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Pathology of AKI

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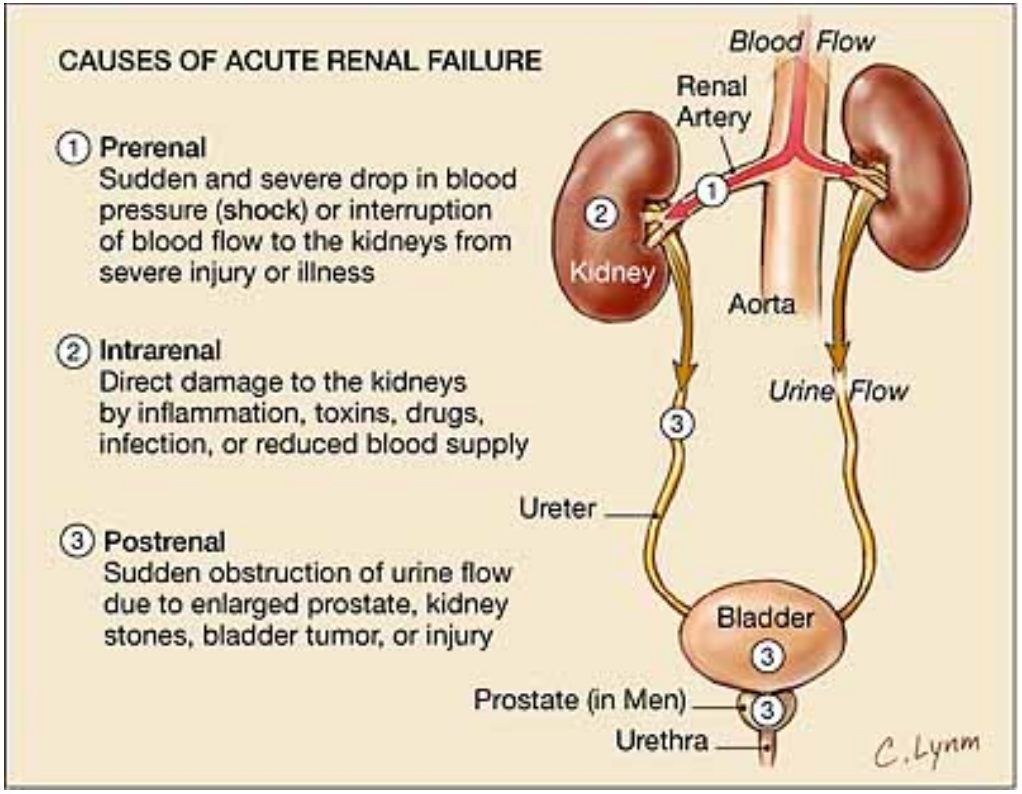
Remember this….

- AKI ≠ Acute tubular injury
- Not all AKI is caused by sepsis or volume depletion
- AKI is caused by an underlying process that must be diagnosed

All kidney disease can be classified according to this scheme



50% Pre-renal

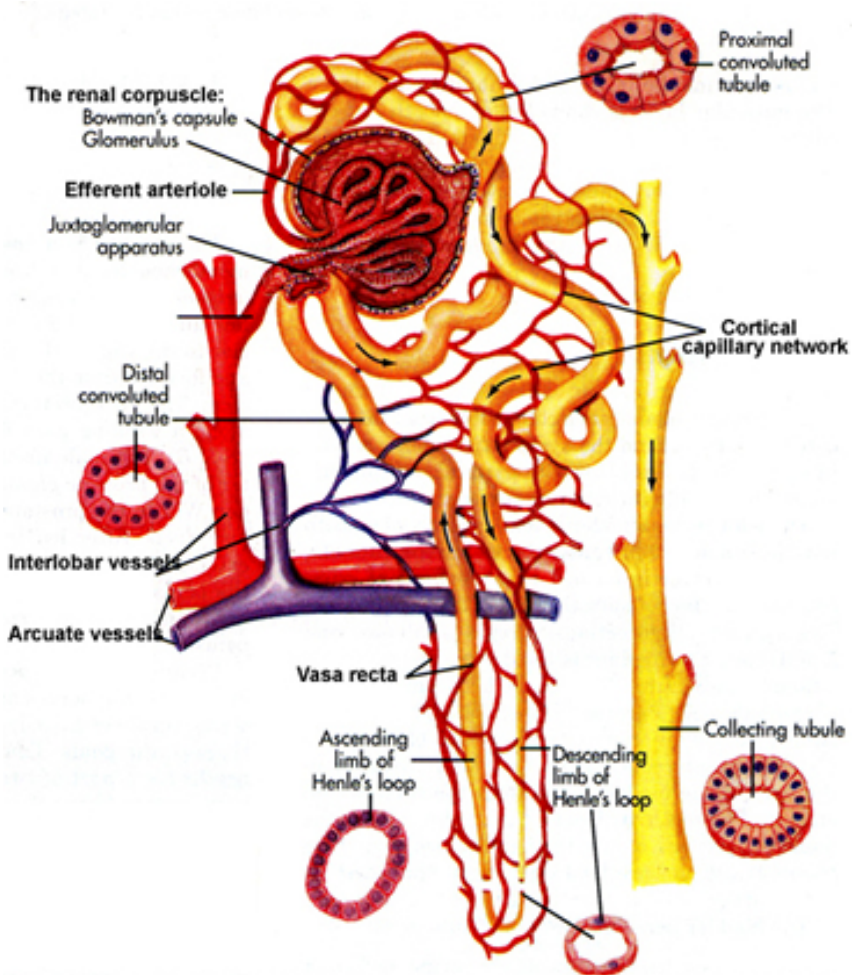
35% Intrinsic

15% Post-renal

Acute kidney injury means a sudden drop in GFR

Parenchymal or intrinsic causes

3 Major kidney compartments :
Glomeruli
Tubules
Blood vessels



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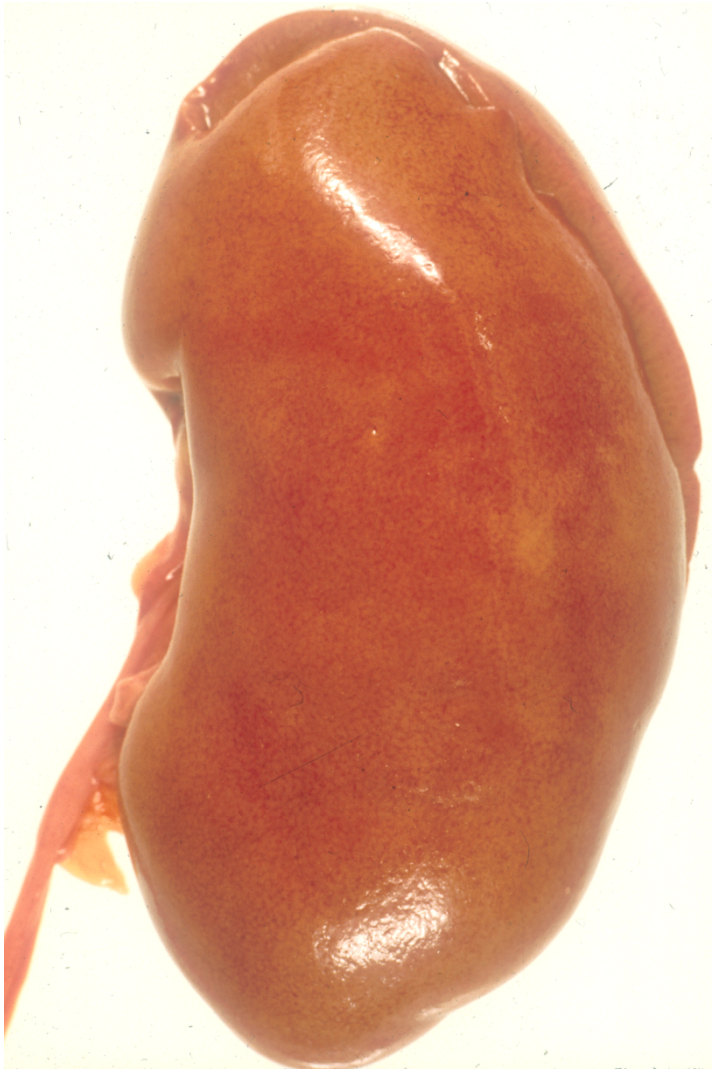

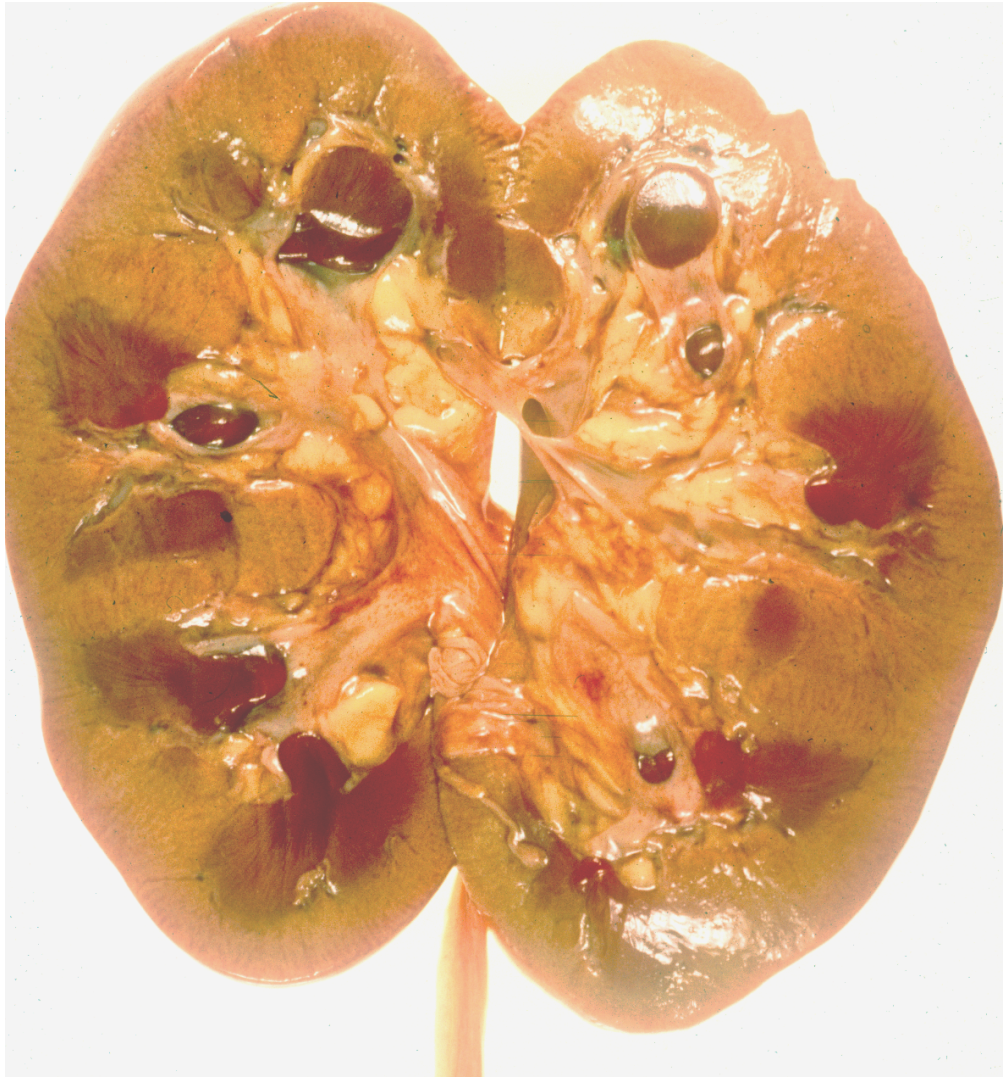

the normal kidney

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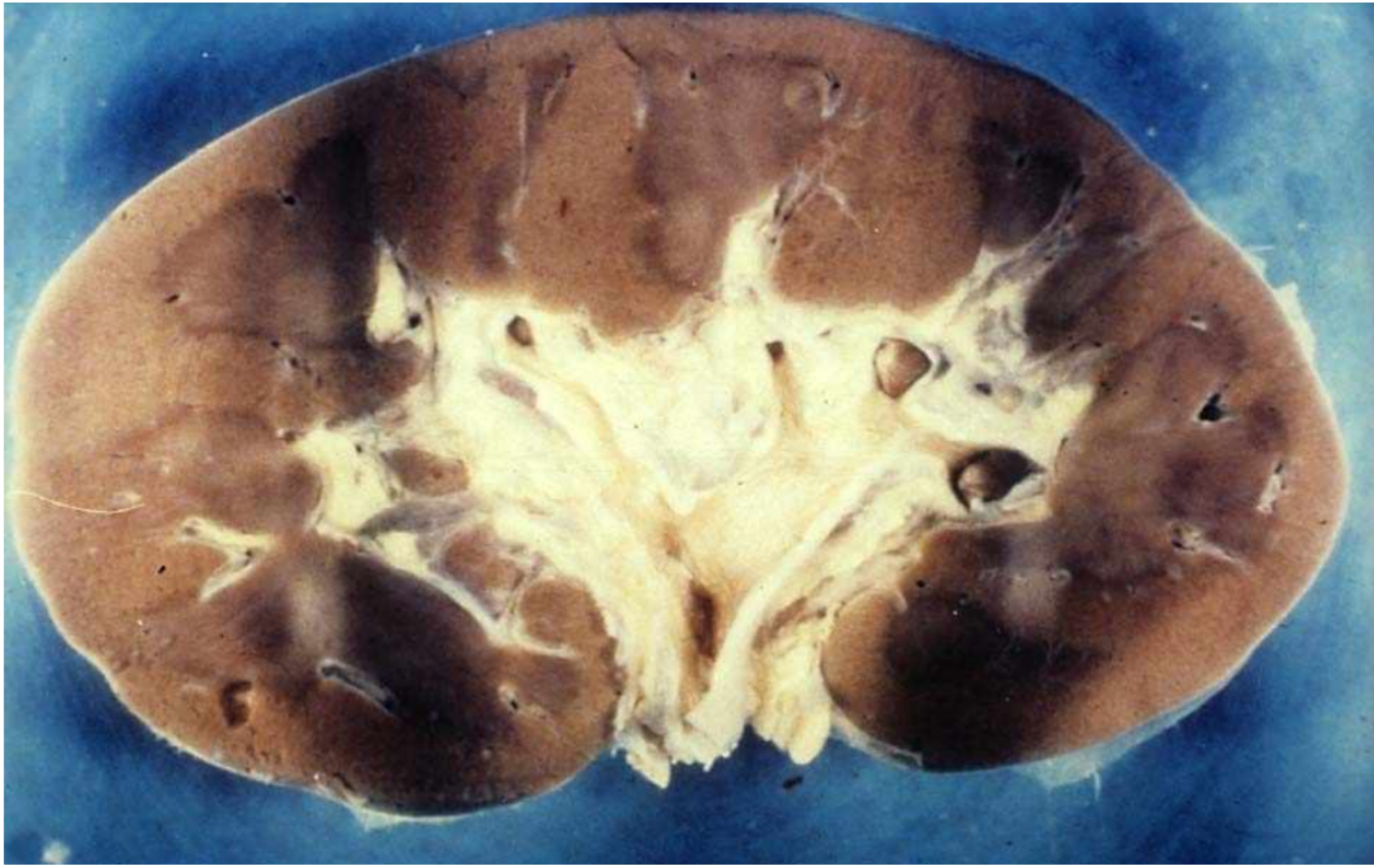
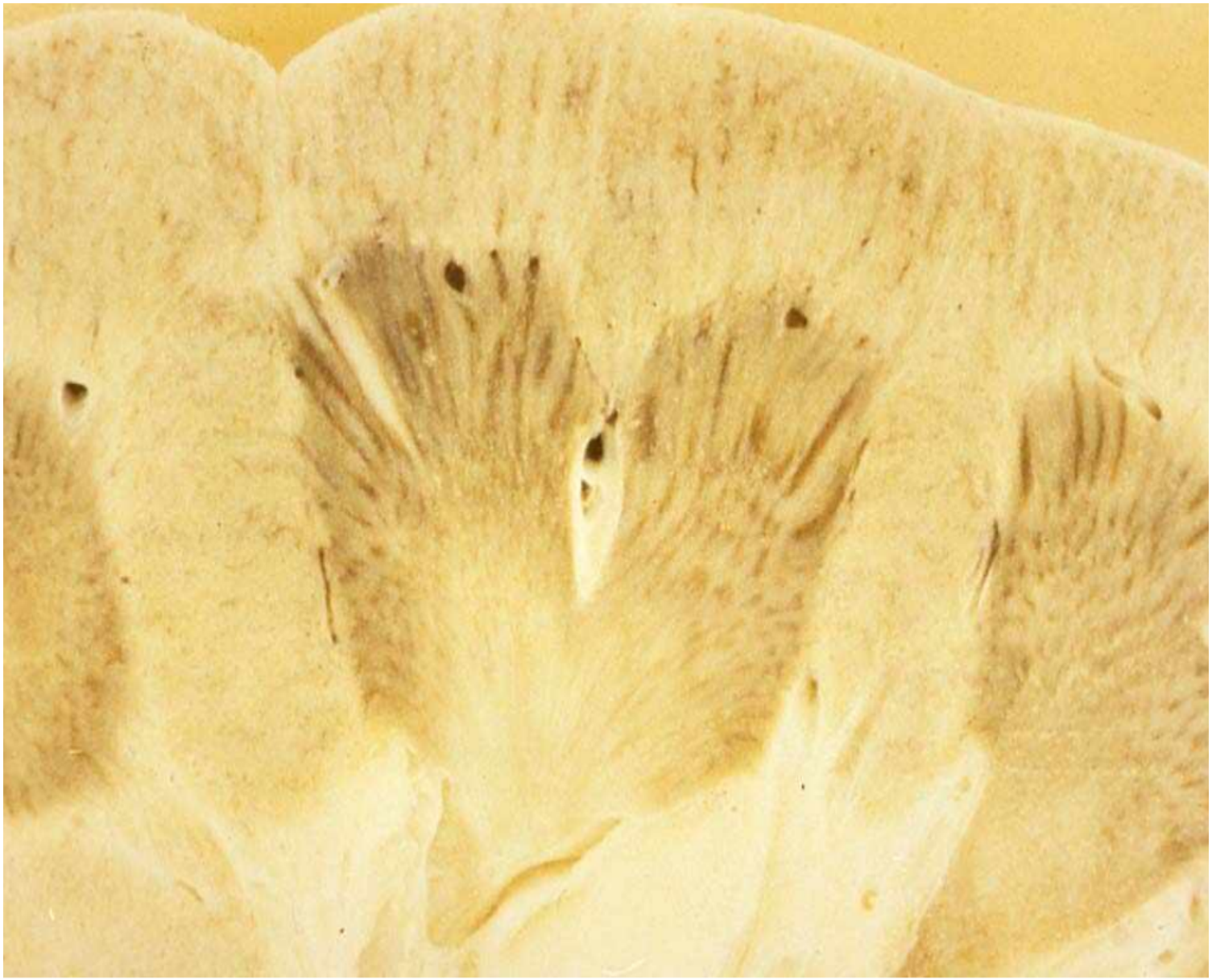
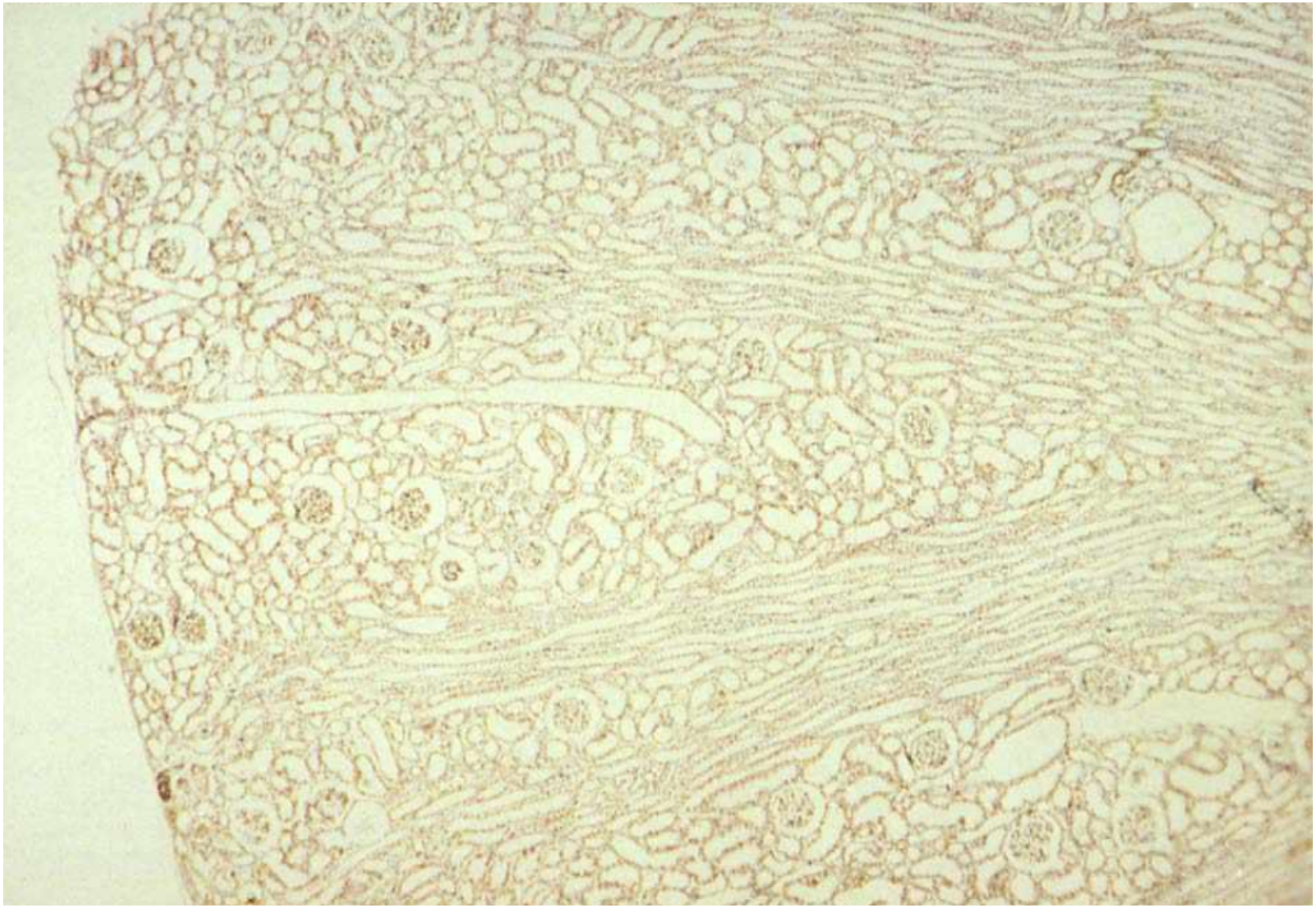


internal structure of the kidney





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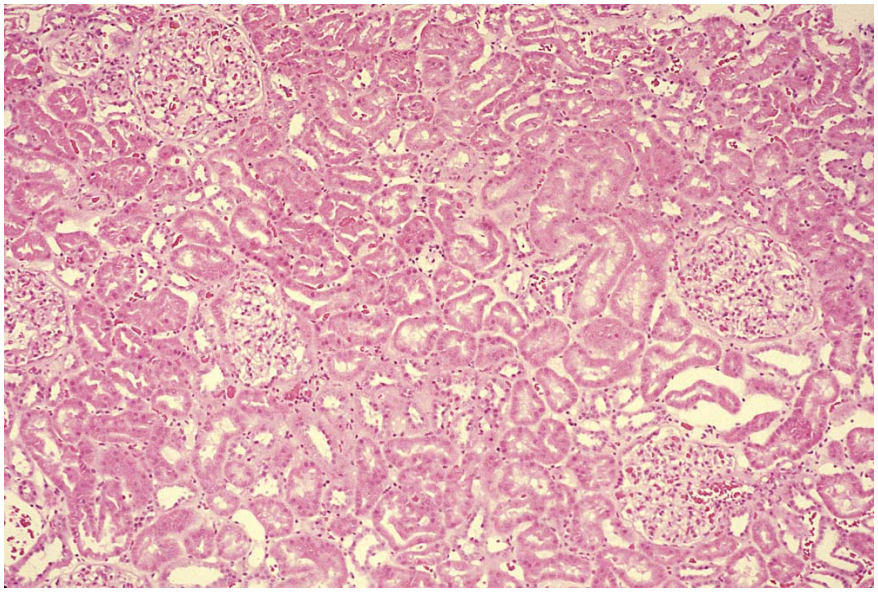
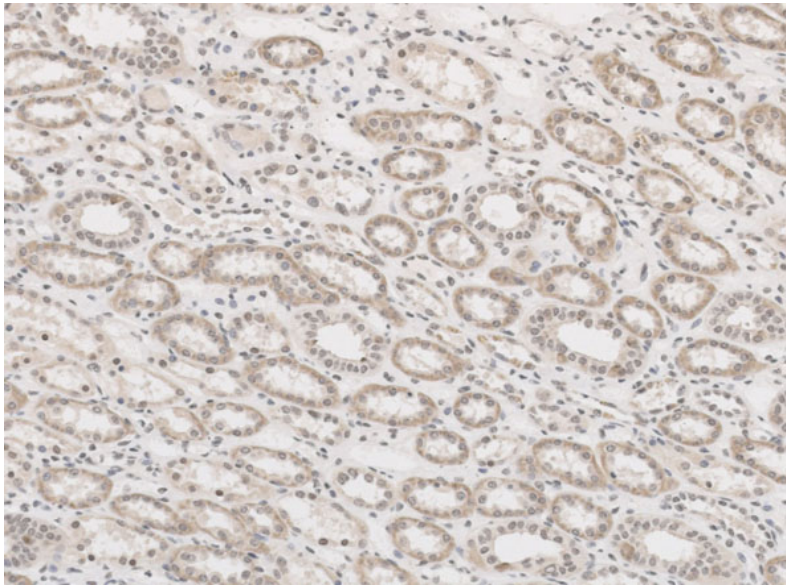
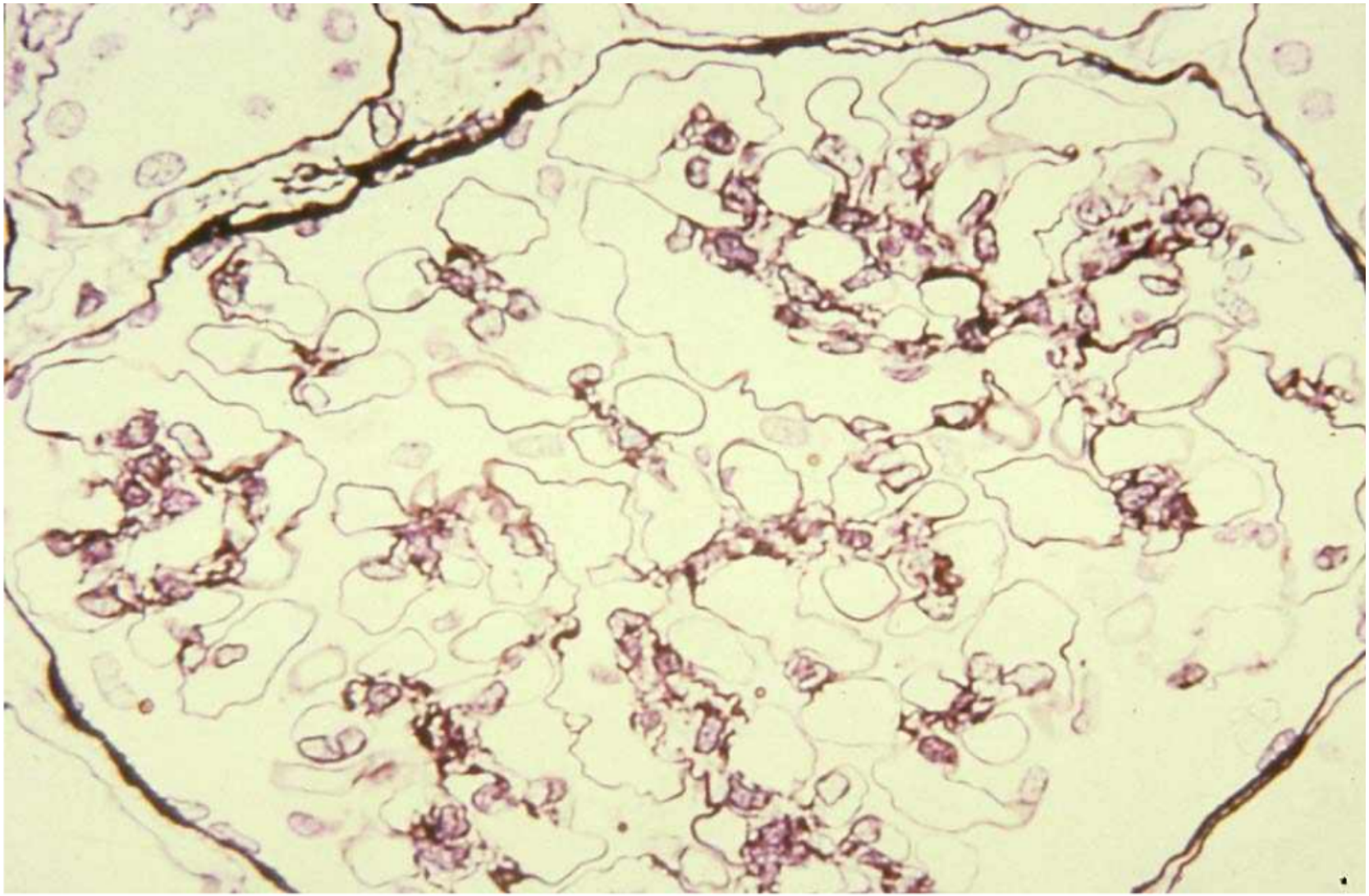


normal cortex



normal medulla



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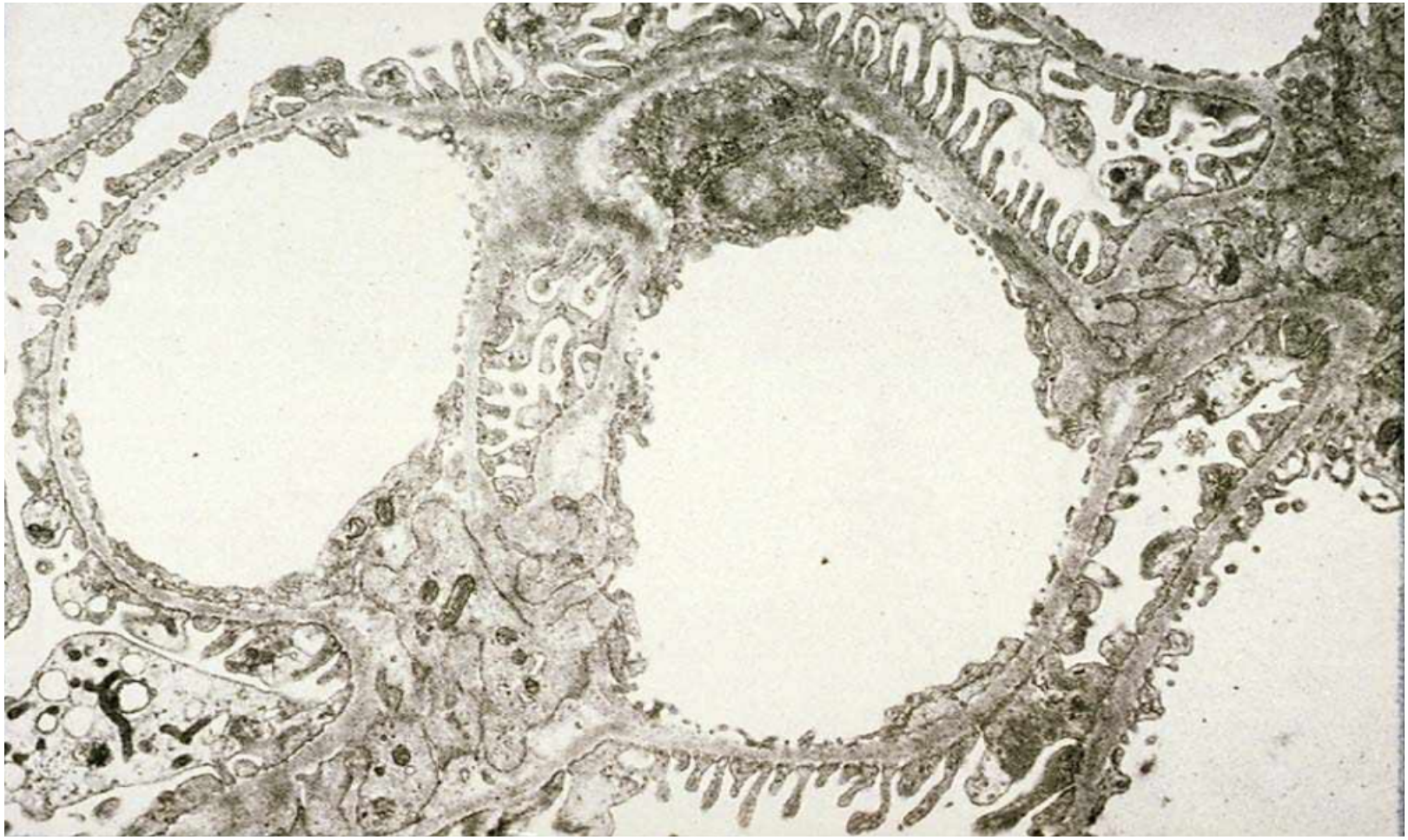

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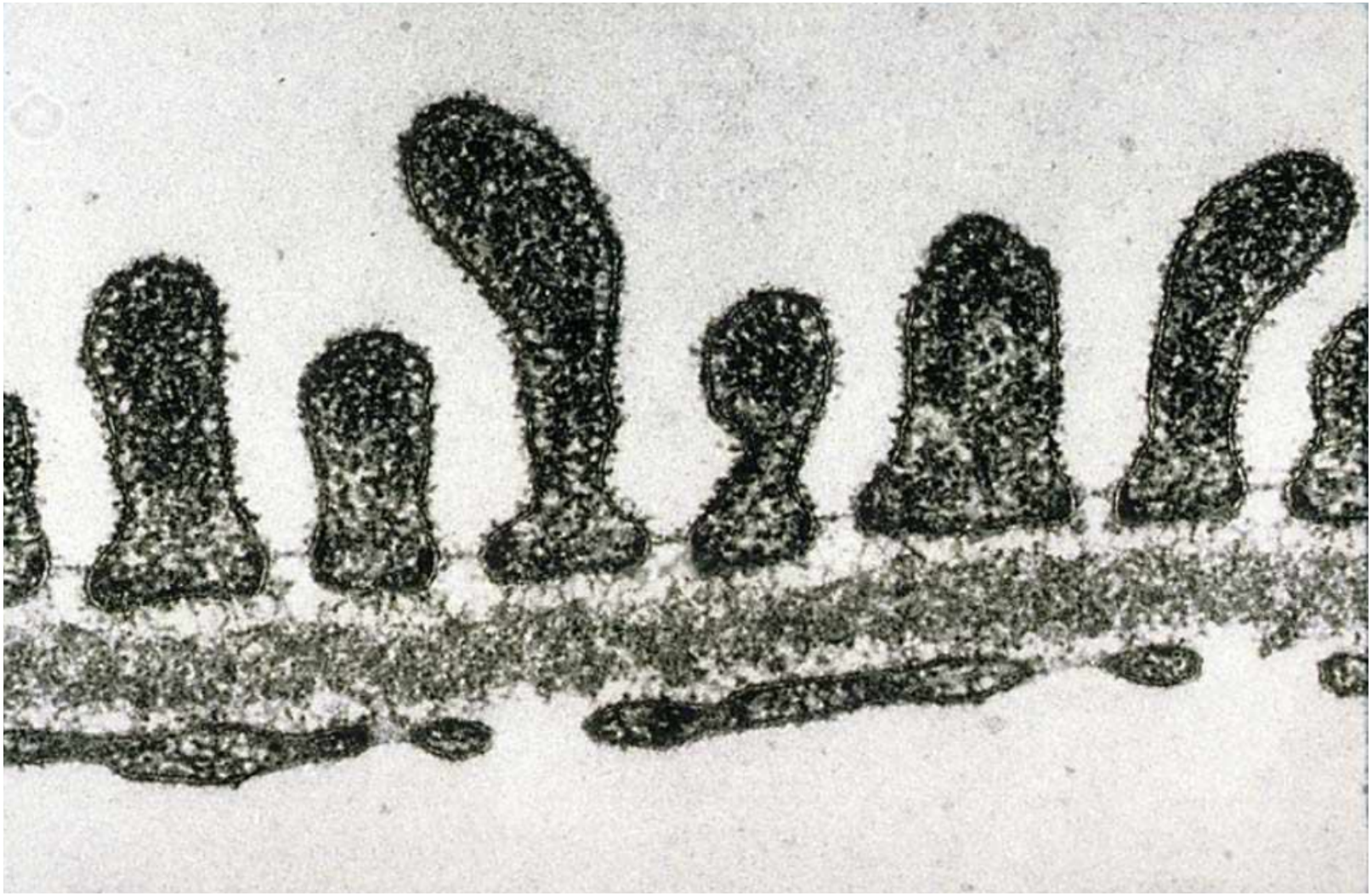

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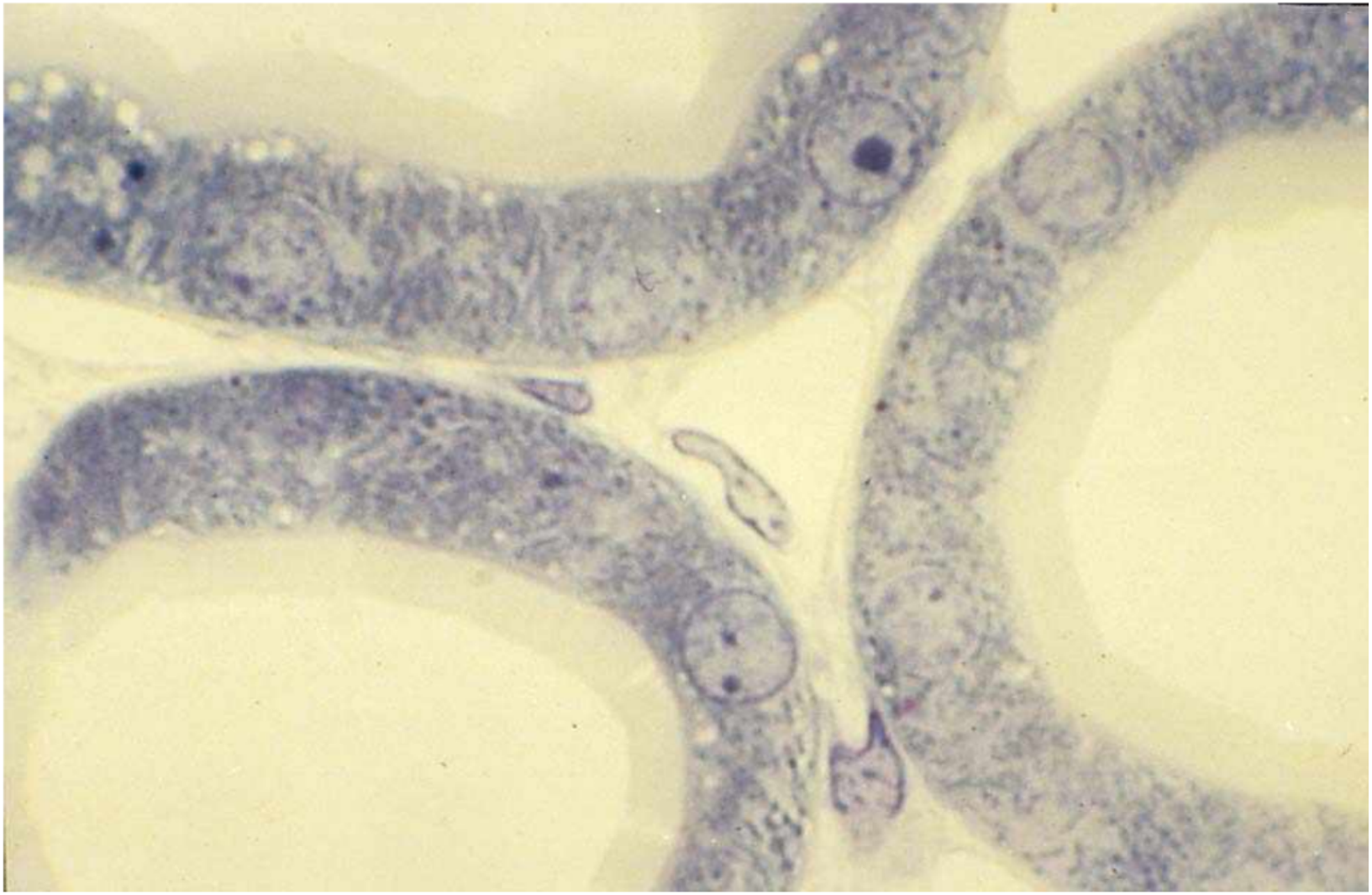

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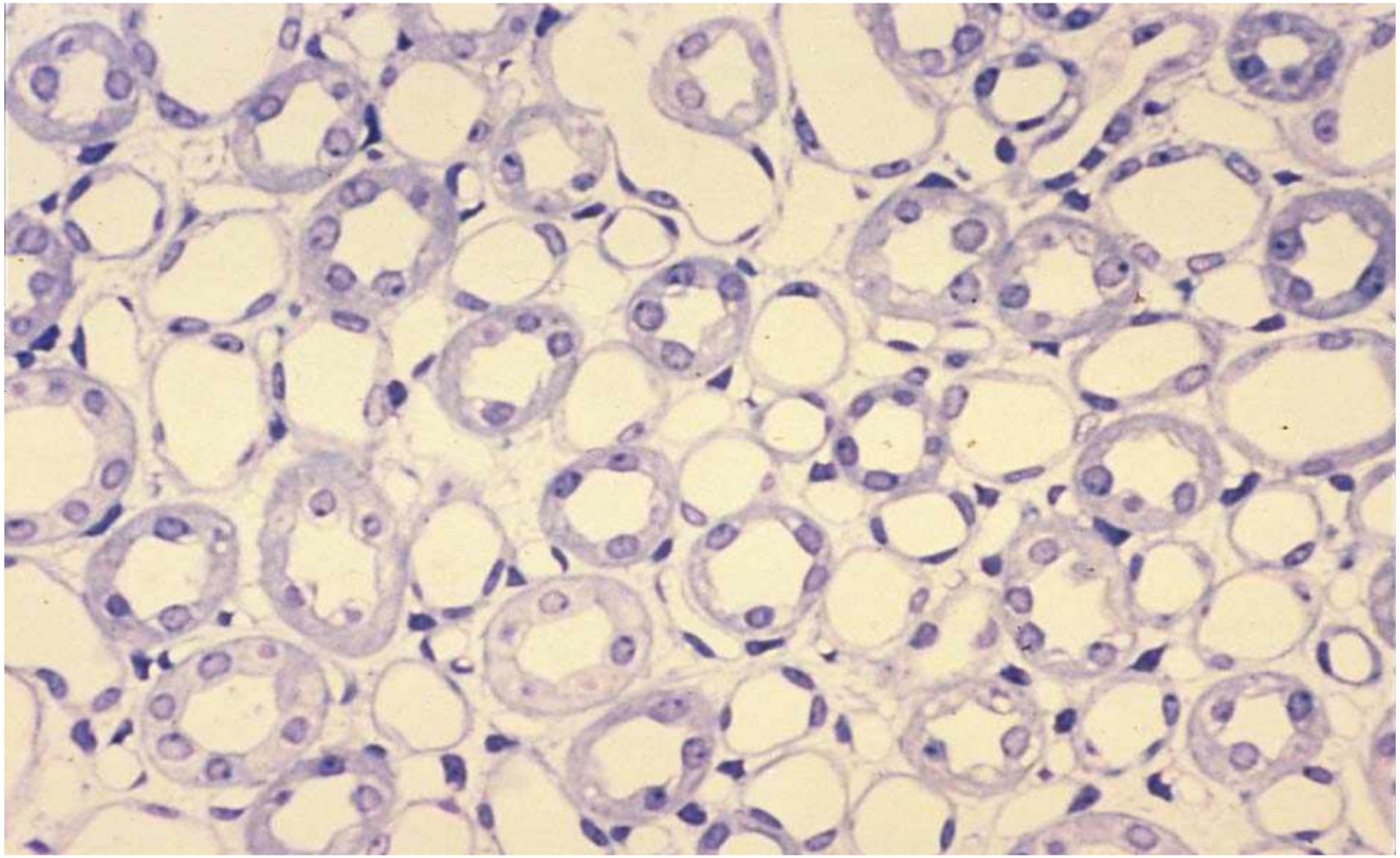

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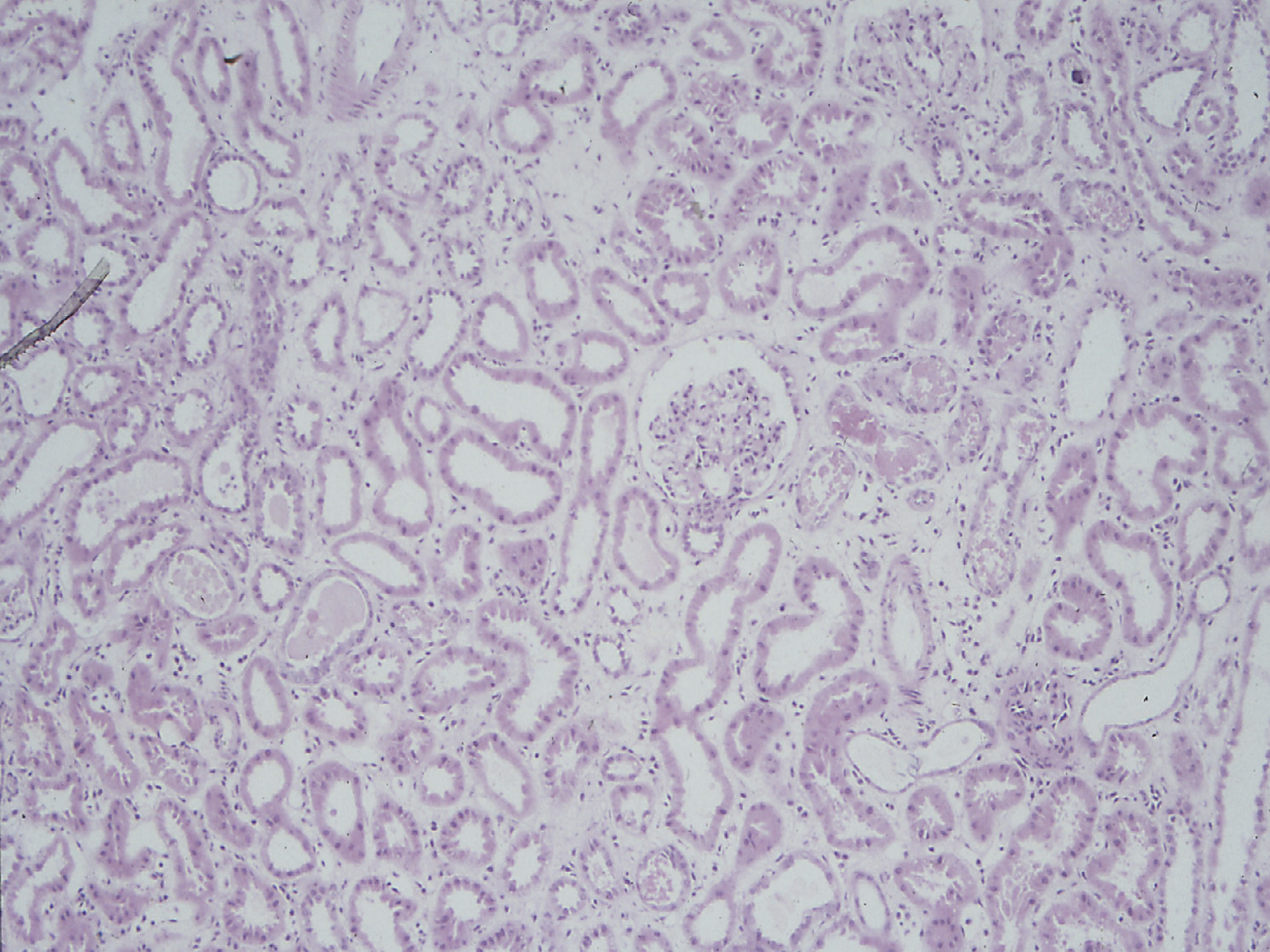
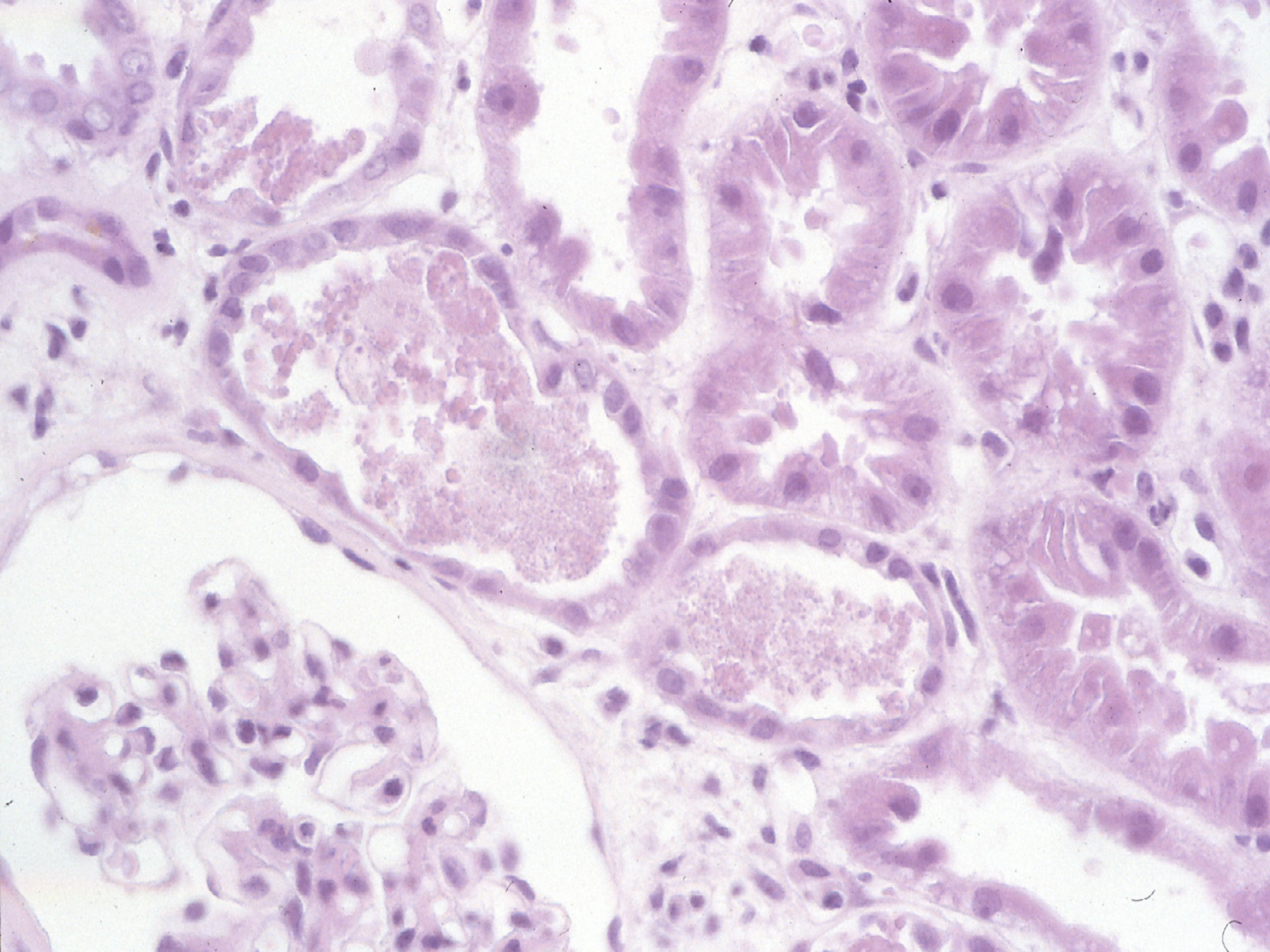
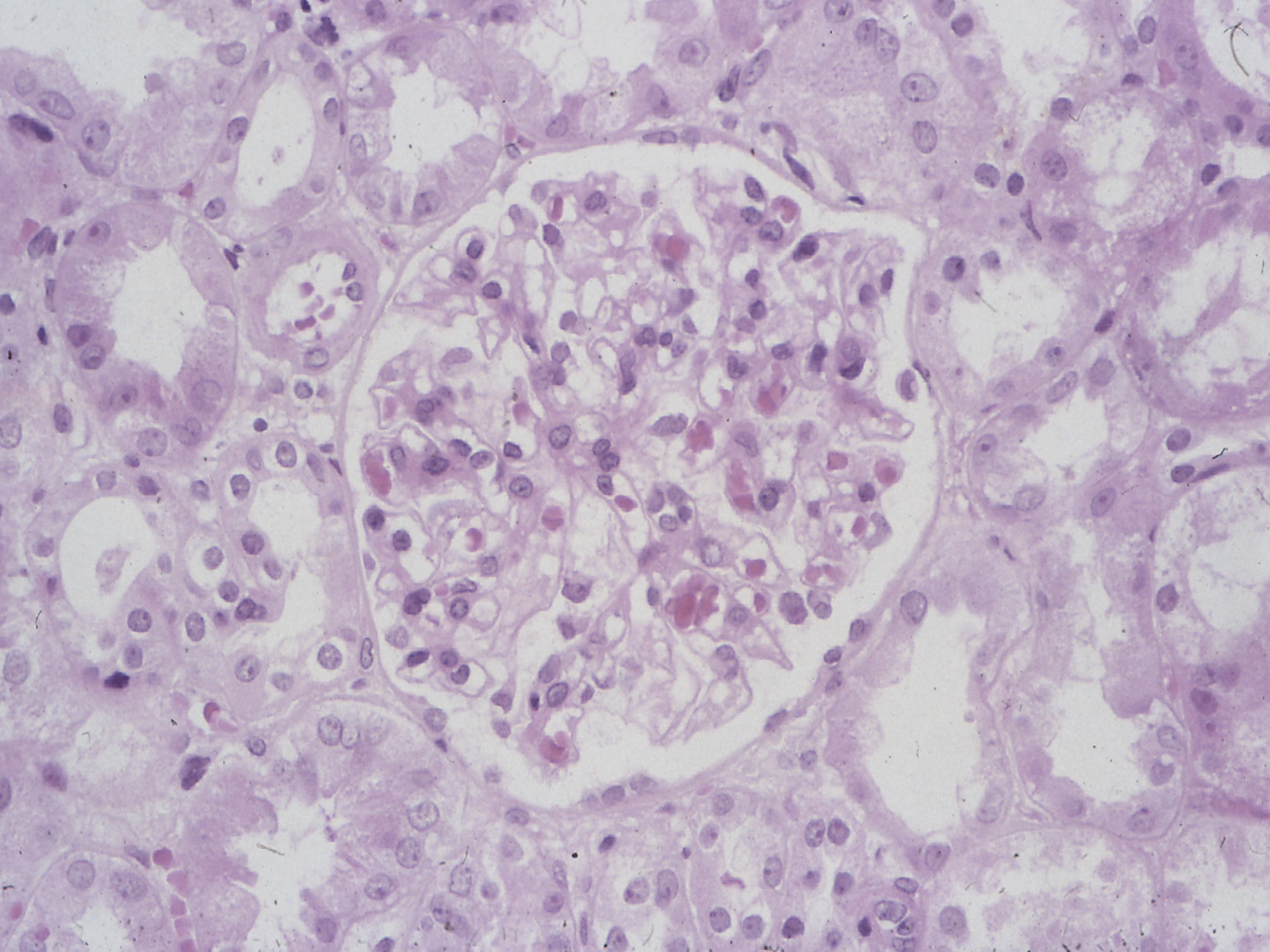
Case 1

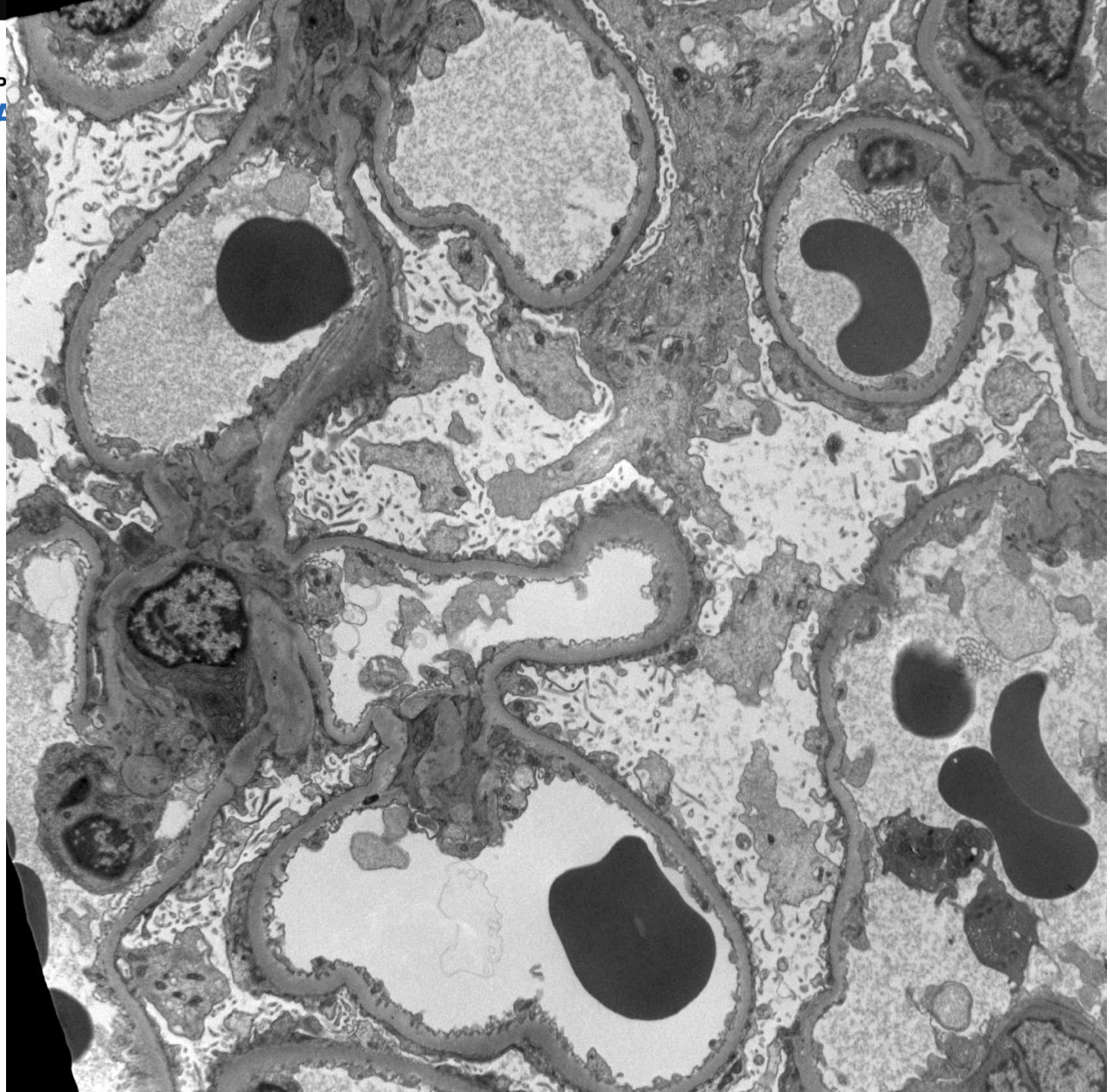
- 71-year-old man
- Admitted in Jan 2014 with SOB and leg swelling over 6 months
- PMH: Angina, Hypertension
- Urine: blood: Nil; protein: ++++
- Total protein 60 g/L, Albumin 20 g/L, Globulin 35g/L, Cholesterol 7.2 mmol/l
- Creatinine 280 mcmol/l
- Urine PCR 1200 mg/mmol

- What further information do you need?
- What investigations would you do ?









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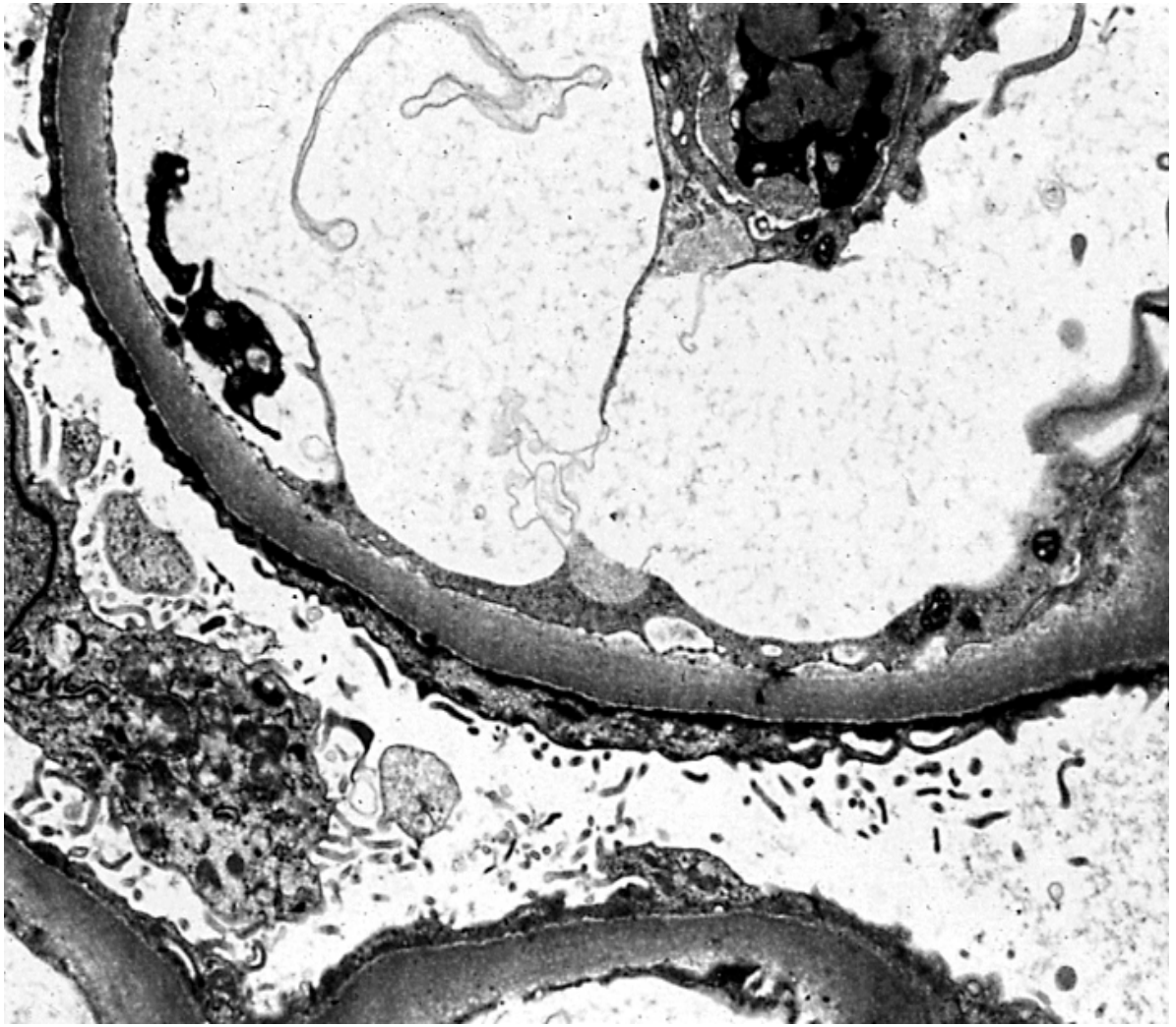
Minimal-Change Disease (EM)
Effacement of the foot processes



MCD and AKI

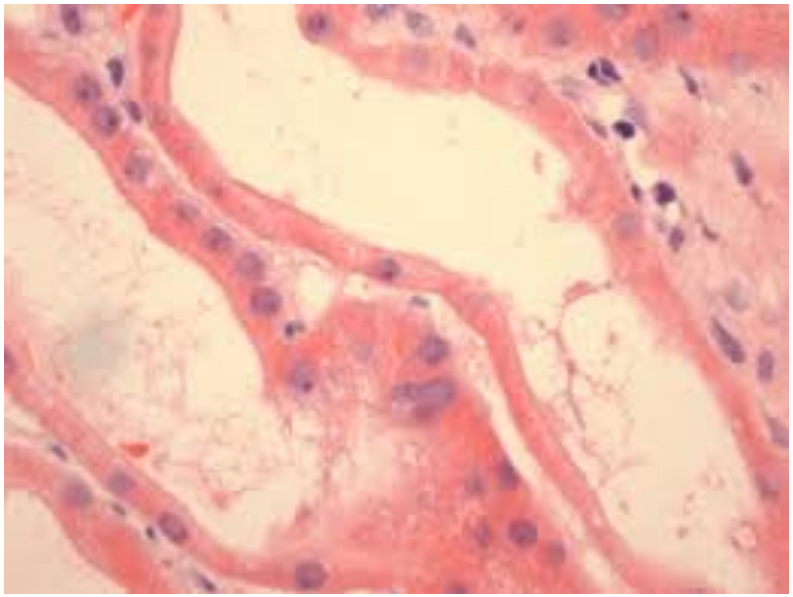
- Smith 1992
- 79 adults MCD and AKI
- Age 58 ± 2 years
- Proteinuria 11.6 ± 0.6 g/day
- Albumin 19 ± 1 g/L
- AKI 29 ± 54 days after onset of nephrosis
- Persisted for 7 weeks
- Plasma volume and Renal blood flow not reduced but ultrafiltration reduced
- ? Ischaemic tissue injury and pre-existing renal abnormalities

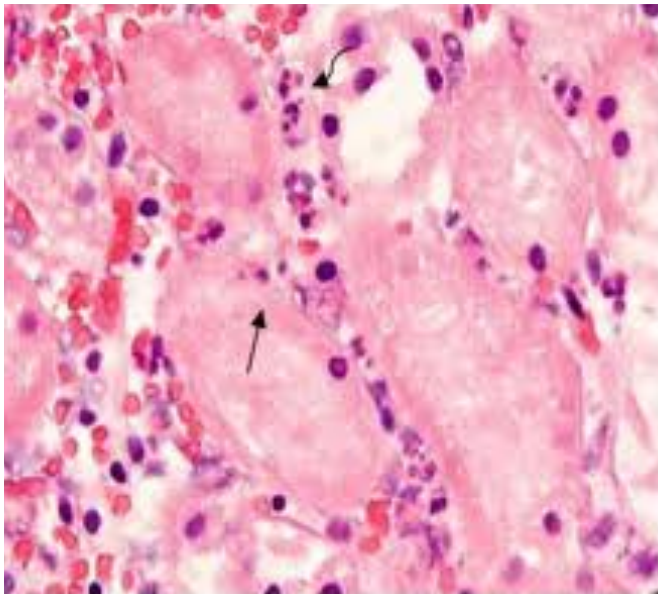
MCD and association with AKI

- Jennette 1990
- 71 adults with MCD
- 21 with Cr>177 vs 50 Cr<133
- Age 59.5 vs 40.3
- Systolic BP 158 vs 138
- Proteinuria 13.5 vs 7.9 g/day
- Greater arteriosclerosis on biopsy
- ATI in 71% vs 0%
- All recovered but may need prolonged RRT

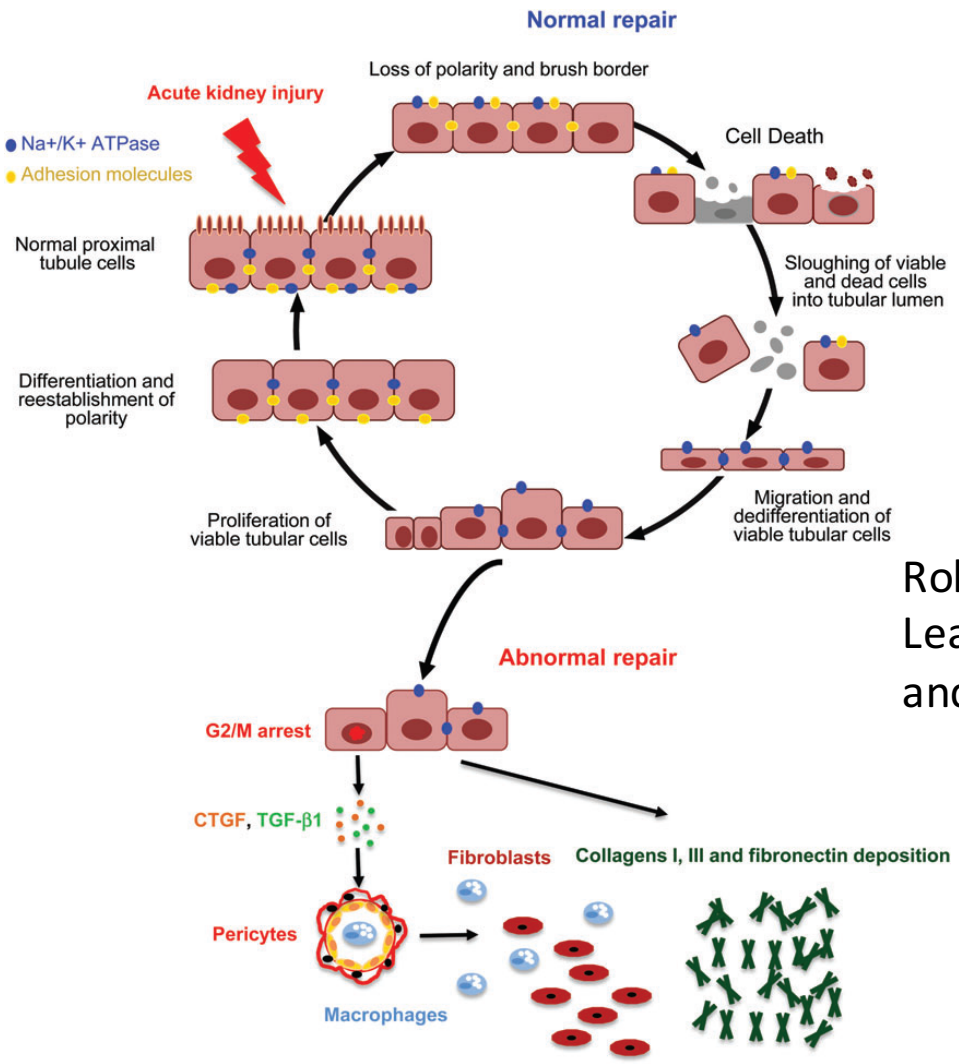
Tubular injury

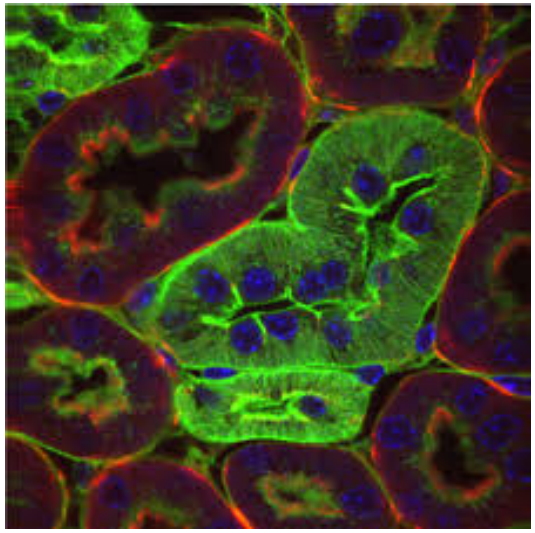
- Acute tubular necrosis(ATN) final common pathway for many processes
- Tubular cell injury leads to sloughing of cells from basement membrane, obstruction of tubular lumen and loss of tubular function
- Often reversible





Tubular repair and progression to CKD



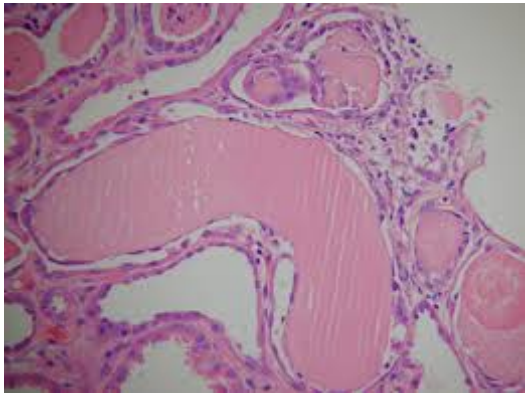


Role of epithelial cell cycle arrest
Leading to production of pro-fibrotic factors and development of CKD

Canaud and Bonventre 2014

Causes of tubular injury

- Hypotension/ischaemia- e.g. sepsis, surgery
- Obstruction- e.g. myeloma, rhabdomyolysis
- Toxicity- drugs eg gentamicin, anti-retrovirals, contrast agents
- Inflammation-e.g. tubulointerstitial nephritis



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Case 2

- A 29 year old woman presented to A/E with abdominal pain, diarrhoea and generalised lethargy
- Noticed a rash on her chest and back in previous week
- No previous medical history
- BP in A/E 180/100
- Investigations
- Hb 6 WCC 8 plts 66
- Creatinine 545 urea 24

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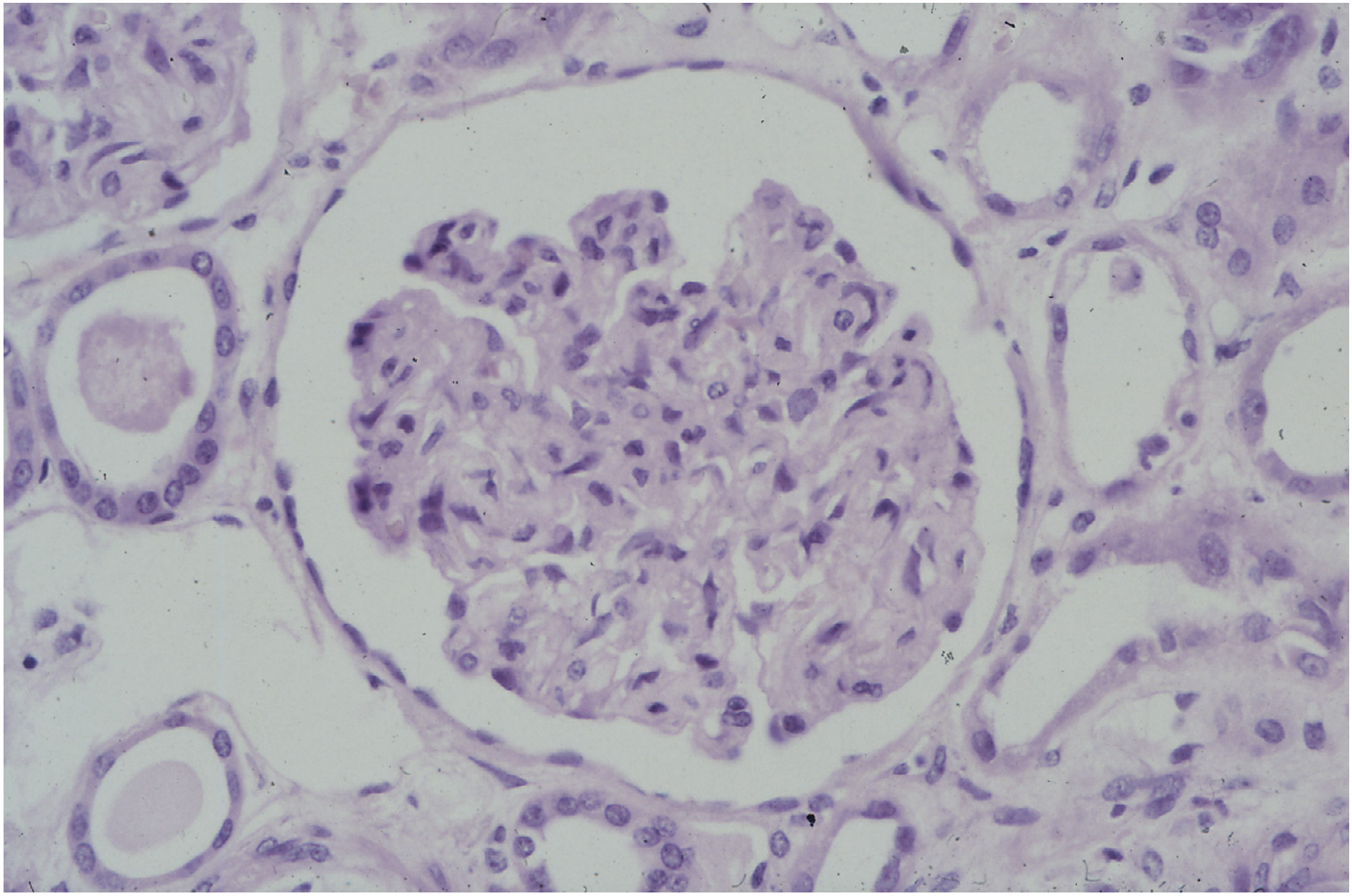
Case 2



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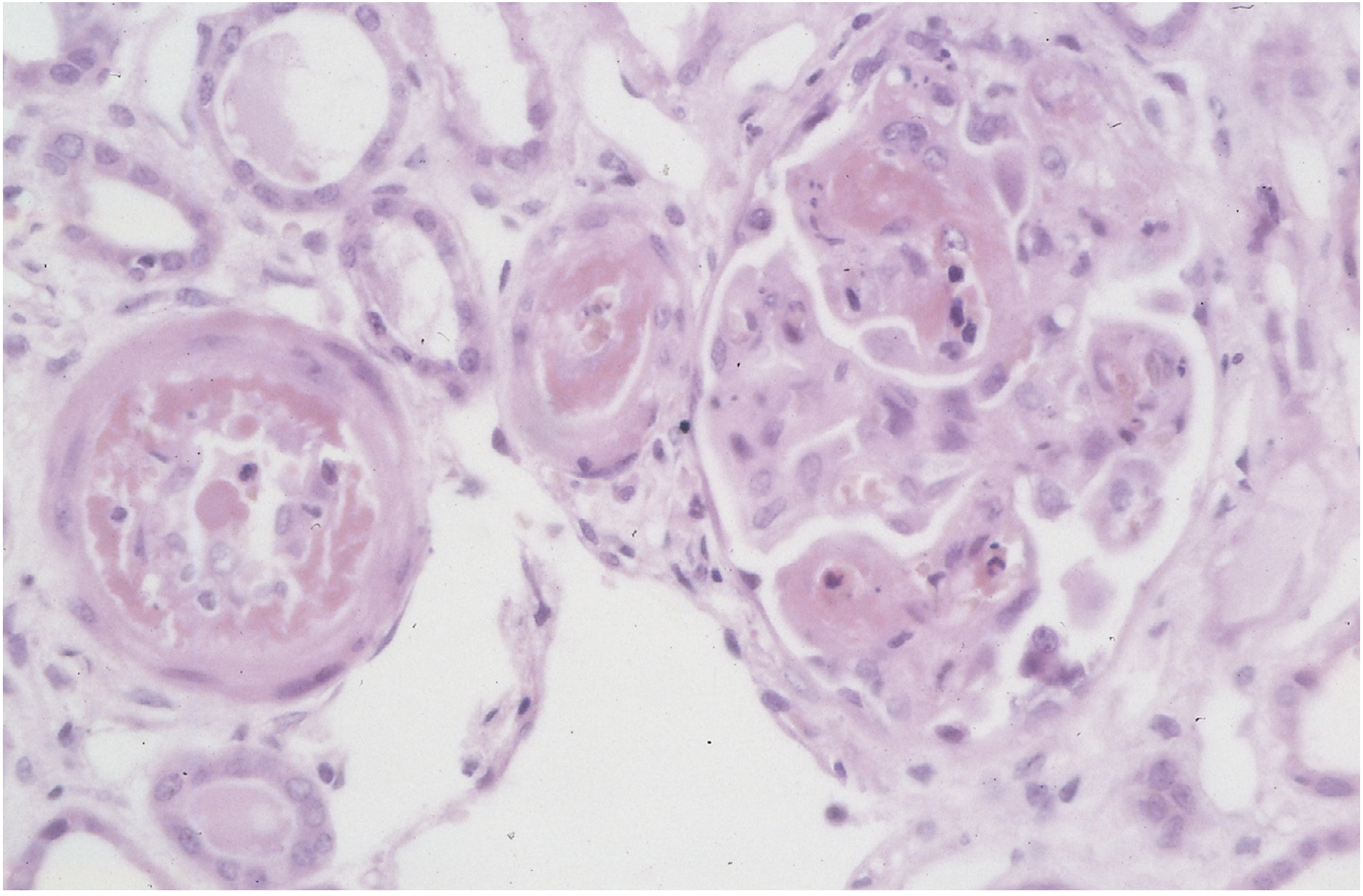
Case 2



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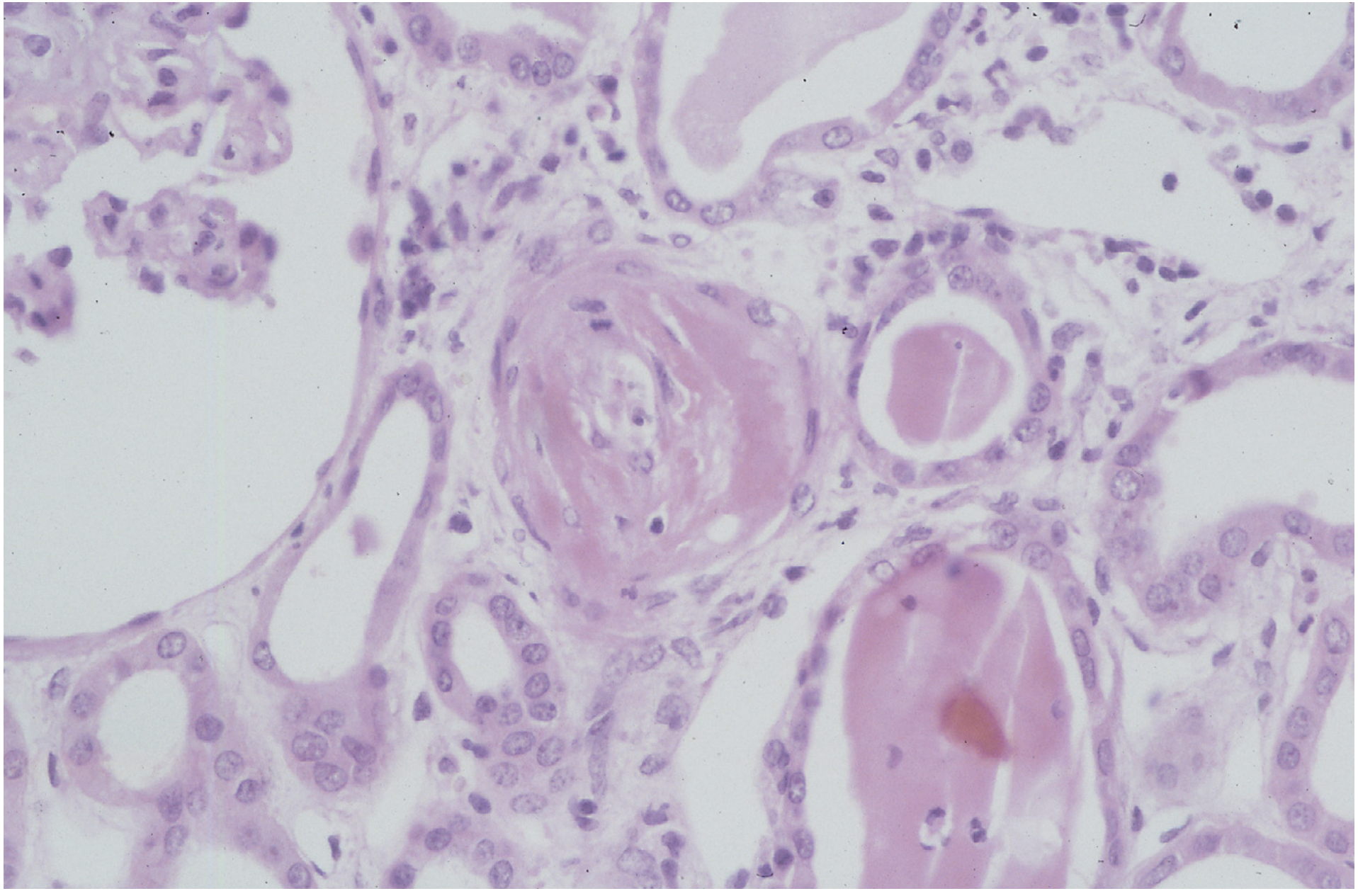
Case 2



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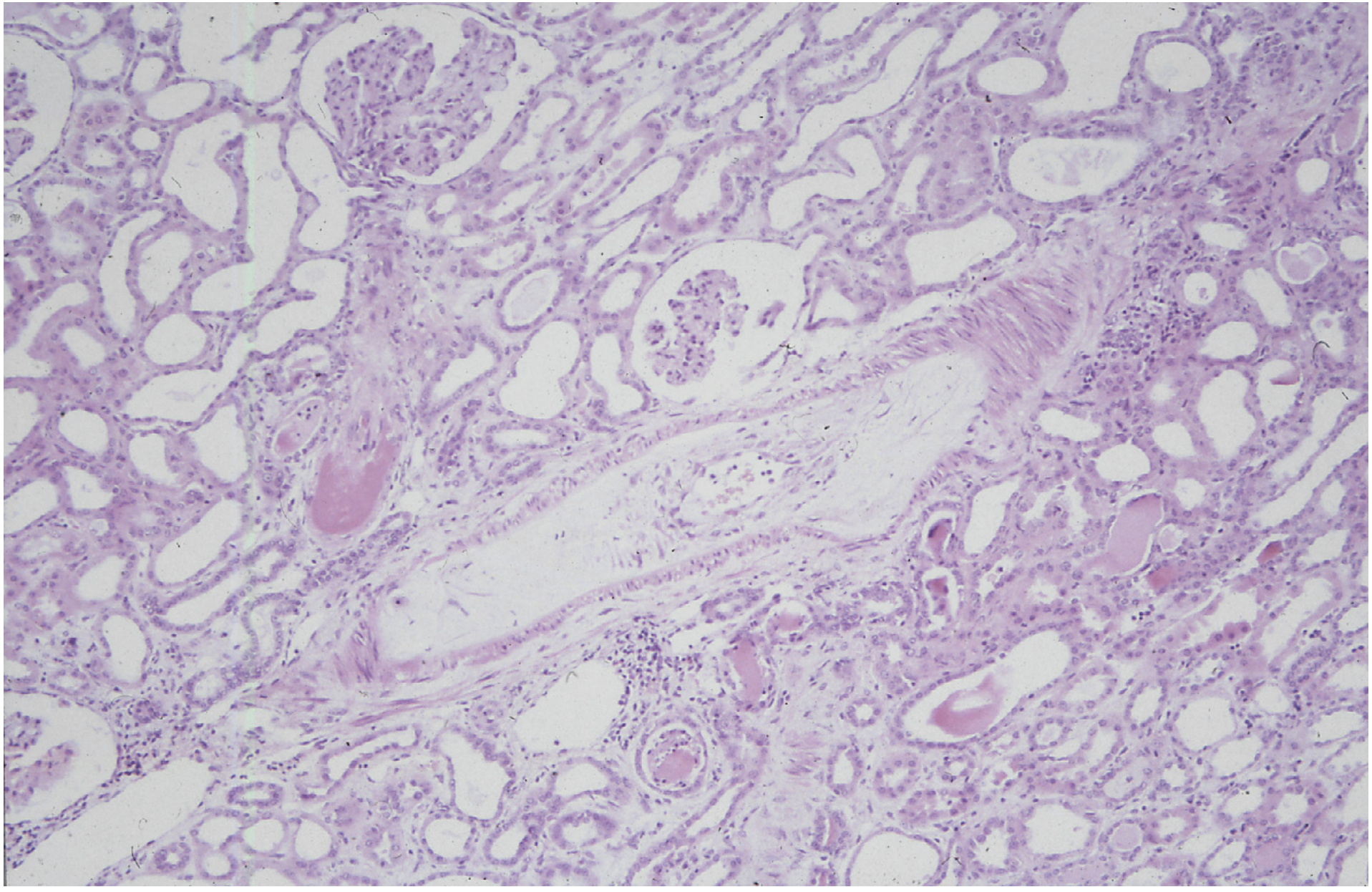
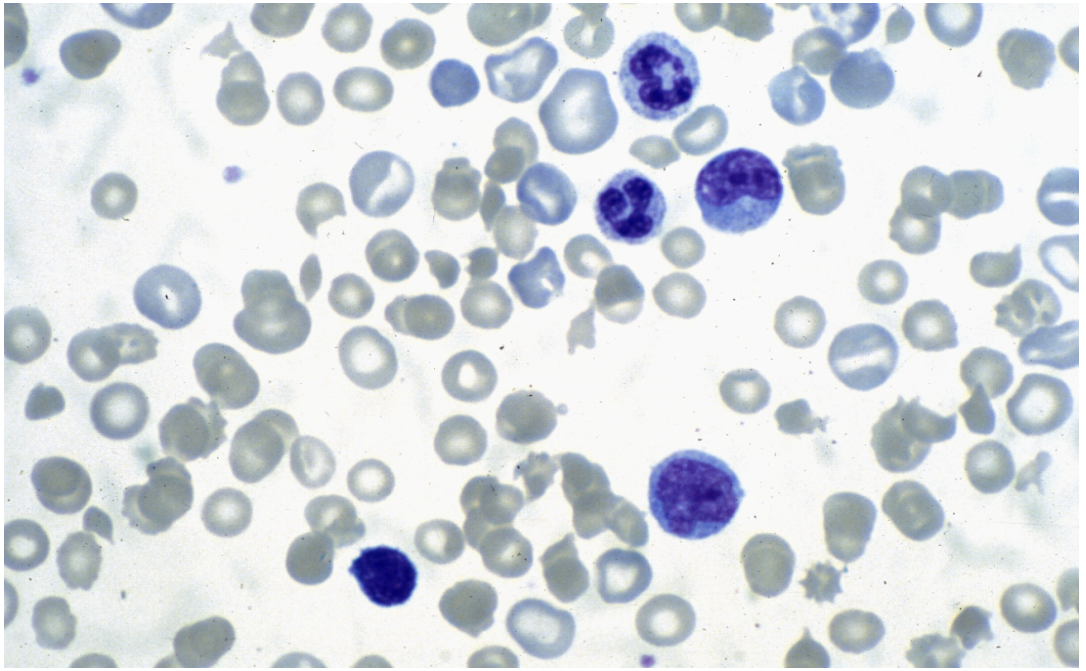
Case 2



Thrombotic microangiopathy

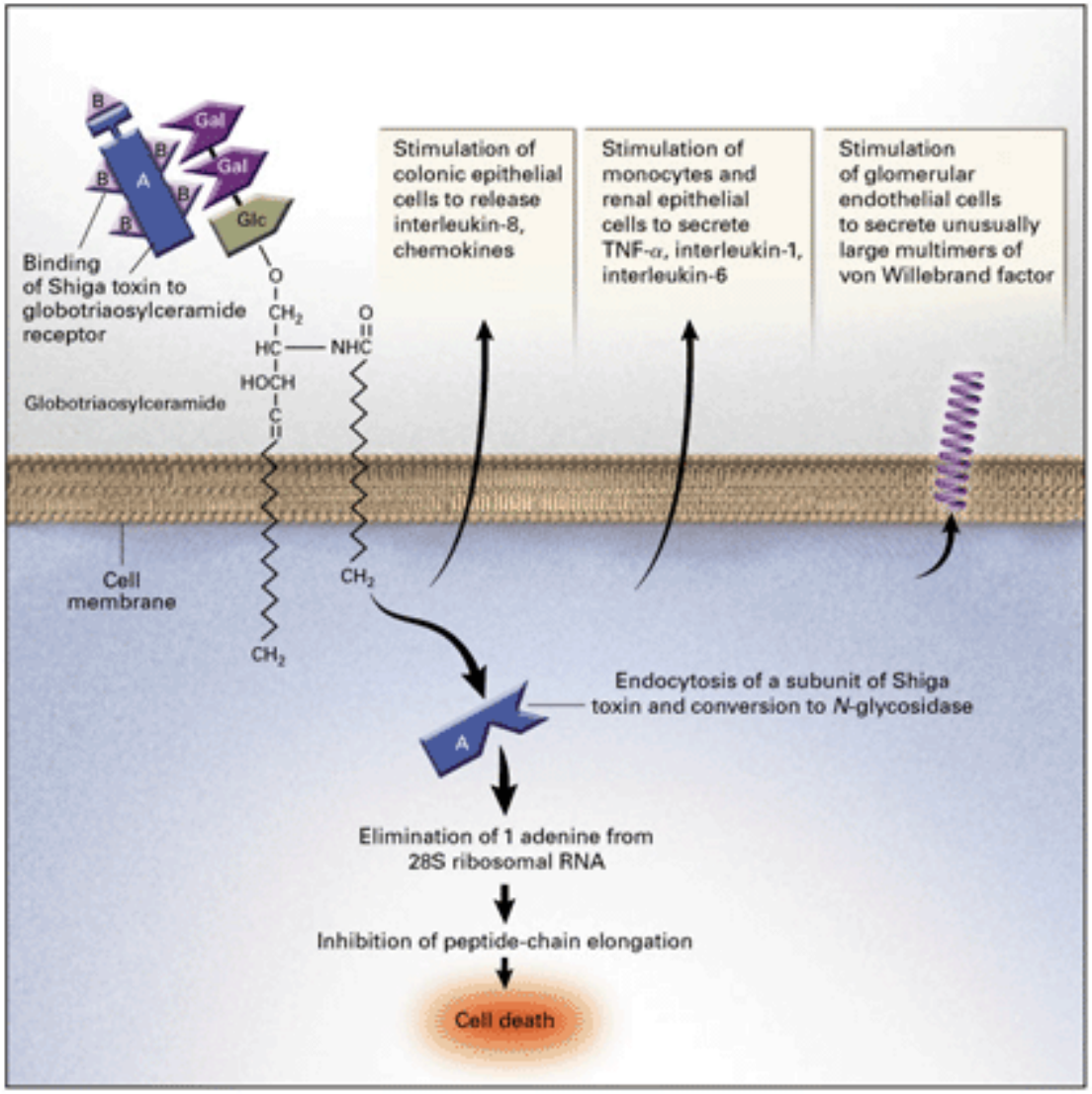
- Association of small vessel thrombi and haemolytic anaemia
- Endothelial damage is underlying process
- May be chronic



Conditions Associated with Thrombotic Microangiopathy

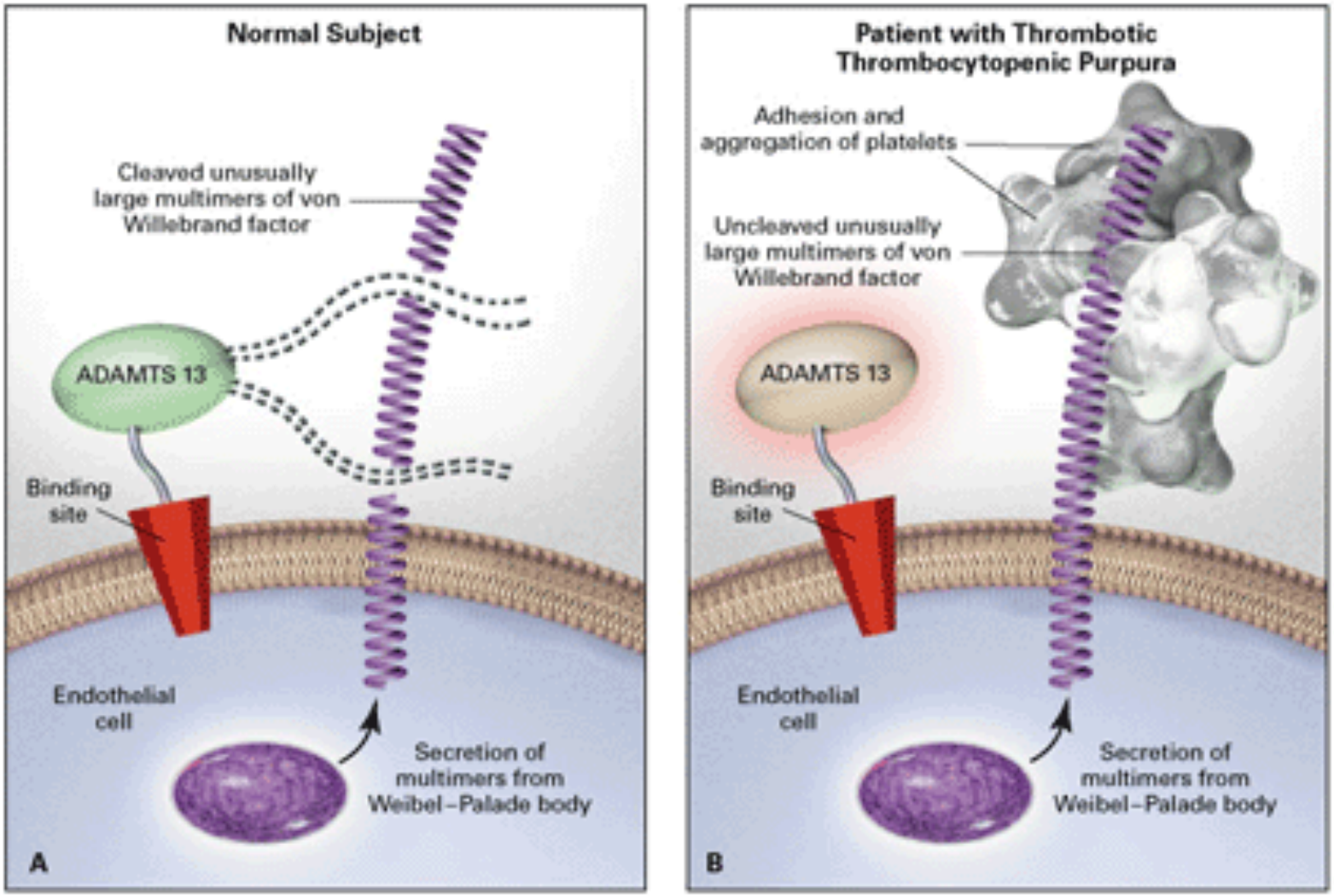
- Accelerated hypertension
- HUS, TTP
- SLE
- Antiphospholipid antibodies
- Progressive systemic sclerosis
- Preeclampsia/eclampsia
- Drug-induced (mitomycin, CyA, FK506)
- Transplant (bone marrow, kidney…)
- Radiation
- Hereditary (complement)

Shiga Toxin and Cell Injury



Moake, NEJM 2002

ADAMTS13 and TTP



Moake, NEJM 2002

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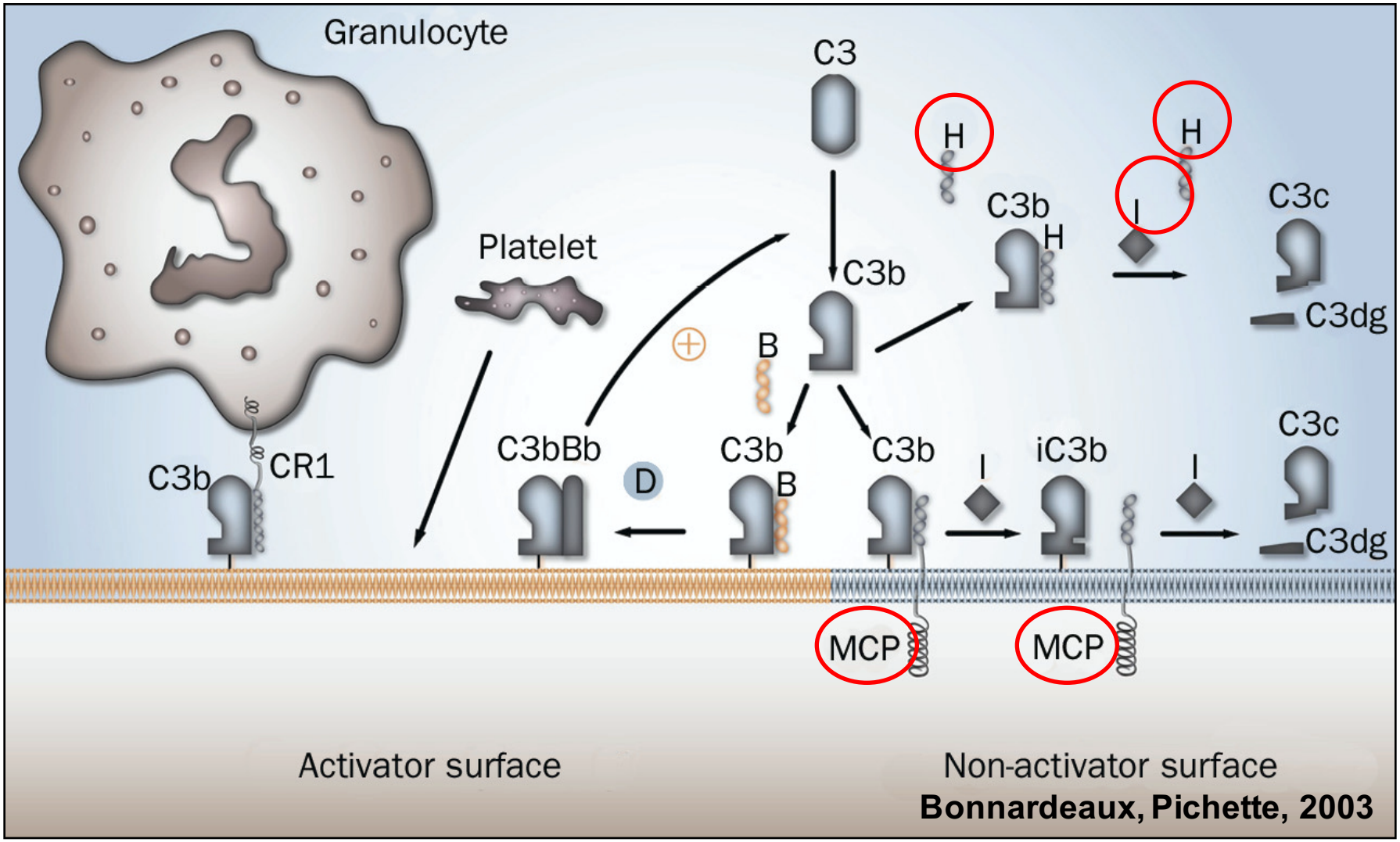
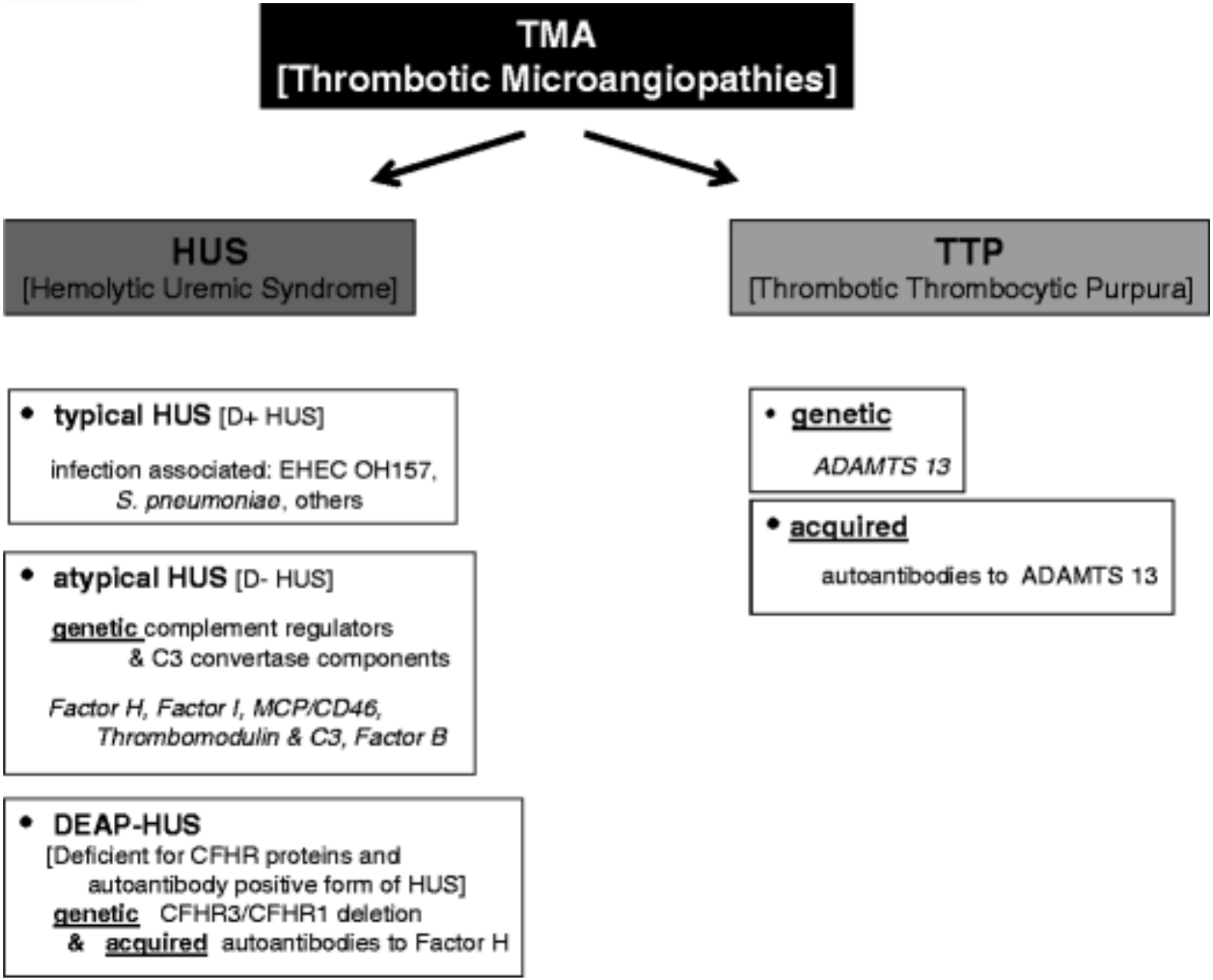
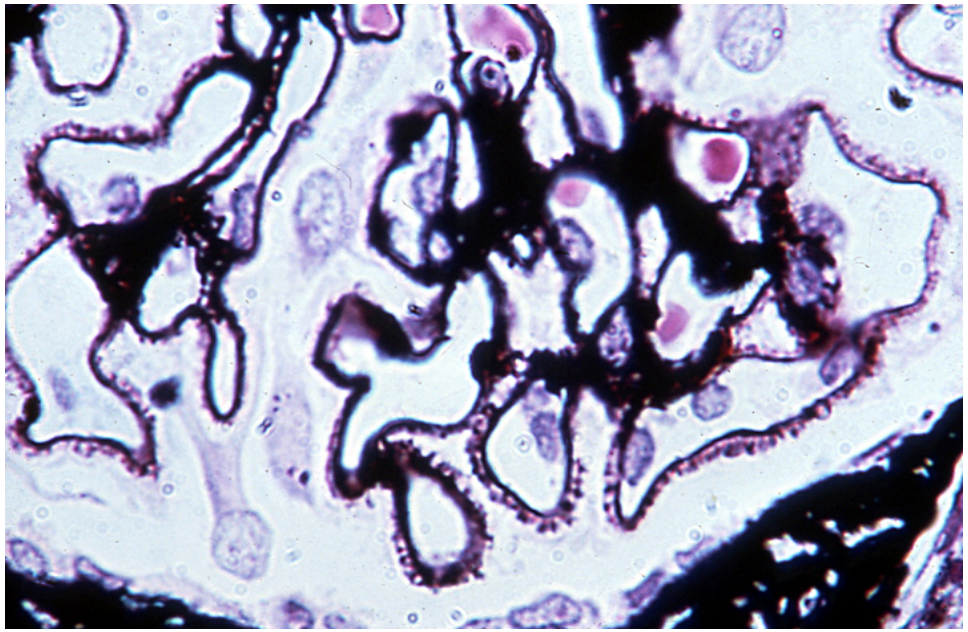
Hereditary HUS and Complement Dysregulation

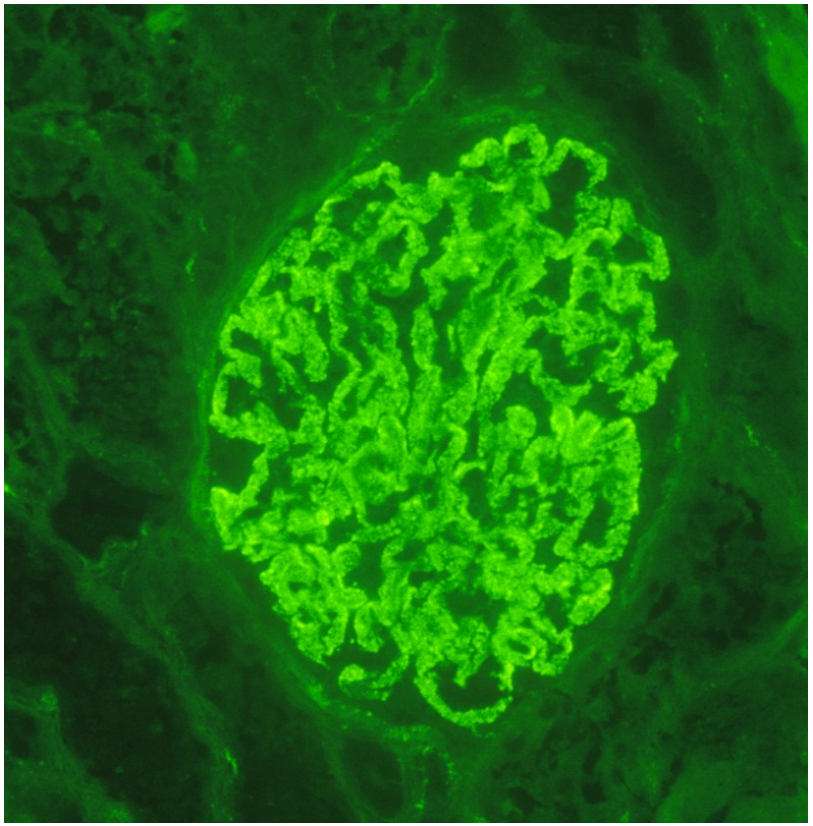



TMA
[Thrombotic Microangiopathies]
HUS
[Hemolytic Uremic Syndrome]
TTP
[Thrombotic Thrombocytic Purpura]
• typical HUS [D+ HUS]
infection associated: EHEC OH157,
S. pneumoniae, others
• atypical HUS [D- HUS]
genetic complement regulators
& C3 convertase components
Factor H, Factor I, MCP/CD46,
Thrombomodulin & C3, Factor B
• DEAP-HUS
[Deficient for CFHR proteins and
autoantibody positive form of HUS]
genetic CFHR3/CFHR1 deletion
& acquired autoantibodies to Factor H
• genetic
ADAMTS 13
• acquired
autoantibodies to ADAMTS 13

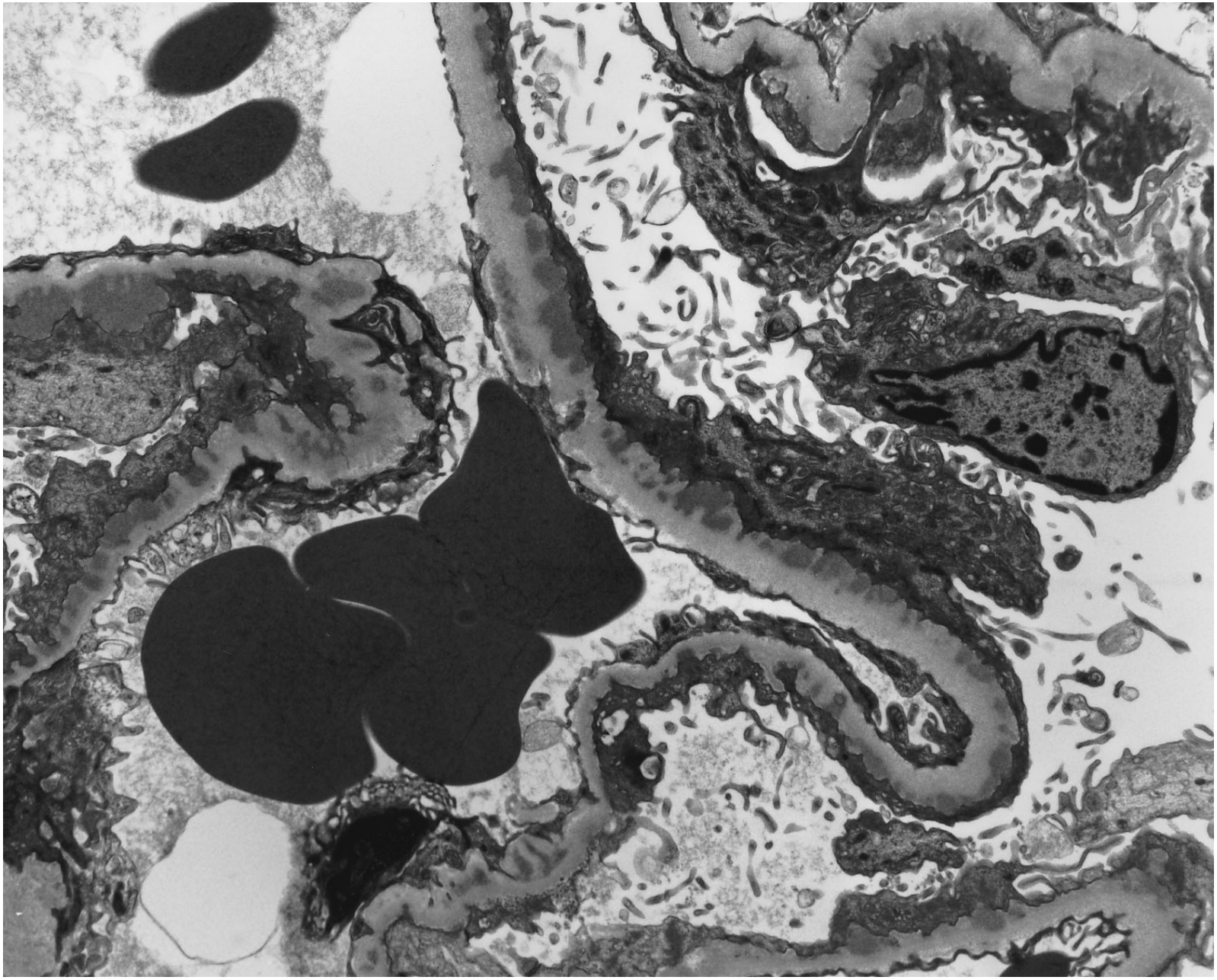
Case 3

- White male age 79
- Presented with nephrotic syndrome
- 24 hour urine protein 5.5g
- Albumin 22g/l
- Serum creatinine 80mmol/l





IgG

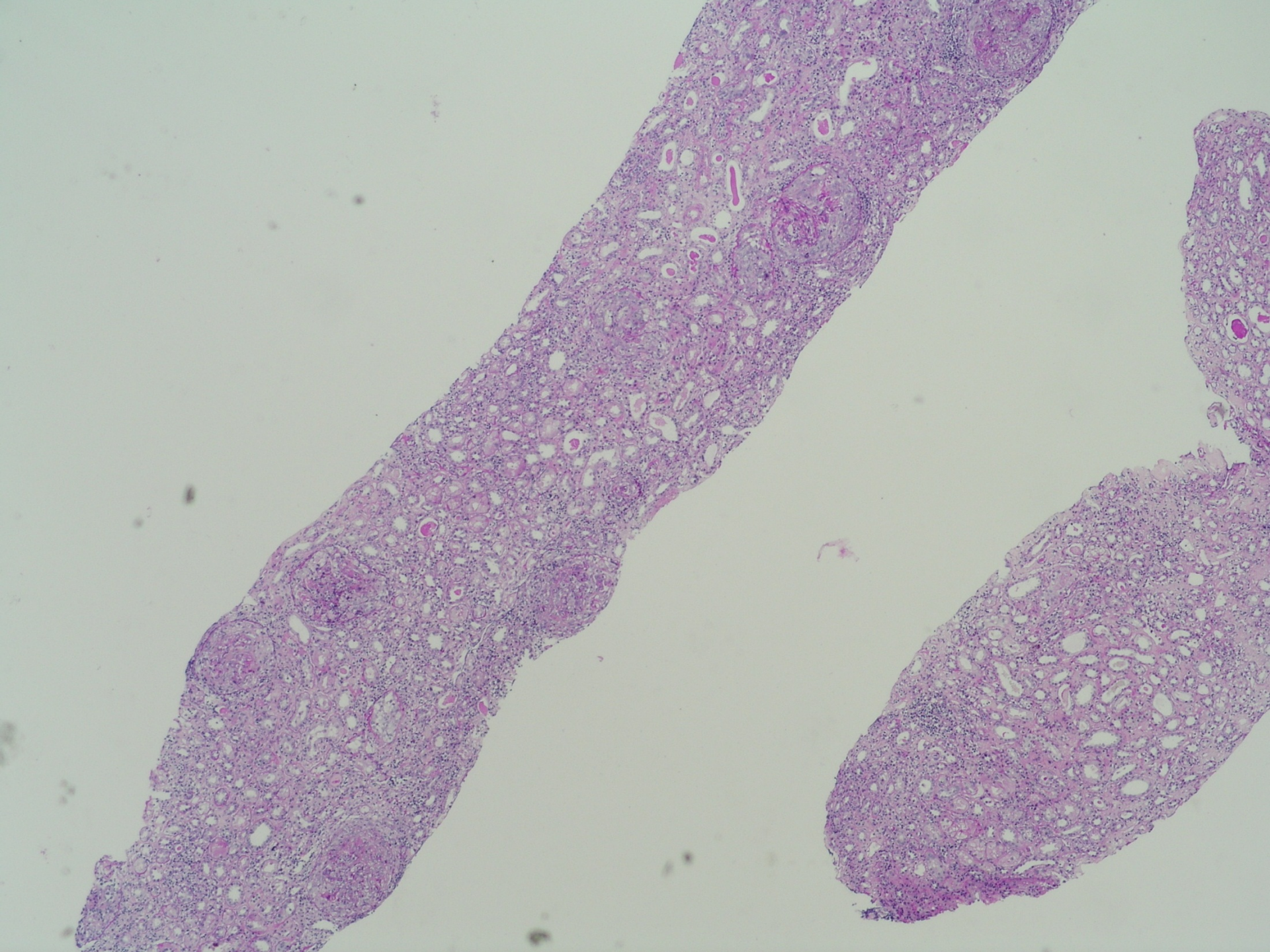


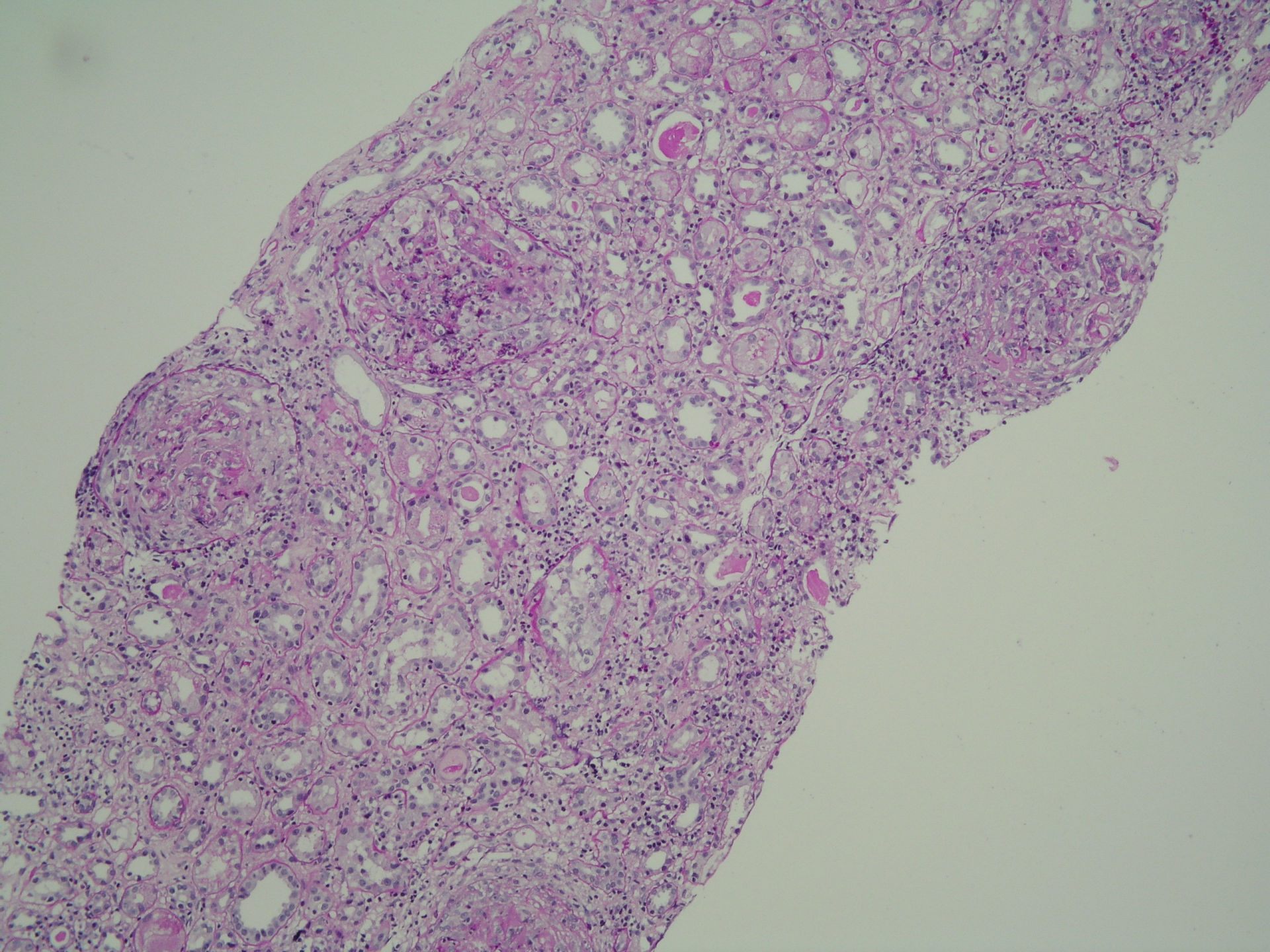
Diagnosis – membranous glomerulonephritis

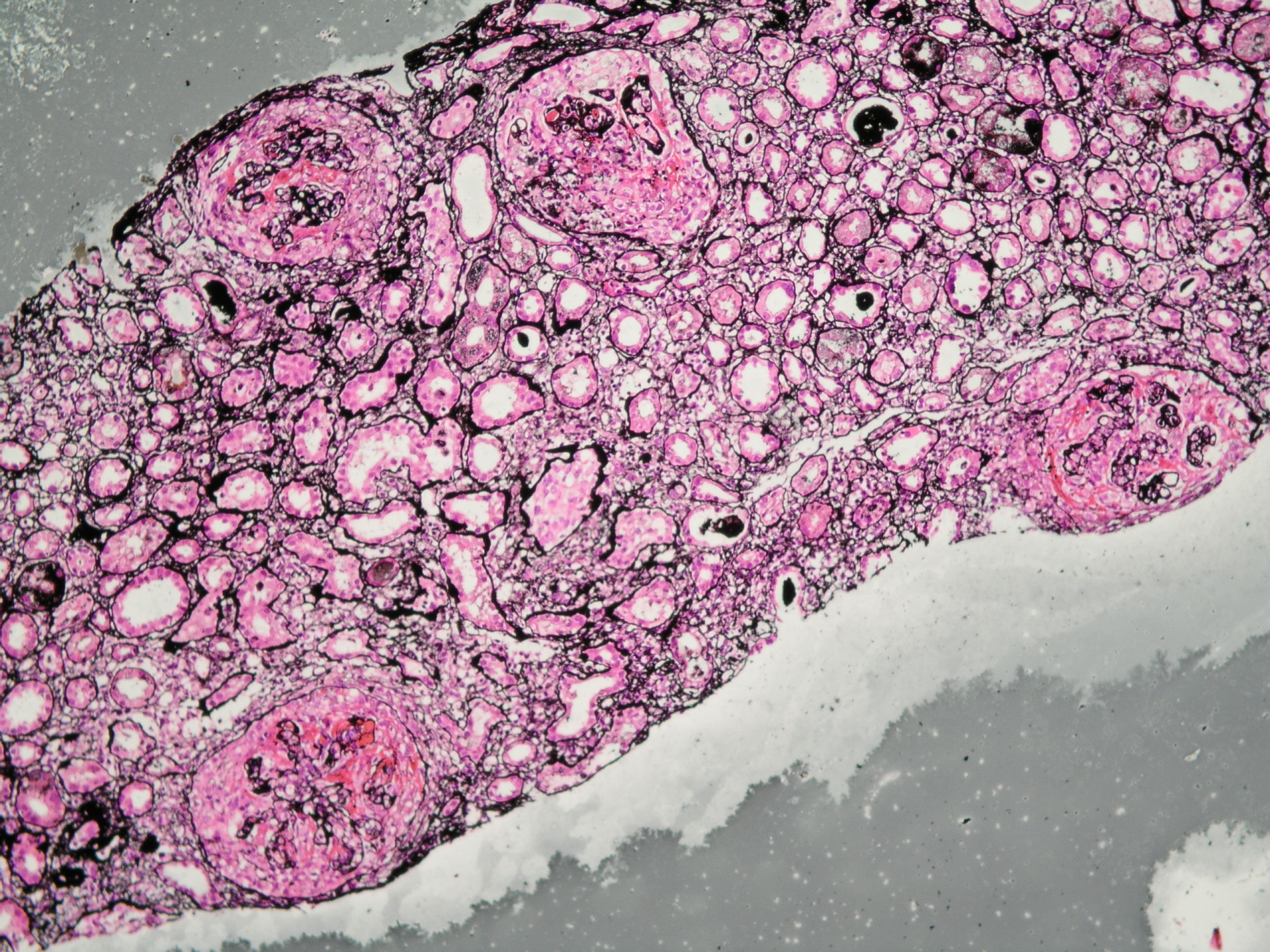
- Treated with diuretics
- No immunosuppression

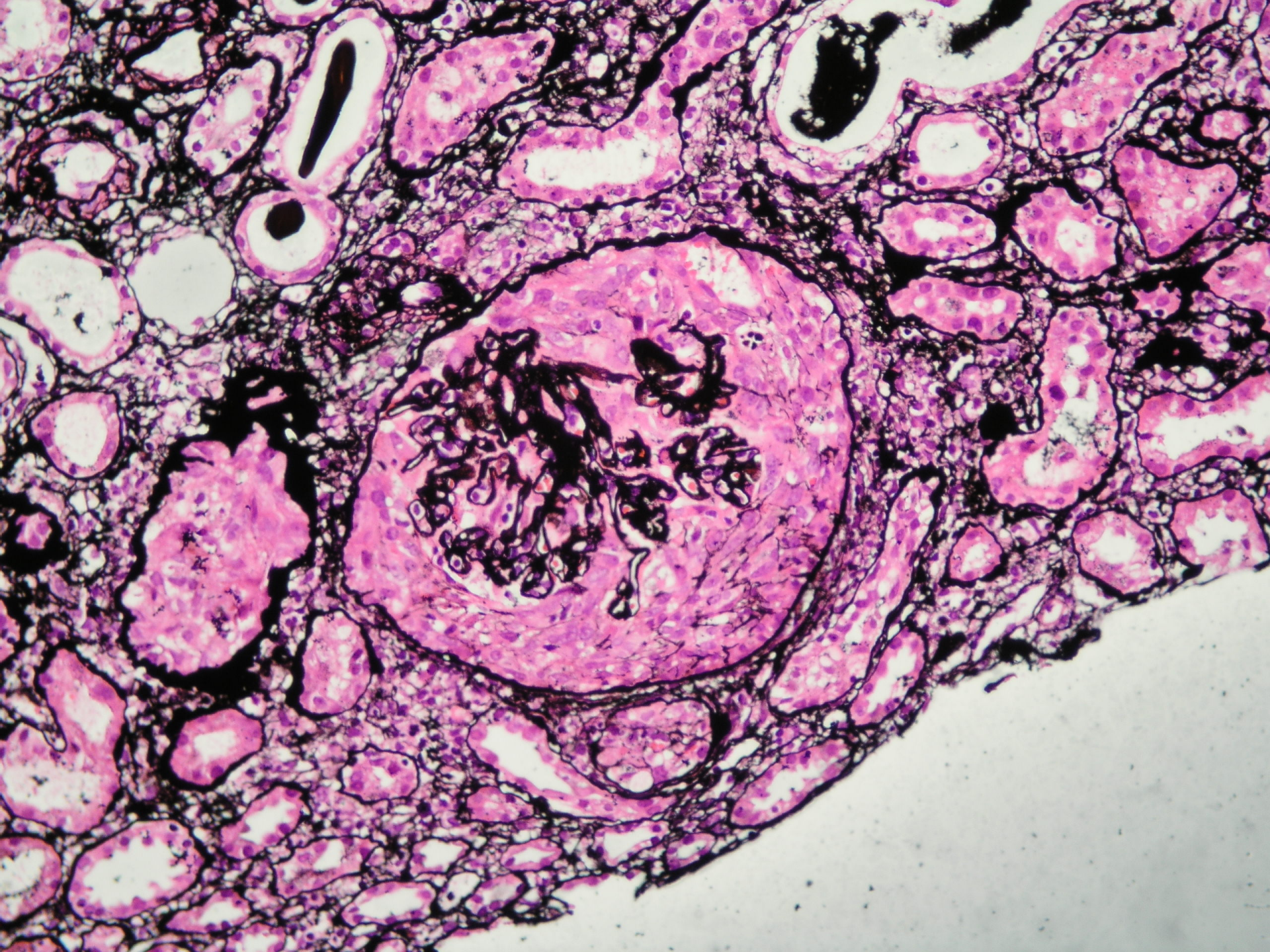
- 8 months later
- Nausea and vomiting
- Anuric for 48 hours
- Creatinine 1400 μmol/l
- Albumin 13g/l
- Started on dialysis

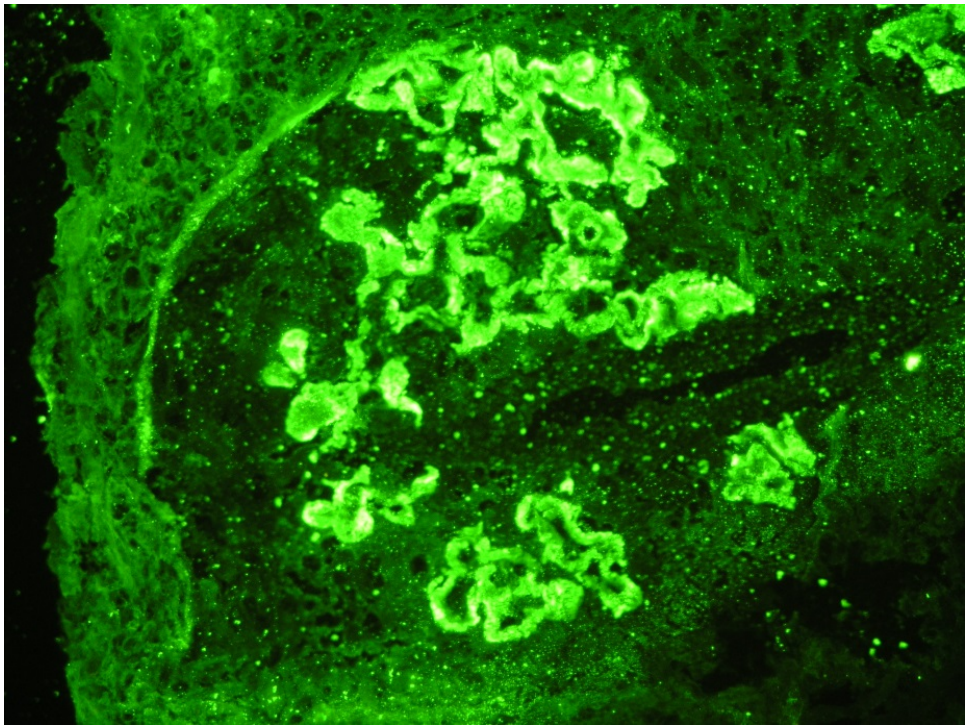
What do you think has happened?





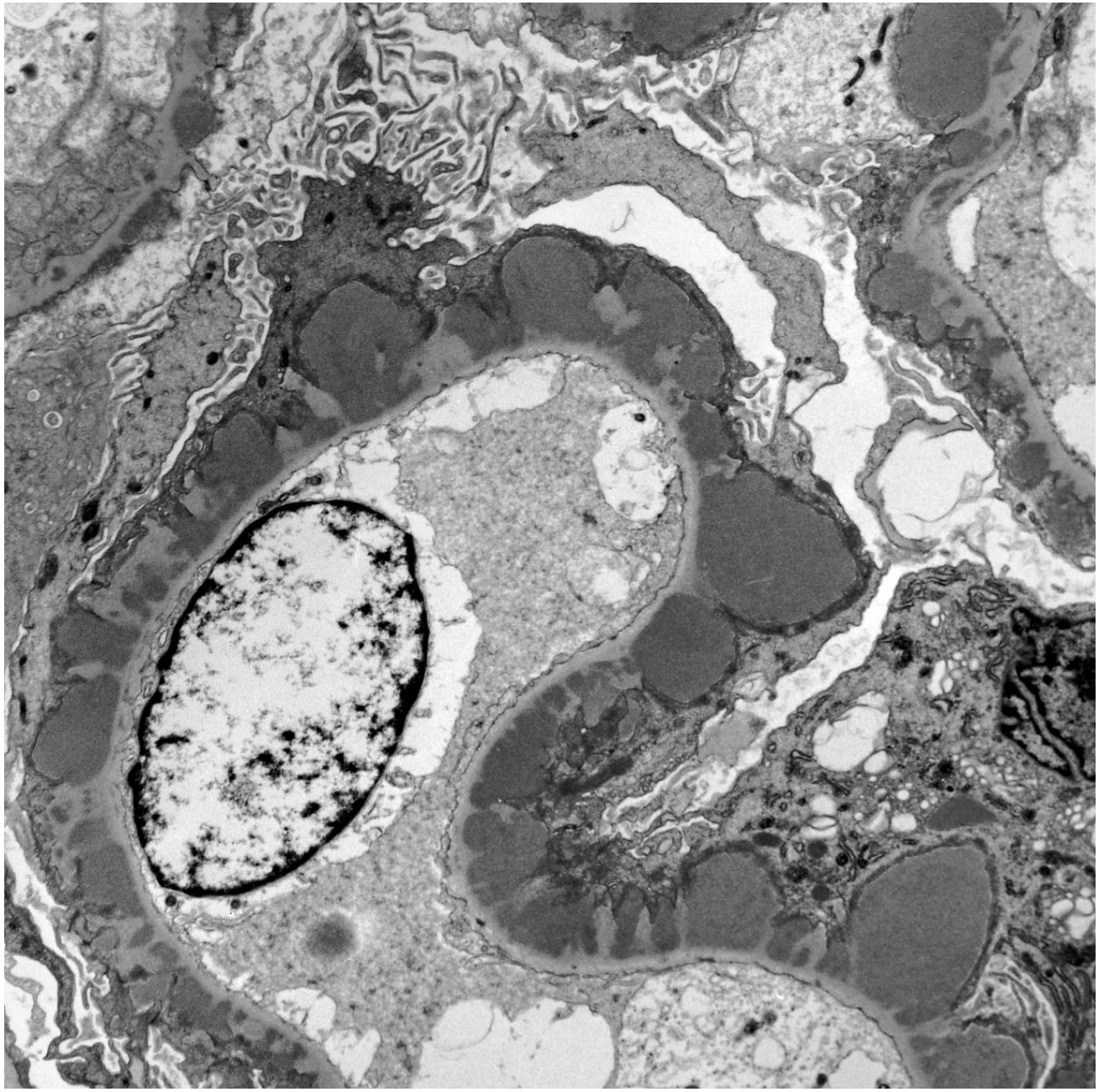






IgG

IgM and C3 showed similar capillary wall staining



Other tests?

- Circulating anti-GBM antibody ELISA

  64% (Normal <15%)

Diagnosis - membranous glomerulonephritis + anti-GBM disease

Crescents in membranous glomerulonephritis

- Very uncommon
- Must exclude SLE
- Most of the reported cases are in association with anti-GBM disease
- Associated with ANCA

Membranous GN and anti-GBM disease

- 17 cases in the literature
- 7/17 membranous preceded anti-GBM
  - Interval 8-17 months
- 7/17 simultaneous

- Our patient declined aggressive treatment

Association of anti-GBM disease with other renal lesions

- Many isolated reports
- Recurrent associations
  - ANCA
  - Membranous GN
  - Diabetic nephropathy
  - Following lithotripsy
  - After renal transplantation in Alport's

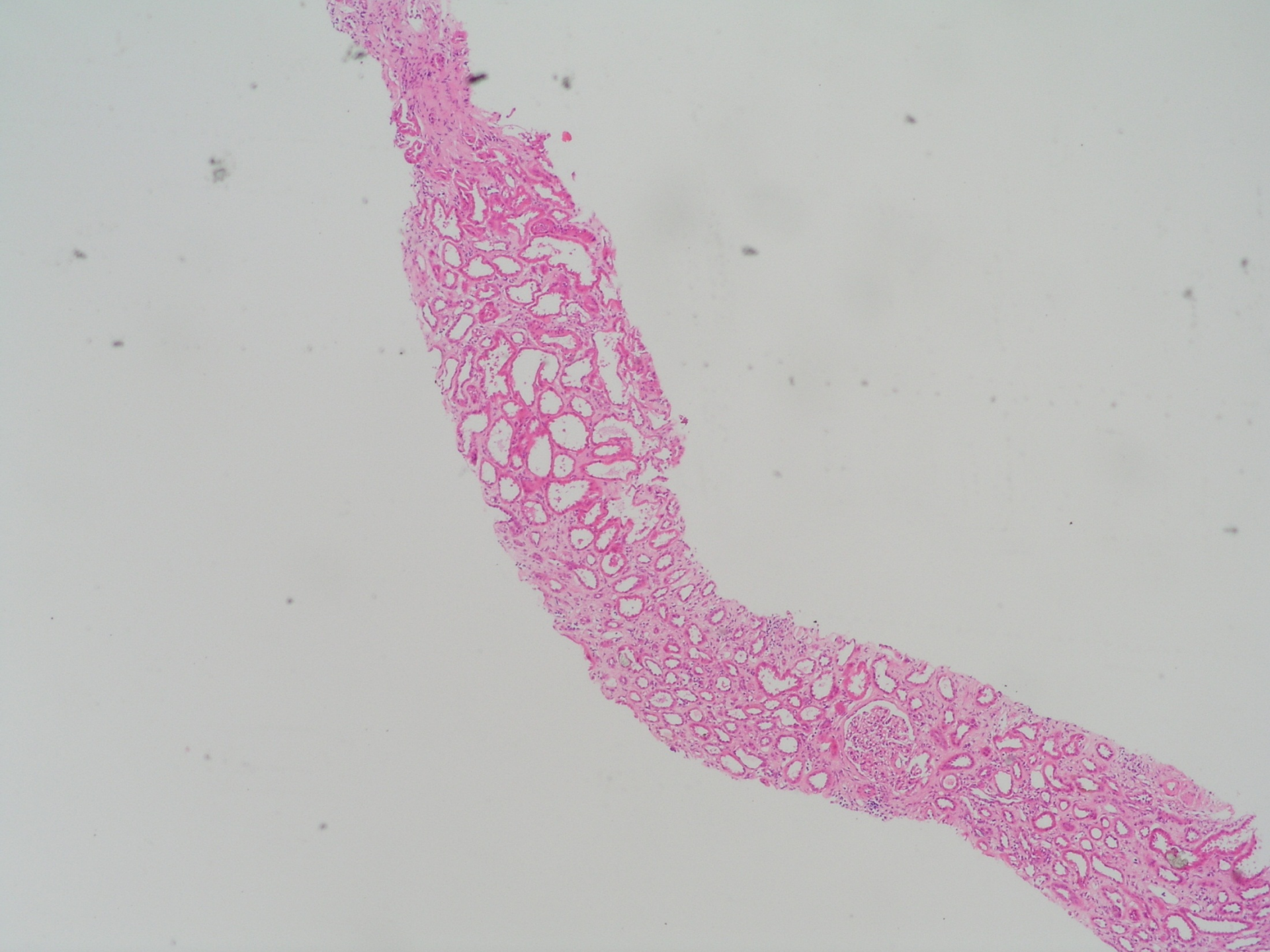
Case 4

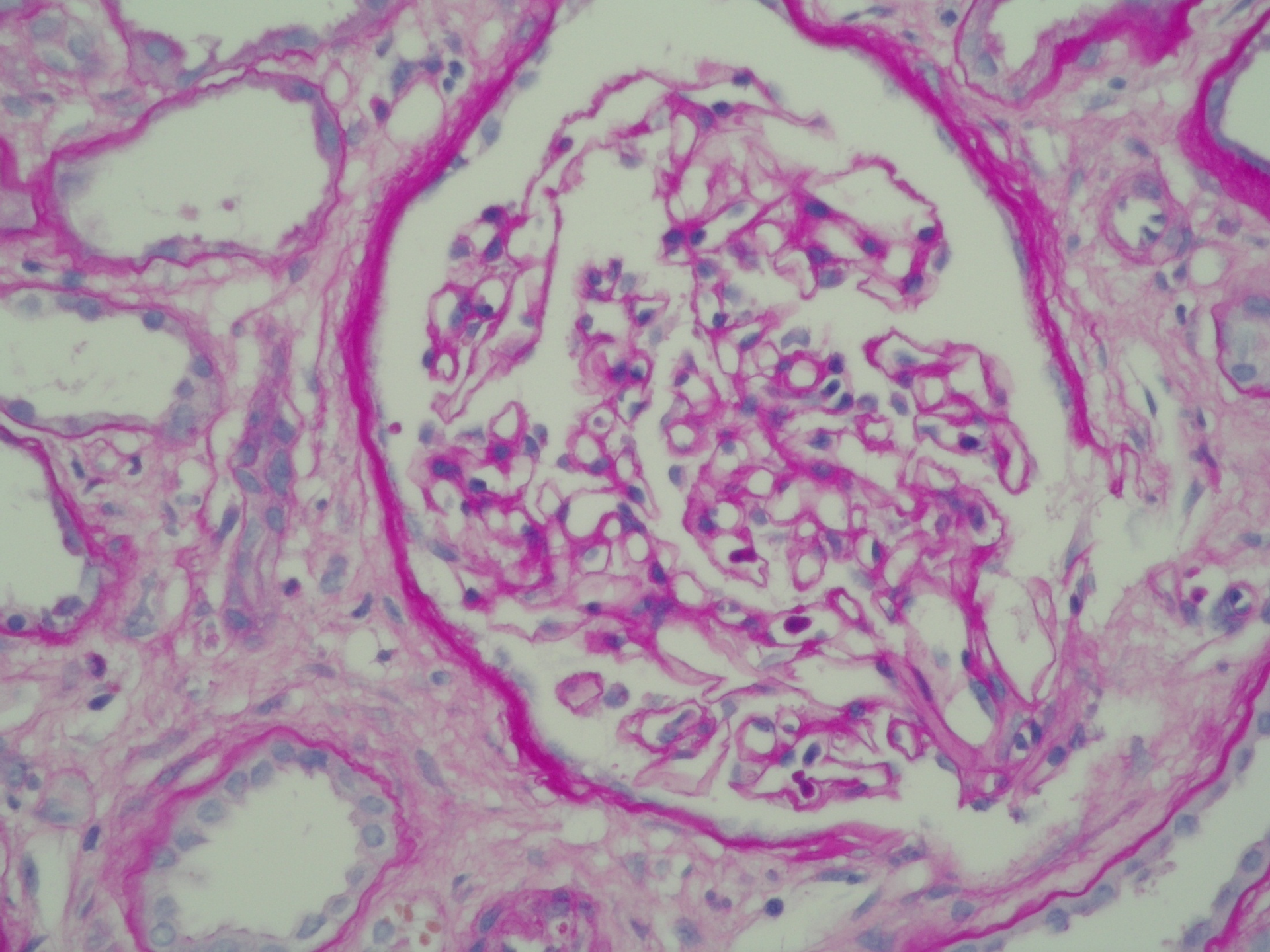
- 44 year old man presented with acute-on-chronic renal failure
- PMH
  - 20 year history of heavy alcohol consumption
  - 14 years ago partial pancreatectomy for chronic pancreatitis
  - Insulin dependent diabetes mellitus
  - Drugs: Insulin, pancreatic supplements

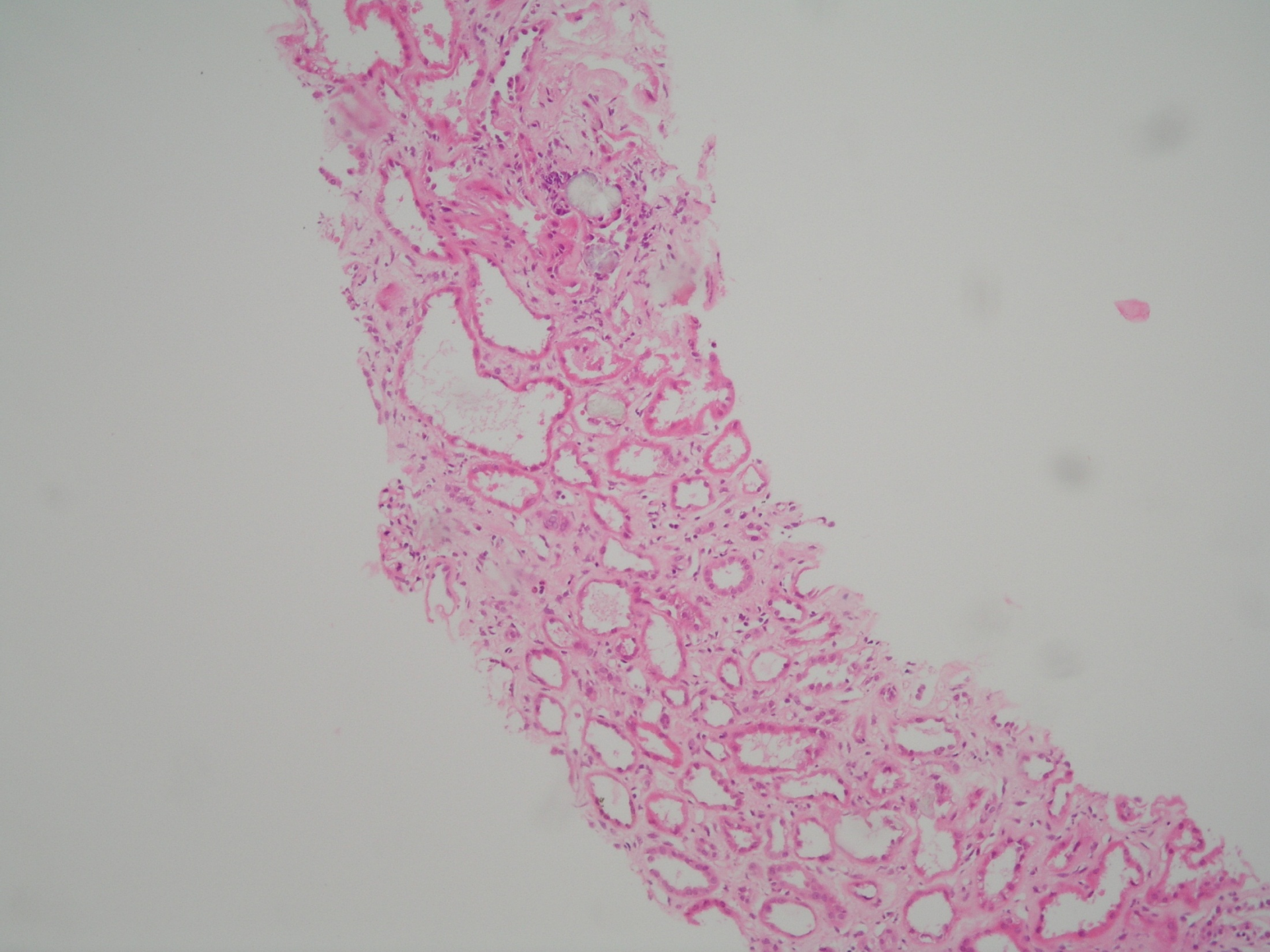
Case 4

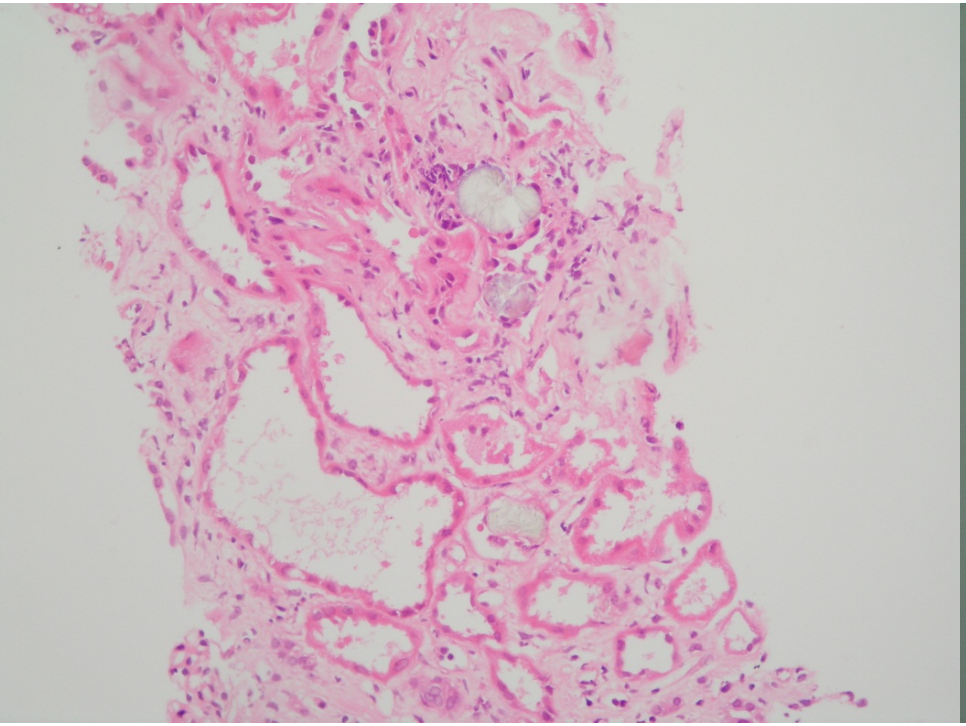
- 2 years before presentation: plasma creatinine: 150 μmol/l. Proteinuria 1g/l
- Presented unwell, malaise, anorexia, BP 110/60
- Sudden deterioration of renal function over 3 weeks to creatinine 560 μmol/l

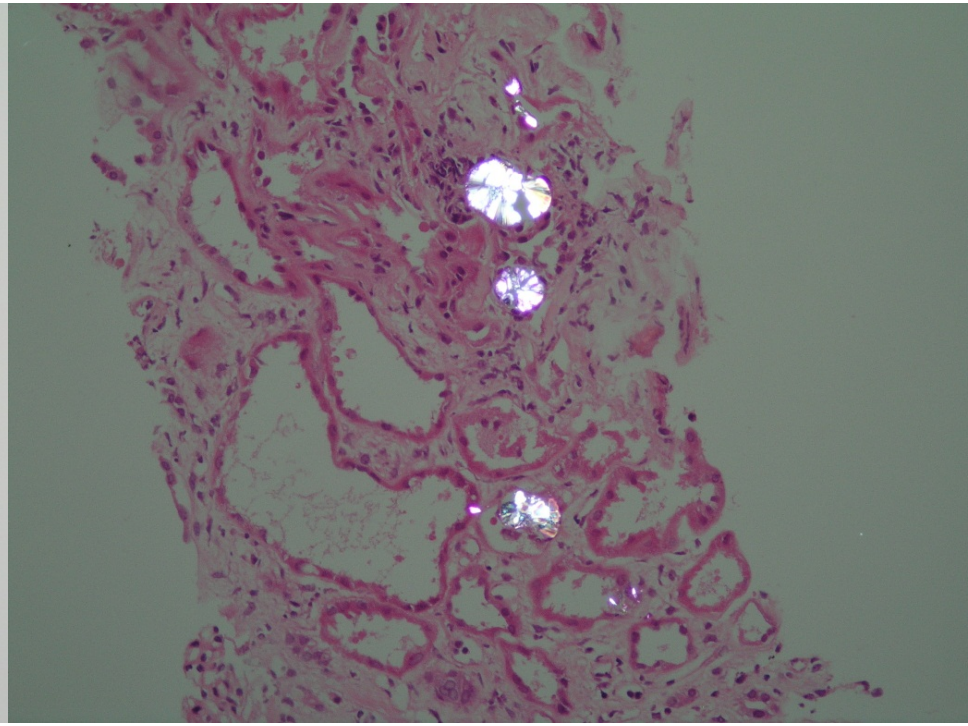
What is the diagnosis?

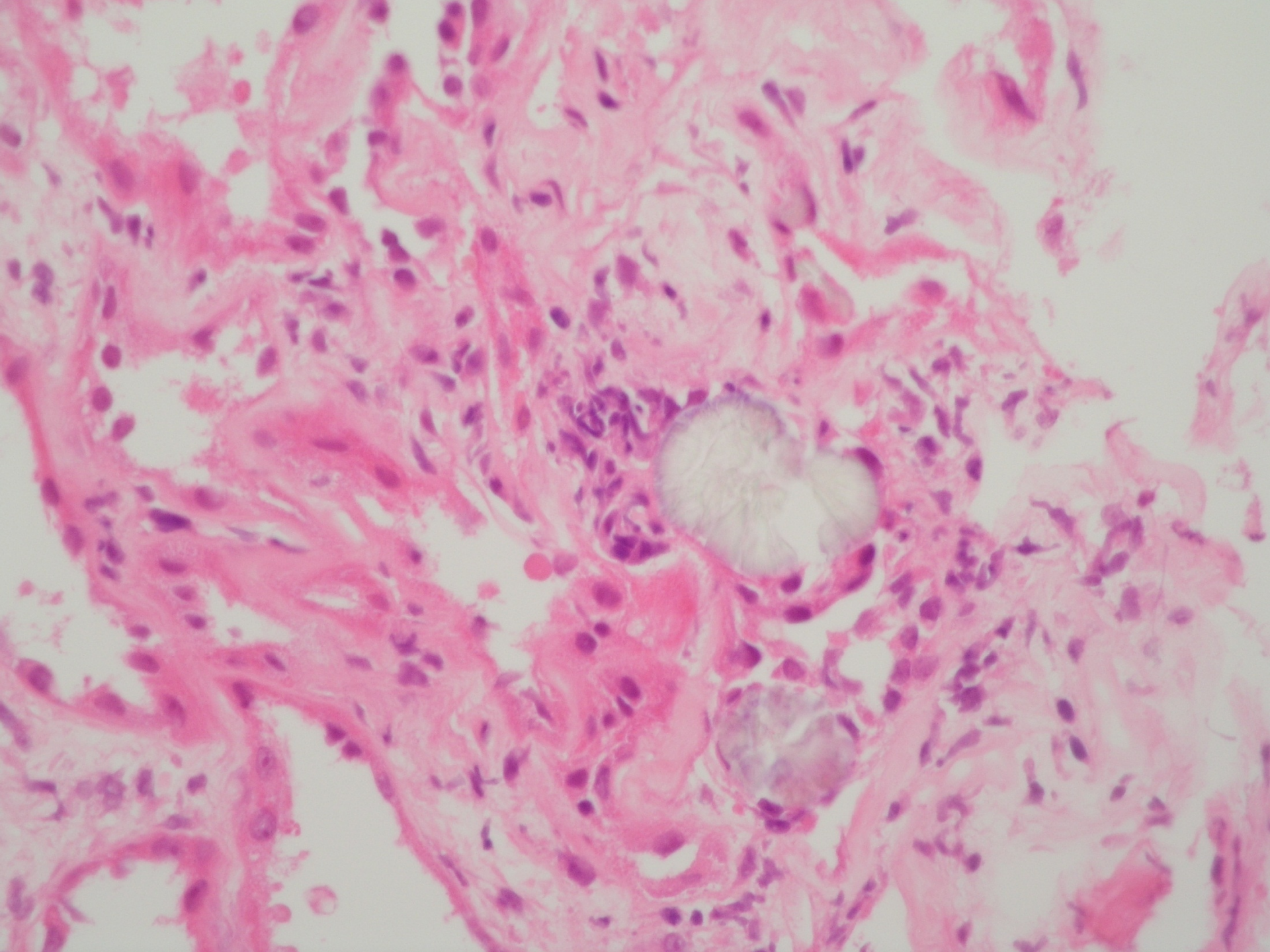












Oxalate nephropathy

- Caused by increased oxalate in urine which precipitates in tubules
- Hyperoxaluria
  - Primary – autosomal recessive enzyme deficiencies
  - Secondary
    - Increased production
    - Increased absorption

Secondary hyperoxaluria

- Increased production
  - Ingestion of ethylene glycol, large amounts of ascorbic acid
- Increased absorption
  - Consequence of fat malabsorption
  - Absorption of oxalate occurs in the colon and is limited by binding of calcium to oxalate in the small bowel
  - In malabsorption calcium binds to free fatty acids allowing increased absortion of oxalate in the colon

Secondary hyperoxaluria

- Described in
  - Cystic fibrosis
  - Coeliac disease
  - Chronic pancreatitis and post-pancreatectomy
  - Dibetic gastroenteropathy
  - “Short bowel” syndrome with intact colon e.g. small bowel resection for Crohn’s disease, jejunoileal bypass for obesity

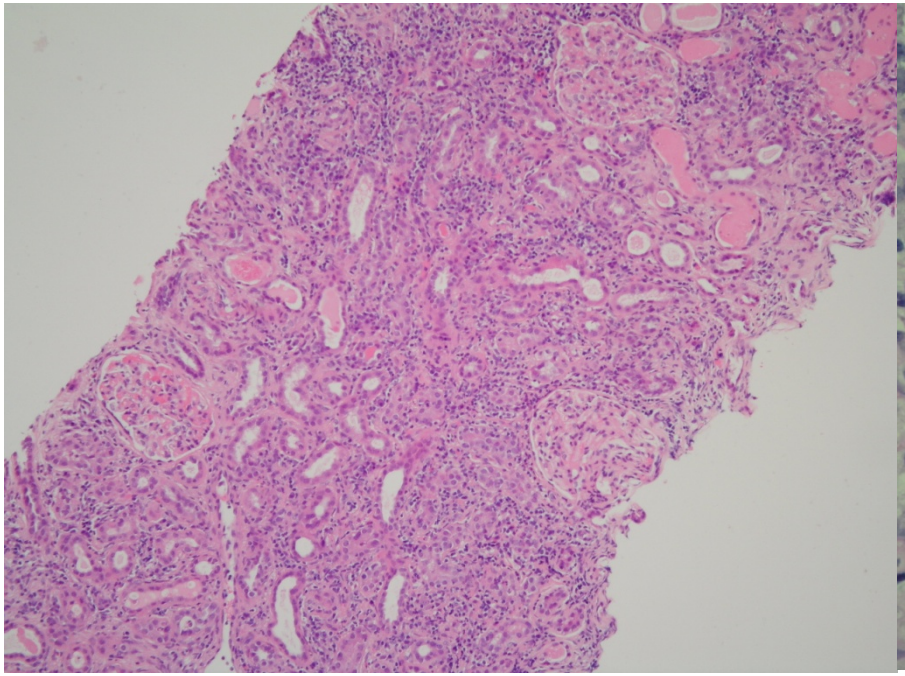
- Our patient admitted that he took his pancreatic supplements irregularly and had frequent episodes of diarrhoea and steatorrhoea

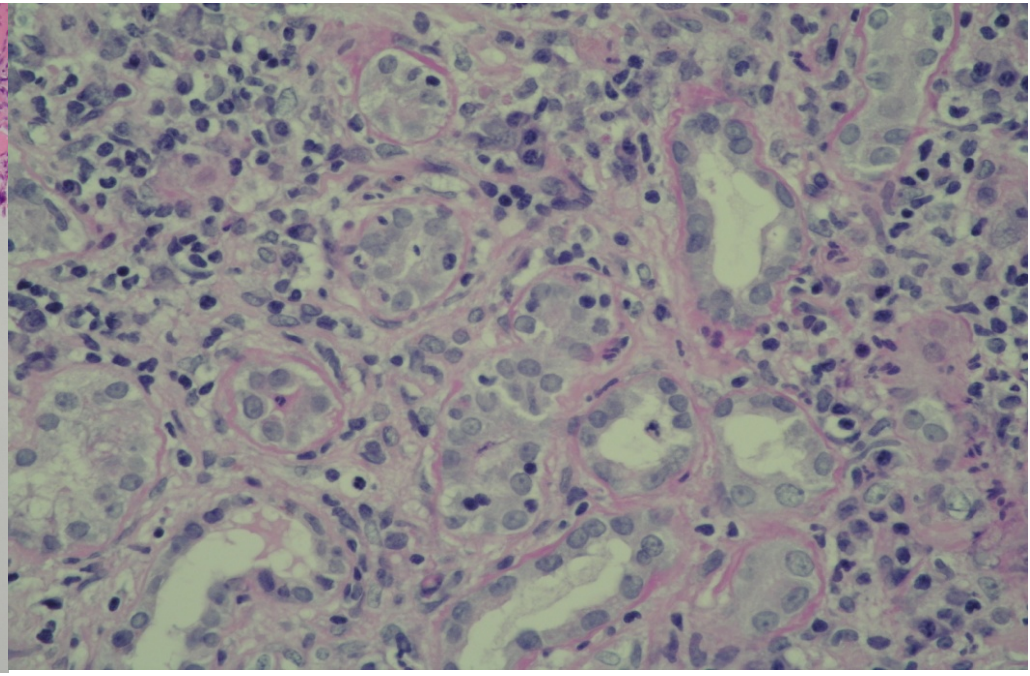
Case 5

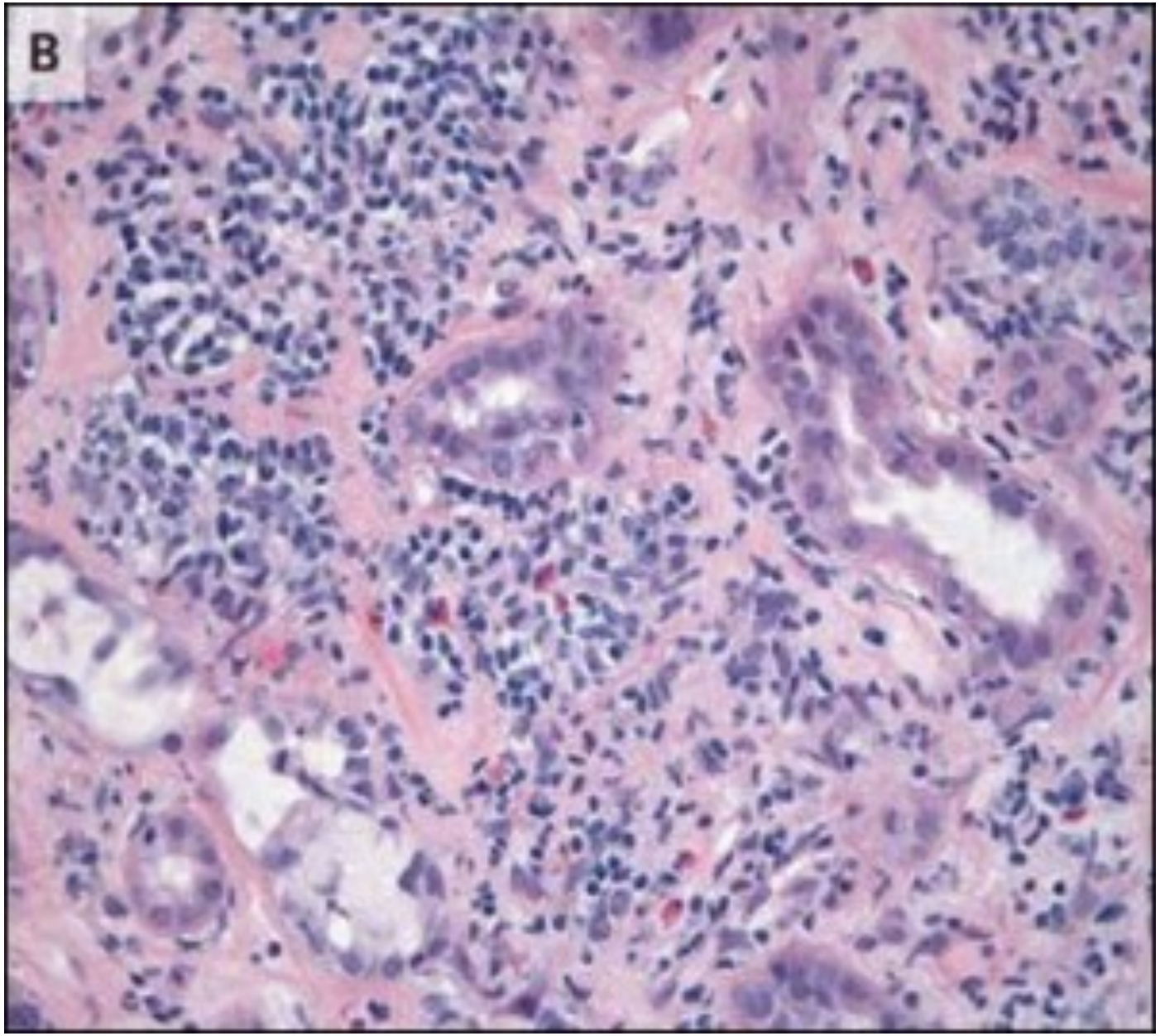
- A 43 year old man previously fit and well presented to GP with tiredness, malaise, arthralgia and was found to have a creatinine of 450μmol/l.
- His was previously fit and well, and a regular runner (30 miles/week, marathons)
- Urine dipstick testing blood(3+) and protein(+) glycosuria(++)

What is your differential diagnosis ?

Tubulointerstitial nephritis






B

Tubulointerstitial nephritis

- Main target – tubules
- Damage caused by lymphocytes, neutrophils, eosinophils, antibodies and complement
- In response to antigens that are expressed in tubules or caught in tubules
- May be autoimmune or secondary to foreign antigens
- Eosinophils may predominate in drug induced causes

Causes of tubulointerstitial nephritis

- Infections: bacterial (TB, streptococcus), viral (CMV, HIV), fungal, parasitic, ricketsial
- Drugs: **anything**, but commonly antibiotics, NSAID, PPI
- Immunological: SLE, Sjogren's, sarcoidosis
- Unknown

Case 6

- 55 year old timber trader visiting Brazil
- Boat caught fire and so did patient and his cousin; Jumped into river
- Sustained 30% burns- arms and legs
- In hospital 10/7
- Rigors on four occasions;
- Short course of ciprofloxacin

Repatriated to UK

- Grossly oedematous, hypertensive, hypoalbuminaemic
- Skin grafting to arms and legs
- Progressive swelling
- Thought to be due to burns
- Treated with albumin and diuretics
- SCr 116 mmol/l; Albumin 24g/dL;
- Differential Diagnosis? Any other tests?

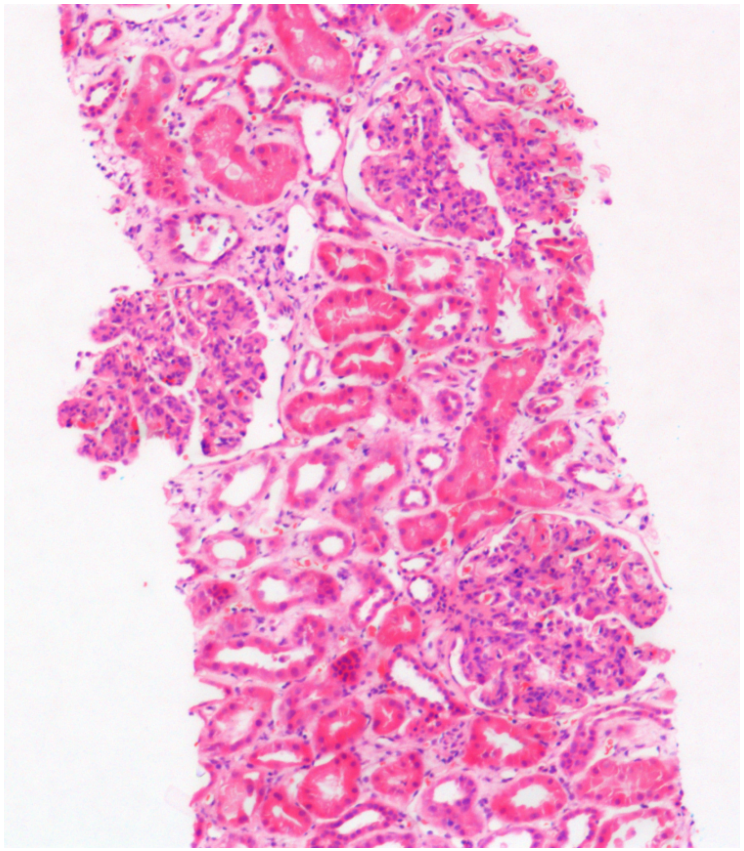
Repatriated to UK

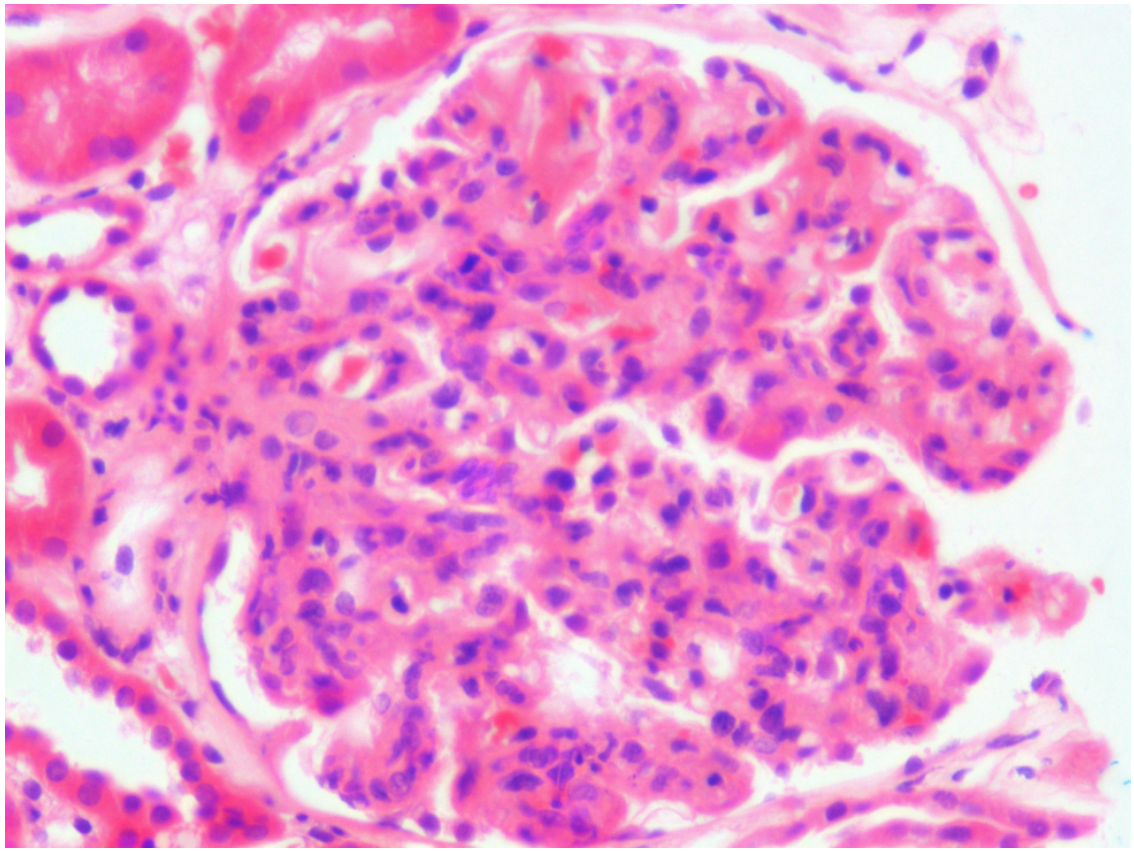
- Grossly oedematous, hypertensive, hypoalbuminaemic
- Skin grafting to arms and legs
- Progressive swelling
- Thought to be due to burns
- Treated with albumin and diuretics
- SCr 116 mmol/l; Albumin 24g/dL;
- Noted to have UPCR 1200 mg/mmol

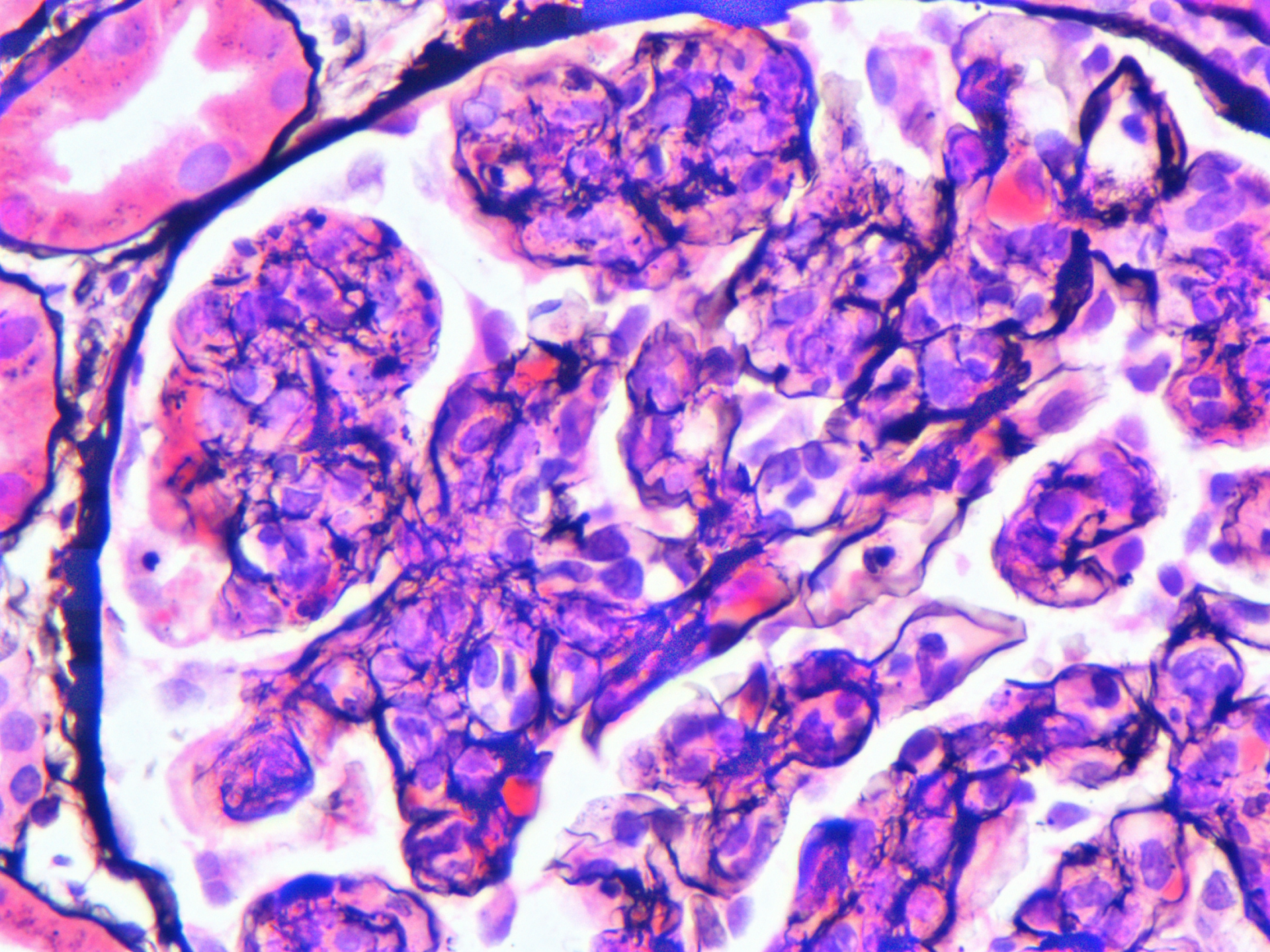
Additional data

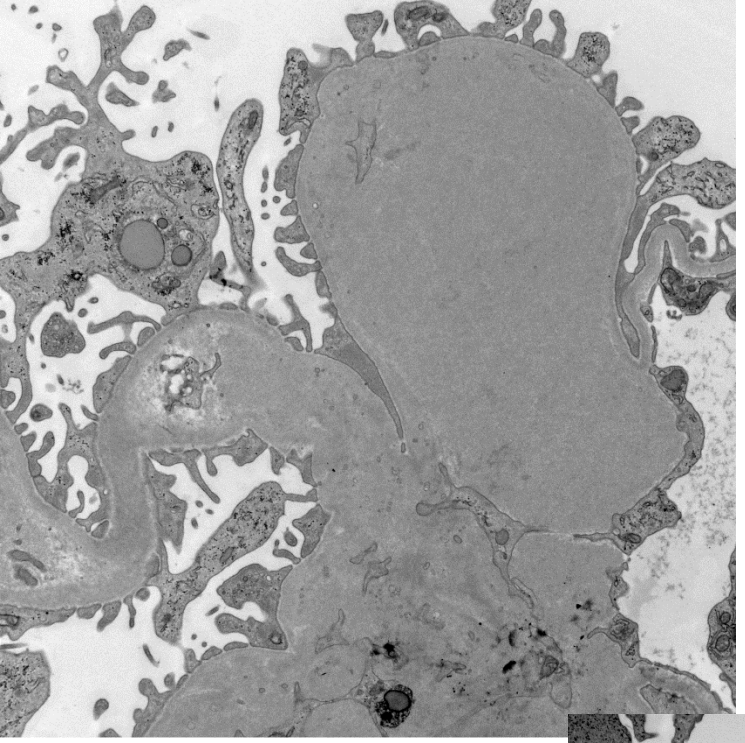
- C3 0.87(0.9-1.8), C4 0.35(0.1-0.4)
- ASOT not elevated
- ANCA, ANA, RhF all negative
- HIV, HCV, HBsAg all negative
- Syphyllis serology negative
- IgG low, no paraprotein
- Creatinine rose gradually- to 174 μmol/l
- What next ?

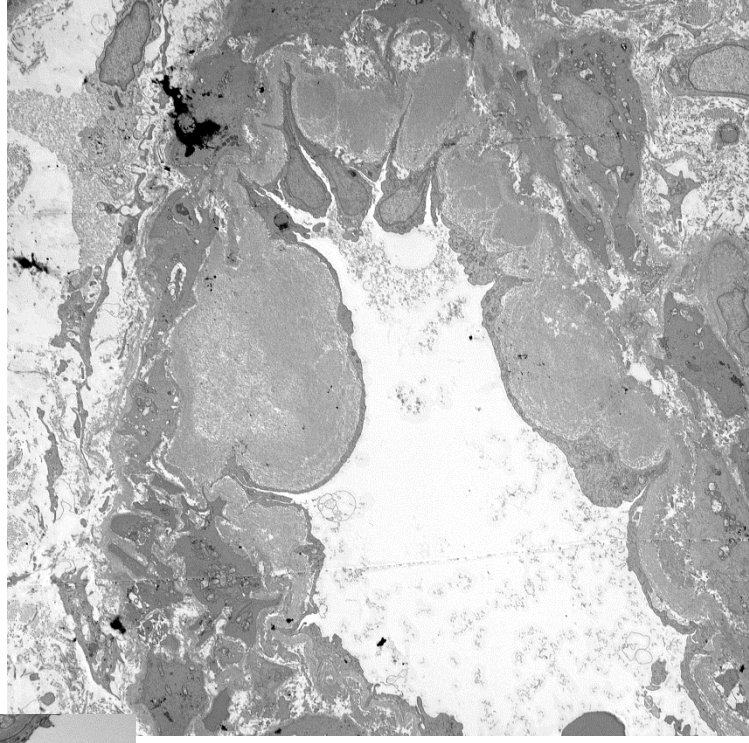
Renal Biopsy:September 2013

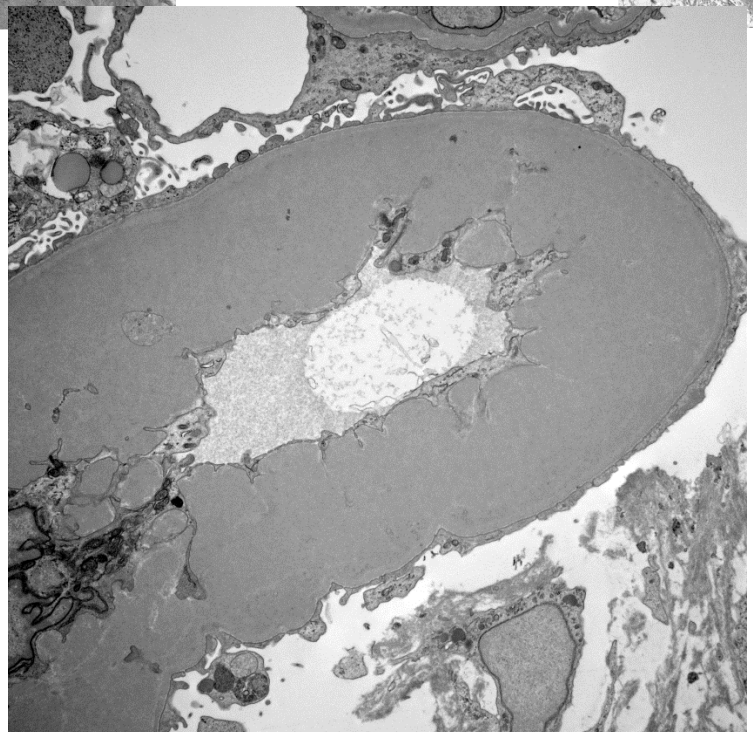




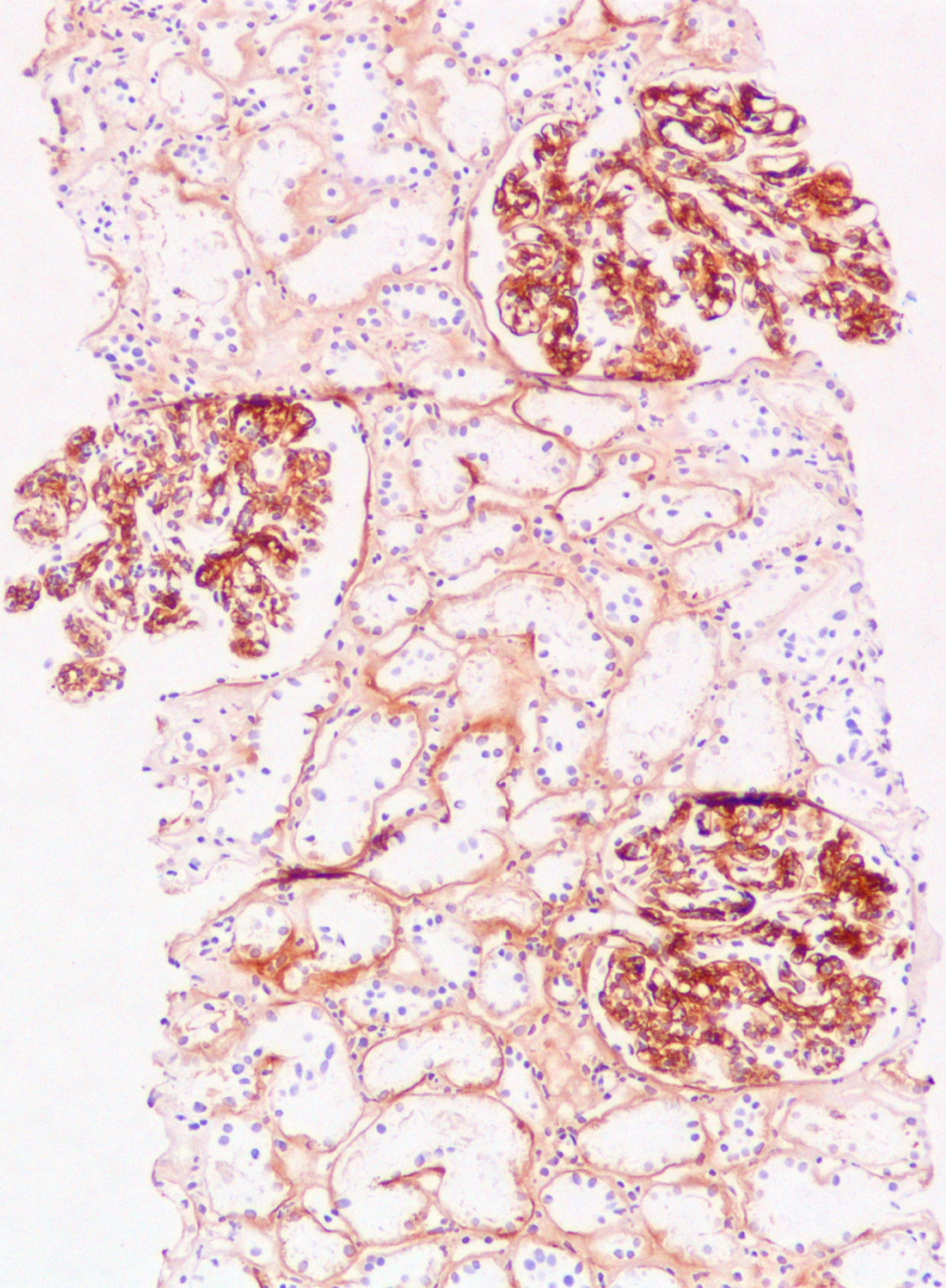




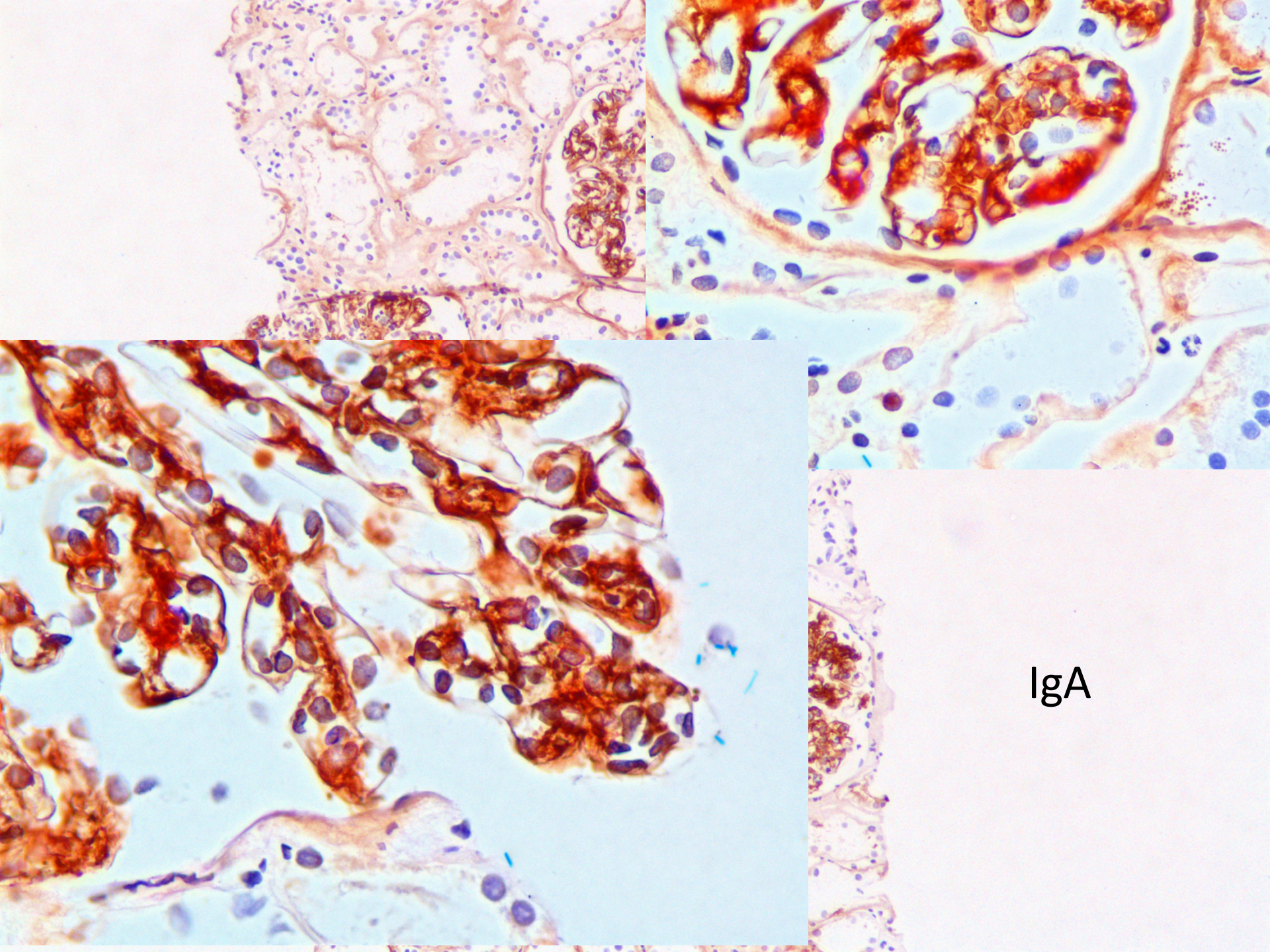




Diagnosis?



IgA


IgA

Diagnosis

- IgA rich atypical post infectious GN
- Infection from river? From burns?

IgA rich PIGN

- Increasingly reported in older patients
- Underlying complement abnormality?
- Often Staph aureus, or MRSA
- Need to treat infection and in limited cases may need immunosuppression

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ROYALFREE

Conclusions

- Intrinsic kidney disease may result in damage to glomeruli, tubules or blood vessels
- More than one compartment maybe affected
- Many intrinsic renal diseases are medical emergencies as delayed treatment leads to irreversible loss of function
- Blood and urinary abnormalities may provide clues as to cause
- Renal biopsy important in demonstrating damage and extent of reversibility