INTRODUCTION
and
CELL INJURY
Lecture 1

Introduction

- PATHOLOGY IS THE STUDY OF DISEASE.
- IT DESCRIBES THE MANIFESTATIONS OF THE DISEASE, ITS PROCESS AND SEQUELAE AND ATTEMPTS TO DETERMINE THE CAUSE (ETIOLOGY) AND UNDERLYING MECHANISM (PATHOGENESIS).

- IT FORMS A BRIDGE BETWEEN BASIC SCIENCE AND CLINICAL PRACTICE.

Pathological anatomy

- Pathological anatomy is a part of pathology. Pathology literally is the study (logos) of suffering (pathos).
- More specifically, it is a bridging discipline involving both basic science and clinical practice and is devoted to the study of the structural and functional changes in cells, tissues, and organs that underlie "diseases".
- By the use of molecular, microbiologic, immunologic, and morphologic techniques, pathology attempts to explain the "whys" and "wherefores" of the signs and symptoms manifested by patients while providing a sound foundation for rational clinical care and therapy.

Definition of Pathology

It is the "scientific study of disease".

"scientific study of the molecular, cellular, tissue, or organ system response to injurious agents."

Pathology serves as a **"bridge"** or **"link"** between the preclinical sciences (**anatomy, physiology, ……etc**.) and the courses in clinical

What is the Disease?

- **It is the** "state in which an individual exhibits an anatomical, physiological, or biochemical deviation from the normal".

Disease may be defined as :

an abnormal alteration of structure or function in any part of the body.

Learning Pathology:

- **General Pathology**
  - Common changes in all tissues. e.g.. Inflammation, cancer, ageing, edema, hemorrhage ….etc.
- **Systemic Pathology**
  - Discussing the pathologic mechanisms in relation to various organ systems e.g. CVS, CNS, GIT…..etc.

What should we know about a Disease?

- Definition.
- Epidemiology – Where & When.
- Etiology – What is the cause?
- Pathogenesis - Evolution of dis.
- Morphology - Structural Changes
- Functional consequences

Pathology

- Management
- Prognosis
- Prevention

Manifestations of Diseases

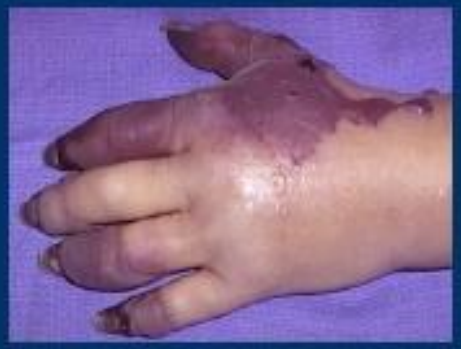
The manifestations of a disease are the sum of the damage done by a harmful agent and the body's response.

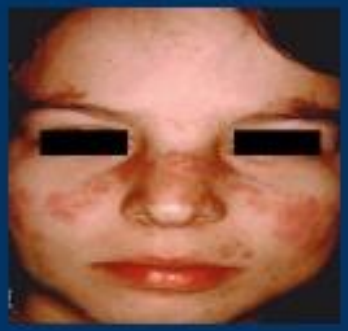
The variation in these components accounts for the great diversity of disease, which can be classified into 4 main groups:

1. Developmental – genetic, congenital
2. Inflammatory - trauma, infection, immune
3. Neoplastic - tumors, cancers
4. Degenerative – ageing
5. Iatrogenic – drug-induced

Manifestations of Diseases

- **Signs** – are objective findings as perceived by an examiner, physician or dentist
- **Symptoms** – are functional manifestations or evidences of a disease process
- **Lesions** – are visible changes produced by a disease in the tissues or organs. They are usually local abnormalities which could be benign, cancerous, gross, occult, or primary.






- **Exacerbations** – a sudden increase in the severity or seriousness of the signs and symptoms during the course of a disease.
- **Remissions** – become less intense at a time.
- **Complications** – unfavorable conditions that arise during the course of a disease
- **Sequelae** – are remote aftereffects produced by a disease.

ETIOLOGY

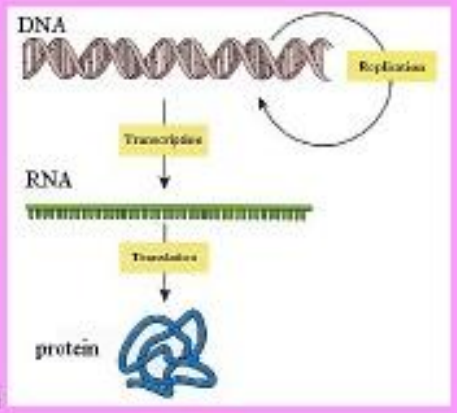
- Cause

vs.

- Risk Factors

ETIOLOGY

Knowledge or discovery of the primary etiology remains the backbone on which a diagnosis can be made and a disease process can be best understood so that a treatment can be prescribed.



THE ETIOLOGICAL FACTORS ARE:

- ENVIRONMENTAL FACTORS
- GENETIC FACTORS
- IINDIRECT CAUSES

ENVIRONMENTAL FACTORS ARE:

- PHYSICAL AGENTS – radiation, trauma or mechanical injury, thermal changes, electrical, nuclear or X-rays, changes in atmospheric pressure
- CHEMICAL AGENTS – chemicals, poisons like venoms or toxins, corrosive agents like strong acids and alkalis
- NUTRITIONAL DEFICIENCES AND EXCESSES
- INFECTIONS AND INFESTATIONS
- ABNORMAL IMMUNOLOGICAL REACTIONS
- PSYCHOLOGICAL FACTORS

GENETIC FACTORS: ABNORMAL GENES

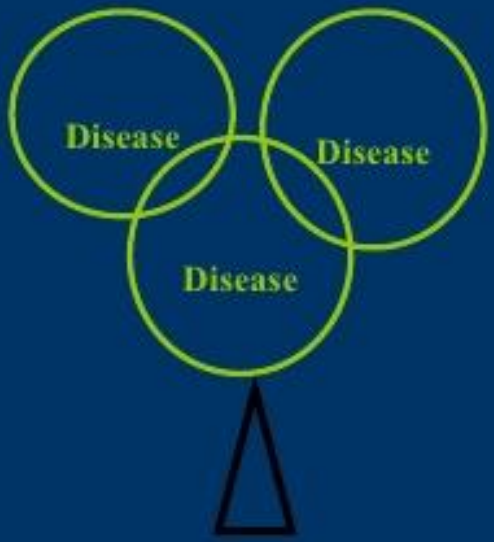
INDIRECT CAUSES: pertain to the predisposing factors like age, age, sex, environment, race, climate, state of nutrition, habits

Etiology

- One etiologic agent

- one disease, as Malaria.

- Several etiologic agents one disease, as diabetes .



- One etiologic agent several diseases, as smoking.

Pathogenesis

The sequence events in the response of the cells or tissues to the etiologic agent, from the initial stimulus to the ultimate expression of the disease,"from the time it is initiated to its final conclusion in recovery or death"

The core of the science of pathology —

the study the

pathogenesis of the disease.

Objects of study of pathological anatomy:

1. Surgical biopsy material;
2. Autopsy material;
3. Tissues and organs from experimental animals.

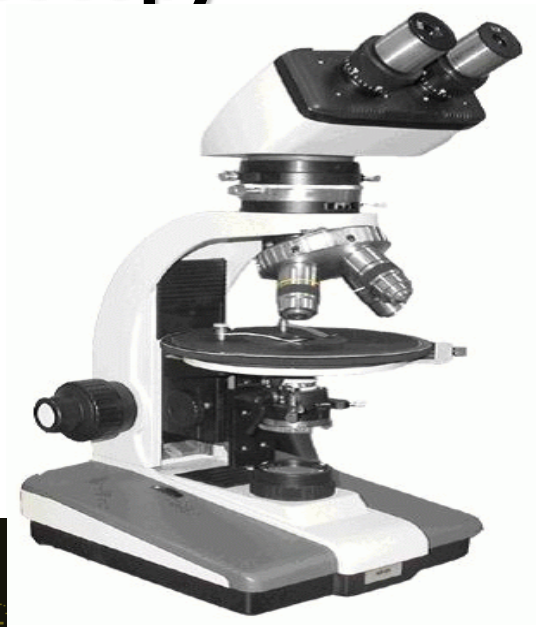
METHODS OF STUDYING PATHOLOGY

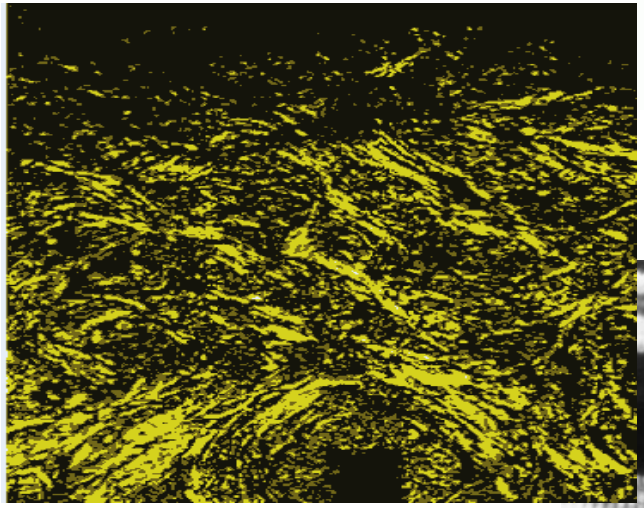
- GROSS EXAMINATION
- LIGHT MICROSCOPY
- IMMUNOCHEMISTRY
- ELECTRON MICROSCOPY
- MOLECULAR BIOLOGY

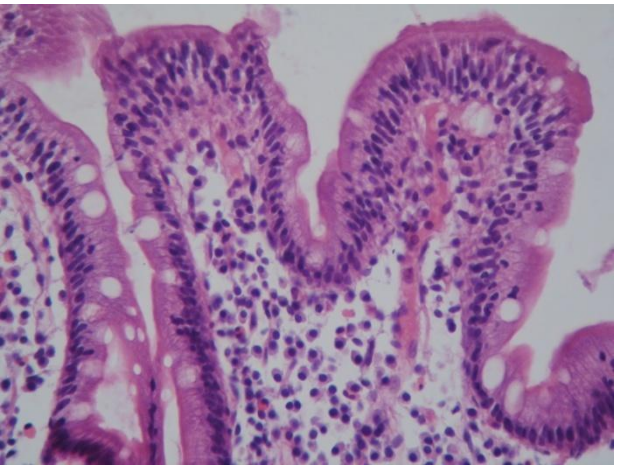
Research methods in pathological anatomy

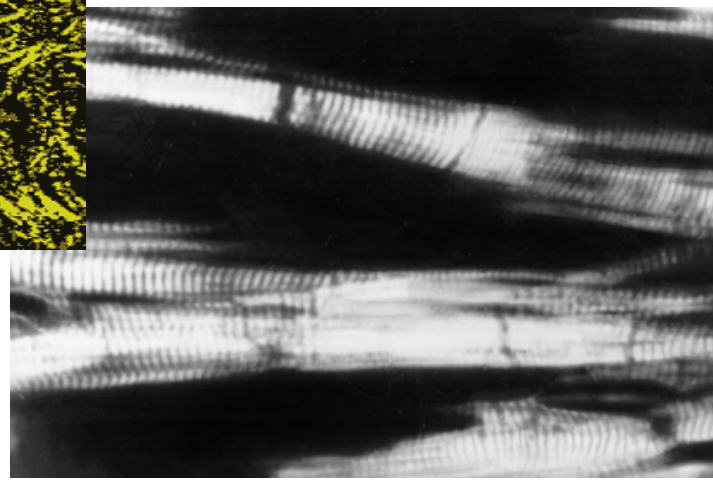
1. Macroscopic examination.
2. Microscopic examination:
   a) light-optical research;
   b) polarizing microscopy;
   c) luminescence microscopy;
   d) histochemical study;
   e) immunohistochemical study.
3. Cytological examination.
4. Electron microscopy.
5. Methods of molecular biology: a) in situ hybridization (nucleic acid detection); b) flow cytometry; c) historadioautography
6. Research of chromosomes.

Light / polarizing microscopy

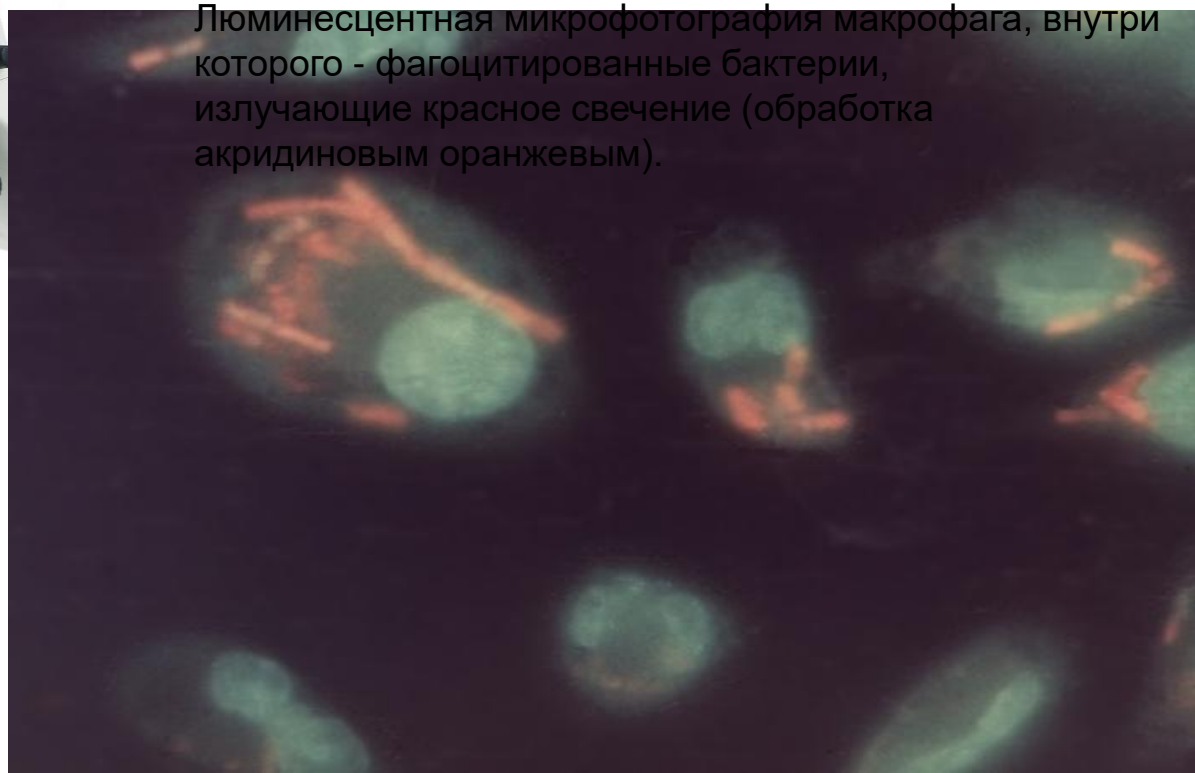






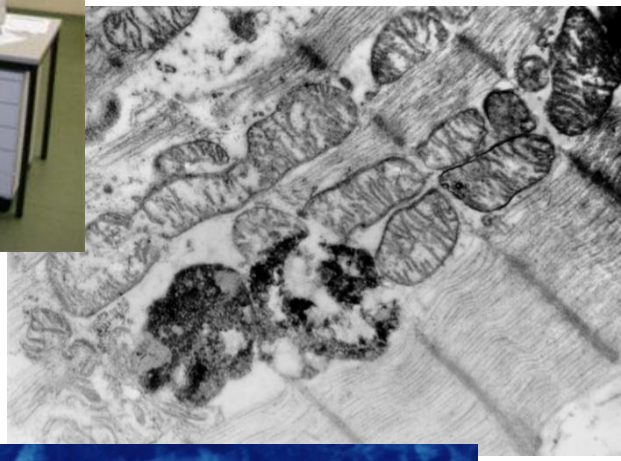


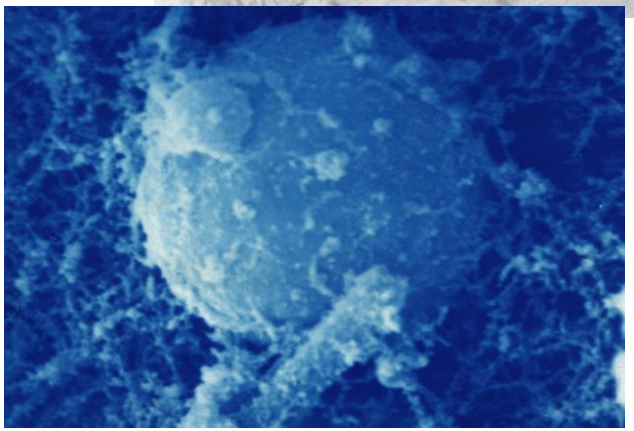
Luminescence microscopy



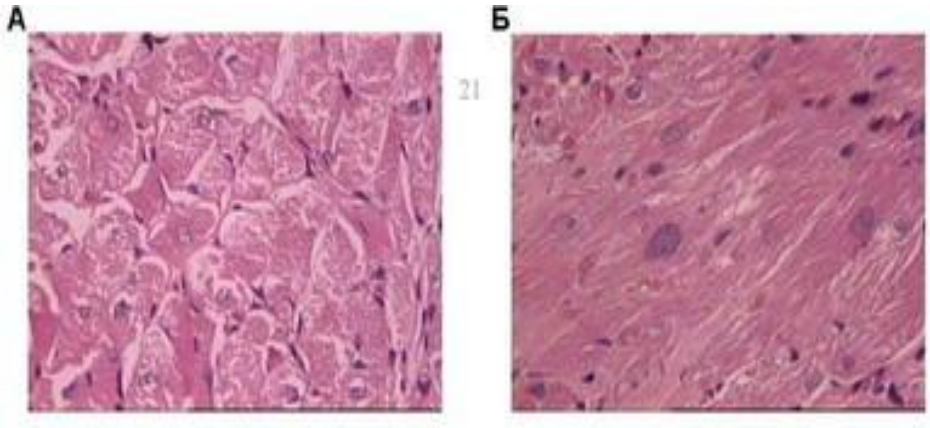
Люминесцентная микрофотография макрофага, внутри которого - фагоцитированные бактерии, излучающие красное свечение (обработка акридиновым оранжевым).

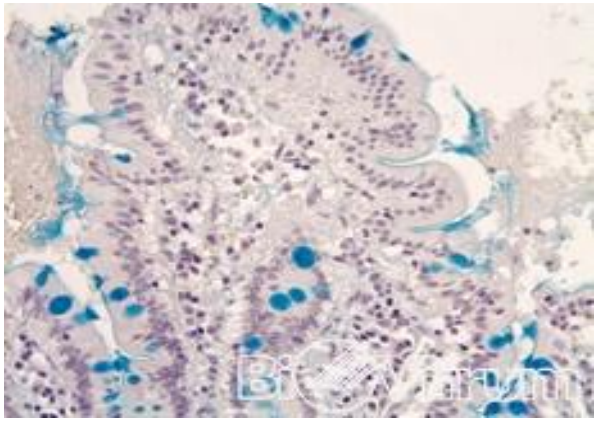
Electron microscopy
(transmission, scanning, scanning electron microscope)

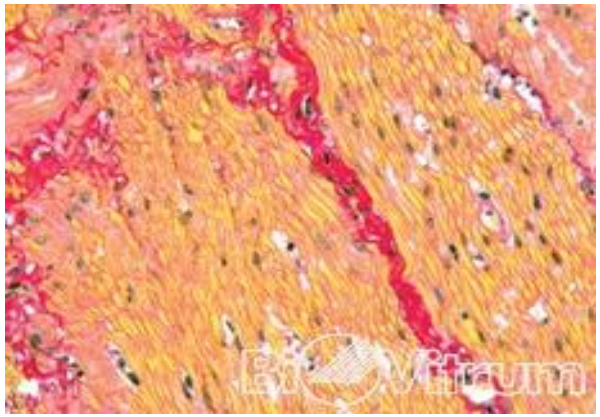


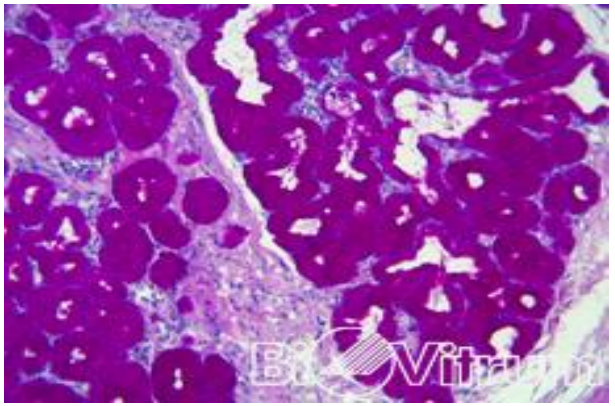


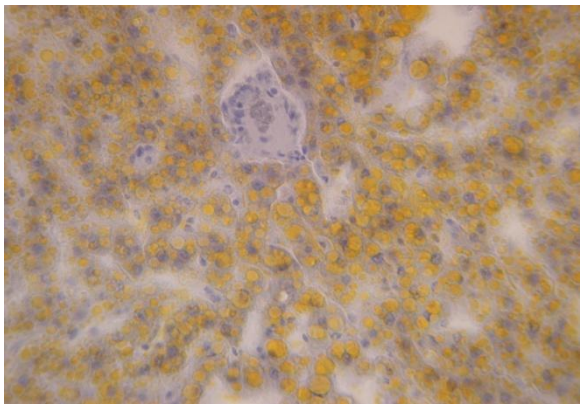
Histochemical examination



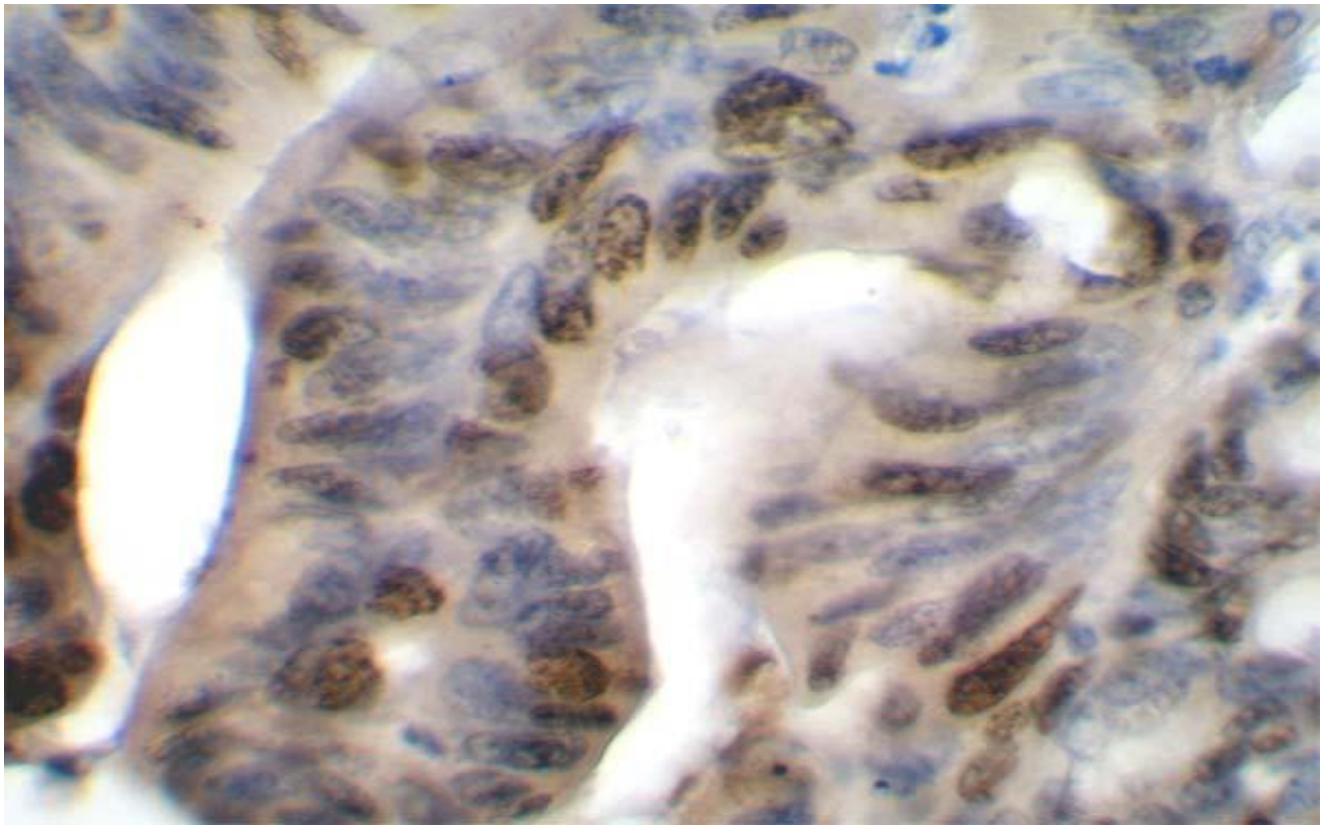








Immunohistochemical study



- **Necropsy:** Gross examination of the animal cadaver by systematic dissection in order to evaluate any abnormal changes **(lesions)** that may be present.
- **Autopsy:** Synonymous to necropsy in human medicine
- ***Biopsy:*** *Removal and examination of tissue*

Research levels in pathological anatomy:

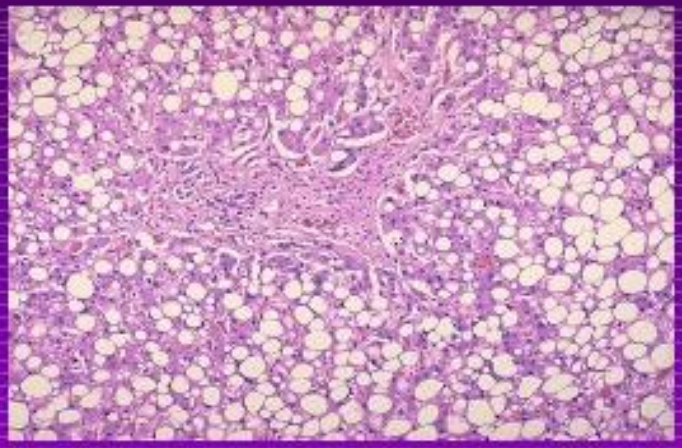
- Organismic level,
- Organ level,
- Systemic level,
- Tissue level,
- Cellular level,
- Molecular level.

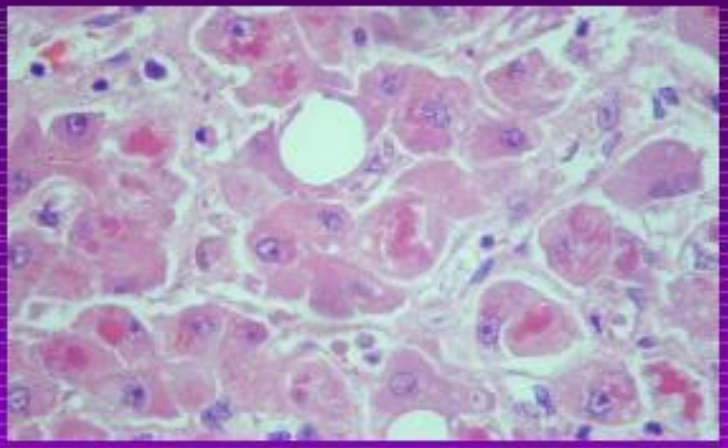
Types of Diseases

- Acute – characterized by a sudden onset or in a rapid course
- Fulminating – an acute fatal disease
- Chronic – slow onset and long duration or having a long course
- Intercurrent – occurs during the course of another disease
- Idiopathic – disease with unknown cause
- Teratogenic – diseases that are cause by drugs that cross the placental barrier and harm the fetus
- Contagious – transmitted by direct, intimate or by skin contact
- Venereal – transmitted by sexual contact
- Infectious – are caused by pathogenic microorganisms
- Communicable – are transmitted by agents, fomites, vector or carrier

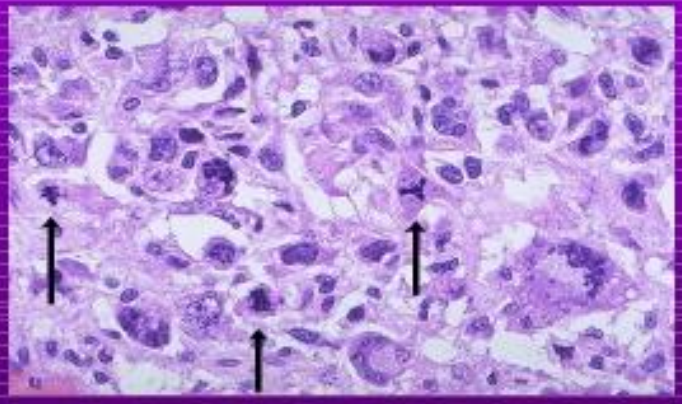
Prognosis

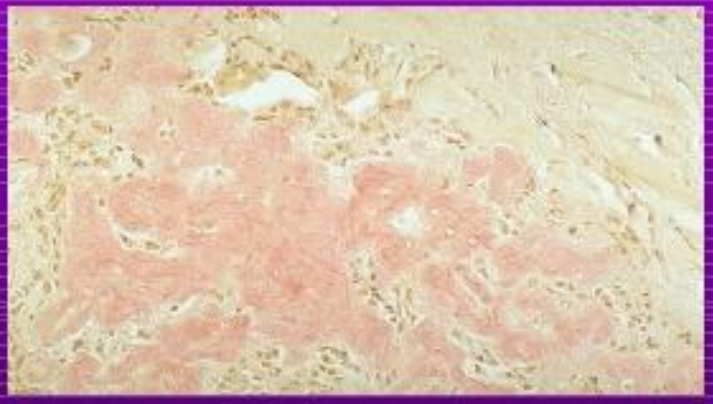
Expected outcome of the disease; it is the clinician's estimate of the severity and possible result/s of a disease.





CELL INJURY





DAMAGE (ALTERATION)

- **Damage or alteration** (from Lat. Alteratio - change) - changes in the structure of cells, intercellular substance, tissues and organs, which are accompanied by a decrease in the level of their vital activity or its termination.

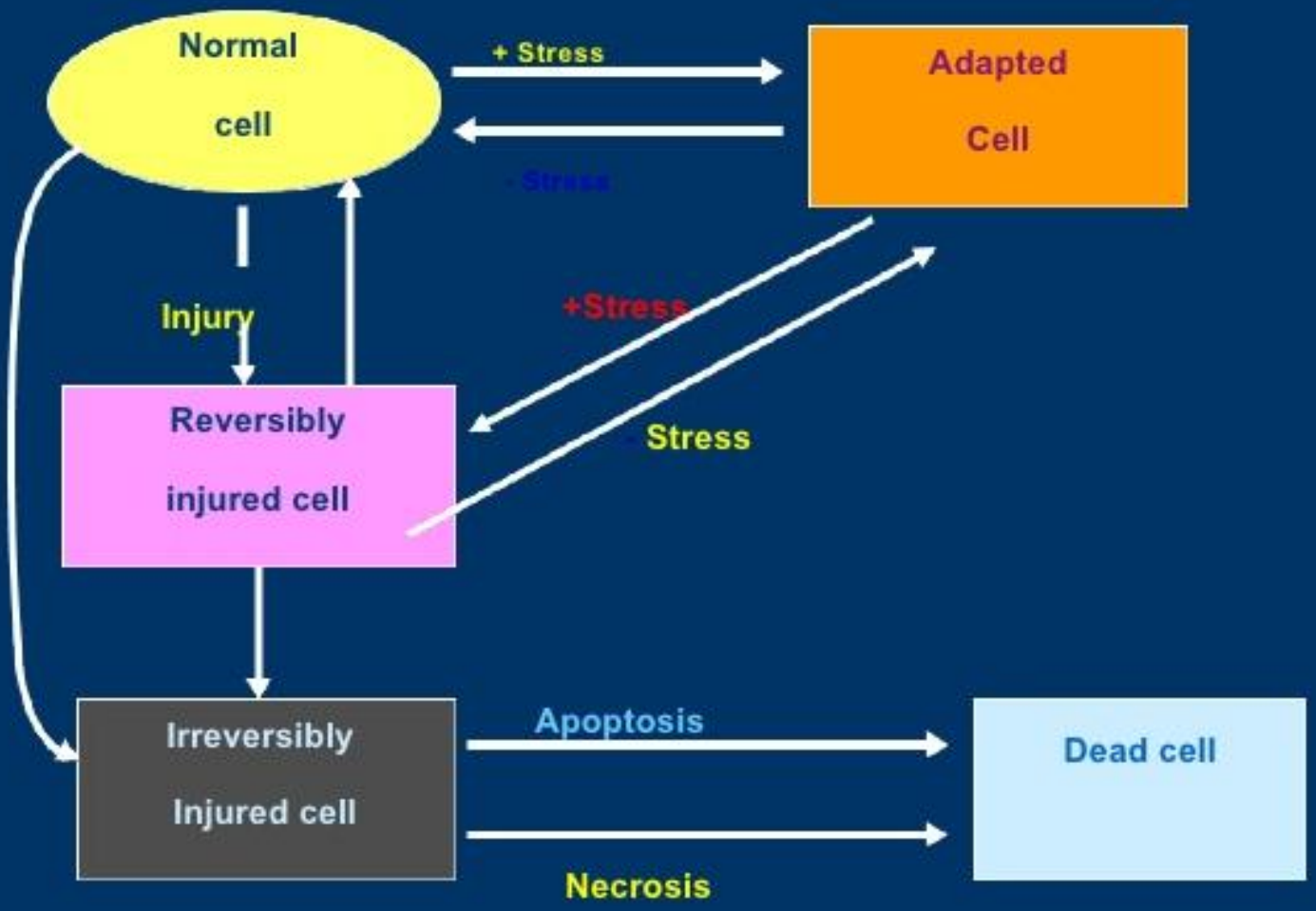
What is cell injury?

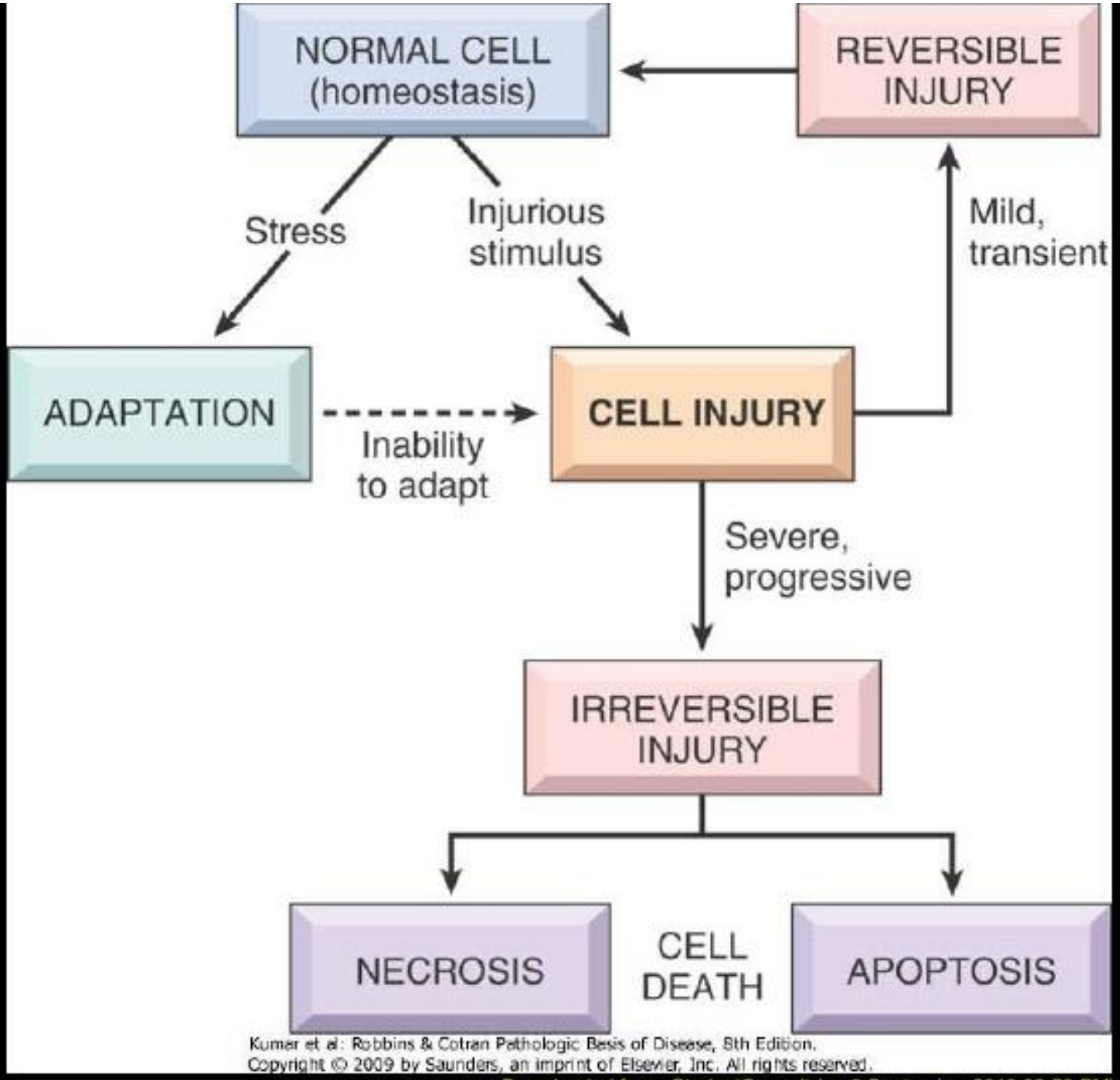
- Cell injury is a sequence of events that occur if the limits of adaptive capability are exceeded or no adaptive response is possible.
- Most common causes are: ischemia, hypoxia, chemical injury, and injury produced by infectious agents

Causes of Cell Injury and Necrosis

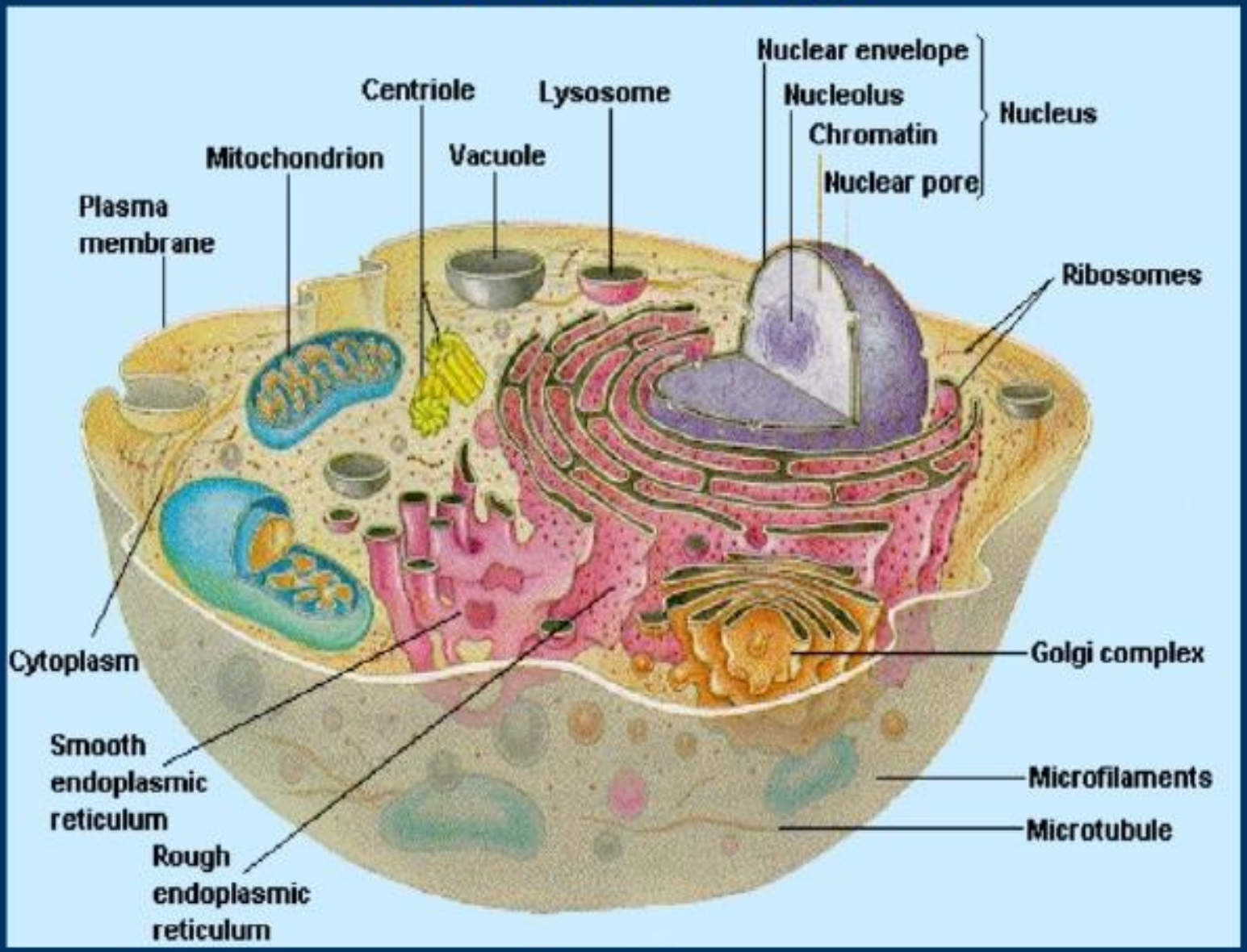
- Hypoxia
  - Ischemia
  - Hypoxemia
  - Loss of oxygen carrying capacity
- Free radical damage
- Chemicals, drugs, toxins
- Infections
- Physical agents
- Immunologic reactions
- Genetic abnormalities
- Nutritional imbalance

Overview


Normal
cell
+ Stress
Adapted
Cell
- Stress
Injury
+Stress
Reversibly
injured cell
- Stress
Irreversibly
Injured cell
Apoptosis
Dead cell
Necrosis

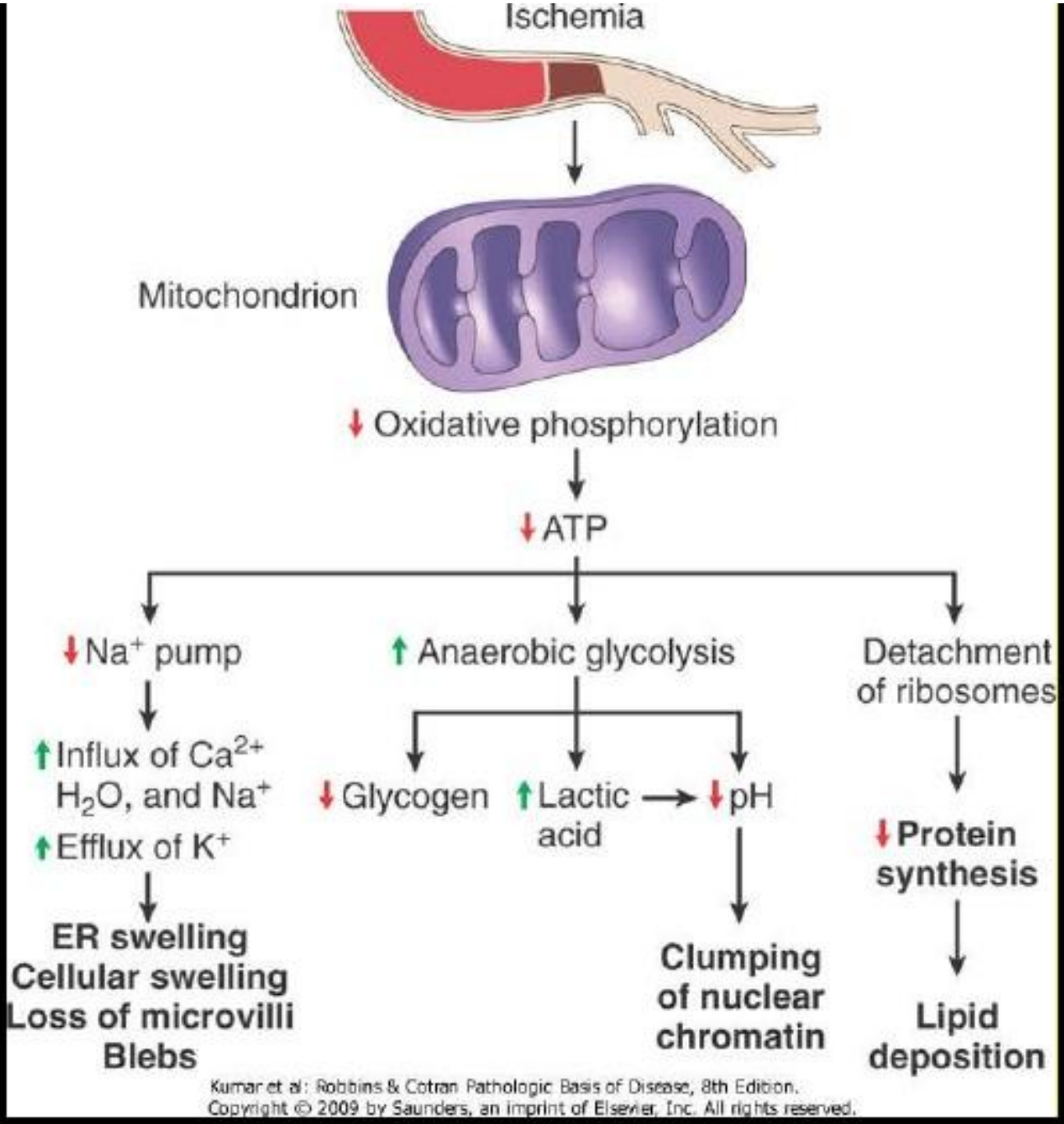


The Normal Cell

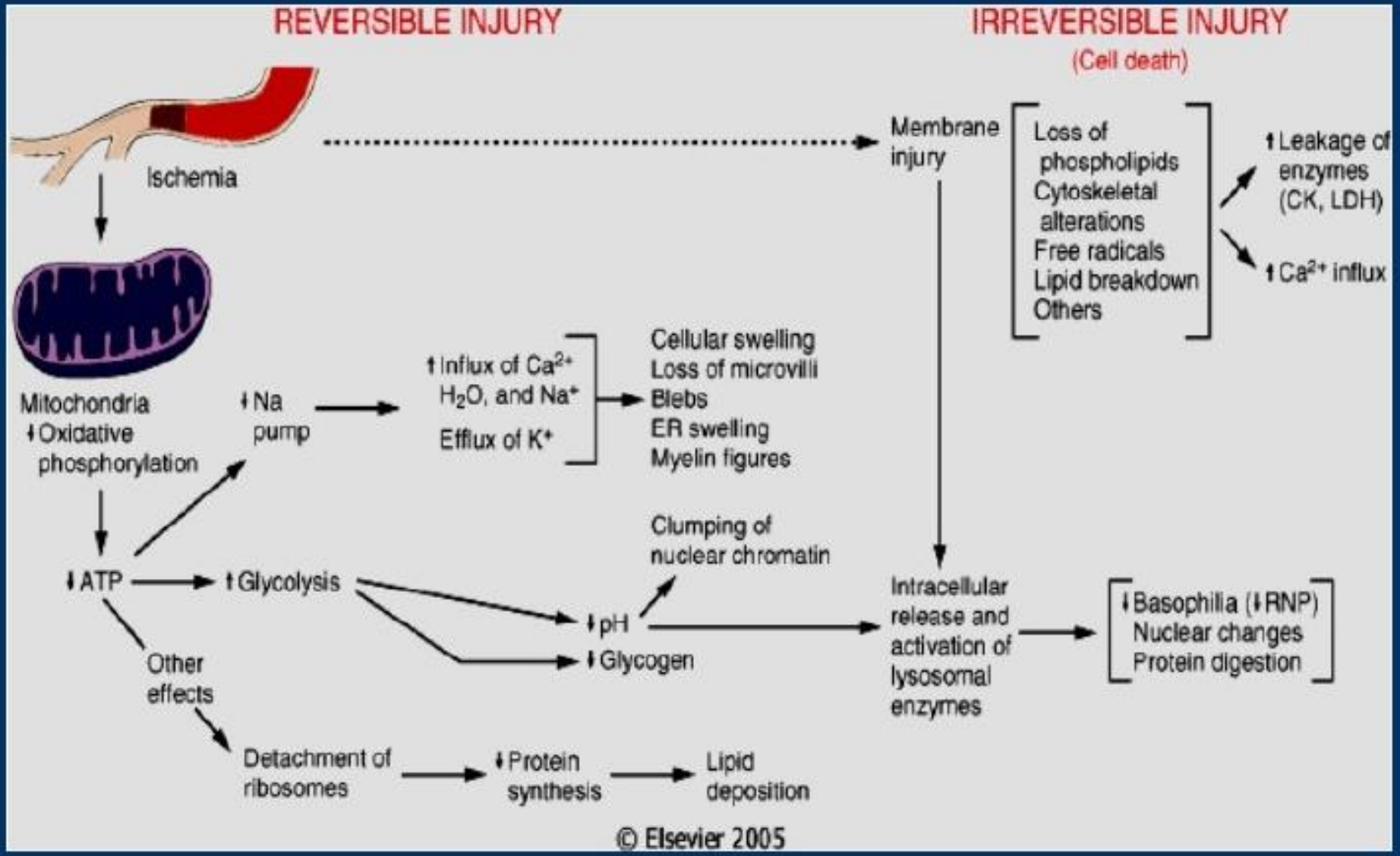


Mechanisms of Cell Injury

- Depletion of ATP
- Mitochondrial Damage
- Influx of Intracellular Calcium and Loss of Calcium Homeostasis
- Accumulation of Oxygen-Derived free radical (*Oxidative stress*)
- Defects in Membrane Permeability

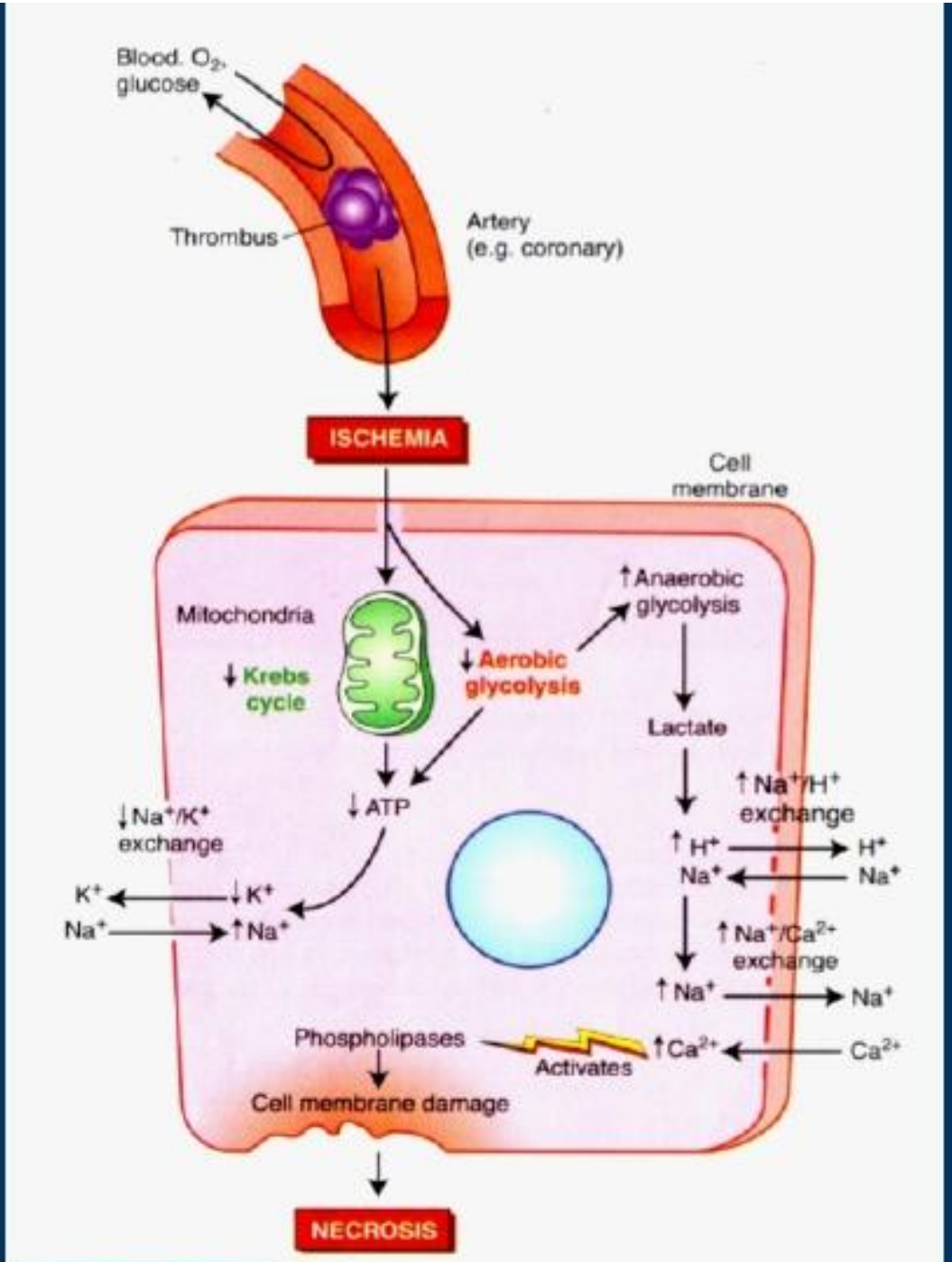


Ischemic Injury



Mechanisms of Cell Injury

Ischemic injury



Examples of Free Radical Injury

- Chemical (e.g., CCl_4, acetaminophen)
- Inflammation / Microbial killing
- Irradiation (e.g., UV rays → skin cancer)
- Oxygen (e.g., exposure to very high oxygen tension on ventilator)
- Age-related changes

Mechanism of Free Radical Injury

- Lipid peroxidation → damage to cellular and organellar membranes
- Protein cross-linking and fragmentation due to oxidative modification of amino acids and proteins
- DNA damage due to reactions of free radicals with thymine

Cell injury and death

- **Reversible hypoxic/ ischemic injury**
  Loss of ATP generation by mitochondria initially results in reversible events:
  - Na+/K+ ATPase membrane pump leads to a loss of ionic and osmotic gradient (↑edCa+2+ Na+, ↓ed K+ and osmotic gain of water) resulting cell swelling & ER dilatation)
  - ↑ed anaerobic glycolysis results in glycogen depletion and lactate accumulation (↓ed pH).
  - Reduced protein synthesis due to ribosome detachment from the RER

The main forms of cell damage

1. Ischemic and hypoxic damage

2. Damage caused by free radicals, including activated oxygen

3. Toxic damage

Classifications of damage

1) by causal factors - ***exogenous*** (biological, including those caused by bacteria, viruses, mycoplasmas, protozoa; physical, chemical) and ***endogenous*** (hypoxia, intoxication, immune damage);

2) Due to the nature of the impact of the damaging factor **- *direct*** and ***indirect***;

3) by the severity of the process **- *reversible*** and ***irreversible***;

4) in terms of prevalence - the number and volume of damaged structures - ***total-cellular*** and ***partial*** (individual structures).

Damage manifestation levels

1) ***Molecular level*** (damage to cellular receptors, enzyme molecules, nucleic acids up to their disintegration);
2) ***Subcellular level*** - ultrastructural (damage to mitochondria, reticulum, membranes and other ultrastructures up to their destruction);
3) ***cellular level*** (various dystrophies due to a violation of different types of metabolism with the possible development of necrosis by the type of rexis or cell lysis);
4) ***tissue and organ level*** (dystrophic changes in most cells and stroma with the possible development of necrosis (like infarction, sequestration, etc.), including the level of tissue complexes or histions, which include vessels of the microvasculature (arteriole, capillaries, venule) and the cells, parenchyma, connective tissue and terminal nerve endings fed by them;
5) ***organismic level*** (a disease with a possible fatal outcome).

Morphology of Cell Injury and Necrosis

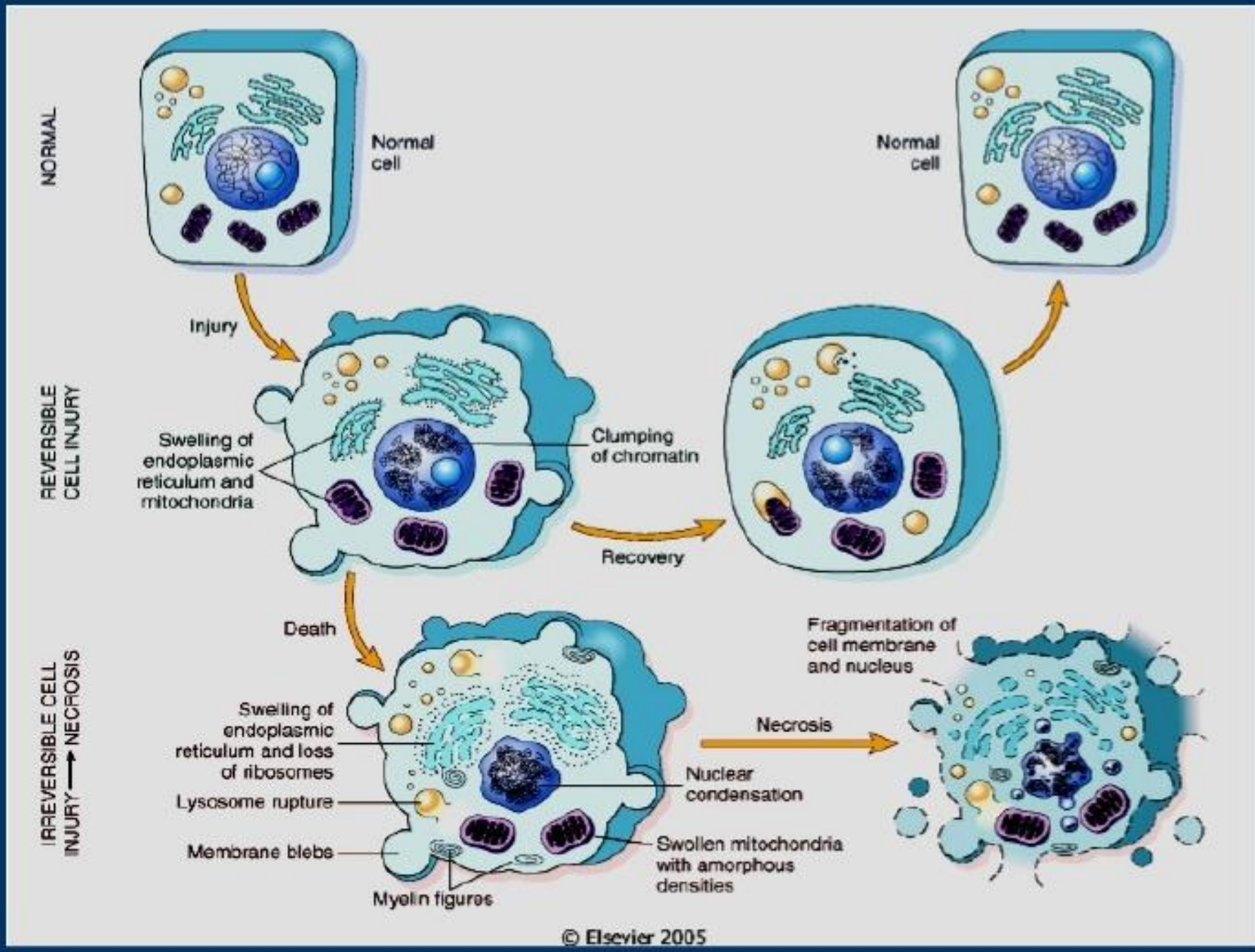
- Cell Injury – Reversible
  – Irreversible
- Cell Death – Necrosis
  – Apoptosis

Reversible Injury -- Morphology

- Light microscopic changes
  - Cell swelling (a/k/a hydropic change)
  - Fatty change
- Ultrastructural changes
  - Alterations of cell membrane
  - Swelling of and small amorphous deposits in mitochondria
  - Swelling of RER and detachment of ribosomes

Cell Injury and Death

- **Reversible Injury**
  - Cell swelling develops when cells are incapable of fluid an ion homeostasis (↓ed function of ATP dependant pumps).
  - Fatty change the accumulation of lipid vacuoles in the cytoplasm.
- **Irreversible injury (Necrosis)**
  - Two basic processes underlie the morphologic changes of necrosis
    - Denaturation of protein
    - Enzymatic digestion of cell components


NORMAL
Normal cell
Normal cell
Injury
REVERSIBLE CELL INJURY
Swelling of endoplasmic reticulum and mitochondria
Clumping of chromatin
Recovery
Death
IRREVERSIBLE CELL INJURY → NECROSIS
Swelling of endoplasmic reticulum and loss of ribosomes
Lysosome rupture
Membrane blebs
Myelin figures
Nuclear condensation
Swollen mitochondria with amorphous densities
Necrosis
Fragmentation of cell membrane and nucleus
© Elsevier 2005

Morphology of Cell Injury

Reversible Injury

Cellular swelling

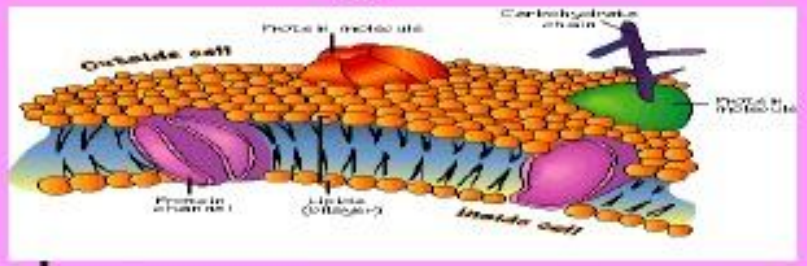
Fatty change

- Plasma membrane alteration
- Mitochondrial Changes
- Dilation of Endoplasmic reticulum
- Nuclear Alteration

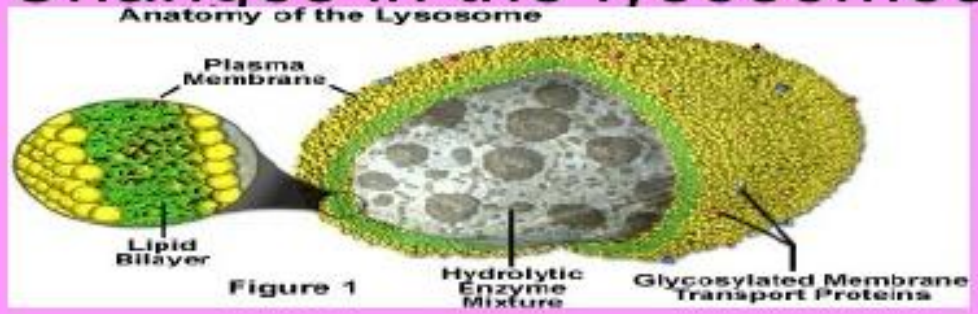
Morphology of Cell Injury

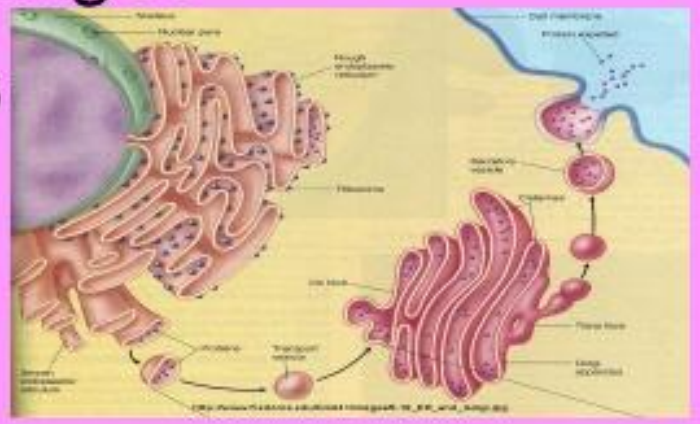
Ultrastructural Changes:

- Alteration in plasma membrane reflecting disturbance in ion and volume regulation induced by loss of ATP

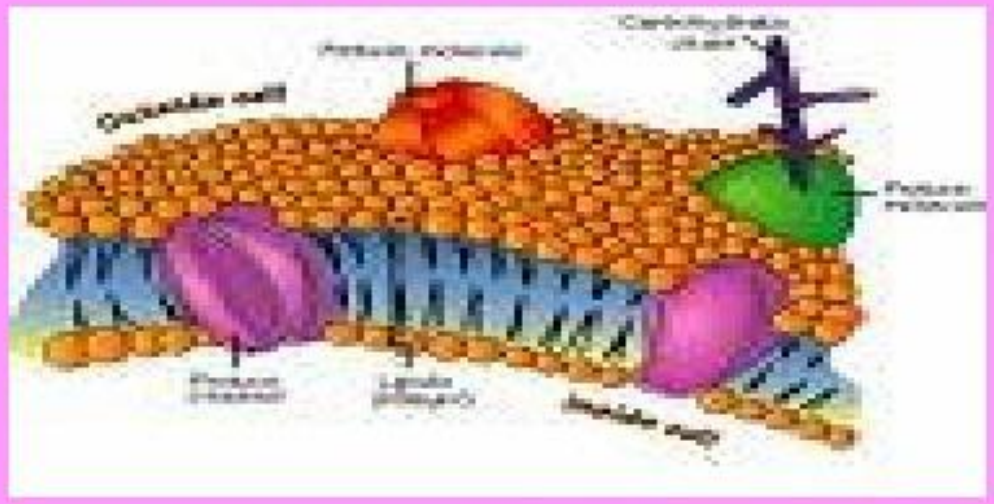


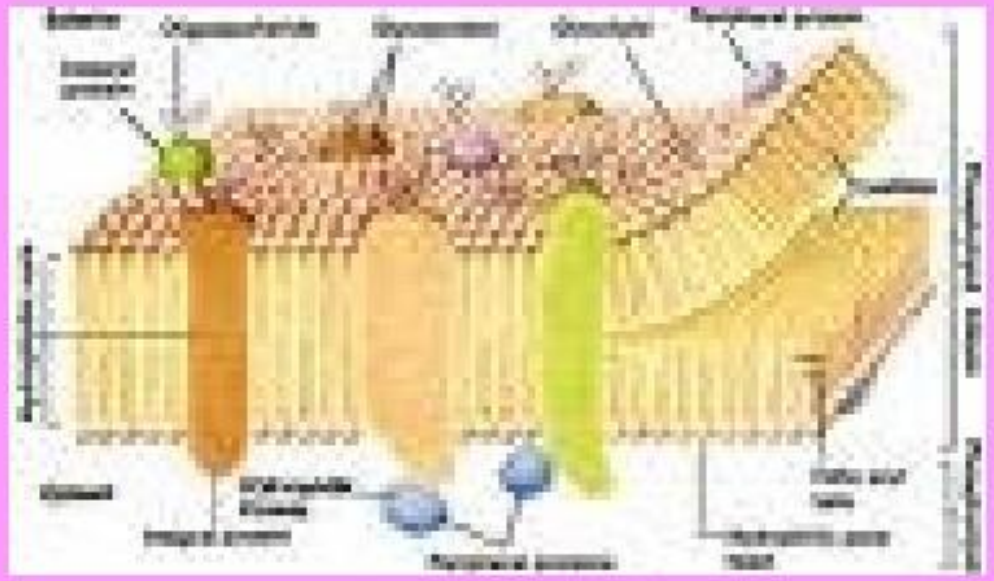
- Mitochondrial changes
- Endoplasmic reticulum changes
- Changes in the lysosomes



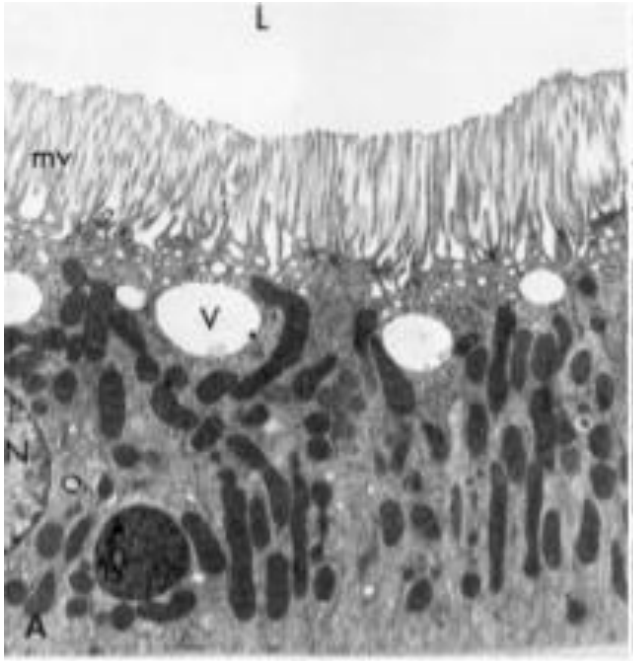


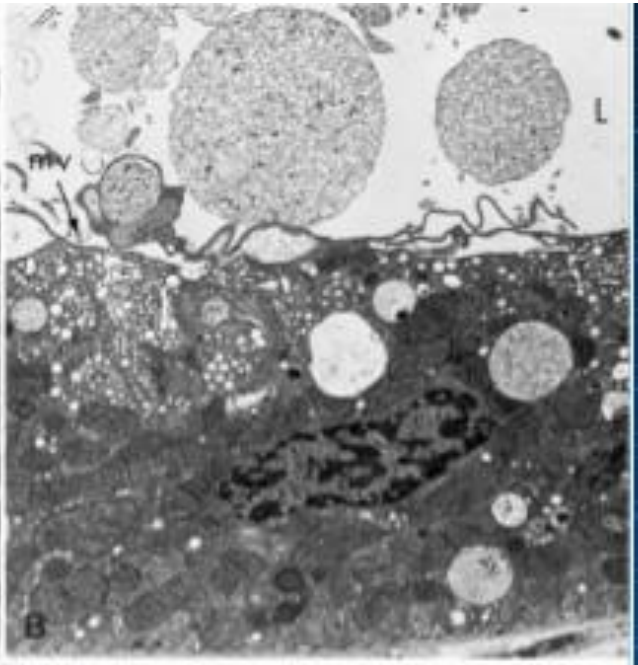
Alteration in the Plasma Membrane



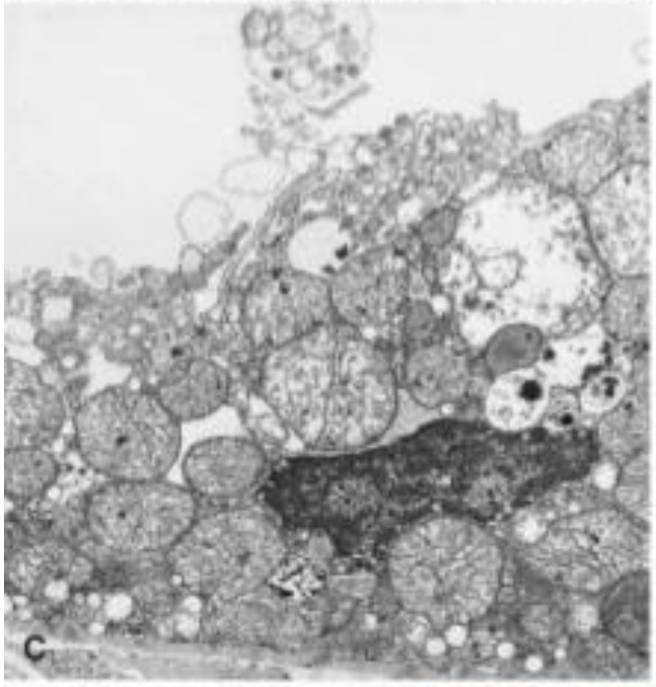


- Cellular swelling
- Formation of cytoplasmic blebs
- Blunting and distortion of microvilli
- Creation of myelin figures
- Deterioration and loosening of intercellular attachments





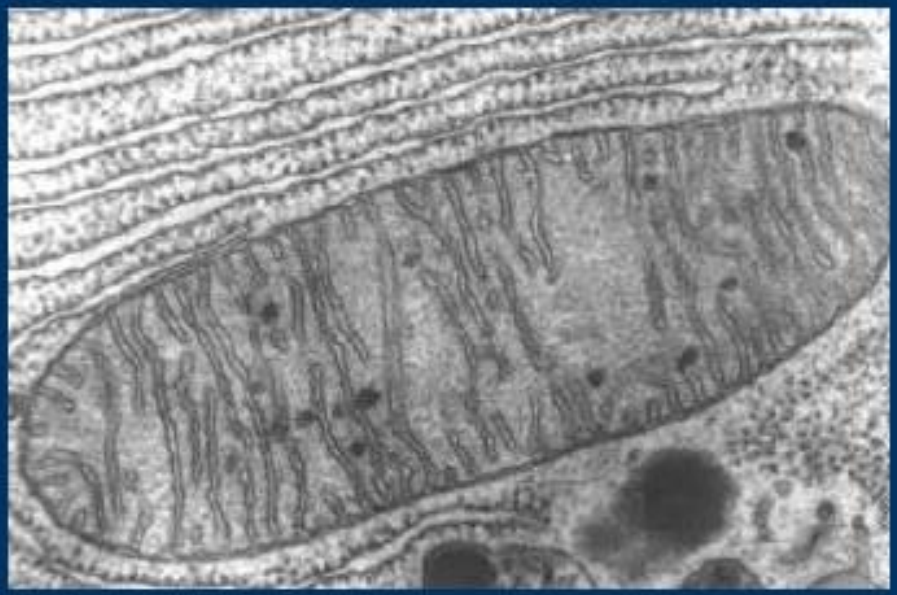
Cell Membrane Injury



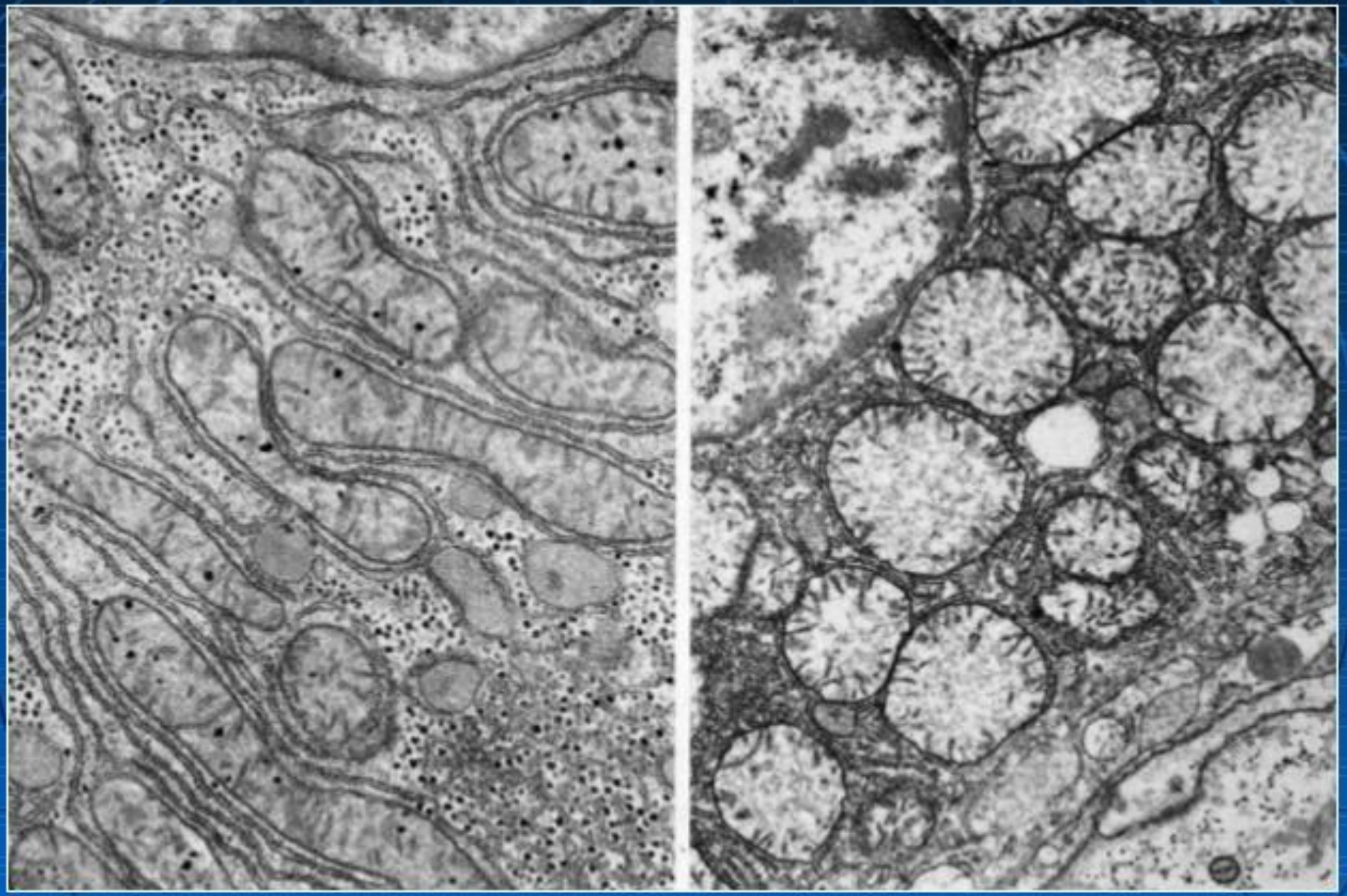
Epithelial cell proximal kidney tubule

A. Normal
B. Reversible ischemic changes
C. Irreversible ischemic changes

Mitochondrial Changes

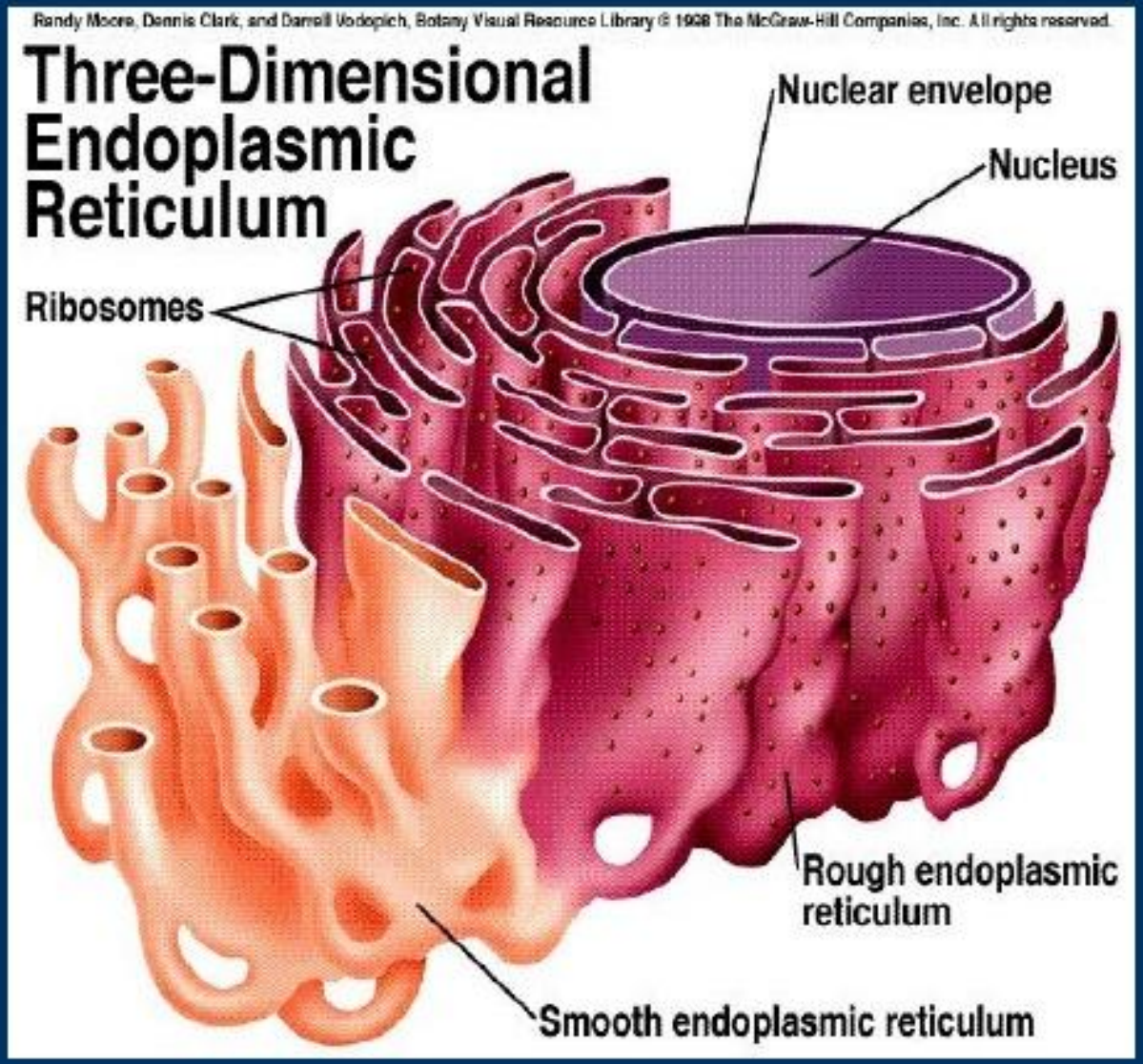


- Early, appears condensed as a result of loss of matrix protein following loss of ATP
- Followed by swelling due to ionic shifts
- Amorphous densities which correlate with the onset of irreversibility
- Finally, rupture of membrane followed by progressing increased calcification

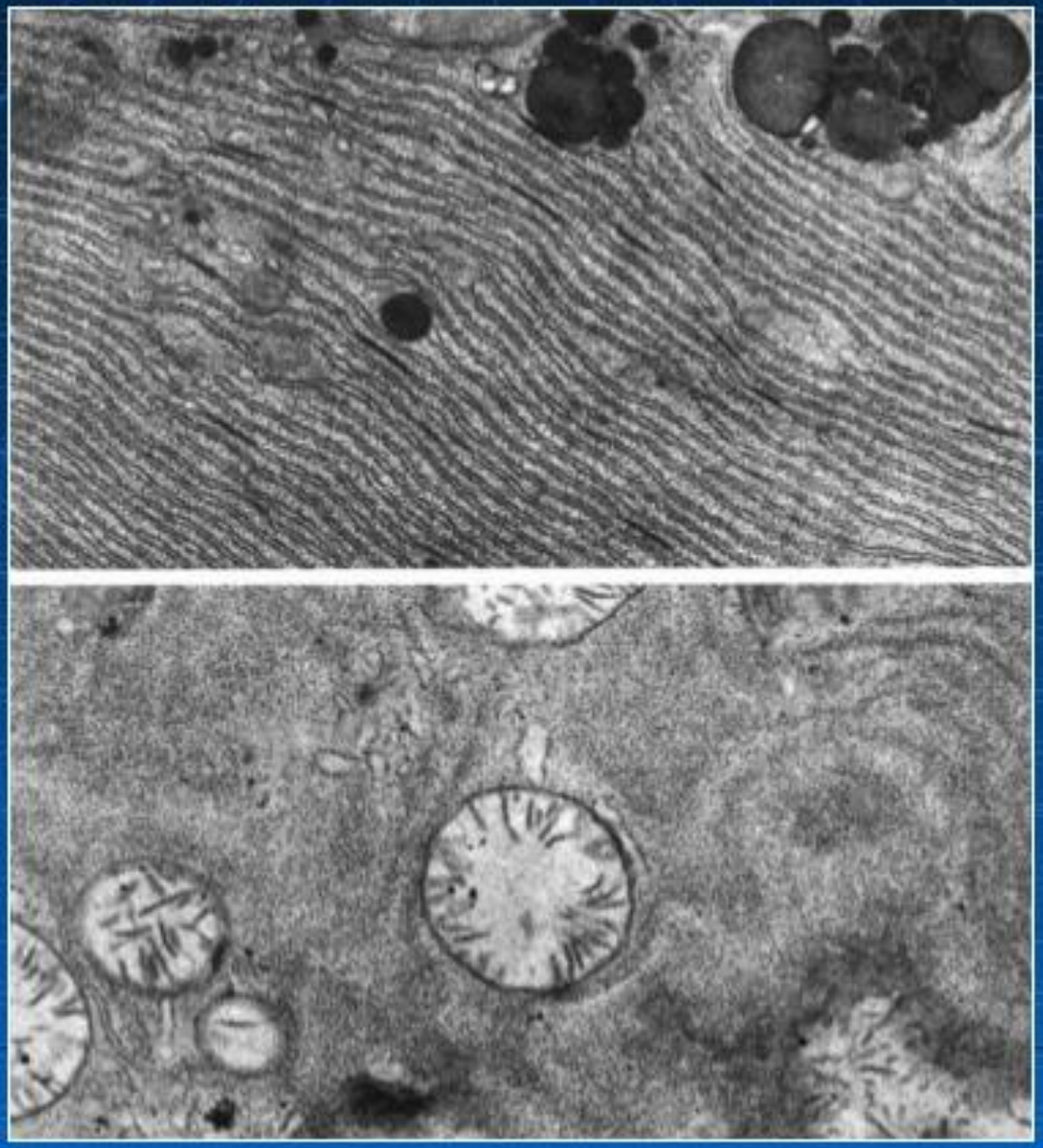


Mitochondrial Injury

Endoplasmic reticulum changes



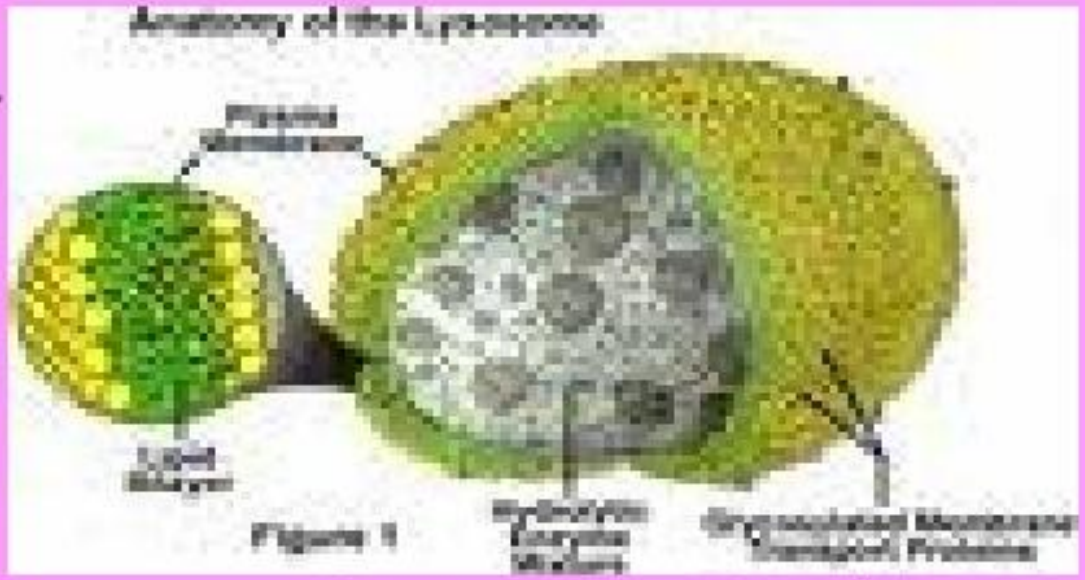
- Dilatation
- Detachment of ribosomes and disaggregation of polysomes with decreased protein synthesis
- Progressive fragmentation and formation of intracellular aggregates of myelin figures

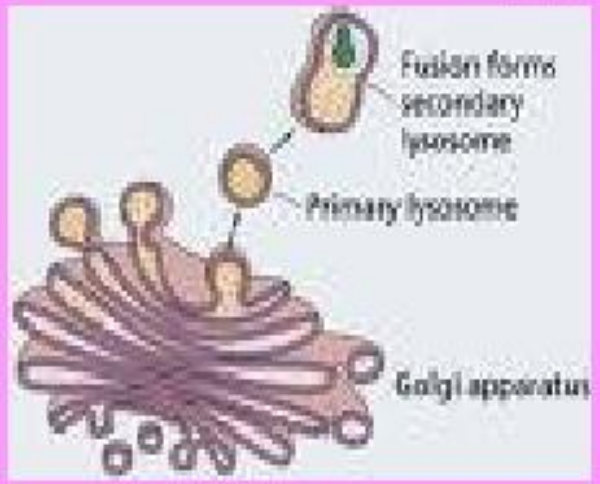


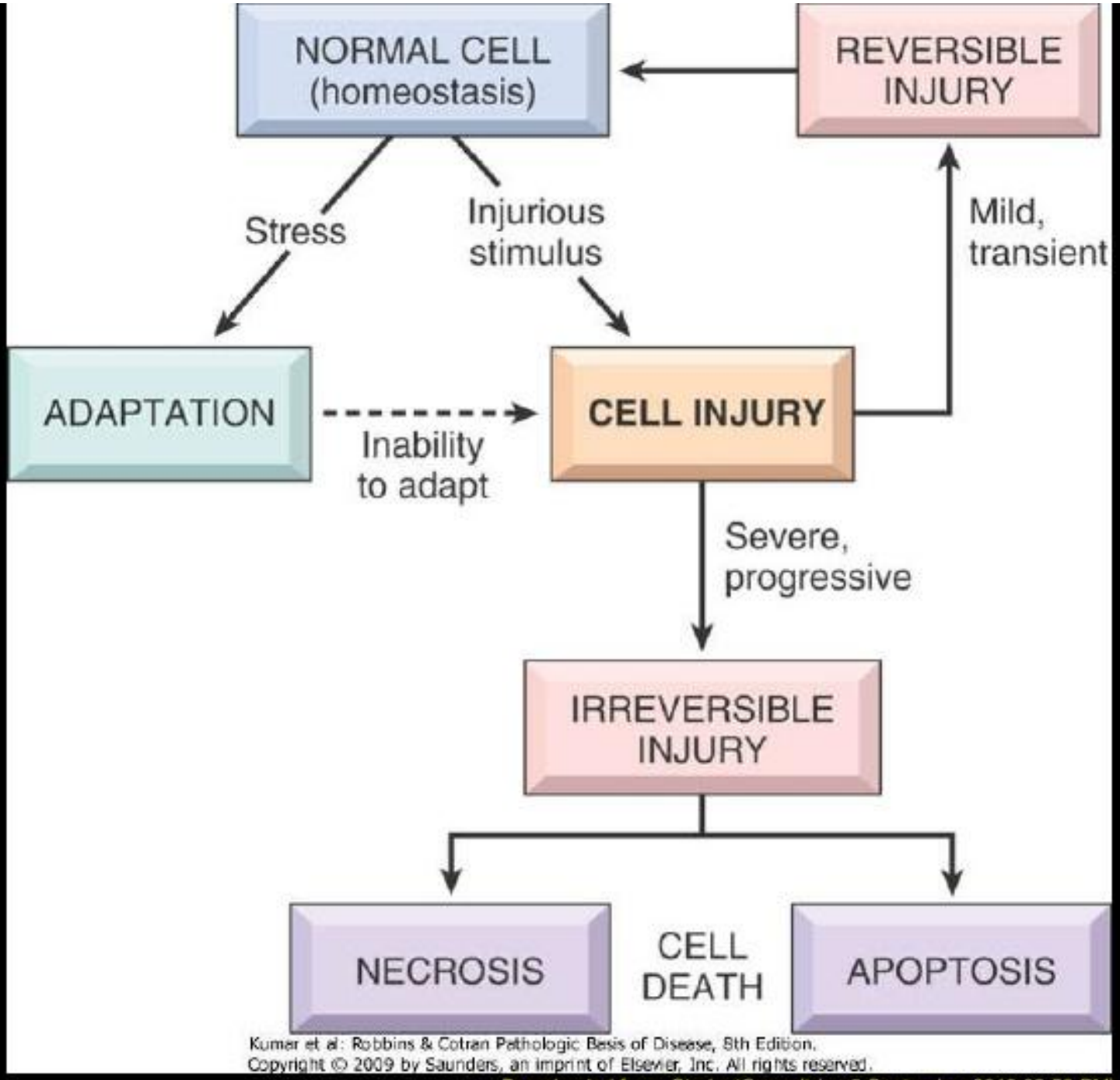
Endoplasmic Reticulum Injury

Changes in the Lysosomes

- Generally appear late
- Swelling → rupture → disappear
- some fused with the autohagic vacuoles (phagosomes) which become apparent within damaged cells







Key Concepts (cont'd)

- Cell injury can be reversible or irreversible
- Reversibility depends on the type, severity and duration of injury
- Cell death is the result of irreversible injury

Morphological manifestations of damage

1. Dystrophy,
2. Necrosis,
3. Apoptosis.

Dystrophy

- Dystrophies are a morphological expression of disorders of tissue (cellular) metabolism, leading to structural changes.

Mechanisms of development of dystrophies

1) ***infiltration*** - the entry of a number of substances into the cell;

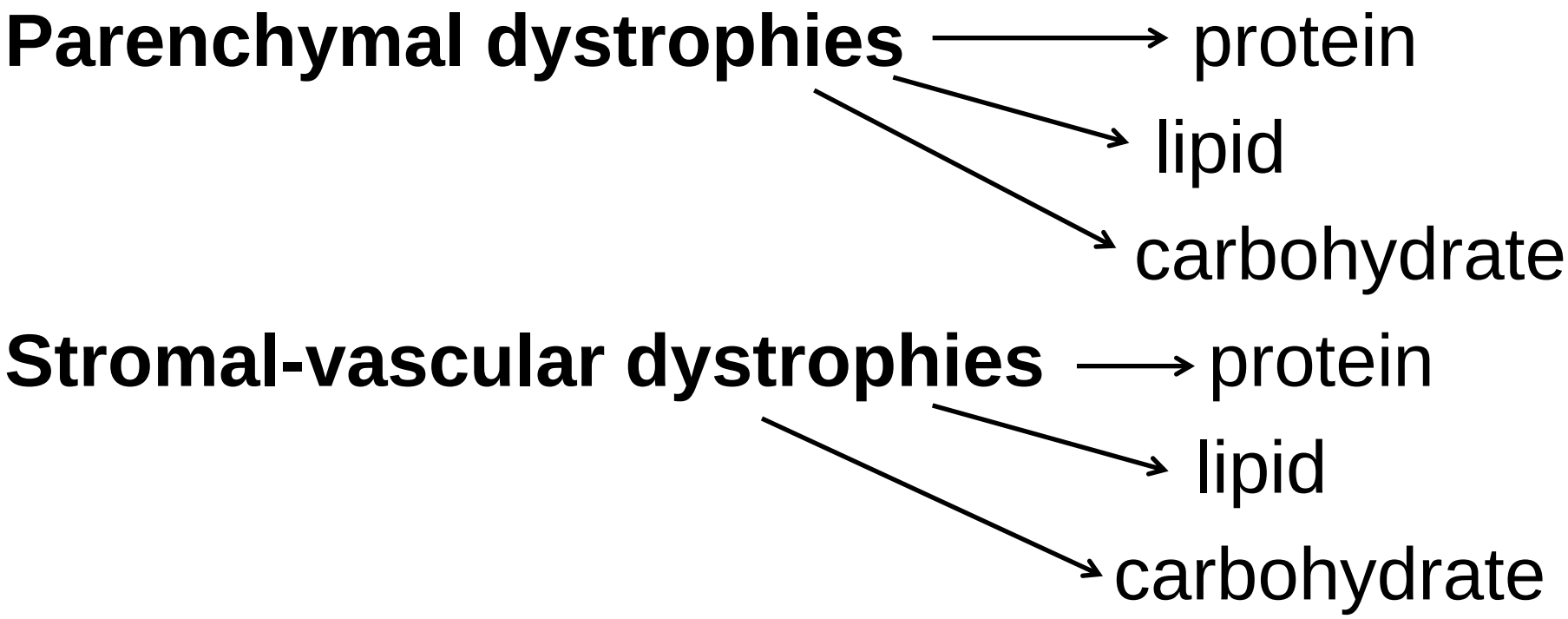
2) ***perverted synthesis*** - synthesis of substances unusual in quantity or abnormal products;

3) ***transformation*** - the transition of one class of substances to another;

4) ***decomposition (phanerosis)*** - the appearance of proteins and lipids in cells during the disintegration of lipoprotein complexes of membranes.

Classification of degenerations

1. Classification in depending on localization of metabolism:
   - parenchymal
   - stromally - vascular
   - mixed
2. Classification in depending on deposition of protein, lipids, carbohydrate , mineral (on predominance of the broken exchange):
   - Proteinous (Dysproteinoses)
   - Fatty (lipidoses)
   - Carbohydrate
   - Mineral
   - Pigmental
3. Classification in depending on prevalence of process:
   - Local
   - System
4. Classification in depending on an origin:
   - Acquired
   - Hereditary


Parenchymal dystrophies
protein
lipid
carbohydrate
Stromal-vascular dystrophies
protein
lipid
carbohydrate

Classifications of reversible injury

classification according to type metabolism abnormality

- Disproteinosis
- Lipidosis
- Carbohydrate abnormality
- Mineral abnormality
- Pigment abnormality

Reversible Injury -- Morphology

- Light microscopic changes
  - Cell swelling (a/k/a hydropic change)
  - Fatty change
- Ultrastructural changes
  - Alterations of cell membrane
  - Swelling of and small amorphous deposits in mitochondria
  - Swelling of RER and detachment of ribosomes

- One of the manifestations of metabolic derangements in cells is the intracellular accumulation of abnormal amounts of various substances.
- The stockpiled substances fall into three categories:

(3) a *normal cellular constituent* accumulated in excess, such as water, lipids, proteins, and carbohydrates;

(4) an *abnormal substance*, either exogenous, such as a mineral or products of infectious agents, or endogenous, such as a product of abnormal synthesis or metabolism;

(5) a *pigment*.

Types of Cell Injury

2. Cloudy or cellular swelling or parenchymatous degeneration
3. Hydrophic swelling
4. Fatty change
5. Hyaline degeneration
6. Lipoidal degeneration
7. Mucoid or mucinous degeneration

REVERSIBLE
Cellular injury

Intracellular accumulation

- **Cellular swelling or hydropic dystrophy**
- **Lipid accumulation**
- **Glycogen accumulation**

ACCUMULATION PATHOLOGY

- LIPID METABOLISM ABNORMALITY
- INTRACELLULAR ACCUMULATION
- STROMAL VASCULAR ACCUMULATION

The most frequent localization of intracellular accumulations of proteins, lipids and carbohydrates is myocardium (cardiomyocytes), liver (hepatocytes), kidneys (nephrocytes).

PROTEINS

- Intracellular accumulations of proteins usually appear as rounded, eosinophilic droplets, vacuoles, or aggregates in the cytoplasm.

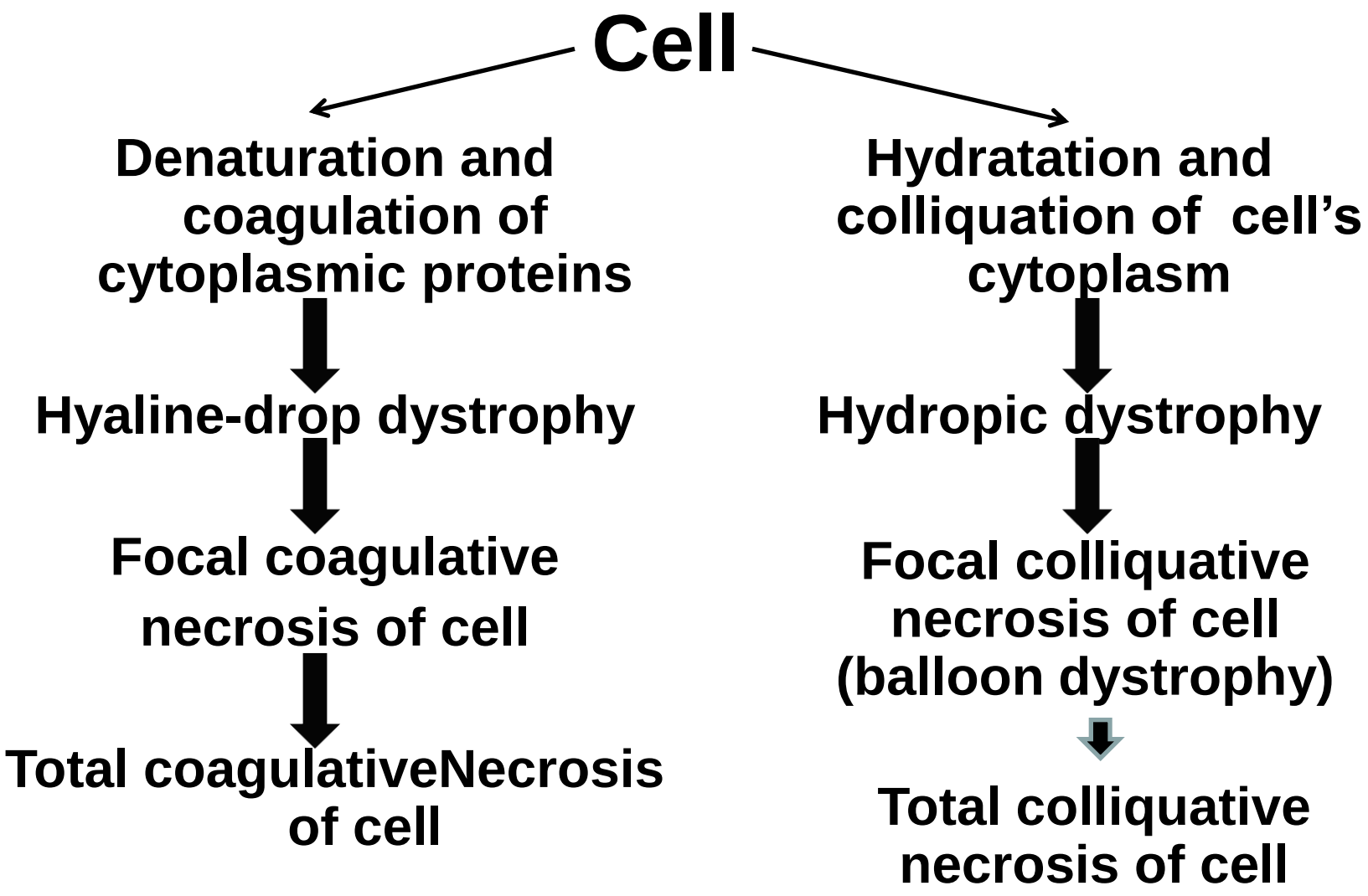
PARENCHYMAL PROTEIN DYSTROPHIES

1. Hyaline droplet dystrophy (degeneration).

2. Hydropic dystrophy (degeneration).

3. Corneous (keratoid) degeneration (hyperkeratosis, leukoplakia).

Parenchymal dysproteinoses, mechanisms.



HYALINE CHANGE

- an alteration within cells or in the extracellular space, which gives a homogeneous, glassy, pink appearance in routine histologic sections stained with hematoxylin and eosin.
- does not represent a specific pattern of accumulation.

Hyaline droplet dystrophy

- the appearance in the cytoplasm of large hyaline-like protein drops, merging with each other and filling the cell body;
- destruction of the ultrastructural elements of the cell.
- In some cases, it ends with focal coagulation cell necrosis.
- often - in the kidneys, rarely - in the liver and very rarely - in the myocardium.

HYALINE DEGENERATION

- Zenker's waxy hyaline masses - typhoid fever; Weil's disease or leptospirosis
- Mallory bodies- nutritional cirrhosis
- Russel bodies- chronic inflammation
- Crooke's hyaline bodies - Cushing's syndrome
- Councilman bodies - yellow fever; viral hepatitis

Hyaline droplet dystrophy

- In the kidneys: accumulation of hyaline drops in nephrocytes;destruction of mitochondria, endoplasmic reticulum, brush border.

- It is based on the insufficiency of the vacuolar-lysosomal apparatus of the epithelium of the proximal tubules, which normally reabsorbs proteins.

- Macroscopically - a picture of the underlying disease.

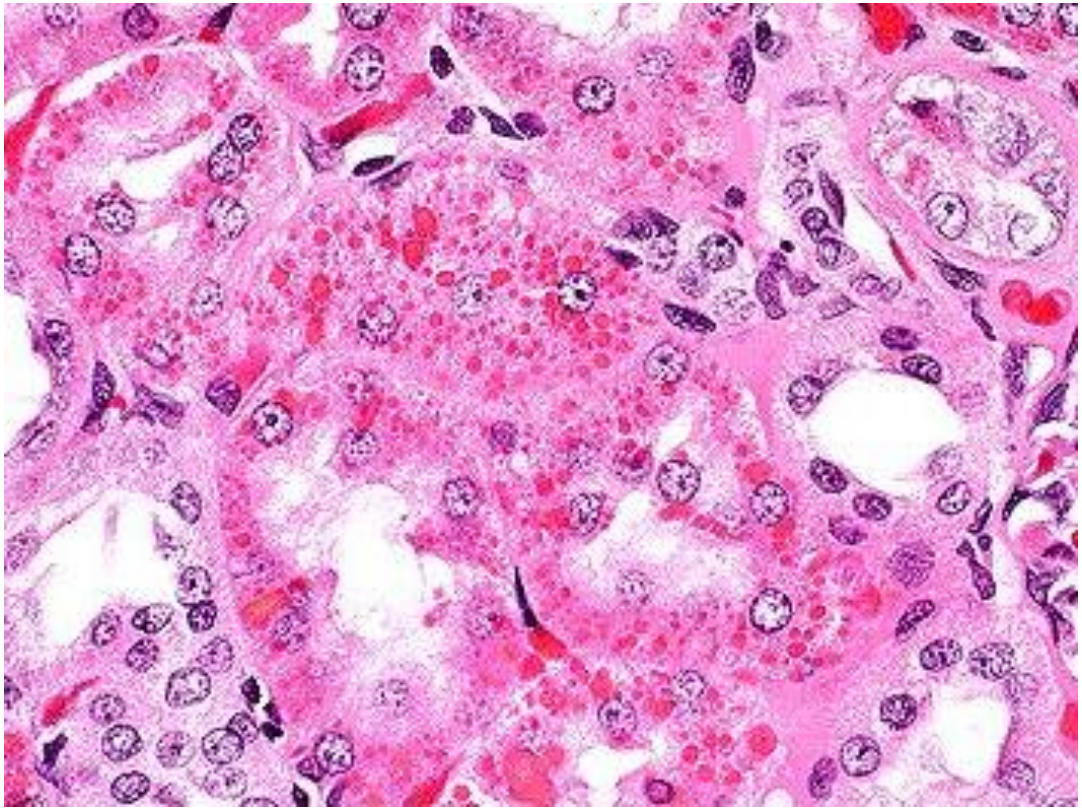
Hyaline droplet dystrophy

- Causes:
- in the kidneys - with nephrotic syndrome, glomerulonephritis, amyloidosis, paraproteinemic nephrosis, diabetic glomerulopathy;

- in the liver - Mallory's little bodies - in alcoholic hepatitis, primary biliary and Indian childhood cirrhosis of the liver, hepatoma, cholestasis.

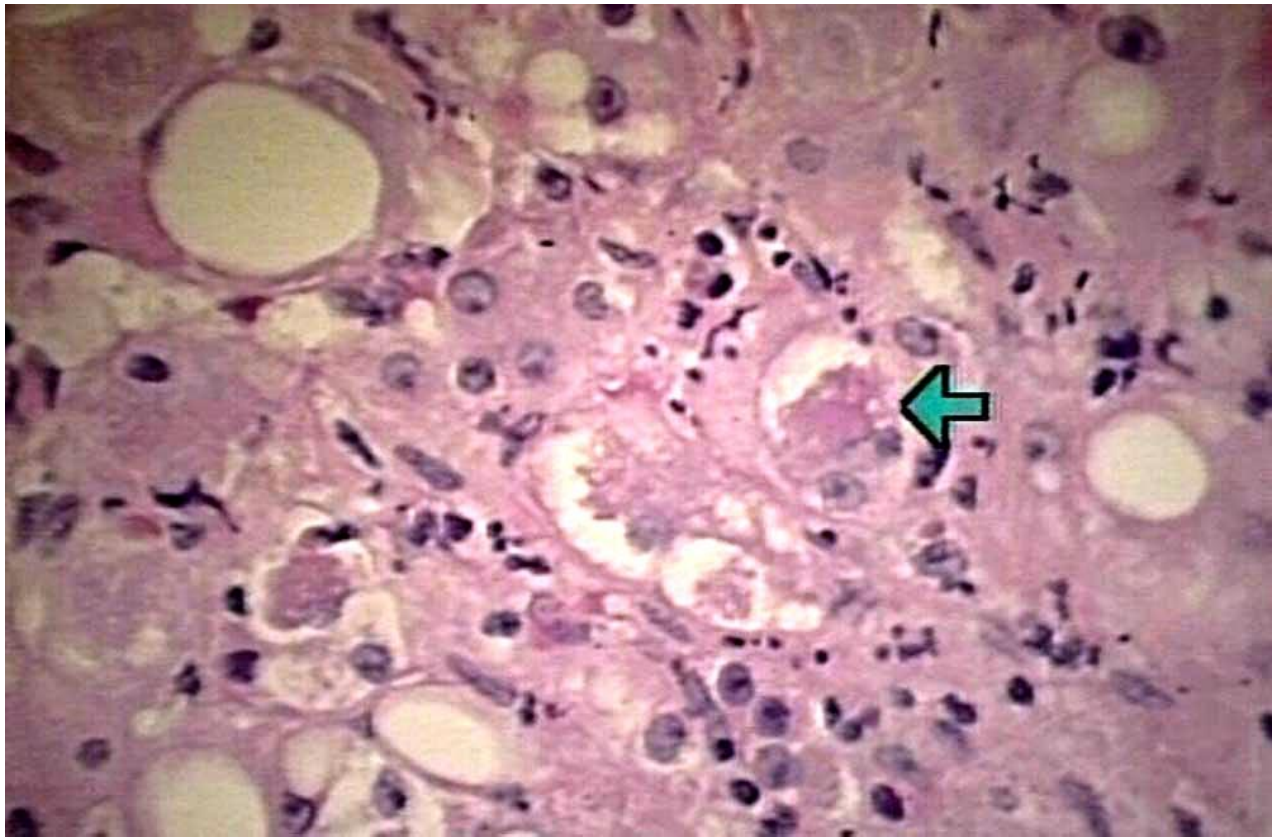
- This type of dystrophy is irreversible and leads to coagulation cell necrosis.

Hyaline droplet dystrophy



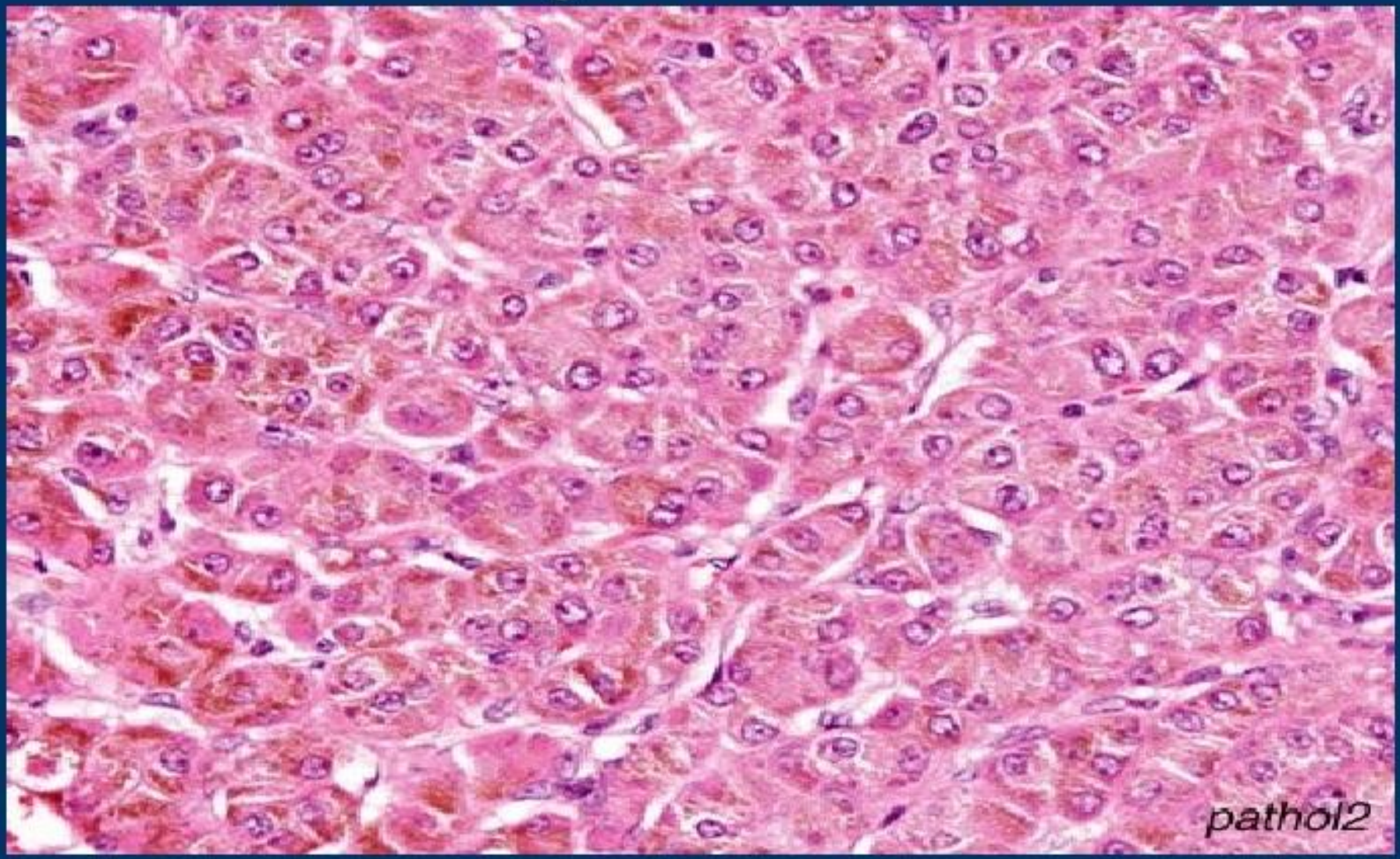
- Micro-: hyaline-like acidophilic protein clumps appear in the cytoplasm of epithelial cells of **renal tubules (kidney**).

Hyaline droplet dystrophy



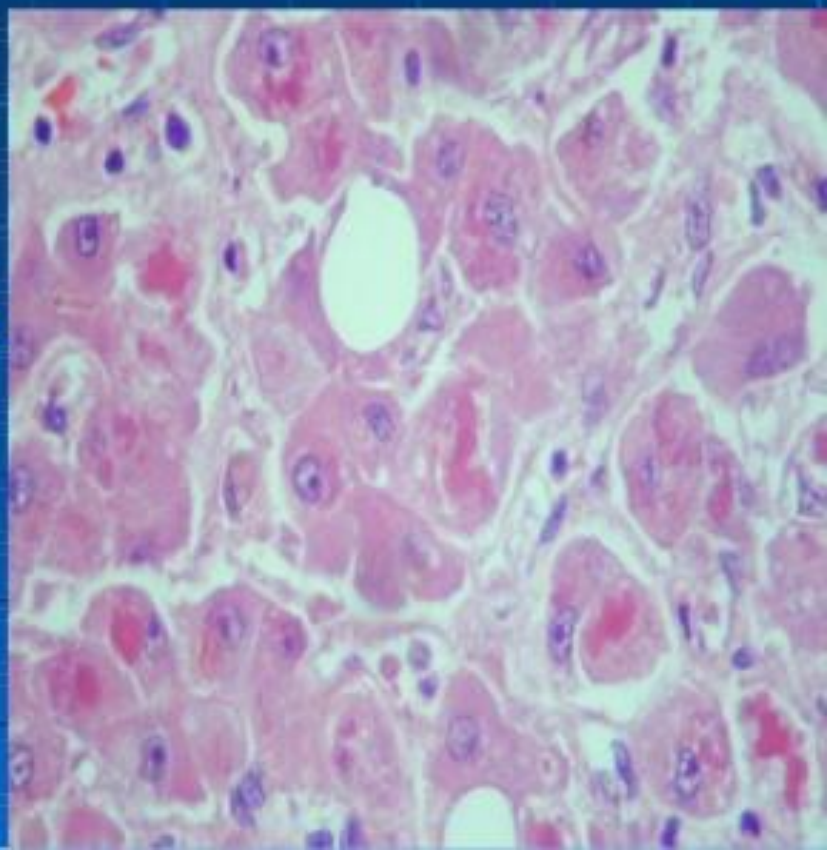
- Micro-: hyaline-like acidophilic protein clumps appear in the cytoplasm the **liver hepatosytes**

CUSHING'S SYNDROME
Crooke's Hyaline bodies-Liver

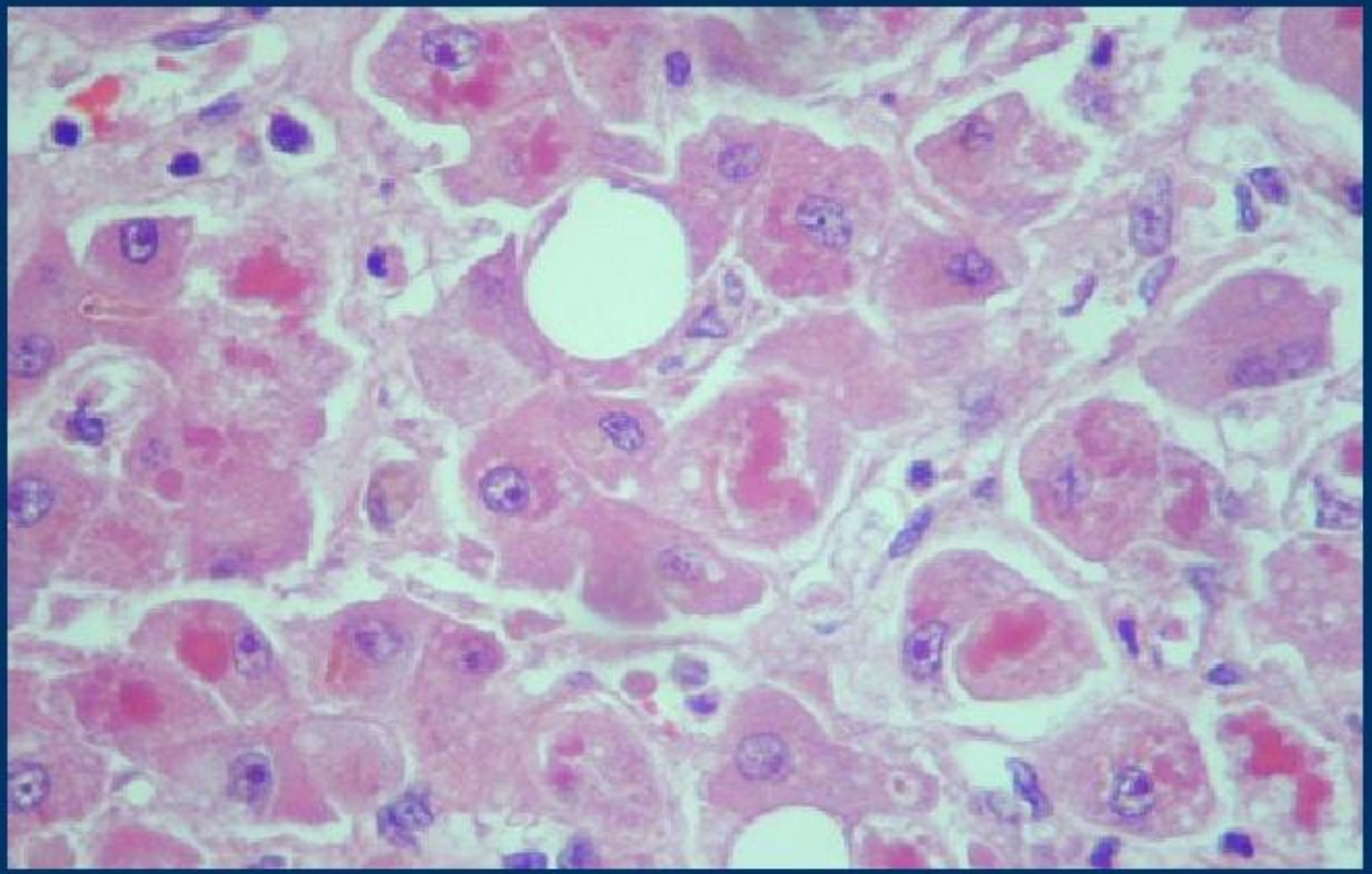


Hyaline droplets dystrophy or degeneration

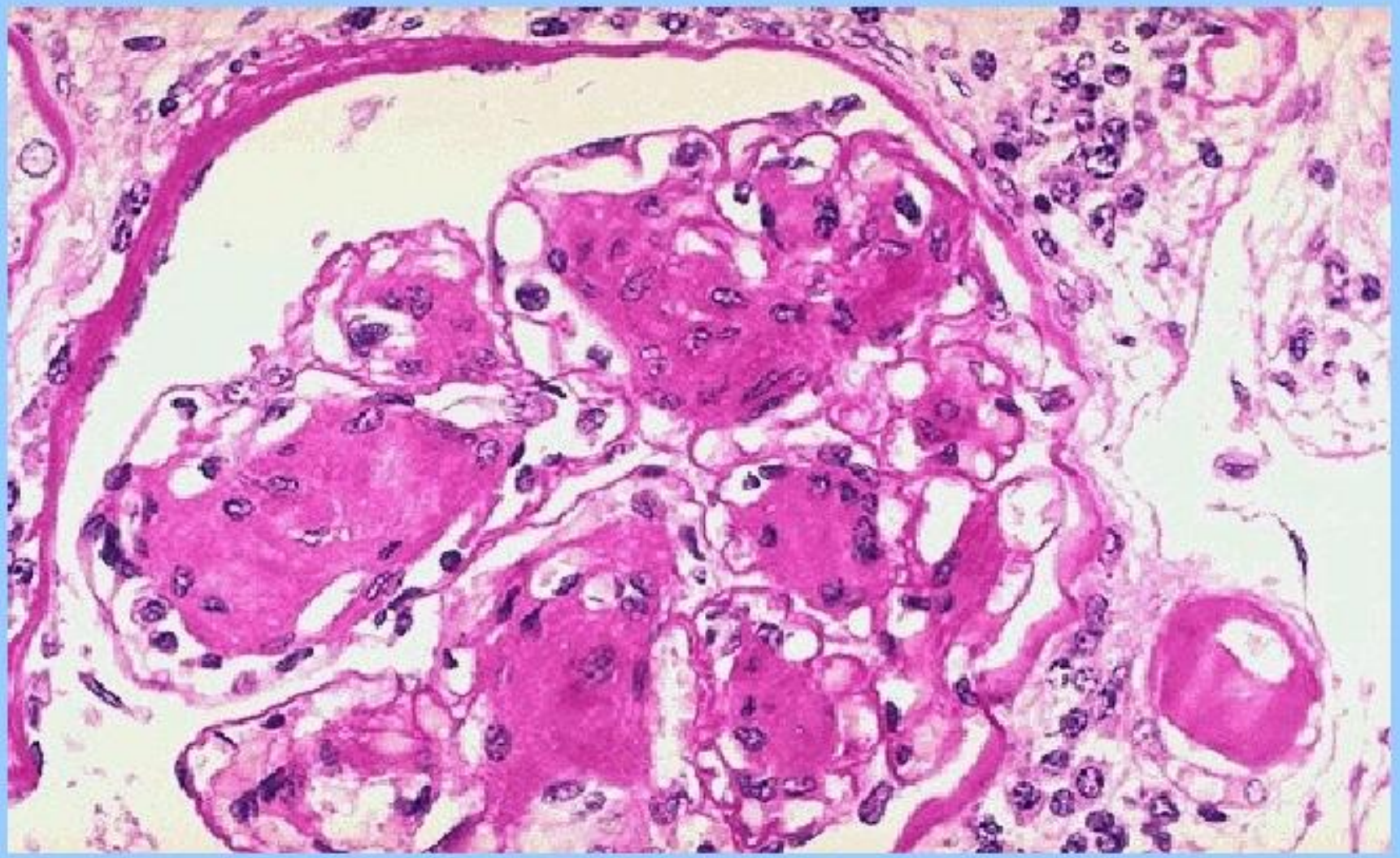
Here are Mallory bodies (the red globular material) composed of cytoskeletal filaments in liver cells chronically damaged from alcoholism

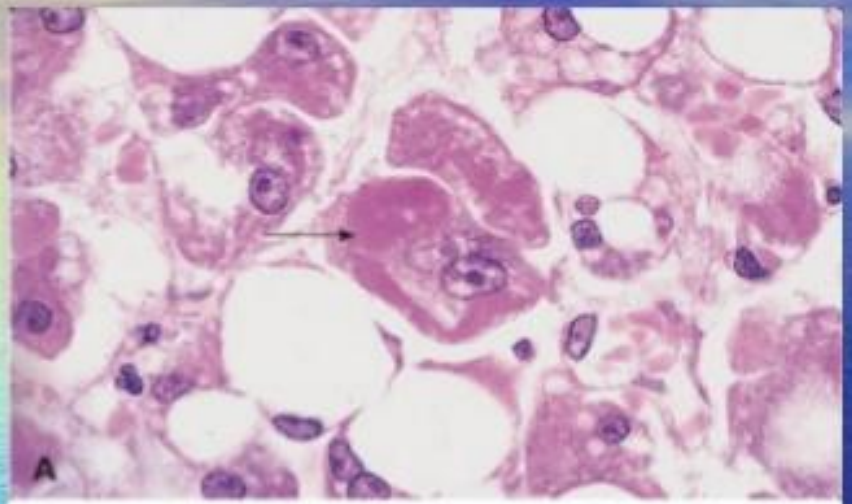


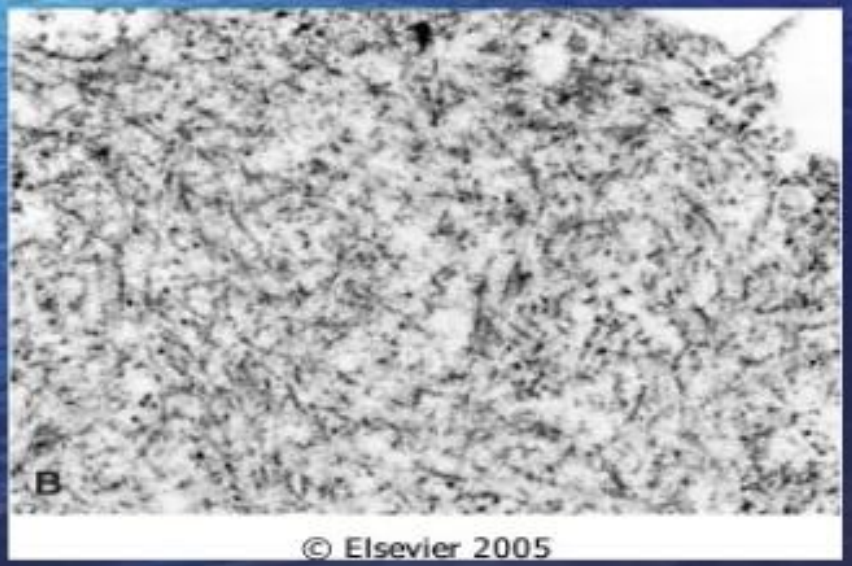
Hyaline Degeneration-Liver



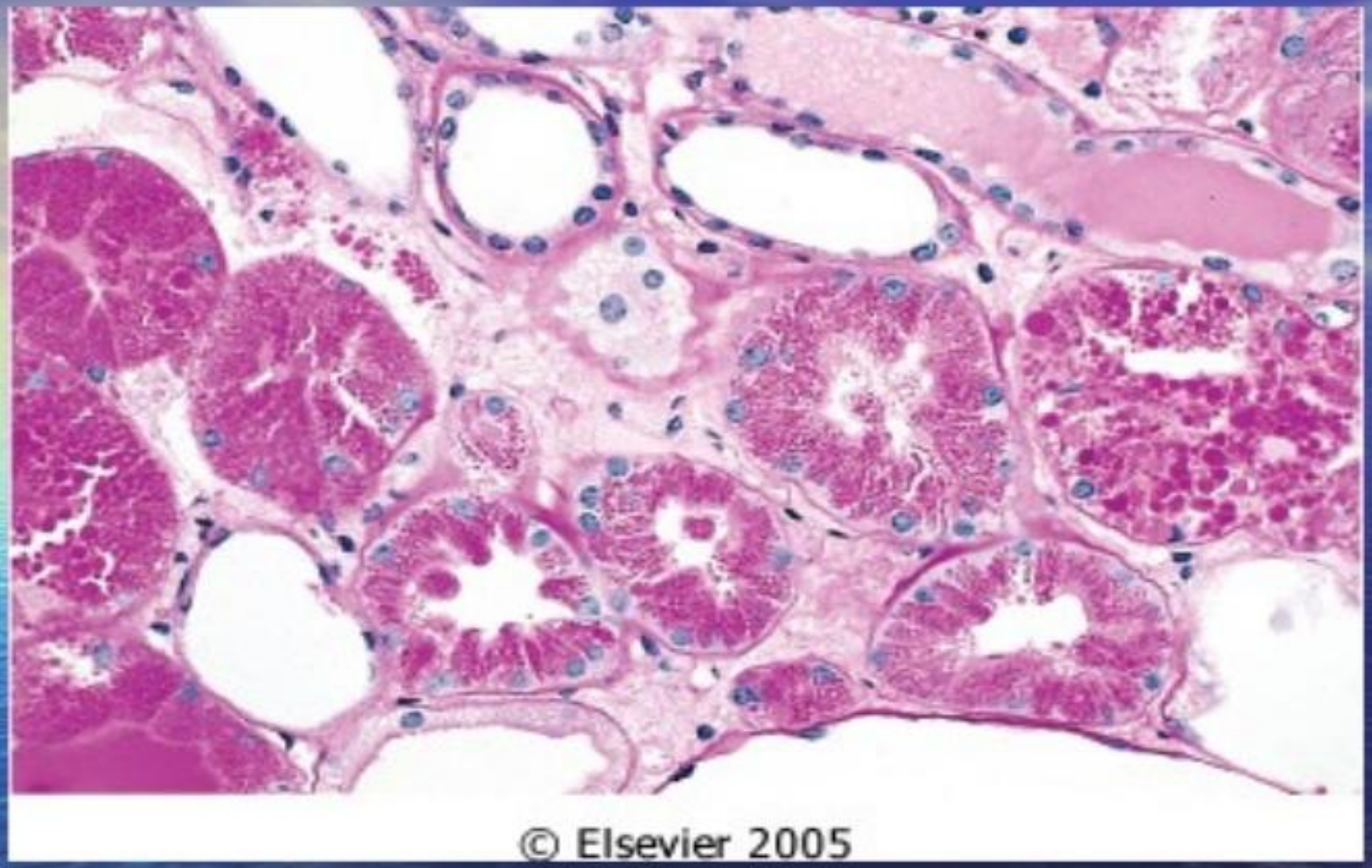
HYALINE DEGENERATION







- Figure 1-34 *A,* The liver of alcohol abuse (chronic alcoholism). Hyaline inclusions in the hepatic parenchymal cell in the center appear as eosinophilic networks disposed about the nuclei *(arrow)*. *B,* Electron micrograph of alcoholic hyalin. The material is composed of intermediate (prekeratin) filaments and an amorphous matrix.



- Figure 1-38 Protein reabsorption droplets in the renal tubular epithelium.

Hydropic (dropsy, vacuolar) dystrophy

- Is characterizws by appearance vacuoles in the cytoplasm of cells that (vacuoles) do not contain fat and glycogen, but filled with cytoplasmic liquid.

- ***Localization:*** epithelium of the renal tubules, skin, hepatocytes (liver), nerve and muscle cells, cells of the adrenal cortex.

- The extreme expression of hydropic dystrophy is ***ballooning degeneration***, in which the cell turns into a huge vacuole filled with fluid,

- outcome - colliquation necrosis.

Cellular swelling or hydropic dystrophy

- Ions disbalance between sodium and potassium with water bubble formation
- Protein infiltration within cells
- Cellular membranes destruction

Hydropic (dropsy, vacuolar) dystrophy

- ***Causes:***

1. hypoxic,
2. heat and cold injuries,
3. malnutrition,
4. ionizing radiation,
5. bacterial toxins (diphtheria, typhoid and streptococcal),
6. toxic substances (phosphorus, arsenic, carbon tetrachloride),
7. viral infections (especially smallpox, viral hepatitis).

Cellular swelling or hydropic dystrophy

Diseases:

- **Infective diseases**
- **Nephropathy**
- **Chronic glomerulonephritis**
- **Alcoholic disease**
- **Alzheimer disease**

Cellular swelling or hydropic dystrophy

Organs are as follow:

- Kidney
- Liver
- Skin (epidermis)
- Brain (neurons)

Hydropic (dropsy, vacuolar) dystrophy

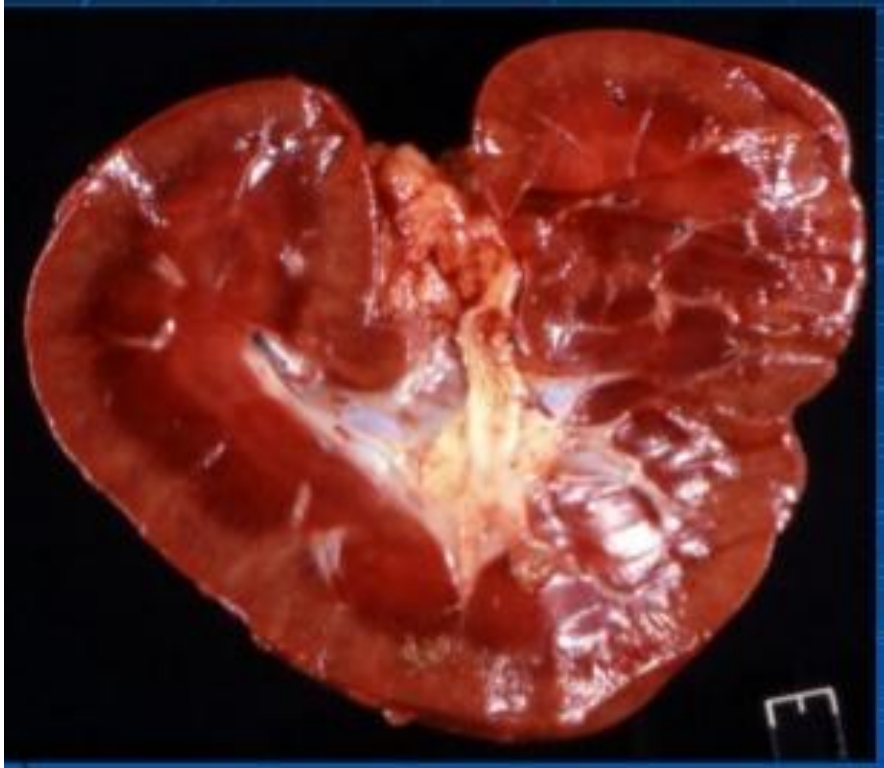
- **In the kidneys**, this is damage to the glomerular filter (glomerulonephritis, amyloidosis, diabetes mellitus), which leads to hyperfiltration and insufficiency of the enzyme system of the basal labyrinth of nephrocytes, which normally provides water reabsorption;
- therefore, hydropic degeneration of nephrocytes is so characteristic of nephrotic syndrome.

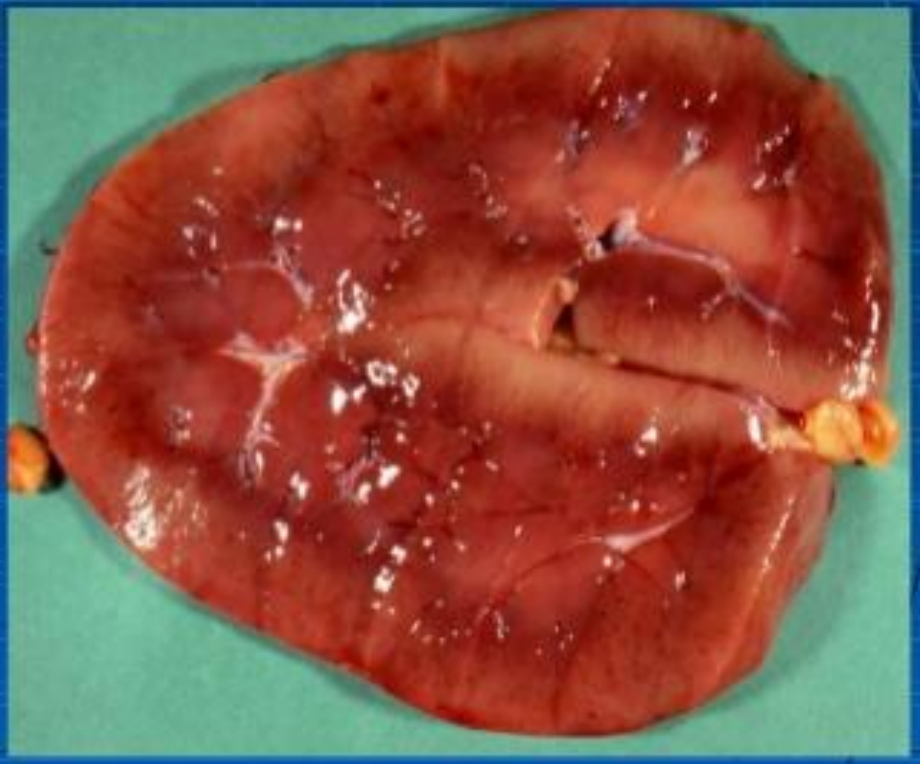
- **In the liver -** with viral and toxic hepatitis, often the cause of liver failure.

- In the epidermis - infection (smallpox), swelling of **the skin** of various mechanisms.

- Vacuolization of the cytoplasm can be a manifestation physiological activity of the cell, which is noted, for example, in the ganglion cells of the central and peripheral nervous system.

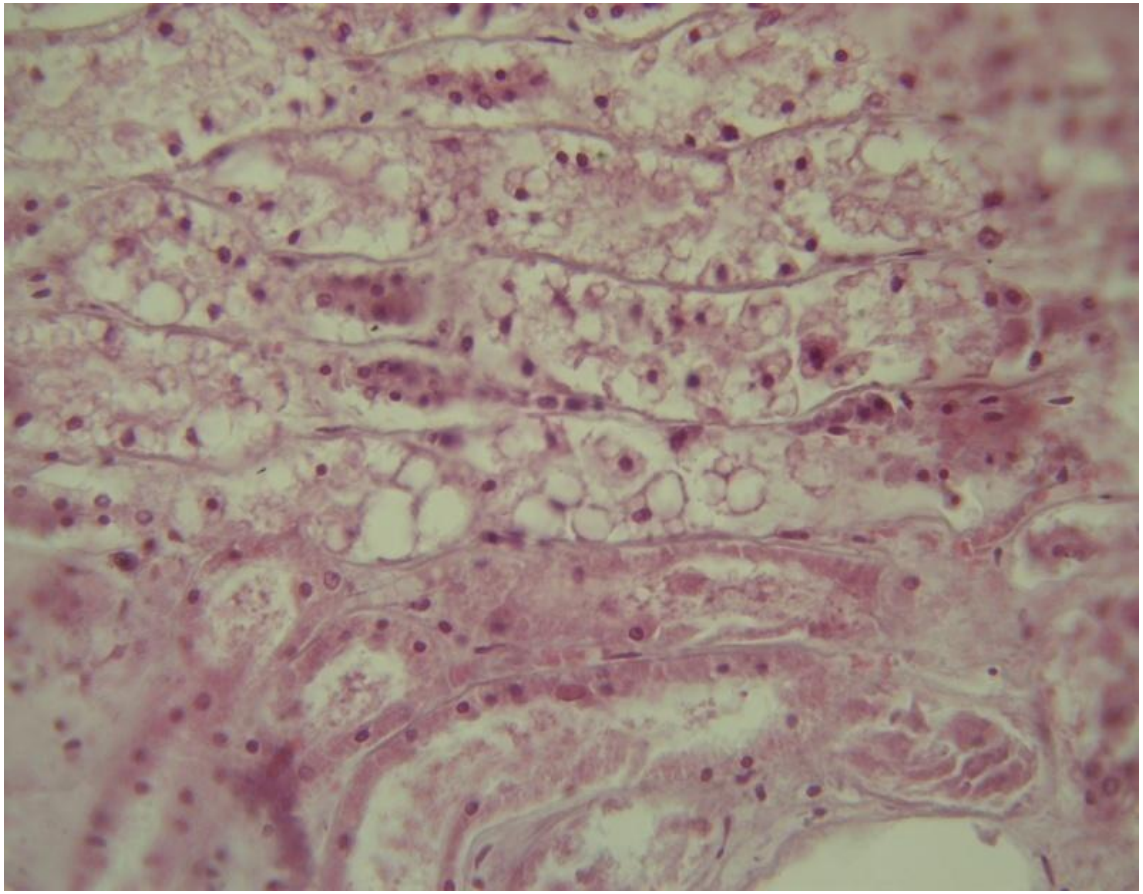
Cellular Swelling





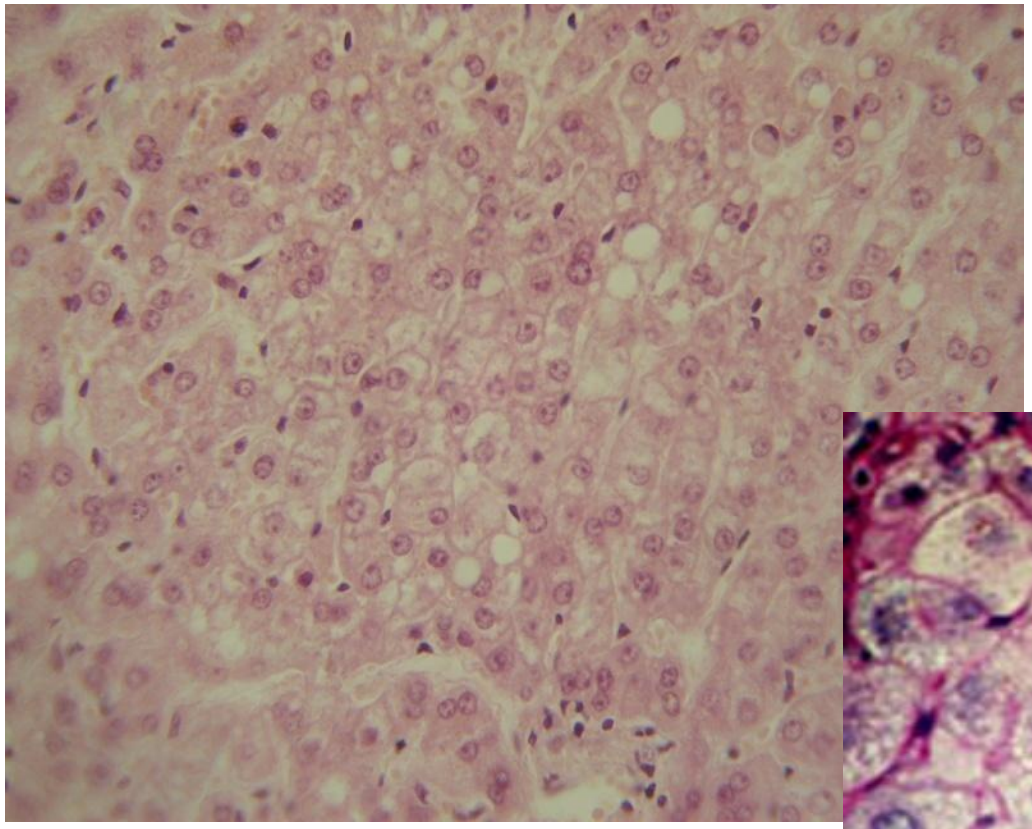
- organ swollen with rounded edges.
- cut surface: tissue bulges and wet / heavy.

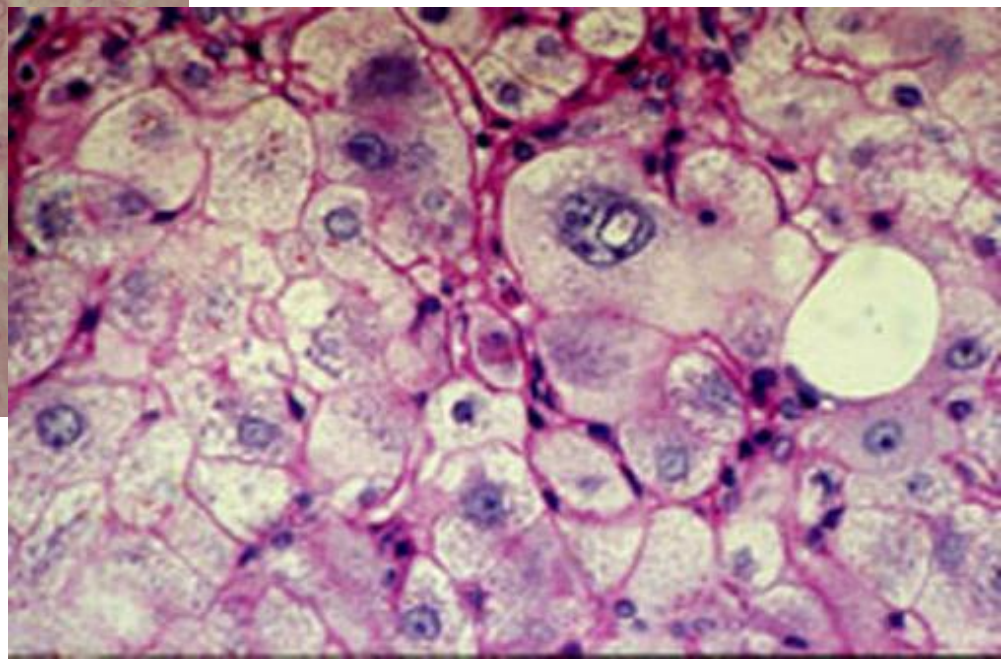
Hydropic (dropsy, vacuolar) dystrophy



- Hydropic degeneration of the kidney

Hydropic (dropsy, vacuolar) dystrophy





- Hydropic degeneration of the liver

Corneous (keratoid) degeneration

- Keratoid dystrophy, or pathological keratinization, - excessive formation of the horny substance in the keratinizing epithelium (***hyperkeratosis, ichthyosis***) or the formation of a keratin substance where it normally does not exist (pathological keratinization on the mucous membranes, ***or leukoplakia***; the formation of "***cancerous pearls***" in squamous cell carcinoma).

- mayn be local or common.

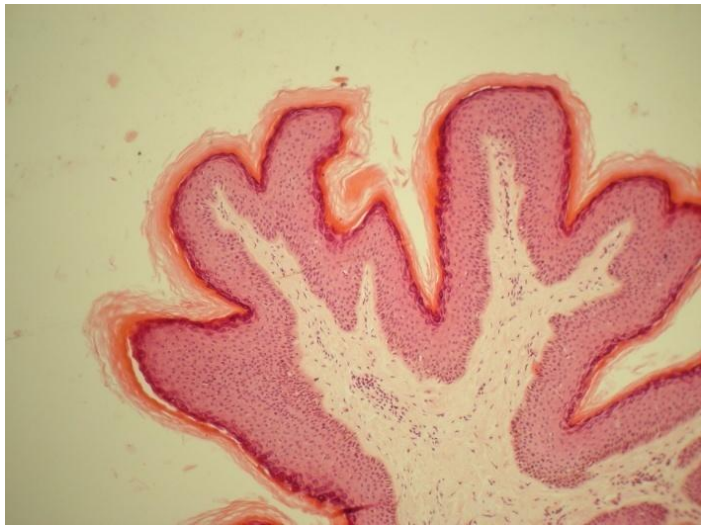
- Causes: disruption of skin development, chronic inflammation, viral infections, vitamin deficiencies, etc.

Corneous (keratoid) degeneration

- ***Outcome:*** elimination of the causative cause at the beginning of the process - to tissue restoration, but in advanced cases - cell death.

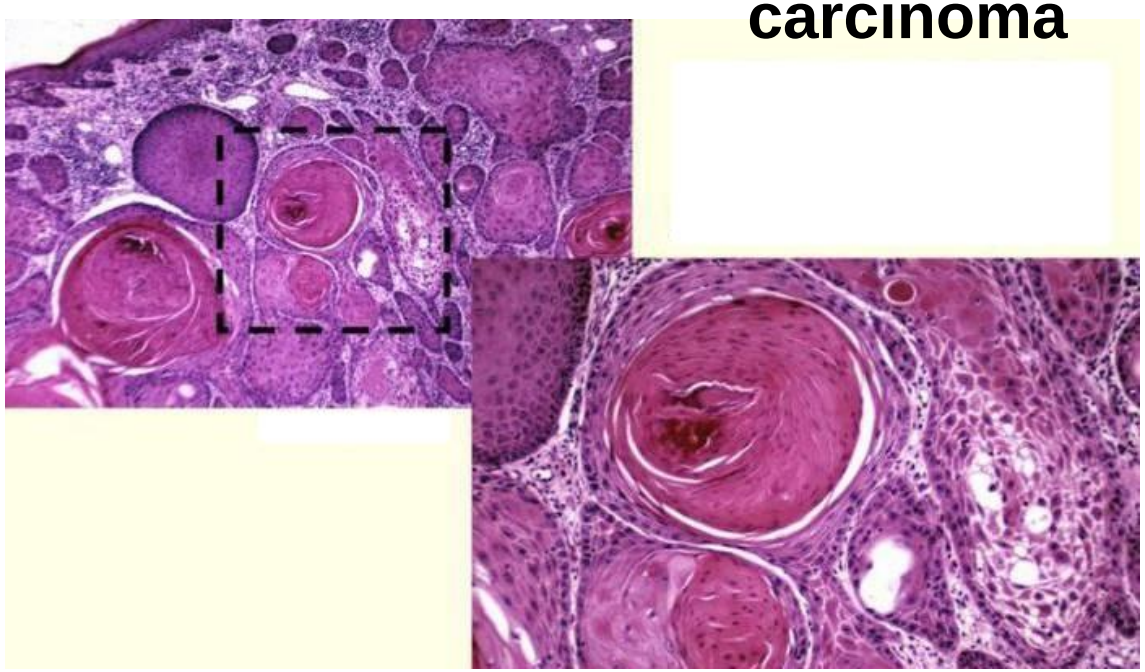
- ***Significance:***
- determined by its degree, prevalence and duration.
- Long-term pathological keratinization of the mucous membrane (leukoplakia) can be the source of the development of a cancerous tumor.
- Acute congenital ichthyosis, as a rule, is incompatible with life.

Corneous (keratoid) degeneration

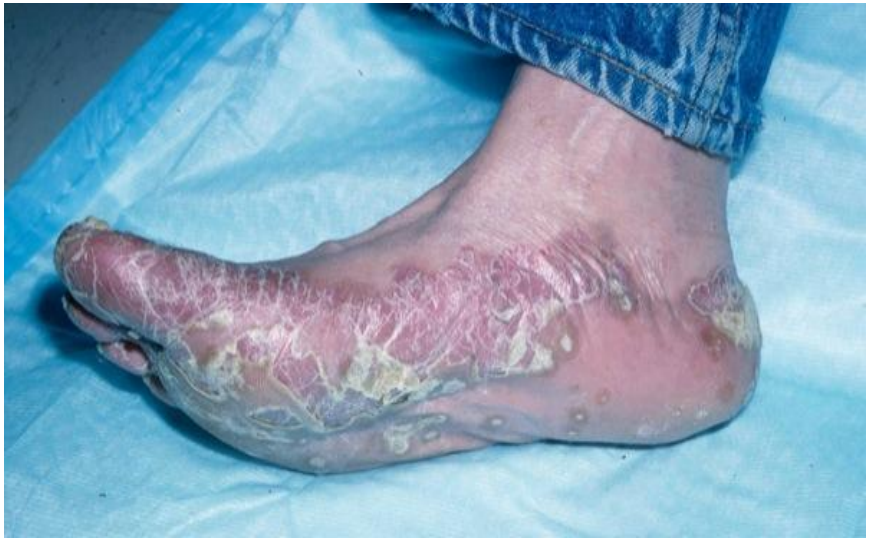


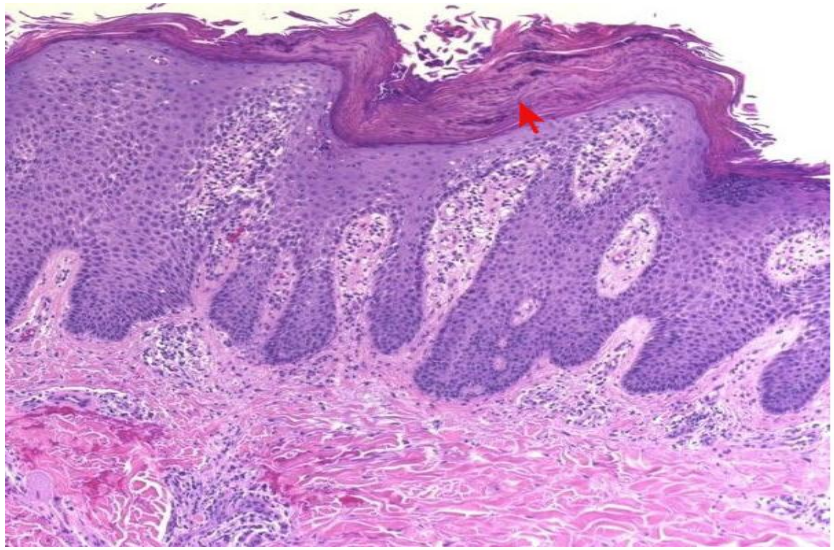
- **Papilloma with hyperkeratosis,**

- **Keratinizing squamous cell carcinoma**



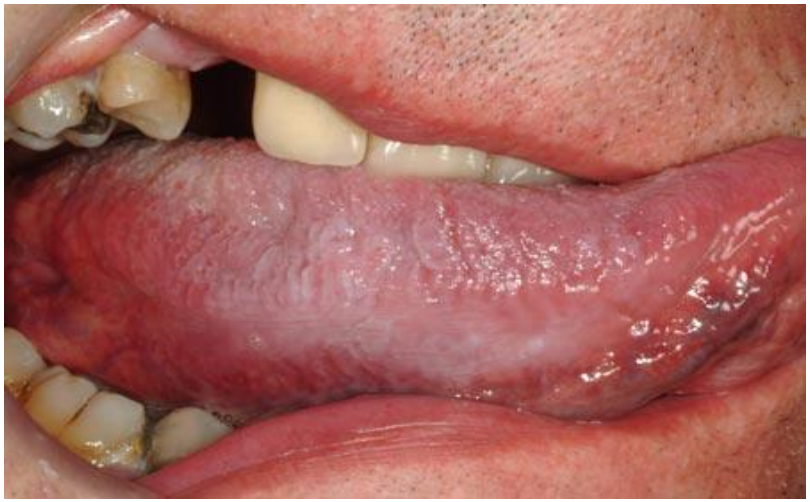
Corneous (keratoid) degeneration

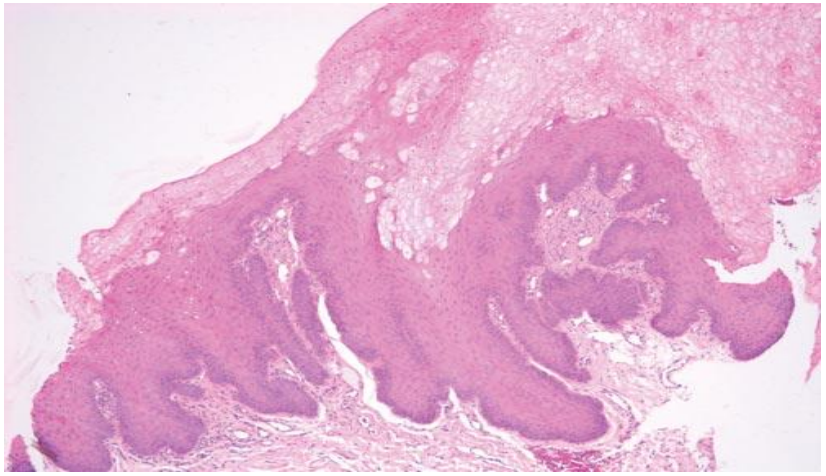




- **Hyperkeratosis**

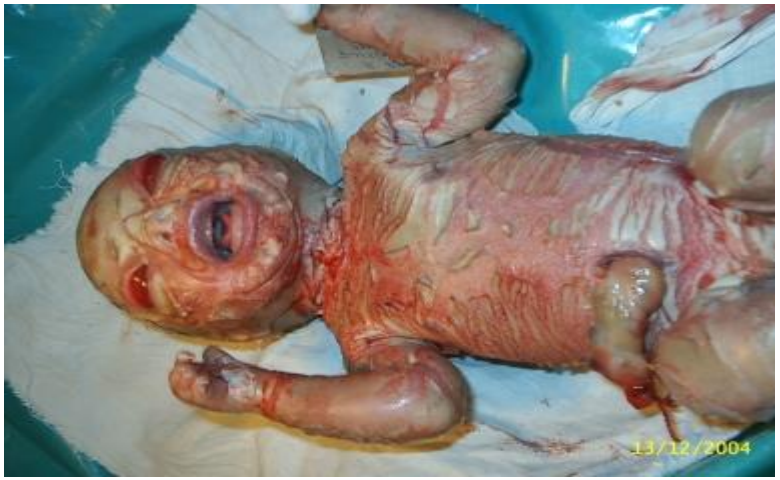
Corneous (keratoid) degeneration

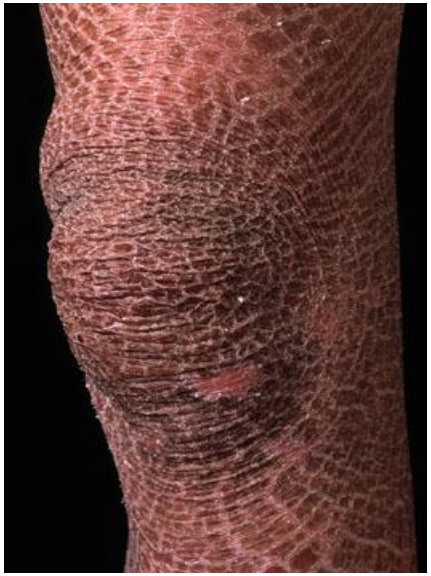


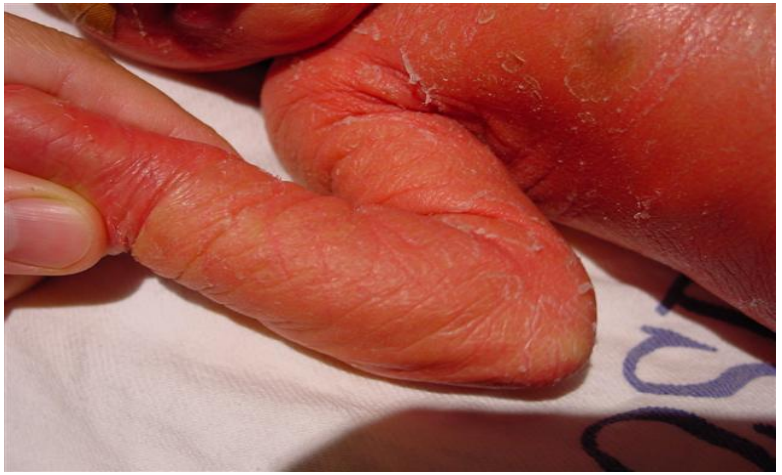


- **Leukoplakia**

Corneous (keratoid) degeneration:
ichthyosis (Harlequin's syndrome)

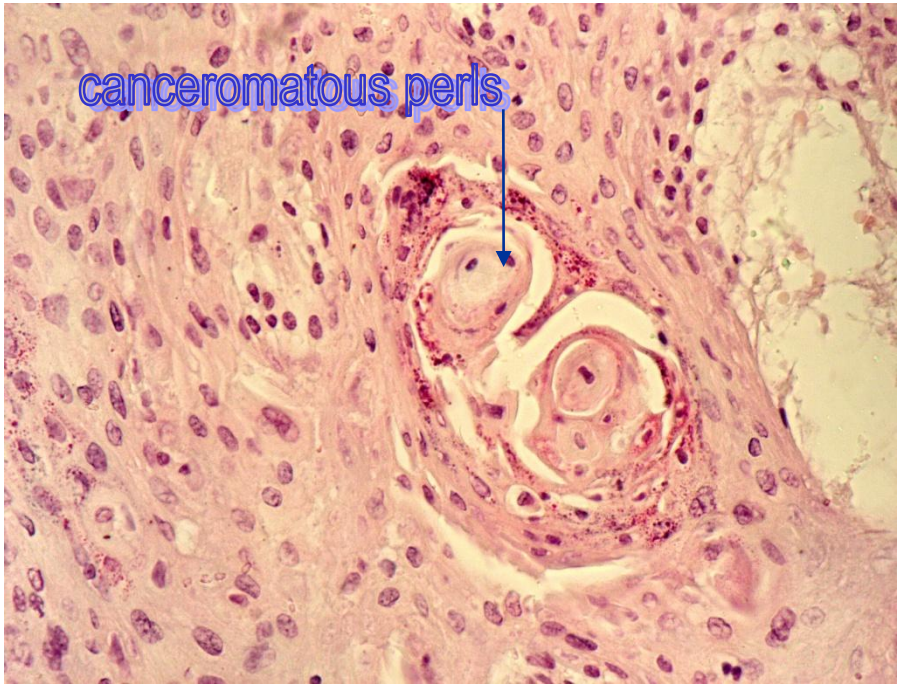


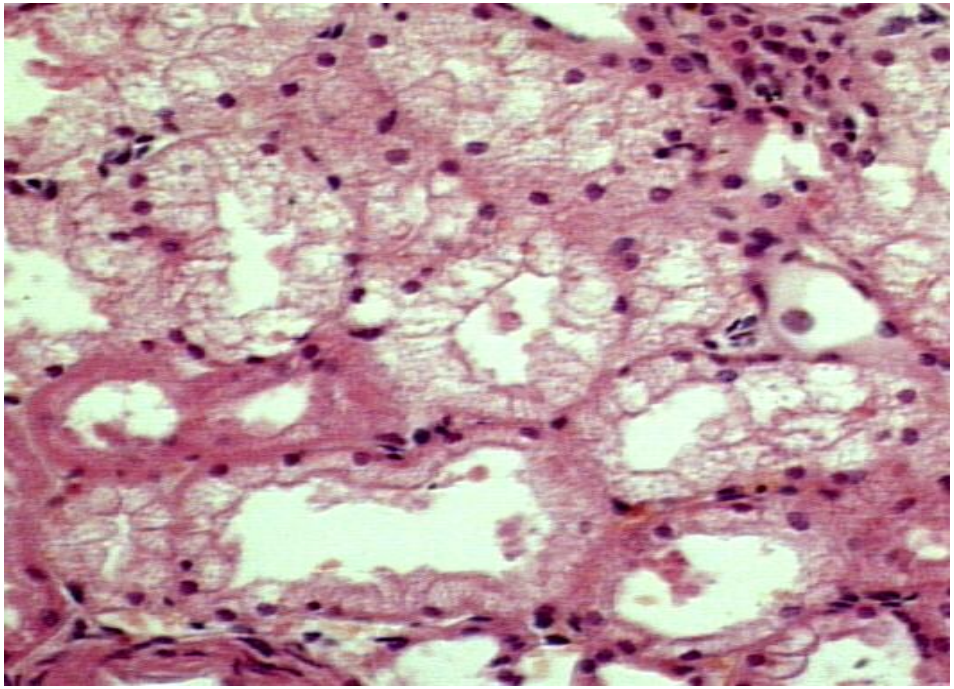


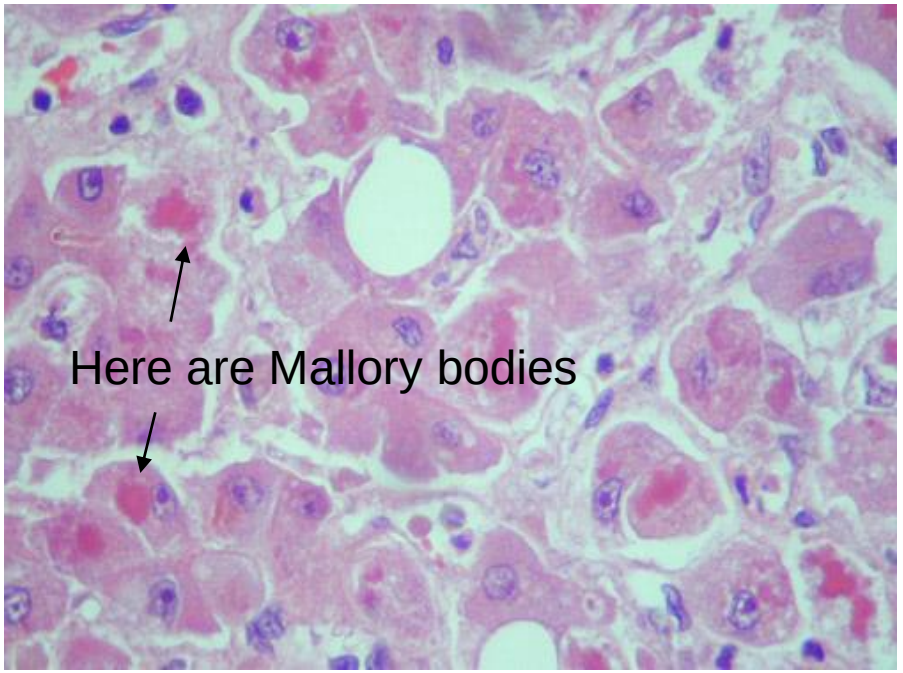


Types of intracellular parenhymatous degenerations

- **Granular**
- **Hyaline-drop**
- **Hydropic (vacuolar, balloon)**
- **Keratoid (horney)**







INTRACELLULAR ACCUMULATION

FATTY CHANGE (STEATOSIS)

PARENCHYMAL LIPIDOSIS IS CHARACTERIZED BY ABNORMAL ACCUMULATION OF TRIGLYCERIDES WITHIN PARENCHYMAL CELLS

ORGANS:

- ***THE LIVER,***
- ***THE MYOCARDIUM,***
- ***THE KIDNEYS.***

FATTY CHANGES IN THE LIVER

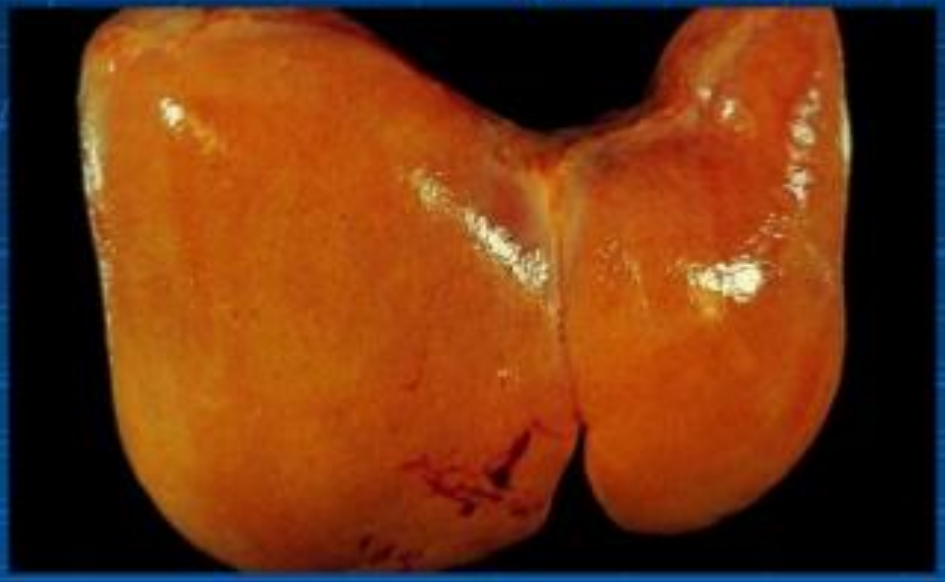
- ETIOLOGY IS TOXINS, PROTEIN MALNUTRITION, DIABETES MELLITUS, OBESITY AND ANOXIA.
- PATHOGENESISIS IS DISBALANCE BETWEEN REMOVE, UTILISATION AND EXCRETION OF LIPIDS BY HEPATOCYTES.

Fatty change or **Steatosis**

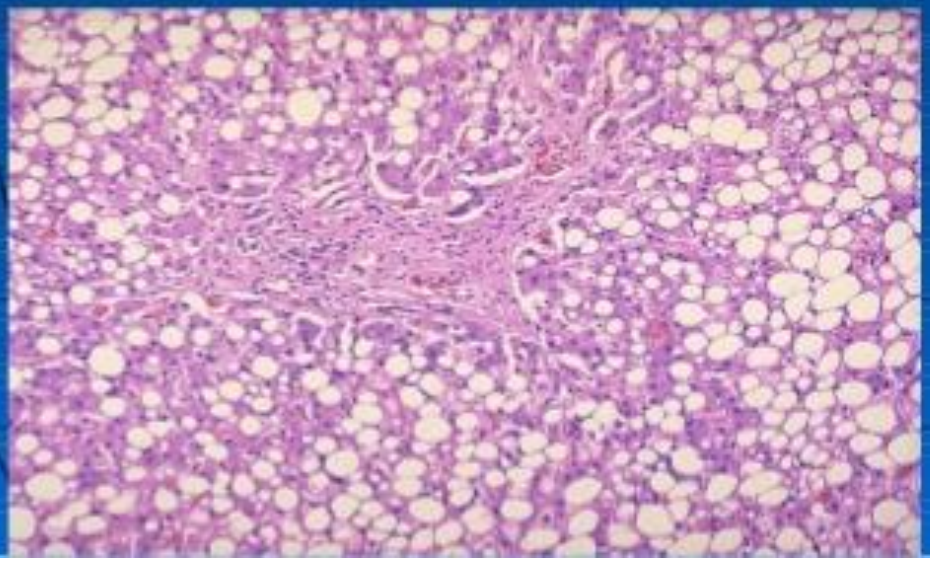
Mechanisms :

1. increase of free fatty acids (starvation, diabetes and chronic ethylism/alcoholism),
2. reduction of free fatty acids oxidation (hypoxia, toxins, chronic ethylism/alcoholism),
3. increase of esterification of free fatty acids into triglycerides (due to increased free fatty acids or reduction of their oxidation, chronic ethylism/alcoholism)
4. reduced export of trygliceride due to deficiency of lipid binding apoprotein (starvation/malnutrition, toxins).

THE STAIN FOR LIPIDS IS NAMED SUDAN THREE

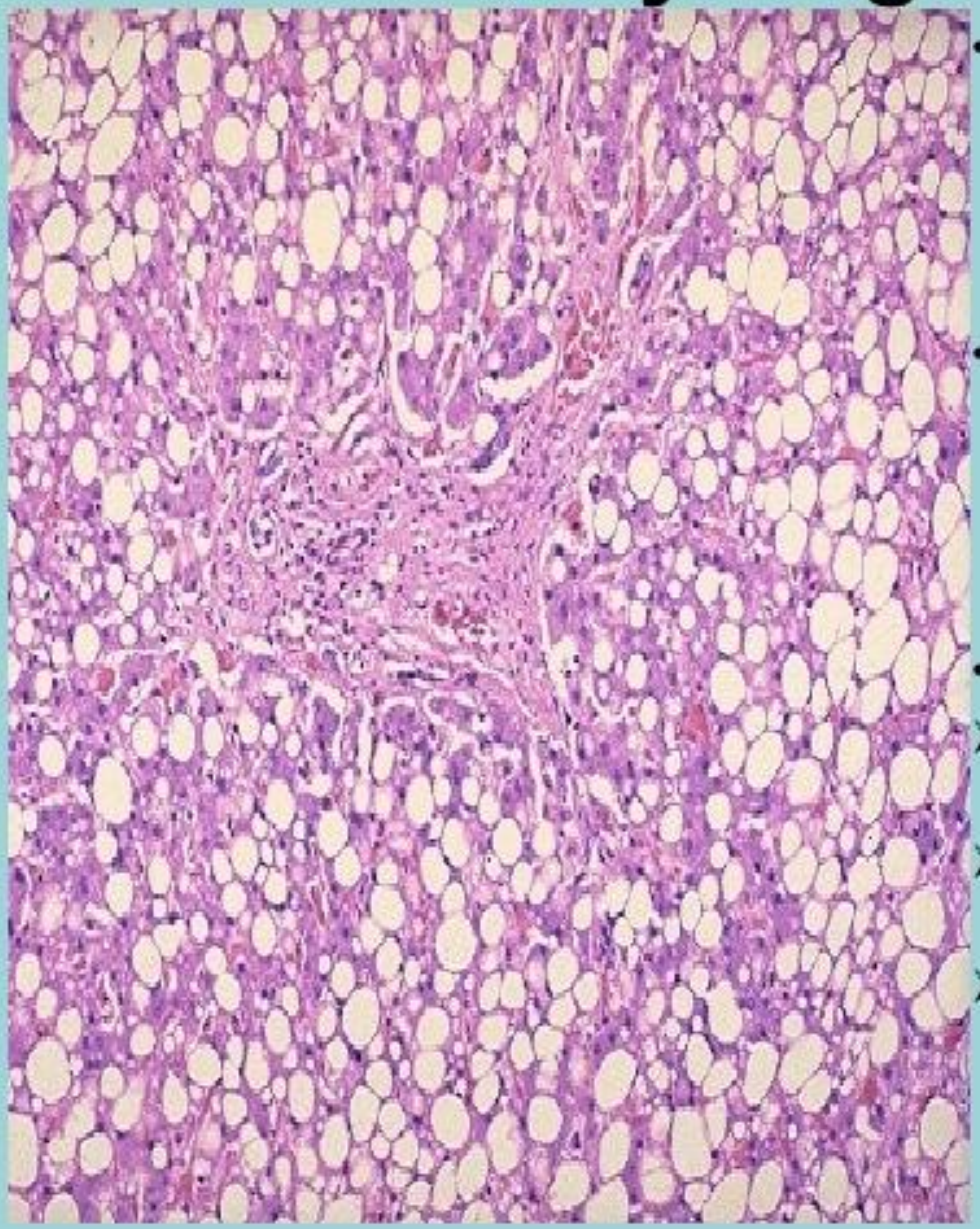


Gross sample



Micro sample
h/e stained

Fatty Degeneration



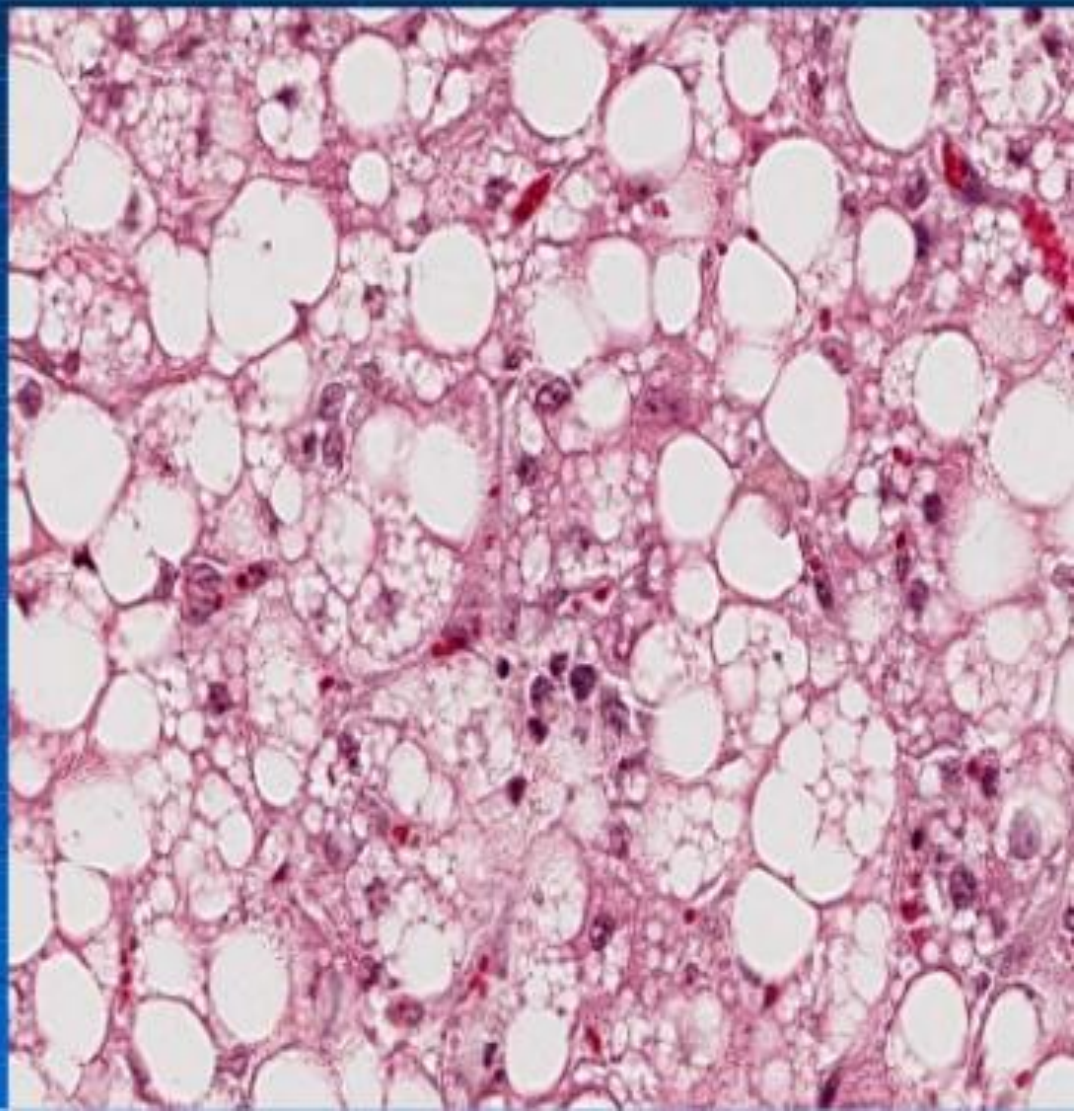
- Fatty degeneration or fatty metamorphosis, steatosis is the abnormal appearance of fat within parenchymal cells.

- It results from hepatotoxic agents such as $C_2 H_5OH$, chloroform, CCl_4, during sever infections, in prolonged anemia and in toxemia of pregnancy.

- Fatty liver is due to:
  - inability of the liver to synthesize phospholipids
  - decreased lipoprotein release from hepatocytes
  - Increased triglyceride production

FATTY LIVER

Hepatic liposis, higher magnification. The well-delineated lipid filled cytoplasmicvacuoles causing swelling of the hepatocytes, usually pushing nucleus to the periphery of the cell. Note, how the vacuoles can be single and large or multiple and small.



Fatty liver (steatosis of the liver)

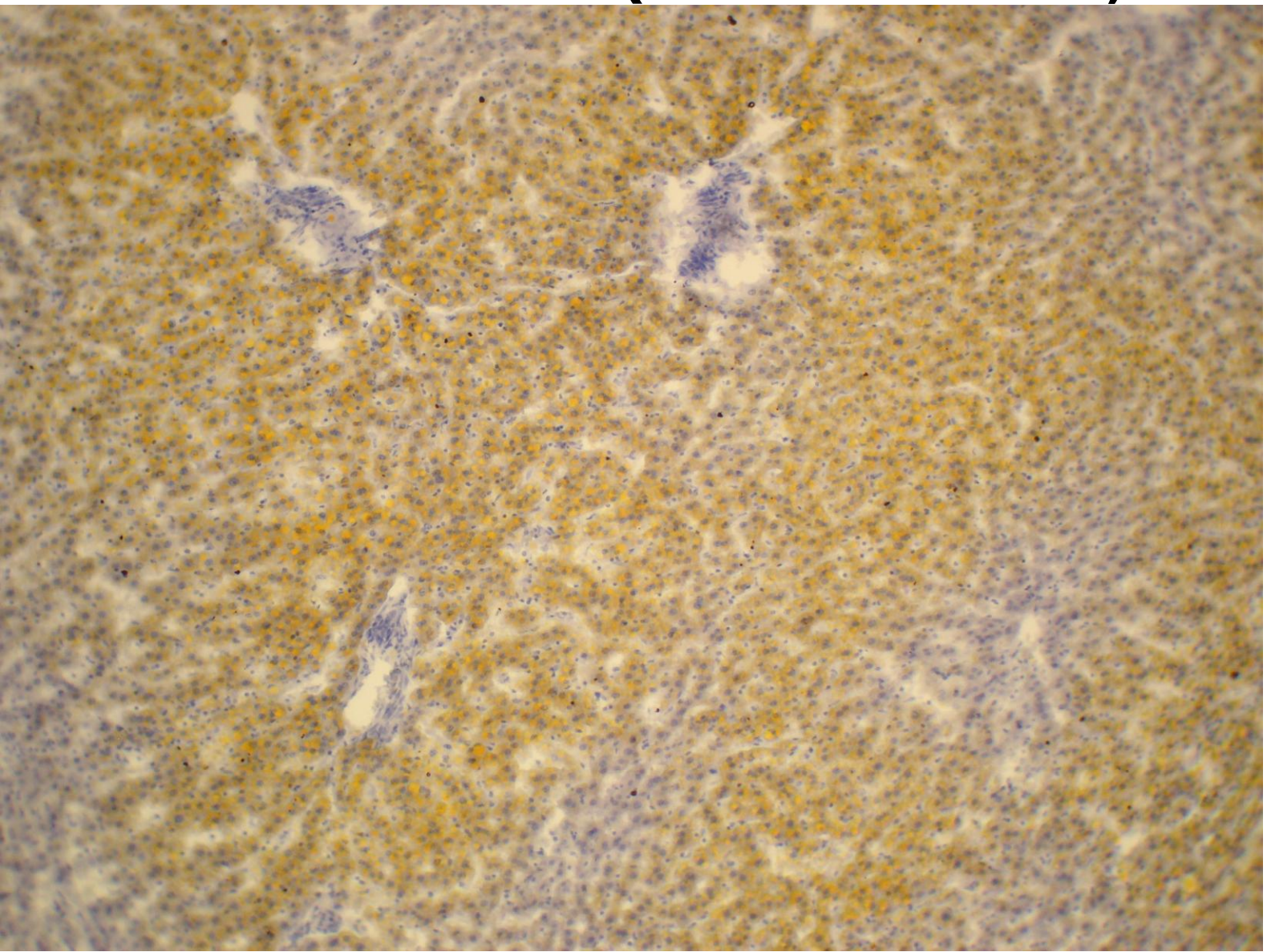
- On histological examination, fat deposits in the liver can be focal or diffuse.

- Depending on the size of the fat droplets, small, medium and large droplet fatty degeneration of hepatocytes are distinguished.

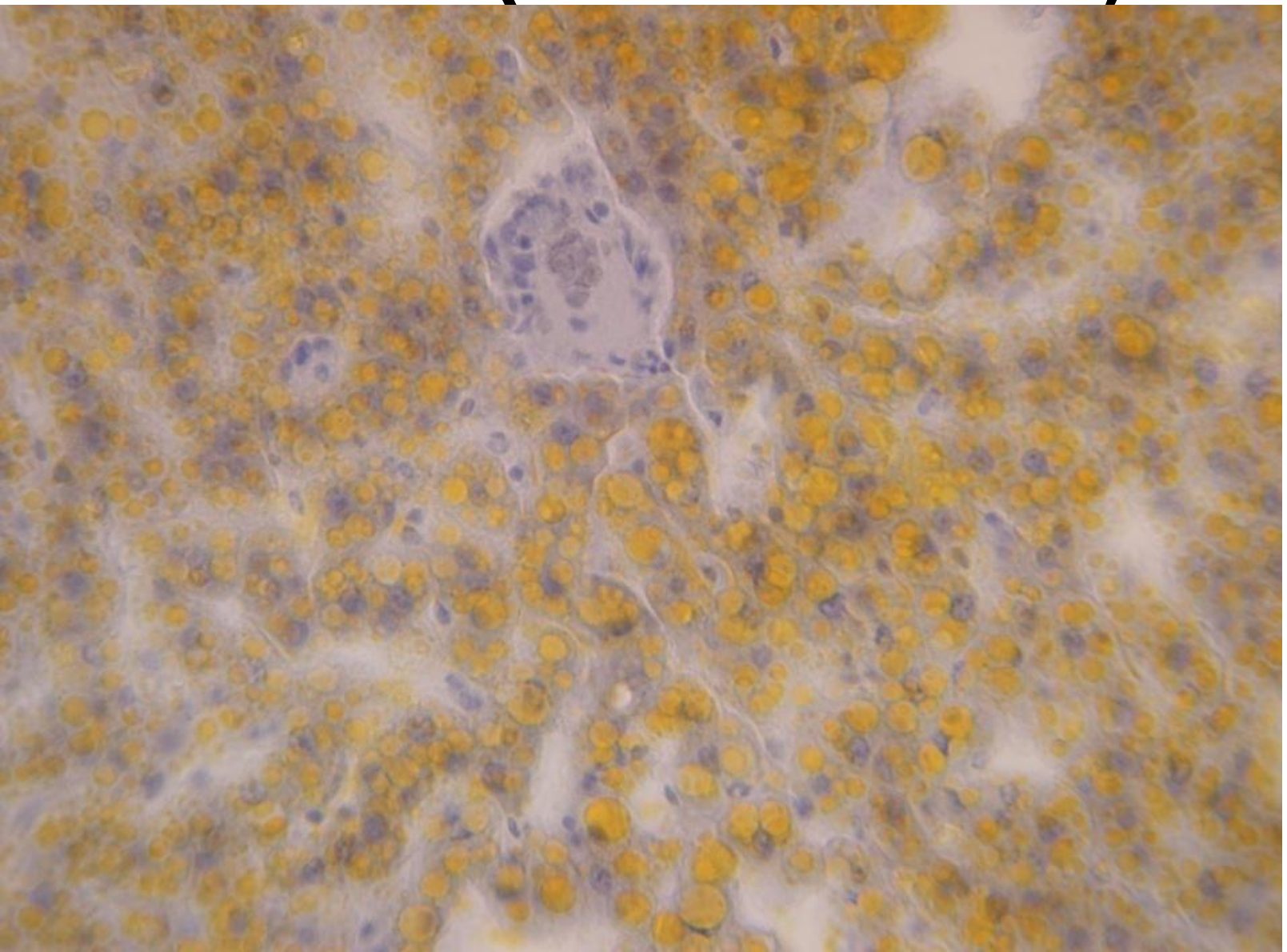
Histochemical stains for identification of fats:

- Sudan III - red-orange color (frozen sections),
- Sudan IV, V - black color,
- Nile blue sulphate - blue or red.

Fatty Liver.
Sudan III (frozen section). X 100.

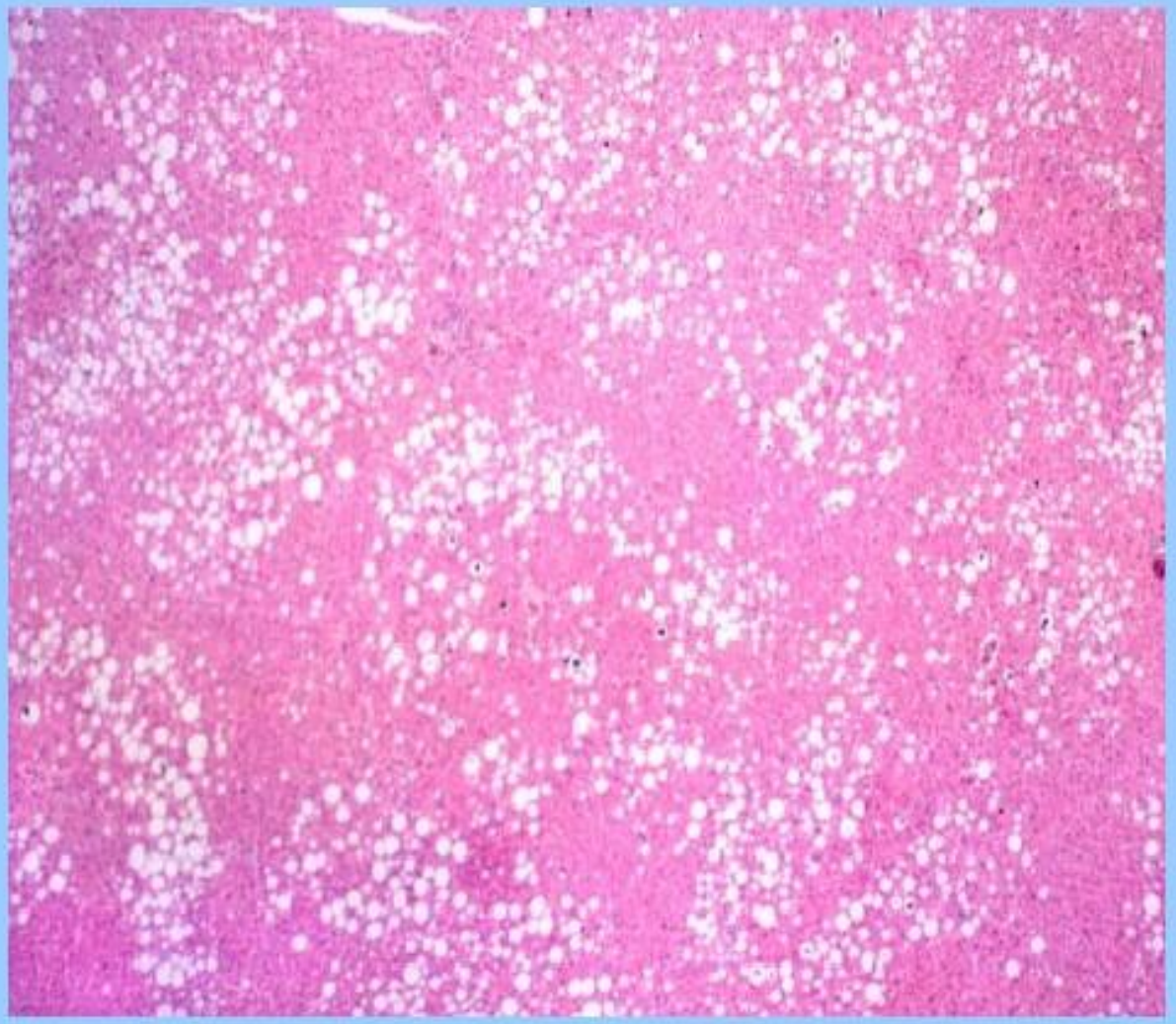


Fatty Liver.
Sudan III (frozen section). X 400



FATTY PHANEROSIS-LIVER

- Fatty phanerosis is the unmasking of invisible fat.
- Lipid accumulates in the liver cells, mainly in the form of triglycerides.



FATTY CHANGES IN THE HEART

ETIOLOGY HYPOXIA, INTOXICATION .

PATHOGENESIS LACK of OXYGEN LEAD TO

decreasing oxidative phosphorylation

anaerobic glycolysis decreasing ATP synthesis mitochondria destruction

inhibition of fatty acid oxidation

toxins cause severe damage of membranes and enzyme systems

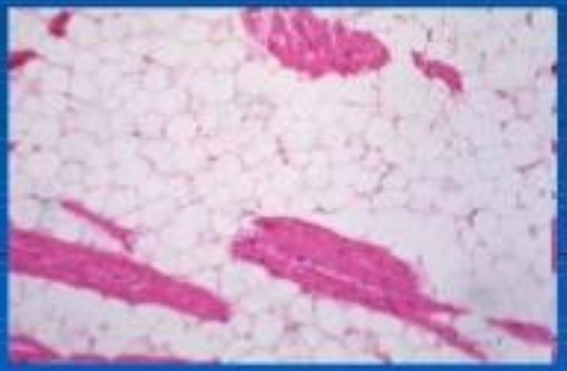
Prolonged moderate hypoxia results in focal intracellular fat deposits

APPEARANT BANDS OF YELLOWED MYOCARDIUM ALTERNATING WITH

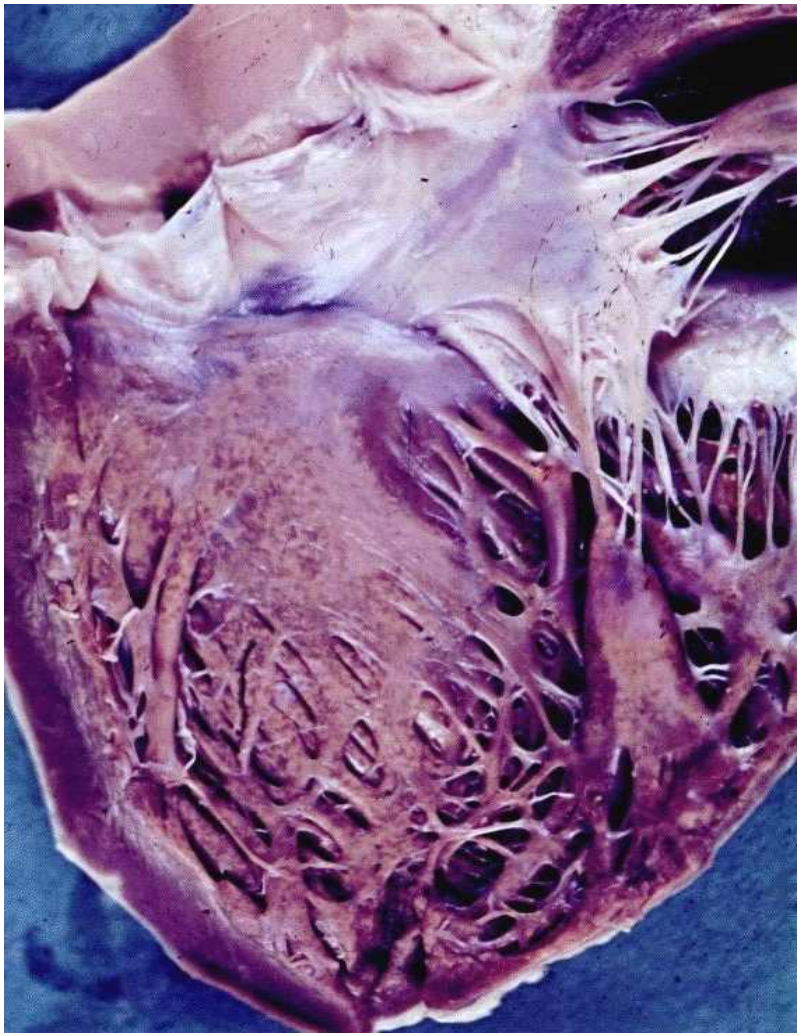
BANDS OF DARKER, RED BROWN UNINVOLVED HEART TIGERET EFFECT´ ± TIGER HEART

Severe fatty change is produced by profound hypoxia with diffused yellow±colored

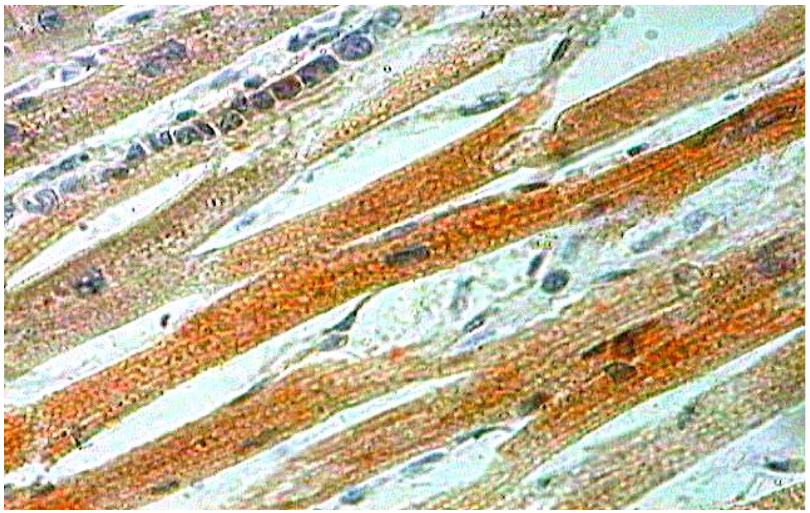
myocardium



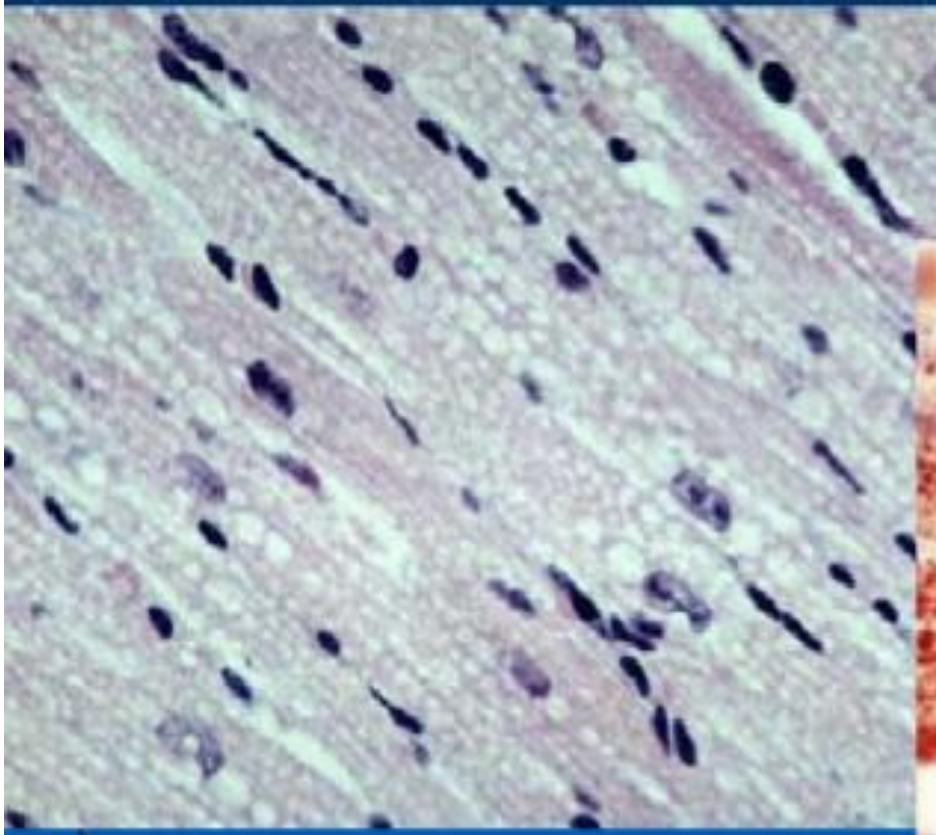
Fatty changes in the heart



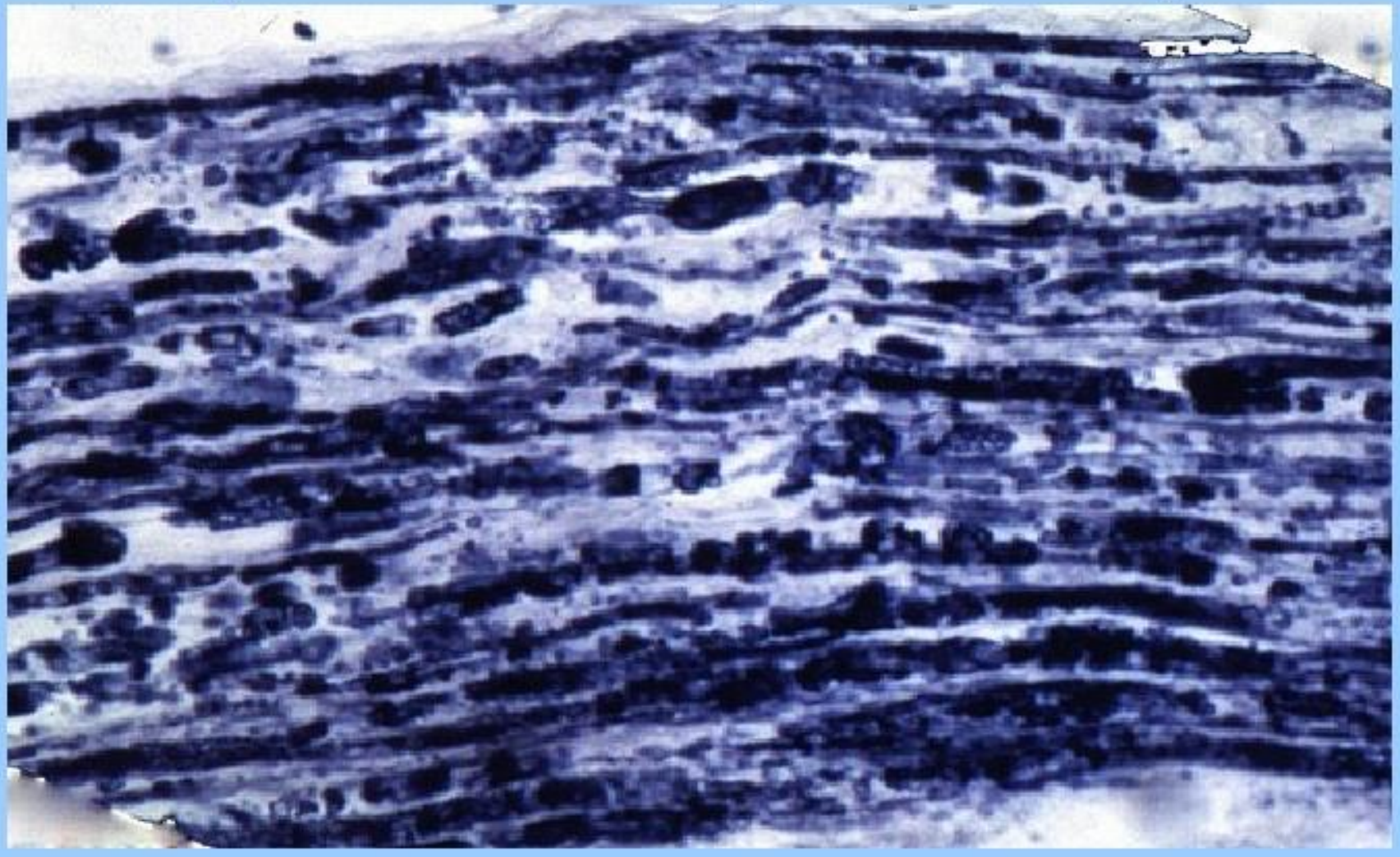
- «Tiger» heart.



FATTY CHANGES IN THE HEART



FATTY DEGENERATION
(Wallerian degeneration)



Fatty degeneration of the kidneys

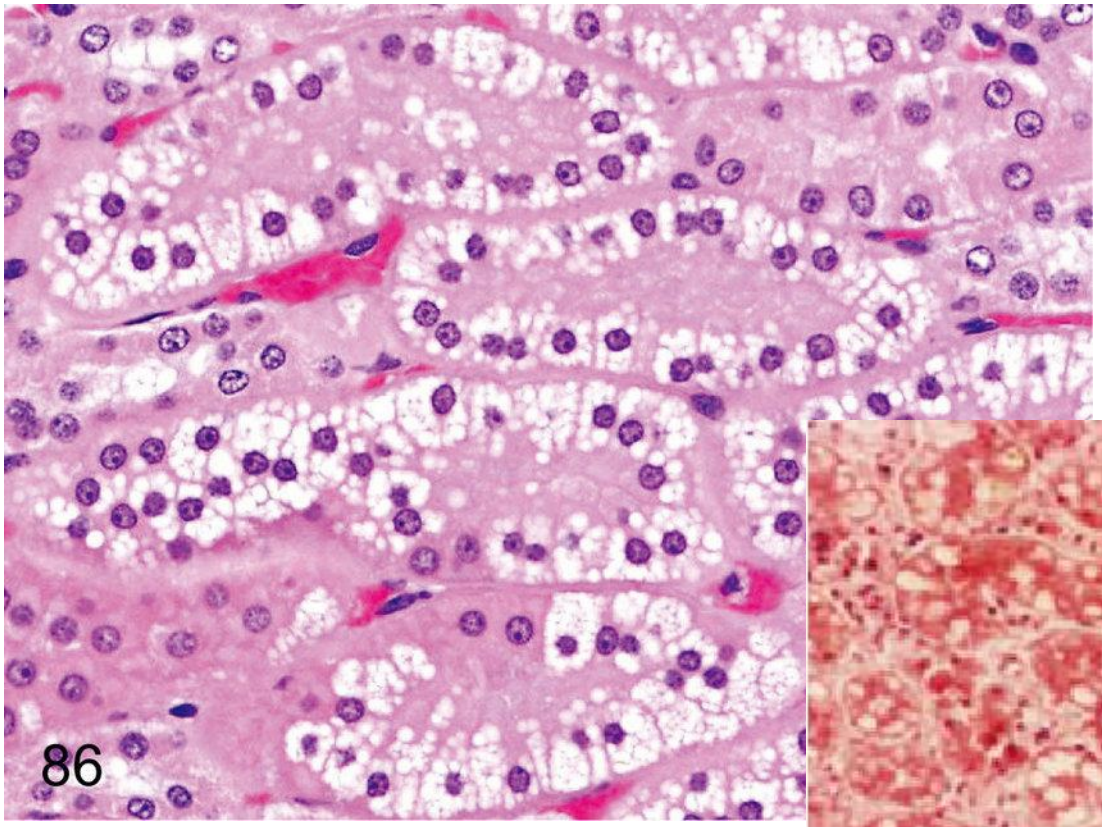
- Under physiological conditions, neutral fats can be found in the epithelium of the narrow segment and collecting ducts.

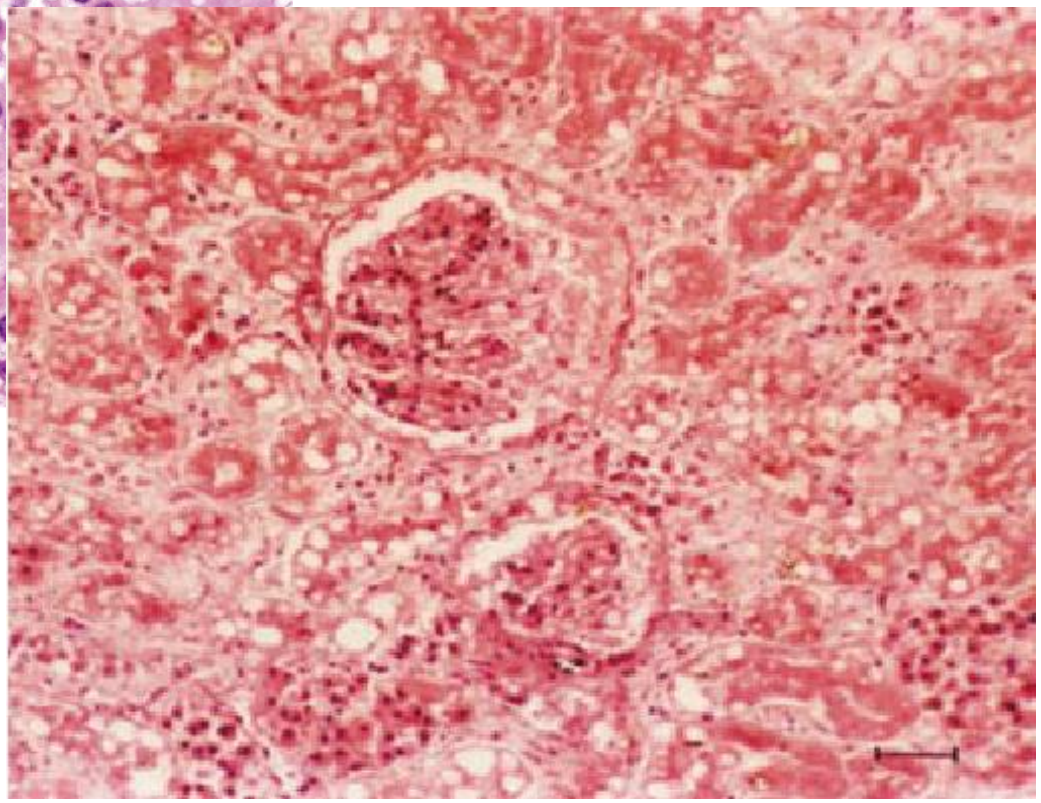
- With the development of fatty degeneration of the kidneys, lipids (neutral fats, cholesterol and its esters, phosphatides) appear in the epithelium of the main divisions of the tubules.

- The most common cause is nephrotic syndrome or chronic renal failure.

- In addition, lipids can accumulate in the epithelium of the kidney tubules in diabetes mellitus, under the influence of phosphorus, carbon tetrachloride, aflatoxin B1.

Fatty degeneration of the kidneys





Stromal-vascular lipidosis

- Stromal-vascular lipidosis includes a violation of the metabolism of fatty tissue and fat depots and a violation of the metabolism of fat (cholesterol and its esters) in the walls of large arteries in atherosclerosis.

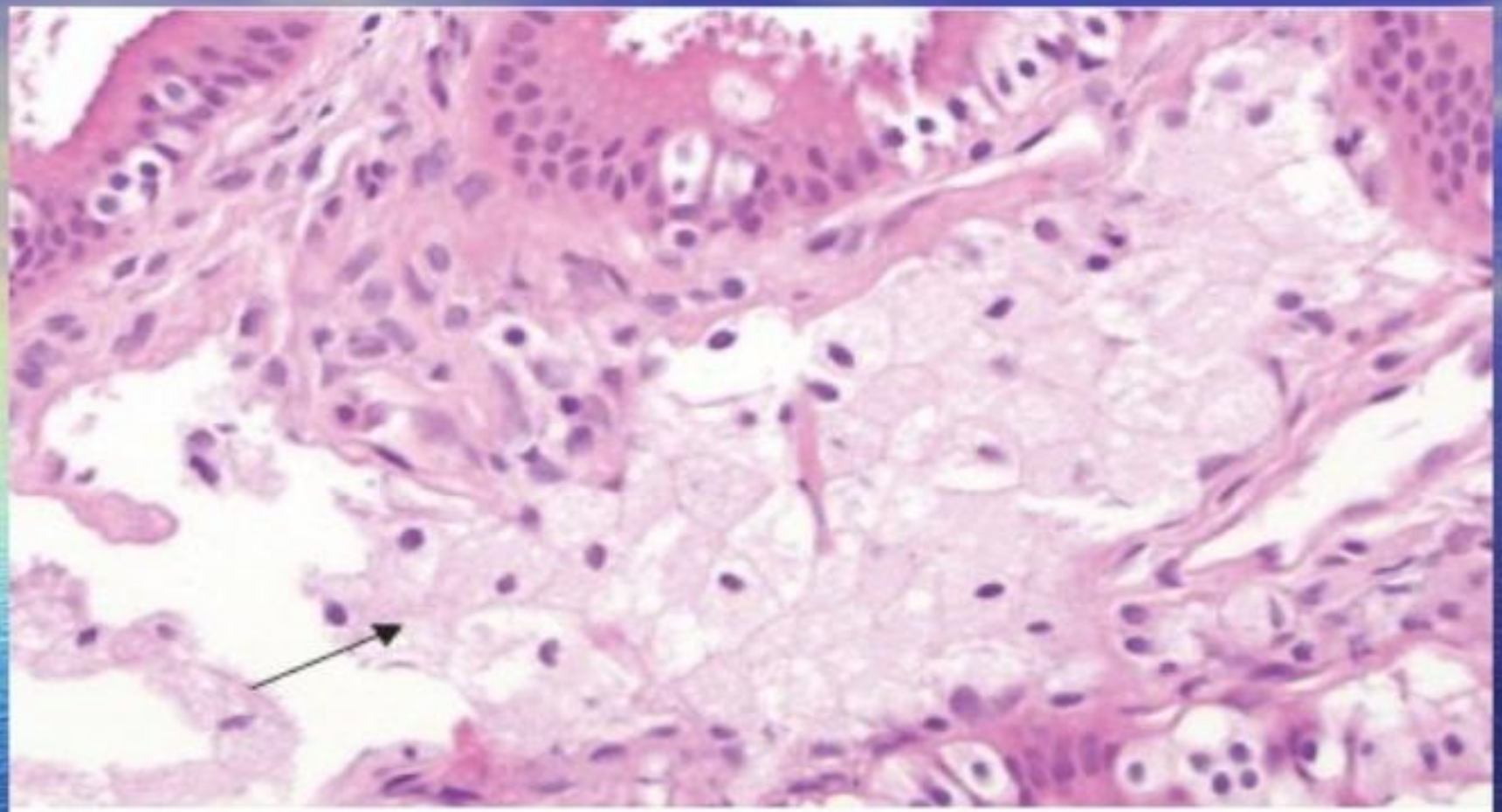
- Excess body weight by 15-20% of the average constitutional, accompanied by an increase in the amount of fat in fat depots: subcutaneous adipose tissue, mesentery, omentum, epicardium, bone marrow, is called ***obesity***.

- A local increase in the amount of fat in the depot (usually subcutaneous tissue) is called ***lipomatosis***.

Cholesterol and Cholesterol Esters

- Accumulations, manifested histologically by intracellular vacuoles, seen in several pathologic processes.

  -i.e. *Cholesterolosis.* Refers to the focal accumulations of cholesterol-laden macrophages in the lamina propria of the gallbladder. The mechanism of accumulation is unknown.

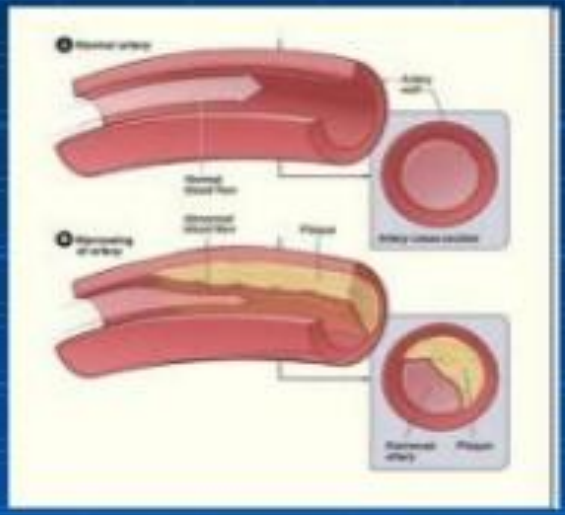


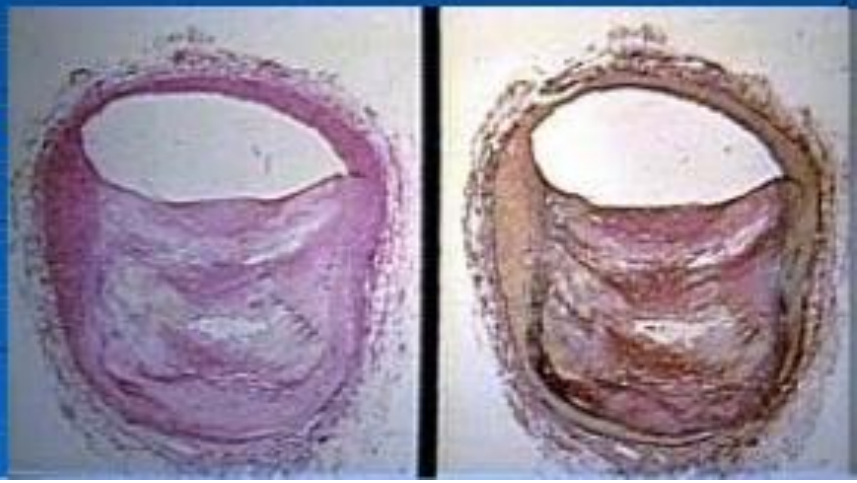
- Figure 1-37 Cholesterolosis. Cholesterol-laden macrophages (foam cells) from a focus of gallbladder cholesterolosis (*arrow*).

FATTY CHANGES IN THE AORTAAND LARGE ARTERY

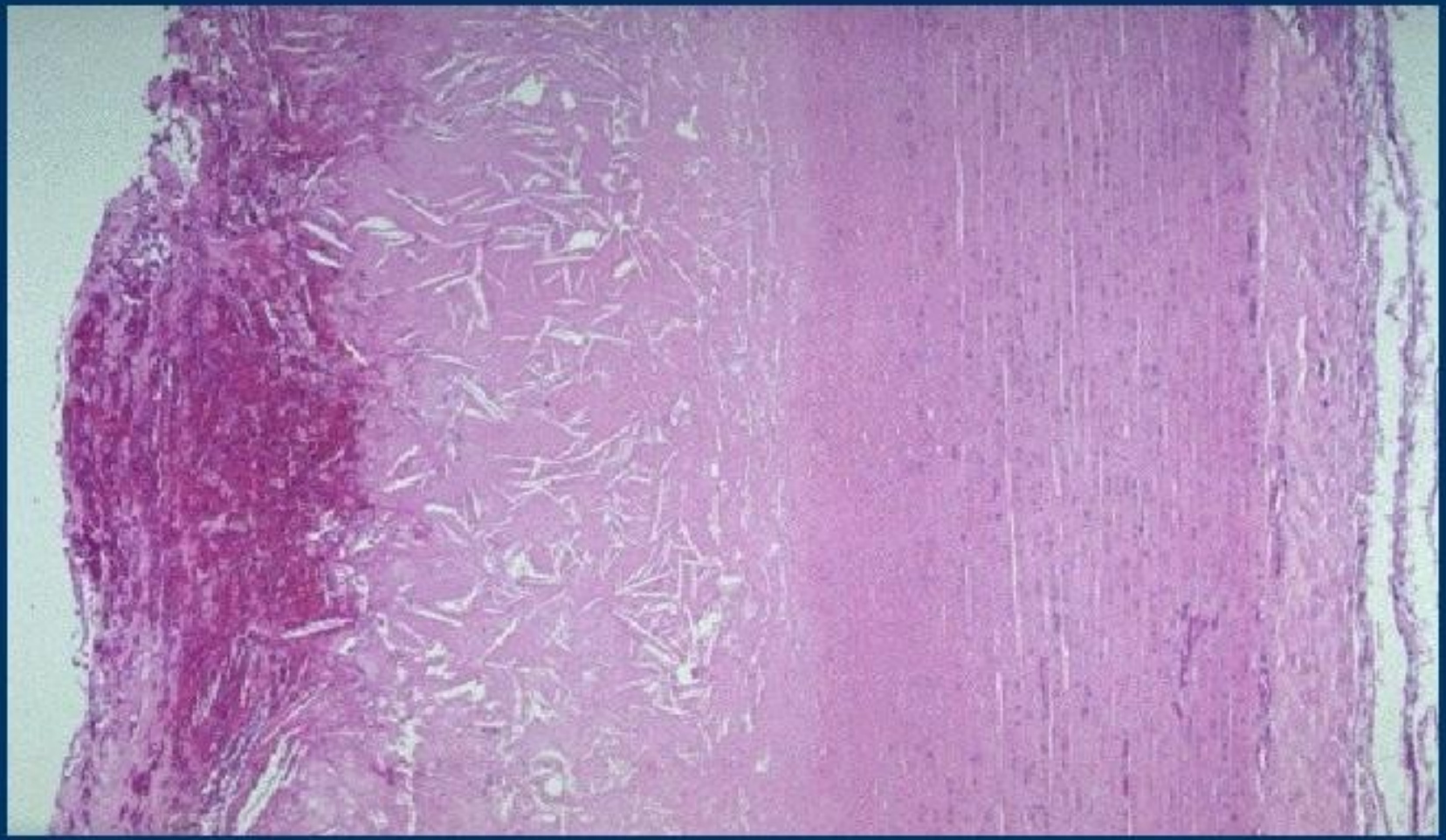
Atherosclerotic plaque contains cholesterol and its esters within macrophages and smooth muscle cells (foam cells).

After cell death, cholesterol and its esters are seen out of cells.



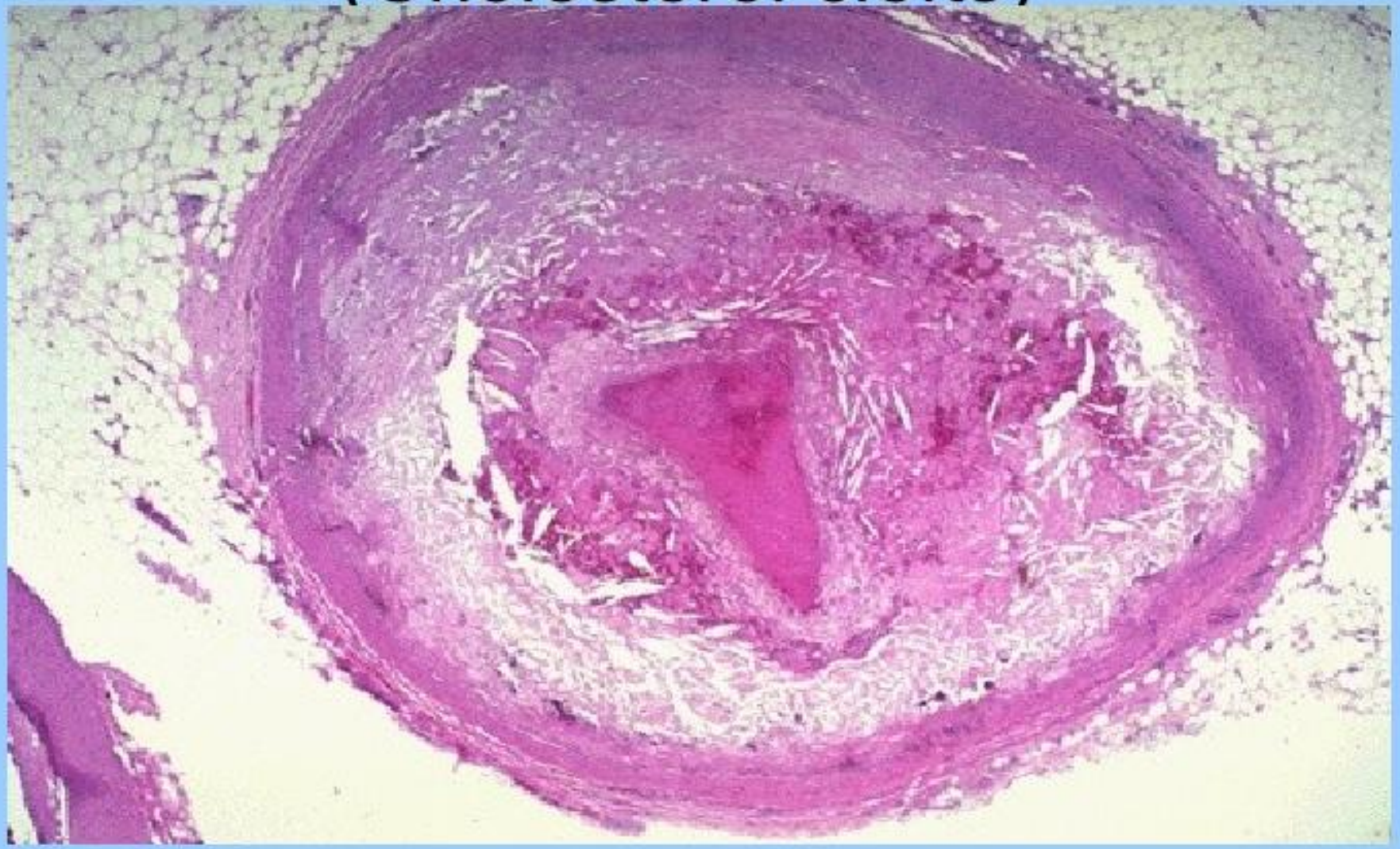


LIPOIDAL DEGENERATION-AORTA



LIPOIDAL DEGENERATION

(Cholesterol clefts)



PARENCHYMATOUS CARBOHYDRATE DYSTROPHIES

Carbohydrates Determined in Cells and Tissues:

1. polysaccharides, of which only glycogen is detected in animal tissues,
2. glycosaminoglycans (mucopolysaccharides) and
3. glycoproteins.

- ***Glycosaminoglycans*** are neutral, strongly associated with proteins, and acidic, which include hyaluronic, chondroitinsulfuric acids and heparin.
- ***Acid glycosaminoglycans*** as biopolymers are capable of entering into fragile compounds with a number of metabolites and transporting them.
- ***Glycoproteins*** are mucins and mucoids.
- *Mucins* form the basis of mucus produced by the epithelium of the mucous membranes and glands,
- *mucoids* are part of many tissues.

- Polysaccharides, glycosaminoglycans and glycoproteins are detected by the ***PAS reaction.***

Carbohydrate dystrophies associated with impaired glycogen metabolism

- The main stores of glycogen are in the liver and skeletal muscles.
- Liver and muscle glycogen is consumed depending on the body's needs ***(labile glycogen***).
- Glycogen of nerve cells, the conducting system of the heart, aorta, endothelium, epithelial integument, uterine mucosa, connective tissue, embryonic tissues, cartilage and leukocytes is a necessary component of cells, and its content does not undergo noticeable fluctuations (***stable glycogen***).
- division of glycogen into labile and stable conditionally.
- Regulation of carbohydrate metabolism - by the neuroendocrine pathway.
- The main role belongs to the hypothalamic region, the pituitary gland (ACTH, thyroid-stimulating, somatotropic hormones), the β-cells of the pancreas (insulin), the adrenal glands (glucocorticoids, adrenaline) and the thyroid gland.

Carbohydrate dystrophies associated with impaired glycogen metabolism

Disorders of glycogen content:

1. a decrease in the amount of glycogen in the tissues,
2. an increase in the amount of glycogen in the tissues,
3. The appearance of glycogen where it is usually not detected.

- These disorders are most pronounced in diabetes mellitus and in hereditary carbohydrate dystrophies - glycogenosis.

Carbohydrate dystrophies associated with impaired glycogen metabolism

- Diabetes mellitus

- the development of the disease is associated with pathology (β-islet cells) of the pancreas,
- there is an insufficient use of glucose by tissues, an increase in its content in the blood (hyperglycemia) and excretion in the urine (glucosuria).

- a sharp decrease in tissue stores of glycogen (in the liver - a violation of glycogen synthesis - infiltration of the liver with fats - fatty degeneration of the liver; at the same time, glycogen inclusions appear in the nuclei of hepatocytes, they become light ("perforated", "empty", nuclei).

Carbohydrate dystrophies associated with impaired glycogen metabolism

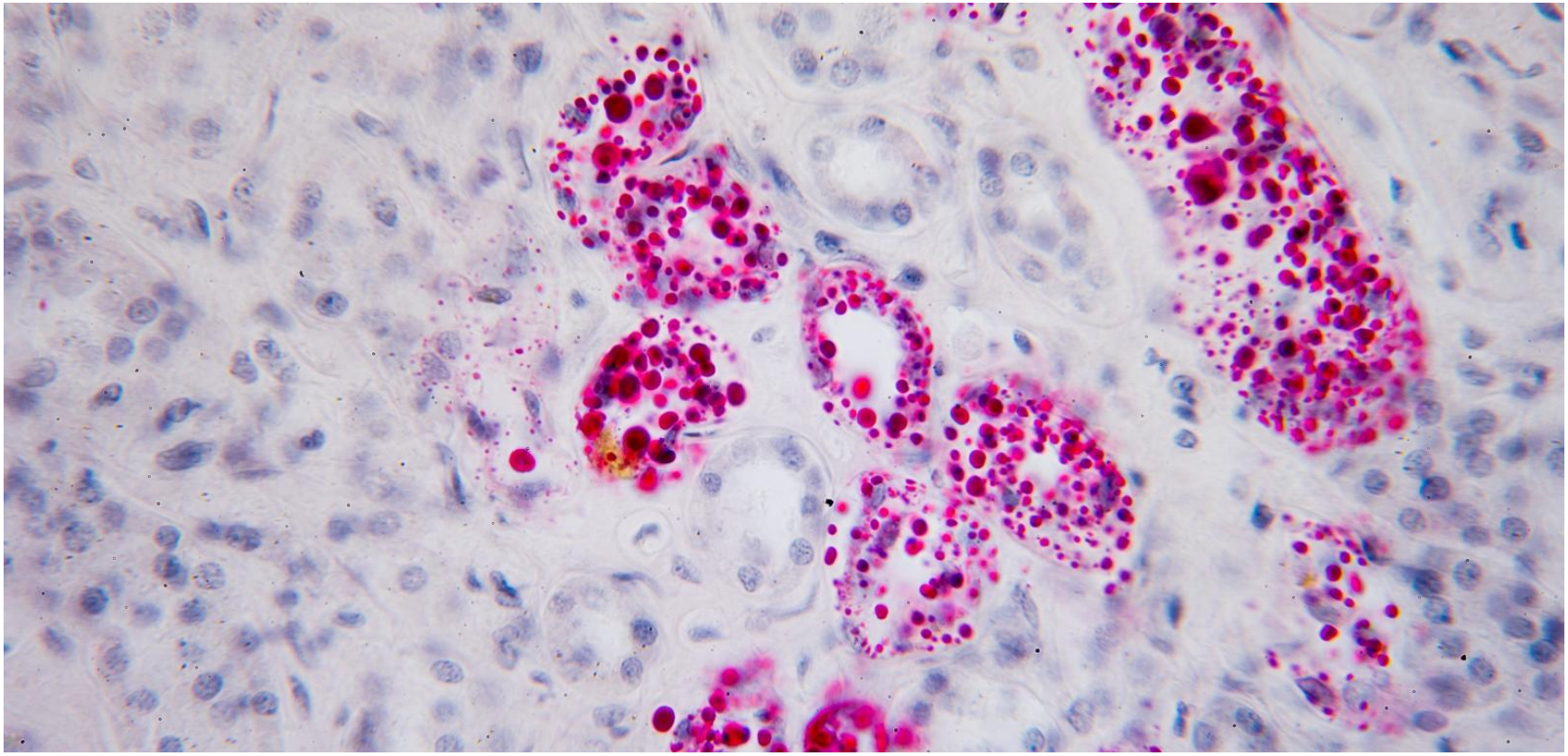
- Diabetes mellitus

- glucosuria - characteristic changes in the kidneys in diabetes: ***glycogenic infiltration of the epithelium of the tubules*** (narrow and distal segments).
- The epithelium is high, with a light foamy cytoplasm; grains of glycogen are also visible in the lumen of the tubules (glucose polymerization in the tubular epithelium during the resorption of glucose-rich plasma ultrafiltrate.
- Changes in the glomeruli - capillary loops, basement membrane - much more permeable to sugars and plasma proteins - intercapillary (diabetic) glomerulosclerosis (as one of the manifestations of diabetic microangiopathy)

Diabetes mellitus

- Hyperglycosemia lead to glycogen accumulation
- within renal tubular
- epithelium Best is stained by
- Carmine Crimson ±
- ±colored granules of glycogen

Glycogenic infiltration of the epithelium of the renal tubules in diabetes mellitus



Carbohydrate dystrophies associated with impaired glycoprotein metabolism

- ***Mucous dystrophy*** is the accumulation of mucins and mucoids, also called mucous or mucus-like substances in violation of the exchange of glycoproteins in cells or in the intercellular substance.

- *Microscopic picture:* increased mucus formation, changes in the physical and chemical properties of mucus.
- Death and desquamation of secreting cells, mucus obstruction of the excretory ducts of the glands - the development of cysts.
- Often in these cases - the addition of inflammation, when the lumens of the bronchi are closed with mucus - the occurrence of atelectasis and foci of pneumonia.

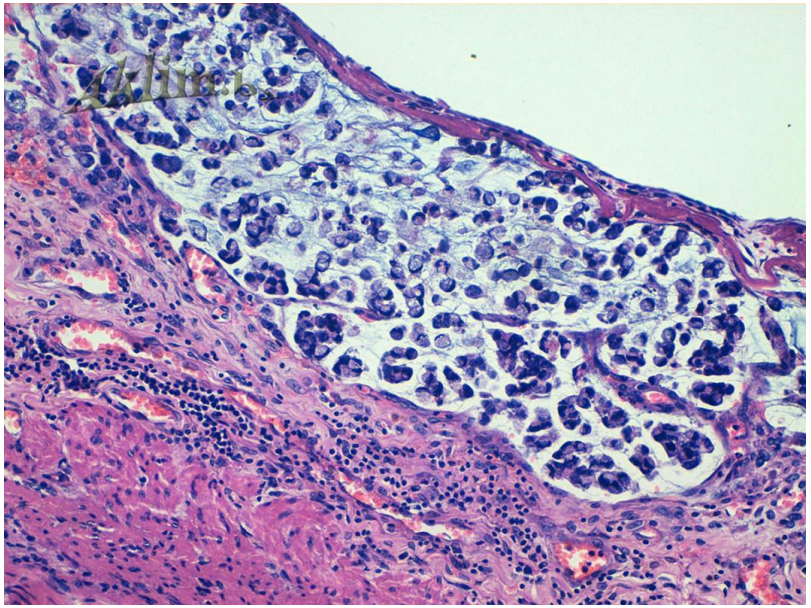
Carbohydrate dystrophies associated with impaired glycoprotein metabolism

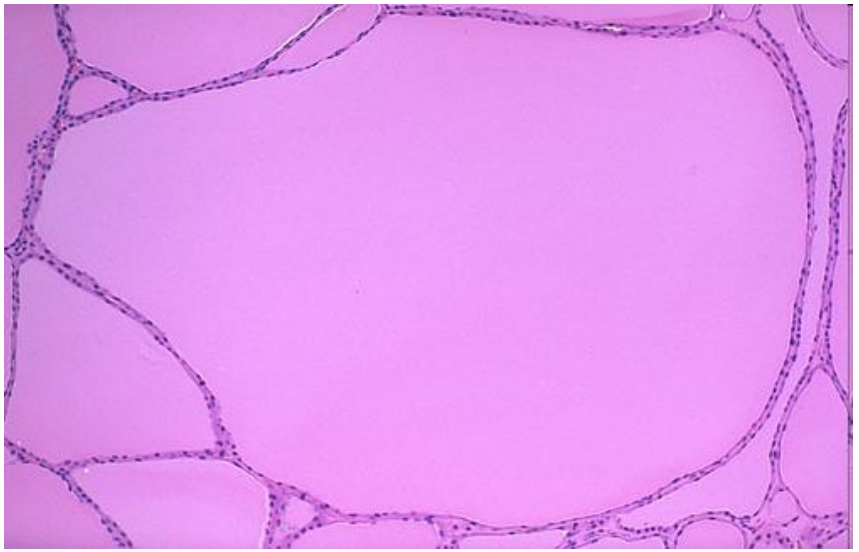
- Sometimes it is not true mucus that accumulates in the glandular structures, but mucus-like substances (pseudomucins).

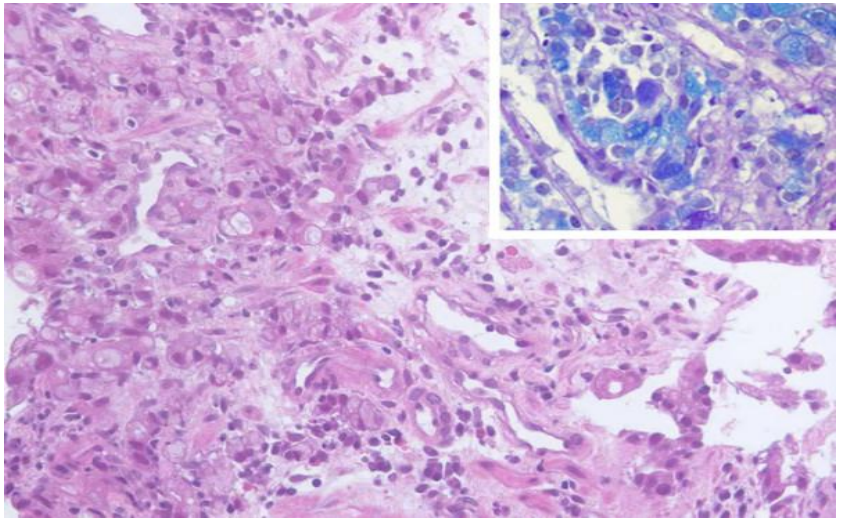
- These substances can thicken and take on the character of a colloid. Then they talk about colloidal dystrophy, which is observed, for example, with colloid goiter.

- The reasons are varied, but more often - inflammation of the mucous membranes as a result of the action of various pathogenic stimuli (Catarrhal inflammation); the formation of mucus in tumor cells.

PARENCHYMATOUS CARBOHYDRATE DYSTROPHIES



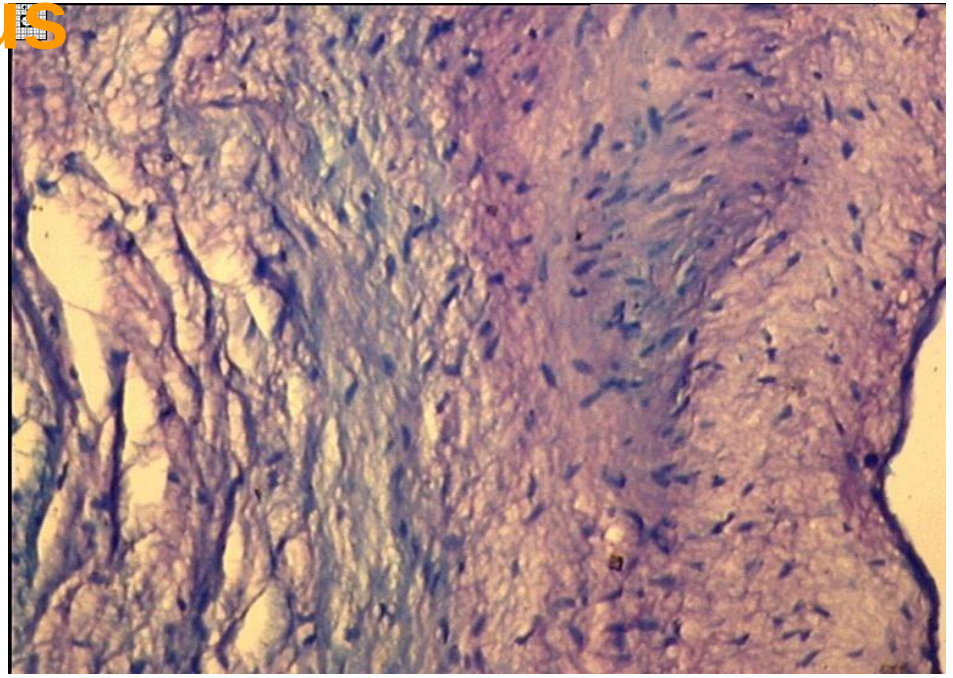


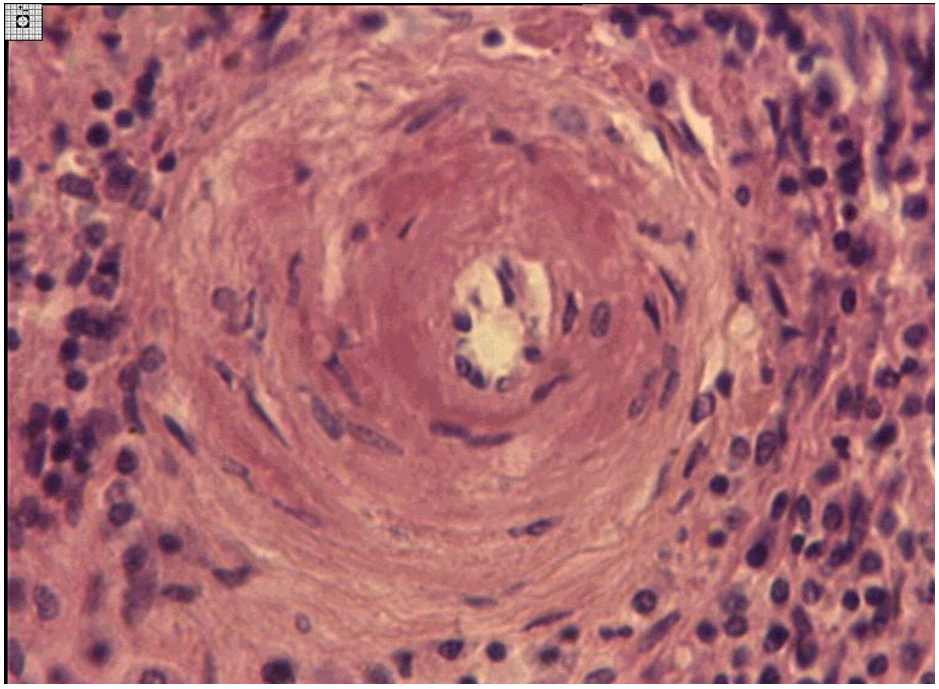


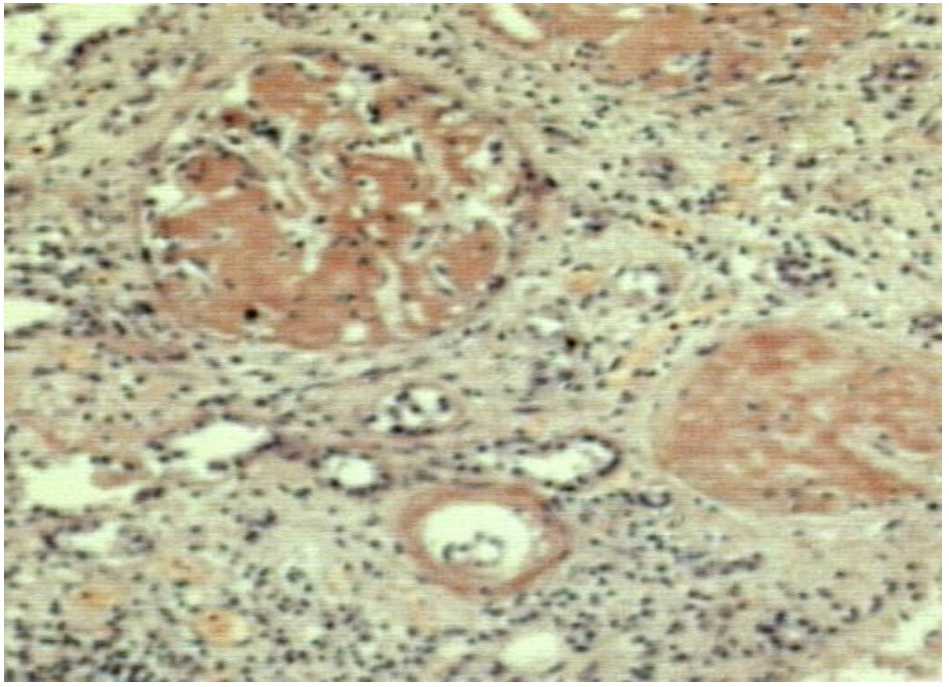
Stroma-vascular degeneration

Extracellular proteinous degenerations

1. Mukoid swelling
2. Fibrinoid changes
3. Hyalynosis
4. Amyloydosis

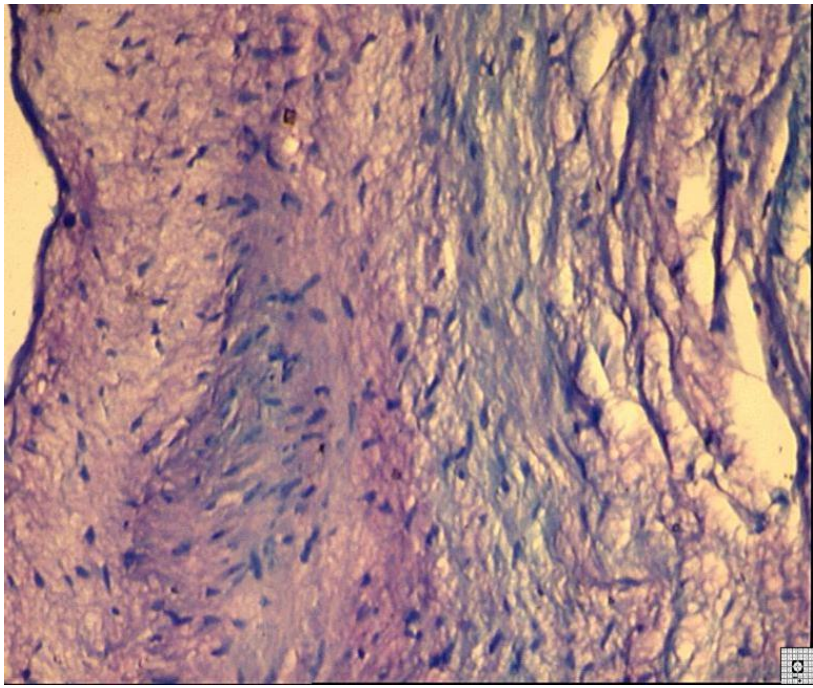






Mucoid swelling

It is reversible disorganization and swelling of perivascular extracellular matrix (disorganization of connective tissue) due to increased vascular permeability, plasmorrhagia and deposition of glucosaminoglycans (GAG).



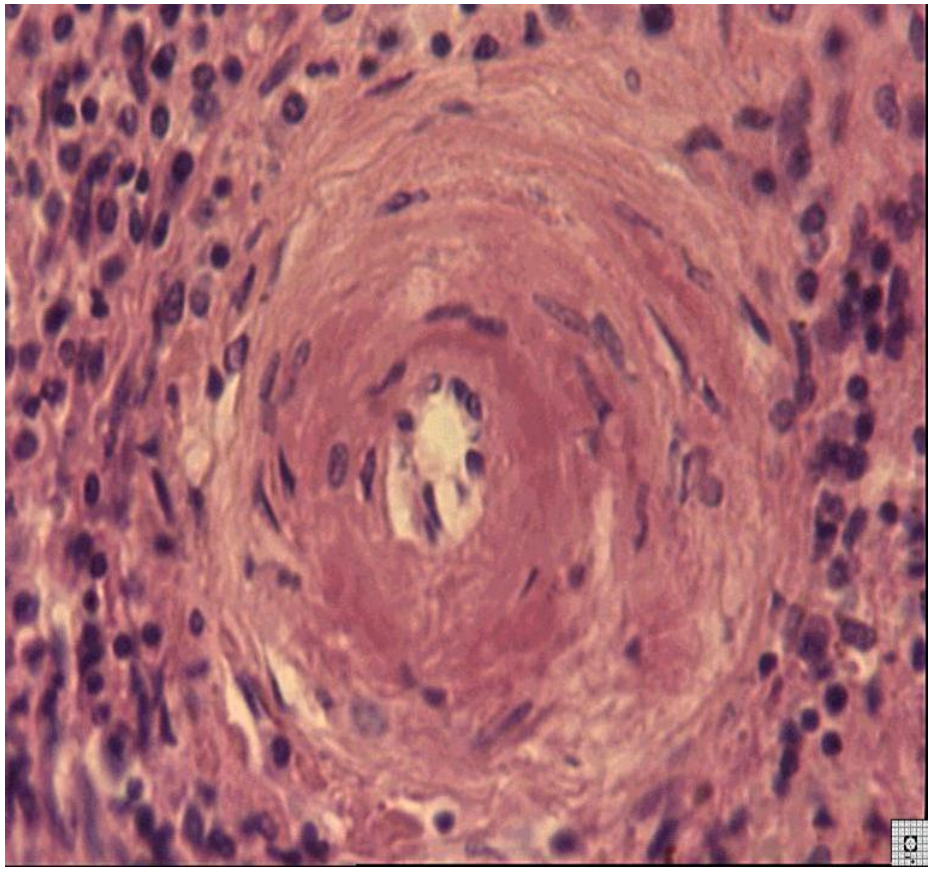
Microscopically: there is the phenomenon of metachromasia. That is basophylic color of basic substances. Collagen fibers save the structure, but swell and undergo to fibrillar destructure.

Gross appearance: tissue or organ is saved.

Process is convertible.

Fibrinoid changes

It is deep and irreversible disorganization of connective tissue, in basis of which destruction of basic substances and fibers. It is accompanied by the sharp increase of permeability of vessels and formation of fibrinoid masses.



Microscopically: the bands of collagen fibers are homogenous, impregnated with plasma proteins.

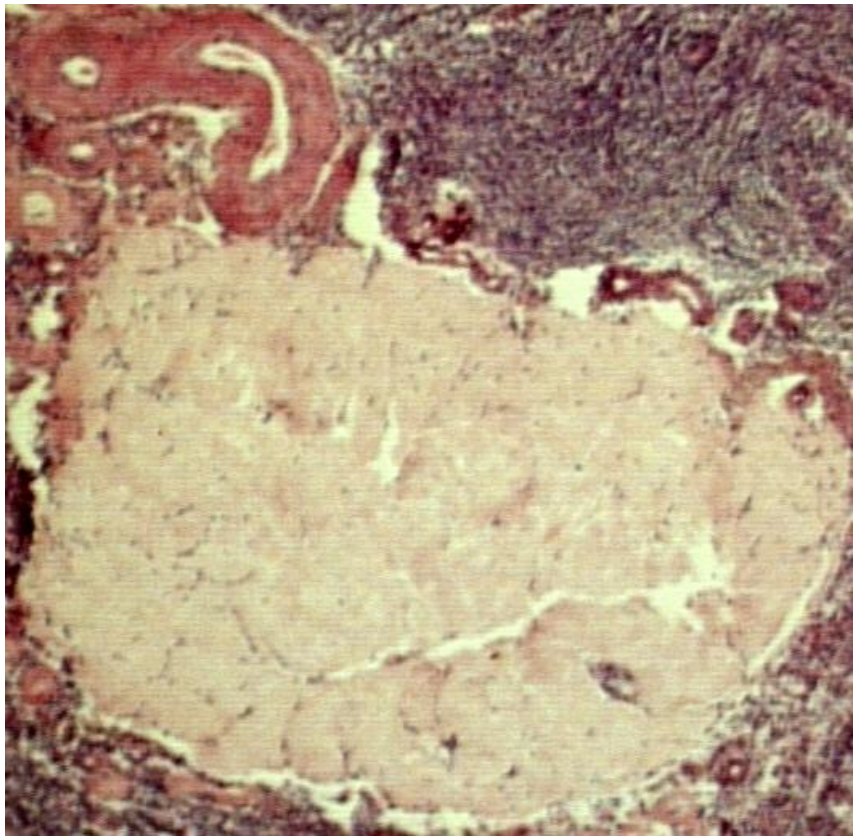
Outcomes: fibrinoid necrosis, hyalinosis, sclerosis.

Hyaline change

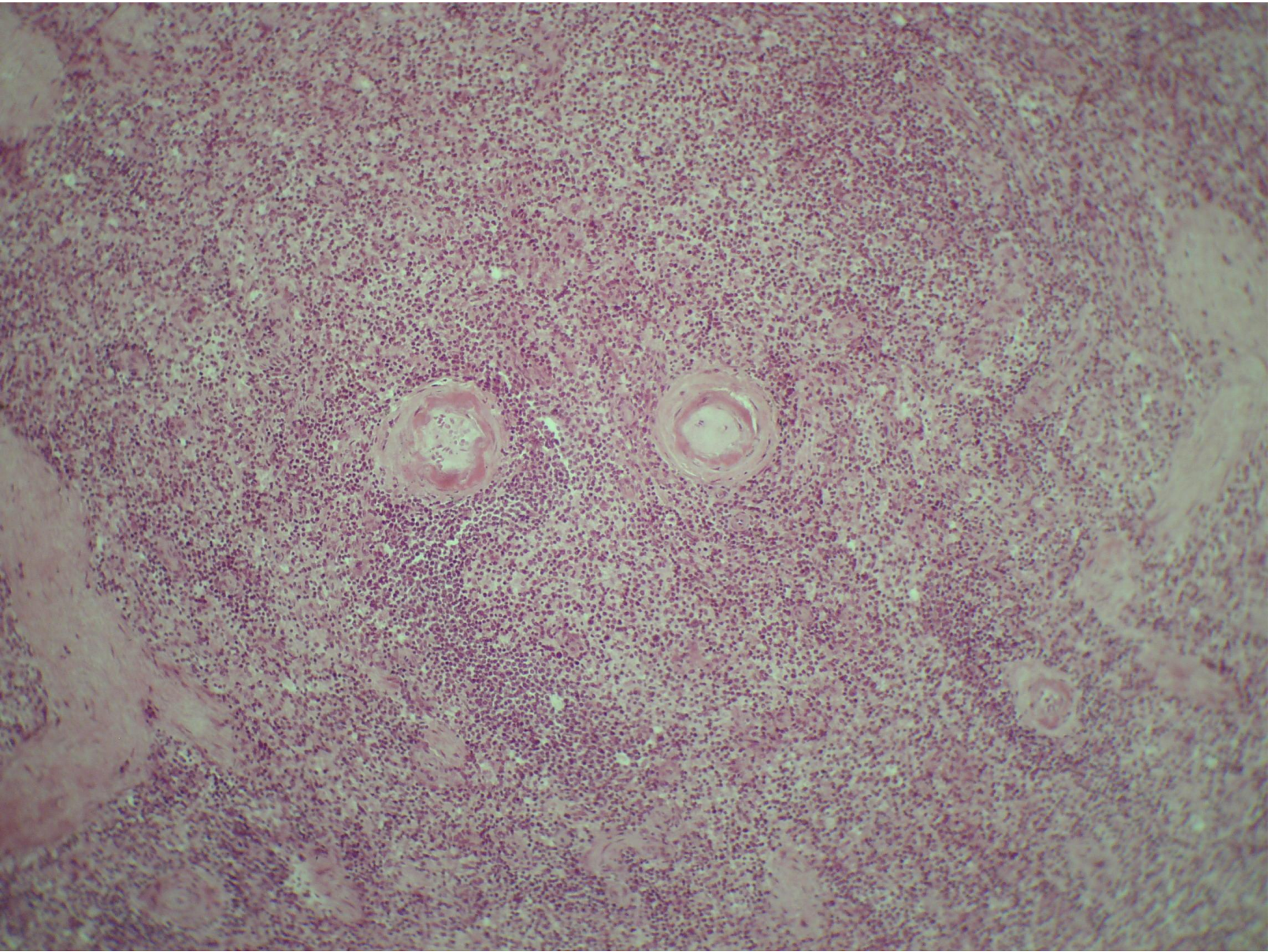
It is an alteration within cells or in the extracellular space, which gives a homogenous, glassy, pink appearance in routine histologic sections stained with H&E.

Hyalinosis is classified according to its localization:

- Vascular hyalinosis (arteries are thickened with sharply narrowed or obliterated lumen)
- Hyalinosis of connective tissue is usually localized; it develops in scars, adhesions, in the areas of chronic inflammation (e.g. *"glazed spleen"*).



Hyalinosis of spleen arteries.
Stained by hematoxilin and eosin. X 100.



The outcome of hyalinosis is irreversible.

Functional significance of hyalinosis is different:

- Vascular hyalinosis may lead to atrophy or sclerosis, infarction of organs.

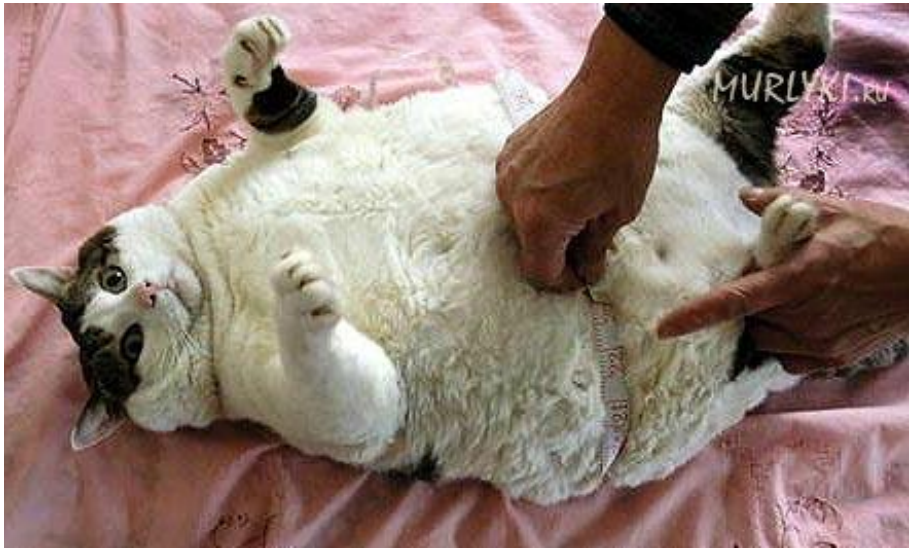
- Local hyalinosis in the cardiac valves results in heart defects.

Stromal vascular lipidoses

- Stromal-vascular lipidoses include a violation of the metabolism of fat, adipose tissue and fat stores and a violation of the metabolism of fat (cholesterol and its esters) in the walls of large arteries in atherosclerosis.

- Excess body weight by 15-20% of the average constitutional, accompanied by an increase in the amount of fat in fat depots: subcutaneous fatty tissue, mesentery, omentum, epicardium, bone marrow, is called ***obesity***.
-
- A local increase in the amount of fat in the depot (more often subcutaneous tissue) is called ***lipomatosis***.

Obesity

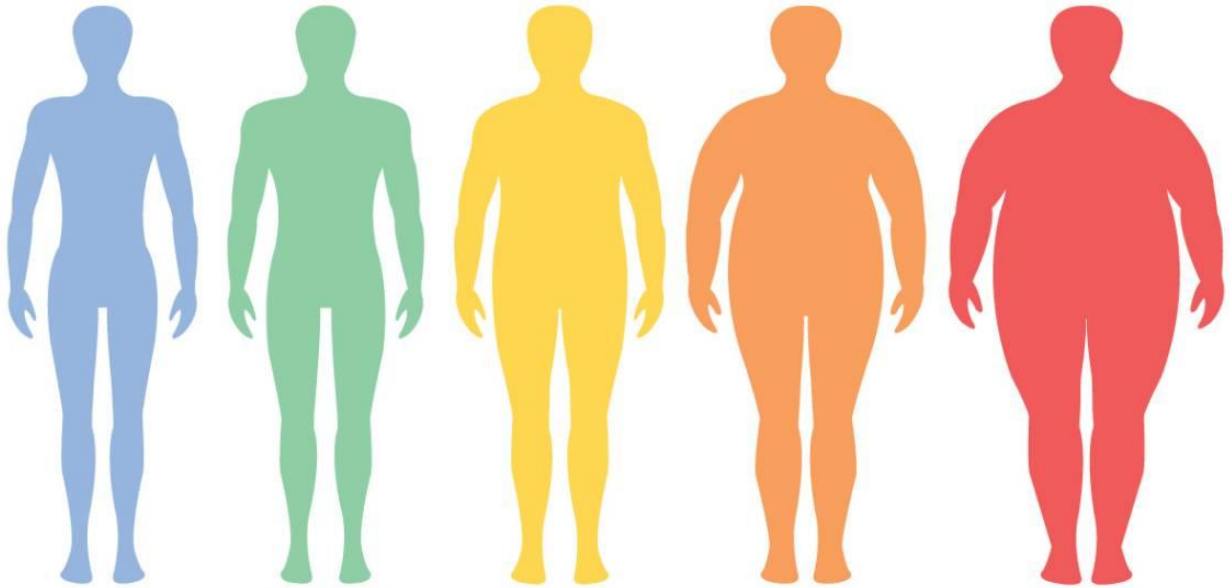


- fat deposition, increase in body weight due to adipose tissue.
- Adipose tissue can be deposited both in places of physiological deposits and in the area of the mammary glands, hips, and abdomen.

When am I obese?

The easiest way to determine whether a person is overweight or obese is through measuring their body mass index (BMI).

$$\text{BMI} = \frac{\text{Weight in kg}}{(\text{Height in m})^2}$$



	Underweight	Normal weight	Overweight	Obese	Morbidly obese
Asians	<18.5	18.5-22.9	23-27.5	27.6-39.9	40 and above
Non-Asians	<18.5	18.5-24.9	25-29.9	30-39.9	40 and above

y Mass Index Interpretation

BMI < 18.5:	Below normal weight
I >= 18.5 and < 25:	Normal weight
MI >= 25 and < 30:	Overweight
MI >= 30 and < 35:	Class I Obesity
MI >= 35 and < 40:	Class II Obesity
BMI >= 40:	Class III Obesity

Predisposing Factors for Obesity

1. Sedentary lifestyle
2. Dehydration
3. Genetic factors, in particular:
   - Increased activity of lipogenesis enzymes
   - Decreased activity of lipolysis enzymes
4. Increased intake of easily digestible carbohydrates:
5. drinking sweet drinksa diet rich in sugars
6. Constantly trying to lose weight through diet
7. Certain diseases, in particular endocrine diseases (hypogonadism, gyrothyroidism, insulinoma)
8. Eating disorders (for example, binge eating disorder), in Russian literature called eating disorders, is a psychological disorder that leads to an eating disorder
9. Tendency to stress
10. Sleep deprivation
11. Psychotropic drugs

Obesity

Depending on the mechanism of development, the following types of obesity are distinguished:

1) alimentary;
2) cerebral (with trauma, brain tumors);
3) endocrine (with Frohlich and Itsenko-Cushing syndrome, adiposogenital dystrophy, hypothyroidism, etc.);
4) hereditary.

Obesity

Obesity stages:

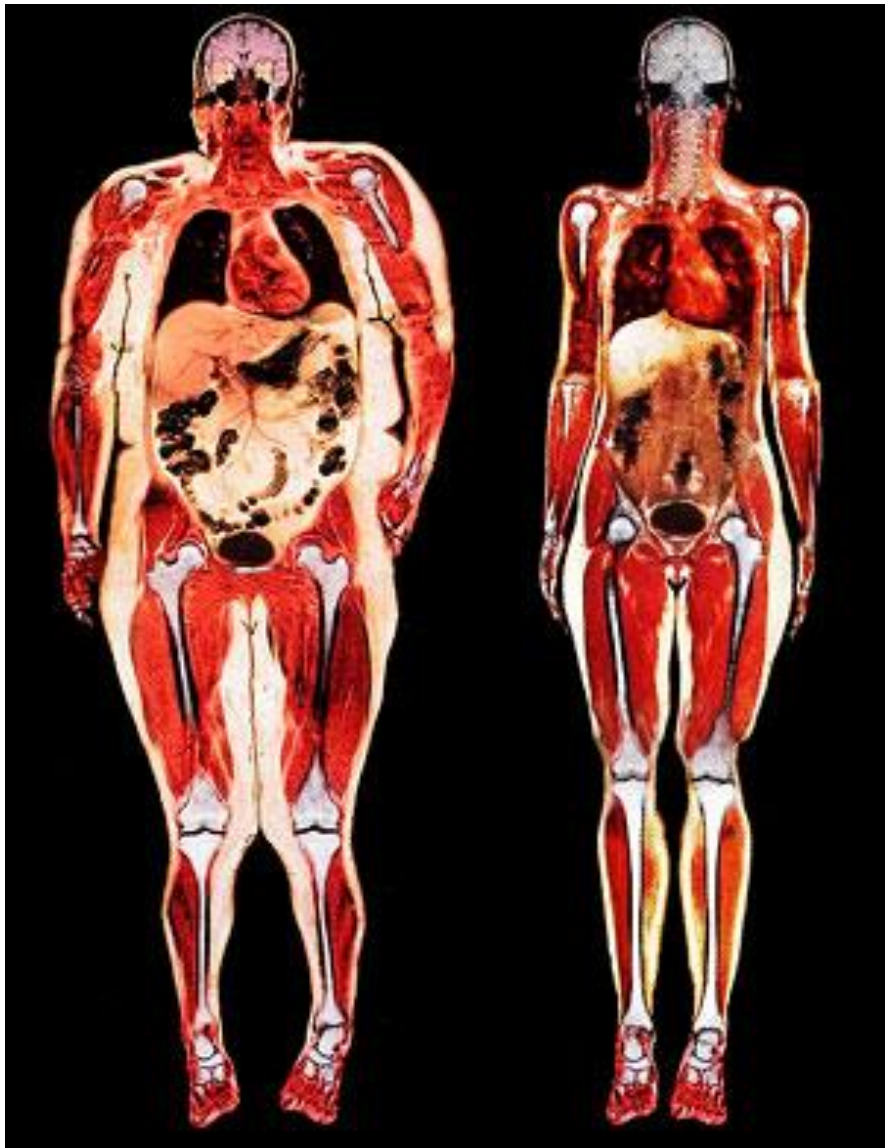
- a) progressive,
- b) stable.

Fat can be located:

1. In the subcutaneous tissue (subcutaneous fat)
2. Around the internal organs (visceral fat).

- Subcutaneous fat in the abdomen + visceral abdominal fat = ABDOMINAL FAT.
- The deposition of fatty tissue in the abdominal region (upper type of obesity, or central obesity) is more clearly associated with morbidity and mortality than lower type of obesity or than the degree of obesity!

Obesity



Obesity

According to the external manifestations of obesity, there are following:

1) Symmetrical type (even distribution of fat);

2) Upper type (face, back of the head, neck, upper shoulder girdle);

3) Medium type (in the abdomen in the form of an apron);

4) Lower type (in the area of the thighs and legs).

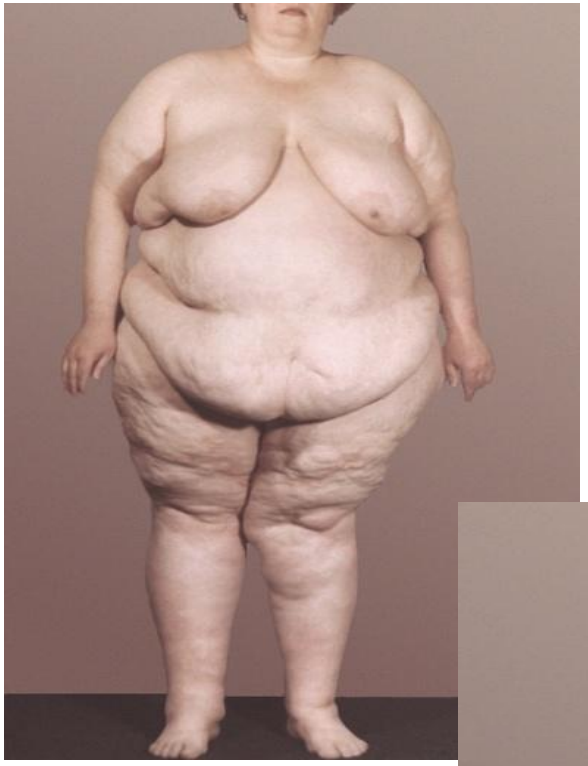
Types of obesity depending on the number of adiposites and their sizes:

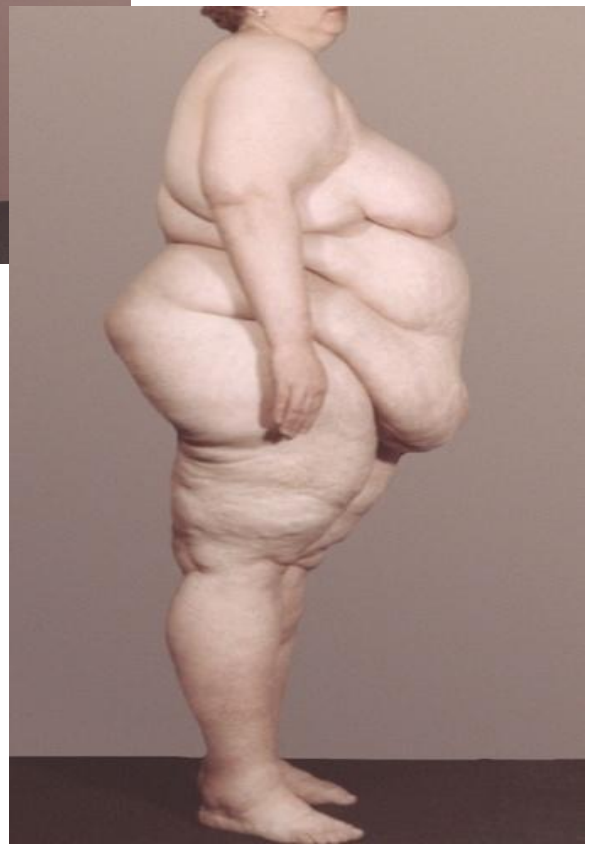
1) hypertrophic variant of general obesity:

- the number of adiposites is not changed;
- adiposites are enlarged and contain several times more triglycerides;
- the course is malignant;

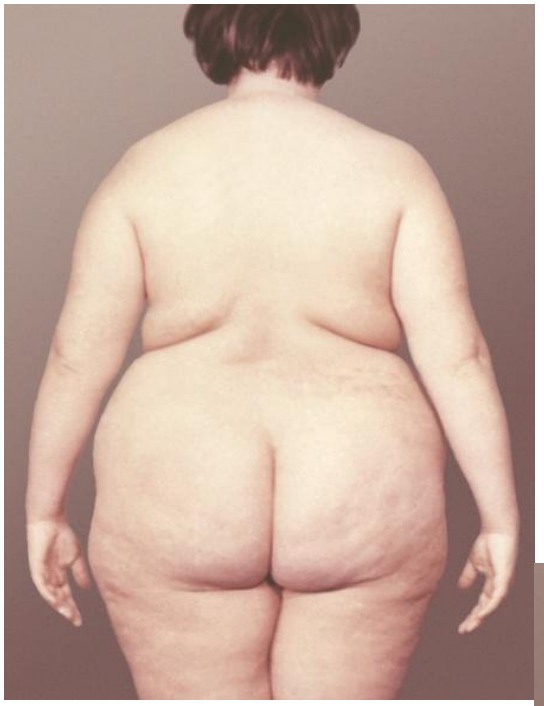
2) ***hyperplastic variant of obesity:***

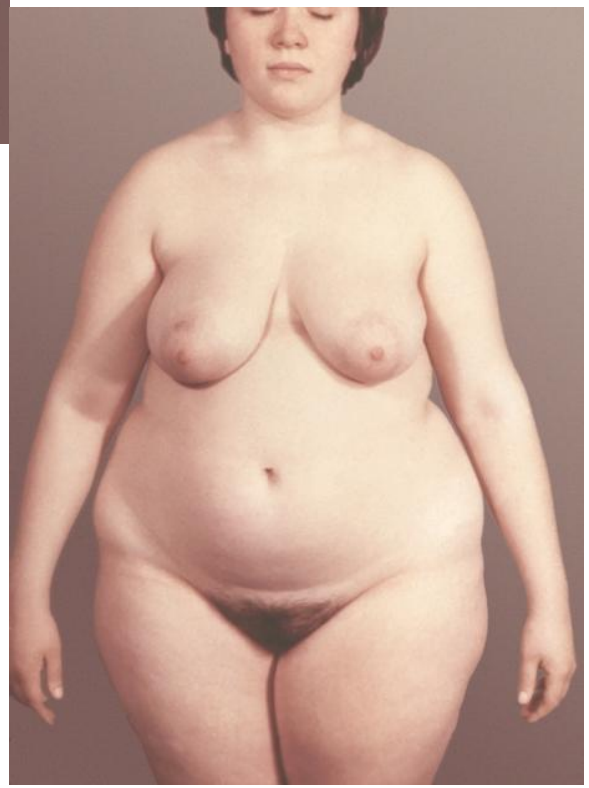
- the number of adiposites is increased;
- the function of adiposites is not impaired;
- the course is benign.





- A patient with pituitary obesity with a predominant deposition of fat on the anterior abdominal wall, hanging in the form of an apron.

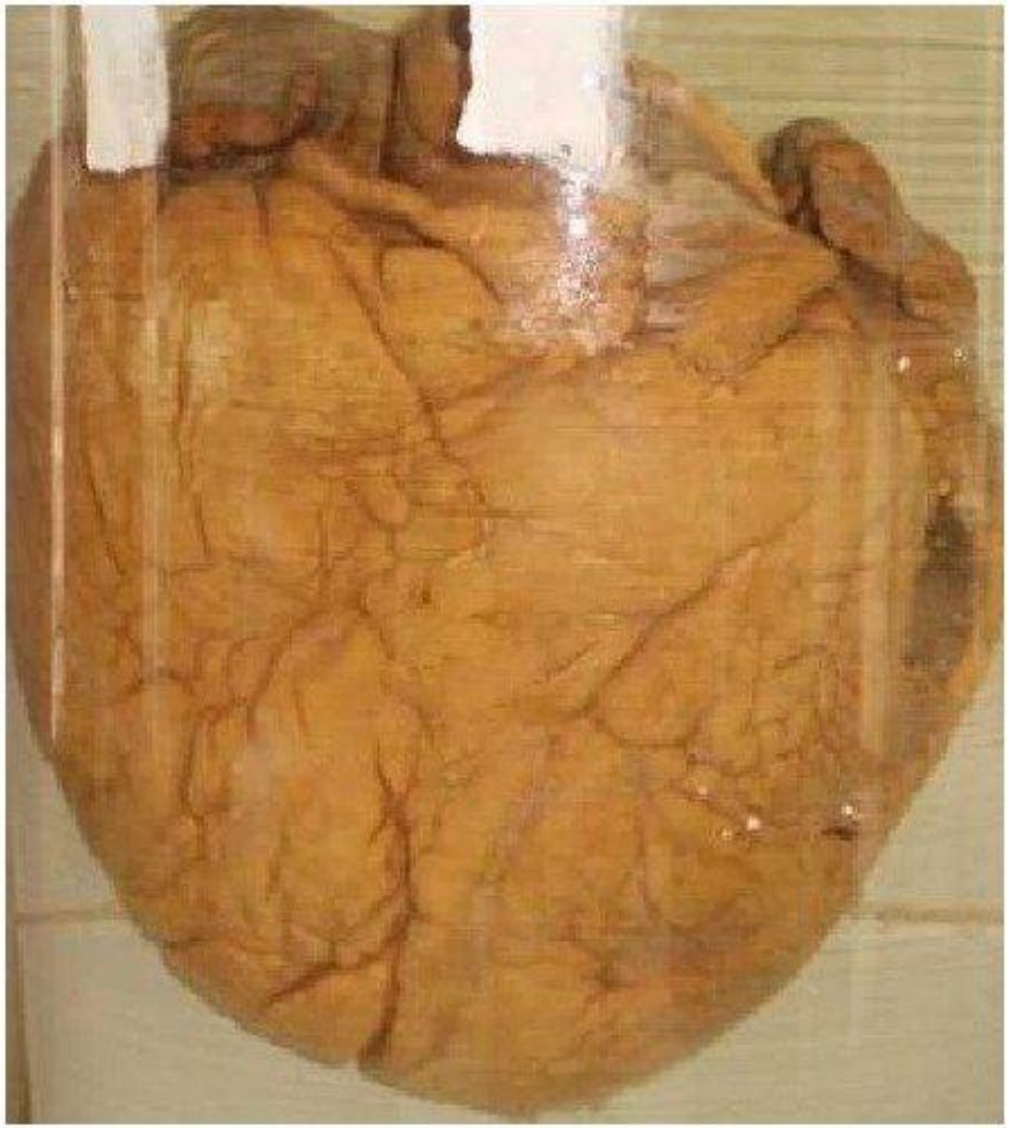




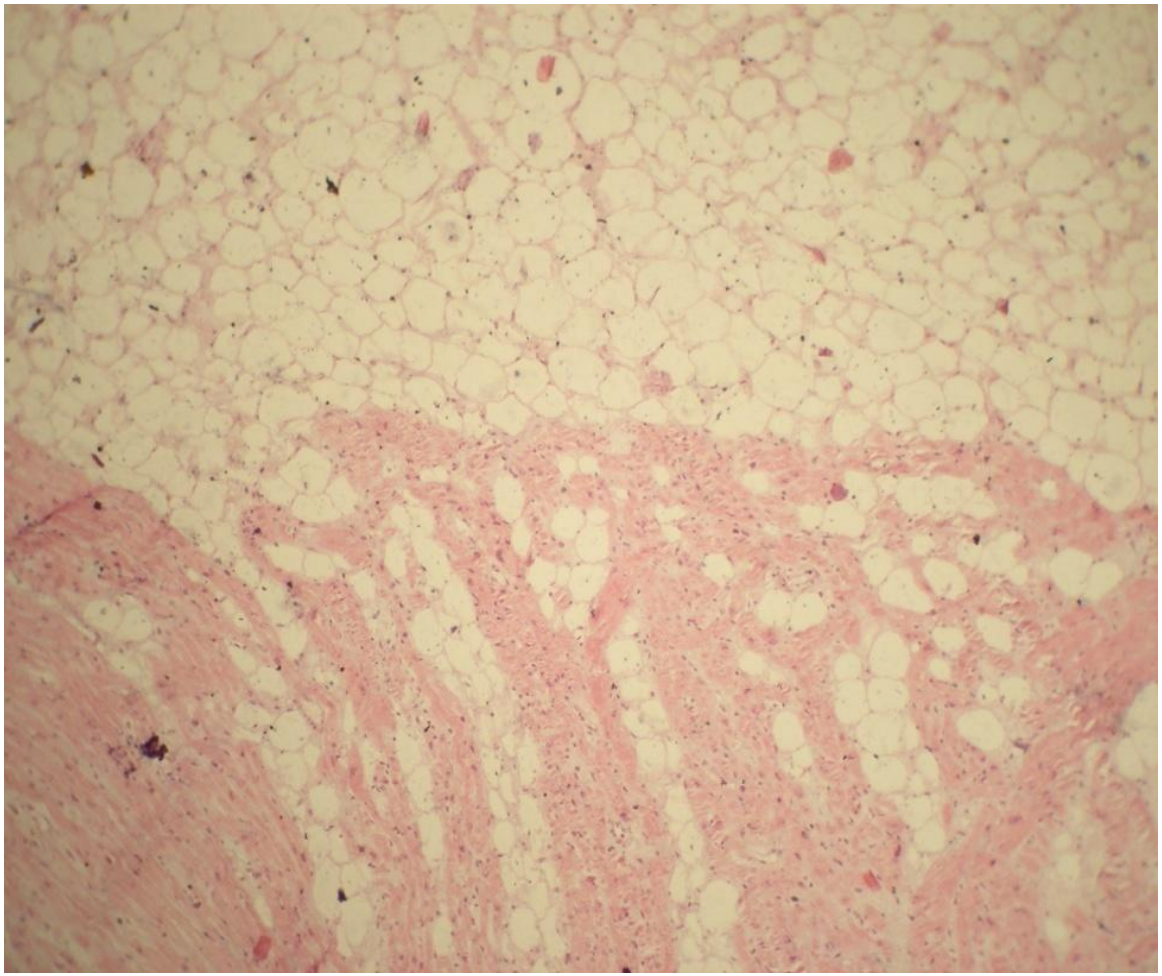
- A patient with exogenous constitutional obesity: relatively even distribution of adipose tissue.

Causes of obesity

Простое ожирение сердца
obesity of a myocardium



Obesity



Simple obesity
of the heart

Complications of obesity

Lipomatosis

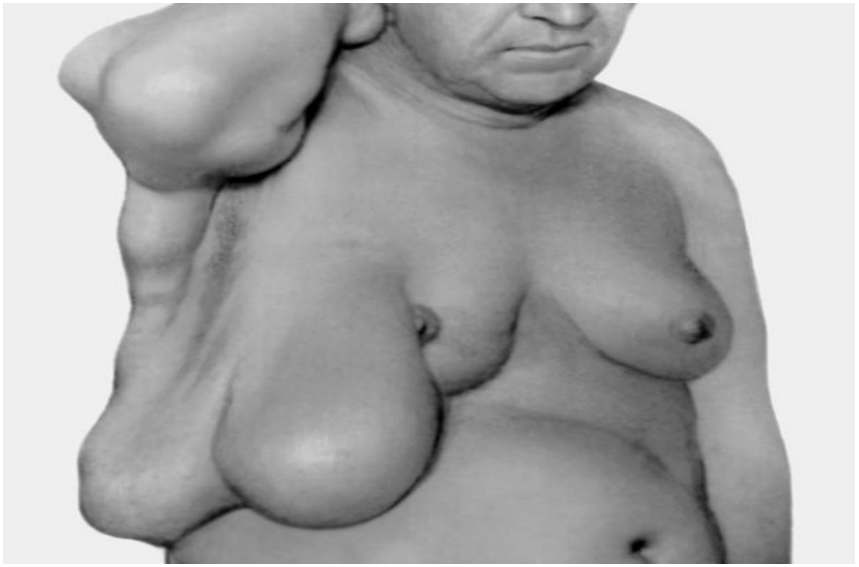
- The increase in the amount of fat in the depot is local in nature;
- Adipose tissue is usually more or less encapsulated, but usually there is no cellular response.
- Lipomatoses include Derkum's disease, Madelung, Roth and Paylaird, Lenu and Benso syndromes.

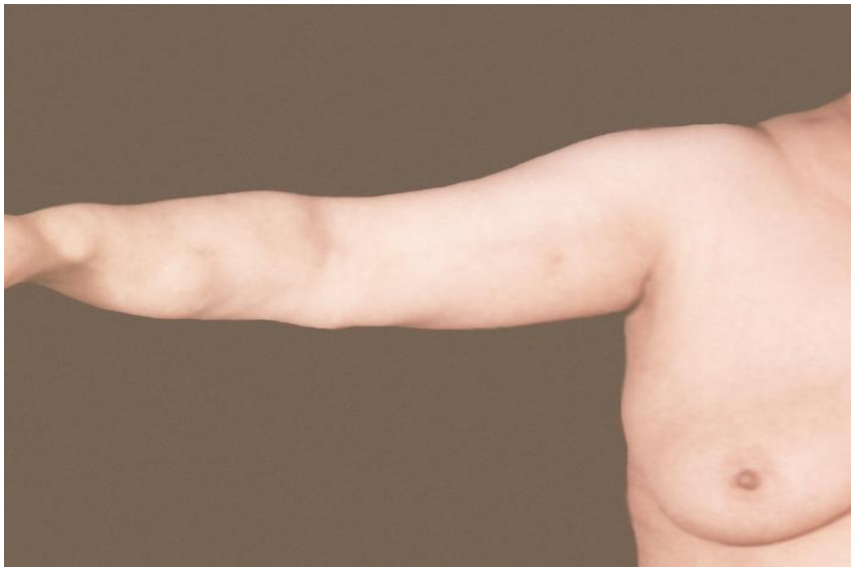
Lipomatosis: Dercum's disease

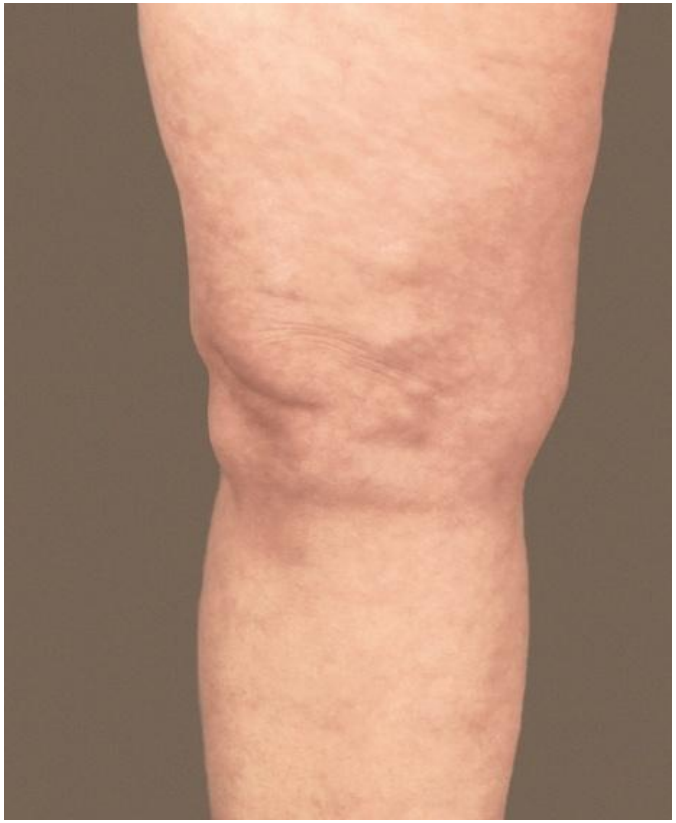
- Most often - in obese women in menopause.
- Presumably, it is based on polyglandular endocrinopathy (the disease is accompanied by atrophy of the endocrine glands).
- Painful nodular fat deposits, similar to lipomas, in the subcutaneous tissue of the thighs, abdomen, and upper extremities.
- In the area of nodes - cyanosis of the skin, impaired sweating, often hemorrhages.
- The structure of wen is characteristic: it is different in size, shape and consistency, the difference from ordinary lipomas is the abundance of vessels with pronounced perivascular lymphoid infiltration and the development of connective tissue (angiofibrolipomas).

- Changes in most of the endocrine glands (sclerosis, atrophy, cystic degeneration), but the most pronounced - in the pituitary gland, thyroid gland, adrenal glands.Lesions of other organs and tissues (for example, osteoporosis, dystrophic changes in sympathetic nodes, etc.) are less characteristic and are, apparently, secondary.

Lipomatosis: Dercum's disease







Lipomatosis: Madelung syndrome

- The reason is unclear.

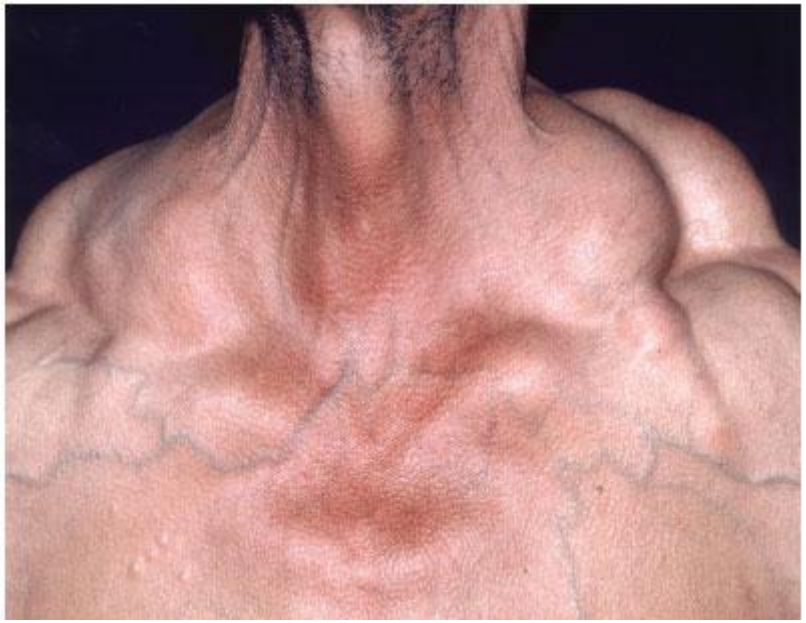
- Various authors associate its development with insufficient function of the thyroid gland, with a tendency to neuro-dystrophic processes, with primary damage to the lymph nodes of the neck, and alcoholism.

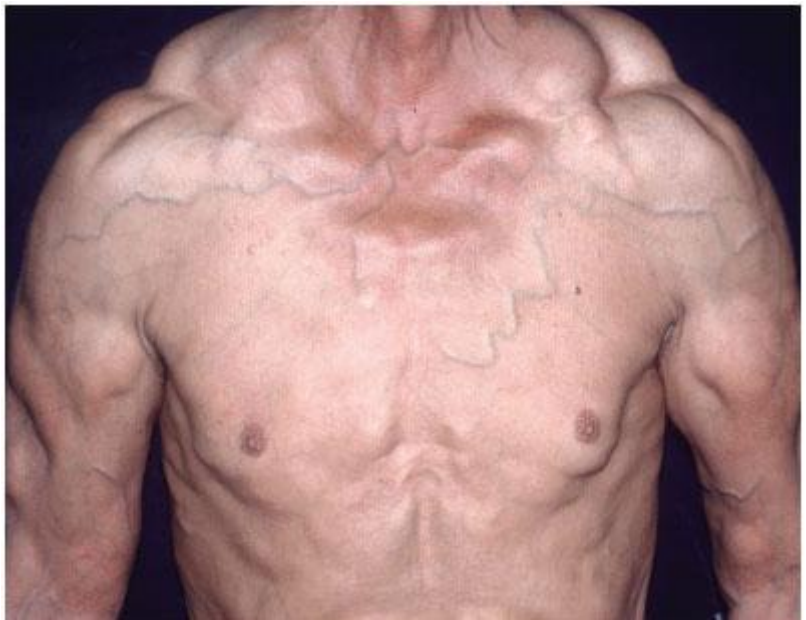
- It is characterized by multiple, diffuse painful growths of adipose tissue in the lymph nodes of the neck with a sharp thickening of the neck, which can lead to difficulty breathing and dysphagia.
- Relapses are possible after surgical treatment.

- Histological examination reveals accumulations of adipose tissue of normal structure.

- The type of inheritance is autosomal dominant.

Lipomatosis: Madelung syndrome



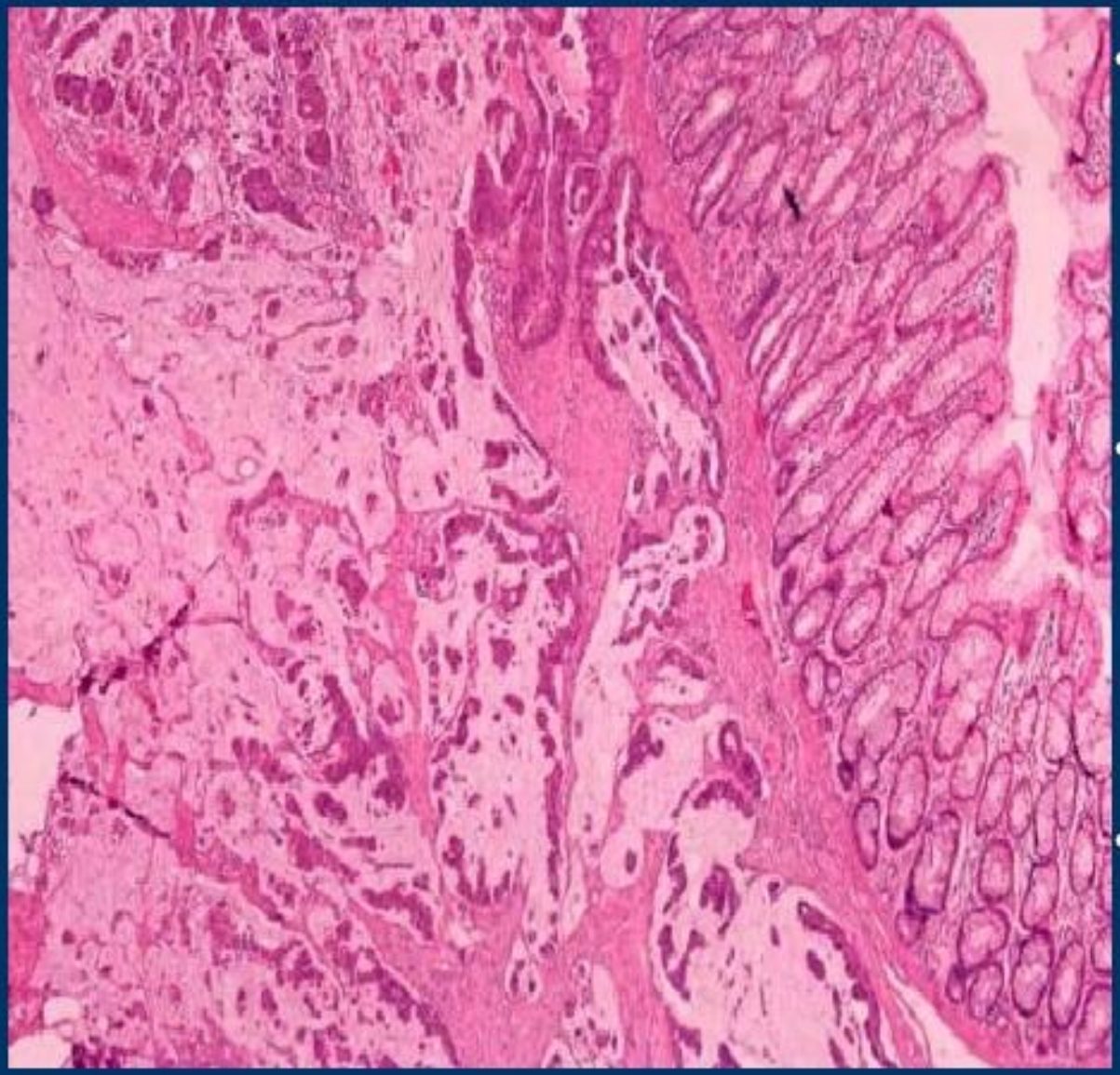


Lipomatosis

- **Roth and Paylaird, Lenu and Benso syndromes:**

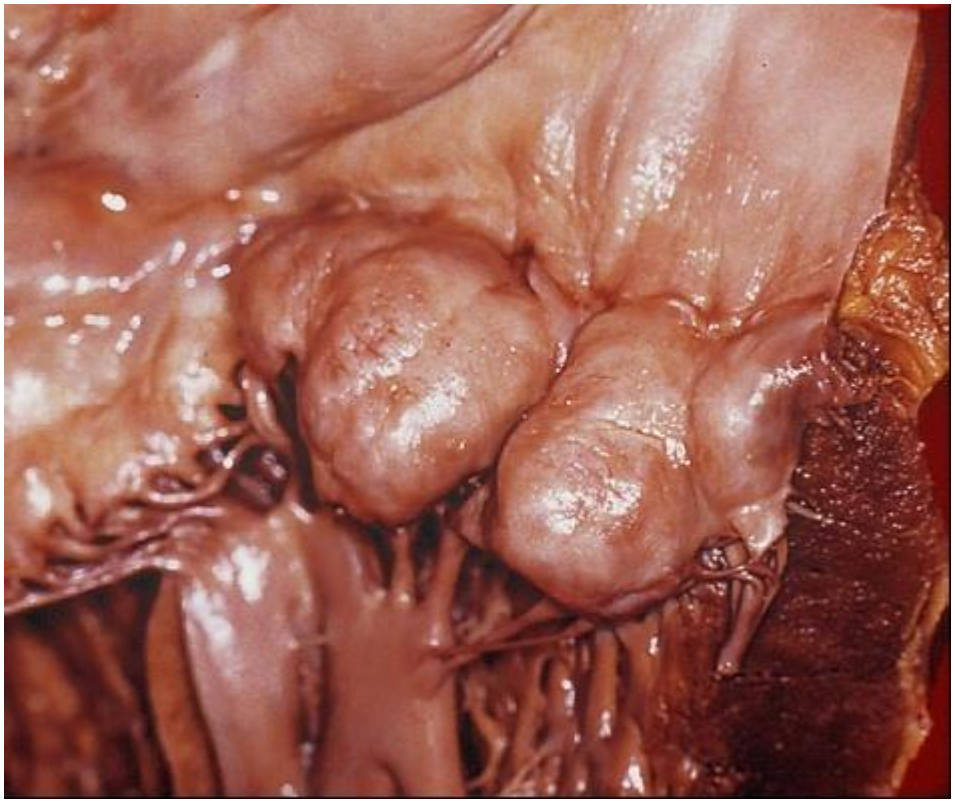
- Refers to symmetric lipomatoses.
- In Roth and Paylair's syndrome, focal fat deposits appear in the lumbar region and on the extremities.
- With Lenu and Benso syndrome - in the neck, abdomen and groin folds.

Mucinous Degeneration-Colon

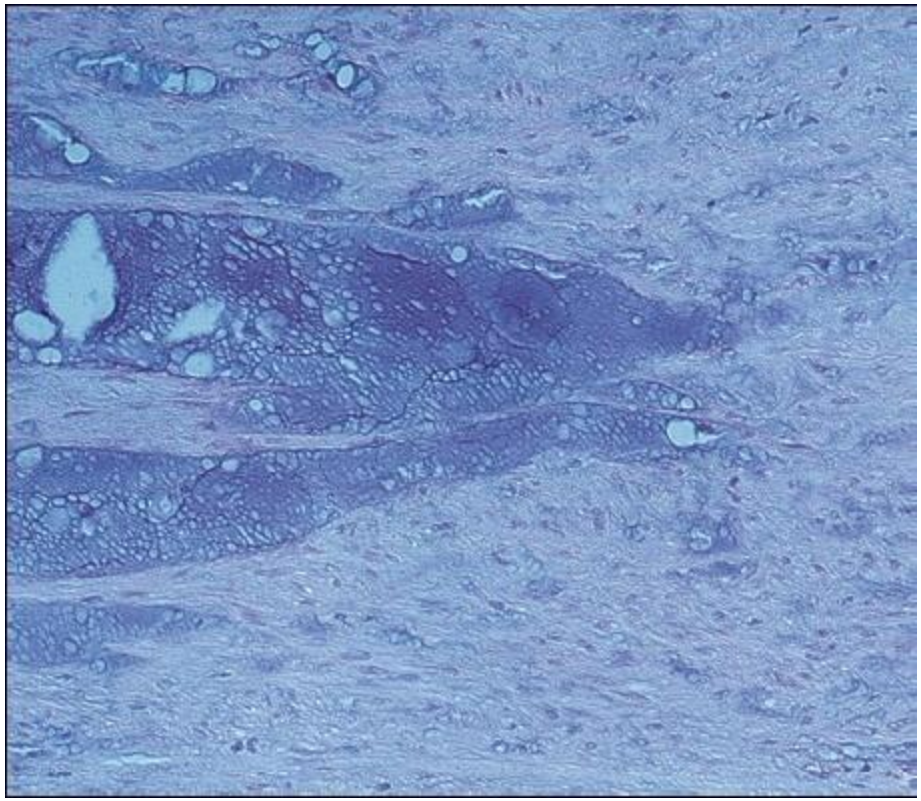


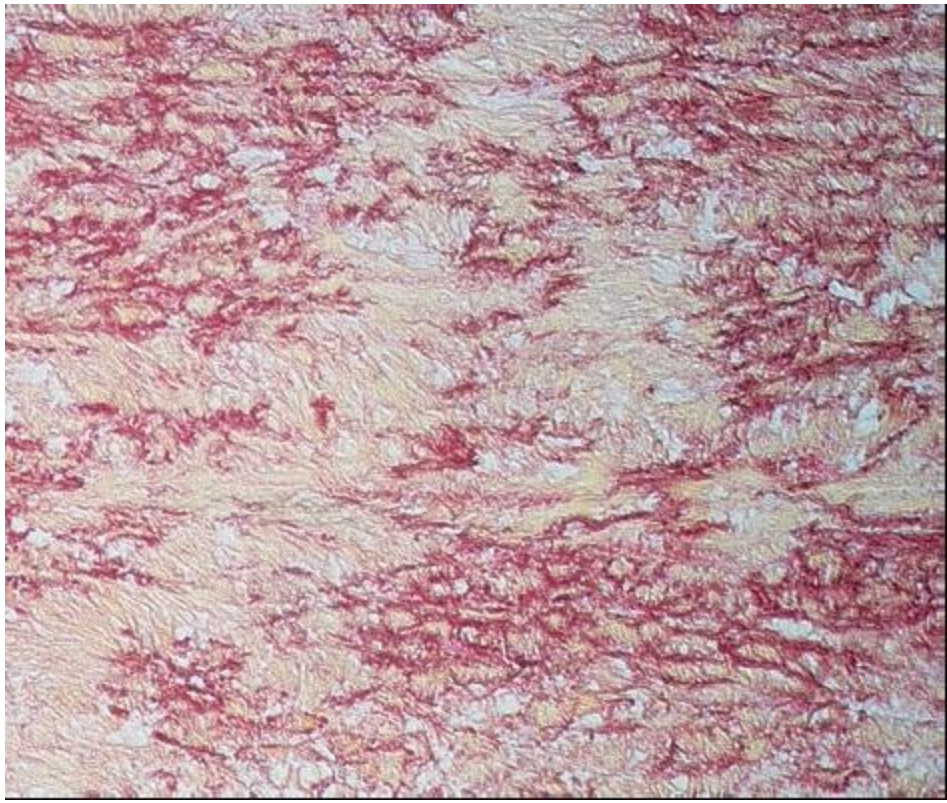
- When there is excessive amount of mucous in unusual location, it is called mucous deg.
- Cancer with high degree of mucous deg are called mucinous carcinoma or the colloid carcinoma.
- Two types of mucin: true mucin and paramucin

Mitral valve prolapse



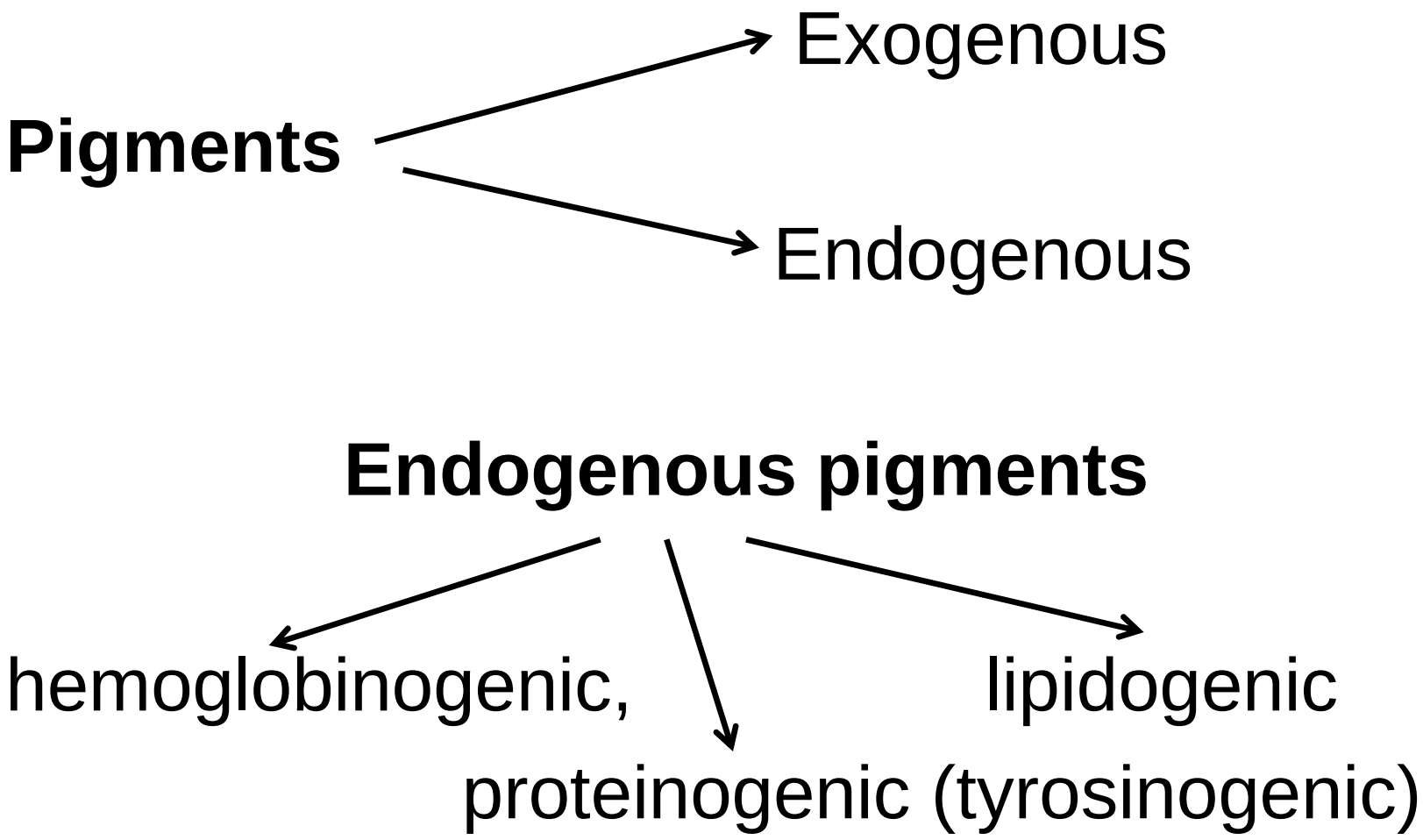
Mucoid degeneration (aorta) (HE) x 150 (aorta; EvG) x 150





Mixed dystrophies

- ***Mixed dystrophies*** are morphological manifestations of impaired metabolism, detected both in the parenchyma and in the stroma of organs and tissues, arising from impaired metabolism of complex proteins - endogenous *pigments (chromoproteins*), *nucleoproteins, lipoproteins and minerals*.


Exogenous
Pigments
Endogenous
Endogenous pigments
hemoglobinogenic,
proteinogenic
lipidogenic (tyrosinogenic)

PIGMENTS

- colored substances, some of which are normal constituents of cells (e.g., melanin), whereas others are abnormal and collect in cells only under special circumstances.

Exogenous Pigments. The most common *exogenous pigment* is *carbon* or coal dust, Accumulations of this pigment blacken the tissues of the lungs *(anthracosis)*

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

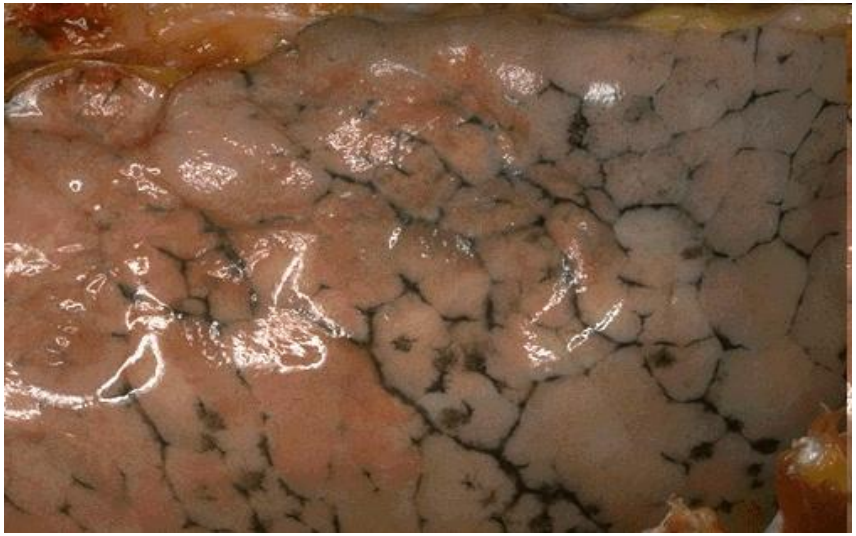
Endogenous Pigments. *Lipofuscin* is an insoluble pigment, also known as lipochrome and wear-and-tear or aging pigment. Its importance lies in its being the telltale sign of free radical injury and lipid peroxidation.

-*Melanin*, is the *only endogenous brown-black pigment*.

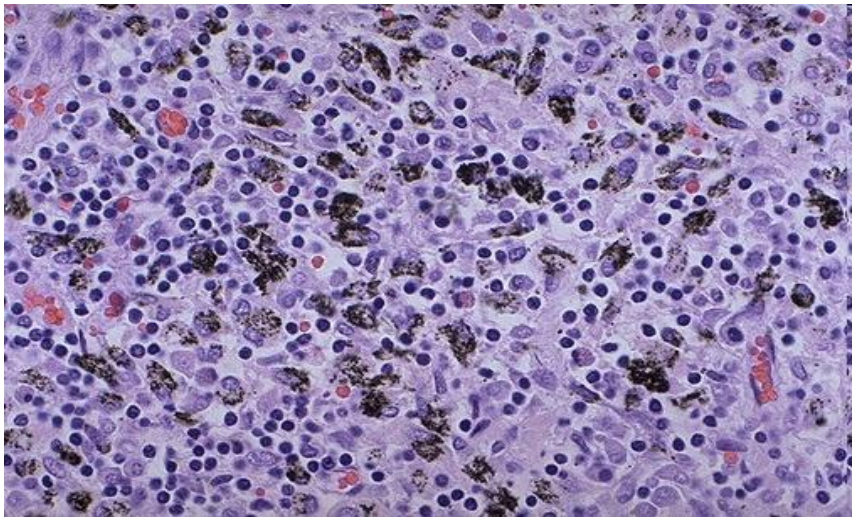
-*Hemosiderin* is a hemoglobin-derived, golden yellow-to-brown, granular or crystalline pigment in which form iron is stored in cells.

Exogenous pigmentation:

Antracosis

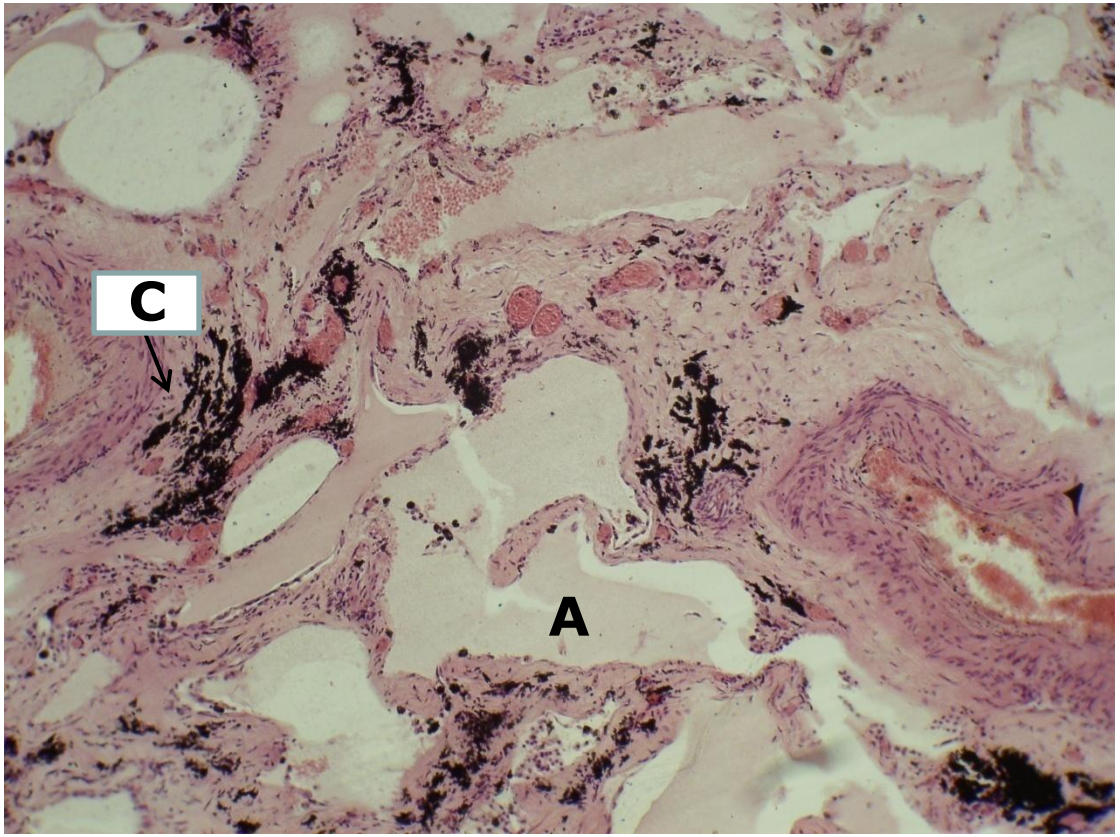


- Antracosis of the lung;



- Antracosis of lymph node. .

Antracosis of the lung



- A – alveoli
- C – carbon depositions

Hemoglobinogenic pigments

- ***Hemoglobinogenic pigments*** are various derivatives of hemoglobin that occur during the synthesis or breakdown of red blood cells.

Normally, the following pigments are formed:

- ferritin,
- hemosiderin,
- bilirubin,
- porphyrins (precursors of heme, can be found in minimal amounts in blood and urine in normal conditions).

In conditions of pathology, the following pigments are formed:

- hematoidin,
- hematins.

Hemoglobinogenic pigments: *Ferritin*

- Ferritin is an iron protein containing the protein apoferritin and a trivalent iron atom in phosphate hydroxide.

- Ferritin molecules are formed intracellularly when iron ions bind to the protein apoferritin:
- a) ***catabolic ferritin*** - is formed during the breakdown of erythrocytes (including physiological) and the destruction of hemoglobin, mainly in monocytic-macrophage cells of the spleen, liver, bone marrow and lymph nodes;
- b) ***anabolic ferritin*** - binds iron ions delivered to the cell from the blood (iron ions are transported by the protein transferritin).

Hemoglobinogenic pigments: *Ferritin*

Histochemical reactions for ferritin:

1. using cadmium sulfate according to the Klochkov method,

2. immunohistochemically using specific antibodies.

3. most often - the reaction of the formation of ***Prussian blue or the Perls reaction*** - a reaction to the detection of salts of iron (III) oxide with the help of iron-cyanide potassium and hydrochloric (hydrochloric) acid.

Hemoglobinogenic pigments: *Hemosiderin*

- ***Hemosiderin*** is a ferritin polymerization product.by chemical structure - colloidal iron hydroxide, combined with mucoproteins of the cell.

- Normally, a small amount of hemosiderin is found in monocytic phagocytes of the bone marrow, spleen and liver; hemosiderin is an intracellular pigment.

- Synthesis - in cells - sideroblasts in specialized organelles - siderosomes.
- Sometimes in sideroblasts - accumulation of a large amount of hemosiderin - destruction of cells and free arrangement of hemosiderin.
- In these cases - phagocytosis of the pigment by macrophages (siderophages).

Hemoglobinogenic pigments: *Hemosiderin*

- Siderosomes are not detected in the cytoplasm of these cells. when stained with *hematoxylin and eosin* - hemosiderin in the form of ***brown granules***,
- with the Perls reaction - in the form of ***greenish-blue granules*** (*Prussian blue*).
- in pathology - excessive formation of ferritin and hemosiderin;

Hemoglobinogenic pigments: *Hemosiderin*

- ***Hemosiderosis*** is a disease that develops with the accumulation of catabolic pigment (formed during hemolysis).

- ***Hemochromatosis*** is a disease resulting from an increased intake of iron into the body and is also accompanied by massive deposits of hemosiderin.

Hemosiderosis

- It occurs with increased hemolysis - the destruction of red blood cells.

Hemosiderosis:

1. Local hemosiderosis,
2. general (common) generalized hemosiderosis.

Hemosiderin is deposited in many organs and tissues, a condition called hemosiderosis.

It is seen with

- 1) increased absorption of dietary iron,
- 2) impaired utilization of iron,
- 3) hemolytic anemias,
- 4) transfusions because the transfused red cells constitute an exogenous load of iron.

Local hemosiderosis

- Occurs with extravascular hemolysis in the foci of hemorrhage;

- Typically: accumulation of hemosiderin in the cells surrounding the hemorrhage: macrophages, leukocytes, endothelium, epithelium;
- a sequential change in the pigments formed during the breakdown of hemoglobin leads to *a change in the color of the hemorrhage*: the *purple-blue color (hemoglobin*) is replaced by *green-blue (biliverdin*), *green-yellow (hematoidin*) and *rusty-brown (hemosiderin*).

Venous congestion

↓

Hypoxia

↓

increased vascular permeability and numerous minor hemorrhages (erythrocyte diapedesis)

↓

formation of hemosiderin in cells(in macrophages, alveolar epithelium)

Local hemosiderosis

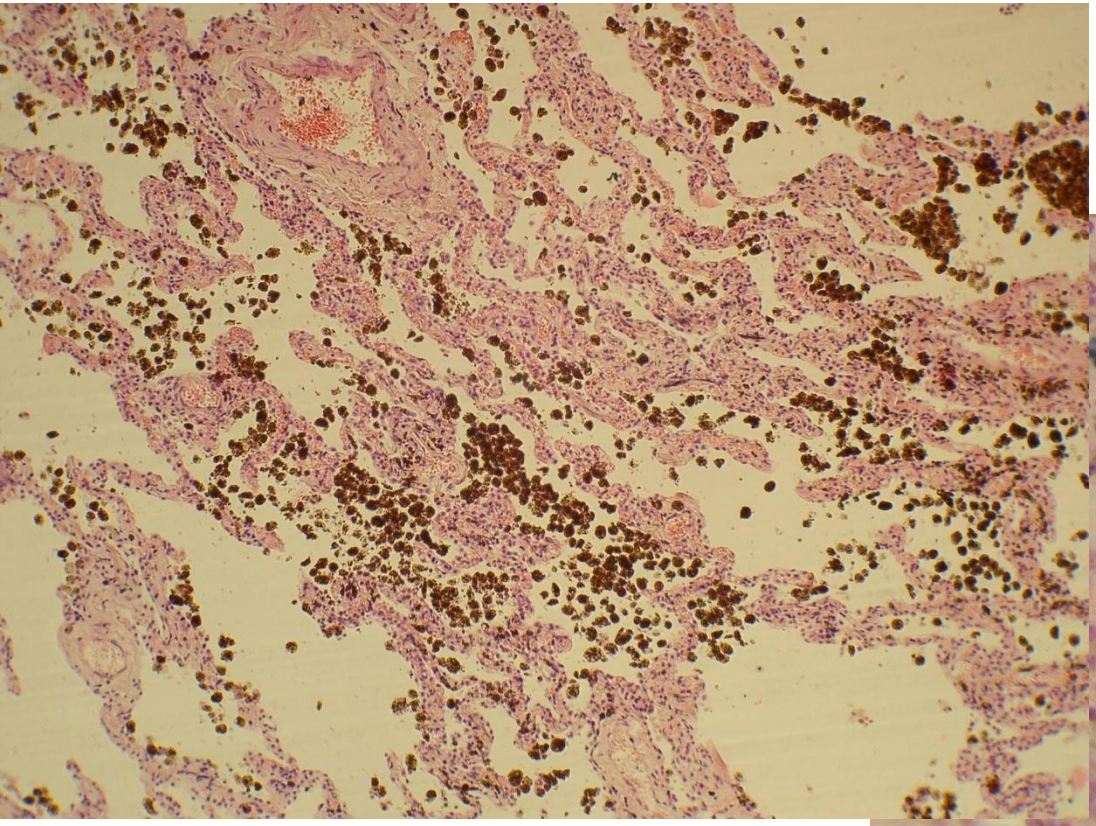
- An example of local hemosiderosis is ***brown induration of the lungs***, which occurs during chronic venous congestion in patients with chronic heart diseases (magpies, cardiosclerosis, etc.).

- *Macroscopic picture:*
- lungs are enlarged,
- dense (induration),l
- n section with numerous brownish blotches and interlayers of connective tissue.

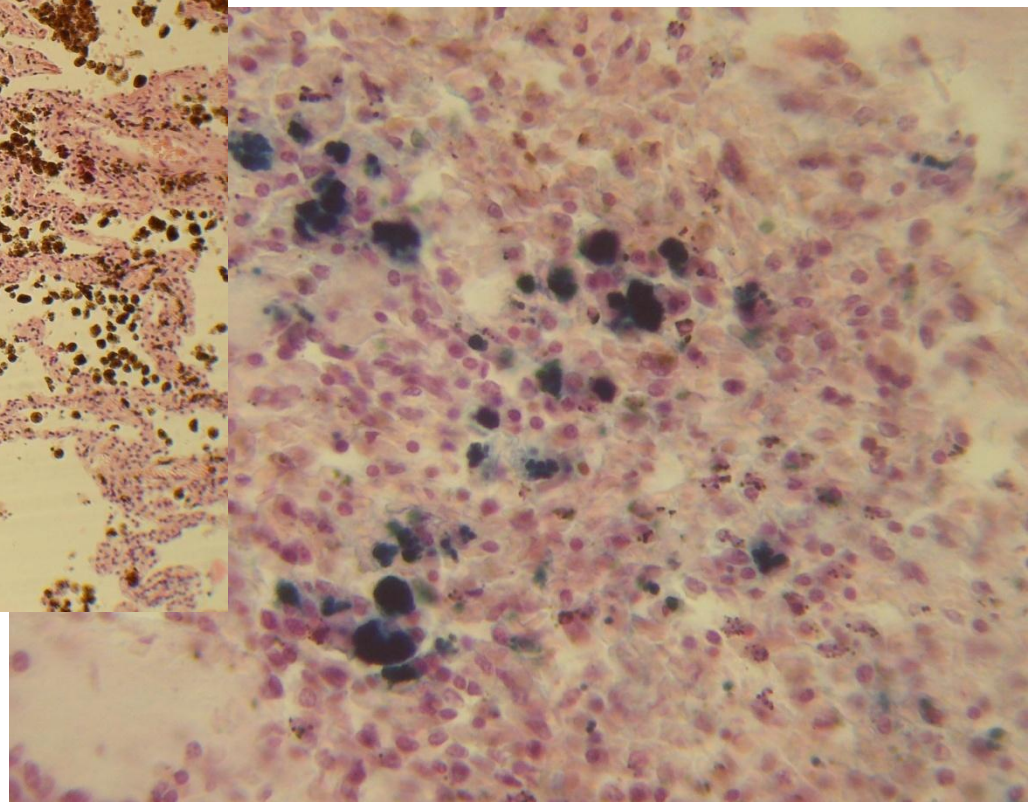
- *Microscopic picture:*
- in the lungs - a large number of cells containing brown pigment, found both in the stroma of the lung and in the lumens of the alveoli and bronchi.
- The interalveolar septa are significantly thickened due to the proliferation of connective tissue.

Hemosiderosis of lung.

H & E. X 100.



- Hemosiderosis of spleen. Perl's method. X 400.



Generalized hemosiderosis

- It occurs with intravascular hemolysis, which develops:

a) in diseases of the blood system (anemia, leukemia, congenital defects of erythrocytes and hemoglobin);

b) in case of poisoning with hemolytic poisons;

c) in infectious diseases (malaria, sepsis, relapsing fever, etc.);

d) in transfusions of incompatible blood and Rh-conflict (hemolytic disease of the newborn).

Generalized hemosiderosis

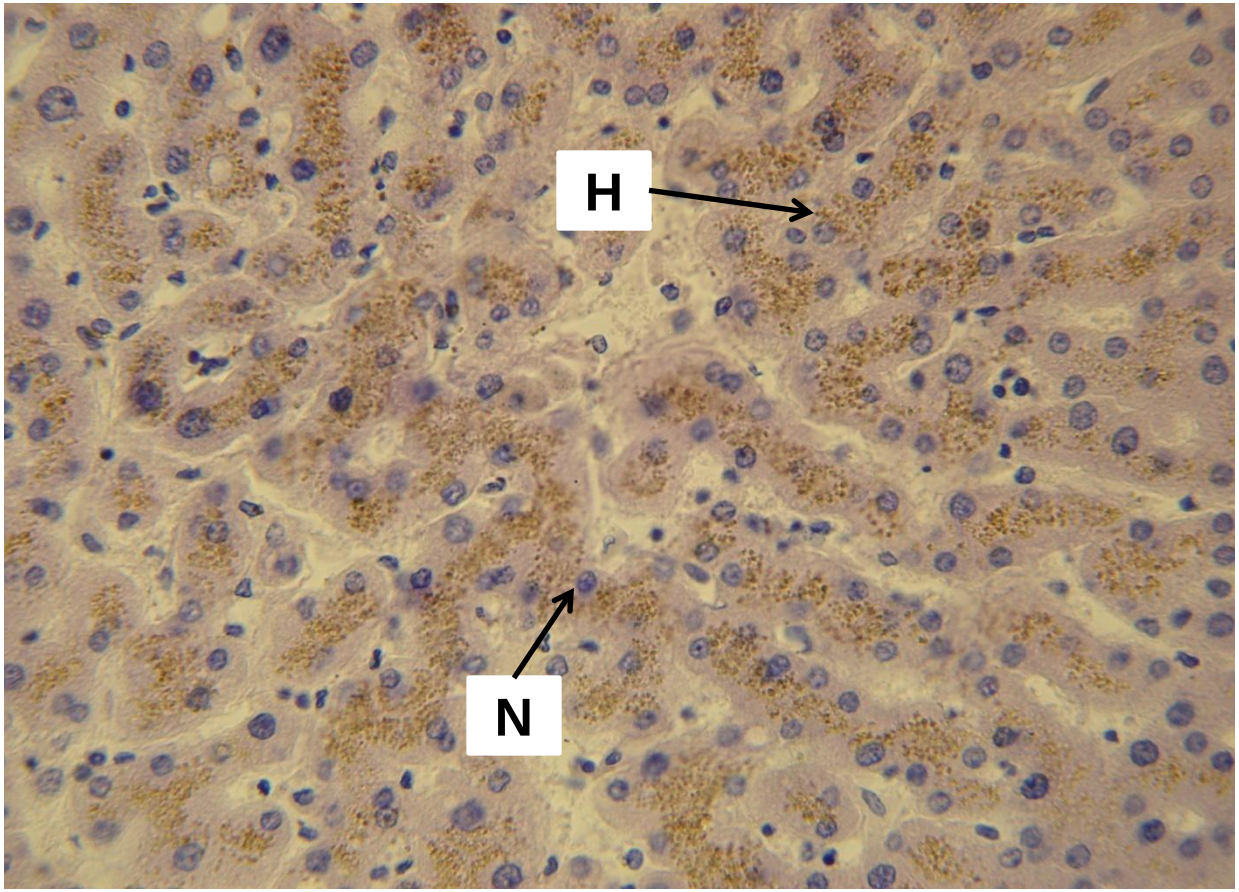
- Hemosiderin -> initially and mainly in mononuclear phagocytes of the spleen, liver, lymph nodes and bone marrow, as well as in macrophages scattered throughout other organs - in the skin, pancreas, kidneys, lungs.

- In the future, hemosiderin -> in the cells of the parenchyma (hepatocytes), and in the stroma of organs and in the walls of blood vessels.

- As the pigment accumulates, the organs acquire a brown (rusty) color.

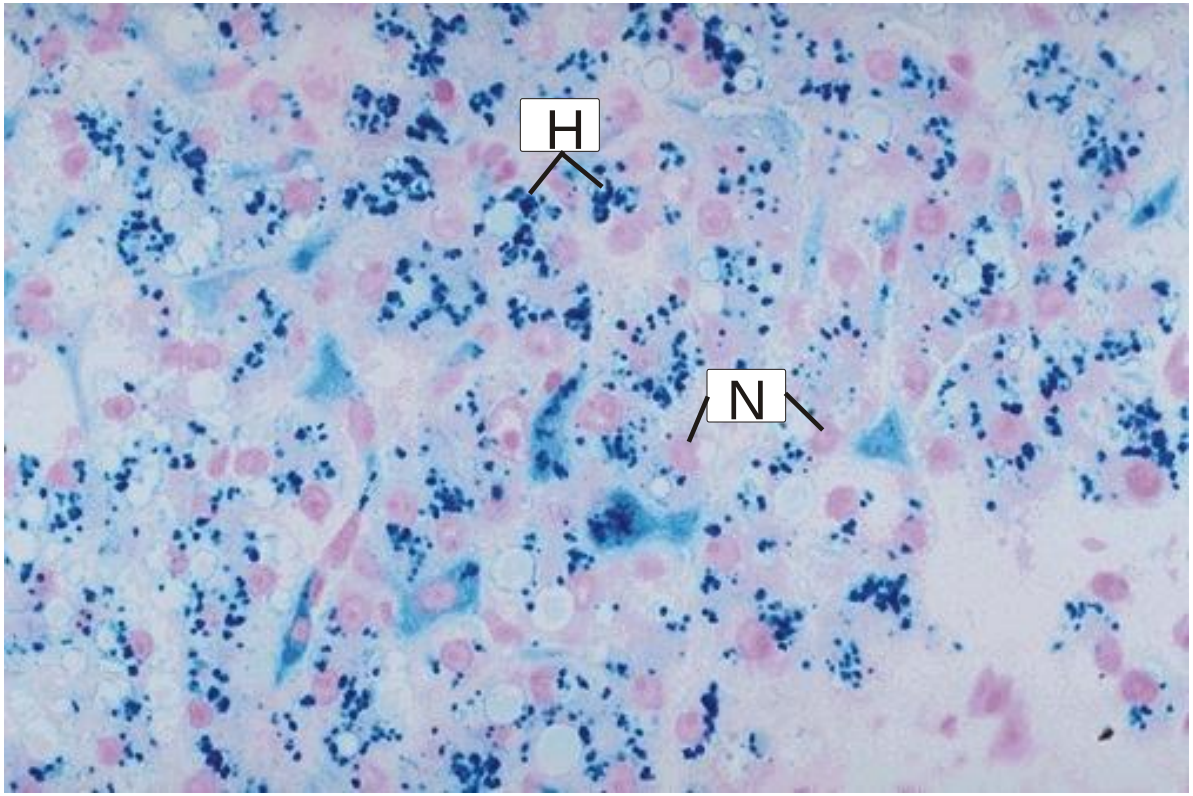
- In most cases, the accumulation of pigment in the organs does not lead to their dysfunction.

Hemosiderosis of liver. H & E. X 400.

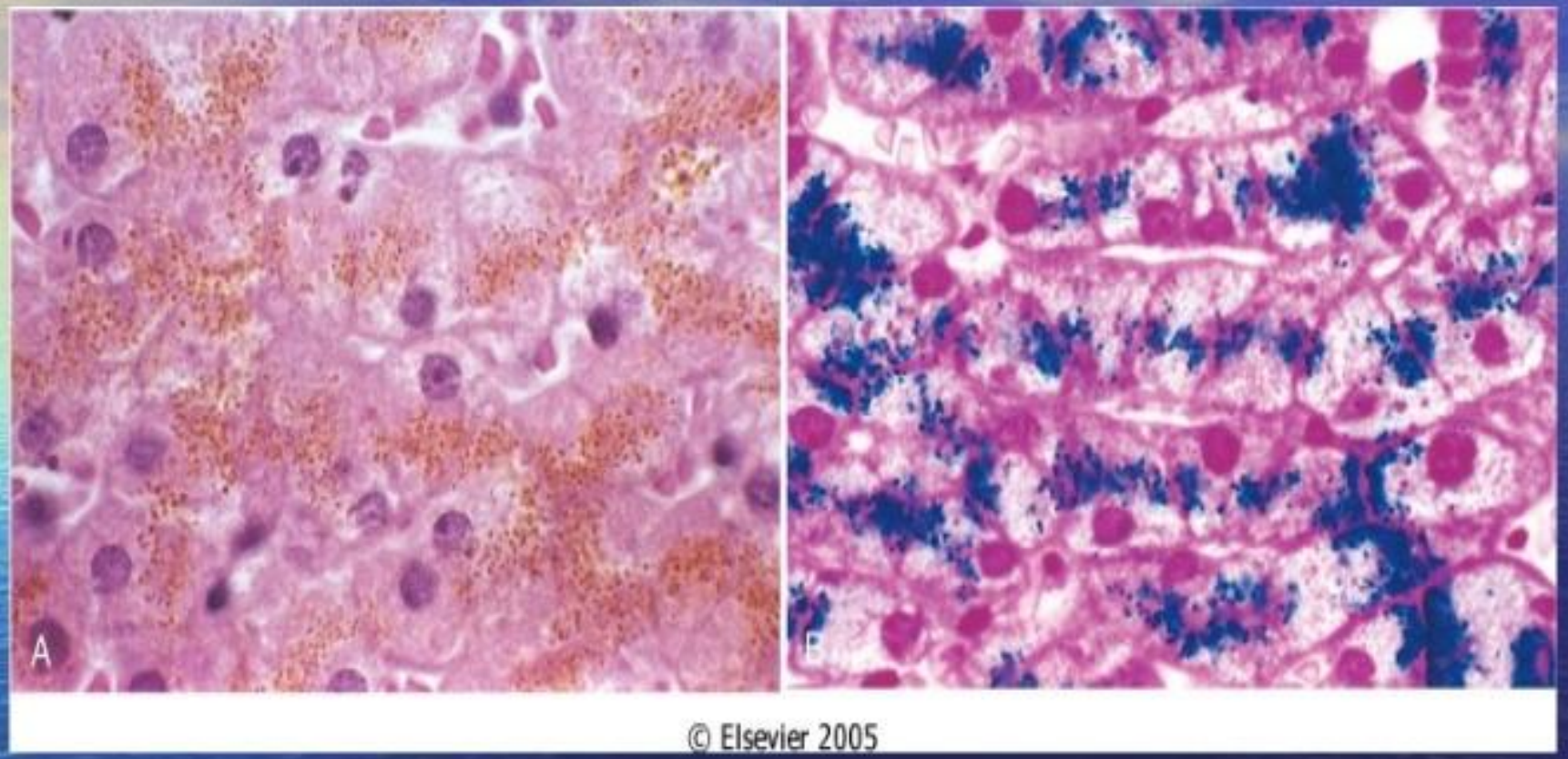


- H – hemosiderin
- N – nucleus of hepatocyte

Hemosiderosis of liver.
Prussian blue. X 520.

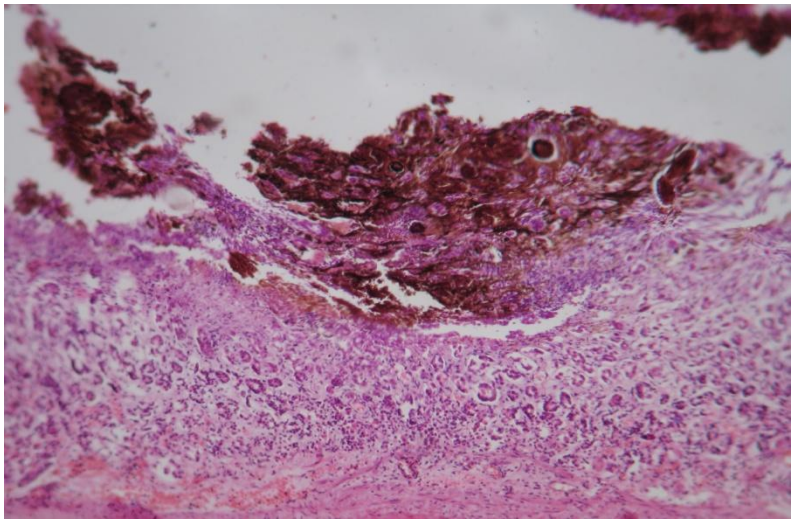


H – hemosiderin
N – nucleus of hepatocyte

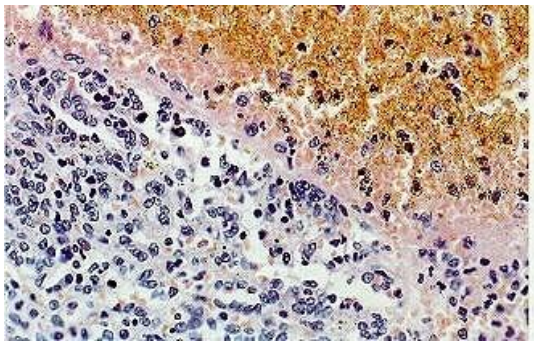


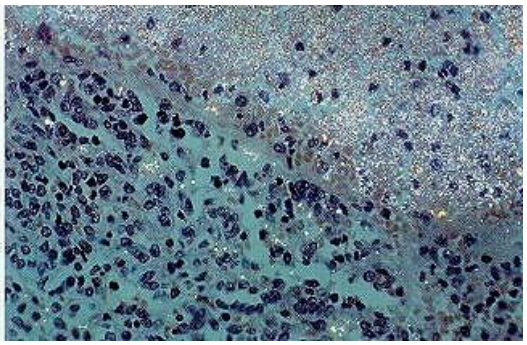
- Figure 1-41 Hemosiderin granules in liver cells. *A*, H&E section showing golden-brown, finely granular pigment. *B*, Prussian blue reaction, specific for iron.

Hematins



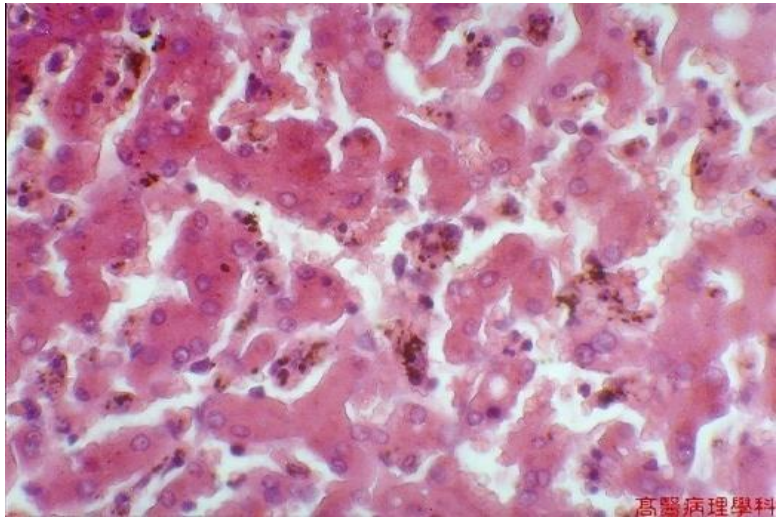
- Hydrochloric acid hematin in gastric erosion;

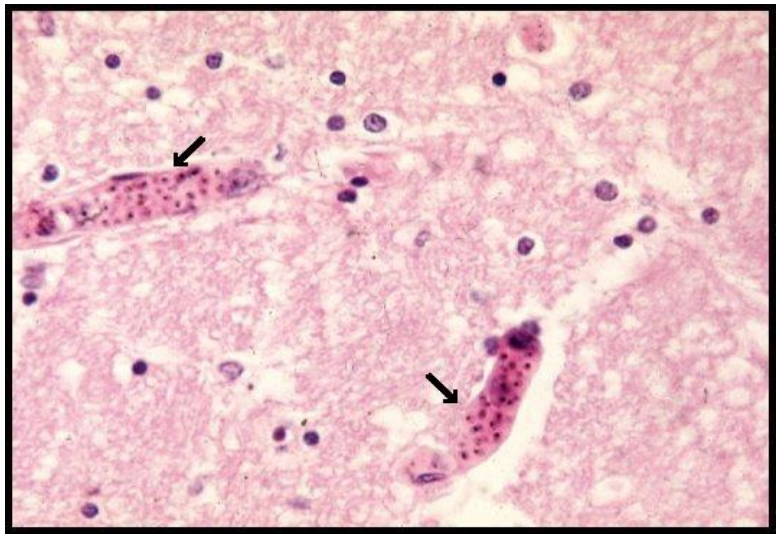




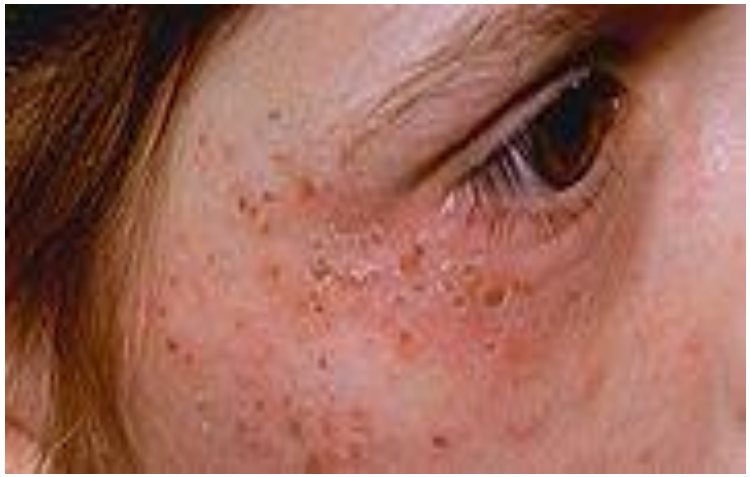
- Formalin pigment.

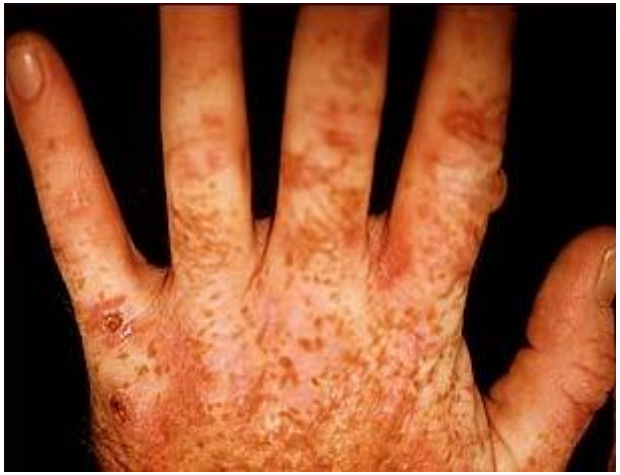
Malaria pigment





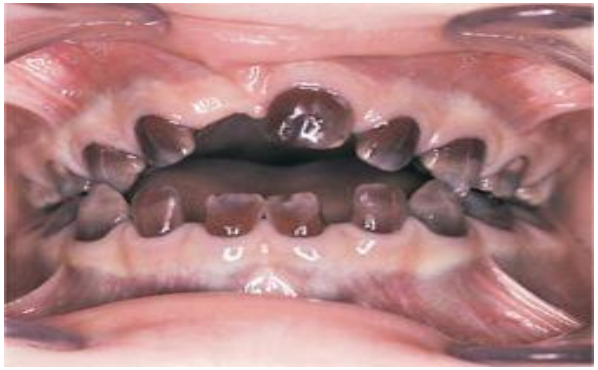
Porphyria



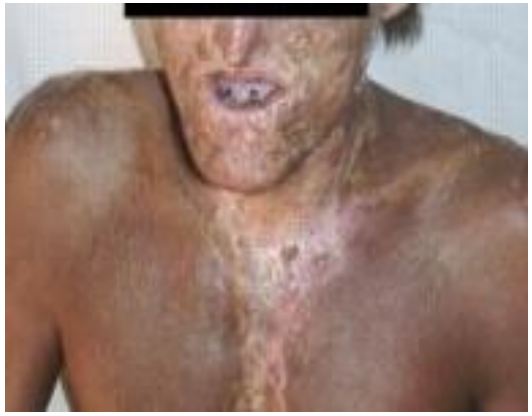


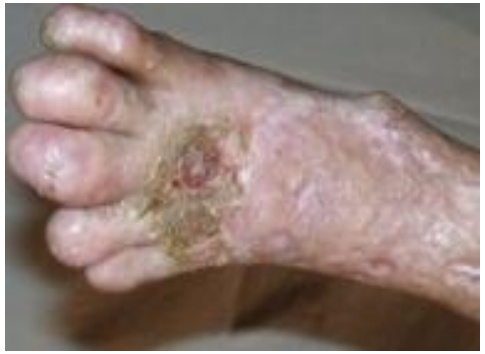
- Porphyria or porphyrin disease is almost always a hereditary disorder of pigment metabolism with an increased content of porphyrins in the blood and tissues and their increased excretion in urine and feces.
- a rare hereditary disease in which the blood pigment hemoglobin is abnormally metabolized.
- Porphyrins are excreted in the urine, which becomes dark; other symptoms include mental disturbances and extreme sensitivity of the skin to light.
- ***Clinical manifestations:***
- photodermatosis,
- hemolytic crises,
- gastrointestinal and neuropsychiatric disorders.

Congenital porphyria

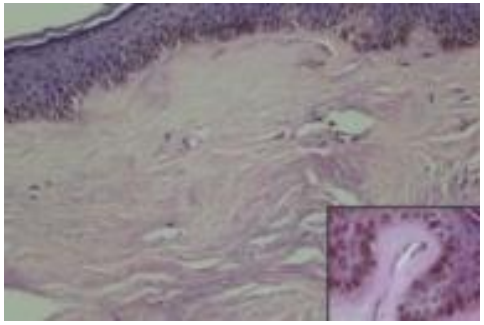


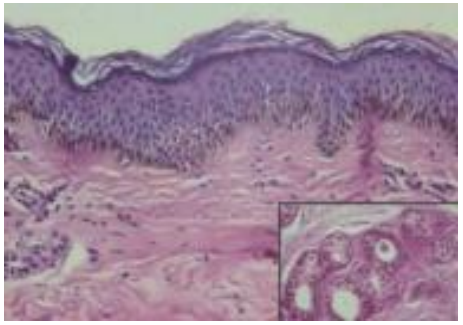
- Brown staining of milk teeth;





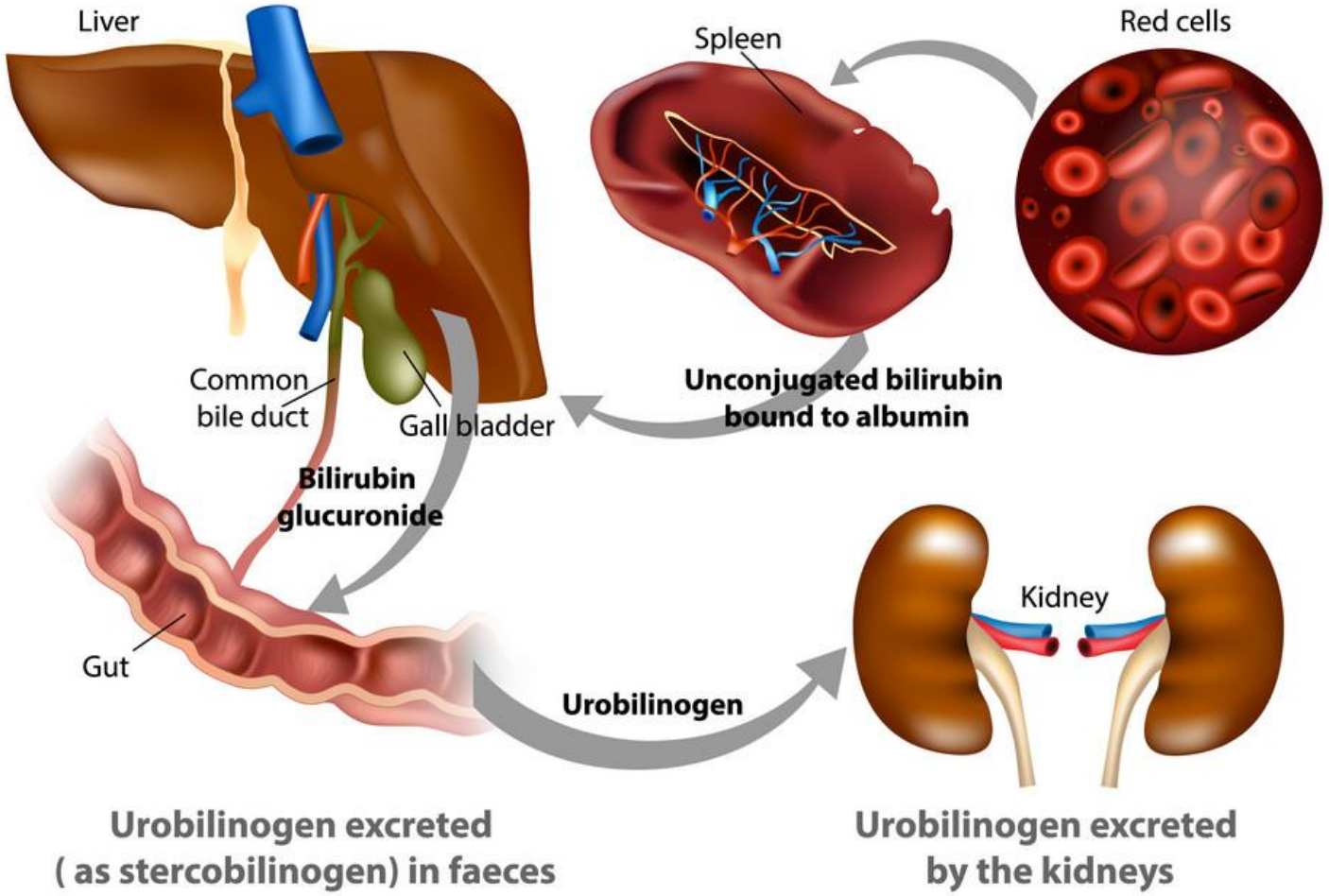
- Ulcers, hypopigmentation, hyperkeratosis and skin fibrosis;





- Fibrosis, deposition of an amorphous substance in the papillary dermis.

Bilirubin



Jaundice

Hemolytic (suprahepatic) jaundice

- It arises in connection with the enhancement of the process of bilirubin formation.
- The indirect (unconjugated) fraction of bilirubin increases.

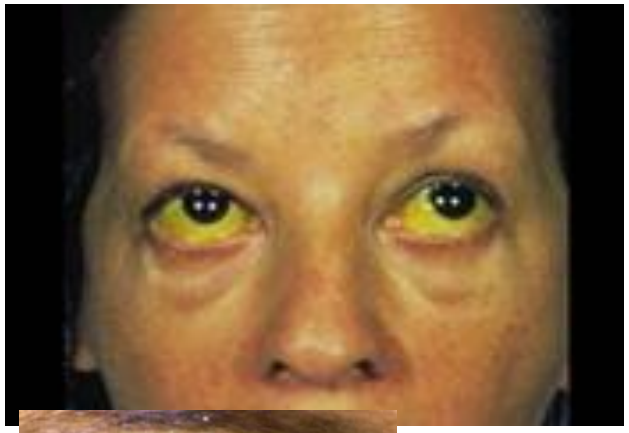
Parenchymal (hepatic) jaundice

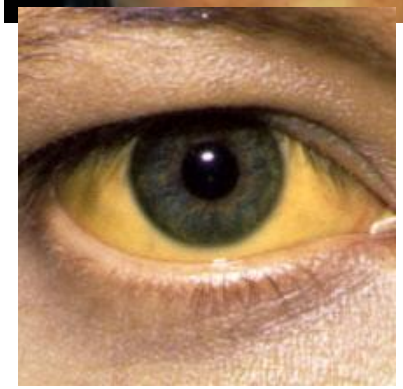
- Development is associated with impaired consumption (capture) of bilirubin by hepatocytes.
- the indirect (unconjugated) fraction of bilirubin increases.

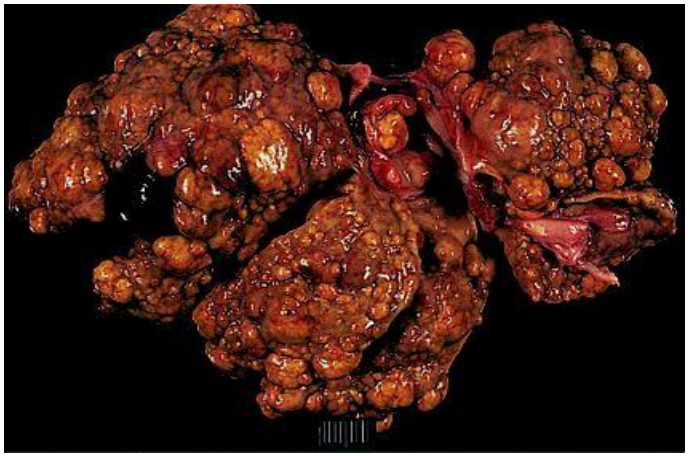
Mechanical (subhepatic) jaundice

- It occurs when there is a violation of the outflow of bile through the extrahepatic bile ducts (obstructive jaundice).

Parenchymal (hepatic) jaundice

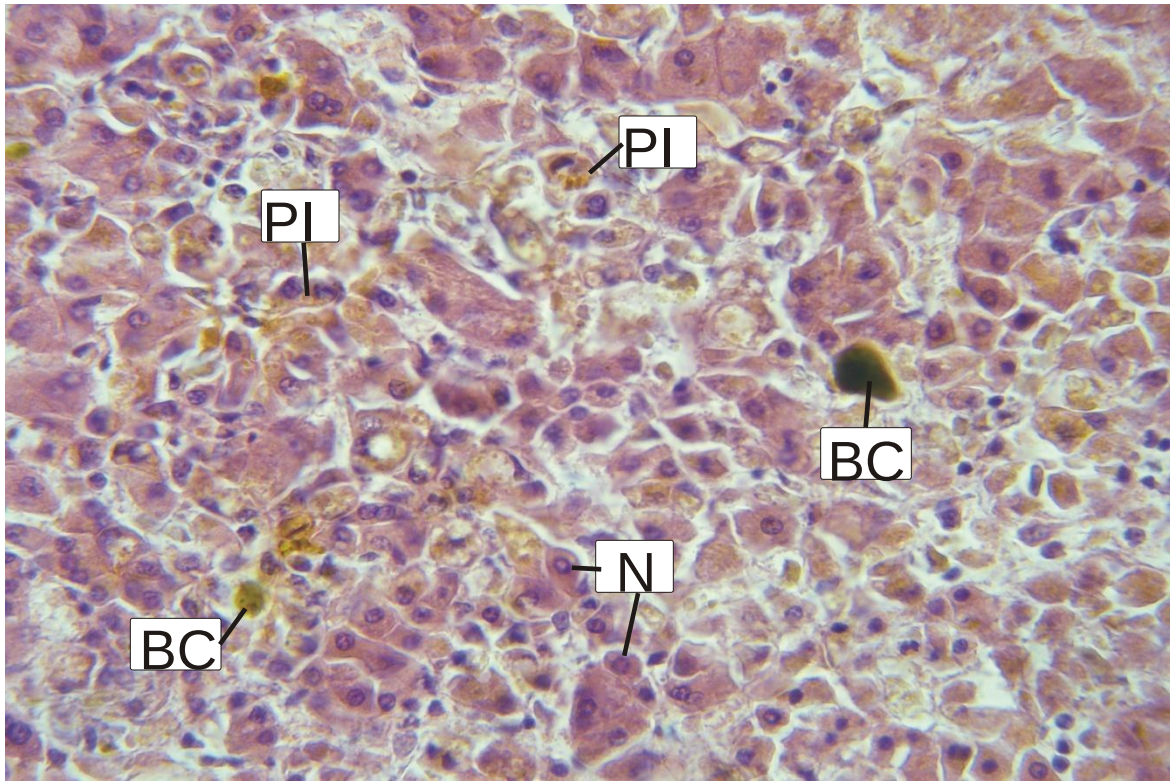






- Liver fibrosis with nodular hyperplasia.

Deposition of bilirubin in the liver. H&E. X 400.



PI - pigment inclusions
BC – distended bile capillaries
N – nuclei of hepatocytes

Common to both obstructive and hepatocellular cholestasis is the accumulation of bile pigment within the hepatic parenchyma. Elongated green-brown plugs of bile are visible in dilated canaliculi, most prominent toward the centers of lobules; this may become panlobular in the most severe cases.

Lipidogenic pigments

Lipidogenic pigments

- lipofuscin,
- vitamin E deficiency pigment,
- hemofuscin,
- ceroid andlipochromes.

- All of them are similar in physical and chemical (histochemical) properties.

- The difference is in their localization: lipofuscin and vitamin E deficiency pigment are in parenchymal cells of organs (lipofuscin is found in nerve cells), and hemofuscin and ceroid are in mesenchymal cells.

Lipofuscin

- An insoluble pigment, also known as aging, wear pigment.
- Forms golden brown granules in the cell.
- Consists of polymers of lipids and phospholipids associated with protein.
- The accumulation of lipofuscin in cells is lipofuscinosis.
- Lipofuscin is most commonly accumulated:in myocardial cells,liver hepatocytes,skeletal muscles with aging or exhaustion, which is accompanied by the development of ***brown organ atrophy***.

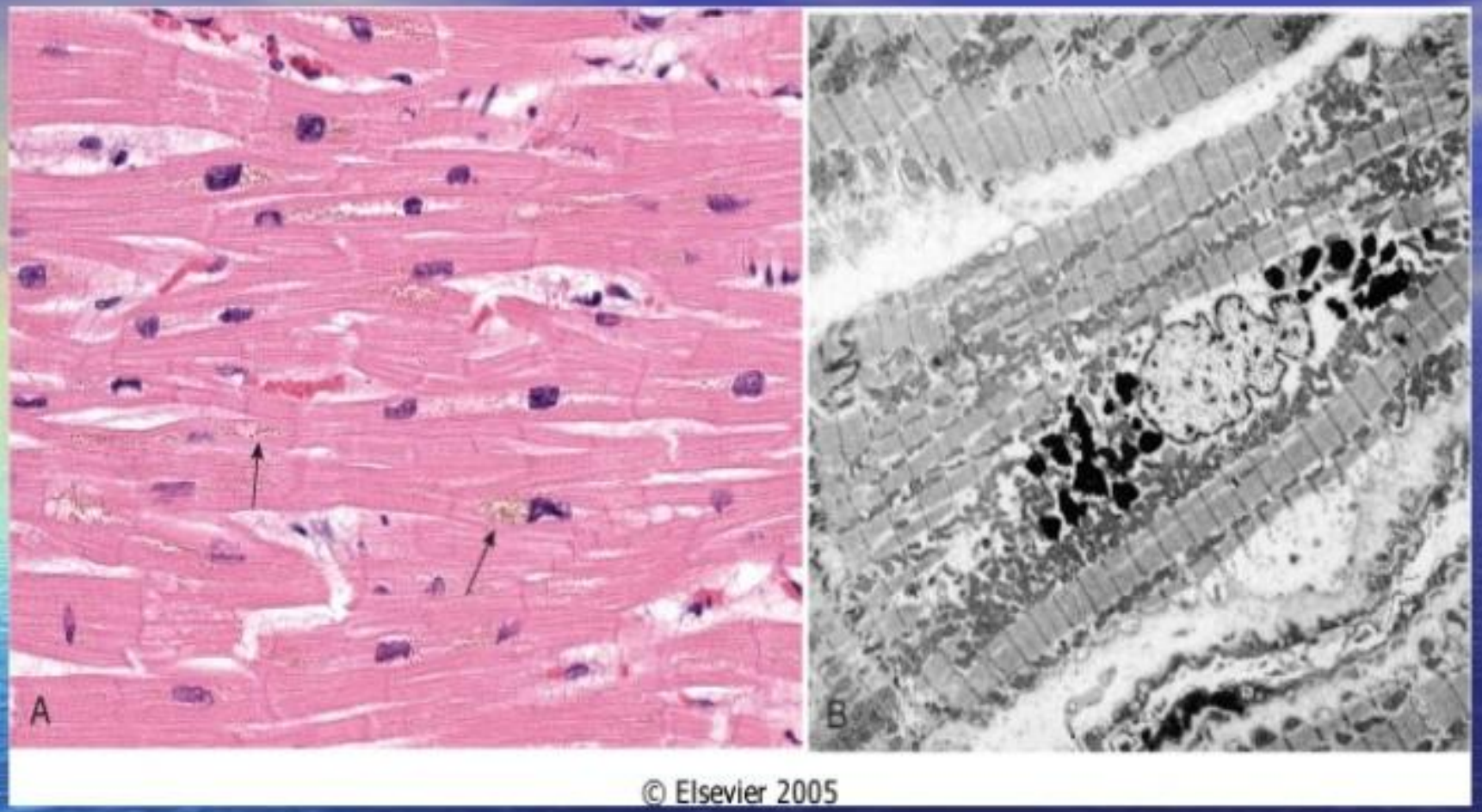
Lipofuscinosis

a) heart (brown myocardial atrophy):

- becomes smallthe amount of adipose tissue under the epicardium is significantly reduced,
- the vessels acquire a crimped course,
- the myocardium is dense, brown;
- microscopically: cardiomyocytes are reduced in size, granules of brown pigment lipofuscin are visible in the cytoplasm,

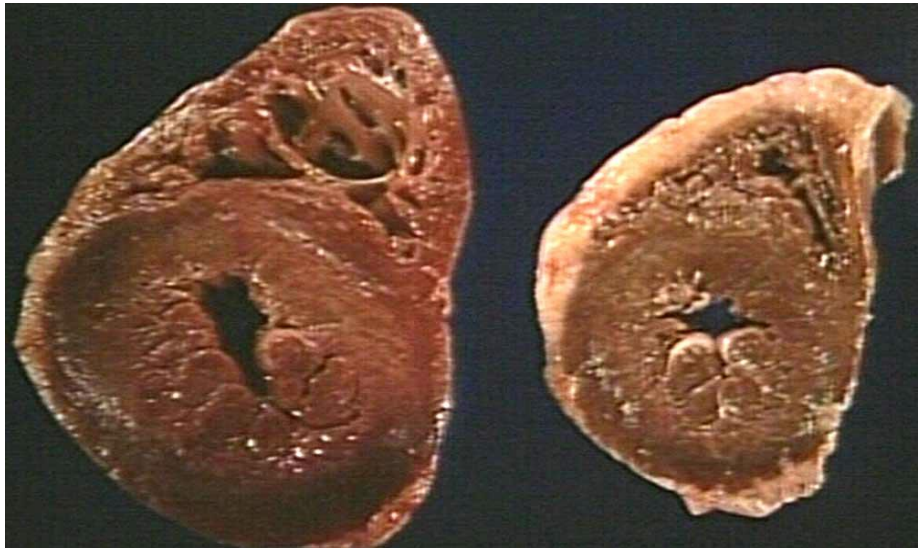
b) liver (brown liver atrophy):

- decreases significantly,
- It’s edge is sharp,
- liver tissue is dense, brown;
- microscopically: the hepatic tracts are sharply thinned, in the cytoplasm of hepatocytes there are numerous brown granules of lipofuscin.

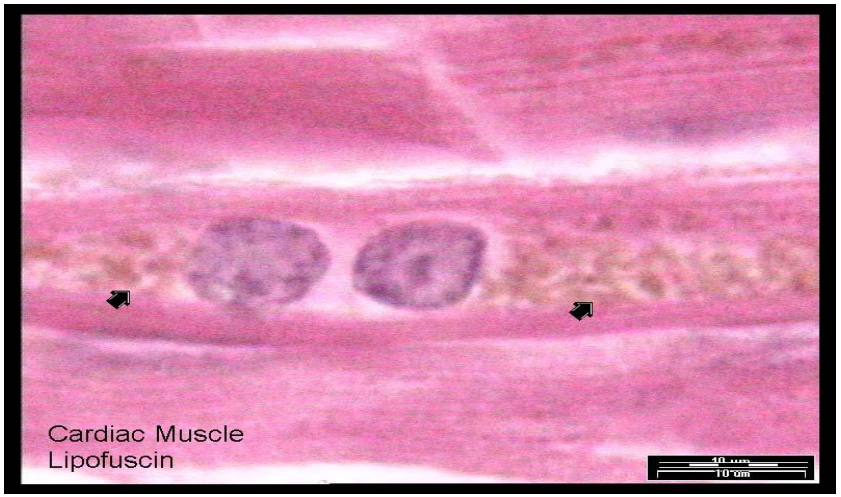


- Figure 1-40 Lipofuscin granules in a cardiac myocyte as shown by *A,* light microscopy (deposits indicated by *arrows*), and *B,* electron microscopy (note the perinuclear, intralysosomal location).

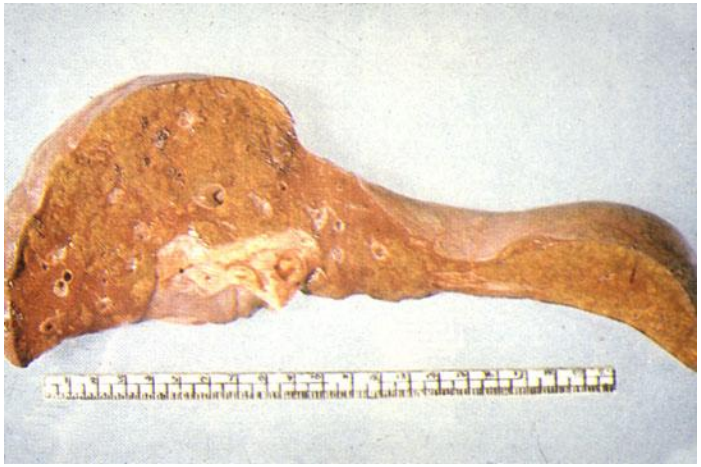
Lipofuscinosis



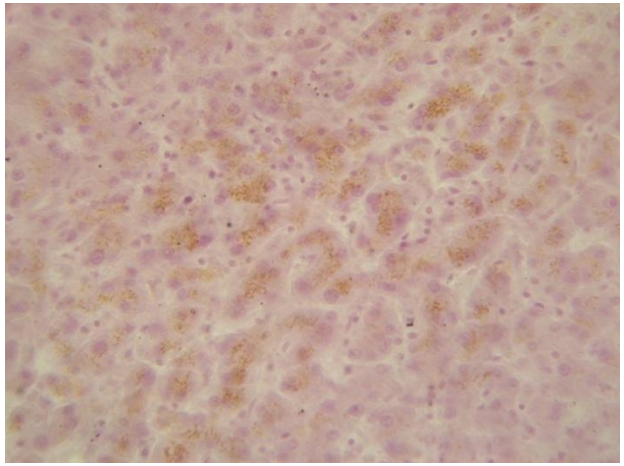
- **Brawn atrophy of myocardium.**

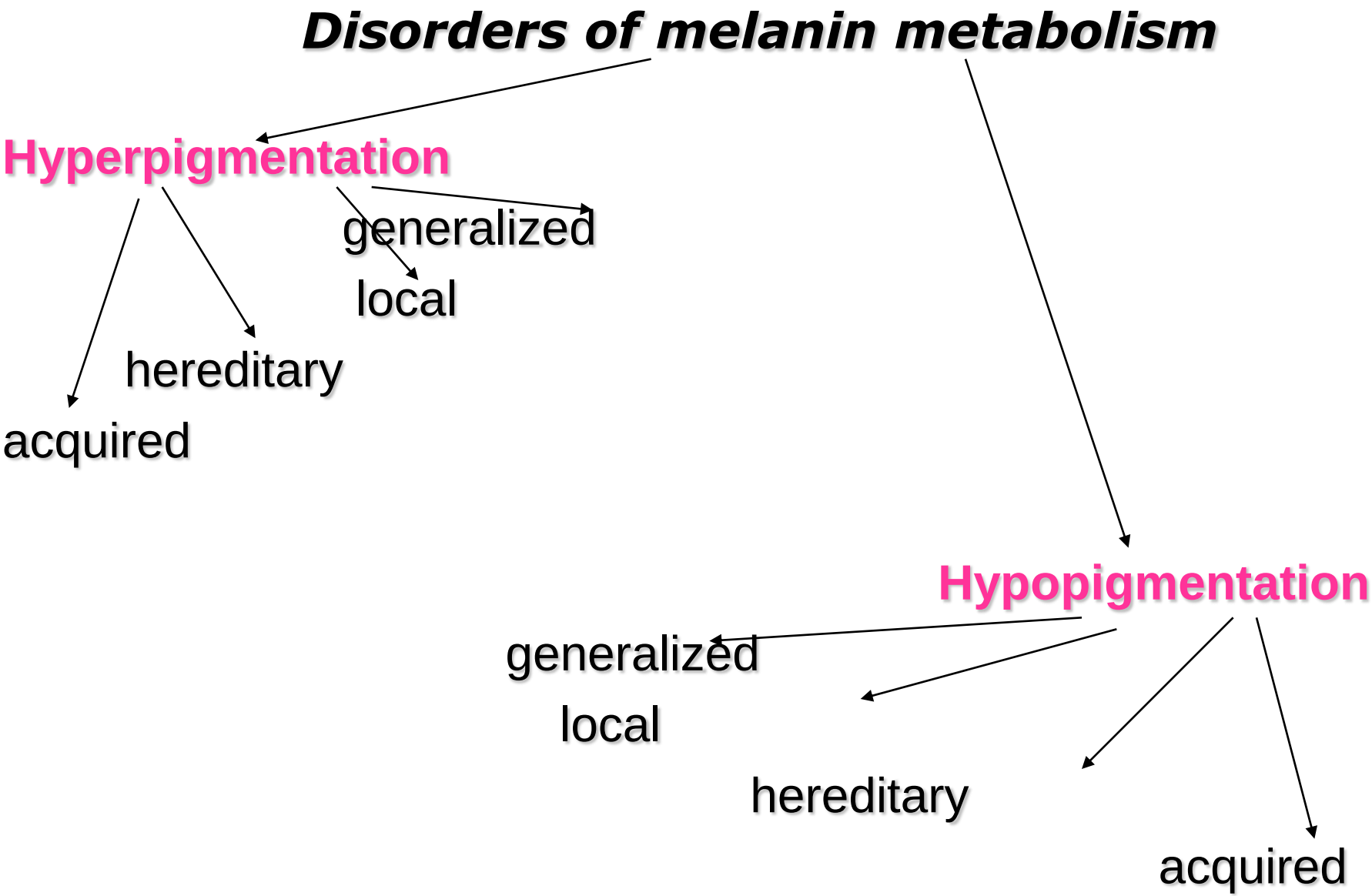


Lipofuscinosis



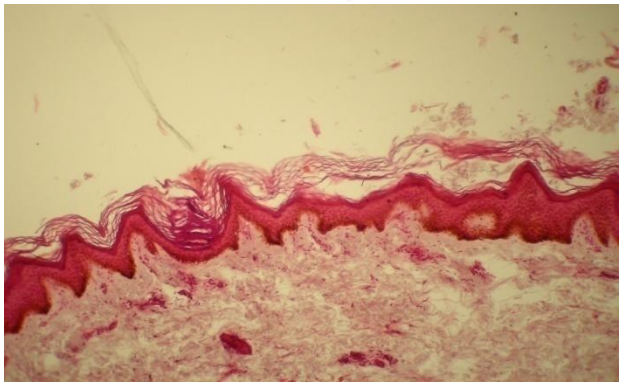
- **Lipofuscinosis of liver**

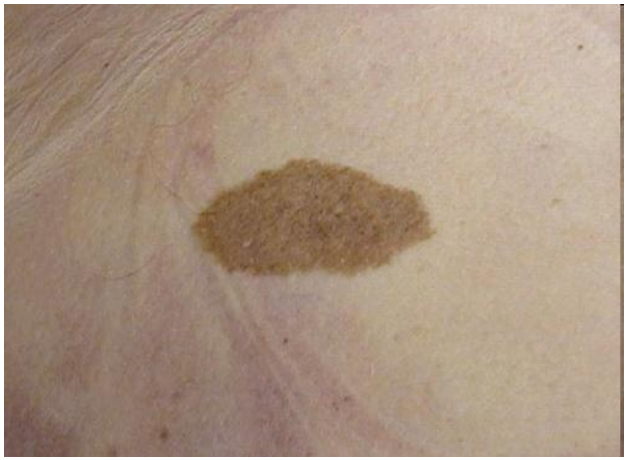



Disorders of melanin metabolism
Hyperpigmentation
generalized
local
hereditary
acquired
Hypopigmentation
generalized
local
hereditary
acquired

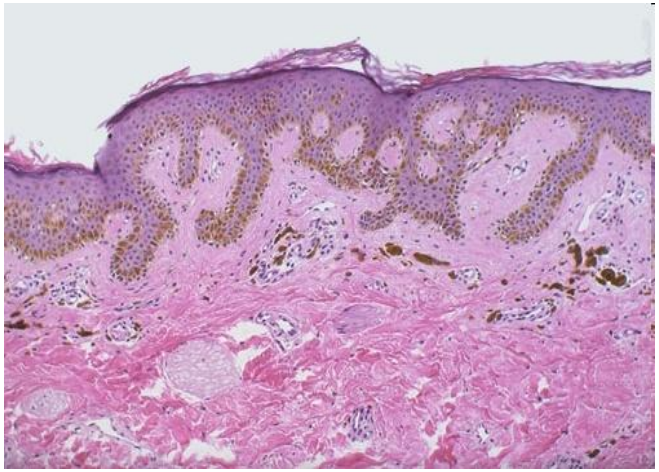
Local hyperpigmentation

- Freckles;
- Melanosis of skin;

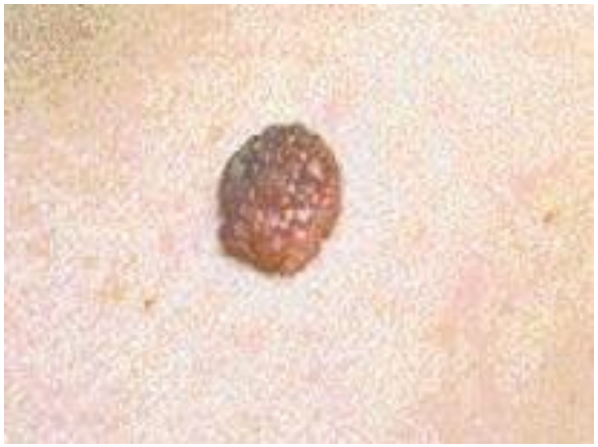




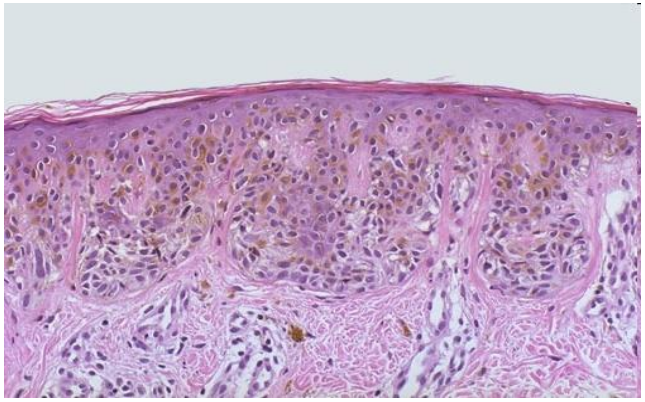
- Lentigo;

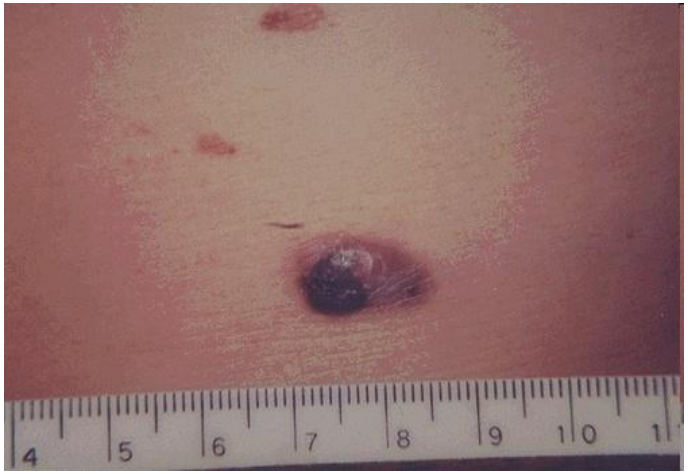


Local hyperpigmentation

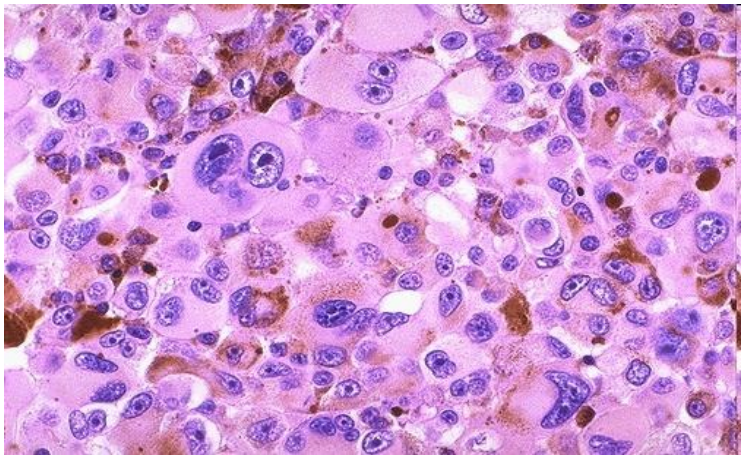


- Pigmental nevus,



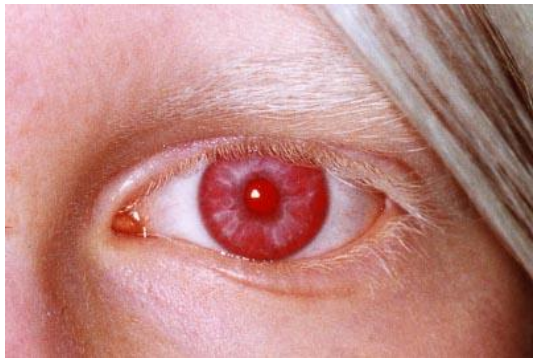


- Melanoma.

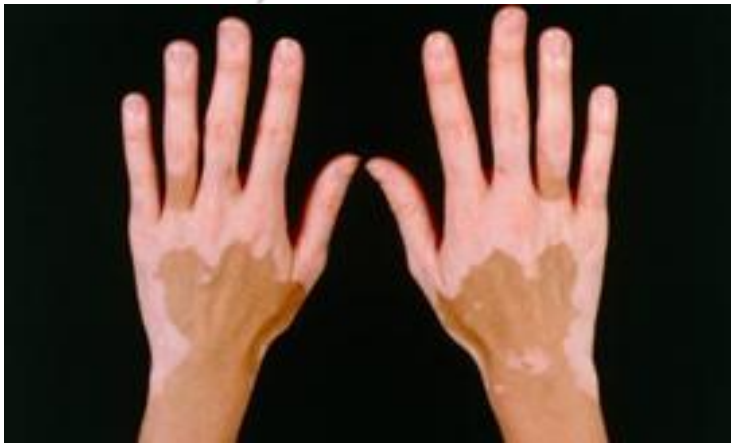


Hypopigmentation

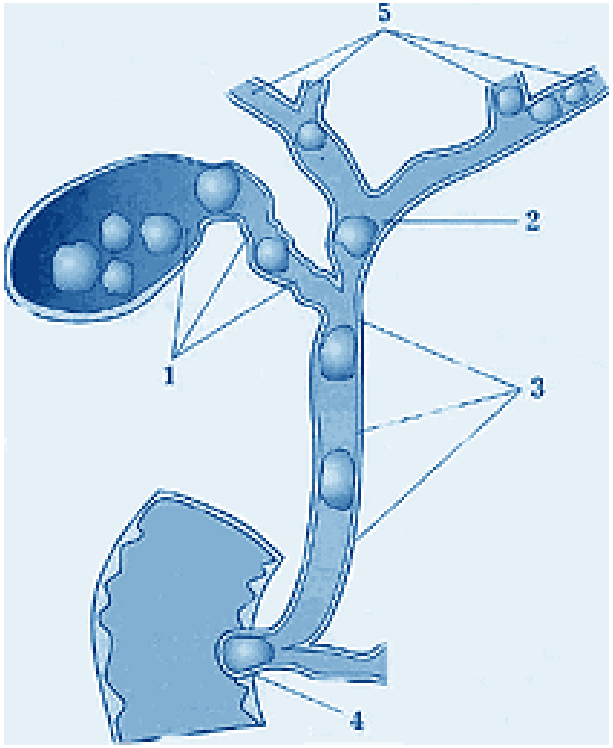
- Albinism;



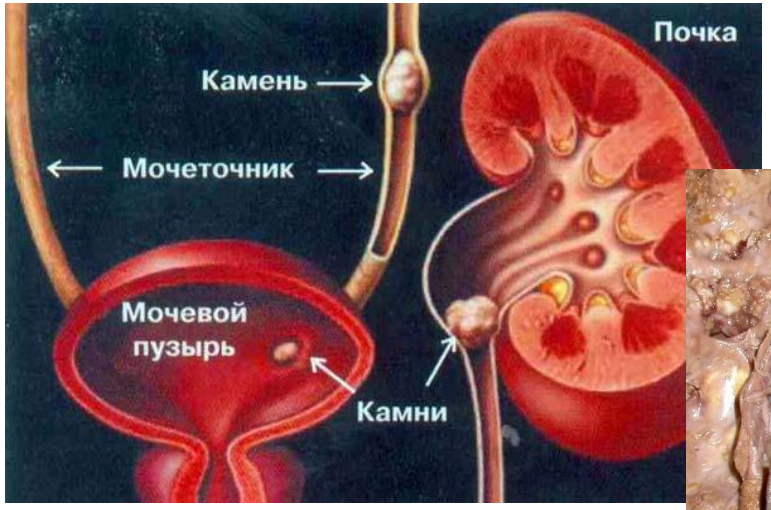
- Vitiligo (acquired leukoderma)

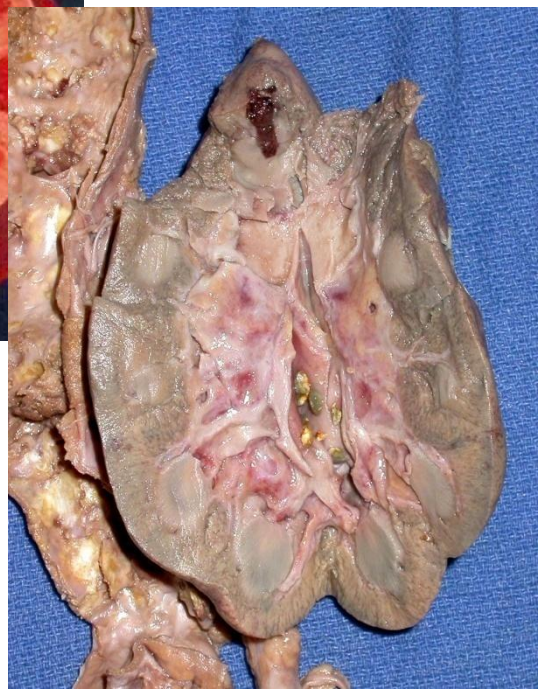


Stones of gall bladder

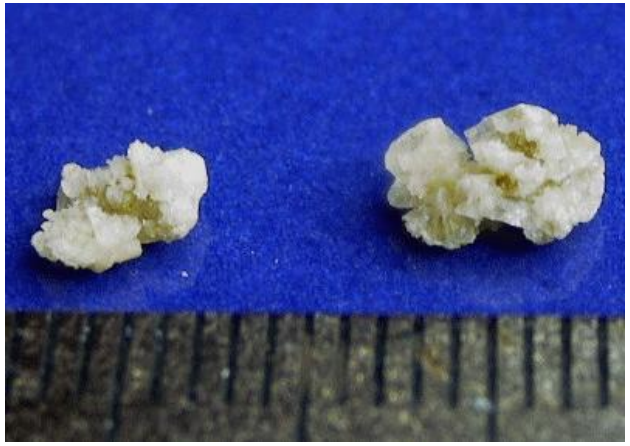


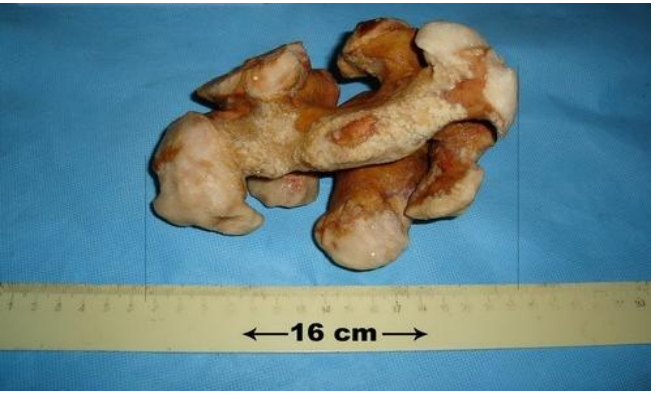
Urolithiasis



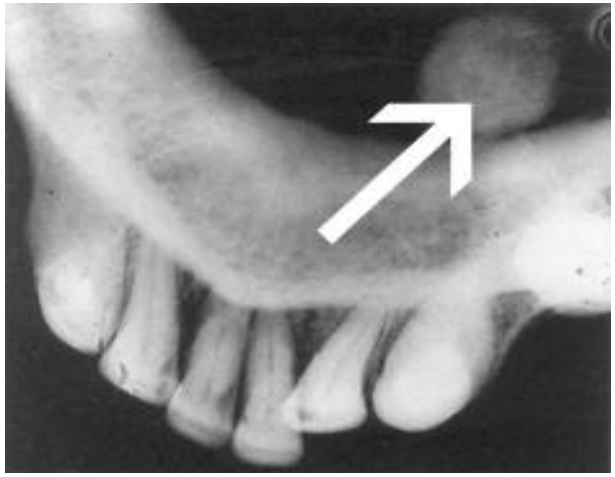


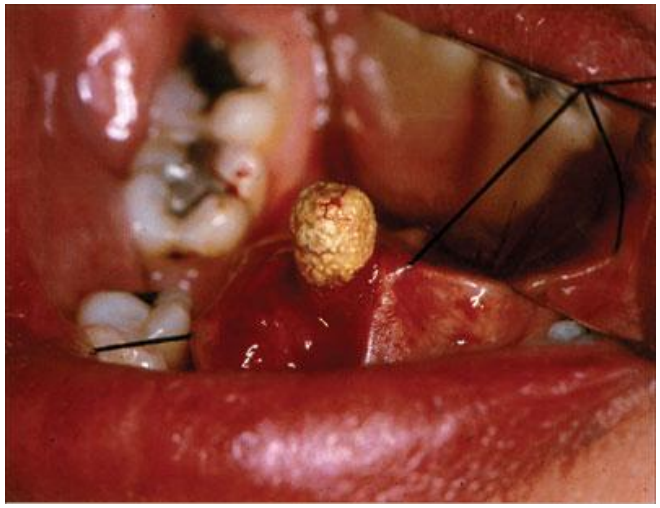
Коралловидный камень почки

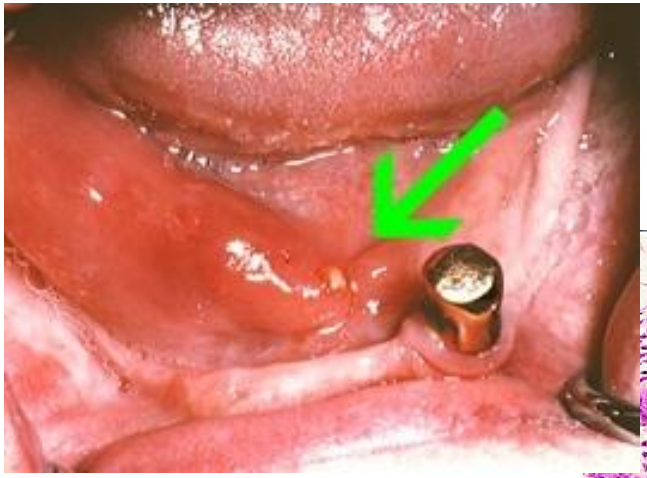


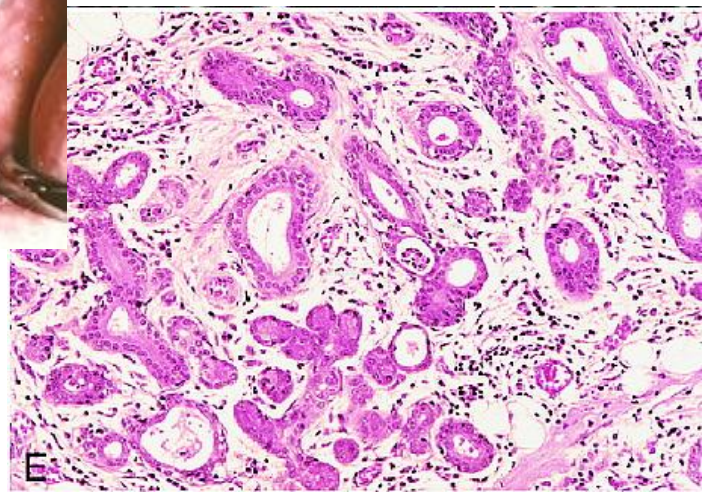


Sialolithiasis









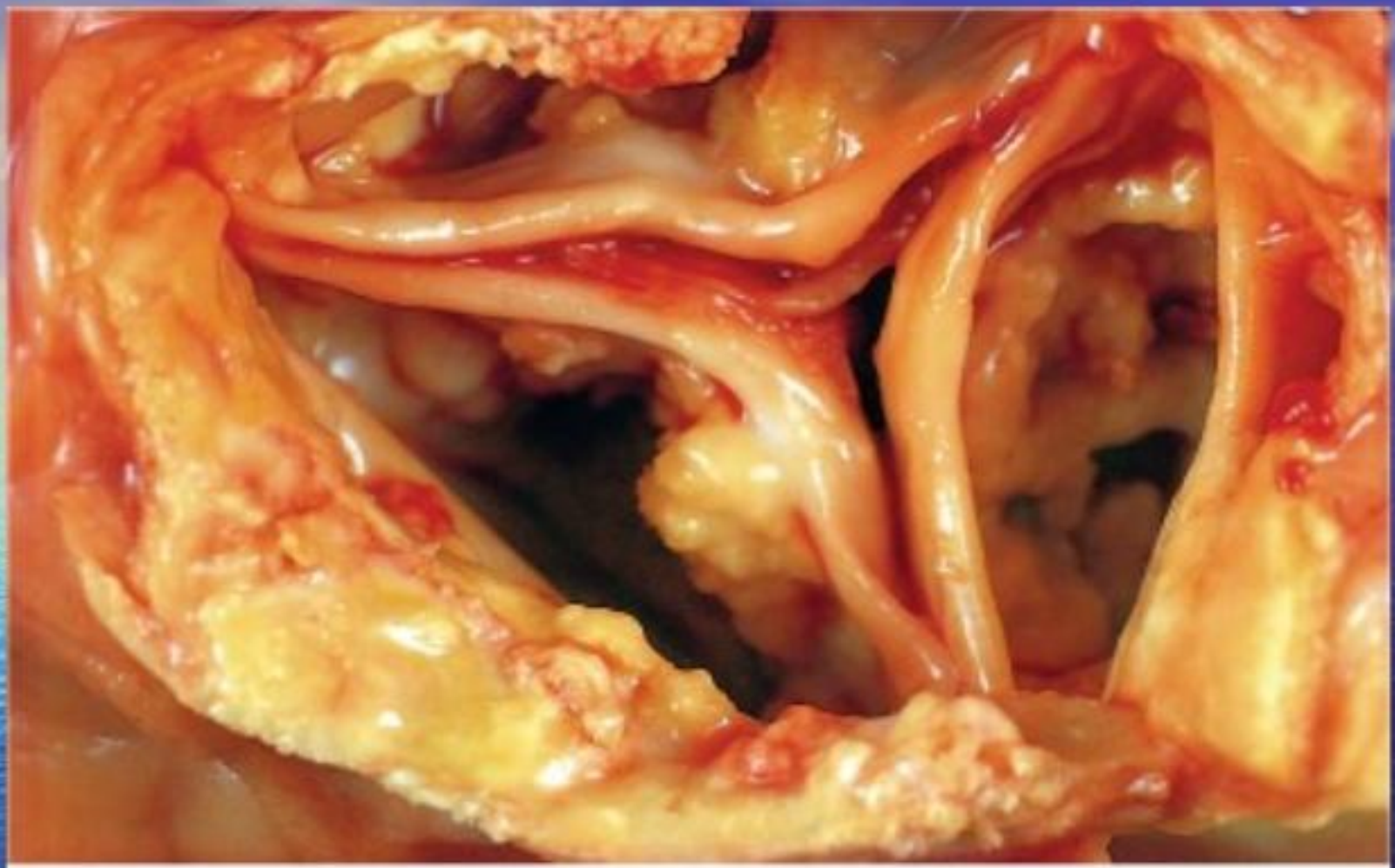
- Evident mononuclea infiltration, destruction of glandular structures, moderate fibrosis.

Pathologic Calcification

- the abnormal tissue deposition of calcium salts, together with smaller amounts of iron, magnesium, and other mineral salts.
- There are two forms of pathologic calcification:

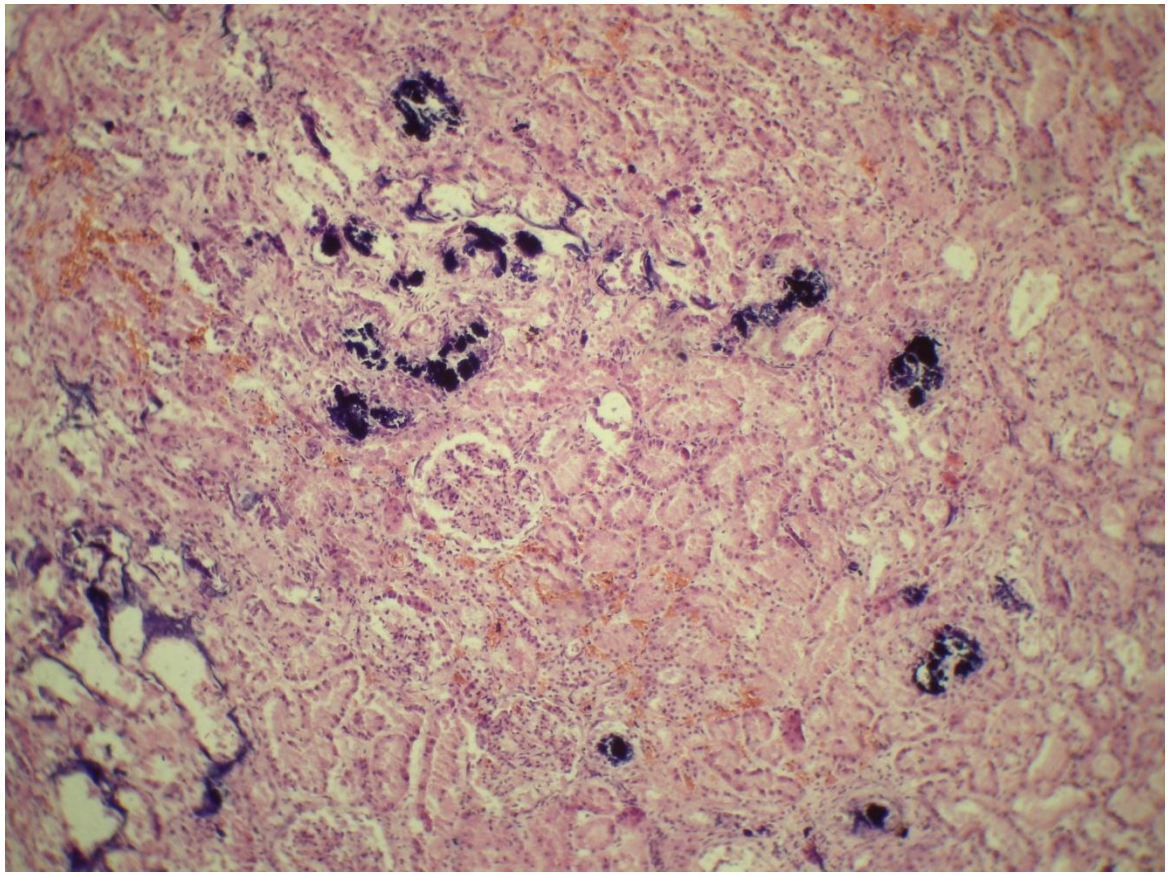
  1. *dystrophic calcification, when the deposition occurs locally in dying tissues* ; it occurs despite normal serum levels of calcium and in the absence of derangements in calcium metabolism.

  2.metastatic calcification, almost always results from hypercalcemia secondary to some disturbance in calcium metabolism.



- Figure 1-42 View looking down onto the unopened aortic valve in a heart with calcific aortic stenosis. The semilunar cusps are thickened and fibrotic. Behind each cusp are seen irregular masses of piled-up dystrophic calcification

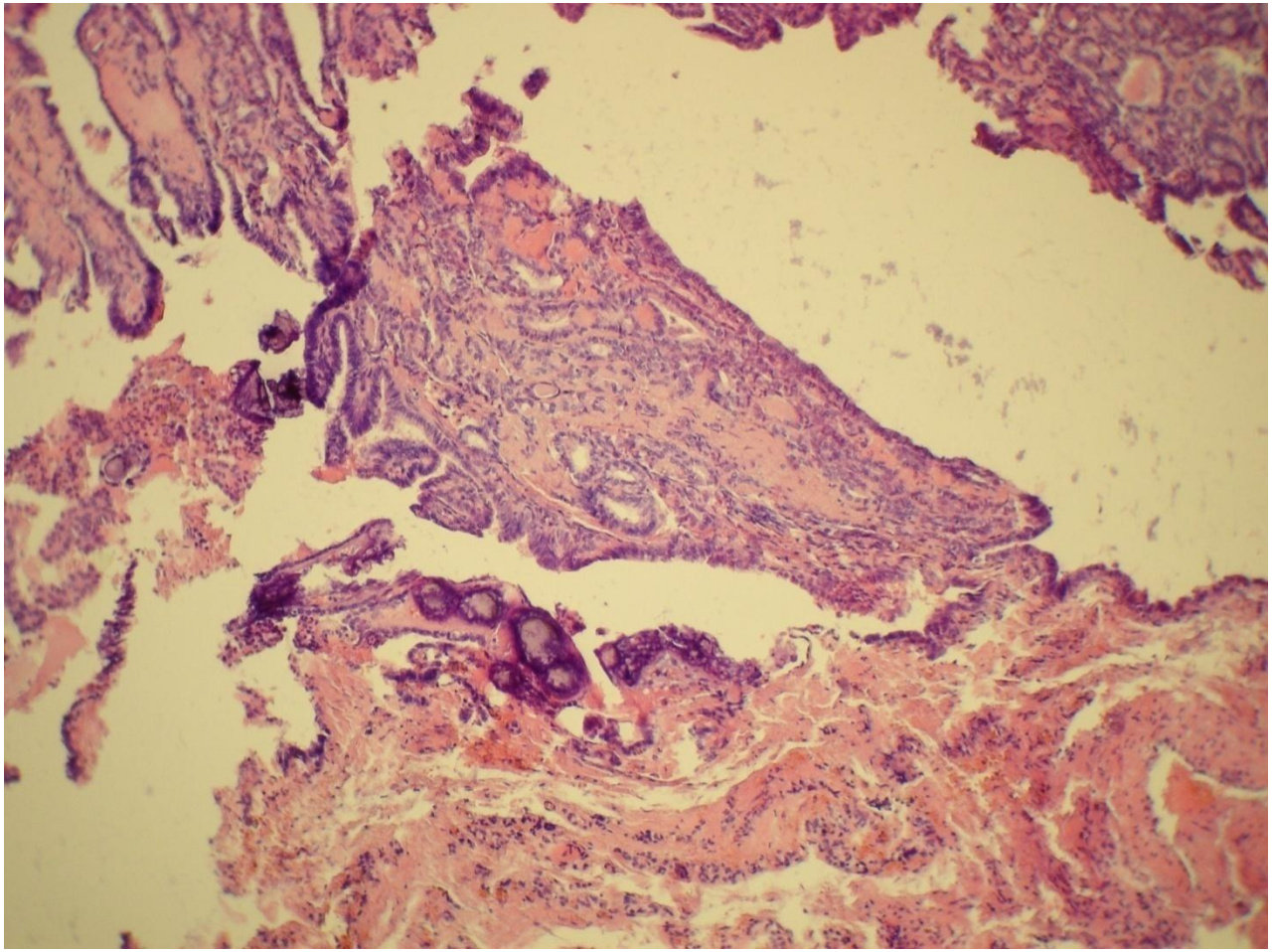
Depositions of calcium salts in the kidney. H&E. X 100.



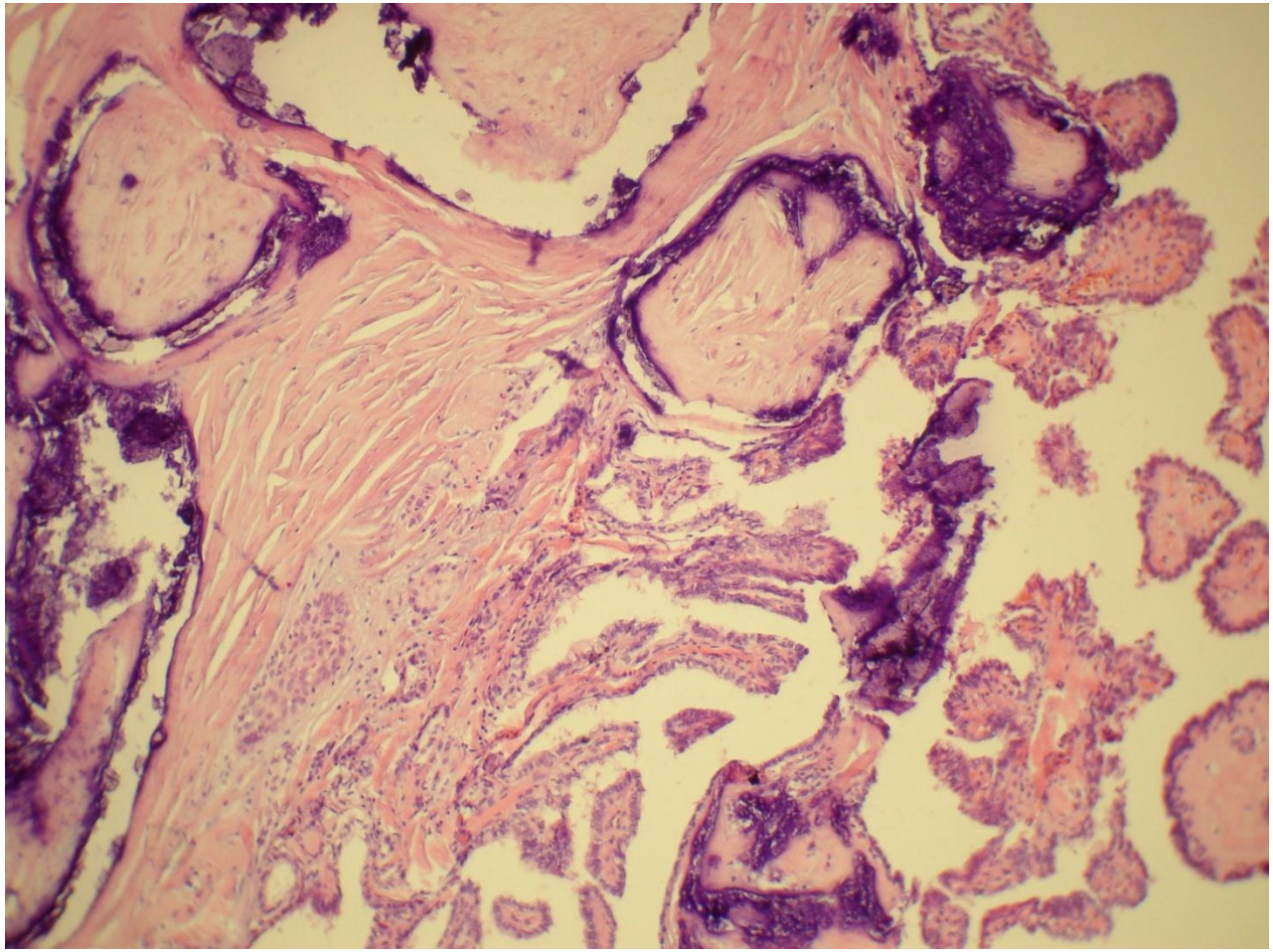
- Metastatic calcification
- Dystrophic calcification

Metastatic calcification appears to begin also in mitochondria except in kidney tubules, where it develops in the basement membranes, probably in relation to extracellular vesicles budding from the epithelial cells.

Depositions of calcium salts in the tyroid gland.
Papillary adenocarcinoma. H&E. X 100.



Depositions of calcium salts in the tyroid gland.
Papillary adenocarcinoma. H&E. X 100.



Gout

- Disease, which develops as a result of violations of purine metabolism and characterized by the deposition of uric acid and its salts in the tissues.
- The frequency of occurrence is 0.04-0.37% of the adult population, of which 93-98% of the patients are men aged 20-50 years.
- There is a hereditary predisposition linked to the sex.

Gout

Mechanisms of occurrence:

- infiltration of tissues with uric acid, in excess contained in the blood and entering the tissues.
- Perverted synthesis, when the primary can be the destruction under the action of unidentified factors of periarticular and some other tissues with the formation of uric acid in them, while a part of it enters the blood, where an increase in its concentration is observed.

Localization of the lesion:

- Joint and periarticular tissues of small joints of hands and feet, knee, elbow, shoulder and other joints;
- Skin of earlobe and prepuce sack;
- Some patients have gouty kidney damage.

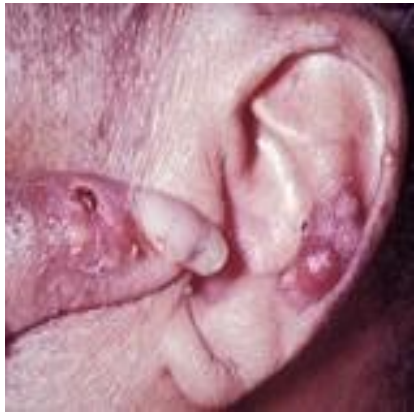
Gout: macroscopic picture

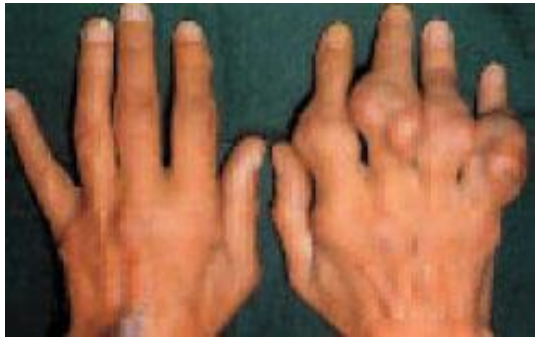
- Periarticular tissues are swollen and often sharply deformed;
- Active and passive movements in the joints are limited;
- The skin above the affected joints is edematic and hyperemic;

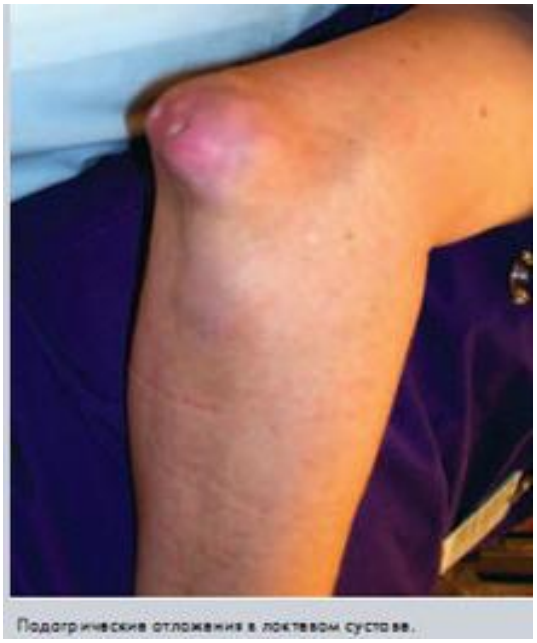
Gout: macroscopic picture - tofus

- Foci of uric acid and urate deposition;
- Foci with a diameter of 0.2-0.6 cm and more;
- Consistency - like a damp school chalk or a dried toothpaste;
- The masses are easily stained with a knife;
- In the epiphyses of bones - rarefaction of bone tissue and its demineralization;
- Around tophus - proliferation of connective tissue;
- Often - purulent bursitis with the formation of external fistulas with the departure of urates in the form of "rice corpuscles."
- With the deposition of urates in the synovial membrane - proliferation of granulation tissue, destruction of articular cartilage with the appearance of a superposition of white color.

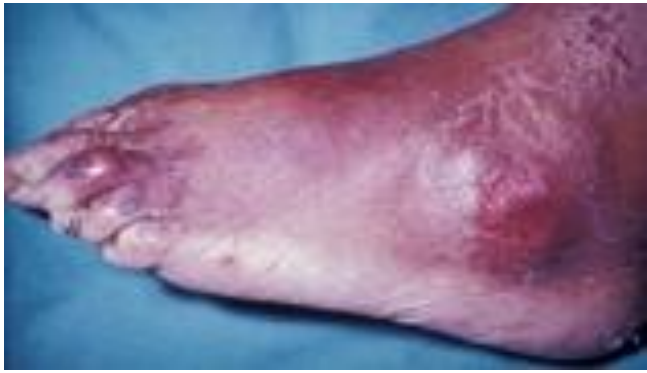
Gout

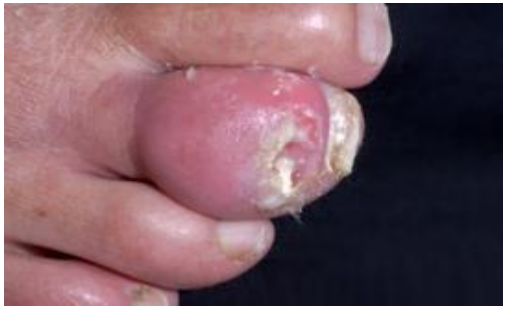


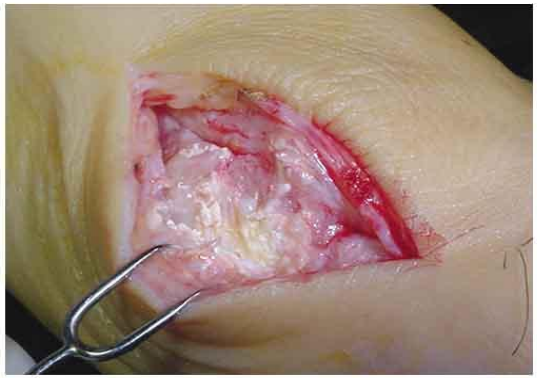




Подагрические отложения в локтевом суставе.



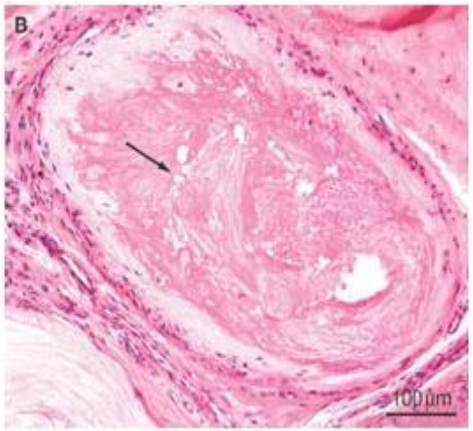


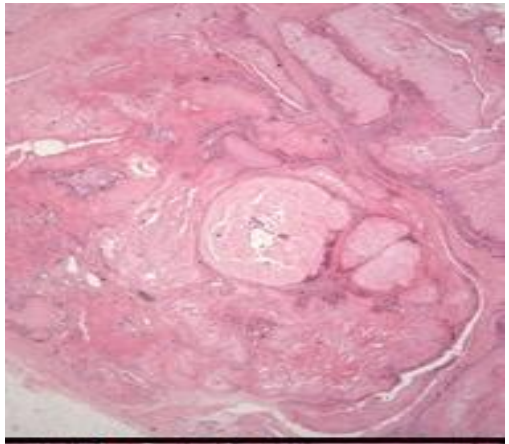


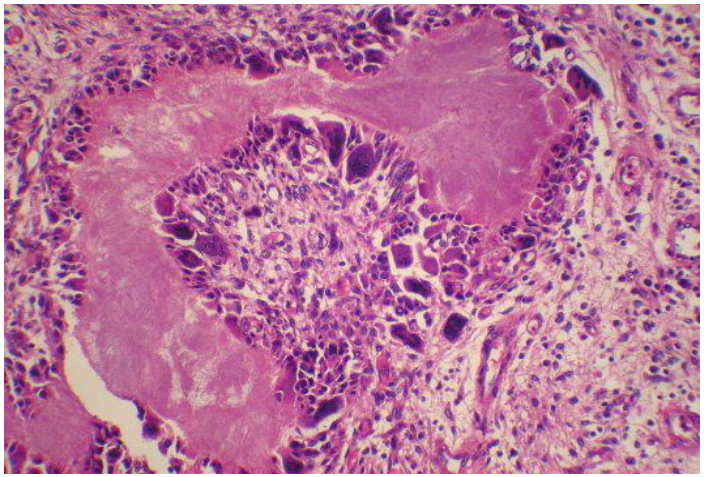
Gout: microscopic picture - tofus

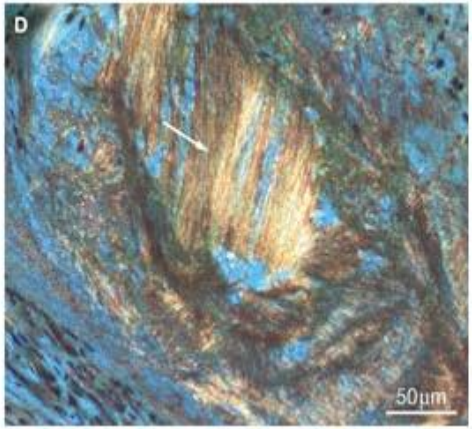
- In tissues - the deposition of needle crystals and amorphous weakly basophilic masses, surrounded by macrophages and giant multinuclear cells such as cells of foreign bodies;
- This is inflammatory aseptic reaction to foreign material;
- Over time, the formation of excess connective tissue around the tofus.

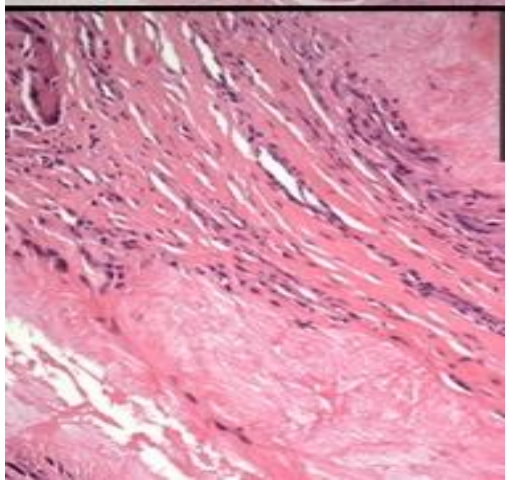
Подагра: тофусы

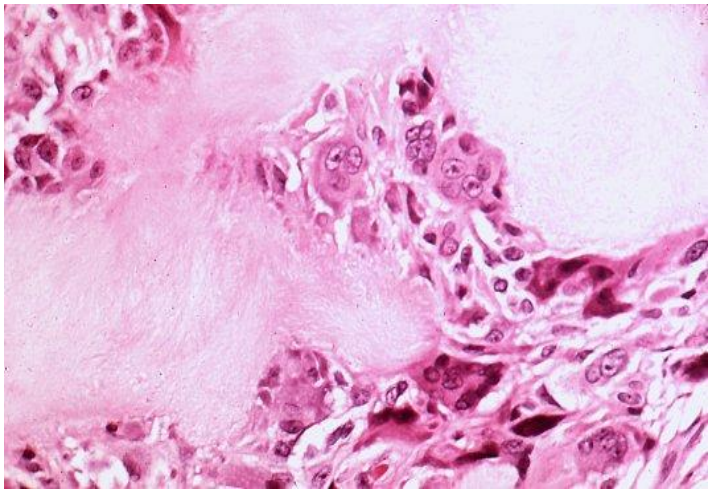




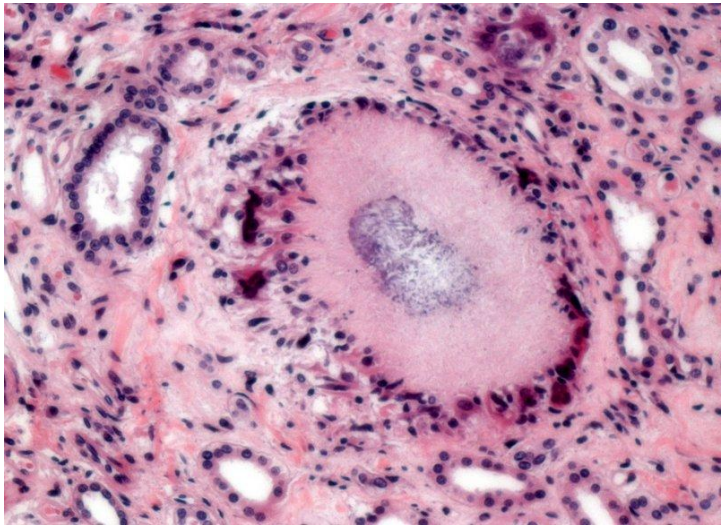








Gout



Gouty kidney:

- The formation of calculi in the pelvis, ureters and bladder,
- In the future - pyelonephritis and nephrosclerosis.

Types of Cell Death

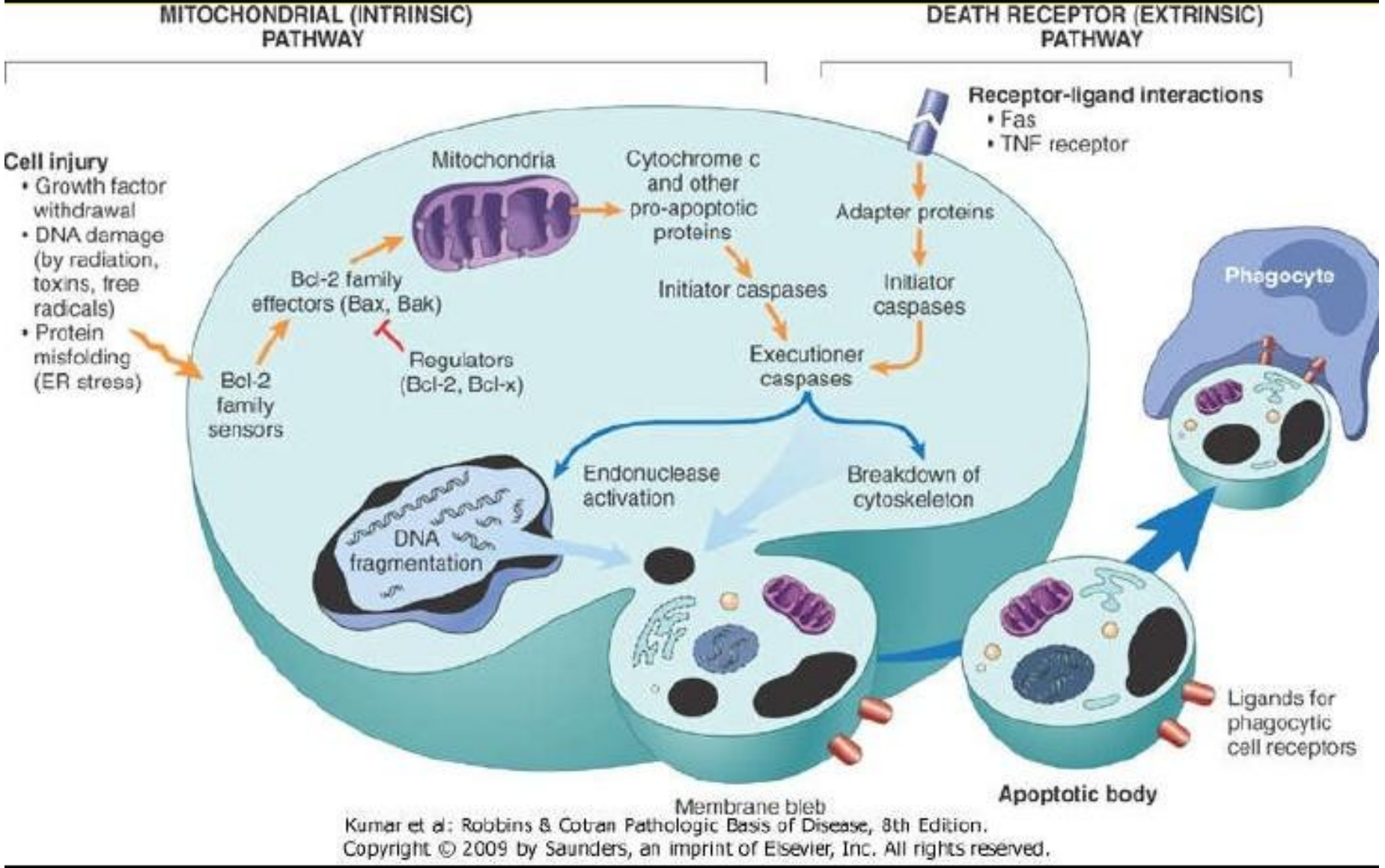
- Apoptosis
  - Usually a regulated, controlled process
  - Plays a role in embryogenesis
- Necrosis
  - Always pathologic – the result of irreversible injury
  - Numerous causes

Apoptosis

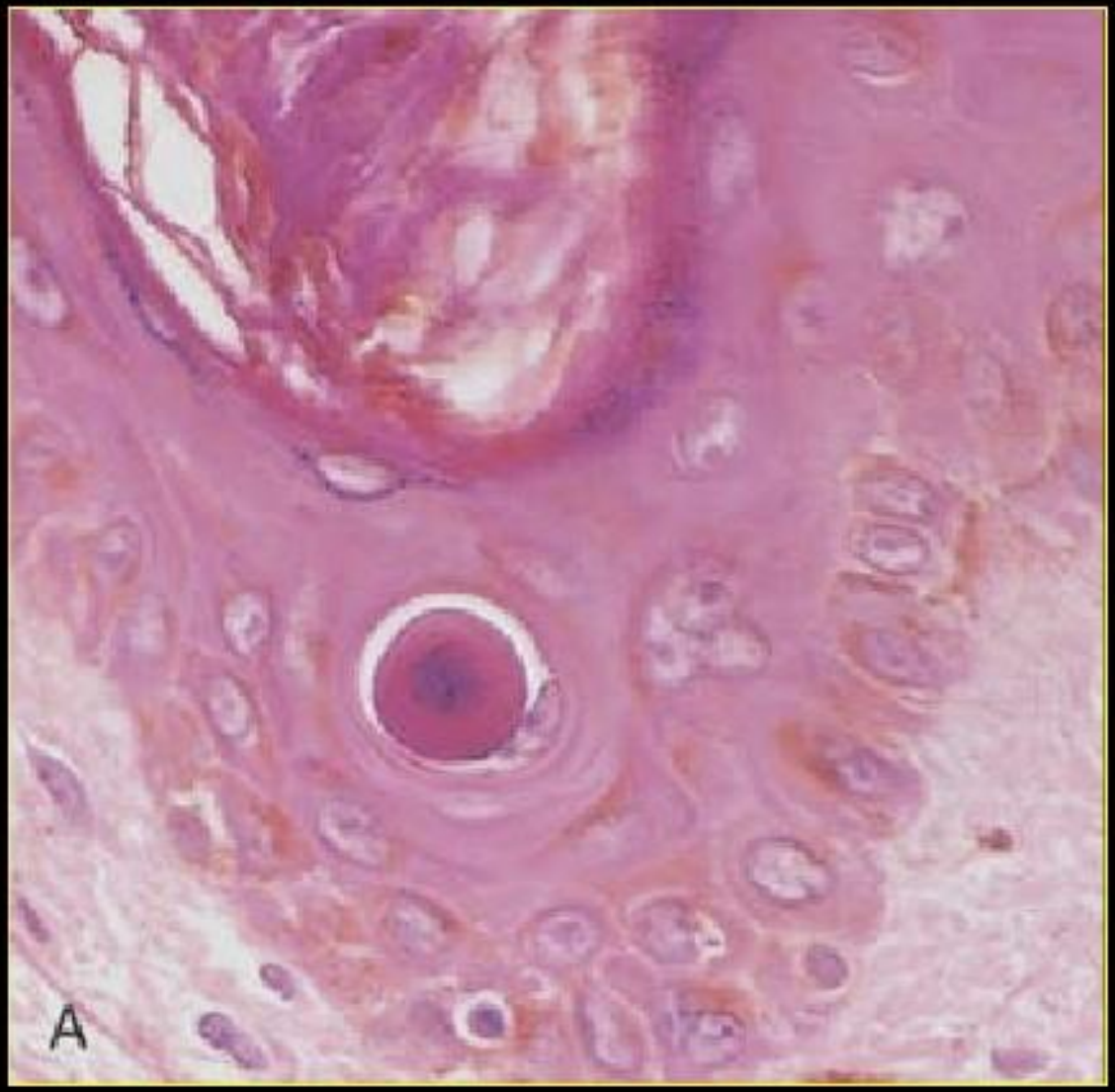
- Involved in many processes, some physiologic, some pathologic
  - Programmed cell death during embryogenesis
  - Hormone-dependent involution of organs in the adult (e.g., thymus)
  - Cell deletion in proliferating cell populations
  - Cell death in tumors
  - Cell injury in some viral diseases (e.g., hepatitis)

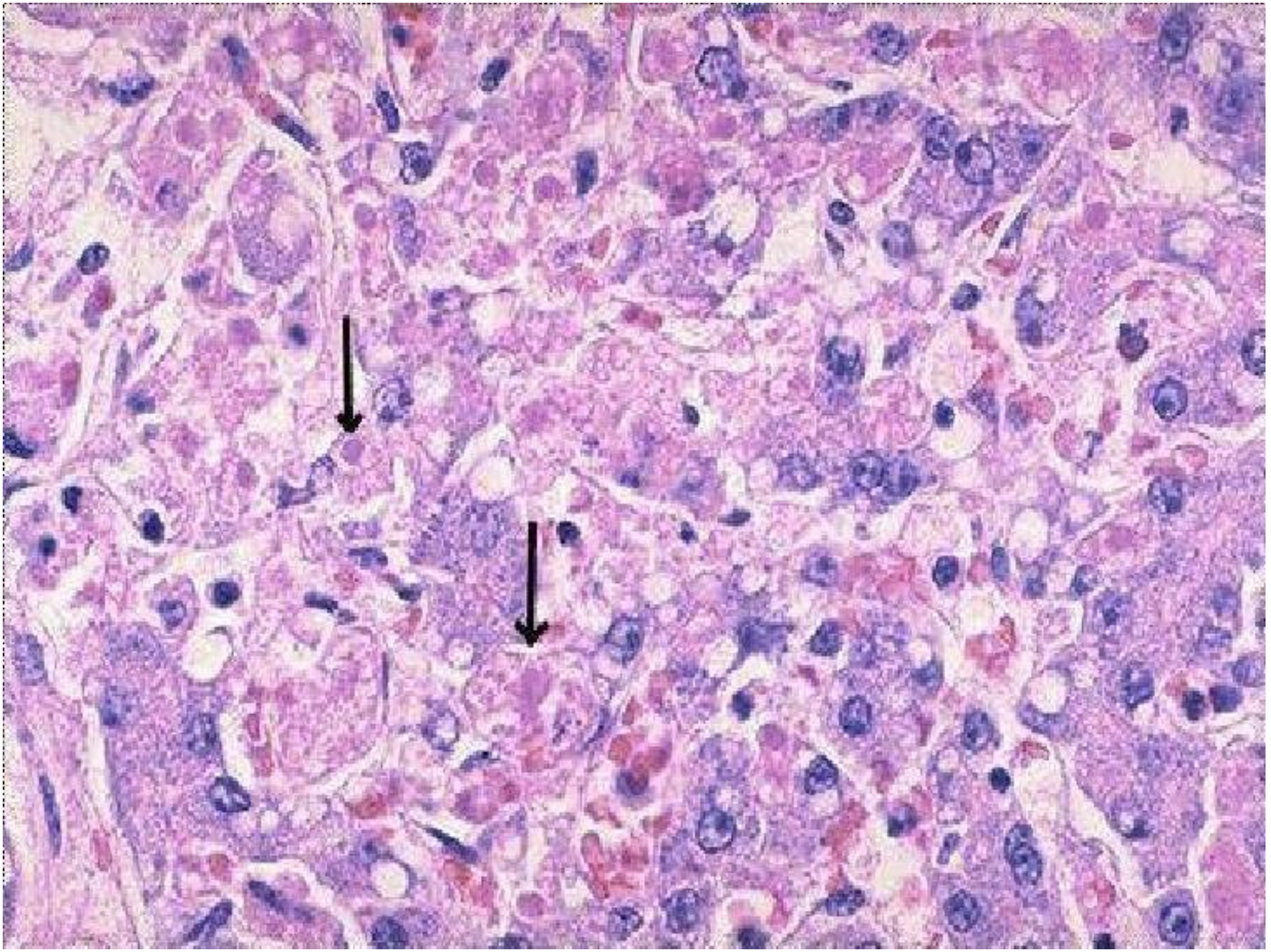
Apoptosis – Morphologic Features

- Cell shrinkage with increased cytoplasmic density
- Chromatin condensation
- Formation of cytoplasmic blebs and apoptotic bodies
- Phagocytosis of apoptotic cells by adjacent healthy cells



Kumar et al: Robbins & Cotran Pathologic Basis of Disease, 8th Edition.





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 pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic, means of or eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage

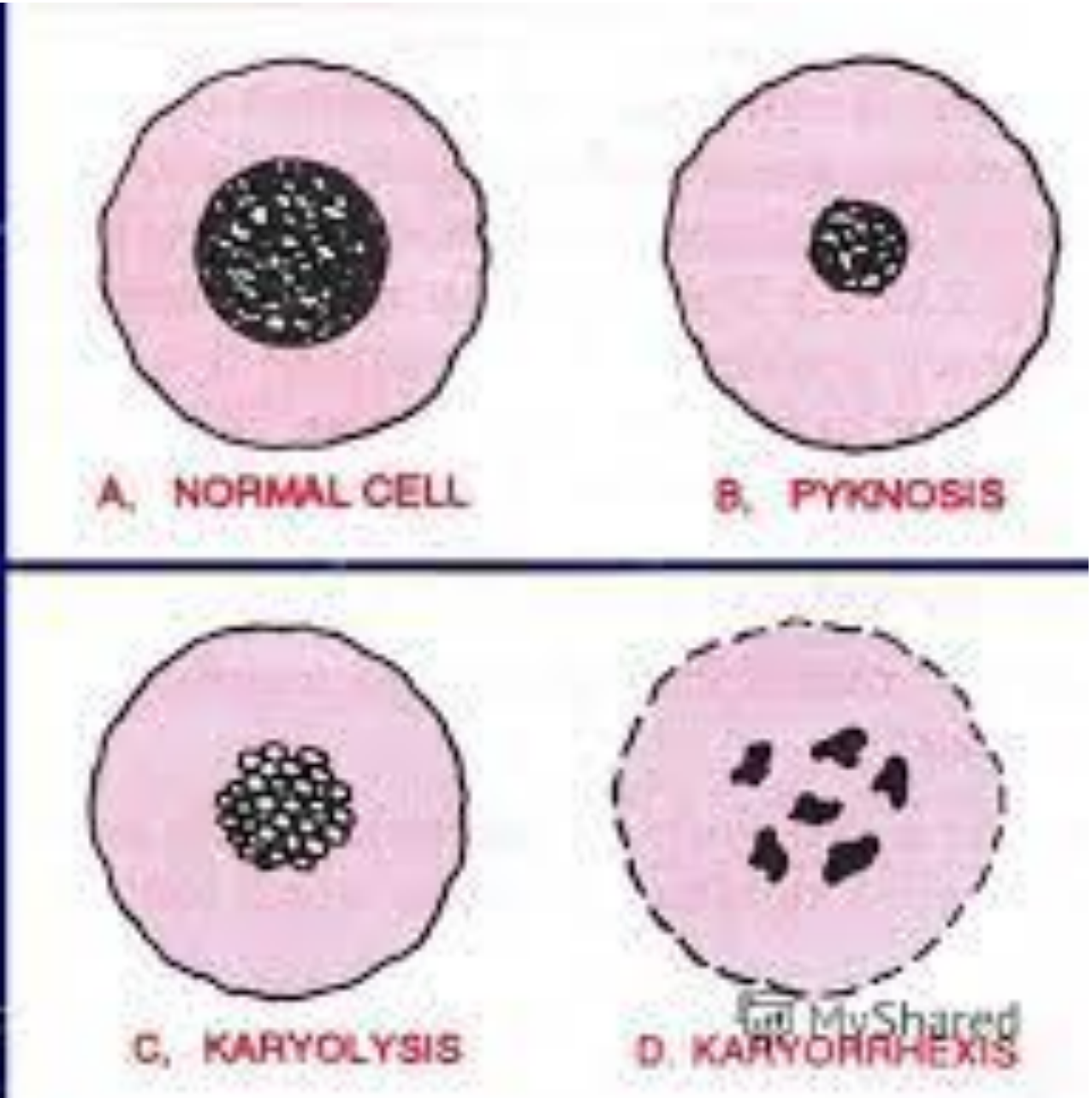
Irreversible Injury -- Morphology

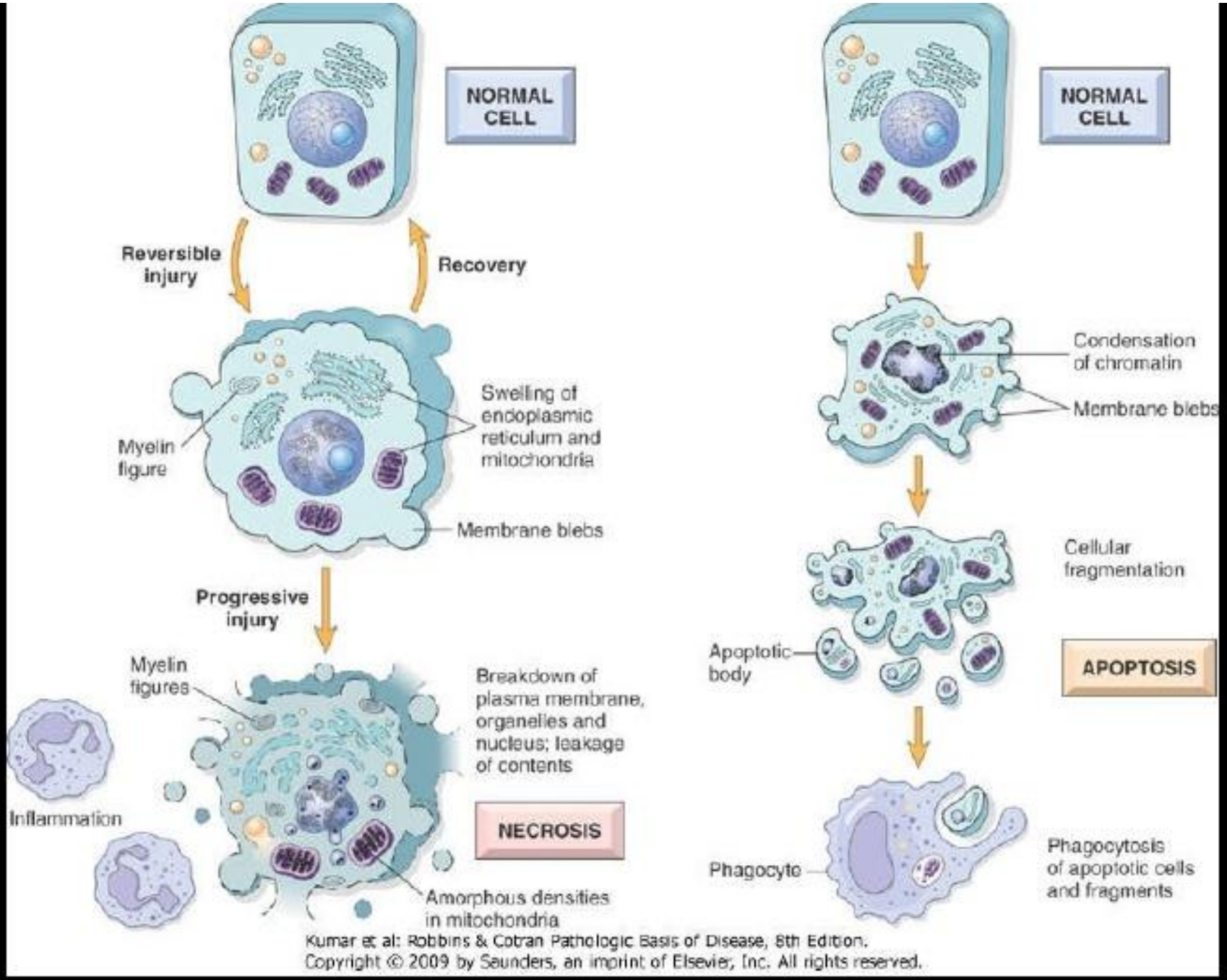
- Light microscopic changes
  - Increased cytoplasmic eosinophilia (loss of RNA, which is more basophilic)
  - Cytoplasmic vacuolization
  - Nuclear chromatin clumping
- Ultrastructural changes
  - Breaks in cellular and organellar membranes
  - Larger amorphous densities in mitochondria
  - Nuclear changes

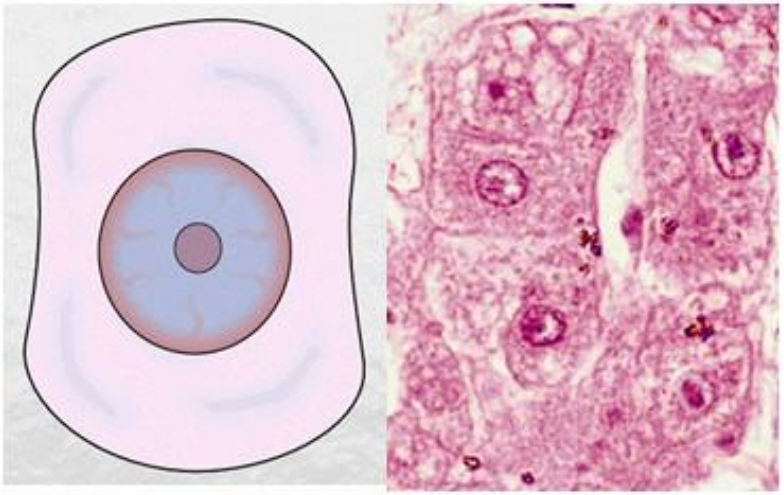
Irreversible Injury – Nuclear Changes

- Pyknosis
  - Nuclear shrinkage and increased basophilia
- Karyorrhexis
  - Fragmentation of the pyknotic nucleus
- Karyolysis
  - Fading of basophilia of chromatin

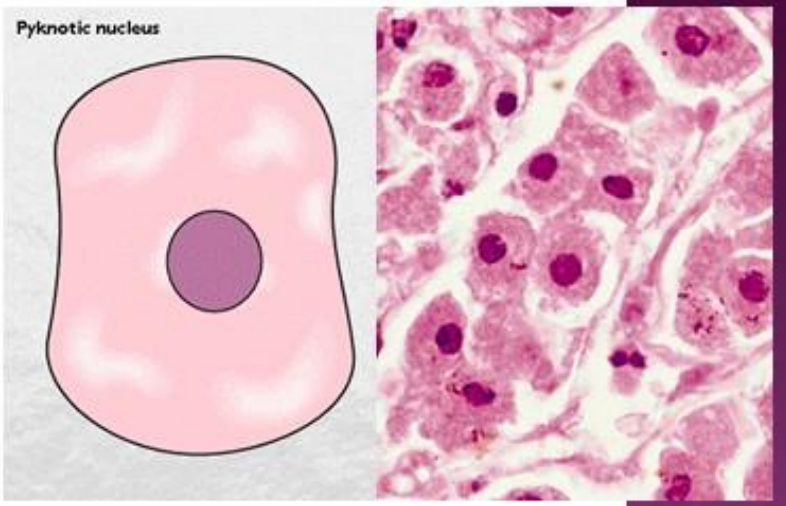
Кариопикноз
кариолизис
и
кариорексис



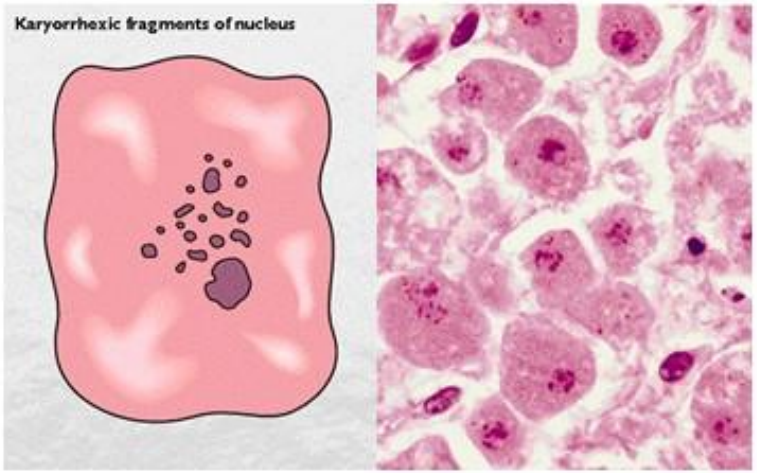




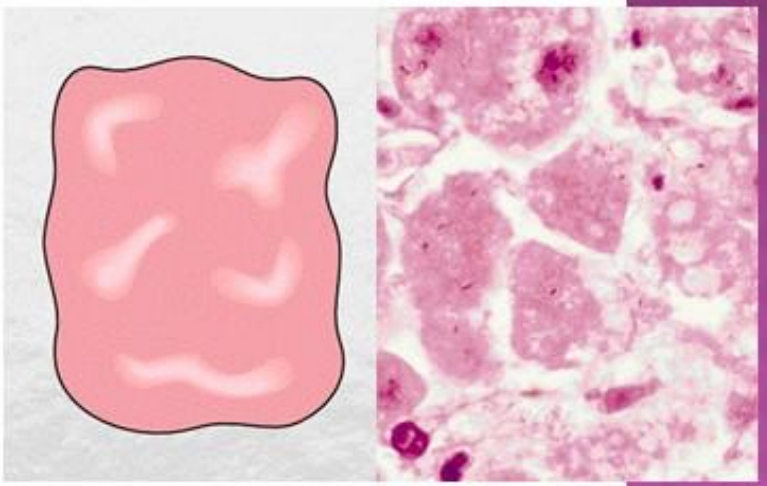
нормальное ядро



кариопикноз



кариорексис



кариолизис

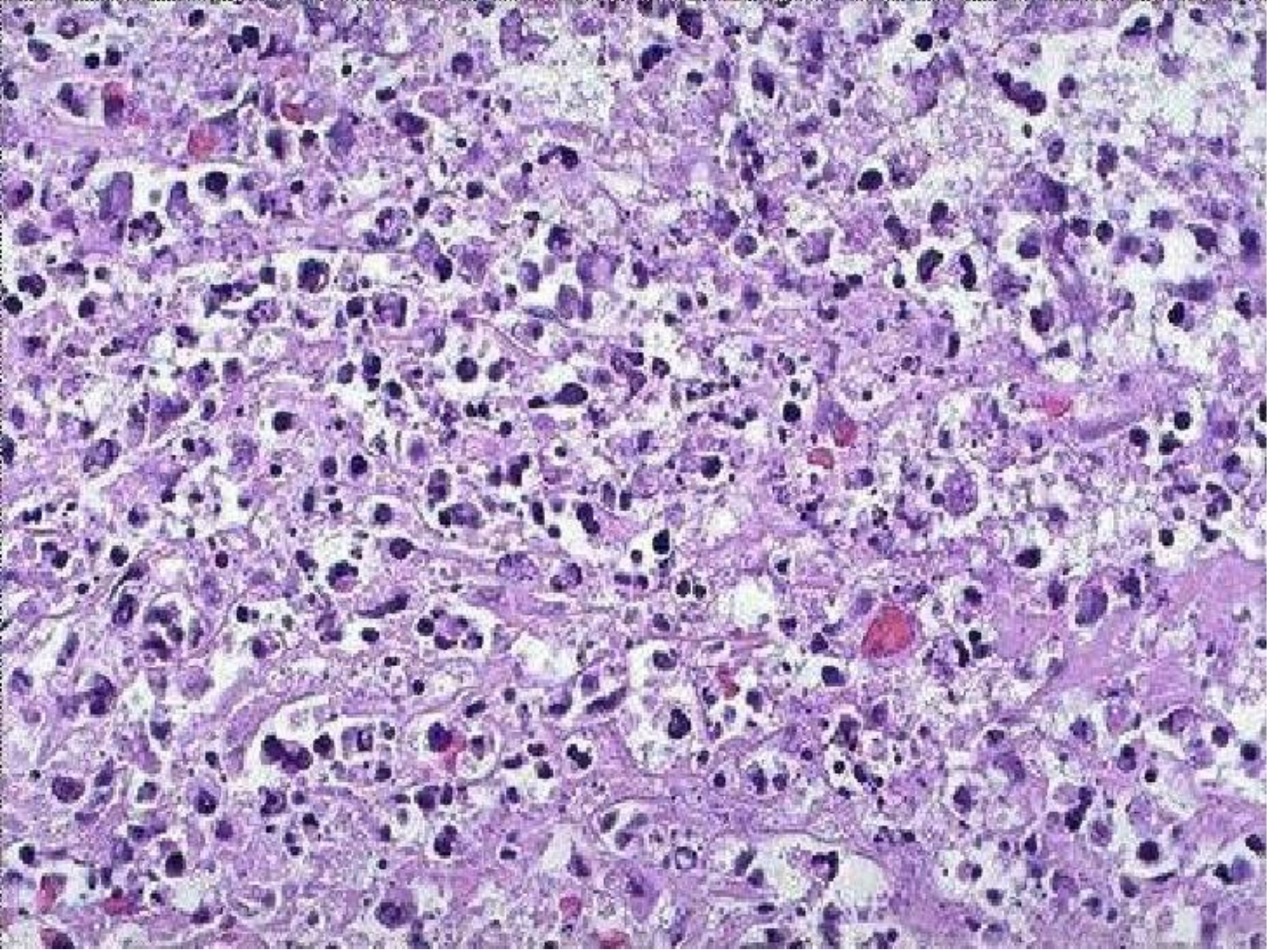
Morphology

- Necrotic cells show increased eosinophilia in hematoxylin and eosin (H & E) stains, attributable in part to the loss of cytoplasmic RNA (which binds the blue dye, hematoxylin) and in part to denatured cytoplasmic proteins (which bind the red dye, eosin).

- The necrotic cell may have a more glassy homogeneous appearance than do normal cells, mainly as a result of the loss of glycogen particles
- When enzymes have digested the cytoplasmic organelles, the cytoplasm becomes vacuolated and appears moth-eaten. Dead cells may be replaced by large, whorled phospholipid masses called myelin figures that are derived from damaged cell membranes

- These phospholipid precipitates are then either phagocytosed by other cells or further degraded into fatty acids; calcification of such fatty acid residues results in the generation of calcium soaps. Thus, the dead cells may ultimately become calcified.

- By electron microscopy, necrotic cells are characterized by discontinuities in plasma and organelle membranes, marked dilation of mitochondria with the appearance of large amorphous densities, intracytoplasmic myelin figures, amorphous debris, and aggregates of fluffy material probably representing denatured protein



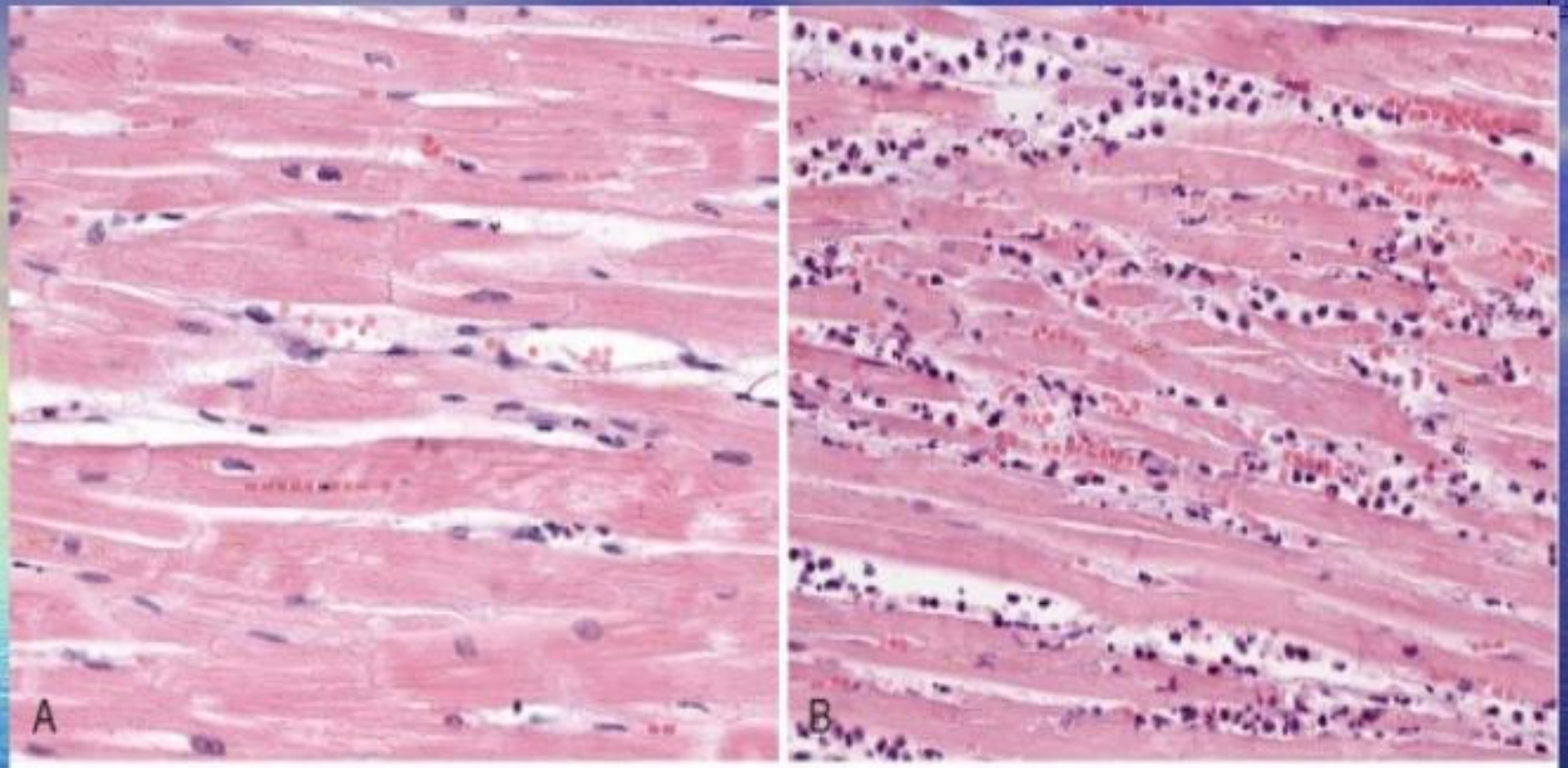
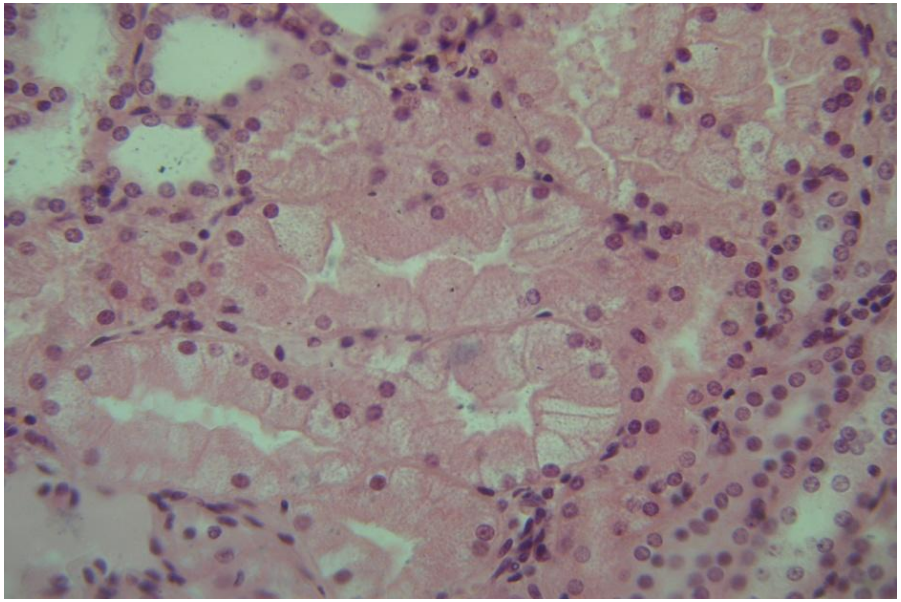
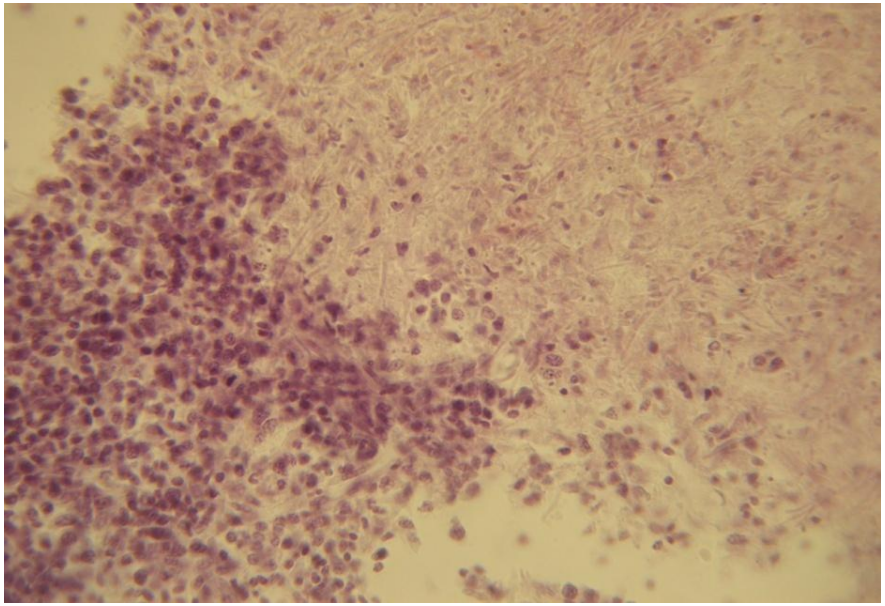


Figure 1-18 Ischemic necrosis of the myocardium. *A*, Normal myocardium. *B*, Myocardium with coagulation necrosis (upper two thirds of figure), showing strongly eosinophilic anucleate myocardial fibers. Leukocytes in the interstitium are an early reaction to necrotic muscle. Compare with *A* and with normal fibers in the lower part of the figure.

Morphology of necrosis

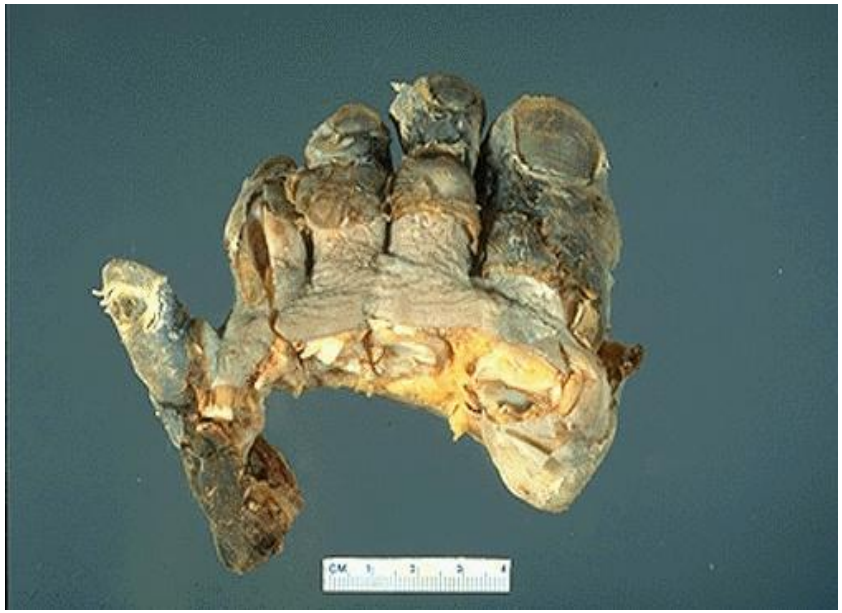


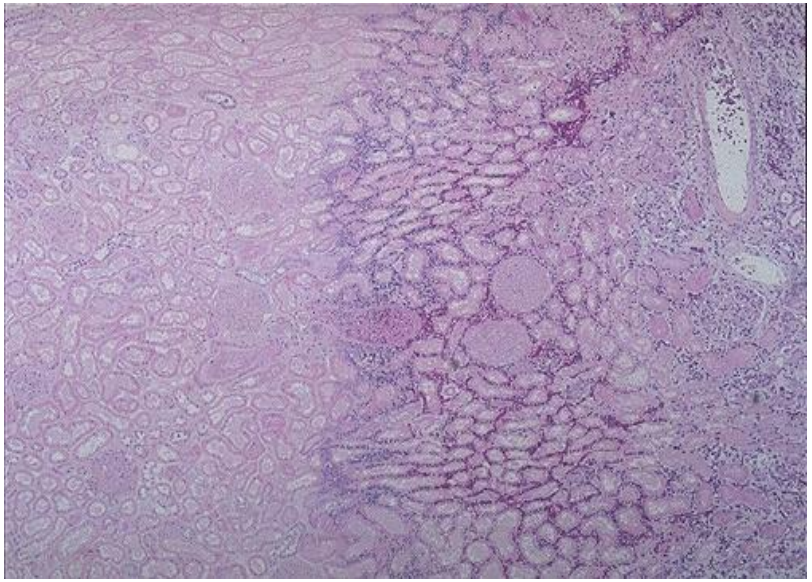
- *Karyolysis of the renal tubular epithelium*



- *Necrosis of the lymphoid tissue of the tonsil in scarlet fever*

Morphology of necrosis





- Zone of necrosis - reactive inflammation (demarcation line) - unchanged tissue.

- ***Demarcation inflammation:***
- View of a red band of plethora with a yellow border adjacent directly to the necrotic tissue;
- Accumulations of leukocytes.

Classification of necrosis according to the cause:

- - traumatic necrosis;
- - toxic necrosis;
- - trophoneurotic necrosis;
- - allergic necrosis;
- - vascular or ischemic necrosis.

Classification of necrosis due to mechanisms of development

- **Direct necrosis** (traumatic, toxic)
- **Indirect necrosis** (trophoneurotic, allergic, vascular)

What are the types of necrosis?

- Coagulation Necrosis
- Liquefactive or Colliquative Necrosis
- Fat Necrosis
- Caseous Necrosis
- Gangrenous Necrosis
- Fibrinoid Necrosis

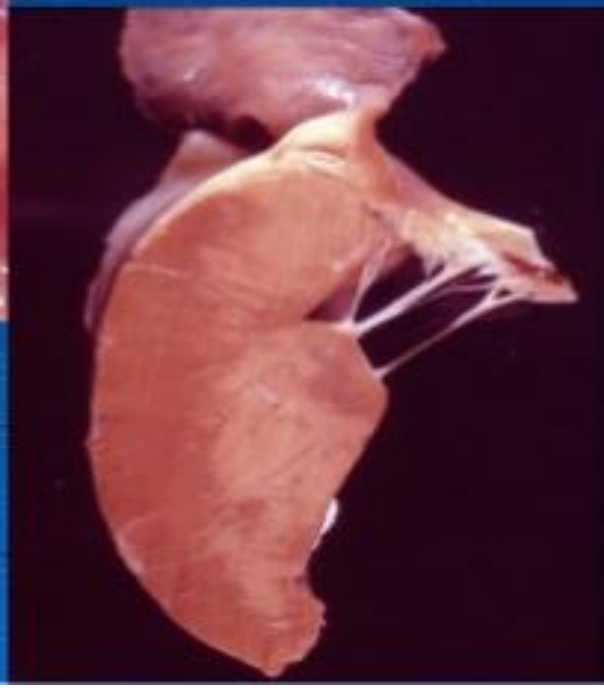
Coagulative Necrosis

- Cell's basic outline is preserved
- Homogeneous, glassy eosinophilic appearance due to loss of cytoplasmic RNA (basophilic) and glycogen (granular)
- Nucleus may show pyknosis, karyolysis or karyorrhexis

Coagulation Necrosis

Gross Appearance

- architecture resembles normal tissue, but colorant texture are different.
- lighter in color (pale) -due to coagulation of cytoplasmic proteins and decreased blood flow (eg infarcts).
- usually firm.
- tissue may be swollen or shrunken.
- may see a local vascular / inflammatory reaction to necrotic tissue.



Coagulation Necrosis

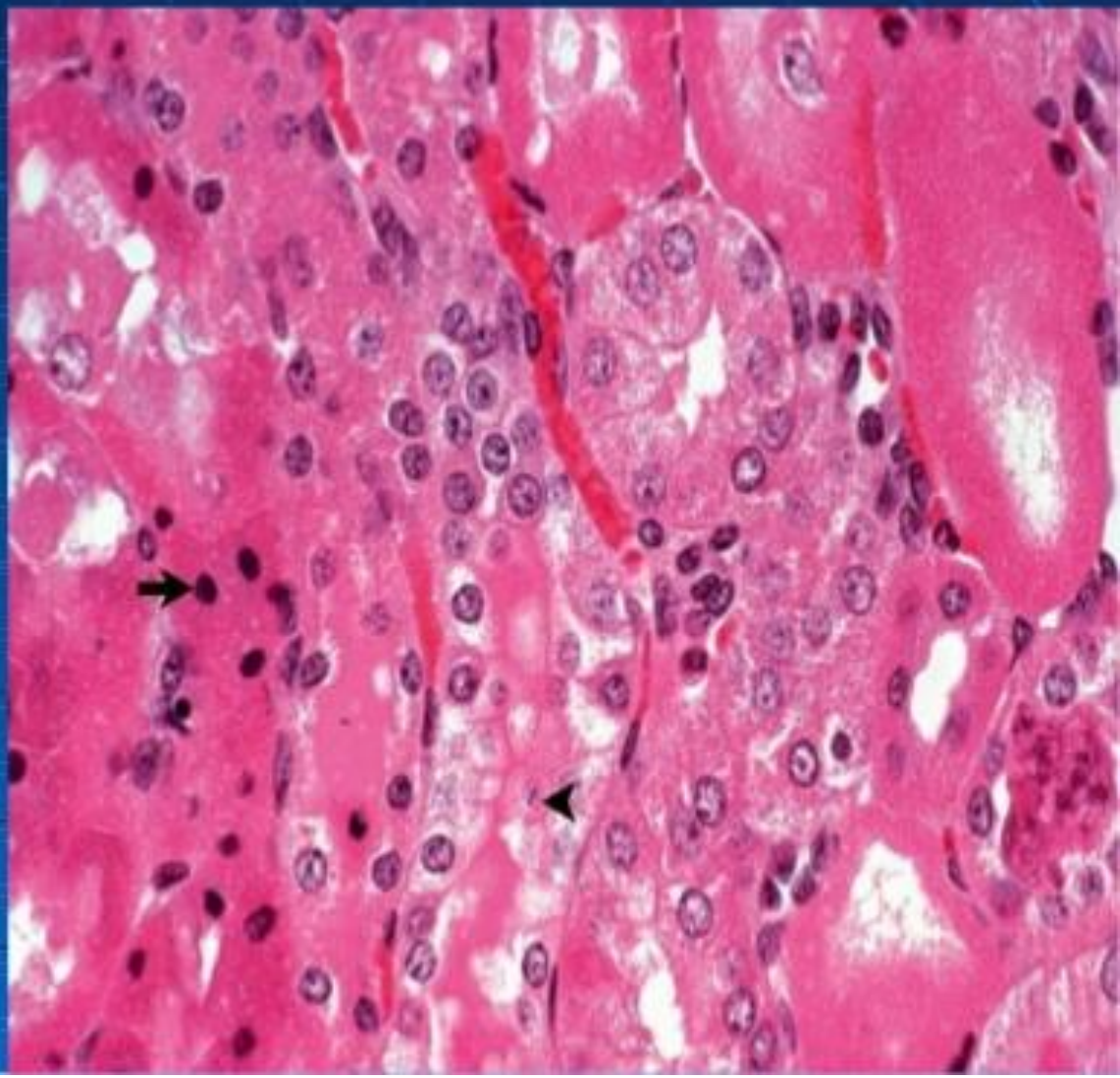
Microscopic Appearance

- original cell shape & tissue architecture is Preserve die dead cells resemble an eosinophilic "shadow" of the original cells.
- cytoplasm: increased eosinophilia (H&E stain)usually hyalinized (homogeneous glassy appearance) may be mineralized.

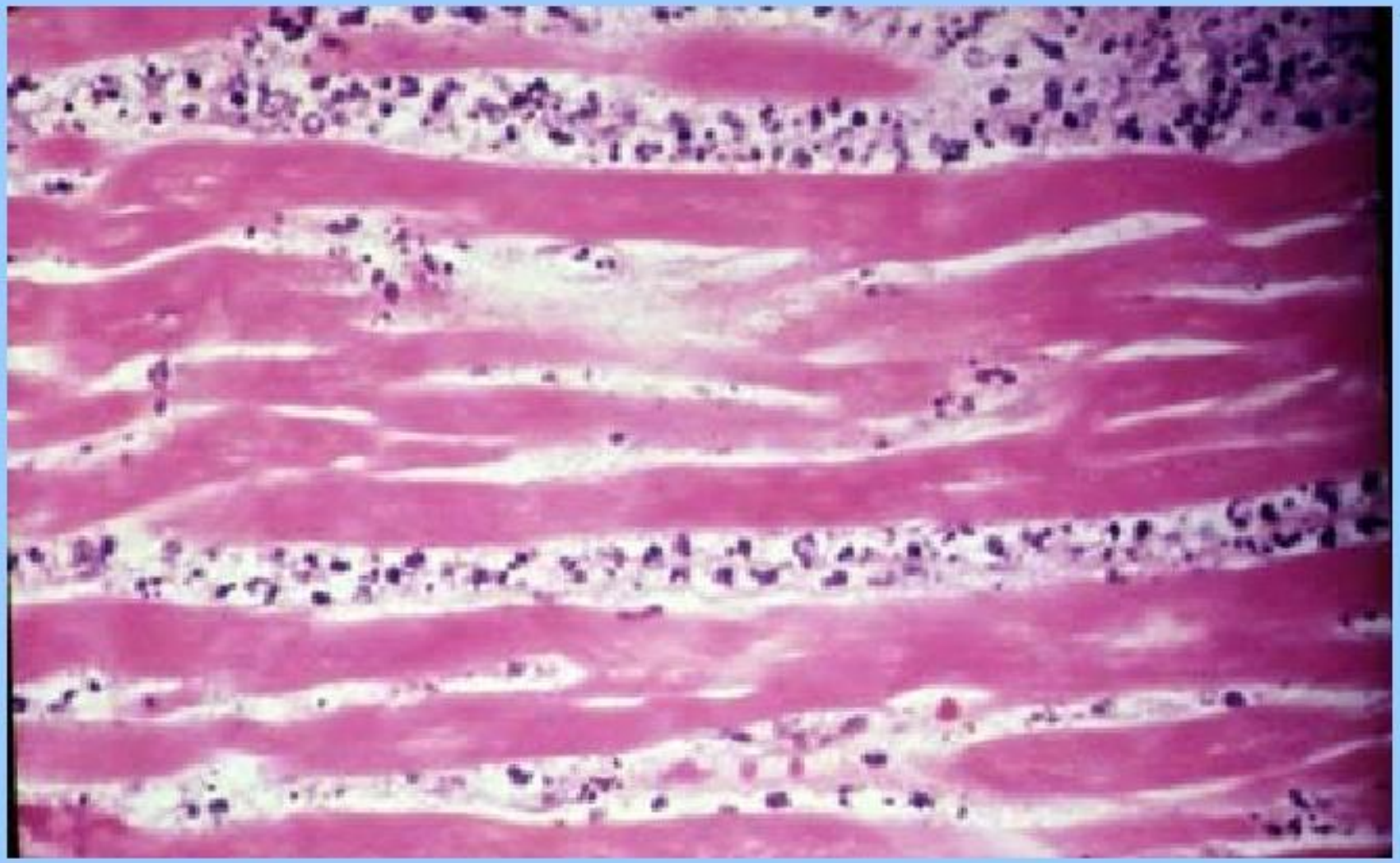
a) Coagulation Necrosis

- nucleus:

1. karyolysi
2. pyknosis
3. karyorrhexis

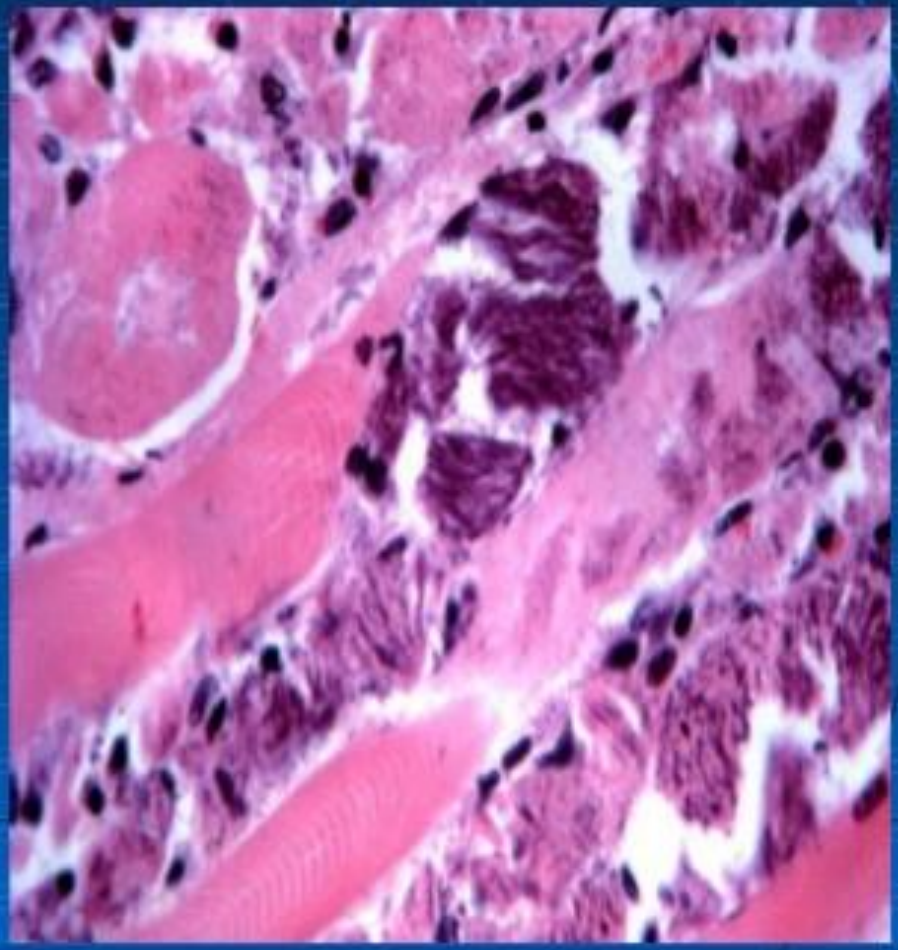


COAGULATION NECROSIS-HEART



Skeletal muscle

note coagulation necrosis of myofibers characterized by fragmentation and hyalinization; also note extensive mineralization (blue-purple staining)



Infarction

- This is necrosis resulting from the cessation of blood supply to a tissue or organ.

- A heart attack is also called circulatory necrosis.

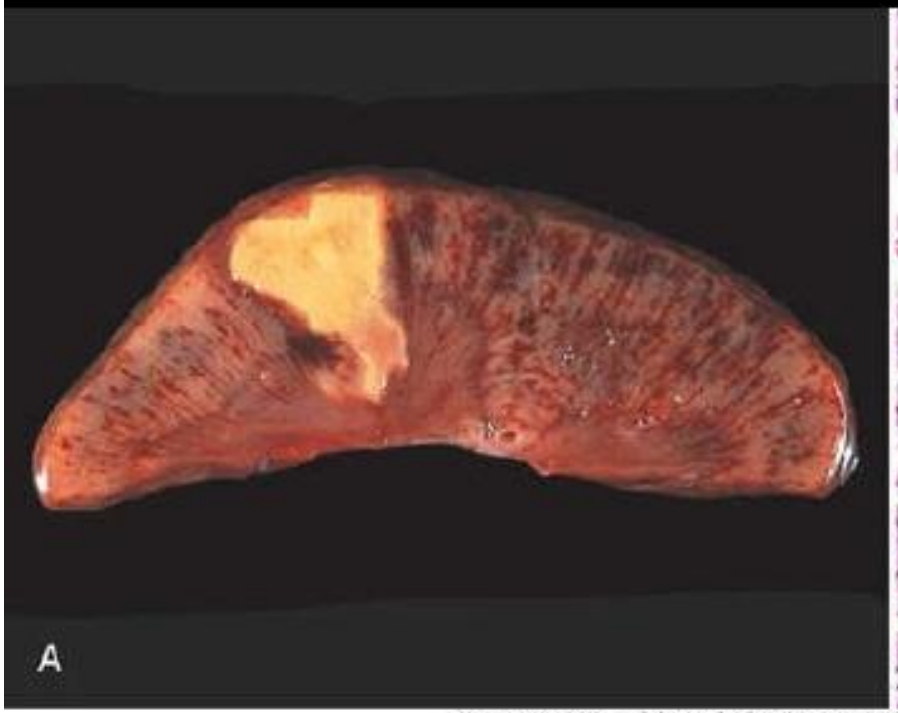
Types of infarction

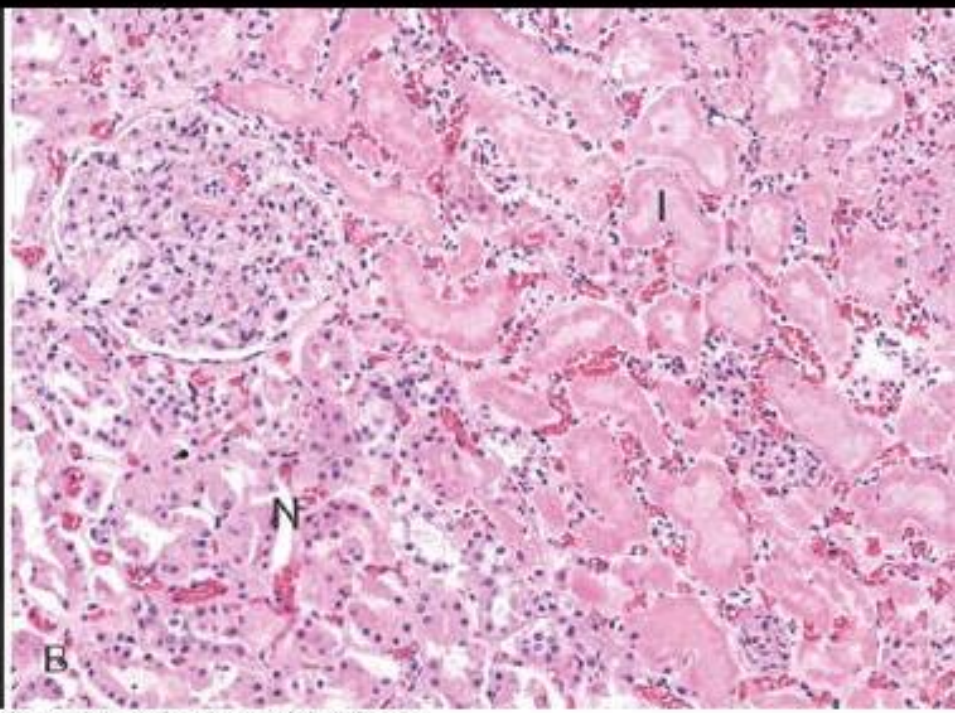
1. ***white (ischemic) infarction***,
2. ***red (hemorrhagic) infarction***,
3. ***white (ischemic) infarction with a hemorrhagic rim (corolla).***

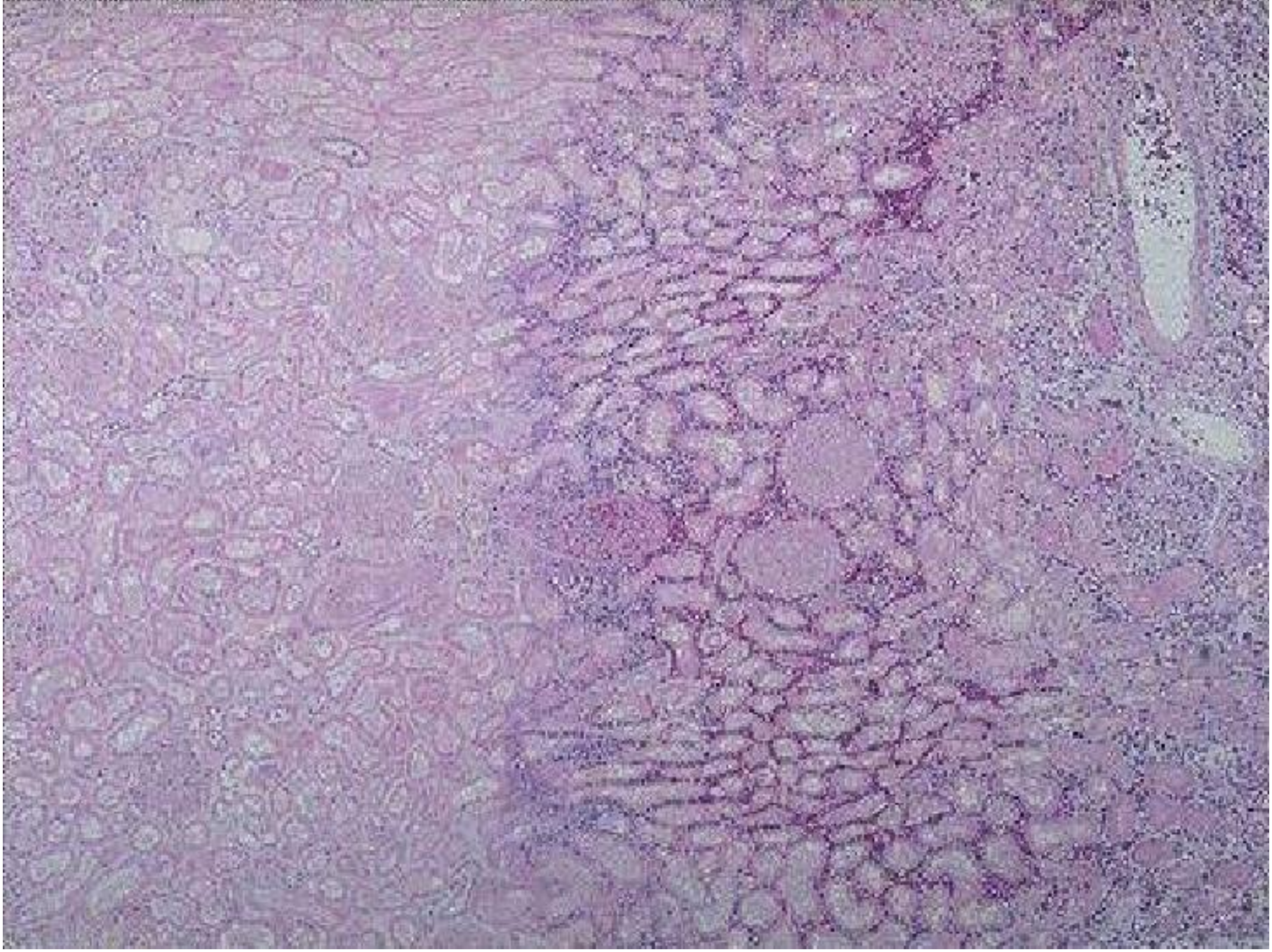
- The difference in the morphology of the types of infarction is due to the unequal mechanisms of their development.
- Macroscopically infarction of any type can be either conical or irregular.
- A conical shape is usually a heart attack that develops in the pool of arteries with a main branching type,
- irregular shape - with loose type.

White (ischemic) infarction

- his type of infarction occurs in the spleen, liver.
- Its development is preceded by the ischemic stage.
- Formed ischemic infarction becomes visible to the naked eye after about 1 day.
- ***Microscopically*** in the infarction zone: necrosis is more often coagulative, less often colliquation type (brain).
- On the periphery, the zone of necrosis is limited by the inflammatory demarcation shaft.







Red (hemorrhagic) infarction

- the area of necrosis is saturated with blood. due to which the site of infarction acquires a dark red color.

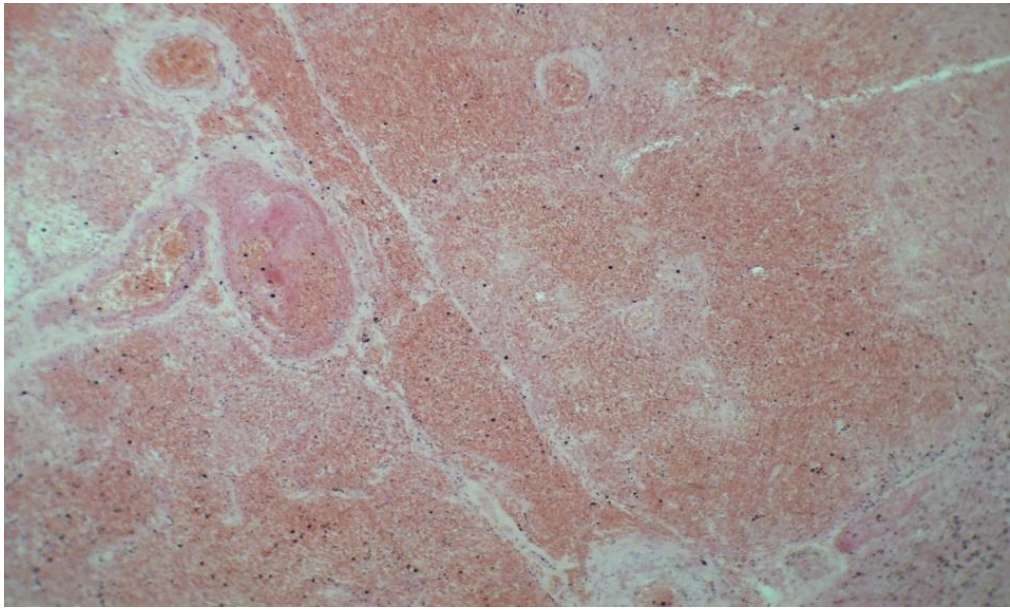
- more often in the lung, brain, intestines.

- Conditions contributing to its development: venous stasis and double blood supply to the organ (from different vascular systems).

- ***Microscopically:*** masses of agglutinated and hemolyzed erythrocytes replacing the destroyed structures of the organ.
- A feature of the perifocal reaction is the presence of a large number of siderophages and hemosiderin lumps.

Red (hemorrhagic) infarction

- *Hemorrhagic pulmonary infarction*

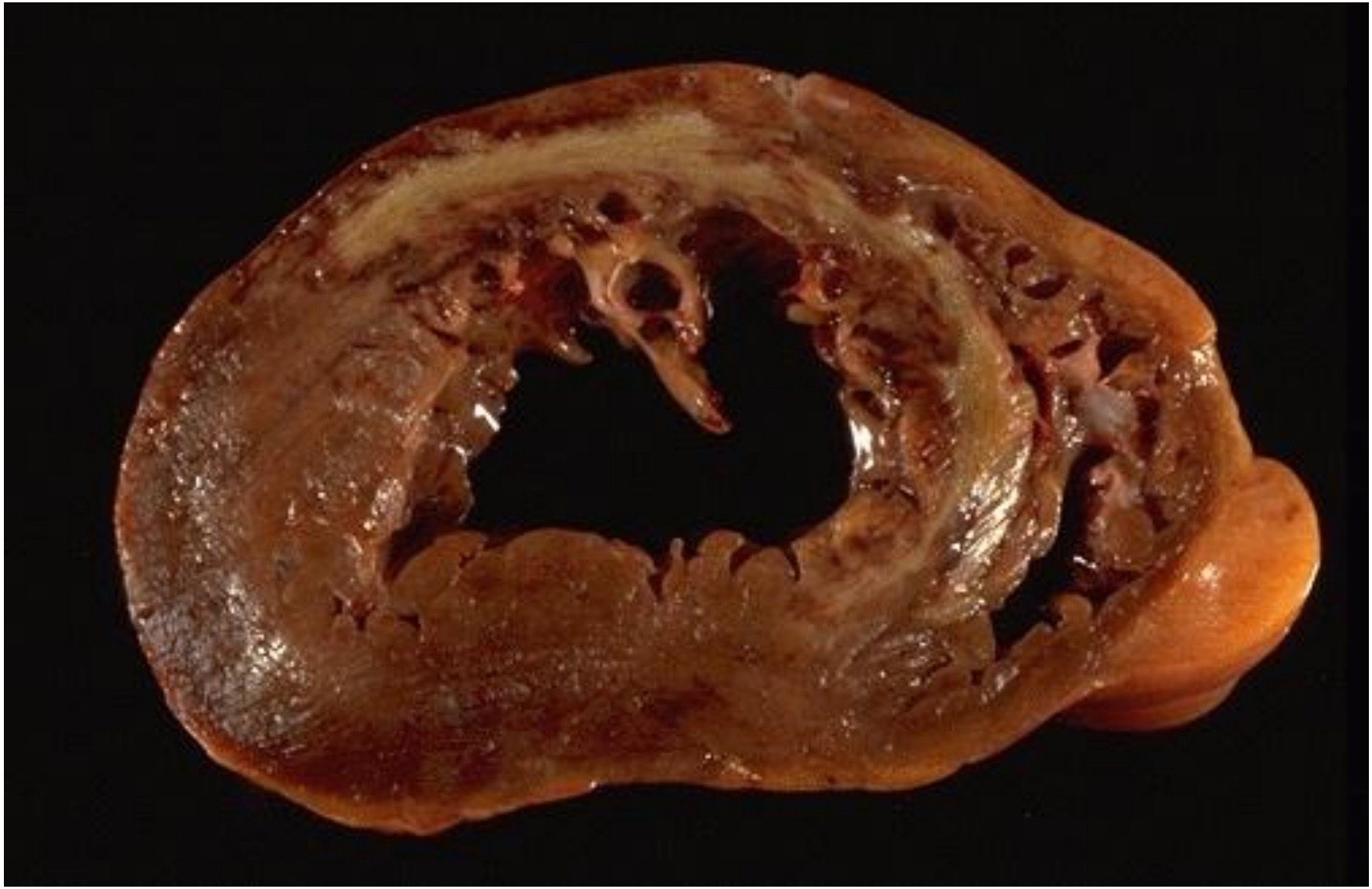


White (ischemic) infarction with a hemorrhagic rim (corolla)

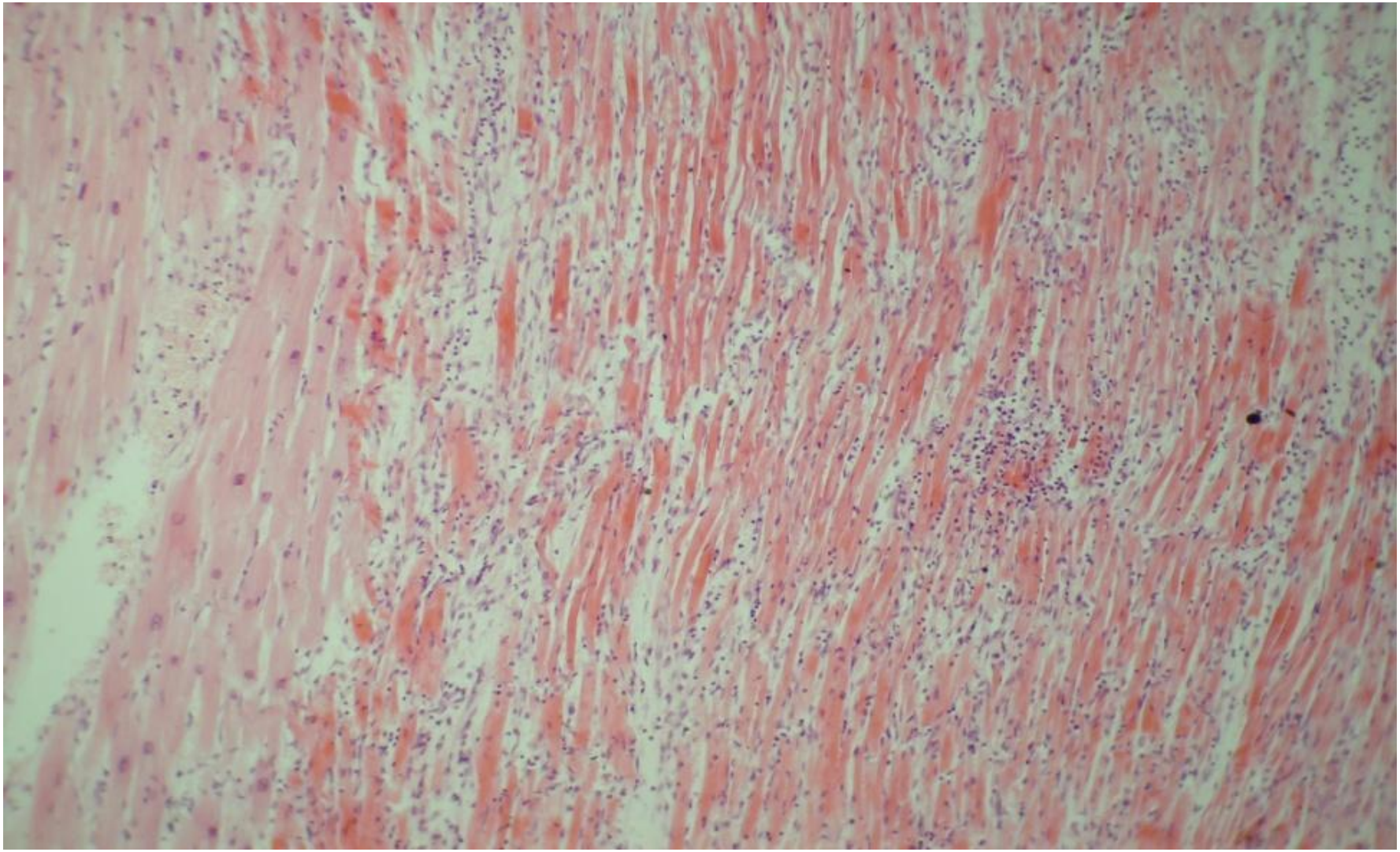
- develops in cases when, during the formation of ischemic necrosis, collaterals and vessels of the marginal zone of the infarction turn on with a delay after their prolonged spasm.

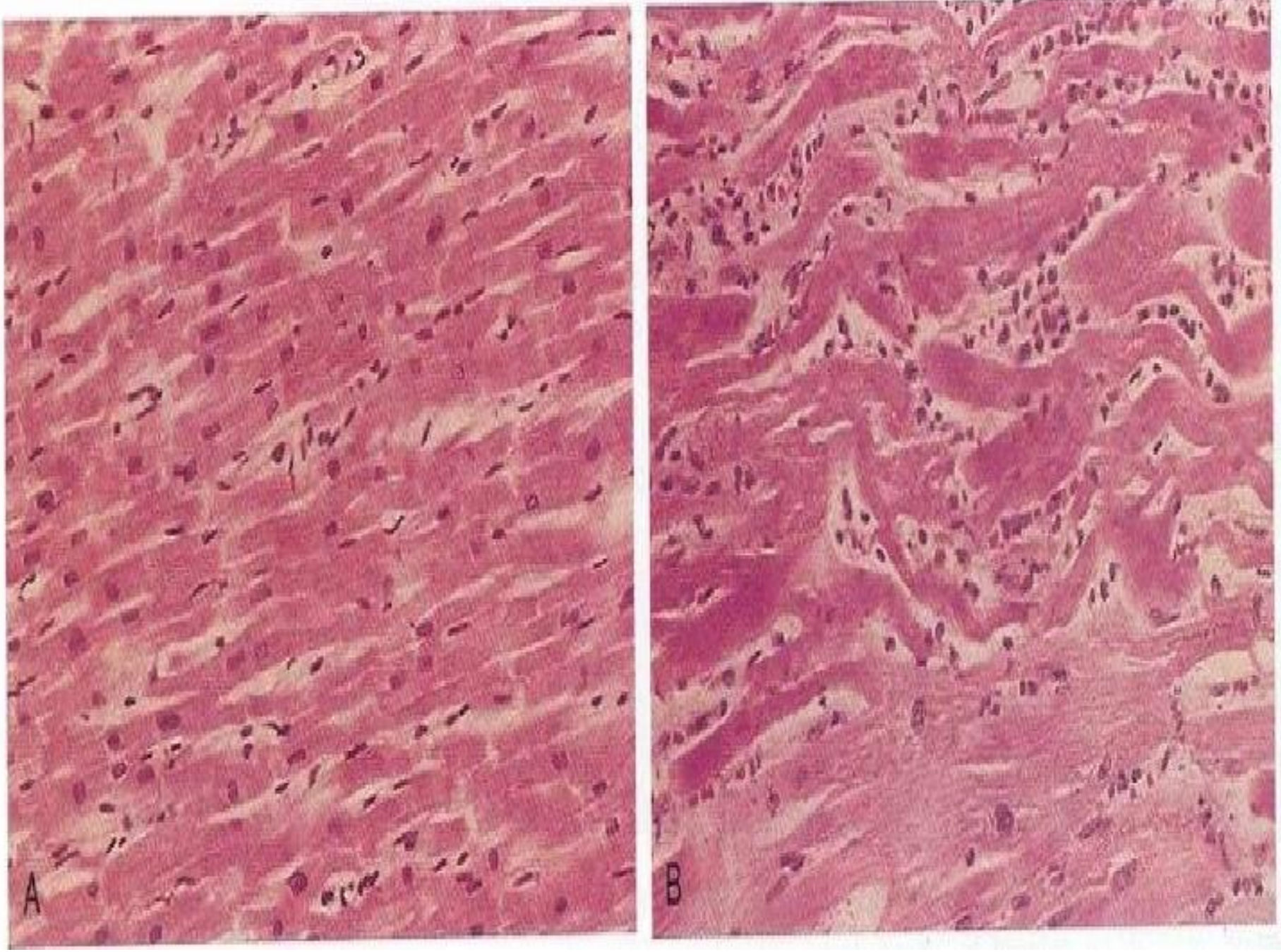
- in the vessels of the marginal zone - paralytic expansion.
- sharp plethora, stasis + outpouring of blood into necrotic tissue.
    - ***This type of infarction is a combination of red and white infarction:***
- in the center - white type infarction,
- on the periphery - red.
- often in the heart and kidneys.

White infarct with hemorrhagic halo: Myocardial infarction



White infarct with hemorrhagic halo: Myocardial infarction



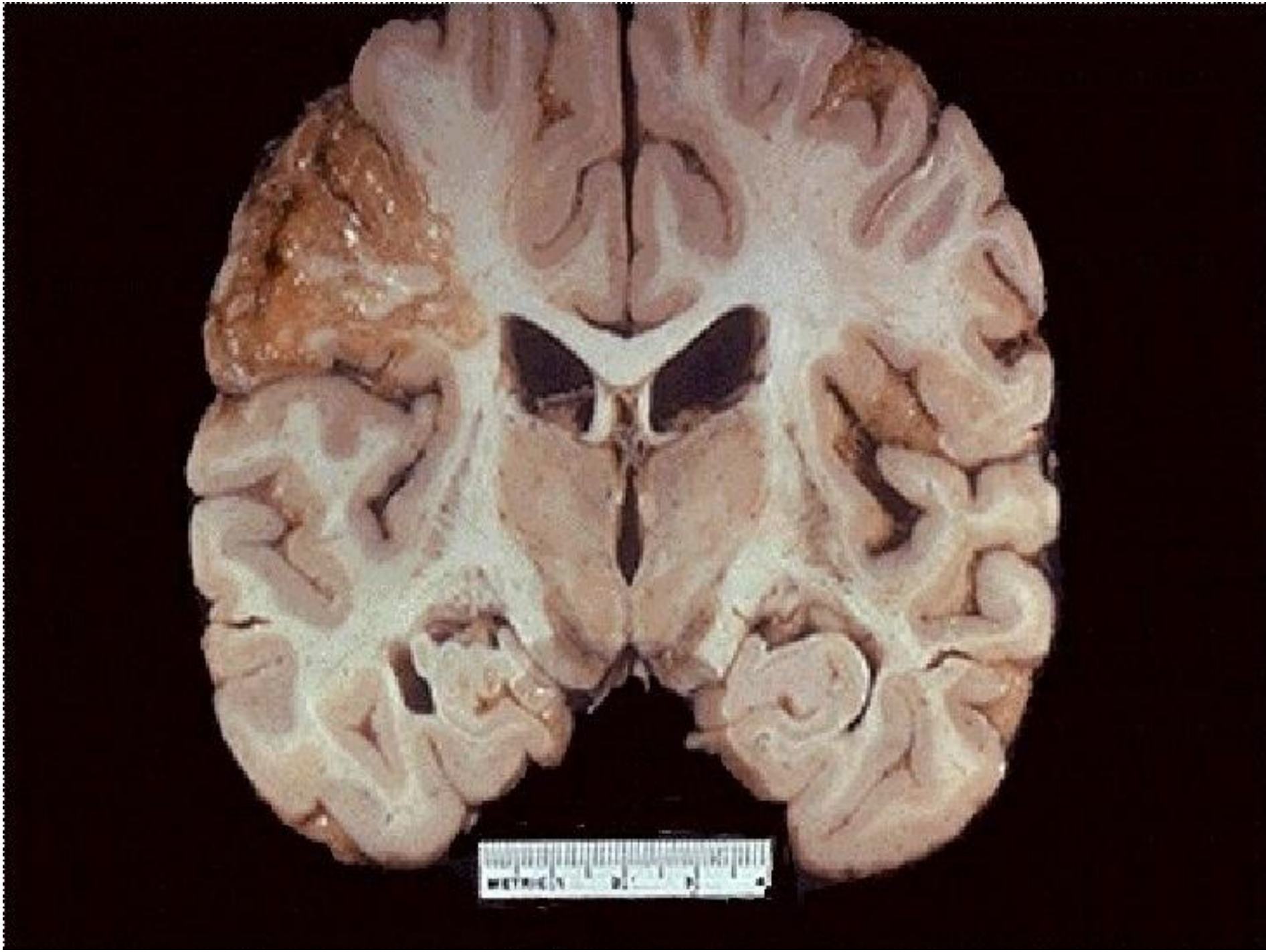

A
B

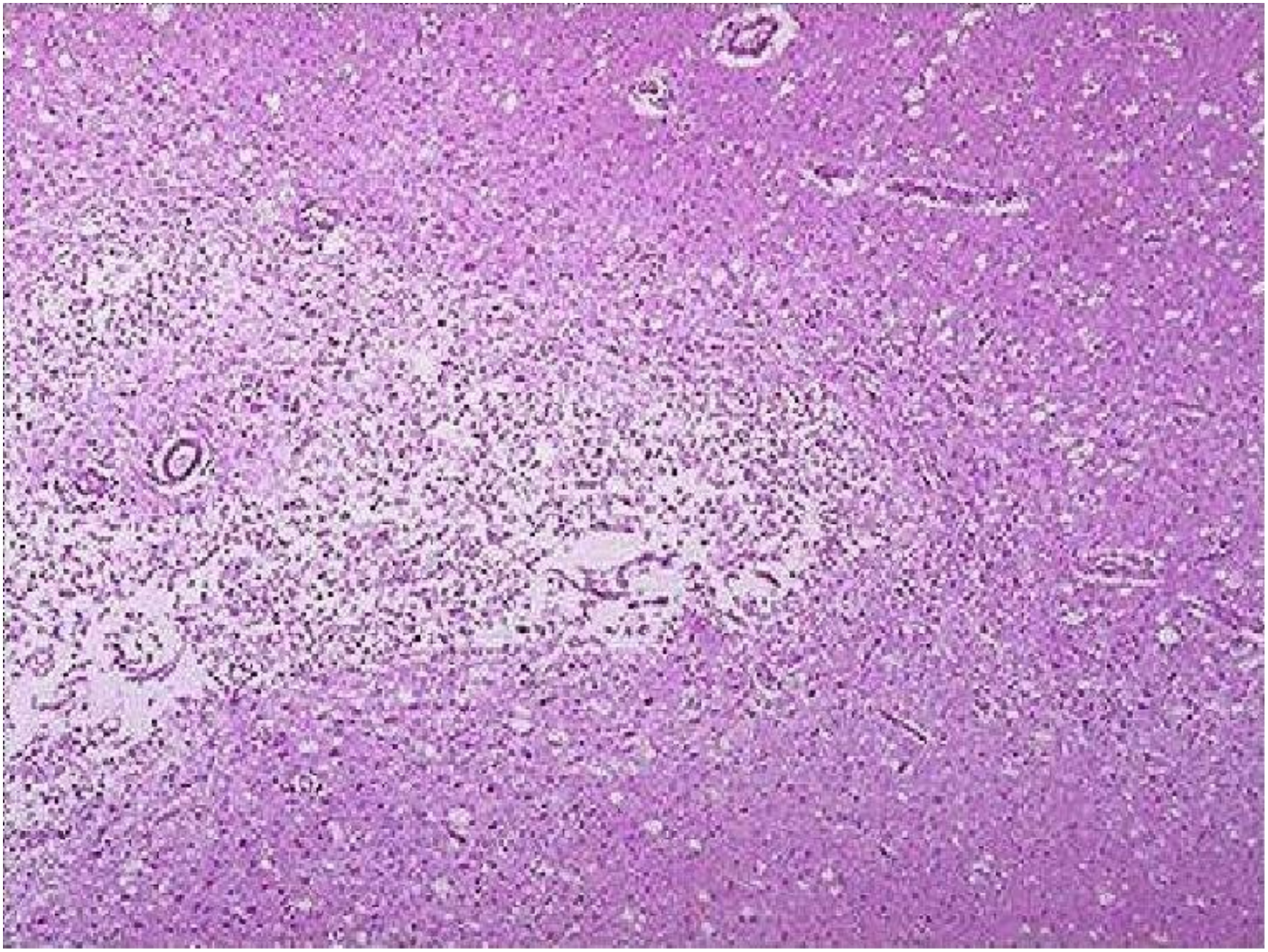
Liquefactive Necrosis

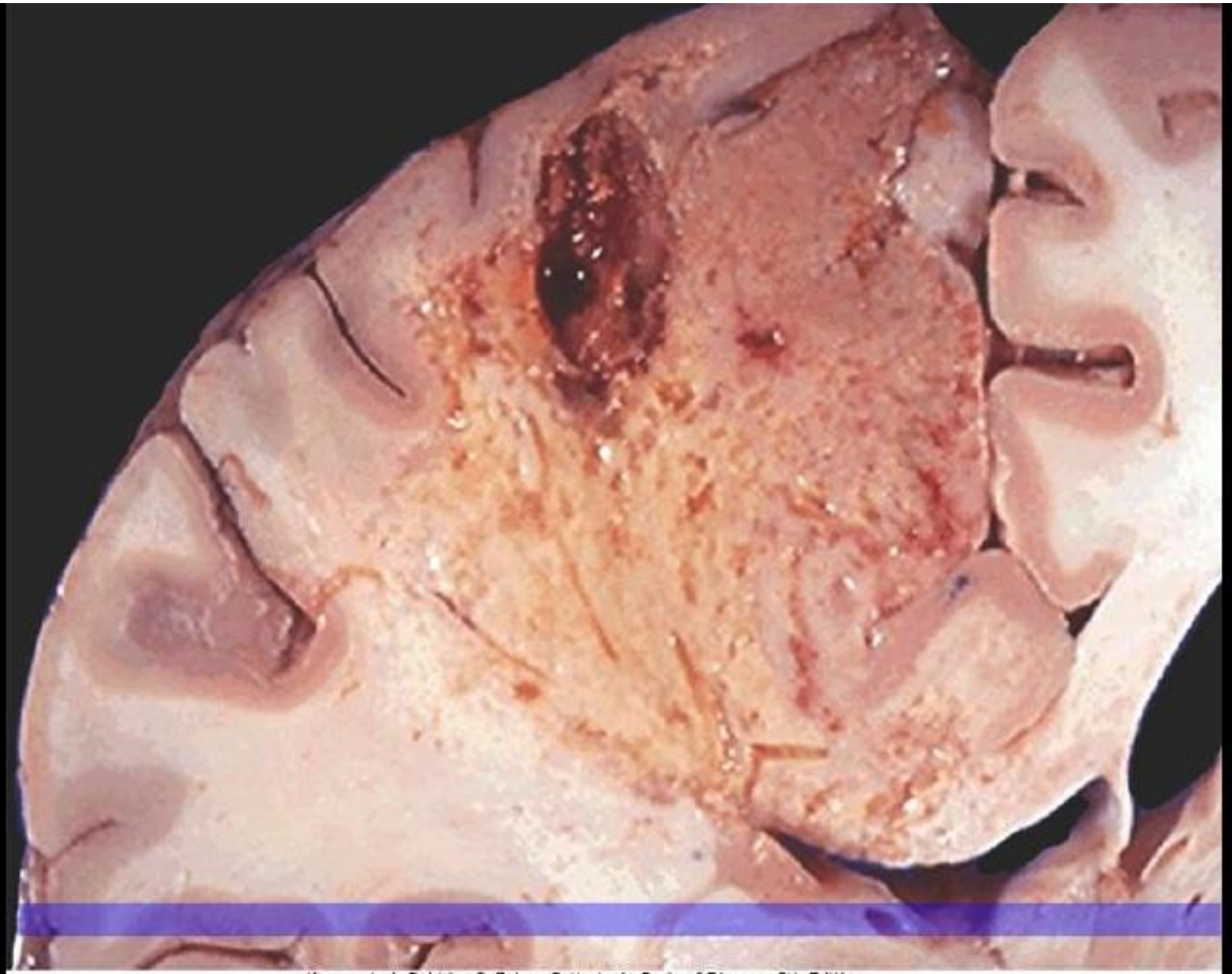
- Usually due to enzymatic dissolution of necrotic cells (usually due to release of proteolytic enzymes from neutrophils)
- Most often seen in CNS and in abscesses

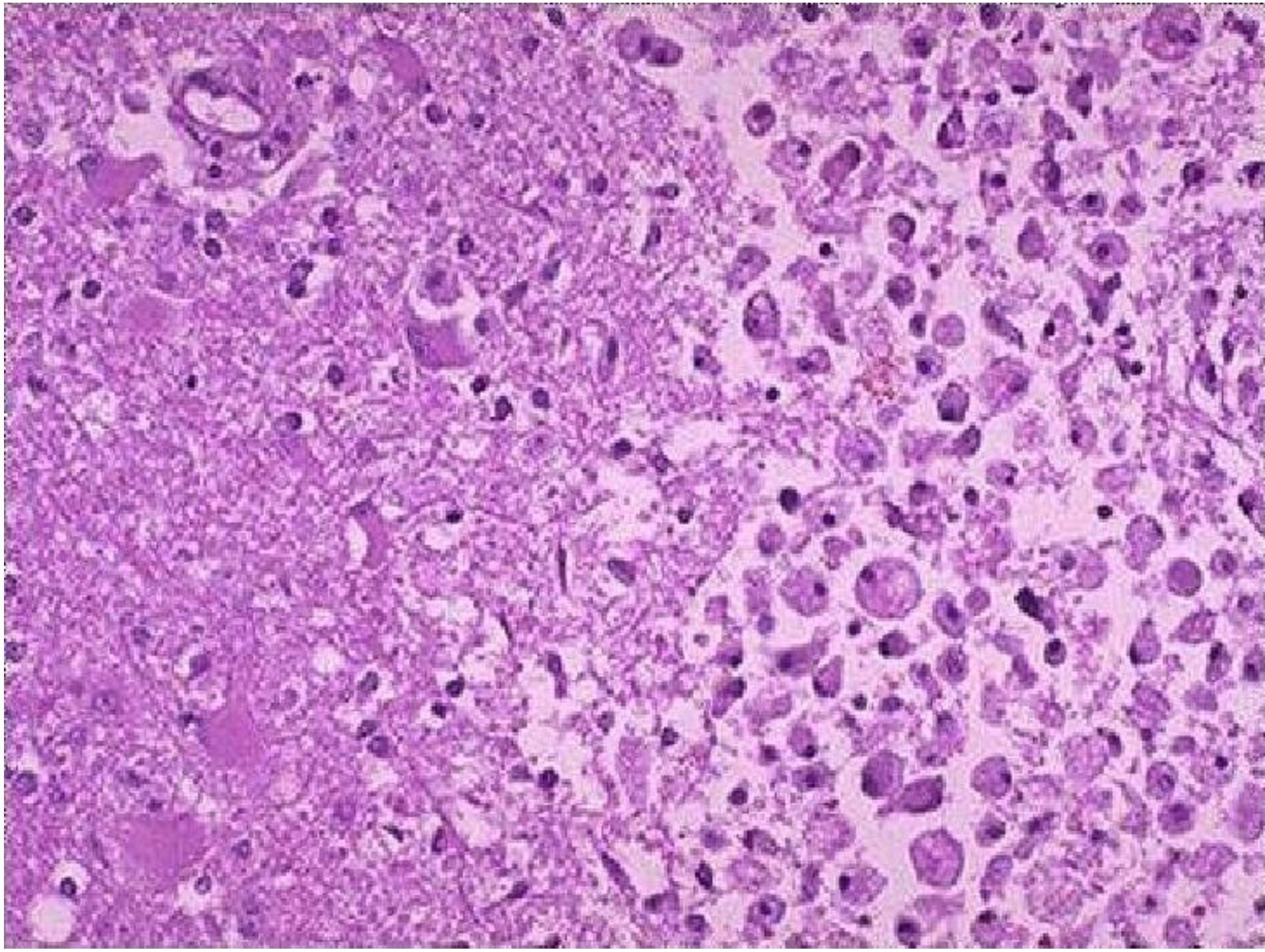
Liquefactive Necrosis

- when enzymatic digestion of necrotic cells predominates.
- esp bacterial infections; neutrophils contain potent hydrolases.
- in hypoxic damage (and other types of damage) of the CNS.
- affected tissue is liquefied to a soft, viscous, fluid mass.
- in acute inflammation, the liquid is often mostly dead WBC's (pus).
- may see degenerate neutrophils and/or amorphous necrotic material.







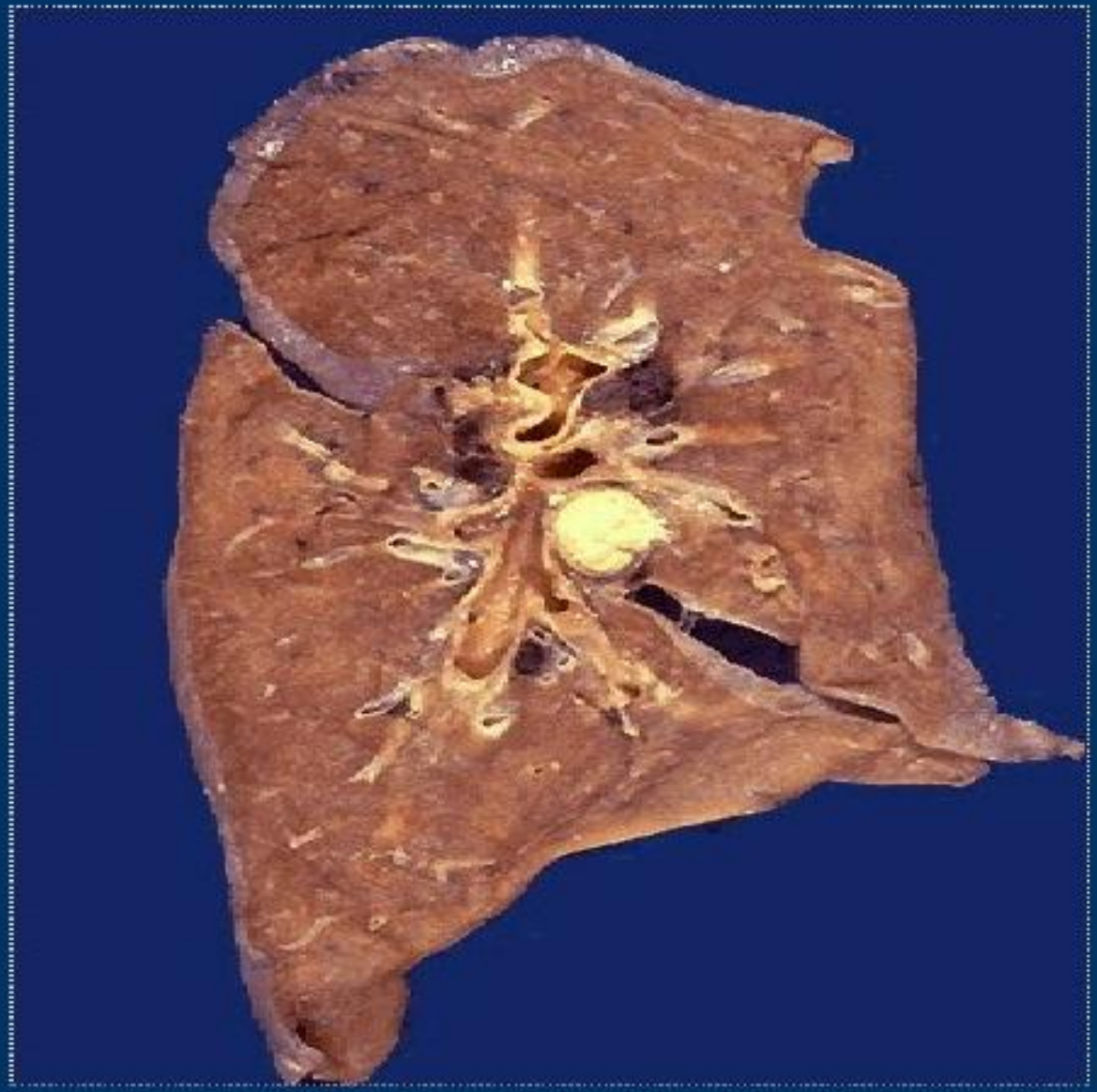


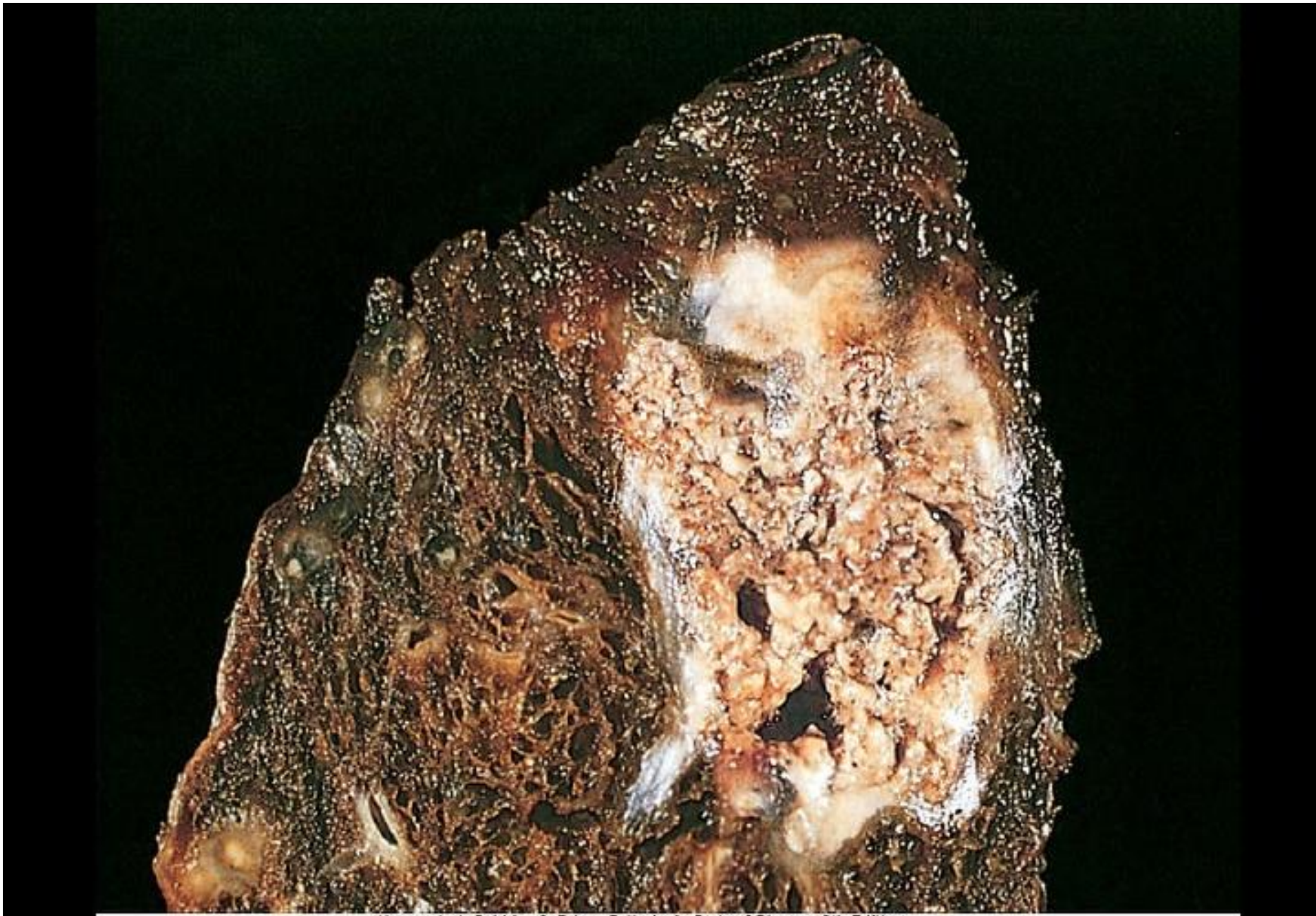
Caseous Necrosis

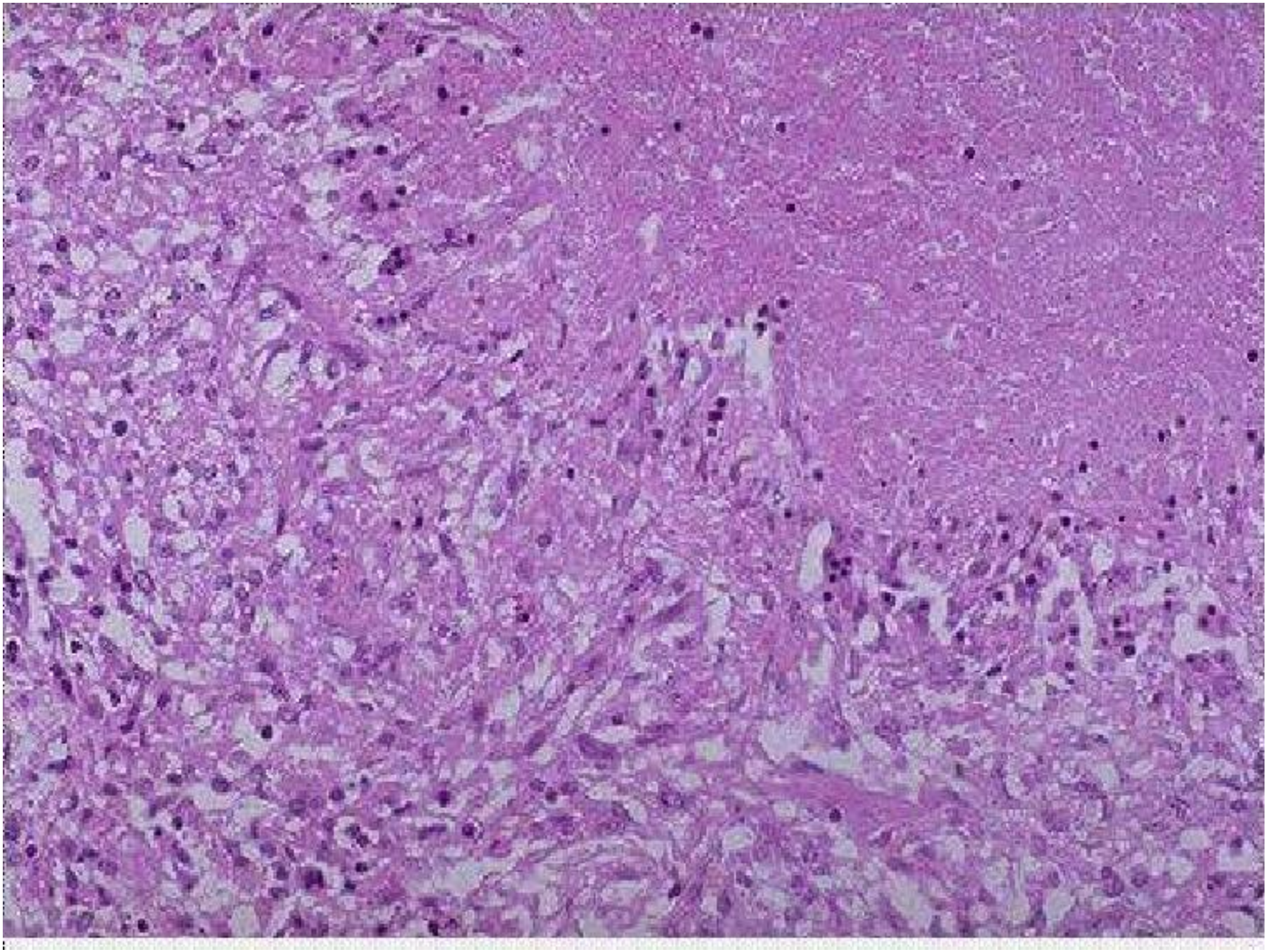
- Gross: Resembles cheese
- Micro: Amorphous, granular eosinophilc material surrounded by a rim of inflammatory cells
  - No visible cell outlines – tissue architecture is obliterated
- Usually seen in infections (esp. mycobacterial and fungal infections)

Caseous Necrosis

- •typical seen with specific bacterial diseases, eg TB, caseous lymphadenitis.
- Gross appearance• grey-white, dry and friable to pasty (caseous = cheese like).
- Microscopic appearance• dead cells persist as amorphous, coarsely granular, eosinophilic debris.• don't retain cellular outline but don't undergo complete dissolution either.







Fat Necrosis

- distinguished by its location in body fat stores.

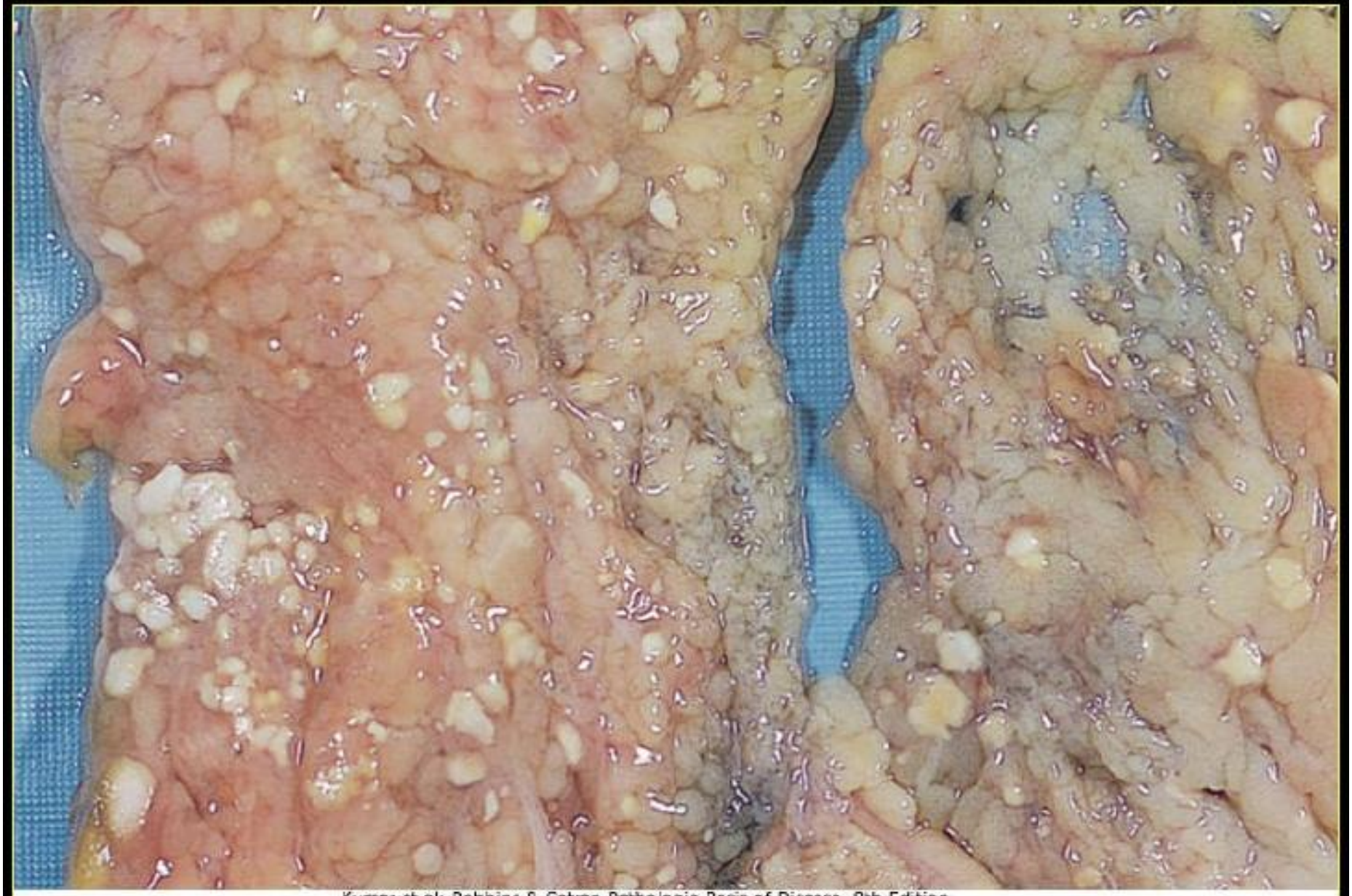
- etiology: inflammation (eg pancreatitis), Vit E deficiency, trauma, idiopathic

Fat necrosis

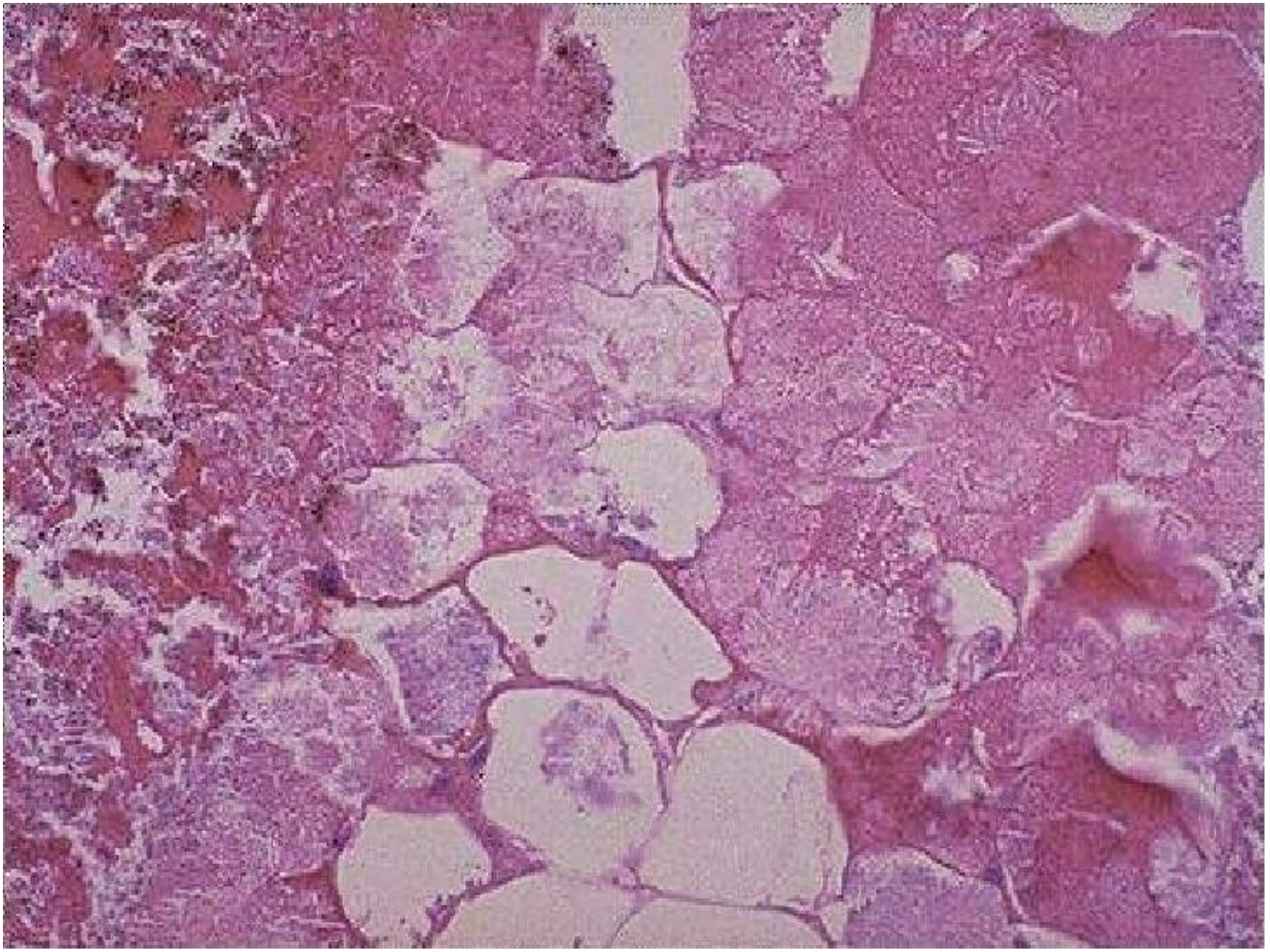
- Enzymatic fat necrosis
- Non-enzymatic fat necrosis

Enzymatic Fat Necrosis

- Results from hydrolytic action of lipases on fat
- Most often seen in and around the pancreas; can also be seen in other fatty areas of the body, usually due to trauma
- Fatty acids released via hydrolysis react with calcium to form chalky white areas → "saponification"



Kumar et al: Robbins & Cotran Pathologic Basis of Disease, 8th Edition.



Non-enzymatic fat necrosis

- in the mammary gland, subcutaneous adipose tissue and in the abdominal cavity.

- Most patients have a history of trauma.= traumatic fatty necrosis (even if trauma is not identified as the underlying cause).

- elicits an inflammatory response characterized by the presence of numerous macrophages with foamy cytoplasm, neutrophils and lymphocytes.

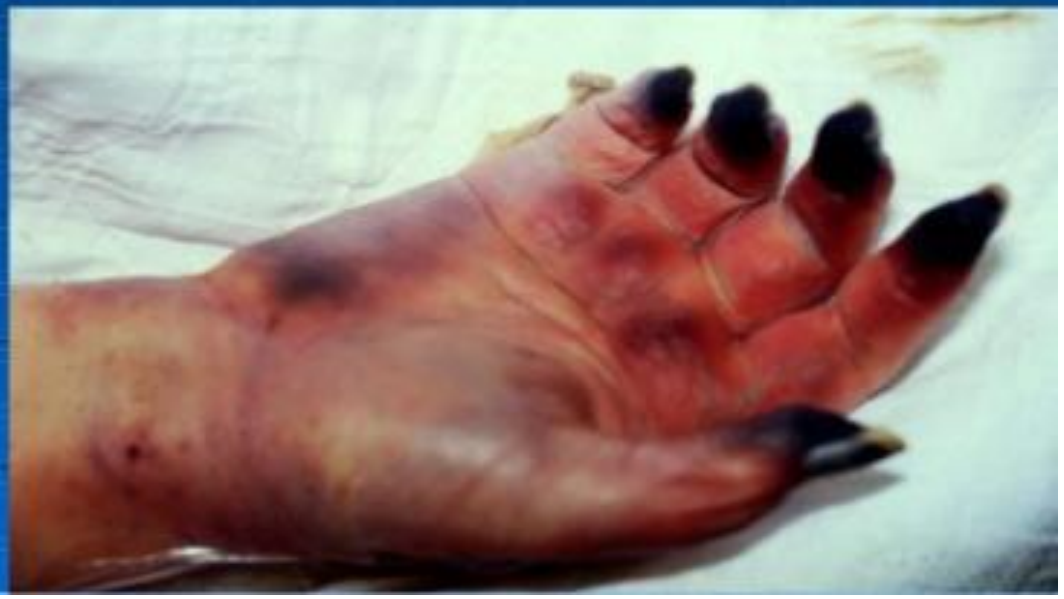
- Then - fibrosis, while this process can be difficult to distinguish from a tumor.

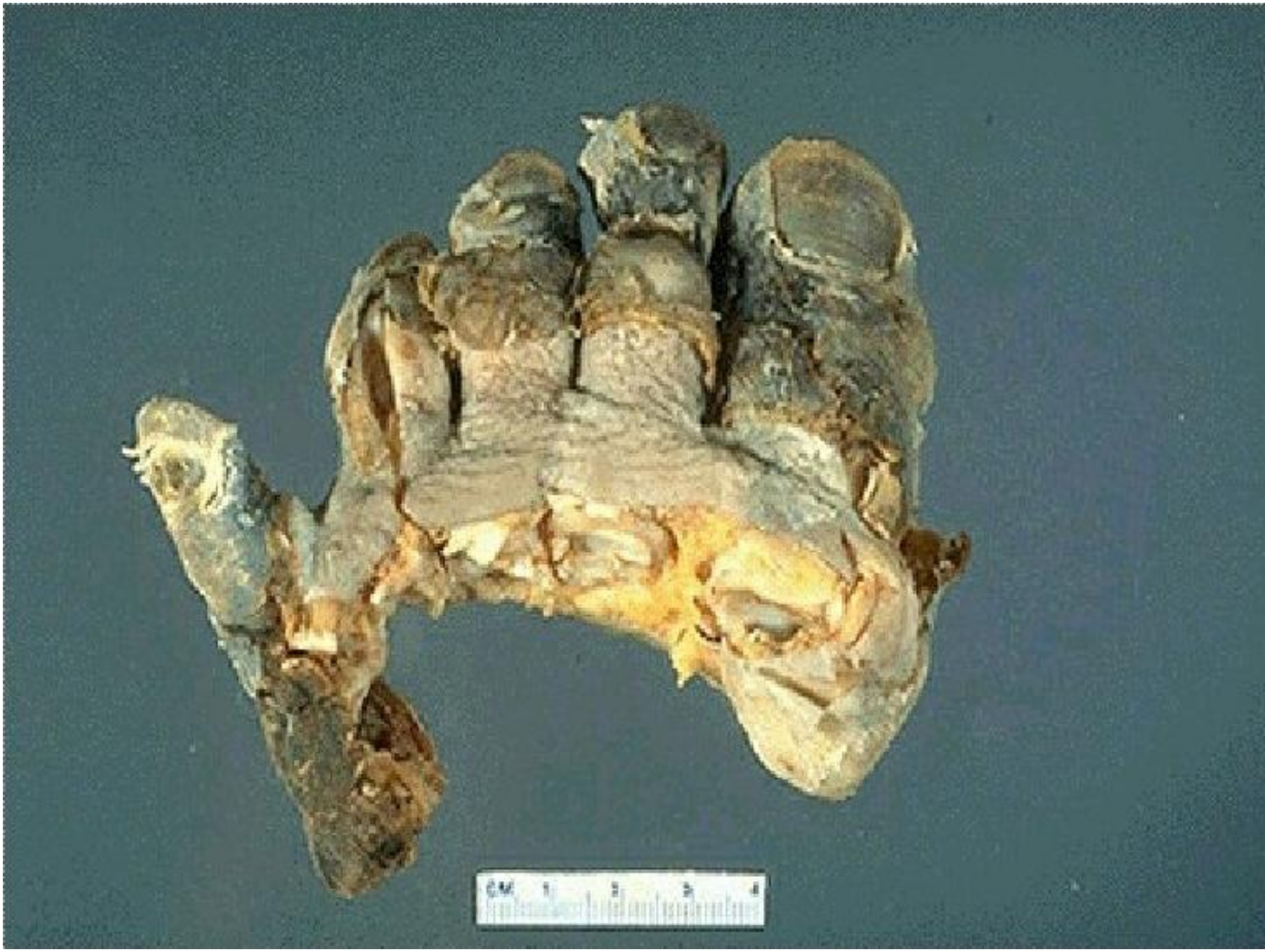
Gangrenous Necrosis

- Most often seen on extremities, usually due to trauma or physical injury
- “Dry” gangrene – no bacterial superinfection; tissue appears dry
- “Wet” gangrene – bacterial superinfection has occurred; tissue looks wet and liquefactive

Gangrenous Necrosis

- definition= necrosis (usually ischemic) of extremities, eg digits, ear tips.
- dry gangrene= coagulation necrosis of an extremity.
- wet gangrene= when the coagulative necrosis of dry gangrene is modified by liquefactive action of saprophytic/putrefactive bacteria.

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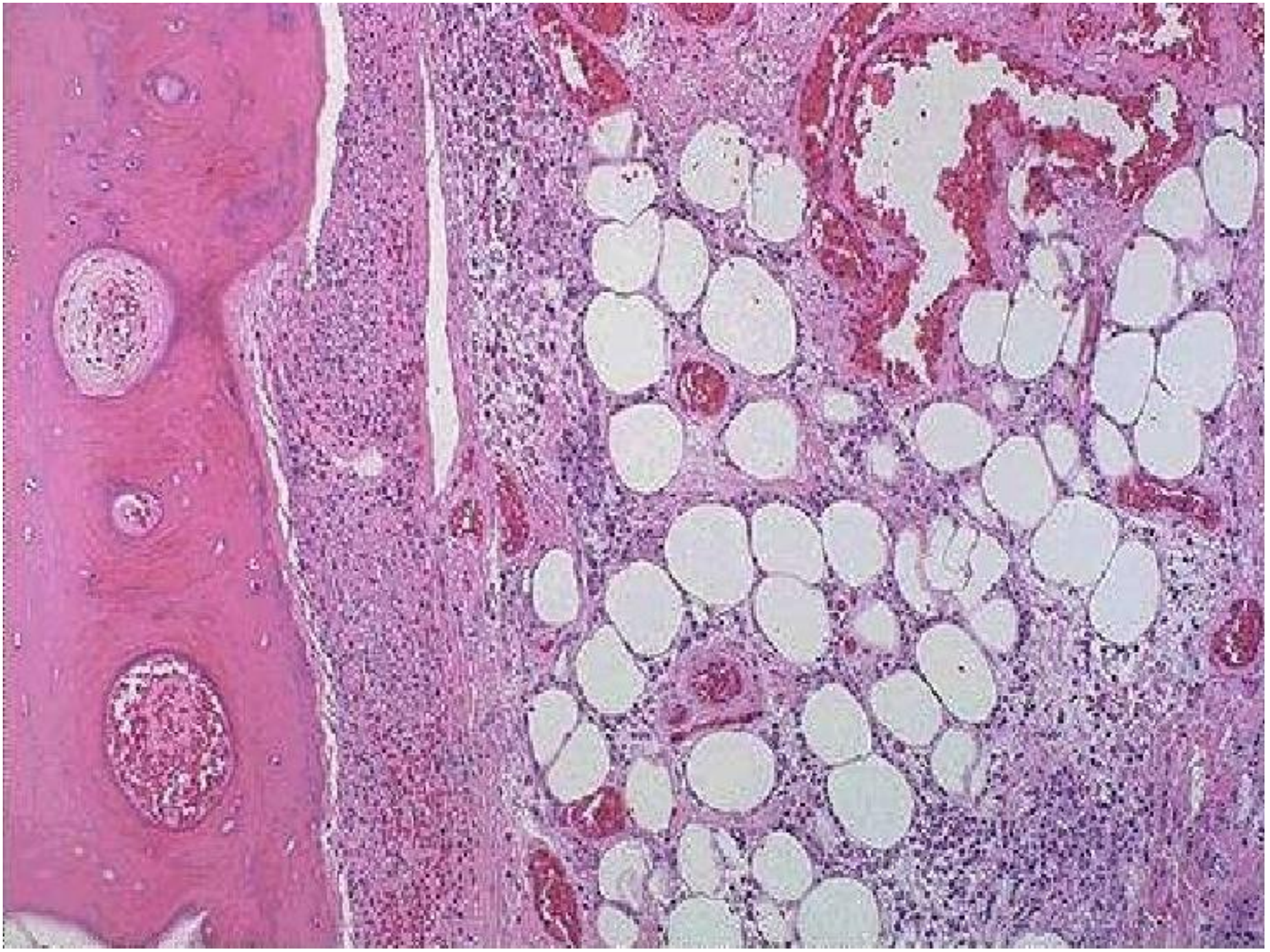
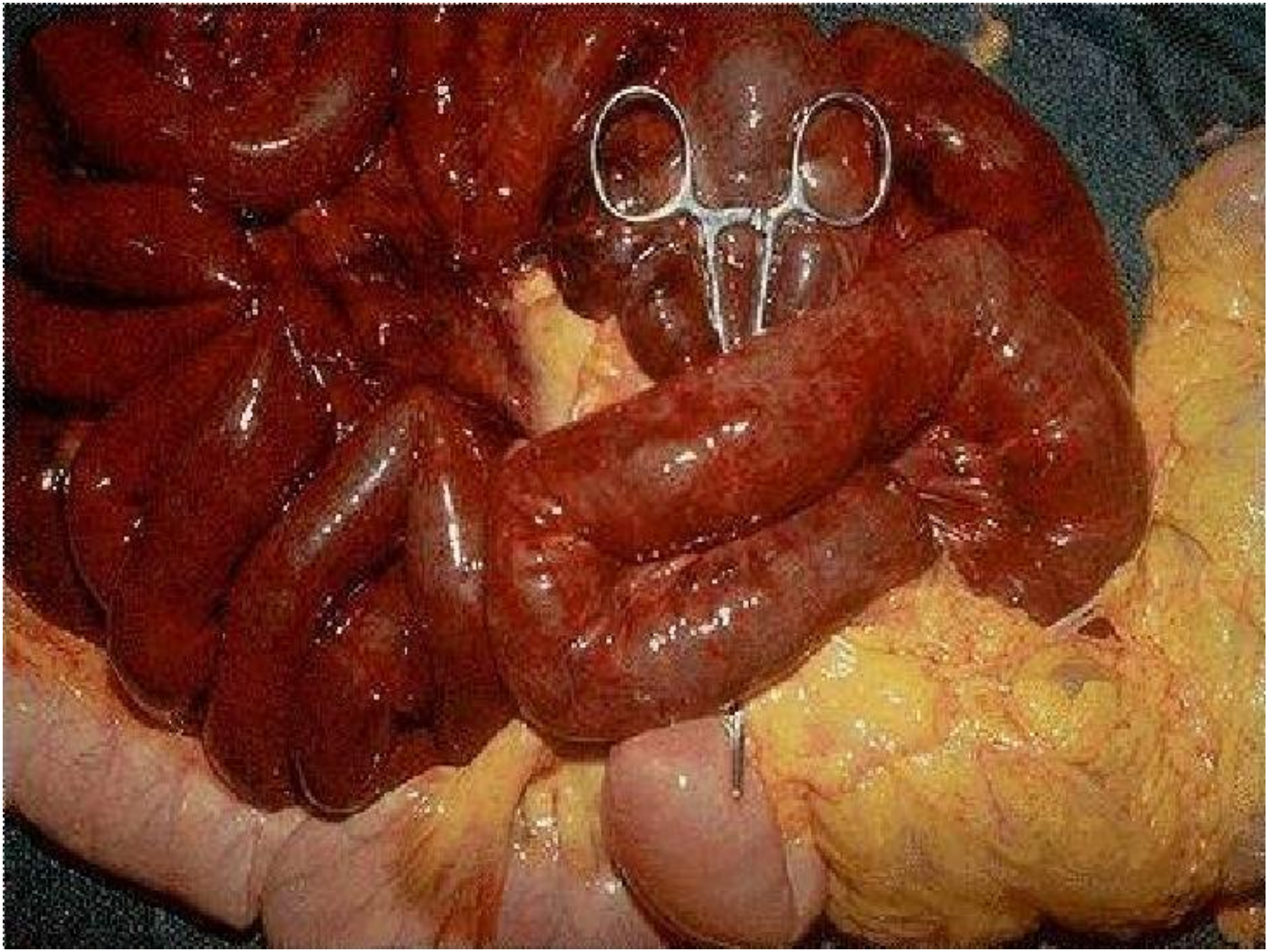


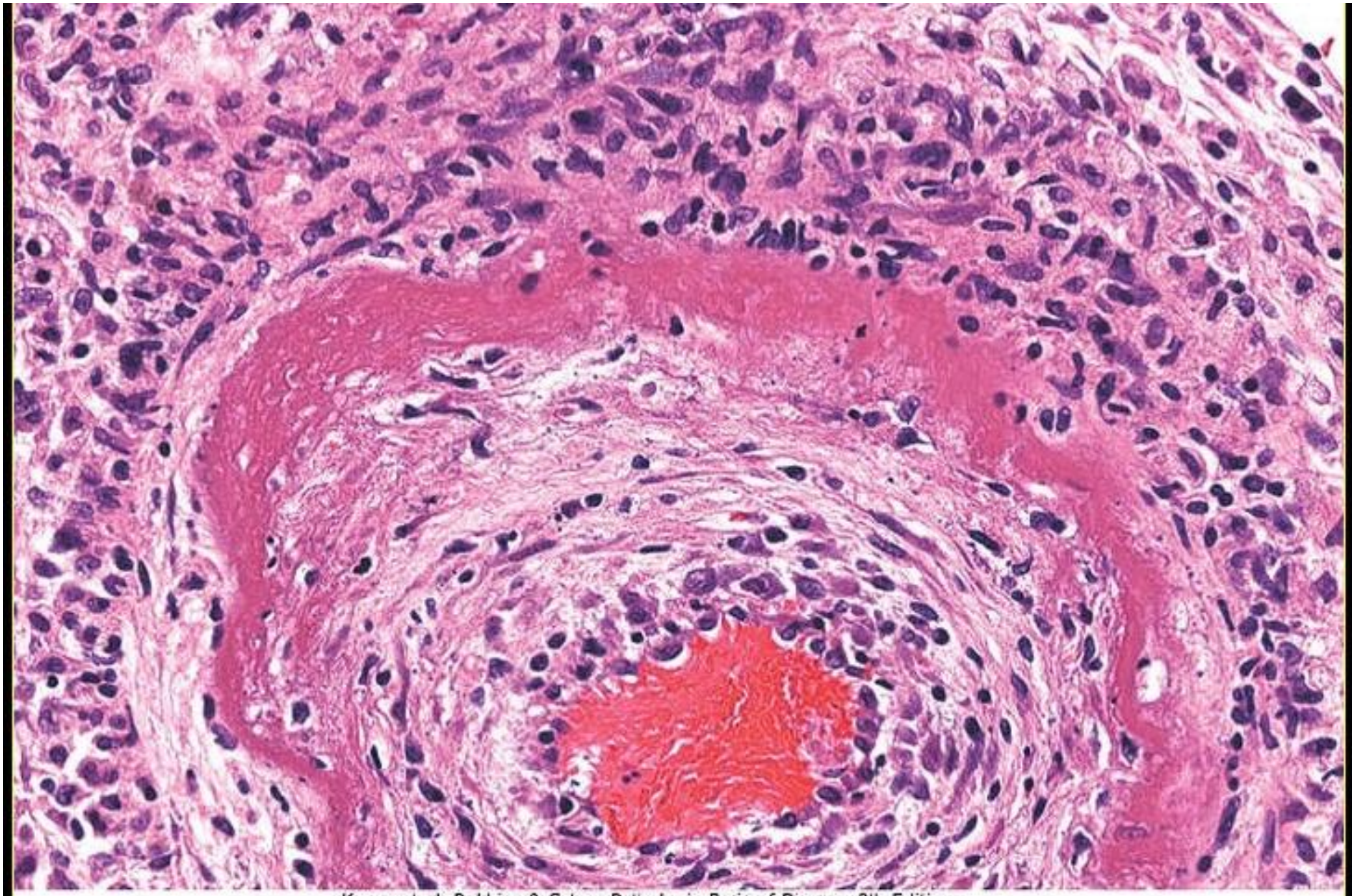


Fibrinoid necrosis

- is a special form of necrosis usually seen in immune reactions involving blood vessels. This pattern of necrosis typically occurs when complexes of antigens and antibodies are deposited in the walls of arteries.

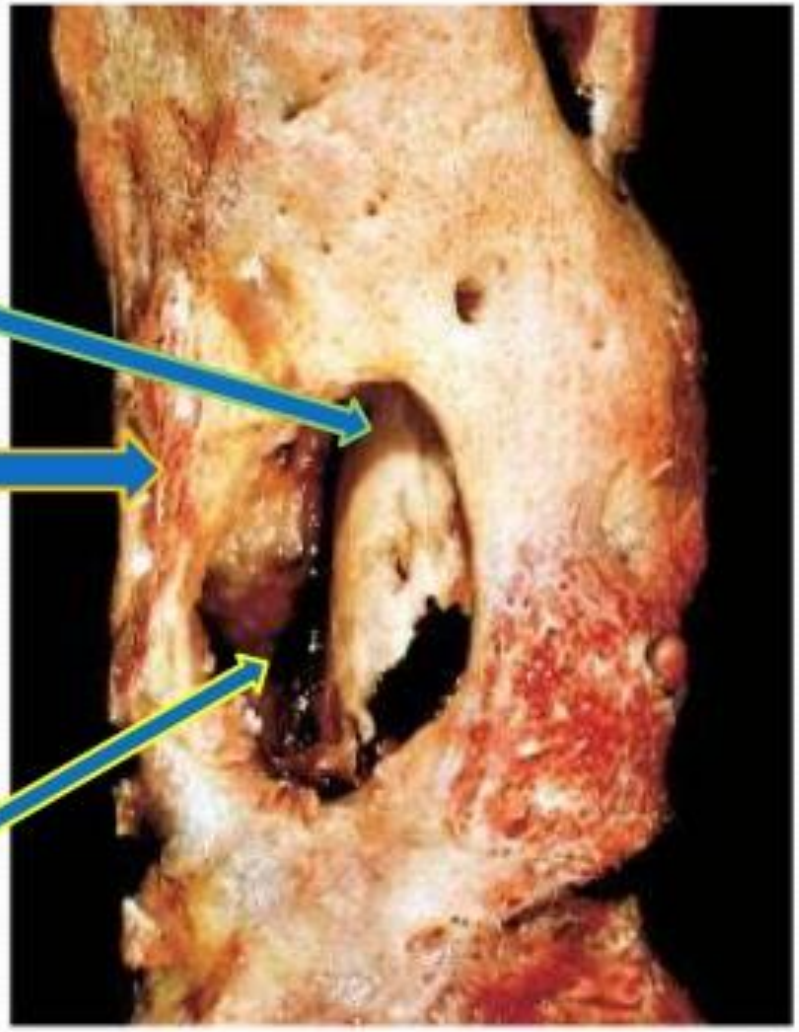
Fibrinoid Necrosis

- Usually seen in the walls of blood vessels (e.g., in vasculitides)
- Glassy, eosinophilic fibrin-like material is deposited within the vascular walls

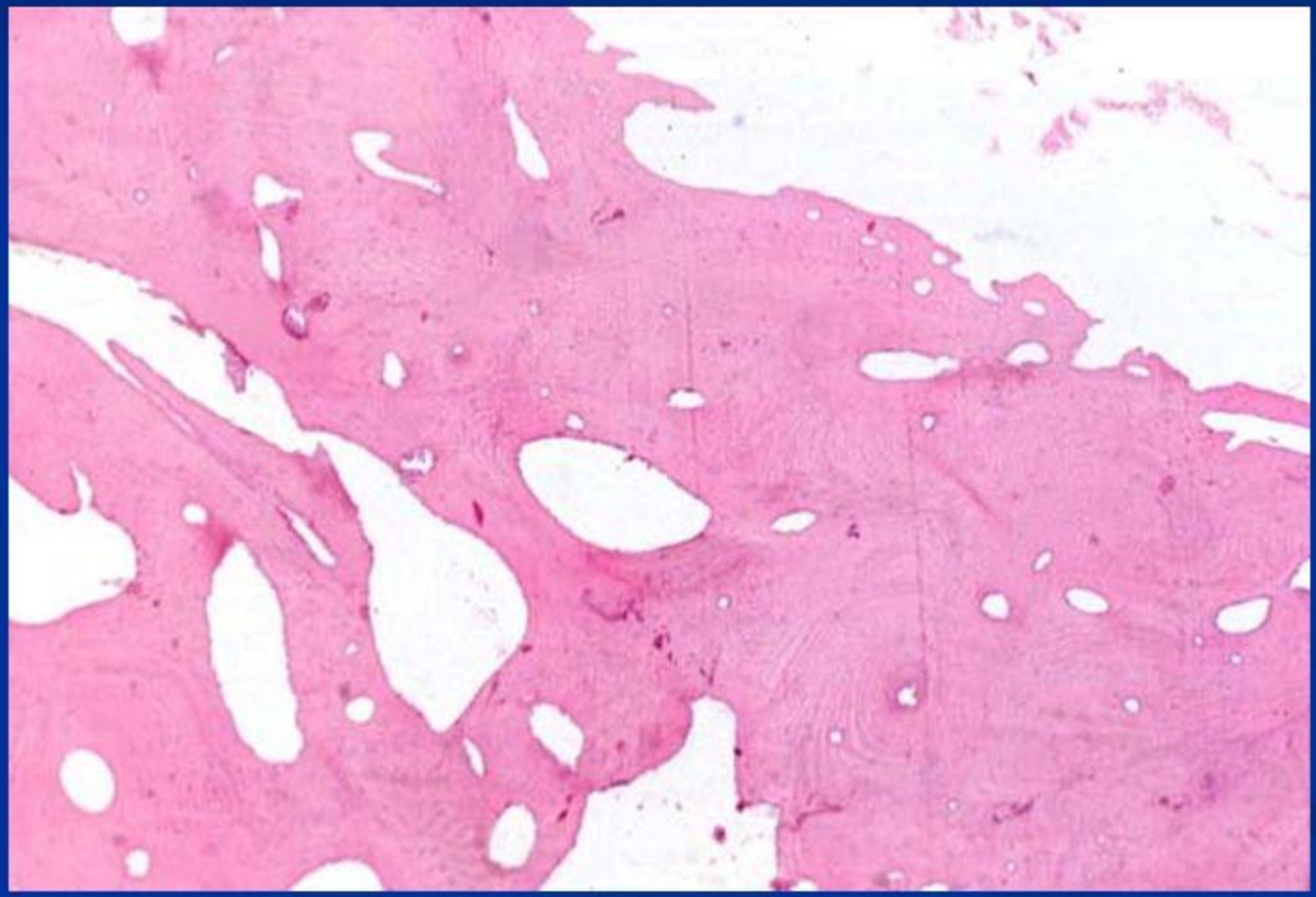


CHRONIC OSTEOMYELITIS

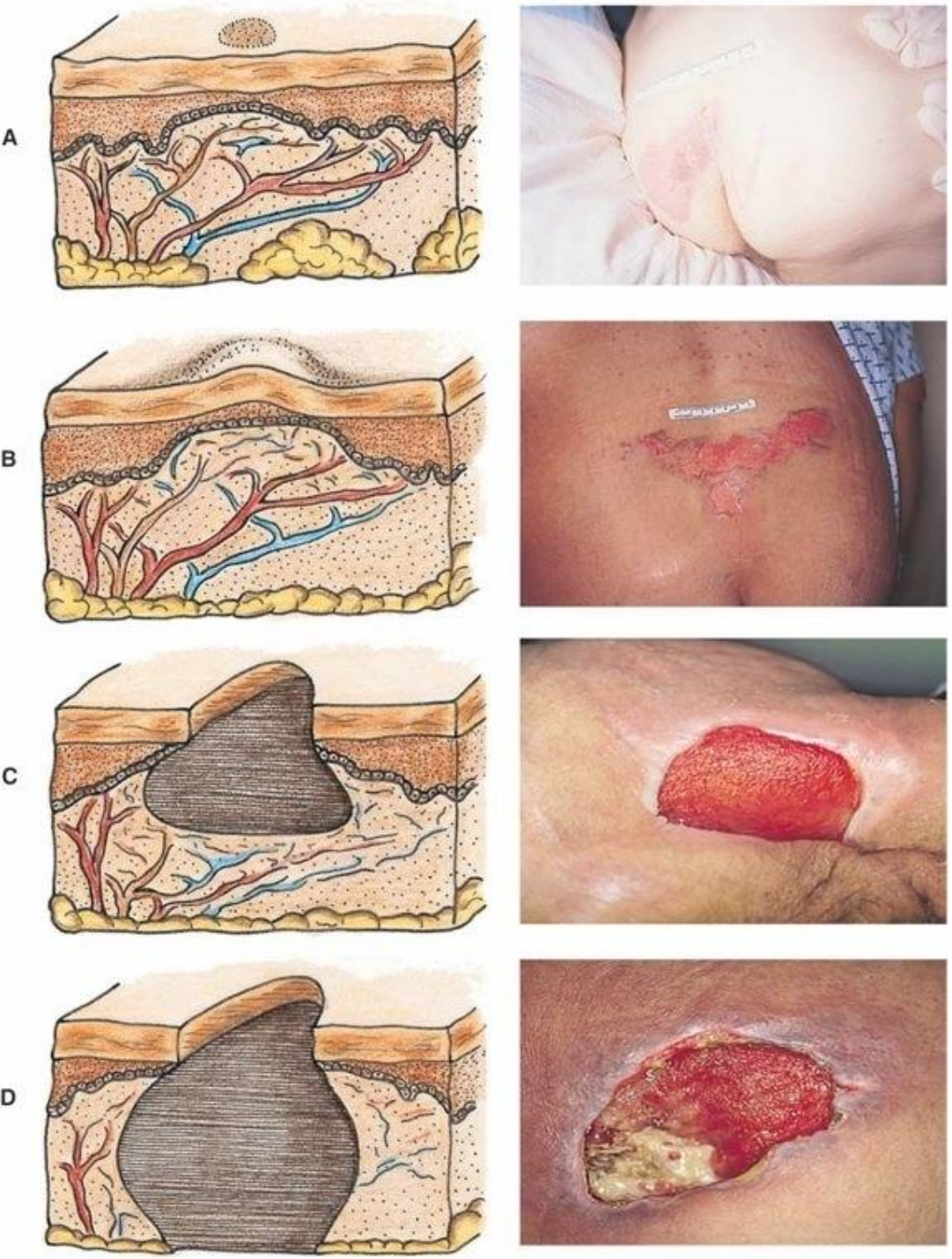
- **Sequestrum** is the necrotic bone that is embedded in the pus/infected granulation tissue.
- **Involucrum** is the new bone laid down by the periosteum that surrounds the sequestra.
- **Cloaca** is the opening in the involucrum through which pus & sequestra make their way out.



Sequestrum (necrotic bone)



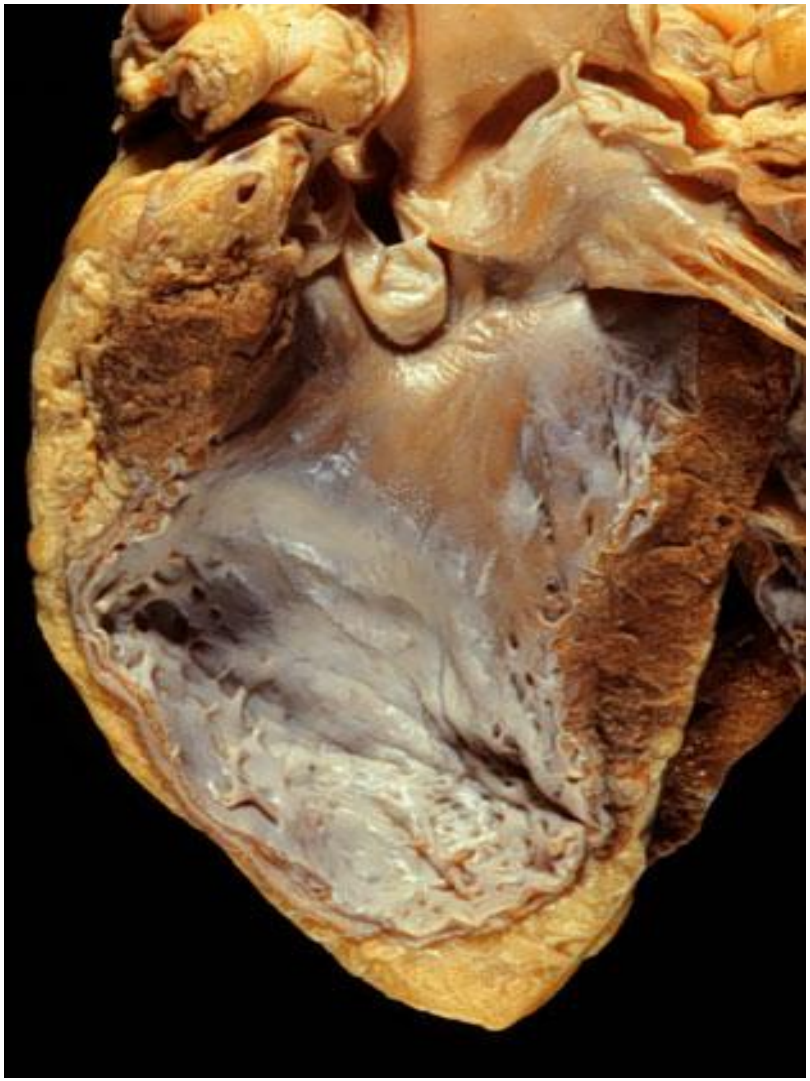
Decubitus

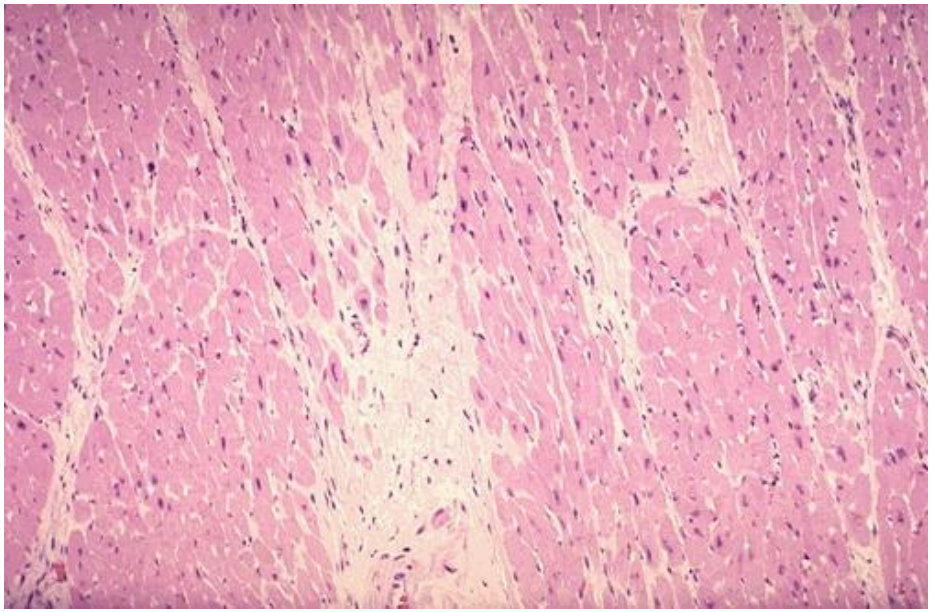


Outcomes of necrosis

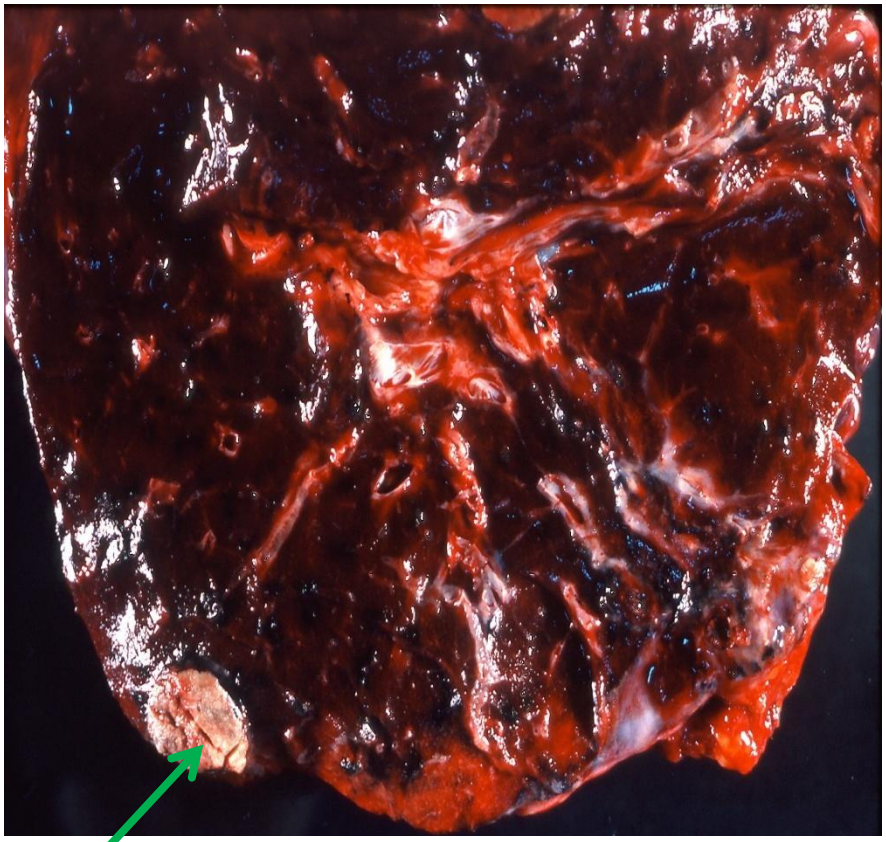
1. tissue regeneration;
2. Organization (formation of coarse fibrous connective tissue = scar);
3. Encapsulation (formation of a capsule around the focus of necrosis);
4. Calcification (calcification, petrification);
5. Ossification (formation of bone tissue);
6. Inlay (deposits of uric acid salts);
7. Hyalinosis;
8. Cyst formation (cavities - the brain);
9. Sequestration;
10. Mutilation (spontaneous rejection of dead parts - a finger);
11. Mummification (fetus)
12. Death due to damage to vital organs.

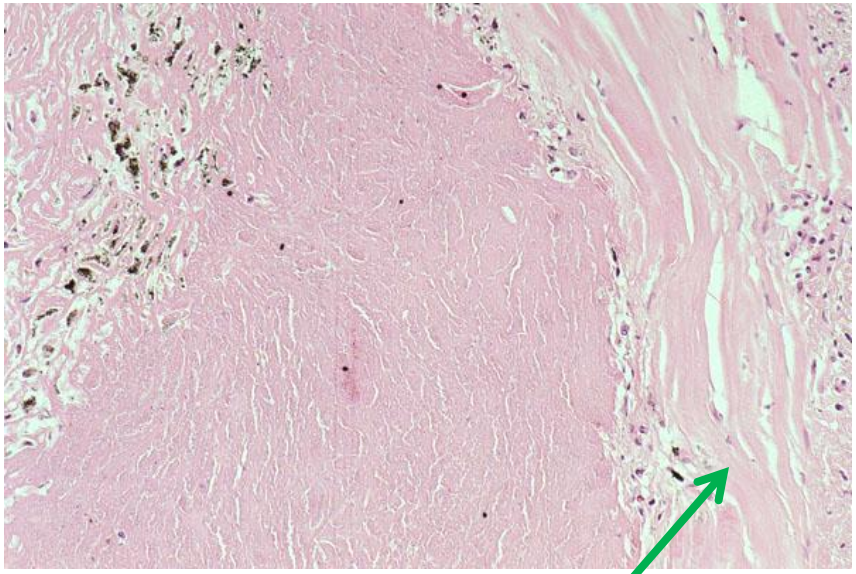
Organization



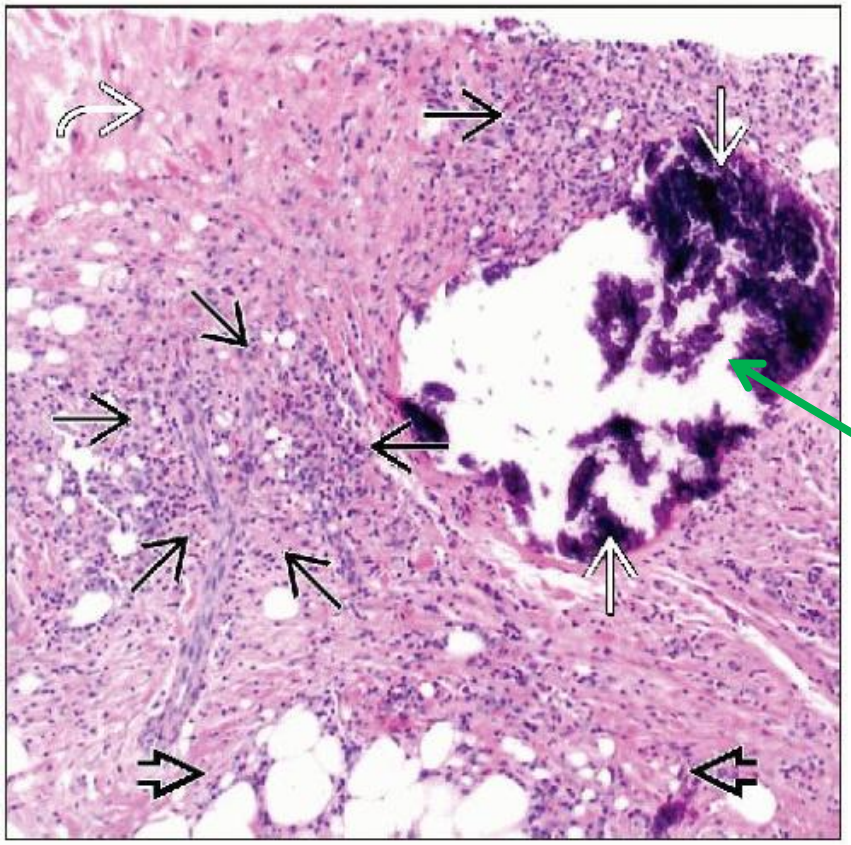


Encapsulation
(healed Ghon's focus)

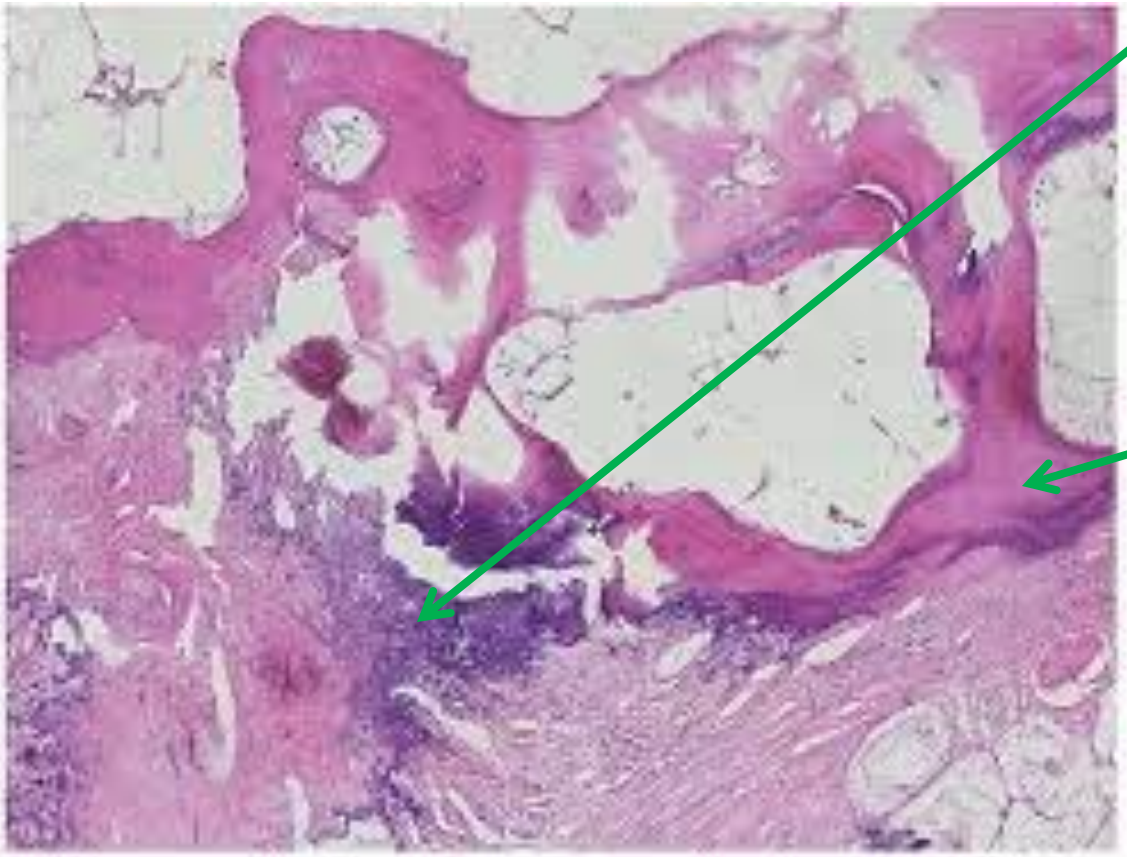




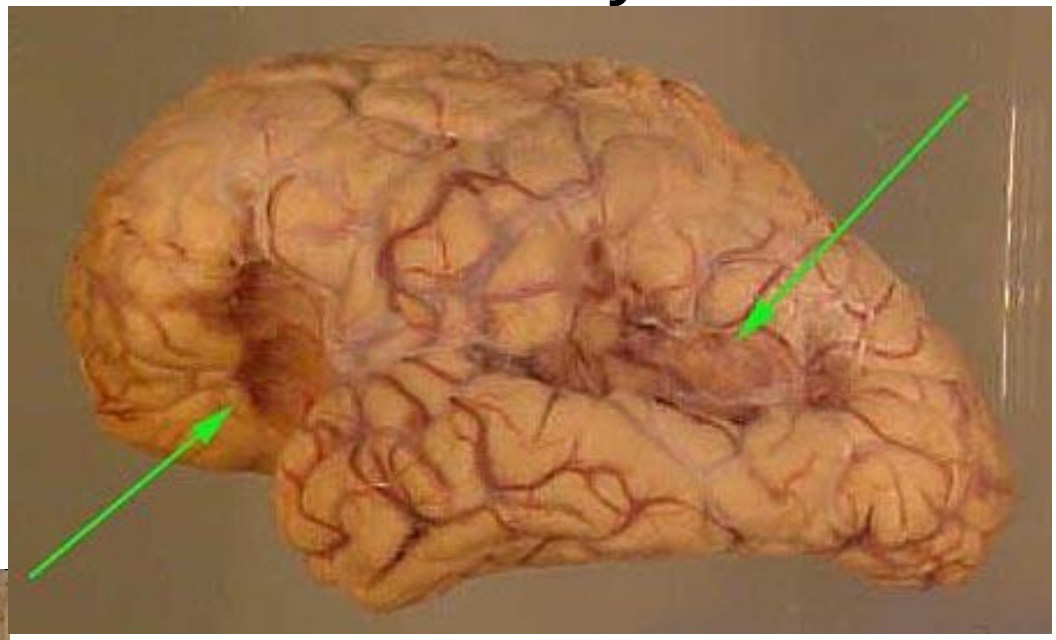
Calcification (in fat necrosis)

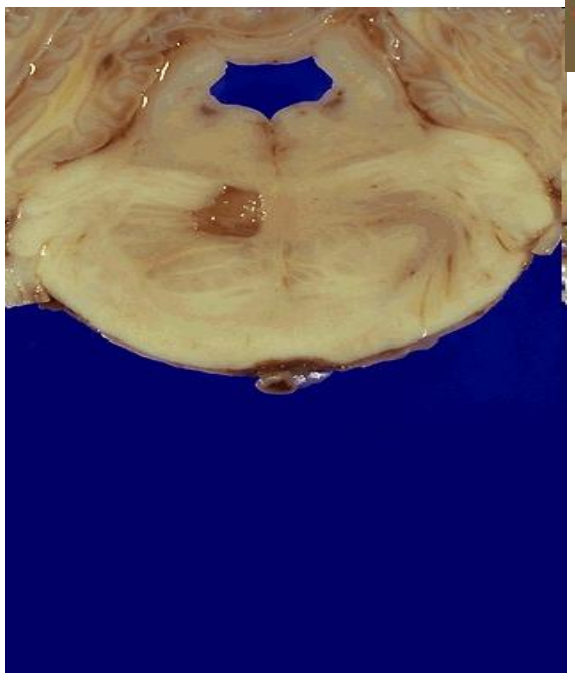


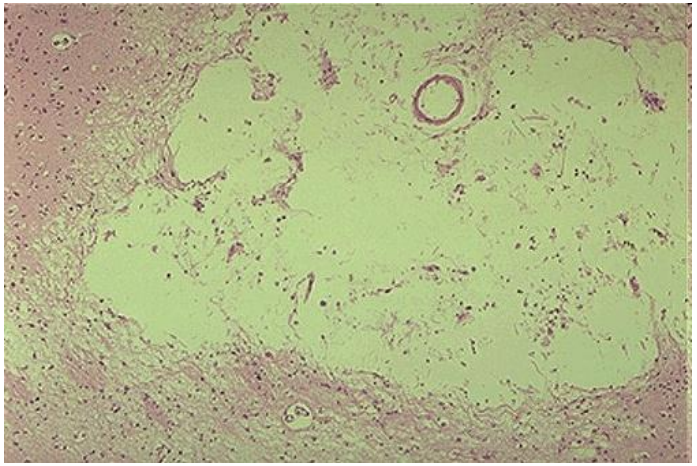
Calcification (1) and ossification (2) (in fat necrosis)



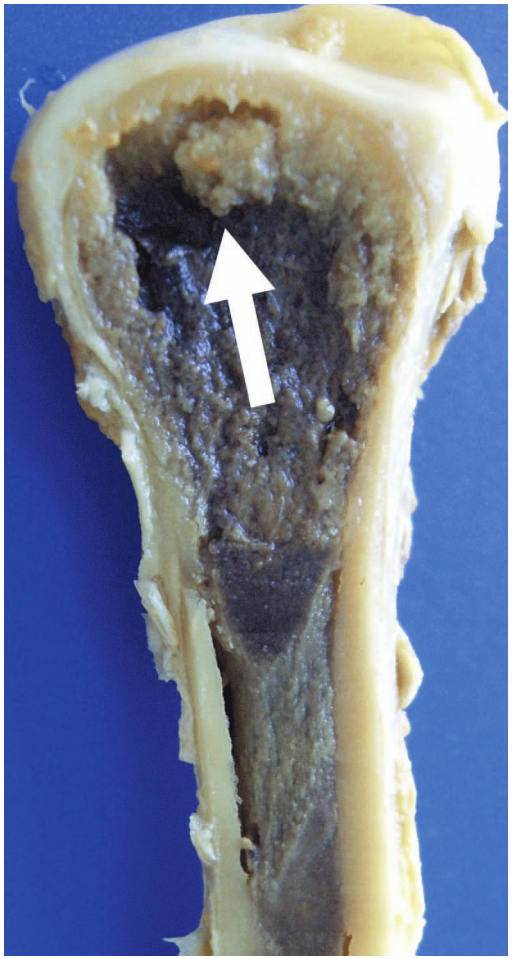
Cyst formation



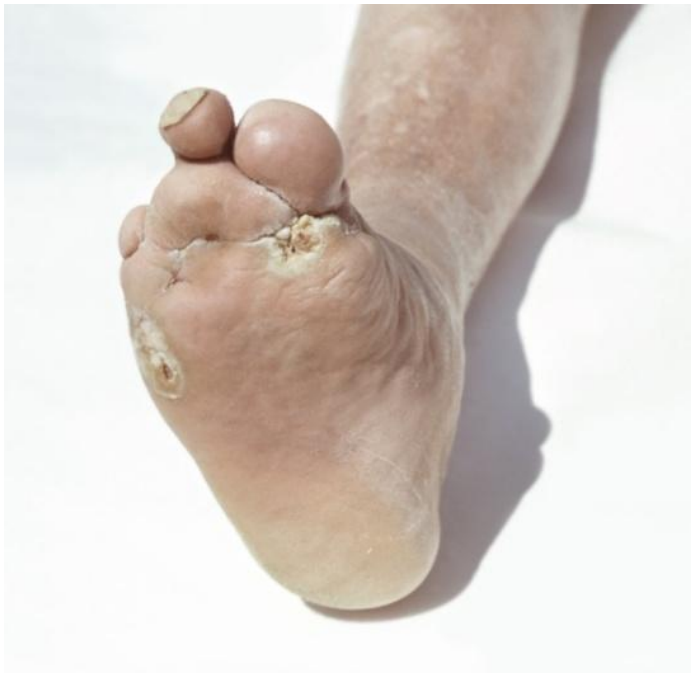


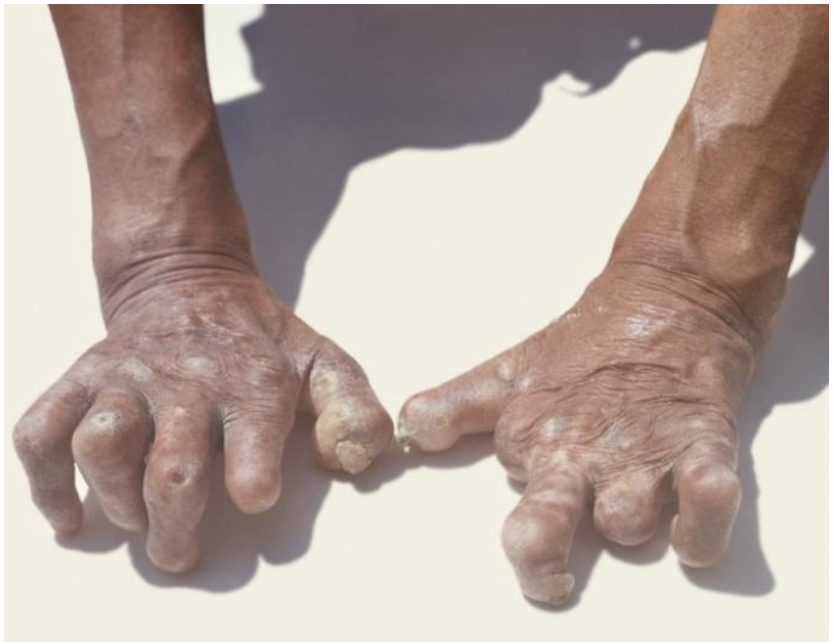


Sequestration (in osteomyelitis)



Mutilation





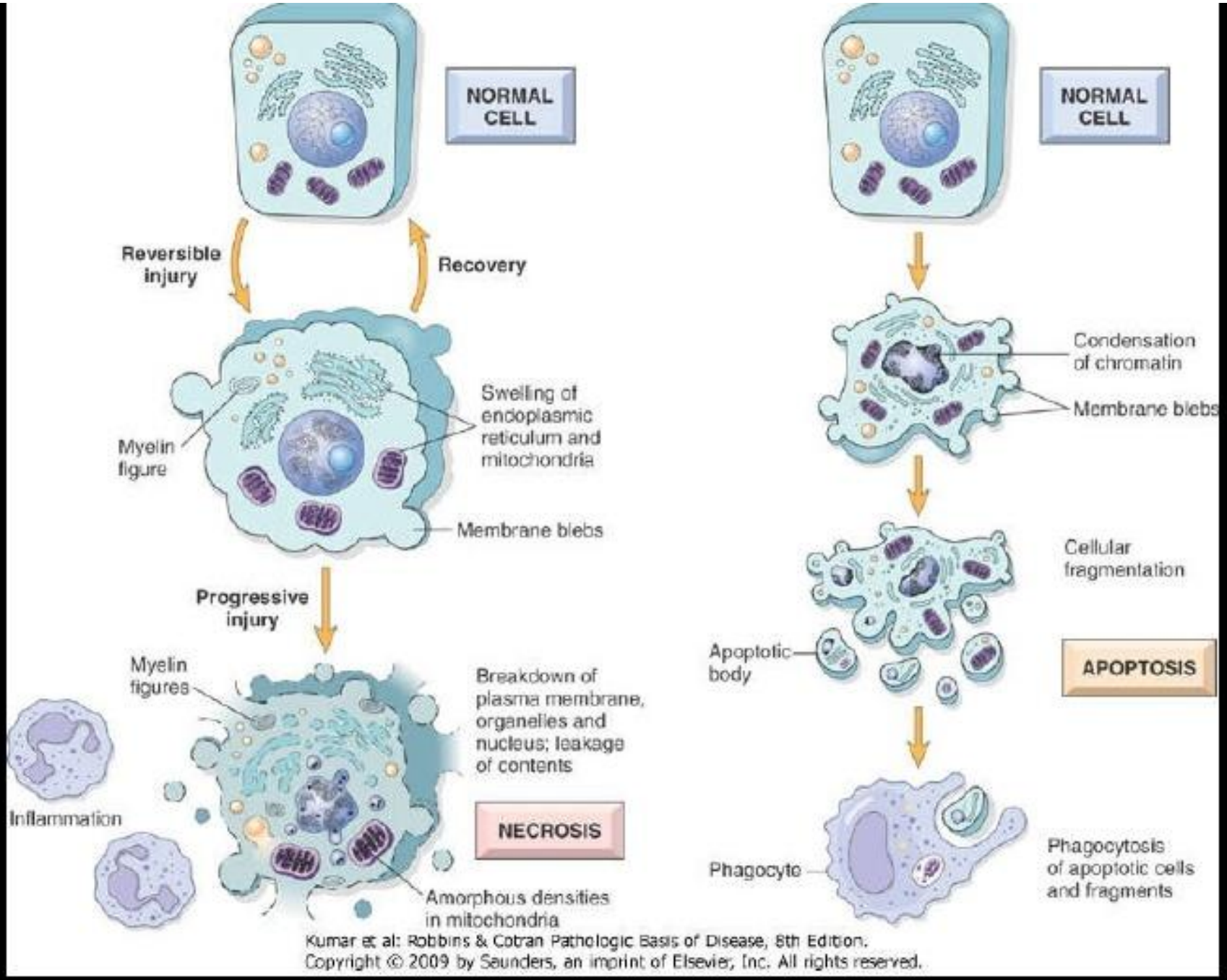
Mummification

Apoptosis

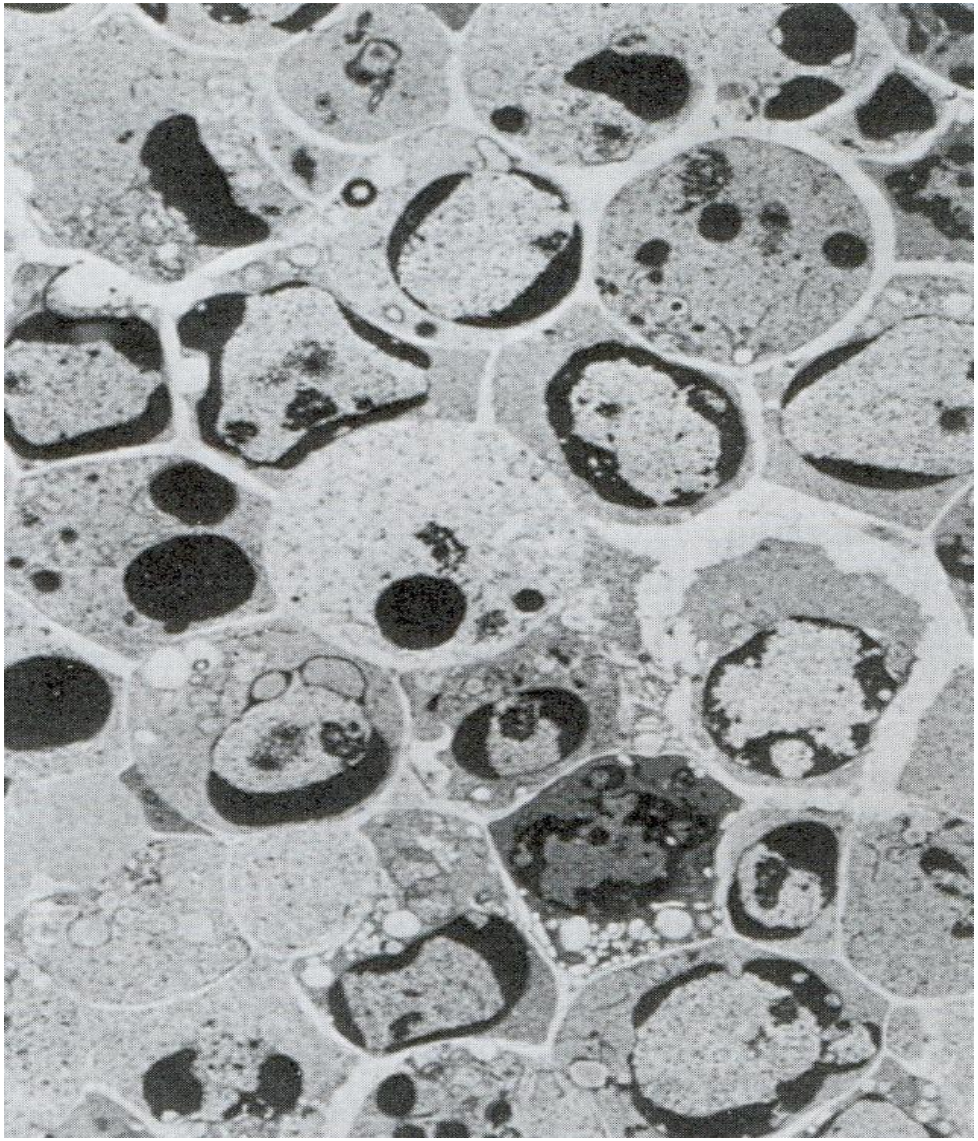
- Involved in many processes, some physiologic, some pathologic
  - Programmed cell death during embryogenesis
  - Hormone-dependent involution of organs in the adult (e.g., thymus)
  - Cell deletion in proliferating cell populations
  - Cell death in tumors
  - Cell injury in some viral diseases (e.g., hepatitis)

Apoptosis – Morphologic Features

- Cell shrinkage with increased cytoplasmic density
- Chromatin condensation
- Formation of cytoplasmic blebs and apoptotic bodies
- Phagocytosis of apoptotic cells by adjacent healthy cells



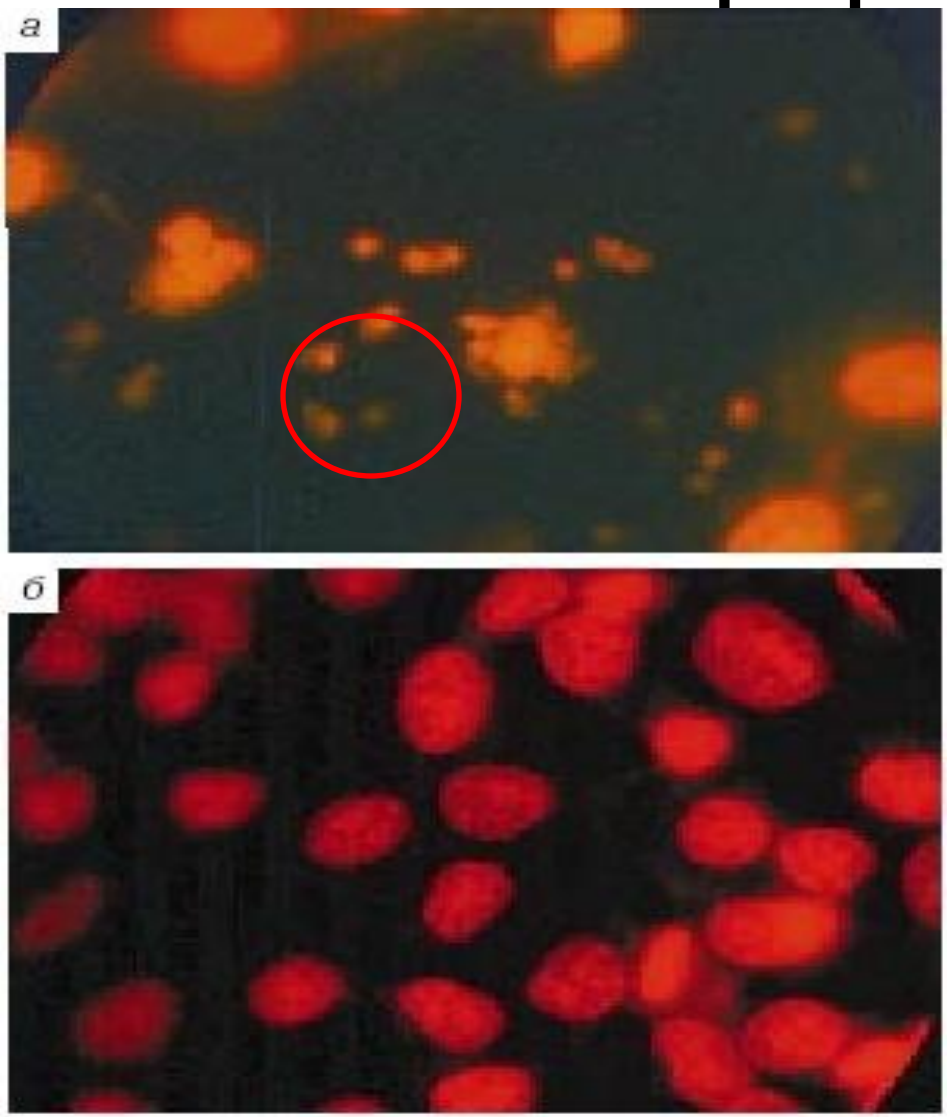
Morphology of apoptosis



Ultrastructural manifestations of apoptosis:

- Condensation of chromatin at the periphery of the nuclei;
- Fragmentation of chromatin;
- Formation of apoptotic bodies.

Apoptosis



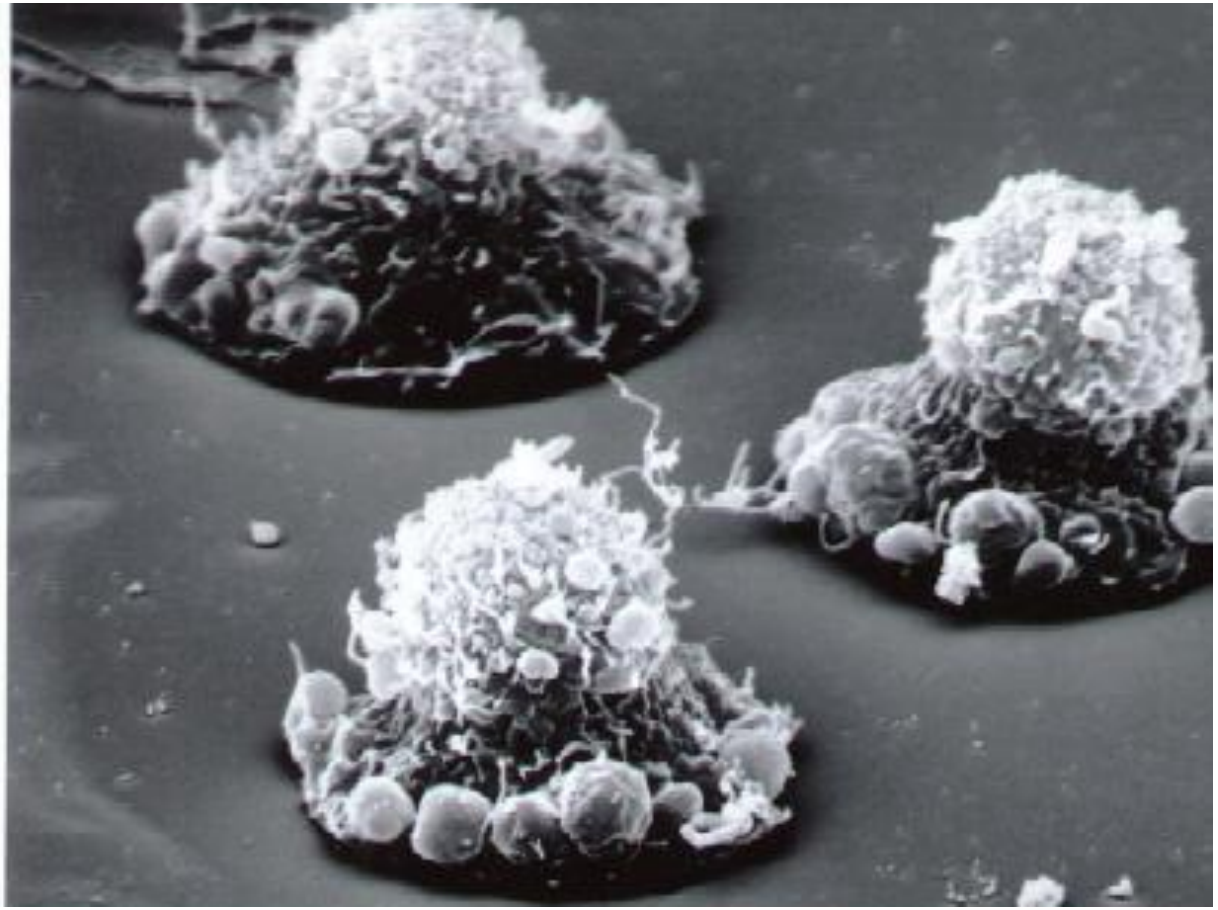
Flow cytometry:

a - cells in a state of apoptosis

b - control cells

A dye that fluoresces under ultraviolet light

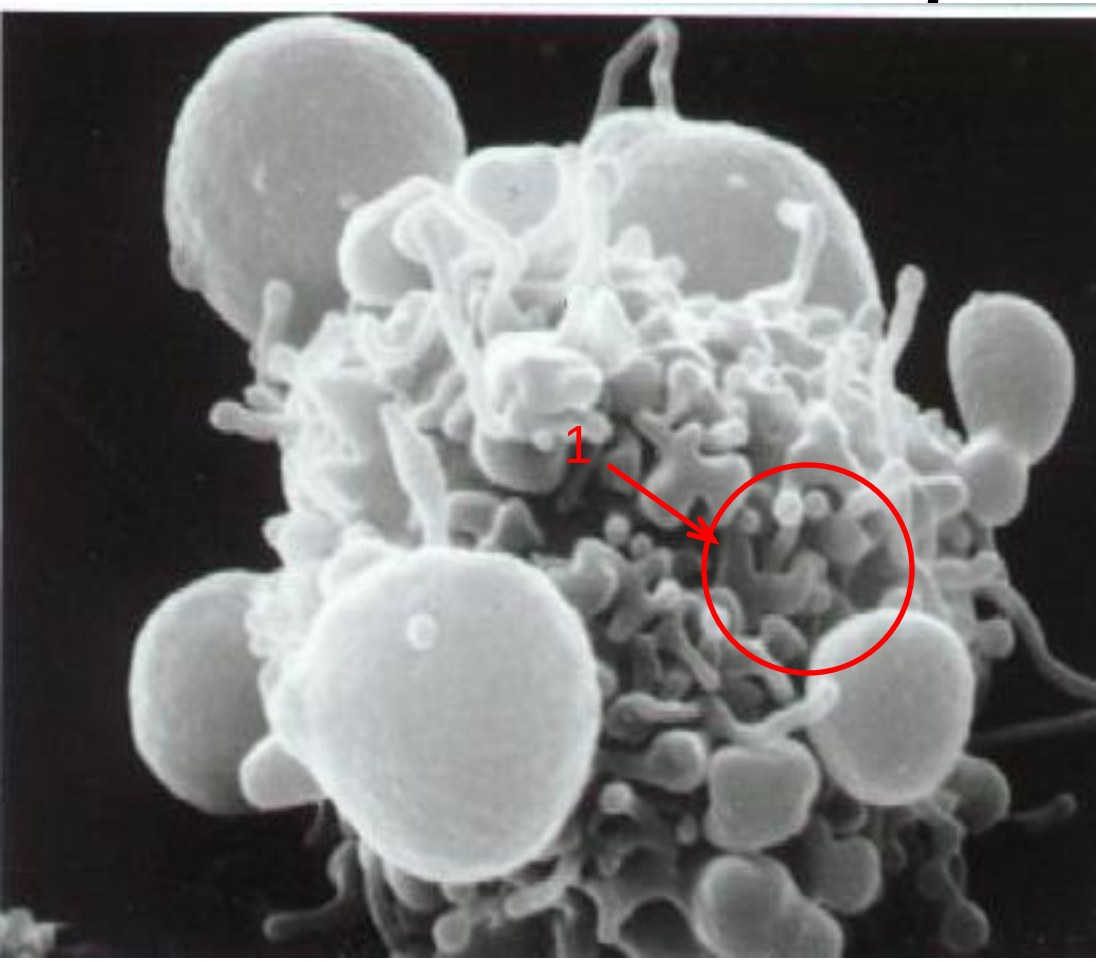
Apoptosis of epithelial cell.



Scanning Electron Microscopy:

- Formation of apoptotic bodies

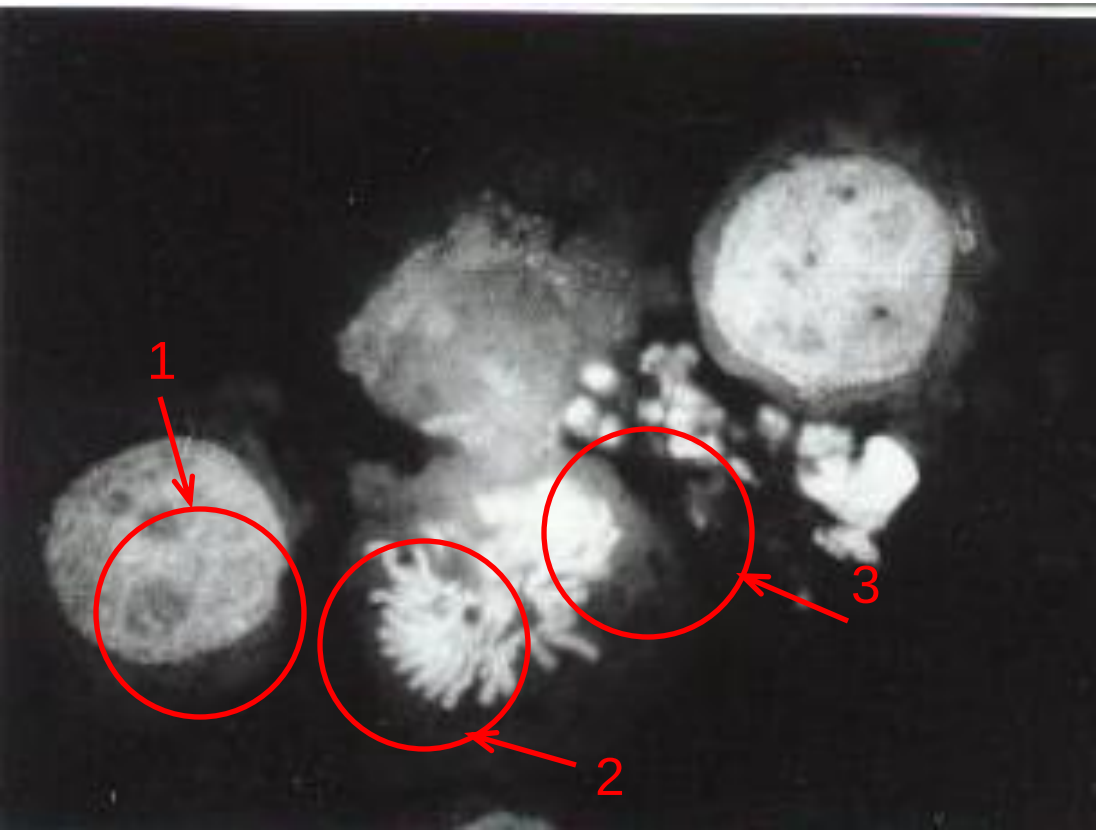
The final stage of apoptosis



Scanning Electron Microscopy:

1- apoptotic bodies

Cells: apoptosis, necrosis, mitosis



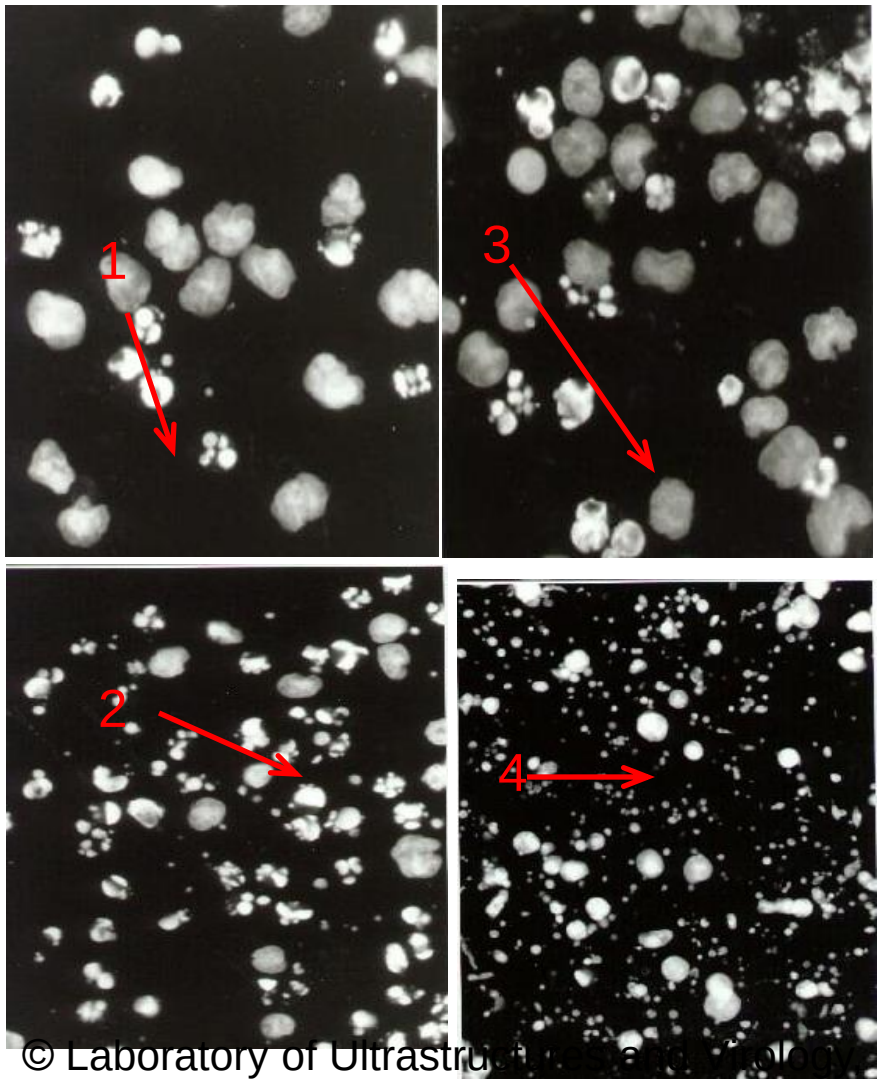
Flow cytometry:

1- norm

2- mitosis

3- apoptosis

Chromatin condensation



Flow cytometry:

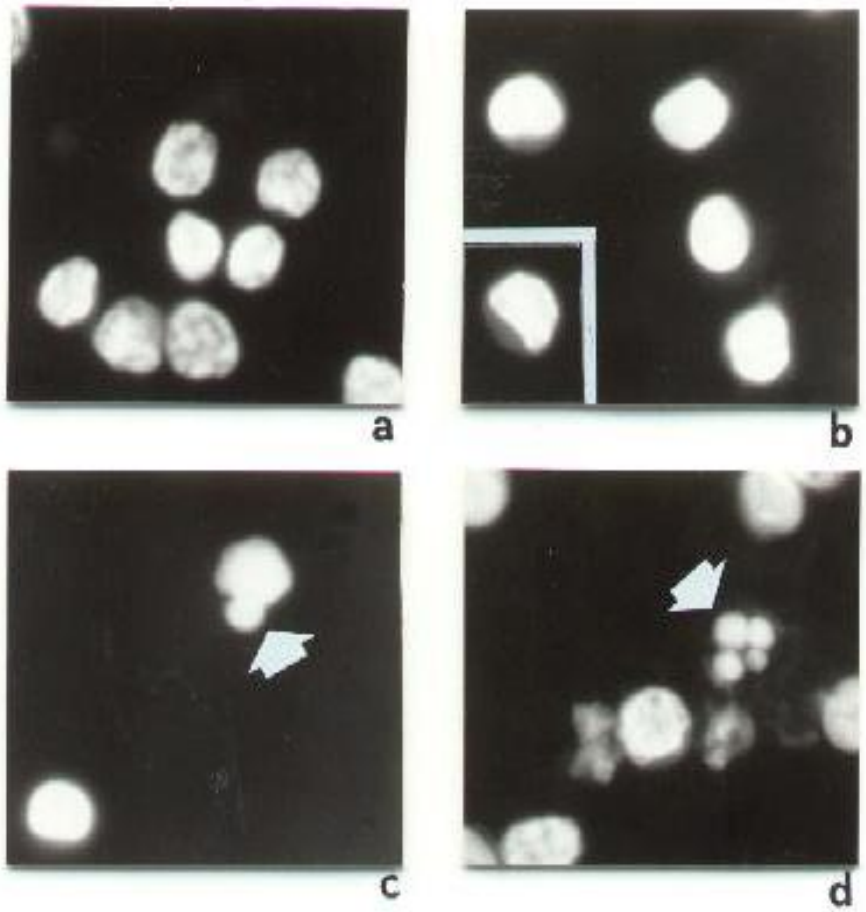
1- loss of connection with the karyolemma

2- chromatin aggregation

3-chromatin dissolution

4- apoptotic bodies

Chromatin condensation



Flow cytometry:

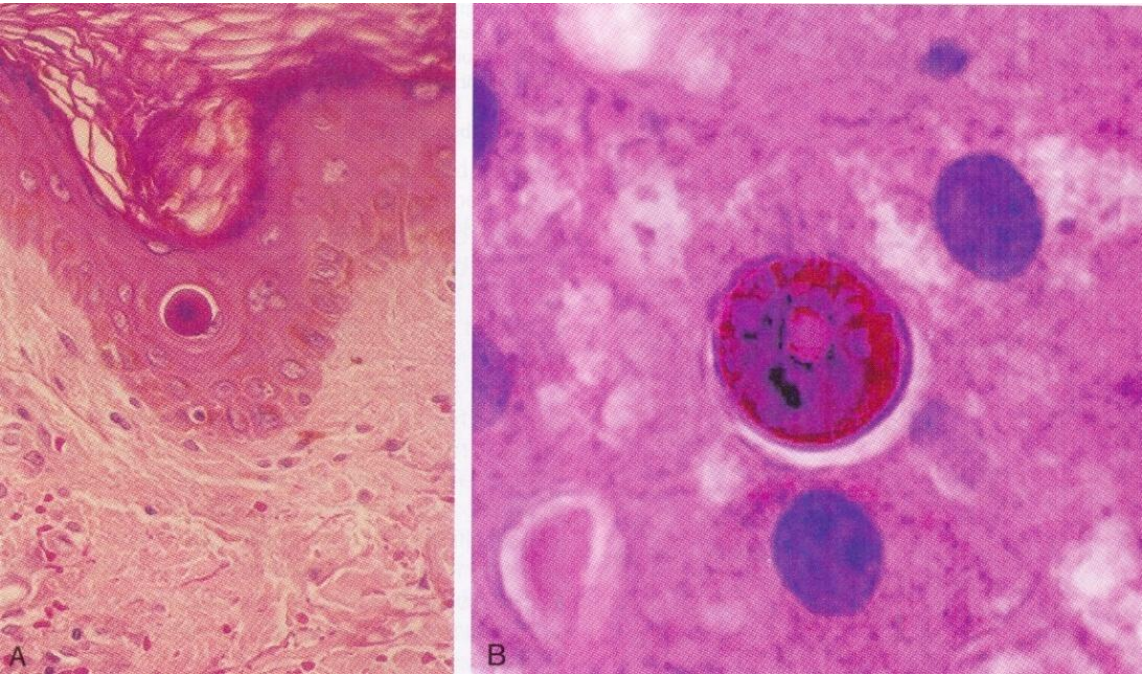
A- norm

B- loss of connection with the karyolemma

C- nuclear decay

D- formation of apoptotic bodies

Morphology of apoptosis



Light microscopy:

- intensely eosinophilic cytoplasm and a small, dark nucleus
- A) Apoptotic cell in the skin with an immunologically mediated reaction;
- B) an apoptotic cell in the liver.

THANK’S