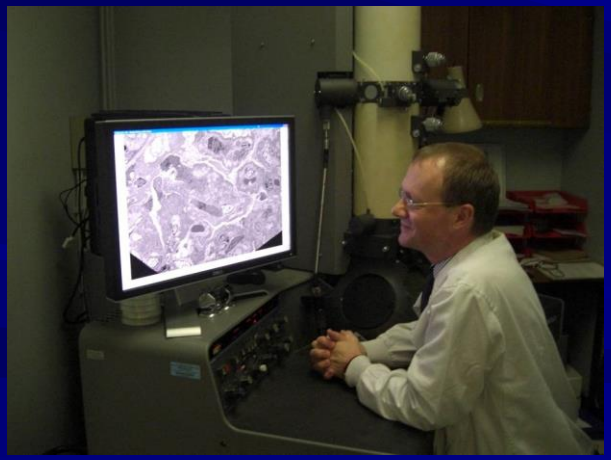
Basic Renal EM workshop

Southampton

September 30th 2011

Renal Ultrastructural Pathology
Lecture 1 A - C



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Renal Ultrastructural Pathology Lecture 1 - Topics

1. Alport’s nephritis
2. Amyloid
3. Capsular adhesion
4. Congenital nephrotic syndrome

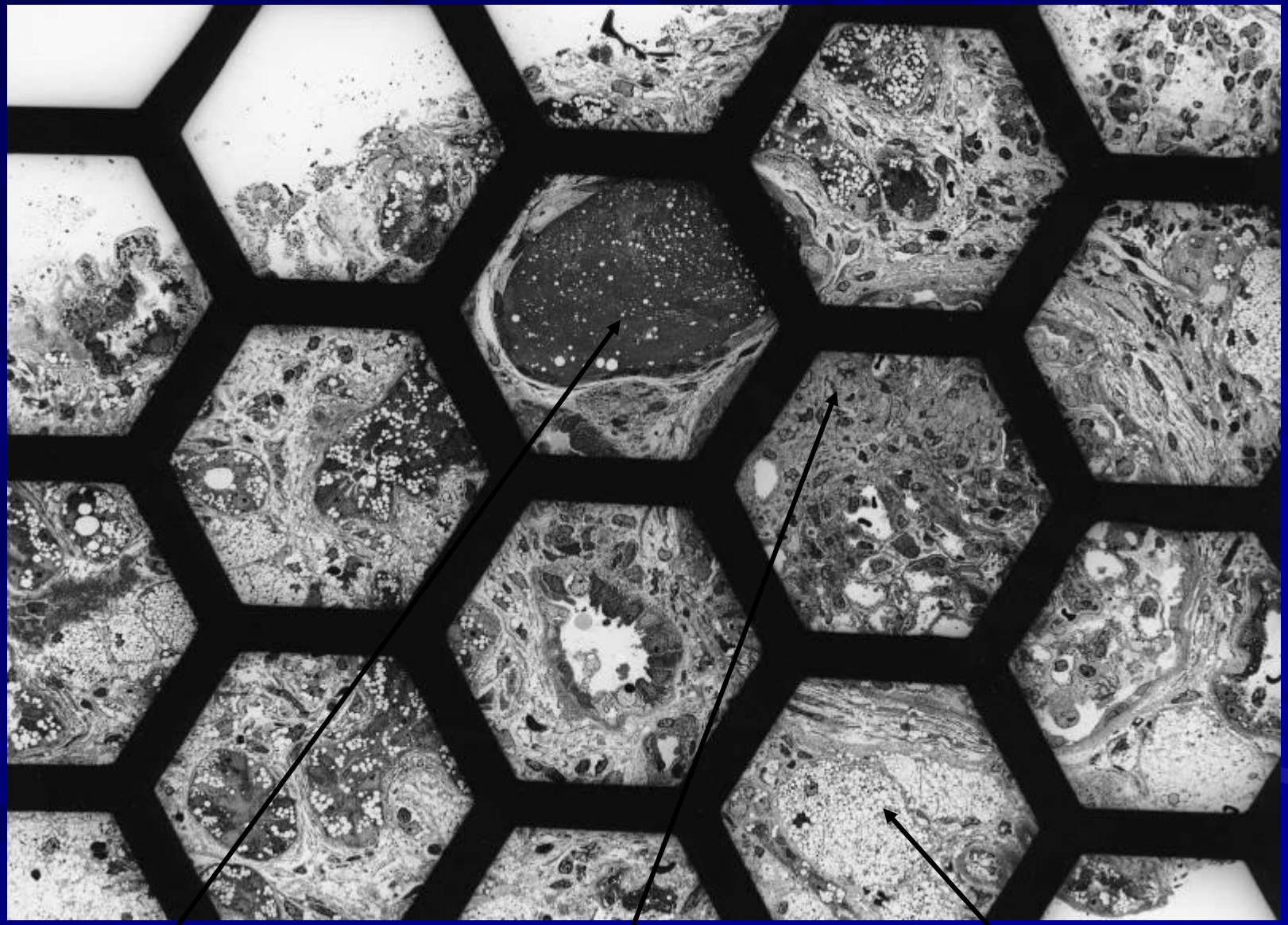
Alport’s nephritis

Alport's nephritis

- Collagen IV gene defect
- Affecting all glomerular basement membranes
- X-linked is most common form (80%) ie results in males being more severely affected, and affected earlier in life. (Col IV alpha 5 & 6)
- Recessively inherited form (Col IV alpha 3 & 4 on chromosome 2)
- Part of syndrome – frequently also affects hearing, occasionally ocular
- Due to GBM defect, persistent microscopic haematuria present

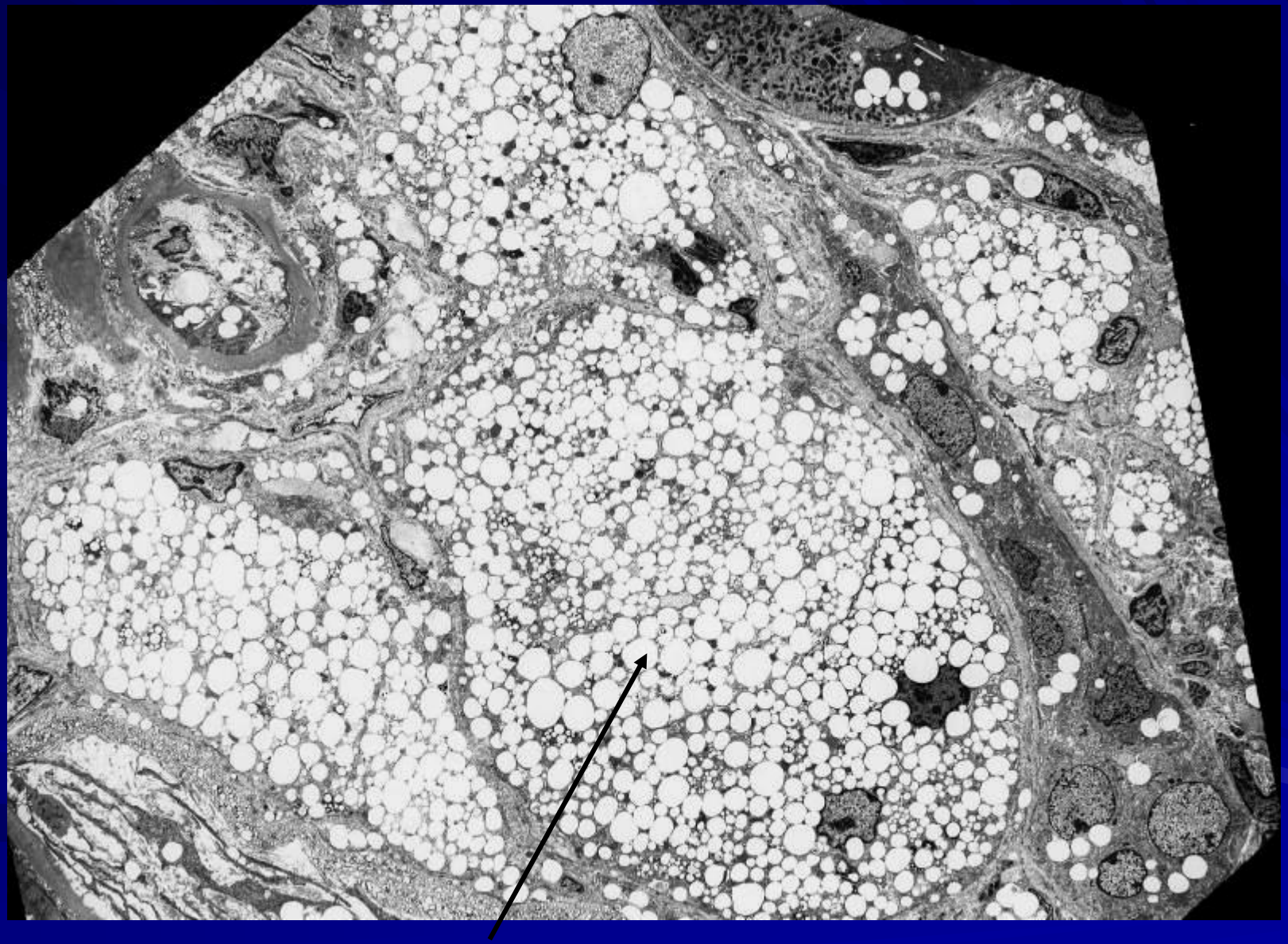
Alport's
25 year old male

End stage Alport's nephritis



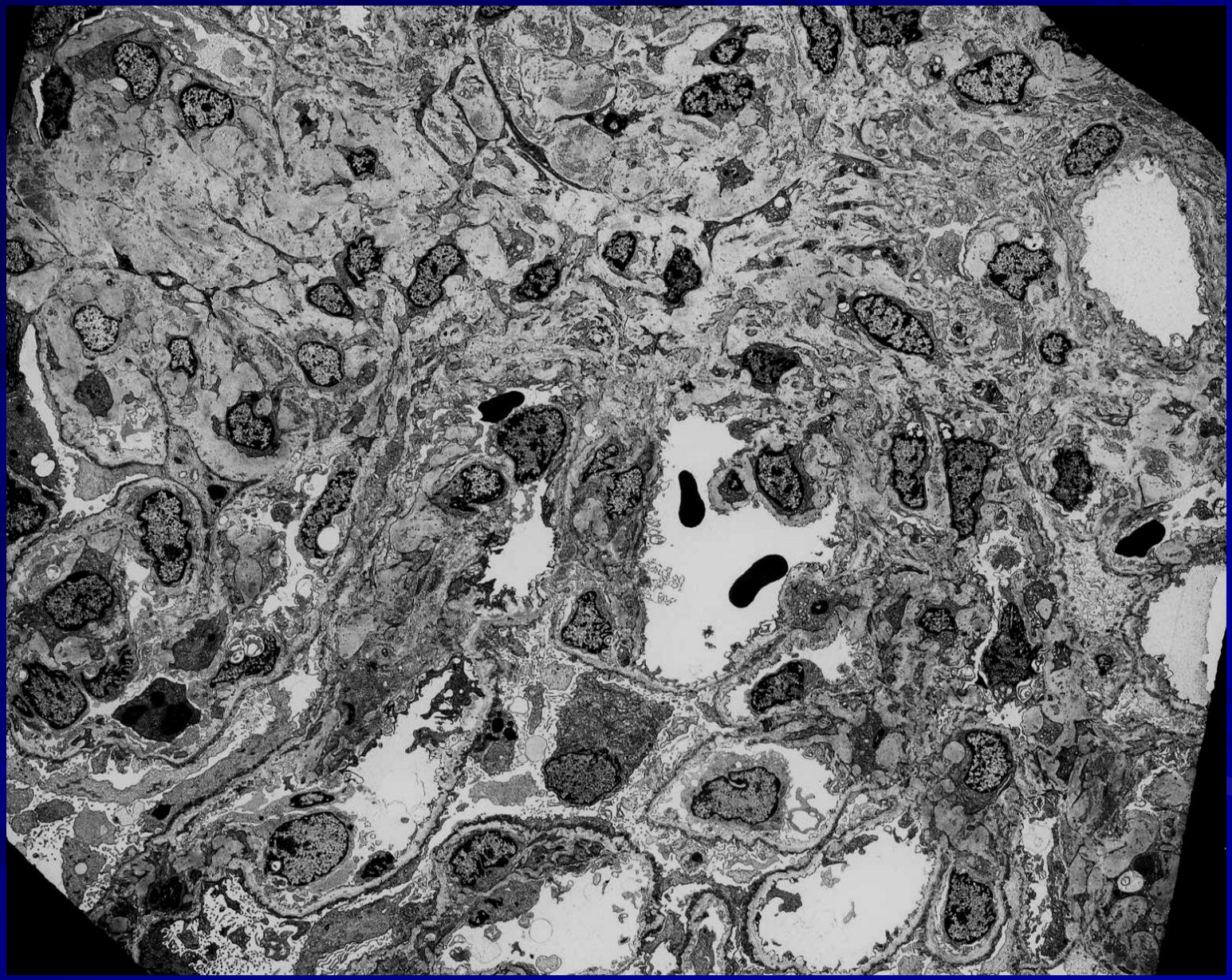
Tubular thyroidisation - Segmental glomerular sclerosis - Interstitial foam cells

Higher magnification of above



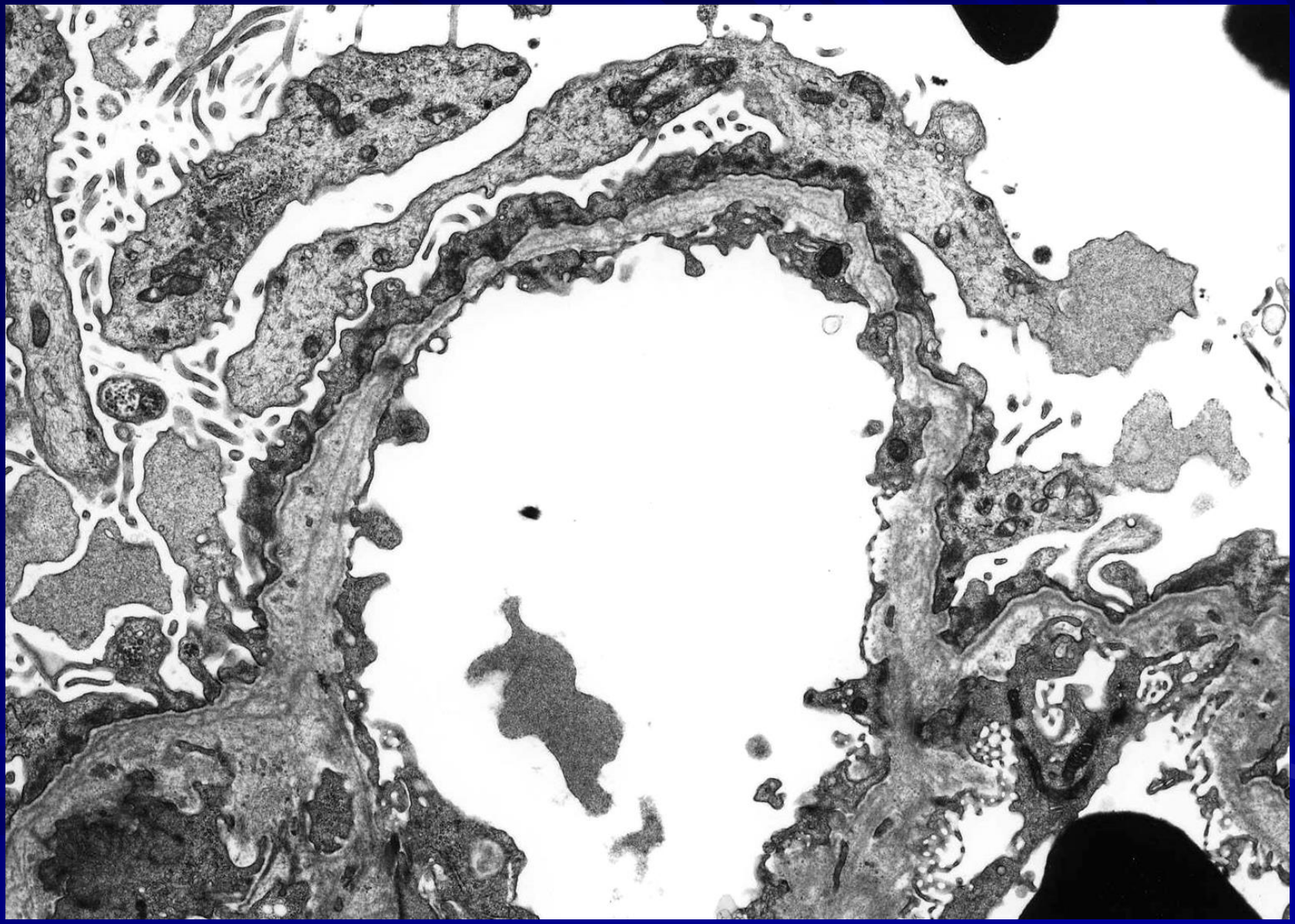
Interstitial foam cells (fibroblasts filled with saturated lipid droplets)

Higher magnification of first Alport's image



Segmental sclerosis, extensive foot process effacement, **all** capillary loops affected

Alport's syndrome

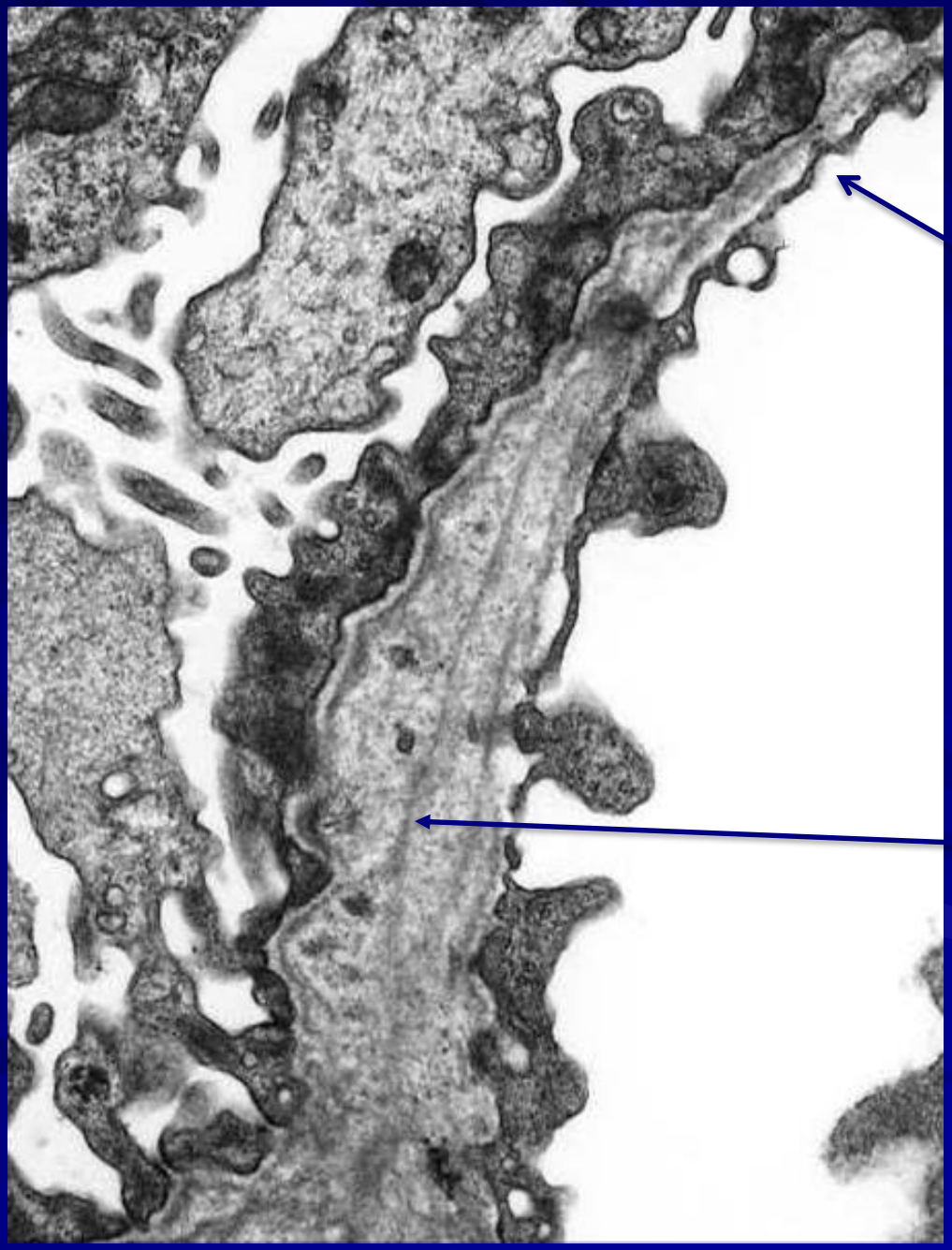


Irregularly thickened GBM

GBM in multiple layers

Alport's syndrome

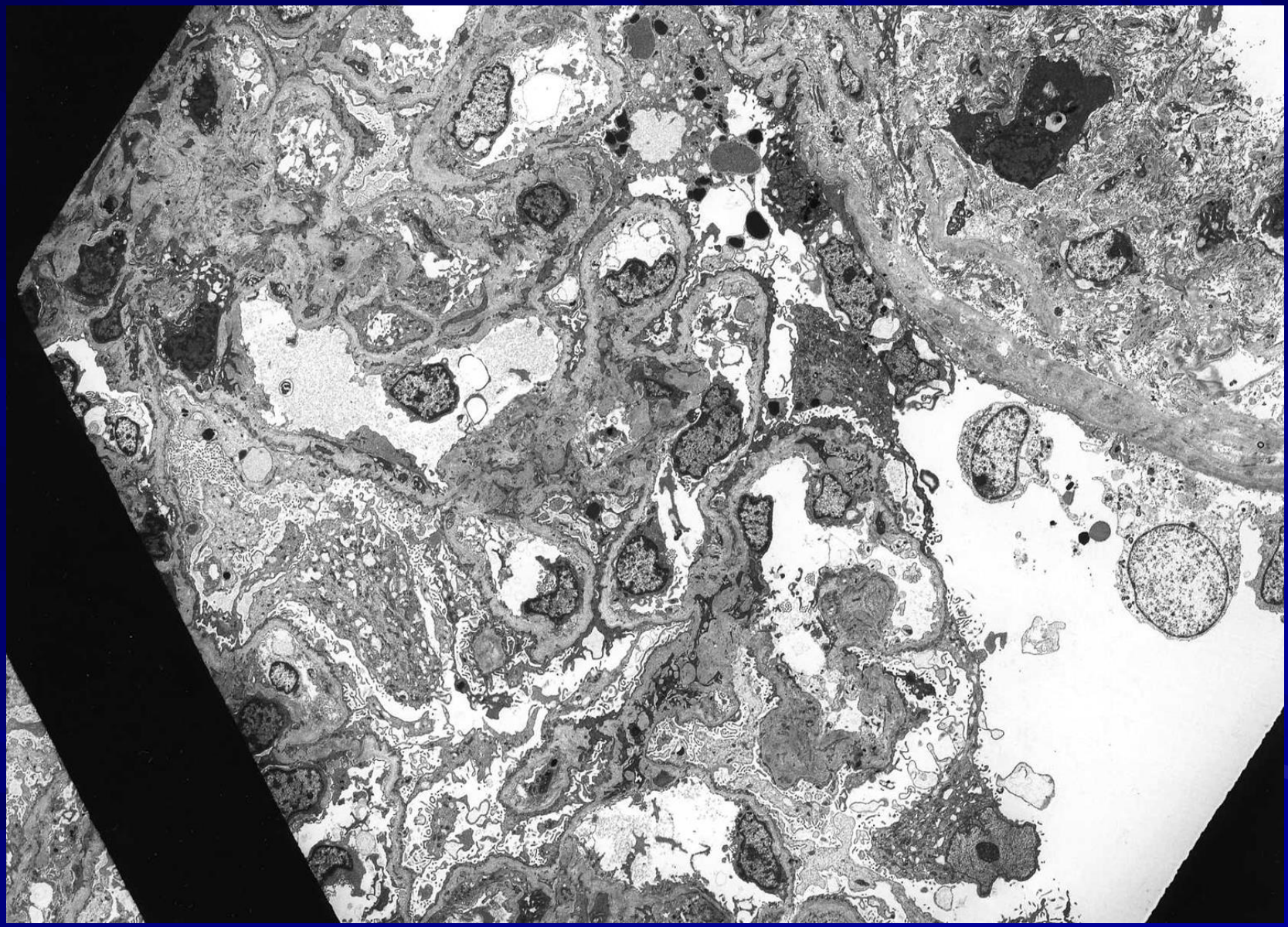
Higher magnification of previous slide



Focally thin GBM

GBM in multiple layers

Alport's
50 year old female



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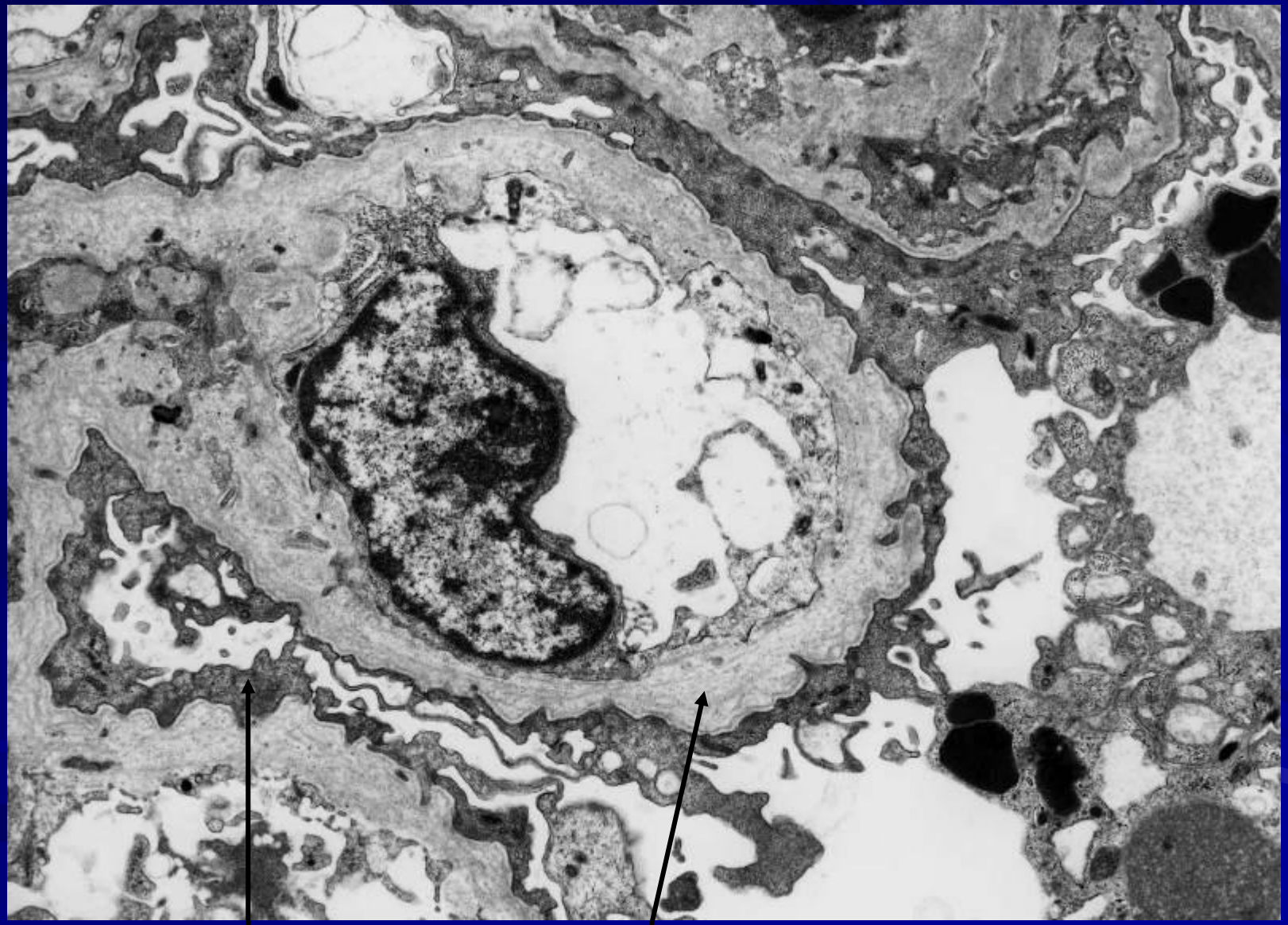
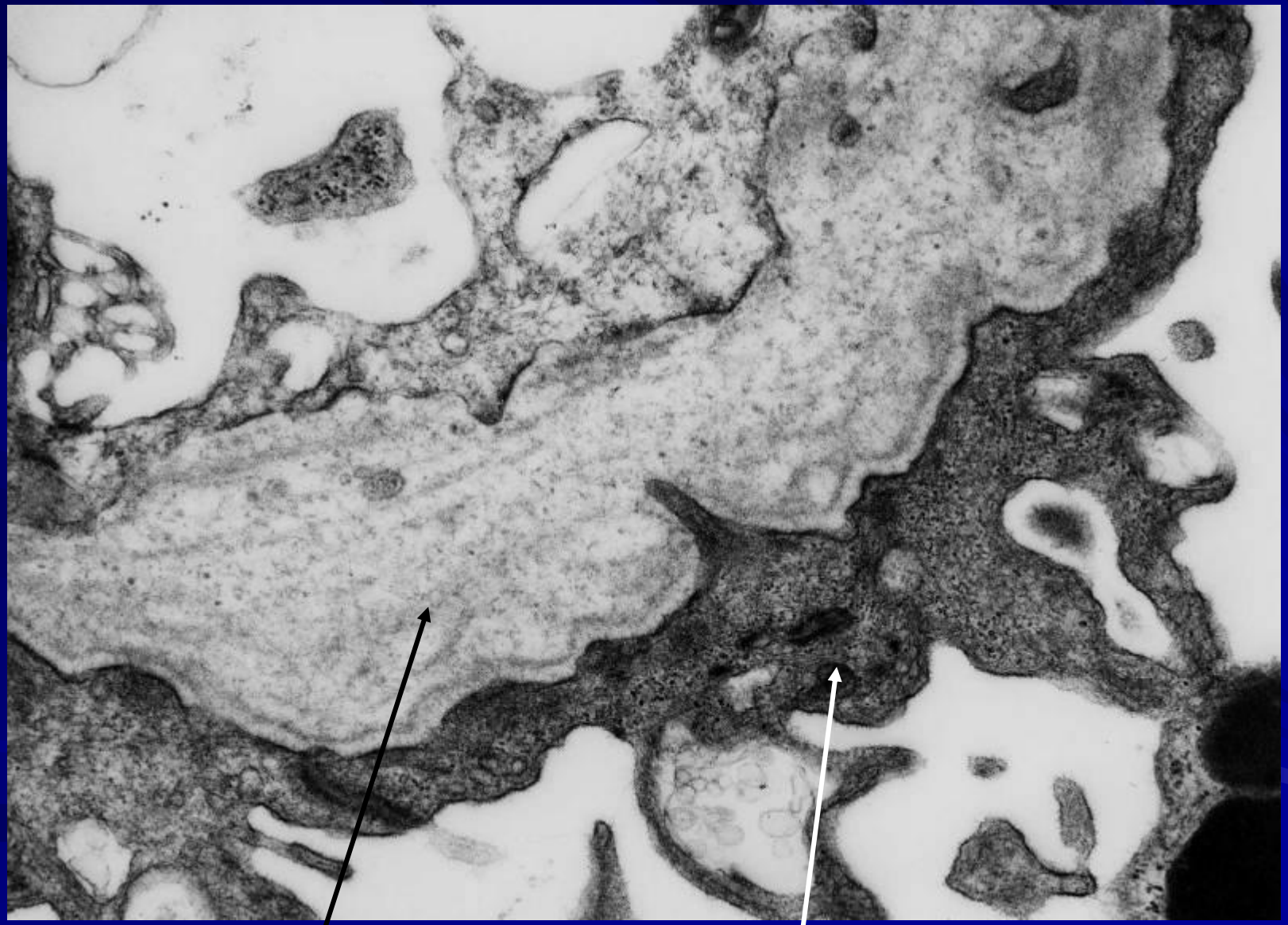


Foot process effacement, lamination of GBM

Higher magnification of previous slide



Lamination/reticulation/reduplication of GBM, foot process effacement

Alport's nephritis

How to diagnose thin basement membrane disease

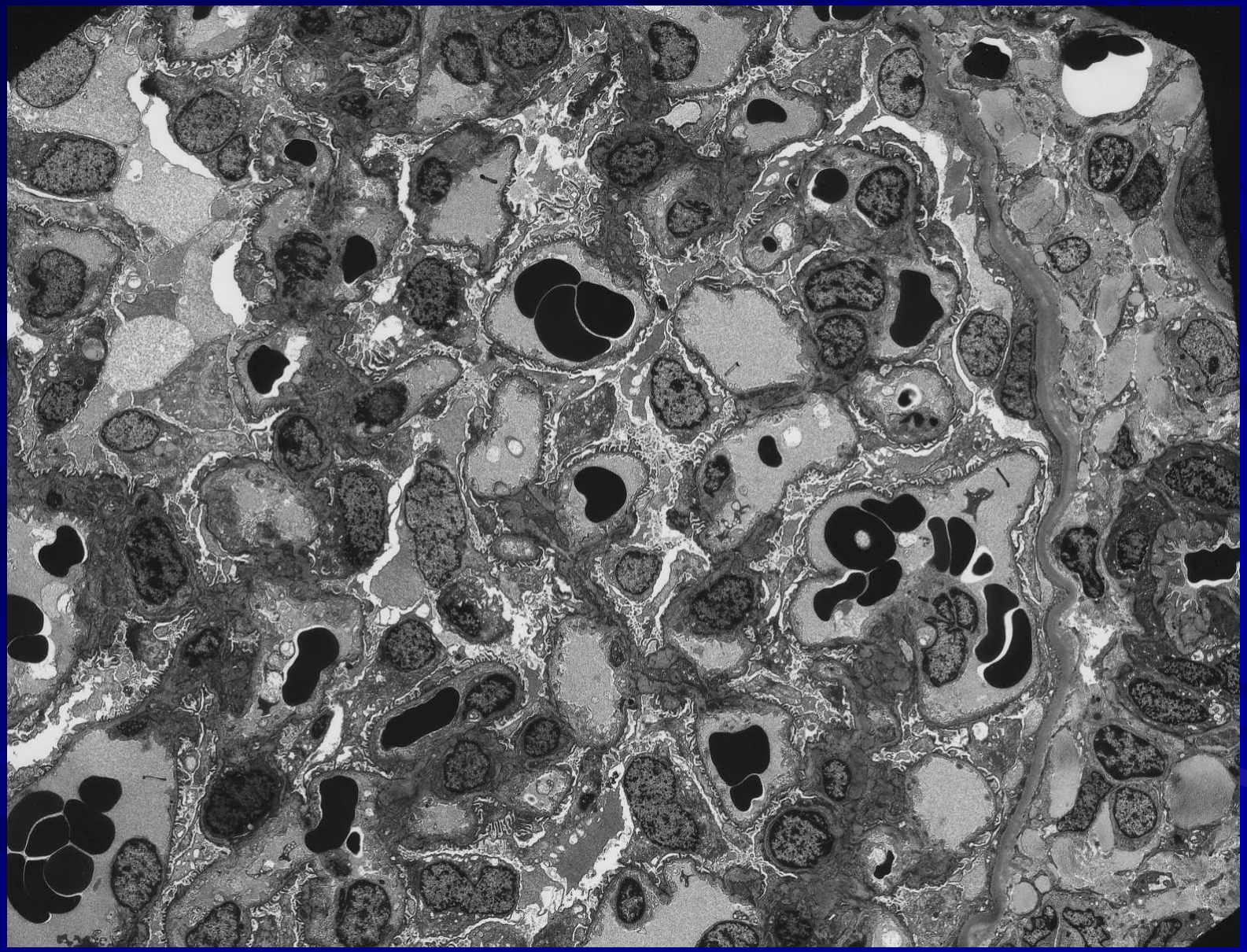
- **All** the GBM's are thin
- All other diagnoses are excluded - especially IgA disease

Genetics

- Either, early X-linked Alport's
- Or, heterozygous autosomal Alport's

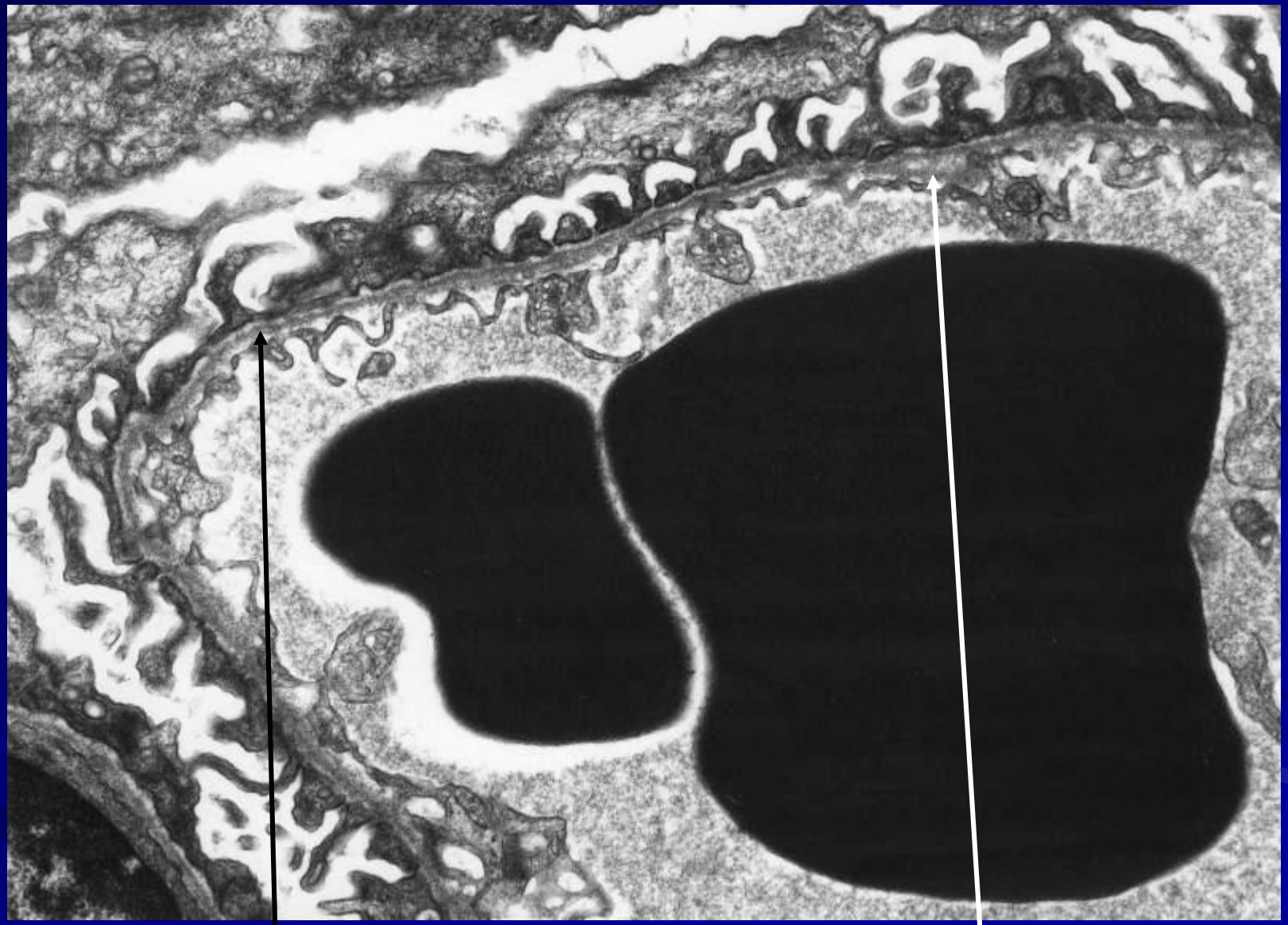
Alport's
14 year old male

14 year old boy with thin GBM, haematuria, but not nephrotic



All GBM's are thin, no deposits

Alport's – 14 year old boy



Thin GBM approx 190nm instead of normal 300nm, with small areas of minor lamination

Renal Amyloid

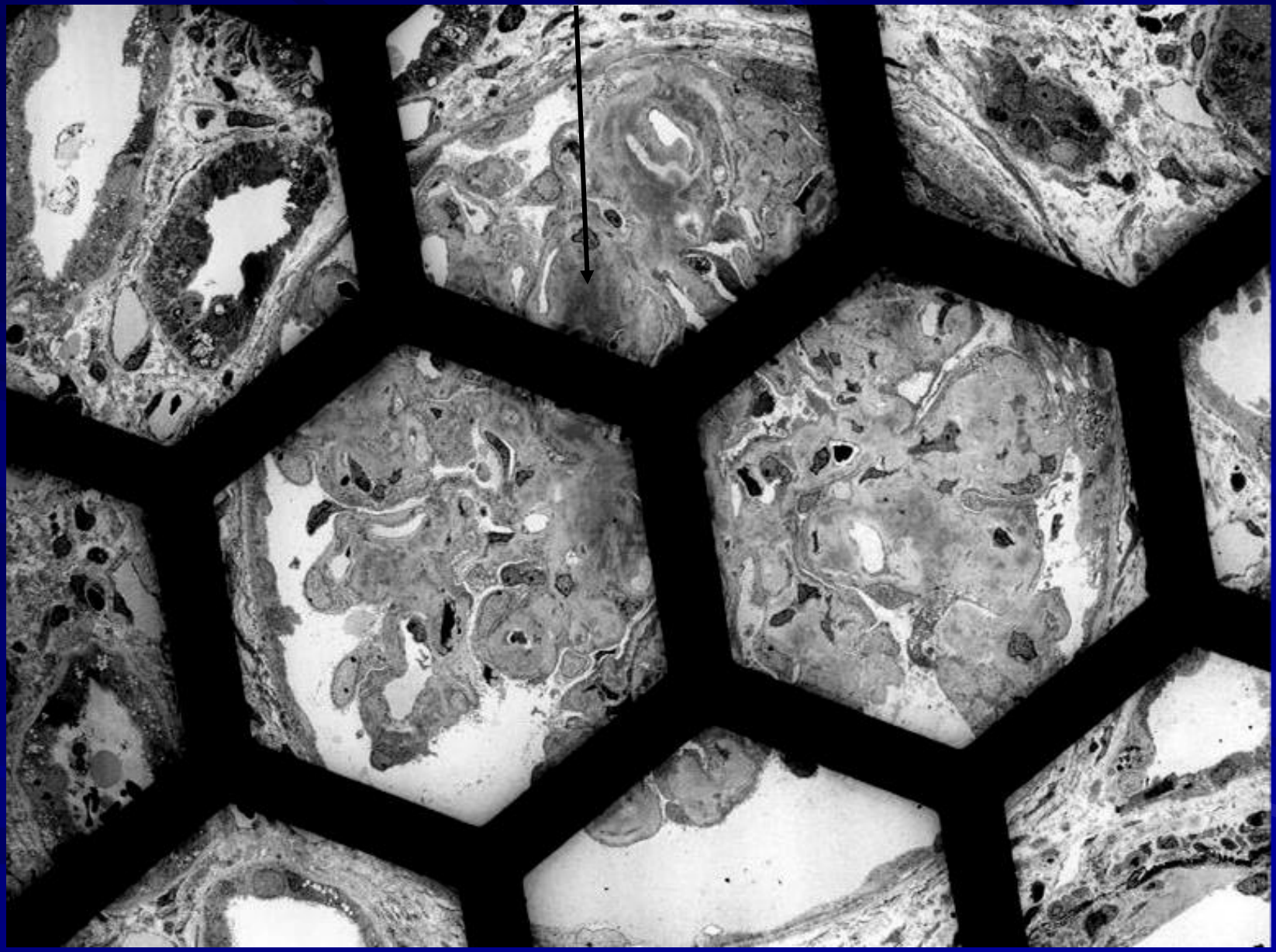
Renal Amyloid

- Electron Microscopy is gold standard test for amyloid

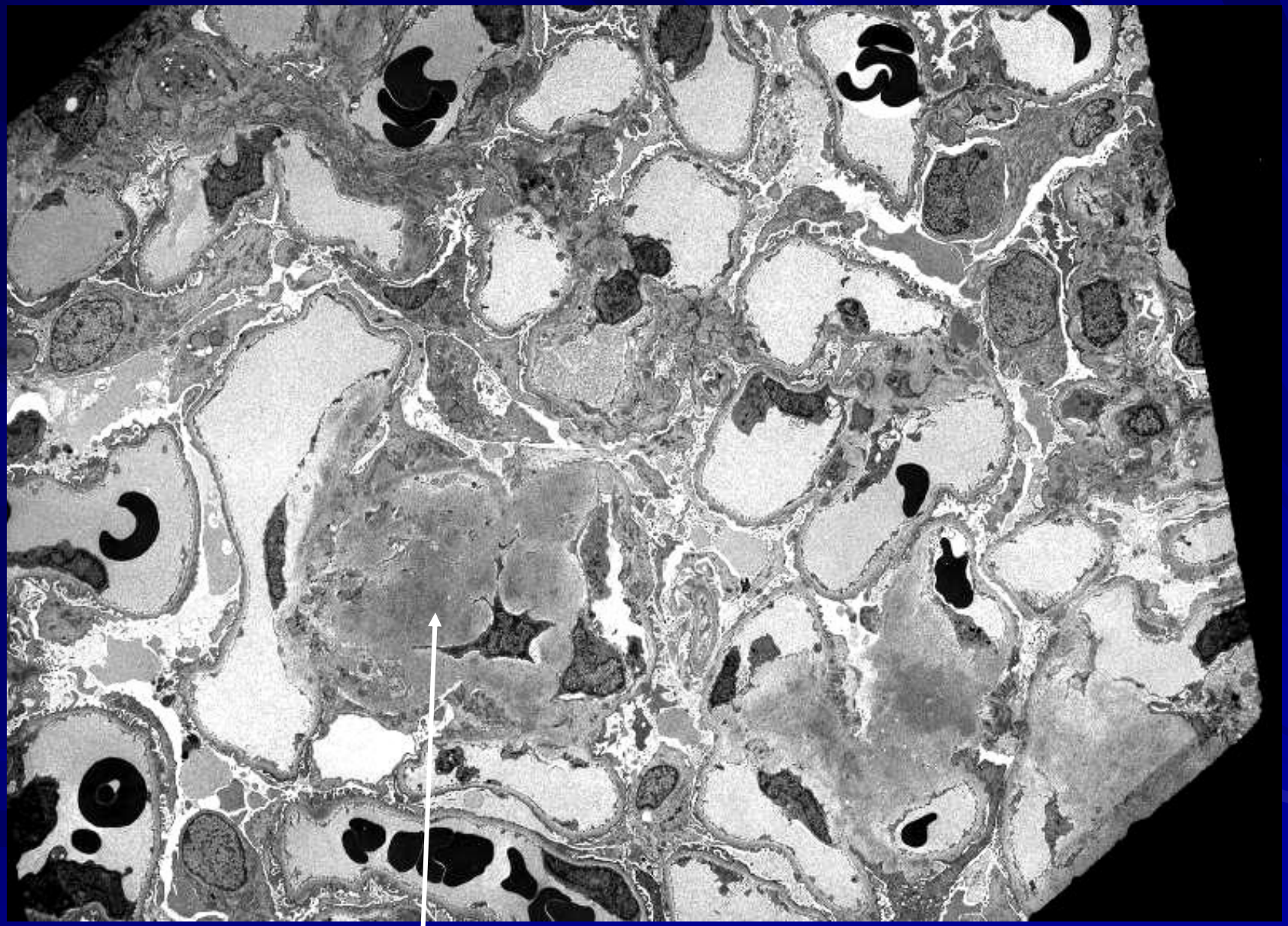
Because

- 10 – 20 % of cases of amyloid, irrespective of type, do not stain with Congo or Sirius Red
- Amount of amyloid can be below amount detected by light microscopy, but still be sufficient to cause severe proteinuria

Amyloid present diffusely in glomerulus

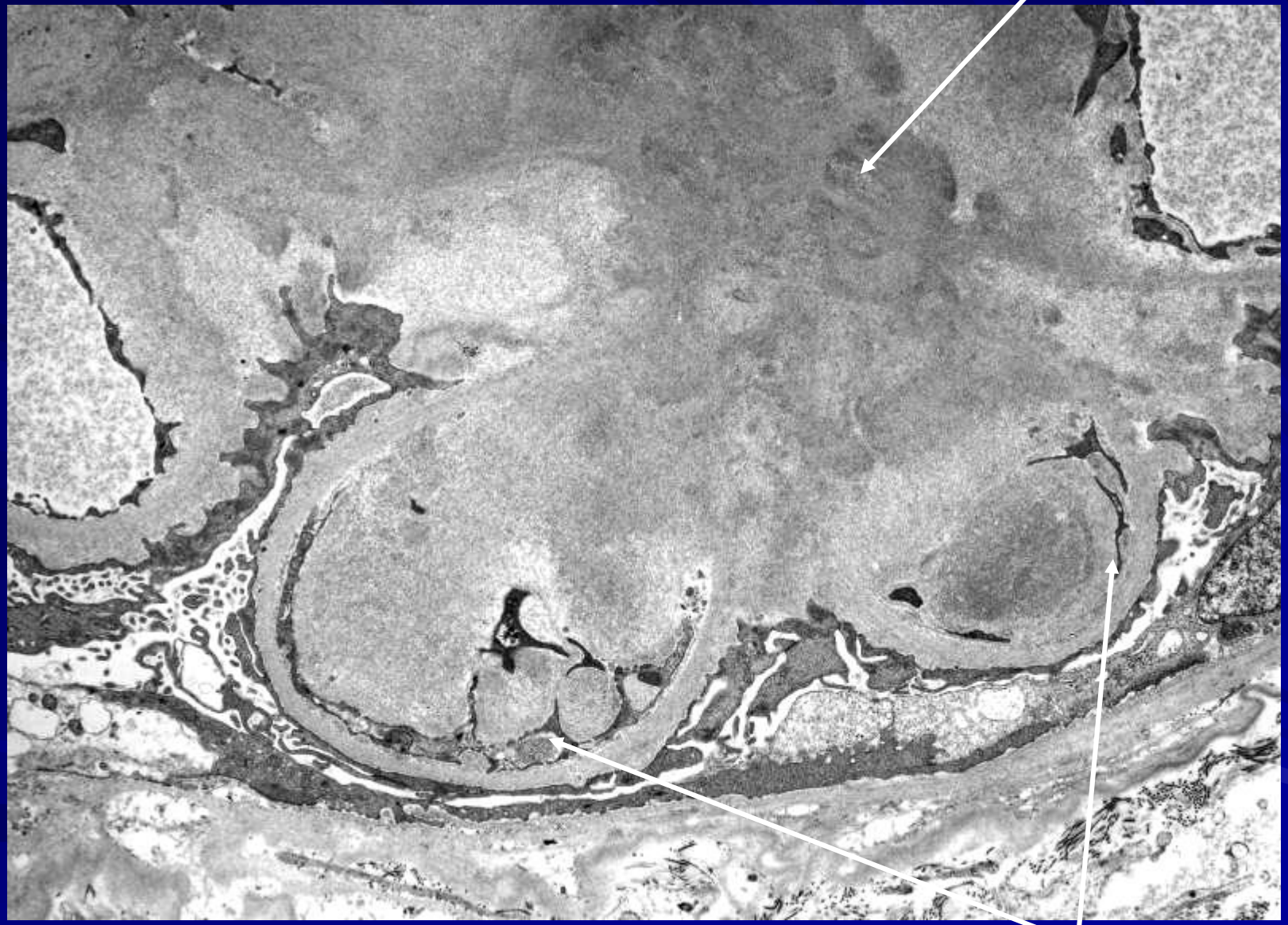


Almost end stage glomerulus



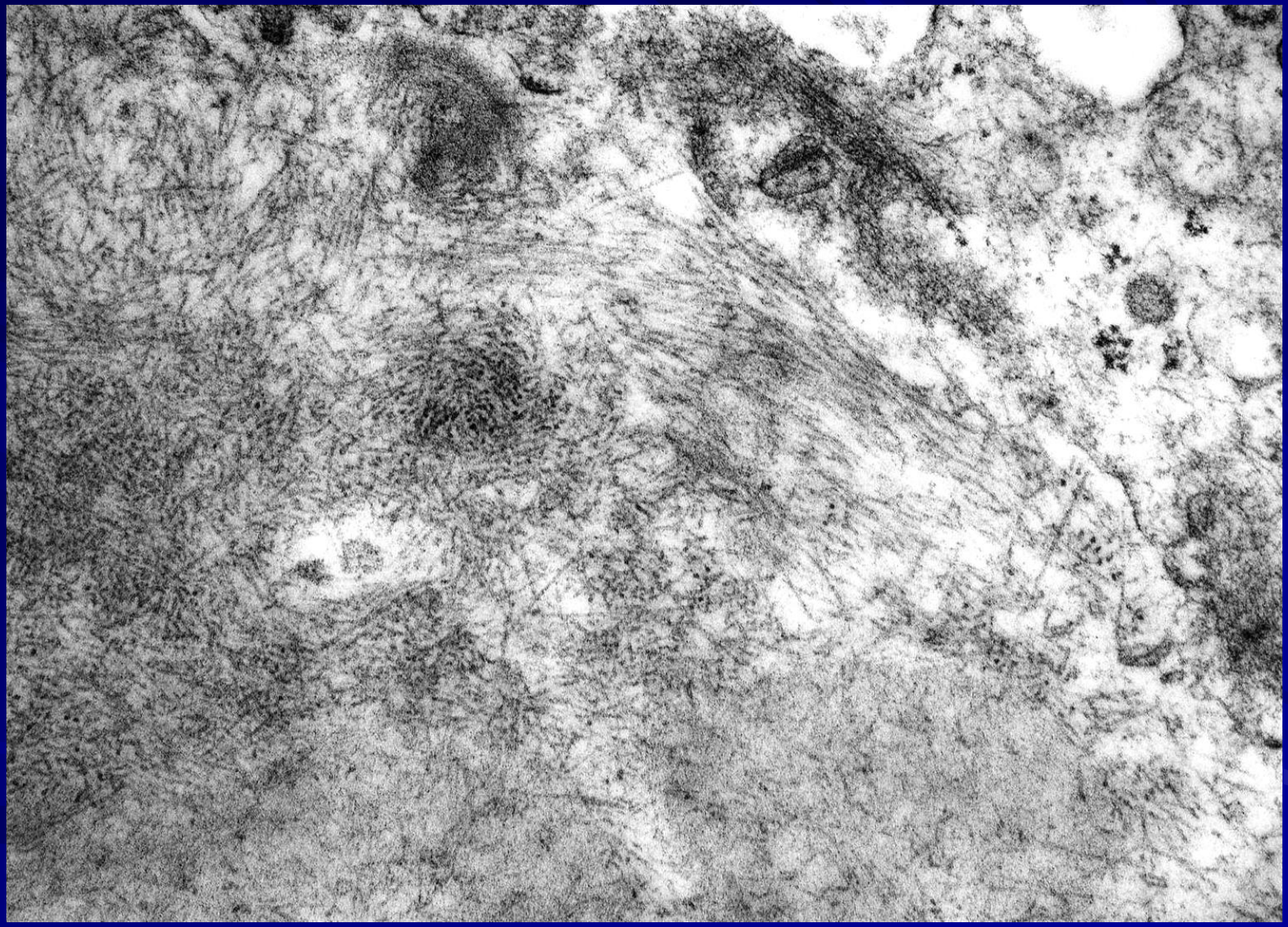
Predominantly mesangial amyloid

Note: variable density of amyloid deposition



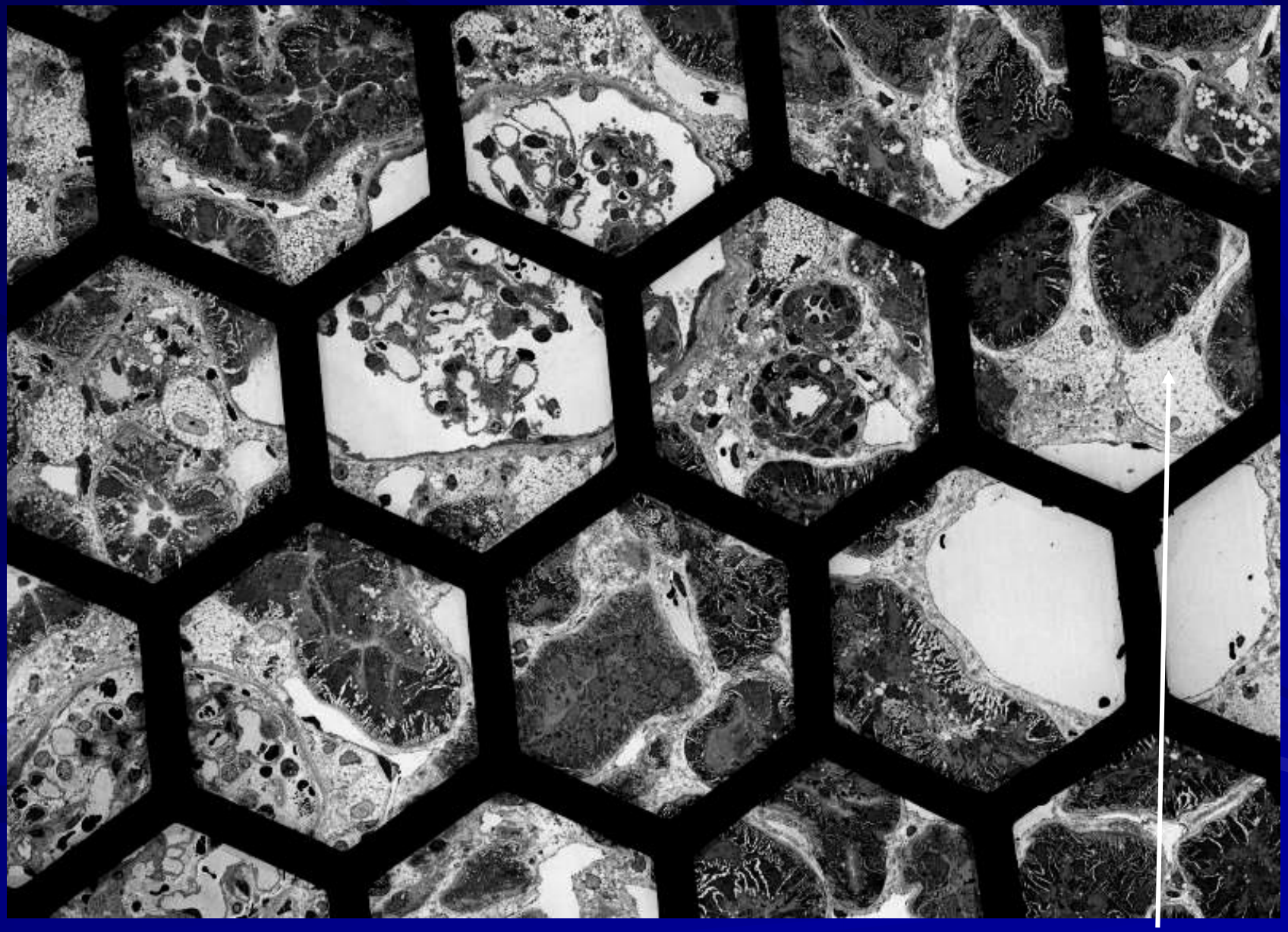
Extensive mesangial deposition of amyloid compromising capillary lumens

Amyloid fibrils



Amyloid fibrils are 7 – 10nm diameter, straight and extracellular

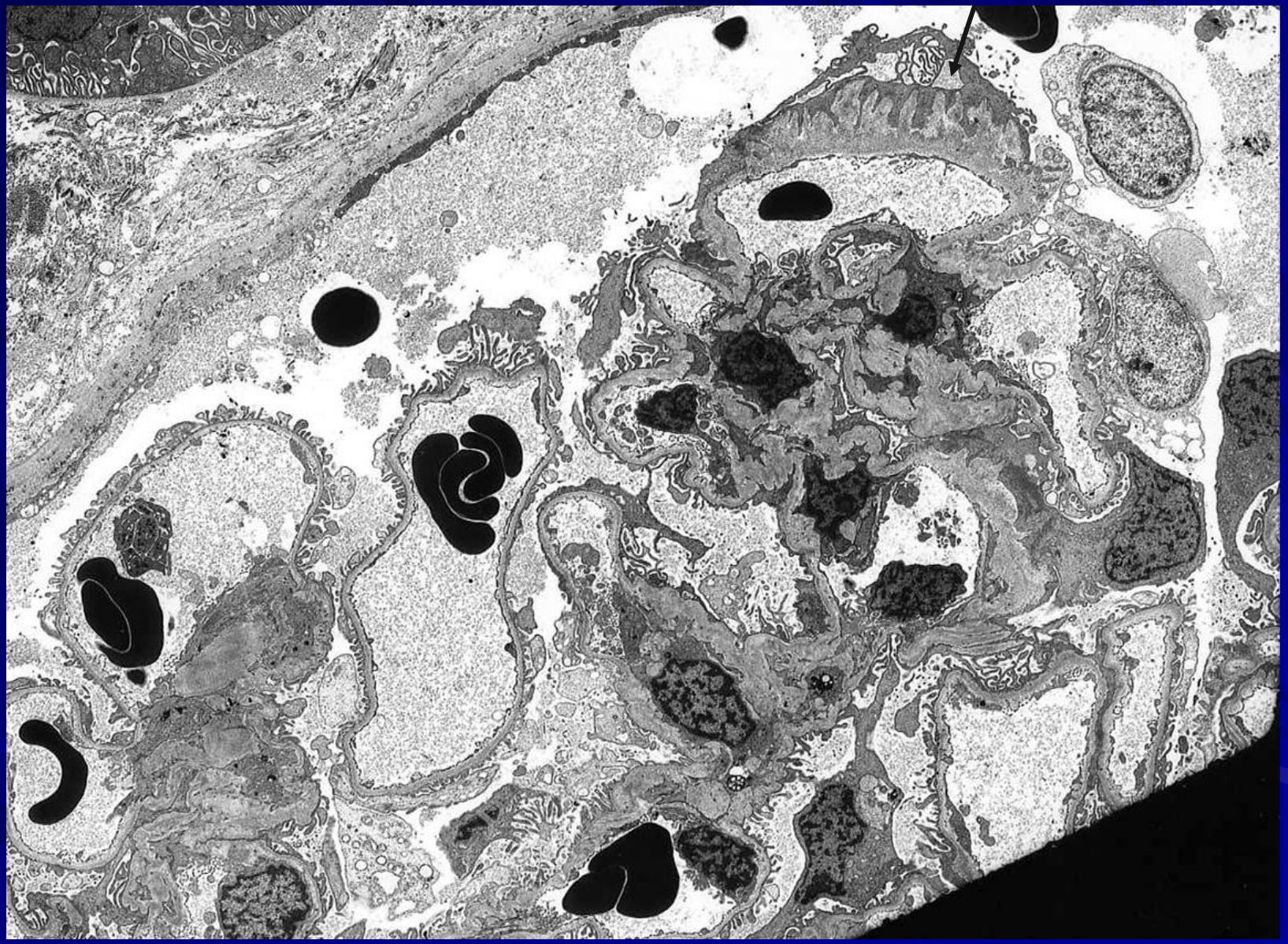
Amyloid in patient with Crohn's disease



Mild disease, but with evidence of chronic proteinuria

Interstitial foam cells

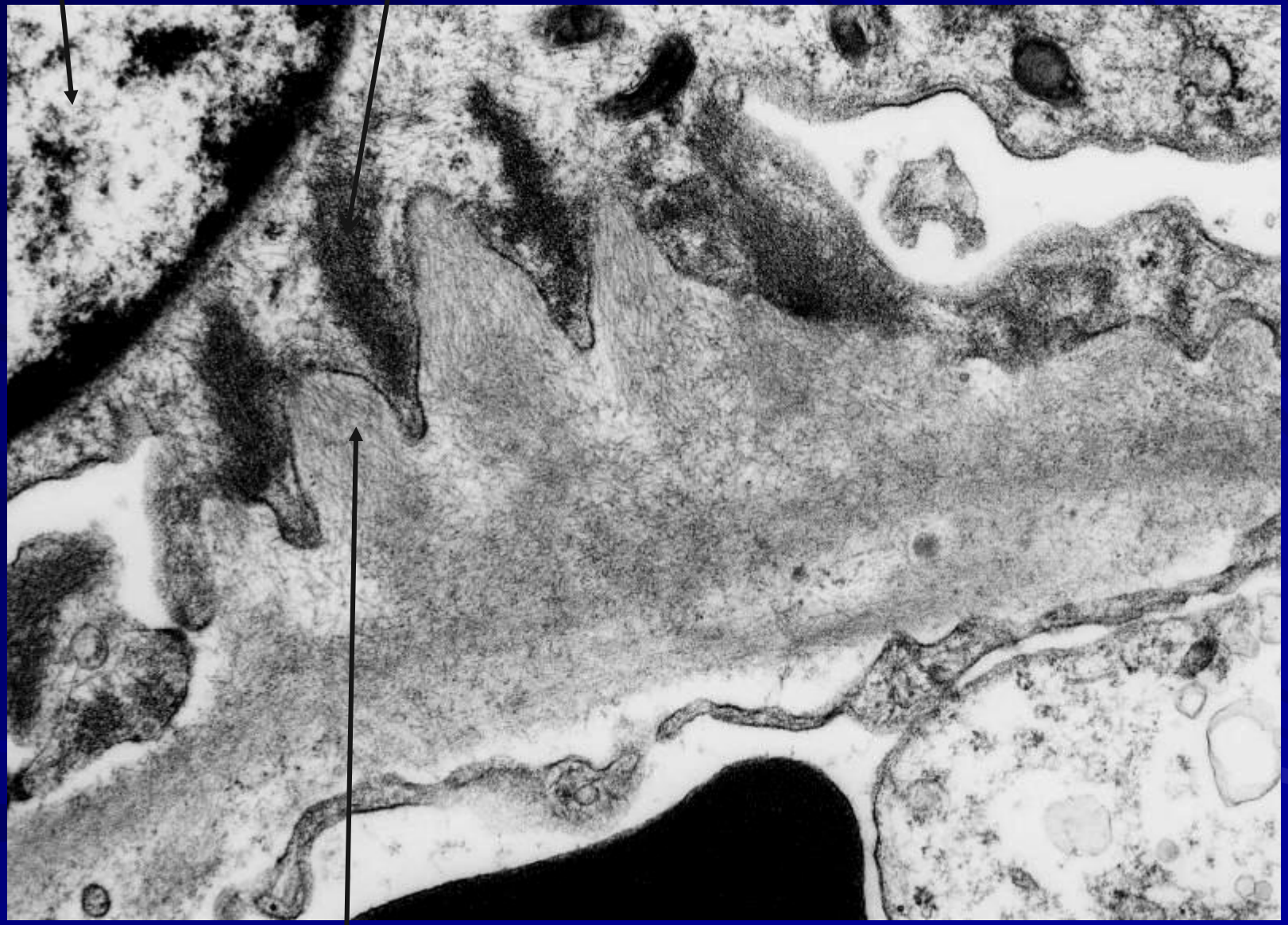
‘Spicular’ on MST stain, amyloid



Podocyte nucleus

Condensed filamentous actin

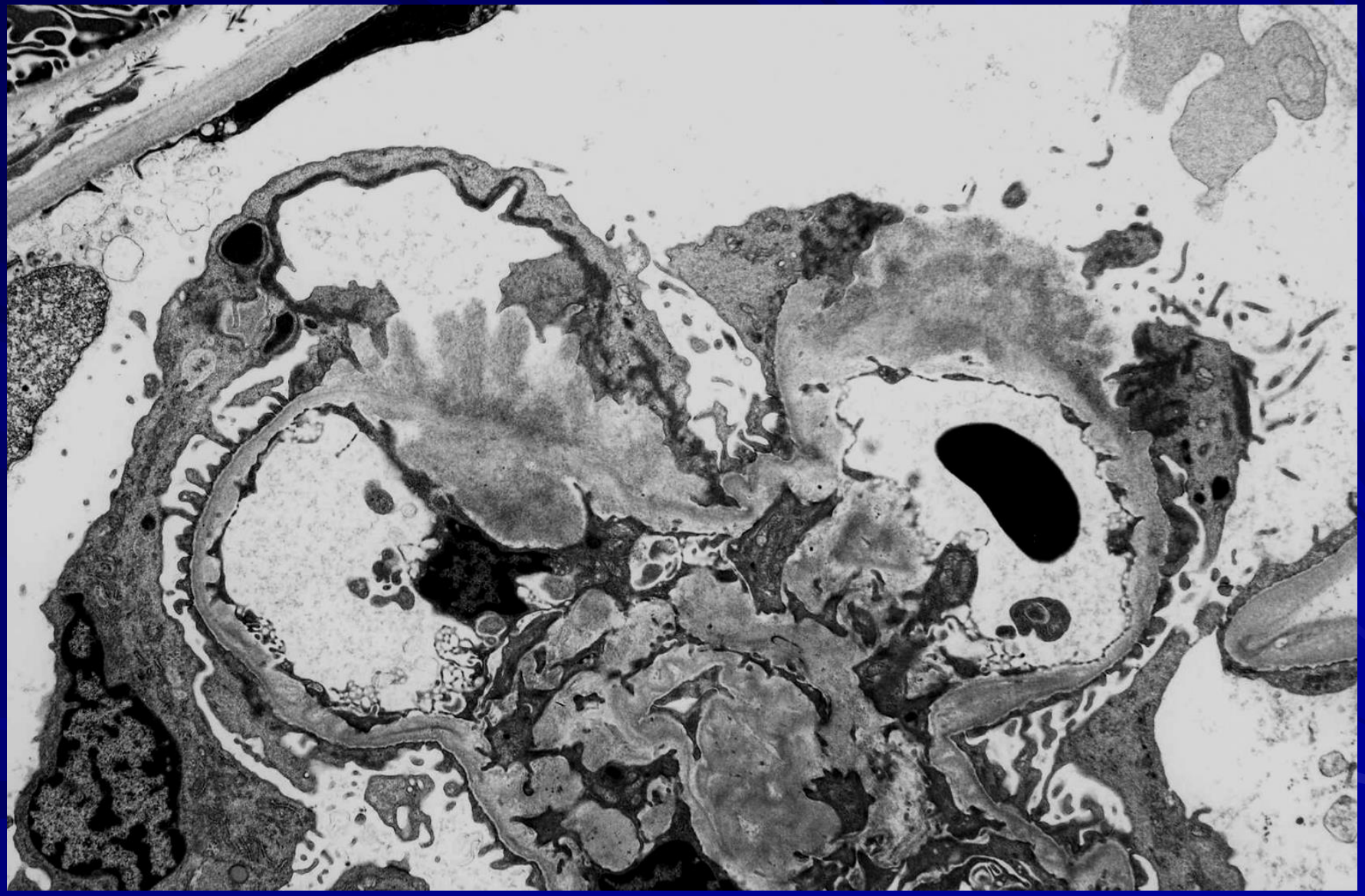
Stage 1



Subepithelial spicular amyloid

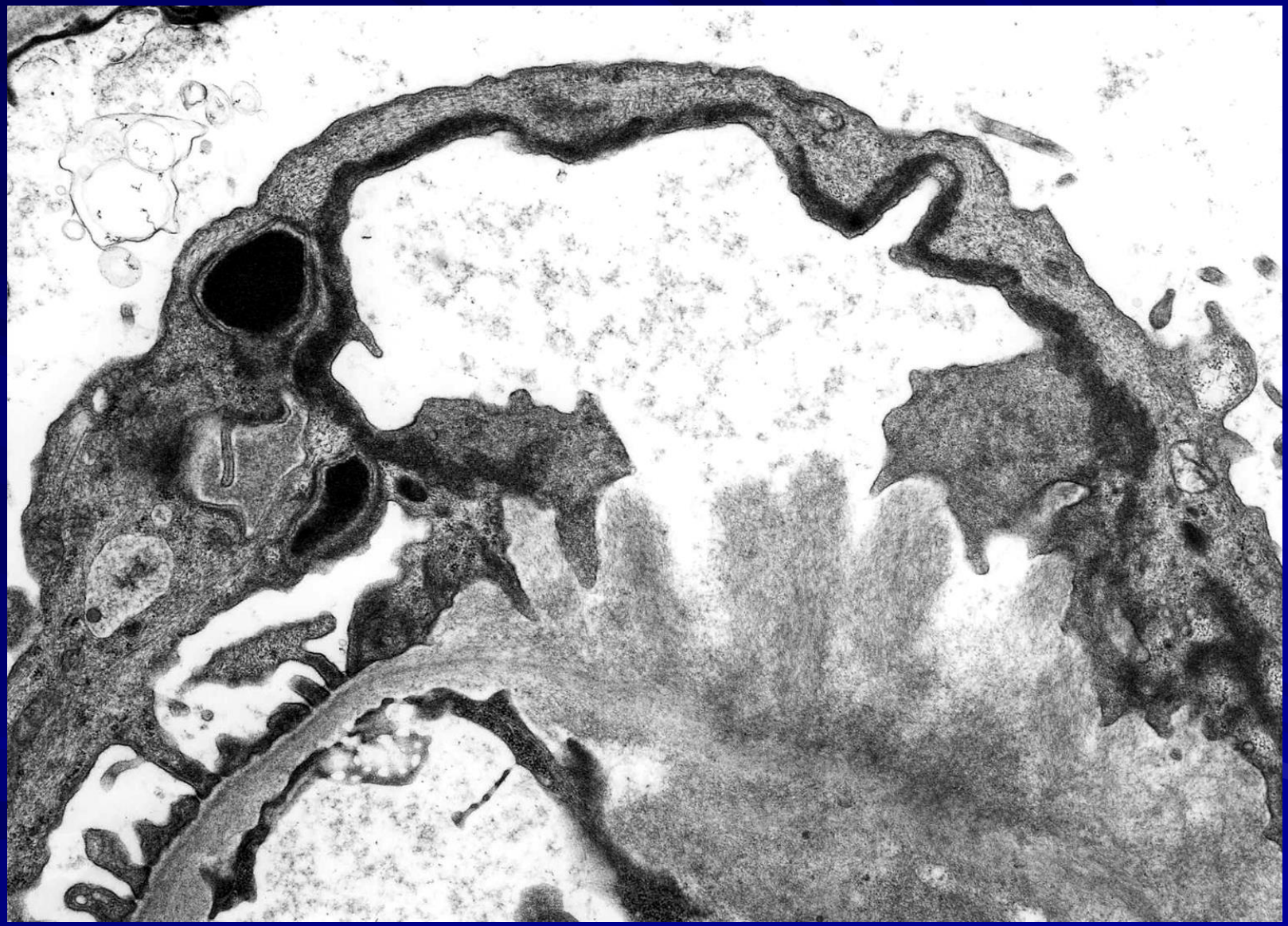
Stage 2

Stage 3



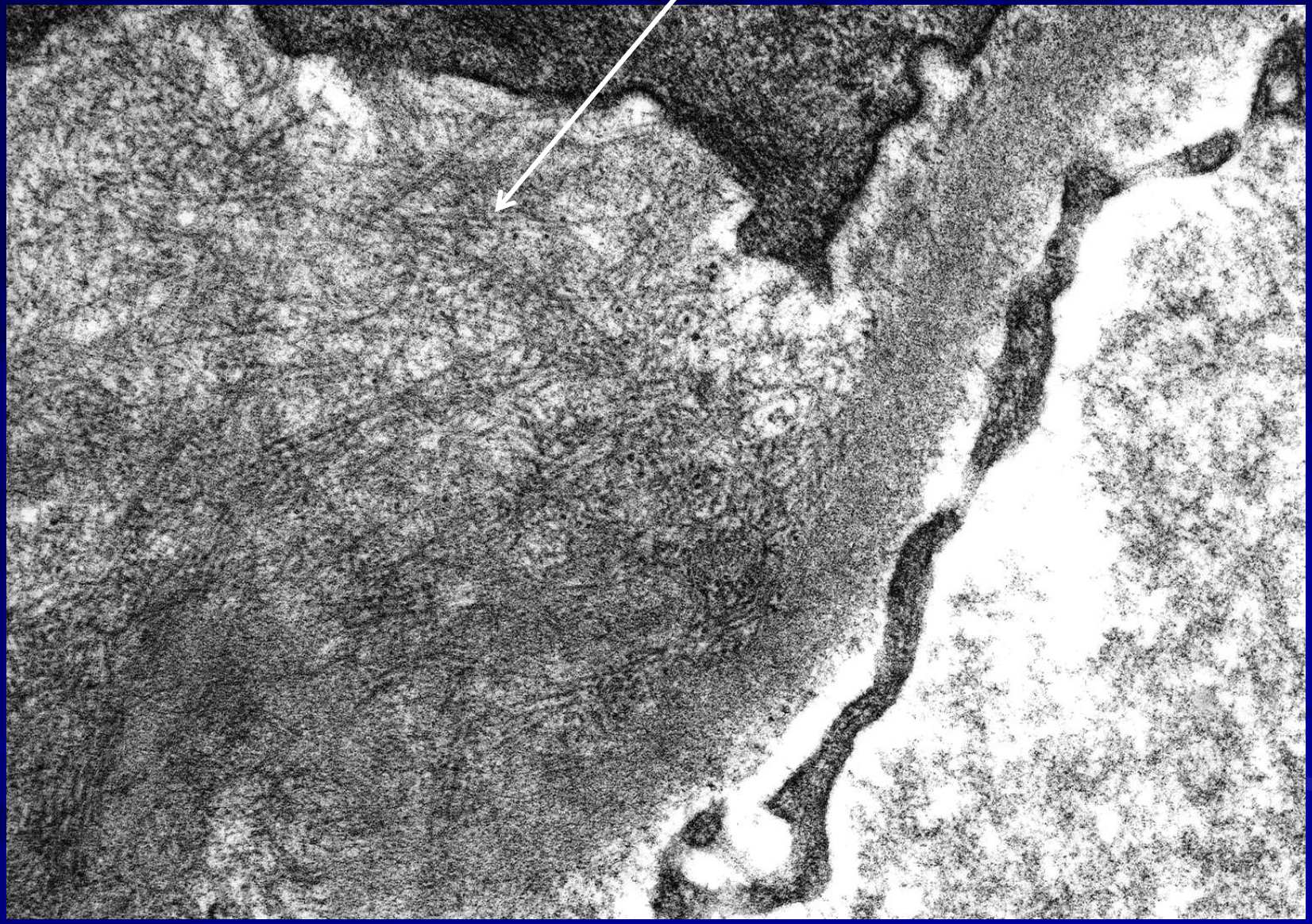
Subepithelial amyloid, at later stages to previous slides

Higher magnification of previous slide at stage 2

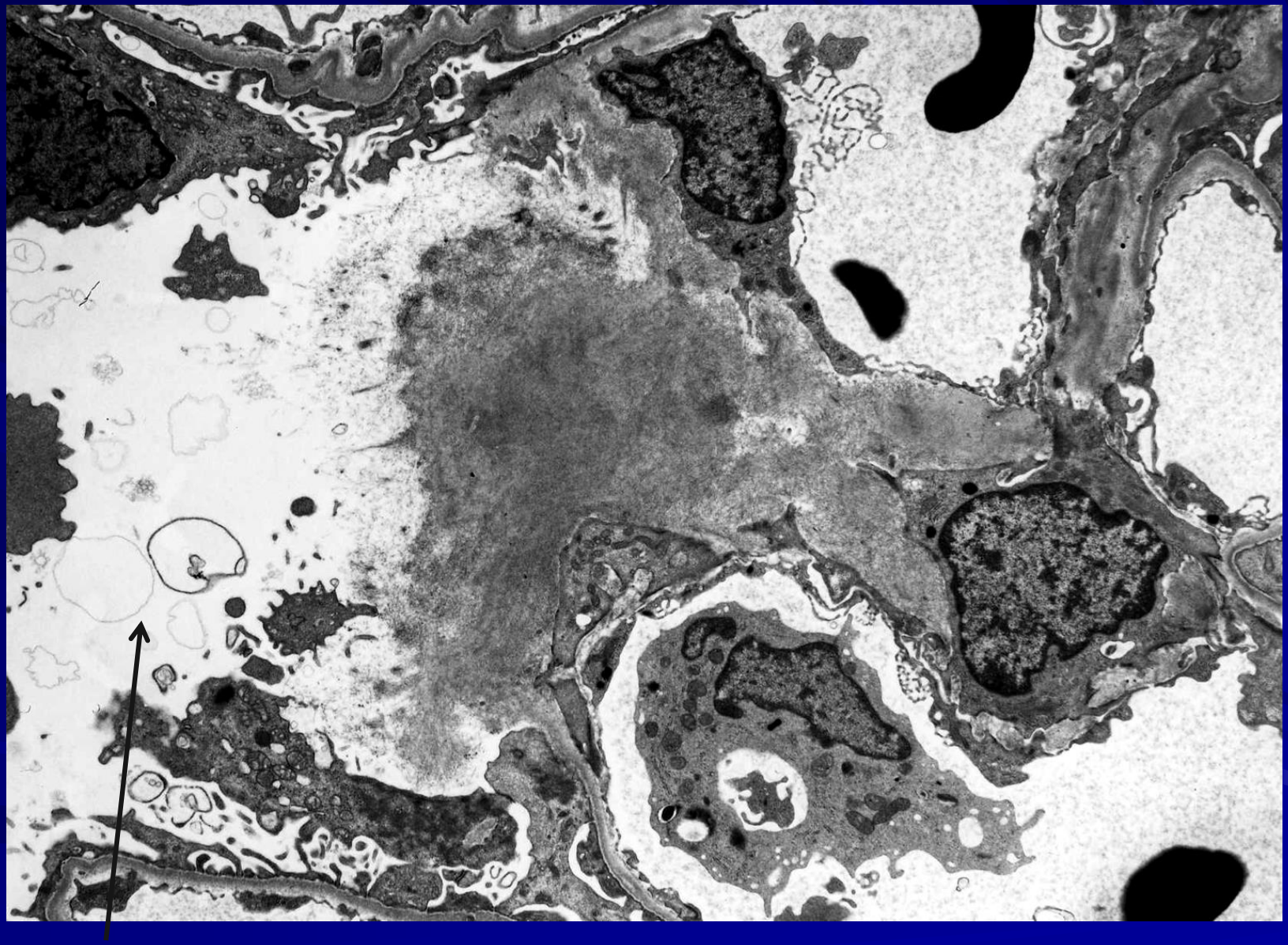


Deposited amyloid fibrils unable to bind to laminin

Higher magnification of subepithelial amyloid fibrils

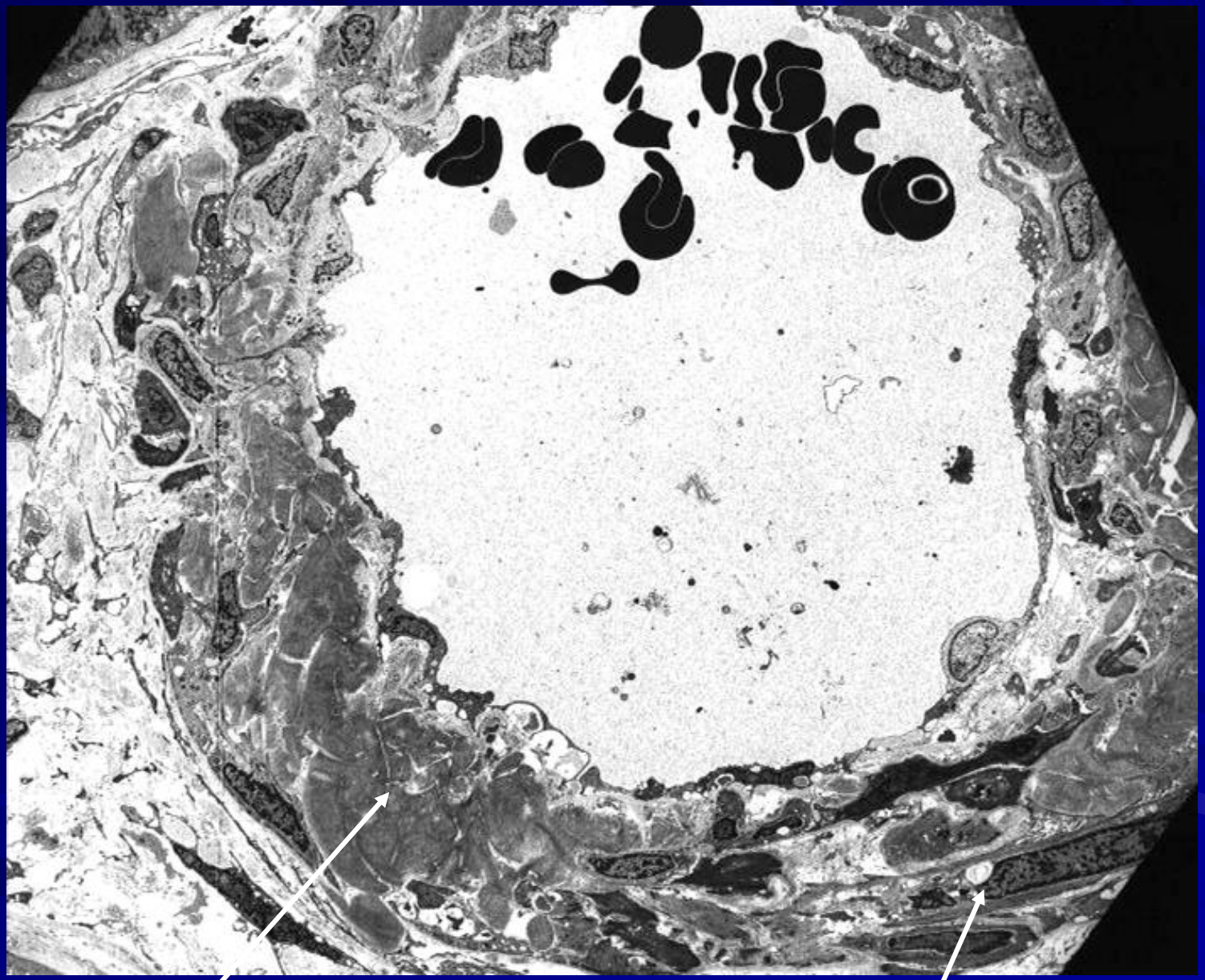


Subepithelial/mesangial amyloid resulting in podocyte loss



Urine space

Stage 3 – visible on tol blue


Perivascular amyloid
Vascular smooth muscle cells

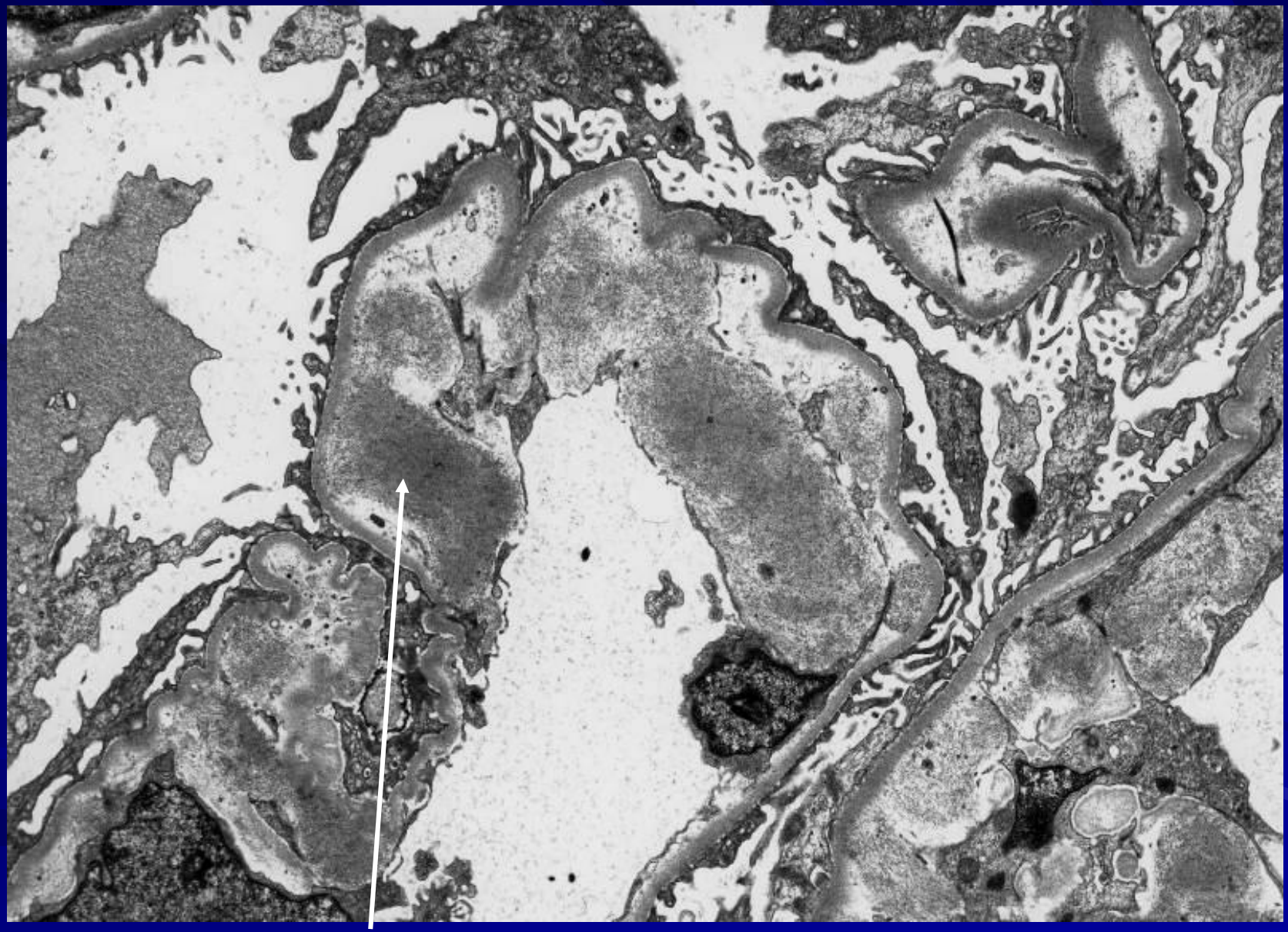
Systemic amyloid can deposit in other locations less commonly, such as..

- Subendothelially
- Renal interstitium
- On tubular basement membrane
- In tubular lumen

Localised amyloid (amyloidoma)

Closely associated with an aggregate of plasma cells in interstitium

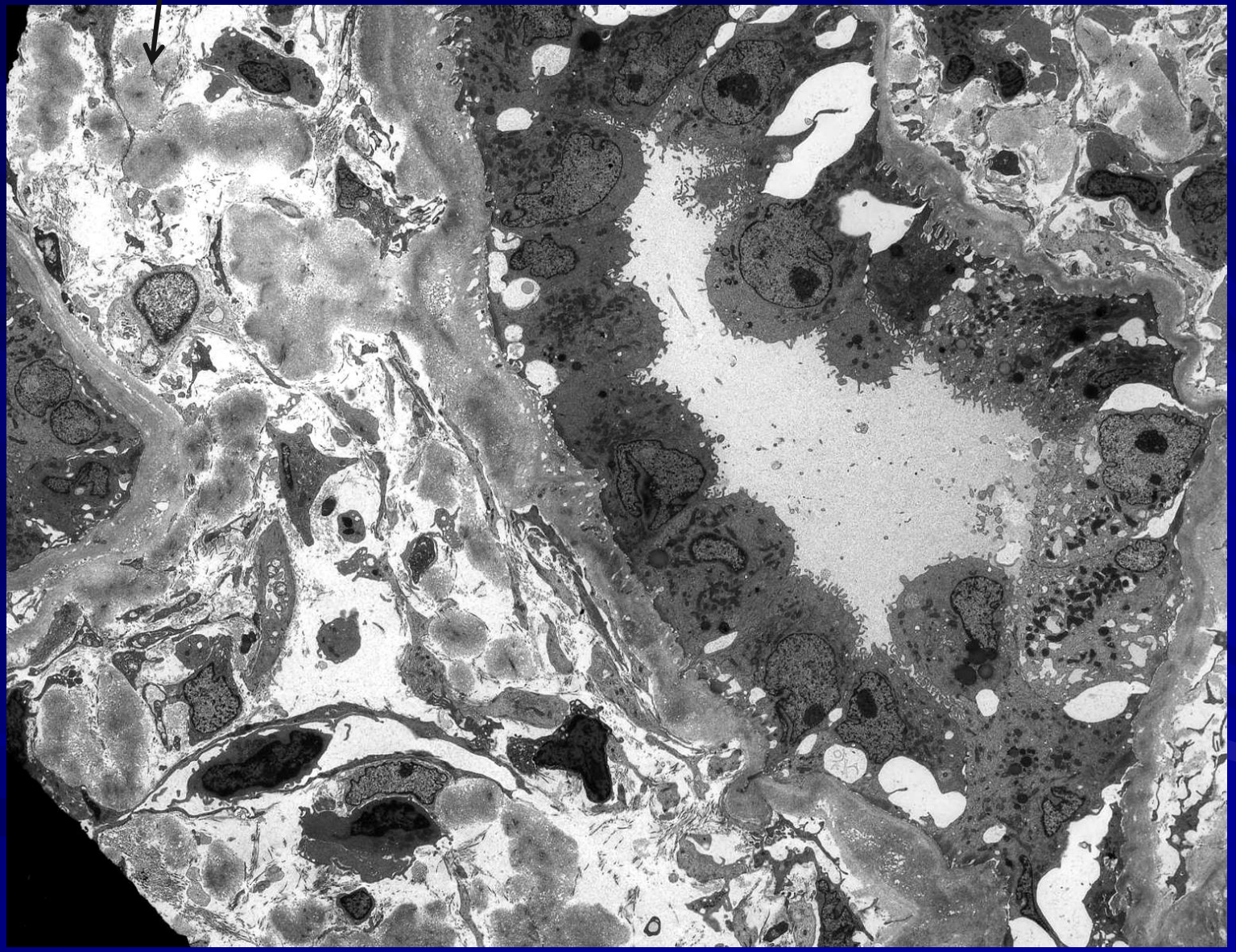
Patient with Porphyria



Subendothelial amyloid

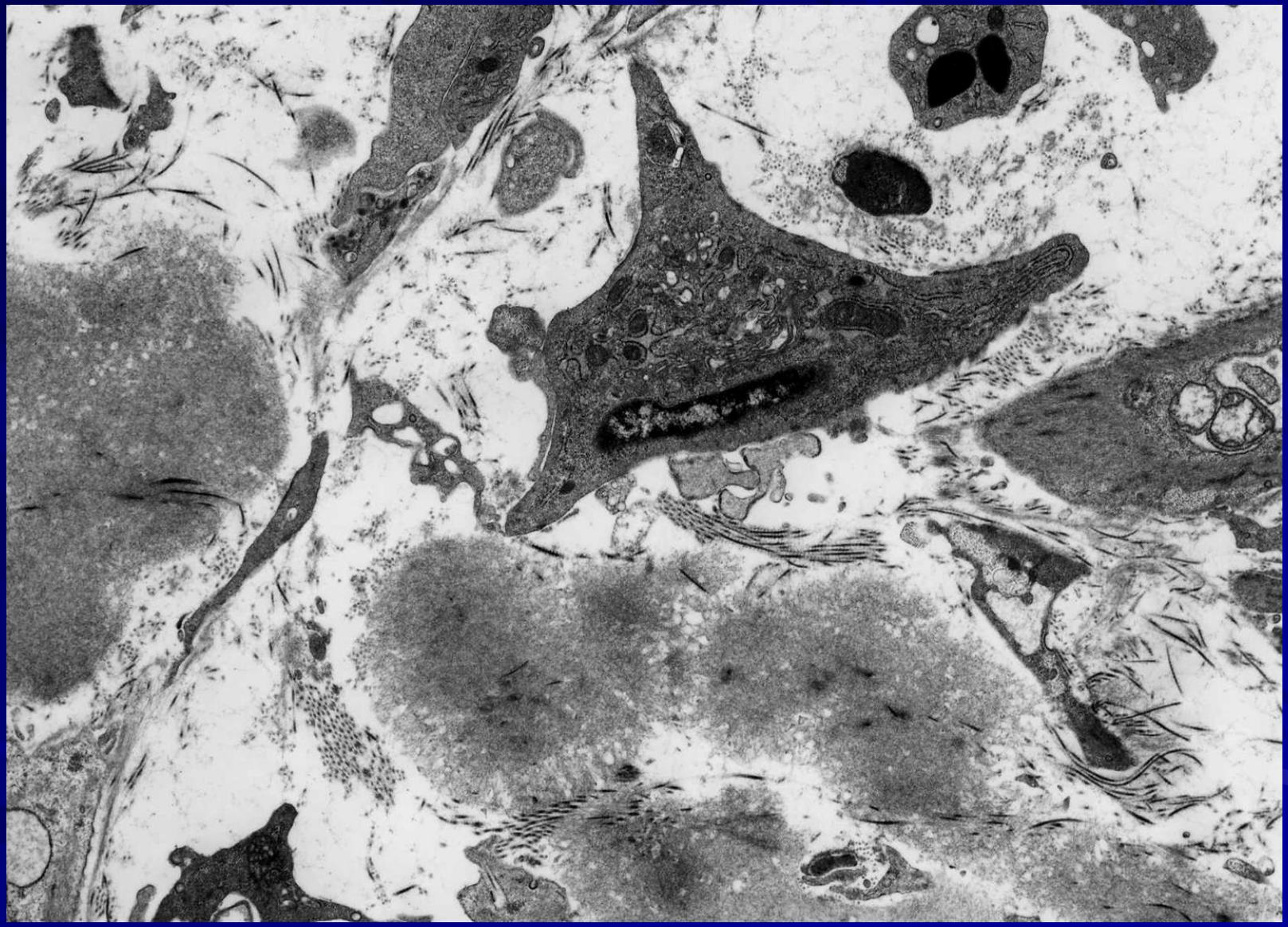
Amyloid in interstitium

Different case to previous slide

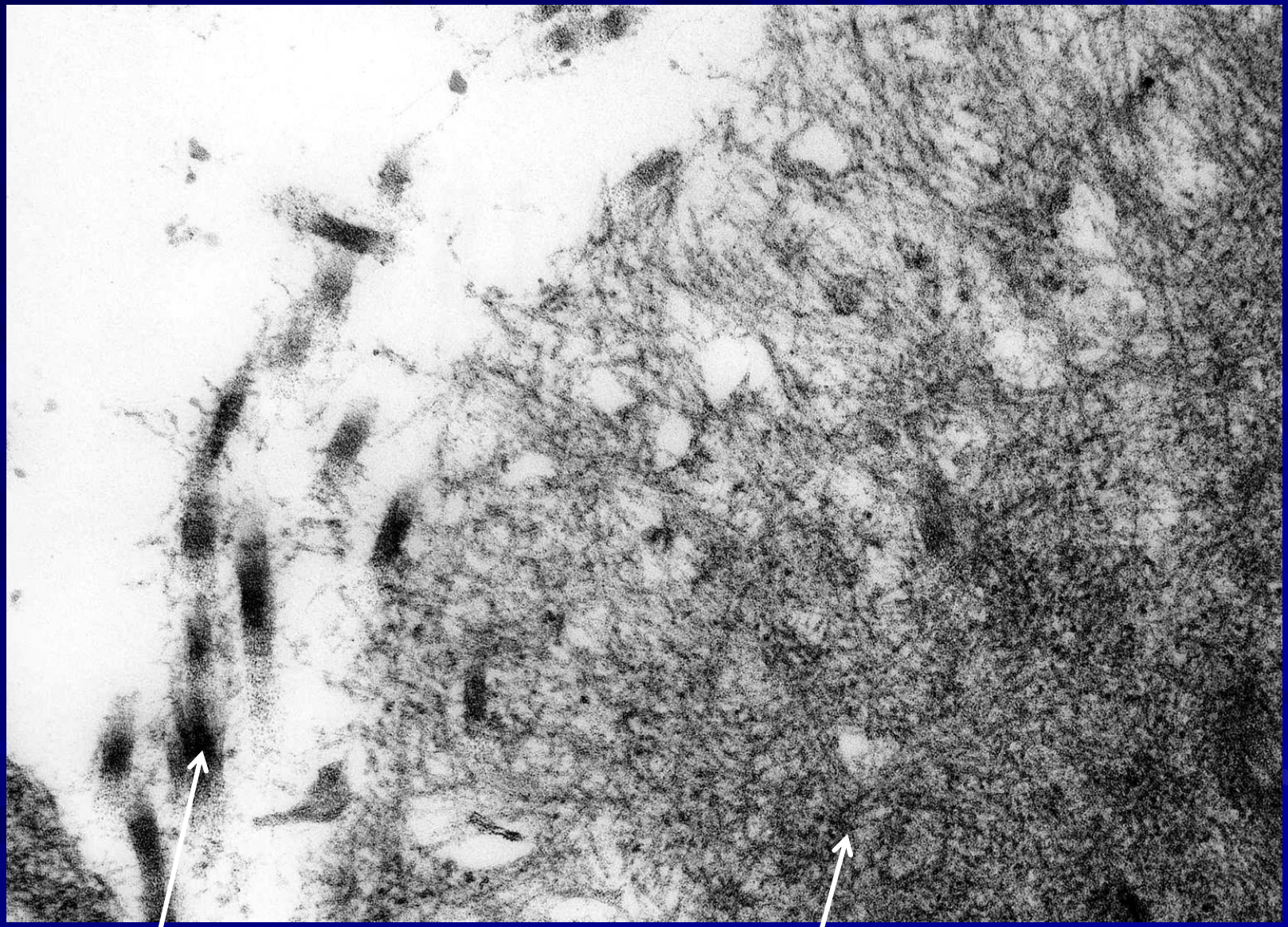


Renal interstitial amyloid

Higher magnification of previous slide

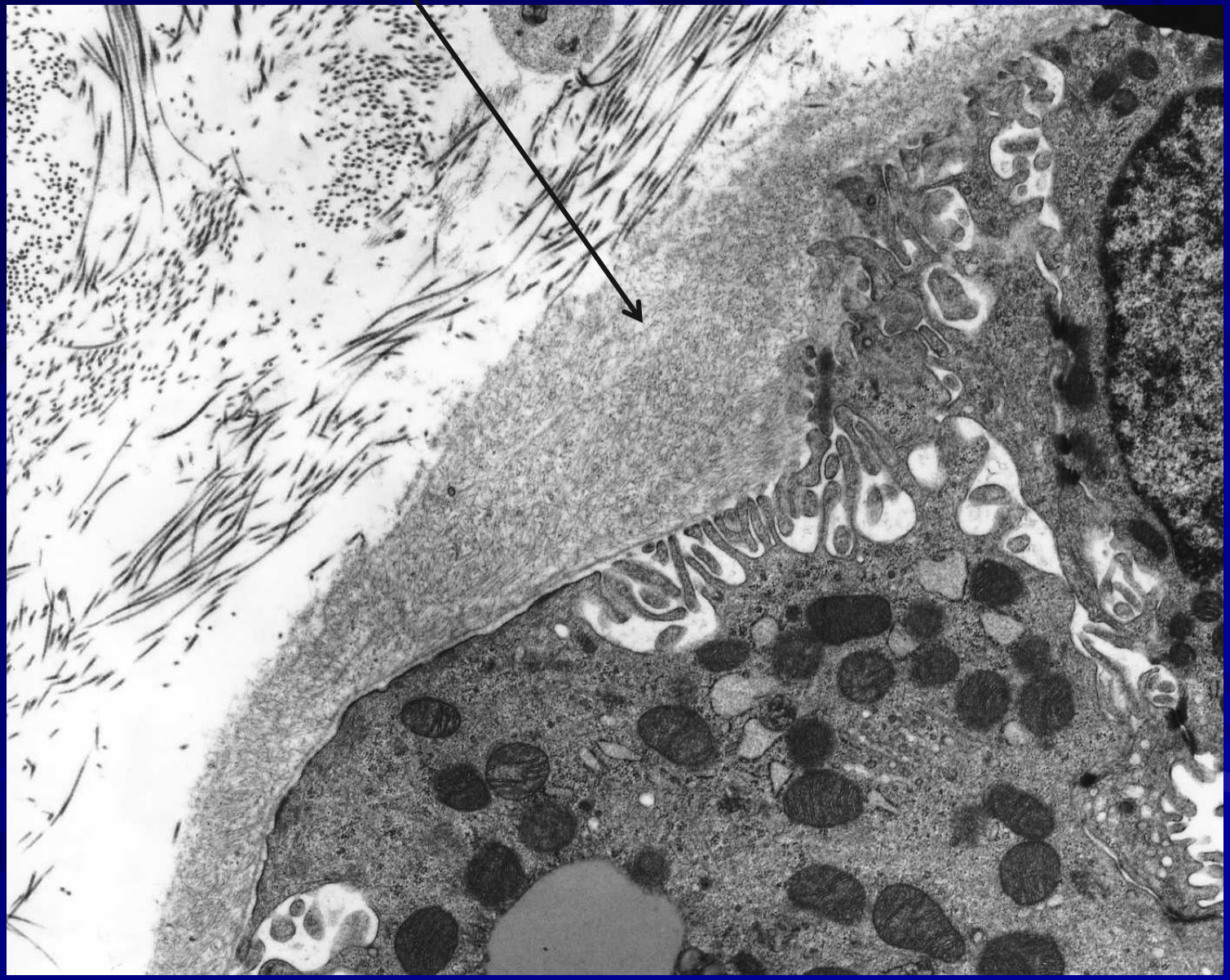


Amyloid in renal interstitium

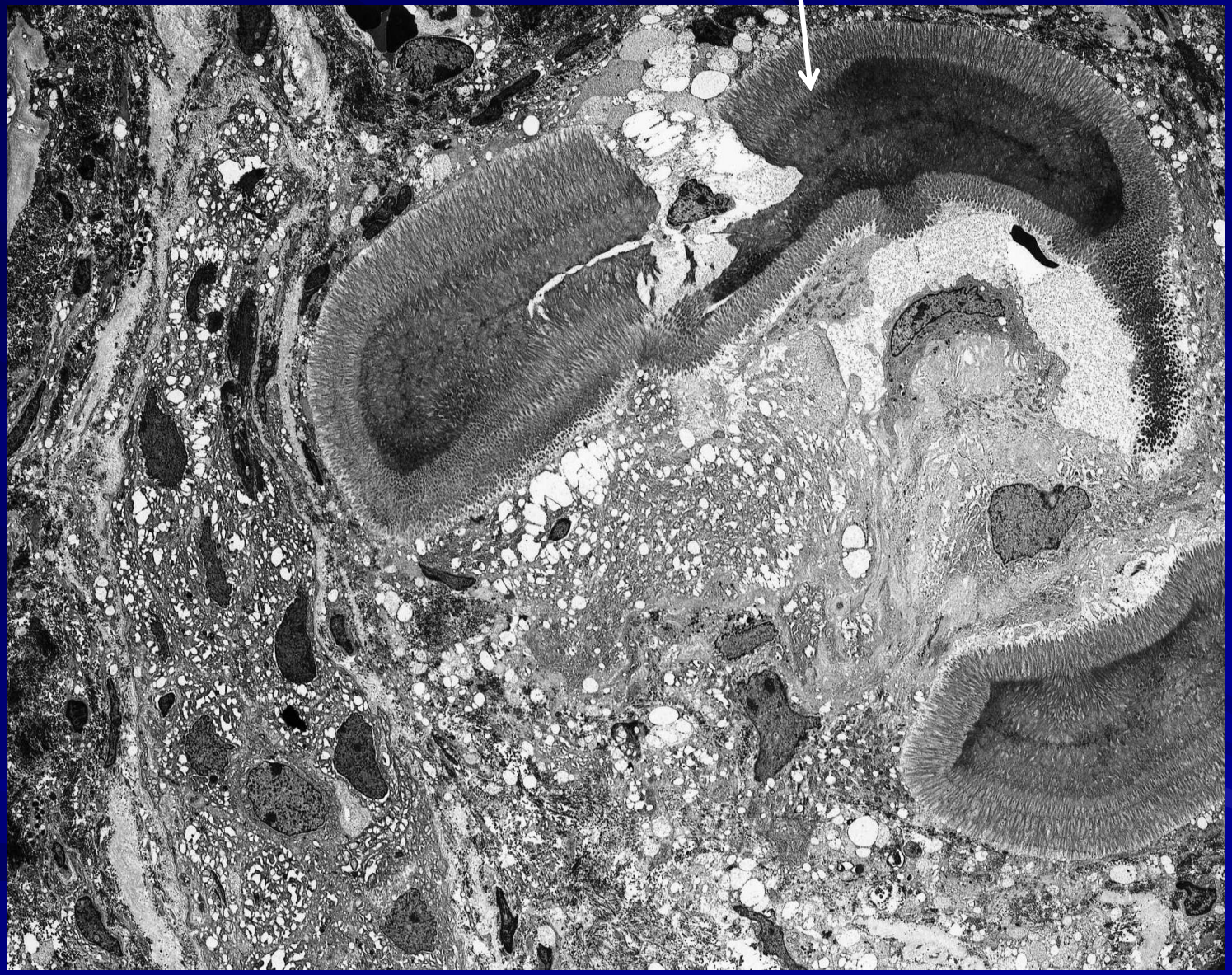


Amyloid on tubular basement membrane

Different case to previous slide

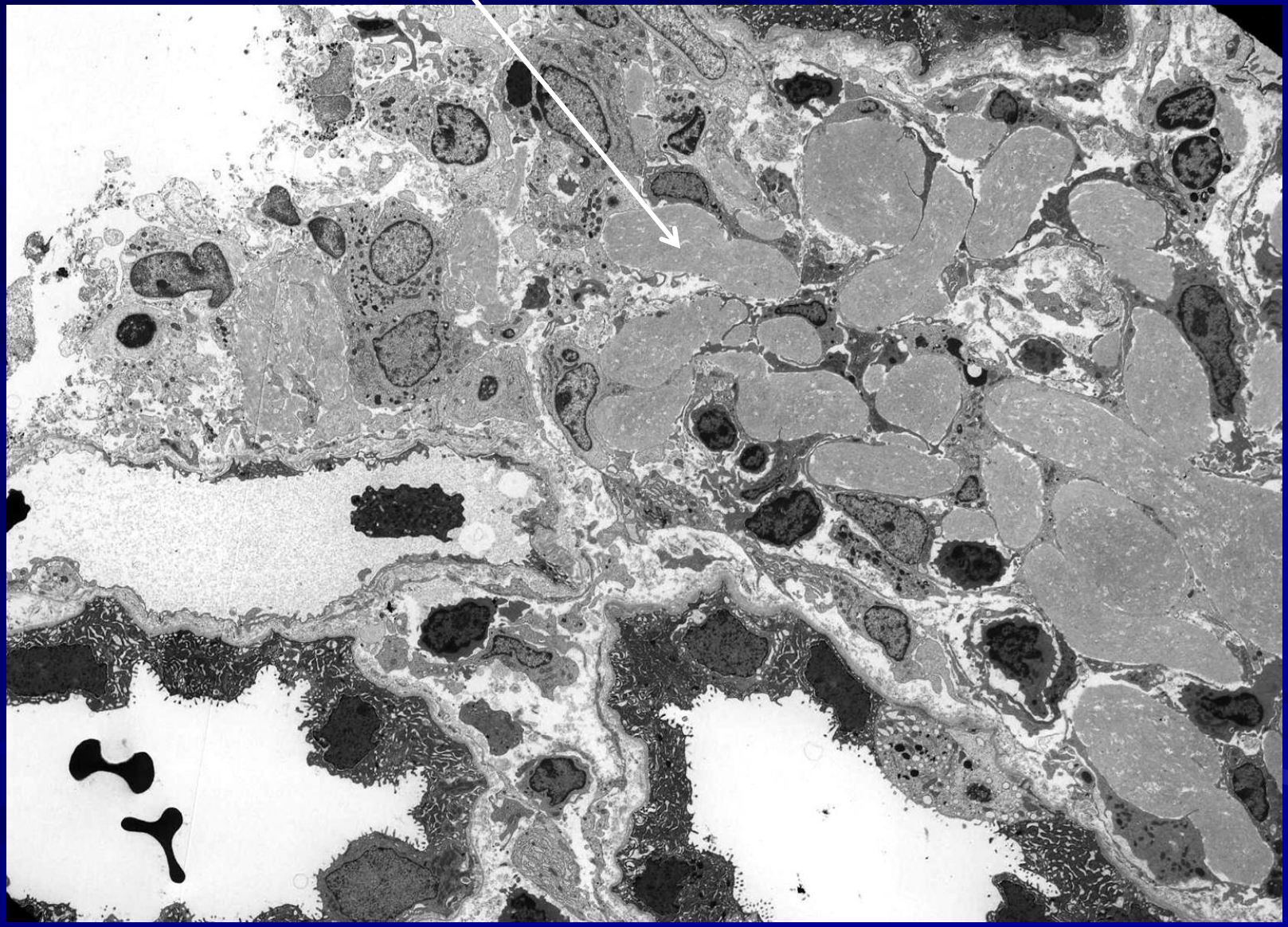


Laminated intratubular lumen, sirius red positive, cast in patient with myeloma



Different case to previous slide

Nodular/localised amyloid associated with aggregate of plasma cells in renal interstitium



Different case to previous slide

Capsular adhesion

Capsular adhesion

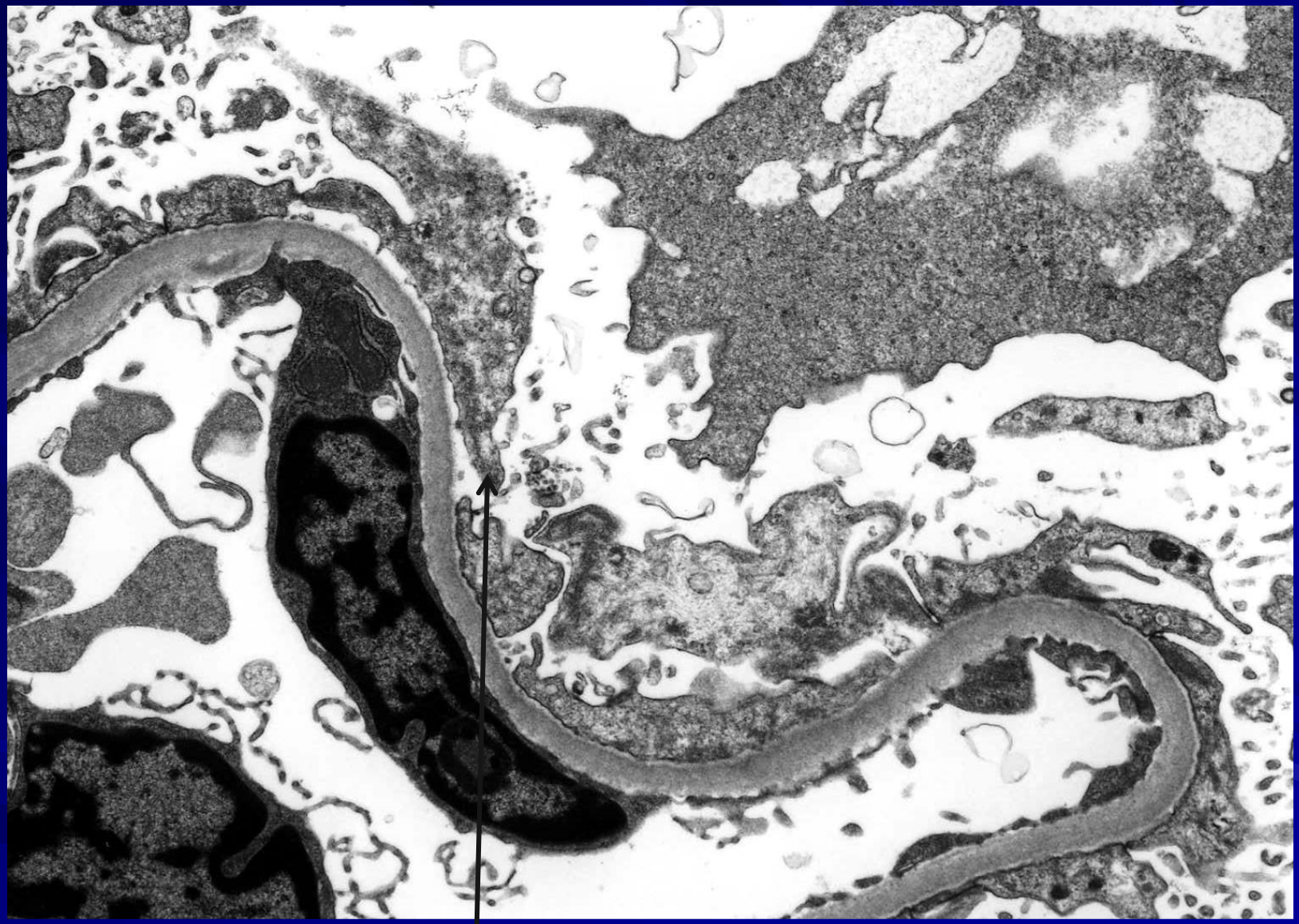
Mechanism

- Podocyte loss associated with severe proteinuria
- If it occurs adjacent to Bowman's capsule
- Apex of parietal epithelial cell adheres to naked GBM

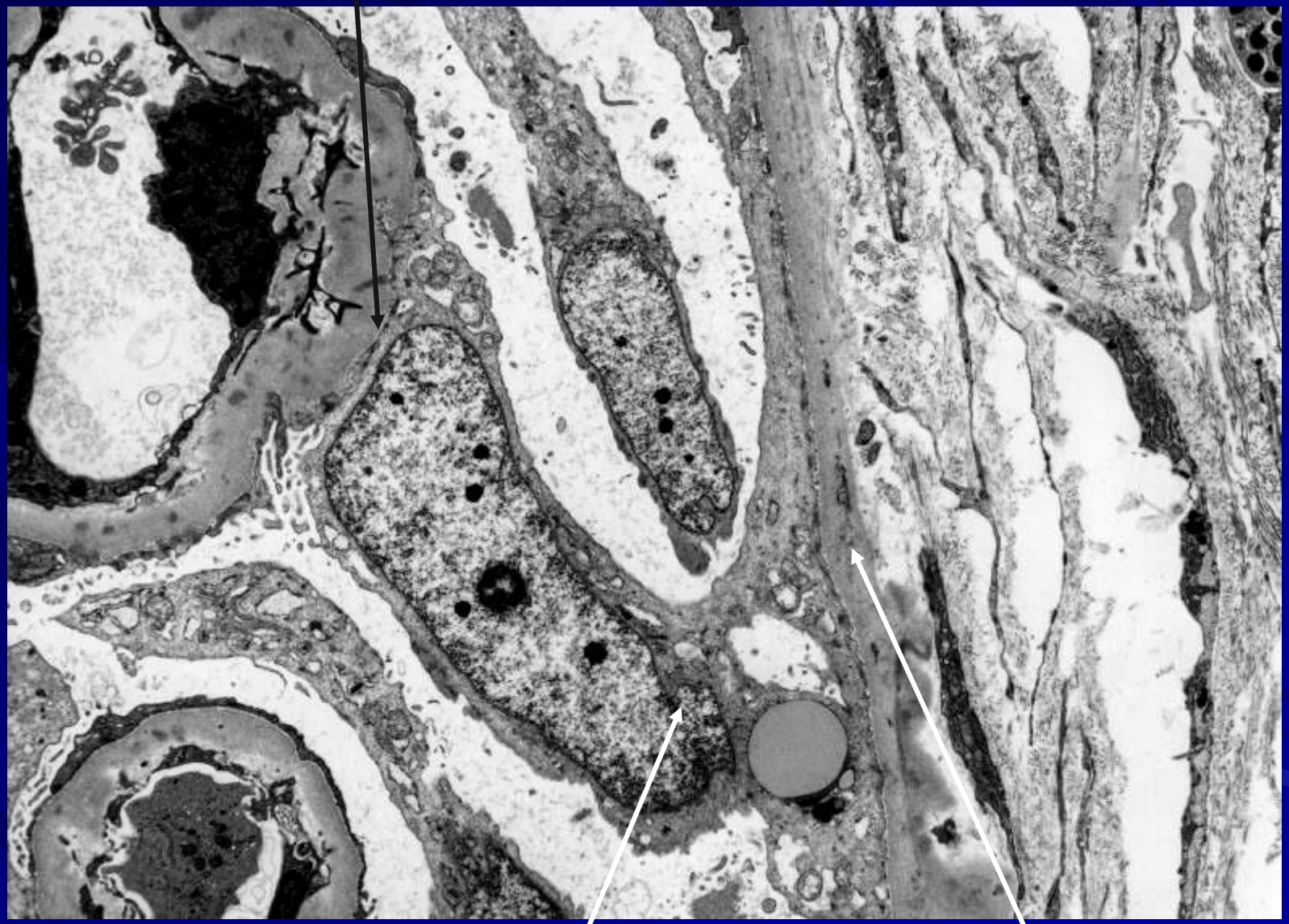
Significance

- Indicator of podocyte damage not caused by lack of adherence.

Capsular adhesion – first stage



Incipient epithelial break – early podocyte degeneration

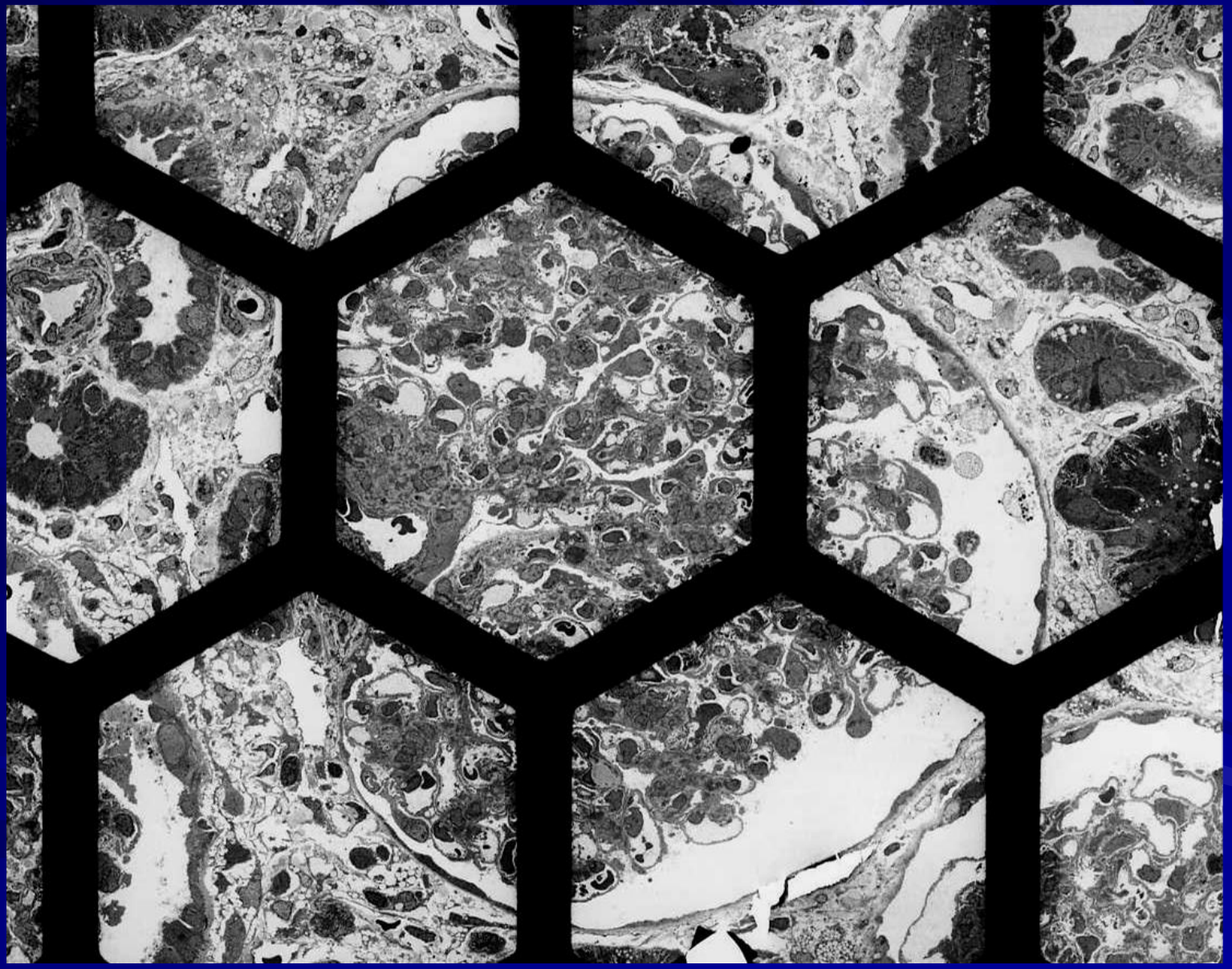

Area of previously denuded GBM
Capsular adhesion – parietal epithelial cell
Bowman's capsule

Congenital nephrotic syndrome

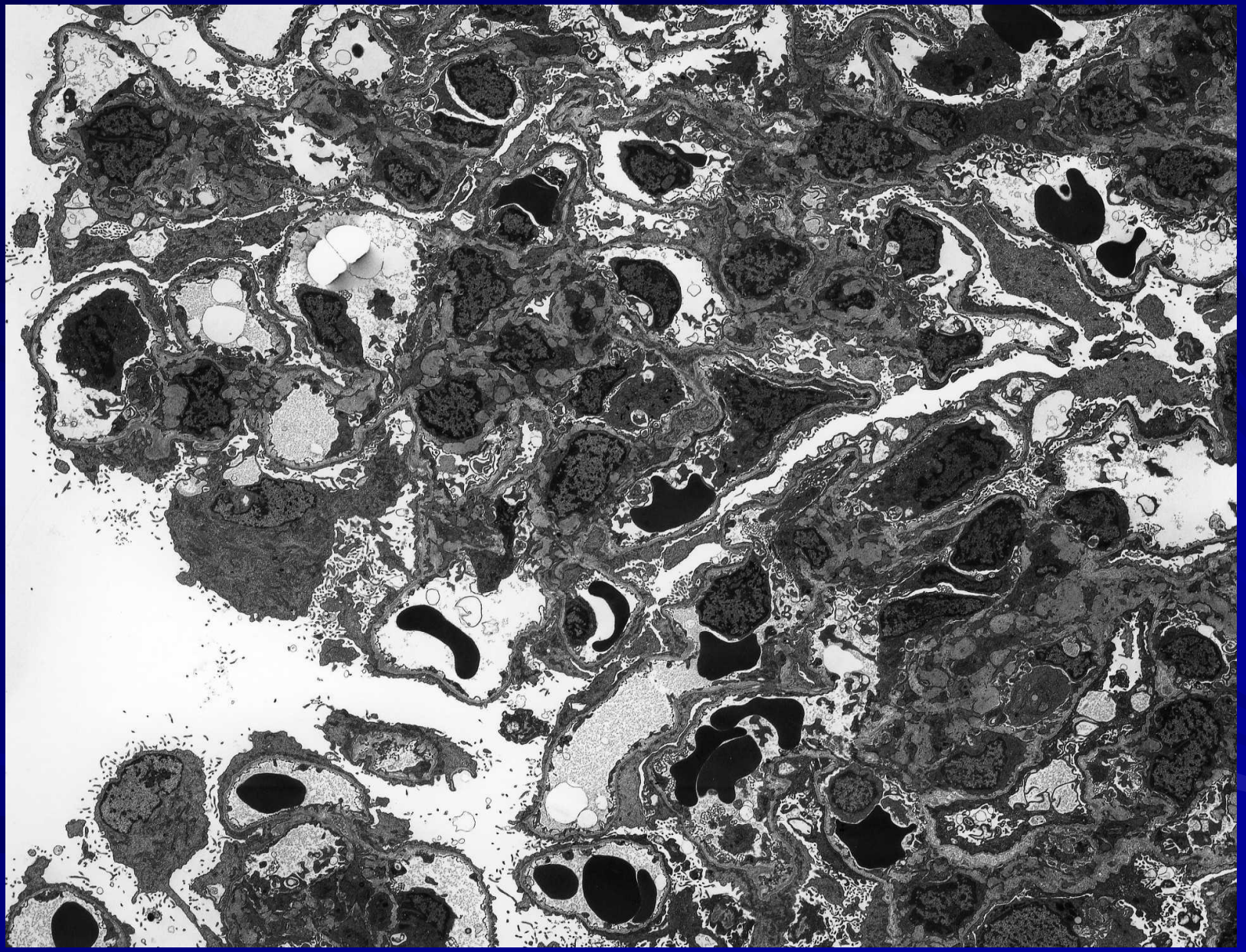
Congenital nephrotic syndrome

- Nephrin gene defect
- Autosomal recessively inherited
- No slit diaphragm seen between podocyte foot processes in most affected individuals
- Survival is rare over the age of 4 – often succumb to Gram negative septicaemia due to hypocomplentaemia
- Transplant only treatment option currently

Congenital nephrotic syndrome

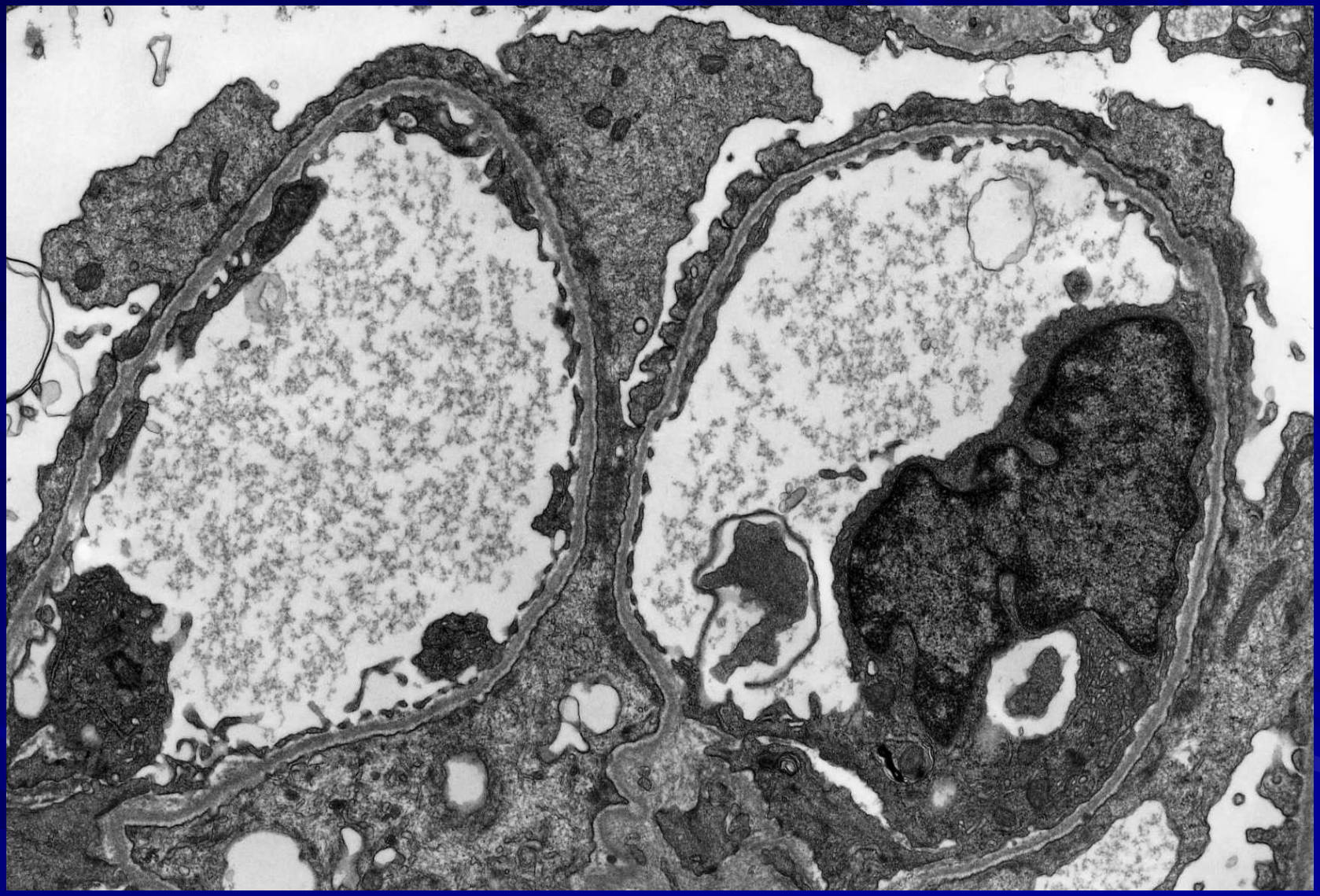


10 month old child – initially thought to have heart failure



100% foot process effacement

Congenital nephrotic syndrome



100% foot process effacement

GBM appears thin due to age of patient – 10 months

Time for a quick break?

‘The mind cannot absorb what the backside cannot endure’

Prince Philip ,The Duke of Edinburgh.