

# RENAL PATHOLOGY IN 2026

## Part I: Nephritic Conditions

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- Professor of Pathology, Harvard Medical School

# Disclosures

No relevant disclosures

# Objectives

- Review the patterns of injury associated with the hematuric conditions and the nephritic syndrome
- Discuss the pathophysiology and differential diagnosis of these patterns of injury



# THE CARDINAL SIGNS OF GLOMERULAR DYSFUNCTION

- Proteinuria [dipstick, 24hr collection, Prot/Cr]
- Hematuria [dipstick, sediment]
- Loss of GFR [sCr; eGFR]

# THE CLINICAL SYNDROMES

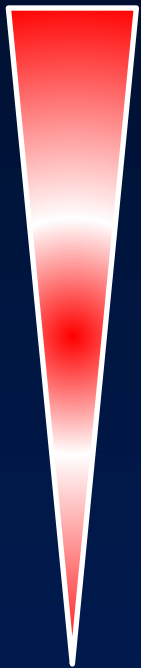
1. The Nephrotic Syndrome

2. The Acute Nephritic Syndrome

3. Rapidly Progressive Glomerulonephritis

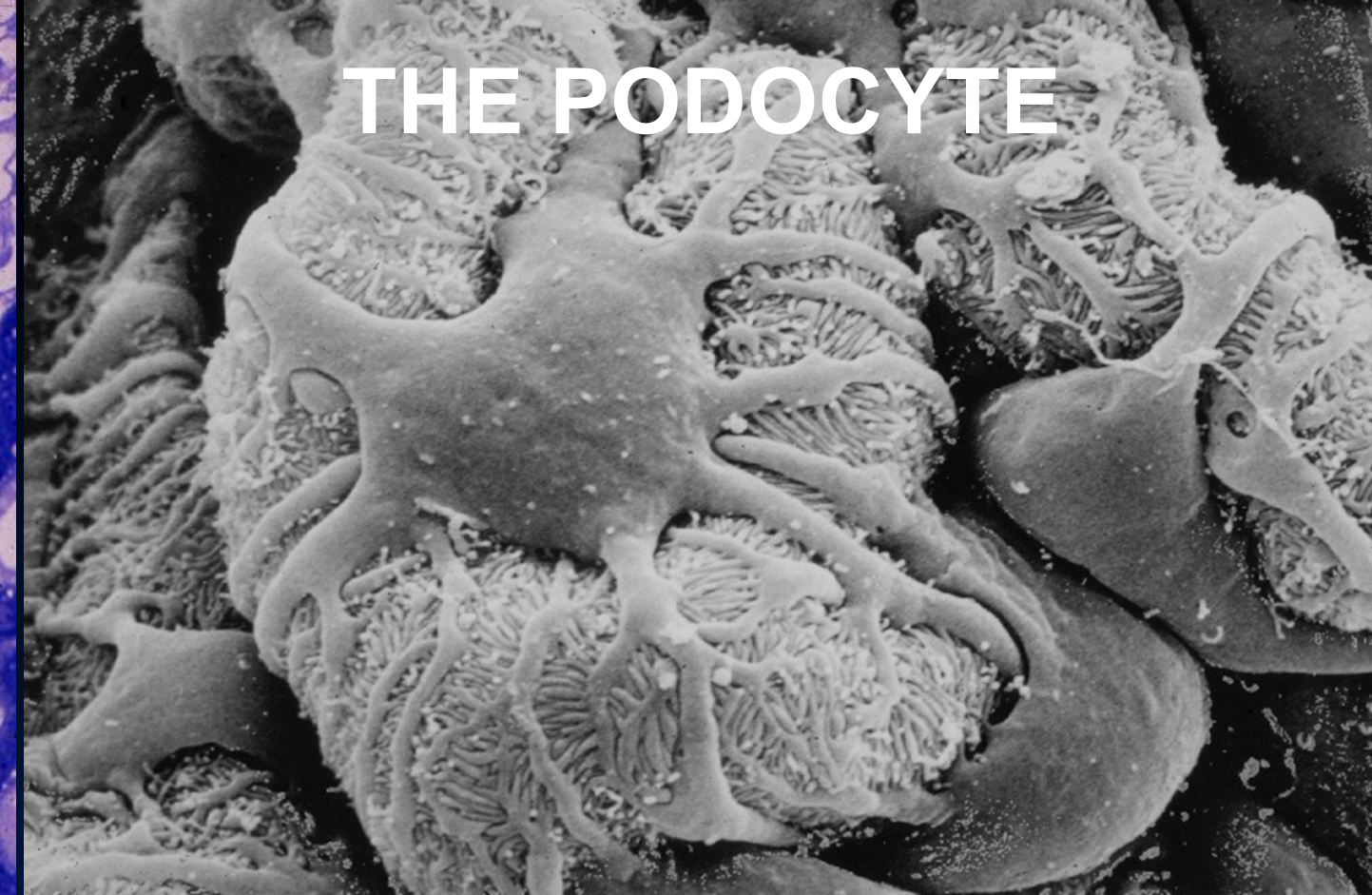
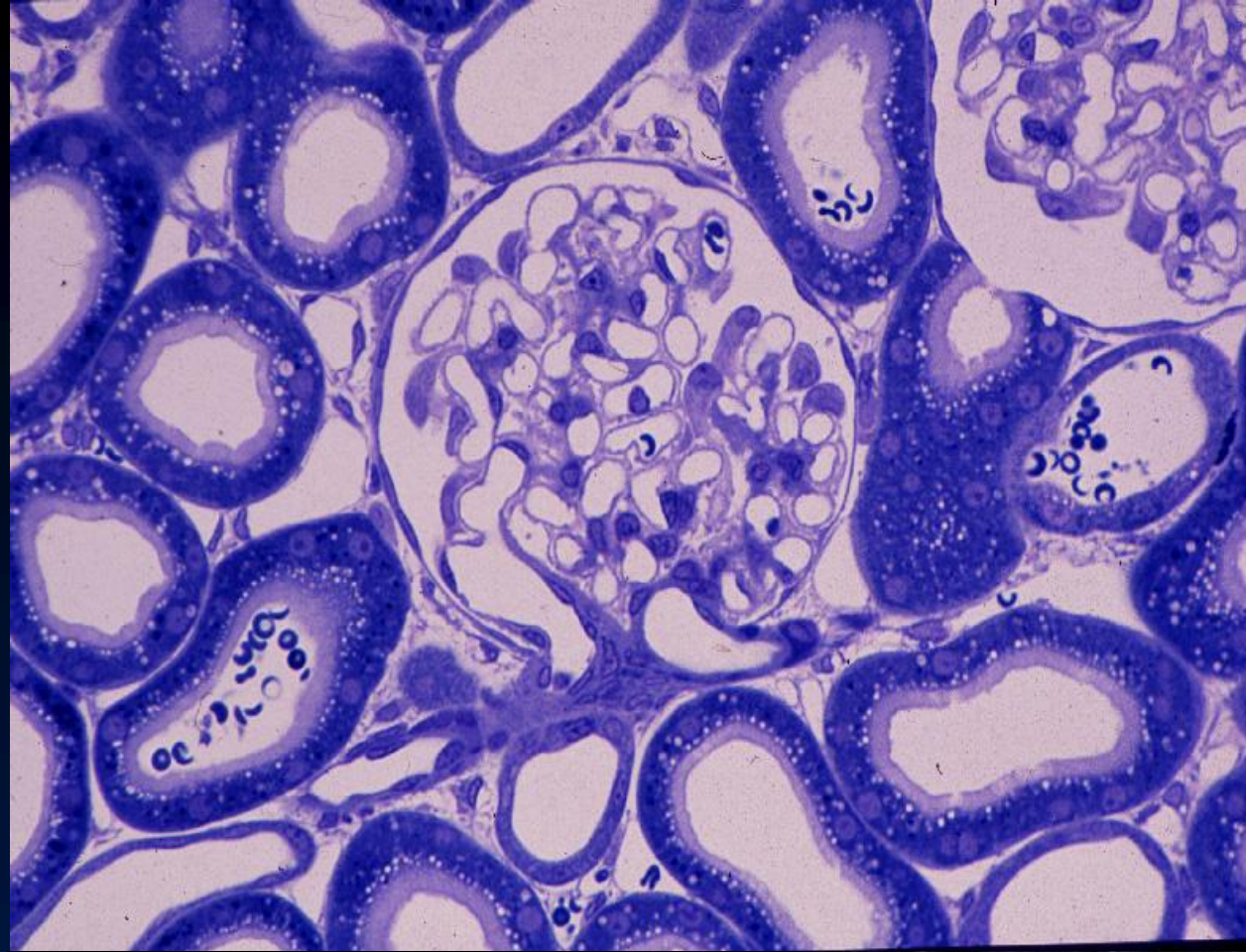
4. Asymptomatic Hematuria / Proteinuria

5. The Chronic Nephritic Syndrome  
(Chronic Renal Failure)

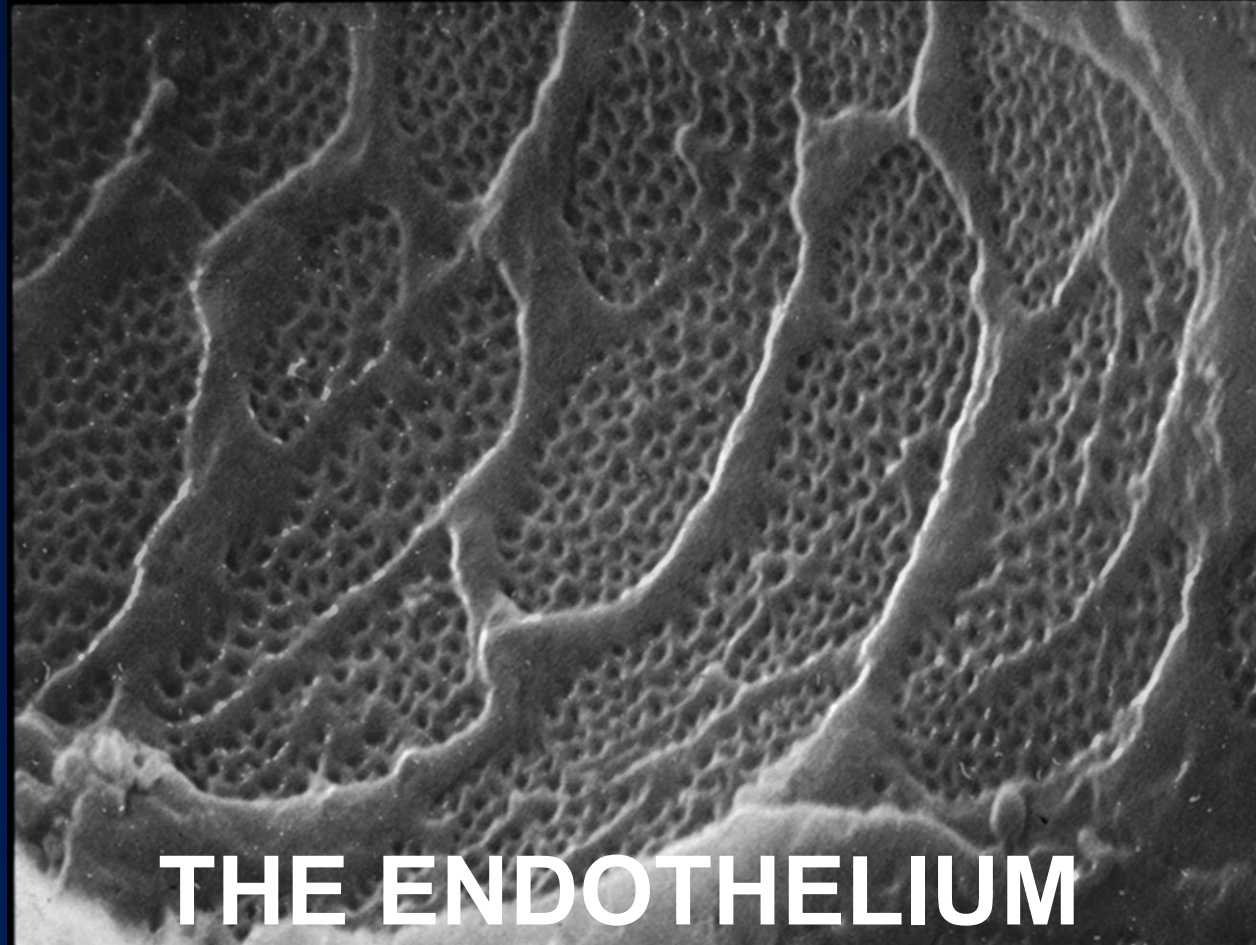




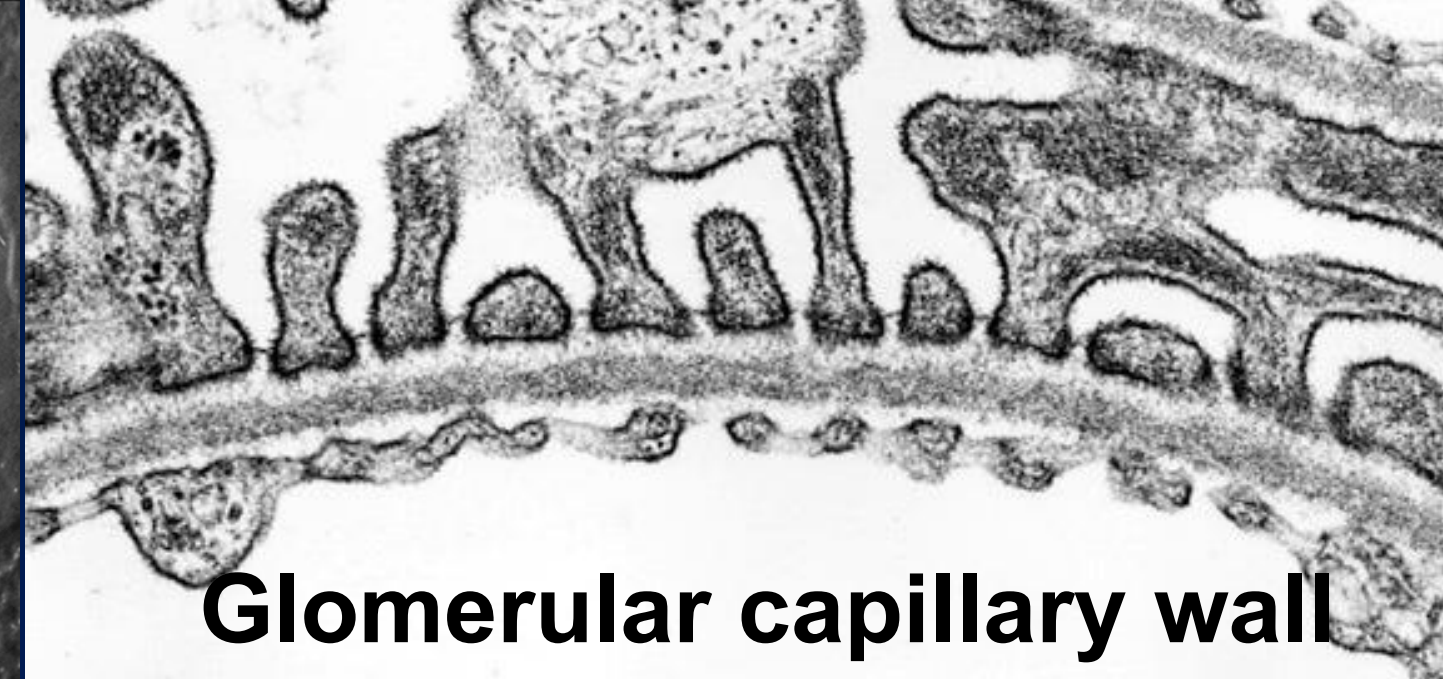
**The unique structural adaptations of  
the glomerular microcirculation**



**THE PODOCYTE**



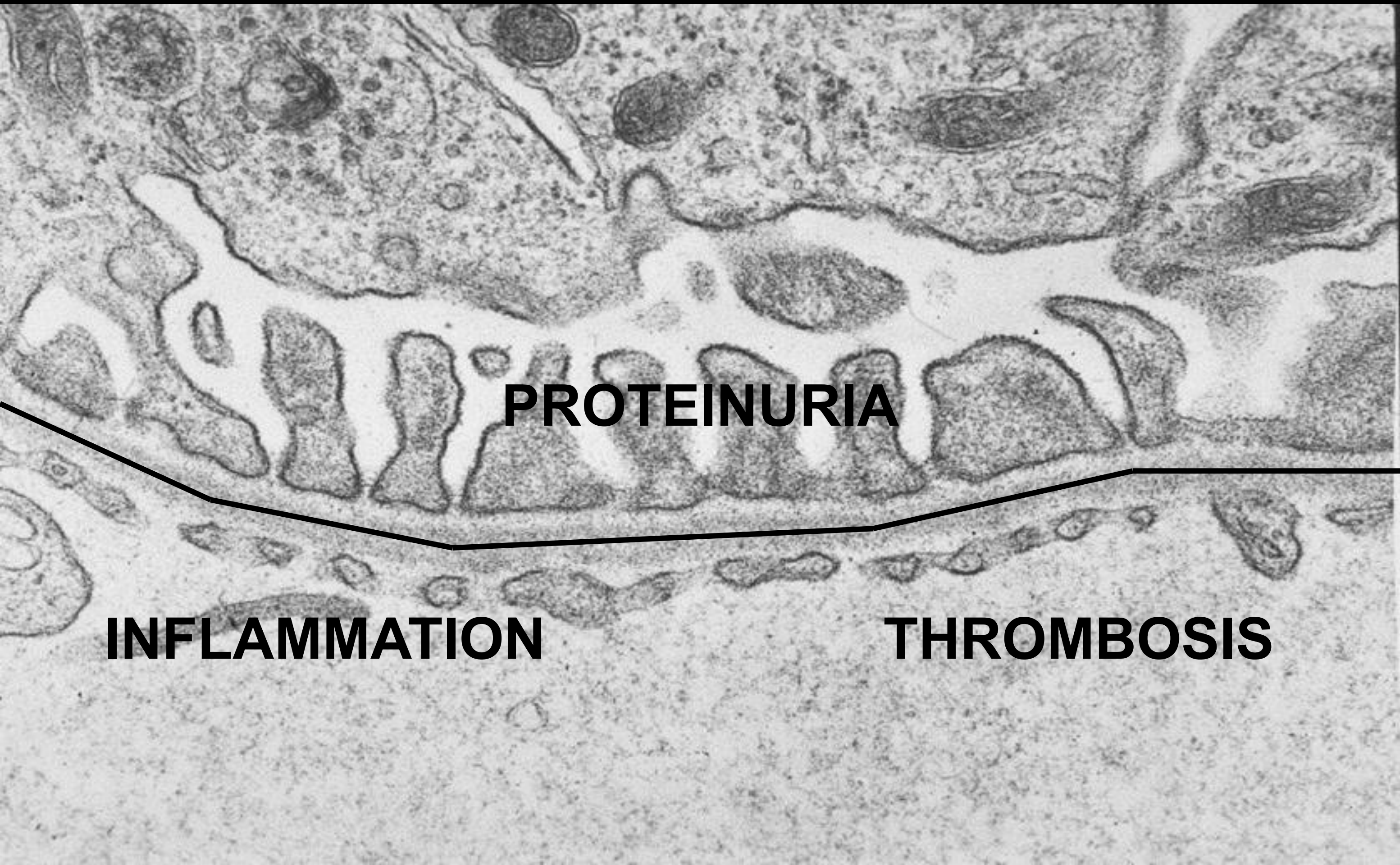
**THE ENDOTHELIUM**



**Glomerular capillary wall**

**Key Target Cells**





**PROTEINURIA**

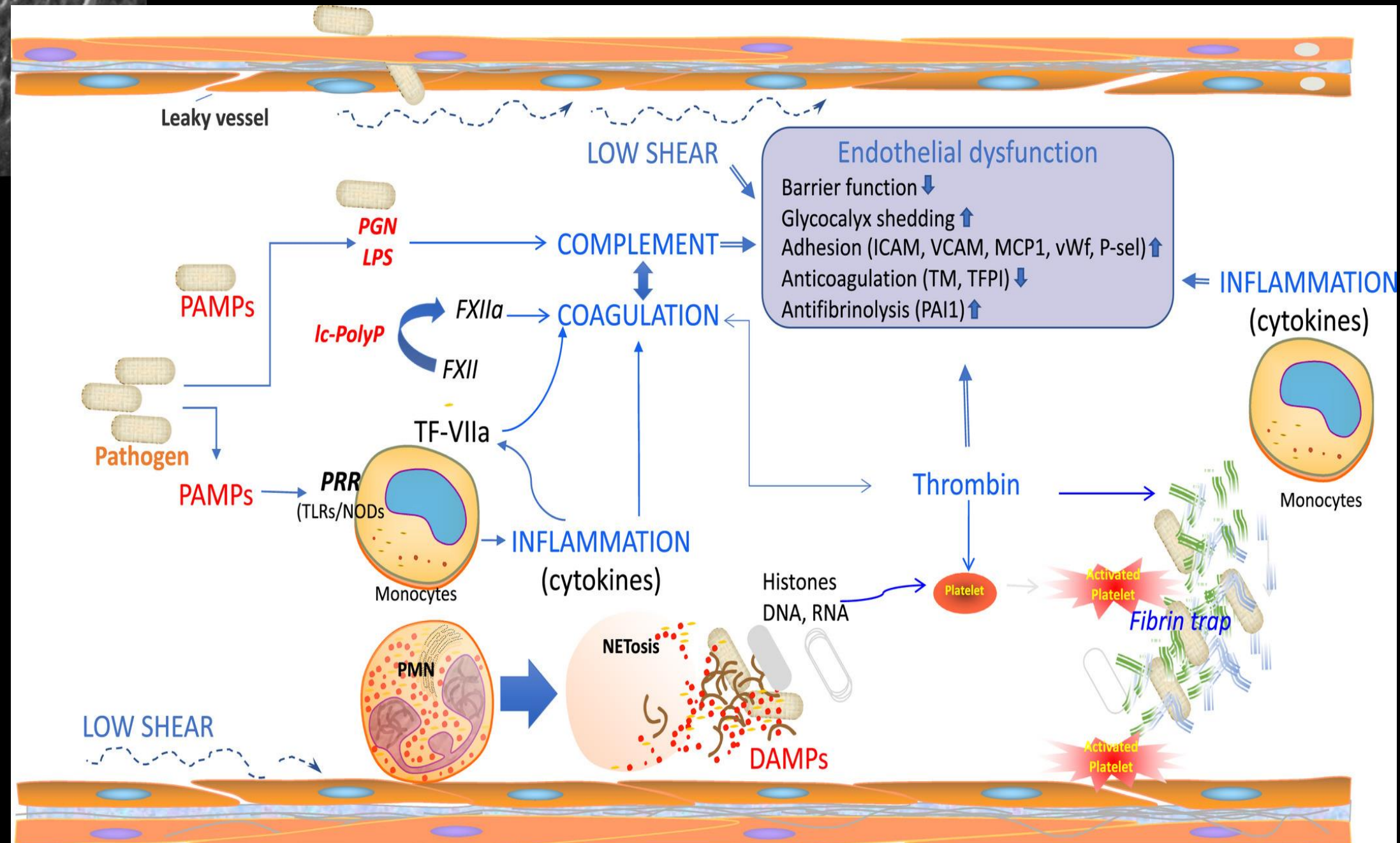
**INFLAMMATION**

**THROMBOSIS**



# THE ROLE OF THE ENDOTHELIUM IN INFLAMMATION AND THROMBOSIS

Frequent overlap of features



# THE CARDINAL SIGNS OF GLOMERULAR DYSFUNCTION

- Proteinuria

- Hematuria

  - **Glomerulitis** (4 basic mechanisms)

    - Inflammation from complement activation via classical pathway by immune complexes in the capillary wall or paraproteins
    - Inflammation by activation of complement via the alternative pathway
    - Inflammation through antibody-dependent cell cytotoxicity
    - Inflammation through cell-mediated immune mechanisms

  - **Capillary fragility** (GBM defects)

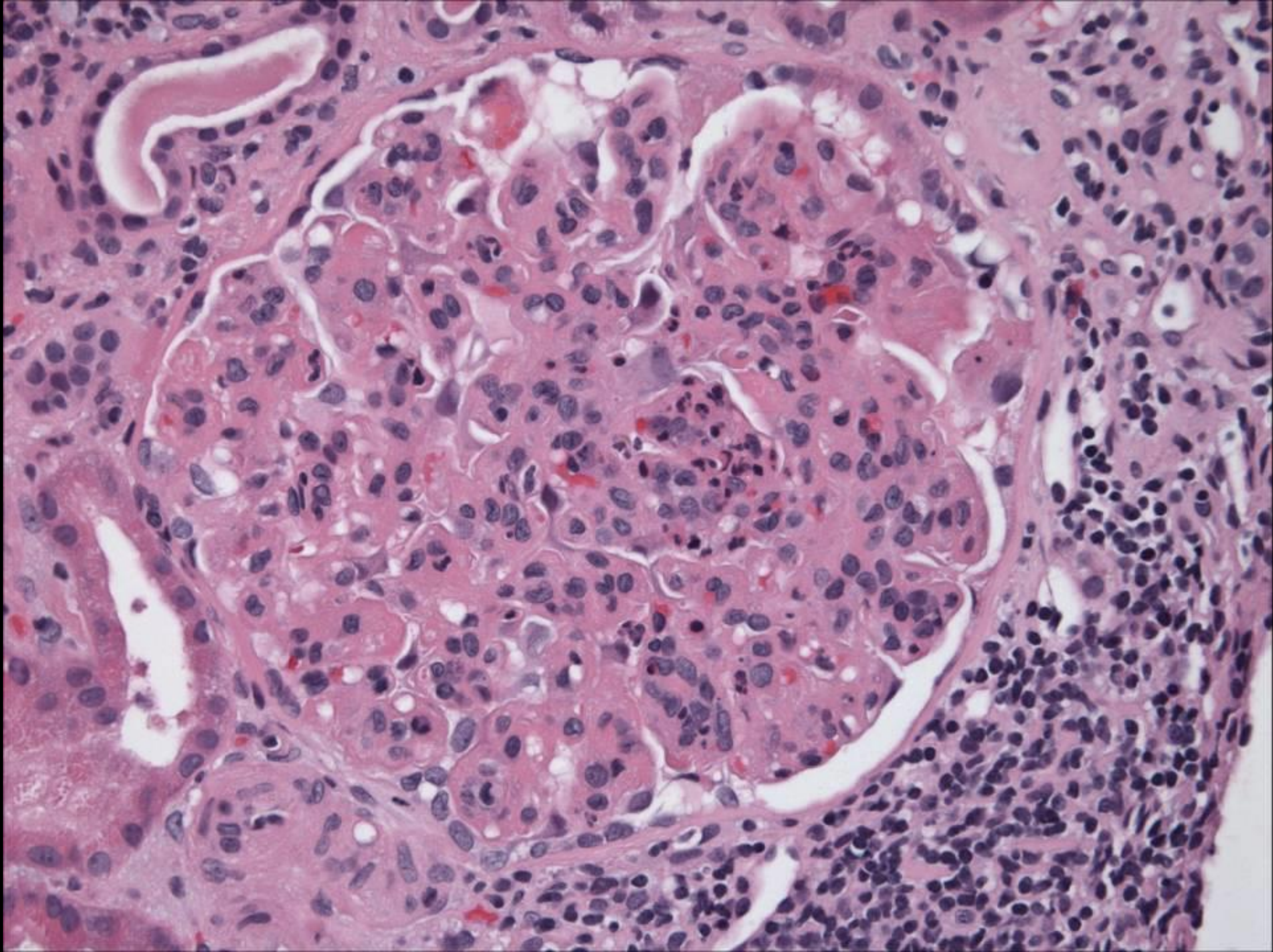
- Loss of glomerular filtration rate

# THE BASIC STRUCTURAL PATTERNS OF GLOMERULAR INJURY

- 1.- Epithelial Cell Disease (Minimal Change Disease)
- 2.- Focal Segmental Glomerulosclerosis
- 3.- Membranous Nephropathy
- 4.- Diffuse Proliferative Glomerulonephritis
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- 9.- Basement Membrane Abnormalities
- 10.- Focal Global Glomerulosclerosis



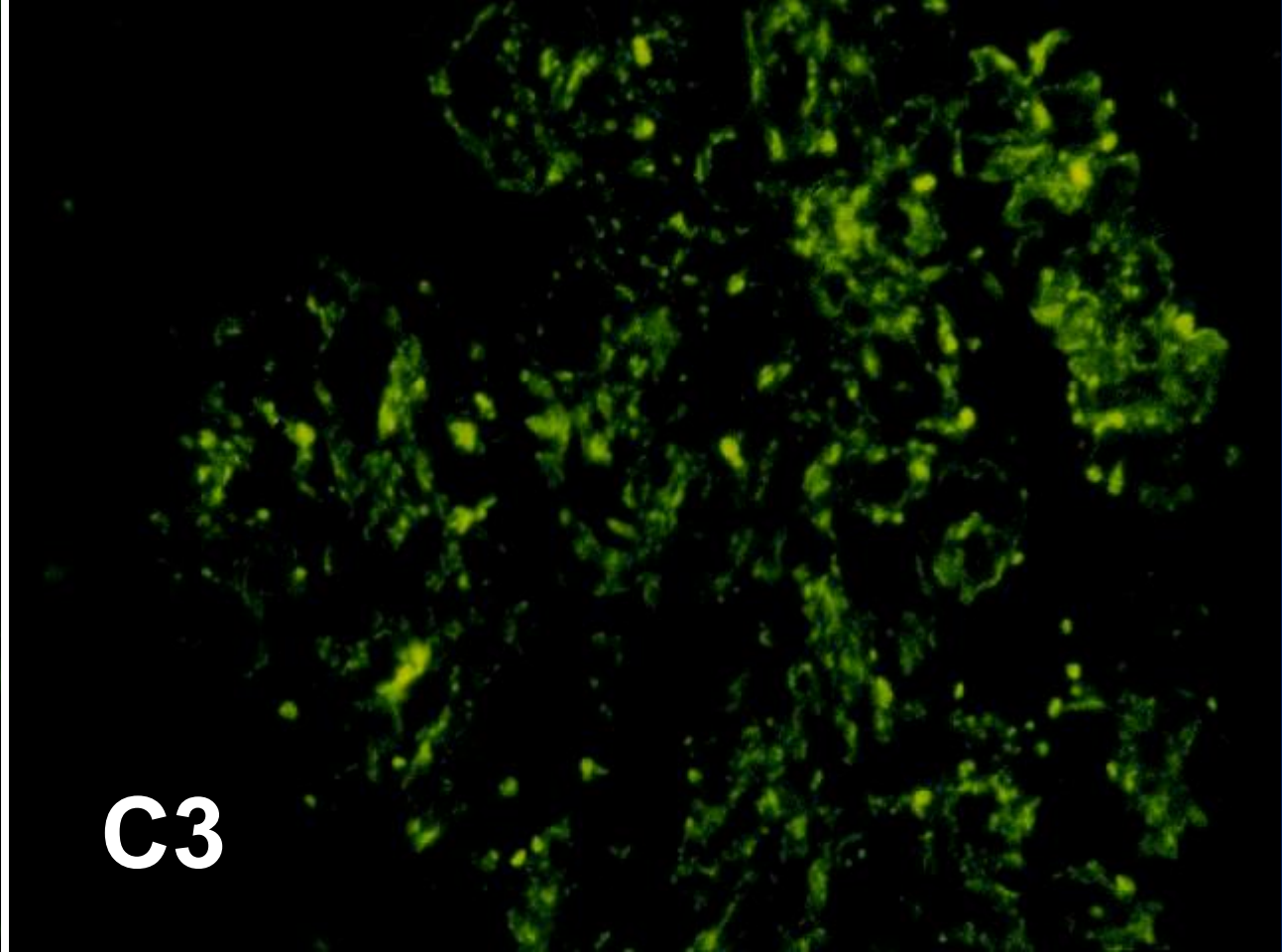
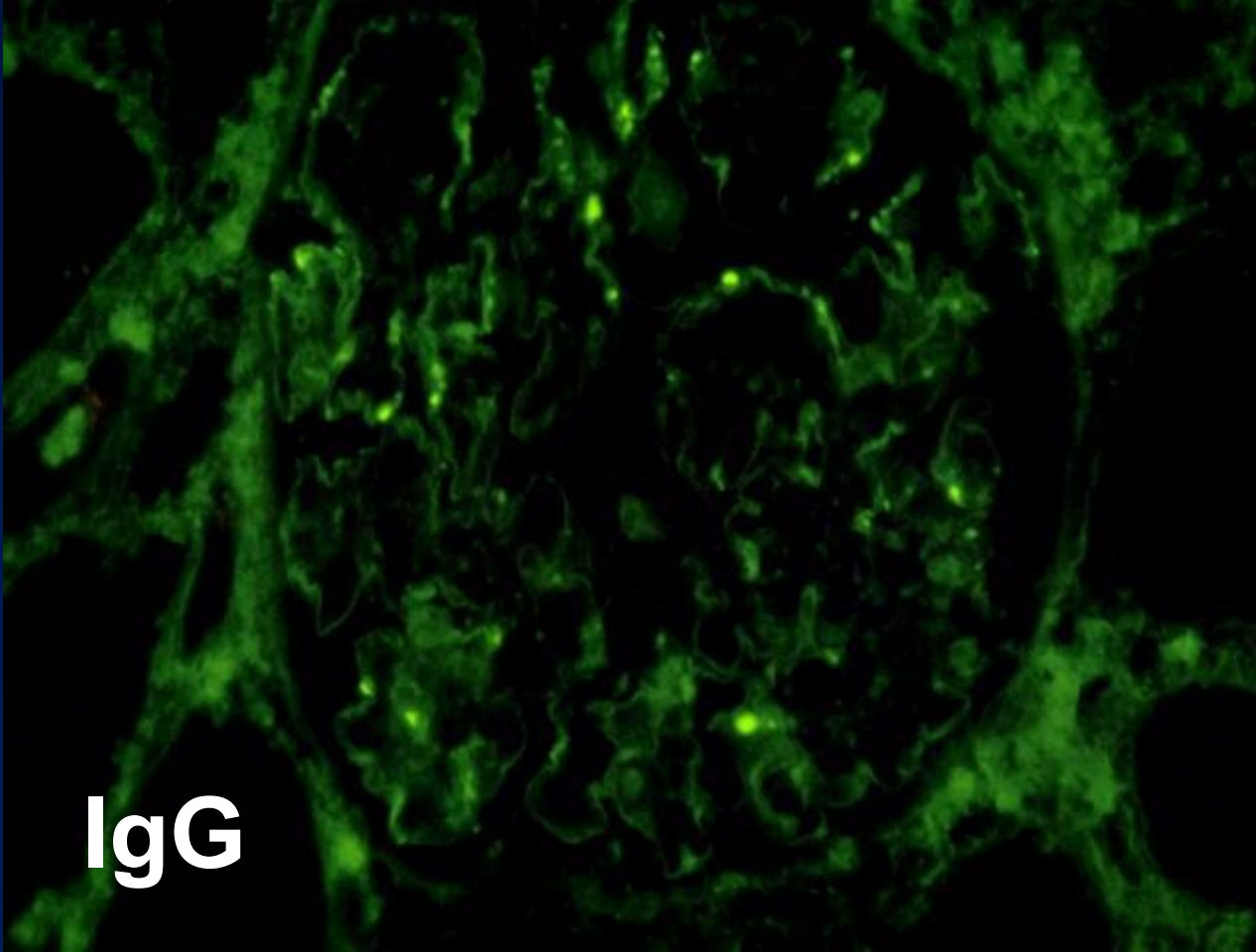
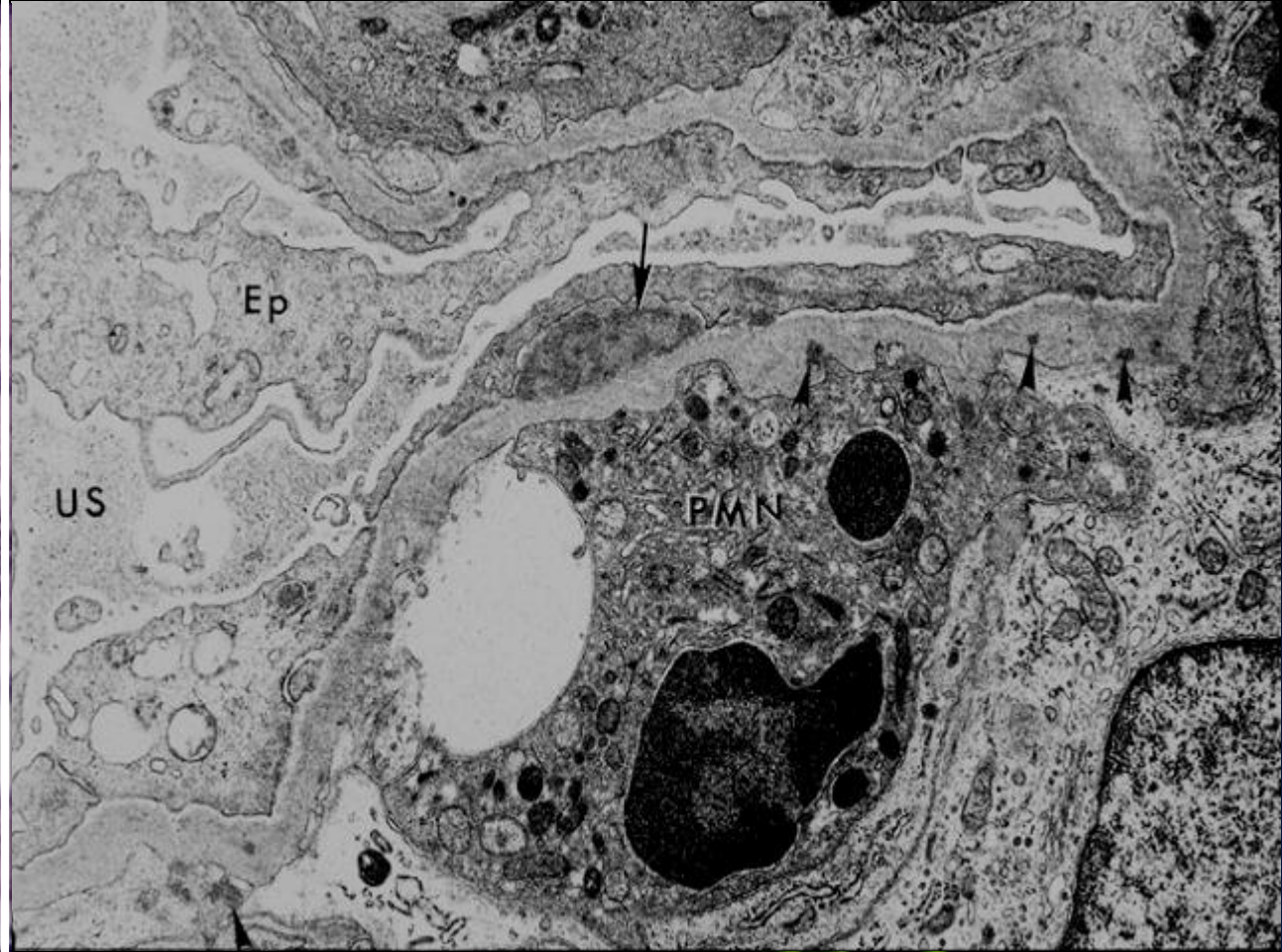
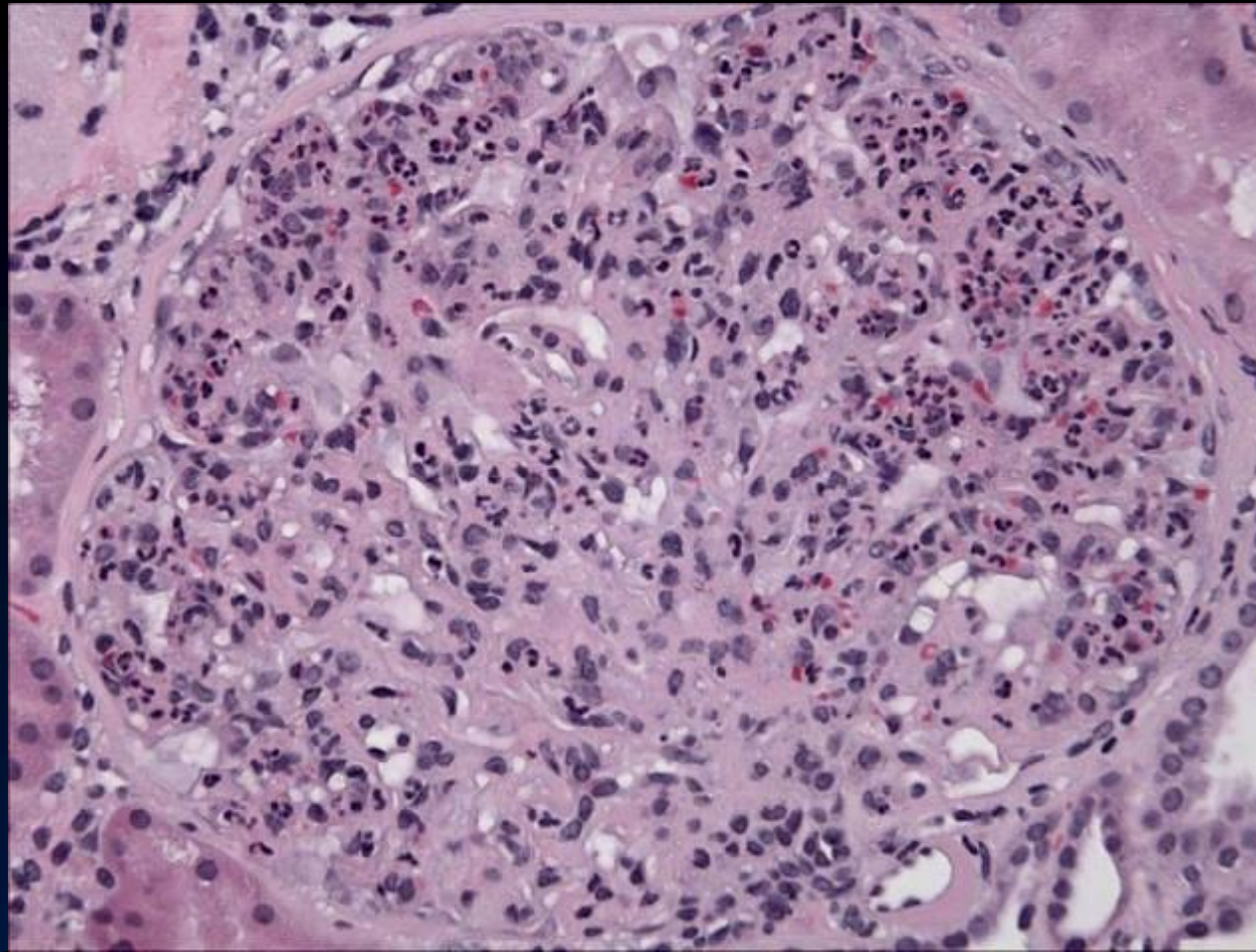
**Diffuse (proliferative) GN**  
**With diffuse endocapillary hypercellularity**





# Post-streptococcal GN

## Infection-associated GN



IgG

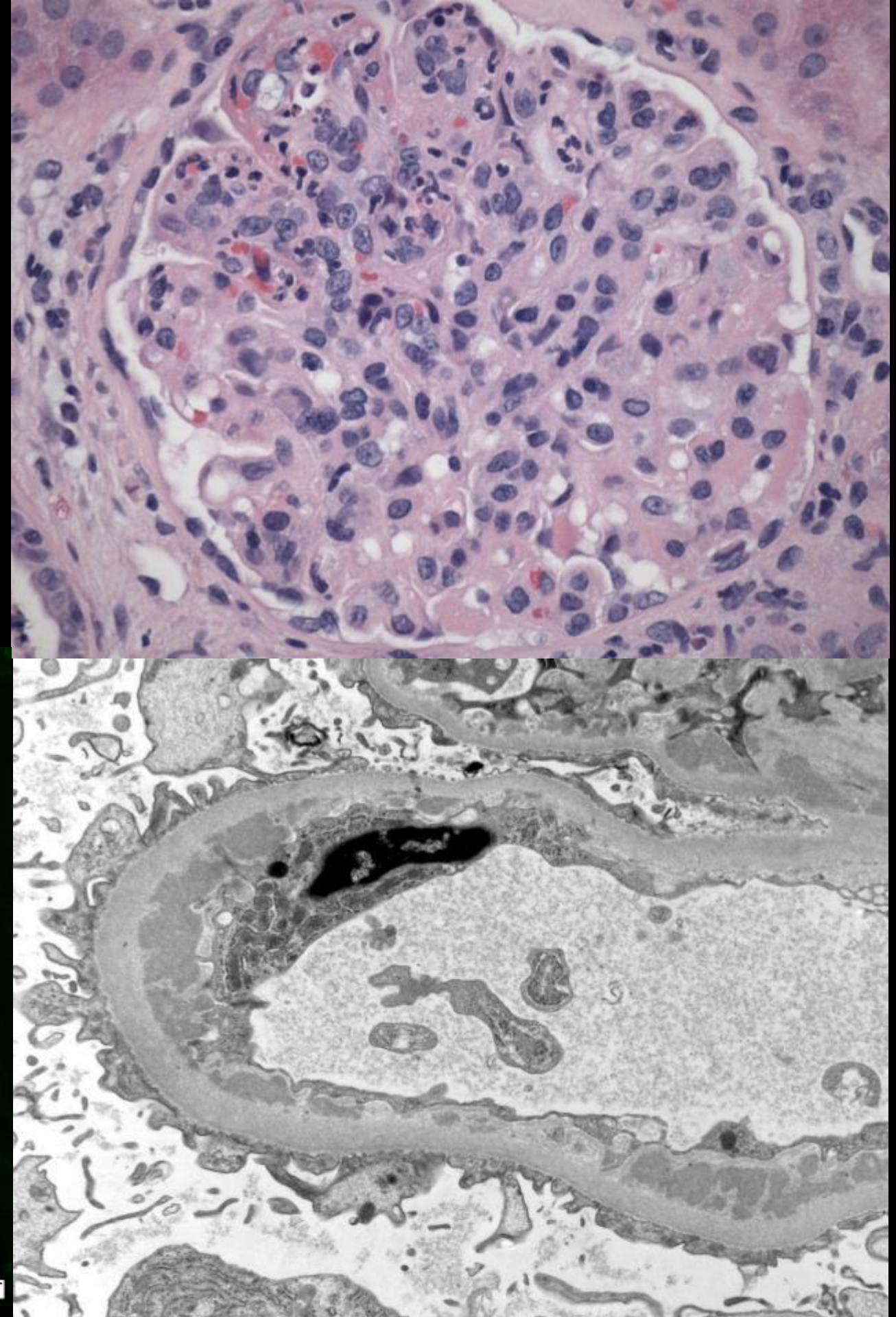
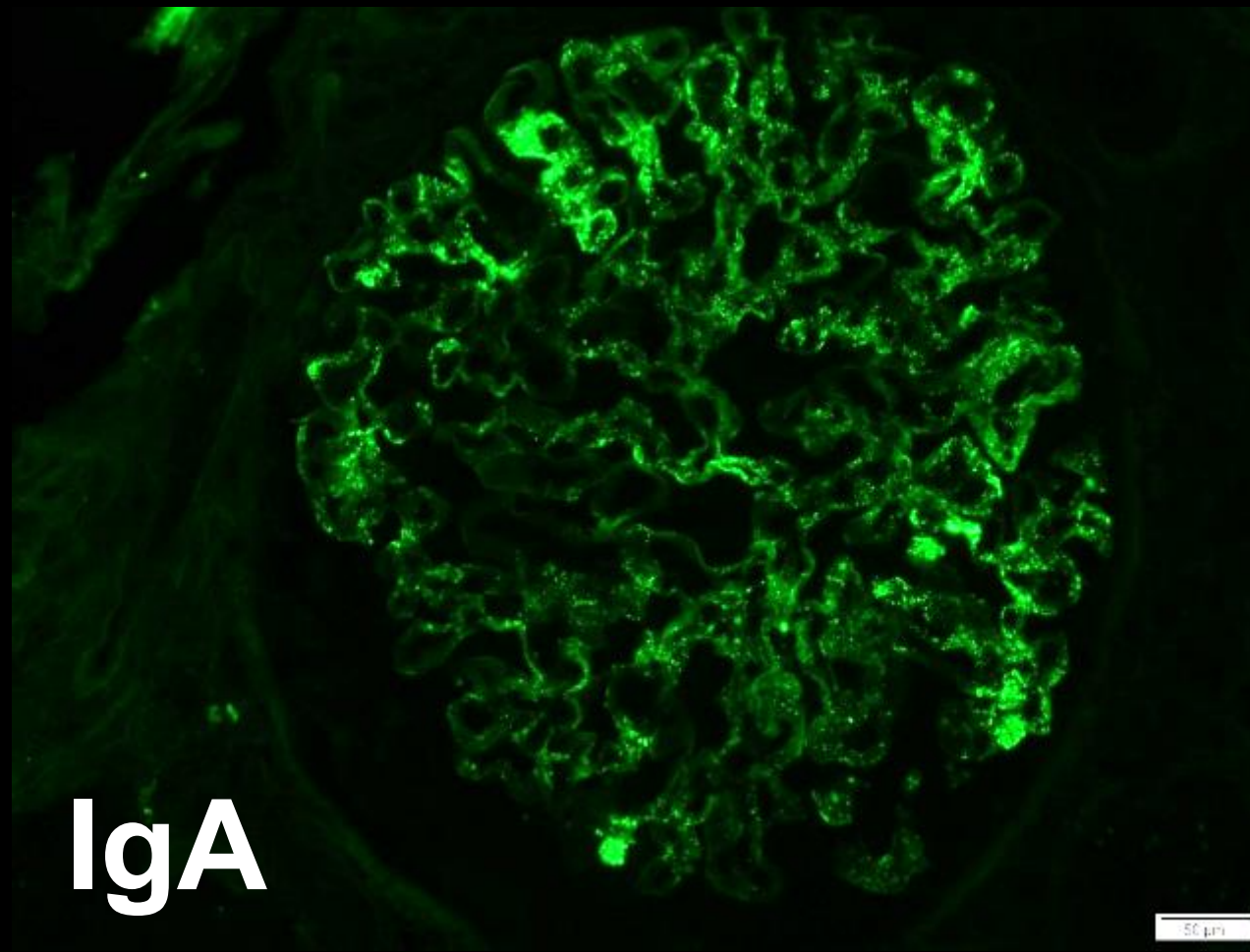
C3



# Staphylococcus aureus (MRSA) skin infection-bacteremia

## IgA-dominant infection-associated GN

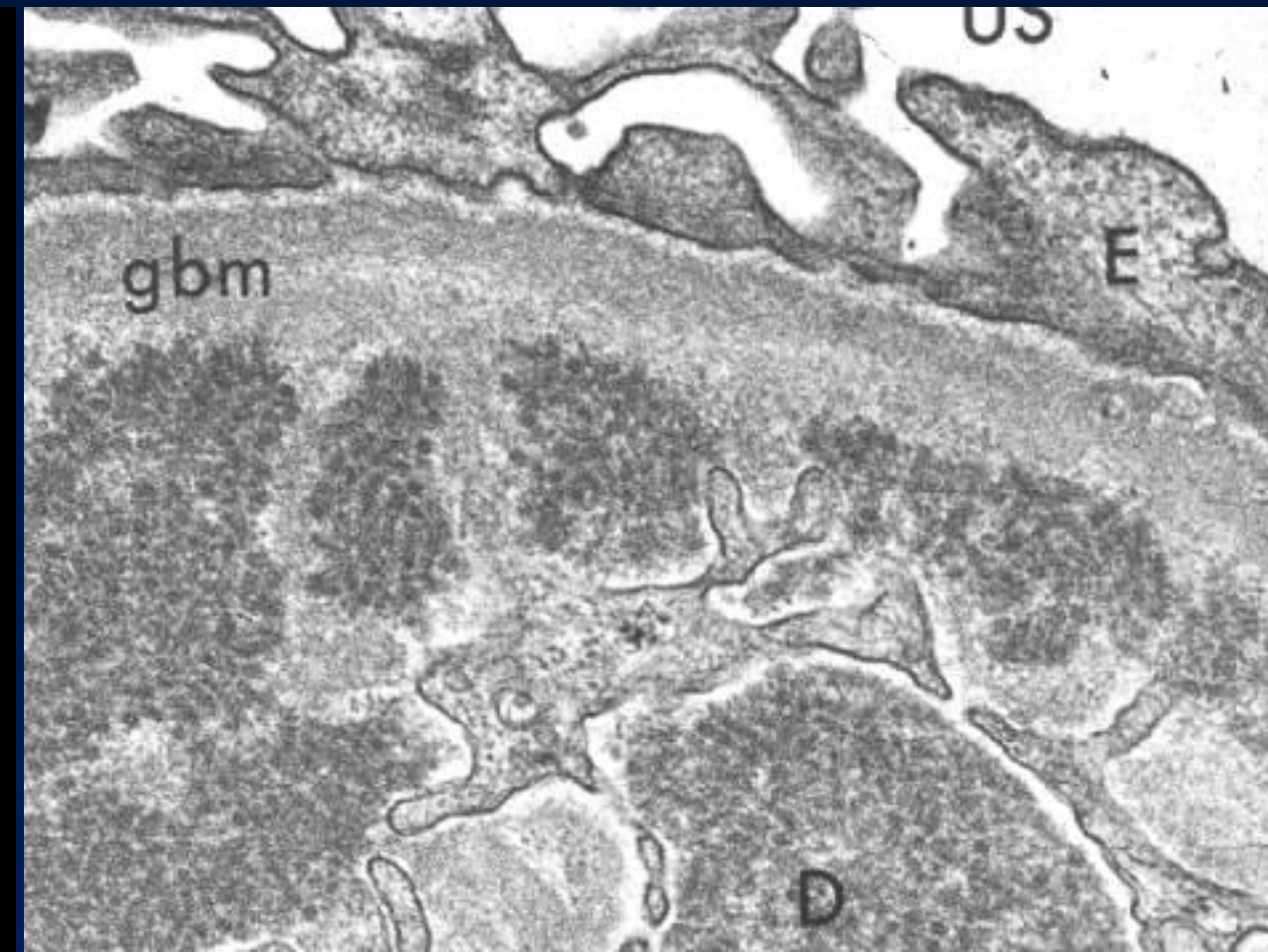
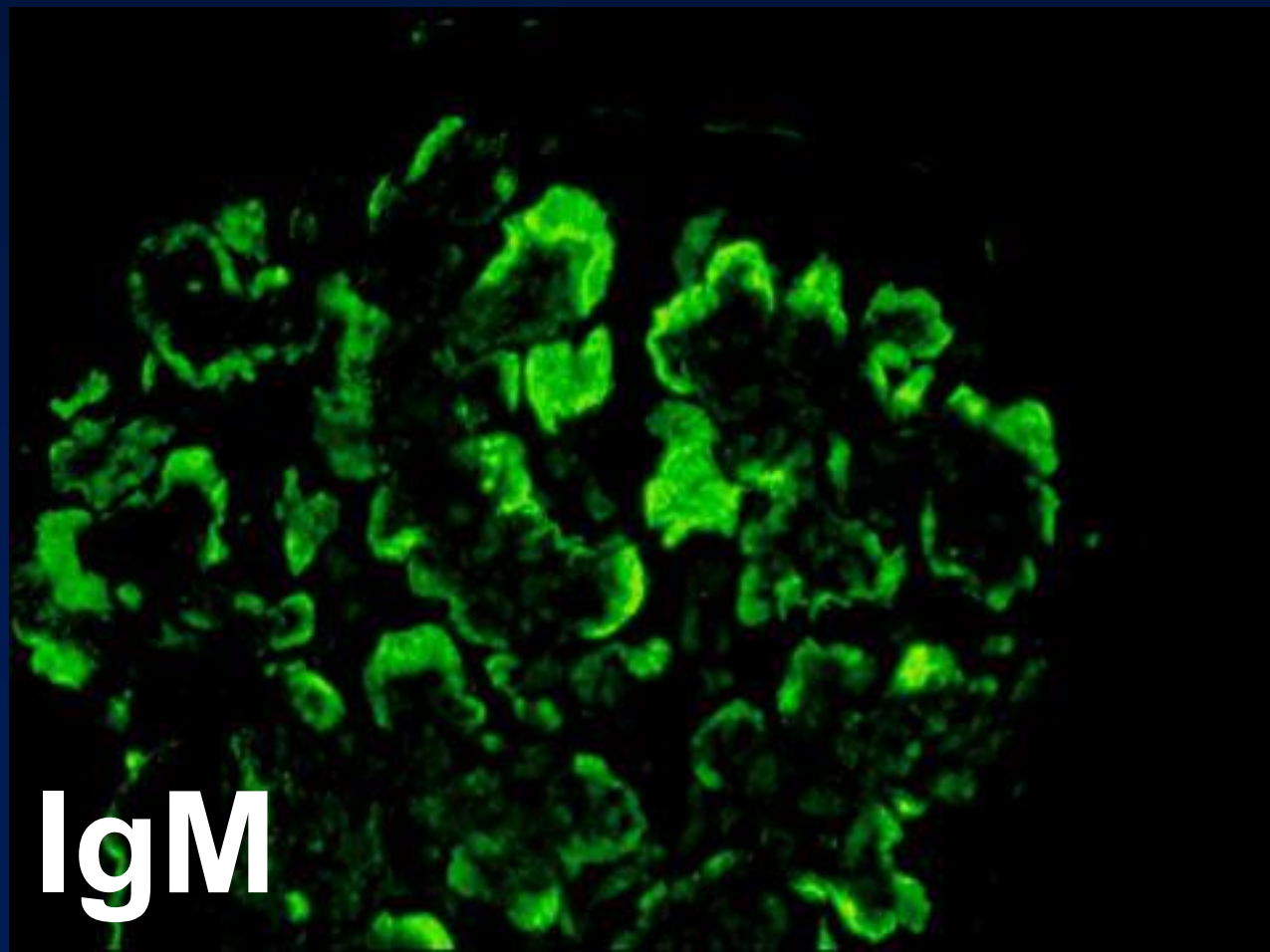
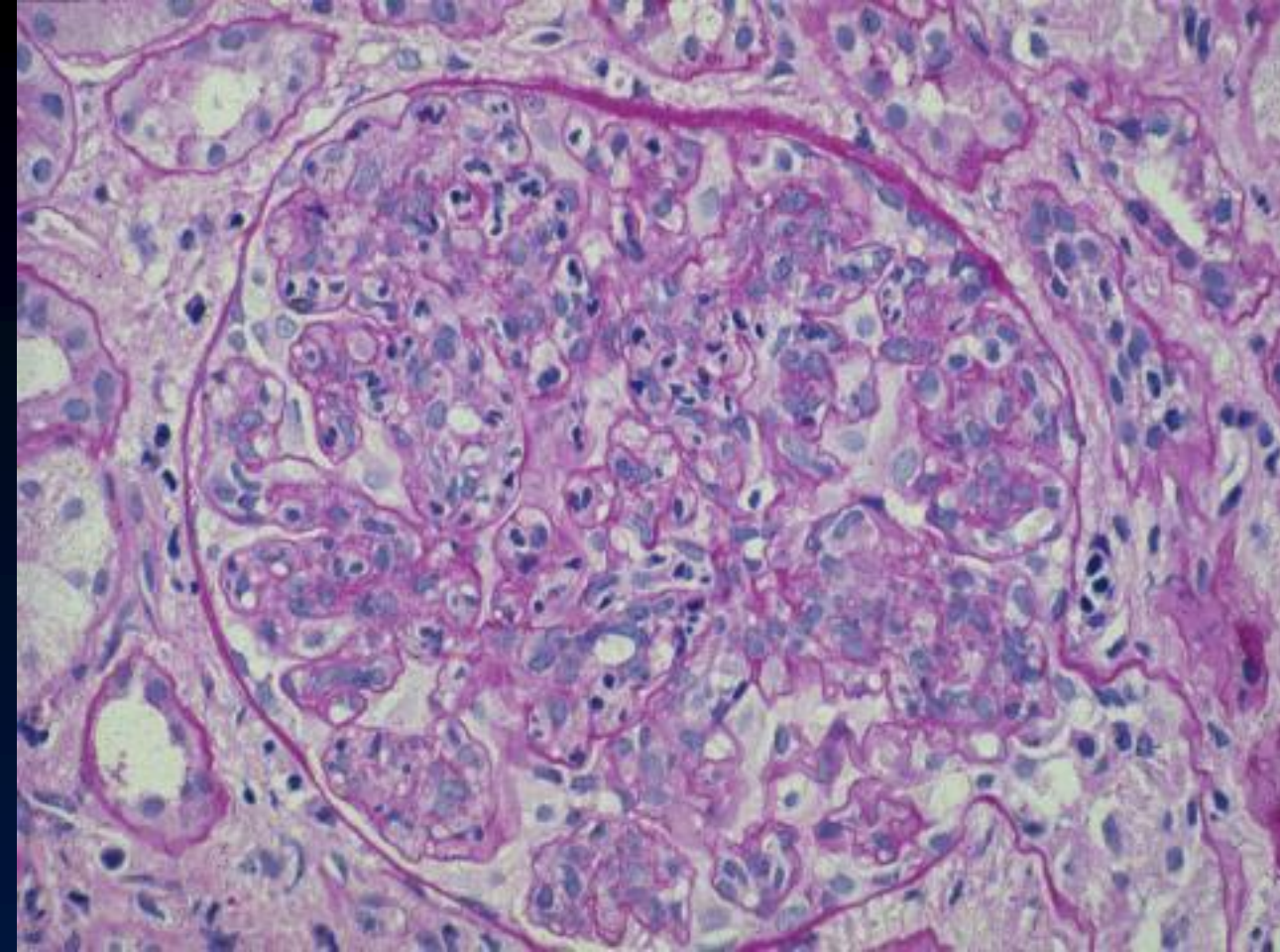
- Diabetic patient with foot ulcer/osteomyelitis
- Patient with polysubstance abuse with endocarditis
- Pneumonia and other respiratory tract infections
- Staphylococcus aureus (MRSA) is the most frequent causative agent
- GN with endocapillary hypercellularity, cellular crescents, subendothelial (mesangial) electron dense deposits





## HepC-associated acute GN

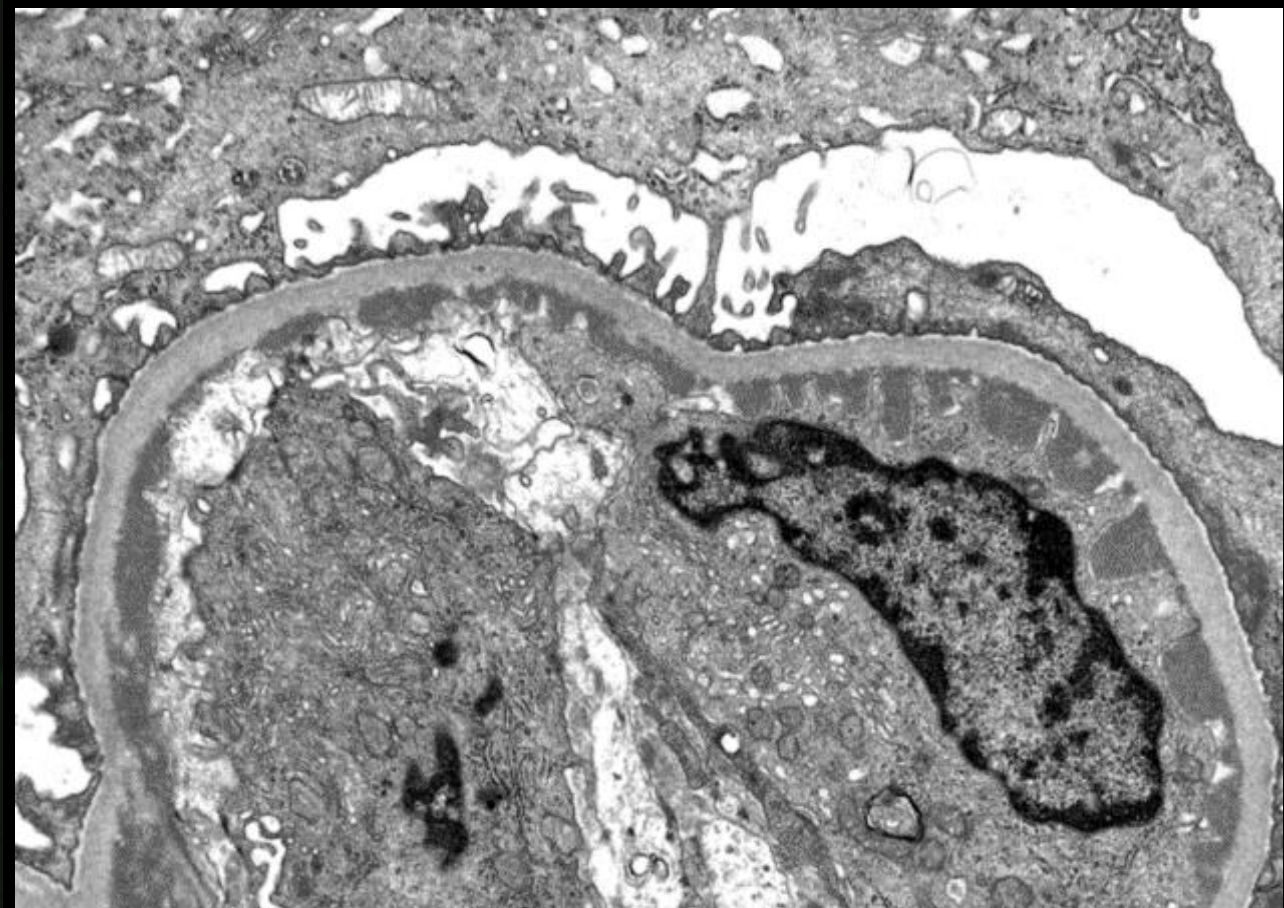
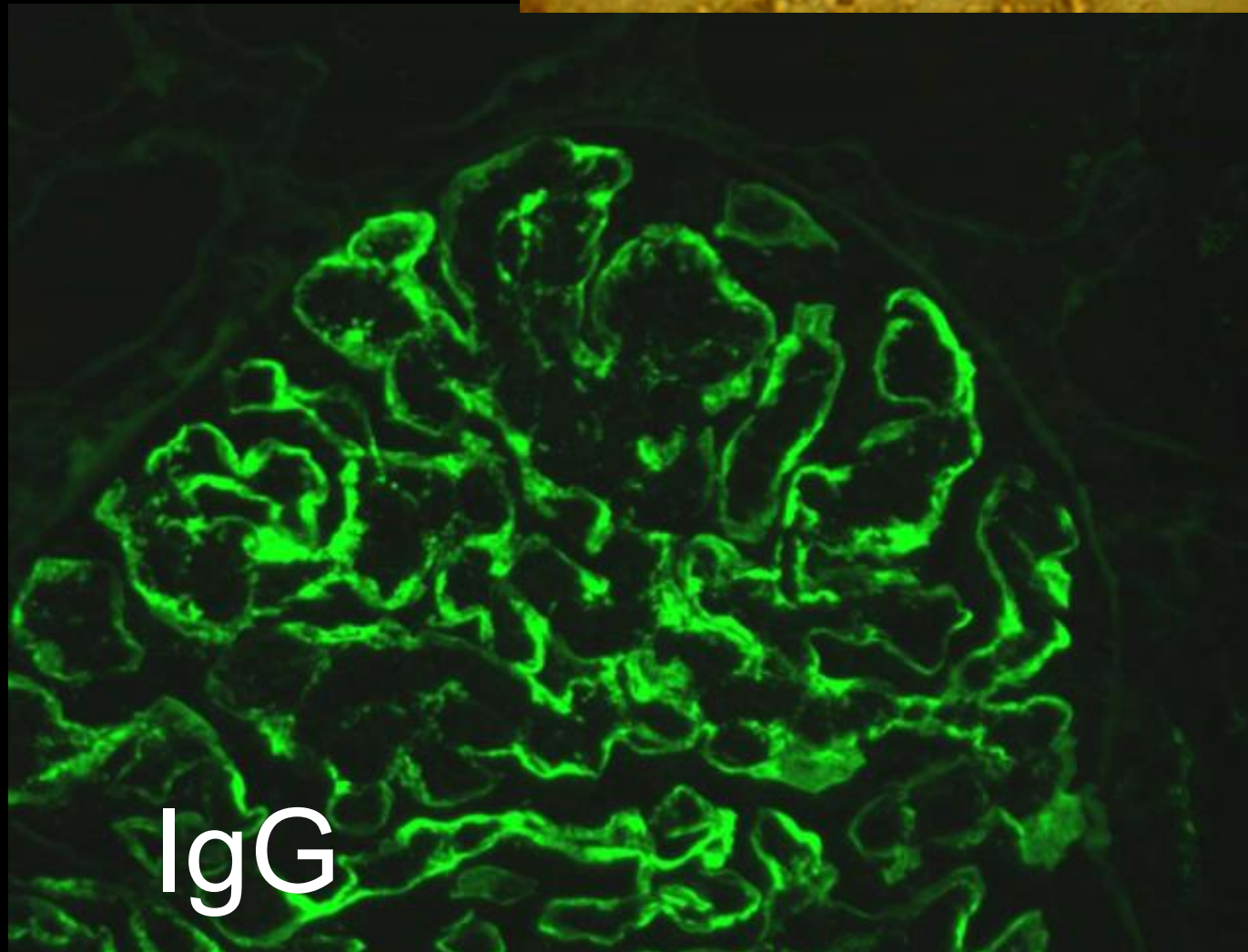
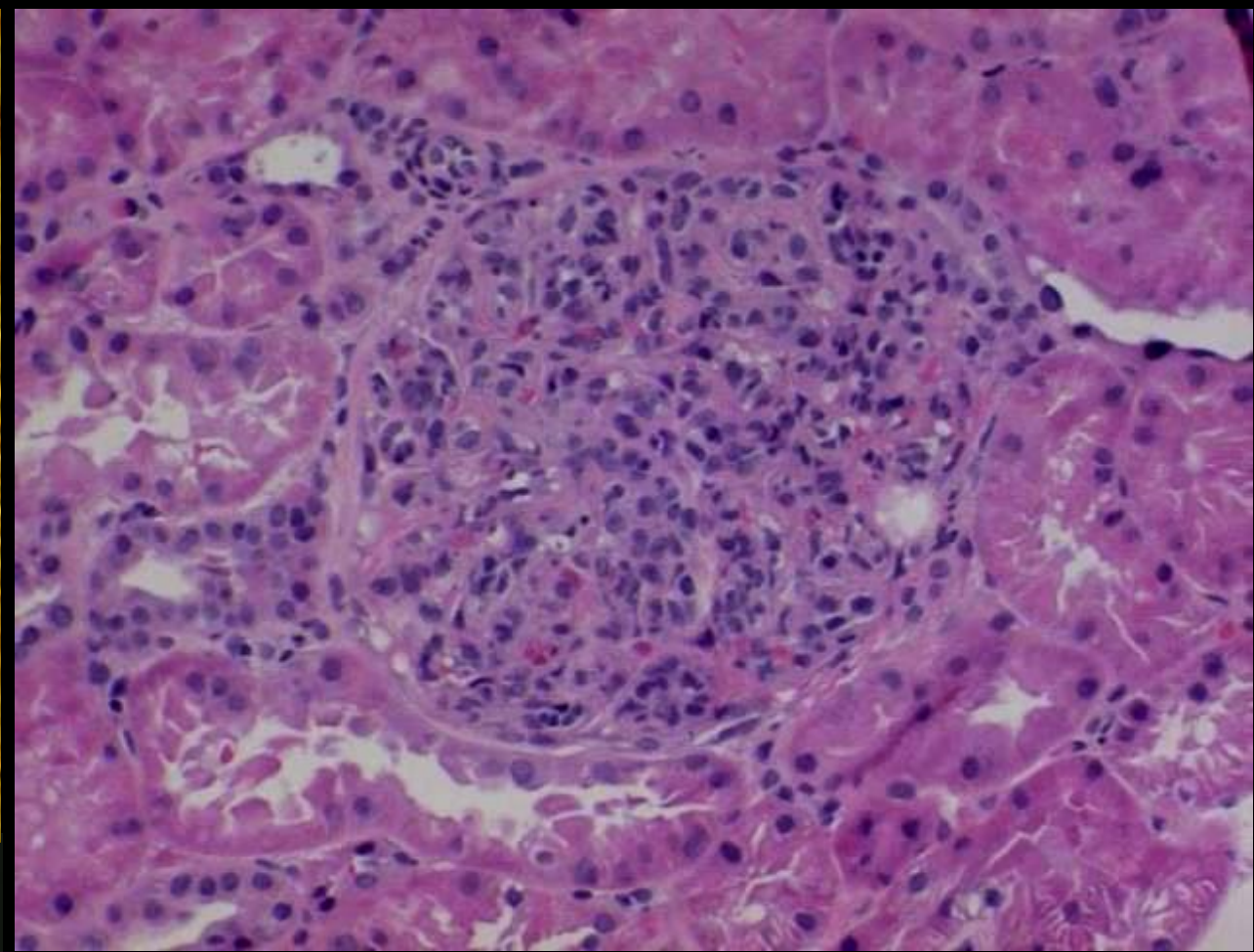
30-year-old man with drug use disorder and recently diagnosed hepatitis C infection. He presents now with a pruritic petechial rash, facial and lower extremity edema, hypertension, and an active urine sediment. His protein-to-creatinine ratio is 5, and he has low C3 complement levels





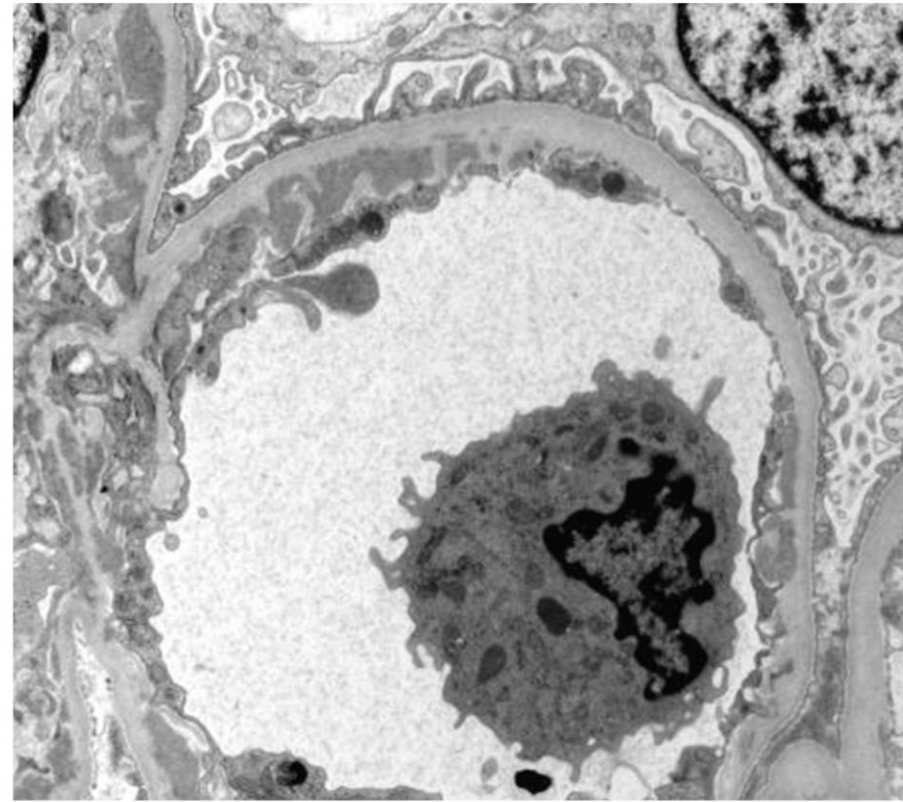
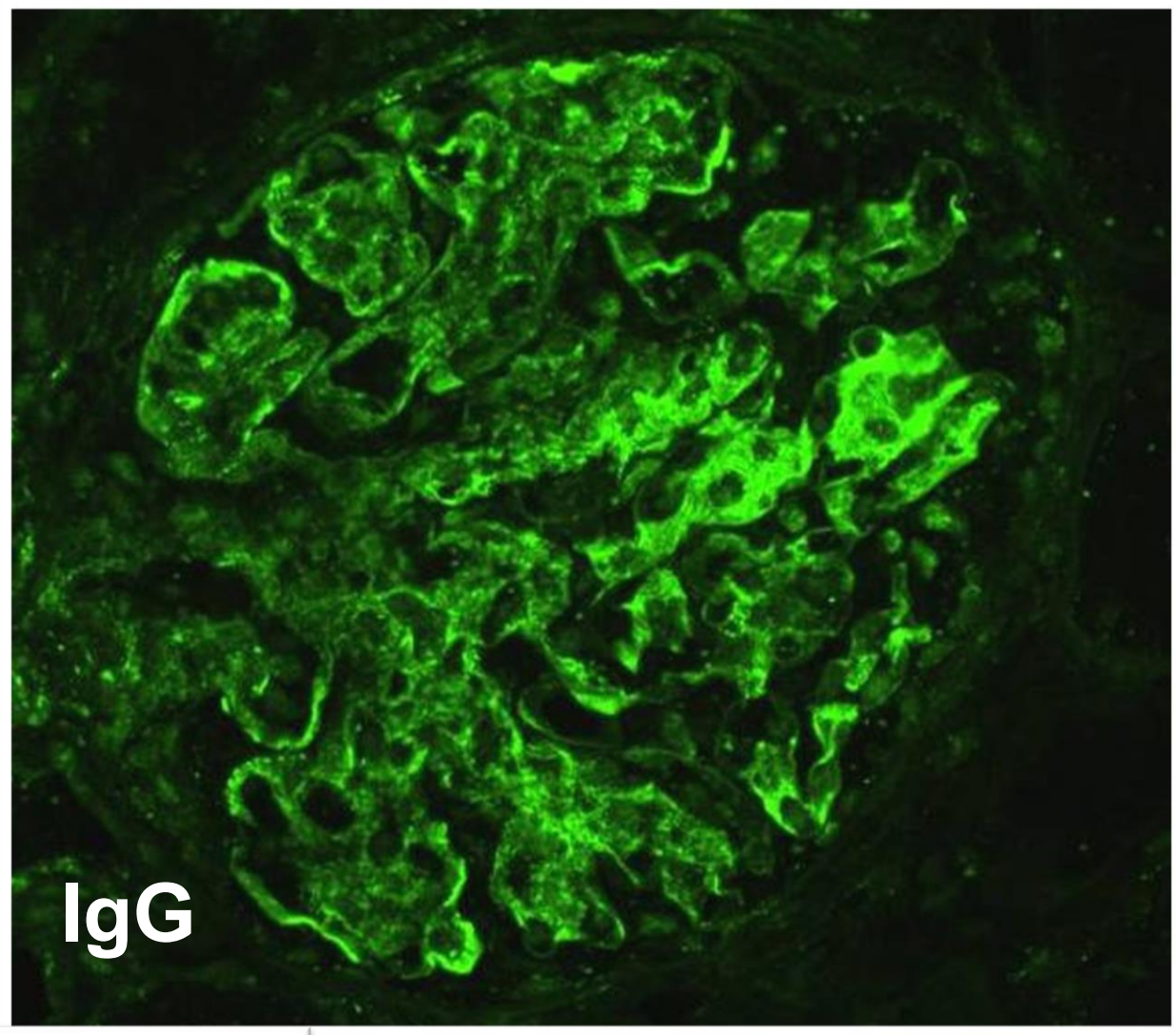
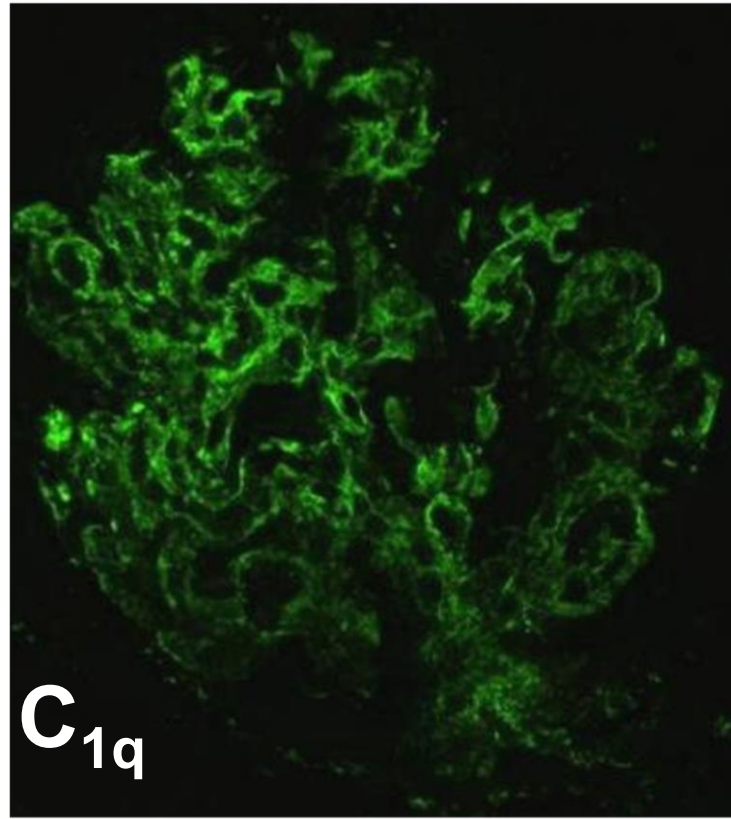
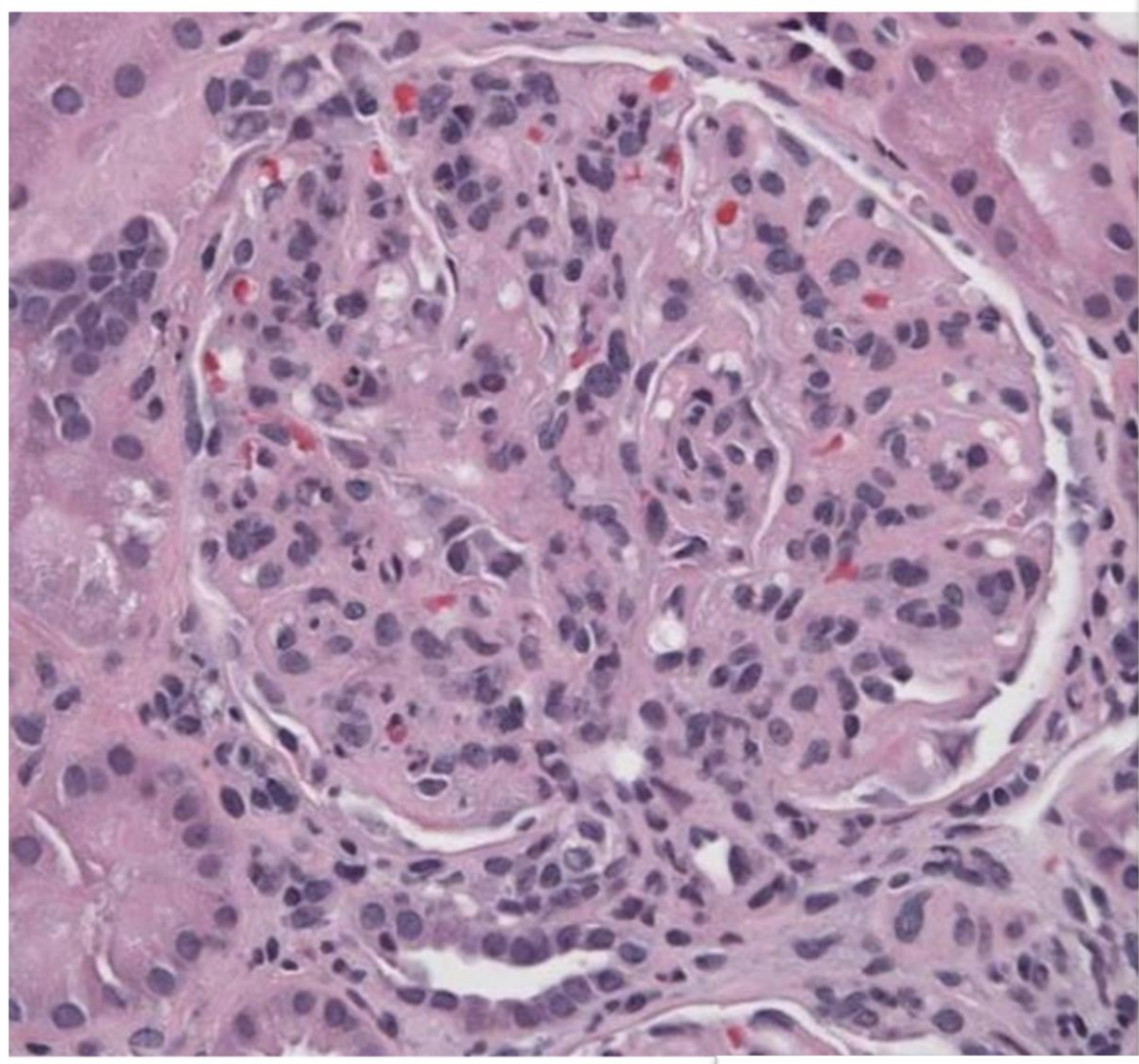
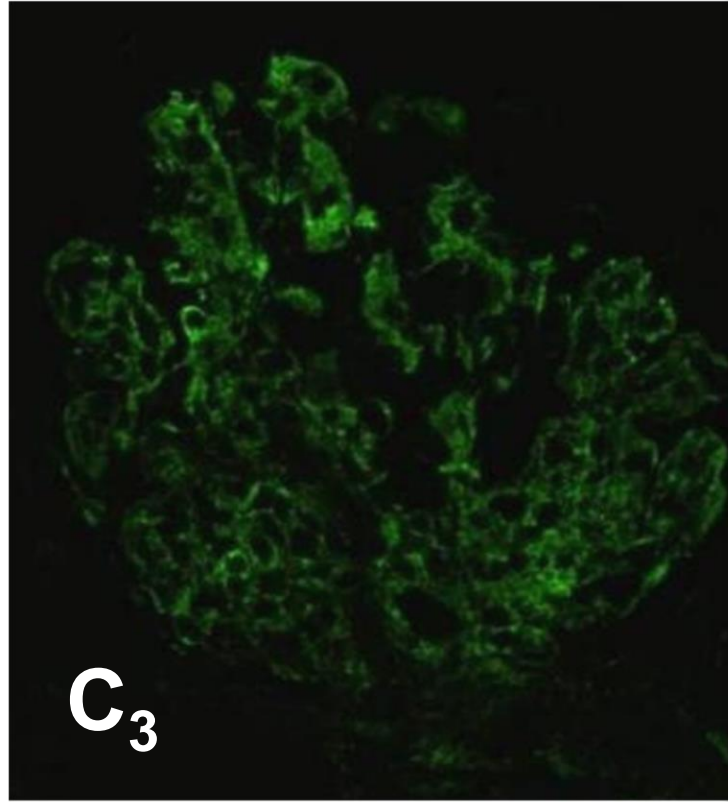
# Infection-associated glomerulonephritis *Strongyloides stercoralis*

44-year-old previously healthy noticed facial swelling, weight gain, and a poorly described rash over both lower extremities. She recently travelled to her native Ethiopia





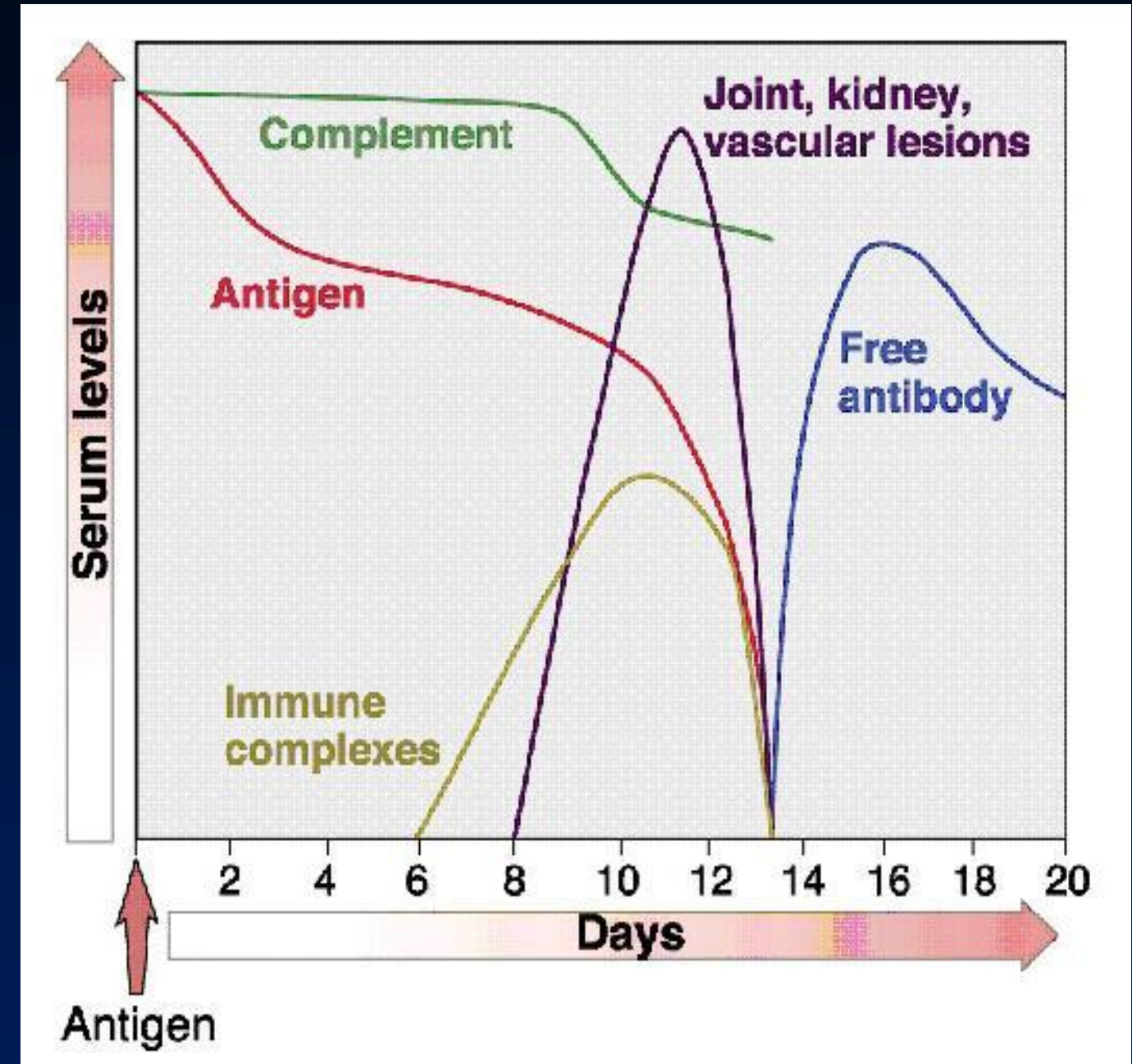
# Diffuse Lupus Nephritis. Class IV





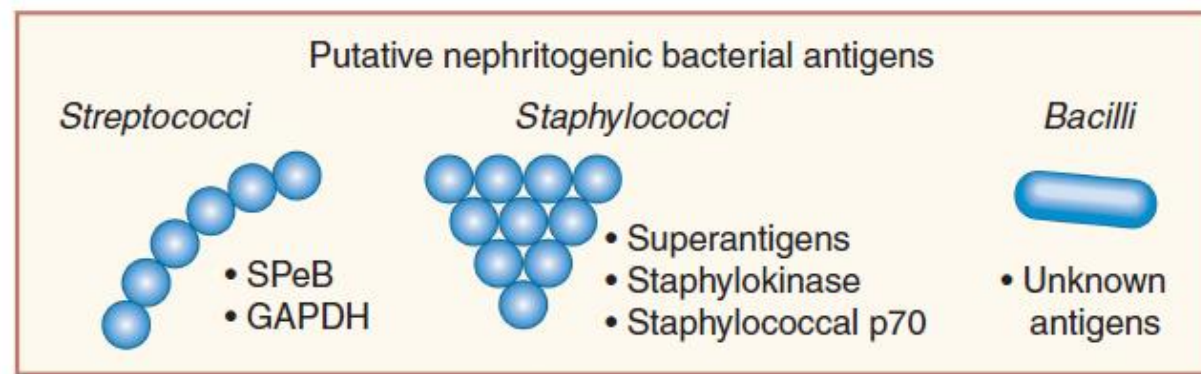
# MECHANISM OF SUBENDOTHELIAL AND MESANGIAL IMMUNE COMPLEX FORMATION.

- Sequential Deposition of Exogenous Planted Antigens and Circulating Antibodies
- Sequential Deposition of Endogenous Planted Antigens and Circulating Antibodies
- **Entrapment of preformed immune complexes from the circulation**
- The effect of the molecular size, charge, and conformation of the target antigen



THE SERUM SICKNESS PARADIGM



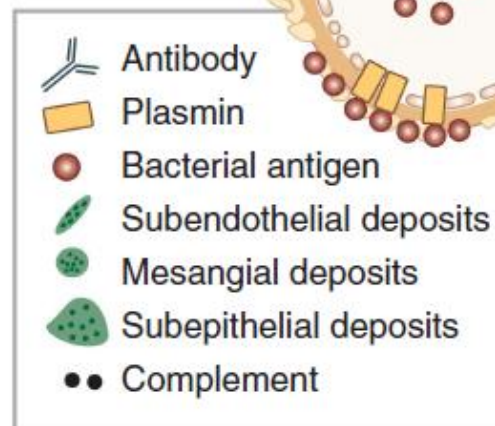


2

• Deposition of circulating bacterial antigen–antibody ICs

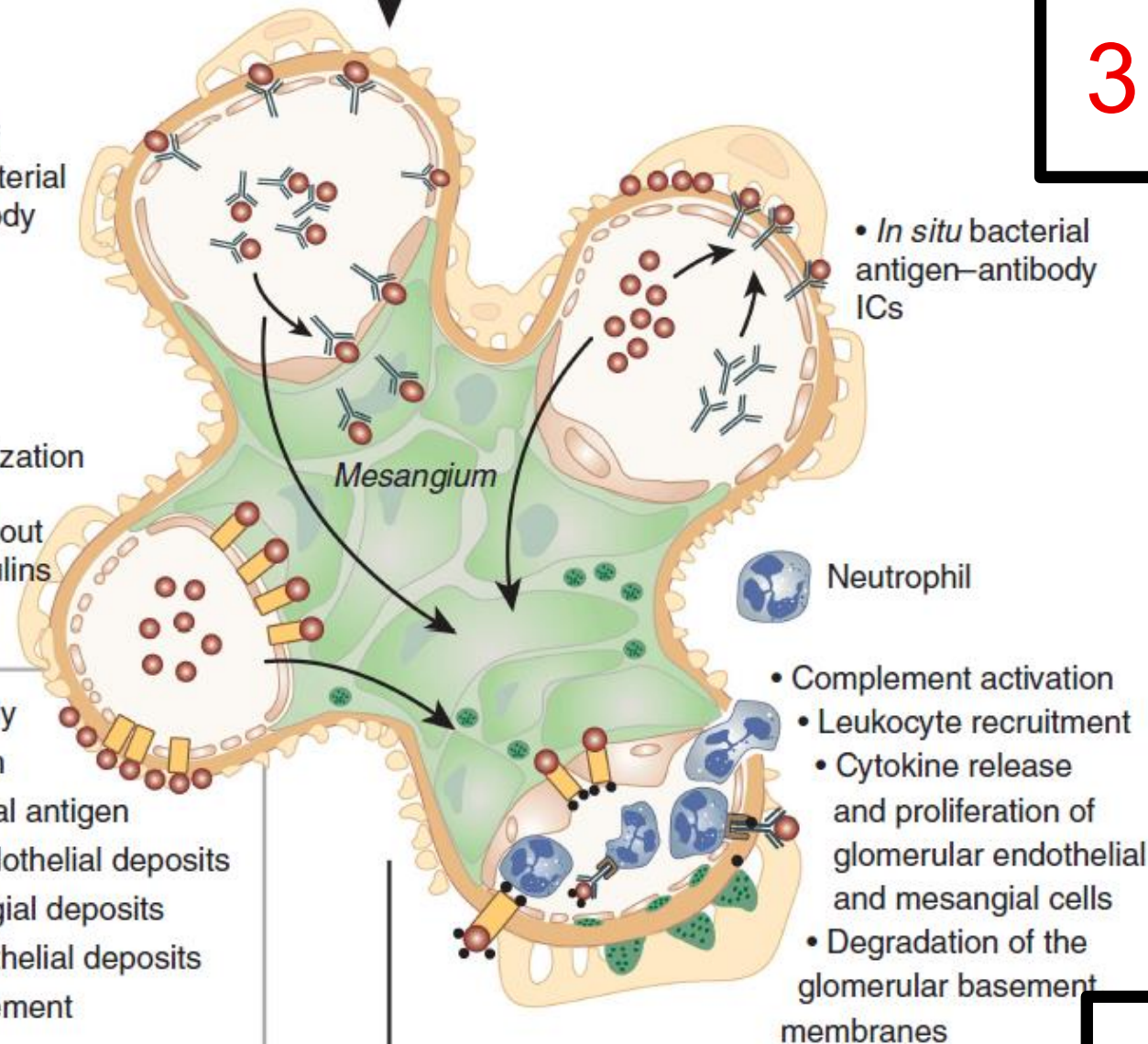
1

• *In situ* localization of bacterial antigens without immunoglobulins



3

• *In situ* bacterial antigen–antibody ICs



4

Host factors  
 • Genetic susceptibility  
 • Abnormalities in the alternative pathway of complement

Infection-related glomerulonephritis

1. Bacterial antigens bind to the capillary wall and mesangial matrix
  2. Excess circulating antigens form immune complex in the circulation setting-up a serum-sickness type immune reaction with large IC depositing in the mesangium and in the subendothelium
  3. When antibodies become available, additional in situ formation of immune complexes form in the subendothelial and mesangial spaces and in the subepithelial space, the latter resulting in hump-like deposits.
  4. These deposits results in:
    - Complement activation
    - Cytokine release
    - Influx of neutrophils resulting in damage and disruption of the GBM
    - Endothelial and mesangial cell proliferation
- Additional host factors may play additional roles in this inflammatory process (genetic susceptibility, abnormalities in alternative complement pathway, pro-coagulant states, etc.)

Nasr S et al. Kidney International (2013) 83, 792–803;



# CONDITIONS ASSOCIATED WITH A DIFFUSE PROLIFERATIVE OR MEMBRANOPROLIFERATIVE PATTERNS OF INJURY

## 1. IMMUNE COMPLEX-MEDIATED DISEASES

### ■ Acute and Chronic infections:

Viral: hepatitis B, hepatitis C and essential mixed cryoglobulinemia

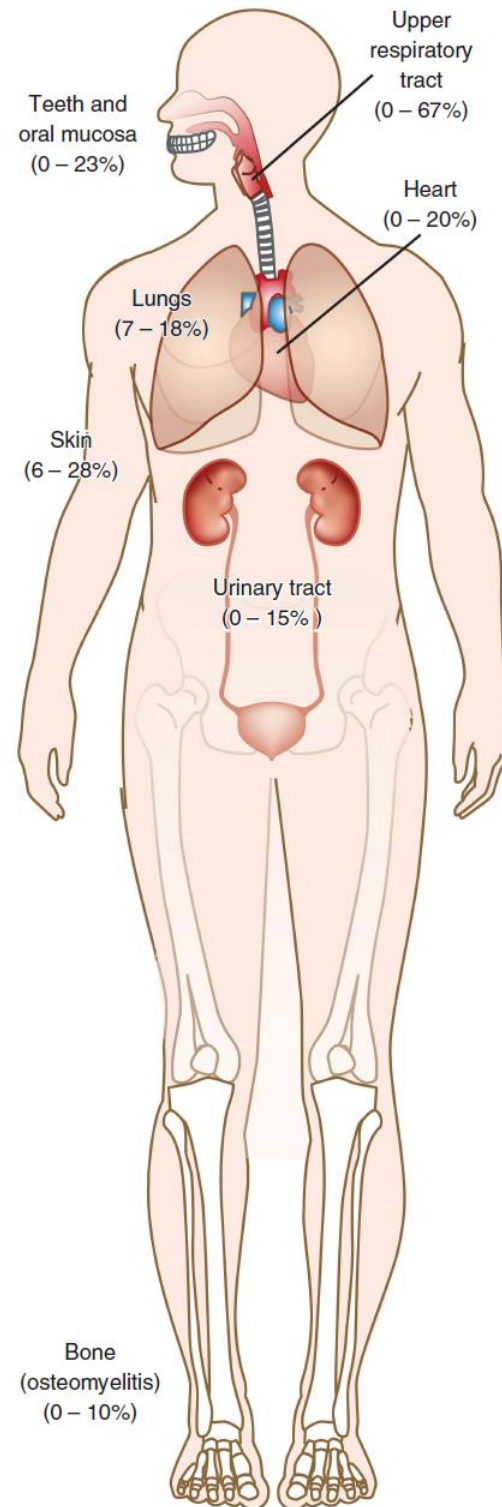
← Bacterial: URI, skin infections, erysipelas, endocarditis, infected ventriculo-atrial (or jugular) shunt, central line infection, multiple visceral abscesses, leprosy, meningococcal meningitis,

Protozoa: malaria, schistosomiasis

Other infections: mycoplasma, Borreliosis, Leishmaniasis;  
Strongyloides stercoralis, other parasites

### ■ Autoimmune diseases:

SLE, Sjögren syndrome, Rheumatoid arthritis, Inherited complement deficiencies, in particular C2 deficiency





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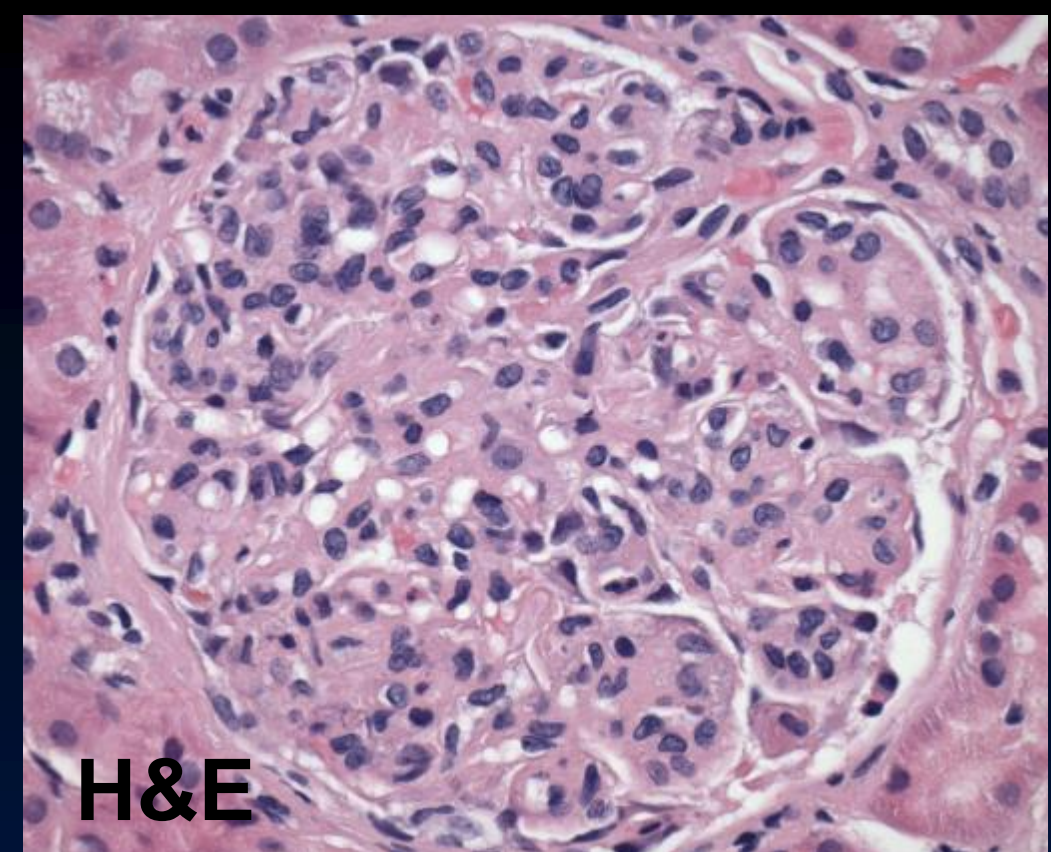


# THE MEMBRANORPOLIFERATIVE PATTERN OF INJURY

- **GLOMERULAR HYPERCELLULARITY**



Increase in the number of cells within the glomerular tuft, mainly mononuclear cells within the capillaries or infiltrating the mesangium.



H&E

- **THICKENING OF THE CAPILLARY WALL**



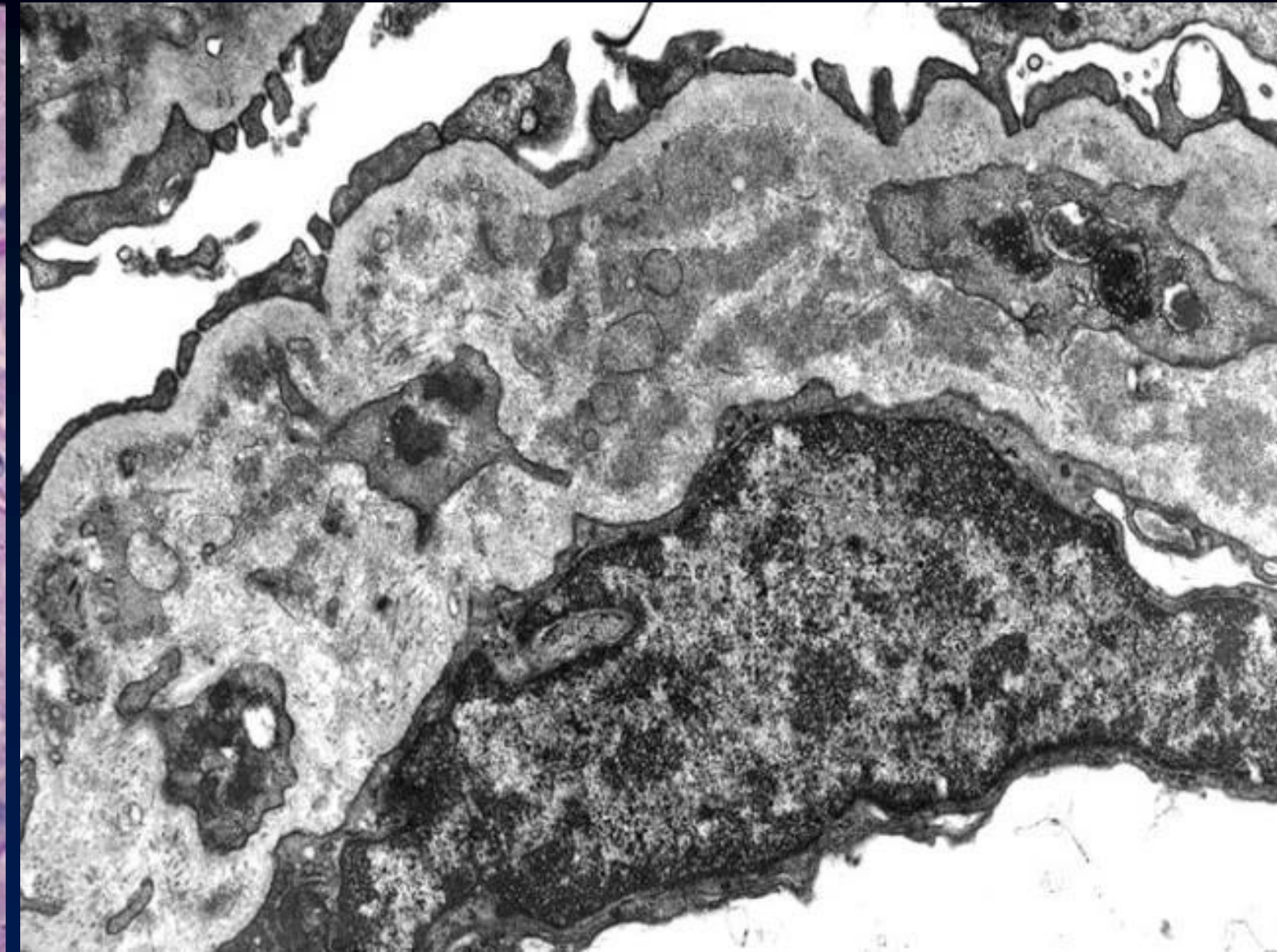
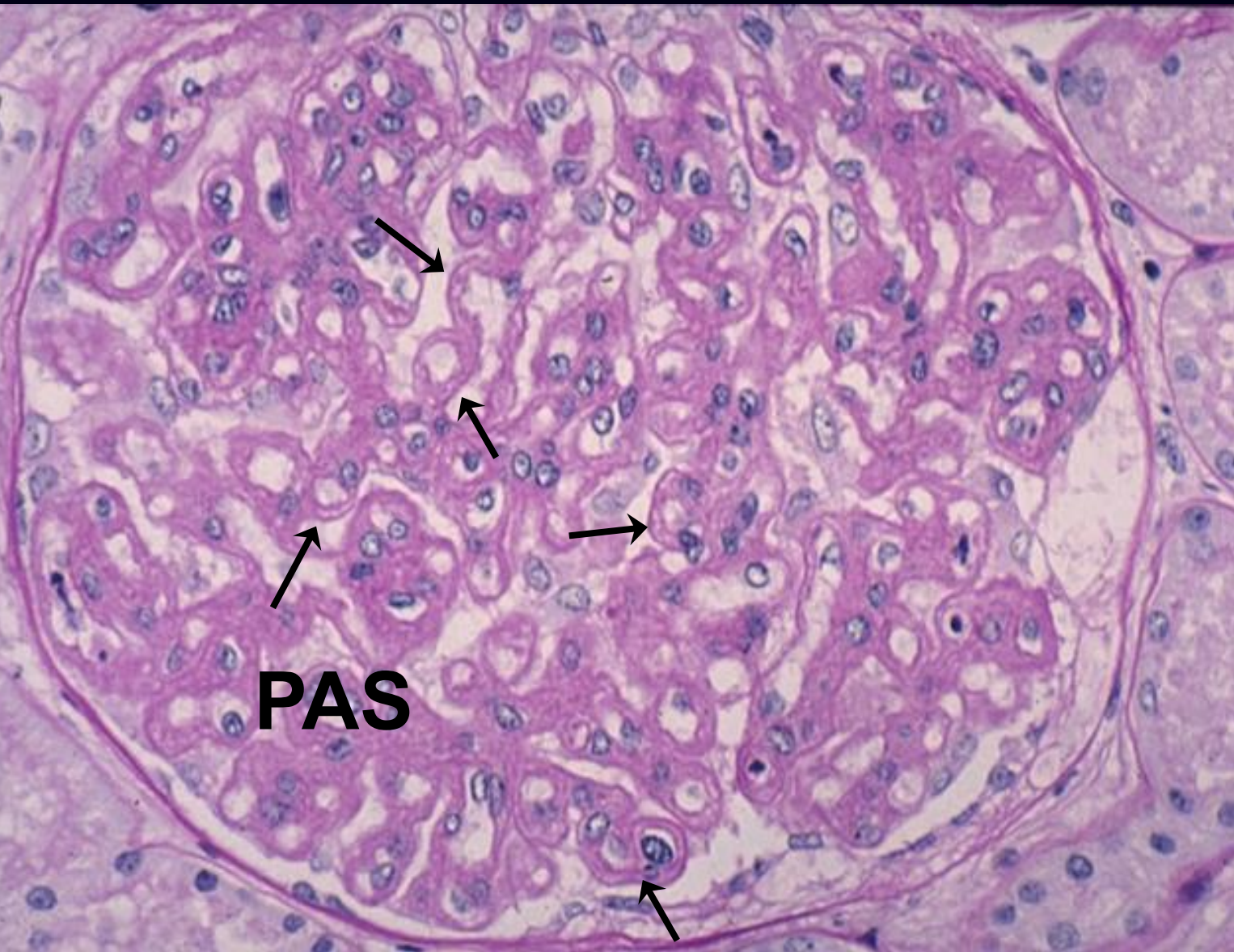
Remodeling of the capillary walls with duplication of the basement membrane, resulting in double contours



Silver methenamine



# THE ULTRASTRUCTURE OF THE DOUBLE CONTOUR



Expansion of the subendothelial space (by protein deposits and/or cell debris), interposition and entrapment of cell projections (inflammatory cells and endothelial cells), and formation of a new basement membrane by the displaced endothelium.



# TRADITIONAL CLASSIFICATION OF MPGN

- **Idiopathic forms of MPGN (unknown association):**

MPGN type I; idiopathic

MPGN type II; Dense deposit disease and  
partial lipodystrophy

MPGN type III; Strife and Anders variant,  
Burkholder variant

- **Secondary MPGN:**

endocarditis (focal embolic GN of Loehlein),  
shunt infections, hepatitis B, hepatitis nonA-  
nonB



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endocarditis (focal embolic GN of Libman),  
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nonB



# **THE MEMBRANOPROLIFERATIVE PATTERN OF INJURY**

## **STRUCTURAL CHANGES:**

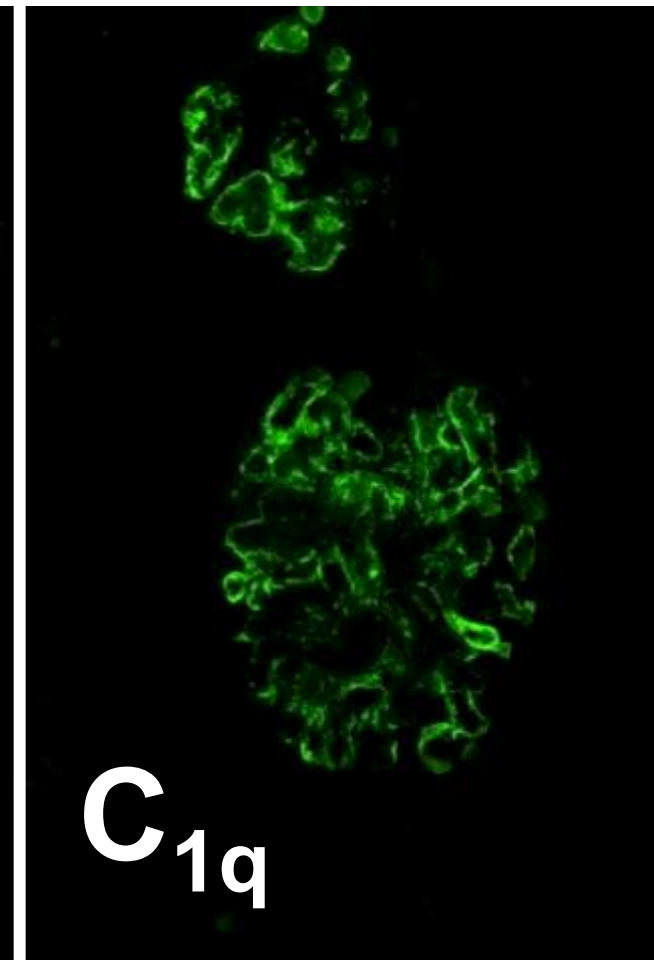
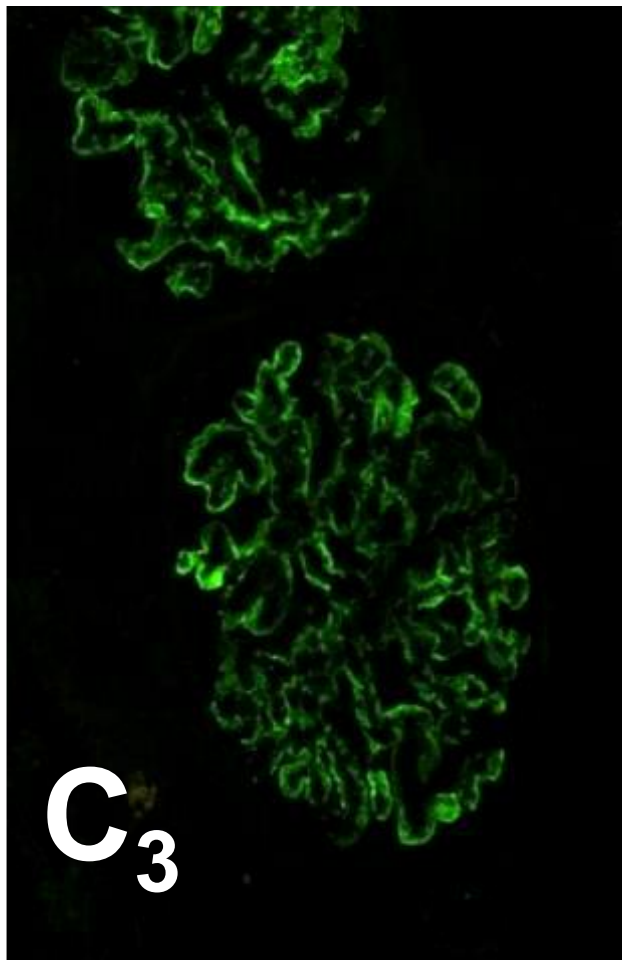
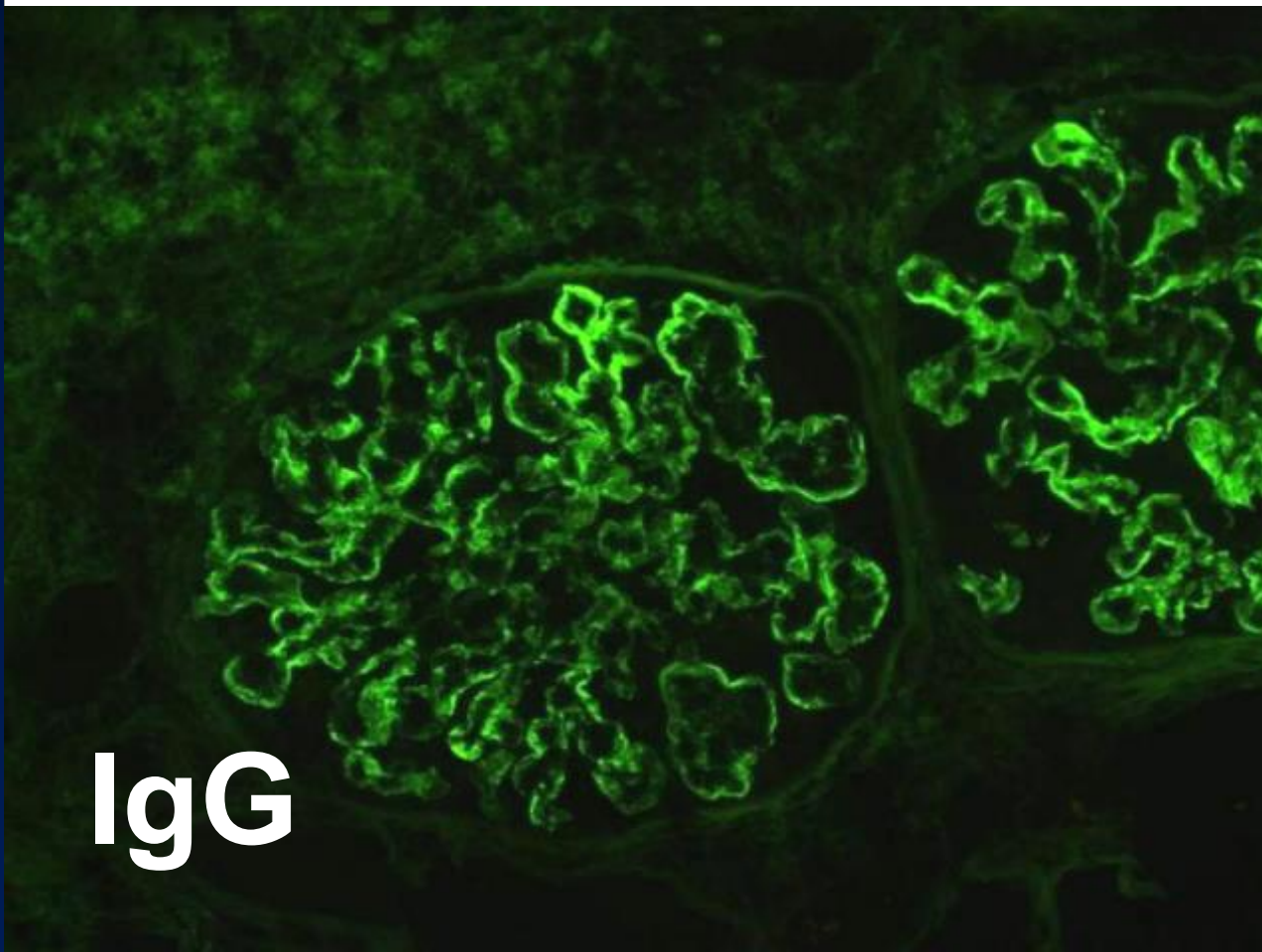
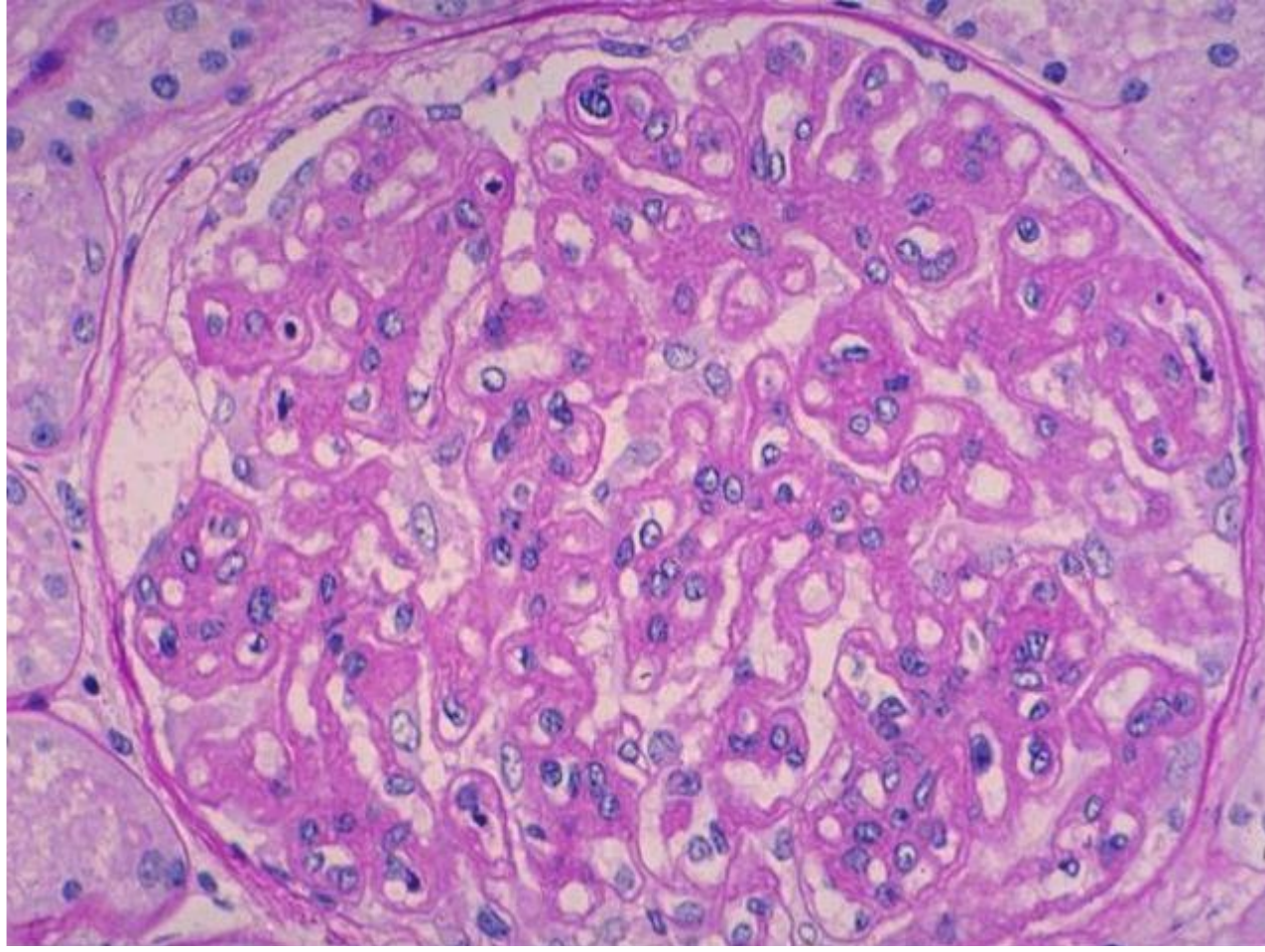
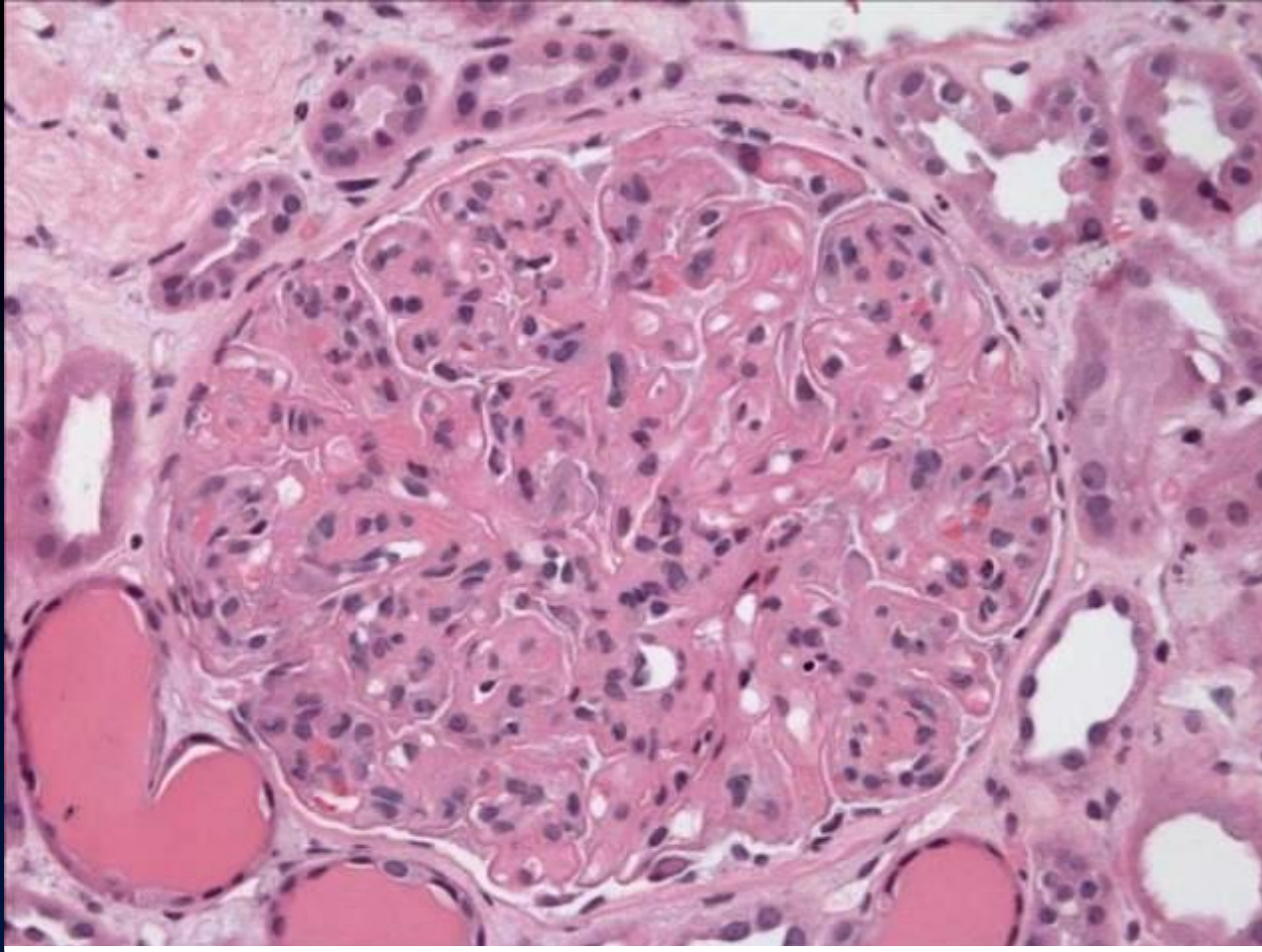
- **HYPERCELLULARITY**
- **CAPILLARY WALL THICKENING (double contours)**

## **CONDITIONS ASSOCIATED WITH THE MPGN PATTERN:**

- **IMMUNE COMPLEX DISEASES**
- **ABNORMALITIES OF COMPLEMENT-  
REGULATORY PROTEINS**
- **THROMBOTIC ANGIOPATHIES**
- **(PARAPROTEIN) DEPOSITION DISEASE**

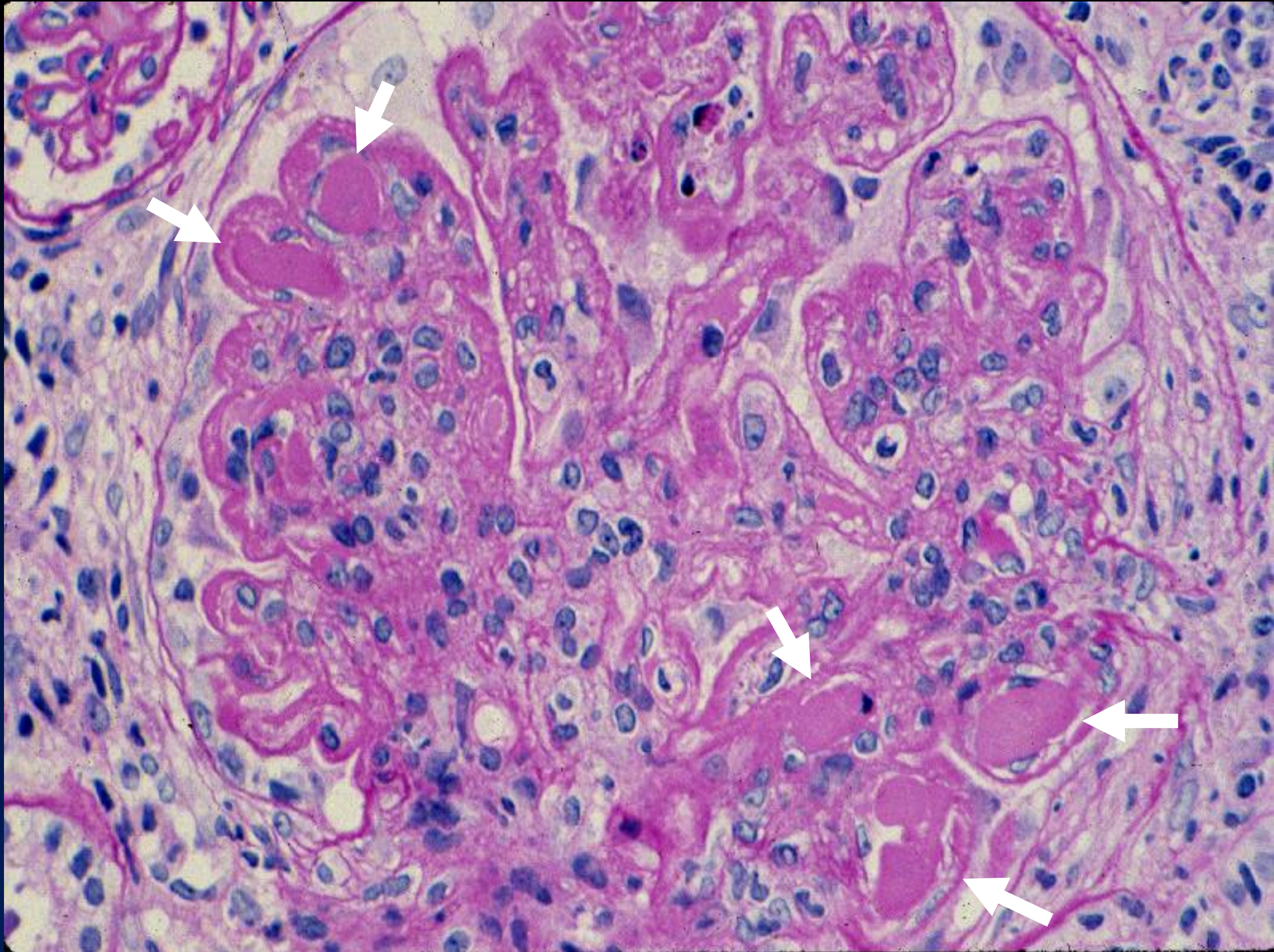


# Immune Complex-mediated GN



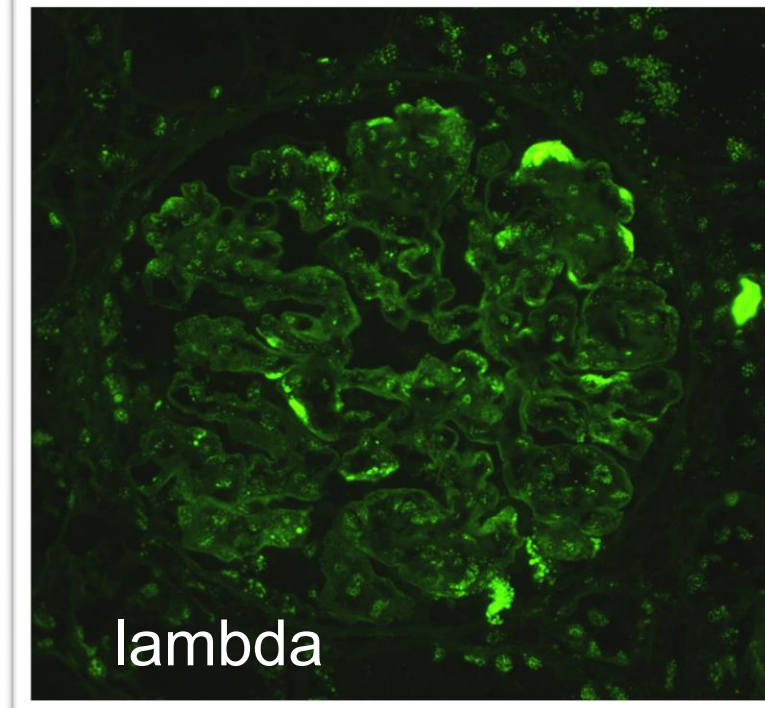
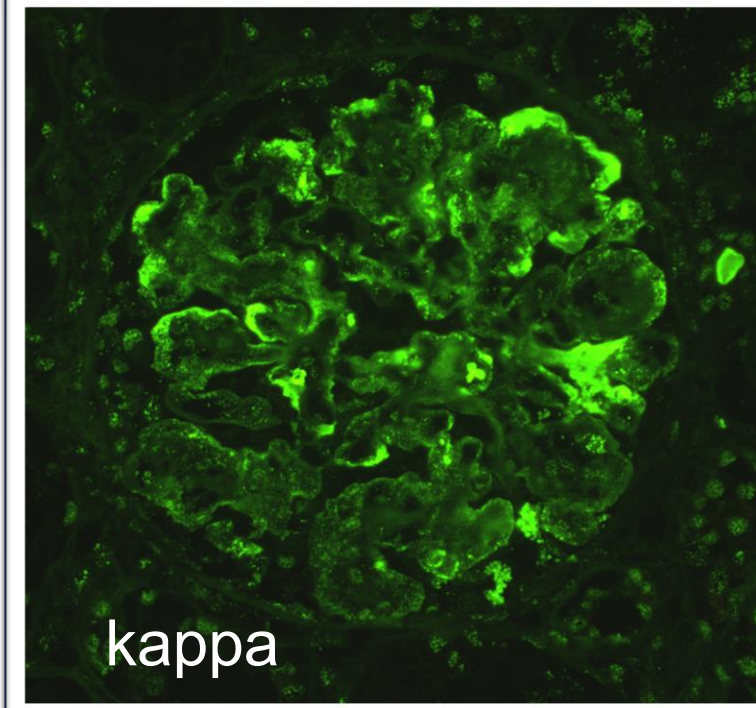
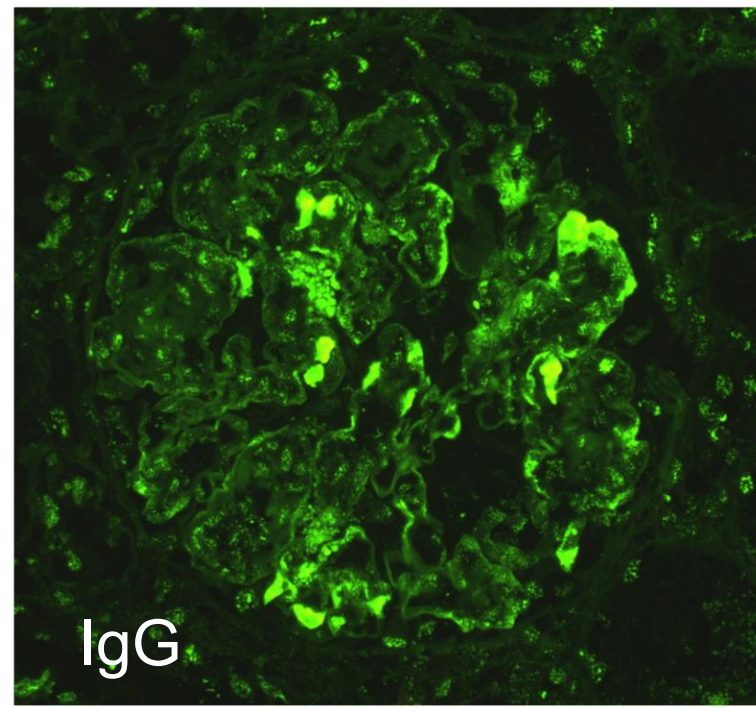
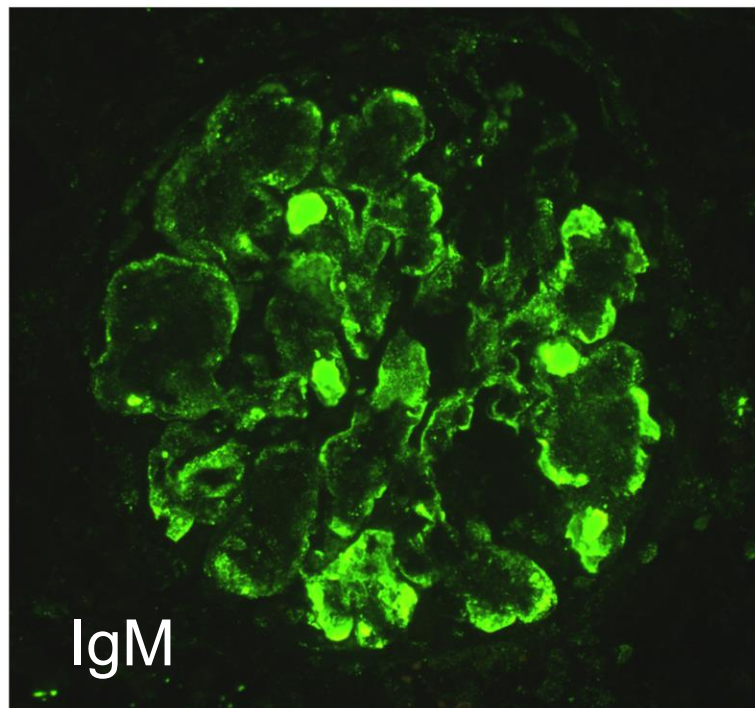
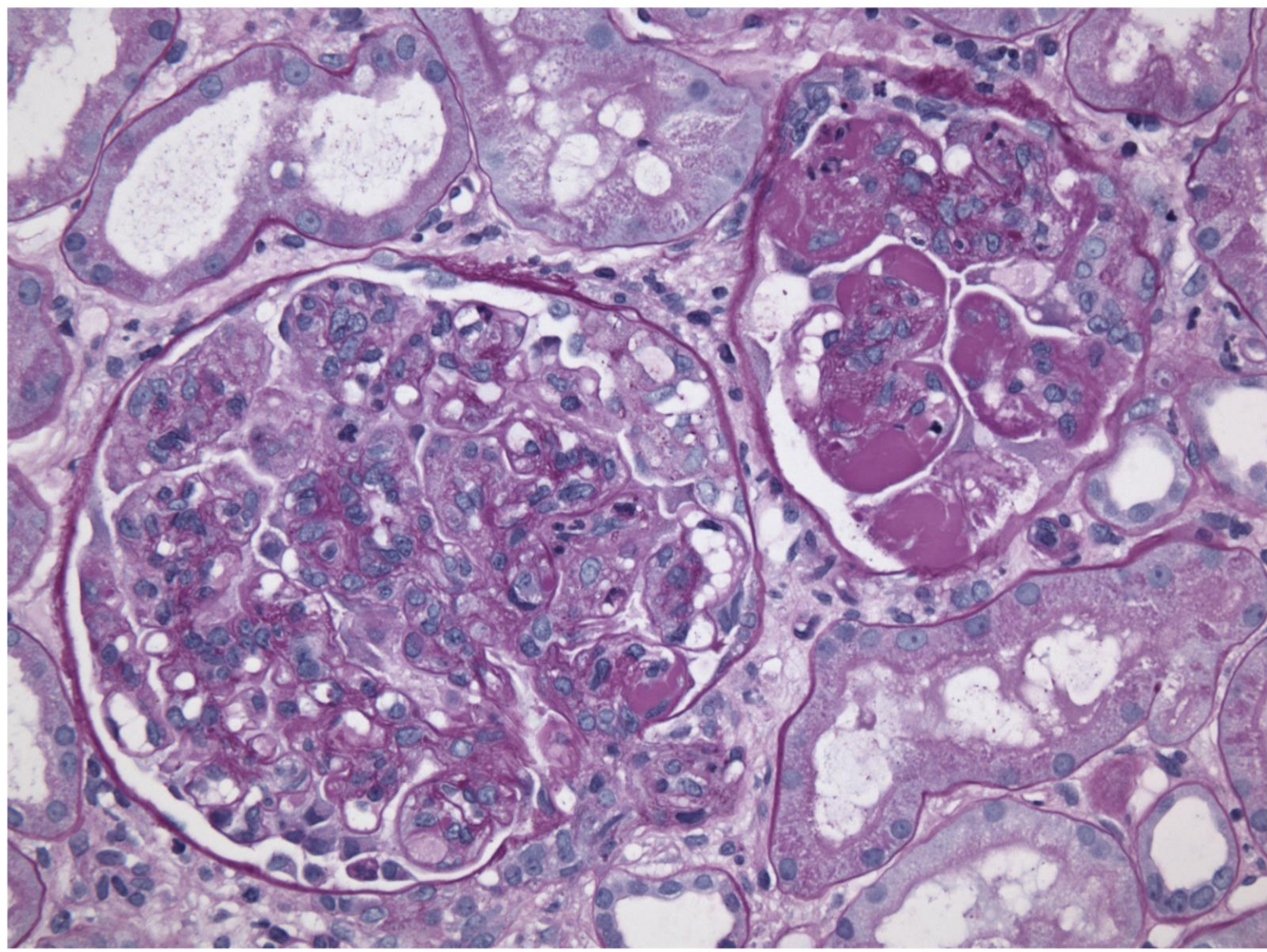


## HepC-associated mixed Cryoglobulinemia

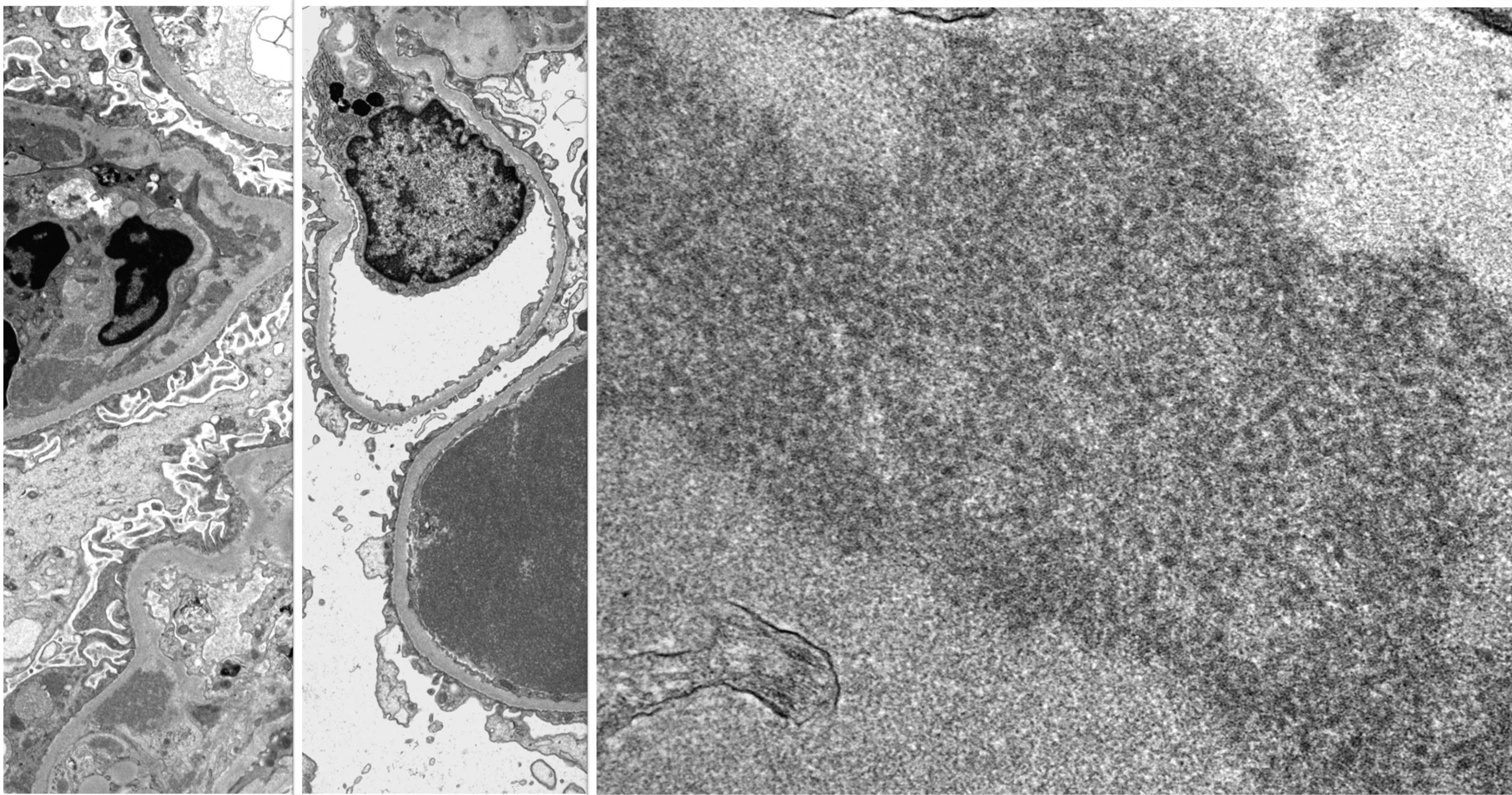




57-year-old man with a history of sicca syndrome, now with several-months history of fatigue. BUN 60, Cr 2.13. WBC 17.3, HCT: 23, Hgb 9.7, Plt 443. PT: 15.3, INR 1.2, PTT 26.9. Ca 8.2, PO4 4.0, alb 2.4; malb/Cr 3887mg; pro/Cr ratio 5; CH50 58, C4 2, C3 51 (all low). ANA+, 1:2560 speckled; hepC ab neg. ANCA neg; anti-Ro, La neg







Sjogren's syndrome-associated mixed cryoglobulinemia



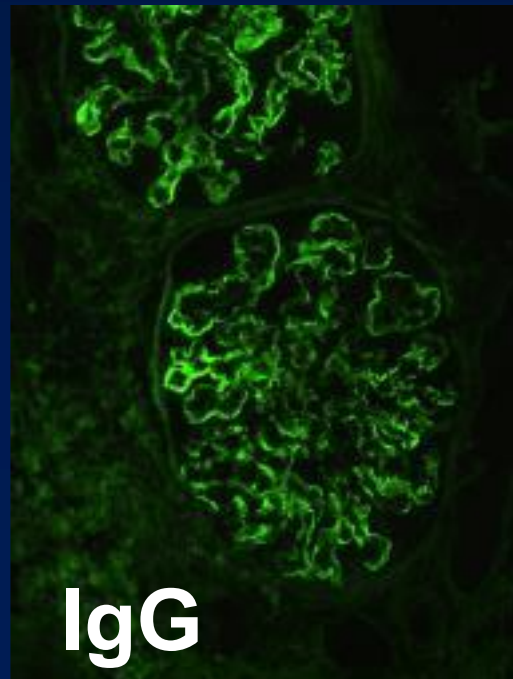
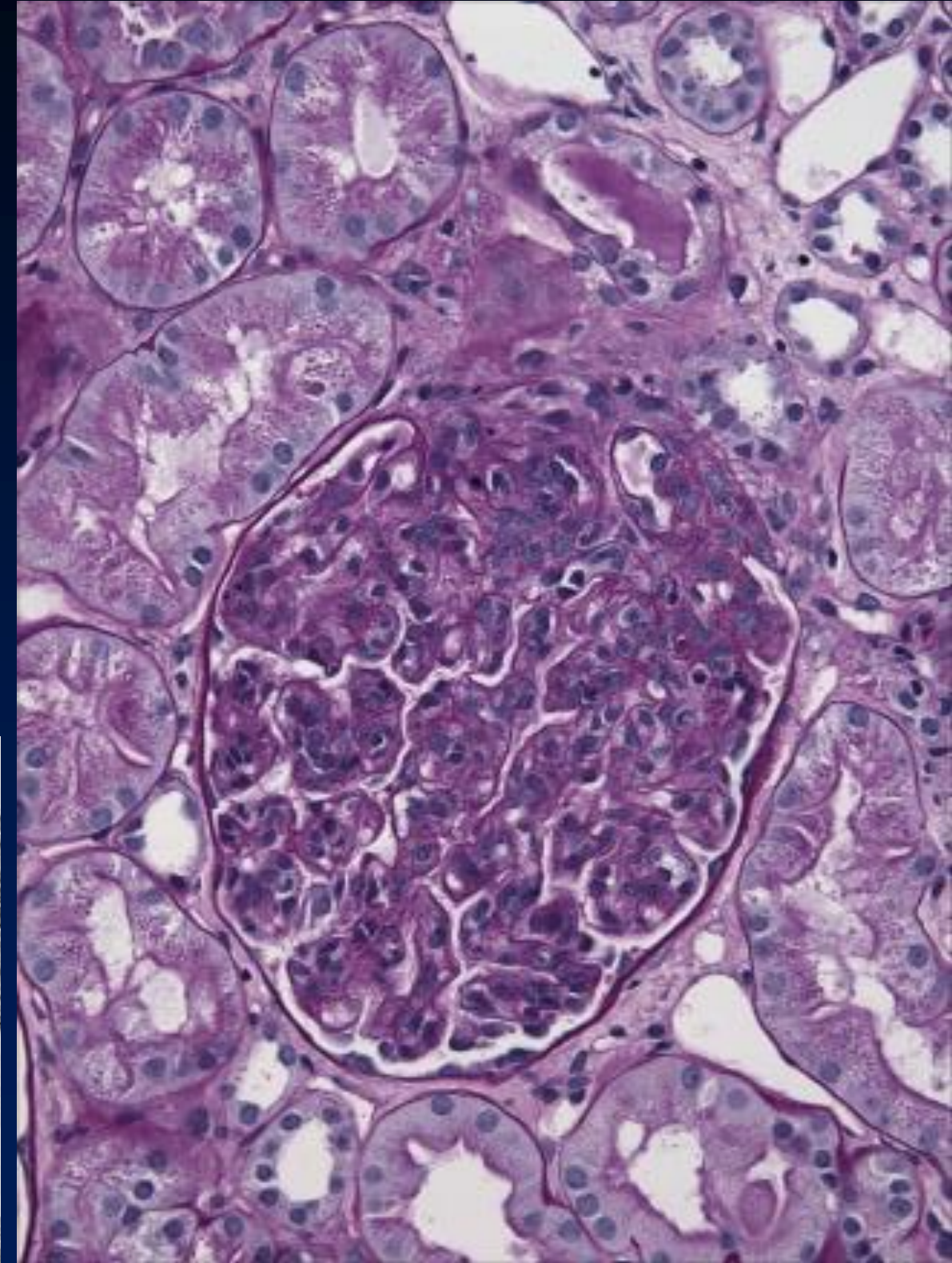
# Lyme Disease-associated GN

*Borrelia burgdorferi*

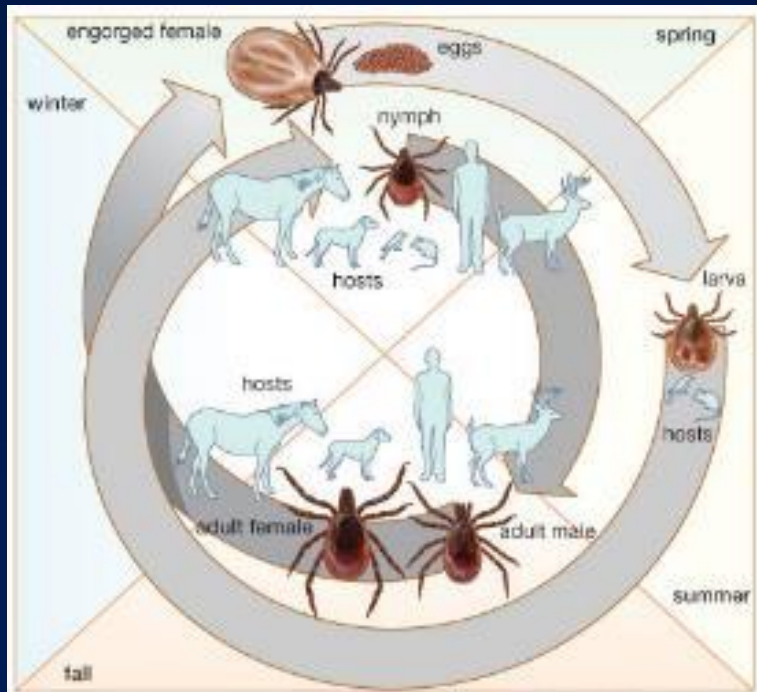
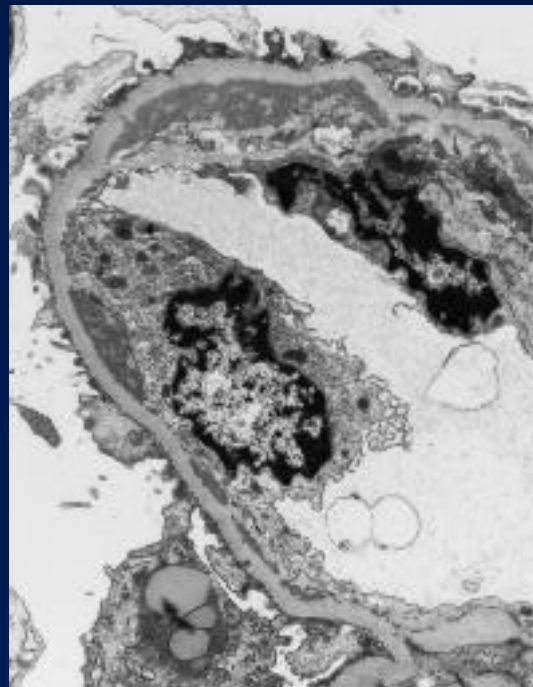
57-year-old woman presents hematuria and proteinuria for several weeks, and recently diagnosed myocarditis; her serum creatinine peaked at 1.5 (baseline 0.9); after the biopsy she was diagnosed recently with Lyme disease



*Ixodes dammini*



IgG





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# THE MEMBRANOPROLIFERATIVE PATTERN OF INJURY

## STRUCTURAL CHANGES:

- HYPERCELLULARITY
- CAPILLARY WALL THICKENING (double contours)

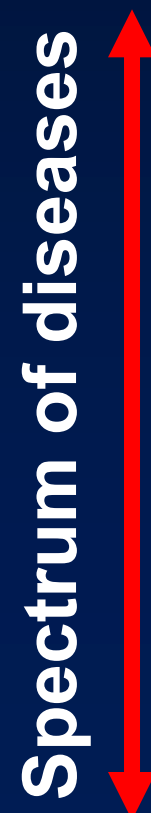
## CONDITIONS ASSOCIATED WITH THE MPGN PATTERN:

- IMMUNE COMPLEX DISEASES
- **ABNORMALITIES OF COMPLEMENT-REGULATORY PROTEINS**
- THROMBOTIC ANGIOPATHIES
- (PARAPROTEIN) DEPOSITION DISEASE



# CONDITIONS ASSOCIATED WITH A MEMBRANOPROLIFERATIVE PATTERN OF INJURY

## 2. DEFECTS IN COMPLEMENT-REGULATORY PROTEINS:

- 
- Spectrum of diseases
- Dense Deposit Disease (DDD)  
(MPGN type II)
  - Glomerulonephritis C3 (GN-C3)
  - Atypical HUS (d-HUS)

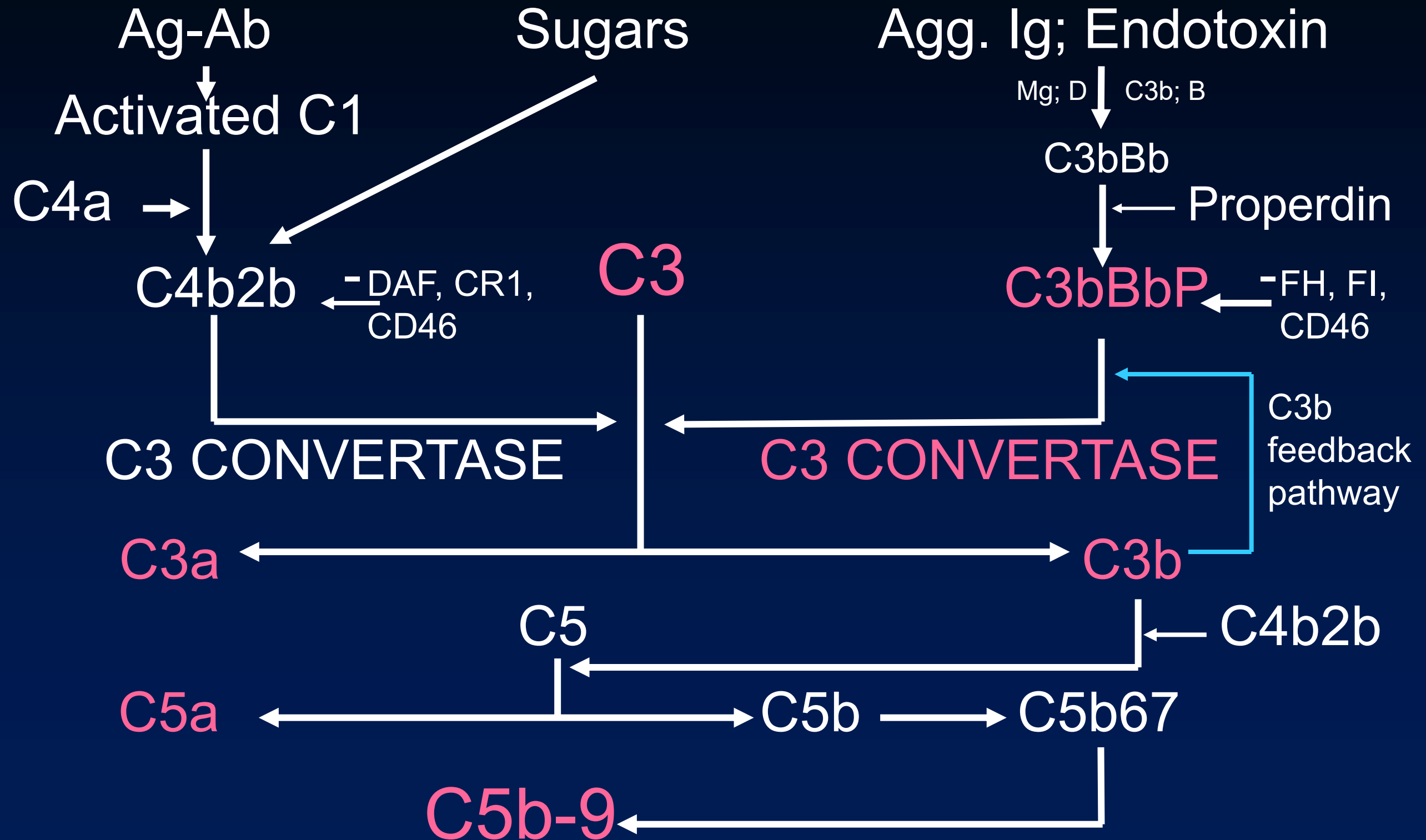


# ACTIVATION OF THE COMPLEMENT SYSTEM

VIA: CLASSIC

LECTIN

ALTERNATIVE



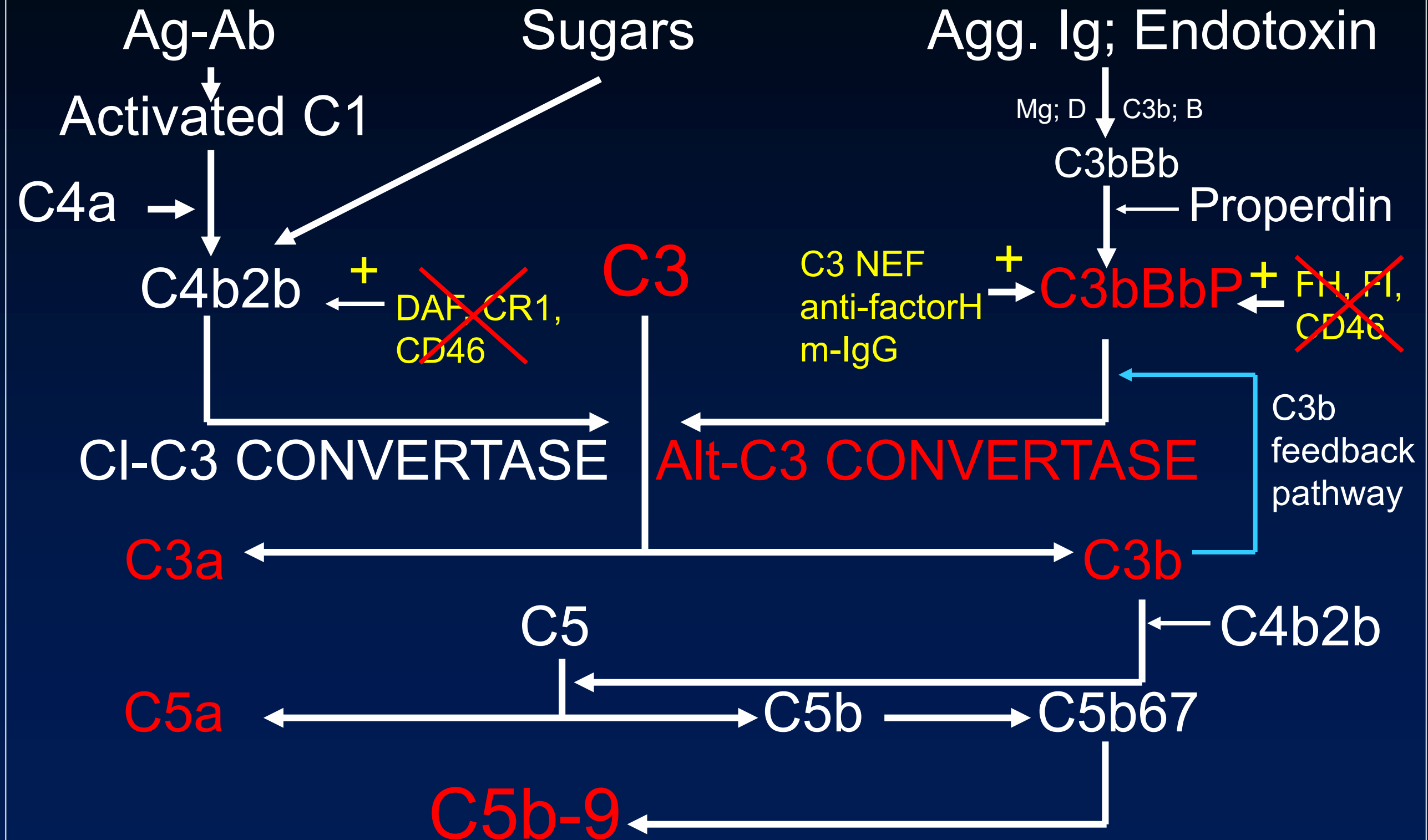


# ACTIVATION OF THE COMPLEMENT SYSTEM

## VIA: CLASSIC

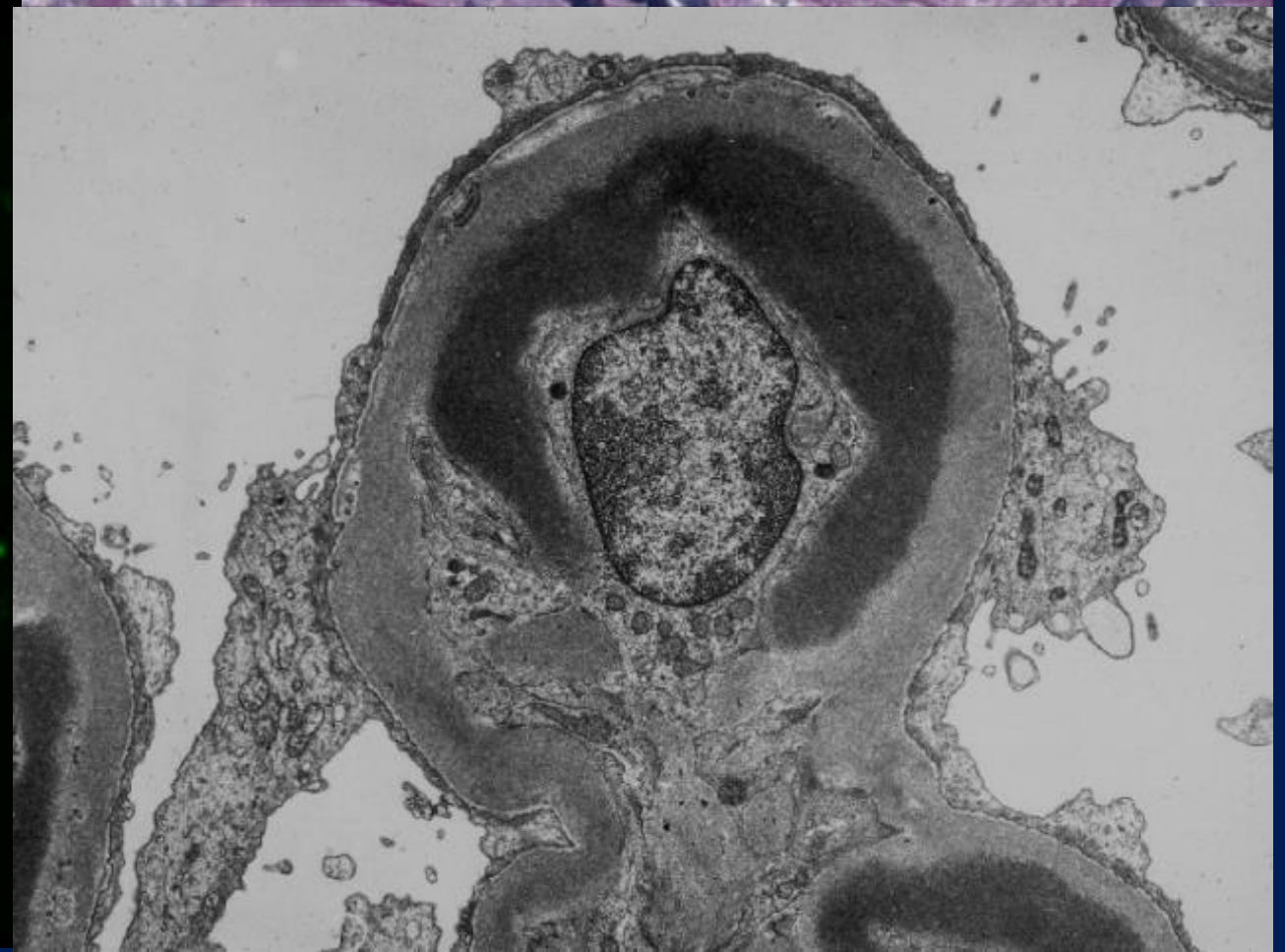
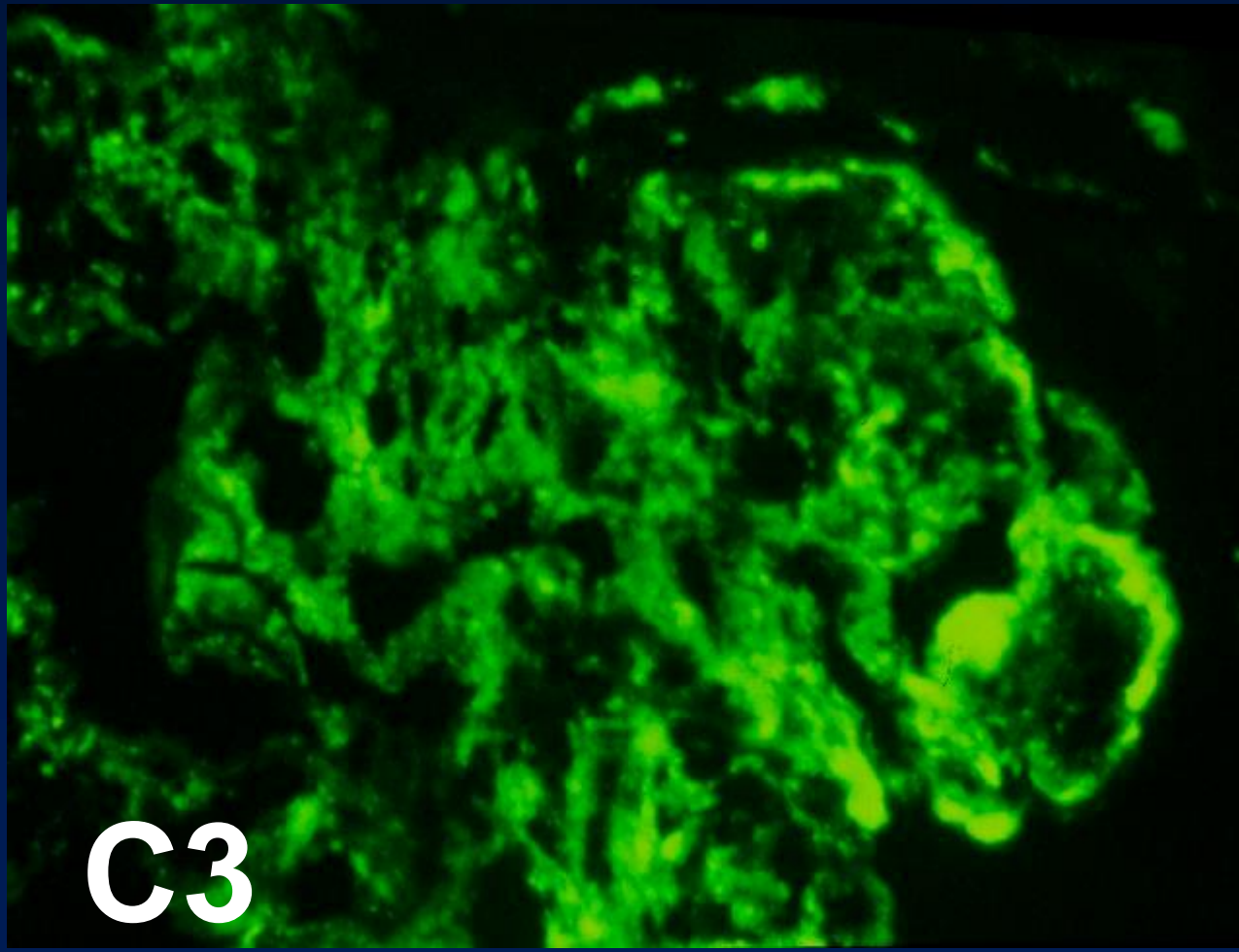
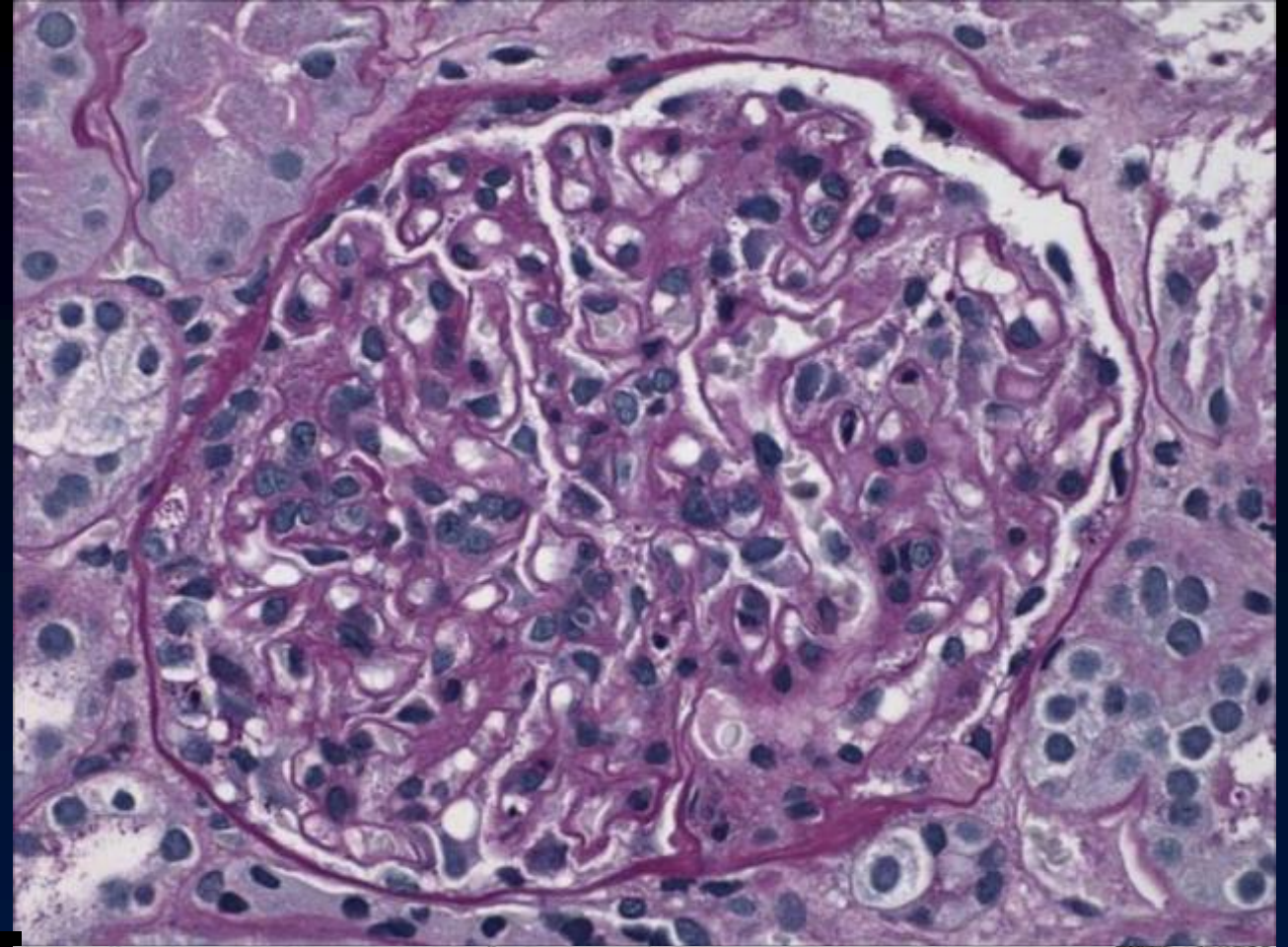
## LECTIN

## ALTERNATIVE





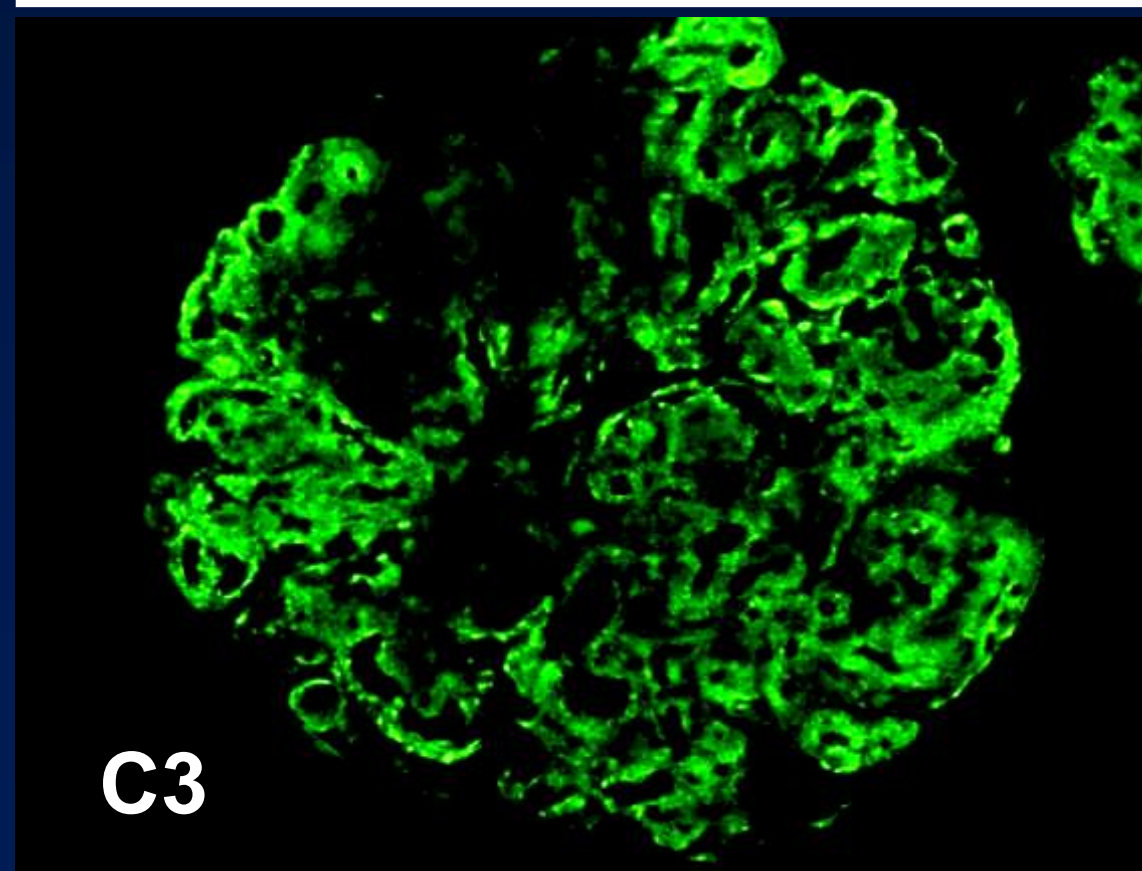
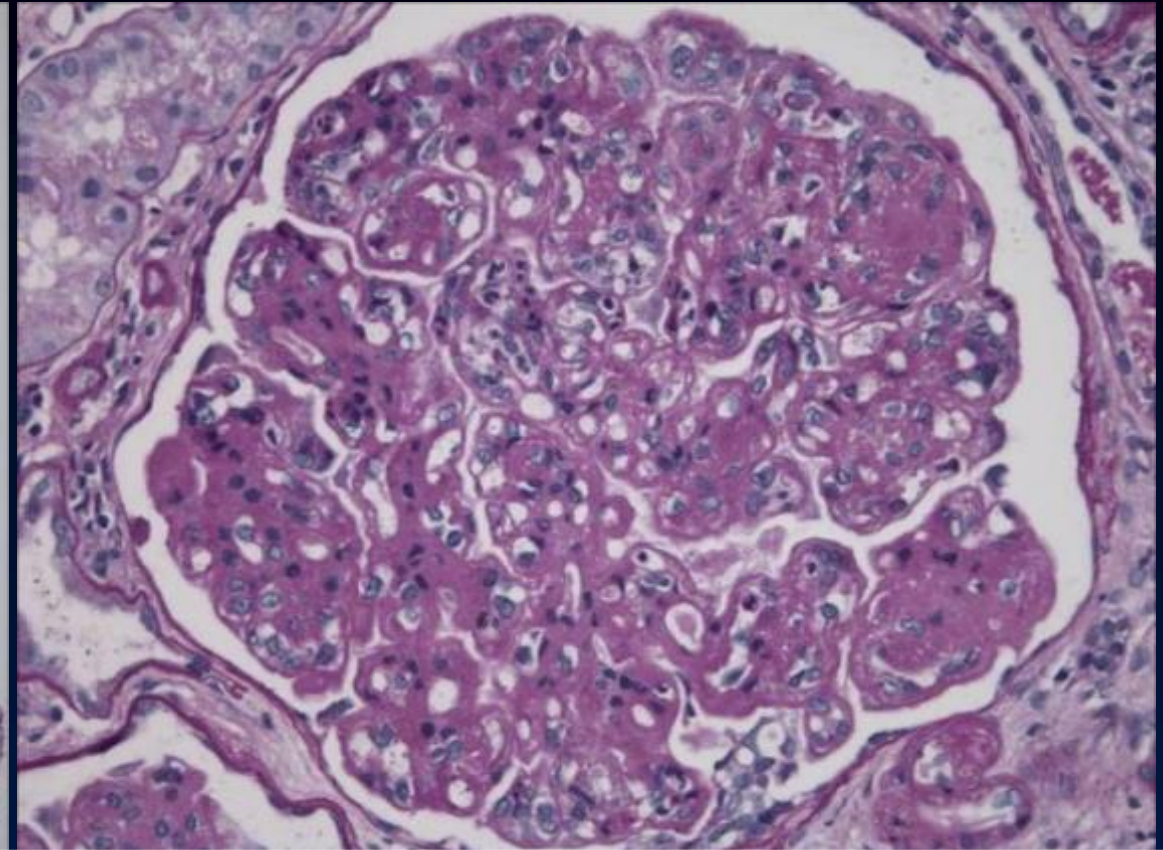
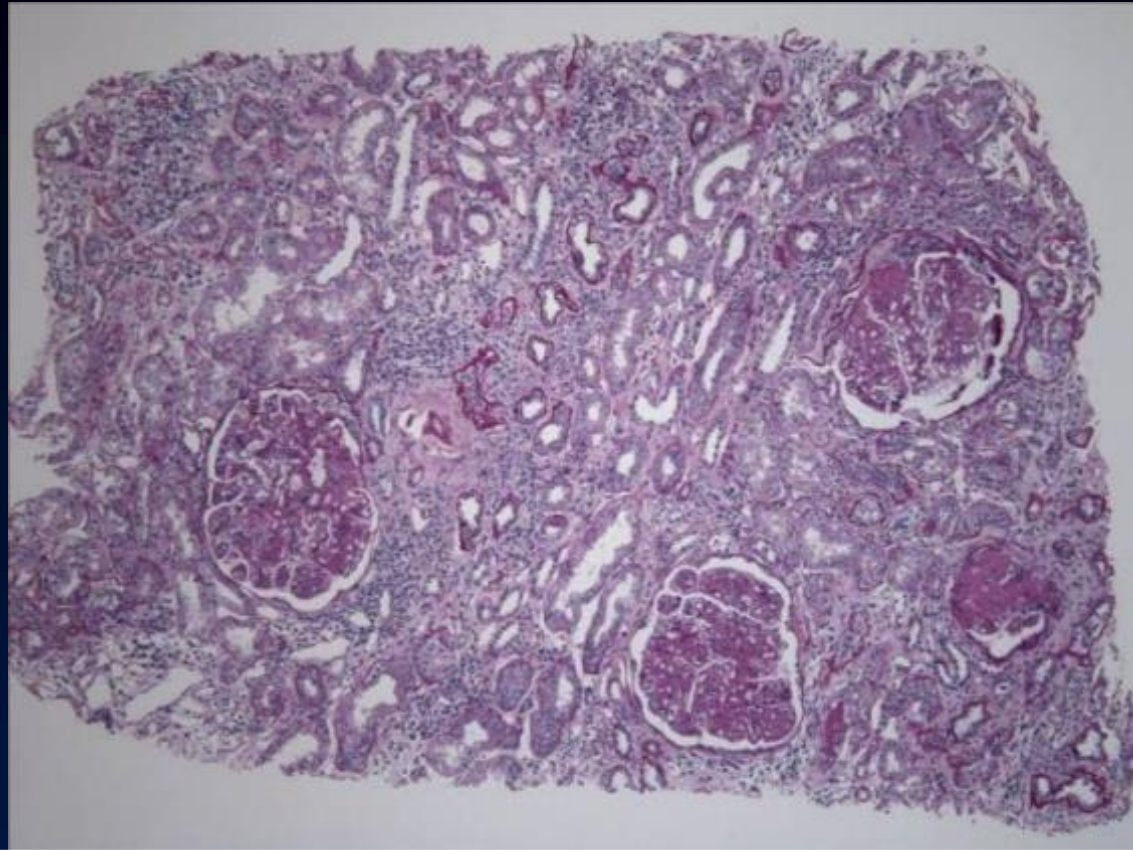
# Dense Deposit Disease



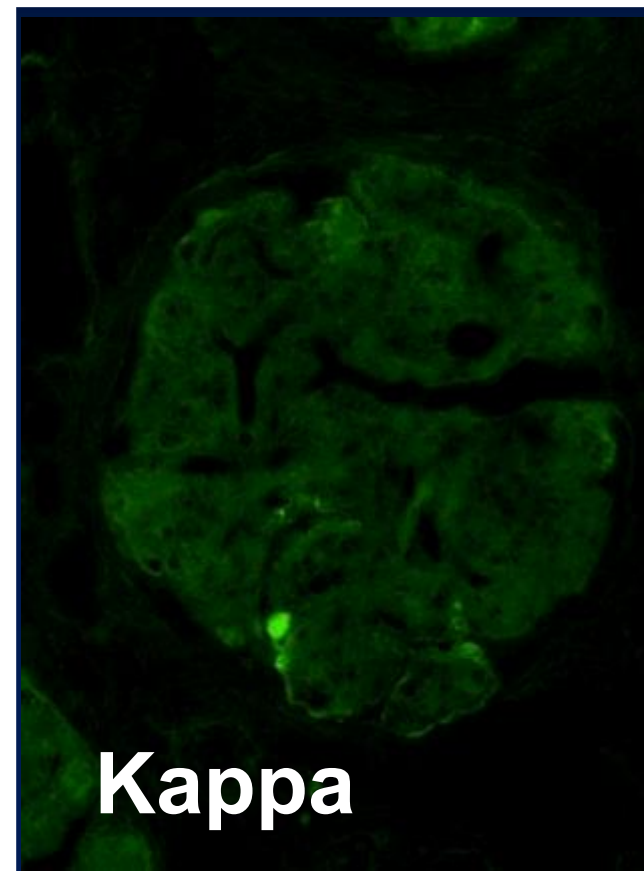


31 y/o woman with h/o hematuria, proteinuria (now ns), hypertension.

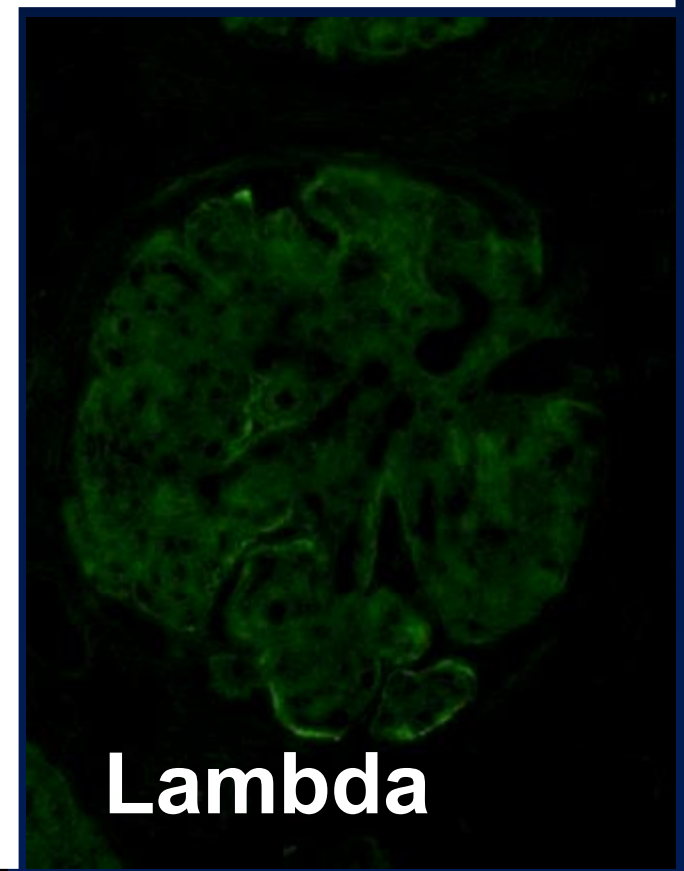
GLOMERULONEPHRITIS C3



C3

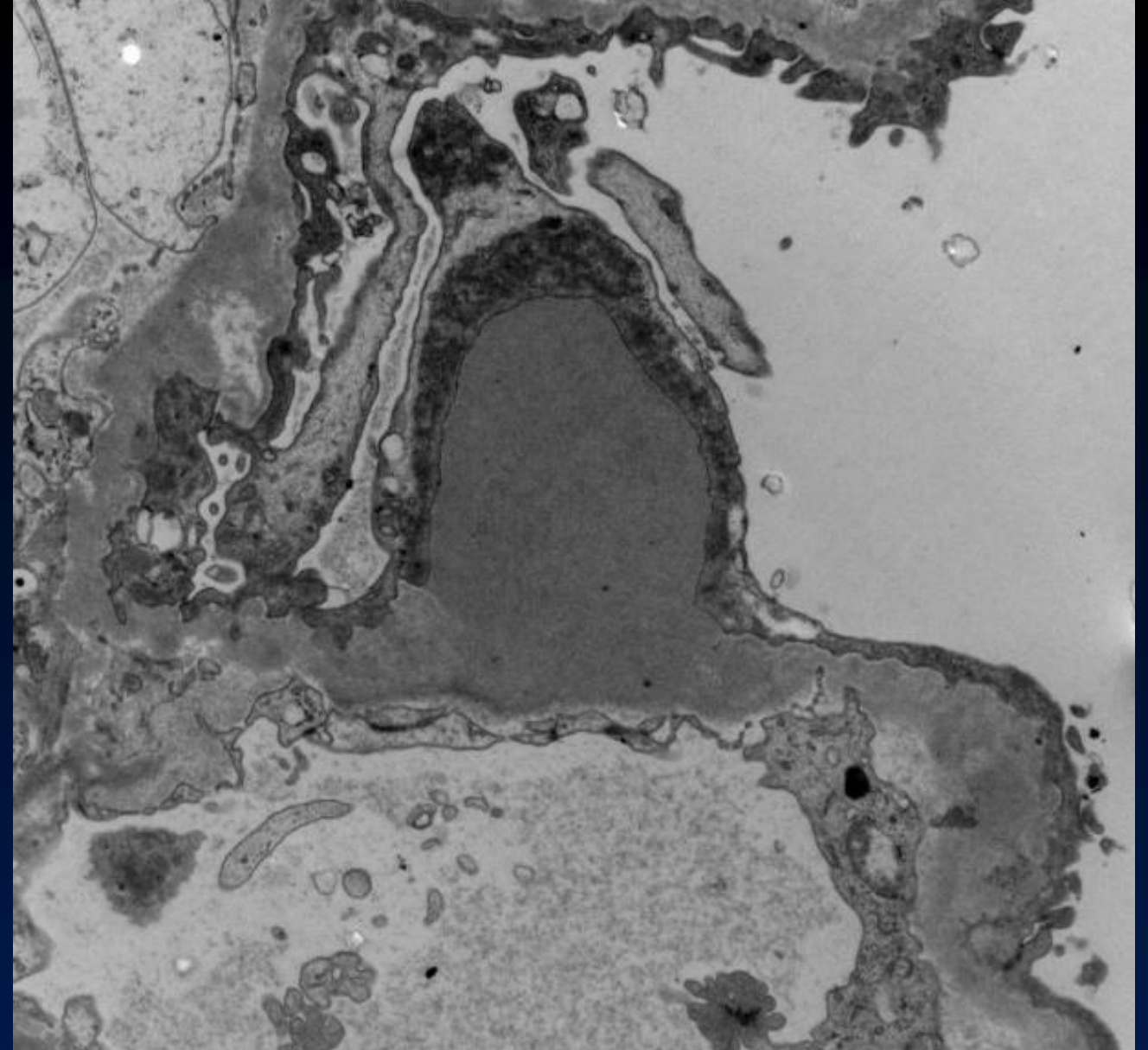
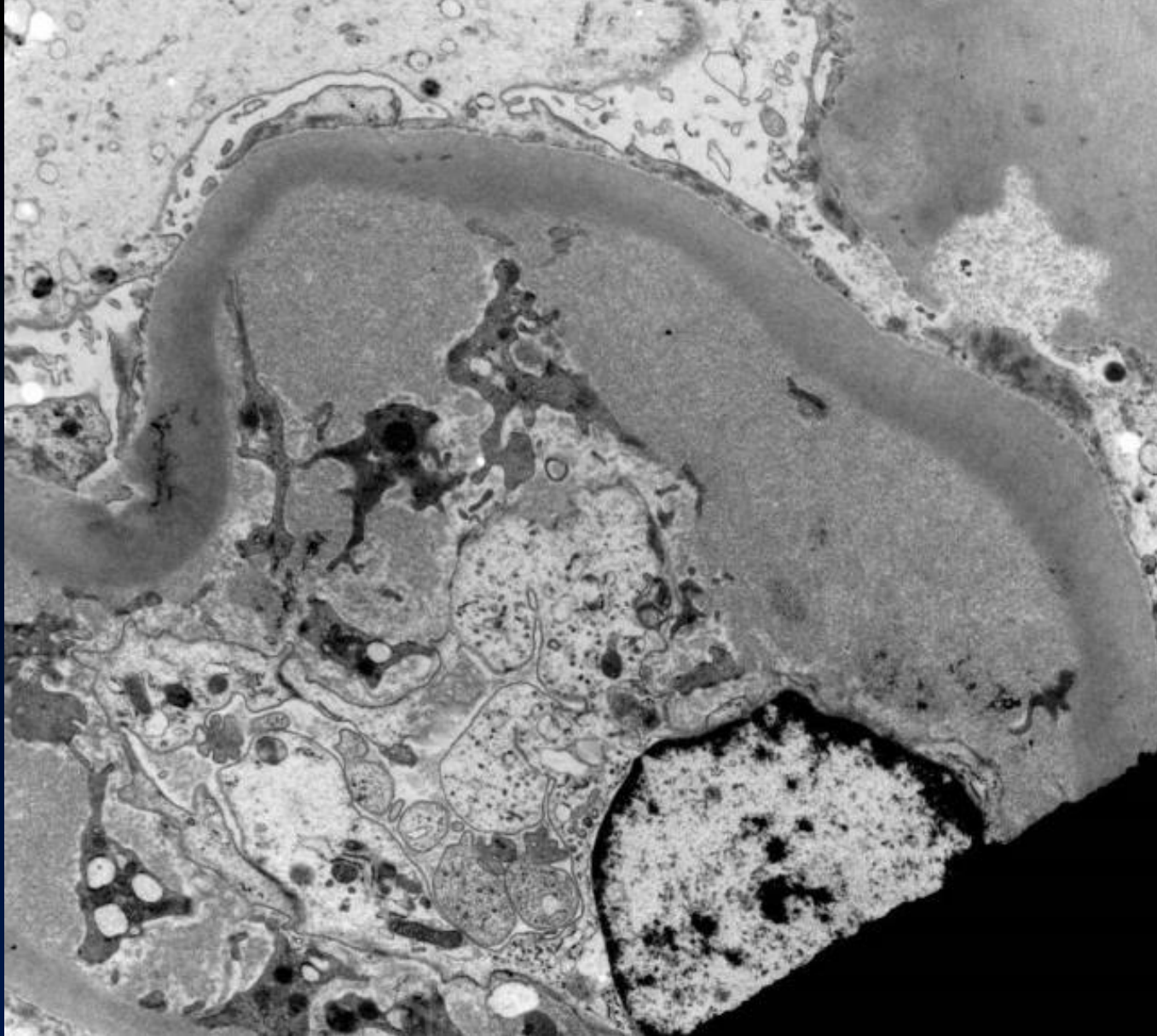


Kappa



Lambda





## CLINICAL RESULTS

### Results: Genetic Tests

| Gene                           | NCBI Reference | Allele 1      | Allele 2      | Result                 |
|--------------------------------|----------------|---------------|---------------|------------------------|
| <i>CFH</i>                     | NM_000186      | normal allele | normal allele | no pathogenic variants |
| <i>CFI</i>                     | NM_000204      | normal allele | normal allele | no pathogenic variants |
| <i>MCP</i>                     | NM_002389      | normal allele | normal allele | no pathogenic variants |
| <i>CFB</i>                     | NM_001710      | normal allele | normal allele | no pathogenic variants |
| <i>C3</i>                      | NM_000064      | normal allele | normal allele | no pathogenic variants |
| <i>CFHR5</i>                   | NM_030787      | normal allele | normal allele | no pathogenic variants |
| MLPA<br>( <i>CFHR1-CFHR4</i> ) | -----          | deletion      | normal allele | heterozygous deletion  |

The presence of C3 Nephritic Factor (C3NeF), an autoantibody to the alternative pathway C3 convertase (C3bBb), ELISA 1:200+ was detected

Soluble membrane attack complex (sMAC) was 0.81 mg/L (<0.3)



# CONDITIONS ASSOCIATED WITH A MEMBRANOPROLIFERATIVE PATTERN OF INJURY

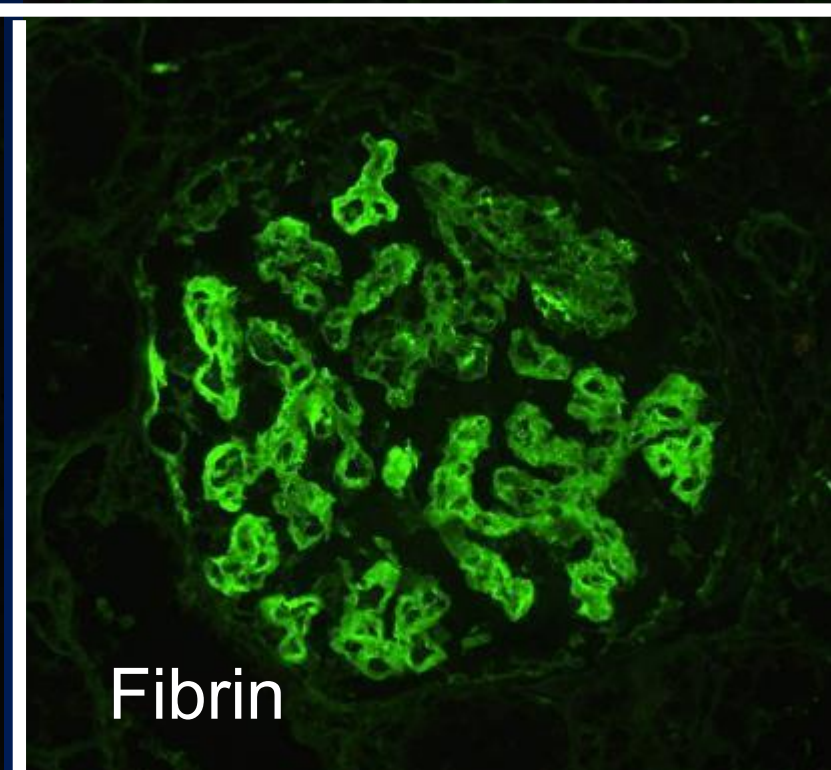
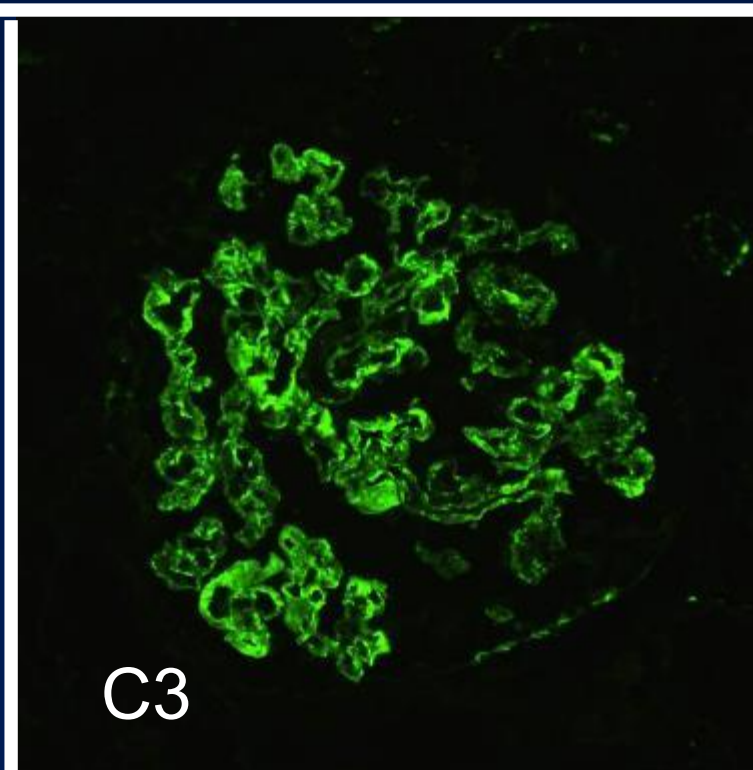
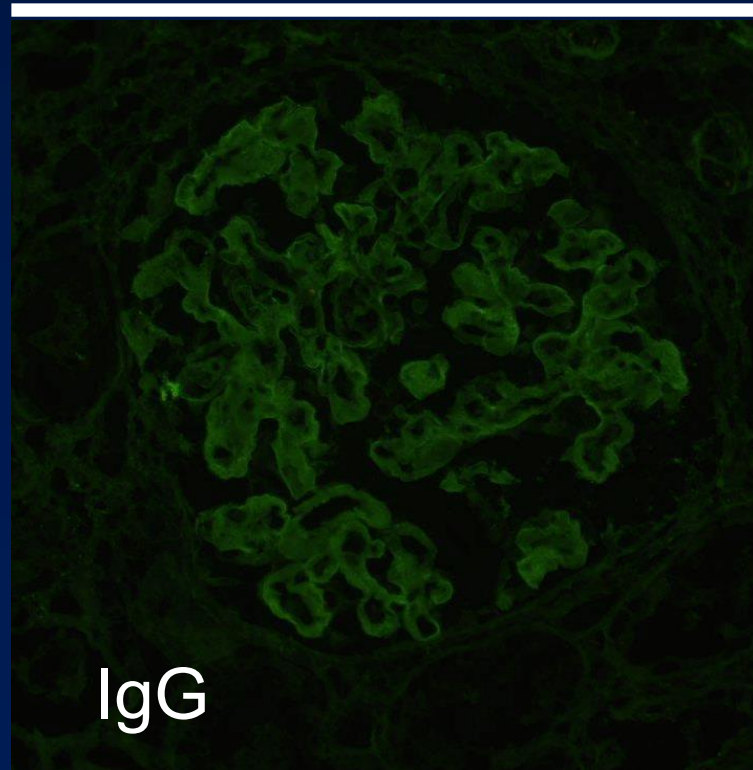
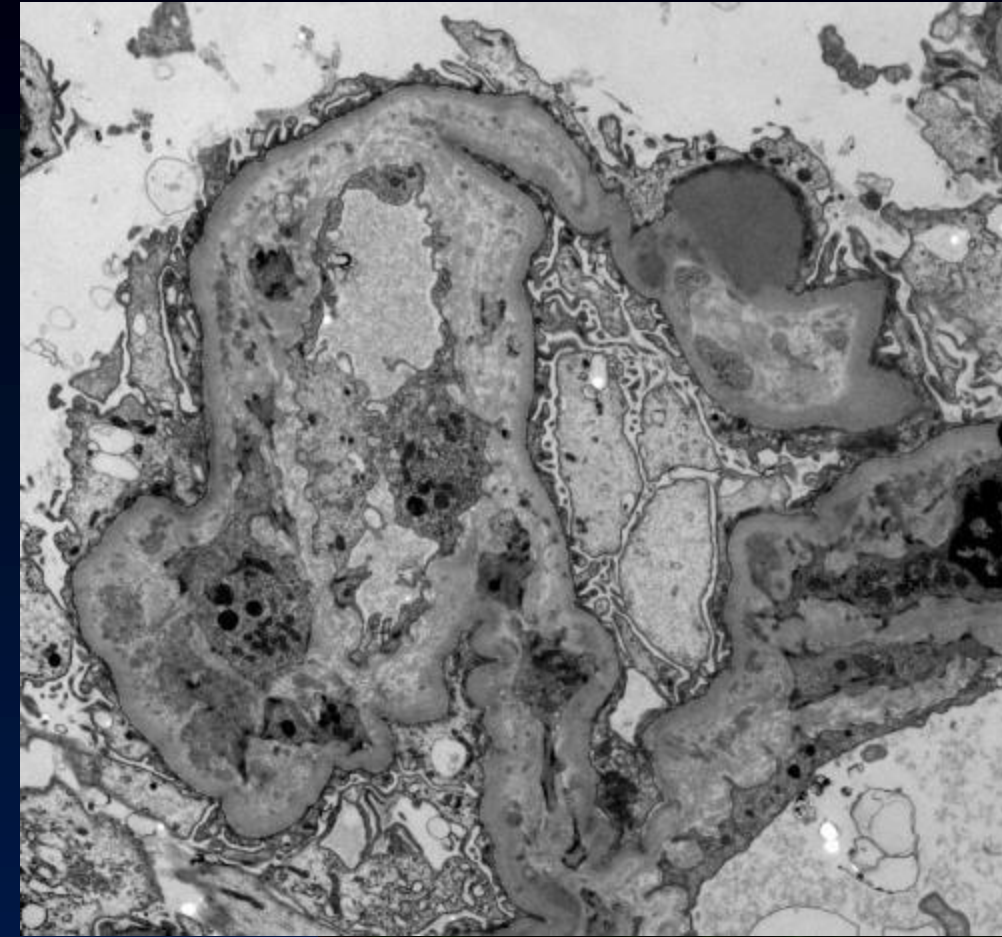
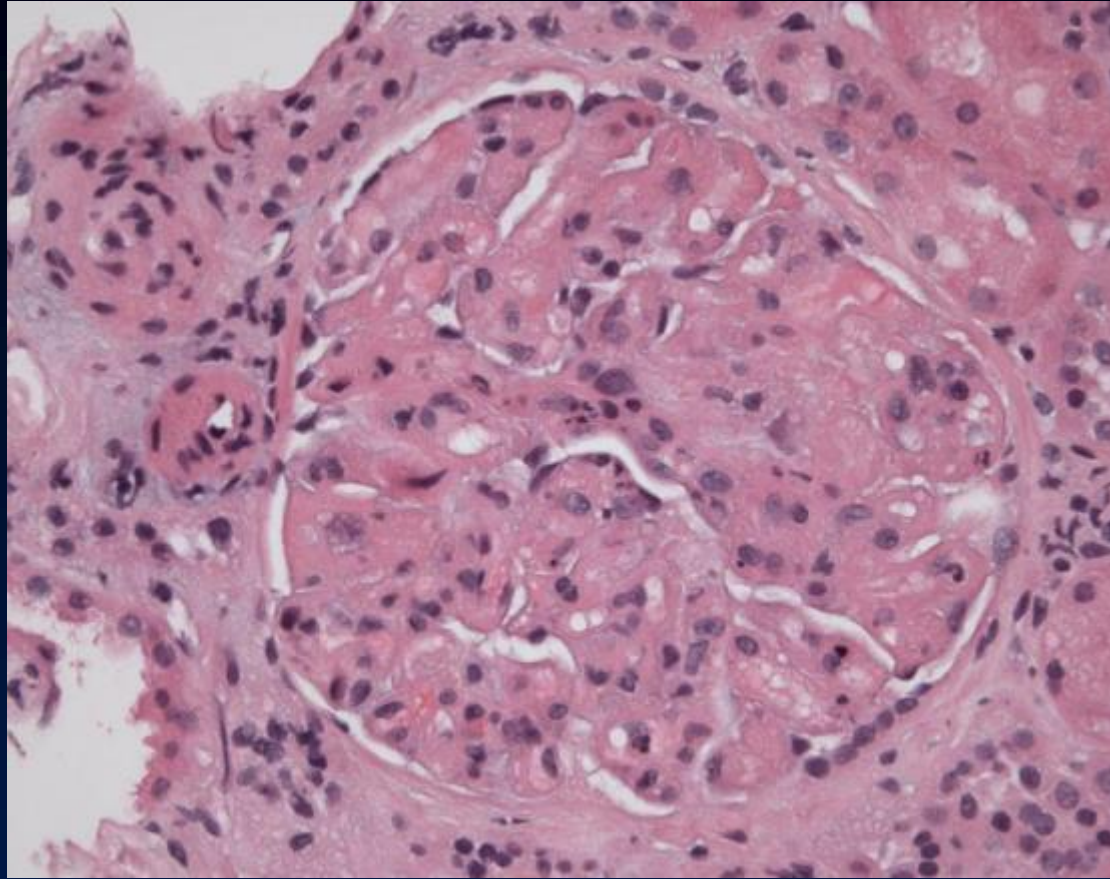
## 2. DEFECTS IN COMPLEMENT-REGULATORY PROTEINS:

- 
- Spectrum of disease
- Dense Deposit Disease (DDD)  
(MPGN type II)
  - Glomerulonephritis C3 (GN-C3)
  - Atypical HUS (d-HUS)
- overlap



Paraprotein-induced Glomerulonephritis C3  
with overlap features of aHUS

88-year-old man recent onset of proteinuria, edema, and kidney failure;  
he has a circulating paraprotein.





**FUNCTIONAL TESTING RESULTS OVERVIEW** *(please see full summary on the following pages)***Complement: Functional Assays and Autoantibodies**

| <i>Date Received</i> | <i>FH autoantibody</i><br>(titer <200 AU) | <i>FB autoantibody</i><br>(titer <200 AU) | <i>Hemolytic Assay</i><br>(<3%) | <i>APFA</i><br>(50% to 130%) | <i>CH50</i><br>(30-90 U/mL) | <i>C3Nef – IFE</i><br>(<7.5%) | <i>C3Nef - C3CSA</i><br>(<20%) | <i>C3Nef - C3CSAP</i><br>(<20%) | <i>C4Nef</i><br>(<20%) |
|----------------------|-------------------------------------------|-------------------------------------------|---------------------------------|------------------------------|-----------------------------|-------------------------------|--------------------------------|---------------------------------|------------------------|
| 12/16/15             | <50 AU                                    | 151 AU                                    | normal (0.2%)                   | 11%                          | 43 U/mL                     | 1+ (8.8%)                     | negative (15%)                 | negative (19%)                  | negative (5%)          |

The activity of the alternative pathway in your patient is low. Consumption or depletion of AP complement proteins will result in a low (abnormal) APFA. Dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) are two ultra-rare renal diseases characterized by fluid-phase dysregulation of the AP that often leads to partial or complete consumption of circulating complement components, including complement C3, factor B, properdin and C5 (see Zhang et al., Defining the complement biomarker profile of C3 glomerulopathy, CJASN 2014). As a consequence, APFA can be low.

Your patient is positive by immunofixation electrophoresis or IFE, an indirect assay measuring whether patient serum contains a factor that cleaves C3 to C3 degradation products. However, direct C3Nef tests (using patient IgG) are negative (negative for C3CSA, C3CSAp and C4Nef, page 3). In these assays, patient-purified IgGs are used to screen for autoantibodies that stabilize membrane bound (pre-formed) AP C3 convertase (C3bBb or C3bBb+Properdin) or CP C3 convertase (C4b2a). As such, your patient carries a yet-to-be-identified factor that can breakdown C3 and lead to very active C3 convertase (high plasma Bb fragment).

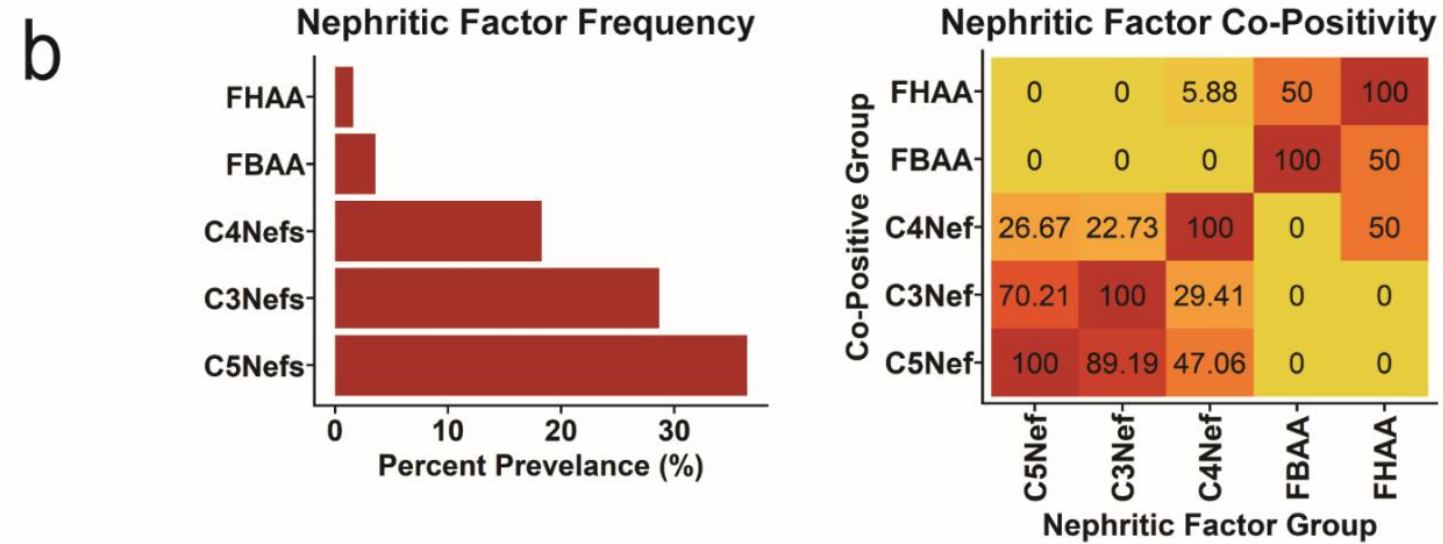
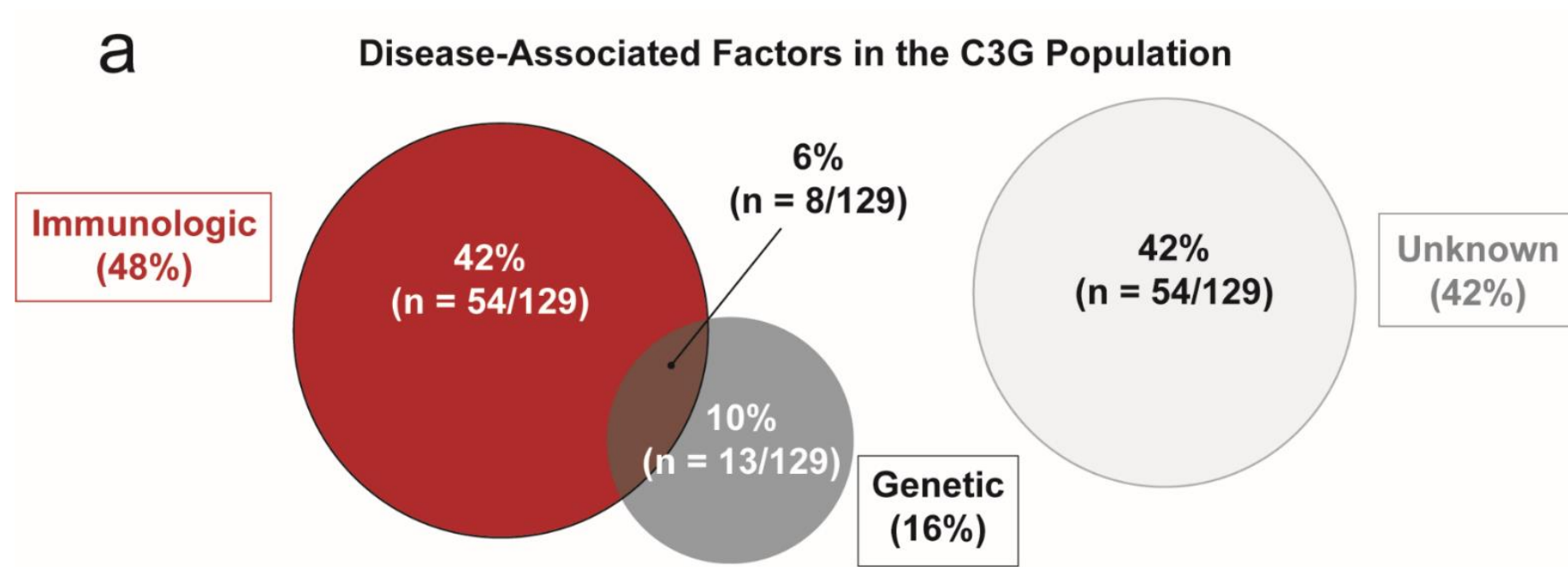
**BIOMARKER TESTING RESULTS OVERVIEW** *(please see full summary on the following pages)***Complement: Biomarker Tests**

| <i>Date Received</i> | <i>C3 Level</i><br>(0.9 – 1.8 g/L) | <i>C3c Level</i><br>(<2.0 mg/L) | <i>C4 Level</i><br>(0.15-0.57 g/L) | <i>Ba Level</i><br>(<1.2 mg/L) | <i>Bb Level</i><br>(<2.2 mg/L) | <i>FB Level</i><br>(22-50 mg/dL) | <i>FH Level</i><br>(45-80 mg/dL) | <i>FI Level</i><br>(16-40 mg/L) | <i>C5 Level</i><br>(10-21 mg/dL) | <i>Properdin Level</i><br>(10-33 mg/L) | <i>Soluble C5b-9</i><br>(<0.3 mg/L) |
|----------------------|------------------------------------|---------------------------------|------------------------------------|--------------------------------|--------------------------------|----------------------------------|----------------------------------|---------------------------------|----------------------------------|----------------------------------------|-------------------------------------|
| 12/16/15             | 1.0 g/L                            | 2.3 mg/L                        | 0.36 g/L                           | 2.7 mg/L                       | 4.5 mg/L                       | 31.2 mg/dL                       | 69.1 mg/dL                       | 34.8 mg/L                       | 21.1 mg/dL                       | 8.6 mg/L                               | 1.03 mg/L                           |

Your patient's C3c, Ba, Bb and soluble C5b-9 levels are high. Plasma levels of complement breakdown products C3c, Ba and Bb are elevated in both DDD and C3GN as compared to controls (both  $p < 0.001$ ), consistent with dysregulation of the C3 convertase. As a result, the C5 convertase is also dysregulated in your patient (high sC5b-9).

Your patient's properdin level is low; consumption of properdin suggests activation of the alternative and terminal pathways of complement.

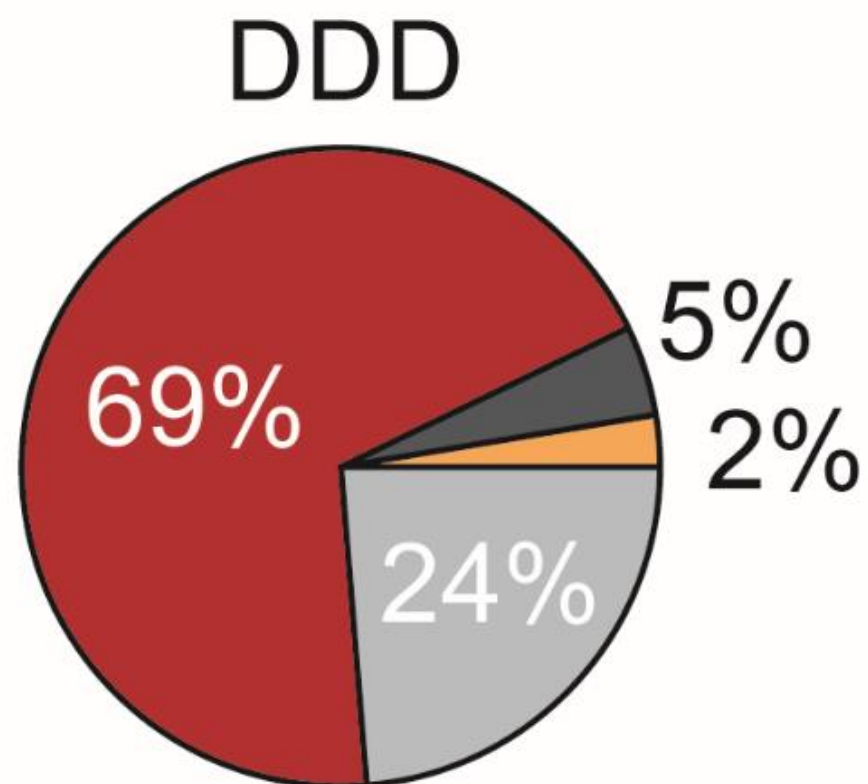
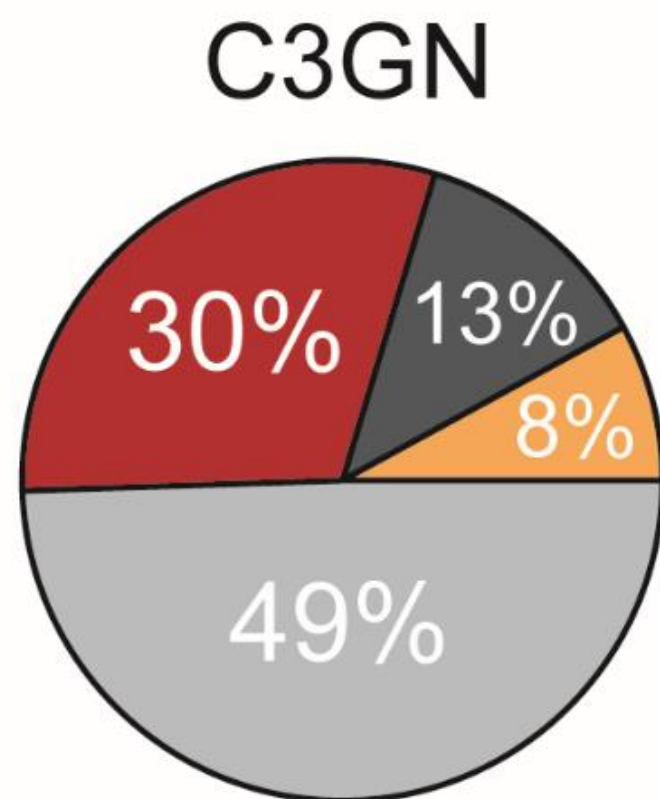




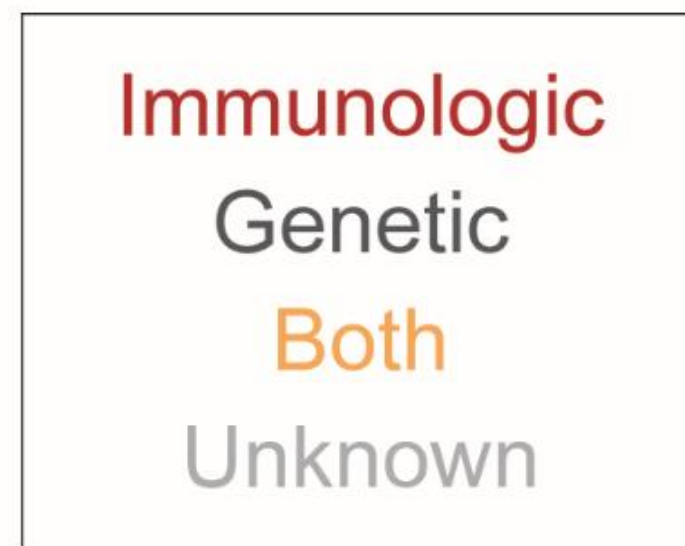
Courtesy Dr. Richard Smith



d



Drivers





# THE MEMBRANOPROLIFERATIVE PATTERN OF INJURY

## STRUCTURAL CHANGES:

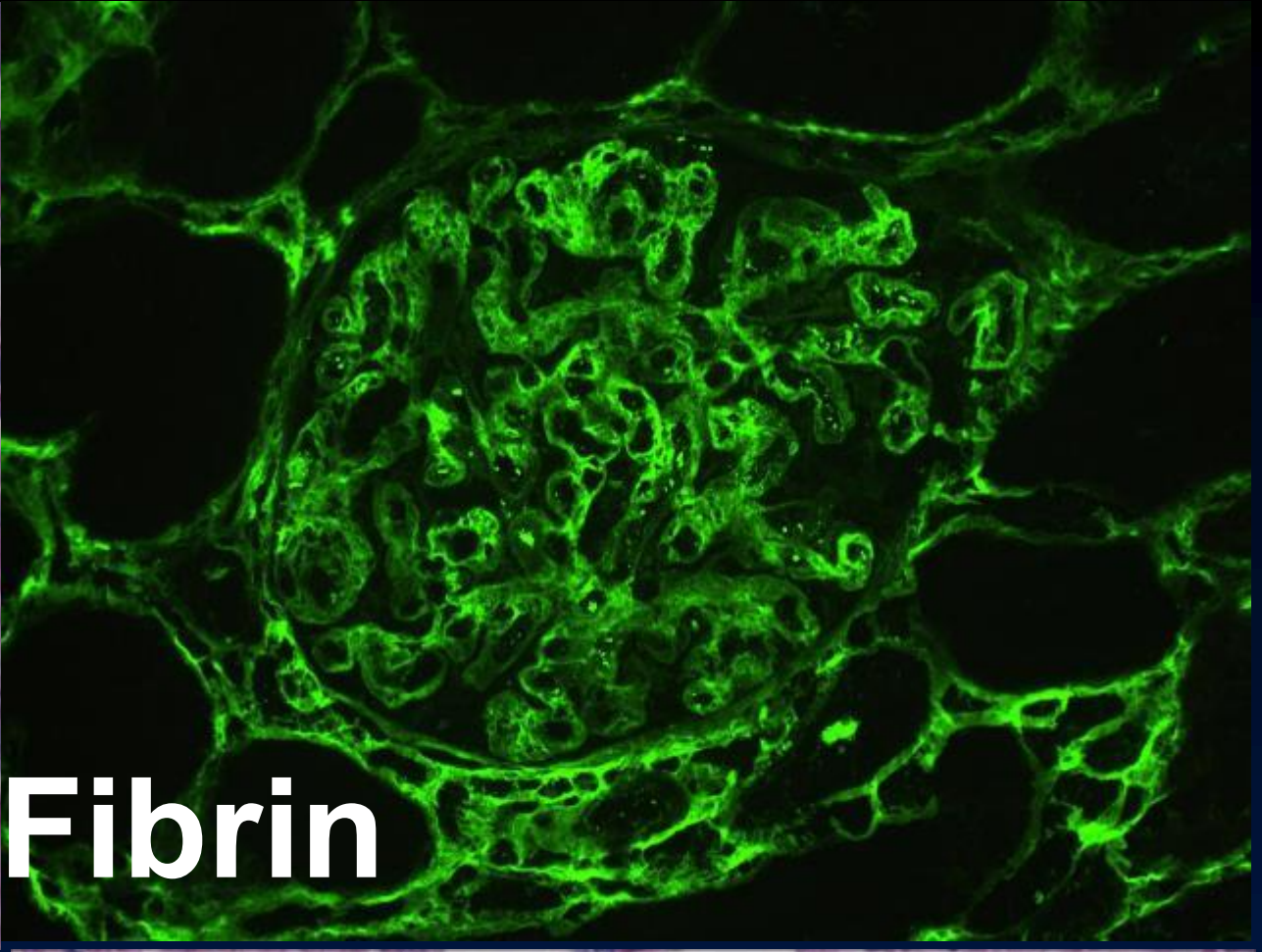
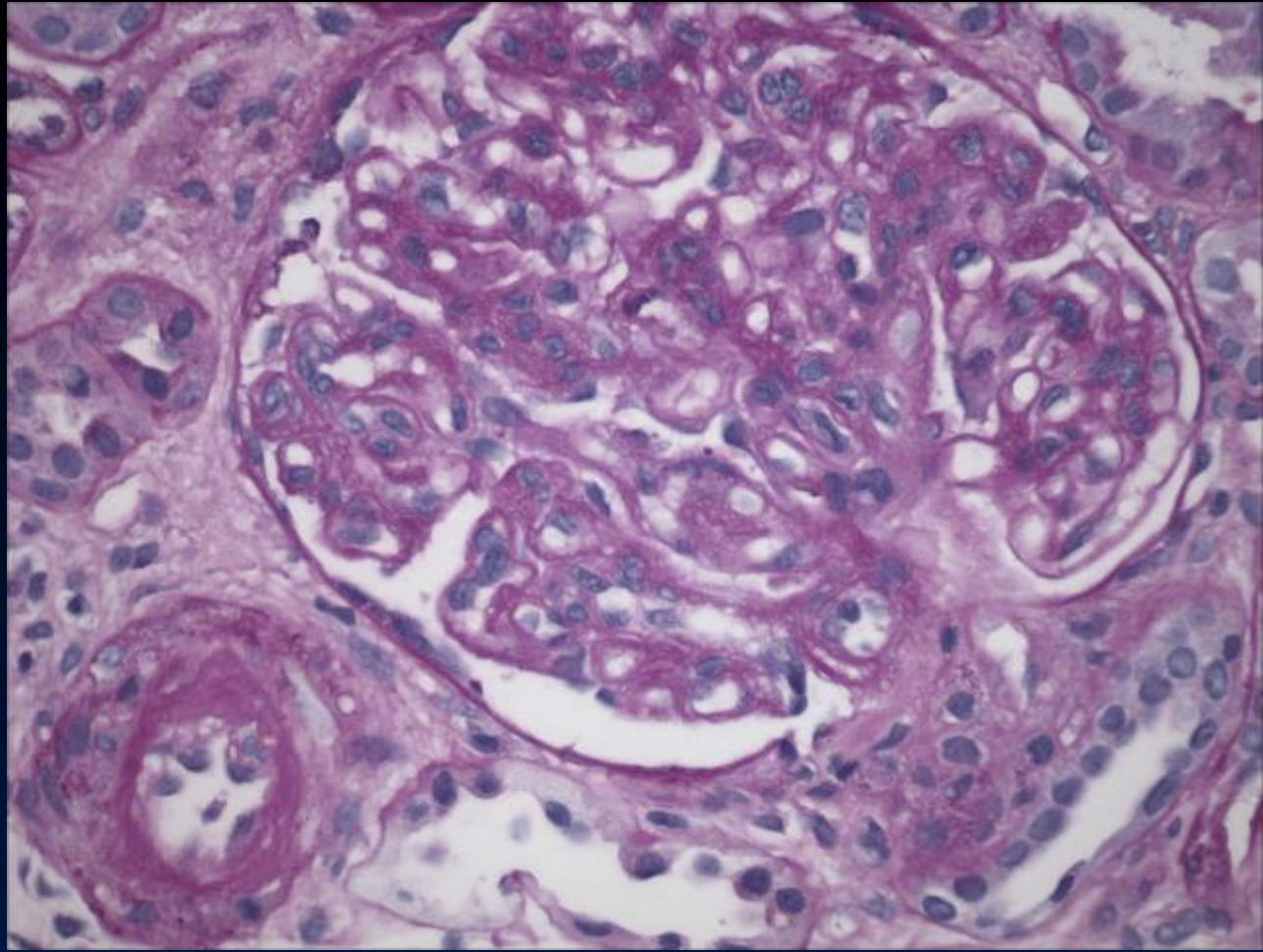
- HYPERCELLULARITY
- CAPILLARY WALL THICKENING (double contours)

## CONDITIONS ASSOCIATED WITH THE MPGN PATTERN:

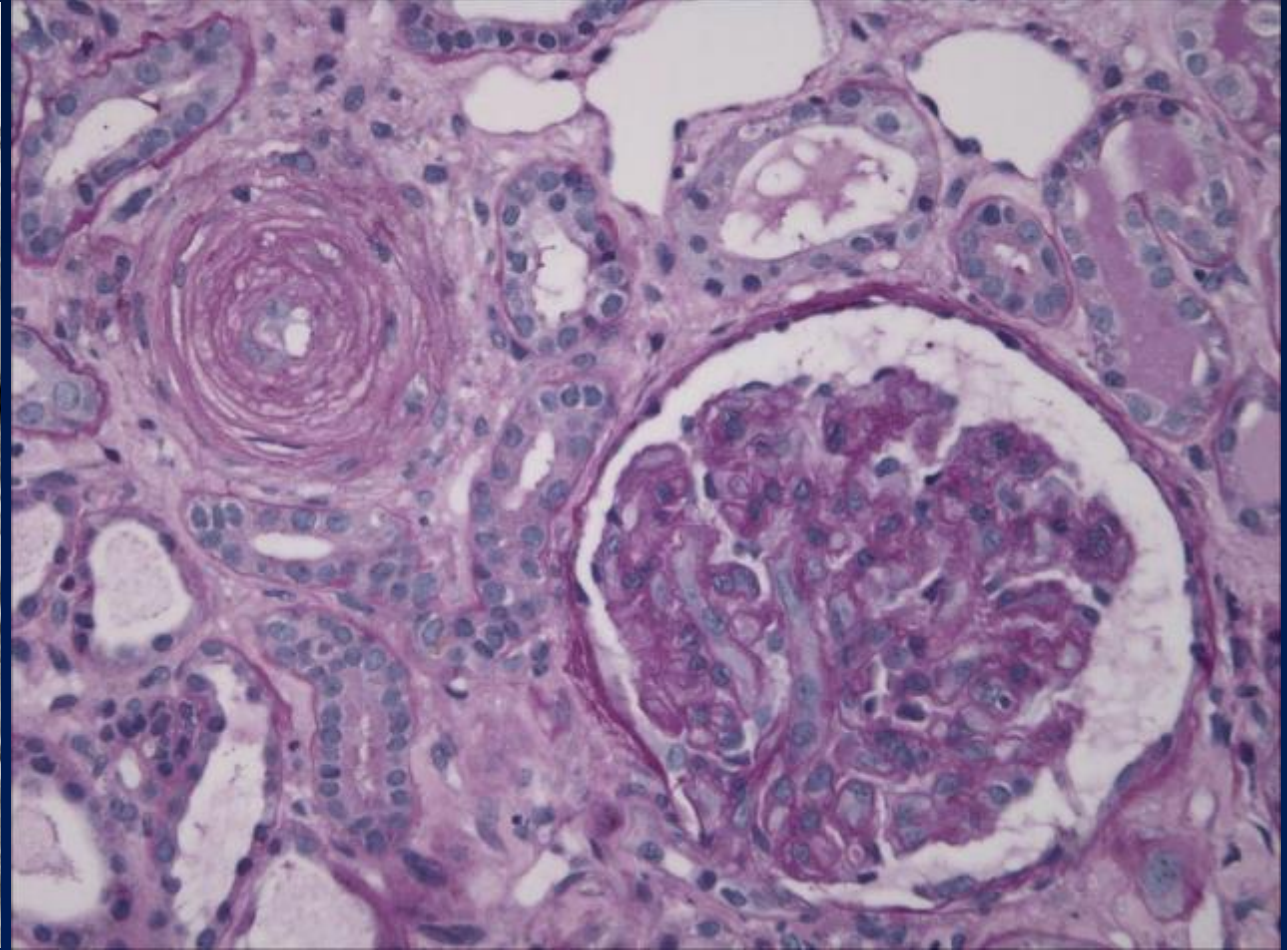
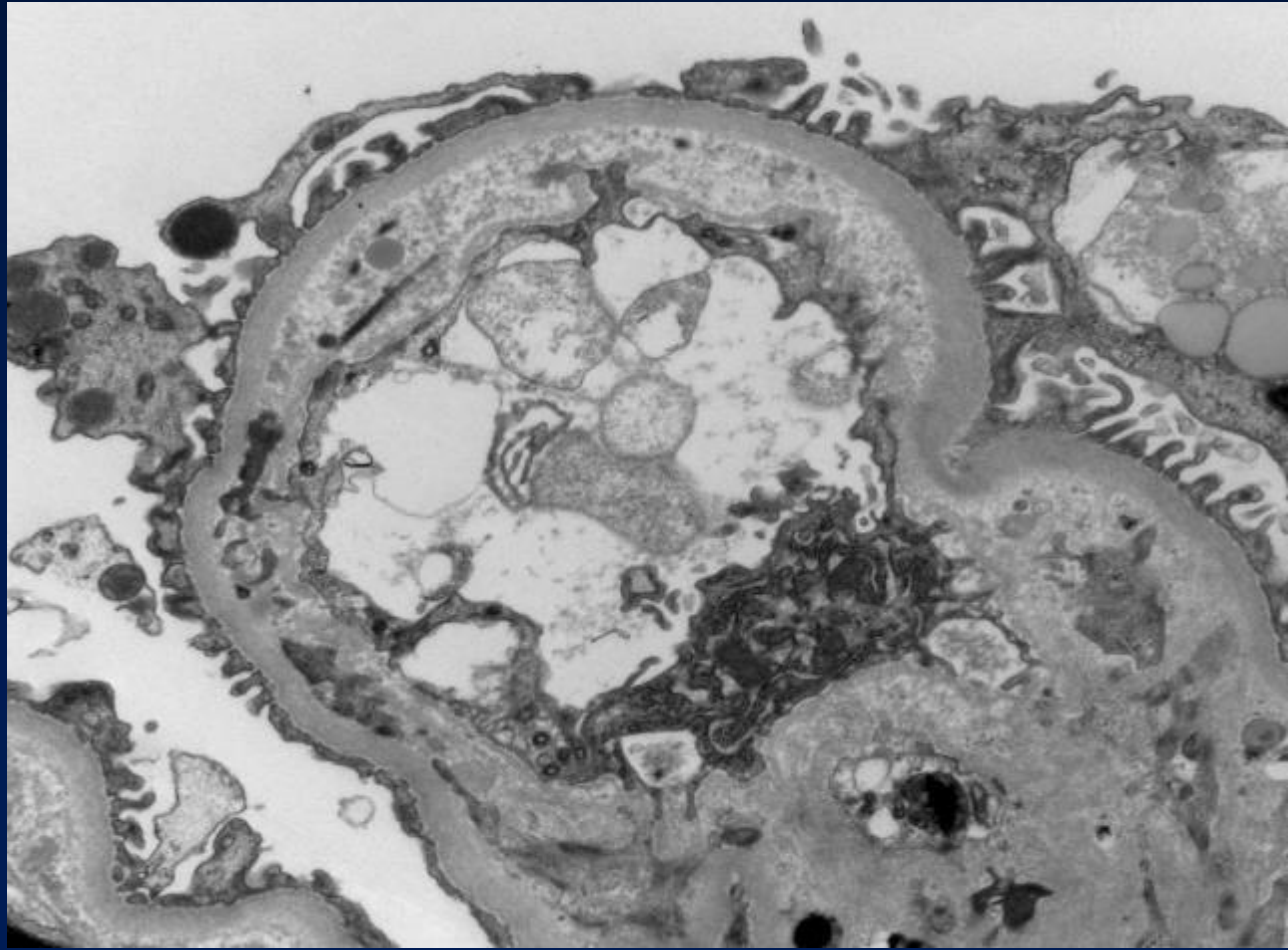
- IMMUNE COMPLEX DISEASES
- ABNORMALITIES OF COMPLEMENT-  
REGULATORY PROTEINS
- **THROMBOTIC ANGIOPATHIES**
- (PARAPROTEIN) DEPOSITION DISEASE



# THROMBOTIC ANGIOPATHIES



**Fibrin**





# **THE ACUTE AND CHRONIC THROMBOTIC ANGIOPATHIES**

- **Complement-mediated TMA**
- **Coagulation-mediated TMA**
- **Metabolism-associated TMA**
- **Autoimmune-mediated and rejection-related TMA**
- **Drug-induced and radiation-associated TMA**
- **Shiga toxin-associated TMA**



# THE MEMBRANOPROLIFERATIVE PATTERN OF INJURY

## STRUCTURAL CHANGES:

- HYPERCELLULARITY
- CAPILLARY WALL THICKENING (double contours)

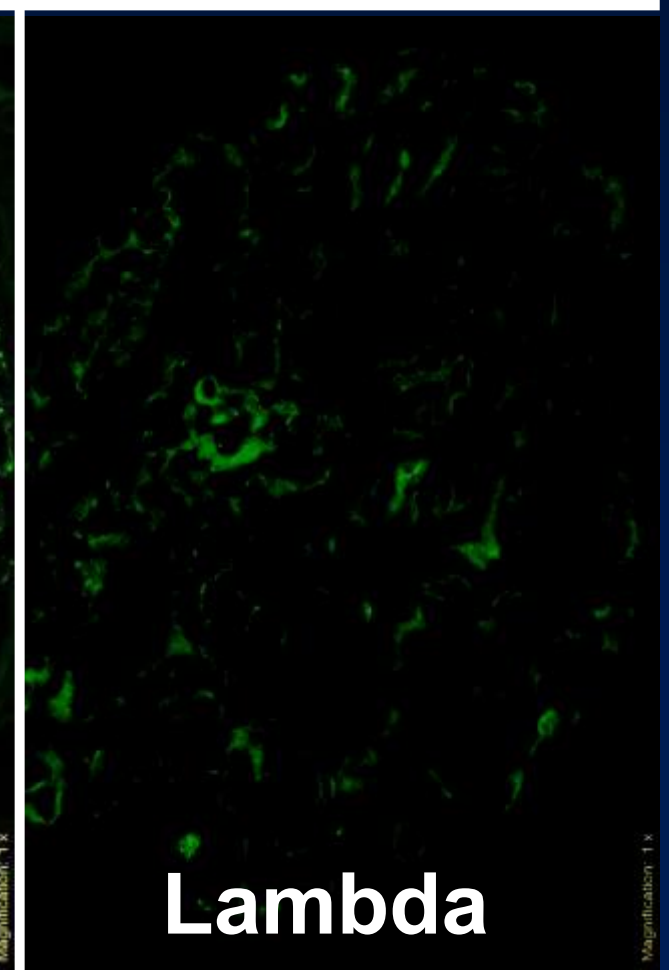
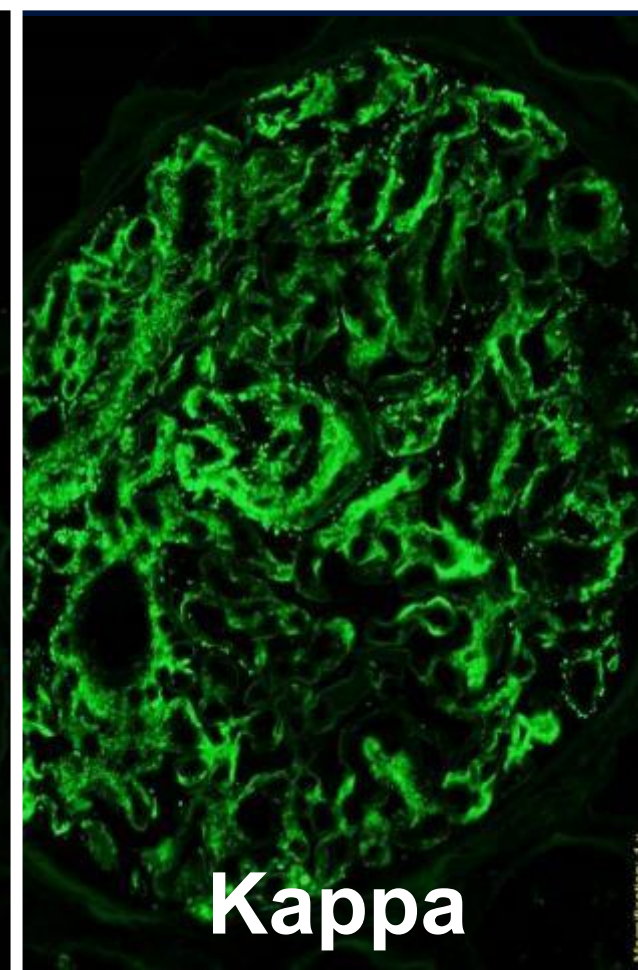
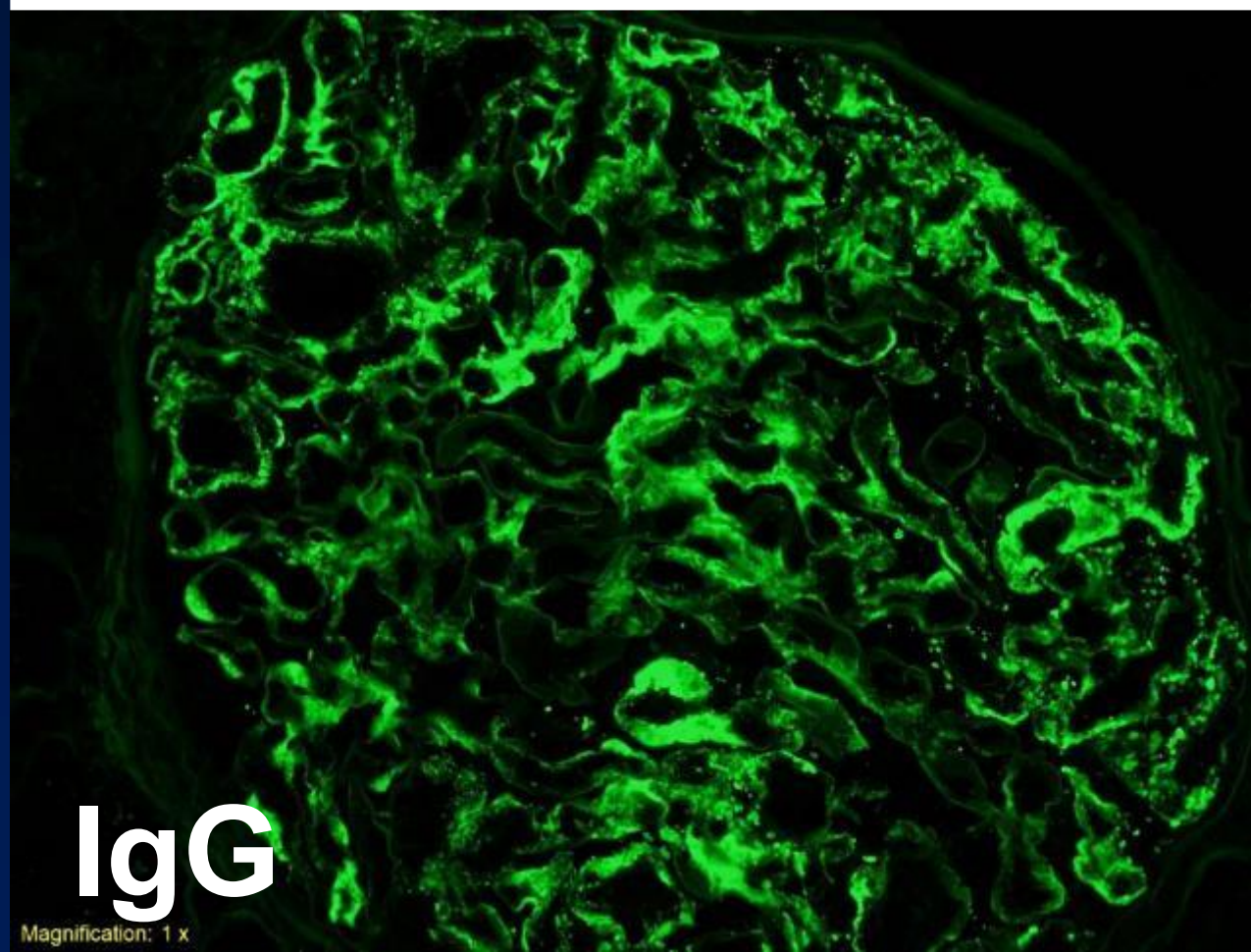
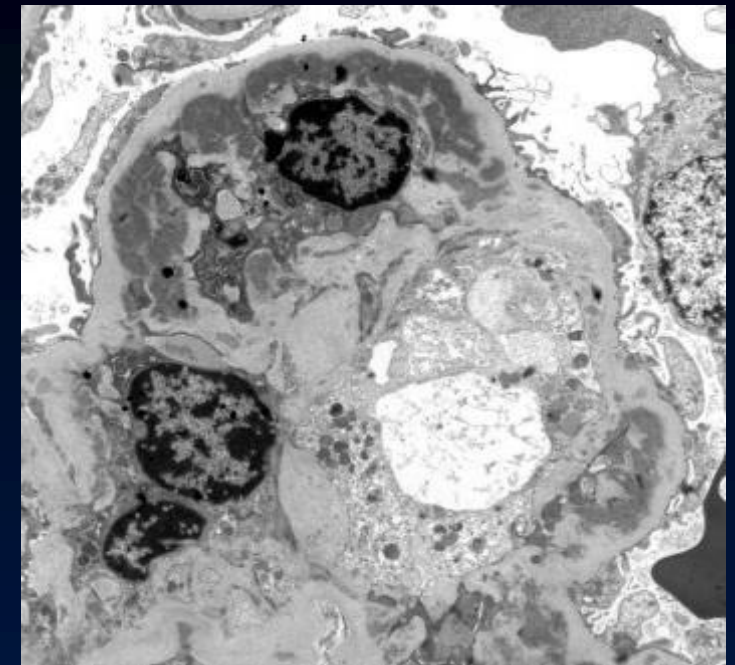
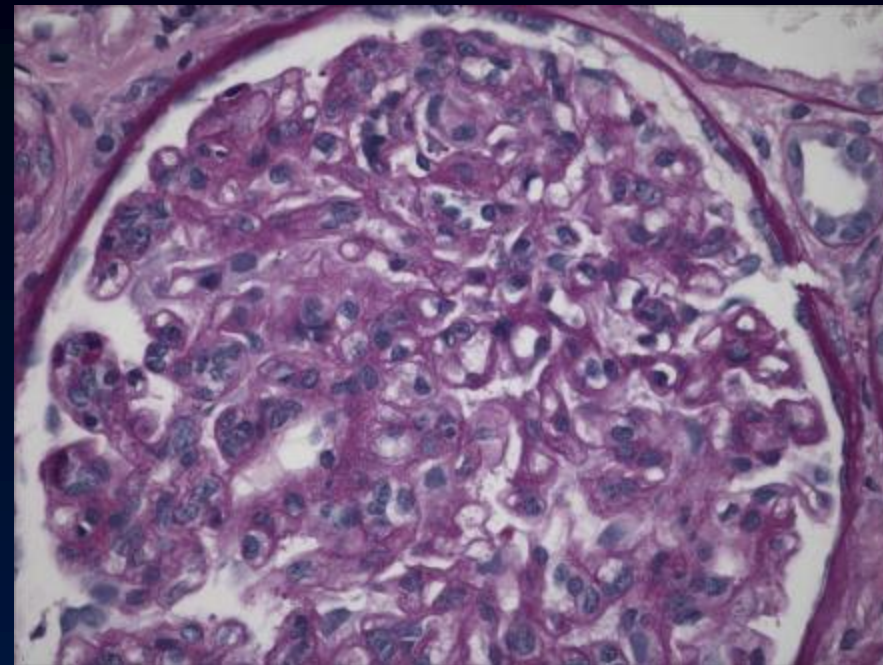
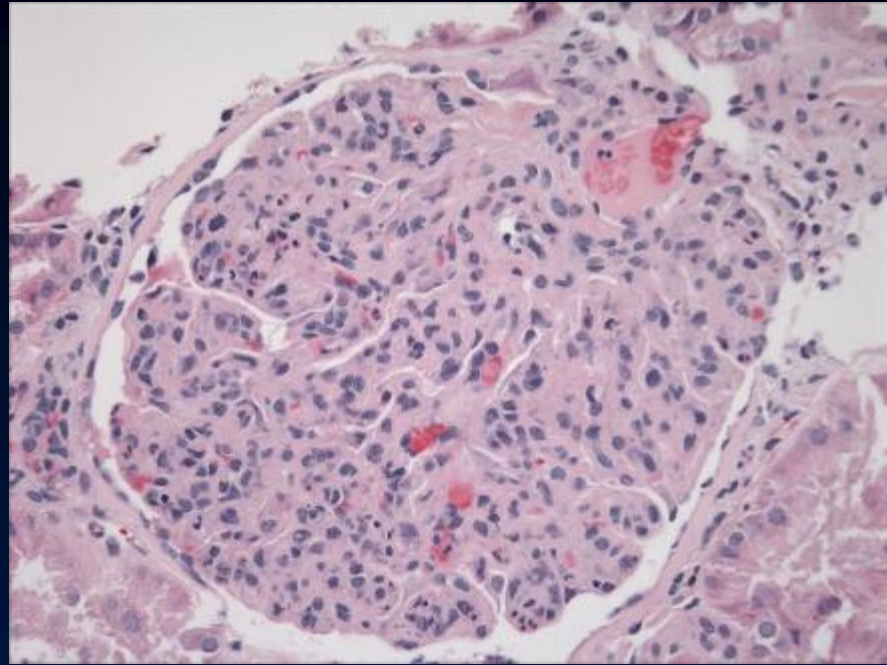
## CONDITIONS ASSOCIATED WITH THE MPGN PATTERN:

- IMMUNE COMPLEX DISEASES
- ABNORMALITIES OF COMPLEMENT-  
REGULATORY PROTEINS
- THROMBOTIC ANGIOPATHIES
- (PARAPROTEIN) DEPOSITION DISEASE

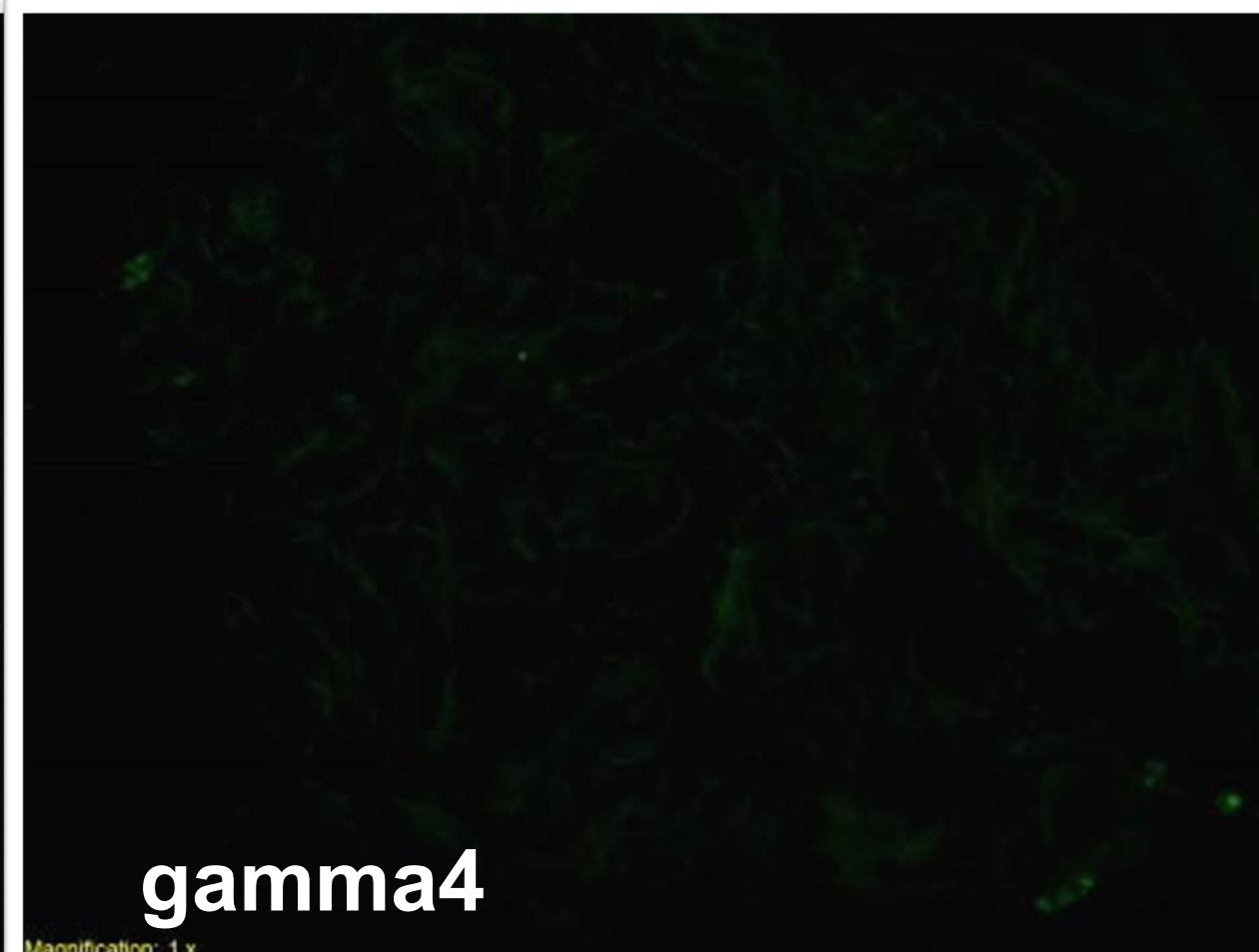
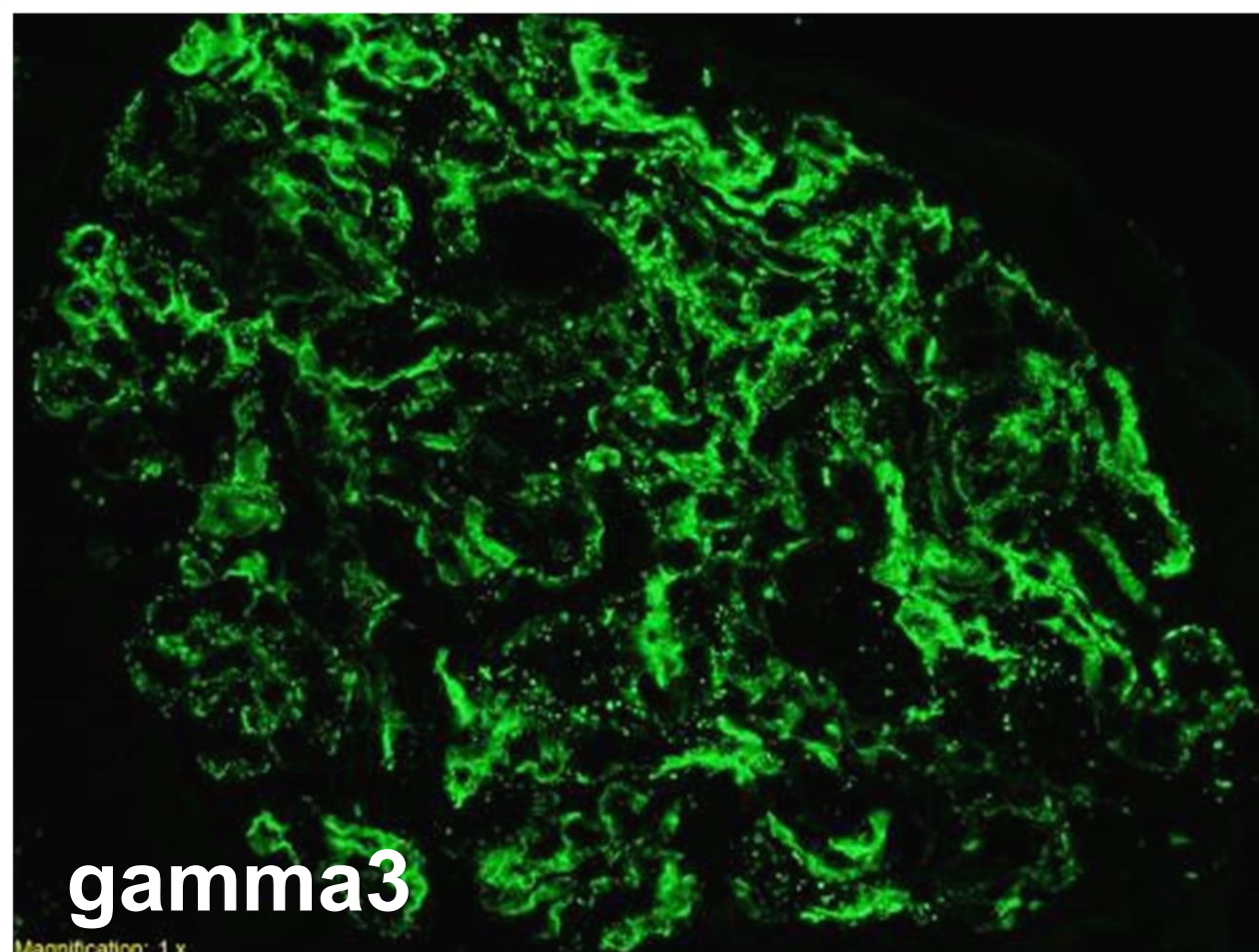
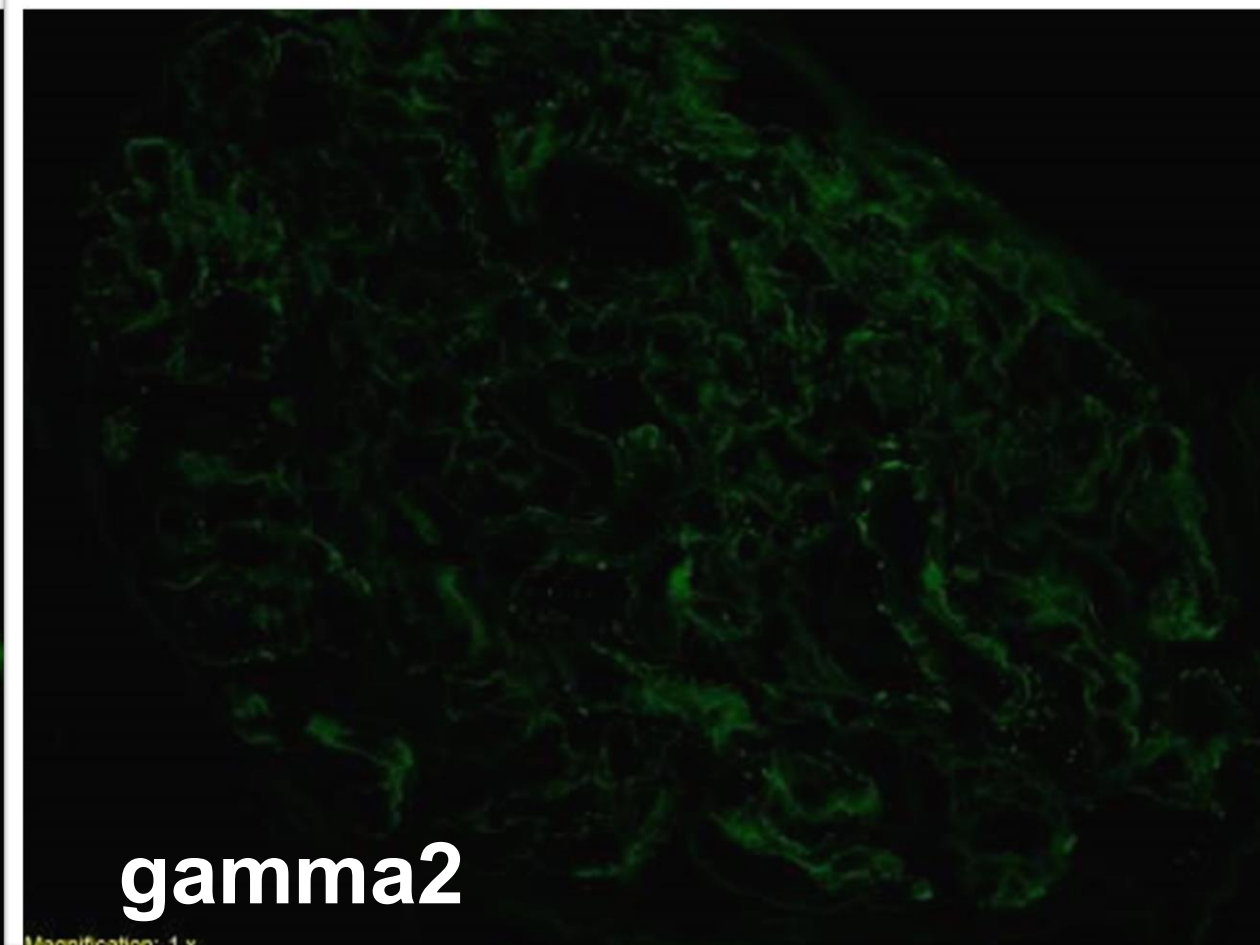
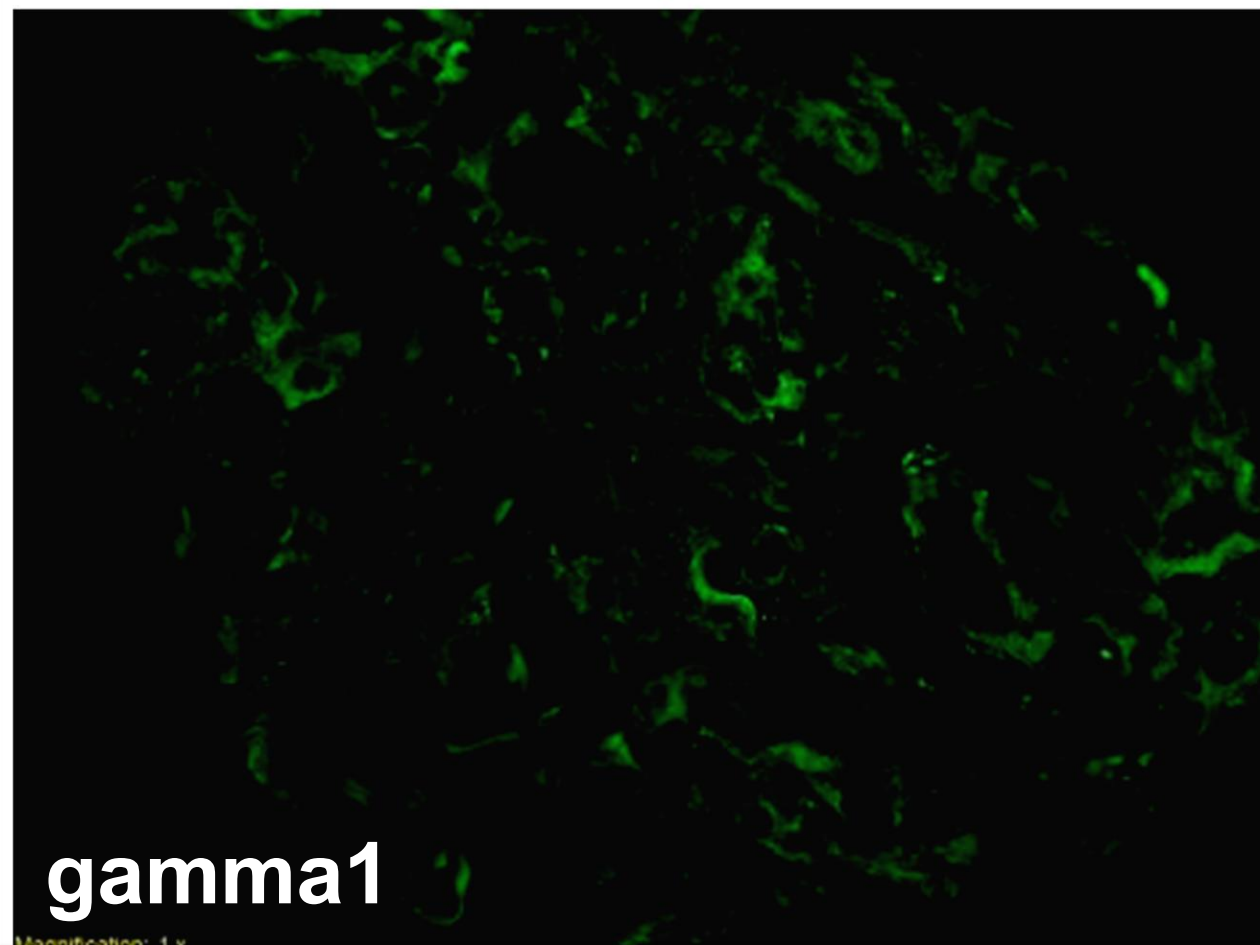


# Monoclonal IgG3/kappa Deposition disease

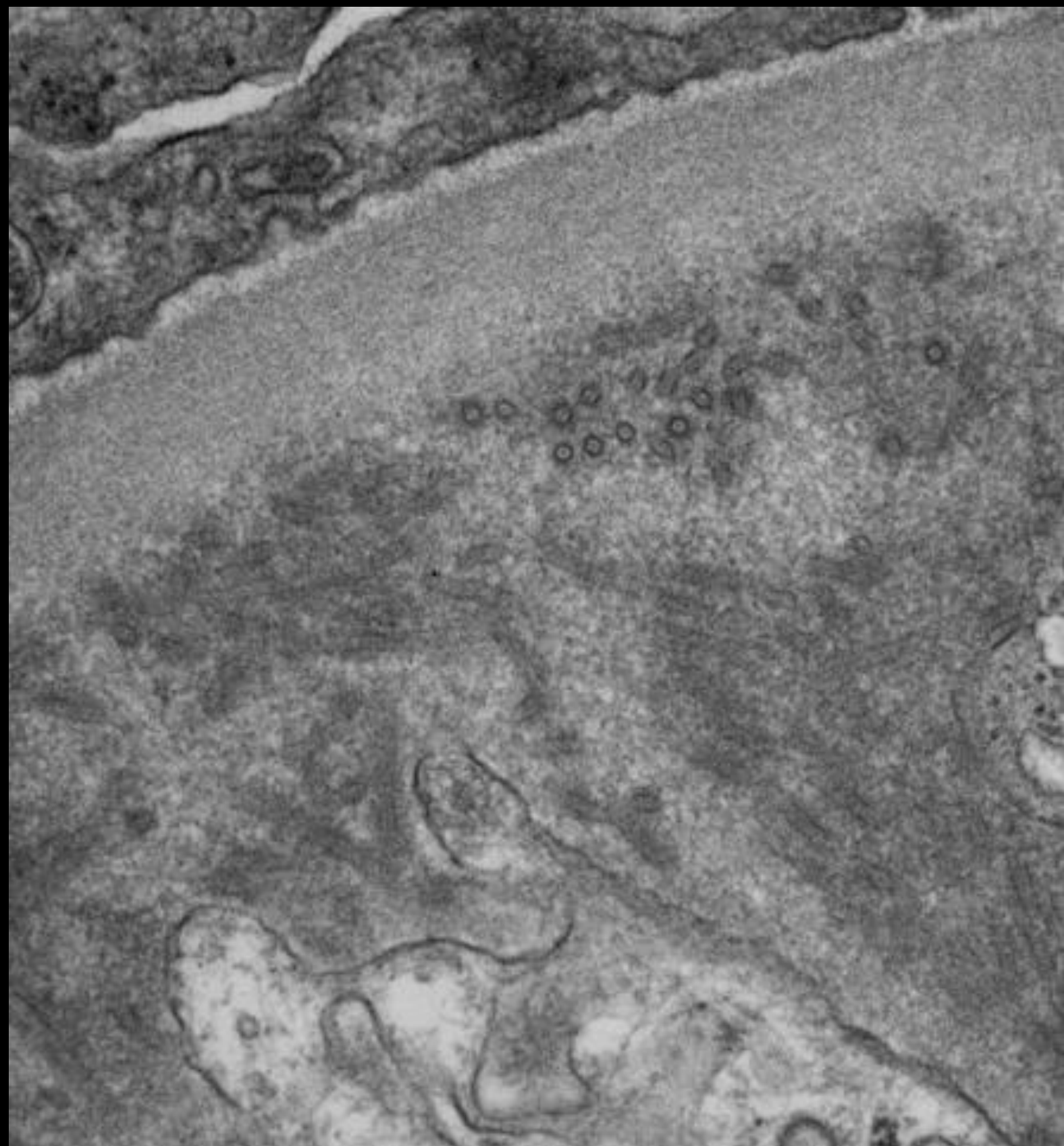
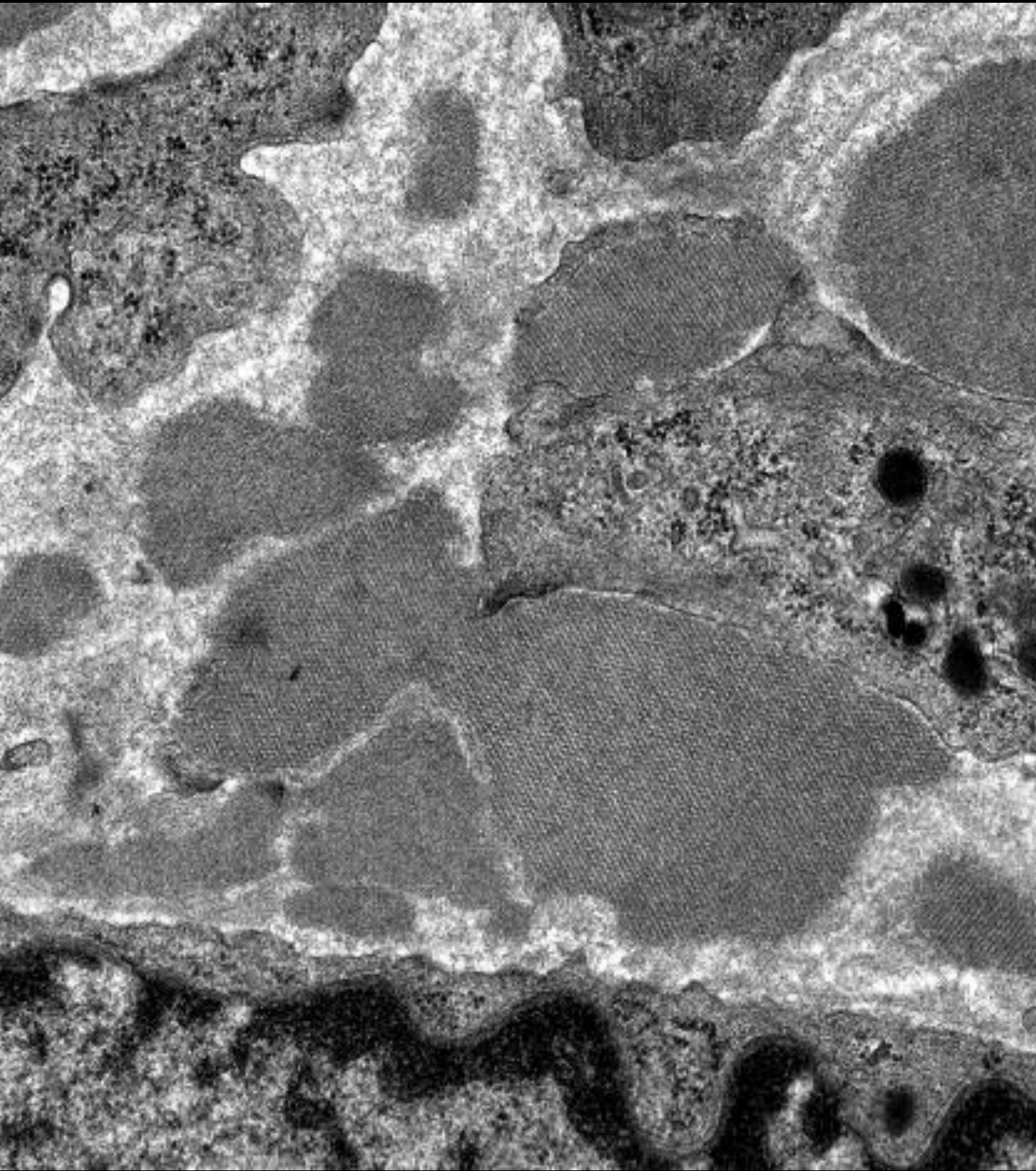
47-year-old woman with HTN and poorly controlled diabetes. The patient presents now with the nephrotic syndrome (proteinuria: 16 grams/24 hours, albumin: 2.5). Recent history of infection treated with amoxicillin for possible UTI. Cr: 2.5 mg/dl.













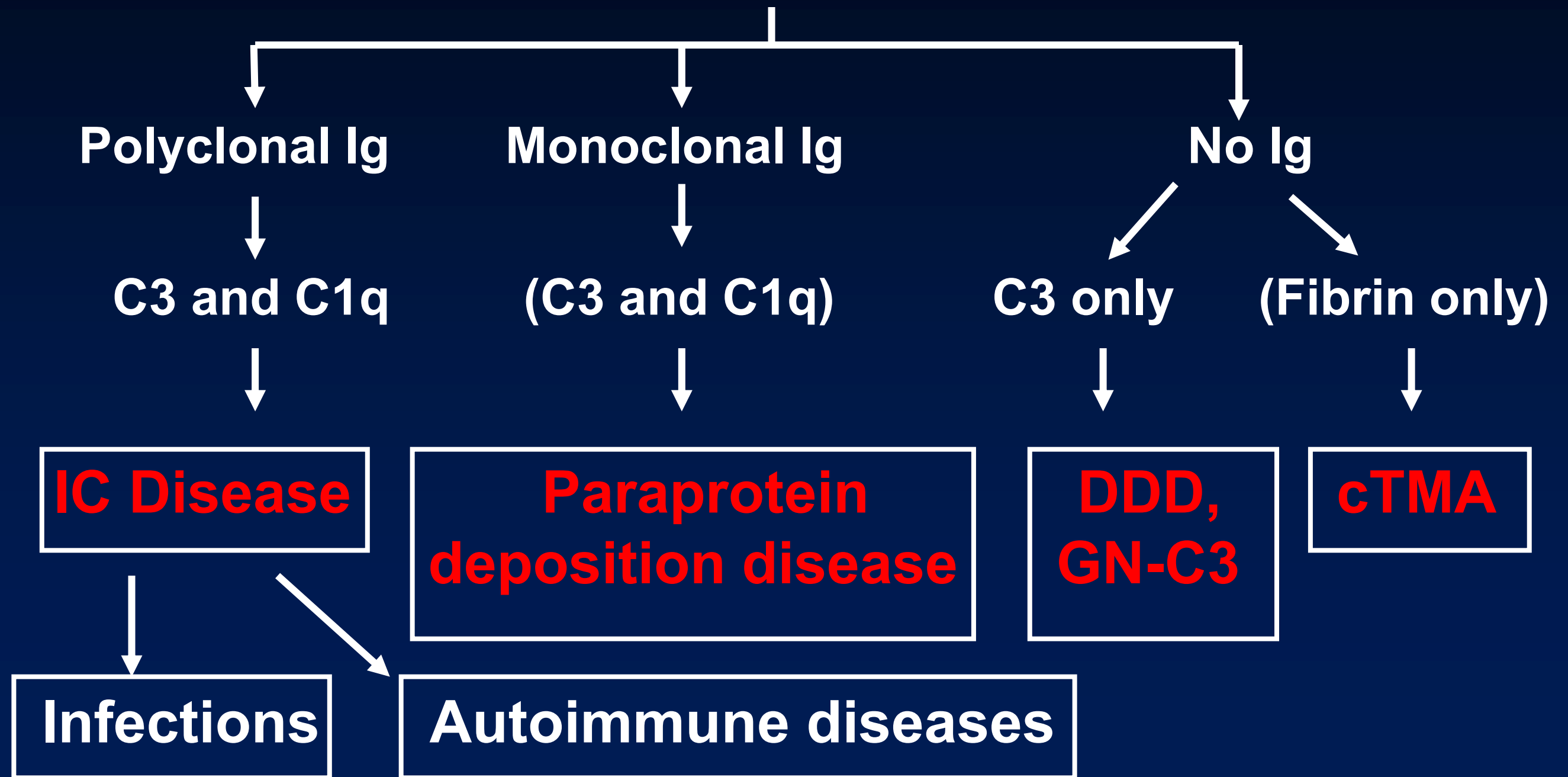
# CONDITIONS ASSOCIATED WITH DYSPROTEINEMIA

- MULTIPLE MYELOMA
  - PLASMA CELLS DYSCRASIA
- 
- CLL
  - SMALL CELL LYMPHOMA
  - FOLLICULAR LYMPHOMA
  - MARGINAL ZONE LYMPHOMA
  - MALT LYMPHOMA
  - MANTLE CELL LYMPHOMA
  - DIFFUSE LARGE CELL LYMPHOMA
  - LYMPHOPLASMACYTIC LYMPHOMA (WALDENSTROM)



# THE MEMBRANOPROLIFERATIVE PATTERN OF GLOMERULAR INJURY

## MPGN PATTERN





# RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Rapid decline in renal function  
(over several days or few weeks)

Active urine sediment

Usually no edema and no hypertension



# THE BASIC STRUCTURAL PATTERNS OF GLOMERULAR INJURY

- 1.- Epithelial Cell Disease (Minimal Change Dis.)
- 2.- Focal Segmental Glomerulosclerosis
- 3.- Membranous Nephropathy
- 4.- Diffuse Proliferative Glomerulonephritis
- 5.- Membranoproliferative Glomerulonephritis
- 6.- Focal Proliferative and Necrotizing  
Glomerulonephritis
- 7.- Crescentic Glomerulonephritis
- 8.- Mesangial Proliferative Glomerulonephritis
- 9.- Basement Membrane Abnormalities
- 10.- Focal Global Glomerulosclerosis

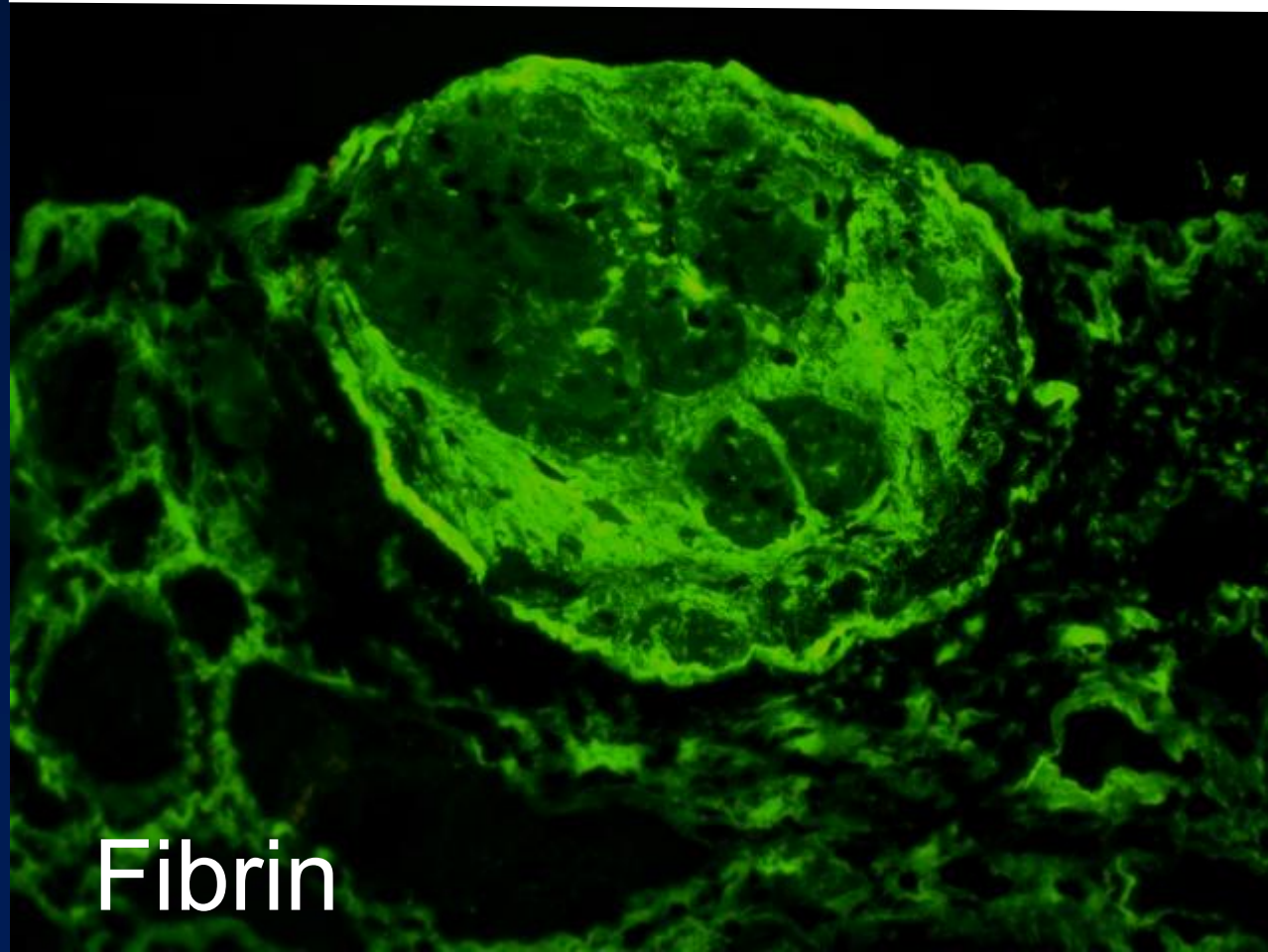
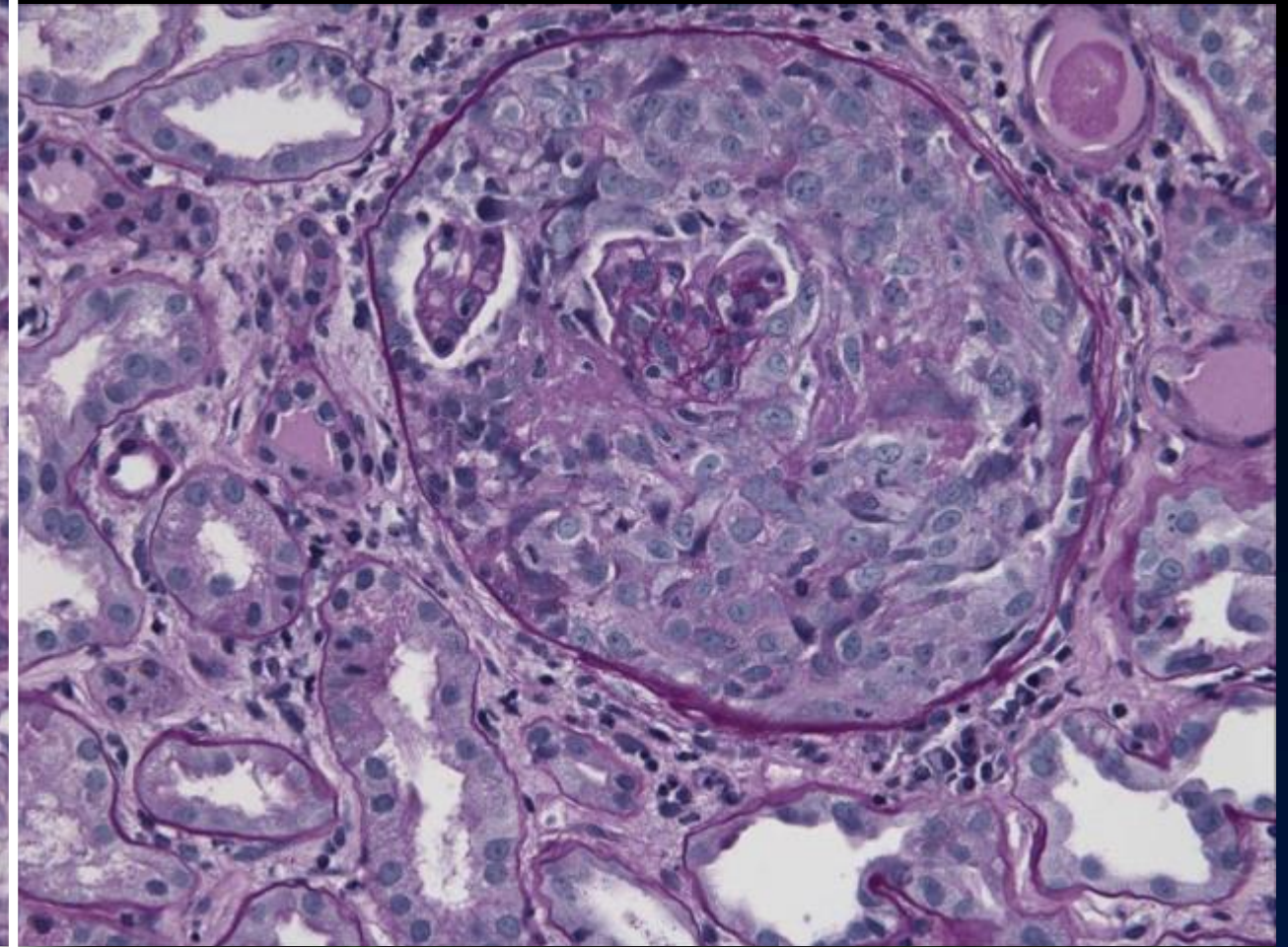
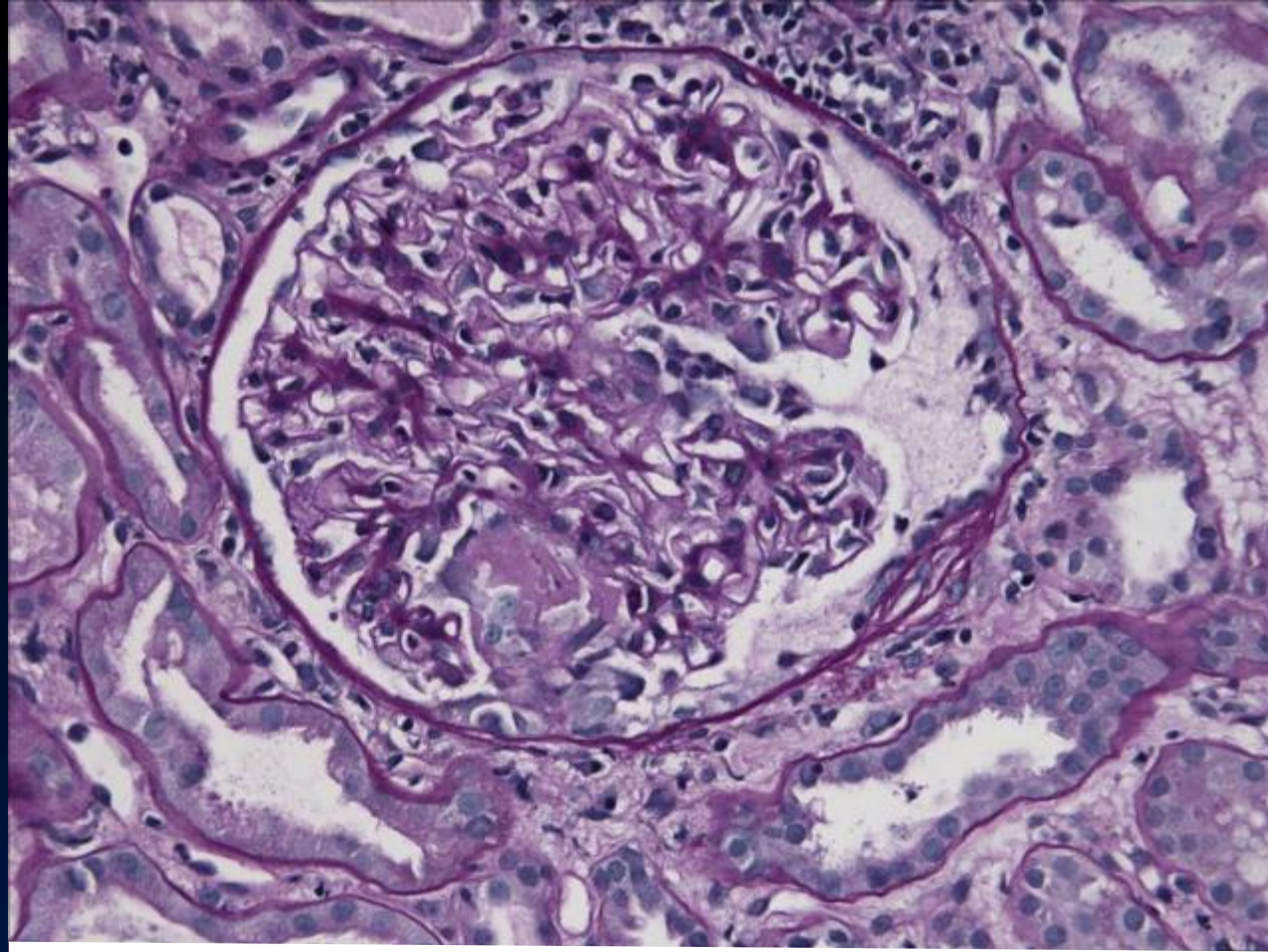


# FOCAL NECROTIZING AND CRESCENTIC GLOMERULONEPHRITIS

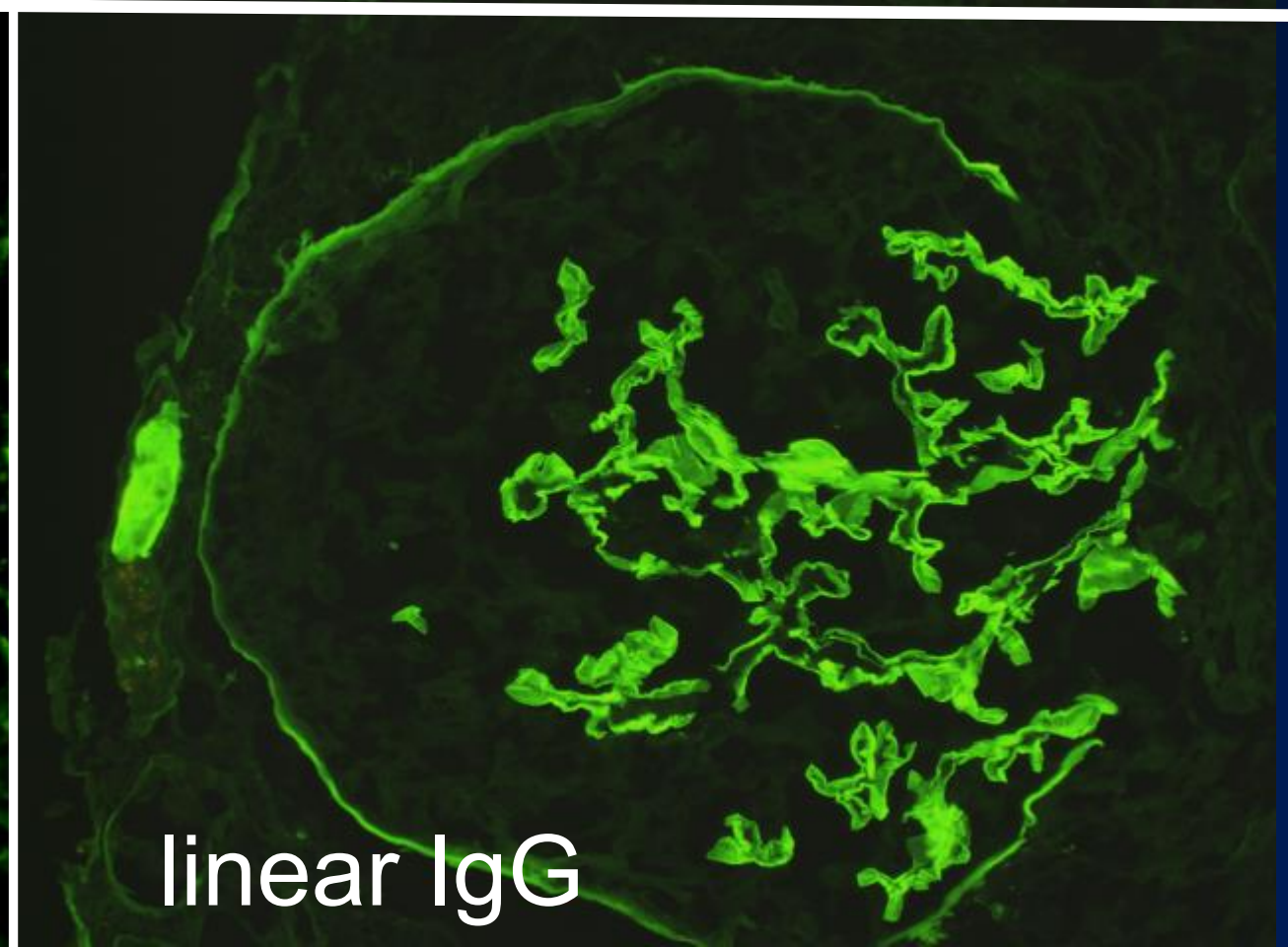
- Idiopathic or primary crescentic glomerulonephritis:
  - Type I, anti-GBM disease
  - Type II, immune complex-mediated
  - Type III, pauci immune polyangiitides (SVV);  
(often ANCA-associated)
    - Microscopic polyangiitis
    - Granulomatosis with polyangiitis
    - Eosinophilic granulomatosis with polyangiitis
    - Drug-induced vasculitides
- Other primary or secondary glomerulonephritides:  
post-infectious GN, IgA nephropathy, MPGN, etc.
- Systemic diseases (SLE, RA, H-S purpura)



# anti-GBM disease



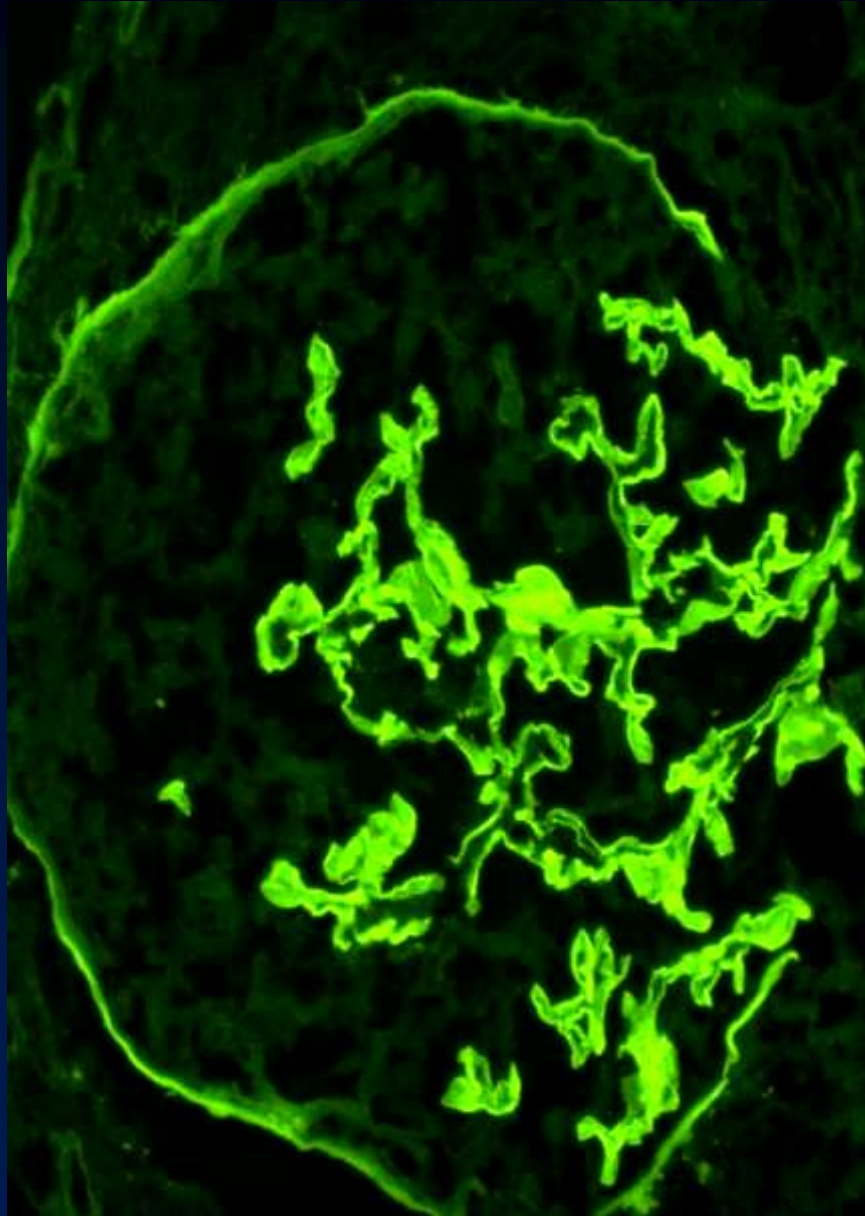
Fibrin



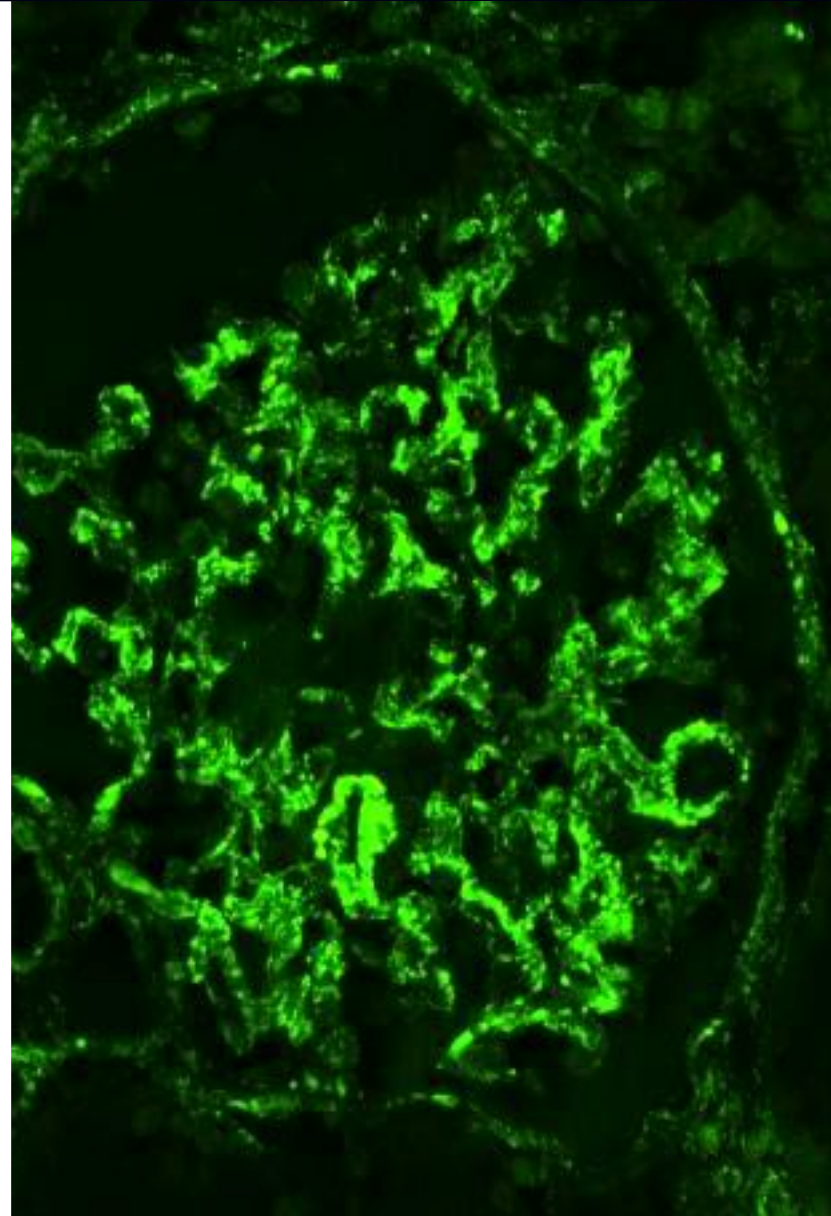
linear IgG



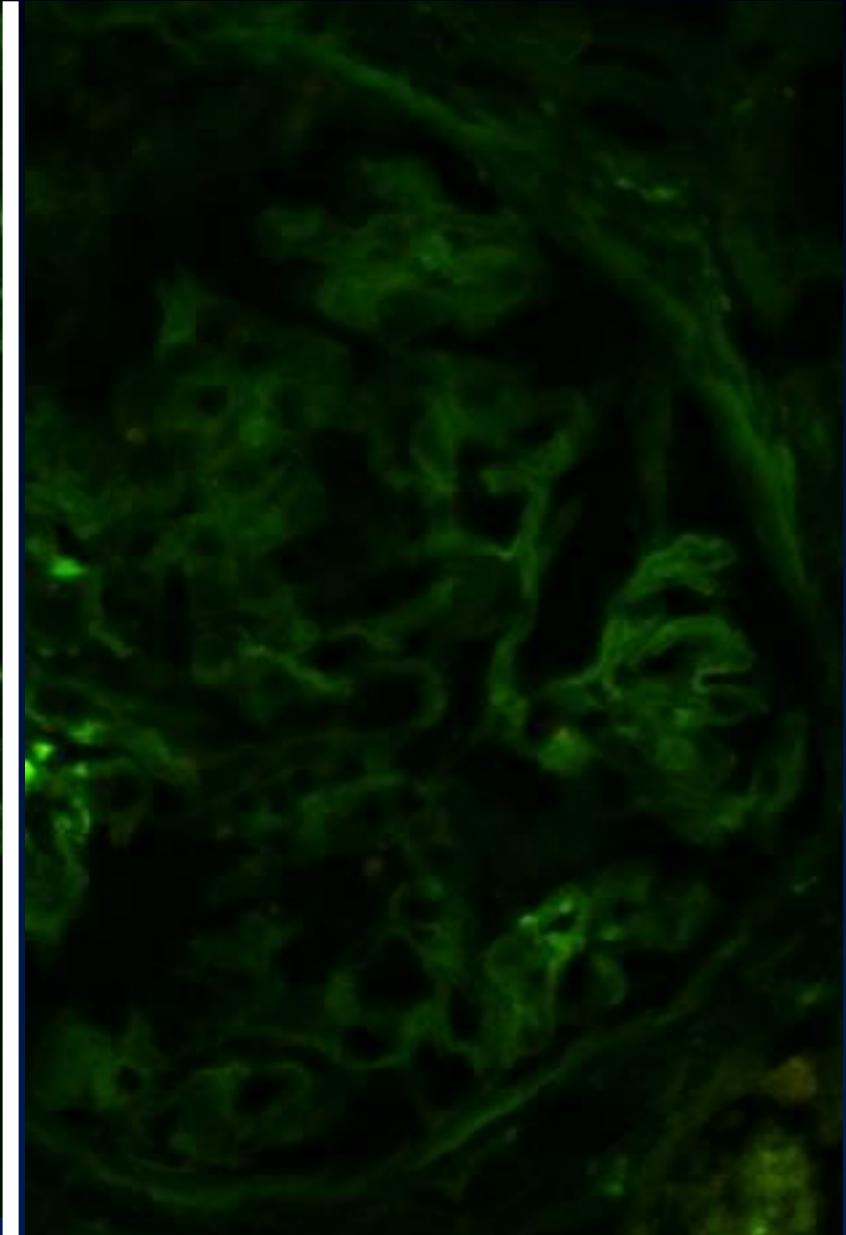
# IMMUNE MECHANISMS OF FOCAL NECROTIZING AND CRESCENT FORMATION



Linear staining for IgG  
Anti-GBM disease  
Goodpasture syndrome



Granular staining for IgG  
Immune-complex  
disease (SLE)

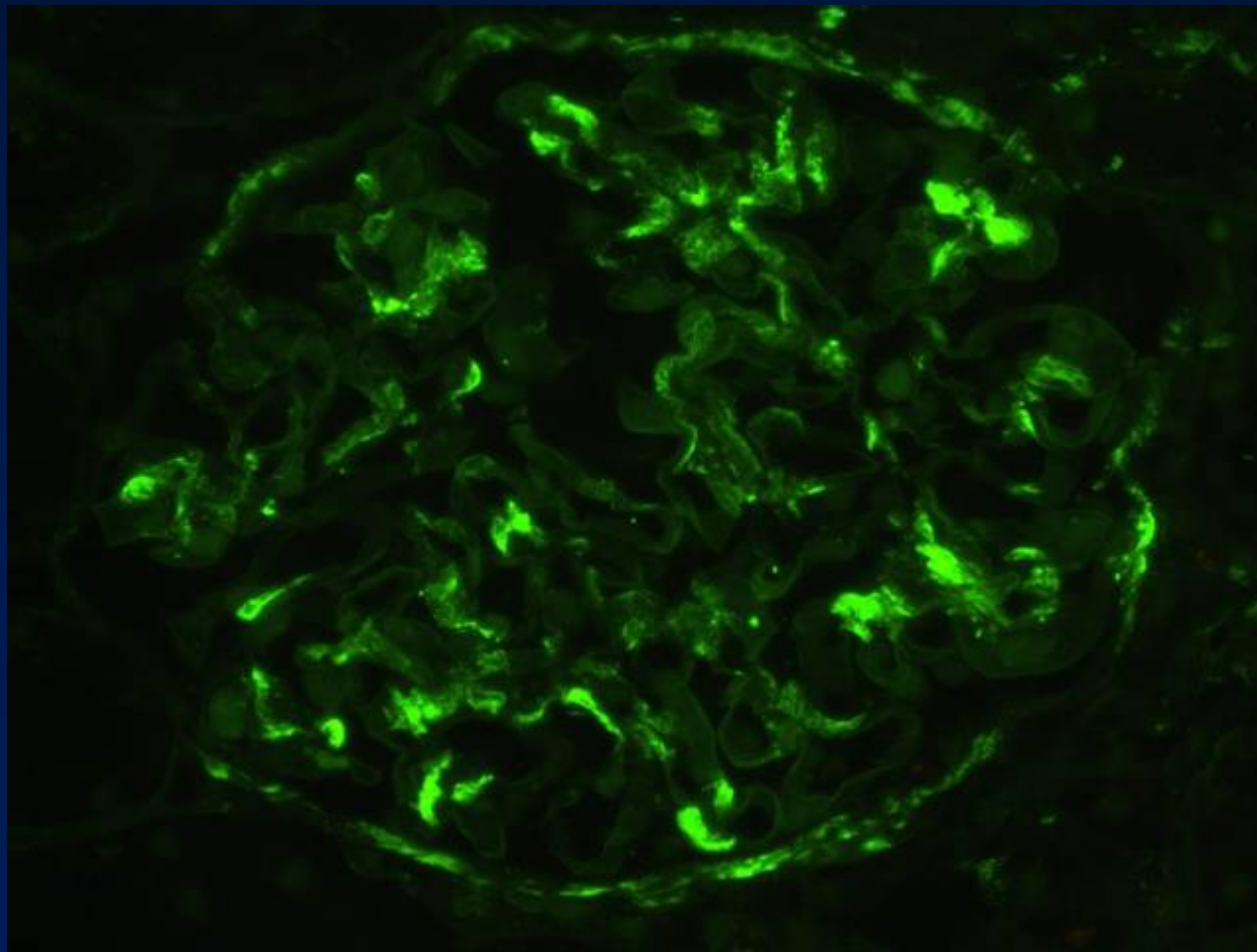
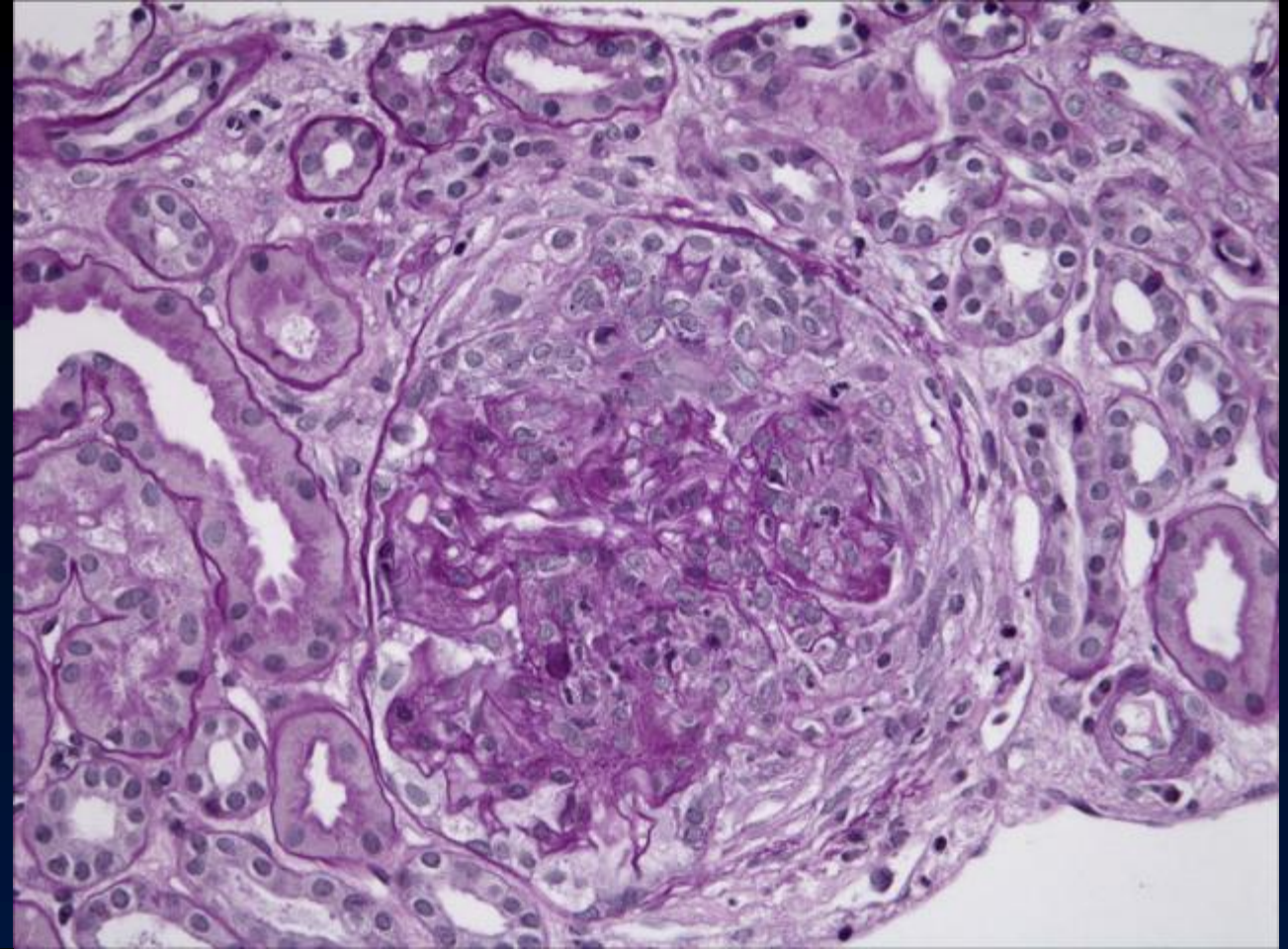


No staining for IgG  
pauci-immune  
disease (usually ANCA)



# Immune complex-mediated crescentic GN

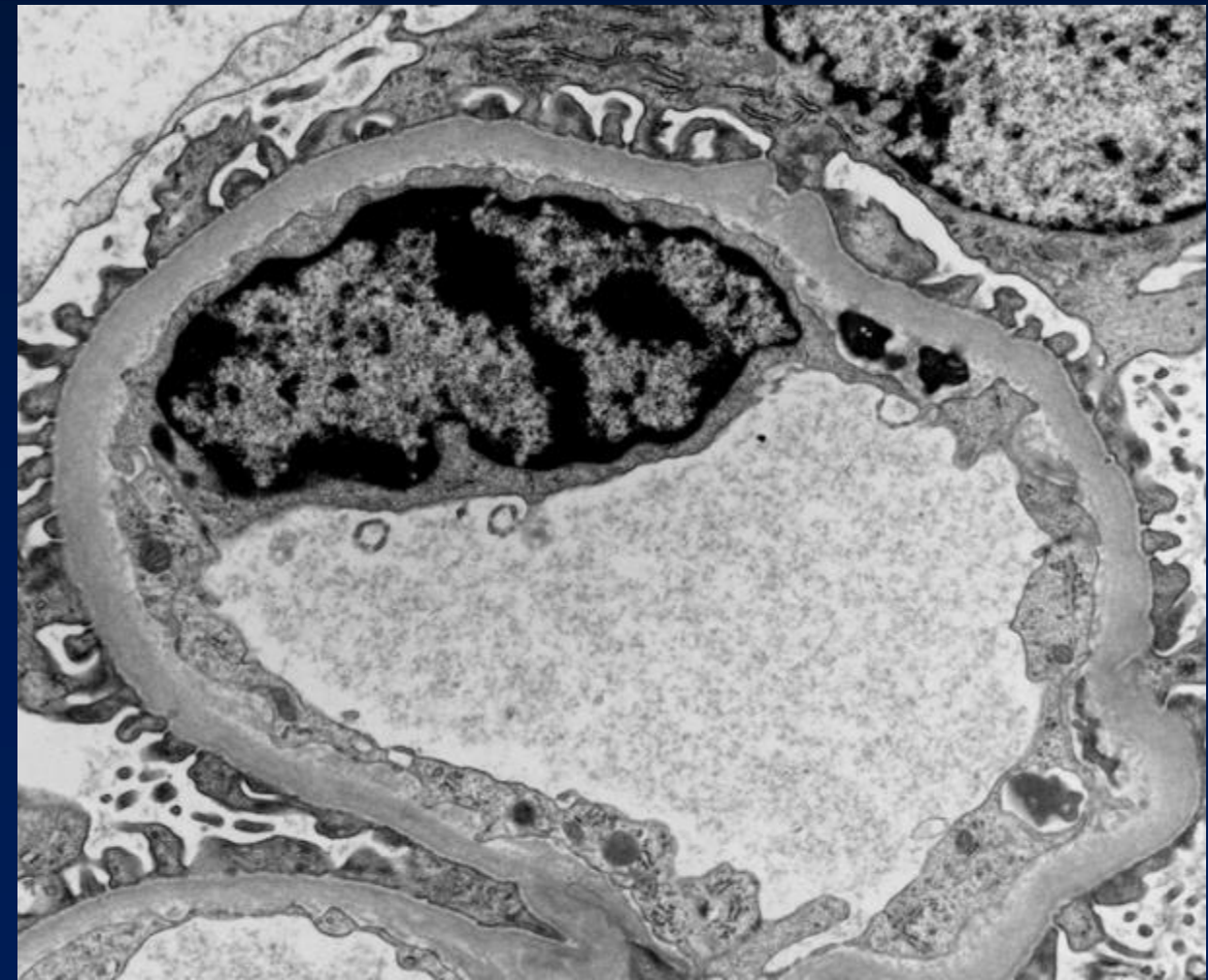
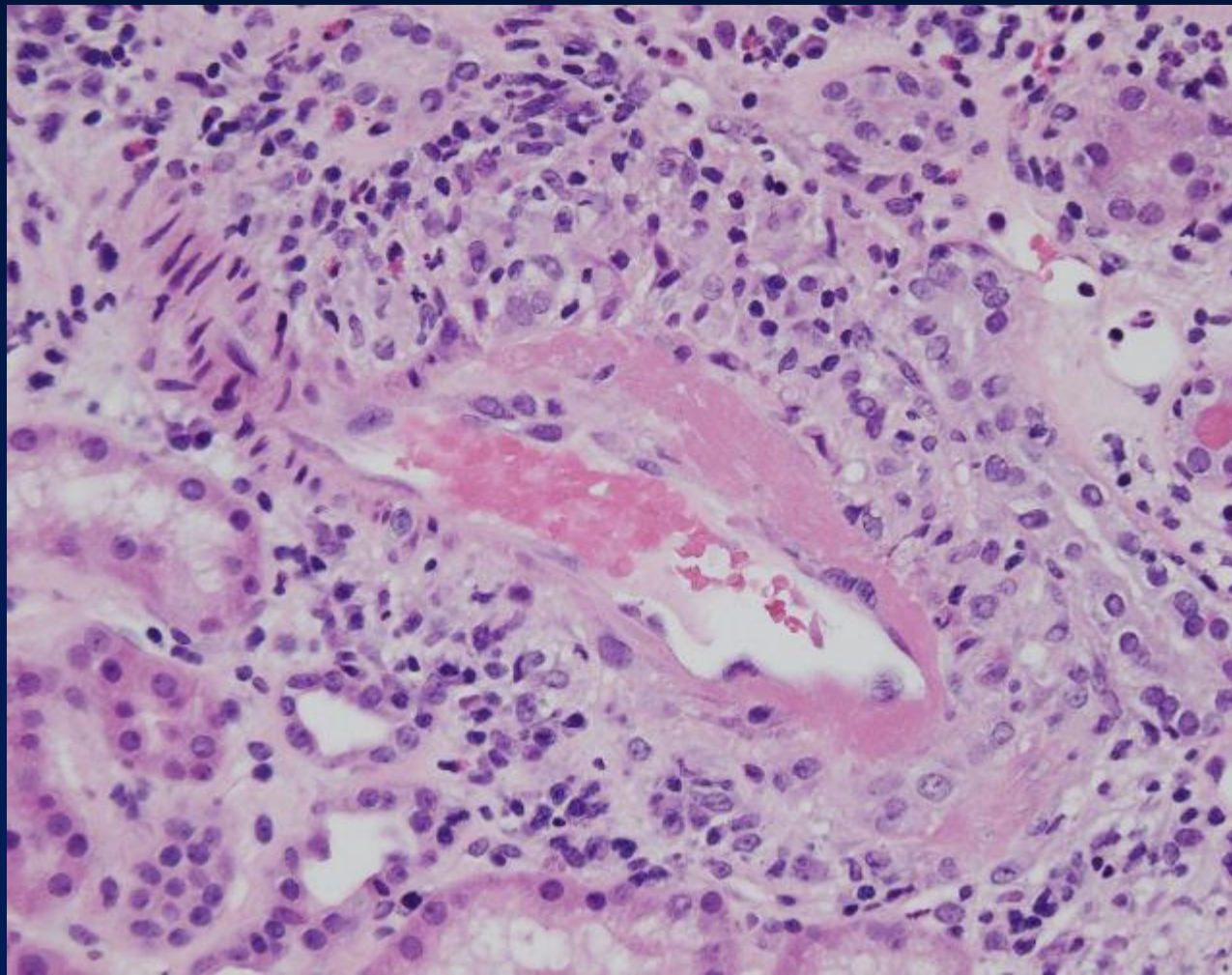
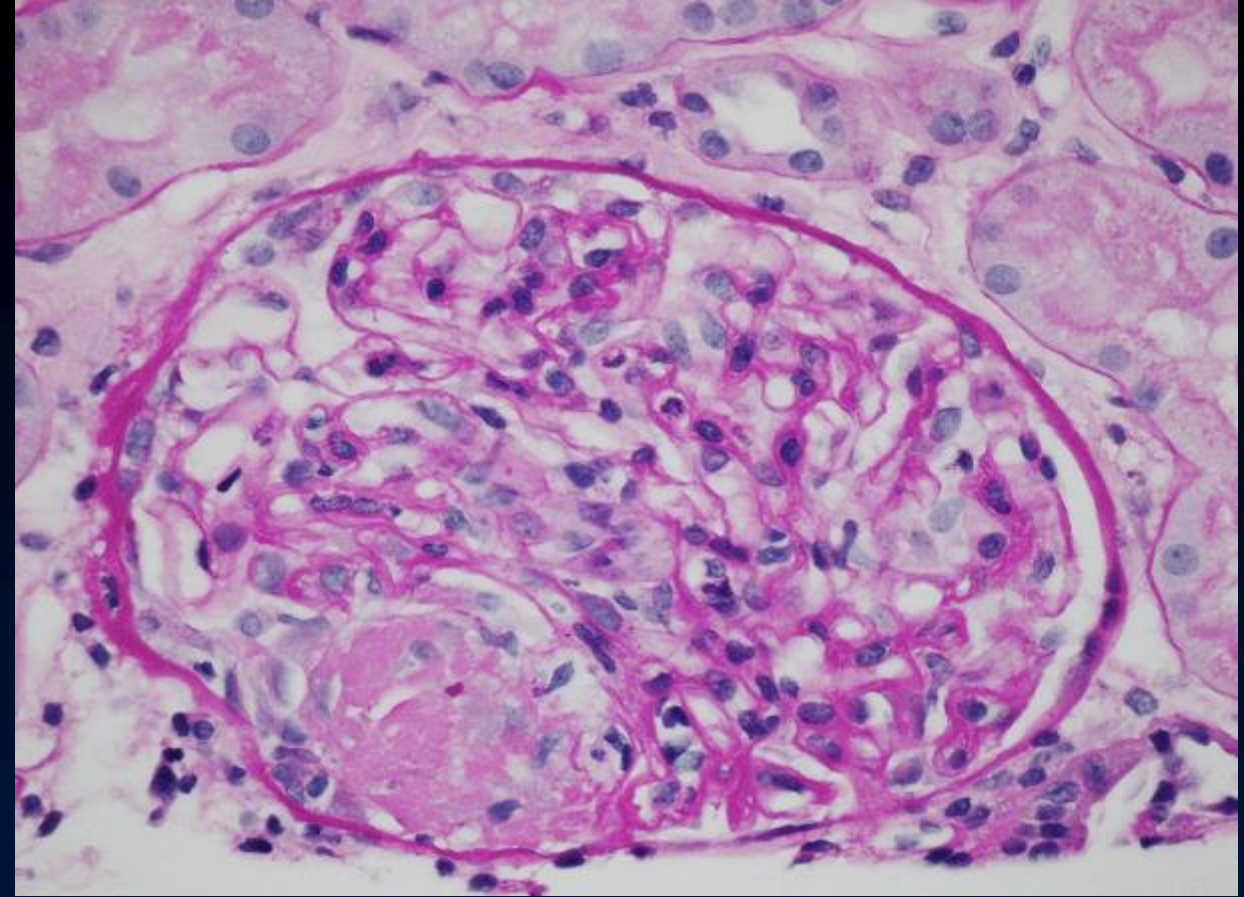
- Lupus nephritis
- IgA nephropathy/HSP
- Infection-associated GN





# Pauci-immune polyangiitis (crescentic GN)

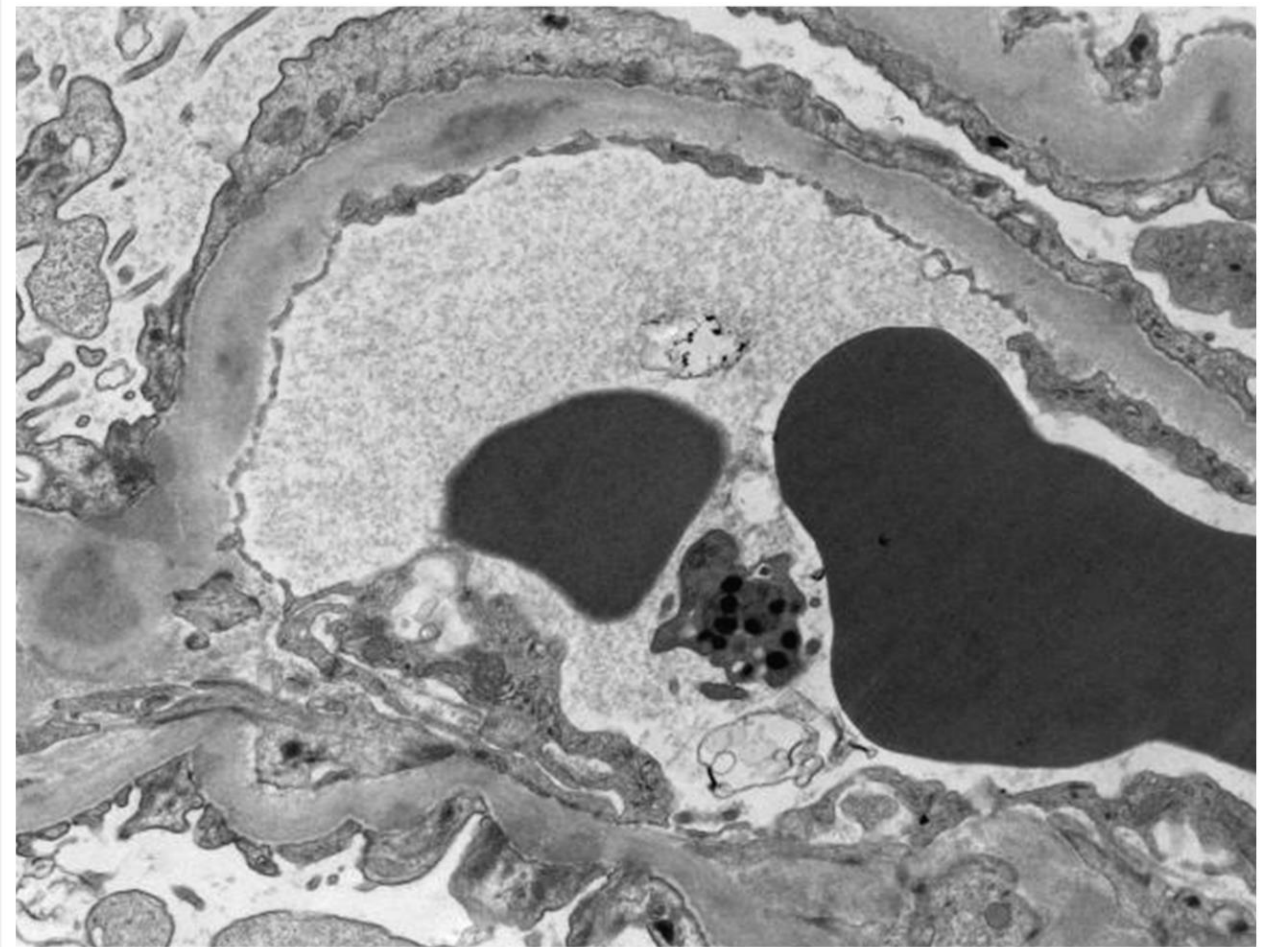
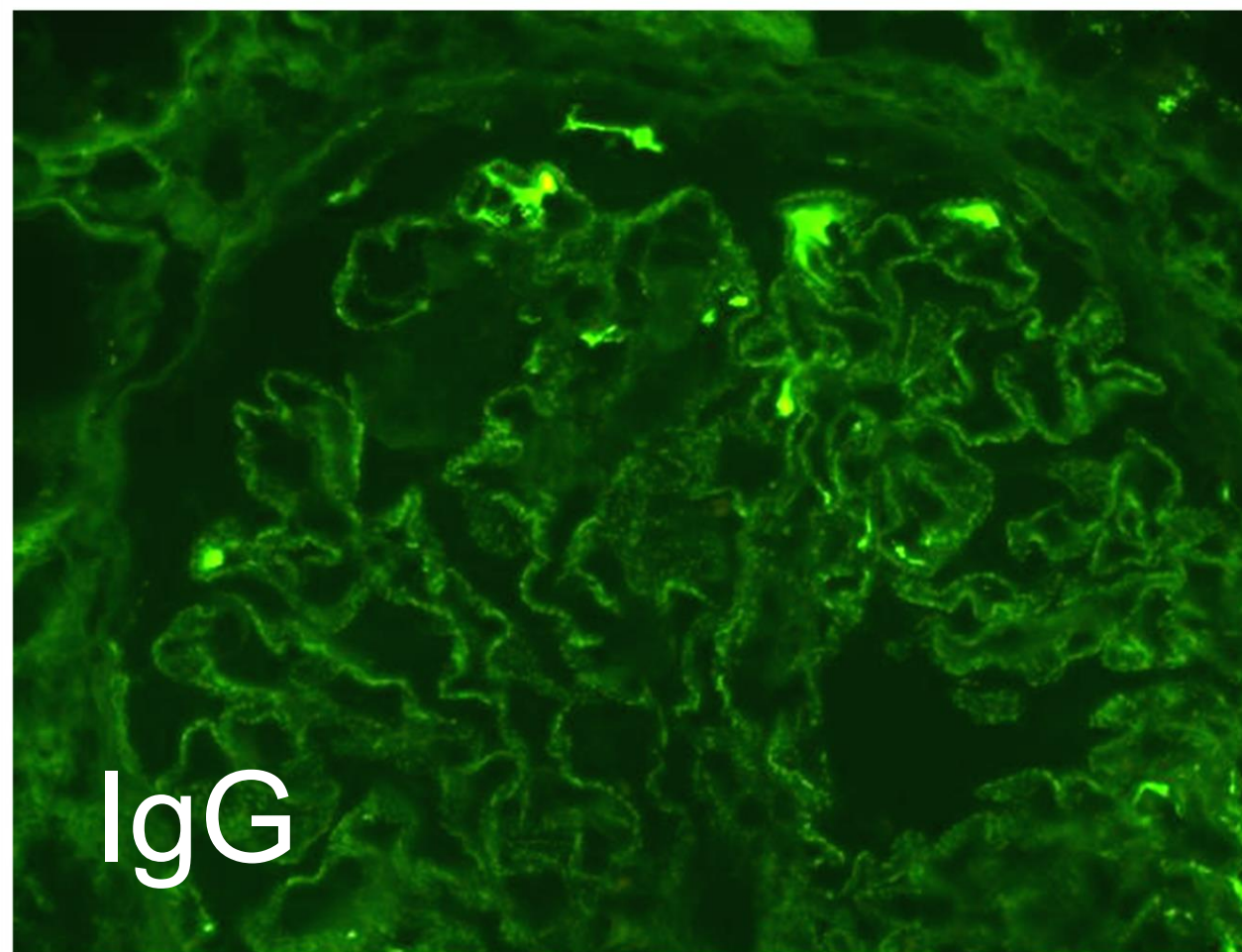
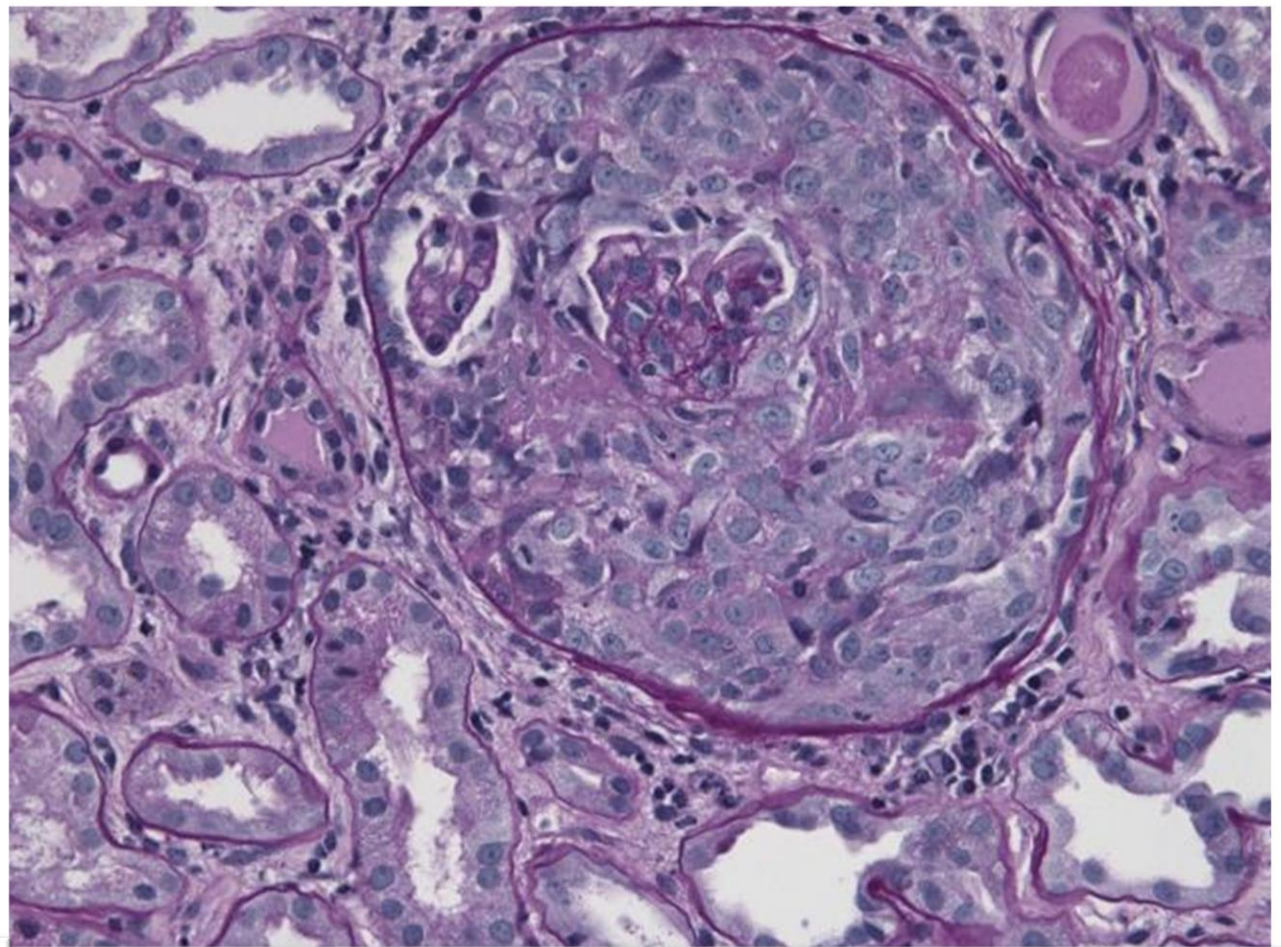
- ANCA-associated microscopic polyangiitis (p-ANCA, MPO)
- Granulomatosis with polyangiitis (c-ANCA, PR3)



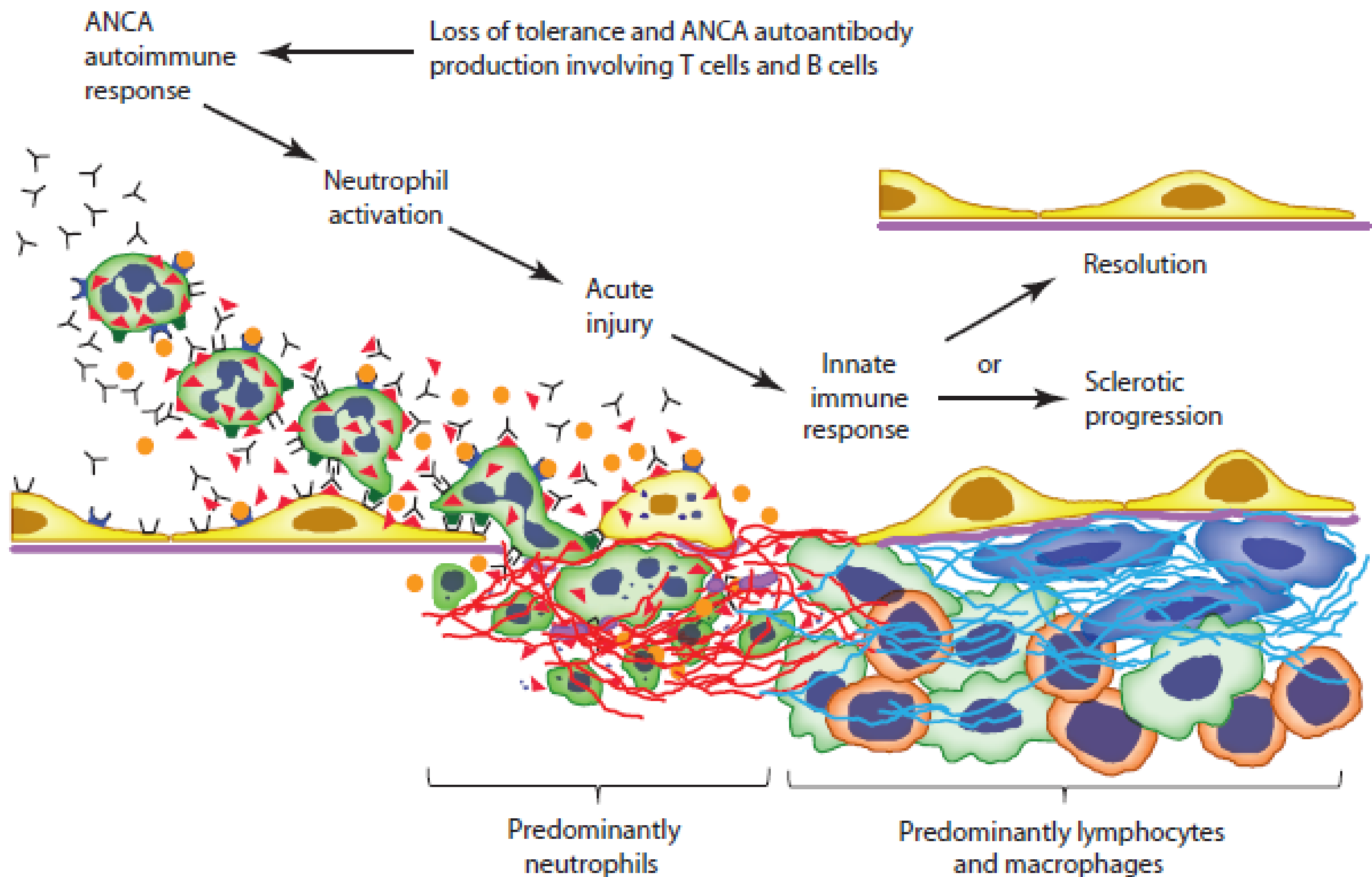


## Drug-induced ANCA crescentic GN:

- Hydralazine
- Propylthiouracil
- Minocycline
- penicillamine,
- cocaine (levamisole, procainamide)







Jennette JC, Falk RJ, Xiao H. Pathogenesis of antineutrophil cytoplasmic autoantibody-associated small vessel vasculitis. *Annu Rev Pathol* 2013; 8:139-60.



# ASYMPTOMATIC HEMATURIA (AND PROTEINURIA)

Hematuria or proteinuria

(persistent microhematuria)

Usually normal renal function

(early during the course)

Usually no hypertension or edema



# THE BASIC STRUCTURAL PATTERNS OF GLOMERULAR INJURY

- 1.- Epithelial Cell Disease (Minimal Change Dis)
- 2.- Focal Segmental Glomerulosclerosis
- 3.- Membranous Nephropathy
- 4.- Diffuse Proliferative Glomerulonephritis
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Glomerulonephritis
- 7.- Crescentic Glomerulonephritis
- 8.- Mesangial Proliferative Glomerulonephritis
- 9.- Basement Membrane Abnormalities
- 10.- Focal Global Glomerulosclerosis



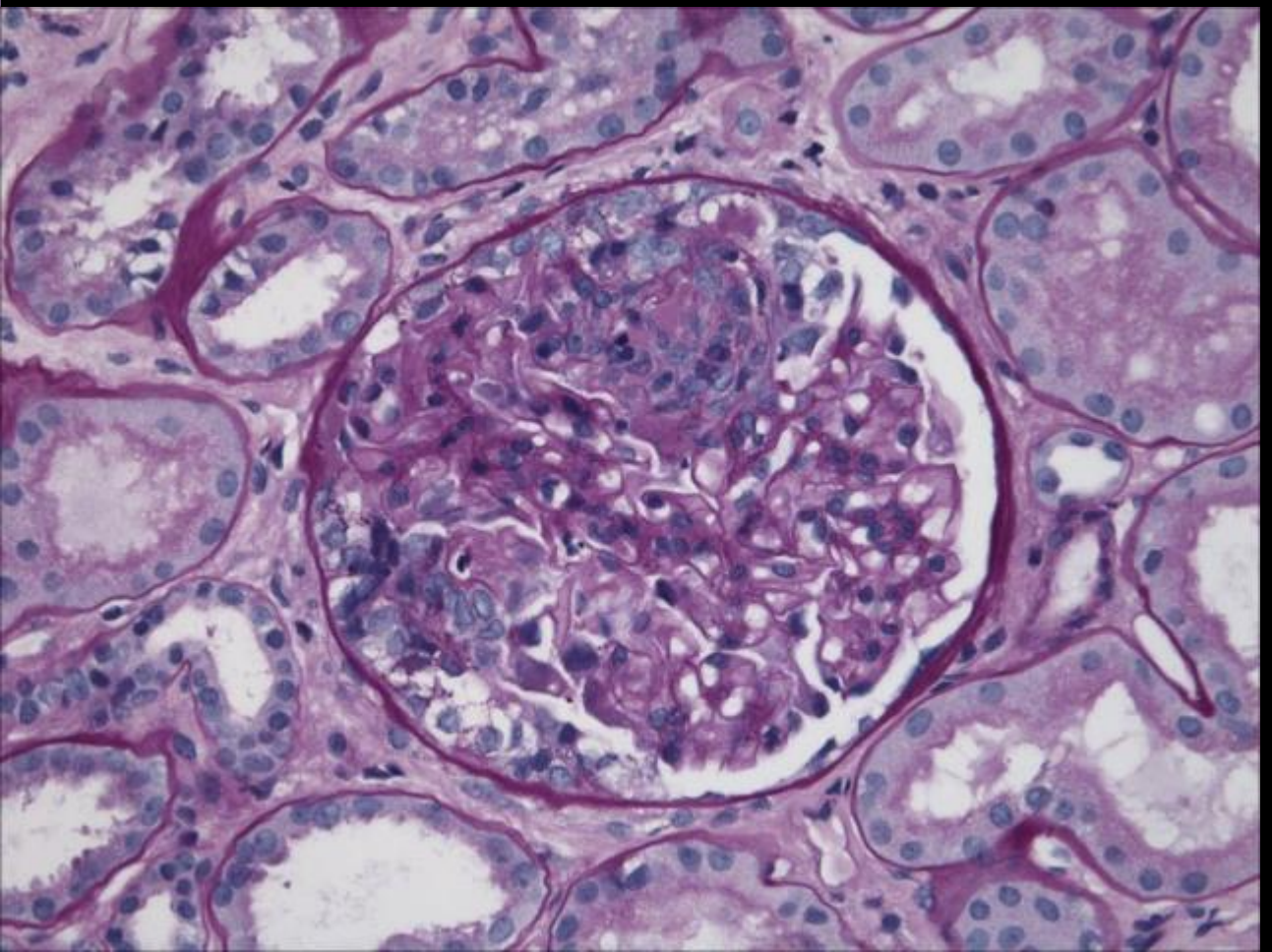
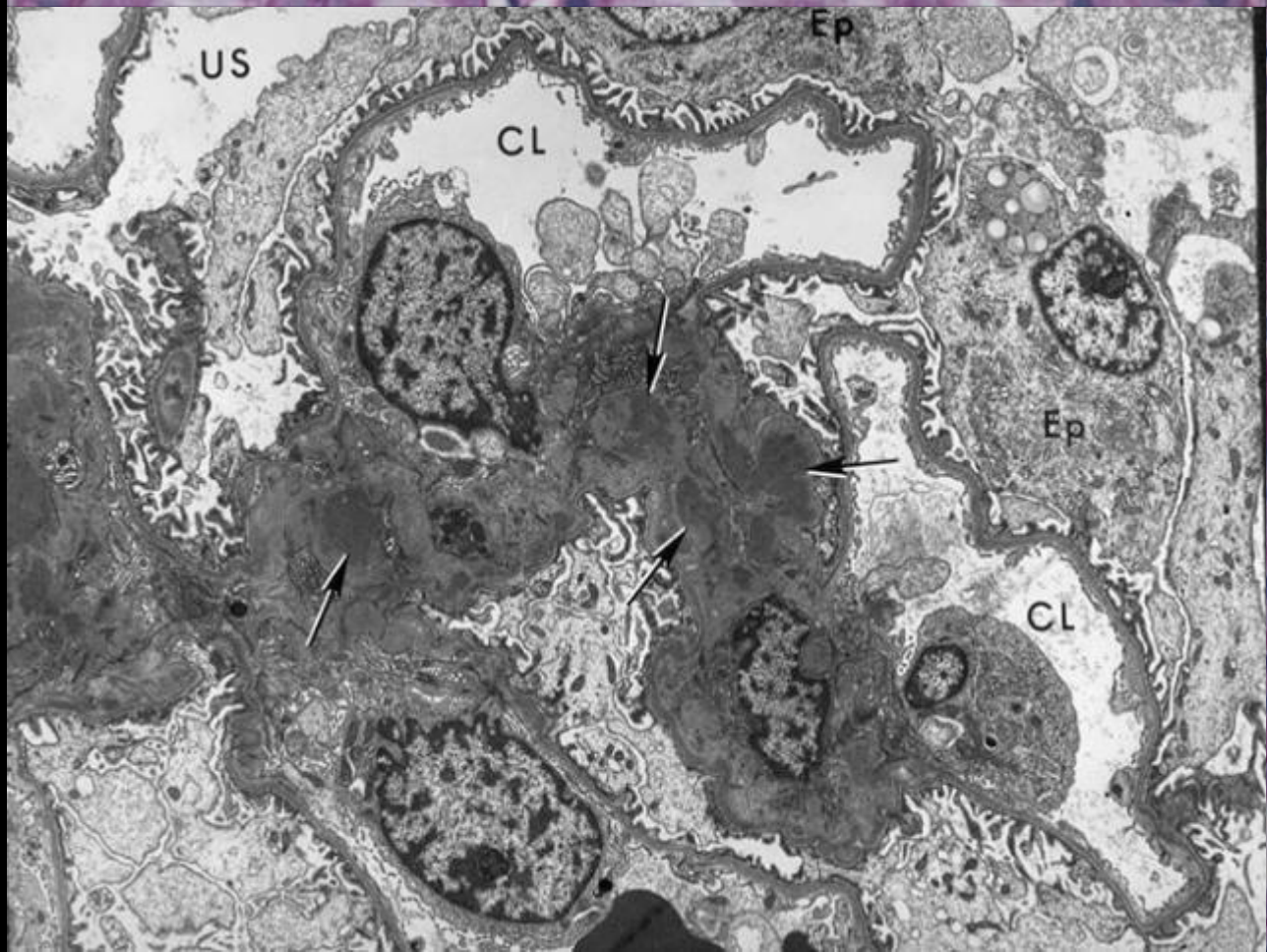
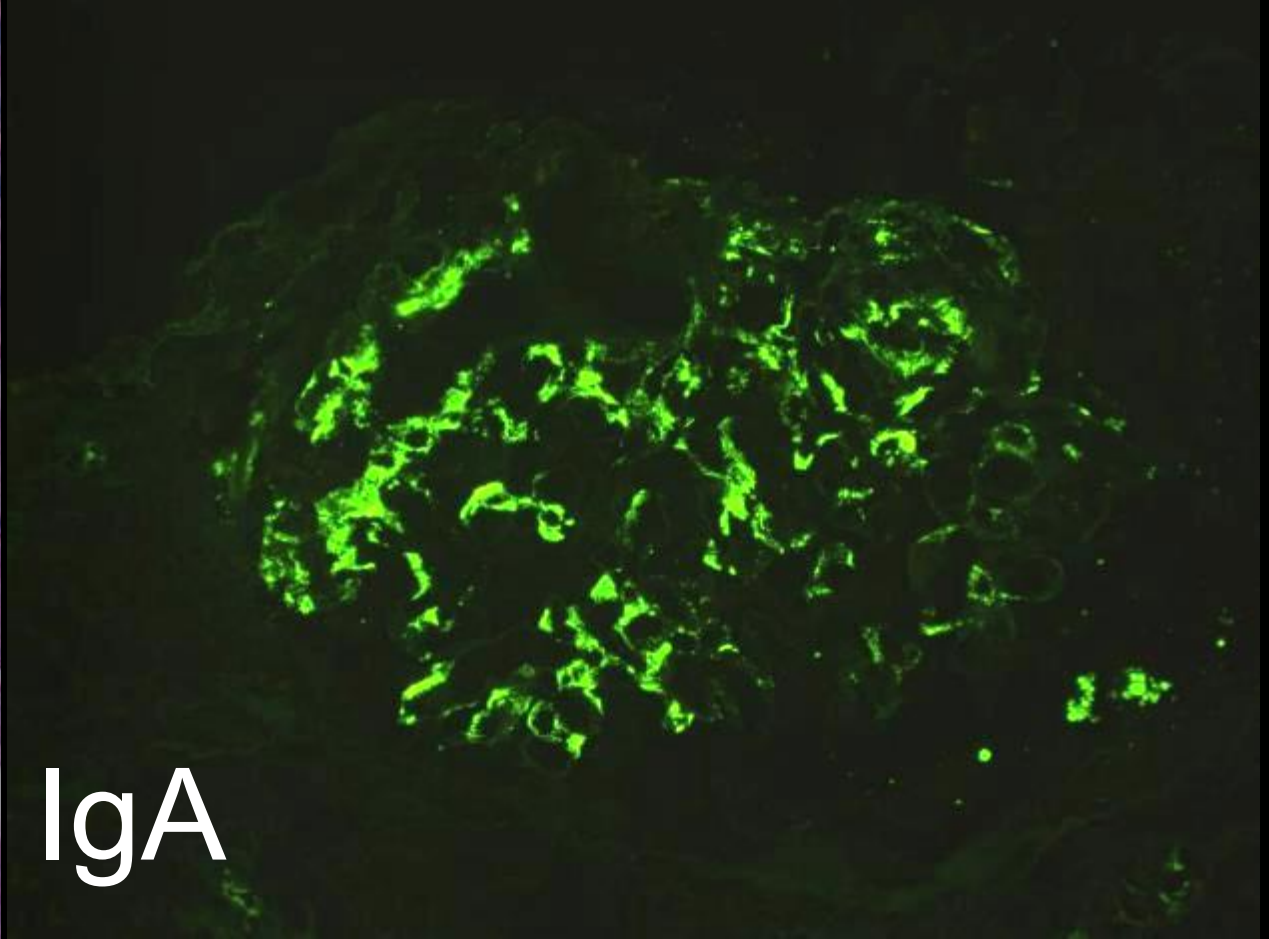
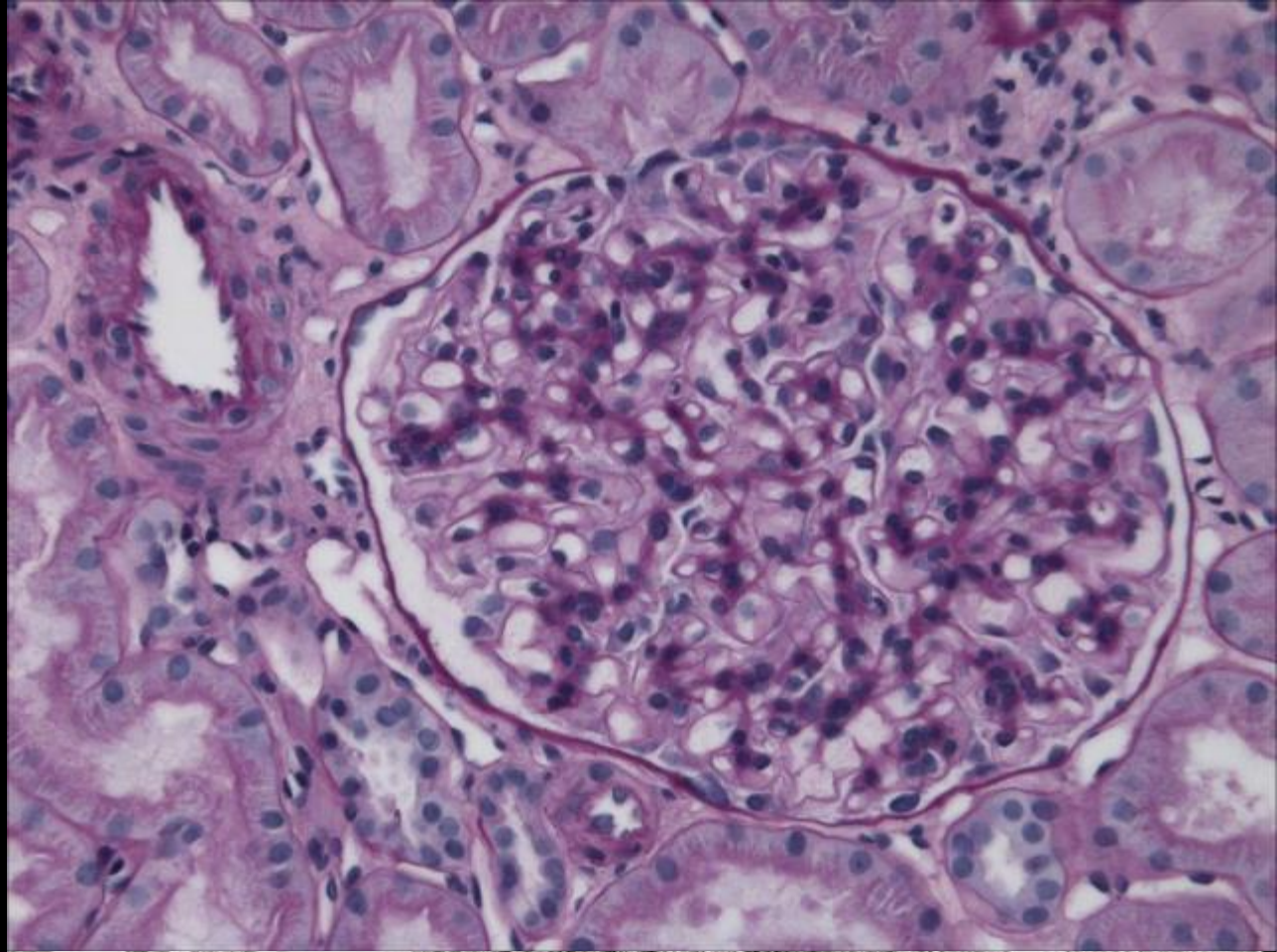
# ASYMPTOMATIC HEMATURIA/PROTEINURIA

## MESANGIOPROLIFERATIVE GLOMERULONEPHRITIS

- IgA Nephropathy
- Recovery phase of a postinfectious glomerulonephritis
- Mesangial proliferative lupus nephritis, SLE WHO Class II, and other IC-mediated diseases
- Idiopathic Mesangioproliferative GN
- Some of the deposition diseases

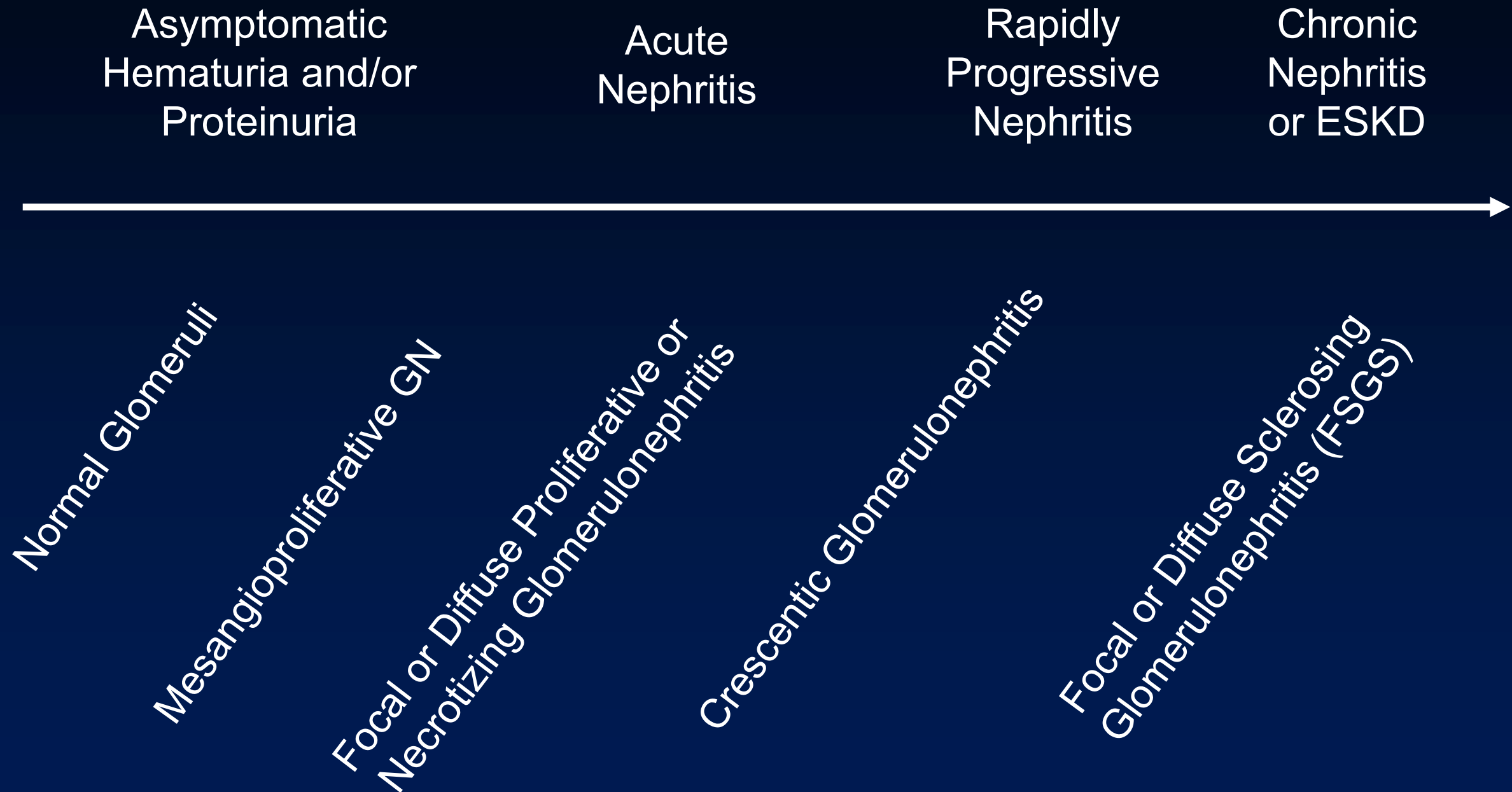


# IgA Nephropathy





# CLINICAL AND MORPHOLOGICAL EXPRESSION OF IgA NEPHROPATHY AND HSP





# Unusual Presentations in IgA Nephropathy

- IgA Nephropathy with gross hematuria and Acute Renal Failure
- IgA Nephropathy with superimposed Nephrotic Syndrome and Minimal Change-like lesions
- IgA Nephropathy with Proteinuria or NS and superimposed Membranous Nephropathy
- IgA Nephropathy with ANCA serology and Necrotizing and Crescentic Glomerulonephritis



# PATHOGENESIS OF IgA NEPHROPATHY AND HSP

A glycosylation defect of the O-linked glycans in the hinge region of IgA1 molecules is believed to:

- reduced clearance from the circulation because of lack of receptor engagement by the abnormal IgA
- increased aggregation of IgA in the circulation resulting in mesangial trapping
- development of immune complex-forming autoantibodies directed against the abnormal IgA
- increased affinity of the abnormal IgA for mesangial matrix



# OXFORD CLASSIFICATION

## M E S T C

1. Mesangial Hypercellularity: average of all glomeruli:

M1 <0.5 M2 >0.5

M0=4 or <4 cells; M1=5 cells; M2=6-7 cells; M3=8 or >8 cells

2. Endocapillary hypercellularity:

E0 E1

3. Segmental sclerosis:

S0 S1

4. Tubular Atrophy and Interstitial Fibrosis:

T0=0-25% T1=26-50% T2=>50%

5. Crescents:

C0=no crescents; C1=1 or more crescents; C2=>25% of glomeruli

# THE CARDINAL SIGNS OF GLOMERULAR DYSFUNCTION

- Proteinuria

- Hematuria

- Glomerulitis

- Inflammation from complement activation via classical pathway by immune complexes in the capillary wall or paraproteins
    - Inflammation by activation of complement via the alternative pathway
    - Inflammation through antibody-dependent cell cytotoxicity
    - Inflammation through cell-mediated immune mechanisms

- Capillary fragility

- Loss of glomerular filtration rate



# CLINICAL CONDITIONS ASSOCIATED WITH GLOMERULAR BASEMENT MEMBRANE ABNORMALITIES

Hereditary nephritis (Collagen type IV):

- Classical Alport syndrome

- Autosomal recessive hereditary nephritis

- Autosomal dominant hereditary nephritis

  - Thin basement membrane disease (TBMD)

Epstein and Fechtner syndromes (myosin HC IIA)

Pierson Syndrome (laminin  $\beta 2$ ) (CNS+eye abn.)

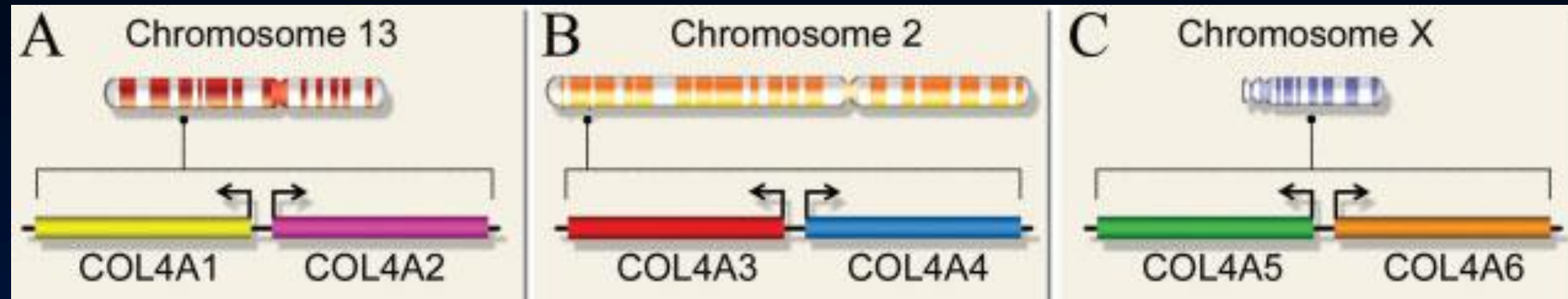
Nail-patella syndrome or hereditary osteo-onychodysplasia (LMX1B, LIM homeodomain transcription factor)

Collagen III glomerulopathy, Fibronectin glomerulopathy

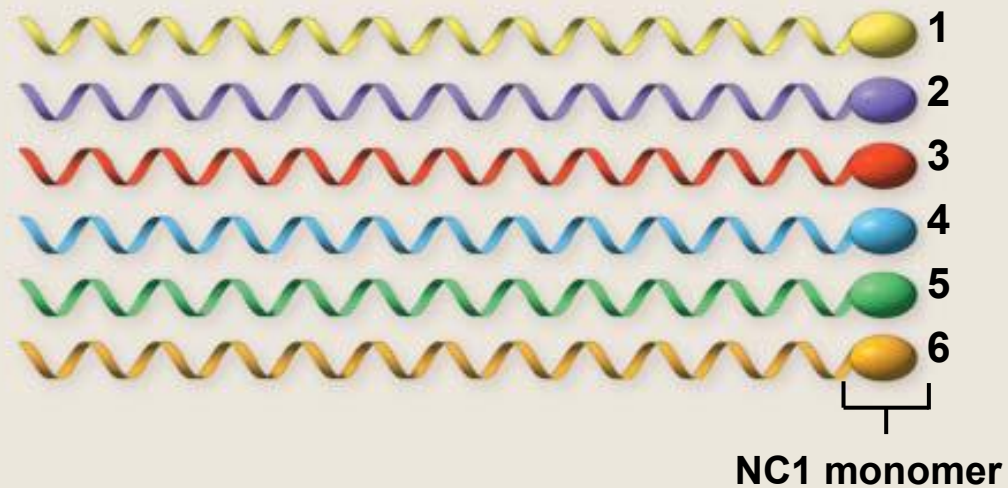
Lecithin-cholesterol acyltransferase deficiency

(Resolving immune complex mediated GN)

# BASEMENT MEMBRANE COLLAGEN GENES AND PROTEINS



## Type IV collagen chains

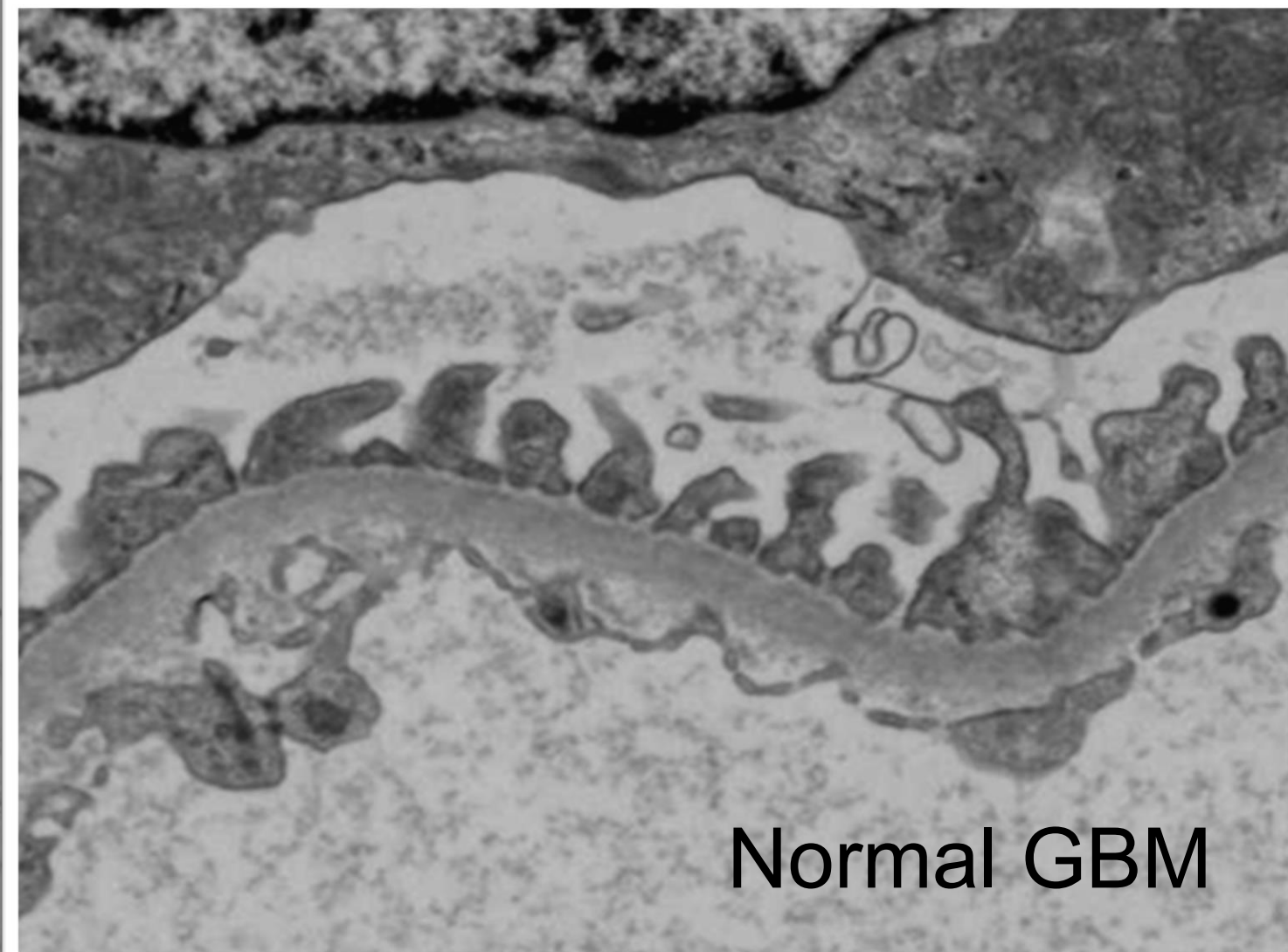
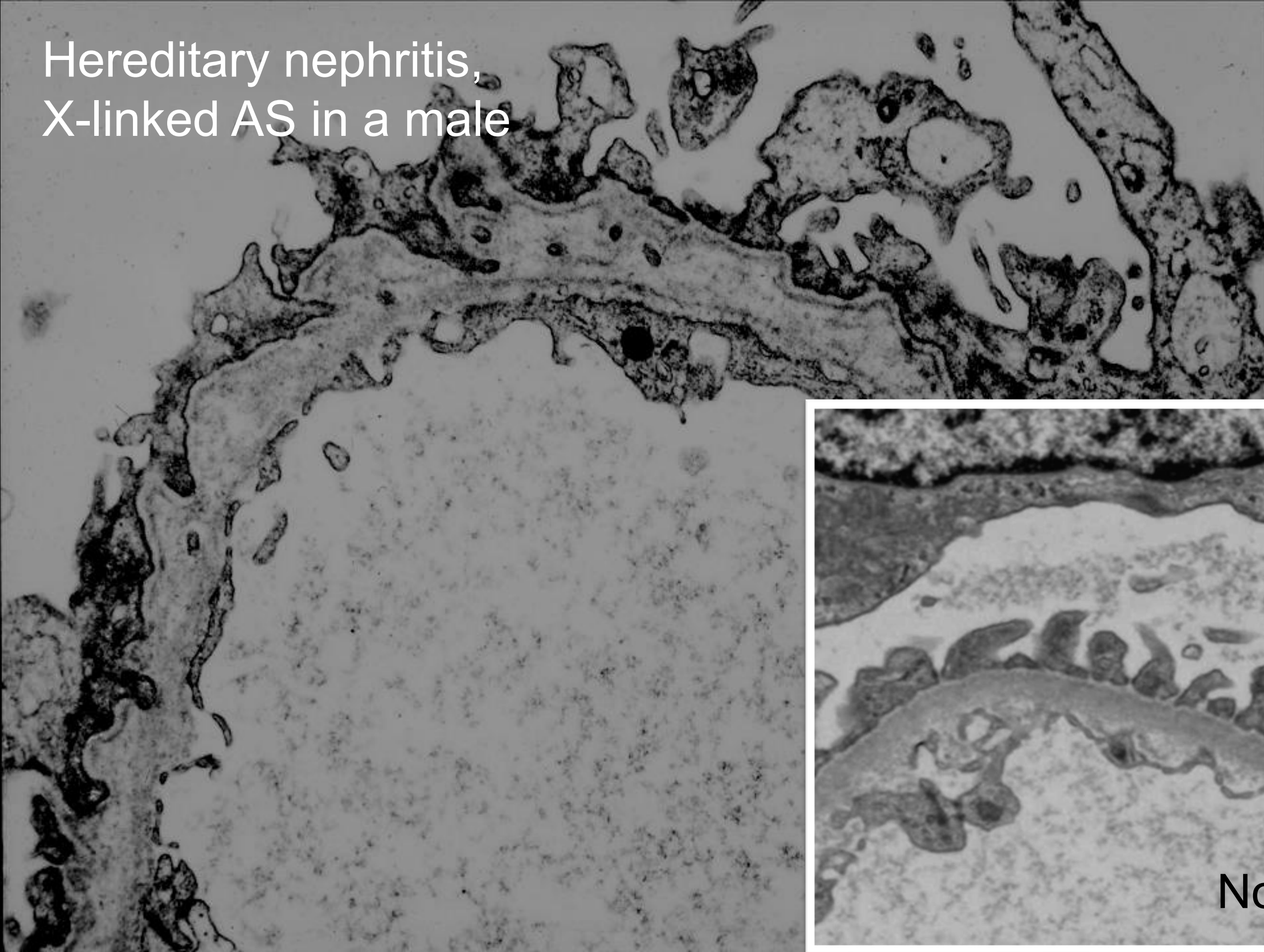


## Protomers

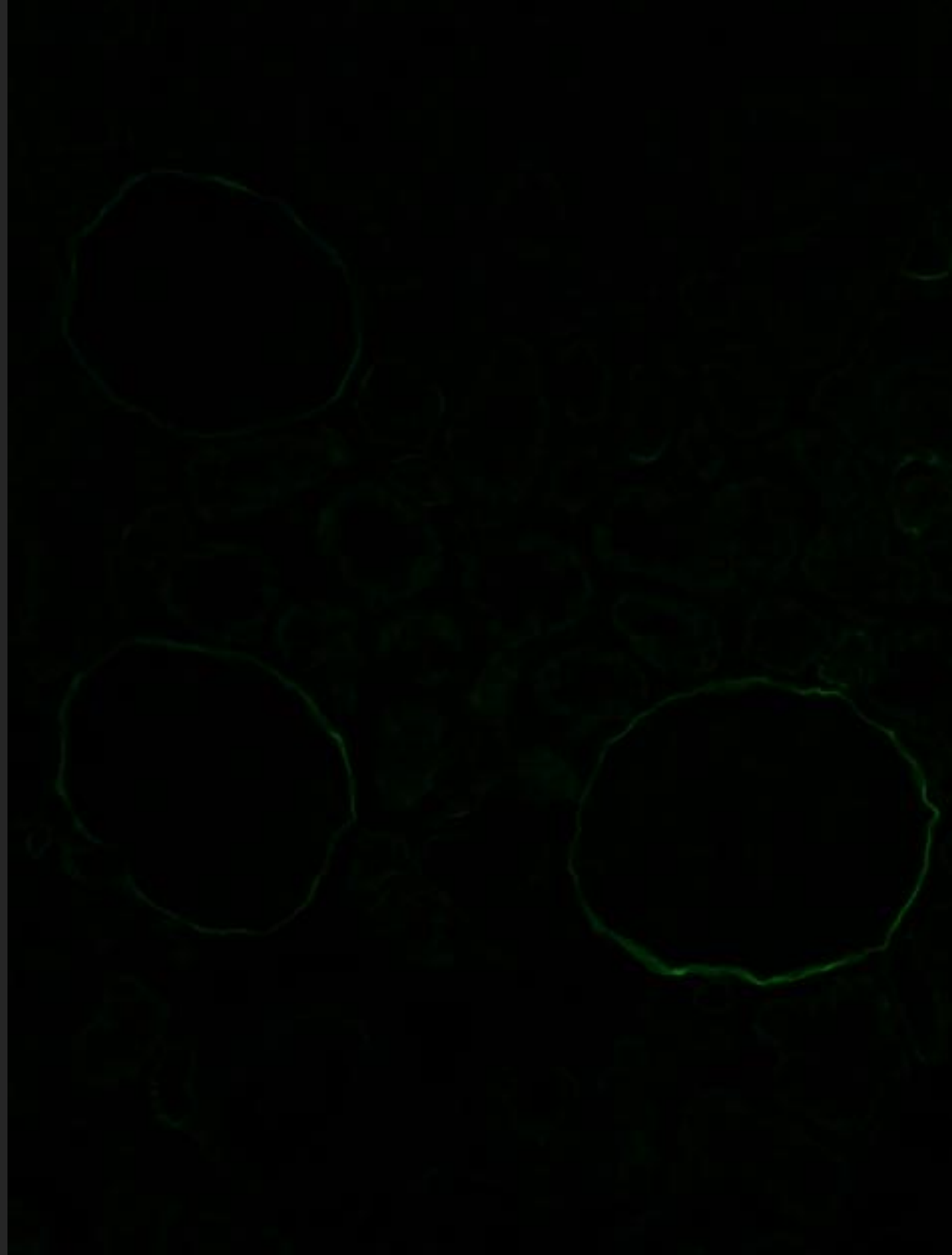




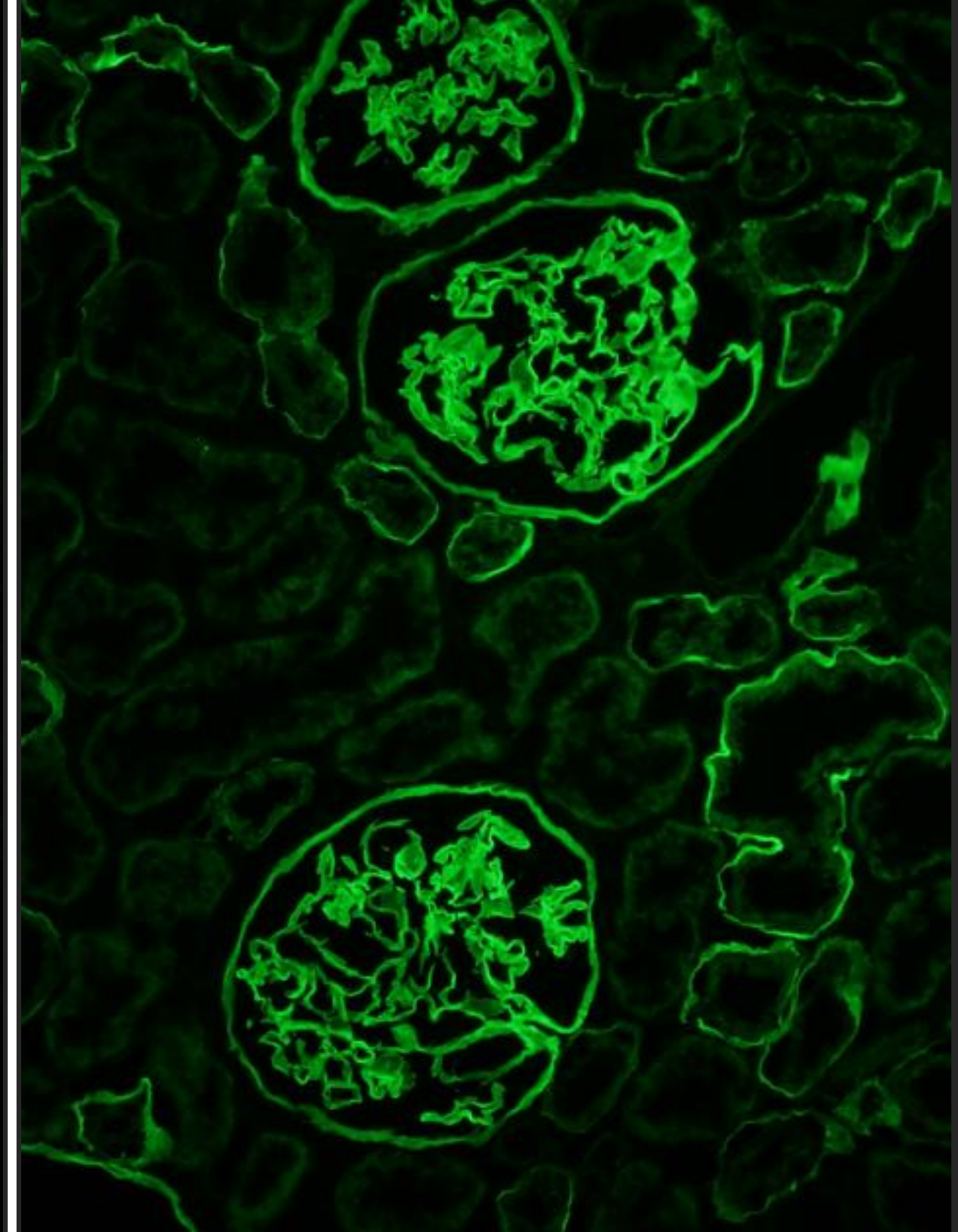
Hereditary nephritis,  
X-linked AS in a male



Normal GBM



**Patient**



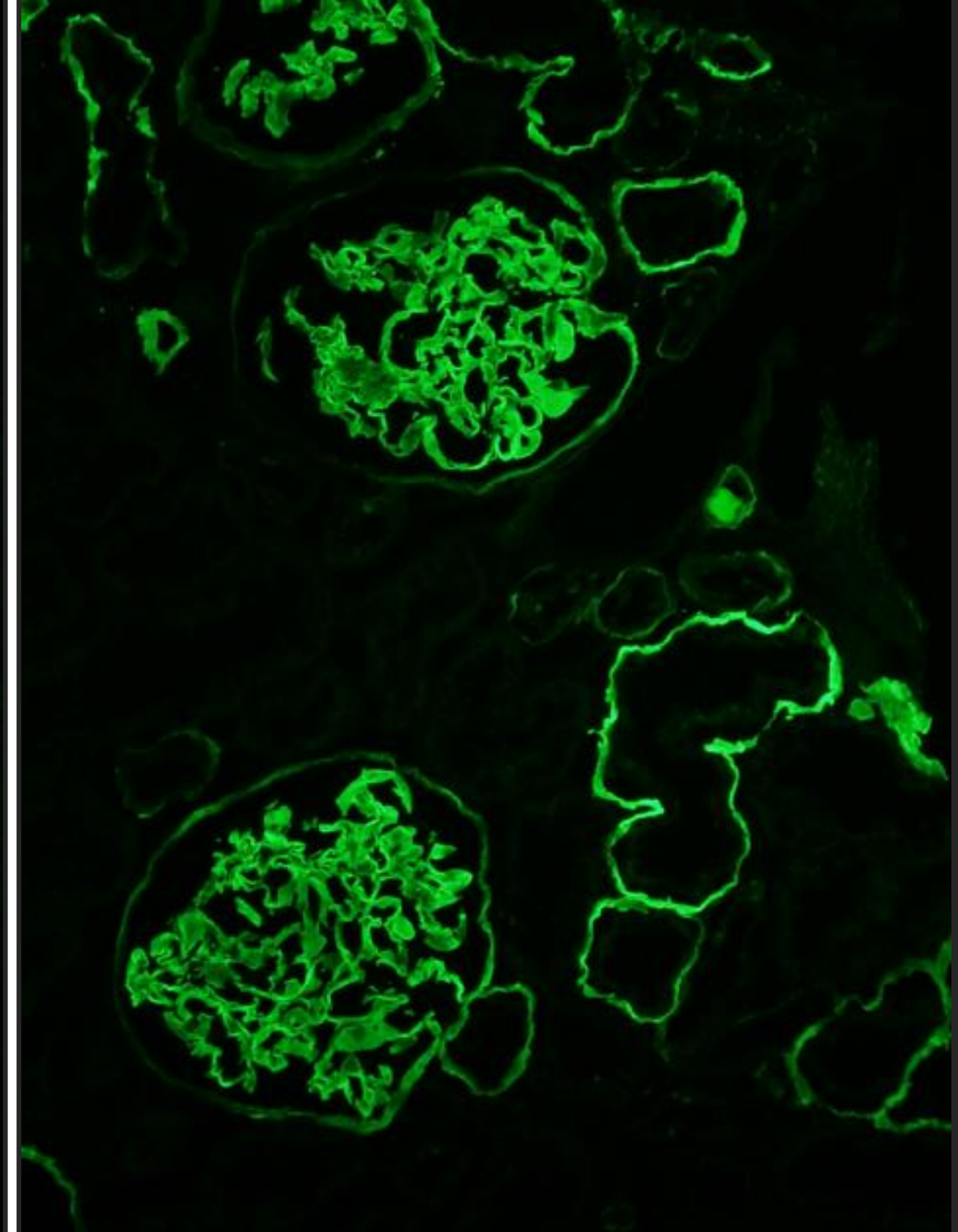
**Normal**

**Alpha5 Collagen IV**





**Patient**



**Normal**

**Alpha3 Collagen IV**

# GENETIC BASIS OF ALPORT SYNDROME

|                               | <b>x-AS-m</b>                                                                      | <b>X-AS-f</b>                                                                                  | <b>ar-AS</b>                                                 | <b>ad-AS</b>                                                 | <b>TBMD</b>                    |
|-------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------|--------------------------------|
| Chromosome                    | <b>X</b>                                                                           | <b>X</b>                                                                                       | <b>2</b>                                                     | <b>2</b>                                                     | <b>2</b>                       |
| Gene Defect                   | <i>COL4A5</i>                                                                      | <i>COL4A5</i>                                                                                  | <i>COL4A3</i><br><i>COL4A4</i>                               | <i>COL4A3</i><br><i>COL4A4</i>                               | <i>COL4A3</i><br><i>COL4A4</i> |
| Collagen chain                | $\alpha 5$                                                                         | $\alpha 5$                                                                                     | $\alpha 3$<br>$\alpha 4$                                     | $\alpha 3$<br>$\alpha 4$                                     | $\alpha 3$<br>$\alpha 4$       |
| Defective<br>protomer network | $\alpha 3,4,5$<br>$\alpha 5,5,6$                                                   | $\alpha 3,4,5$<br>$\alpha 5,5,6$<br>mosaic                                                     | $\alpha 3,4,5$                                               | $\alpha 3,4,5$                                               | $\alpha 3,4,5$                 |
| Negative stain<br>Kidney      | anti- $\alpha 3$ ,<br>anti- $\alpha 4$ ,<br>anti- $\alpha 5$ ,<br>anti- $\alpha 6$ | anti- $\alpha 3$ ,<br>anti- $\alpha 4$ ,<br>anti- $\alpha 5$ ,<br>anti- $\alpha 6$<br>(mosaic) | anti- $\alpha 3$ ,<br>anti- $\alpha 4$ ,<br>anti- $\alpha 5$ | anti- $\alpha 3$ ,<br>anti- $\alpha 4$ ,<br>anti- $\alpha 5$ | normal                         |
| Negative stain<br>Skin        | anti- $\alpha 5$ ,<br>anti- $\alpha 6$                                             | anti- $\alpha 5$ ,<br>anti- $\alpha 6$<br>(mosaic)                                             | normal                                                       | normal                                                       | normal                         |

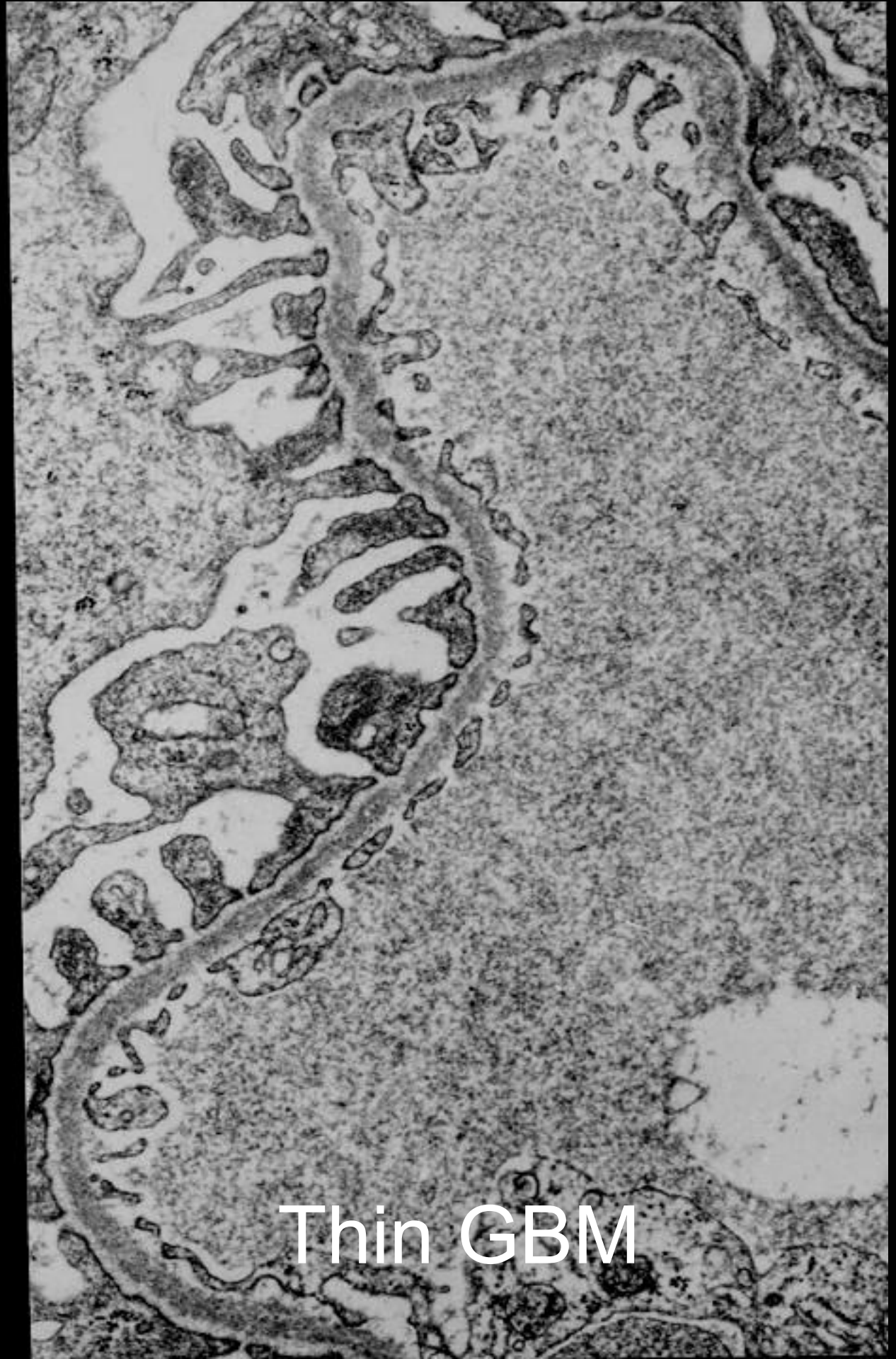


# CLINICAL PRESENTATION OF AS

|                            | <b>x-ASm</b>                                | <b>X-ASf</b>                            | <b>ar-AS</b>                             | <b>ad-AS</b>           | <b>TBMD</b>                      |
|----------------------------|---------------------------------------------|-----------------------------------------|------------------------------------------|------------------------|----------------------------------|
| Microhematuria             | <b>+(100%)</b>                              | <b>+(&gt;90%)</b>                       | <b>+(100%)</b>                           | <b>+</b>               | <b>+(&gt;50%)</b>                |
| Macrohematuria             | <b>+</b>                                    | <b>±</b>                                | <b>±</b>                                 | <b>±</b>               | <b>-</b>                         |
| Proteinuria                | <b>+</b>                                    | <b>±</b>                                | <b>+</b>                                 | <b>+</b>               | <b>-</b>                         |
| ESRD                       | <b>50% (25y)<br/>80%(40y)<br/>100%(60y)</b> | <b>12%(45y)<br/>30%(60)<br/>40%(80)</b> | <b>Variable</b>                          | <b>Variable</b>        | <b>? Similar to general pop.</b> |
| Sensorineural hearing loss | <b>80-90%;Late childhood adolescence</b>    | <b>Sometimes adult</b>                  | <b>80-90%;Late childhood adolescence</b> | <b>sometimes adult</b> | <b>No</b>                        |
| Ant. Lenticonus            | <b>15-20% Late adolesc</b>                  |                                         | <b>15-20% Late adolesc</b>               |                        | <b>No</b>                        |
| Perimacular flecks         | <b>+</b>                                    |                                         | <b>+</b>                                 |                        | <b>No</b>                        |



Normal GBM



Thin GBM



# THE BASIC STRUCTURAL PATTERNS OF GLOMERULAR INJURY

- 1.- Epithelial Cell Disease (Minimal Change Disease)
- 2.- Focal Segmental Glomerulosclerosis
- 3.- Membranous Nephropathy
- 4.- Diffuse Proliferative Glomerulonephritis
- 5.- Membranoproliferative Glomerulonephritis
- 6.- Crescentic Glomerulonephritis
- 7.- Focal Proliferative and Necrotizing Glomerulonephritis
- 8.- Mesangial Proliferative Glomerulonephritis
- 9.- Basement Membrane Abnormalities
- 10.- Focal Global Glomerulosclerosis

# NEPHRITIC CONDITIONS

**PATTERN OF INJURY - IF FINDINGS - EM CHANGES**

Immune Complex  
Diseases

mlg-associated  
Diseases

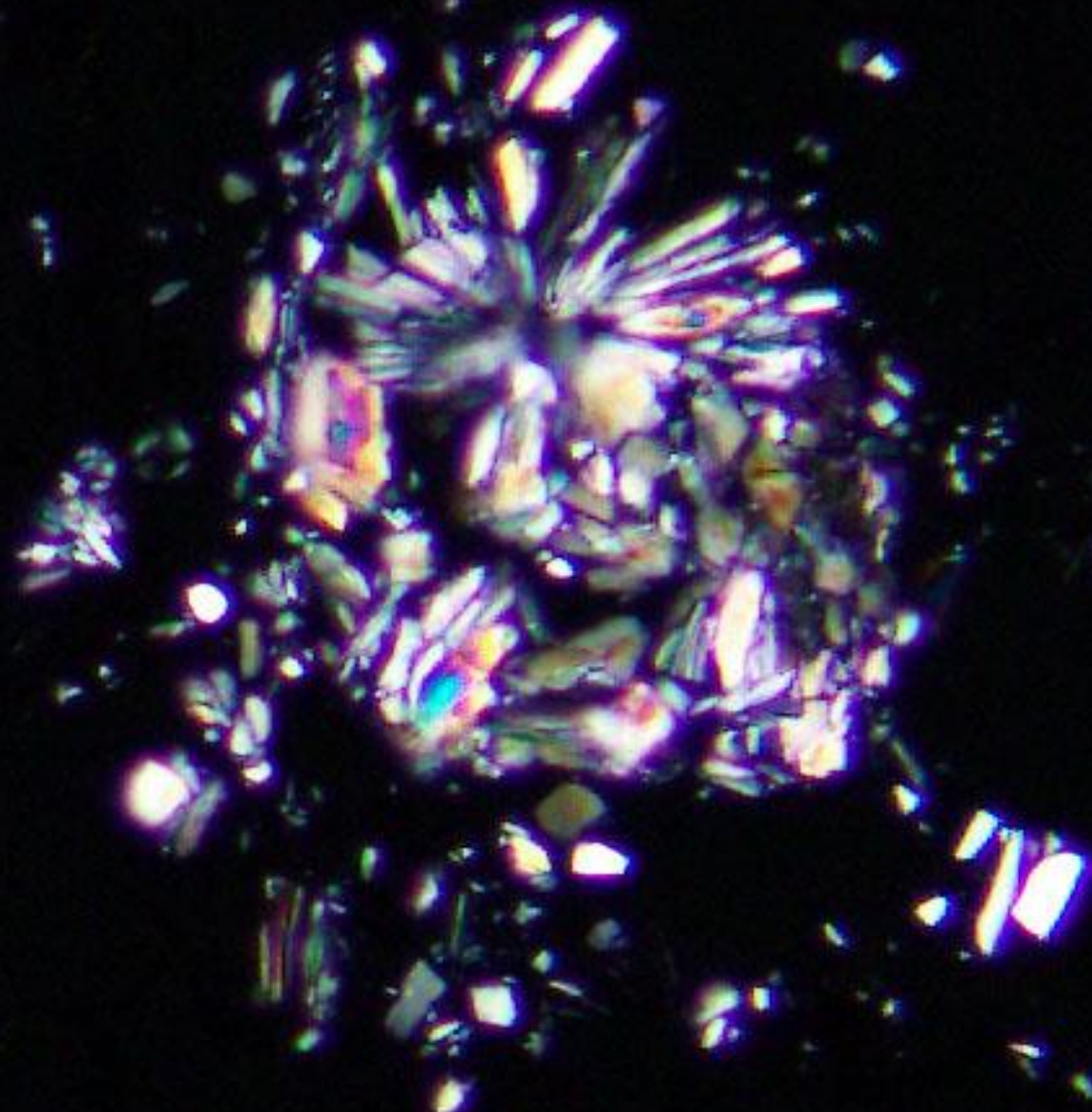
Complement  
abnormalities

Thrombotic  
Angiopathies

Genetic defects  
of the GBM

Rational Therapy





Thank you