Pathological Calcification & Amyloidosis

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Pathological Calcification

- **Definition:** It is the abnormal tissue deposition of calcium salts, together with smaller amounts of iron, magnesium and other mineral salts.
- **Two forms of calcification**
  - Dystrophic calcification – seen in dead tissue
  - Metastatic calcification – seen in live tissue

- **Dystrophic calcification** is when the depositions occurs in dying tissue, it is known as dystrophic calcification.
- It occurs despite normal normal serum calcium & in absence of derangements in calcium metabolism.
- **Metastatic calcification** is the deposition of calcium salts in normal tissue.
- Results from hypercalcemia secondary to disturbance in calcium metabolism.

Dystrophic Calcification

- Dystrophic calcification is deposition of calcium salts in dead and degenerated tissues with the absence of a systemic mineral imbalance.
- It is often associated with trauma, infection, or inflammation and rarely appears in the head and neck area.

Pathogenesis is in 2 Phases

- The pathogenesis of dystrophic calcification is known to involve intracellular or extracellular initiation and propagation.
- Initiation phase
  - Intracellular calcification is initiated with dead or dying cells that are not able to regulate intracellular calcium.
  - Occurs in the mitochondria of necrotic cells with the creation of a microcrystals.
  - Extra Phospholipids in matrix

- Propagation is the phase in which minerals deposited in the initiation phase are propagated to form mineral crystals.
- It depends on concentration of calcium^{++} phosphates & other proteins in the extracellular space

Etiologies of calcium deposits

- **Caseous necrosis**
  - Tuberculous lesions, lymph nodes, lungs
- **Liquefaction necrosis**
  - In chronic abscesses may get calcified in brain
- **Fat necrosis**
  - Following acute pancreatitis
  - Traumatic fat necrosis in breast results in deposition of calcium soaps.
- **Infarcts may undergo dystrophic calcification.**

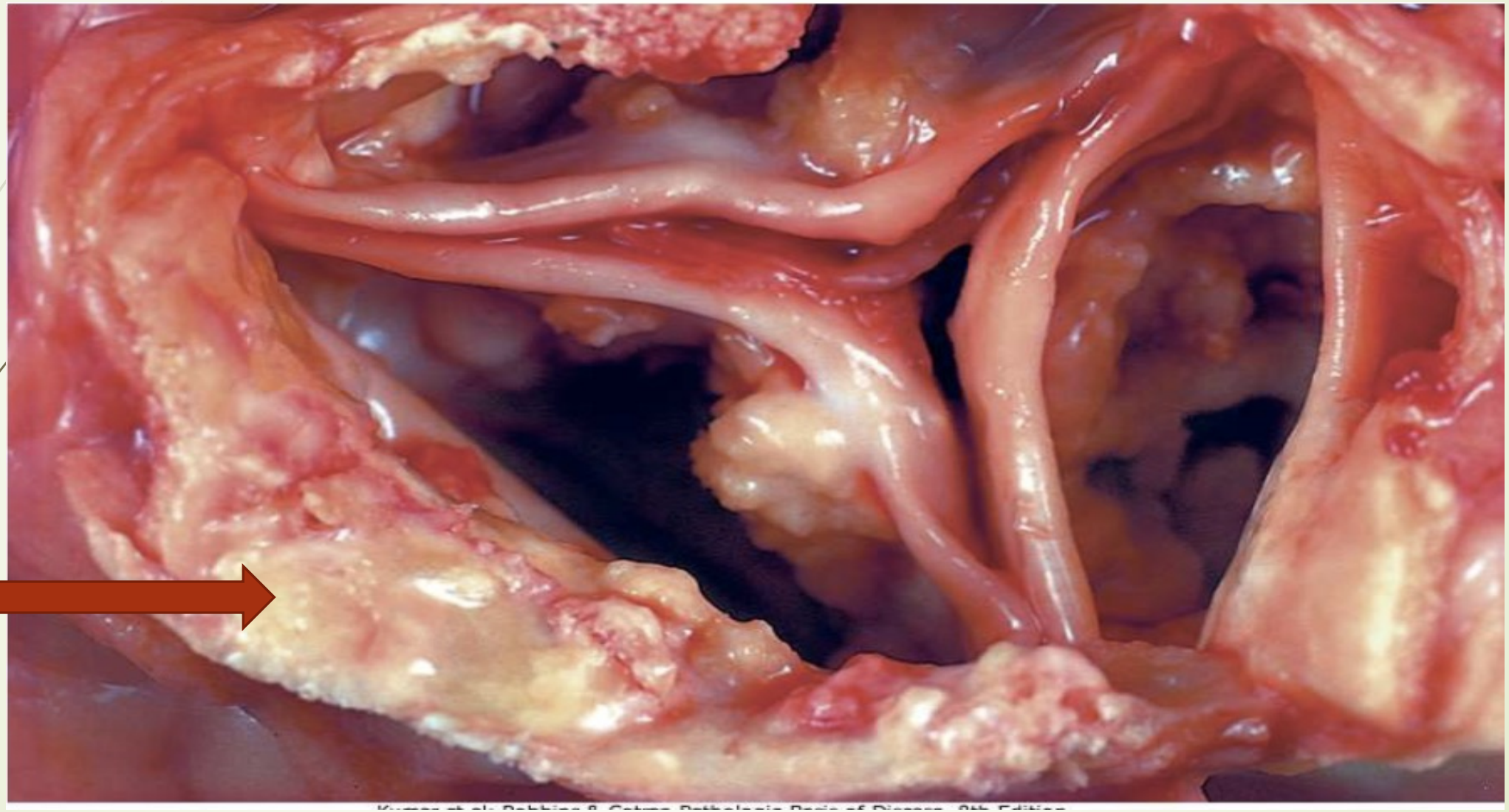
- **Thrombi**
  - Especially in veins may produce phleboliths
  - Can be in thrombophlebitis
- **Hematomas** near bones may undergo dystrophic calcification.
- **Dead parasites**
- **Dense old scars** may undergo hyaline degeneration & subsequent calcification.
- **Atheromas** in aorta and coronaries frequently undergo calcification.

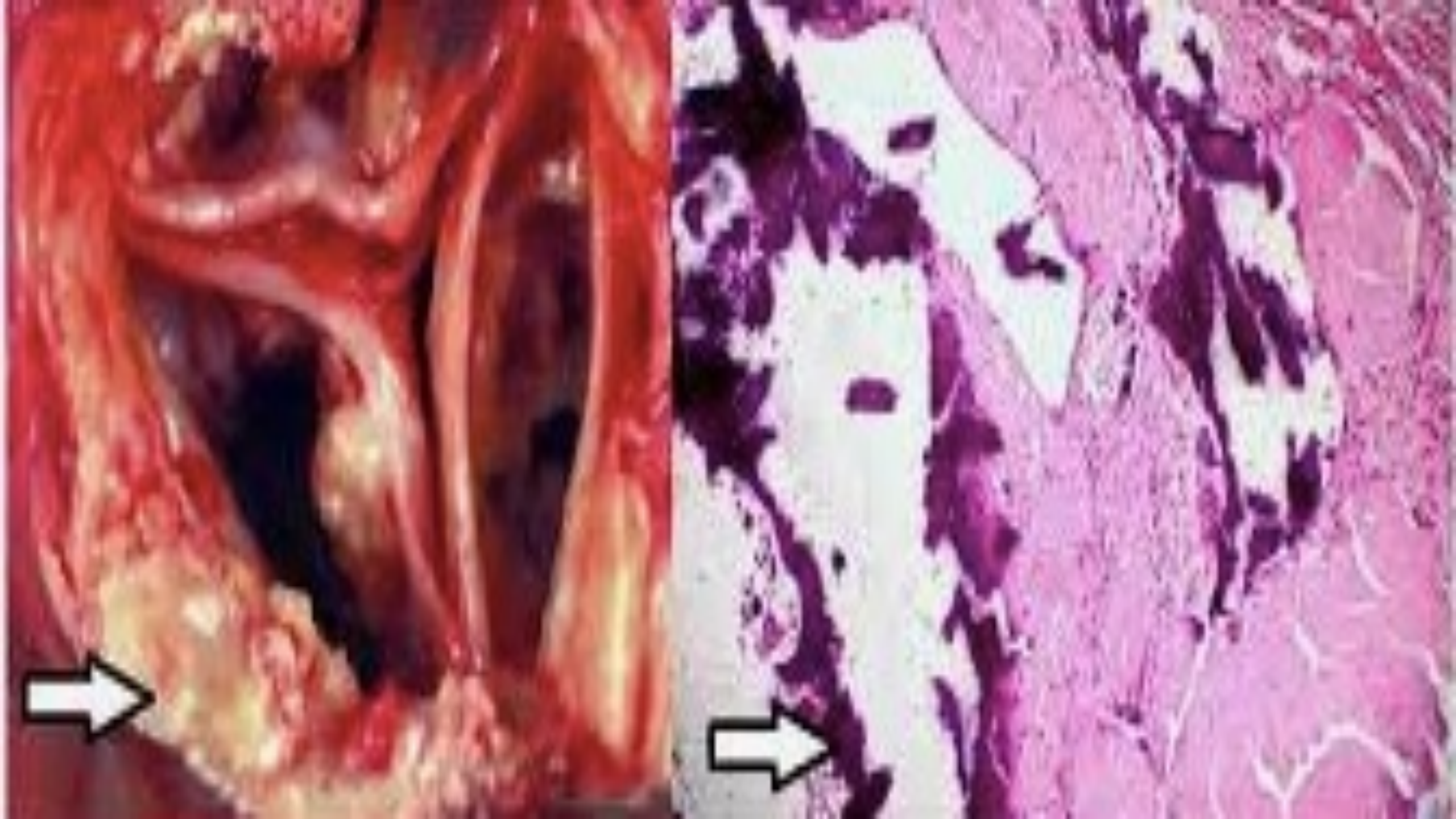
- **Monckeberg sclerosis** show calcification in tunica media of muscular arteries in elderly people.
- **Cysts** over a long time
- **Calcinosis cutis**
  - Irregular nodules of calcium salts in skin and subcutaneous tissue.
- **Senile degenerated changes**
  - In senile dementia may be accompanied by dystrophic calcification.

Stroma of tumors

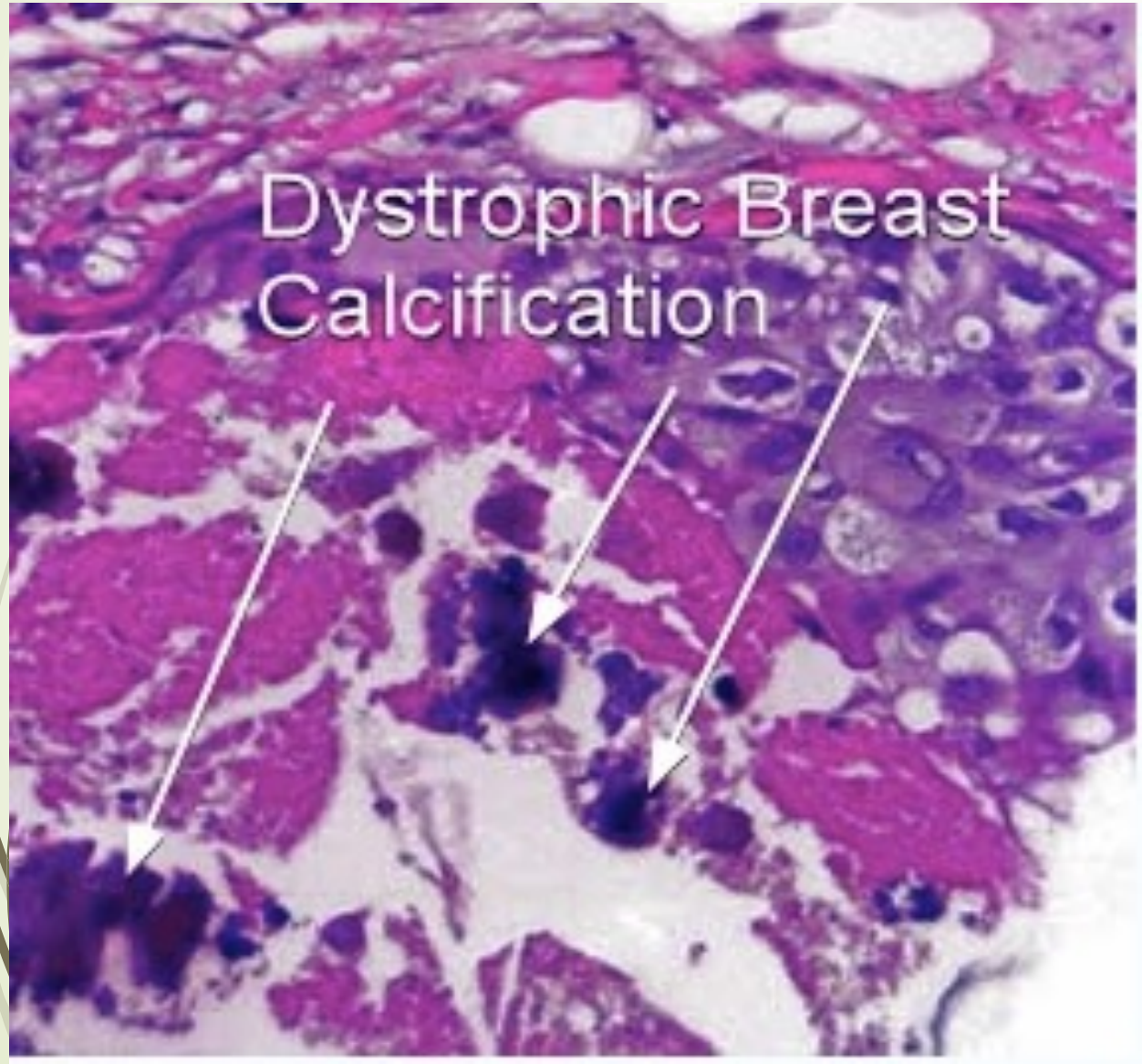
- Such as uterine fibroids
- In breast cancer
- In thyroid cancer
- These depositions are referred to as Psammoma bodies which are round, microscopic collections of calcium salts.
- Their name is derived from the Greek word for sand because they resemble grains of sand.

Dystrophic calcification in wall of aortic valve

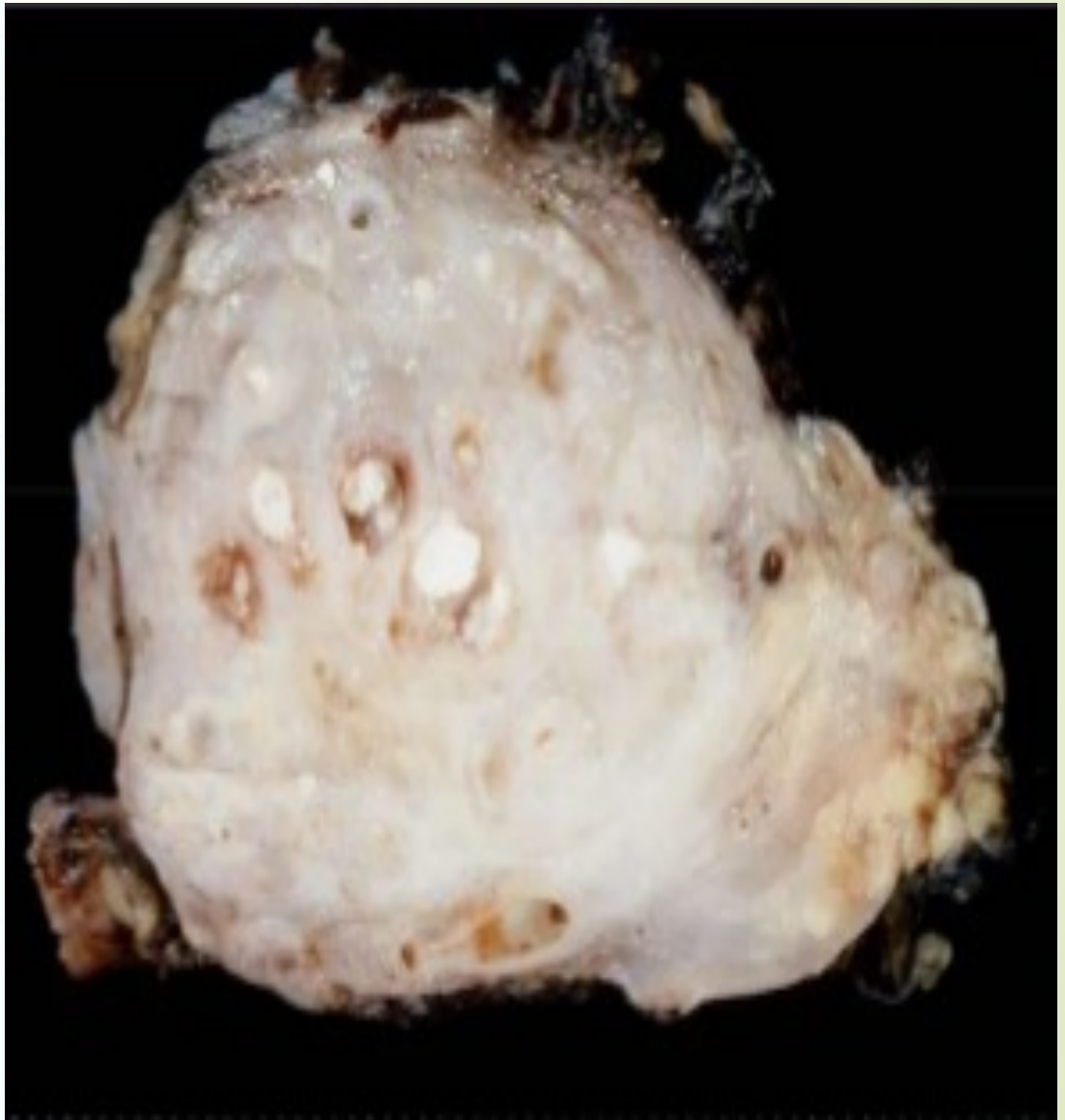




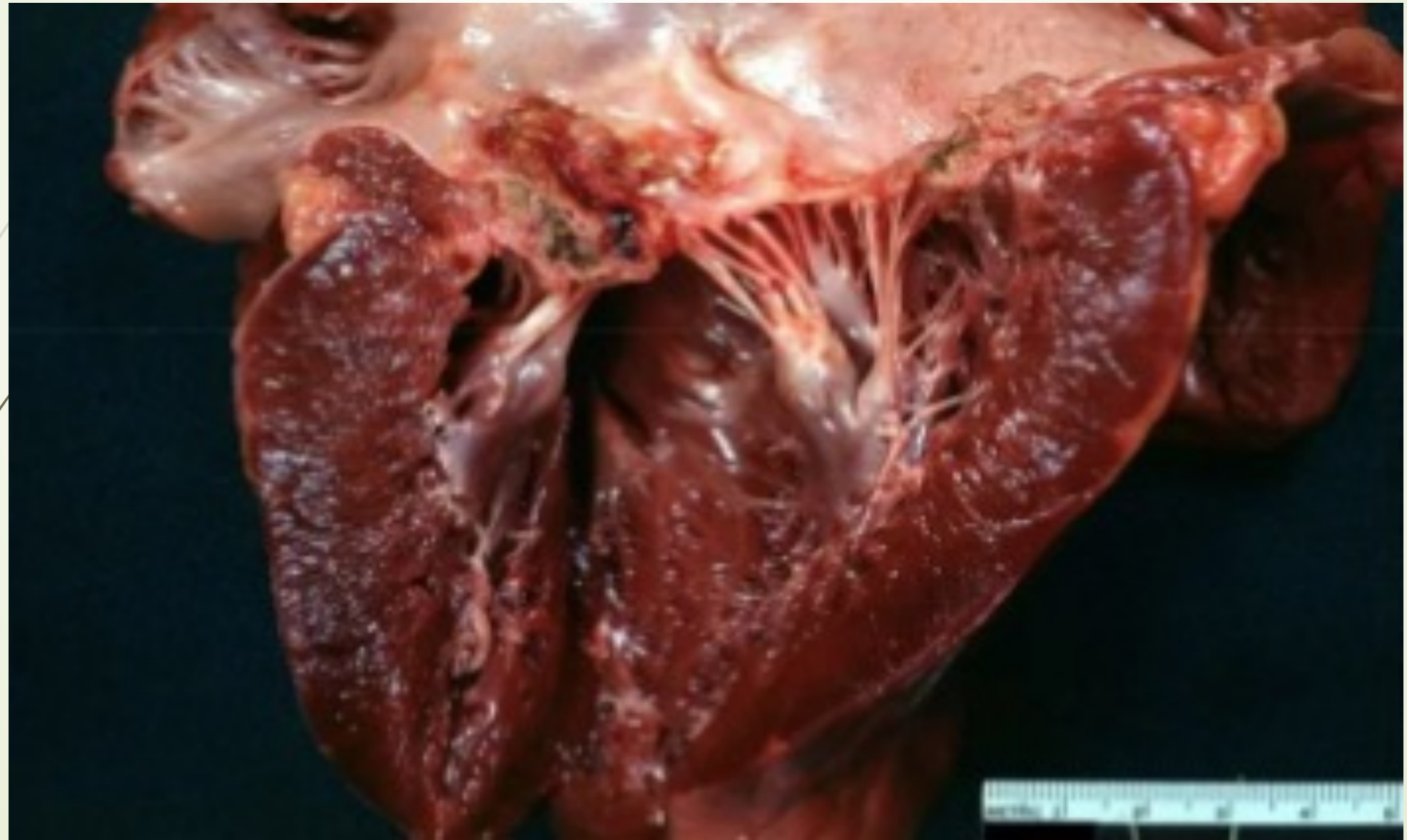
Dystrophic breast calcifications

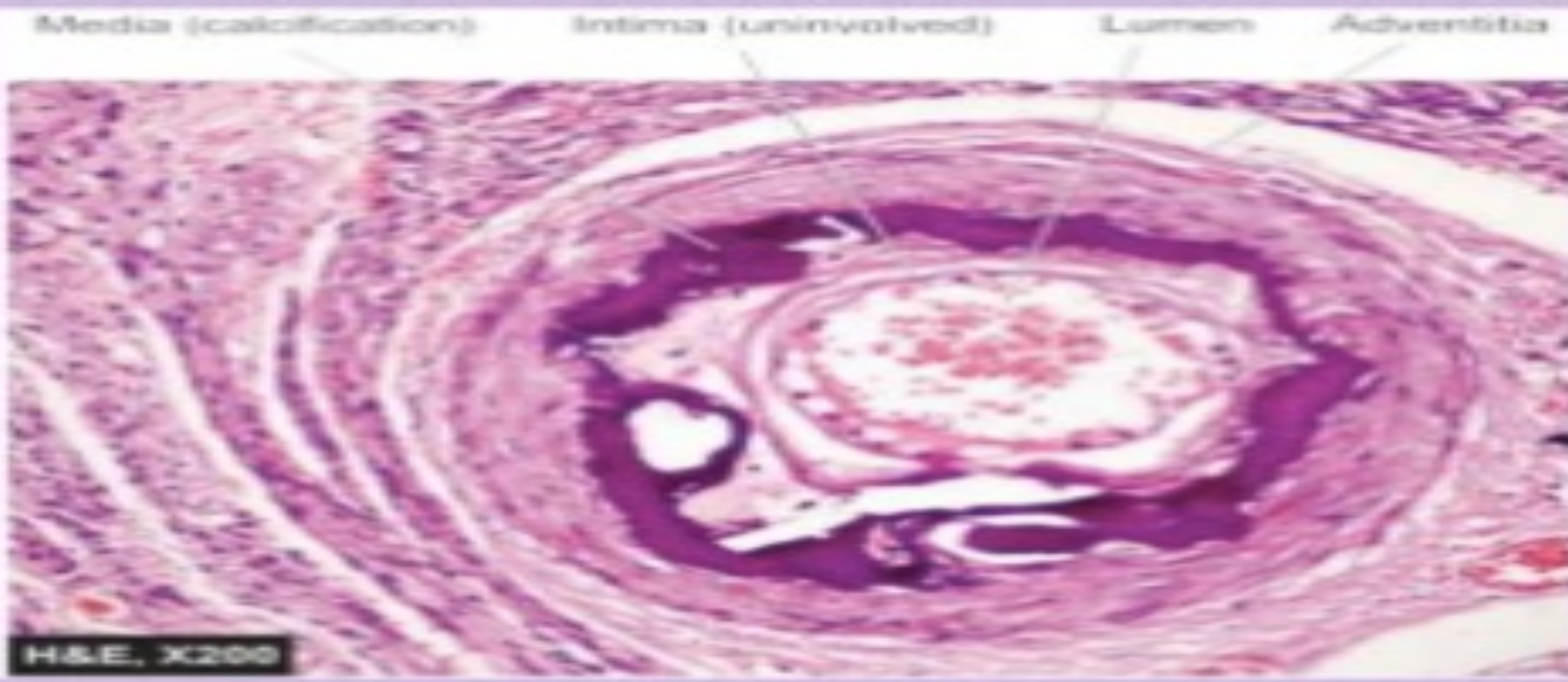


Dystrophic calcification of pancreas parenchyma

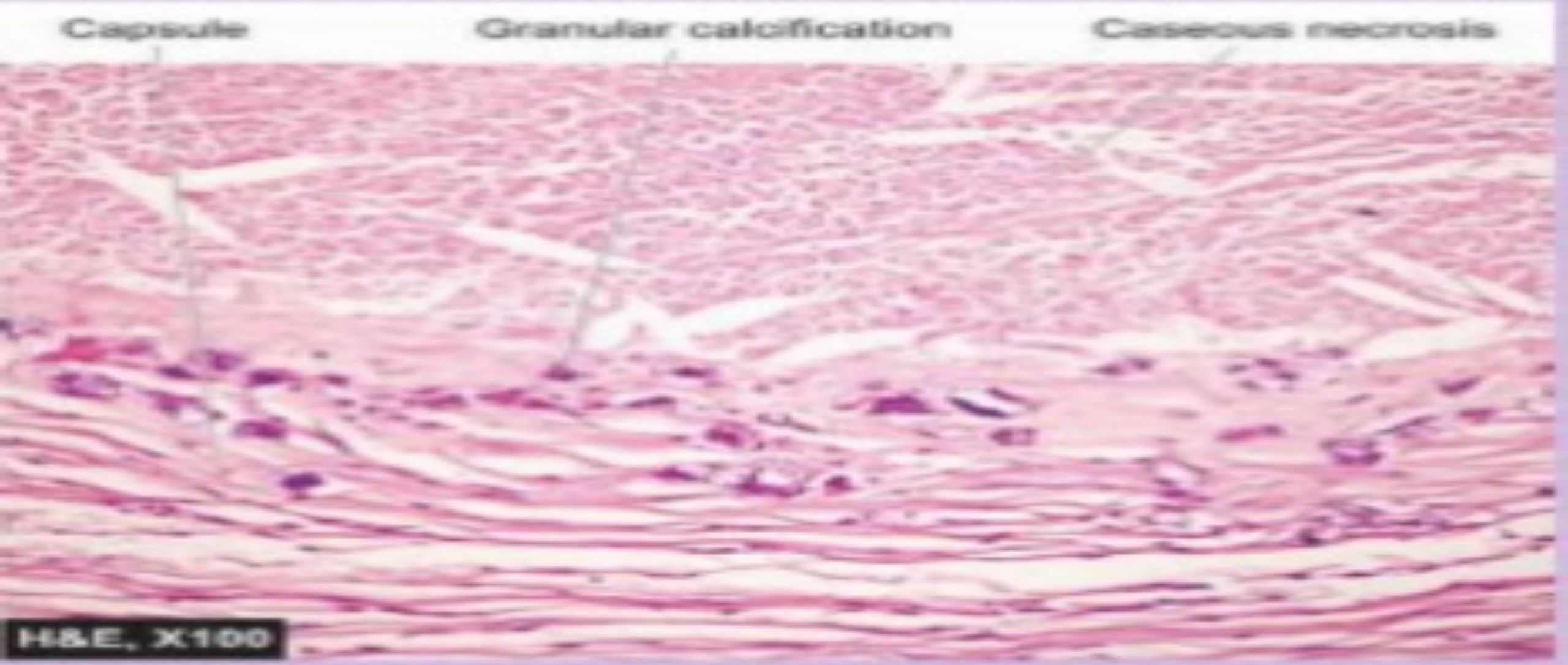


Dystrophic calcification seen in mitral stenosis

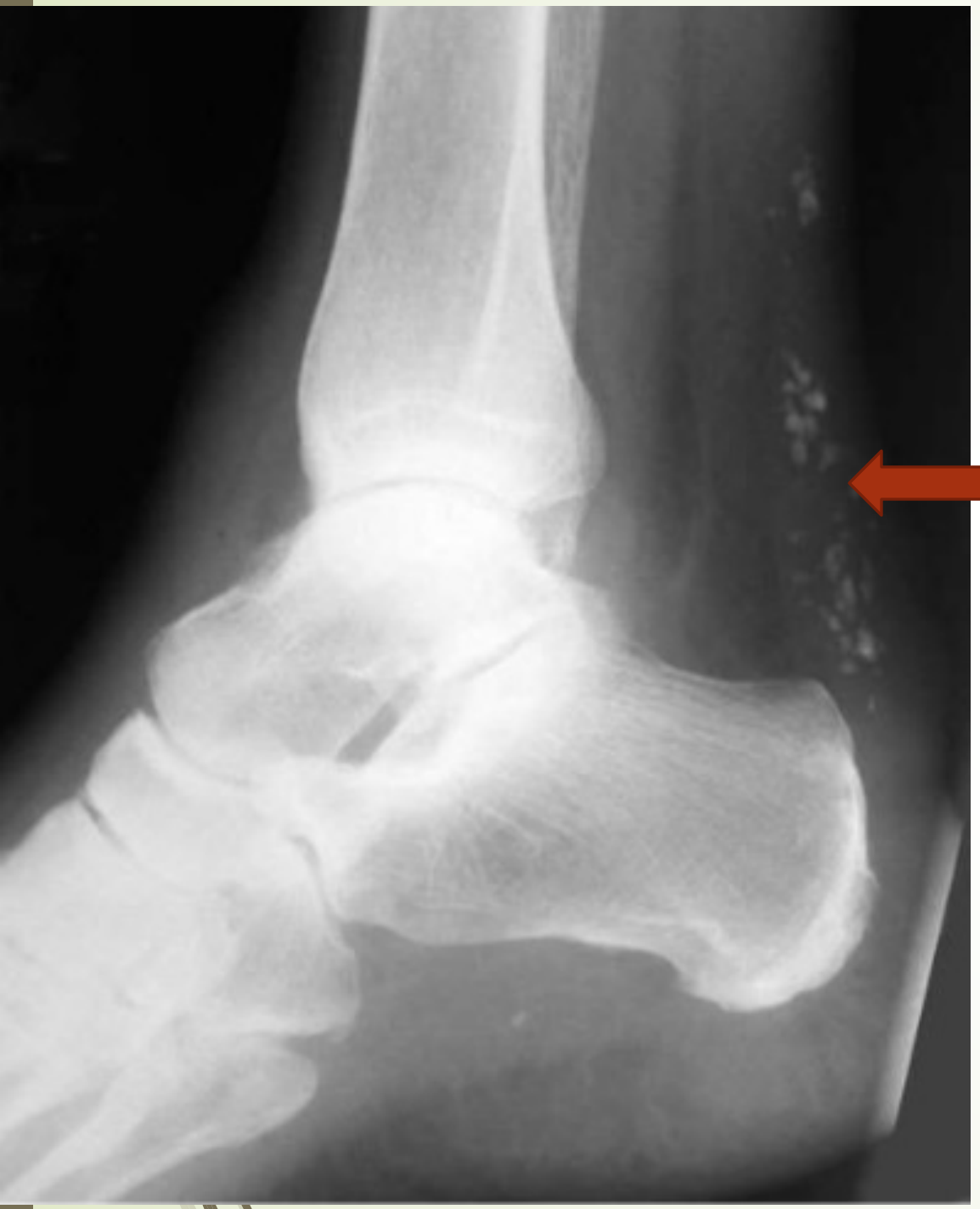




Degenerated tunica media of muscular artery of uterine myometrium in **Mönckeberg's arteriosclerosis**



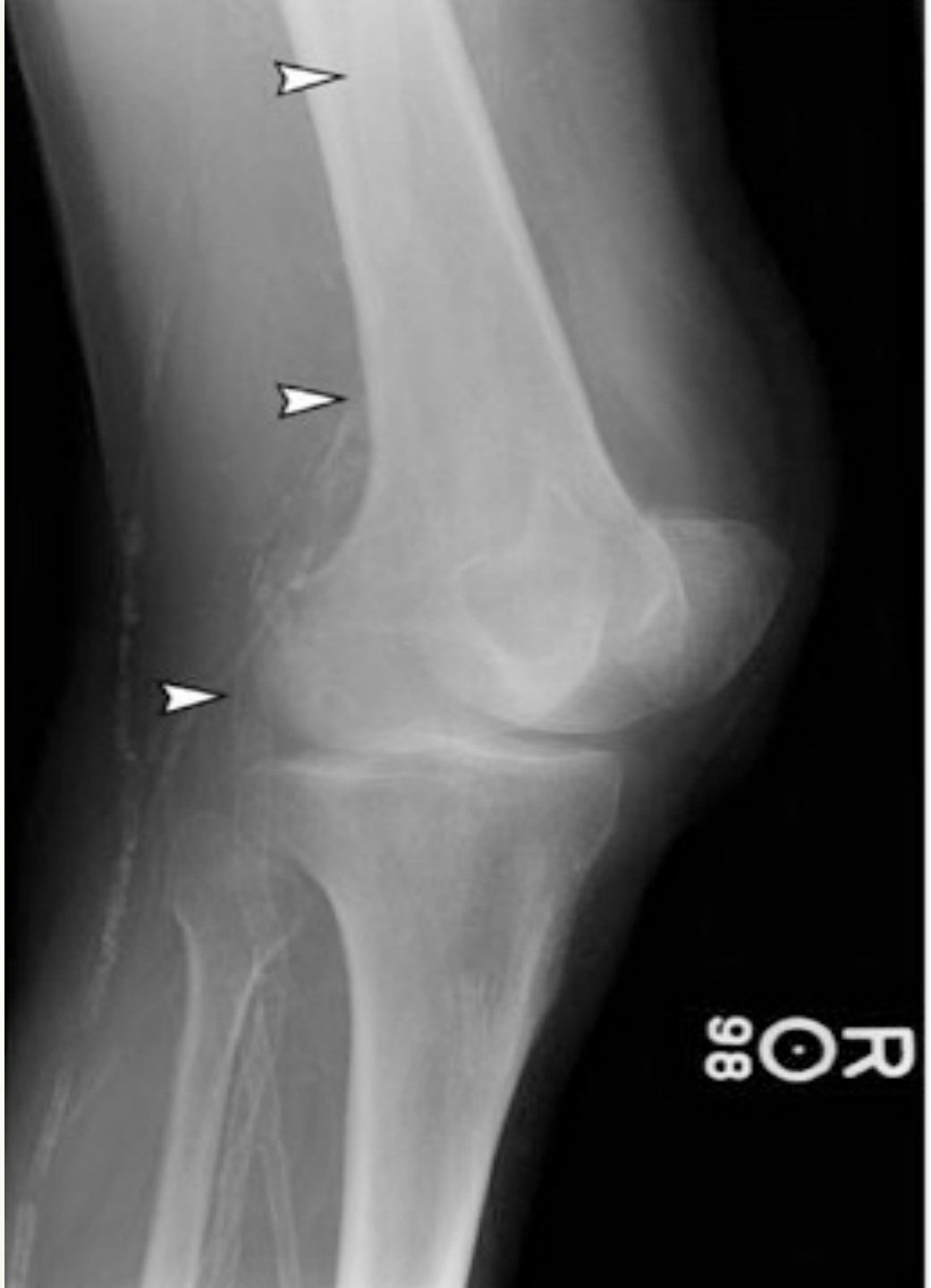
Caseous necrosis in tuberculous lymph node. In H & E, the deposits are basophilic granular while the periphery shows healed granulomas.



Dystrophic calcification in the Calcaneal tendon after repeated traumatic injury.

Mönckeberg's arteriosclerosis in 70-year-old man with recent history of falling and knee pain.

Lateral radiograph of knee revealing extensive calcification of femoral and popliteal arteries that appears with “railroad track” pattern (arrowheads), indicating Mönckeberg's arteriosclerosis.



Metastatic Calcification

- The deposition of calcium salts in normal tissue.
- Results from hypercalcemia secondary to disturbance in calcium metabolism.
- Excessive mobilization of calcium from the bone.
- Excessive absorption of calcium from the gut.

- Excessive mobilization of calcium from the bone.
  - Hyperparathyroidism secondary to parathyroid adenoma, or secondary such as from parathyroid hyperplasia, chronic renal failure.
  - Bony destructive lesions such as multiple myeloma, metastatic carcinoma.
  - Prolonged immobilization of a patient results in diffuse atrophy of the bones and hypercalcemia.

- Excessive absorption of calcium from the gut.
  - Hypervitaminosis D
  - Milk alkali syndrome
  - Hypercalcemia of infancy
- Metastatic calcification may occur in any normal tissue of the body but affects
- Kidney, Lungs, Stomach, Blood vessels, Cornea.
- Pathogenesis: relatively high pH favors precipitation of the calcium.

Features	Dystrophic Calcifications	Metastatic Calcifications
Definition	Deposition of calcium salts in dead & degenerated tissue.	Deposition of calcium salts in normal tissue.
Calcium metabolism	Normal	Deranged
Serum calcium levels	Normal	Hypercalcemia
Causes	Necrosis, Infarcts, thrombi, hematomas, dead parasites, old scars, atheroma, Monckebrg`s sclerosis, calcinosis cutis	Hyperparathyroidism, prolonged immobilization, hypervitaminosis D, milk alkali syndrome, hypercalcemia of infancy

Amyloidosis

- Amyloidosis is a rare disease that occurs when an abnormal protein, called amyloid, builds up in the organs and interferes with their normal function.
- Organs that may be affected include the heart, kidneys, liver, spleen, nervous system and digestive tract.

Amyloidosis

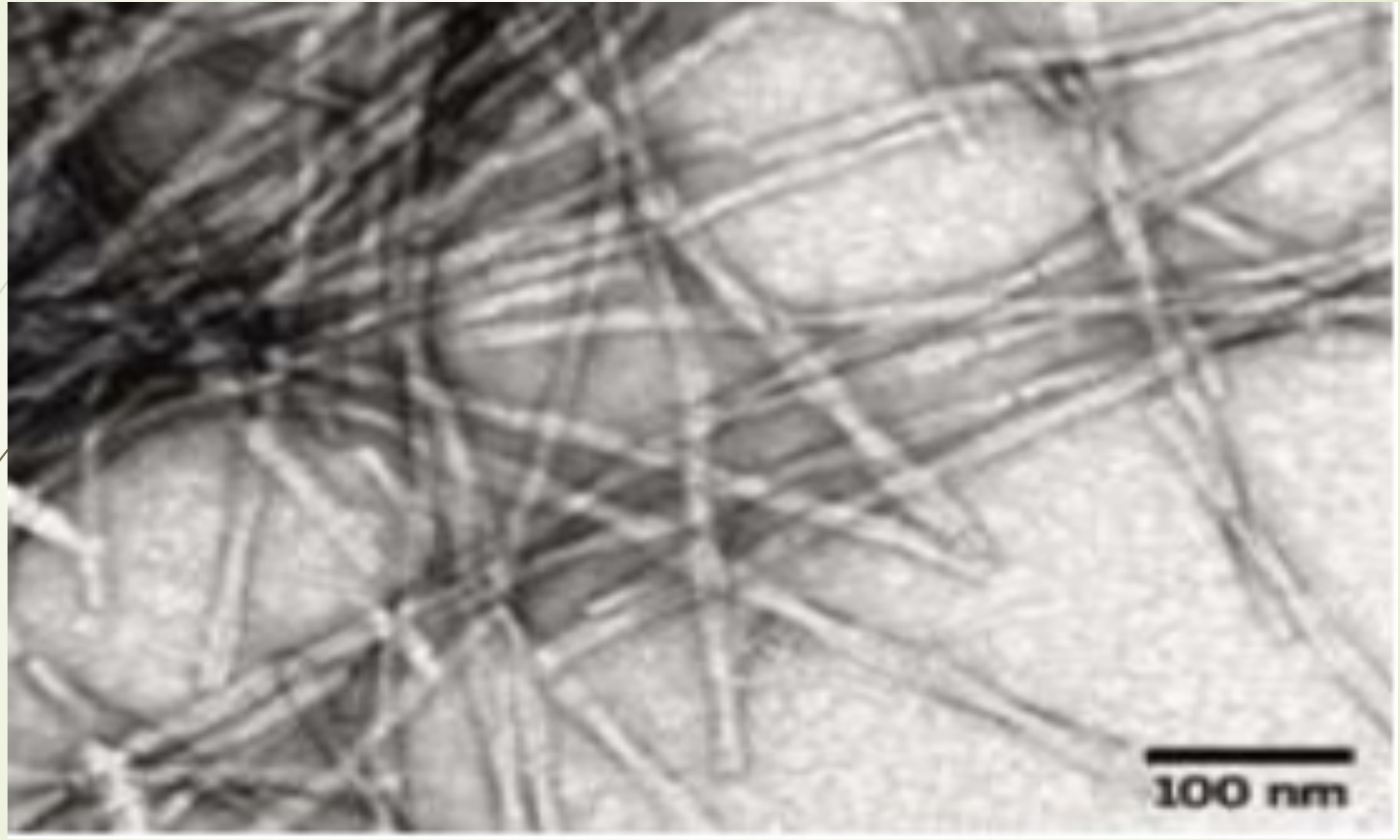
- Functional amyloids play a beneficial role in a variety of physiologic processes (eg, long-term memory formation, gradual release of stored peptide hormones).
- Amyloidosis results from the accumulation of pathogenic amyloids—most of which are aggregates of misfolded proteins—in a variety of tissues.

Amyloidosis

- Some varieties of amyloidosis occur in association with other diseases.
  - These types may improve with treatment of the underlying disease.
- Some varieties of amyloidosis may lead to life-threatening organ failure.
- Treatments may include chemotherapy similar to that used to combat cancer.
- Some people may benefit from organ or stem cell transplants.

Amyloidosis

- Amyloidosis is a clinical disorder caused by extracellular and/or intracellular deposition of insoluble abnormal amyloid fibrils that alter the normal function of tissues.
- Amyloid fibrils are protein polymers comprising identical monomer units.
- Amyloid fibril protein occurs in tissue deposits as rigid, non-branching fibrils 7-to 10 nm in dm


100 nm

Risk factors leading to amyloidosis

- Age, the most common age group involved is 50 or older people except for the younger age group.
- In family history, some amyloidosis is hereditary.
- The majority of the patients are male.
- Dialysis of the patient also leads to amyloidosis.
- Chronic diseases predispose to amyloidosis.

Complications of Amyloidosis

- **Kidney**
  - Will ultimately lead to renal failure.
  - Kidney size may be normal or enlarged.
  - Amyloid deposits in the glomeruli.
  - Amyloidosis is also seen in the interstitium and the wall of blood vessels

- **Cardiovascular**
  - Leads to heart failure and arrhythmias.
  - The heart size may increase from minimum to moderate enlargement.
  - Amyloid deposits are found in the myocardium.
- **Spleen**
  - May be enlarged moderately to a large size.
  - Amyloid deposit is limited to splenic follicles and giving sago spleen appearance.

- **Liver**
  - Amyloidosis causes massive enlargement.
  - The amyloid deposit first appears in the space of Disse (area between hepatocytes and sinusoids)
  - Later on, encroach the adjacent liver parenchyma.
  - In late stages involve the sinusoids.
- **Central nervous system**
  - Leads to various types of complications like diarrhea, constipation, numbness of fingers, and dizziness.

6 Main Groups of Amyloids

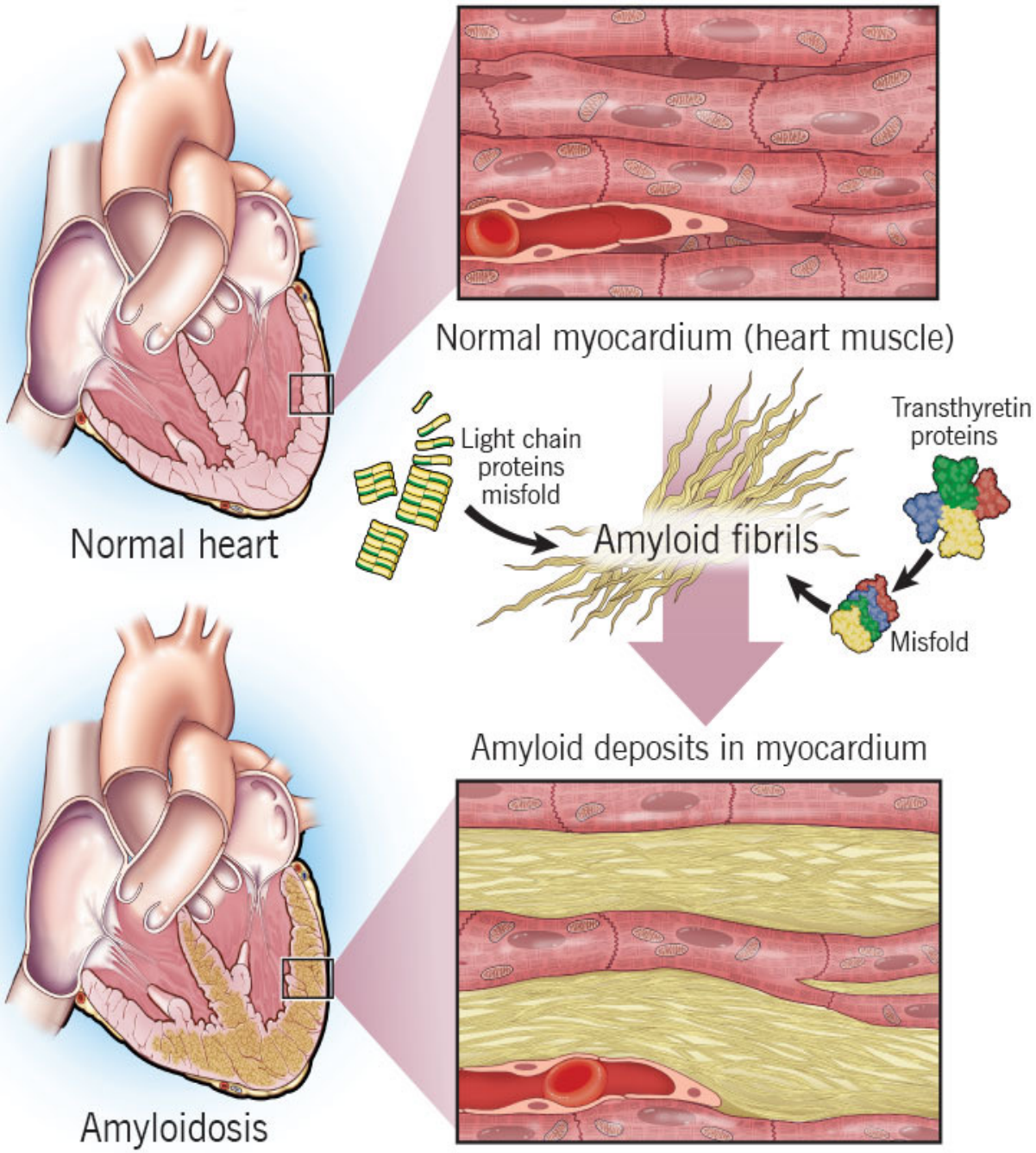
- AL - Amyloid Light Chain Type
- AA - Amyloid Associated Proteins
- AF - Amyloid Familial Type
- AH - Amyloid Hemodialytic Type
- AE - Amyloid Endocrine Type
- AS - Amyloid Senile Cerebral Type

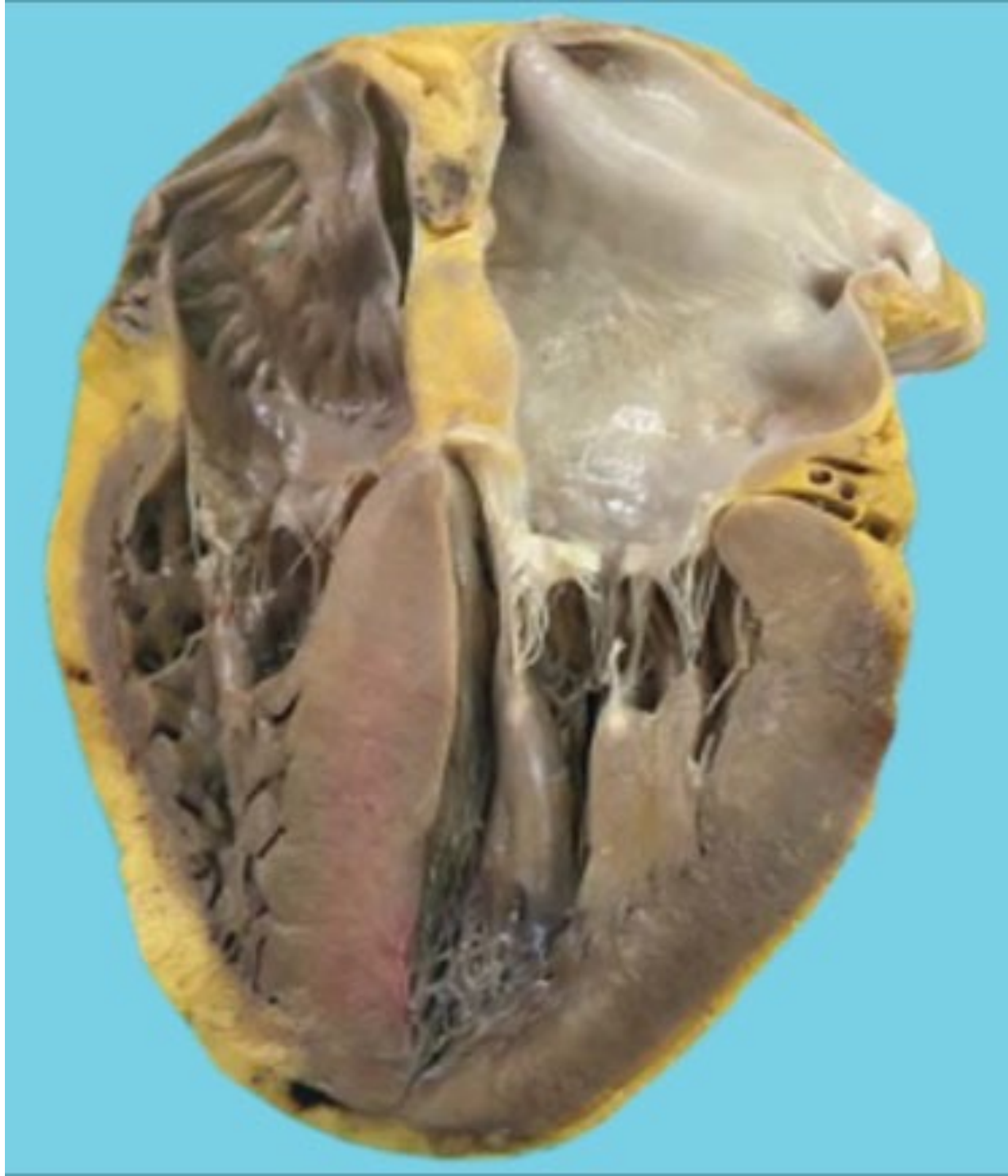
AL (Primary) Amyloidosis

- AL (primary) amyloidosis is the most common form of the disease.
  - The body's immune system produces abnormal forms of antibodies called "light chains," (the "L" in "AL" amyloidosis).
- Bone marrow plasma cells produce antibodies that fight infections.
  - If a plasma cell becomes cancerous, it may produce extra pieces of antibodies called "light chains" (the "L" in "AL" amyloidosis).
  - These light chains circulate in the bloodstream, and can deposit in organs throughout the body, causing organ damage.

- Some of the most common organs affected by AL (primary) amyloidosis include:
  - Heart
  - Kidneys
  - Nerves
  - Gut
  - Skin/soft tissue
  - Tongue
- Life expectancy depends on each individual's specific case – and most importantly on the degree of heart involvement.

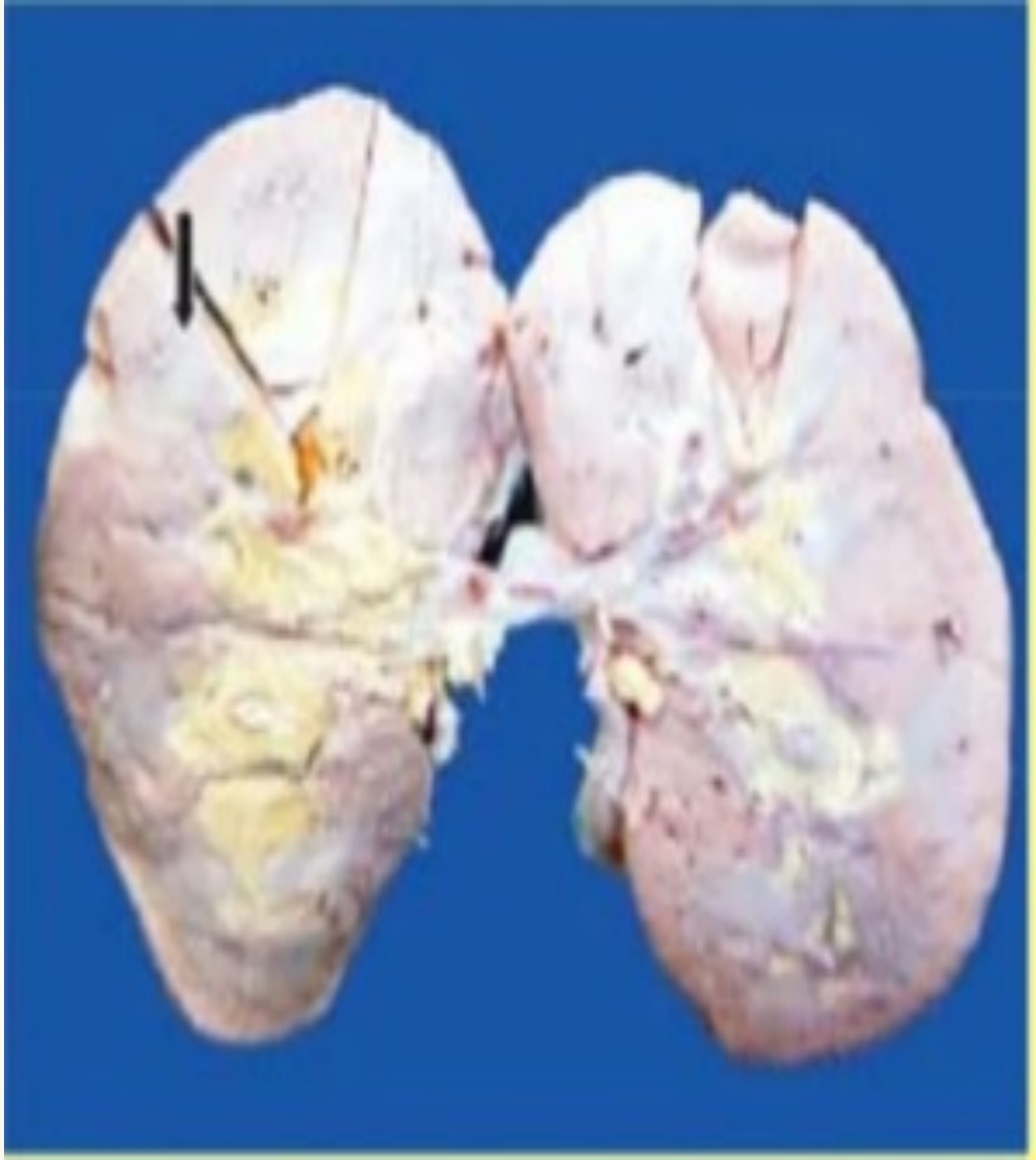
- **AL (primary) amyloidosis treatment options**
- Treatment of AL (primary) amyloidosis has two goals:
  - Improve the function of the involved organs (such as the heart)
  - Decrease the production of the abnormal light chains

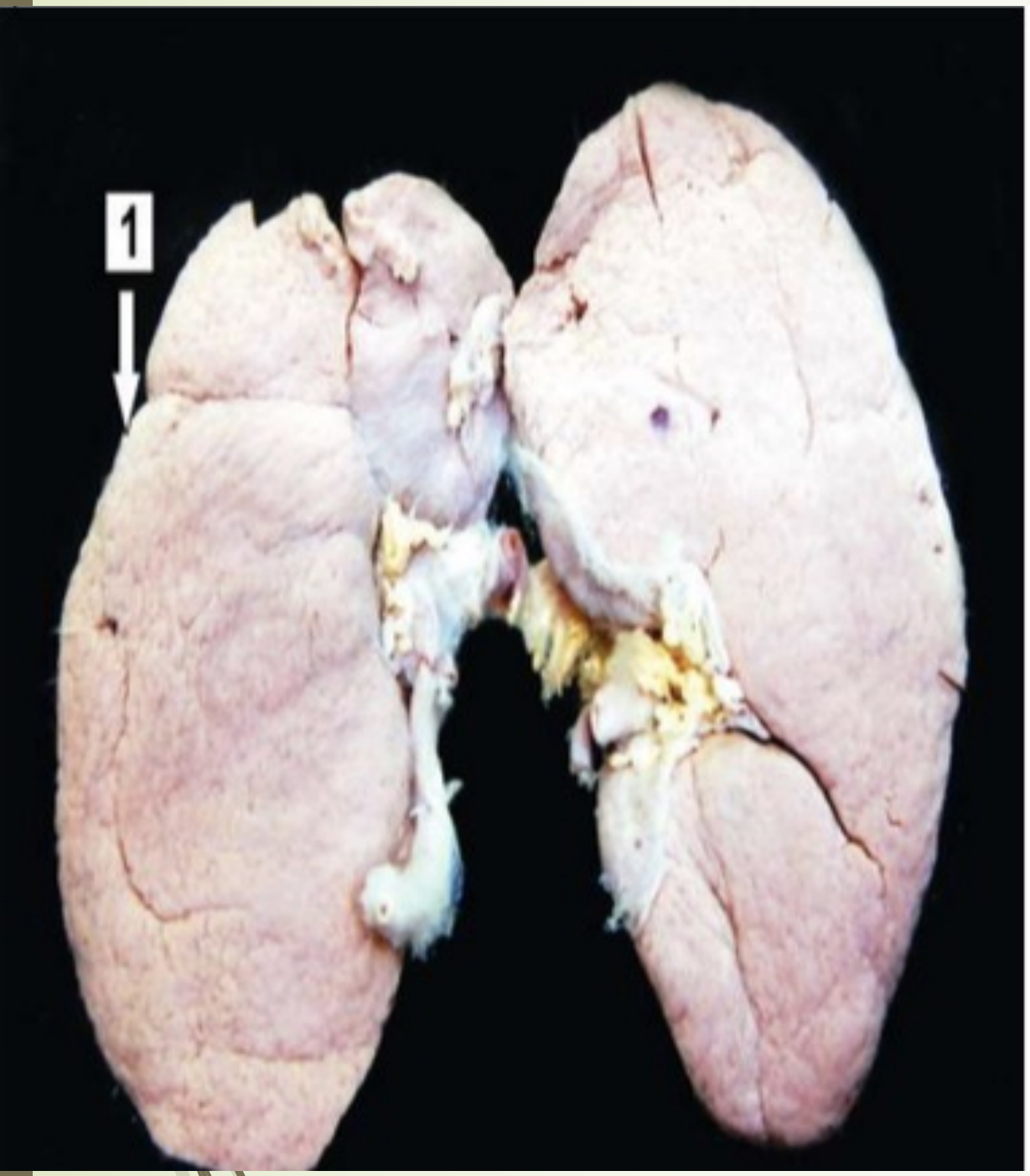

Normal myocardium (heart muscle)
Normal heart
Light chain proteins misfold
Amyloid fibrils
Transthyretin proteins
Misfold
Amyloid deposits in myocardium
Amyloidosis
©2021 Cleveland Clinic



Amyloidosis of Kidney

Sectioned section shows loss of corticomedullary distinction and pale waxy translucence

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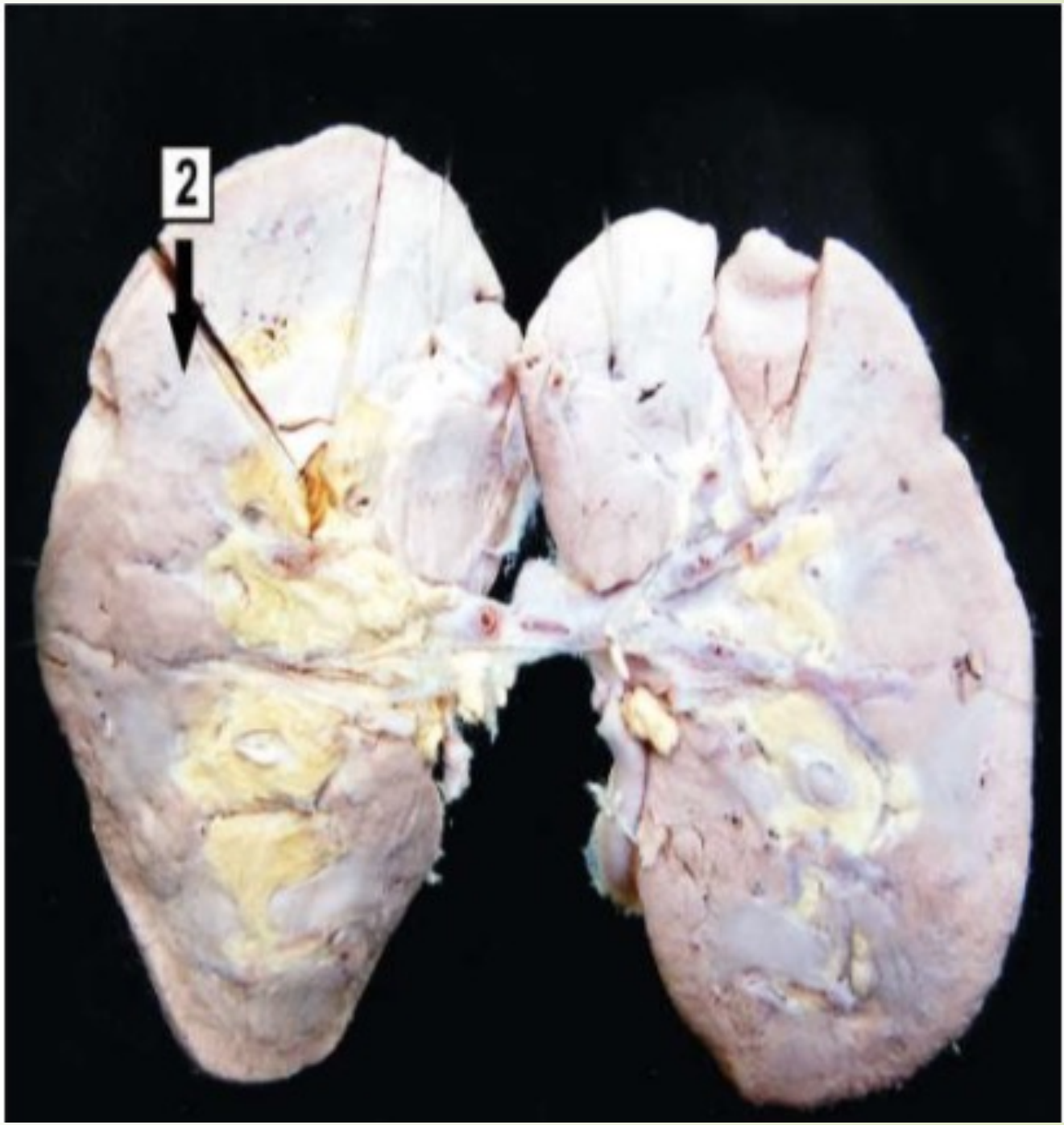
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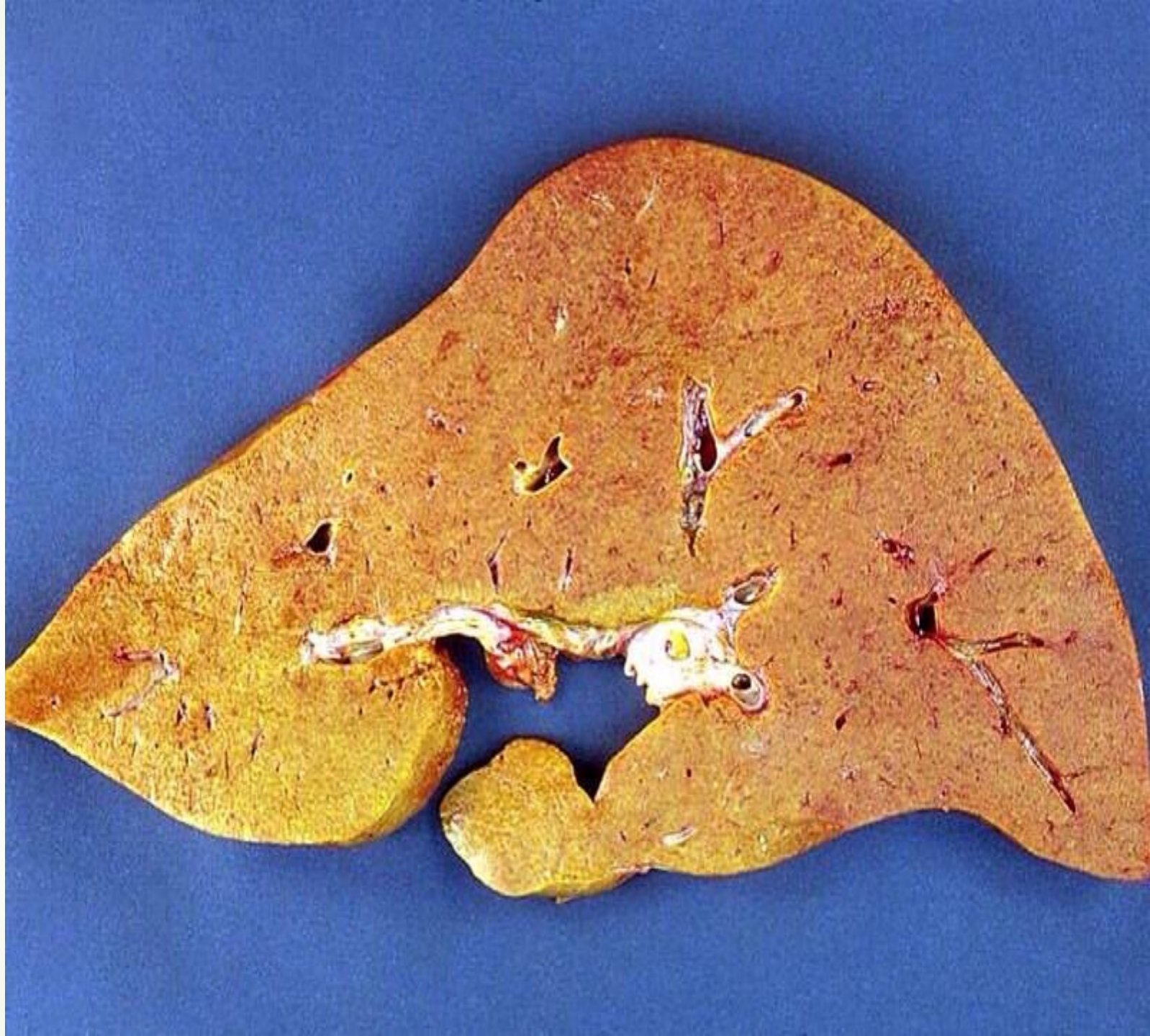
Amyloidosis of liver

- Amyloid deposits are seen in pink and red from the congo dye



AA (Secondary) Amyloidosis

- AA (secondary) amyloidosis is characterized by a protein called "serum amyloid A."
- This protein is produced by the body in response to inflammation or infection.
- High levels of the protein do not cause amyloid deposits over the short term, but can lead to amyloid deposits over a long period of time.
  - For this reason, diseases which lead to chronic states of inflammation or to chronic states of infection can result in AA amyloidosis deposits over several years.

- AA (secondary) amyloidosis commonly affects:
  - Kidneys
  - Liver
  - Spleen
- Treatment targets the cause of the inflammation or infection – for example, controlling rheumatoid arthritis with immune suppressants, or treating chronic tuberculosis with appropriate antibiotics.

AF - Familial Amyloidosis

- Familial amyloidosis is an inherited disease, where the body makes a mutant form of a protein called "transthyretin."
- Familial amyloidosis most commonly affects the heart and nerves.
  - Other organ involvement may occur, but is uncommon.
- Though it is a very serious disease, the prognosis for familial amyloidosis is overall better than AL amyloidosis, as it usually progresses at a slower rate.

- **Treatment for familial ATTR amyloidosis**
  - As the liver produces the mutated transthyretin protein, a liver transplant may be a treatment option, if the disease is caught early enough.
  - Patients with severe heart involvement may benefit from a heart transplant.

AS - Amyloid Senile Cerebral Type

- Senile amyloidosis is similar to familial amyloidosis, except the protein that is deposited is the normal, non-mutated transthyretin protein.
- As a result, patients only develop the disease in older age, usually at 65 years of age or older. Because amyloid deposits accumulate slowly in this form of the disease, the prognosis is generally better than AL (primary) amyloidosis and familial ATTR amyloidosis.

- Amyloidosis is associated with the aging process.
- This is also called senile amyloidosis, and most often, the heart is involved, called senile cardiac amyloidosis.
- This may also be found in the pancreas and brain.
- Nodular or infiltrative amyloid deposits s are seen in the skin, lungs, trachea, and endocrine organs (thyroid medullary carcinoma) and in long-standing diabetics (pancreas).
- These patients are usually asymptomatic except for cardiac form.

Treatment of Amyloidosis

- There is no definite treatment or cure for amyloidosis.
- Treatment can limit the production of amyloid protein.
- There is the symptomatic treatment for nephrotic syndrome and cardiac failure.
- Colchicine may be helpful for familial Mediterranean fever.
- Chemotherapy may show some benefits in AL amyloidosis.

Prognosis of Amyloidosis

- It depends upon the type of amyloidosis and the organ involved.
- In generalized amyloidosis, the prognosis is poor, with mean survival after the diagnosis is 1 to 3 years.
- Microscopic and focal deposits in older people are of no clinical significance.
- Widespread deposits are progressive and fatal.

- AL (most common) Amyloid patients with cardiac involvement have a worse prognosis and, in untreated cases, is less than the survival is one year.
- AA (secondary) amyloid patients survive 2 to 4 years.
- ATTR (familial) amyloid patients survive for 15 years.
- Overall, the average life expectancy is 11 years from the time of diagnosis.
- For patients with multiple myeloma-associated amyloidoses, the prognosis is poor.