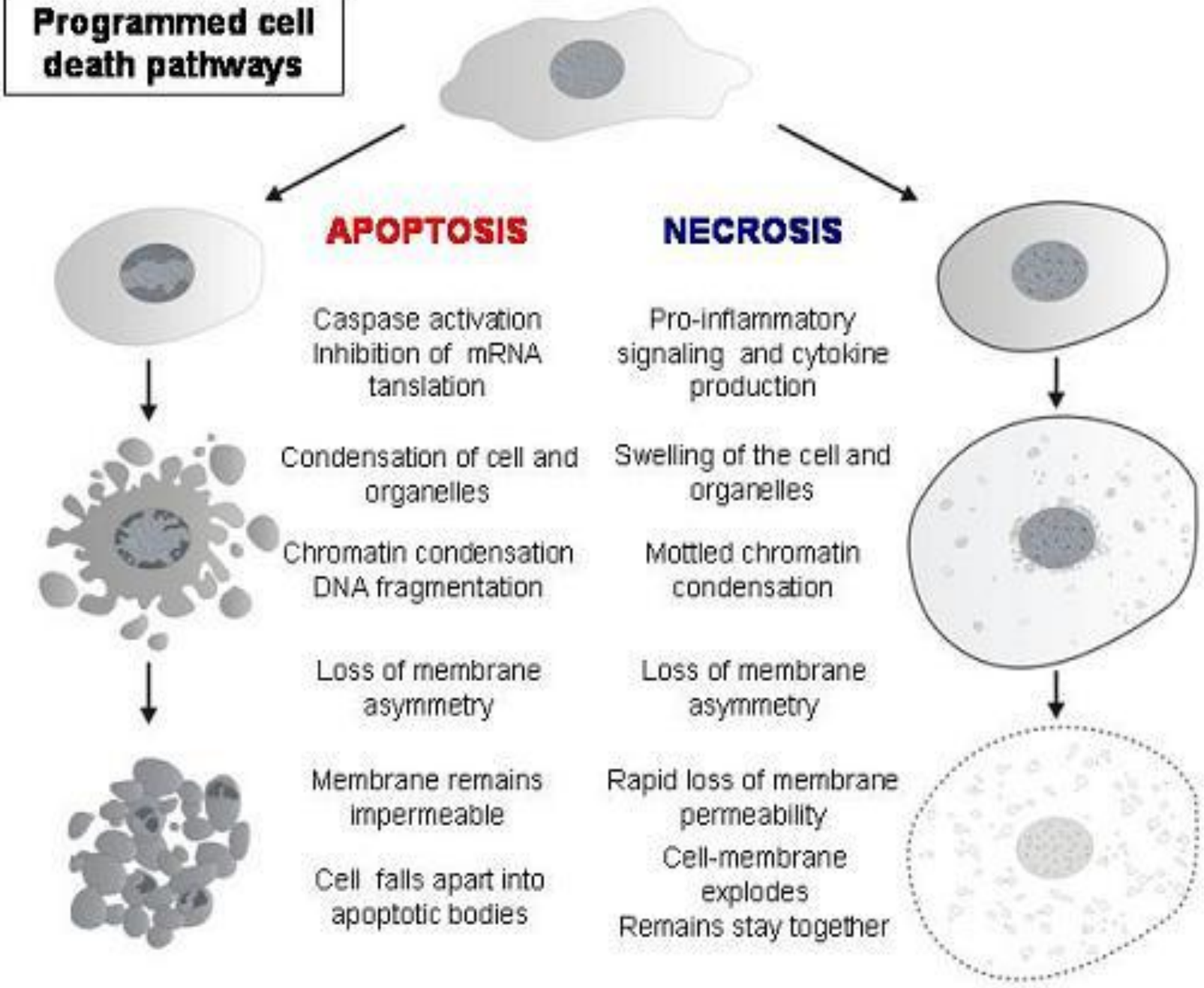


- **Occurrence:**

1. Occur in normal cell turnover.
2. Programmed cell destruction during embryonic development (e. interdigital clefts).
3. Endocrine dependent involution of tissues e.g. shedding endometrium during the menstrual cycle and regression of breast after weaning.

4. **In pathological conditions e.g.:**
    a. Radiation cell injury.
    b. Cell death by cytotoxic T lymphocytes.
    c. Liver cells in viral hepatitis.
    d. Reduction of cell number in pathological atrophy.

Programmed cell death pathways



	Necrosis	Apoptosis
Stimulus	- Always pathologic - (Hypoxia, Toxins,.....)	- Physiologic and - Pathologic conditions
Number of cells	- Group of cells	- Single cells
Histologic picture	- Cellular swelling - Rupture of cell & release of cellular contents	- Cell shrinkage - Chromatin condensation - Formation of apoptotic bodies
Tissue reaction	- Inflammation	- No inflammation - Phagocytosis of apoptotic bodies

GANGRENE:

- **Definition:**
- Gangrene is massive tissue necrosis followed by putrefaction.

- **Causes:**

1. ***Necrosis:*** Is caused by sudden ischemia or bacterial toxins.
2. ***Putrefaction:*** Is caused by saprophytic bacteria which breaks down the protein of the necrotic tissue liberating hydrogen sulphide that gives the tissue a foul odor.

- Hydrogen sulphide unites with the iron of hemoglobin forming iron sulphide that stains the gangrenous tissue black color.

- The classification of gangrene into dry and moist depends on the amount of blood and tissue fluids in the part affected at the time of its death.
- Dry gangrene occurs in parts poor in the blood supply and tissue fluids, while moist gangrene occurs in parts rich in blood supply and tissue fluids.

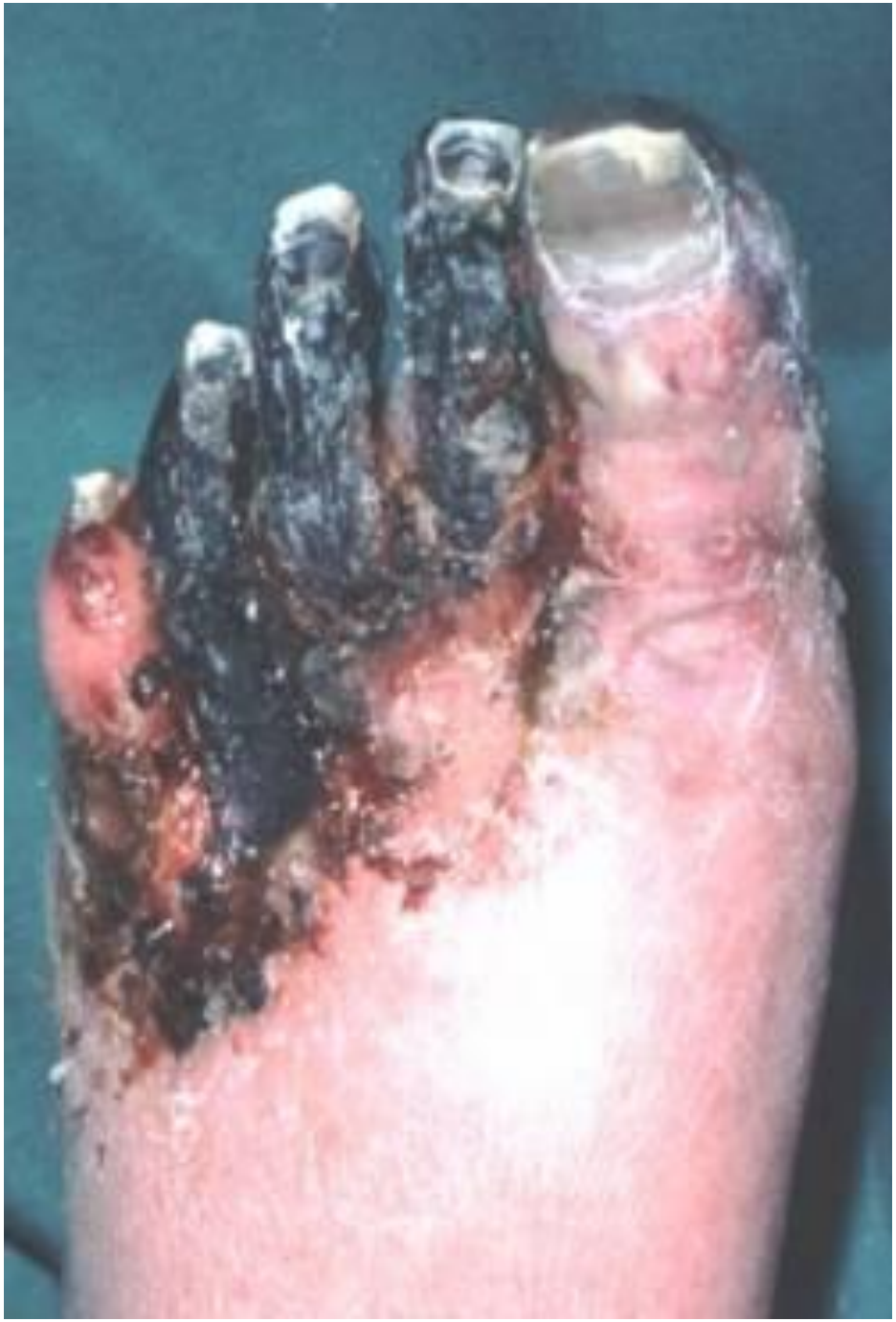
DRY GANGRENE

- Dry gangrene of a limb results from occlusion of its artery by:

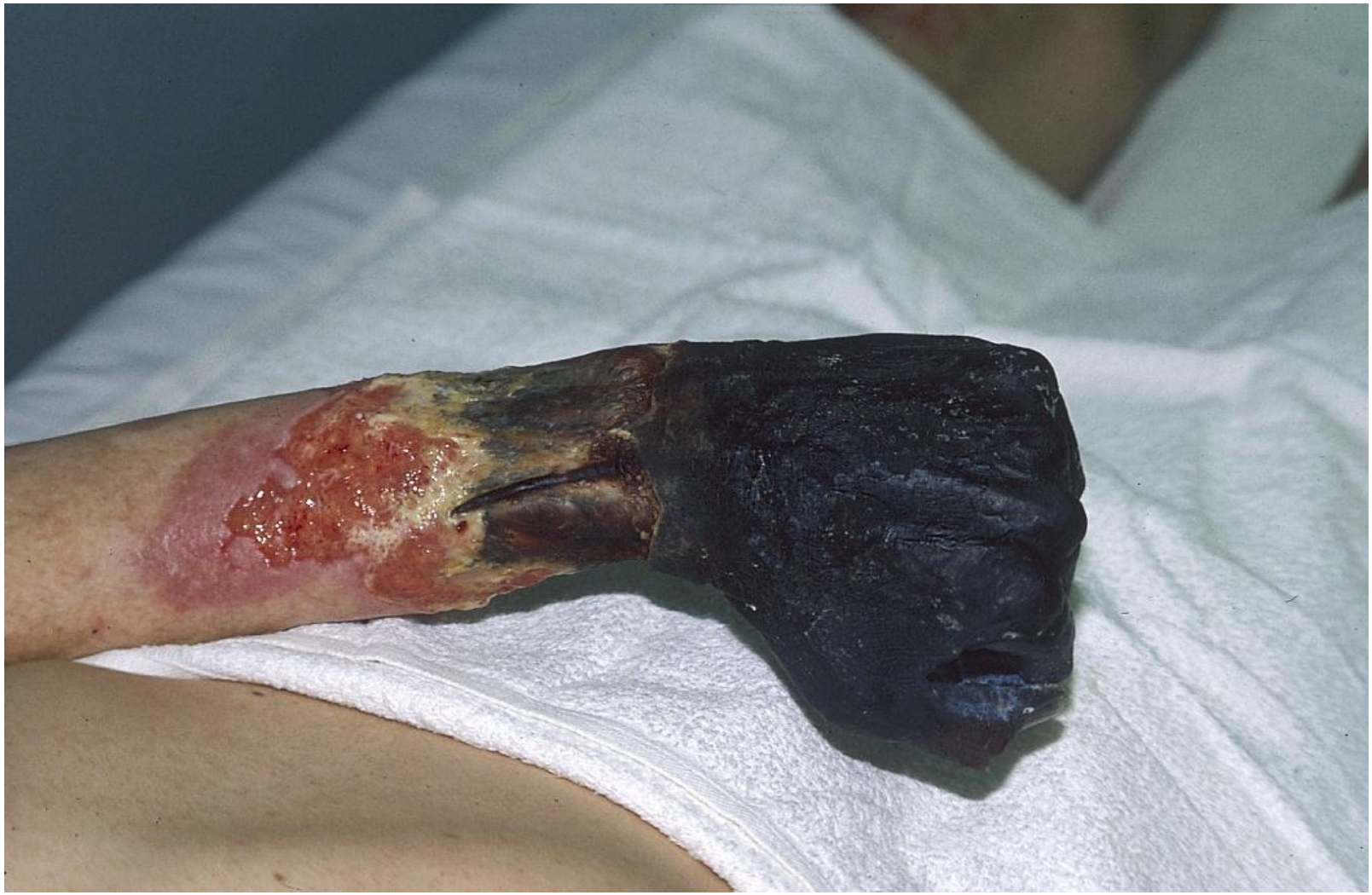
1. Thrombus.
2. Embolus.
3. Thromboangitis obliterans (Buerger's disease).
4. Ergot poisoning and Raynaud's disease which cause spastic occlusion.
5. Surgical ligature.

- When the main arterial supply of a limb is cut off and the circulation is poor, gangrene occurs.
- As the arterial supply is only occluded venous and lymphatic drainage and surface evaporation occur, so gangrene will be of the dry type.
- The commonest example of dry gangrene is senile gangrene of the lower limb.

Dry Gangrene



DRY GANGRENE:



SENILE GANGRENE

- Usually affects old males.
- ***Predisposing factors:***

1. Atherosclerosis common in old age, predisposes to arterial thrombosis and poor collateral circulation.
2. Weak heart action and low blood pressure causes vascular stasis
3. Low body resistance due to nutritional disturbances, nephritis, anemia etc.

- ***Pathological features:***
  The gangrenous process follows the following steps:

1. Arterial occlusion occurs either spontaneously or as a result of slight injury as that caused by a tight shoes.
2. Distal to the occlusion massive necrosis occurs.

- The affected part is pale and cold due to ischemia.
- Sensations are lost.

- Later on the necrotic area stains red by the blood escaped from the necrotic vessels.
- Drainage and evaporation of blood and tissue fluids causes dryness of the dead part.
- It becomes shrunken and mummified.

3. Saprophytic bacteria as bacillus subtilis and diphtheroids invade the necrotic tissue and causes putrefaction

- They act on the dead proteins liberating hydrogen sulphide which causes bad odor.
- Hydrogen sulphide units with iron released from the decomposed hemoglobin and forms iron sulphide which stains the gangrenous part black.

- The gangrenous process advances slowly along the limb because the part irritates the living one and initiates inflammation of its tissue with thrombosis of its vessels and further tissue necrosis and extension of the gangrene.

- When gangrene reaches a level with good blood supply it stops.
- The toxic products of putrefaction act as an irritant and cause a zone of acute inflammation in the neighboring healthy part.
- It appears as a narrow red line between the healthy and gangrenous part called ***line of demarcation***.

- From the healthy side granulation tissue grows towards the gangrenous part with the formation of a groove on the surface called ***line of separation***.
- This groove may slowly deepens until it separates the gangrenous part leaving a ***conical stump***.
- The stump is conical as the gangrene spreads higher up in the skin and subcutaneous tissue than in the muscles and bone as the blood supply of the skin and subcutaneous tissue is less abundant.

MOIST GANGRENE:

- Moist or wet gangrene is caused by sudden arterial and venous occlusion.
- It occurs mainly in internal organs as the intestine from which no evaporation of fluids can occur

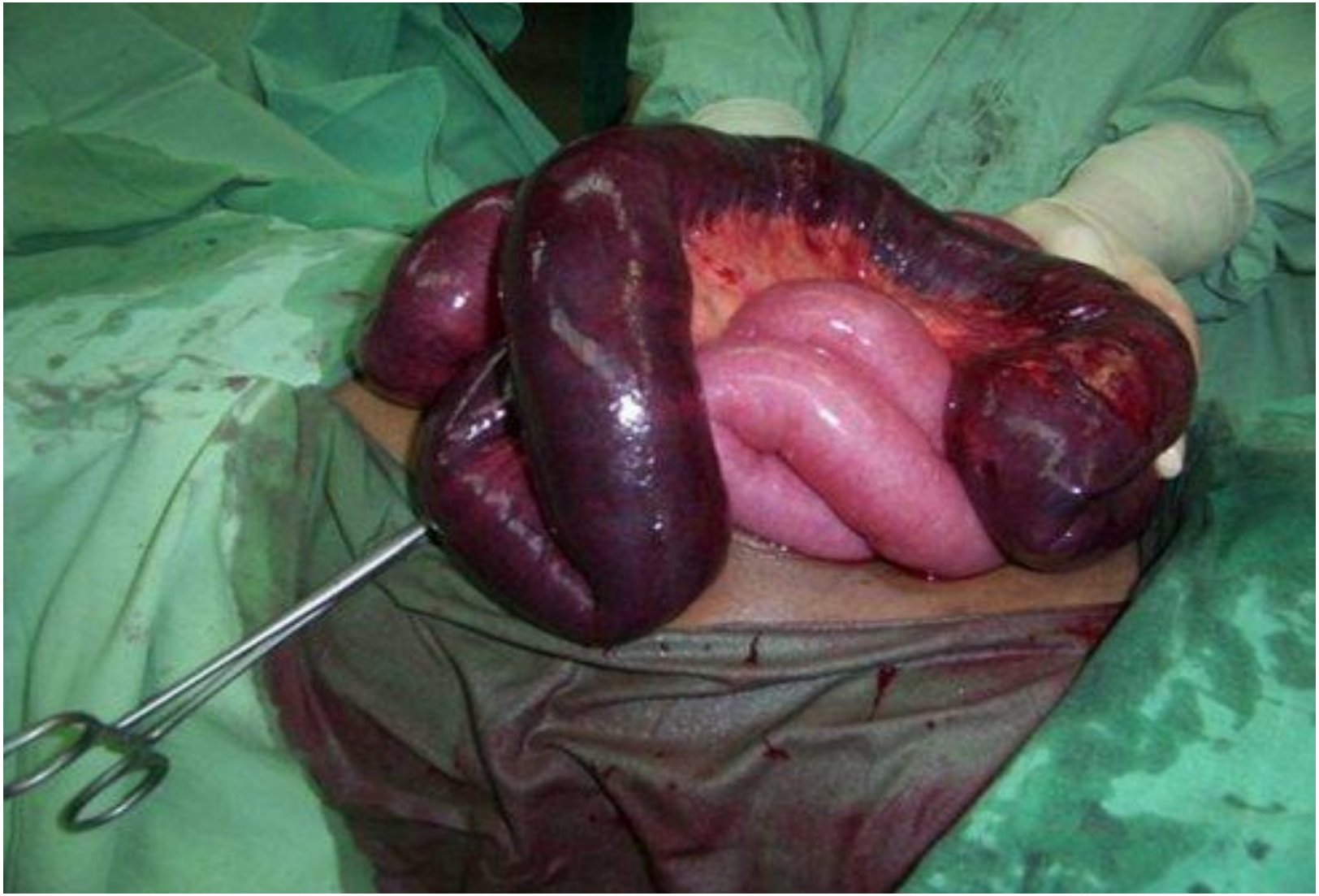
- The presence of tissue fluids aid rapid putrefaction.
- Gangrene spreads rapidly.
- The line of demarcation is poor and the line of separation is absent.
- The toxemia is severe.

MOIST GANGRENE OF THE INTESTINE:

- May develop in strangulated hernia, intussusceptions, volvulus and mesenteric arterial occlusion.
- In the first three conditions venous obstruction occurs first.
- The affected loop shows congestion and edema.

- It appears dark red and swollen.
- Next arterial occlusion occurs and the loop undergoes necrosis.
- The necrotic loop is invaded by putrefactive bacteria from the intestinal lumen and putrefaction occurs rapidly.
- The loop stains black with iron sulphide.
- Toxemia is severe and the patient suffers from acute intestinal obstruction and peritonitis.

GANGRENE OF THE INTESTINE



MOIST GANGRENE OF THE LIMB:

- May follow severe crushing injury, as both artery and vein are occluded by thrombosis and hematoma at the site of damage.
- Also gangrene of the limb may be moist in diabetic patients.

DIABETIC GANGRENE:

- ***Causes:***
- More common in diabetic females after the age of 45.
- Diabetic hyperlipemia causes early development of atherosclerosis followed by arterial occlusion.

- ***Pathology:***
- Diabetic gangrene is initiated by mild injury and starts on the big toe or the sole of the foot.
- At first gangrene is dry, but becomes moist and edematous as tissue hyperglycemia and poor body resistance help multiplication of the bacteria followed by inflammatory occlusion of the vessels.

- This type of gangrene spreads rapidly.
- The line of demarcation is poor and there is little tendency to self limitation.
- Toxemia is severe.

	Dry Gangrene:	Moist Gangrene:
Cause:	Occlusion of an artery only	Occlusion of both artery and vein
Site:	Limbs	Internal organs and limbs
Gross picture:	The gangrenous part is dry & mummified	The gangrenous part is edematous & swollen
Putrefaction:	Slow	Rapid
Toxemia	Mild	Severe
Line of demarcation	Prominent	Poor
Line of separation	Prominent	Absent

INFECTIVE GANGRENE:

- A subtype of moist gangrene in which bacteria cause both tissue necrosis and putrefaction.
- Pathogenic bacteria cause tissue necrosis by its toxins.
- Next saprophytic bacteria act on the dead protein causing putrefaction.

- **Types:**

1. **Lung Gangrene**
2. **Cancrum Oris:**

- Infective gangrene of the cheeks of debilitated children recovering from fevers, caused by Treponema vincenti and bacillus fusiform.
- Toxemia is severe and bronchopneumonia may result from aspiration of the septic necrotic tissue.

3. **Noma Pudendi:**

- Infective gangrene which affects the subcutaneous tissue of inguinal region, labiae in females and scrotum in males.

4. **Phagedena:**

- Gangrene on top of syphilitic chancre or soft sore.
- The lesion is confined to the genital organs.

5. **Synergistic Gangrene:**

- May complicate wounds draining deep seated abscesses caused by a symbiosis between non-hemolytic streptococcus and a hemolytic staphylococcus, neither of which alone produces disease.

5. **Bed Sores:**

- Skin ulcers over the bony prominences (sacrum and greater trochanter) due to prolonged bed rest as in paralysis or bone fracture.
- The ulcers are due to blood stagnation and thrombosis of the vessels followed by tissue necrosis.
- Bacterial infection causes putrefaction in the ulcers.

GAS GANGRENE:

- Gas gangrene is a moist gangrene mainly of muscles occurring in deep wounds contaminated by manured soil containing anaerobic spores.
- Tissue destruction causes local ischemia which favors germination of the spores.
- The organisms are of two types:

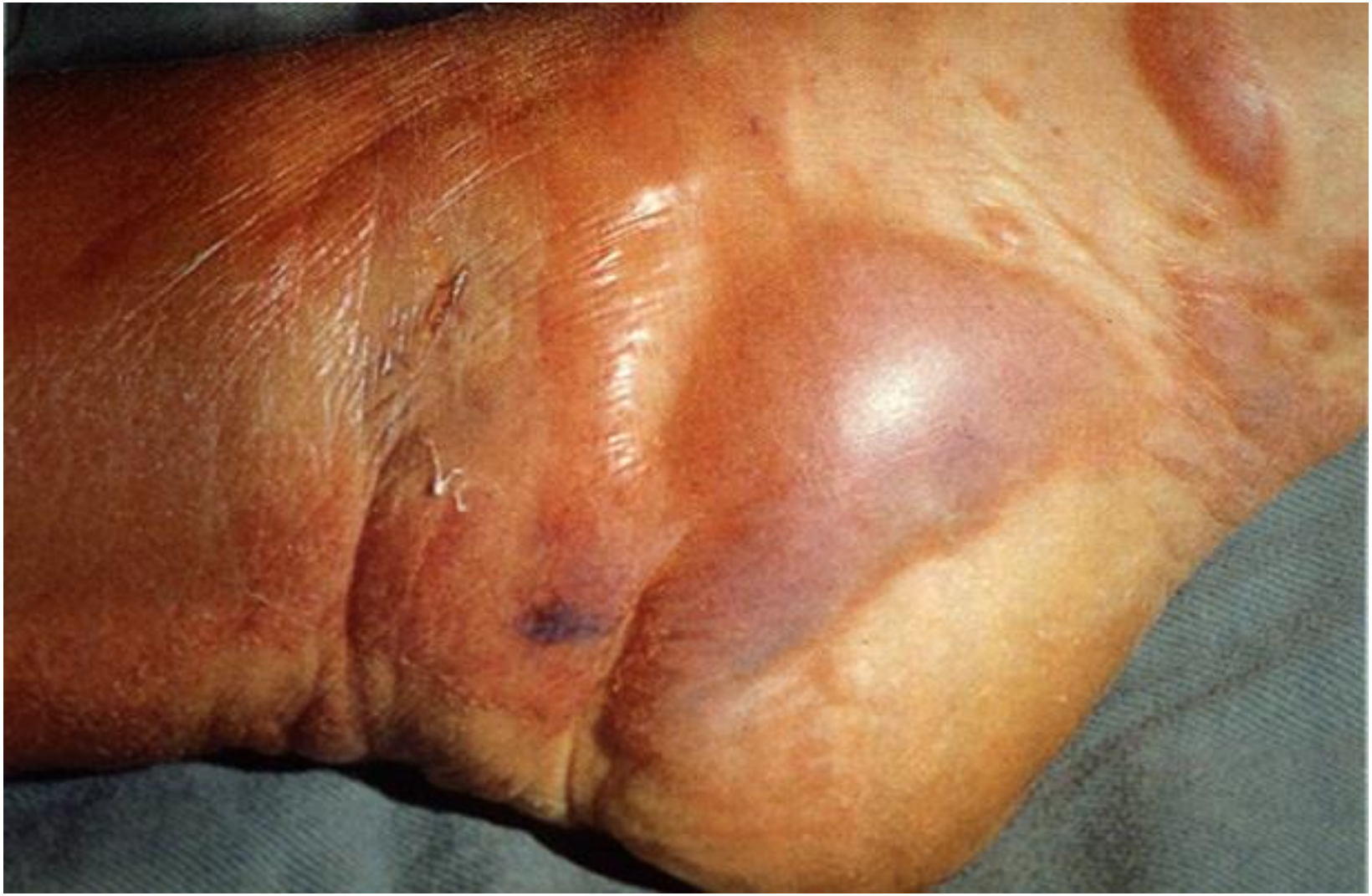
1. ***Saccharolytic bacteria:***

- e.g. Clostridium welchii and Cl. Edematiens; that produce powerful toxins and enzymes, hyaluronidase, hemolysins, cytolysins and lecithinase.
- Hyaluronidase dissolves the tissue cement substance allowing spread of the other toxins.
- The toxins cause necrosis of the muscles and hemolysis of the RBCs.
- The necrotic muscles stain red by the liberated hemoglobin.

2. ***Proteolytic bacteria:***

- e.g. Cl. sporogens and Cl. Histolyticum; that produce putrefaction in the dead muscles.
- Hydrogen sulphide forms and gives the gangrenous part a foul odor and accumulates between the muscle fibers.
- With the formation of iron sulphide the muscles stain black.
- Gas gangrene is highly fatal due to the severe toxemia which causes degeneration and necrosis in parenchymatous organs.

GAS GANGRENE:




Thank you