# AMYLOIDOSIS

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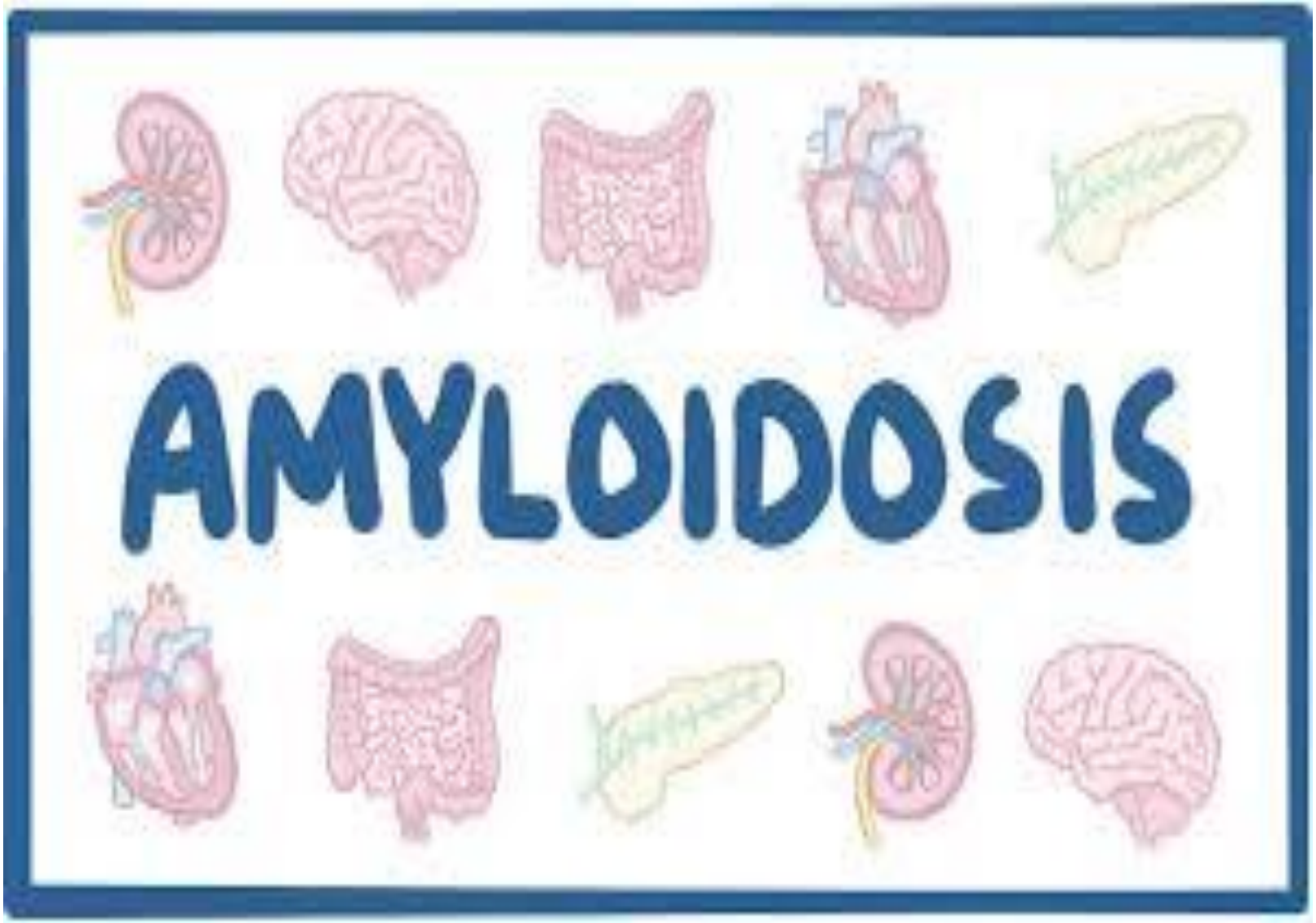
- PA3.1 Describe the pathogenesis and pathology of amyloidosis
- PA3.2 Identify and describe amyloidosis in a pathology specimen

# Specific learning Objective

At the end of the session the II MBBS student shall be able to

- Classify Amyloidosis
- Describe pathogenesis of Amyloidosis


AMYLOIDOSIS

# AMYLOIDOSIS

- It is group of diseases characterized by **extracellular** deposition of insoluble fibrillary proteinaceous substance called amyloid.

- On light microscopy – homogenous, structureless and eosinophilic hyaline material.

- Amyloid- common morphological appearance, staining properties and physical structure but variable biochemical composition.

- Condition associated with a number of inherited and inflammatory disorders
- Extracellular deposits of fibrillar proteins
- Responsible for tissue damage and functional compromise.

# Nature of Amyloid

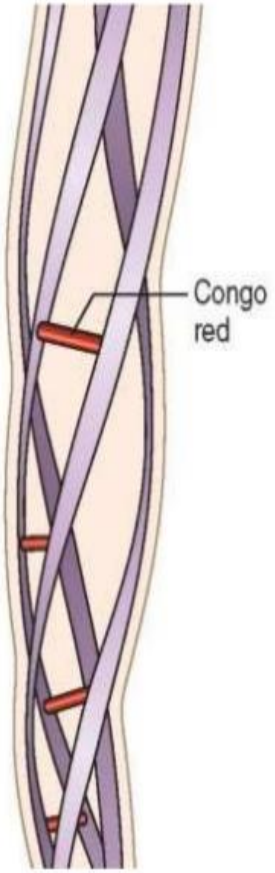
- Electron microscopy

  Nonbranching fibrils of indefinite length w
  diameter appoximately 7.5 – 10 nm.
- Chemically,

  95%- paired filaments of **Fibrillary protei**

  5 % - P component and other glycoproteir
- X-ray diffraction & Infrared spectroscopy

  Cross beta pleated configuration



- These abnormal fibrils are produced by the **aggregation of misfolded proteins**( which are soluble in their normal folded configuration)
- The fibrillar deposits bind a variety of proteoglycans and glycosaminoglycans, including heparin sulfate and dermatan sulfate and plasma proteins - serum amyloid P component (SAP)

- The presence of **abundant charged sugar groups** in these adsorbed proteins gave the deposits staining characteristics that were thought to resemble starch (amylose)

# Types of Fibrillary proteins

1.AL proteins: whole light chains or fragments of light chains- Primary Amyloidosis

2.AA proteins: derived from Serum amyloid associated proteins which are acute phase reactant proteins synthesized in liver.- Secondary amyloidosis.

3. ATTR -Transthyretin/Amyloid familial pre-albumin

transports thyroxine and retinol

4.A $\beta_2$ microglobulin/Haemodialysis associated amyloid

Seen in patients receiving long term Haemodialysis.

5.Aβ- amyloid/Cerebral amyloid

In Alzheimer's disease

6.Hormone precursor/Endocrine amyloid

Procalcitonin and proinsulin

7.Prion Proteins- APrP

# Classification of amyloidosis

I] On basis of cause:

Primary - AL

Secondary - AA

II] On basis of Histology

Pericollagenous - AL

Perireticulin - AA

III] On the basis of clinical location:

Pattern I – Tongue, Heart, Bowel, skeletal & smooth muscle, skin and nerves

Pattern II – Liver, spleen, kidney & adrenals

Mixed – Pattern I & II

## IV] Clinicopathological–

### 1. Systemic amyloidosis (Generalized)

- Primary - AL
- Secondary(reactive) - AA
- Haemodialysis associated – A$\beta_2$M
- Heredofamilial associated –

✓ Hereditary polyneuropathies: ATTR

✓ Familial Mediterranean fever: AA

✓ Rare hereditary forms

## 2. Localised amyloidosis

- Senile cardiac- ATTR
- Senile cerebral – Aβ , APrP
- Endocrine –

✓Medullary carcinoma: Procalcitonin

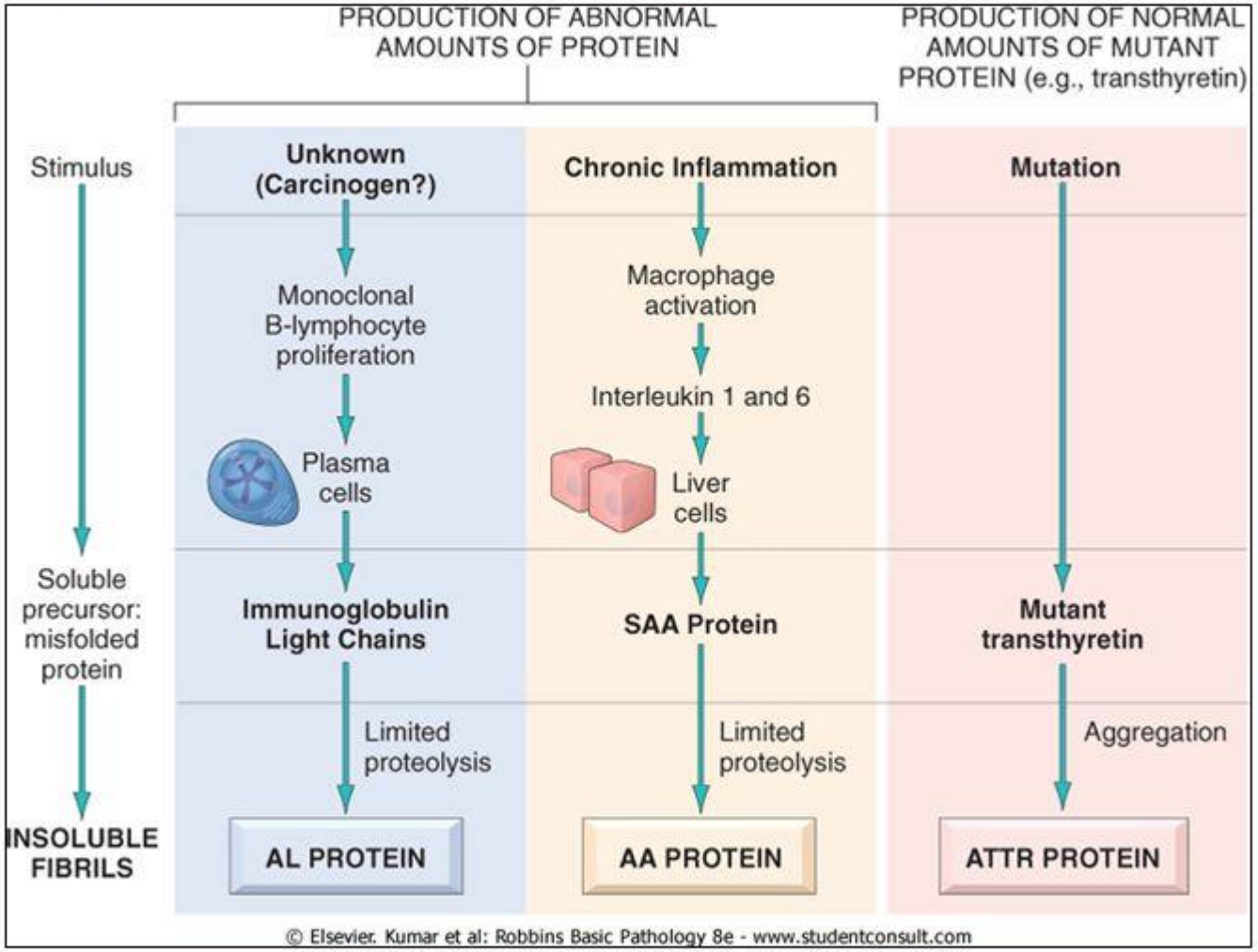
✓Type 2 diabetes mellitus: Proinsulin

❑Tumor forming

# Pathogenesis

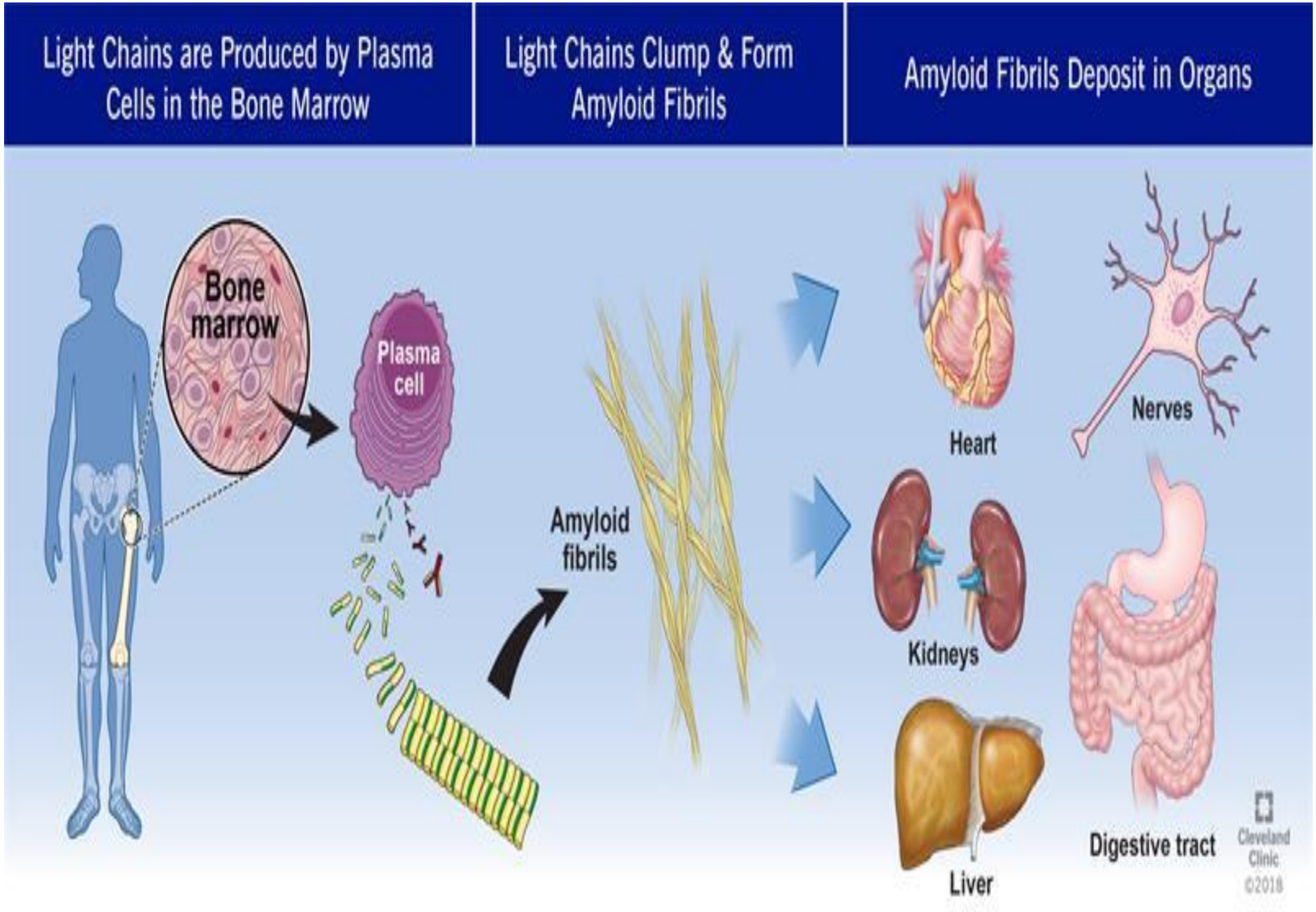
- Abnormal folding of proteins
- Insoluble ,aggregate and deposit as fibrils in extracellular tissues
- Normally, misfolded proteins are degraded intracellularly in proteosomes or extracellularly by the macrophages

# Pathogenesis of Amyloidosis



# 1.Primary amyloidosis

- Occur without predisposing disease
- AL amyloid
- Heart, skin, bowel & skeletal muscle
- Associated plasma cell dyscrasias- Multiple myeloma & other monoclonal proliferation


Light Chains are Produced by Plasma Cells in the Bone Marrow
Light Chains Clump & Form Amyloid Fibrils
Amyloid Fibrils Deposit in Organs
Bone marrow
Plasma cell
Amyloid fibrils
Heart
Nerves
Kidneys
Liver
Digestive tract
Cleveland Clinic
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# 2.Secondary amyloidosis

- Associated with primary predisposing disease –TB, bronchiectasis, chronic osteomyelitis,leprosy, syphilis,inflammatory bowel disease, ankylosing spondylitis, RA etc
- AA amyloid
- Abd. Viscera – Liver, spleen, kidneys

# 3.Haemodialysis associated Amyloidosis

## Haemodialysis associated Amyloidosis

- patients receiving long term haemodialysis
- joints, synovium, ligaments, bones or systemic
- A$\beta_2$ microglobulin

# 4.Heredofamilial amyloidosis

- FMF: Familial Mediterranean Fever

➢Mediterranean region

➢Periodic attacks of fever and polyserositis

➢ AA amyloid

➢ Scattered in arteries throughout the body

- Hereditary polyneuropathic type:

➢Peripheral nerves affected the most

➢ATTR

# Localized Amyloidosis

- **Senile cardiac amyloidosis:**

Heart & aorta , ATTR

- **Senile cerebral amyloidosis**:

Walls of cerebral blood vessels, Aβ , APrP

- **Endocrine amyloidosis**:

Medullary Ca of thyroid, Procalcitonin

Islet cell tumor of pancreas, Proinsulin

# Morphology

- **Gross**

-Organ is enlarged,firm and pale.

-C/S: Waxy

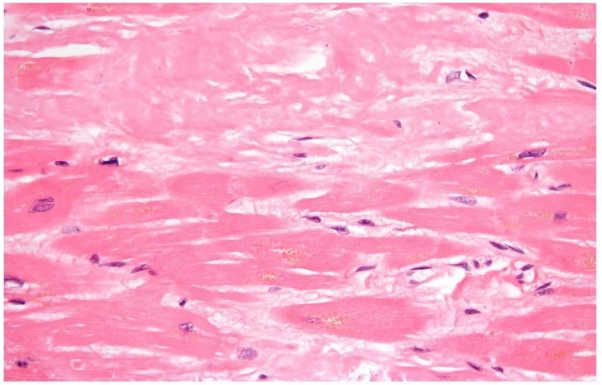
Lugol’s iodine: Mahogany brown

:dilute sulfuric acid- blue

- **Light microscopy**

H & E stain: Extracellular, homogenous, structureless,eosinophilic,hyaline material

High magnification micrograph of senile cardiac amyloidosis on H&E stain. The micrograph shows amyloid (extracellular fluffy pink material) and abundant lipofuscin (yellow granular material).



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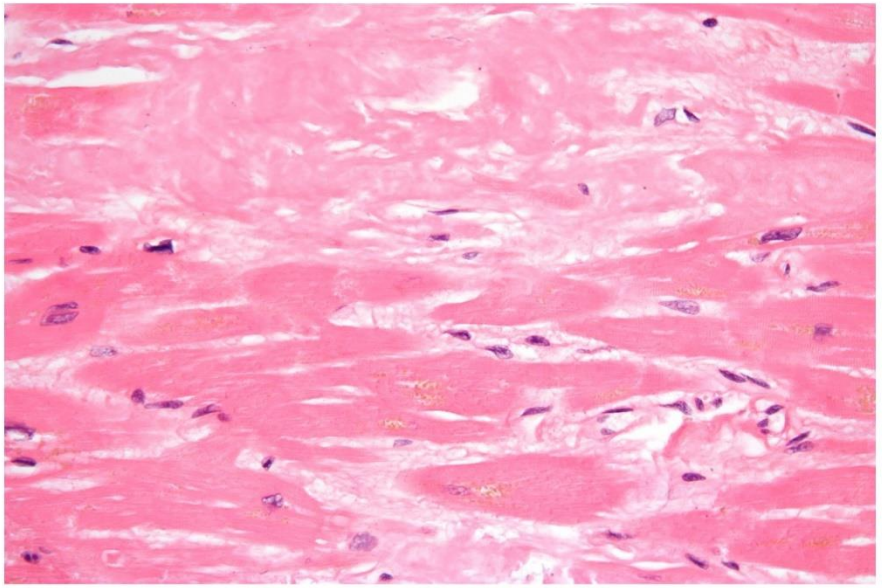
Cardiac Amyloidosis 8

High magnification micrograph of senile cardiac amyloidosis on H&E stain. The micrograph shows amyloid (extracellular fluffy pink material) and abundant lipofuscin (yellow granular material).



# Staining of amyloid

- H & E stain – Extracellular, homogeneous, structureless, eosinophilic, pink hyaline material

# Special stains:

- Congo red
  - Amyloid: red and specific apple
  - green fluorescence in polarized light.

or

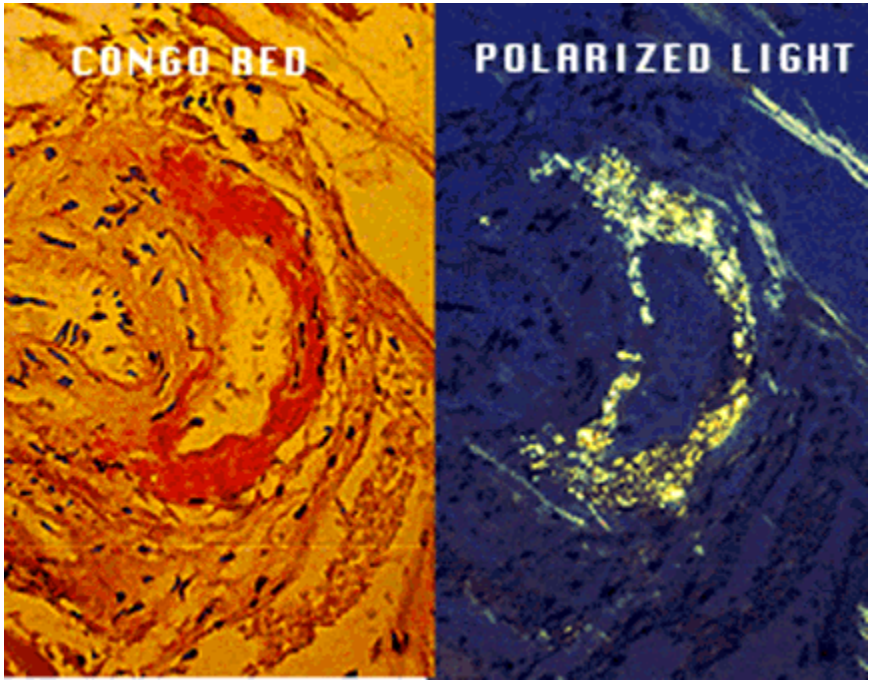
Normal tissue: pale pink red:

No fluorescence.

AL – permangnate resistant

AA – permangnate sensitive

# Amyloid – Special stains



# Additional special stains:

- Van Gieson – Khaki colour
- Metachromatic stain (Crystal violet Or Methyl violet) – rose pink
- Fluorescent stain – fluorescent yellow color
- Sulphated Alcian blue – blue green color
- Immunohistochemistry – antibodies specific to fibril protein. anti AA, anti – AP, anti – lambda and anti - kappa

# Amyloidosis of Kidney

- Grossly

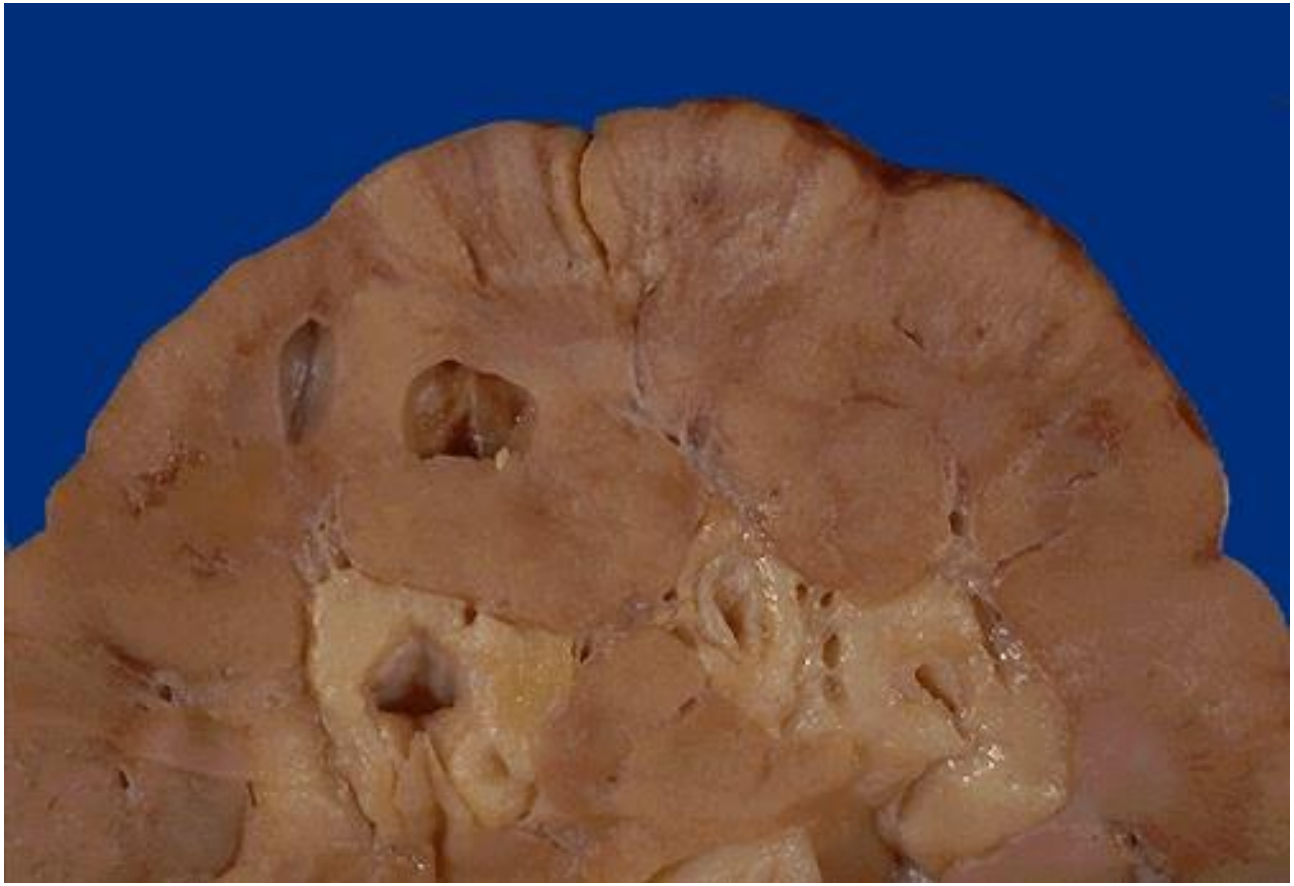
  Normal, enlarged or contracted

- Microscopically

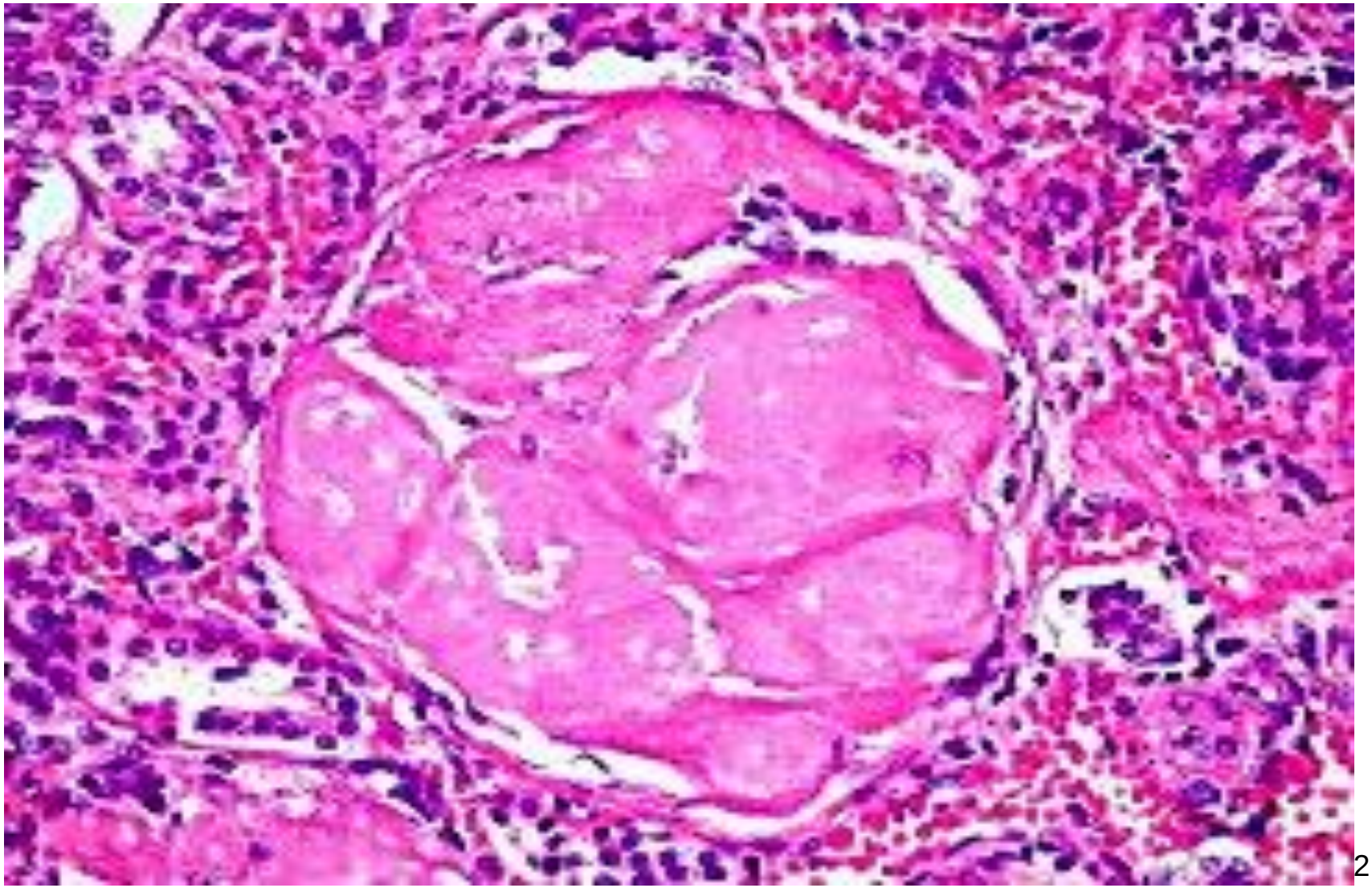
  In the glomeruli on the basement membrane of glomerular capillaries– increase in permeability – Nephrotic syndrome

  In the tubules & walls of vessels

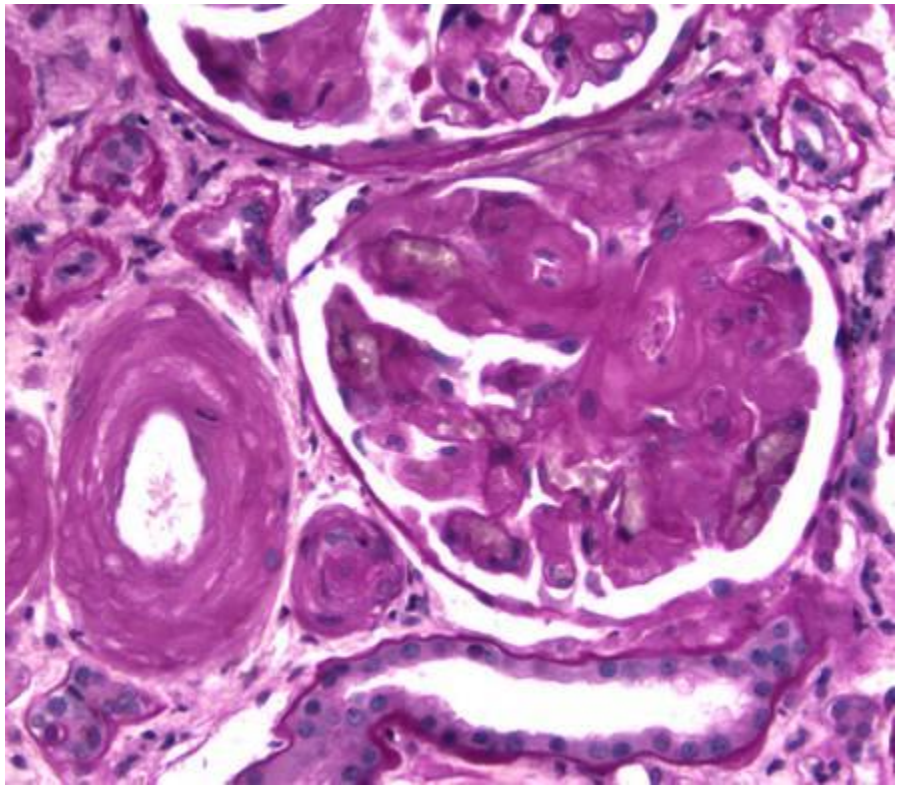
Here is a chronic renal disease that may actually increase the size of the kidney. This is amyloidosis. Pale deposits of amyloid are present in the cortex, most prominently at the upper center.



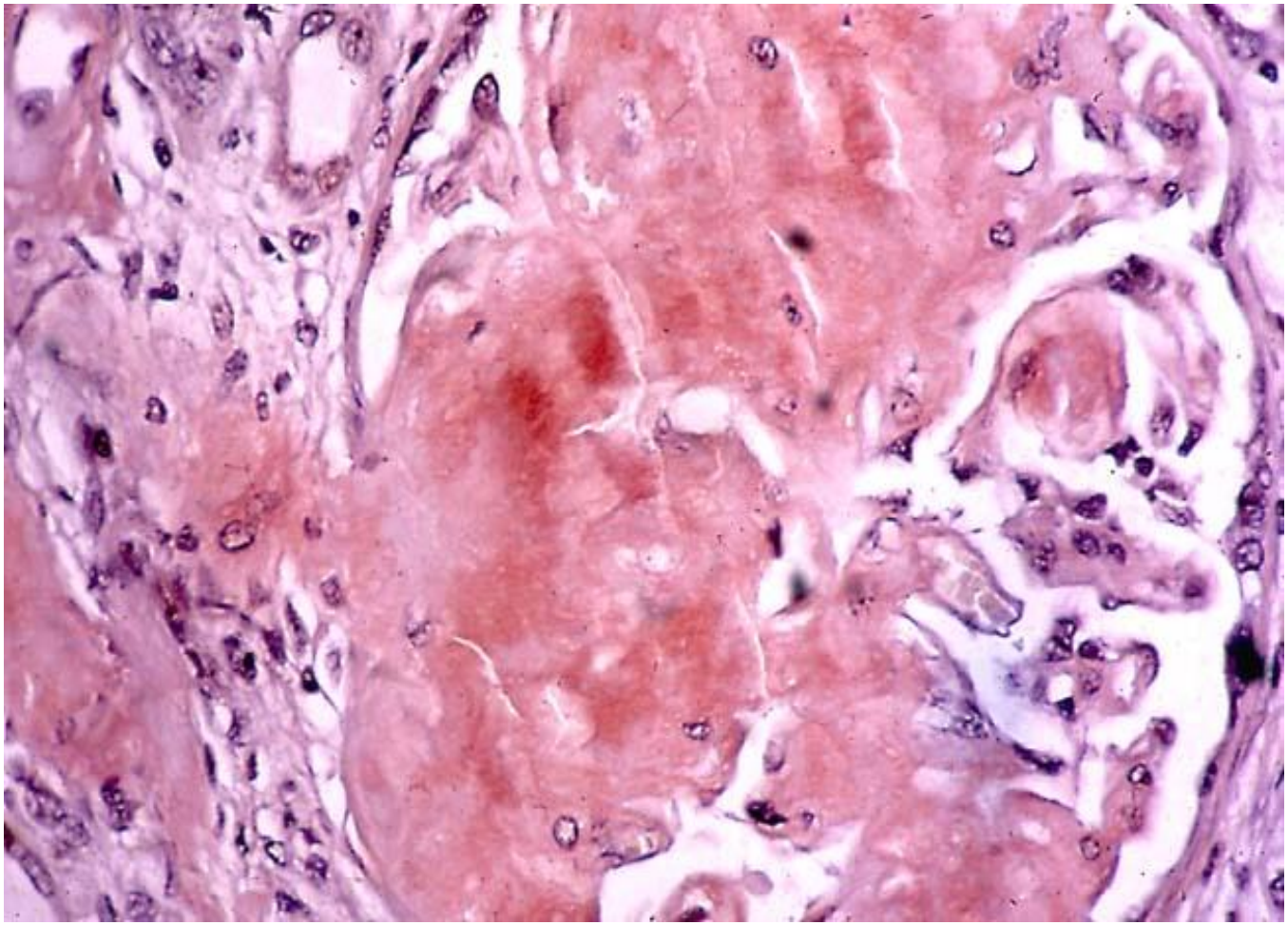
# Amyloid kidney



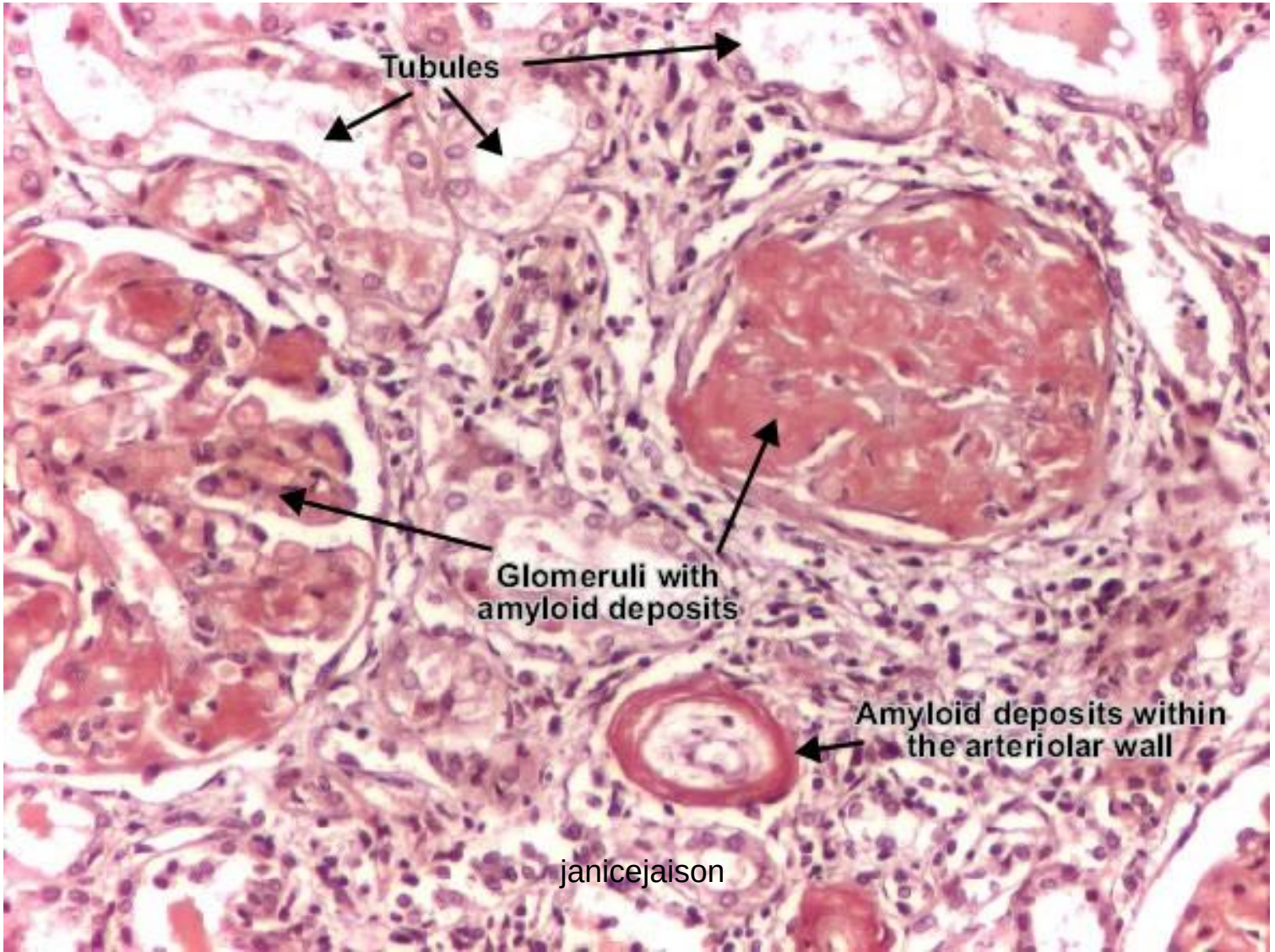
# Amyloid kidney



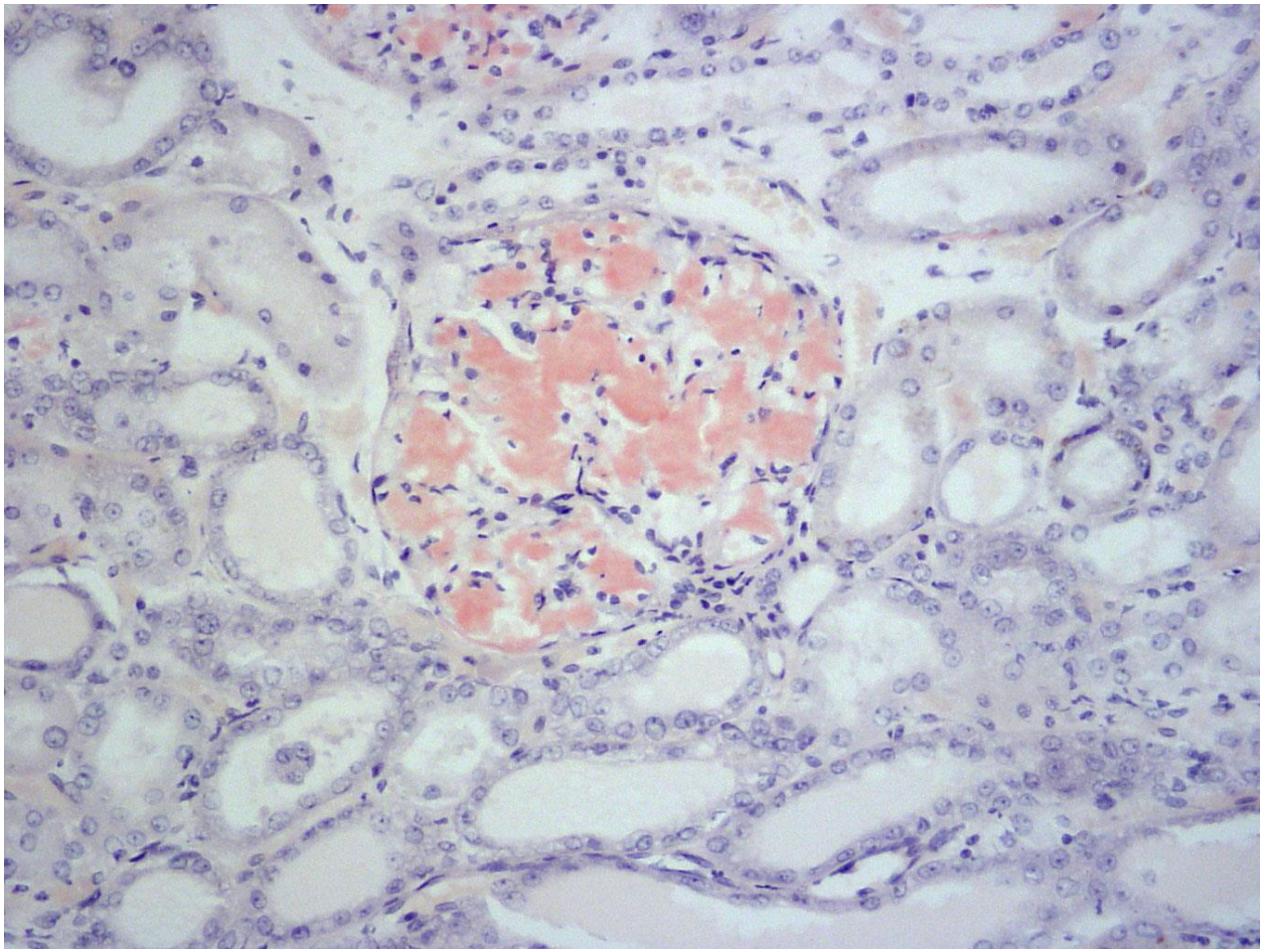
# Amyloid kidney on Congo red



# Amyloid kidney on Congo red



# Amyloid kidney on Congo red



# Amyloidosis of Spleen

I] Sago spleen –

Splenomegaly not marked

C/S: translucent pale & waxy nodules

Microscopically – in walls of arterioles of white pulp

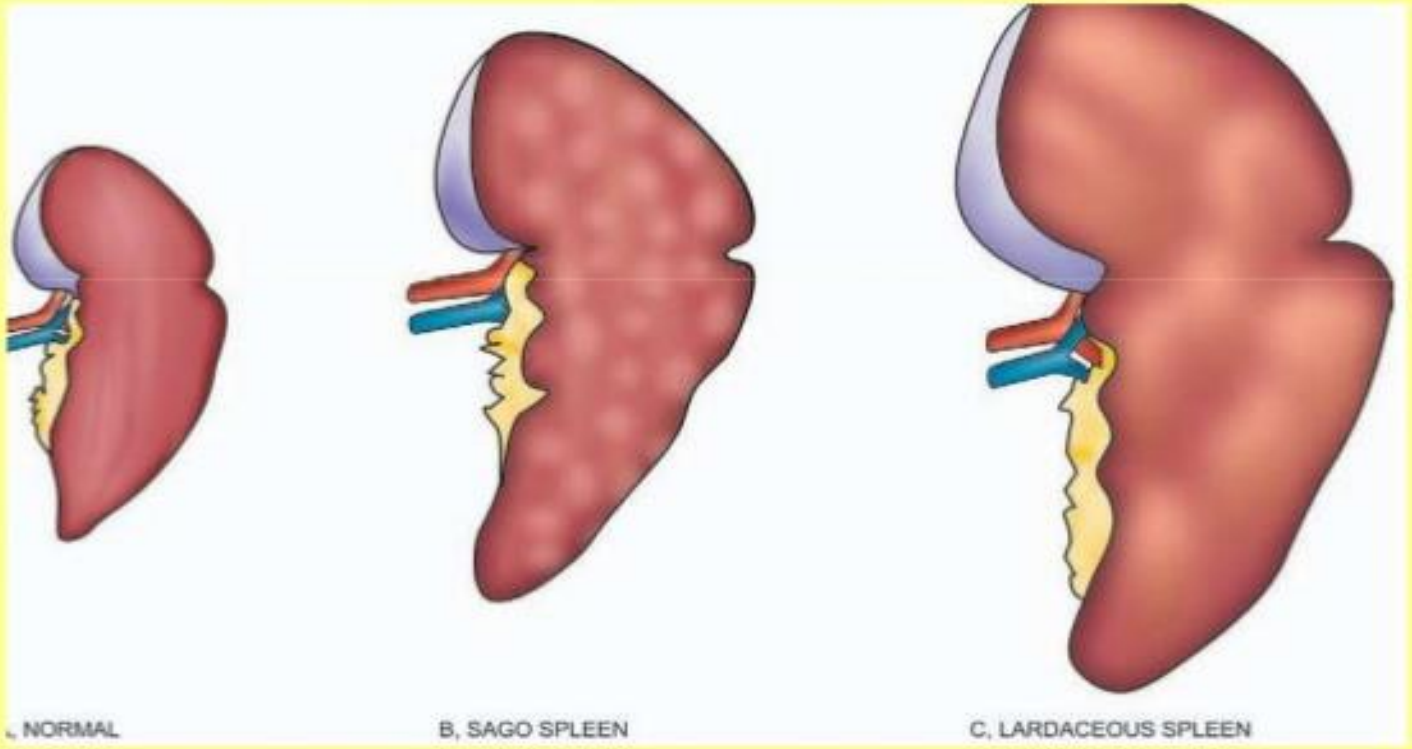
II] Lardaceous spleen –

Moderate to marked splenomegaly

C/S: map like areas of amyloid

Microscopically –in the walls of splenic sinuses & small arteries & in connective tissue of red pulp

# Amyloidosis of the spleen

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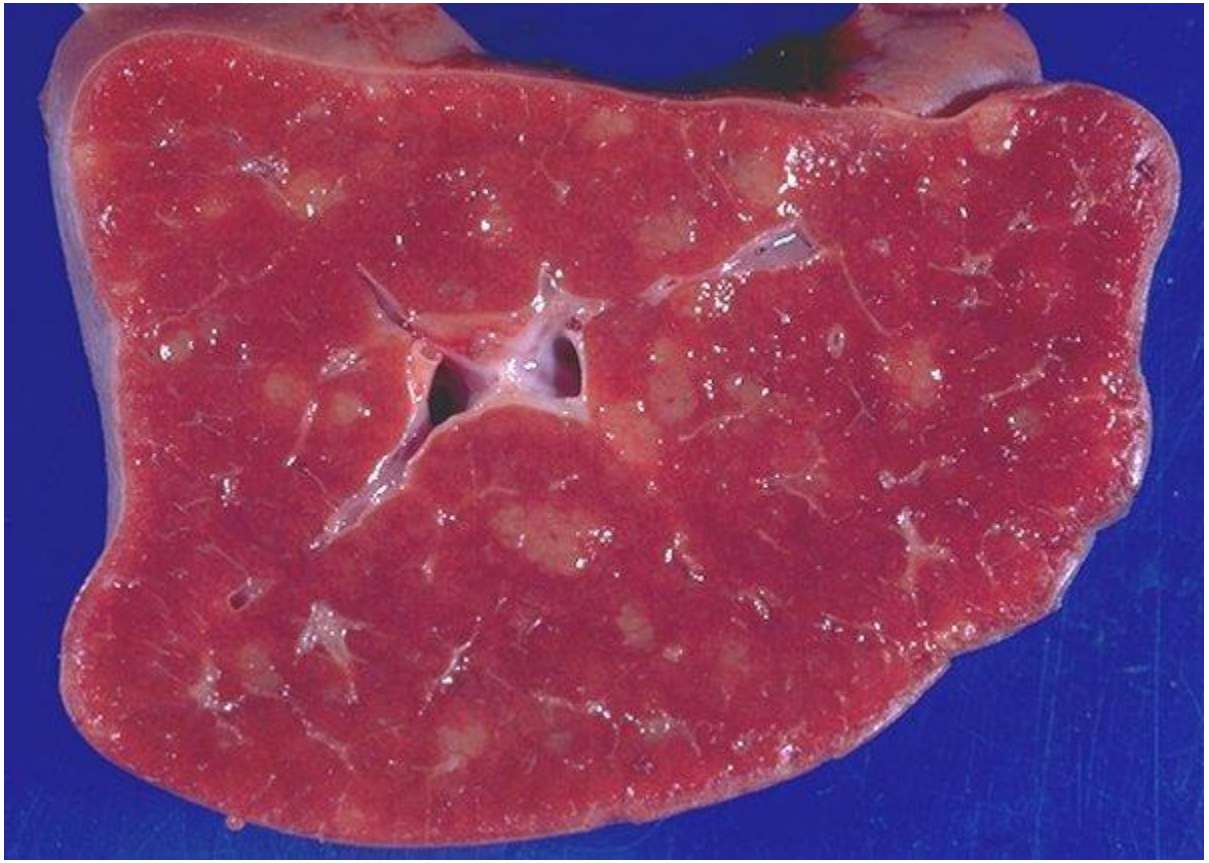
# Gross of amyloid spleen



# Amyloidosis of Liver

- Grossly –

  Enlarged, pale waxy & firm

- Microscopically –

  Initially in the space of Disse

  then compress cords of hepatocytes

  hepatocytes shrunken & atrophic

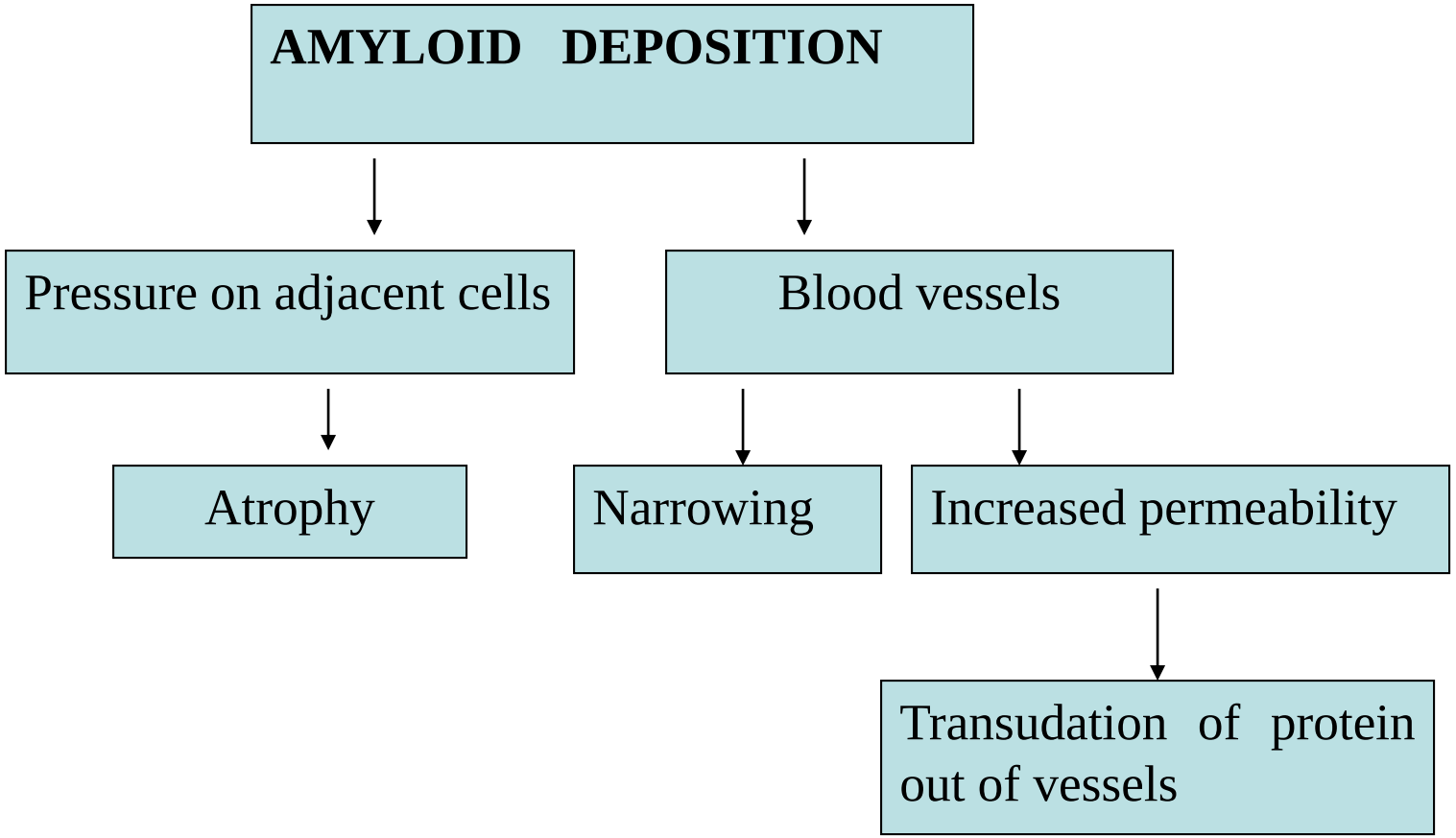
## Amyloidosis of Heart

Primary type seen in systemic amyloidosis.

## Amyloidosis of gastrointestinal tract.

- Seen from oral cavity to anus.
- Deposits around blood vessels.
- In later cases amyloid in bowel wall.
- Tongue – macroglossia.

# Pathological effects



# Diagnosis of amyloidosis

- Biopsy – Kidney

  - Rectum / Gingiva / Abdominal fat

# Prognosis

- Generalized amyloidosis – poor
- Secondary amyloidosis – better
- Renal failure & cardiac arrhythmia are causes of death.

## Amyloidosis

| | |
|---|---|
| Etiology | **Primary:** Associated with plasma cell dyscrasias.<br>**Secondary:** Occurs as a complication to underlying chronic infections (ie, TB, osteomye or chronic inflammatory diseases (ie, RA, IBD). |
| Pathology and Pathophysiology | **Primary:** Deposition of monoclonal immunoglobulin light chains (**AL protein**), usua **heart**, **GI tract**, muscle, nervous system, and **kidneys**.<br>**Secondary:** Deposition of **AA protein**, which is derived from apolipoprotein precu usually involves **kidneys**, **GI tract**, and skin.<br>*Histopathology:* **Apple-green birefringence** of amyloid protein on Congo red stain.<br>*Pathophysiology:* Impaired organ function caused by **infiltration of tissues with ins protein fibrils**. |
| Clinical Manifestations | Symptoms are related to malfunction of organ involved (eg, nephrotic syndrome, renal restrictive cardiomyopathy, arthritis, neuropathy, intestinal malabsorption, respiratory |
| Treatment | **Primary:** Melphalan and prednisone; organ transplant followed by bone marrow tra<br>**Secondary:** Aggressive treatment of predisposing disease. |
| Notes | Other diseases with amyloid deposition include Alzheimer disease (amyloid β- Portuguese type of polyneuropathy (transthyretin), nephropathic hereditary am |

A 56-year-old man with a past medical history significant for multiple myeloma develops flank pain and oliguria. Upon further history, you learn that he has also developed progressive shortness of breath on exertion over the past 6 months. He is admitted to the hospital, where test demonstrates renal failure in addition to evidence of a restrictive cardiomyopathy. When a fat biopsy shows apple-green birefringence under polarized light on Congo red stain.