CELL DEATH

Occurs when cells loose recovering capabilities, due to persistent damage.

There are two distinct types of cell death, which differ in morphology, pathogenesis and meanings:

NECROSIS **APOPTOSIS**

NECROSIS (pathological death)

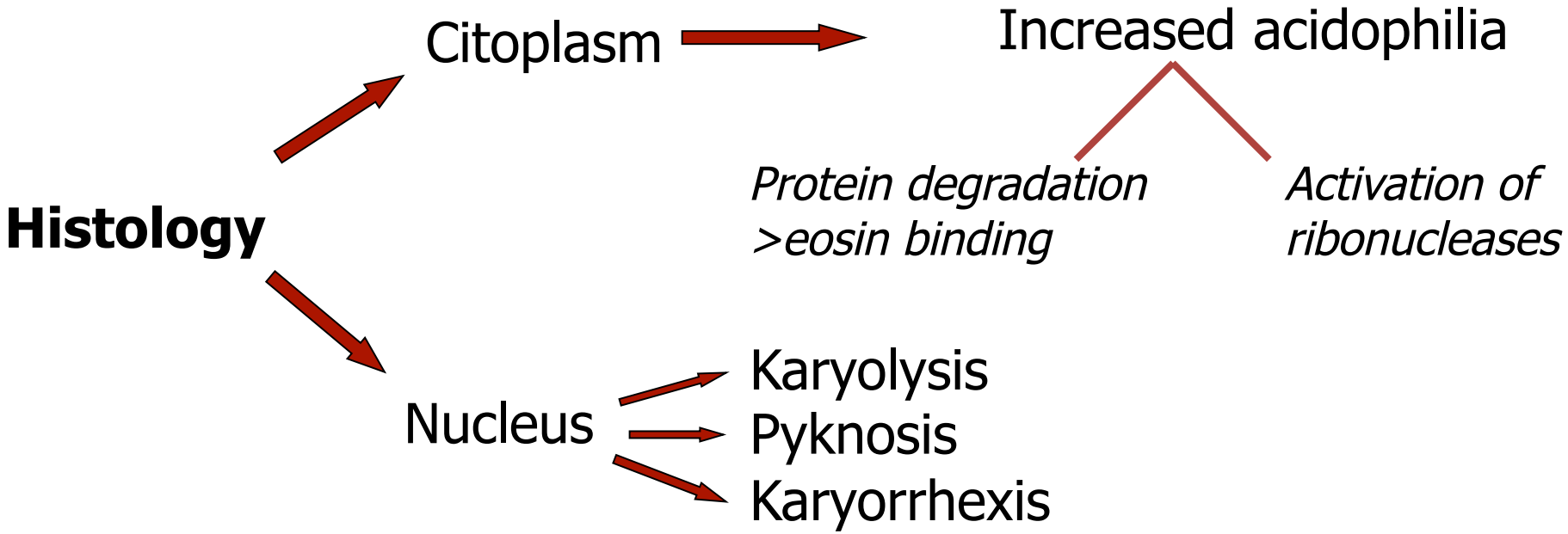
Sum of morphological alterations consequent to cell death, which lead to disappearance of the cyto-histological characteristics of tissues

Mechanisms: **Coagulation of cellular protein**
Autolysis (Lysosomal enzymes)
Eterolysis (Lysosomal enzymes from leukocytes)

Loss of cellular integrity with release of its content into the extracellular environment and subsequent inflammatory reaction

- Time-dependent process: 1-8 hours.
- Simultaneously involves a high number of cells

Macroscopic appeareance: depends on mechanisms is used and site



Biochemistry: *>Na^+,Ca^+ ions < K^+ ions > intracellular H_2O, < cellular respiration*
Appeareance of digestive polypeptides (cytoplasmatic granules).
Phospholipids accumulation due to damaged cellular membranes

Phagocytosis

Release of fatty acids
Calcification (calcium soaps)

M.E.: Discontinuity of plasma membrane
Mitochondria: *swelling, crests fragmentation.*
Ribosomes reduction. Fragmentation and reduction of R.E.R

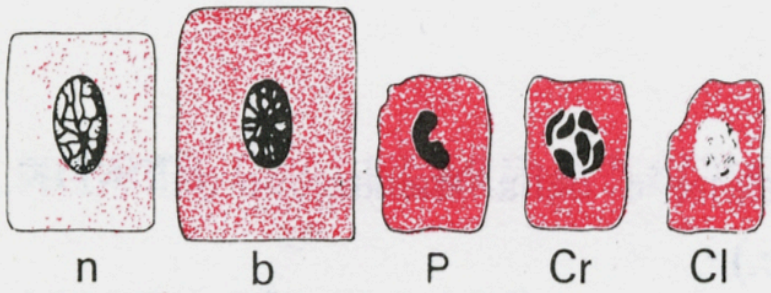
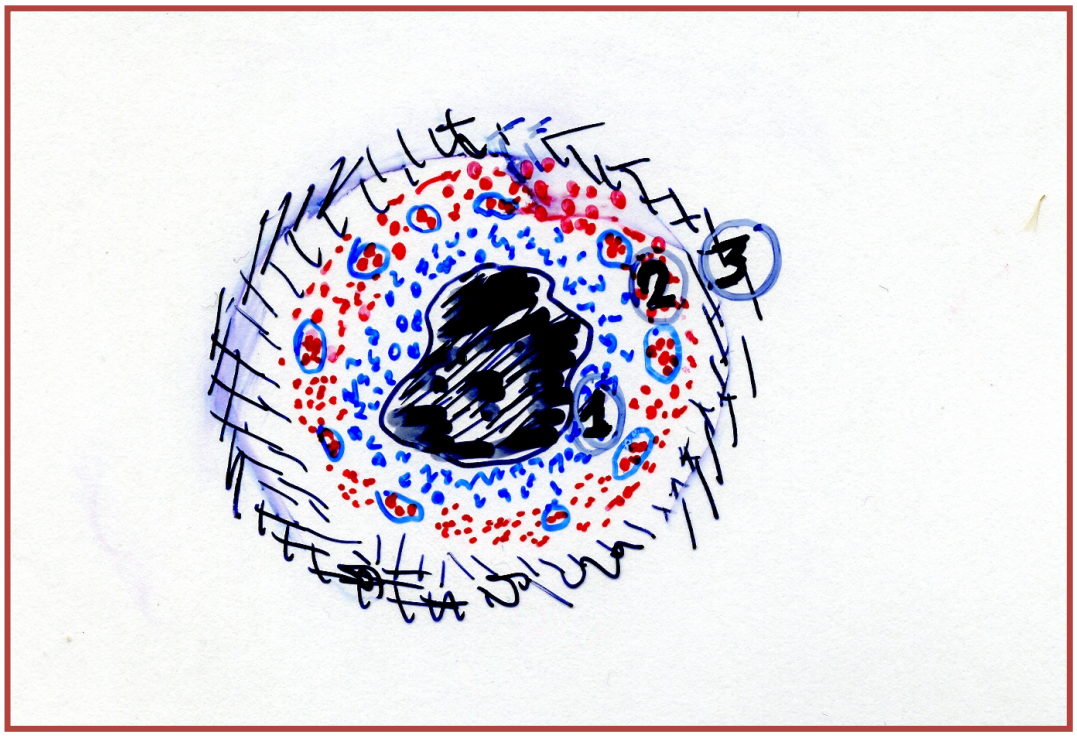


Fig. 47. Alterazioni cellulari regressive. n = cellula normale. b = stadio prenecrotico: cellula con citoplasma acidofilo e reticolo cromatinico addensato. P = picnosi del nucleo. Cr = carioressi; Cl = cariolisi.

Morte cellulare non equivale a necrosi



Evolution of a necrotic focus:

- Granulocytes-inflammatory reaction (yellowish edge close to necrosis)
- Hyperemic red ring with small haemorrhagic extravasation
- Suffering tissue in the peripheral area

EVOLUTION OF NECROTIC FOCUS

- Phagocytosis of cell debris by macrophages
- Simultaneous proliferation of endothelial cells (neoangiogenesis), fibroblasts, lymphocytes and plasma cells at the periphery of necrotic areas

} Granulation tissue

- Progressive reduction of the vascular and cellular components, increase of collagen fibers

↓

REPAIRING SCAR

MORPHOLOGICAL FEATURES OF NECROSIS

- **COAGULATIVE NECROSIS**
- **COLLIQUATIVE N.**
- ENZYMATIC N.
- CASEOUS N.
- FAT NECROSIS
- FIBRINOID N.
- GANGRENOUS N.

COAGULATIVE (*Ischemic*) NECROSIS:

Prevalence of denaturating events and protein coagulation
Inactivation of proteolitic enzymes
Water loss and ***cell mummification***

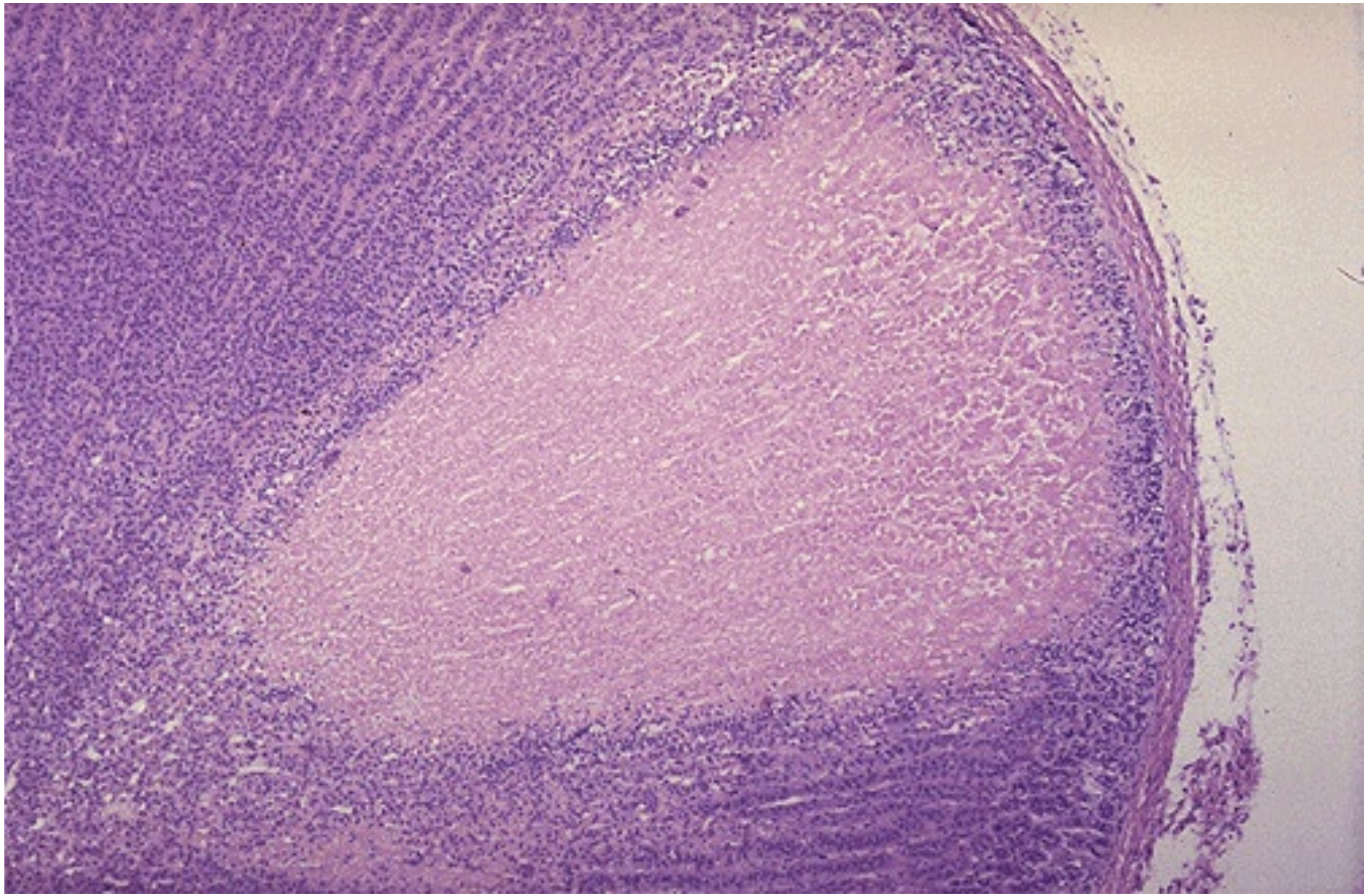
Macroscopic features: pale tissues, opaque, increased thickness
gray-white color

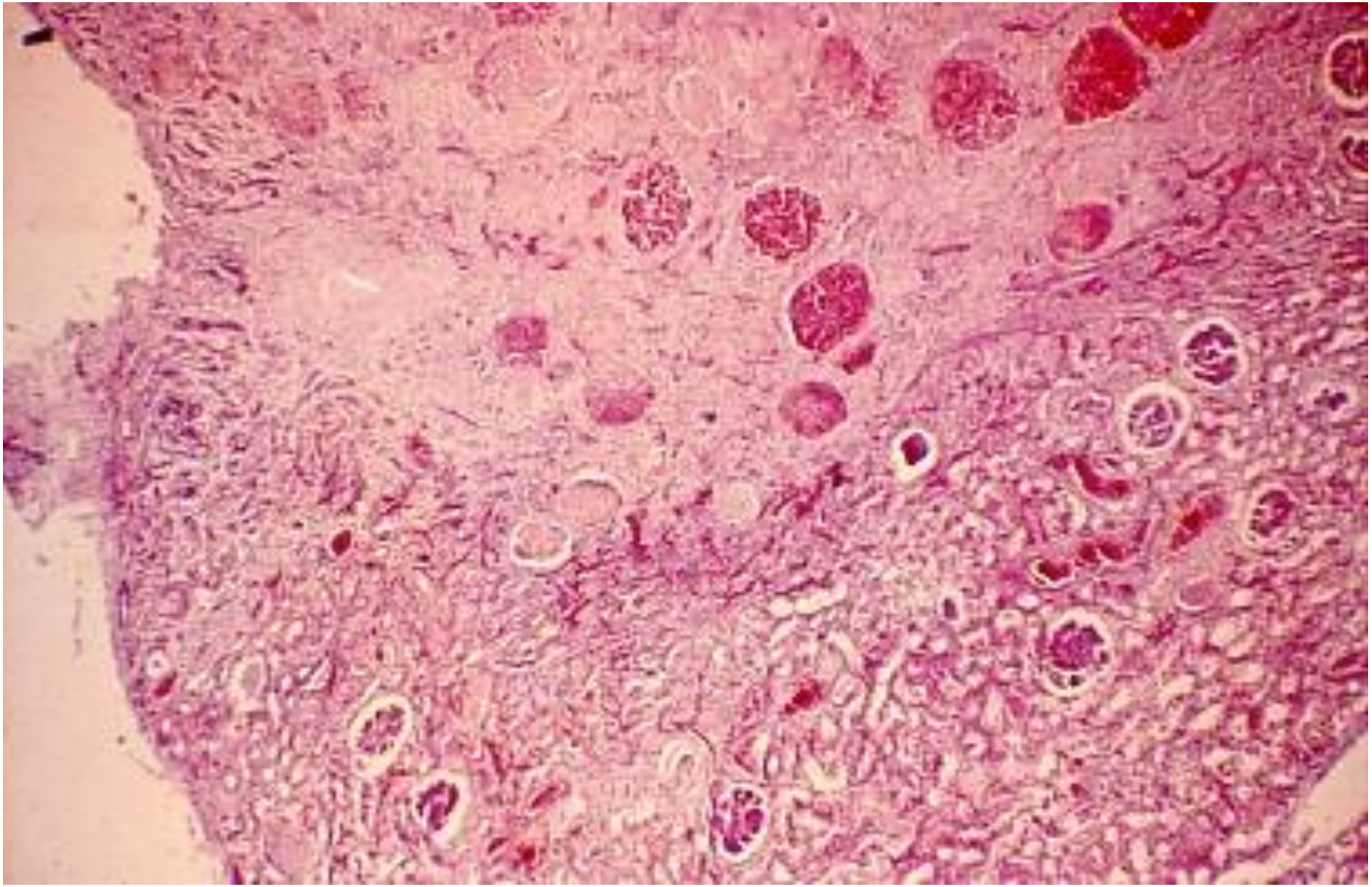
Microscopic features: Structure initially preserved. Homogeneous cytoplasm

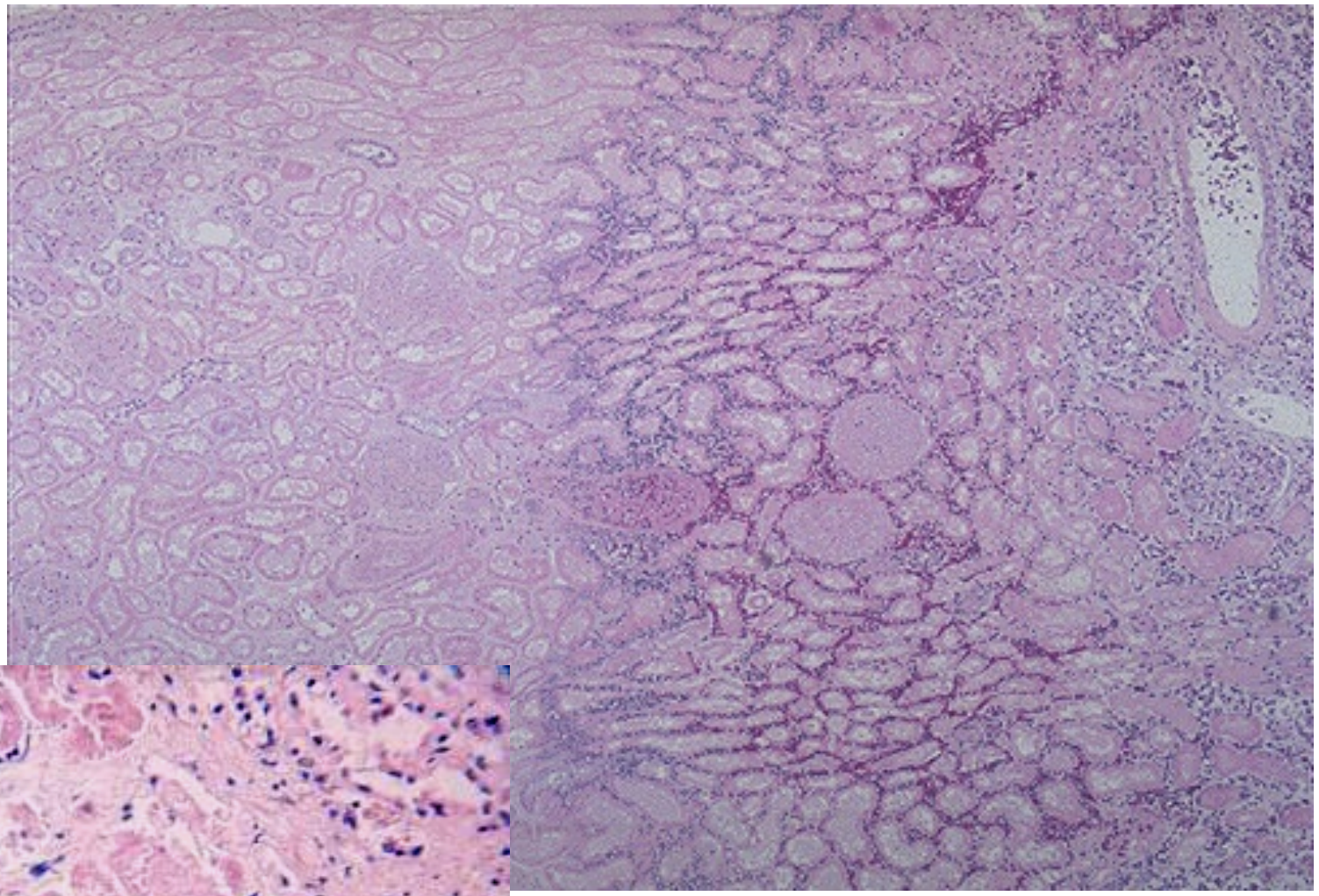
Causes: ischemia, physical and chemical agents

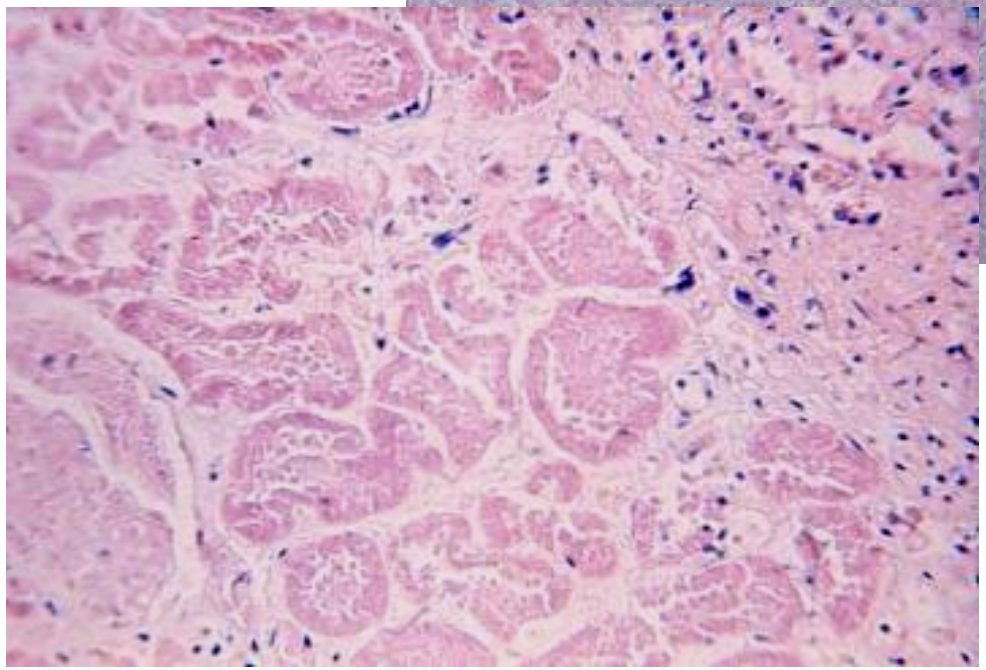
Sites: heart, kidneys, spleen, neoplasms ecc.

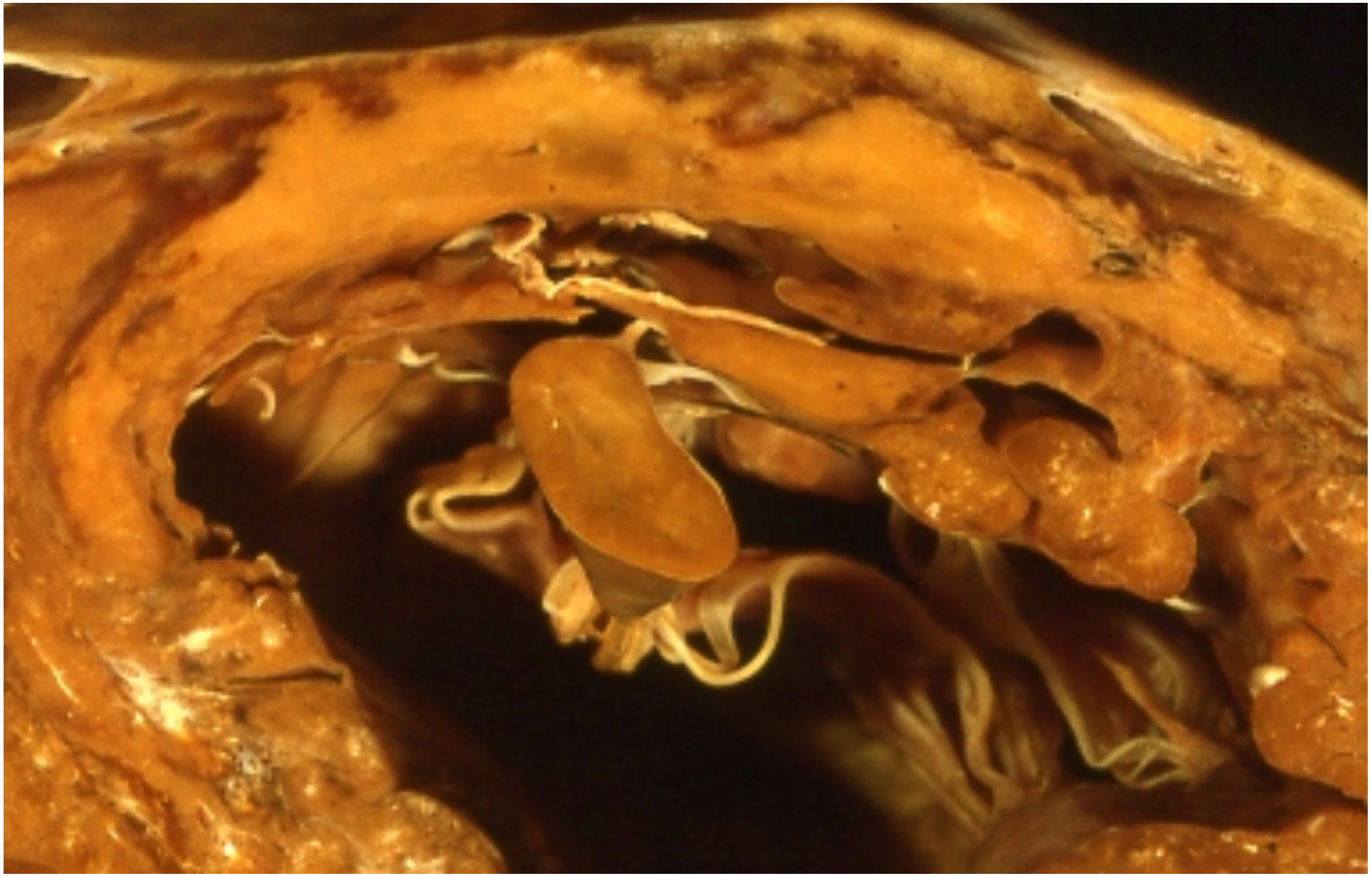
Tissue reactions: Neutrophils and macrophages close to the lesion.

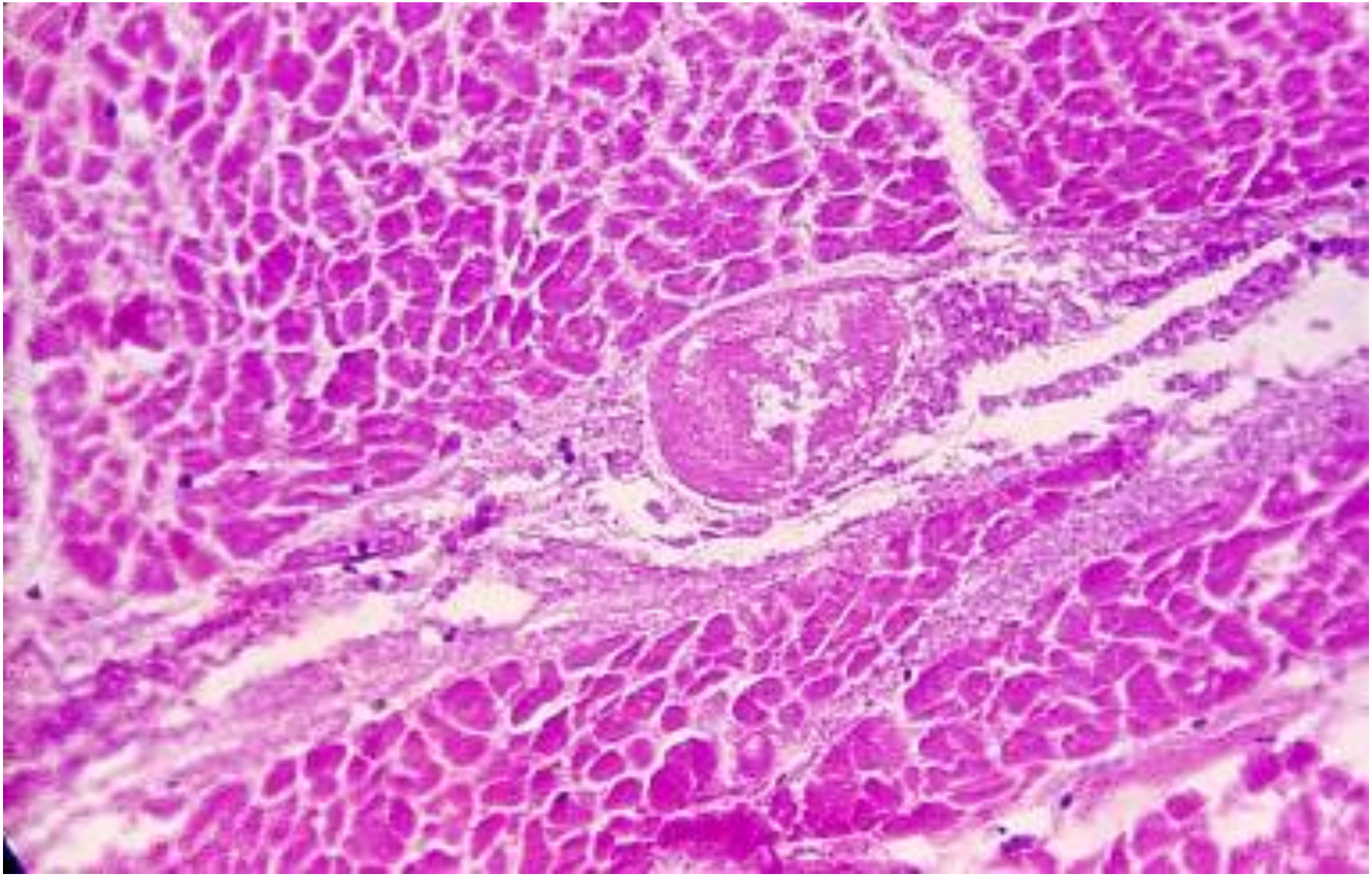


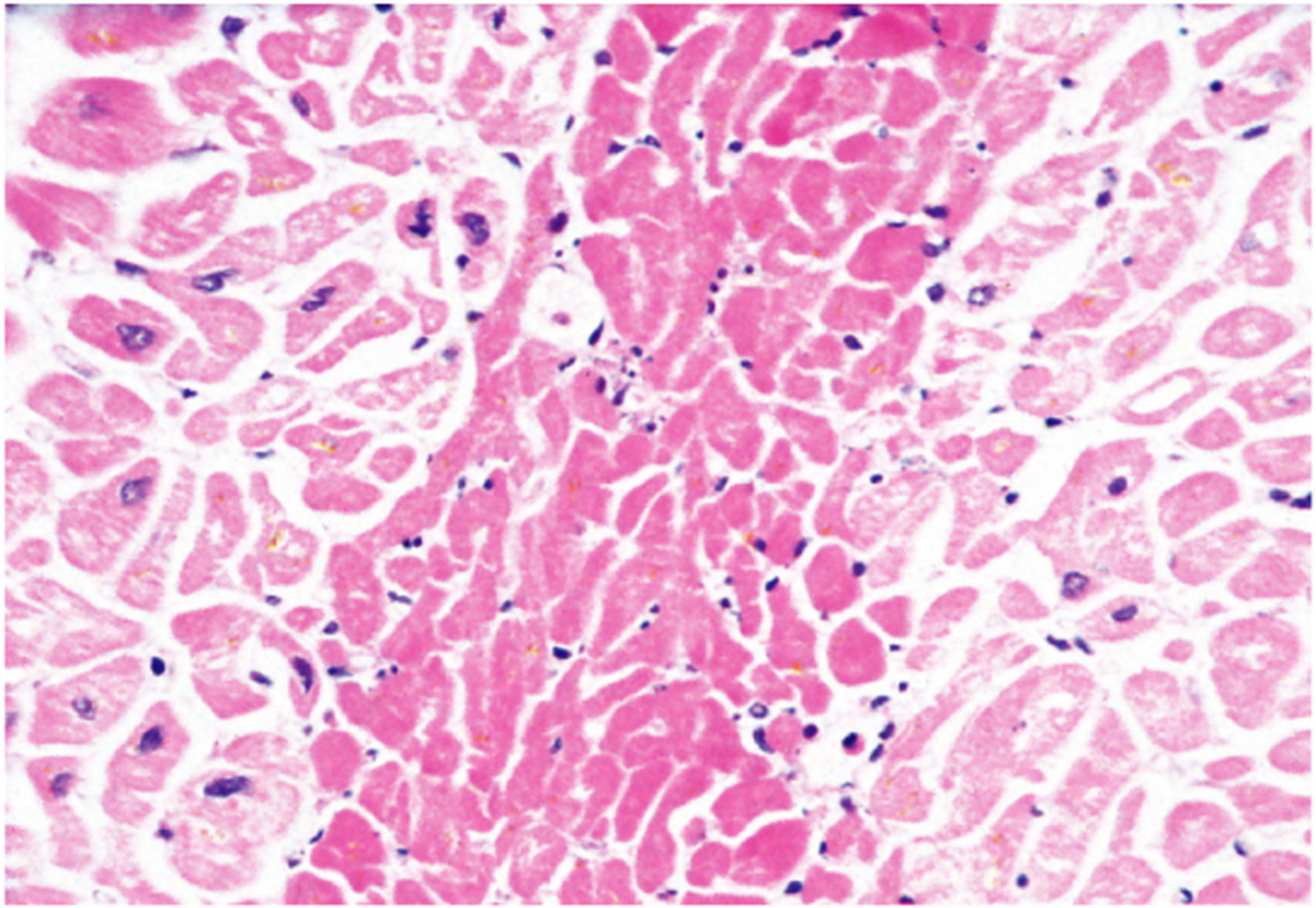


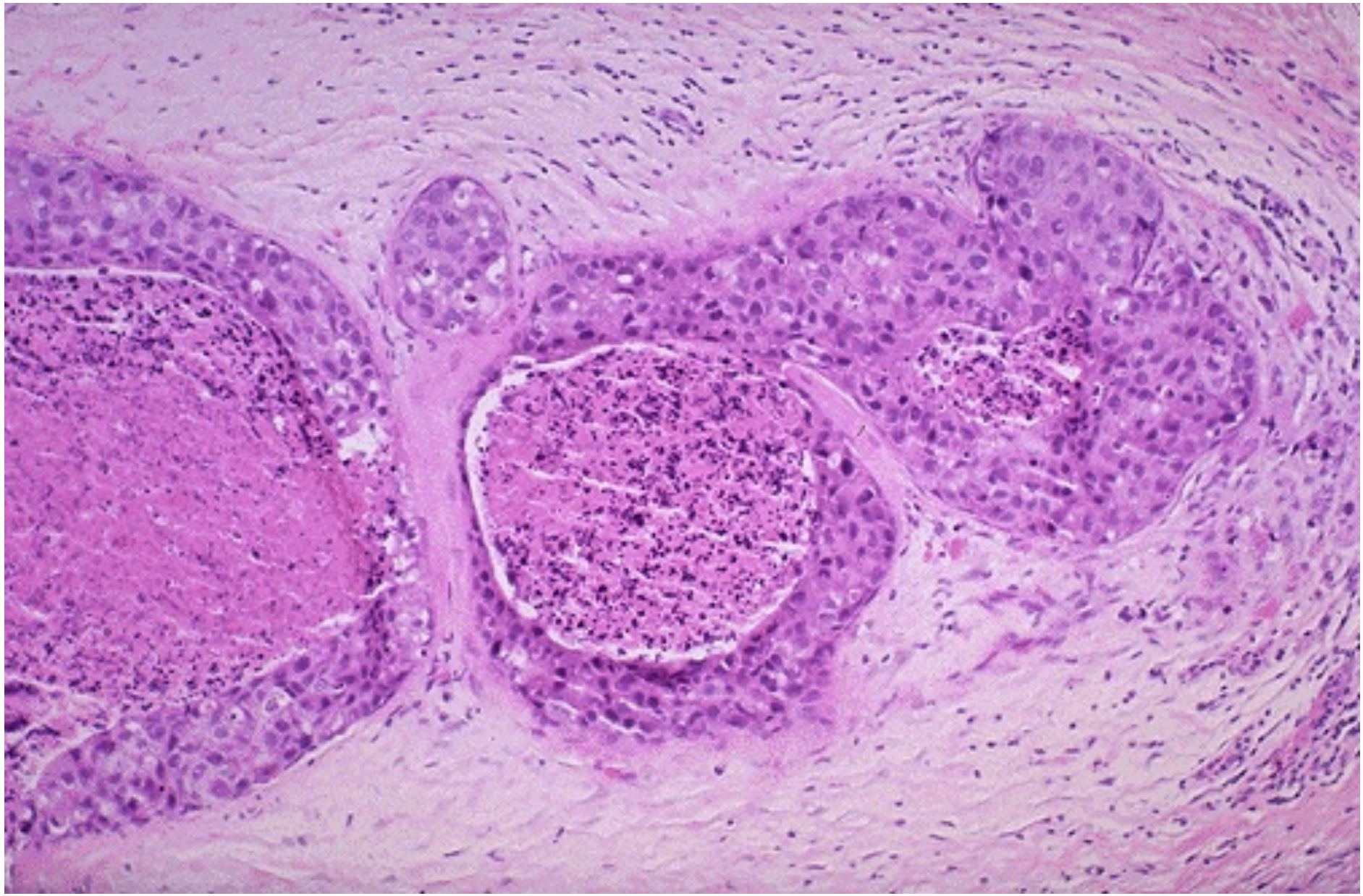


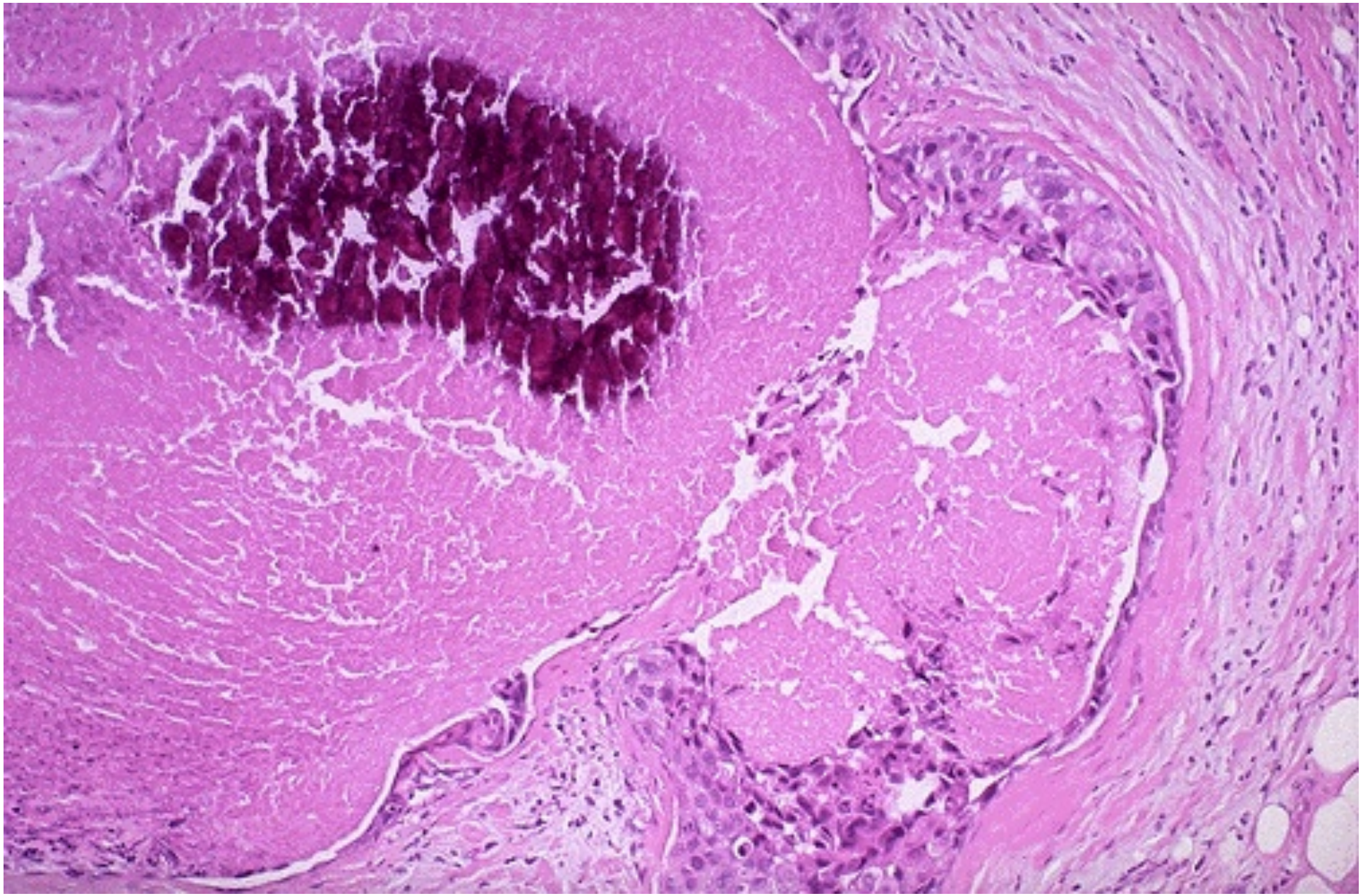












COLLIQUATIVE (*Enzymatic*) NECROSIS

prevalence of autolytic phenomena

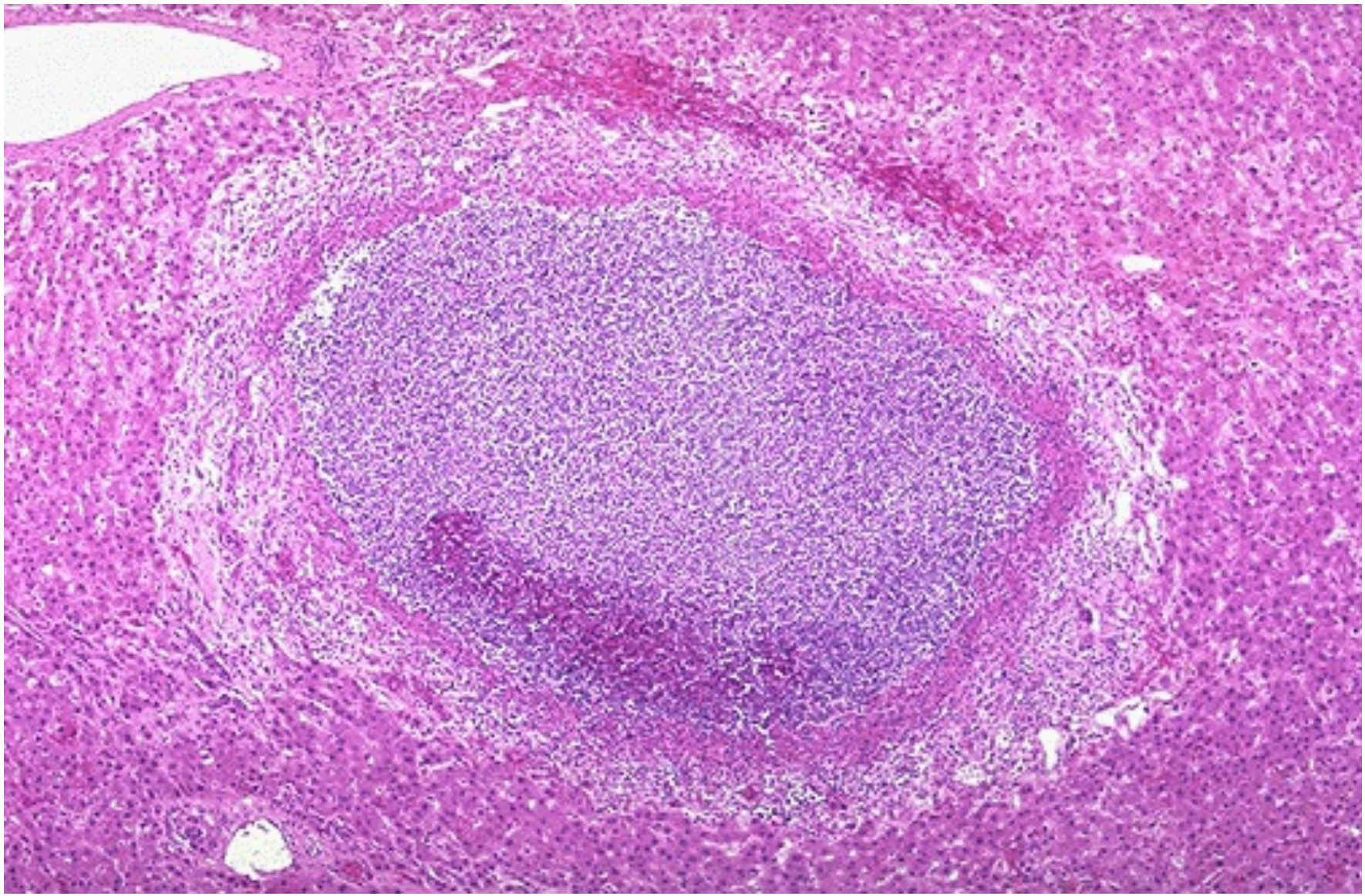
Macroscopic features: rapid destruction of tissues, presence of dense material (Pus)

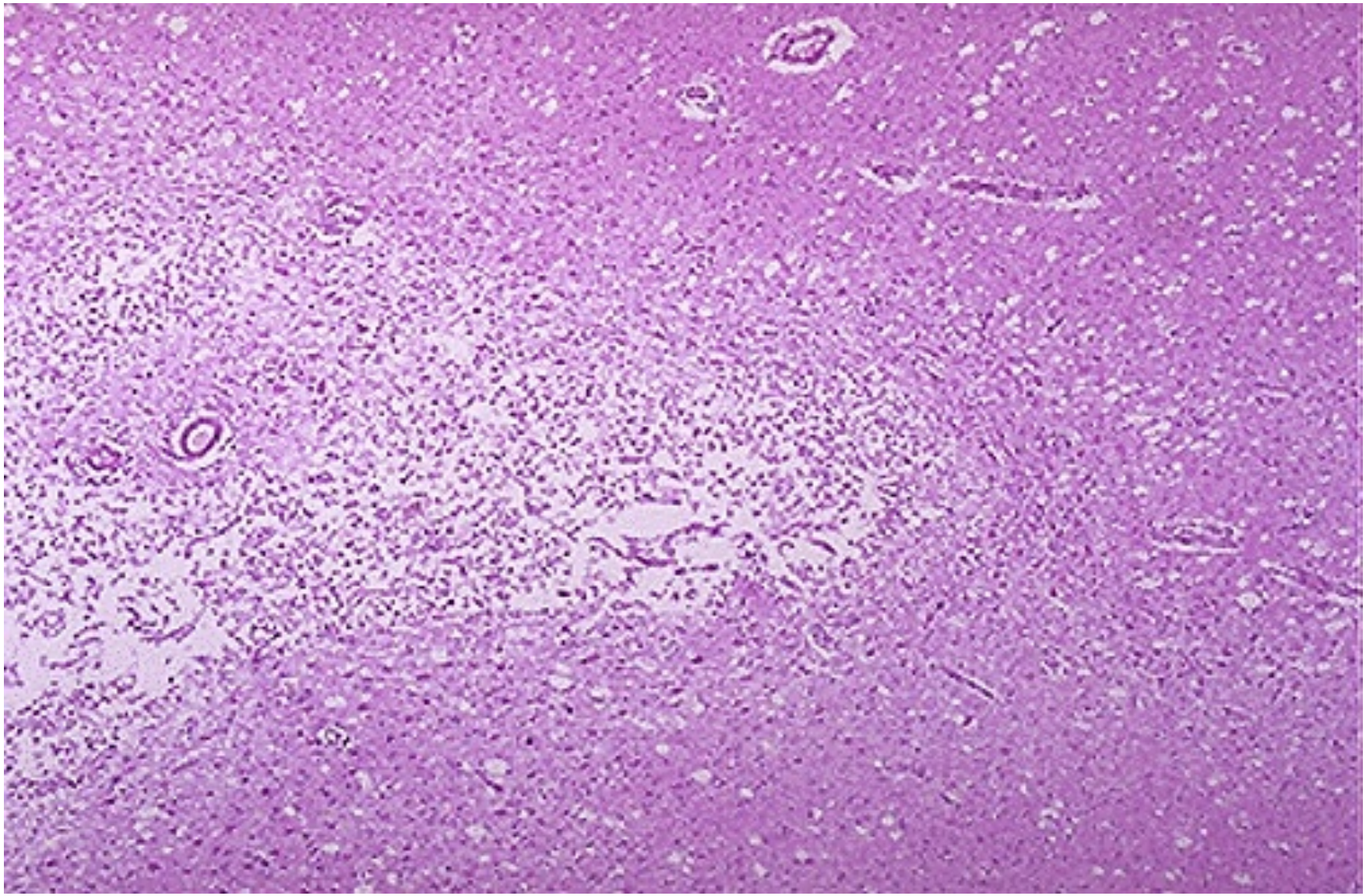
Microscopic features: rapid disappearance of cellular borders. Nuclear debris, cellular debris, regression of granulocytes.

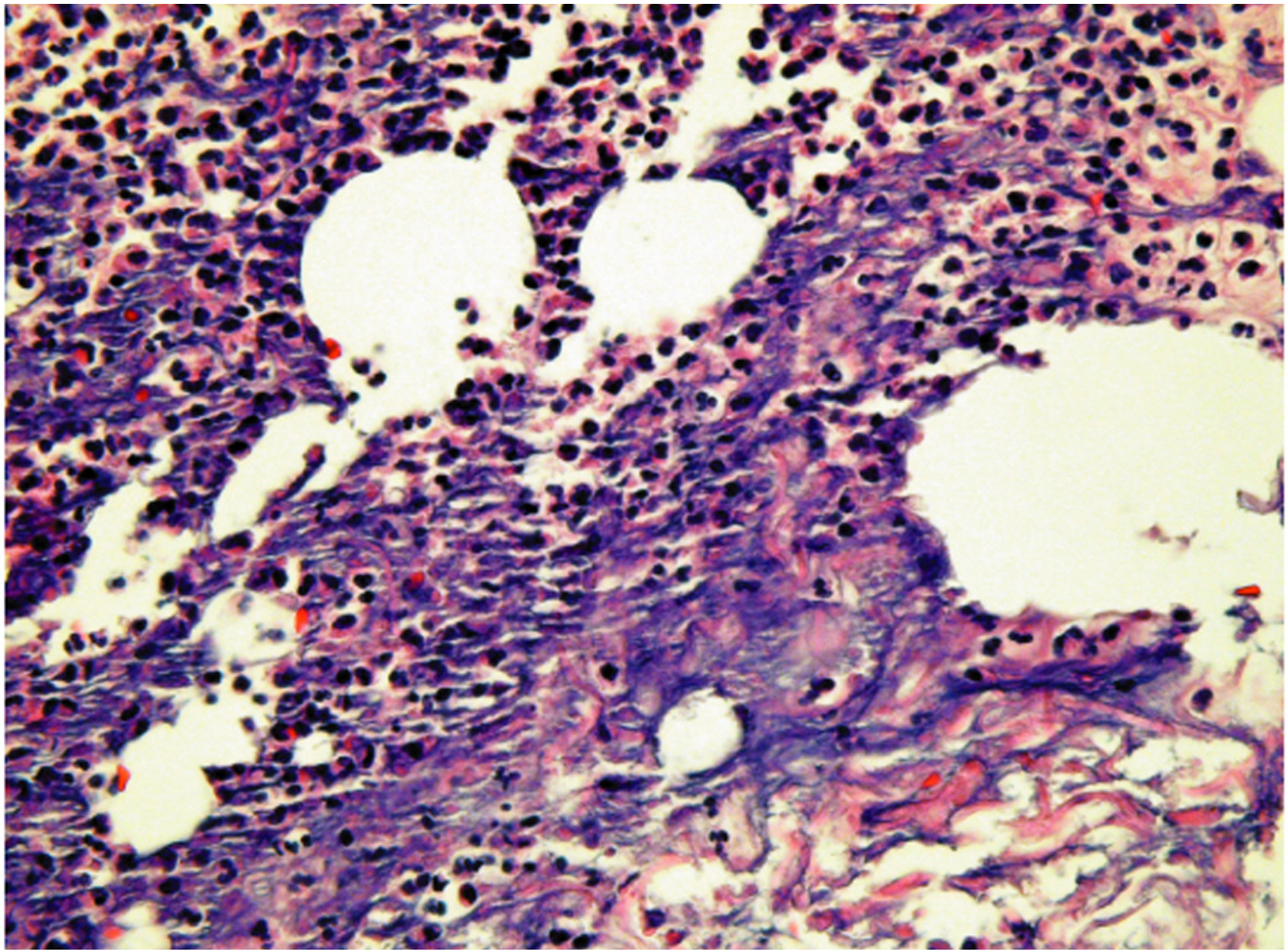
Causes:

- Acute infections - suppurative inflammation
- Anoxia (CNS: softening of white matter)

Locations: ubiquitous







Caseous necrosis

Necrosis due to coagulation + lipidic complex (capsules of destroyed bacilli)

Melted cheese appeareance

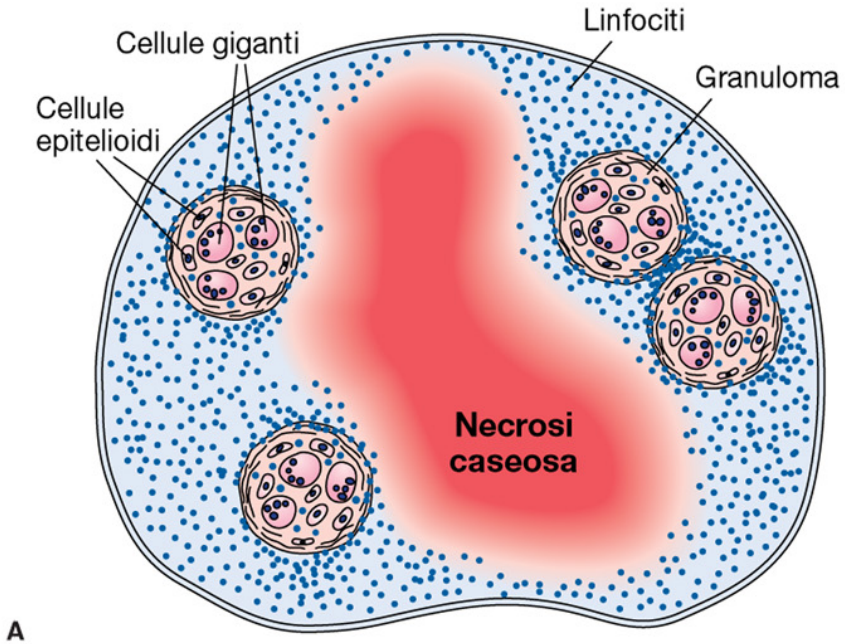
Macro: semifluid-tissue

Micro: areas of amorphous and acidophilic material

(surrounded by granulomatous reaction), sometimes cellular debris are present

Frequent calcification.

Infectious granulomatous diseases :TBC, leprosy, syphilis



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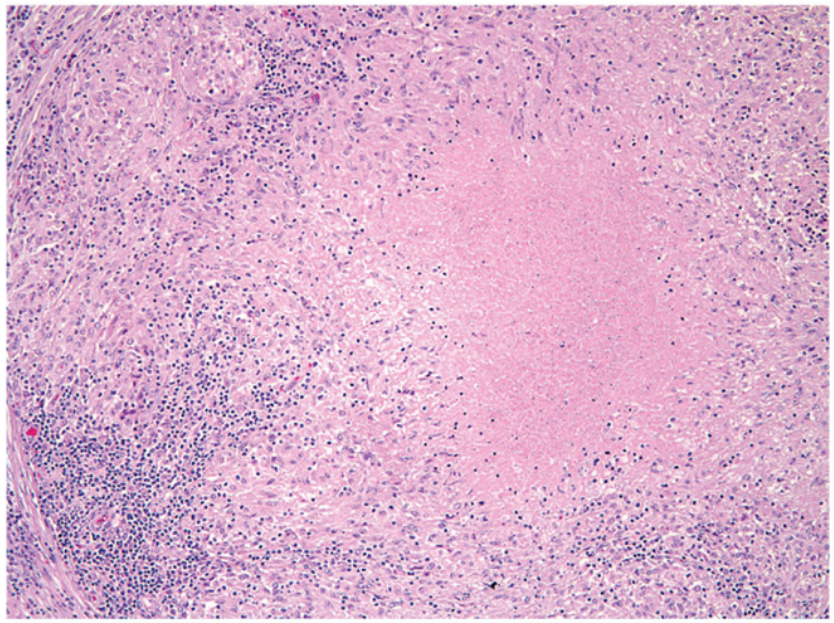

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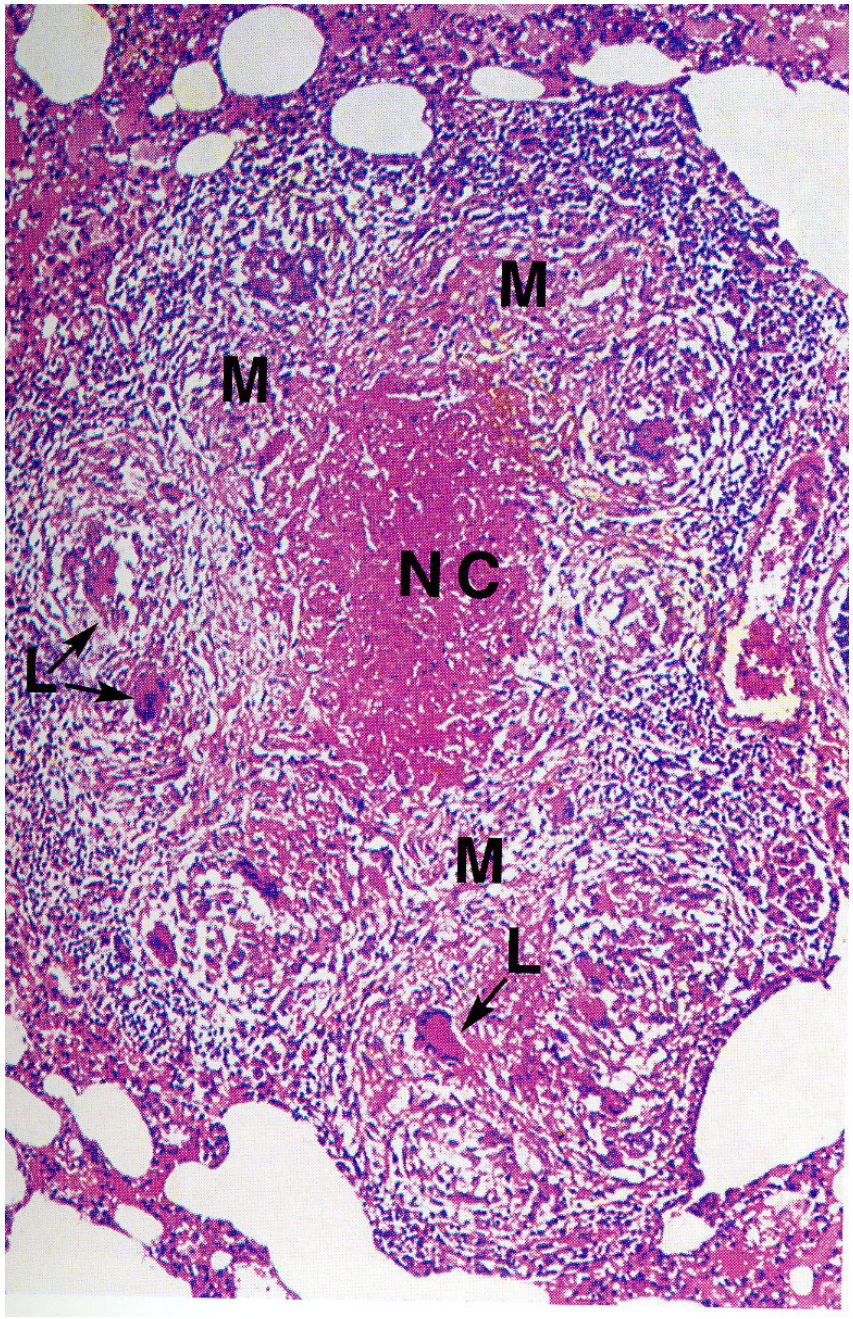
Rubin, Patologia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- **Liponecrosis:** destruction of adipose tissue with subsequent release of neutral fats (macrophagic reaction)

- **Steatonecrosis:** (enzymatic necrosis):destruction and digestion of adipose tissue due to lipase action, release of fatty acids
- **Fibrinoid necrosis:** Frequent in immune-complex disease (AA complex + fibrin)

- **Gangrenous necrosis:** Due to ischemia (thrombosis, arteriophaties) + Gram- bacterial (C. Welchii) infection

Apoptosis

Genetically programmed cell death in response to molecular signals, internal or external to the cell

- **Physiological** event, normal tissue homeostasis (labile tissues)
- Removal of damaged cells : healthy cells inactivate functional genes and activate genes that lead to death

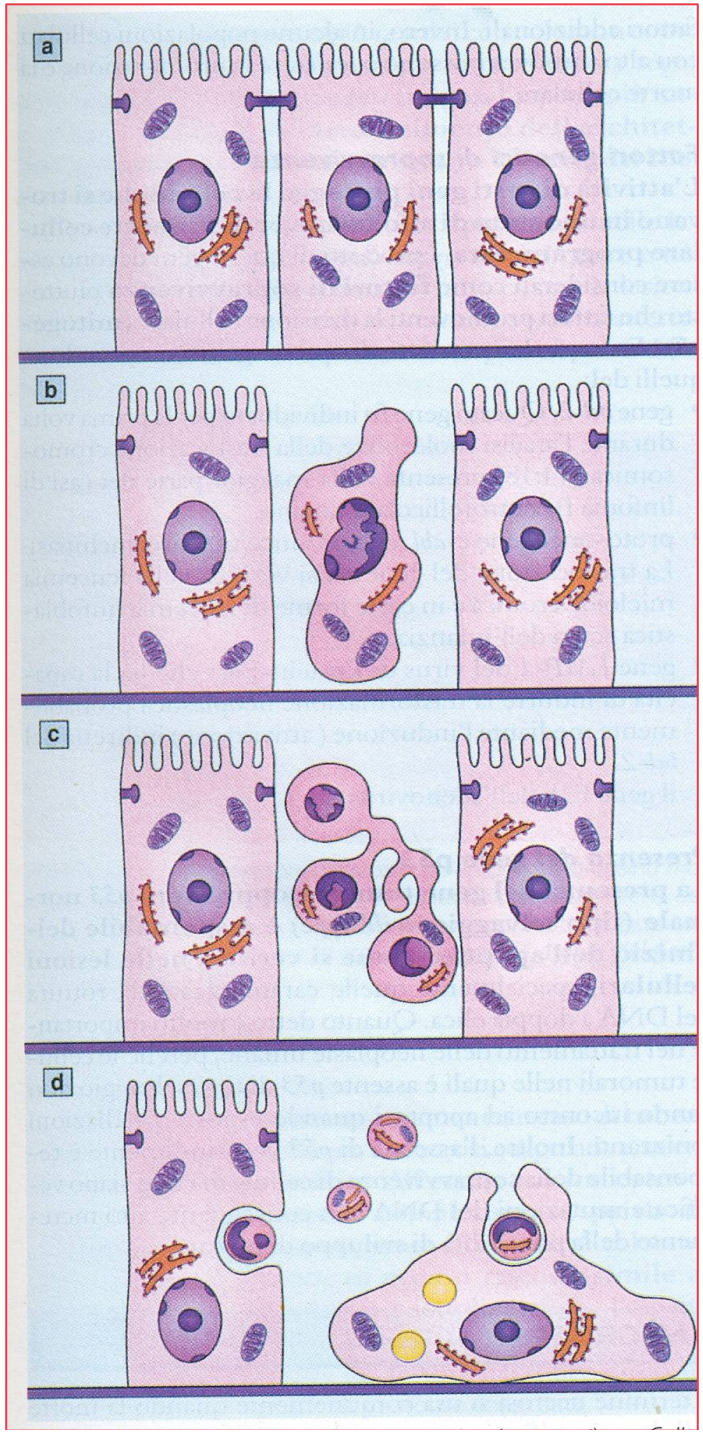
- apoptotic genes
- genes promoting cell death
- genes controlling phagocytosis and digestion of dead cells

APOPTOSIS

Spontaneous phenomena
- Embryogenesis
- Hormonal causes
- Tumors
- Immune disorders
- Viral infections

Increased by
- Chemotherapeutic drugs
- Radiation therapy
- Hypothermia
- Therapies that block or inhibit hormones

MORPHOLOGY OF APOPTOSIS



APOPTOSIS / NECROSIS HISTOLOGICAL FEATURES

APOPTOSIS

- Single or few cells
- Chromatin leaning the nuclear membrane + dense cytoplasm
- Convolution of nuclear membrane
- Fragmentation of nucleus into particles surrounded by double membrane: **apoptotic bodies**
- Phagocytosis of apoptotic bodies
- Lysosomal digestion
- Rapid event
- Tumors: everywhere

NECROSIS

- Areas of contiguous cells
- Irregular thickening of chromatin
- Gradual disappeareance of nuclear membranes
- Preservation of nuclear and cellular shape
- Swelling and disintegration
- Phagocytosis + **inflammation**
- Slow event over time
- Tumors: central areas

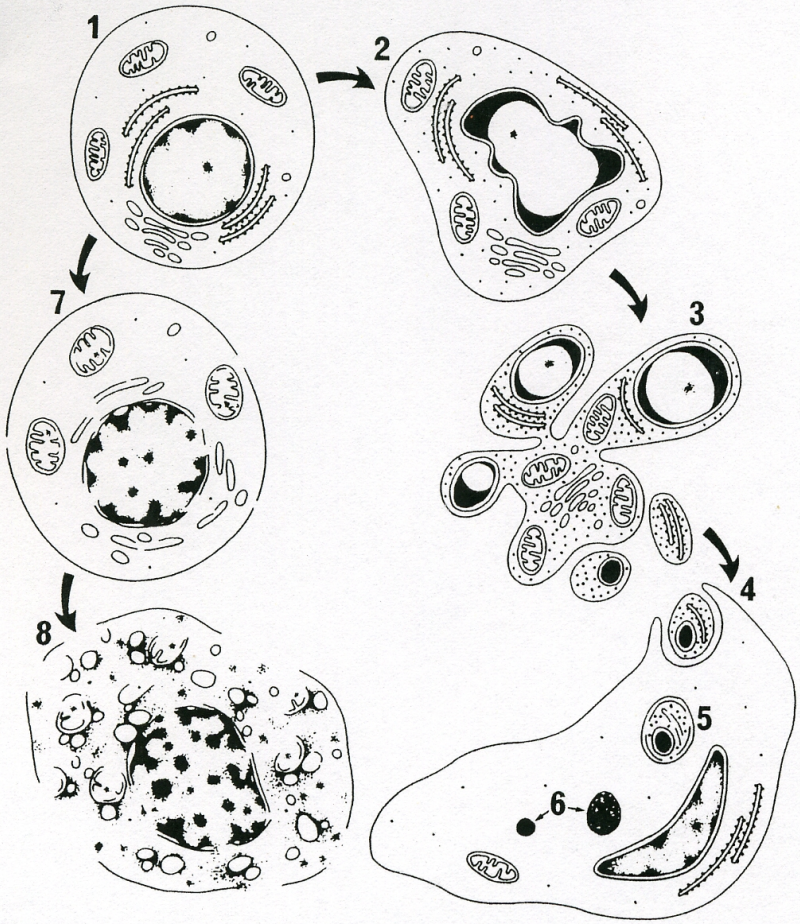
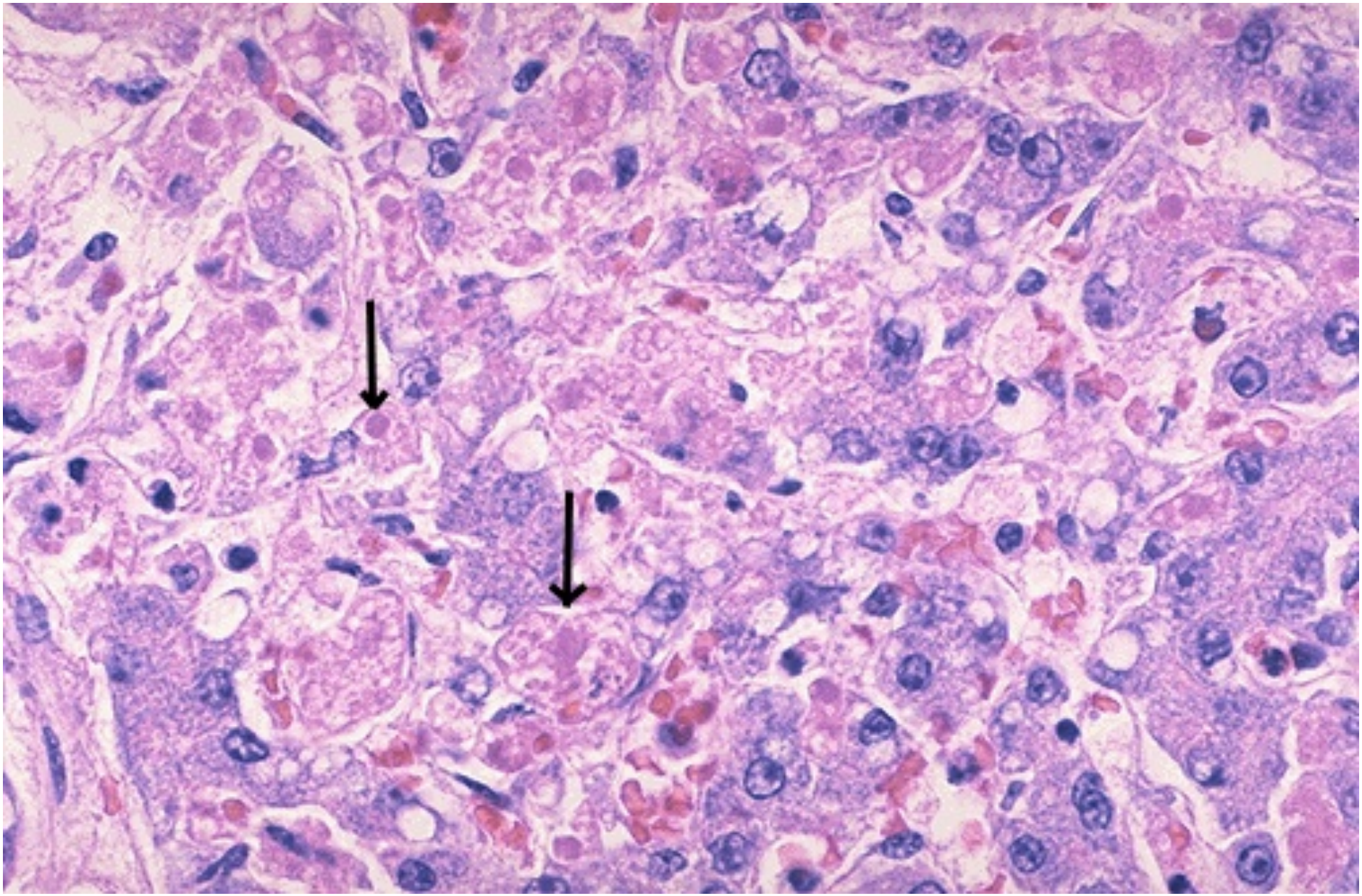
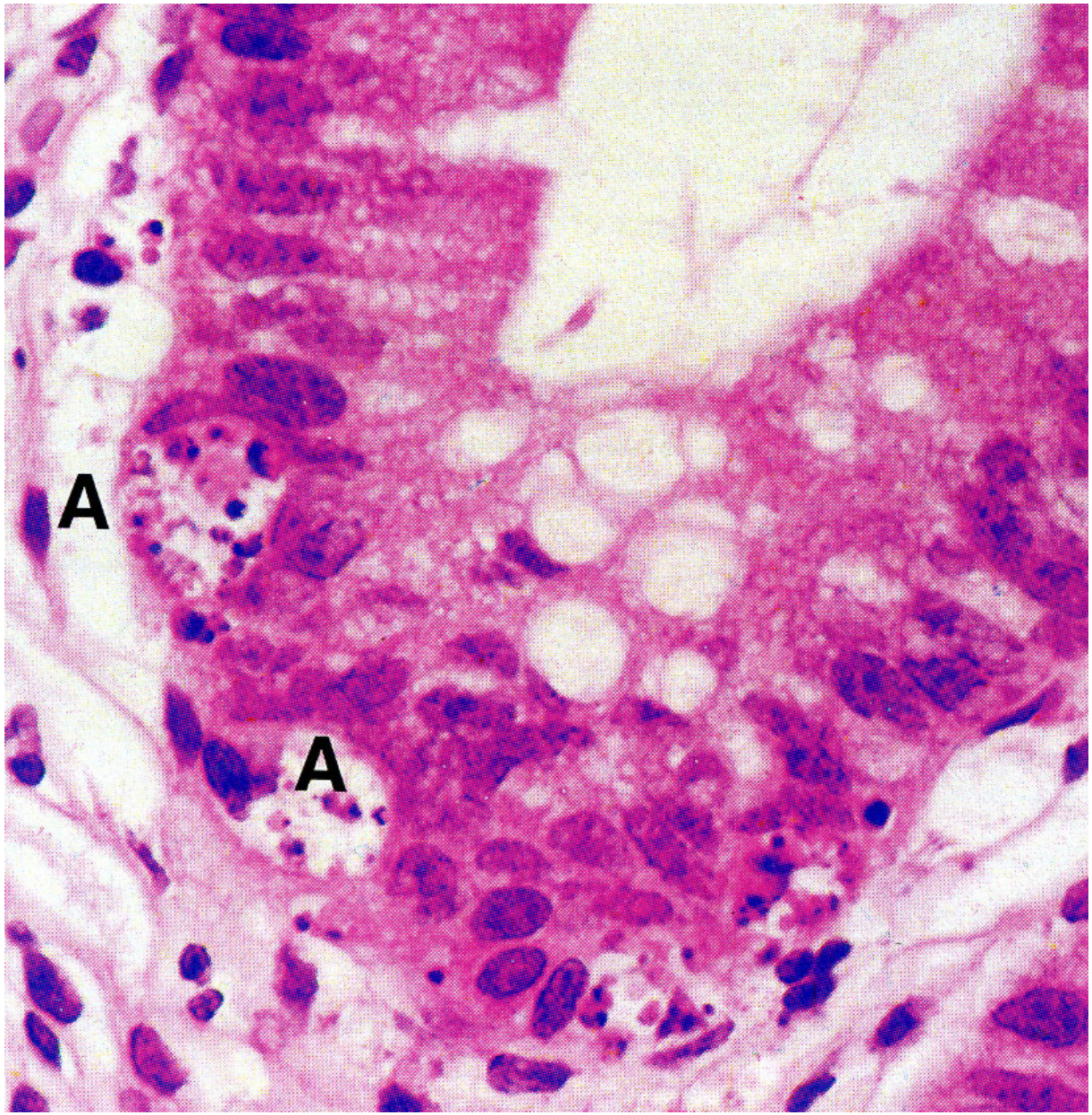


Figure 1. Diagram illustrating sequence of ultrastructural changes in apoptosis (2–6) and necrosis (7 and 8). (1) Normal cell. Early apoptosis (2) is characterized by compaction and margination of nuclear chromatin, condensation of cytoplasm, and convolution of nuclear and cell outlines. (3) At a later stage, the nucleus fragments, and protuberances that form on the cell surface separate to produce apoptotic bodies, which (4) are phagocytosed by nearby cells and (5 and 6) degraded within lysosomes. (7) The development of necrosis is associated with irregular clumping of chromatin, marked swelling of organelles and focal disruption of membranes. (8) Membranes subsequently disintegrate, but the cell usually retains its overall shape until removed by mononuclear phagocytes.

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BIOCHEMICAL MECHANISMS OF APOPTOSIS

Intrinsic or mitochondrial way Extrinsic way (death receptors)

- Activation of endocellular proteases "caspase" (initiator and effector)
- Activation of endogenous endonucleases
- Splitting of DNA into fragments that can be observed by electrophoresis ("ladder" appearance)

(NECROSIS: DNA fragmentation without any particular appearance)

Cytoplasmic condensation:

- Modification of the cytoskeleton (Beta tubulin)

⇩

Protuberance of cytoplasmic membrane

- Increased bonds between proteic chains

⇩

Stability of apoptotic bodies in the extracellular space

Phagocytosis: rapid event (specific membrane receptors on macrophages)
Failure of cell lysis: no inflammation

TISSUE CALCIFICATION: accumulation of calcium salts.

- **MACROSCOPIC APPEARANCE**: small whitish granulations

- **MICROSCOPIC APPEAREANCE**: basophilic granules

- **CHEMISTRY**: phosphate, oxalates, calcium carbonate
  Particular aspect: "onion bulb"

- Frequent in many diseases.
- Tissue dysfunction (distrophy)
- Calcium precipitates in the form of phosphate (90%) and carbonate/oxalate (10%)
- Von Kossa staining

- TYPES OF CALCIFICATION:
  - DYSTROPHIC
  - METASTATIC
  - UNKNOWN ETIOLOGY (IDIOPATHIC)

A) Secondary or dystrophic calcifications:

Accumuation of calcium salts in damaged or necrotic tissues.

→ Necrosis
Atherosclerosis
Organized thrombi
Sclerotic scars
Tumors

MECHANISM: cellular necrosis → phosphate release → calcium phosphate,
Increased alkalinity in necrotic tissue.
Release of fatty acids → soaps of insoluble calcium

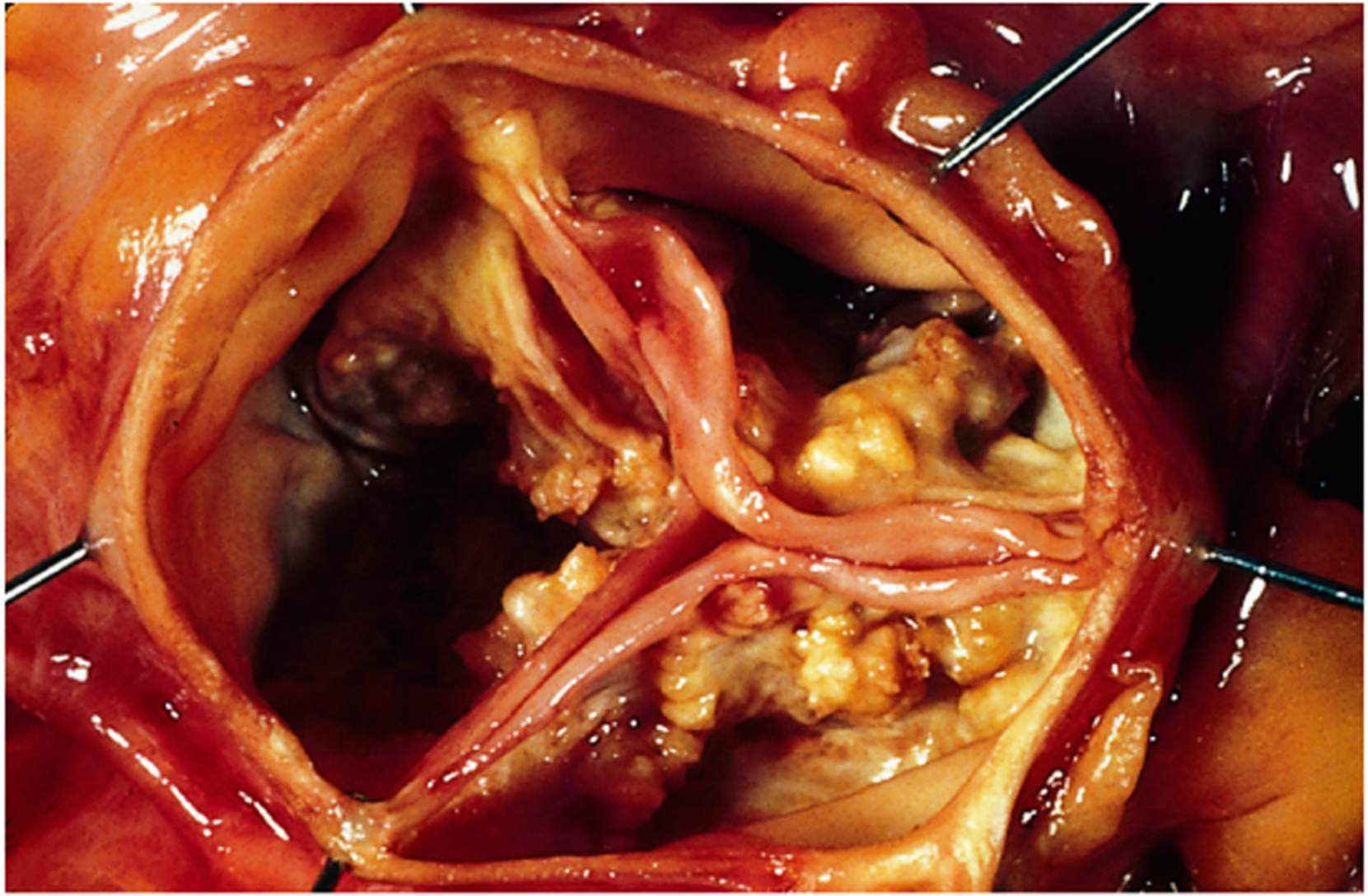
B) Metastatic calcification in hypercalcemia

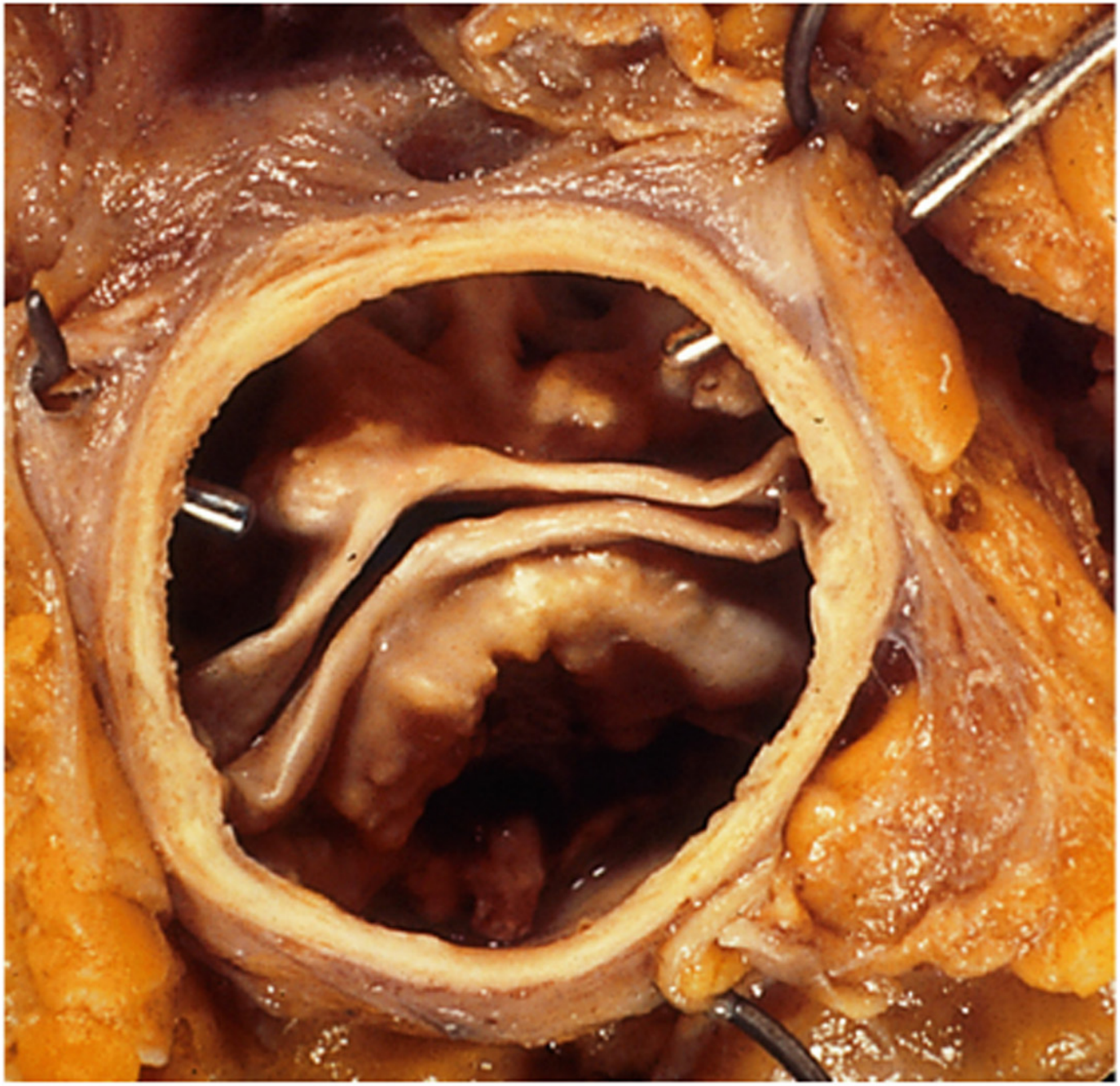
Calcinosis universalis: depots of calcium salts in all tissues

Hyperparathyroidism
Osteolytic bone metastases
Hypervitaminosis (vitamin D)
Bone atrophy (osteoporosis)
Nephropathy

C) Idiopathic calcification:

- Localized subcutaneous calcinosis.
- Interstitial calcinosis(joints); myositis ossificans
- TRAUMA?





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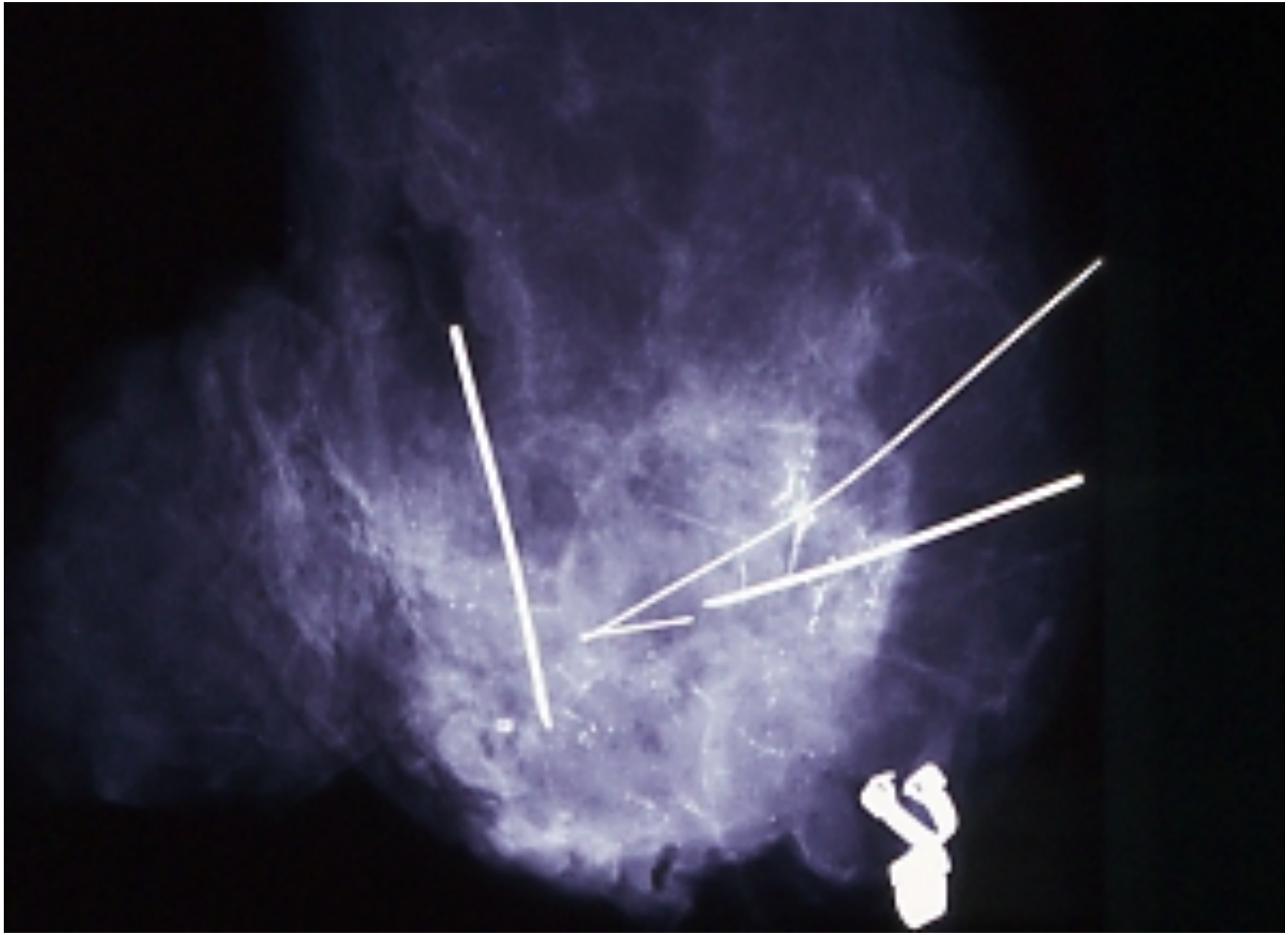

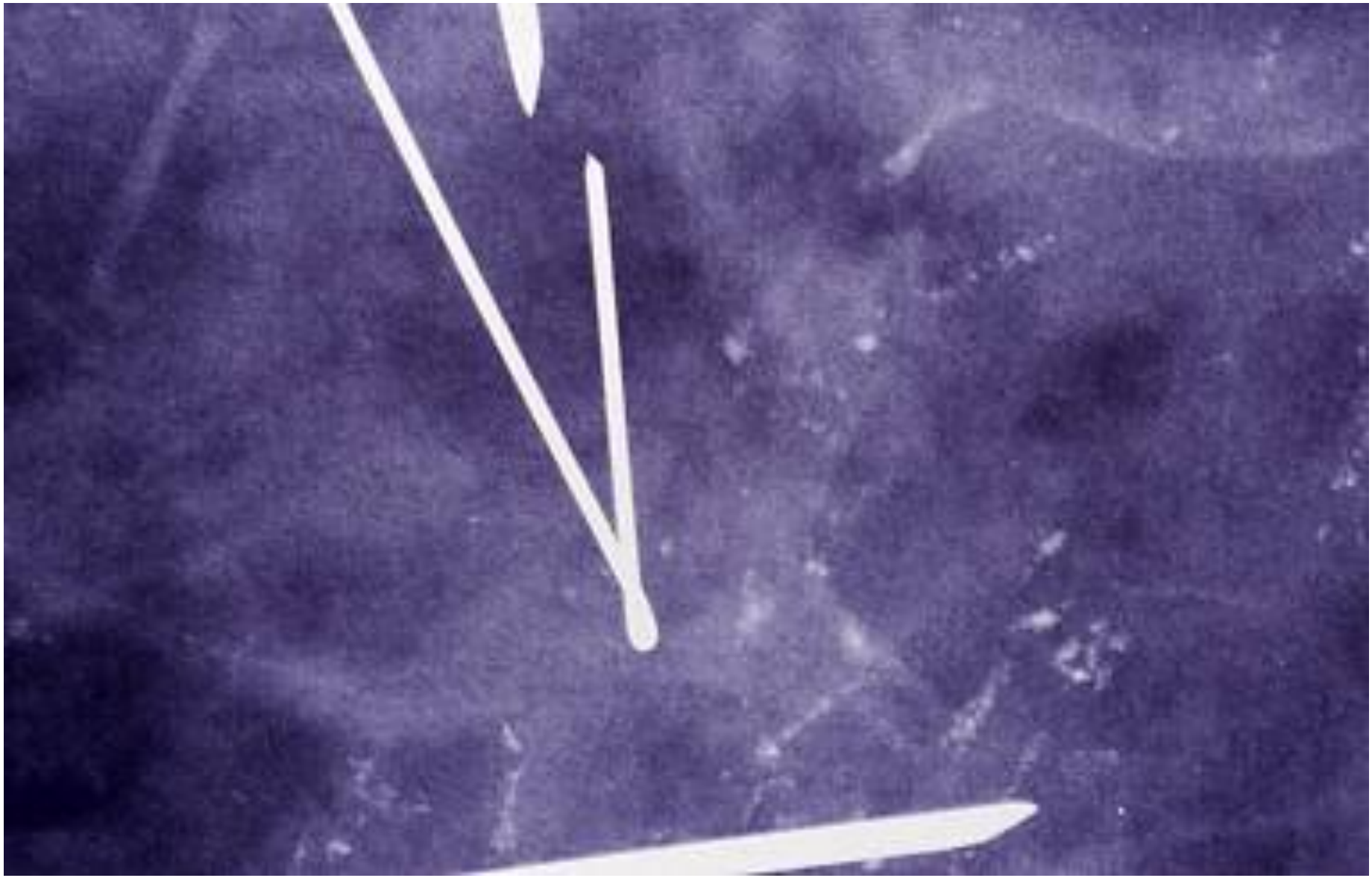

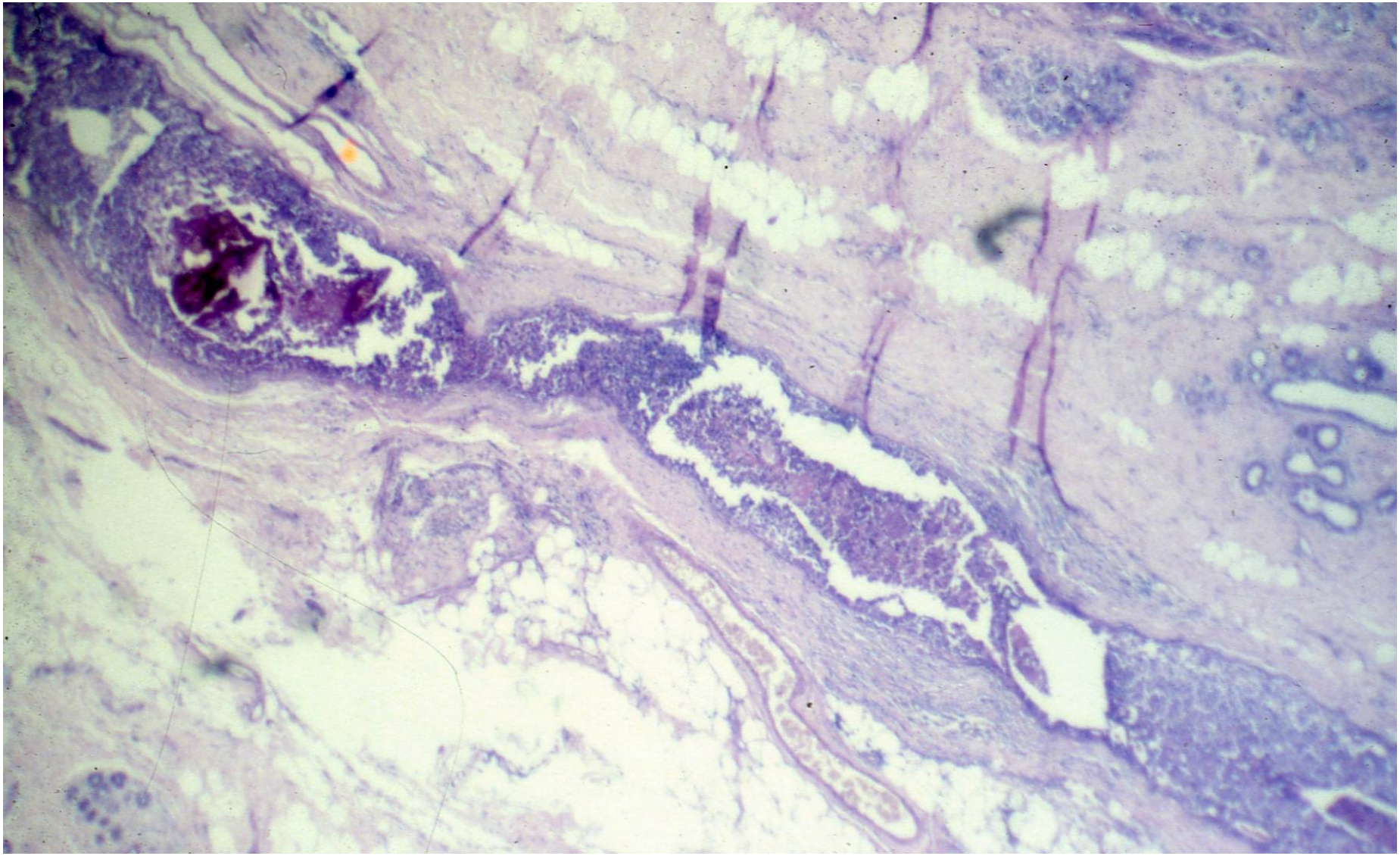

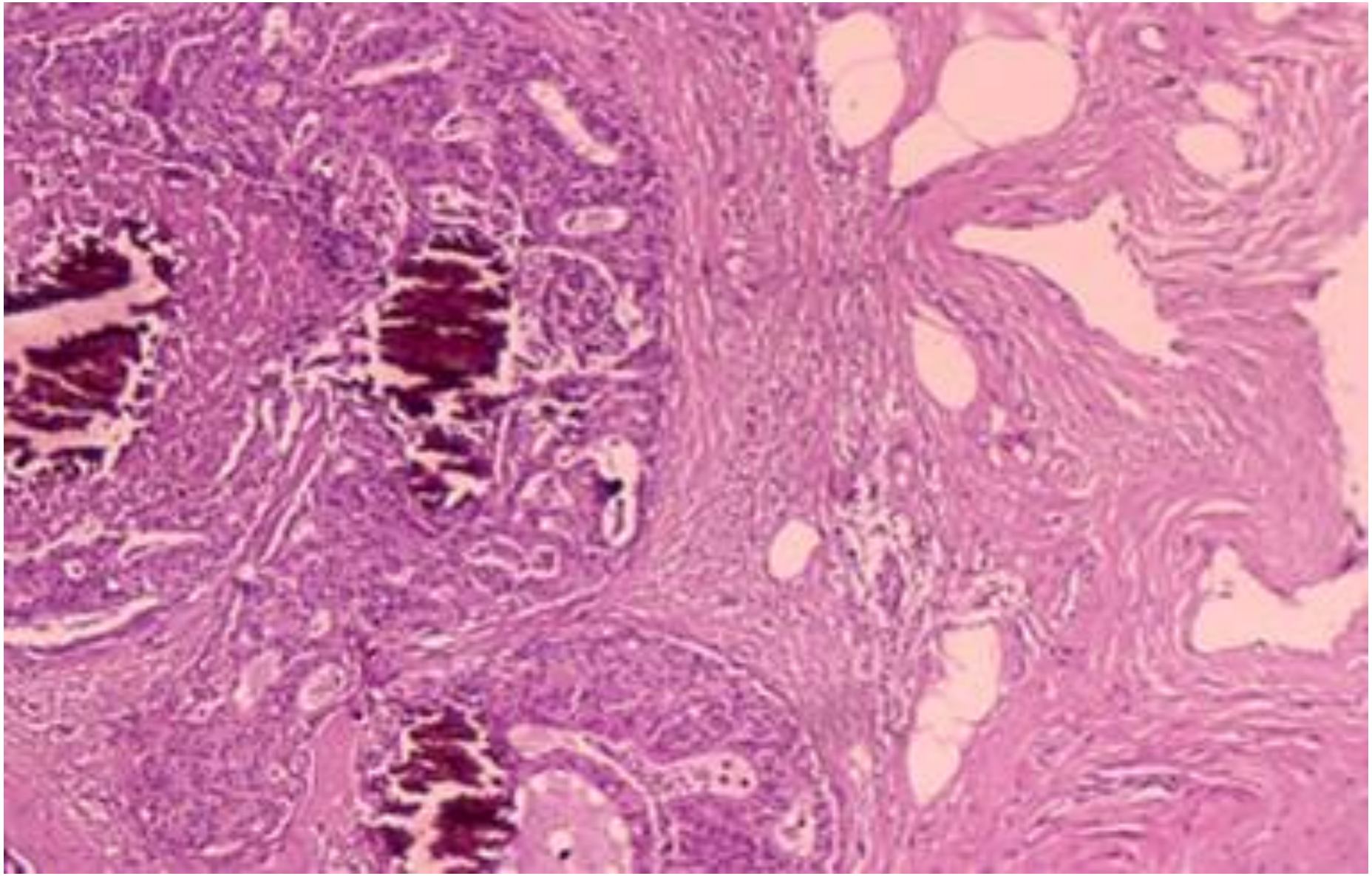

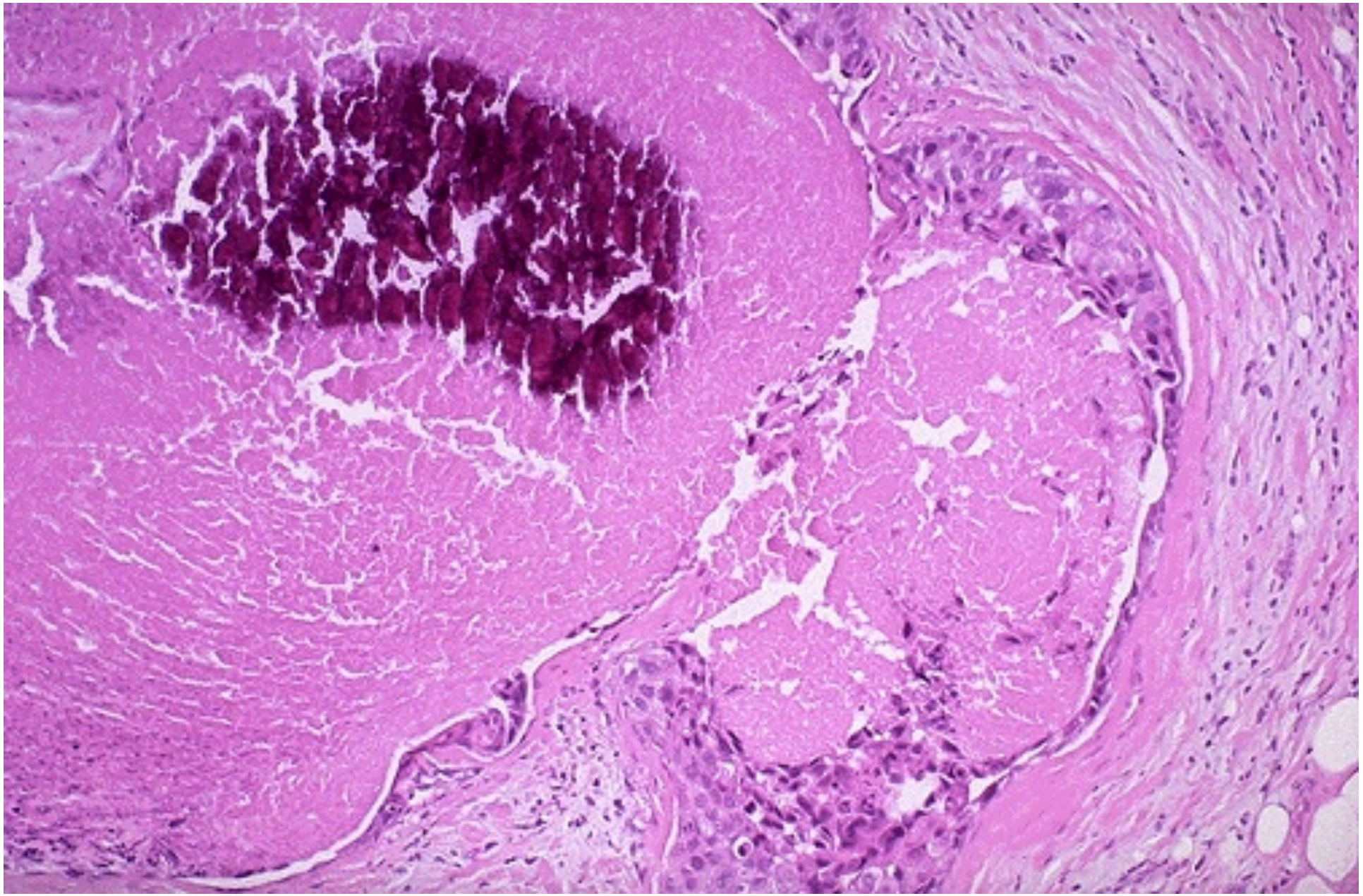

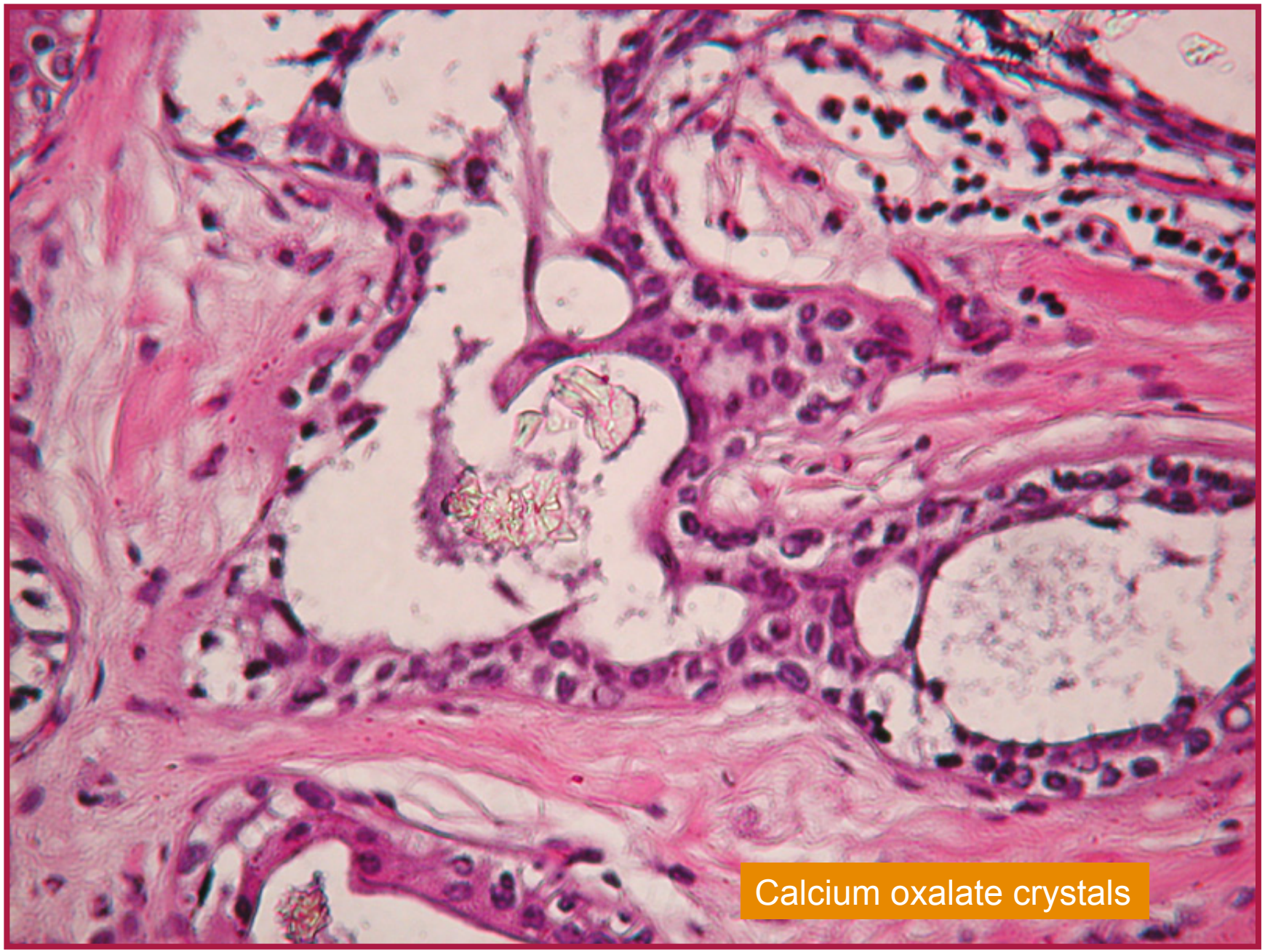
Calcium oxalate crystals