

# RENAL PATHOLOGY IN 2025

## 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

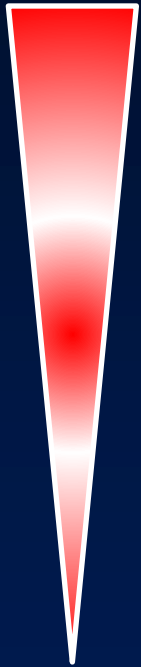
1. The Nephrotic Syndrome

2. The Acute Nephritic Syndrome

3. Rapidly Progressive Glomerulonephritis

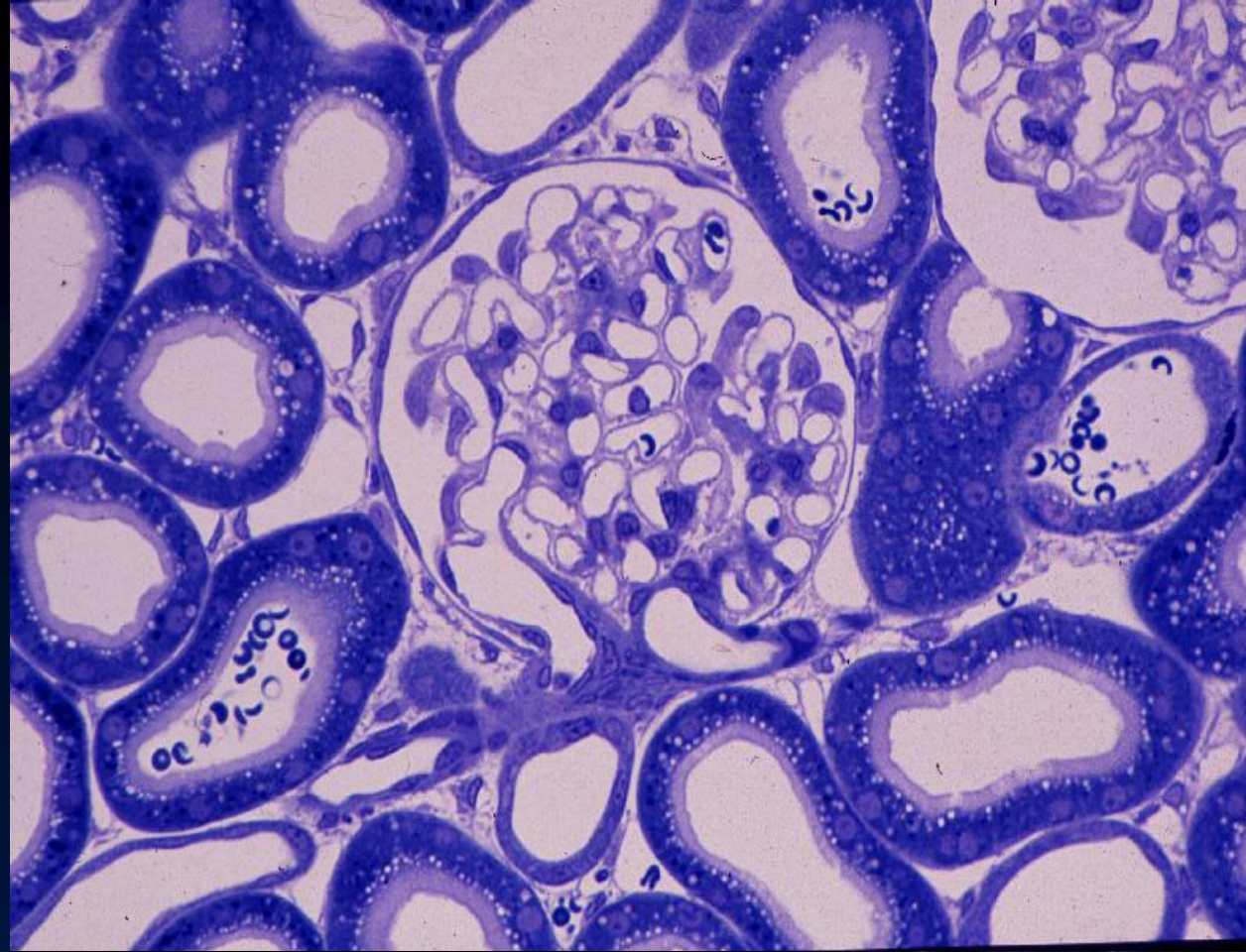
4. Asymptomatic Hematuria / Proteinuria

5. The Chronic Nephritic Syndrome  
(Chronic Renal Failure)

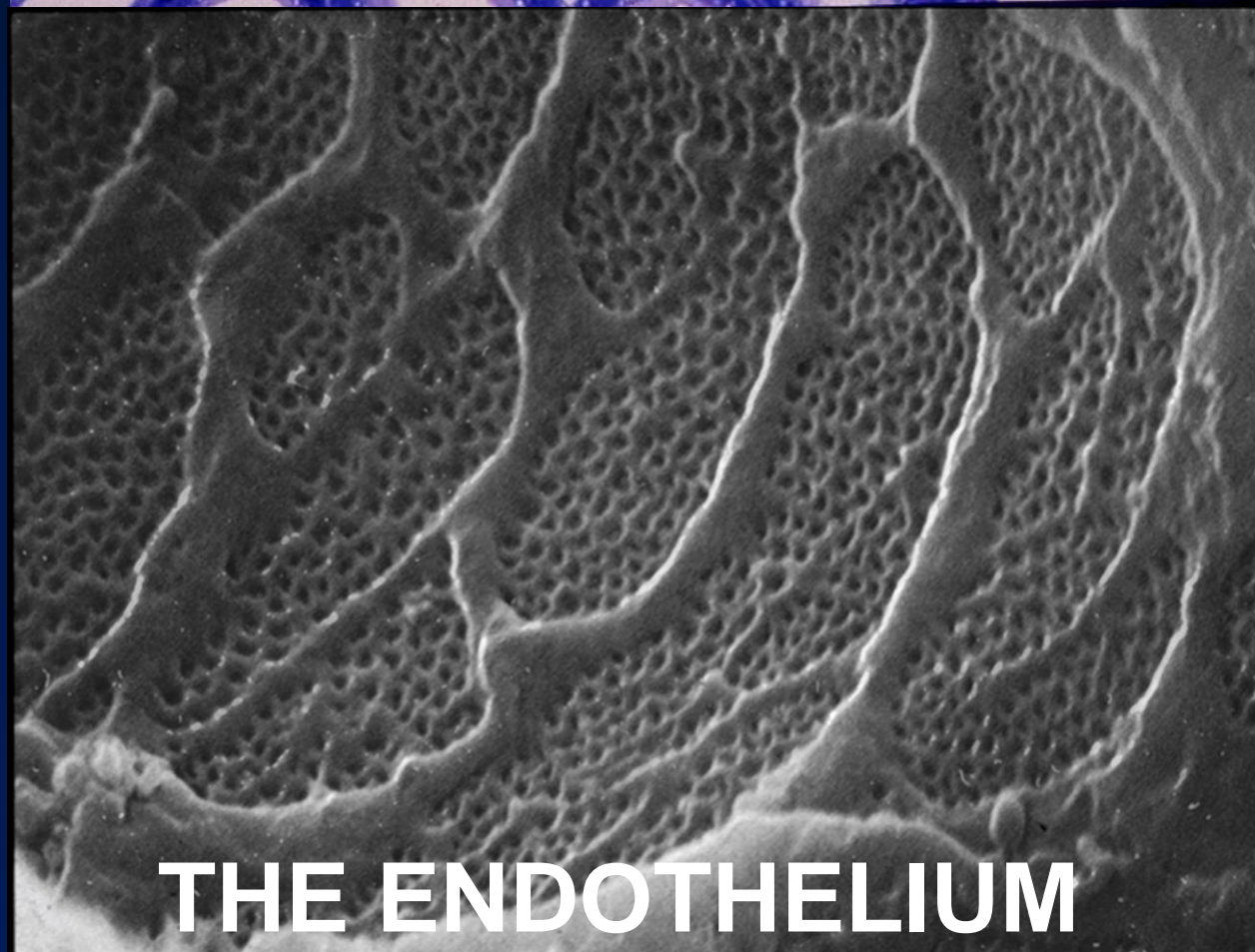




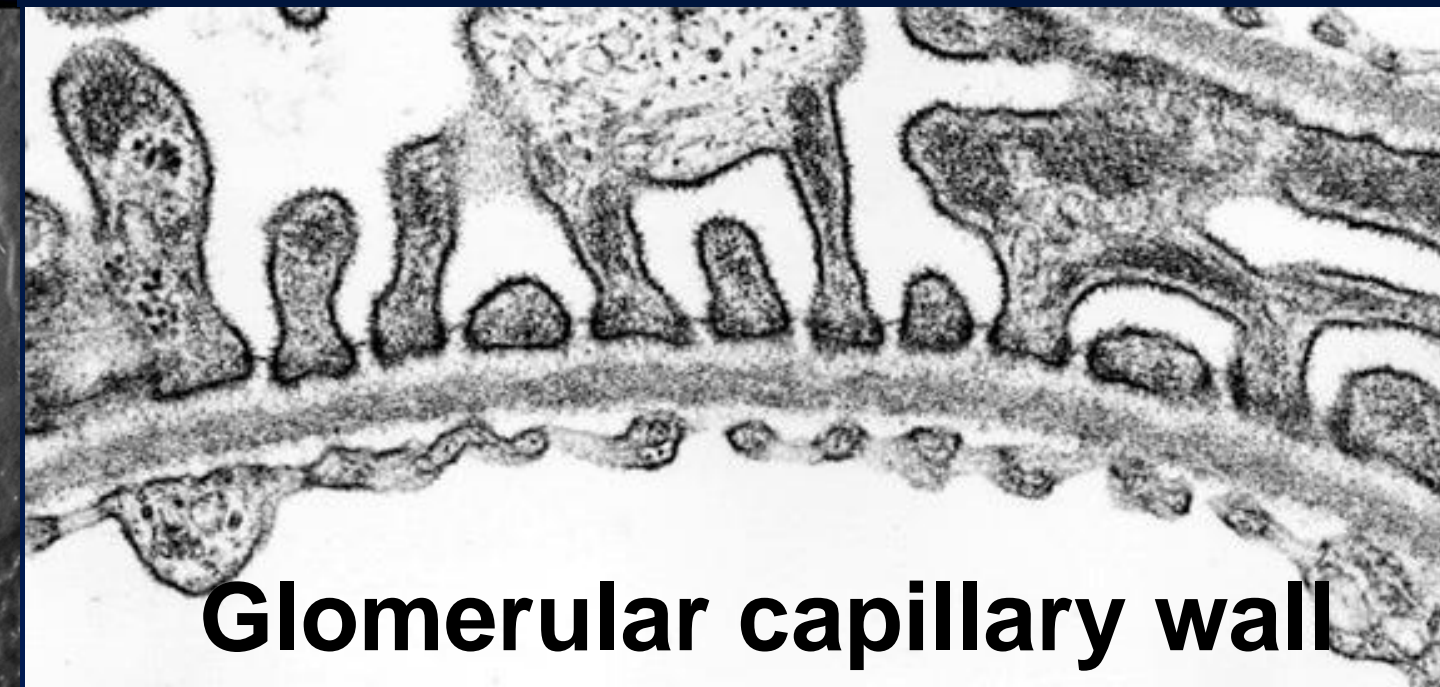
# The unique structural adaptations of the glomerular microcirculation



**THE PODOCYTE**



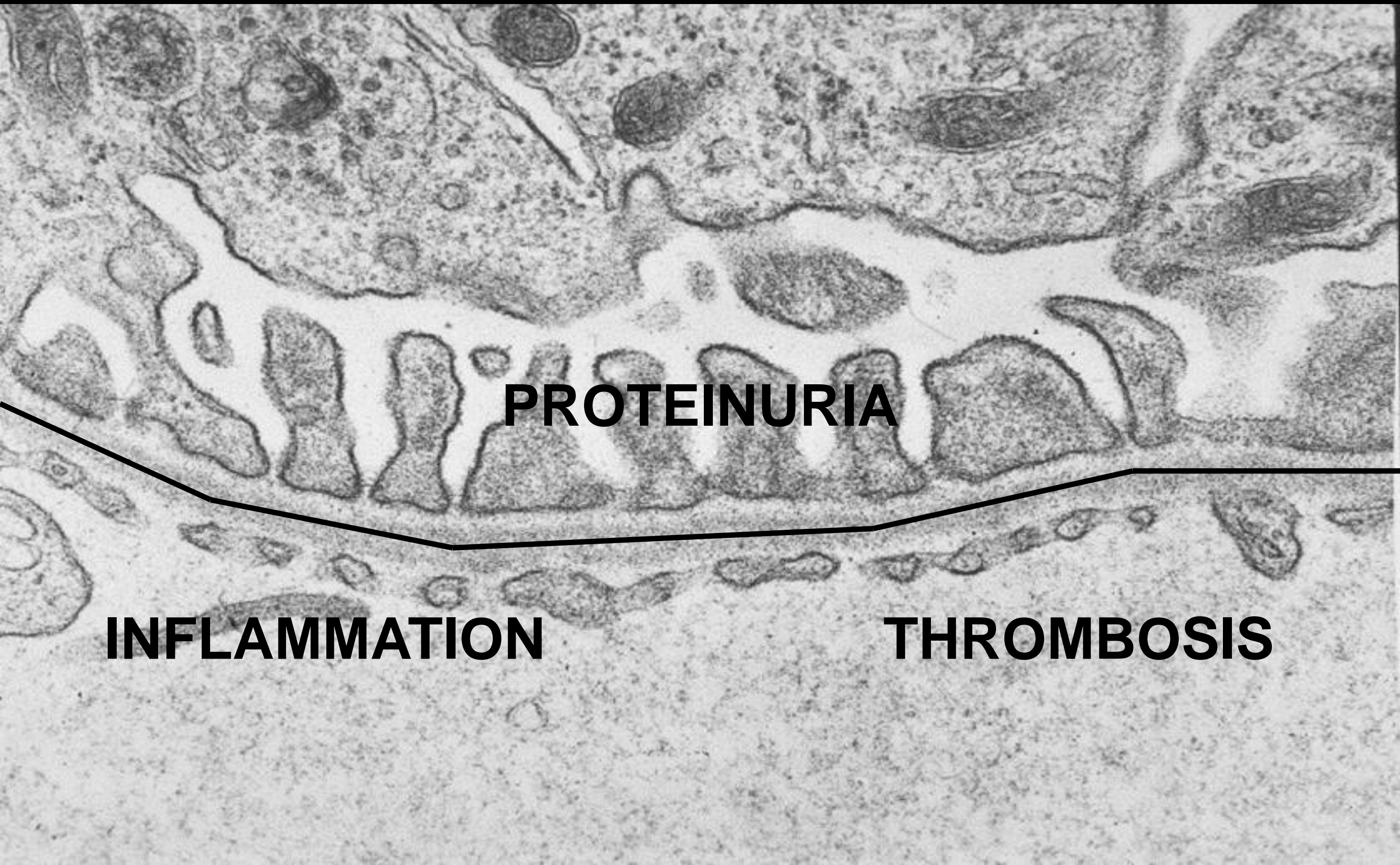
**THE ENDOTHELIUM**



**Glomerular capillary wall**

**Key Target Cells**





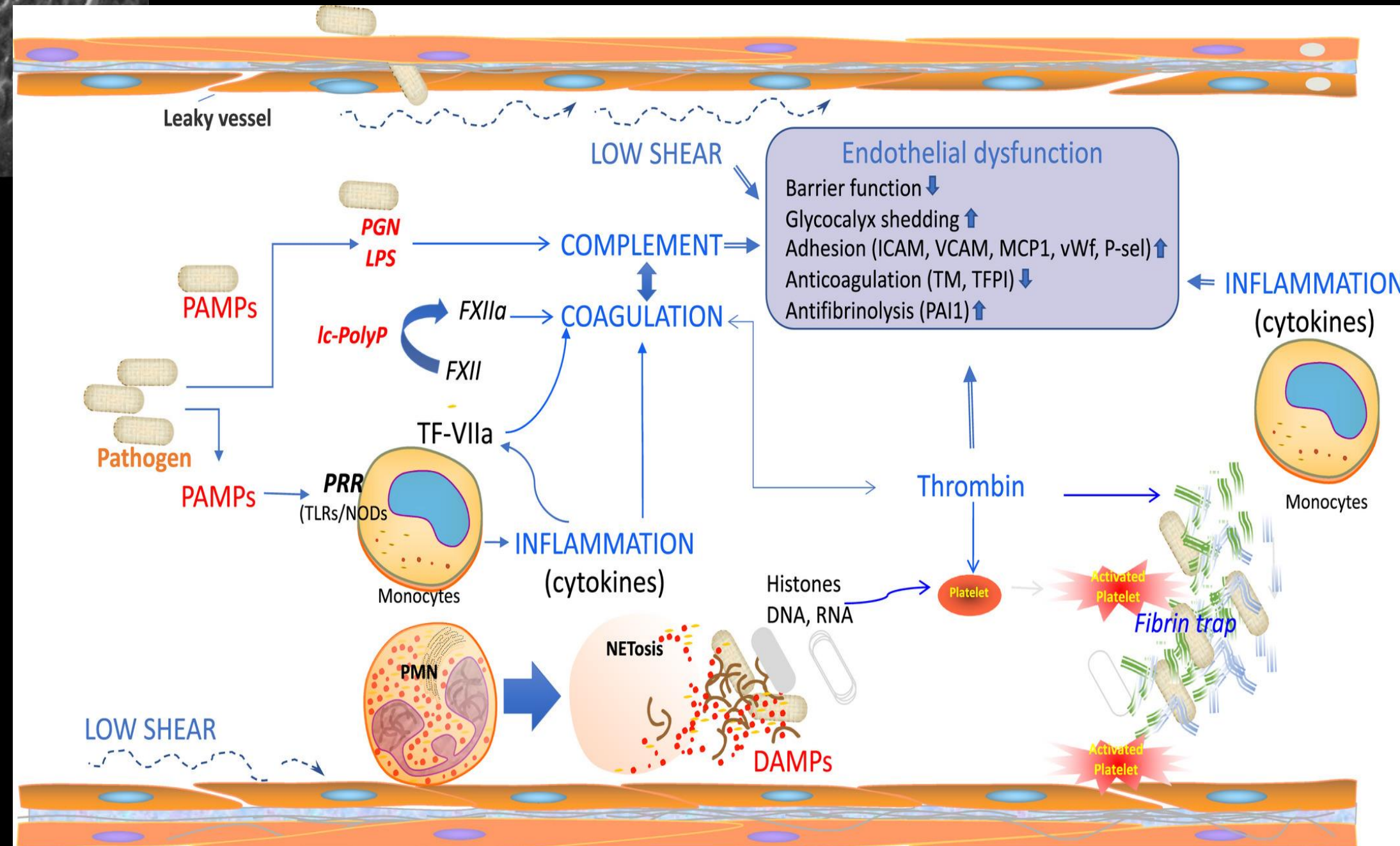
**PROTEINURIA**

**INFLAMMATION**

**THROMBOSIS**



# THE ROLE OF THE ENDOTHELIUM IN INFLAMMATION AND THROMBOSIS



# 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

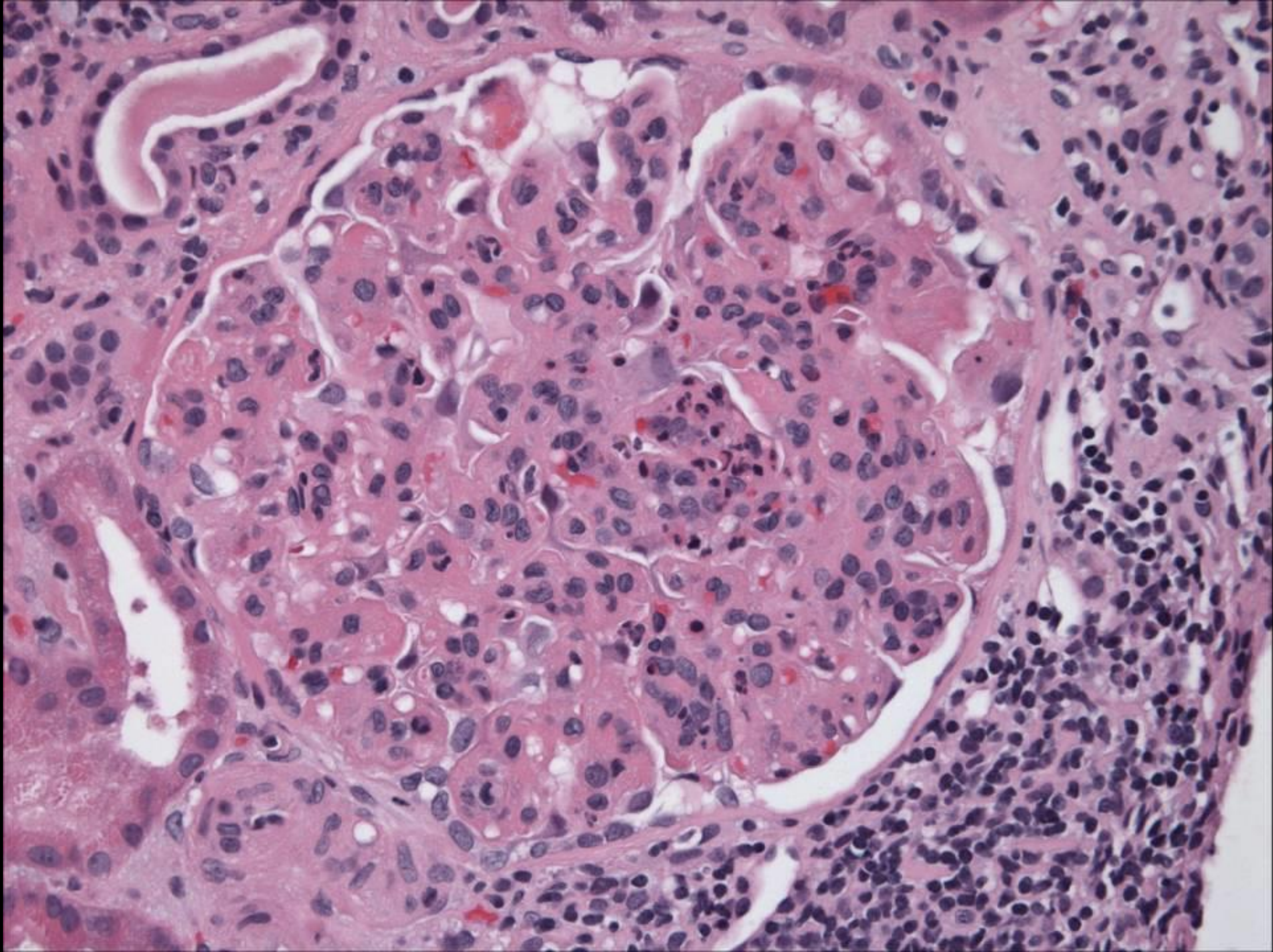
- Loss of glomerular filtration rate

# 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



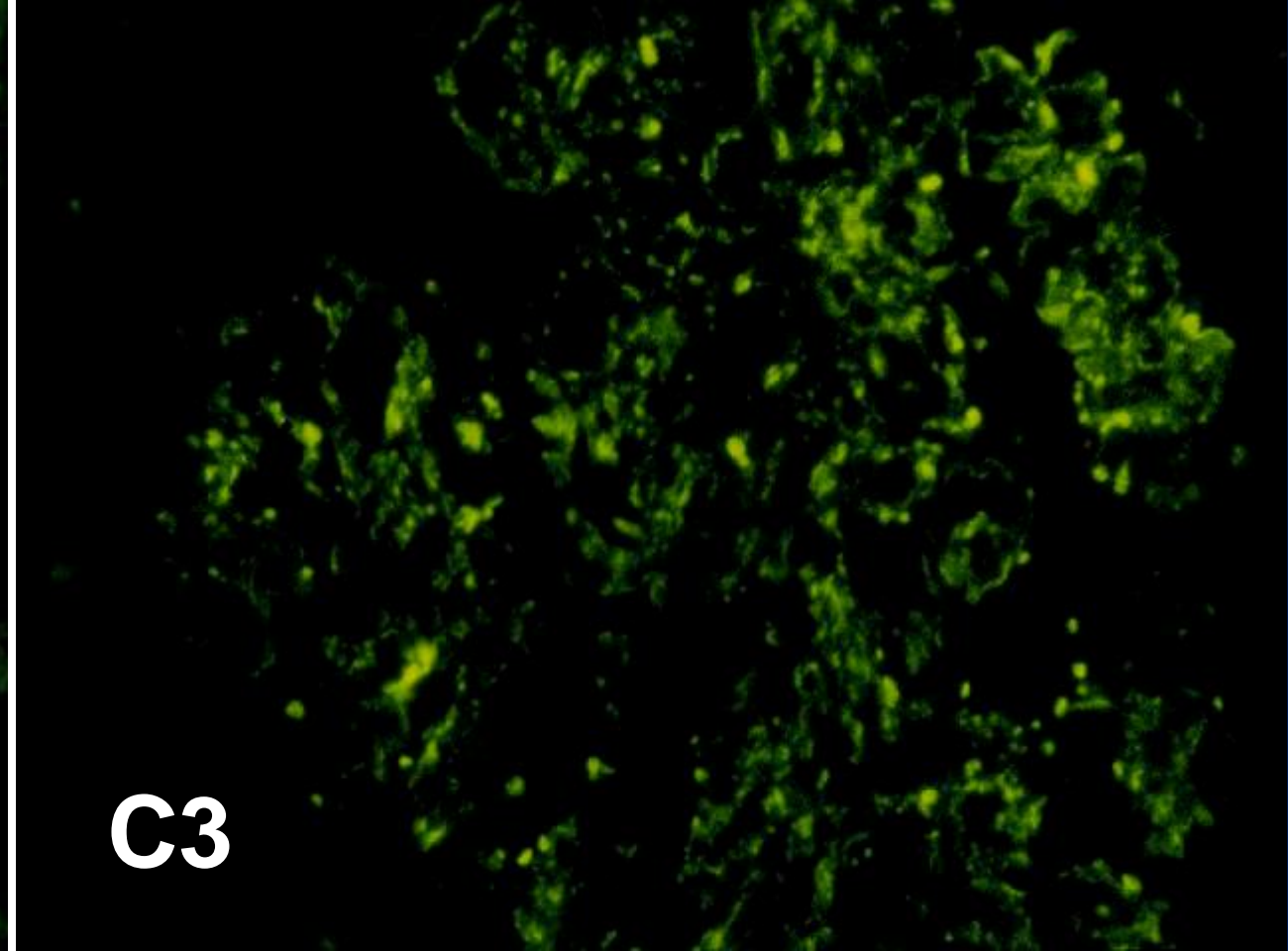
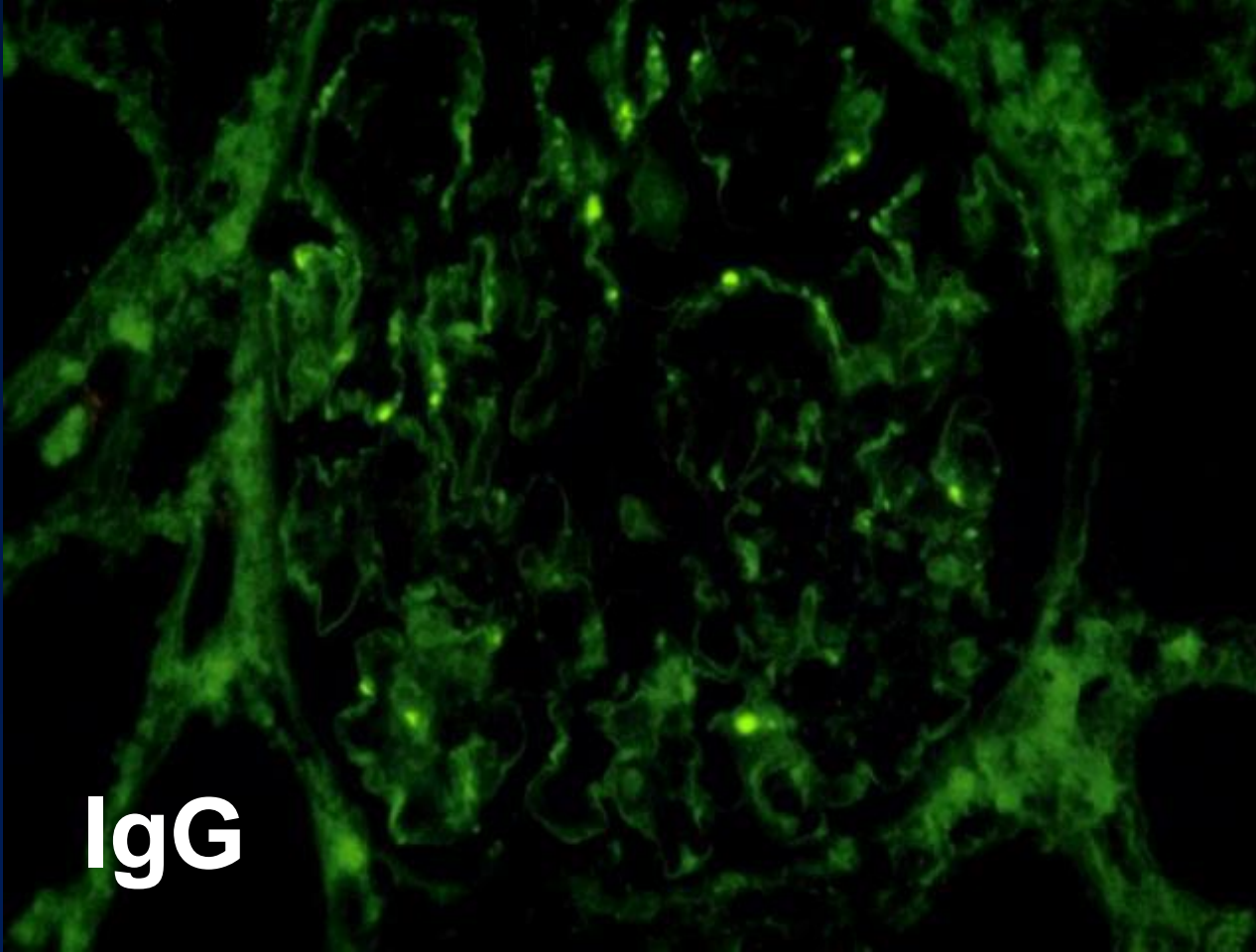
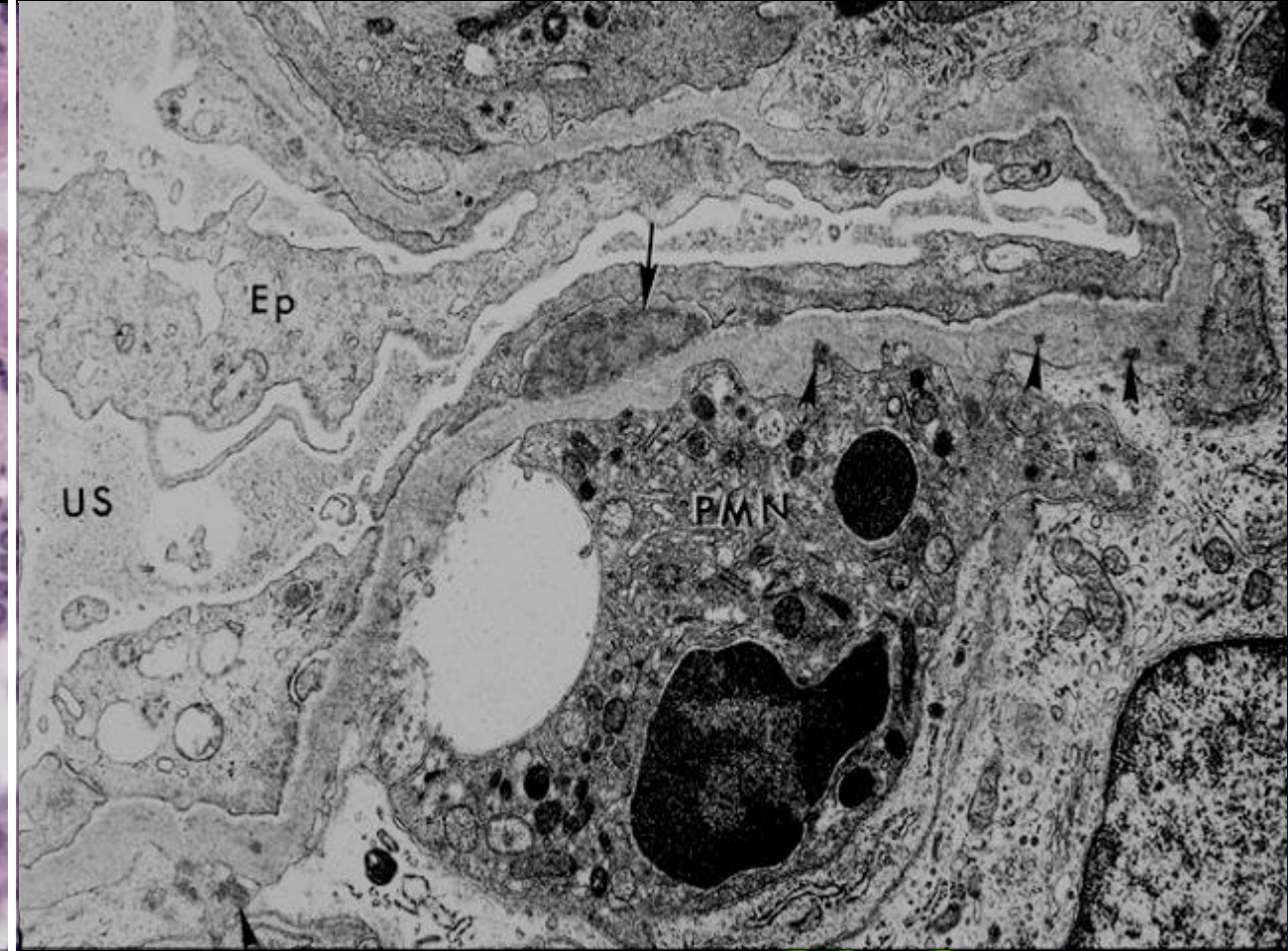
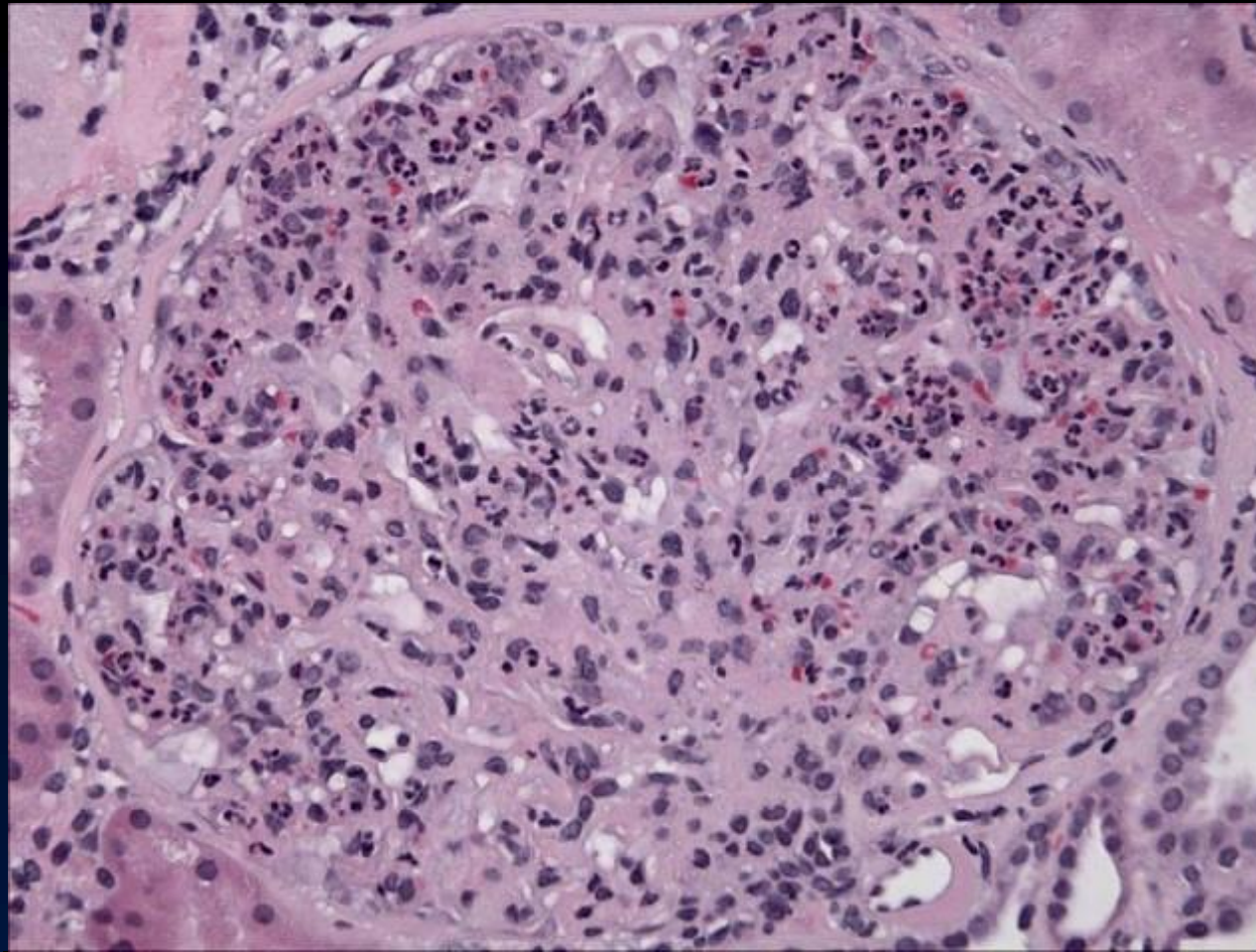
**Diffuse proliferative GN**  
**With diffuse endocapillary hypercellularity**





# Post-streptococcal GN

## Infection-associated GN

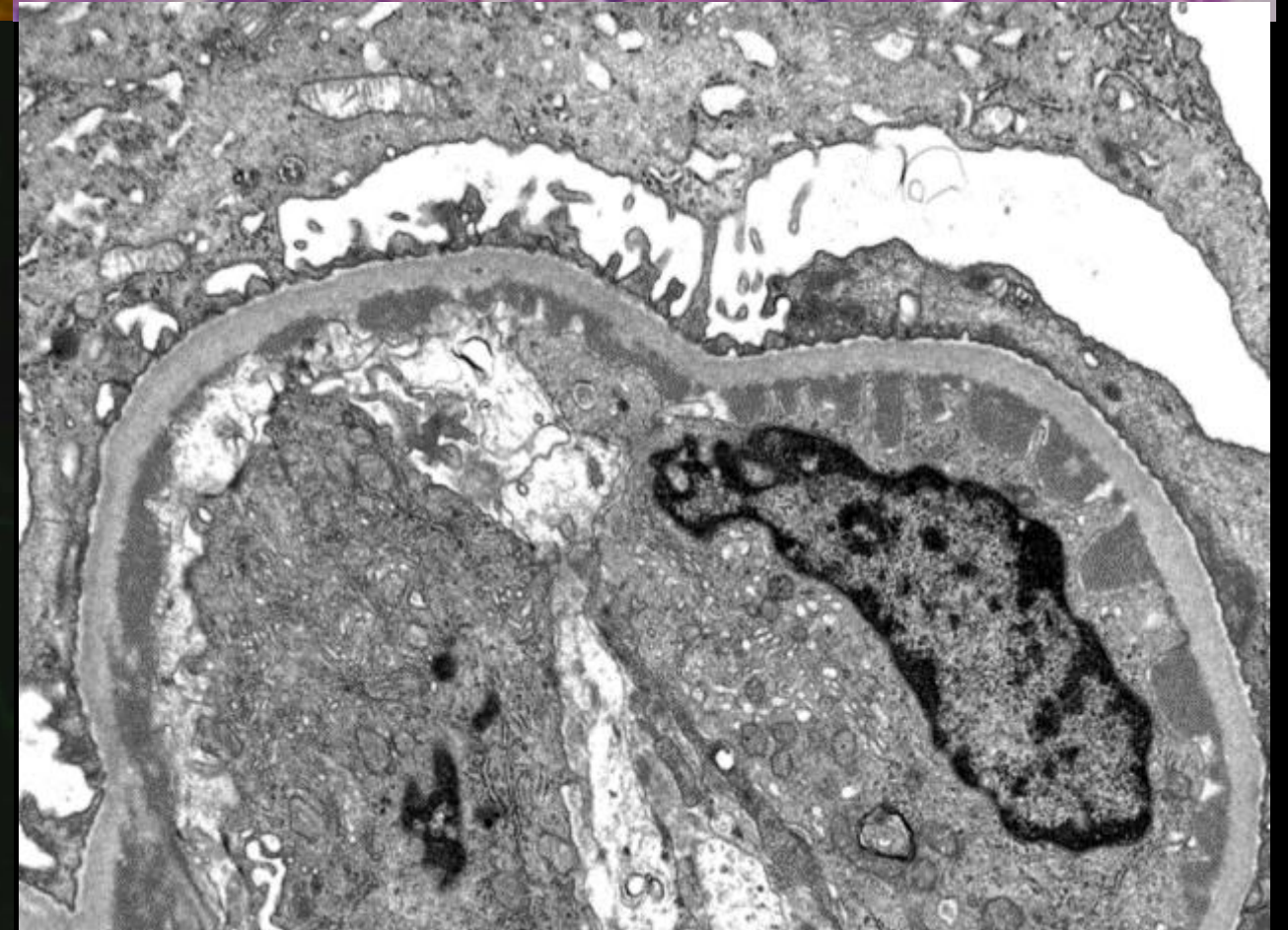
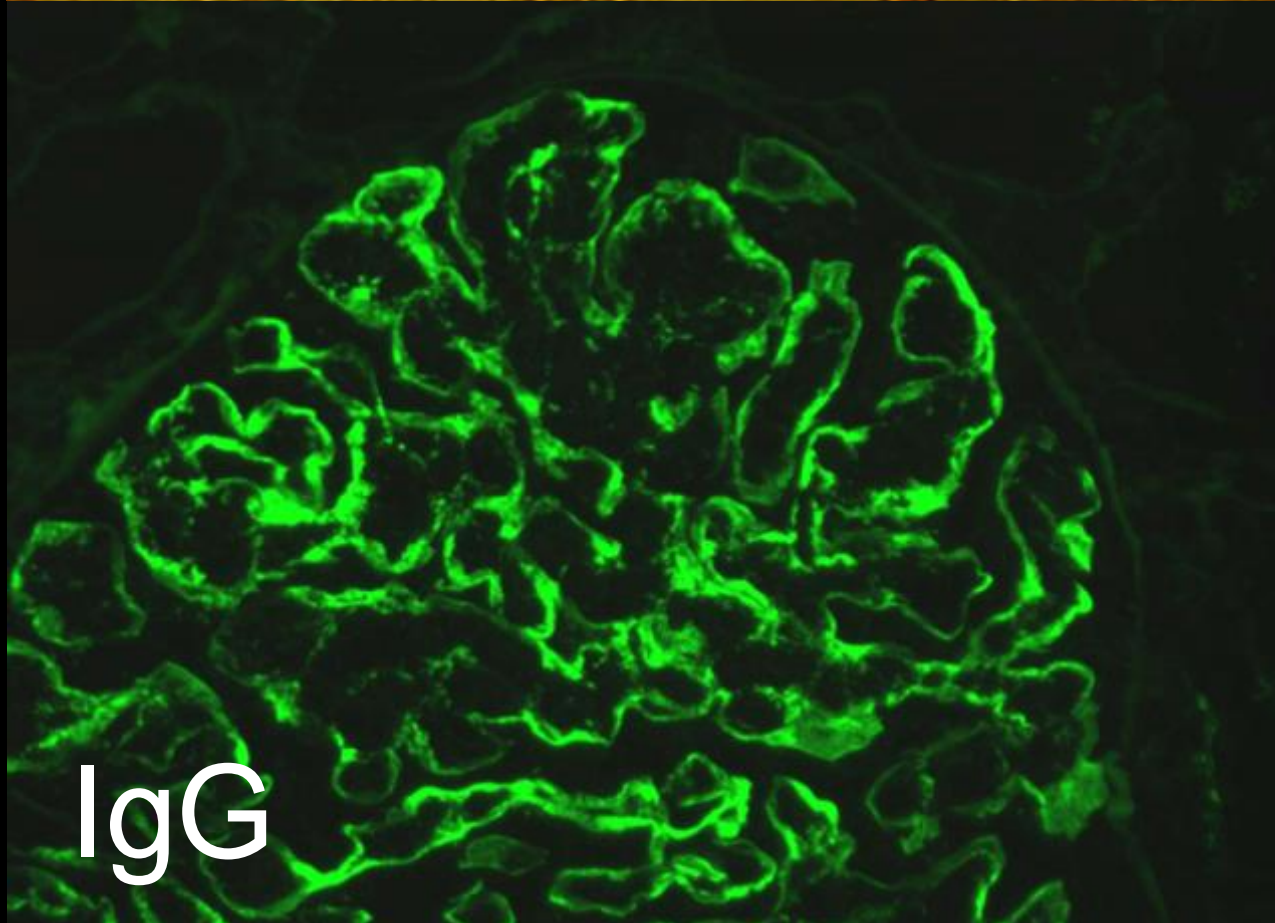
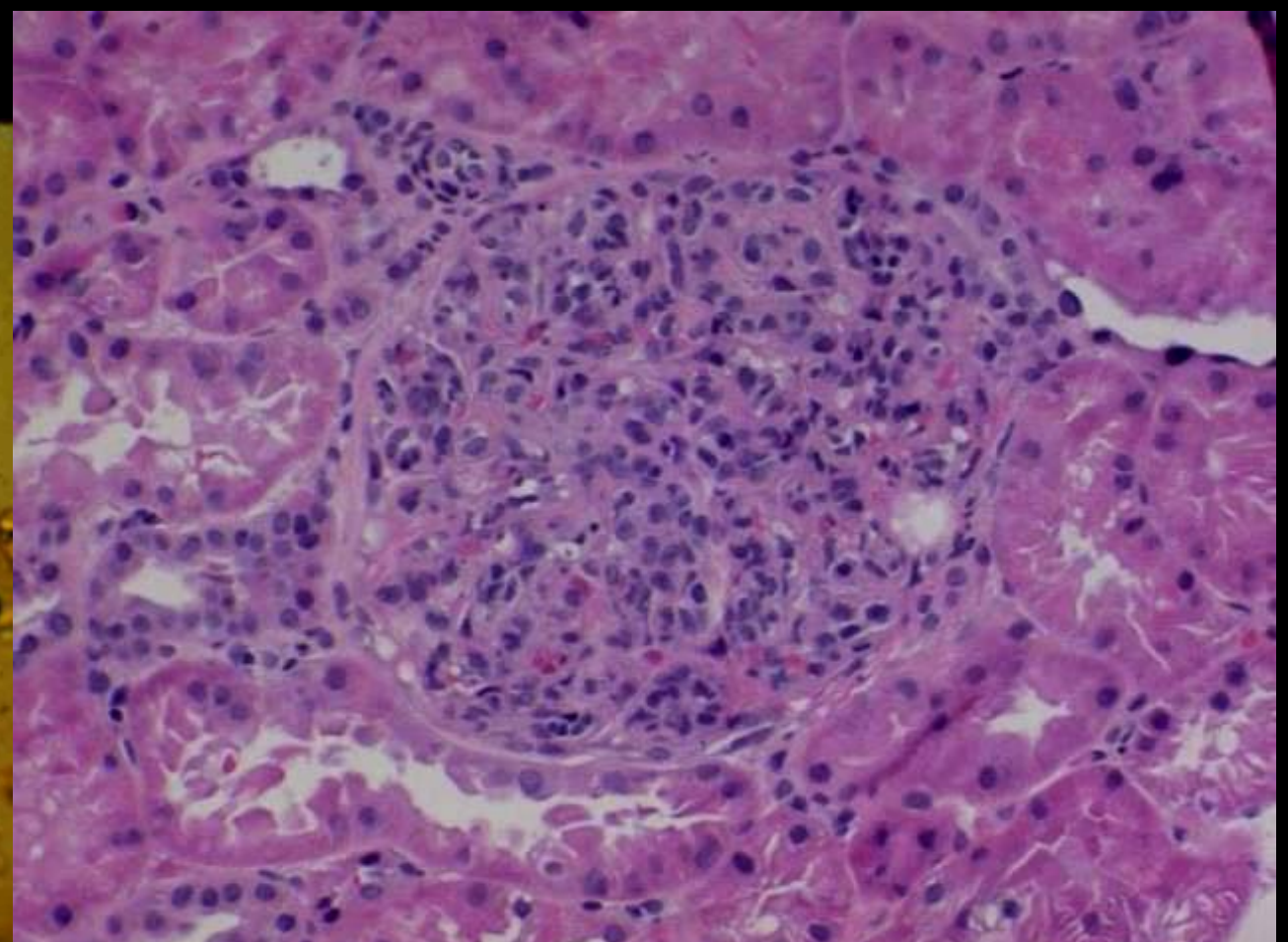


IgG

C3



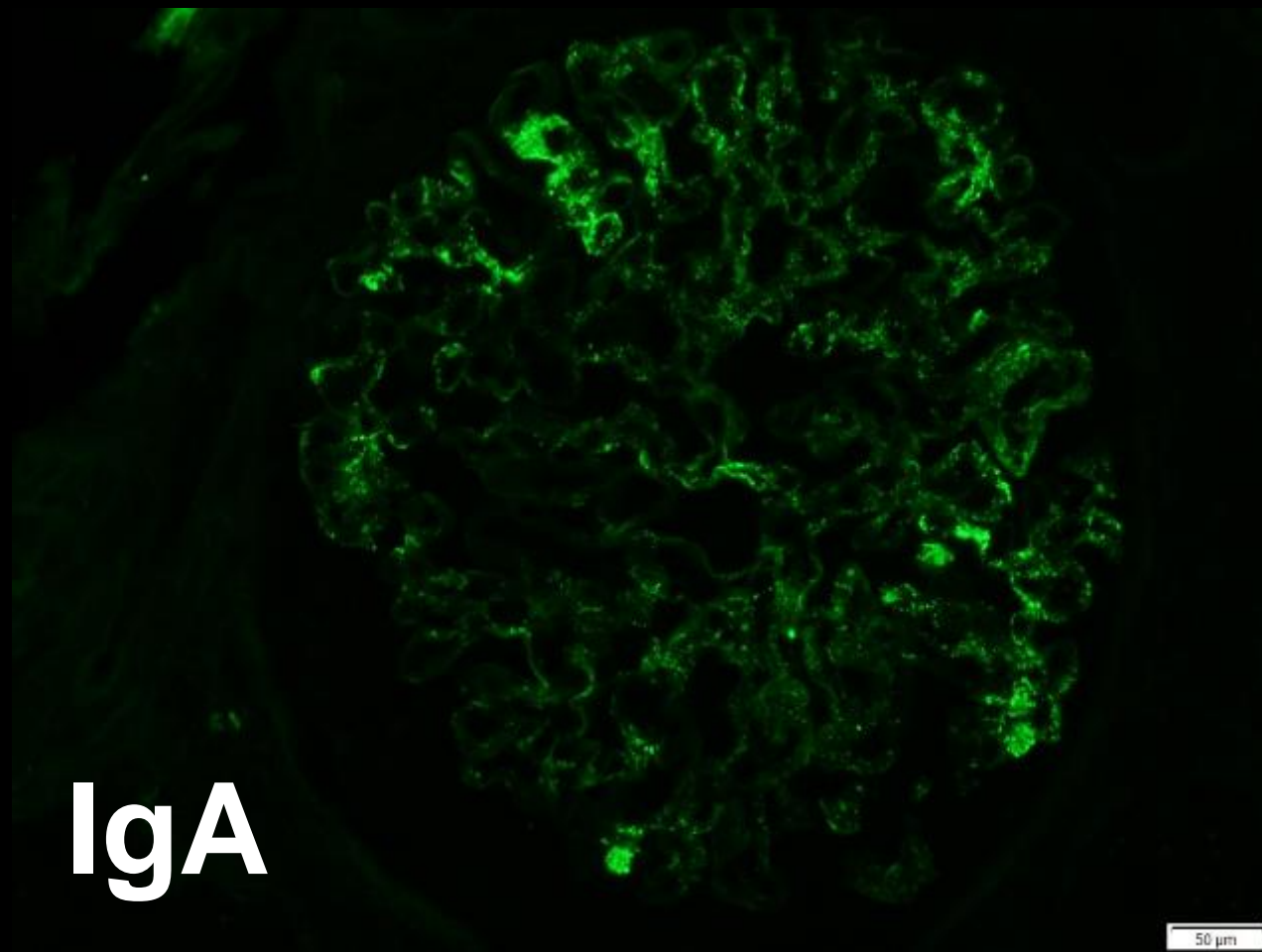
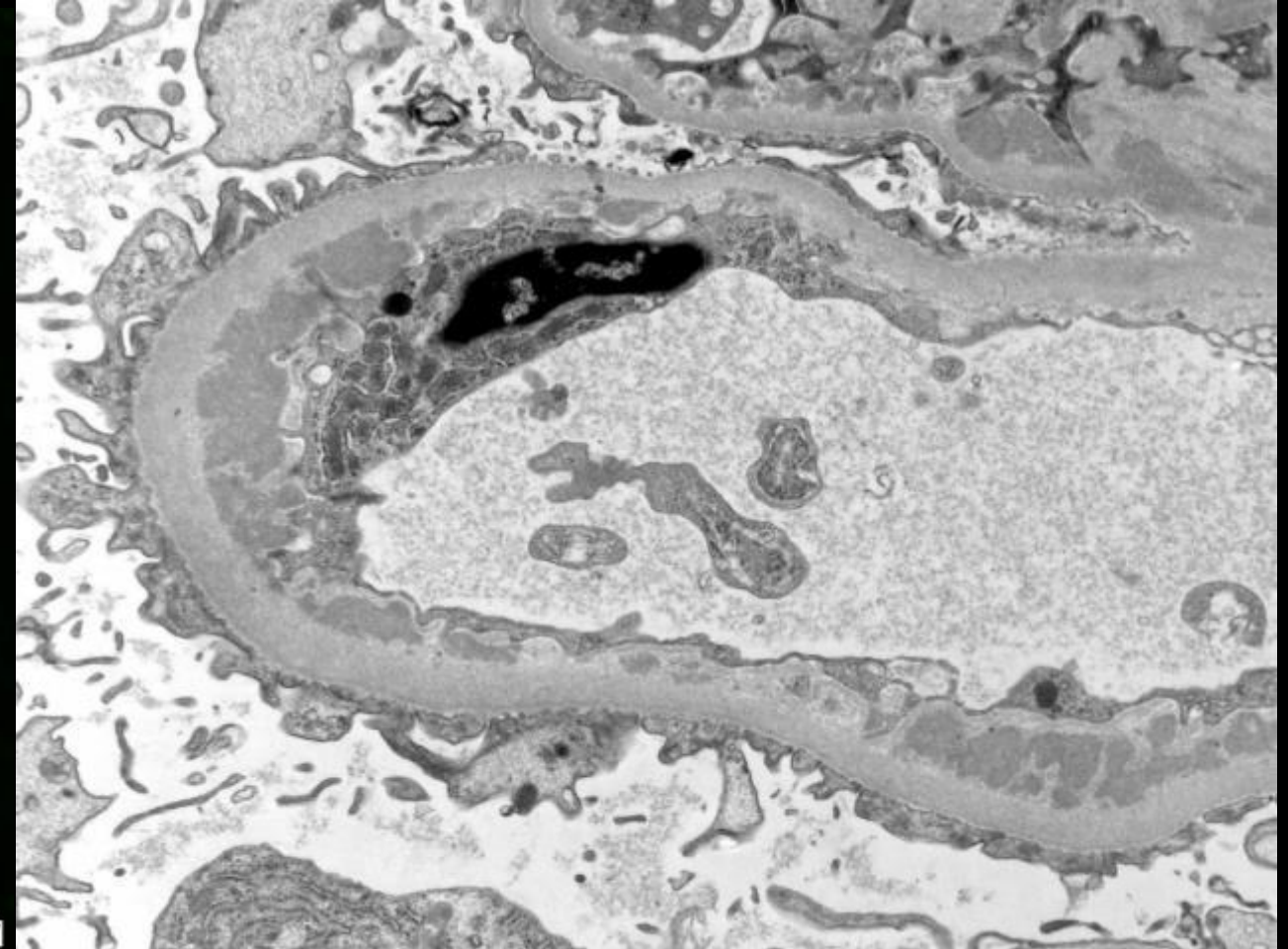
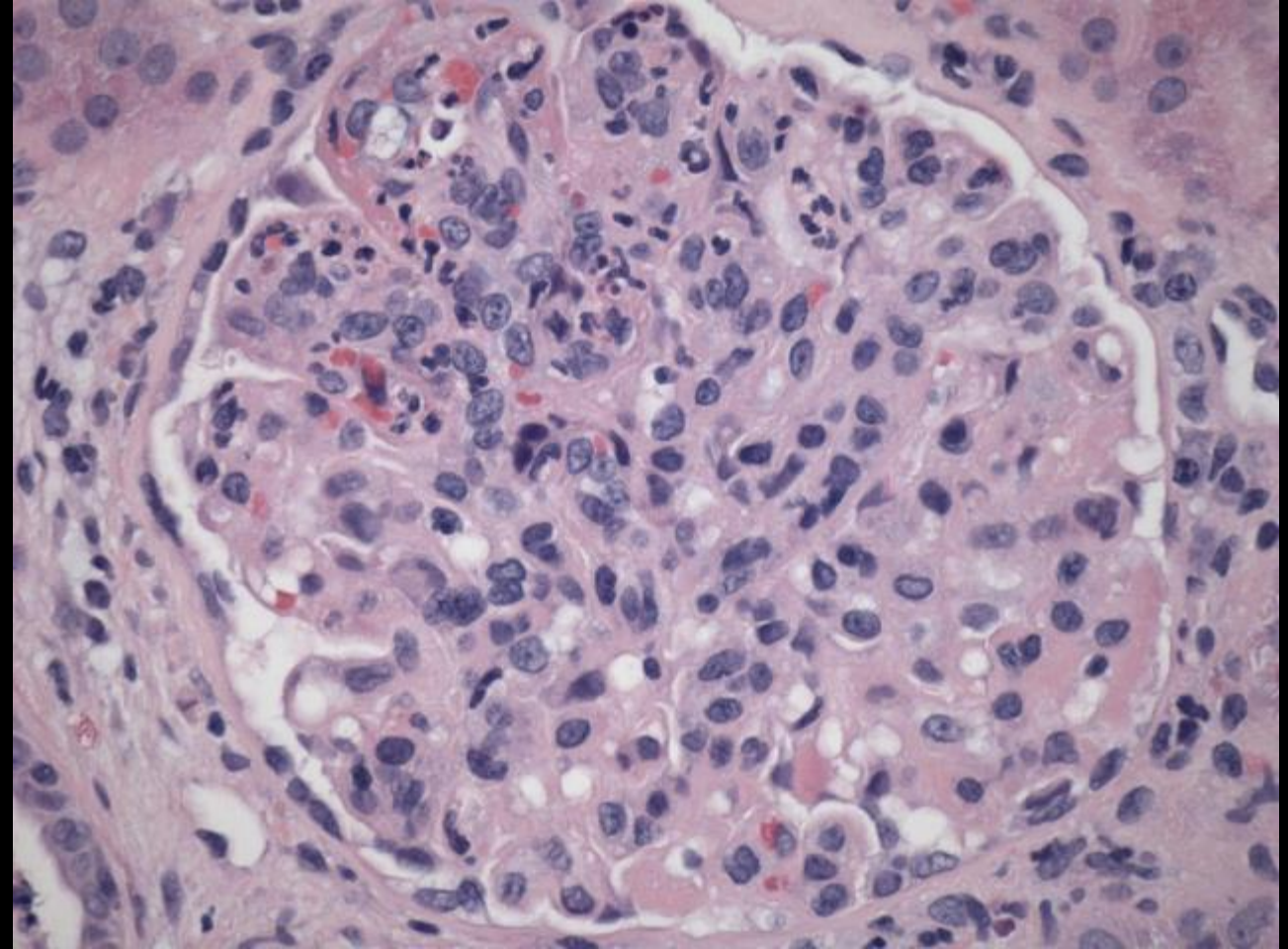
# **Strongyloides stercoralis**





## IgA-dominant infection-associated GN

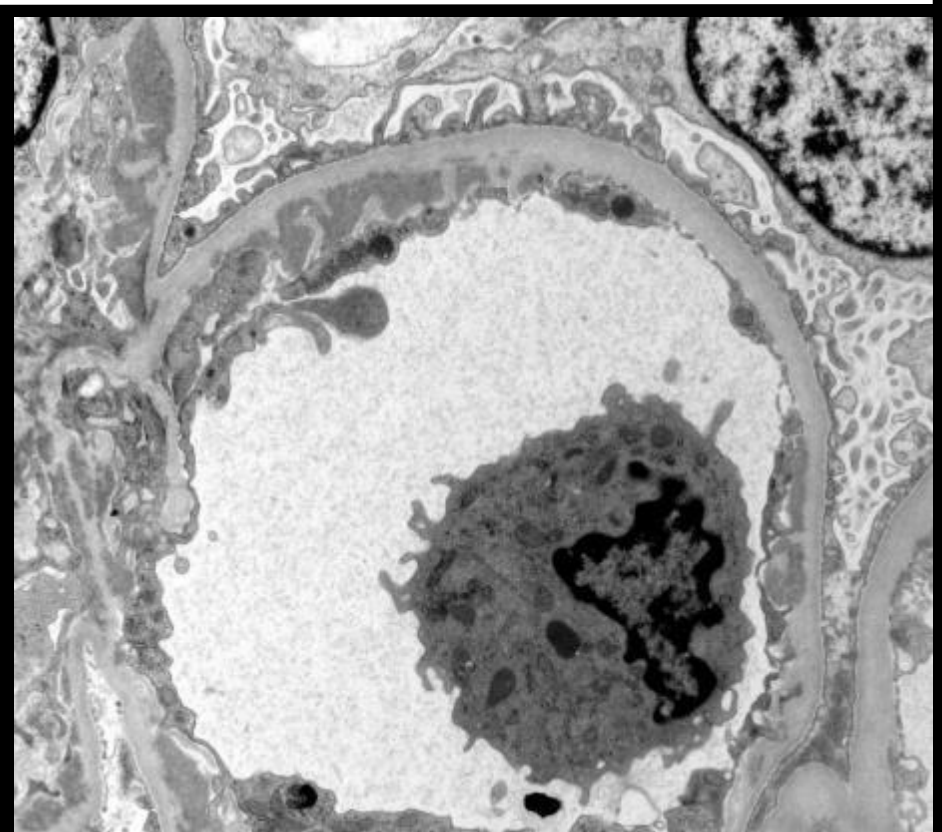
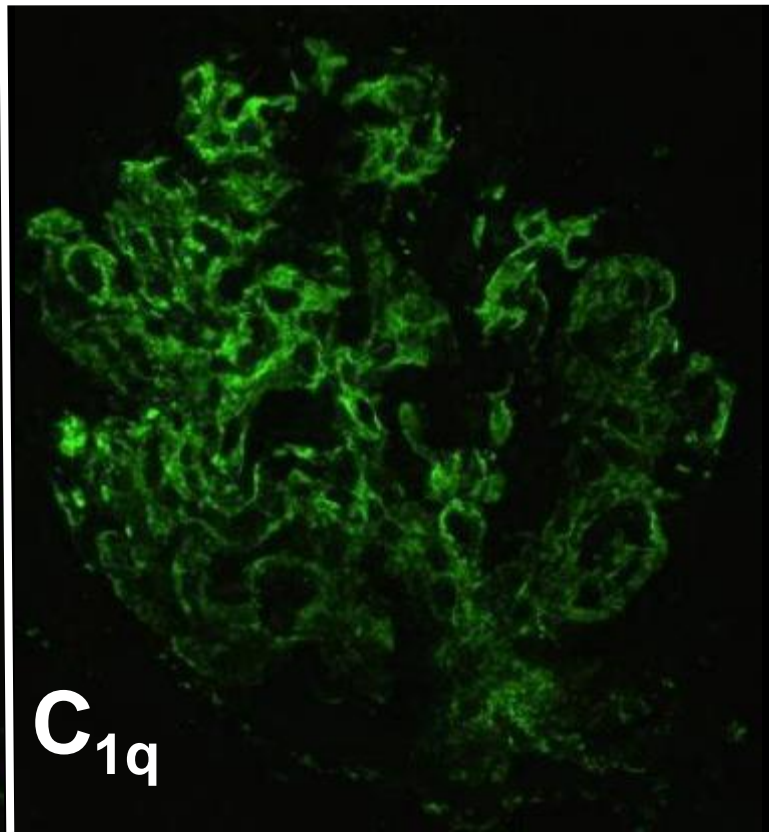
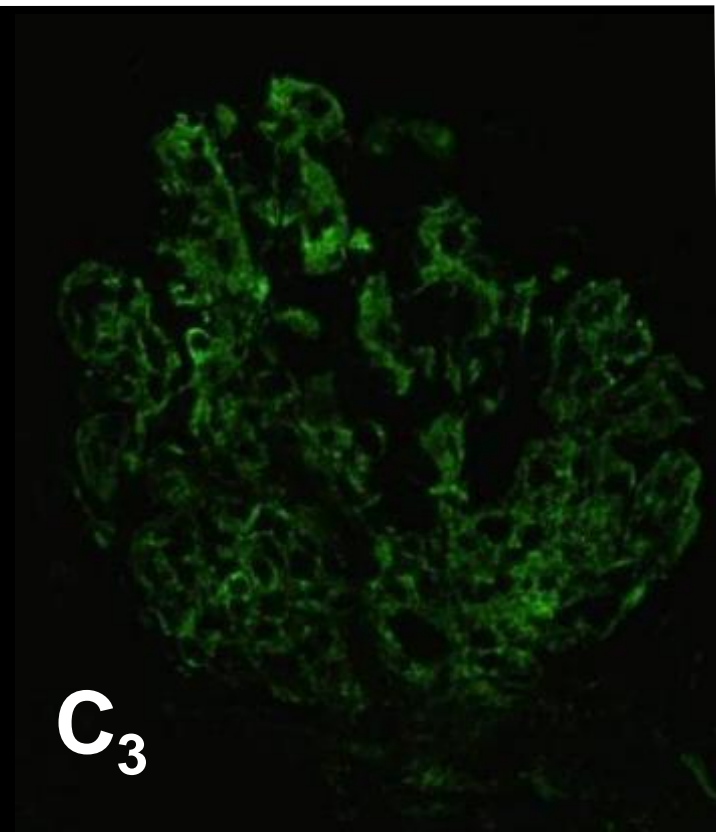
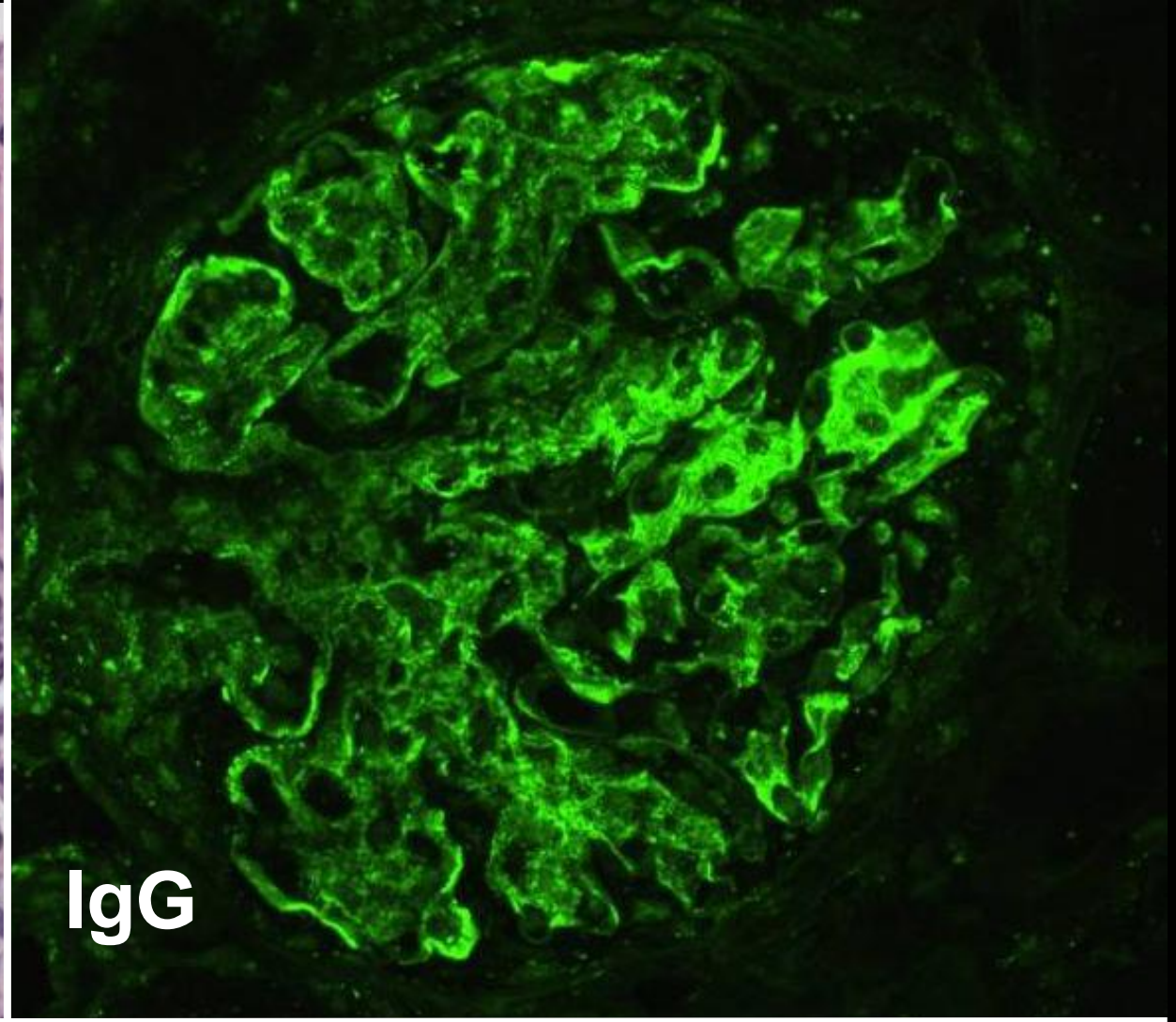
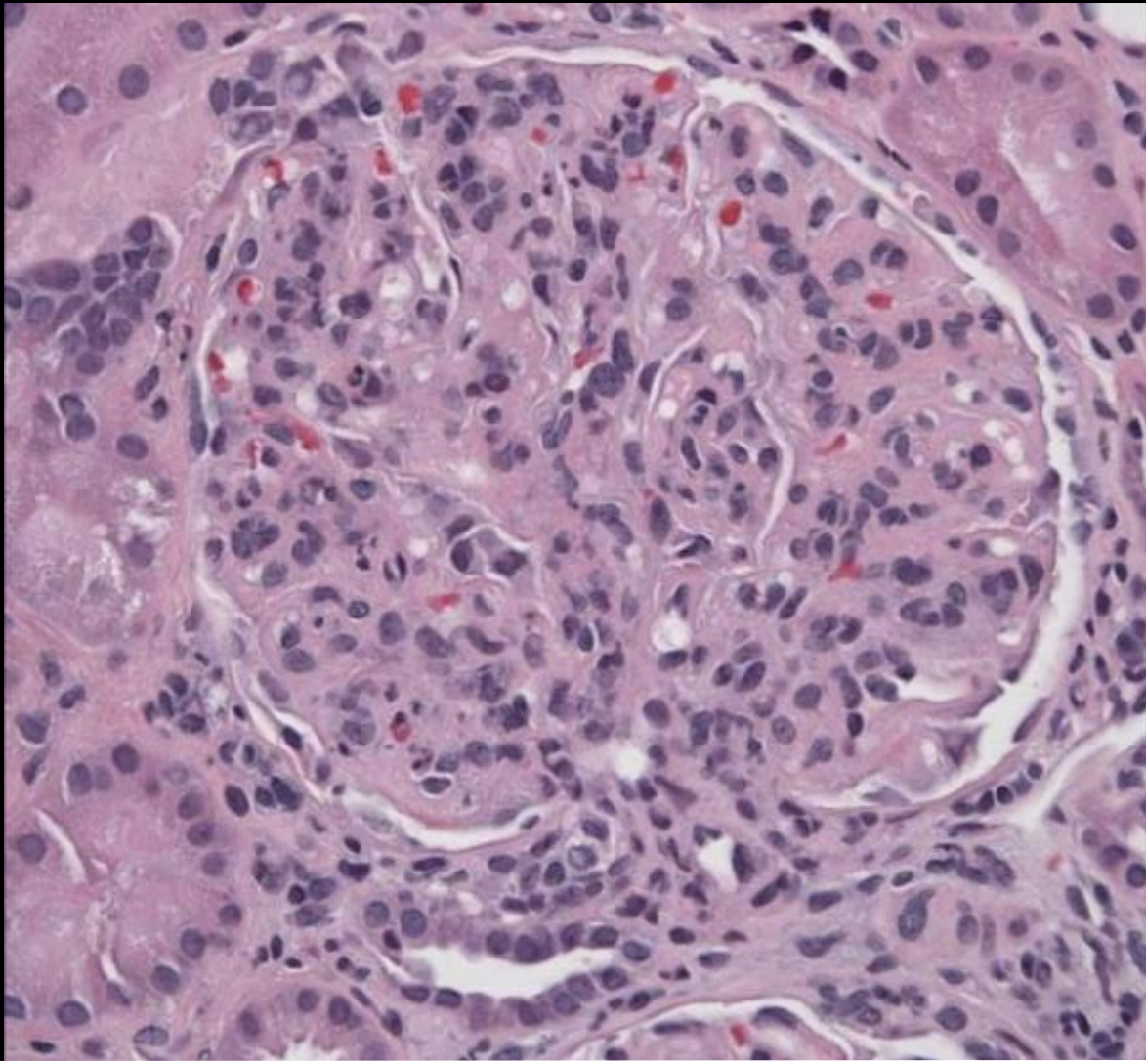
- Diabetic patient with foot ulcer/osteomyelitis
- Patient with polysubstance abuse with endocarditis
- Pneumonia and other respiratory tract infections
- Staphylococcus aureus (MRSA) is the most frequent causative agent
- GN with endocapillary hypercellularity, cellular crescents, subendothelial (mesangial)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



**IgA**



# Lupus Nephritis





# 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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# 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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# **THE MEMBRANOPROLIFERATIVE PATTERN OF INJURY**

## **STRUCTURAL CHANGES:**

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

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

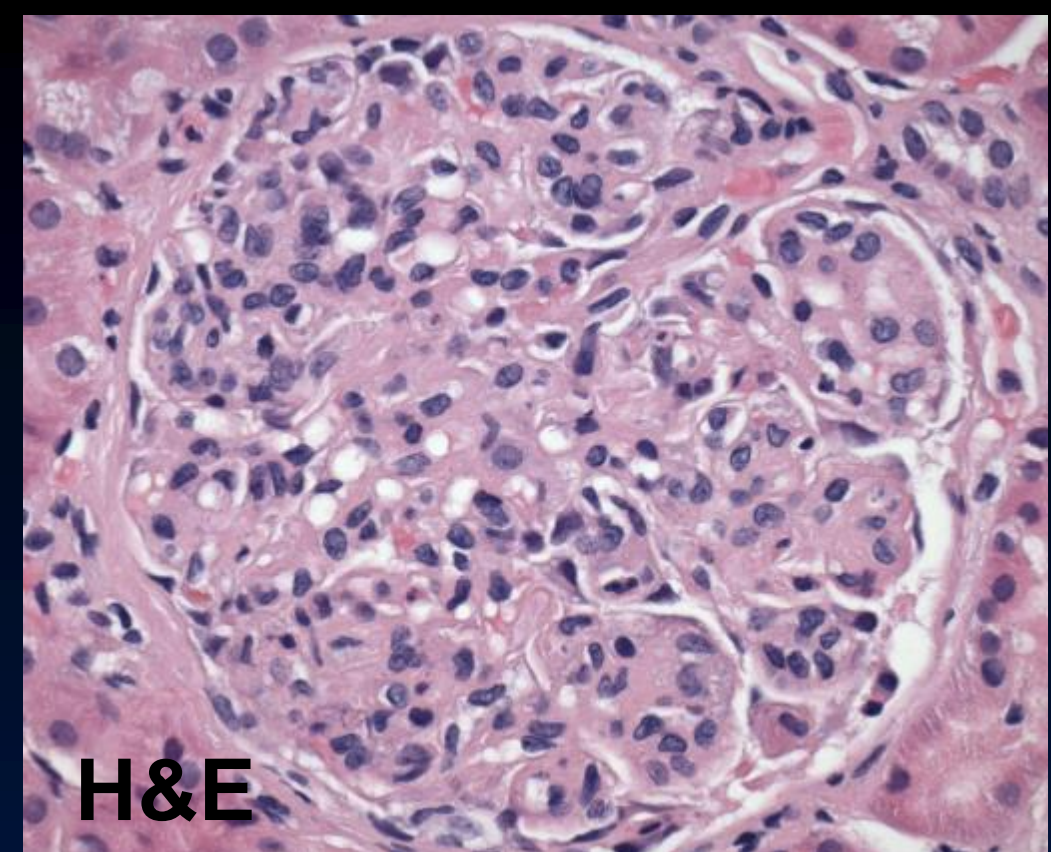
- **IMMUNE COMPLEX DISEASES**
- **ABNORMALITIES OF COMPLEMENT-  
REGULATORY PROTEINS**
- **THROMBOTIC ANGIOPATHIES**
- **(PARAPROTEIN) DEPOSITION DISEASE**

# THE MEMBRANOPROLIFERATIVE 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**



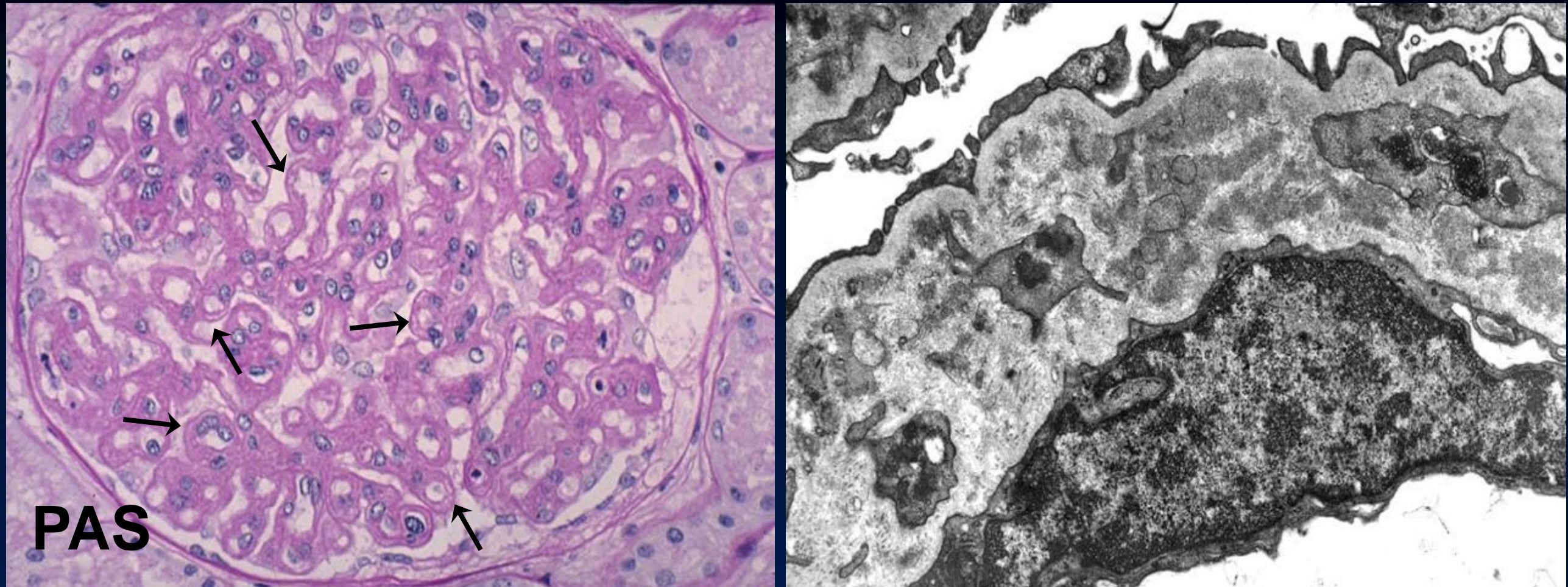
Remodeling of the capillary walls with duplication of the basement membrane, resulting in double contours



Silver methenamine



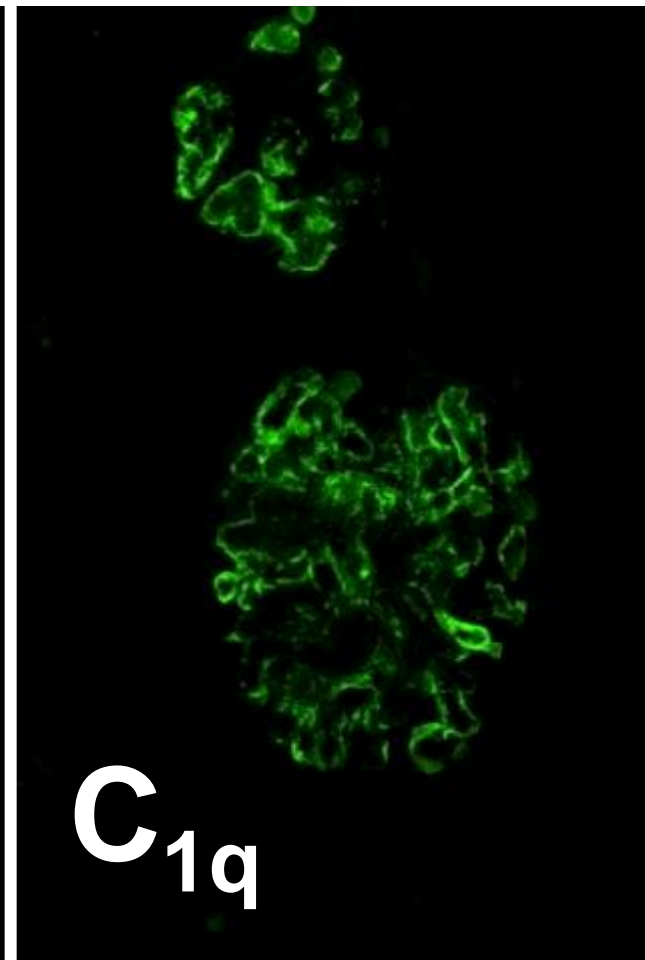
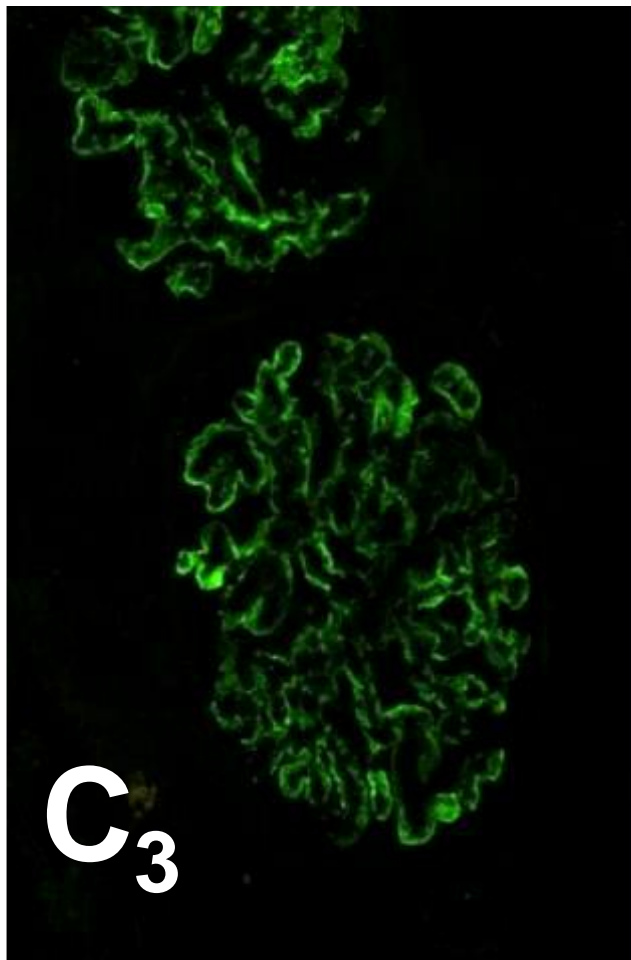
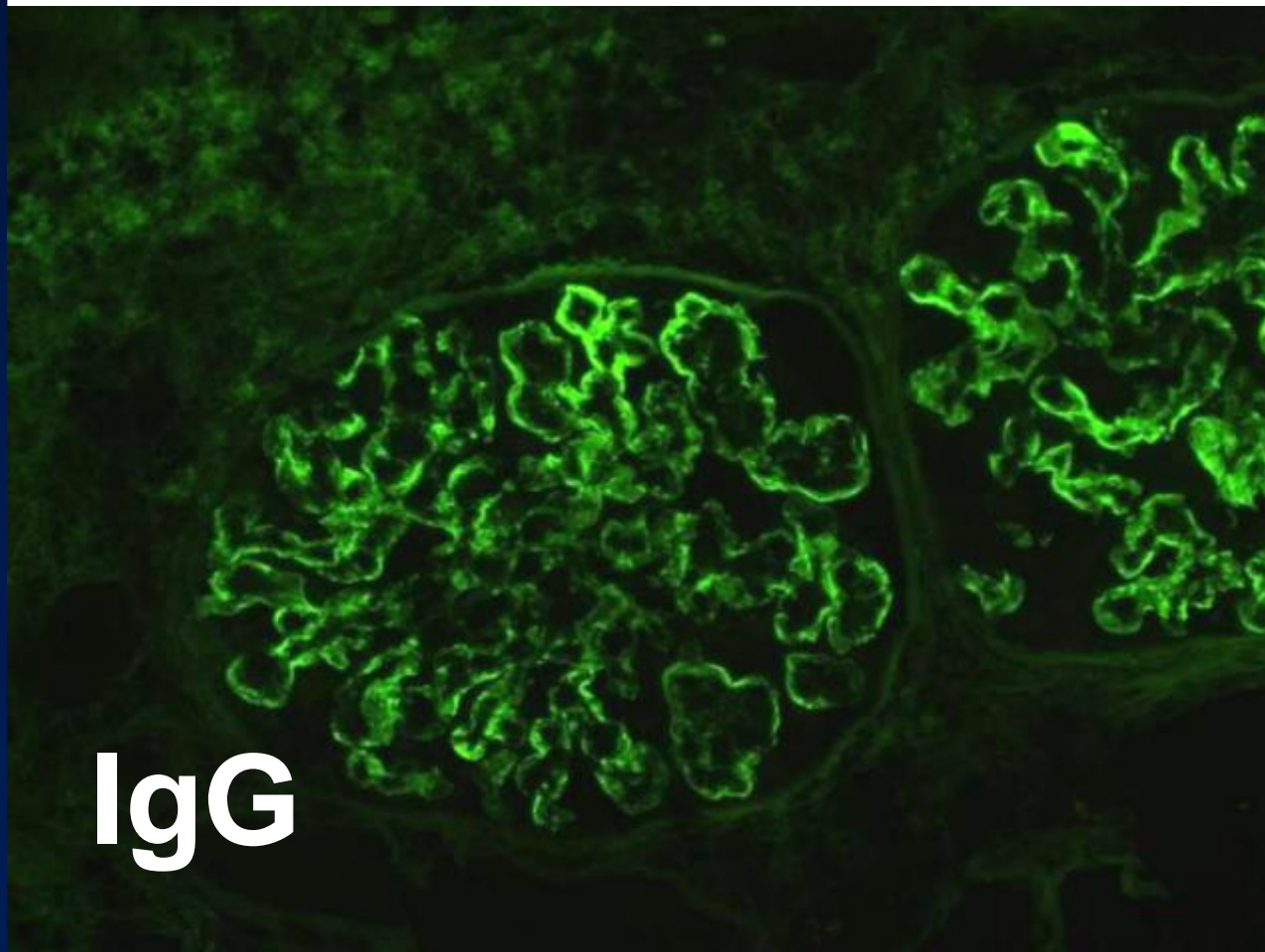
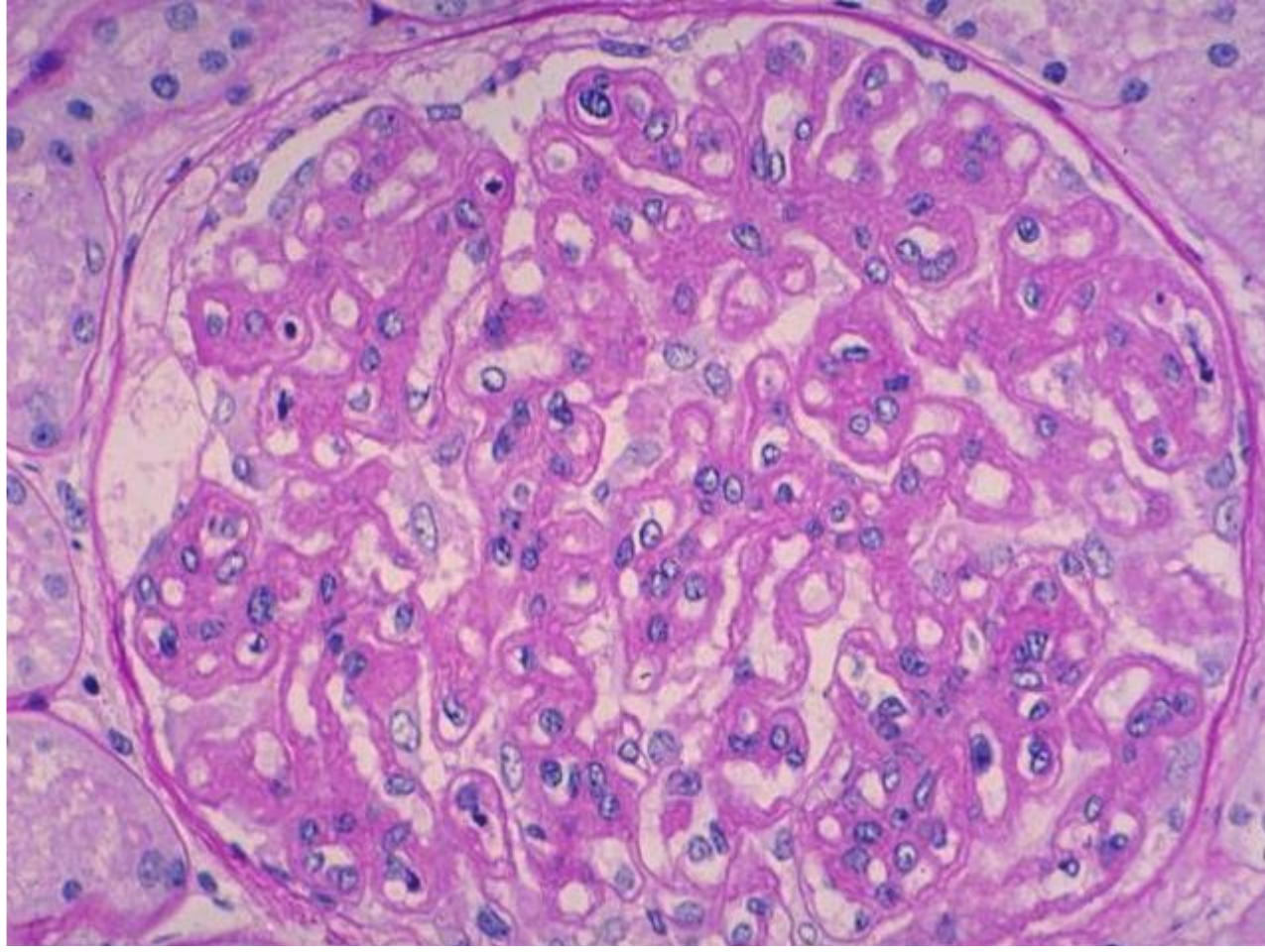
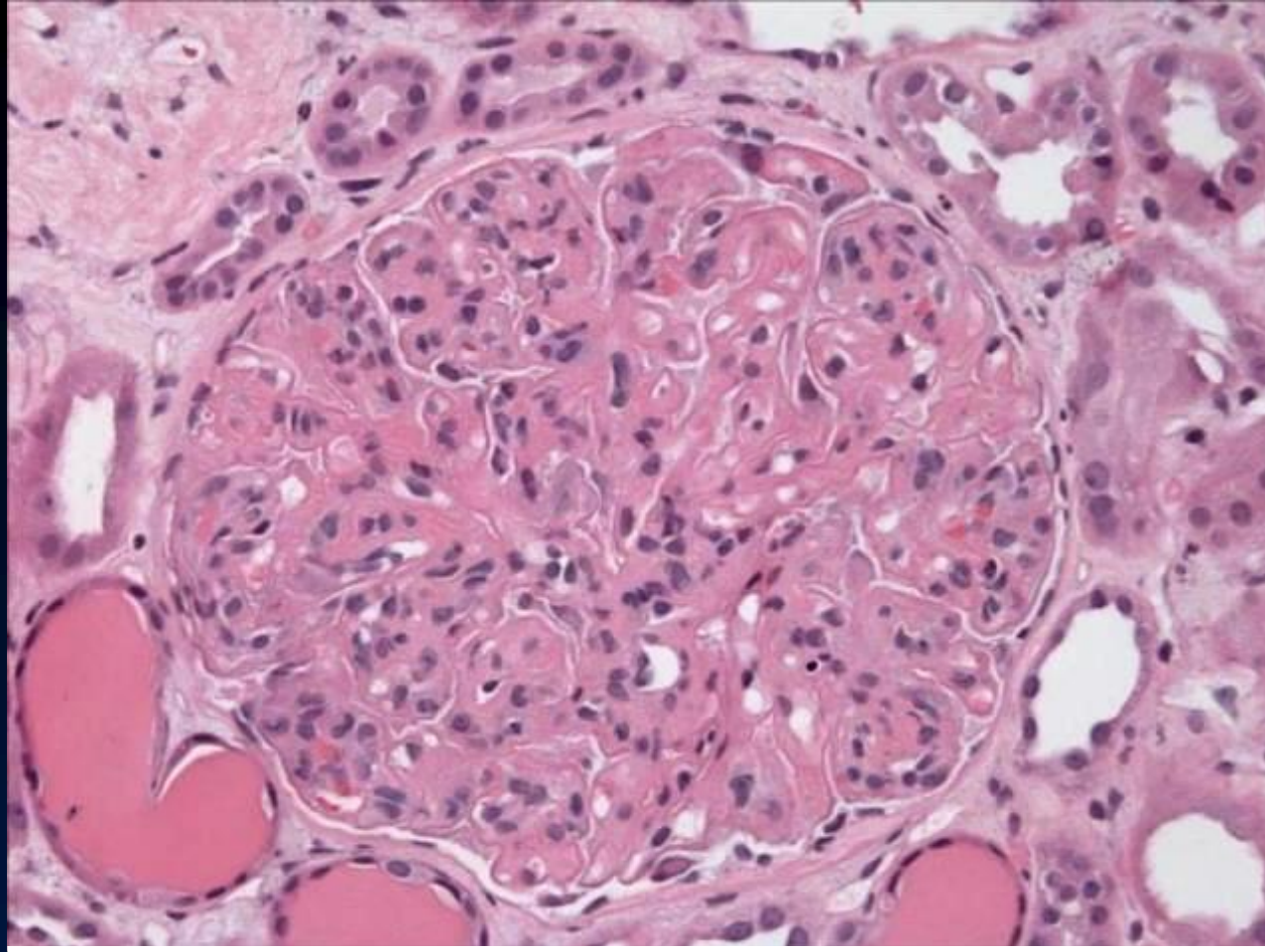
# THE ULTRASTRUCTURE OF THE DOUBLE CONTOUR



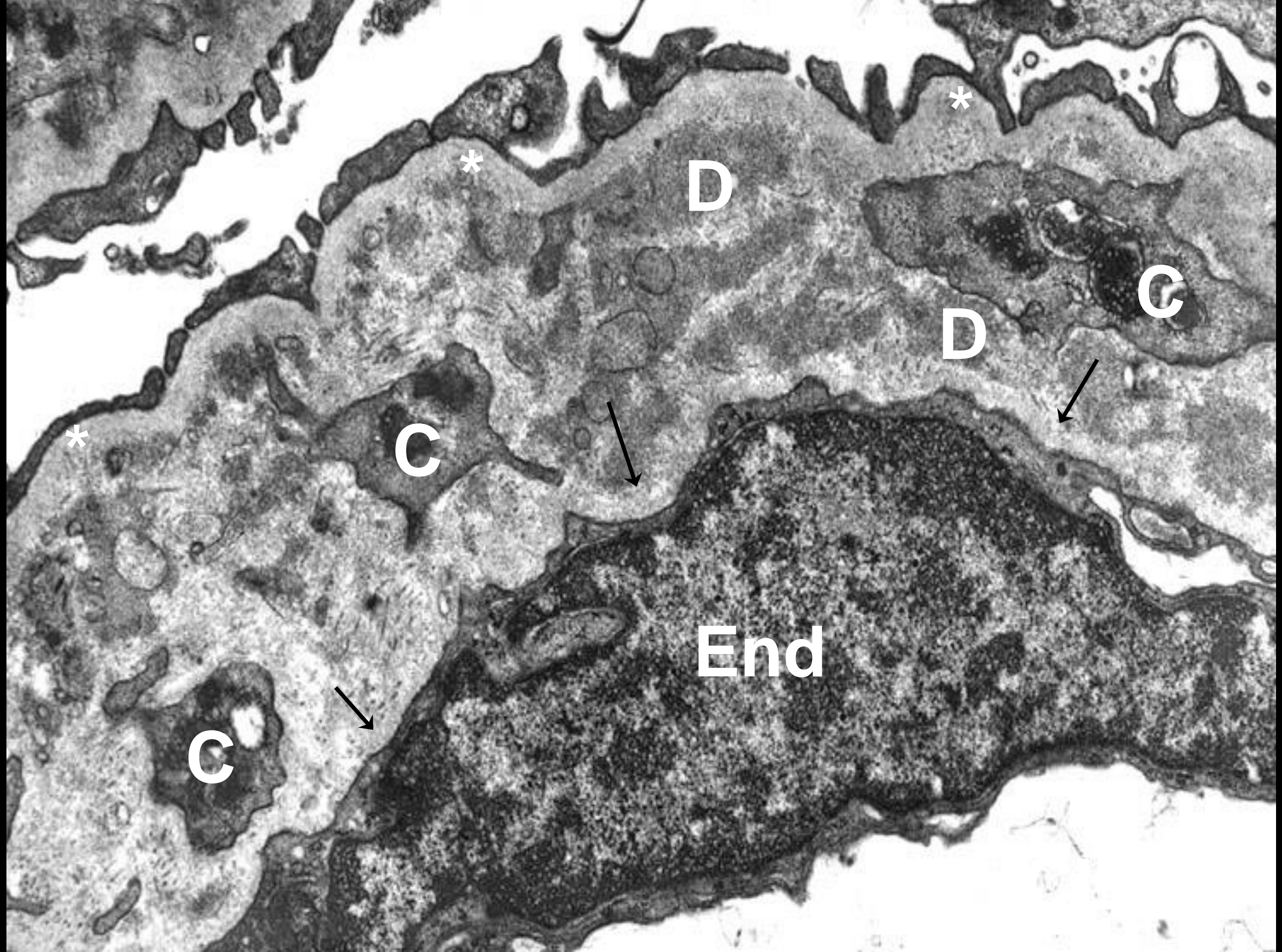
Expansion of the subendothelial space (by protein deposits and/or cell debris), interposition and entrapment of cell projections (inflammatory cells and endothelial cells), and formation of a new basement membrane by the displaced endothelium.



# Immune Complex-mediated GN

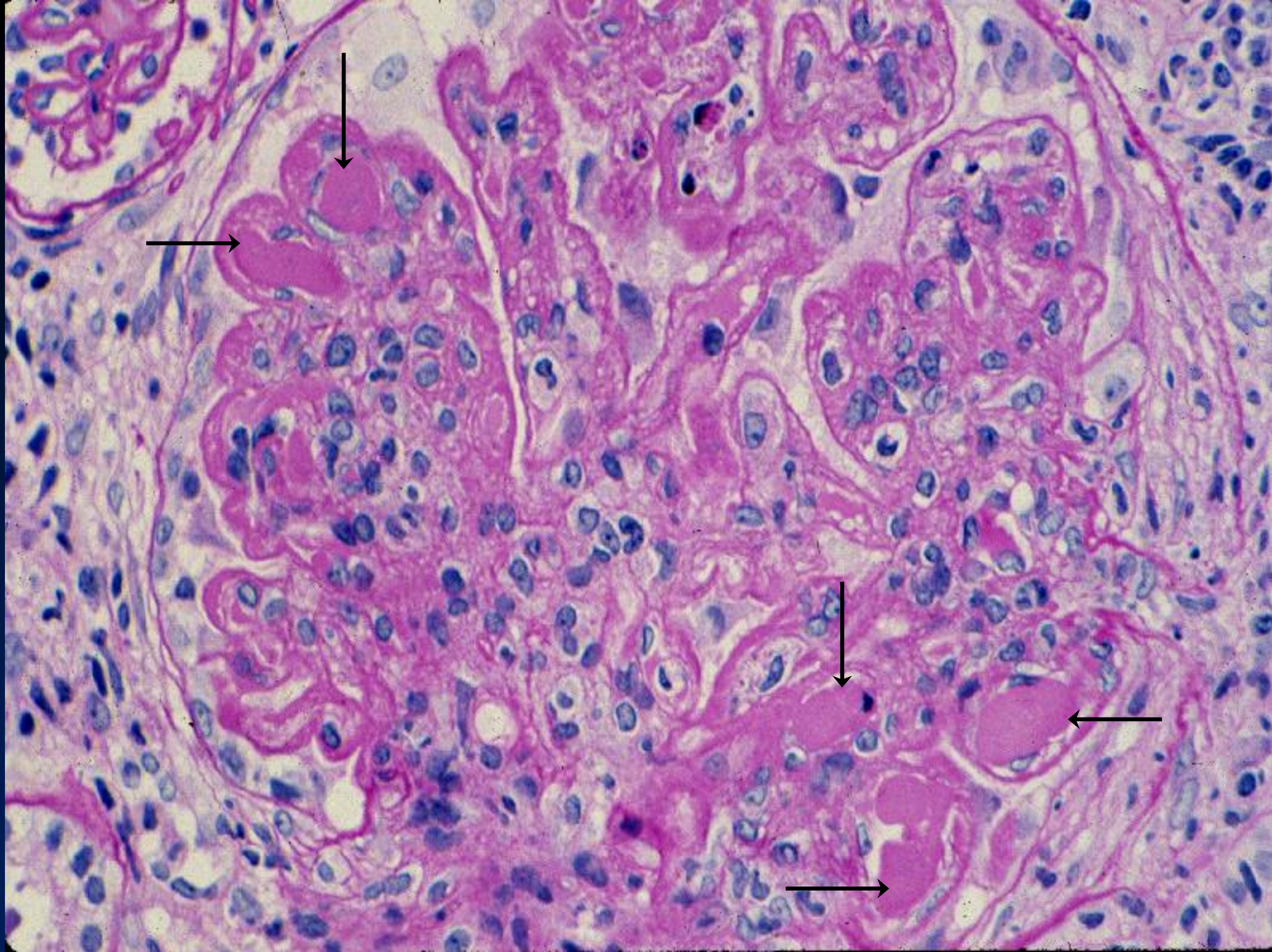






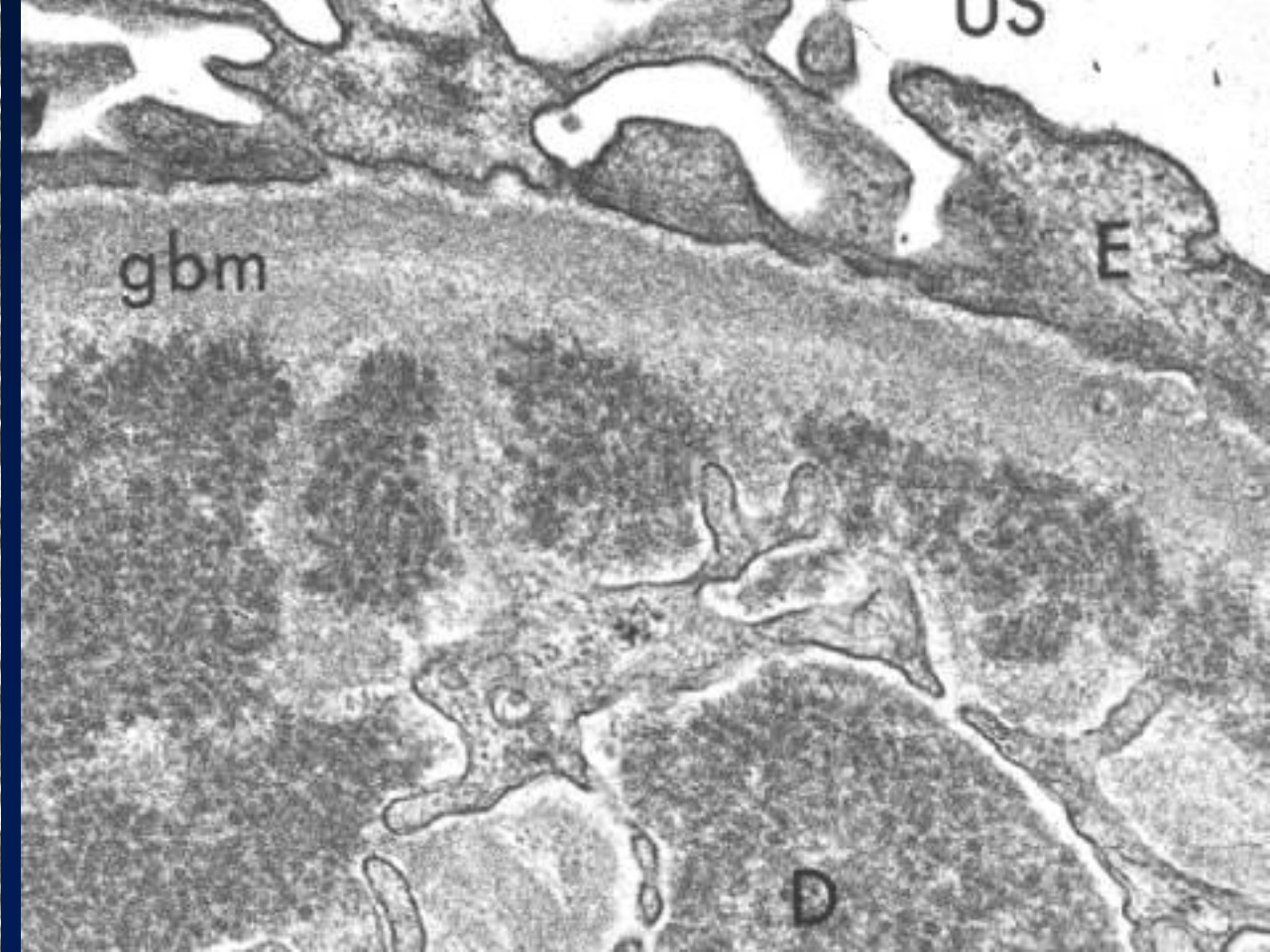
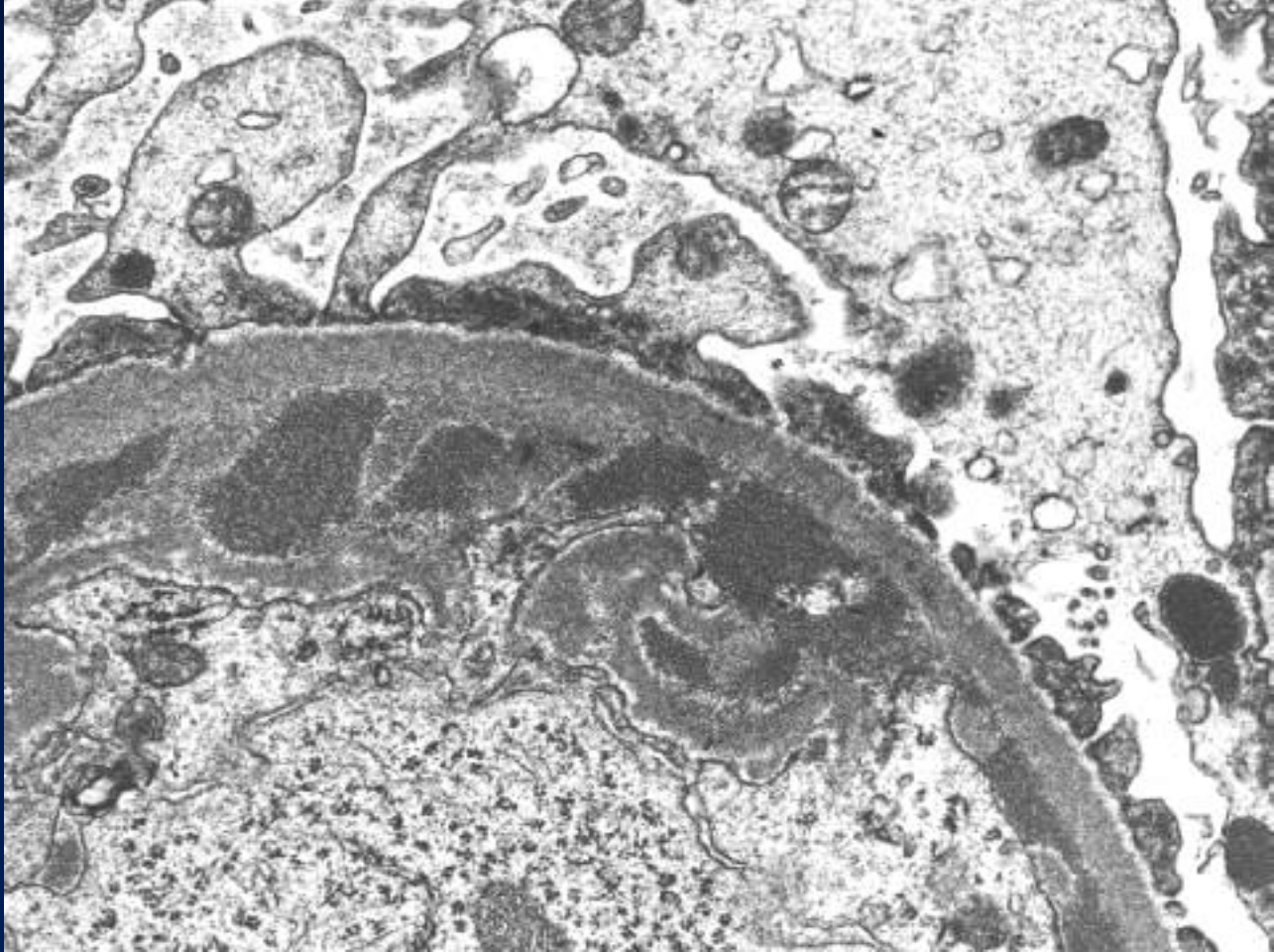
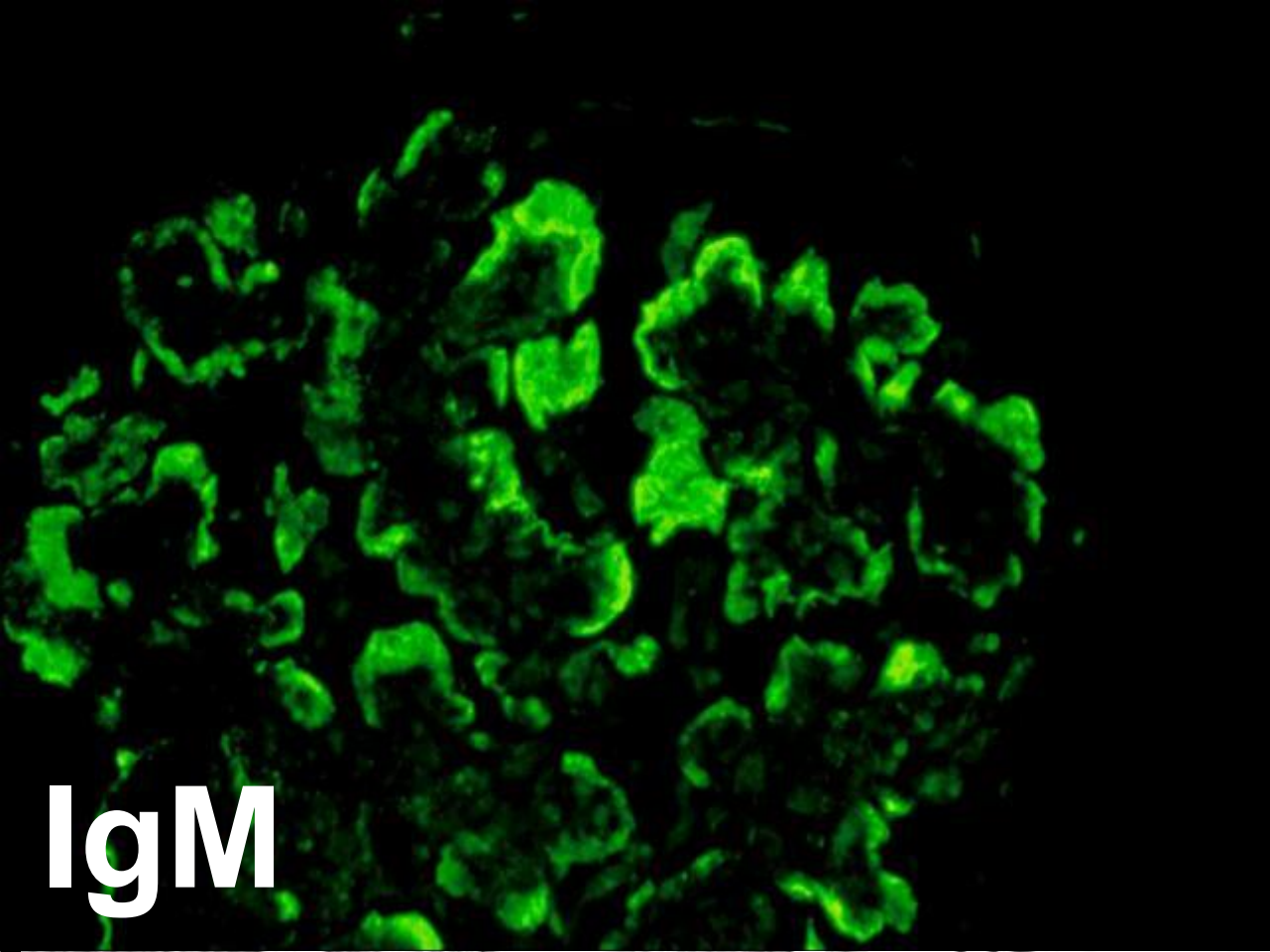
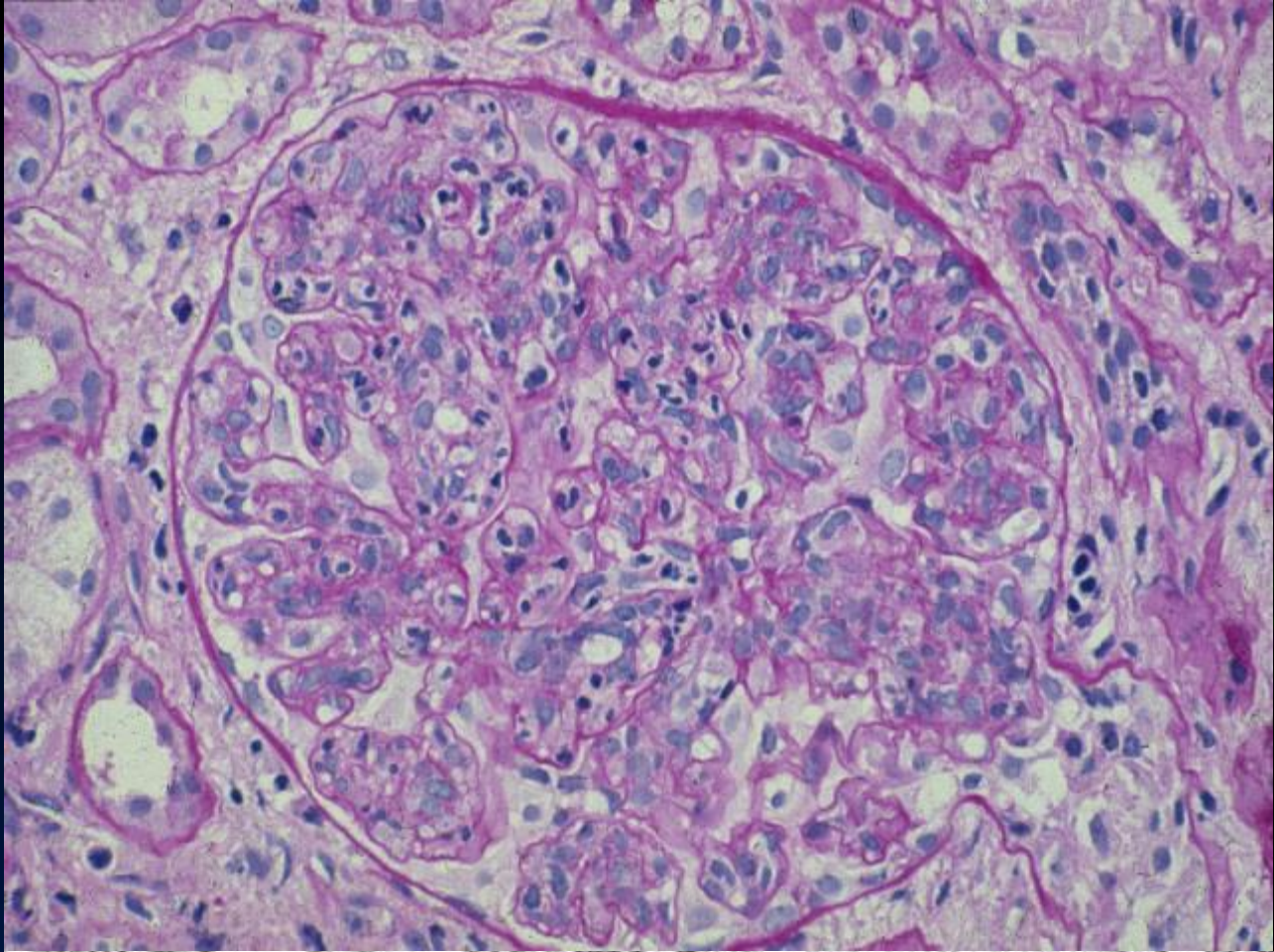


## HepC-associated Cryoglobulinemia



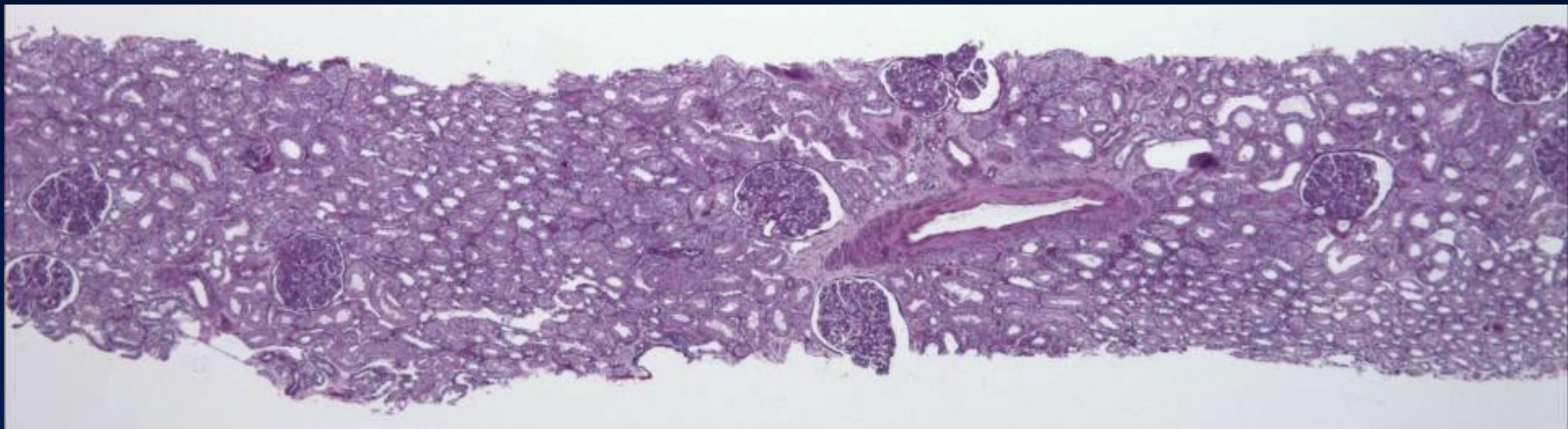


# HepC-associated acute GN



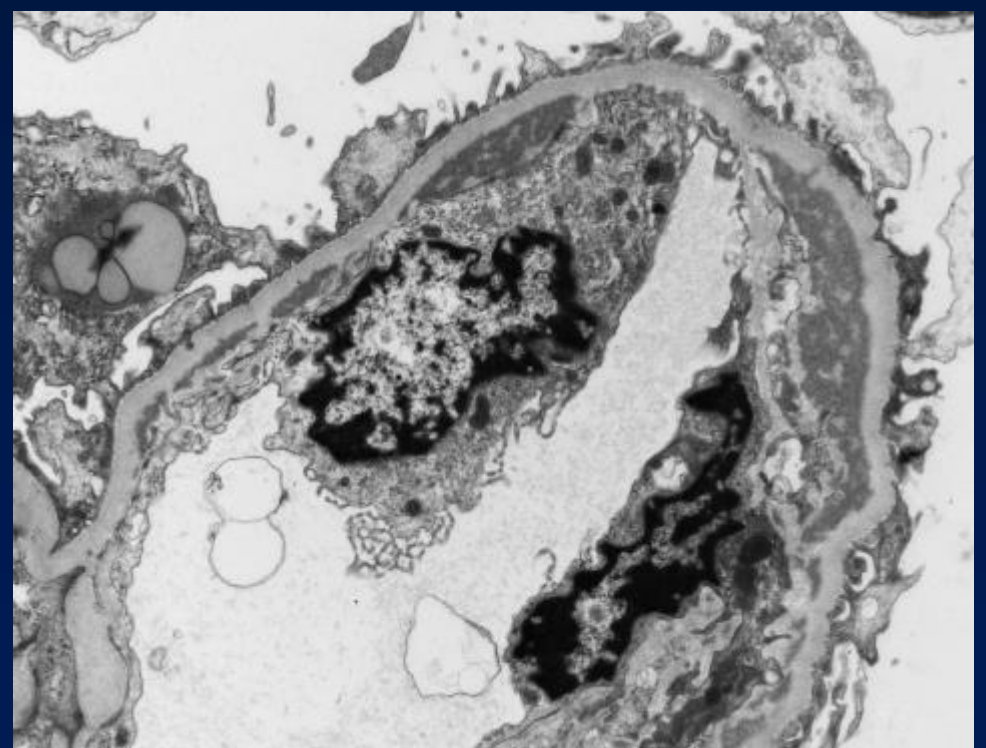
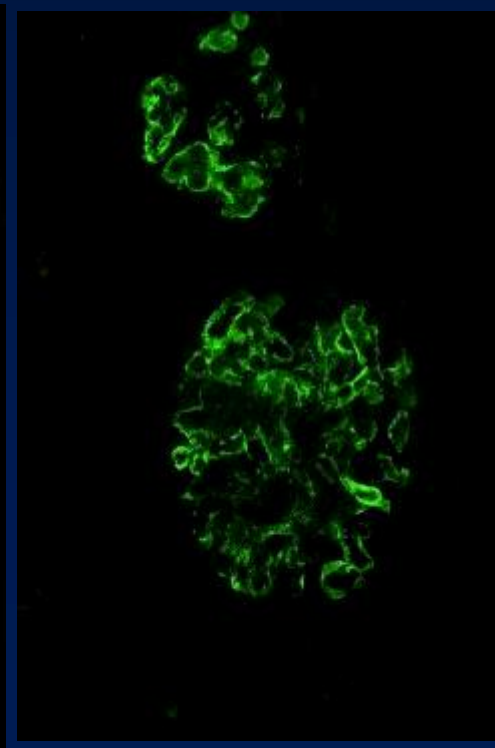
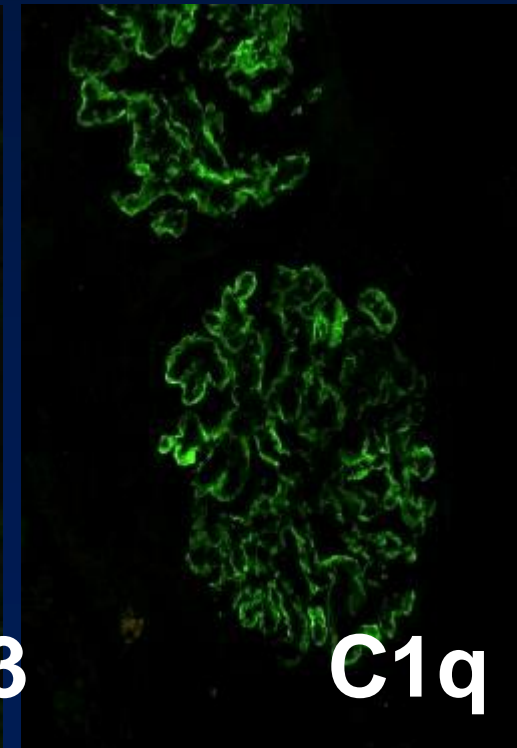
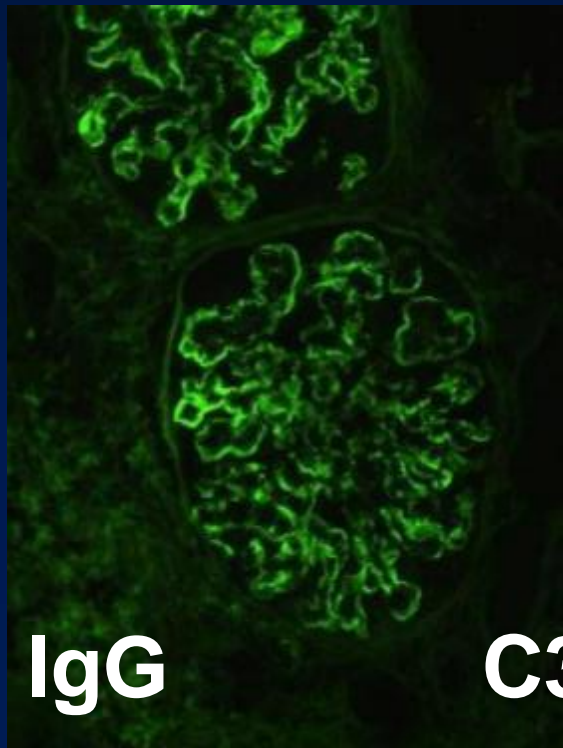
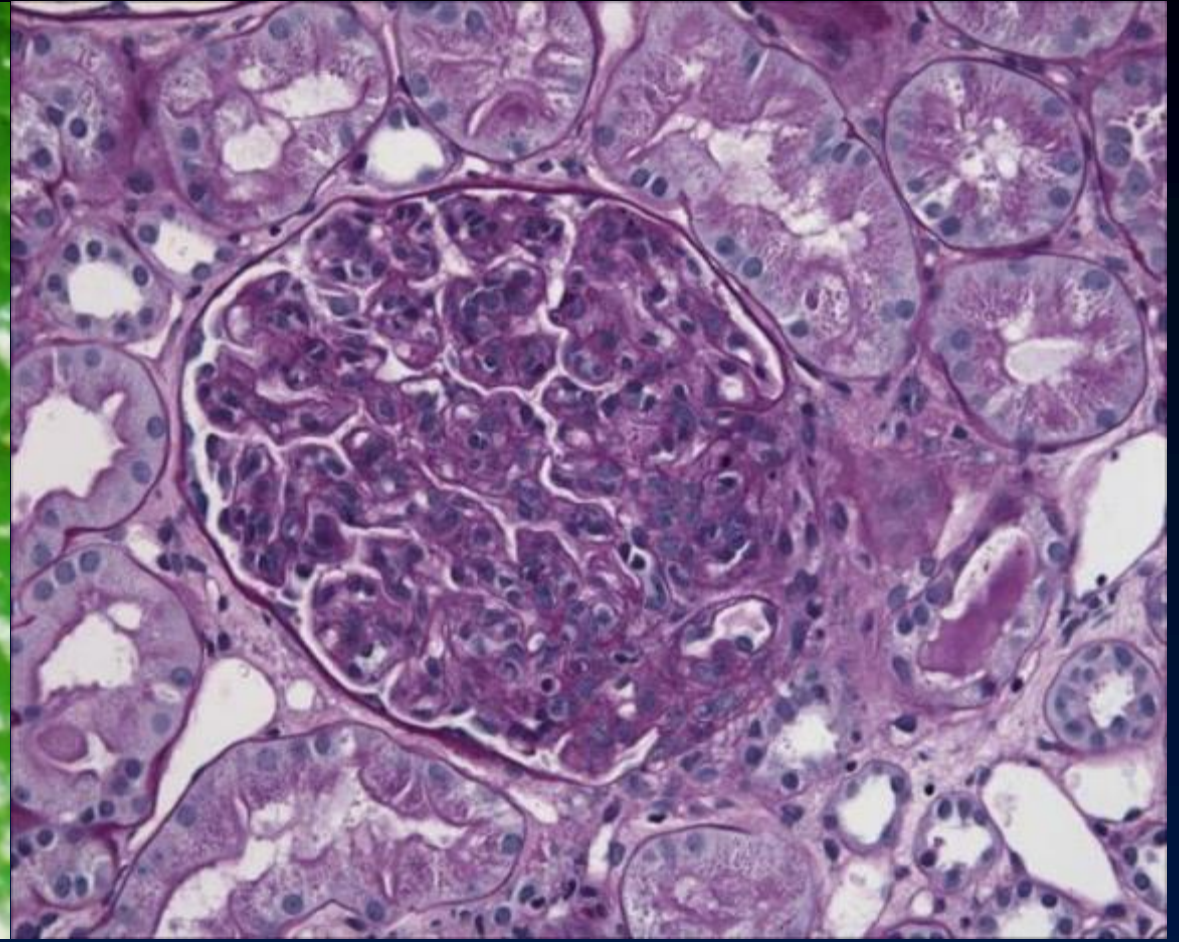


**57-year-old woman with recently-diagnosed myocarditis due to Lyme disease presents now with hematuria and proteinuria; her serum creatinine peaked at 1.5 (baseline 1)**





# Lyme Disease-associated MPGN





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

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Strongyloides stercoralis, other parasites

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

# **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:

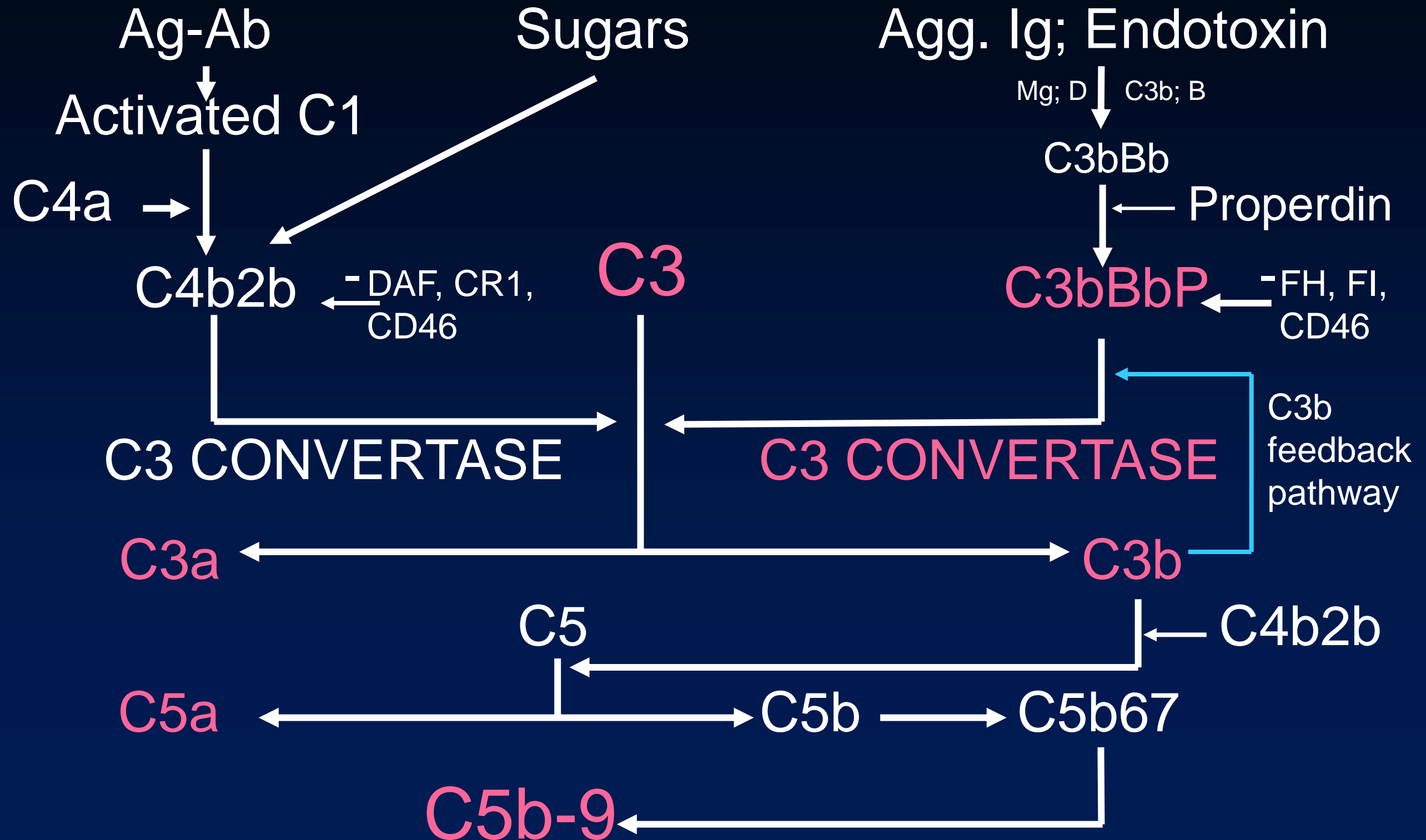
- 
- Spectrum of diseases
- Dense Deposit Disease (DDD)  
(MPGN type II)
  - Glomerulonephritis C3 (GN-C3)
  - Atypical HUS (d-HUS)

# ACTIVATION OF THE COMPLEMENT SYSTEM

VIA: CLASSIC

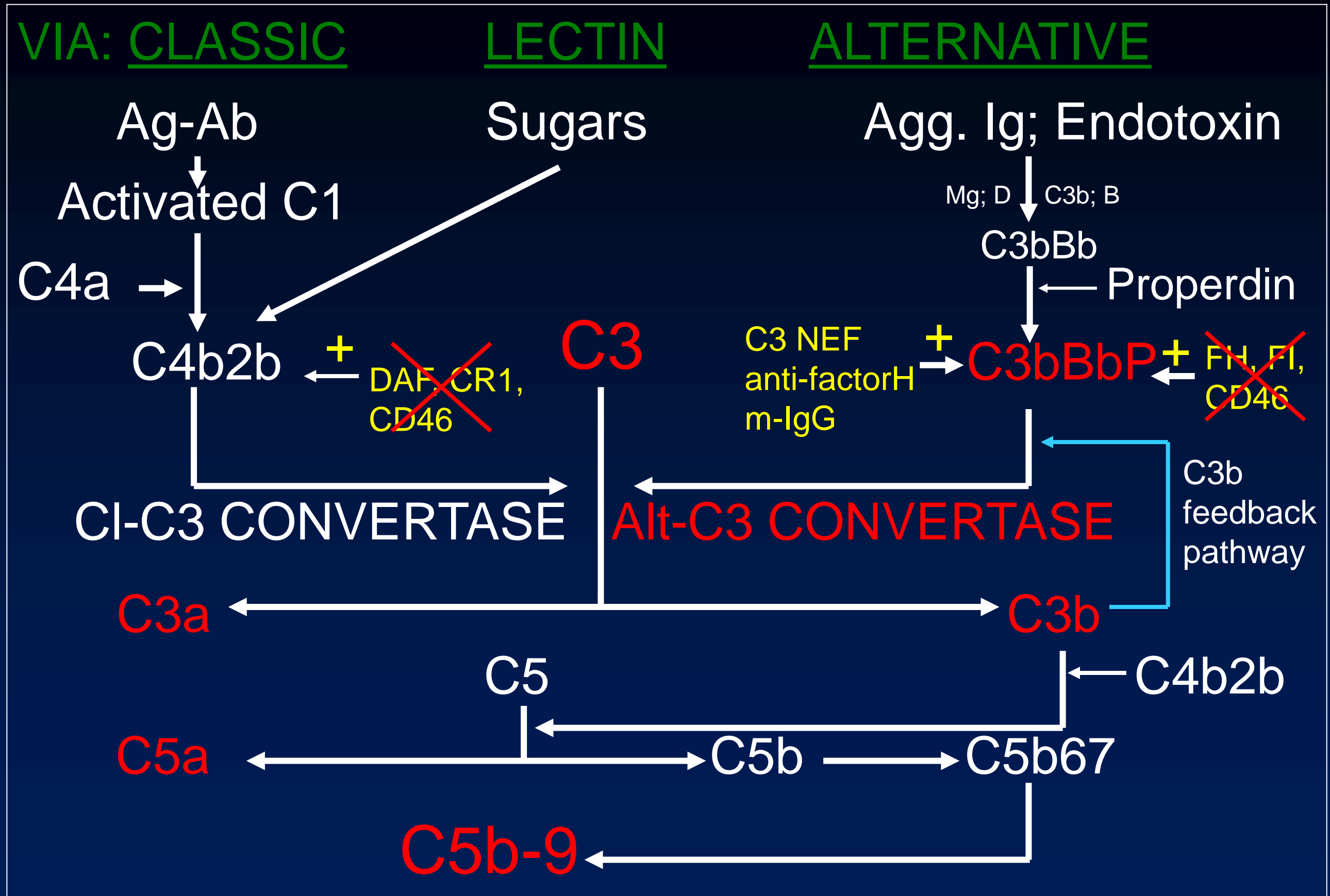
LECTIN

ALTERNATIVE

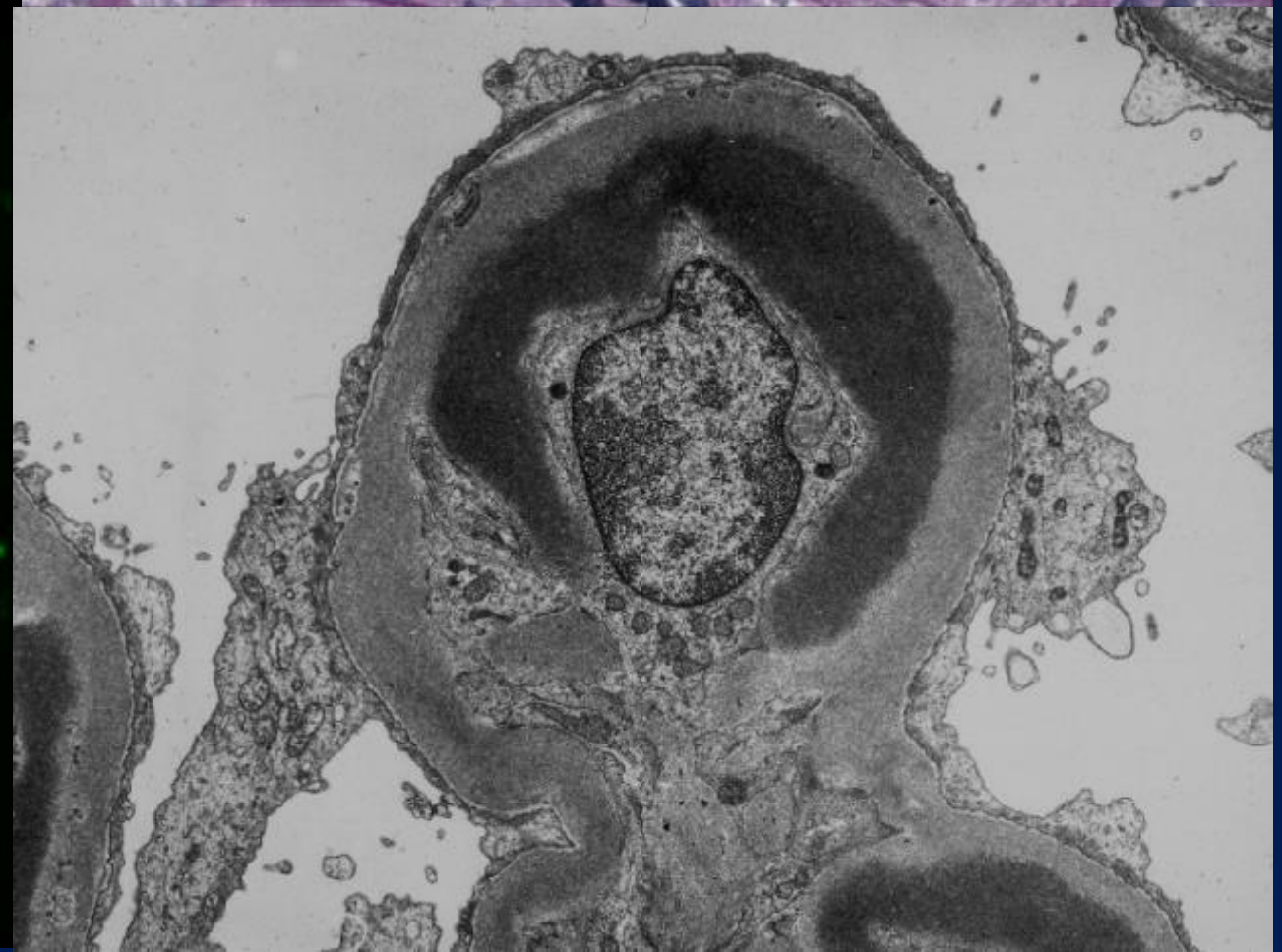
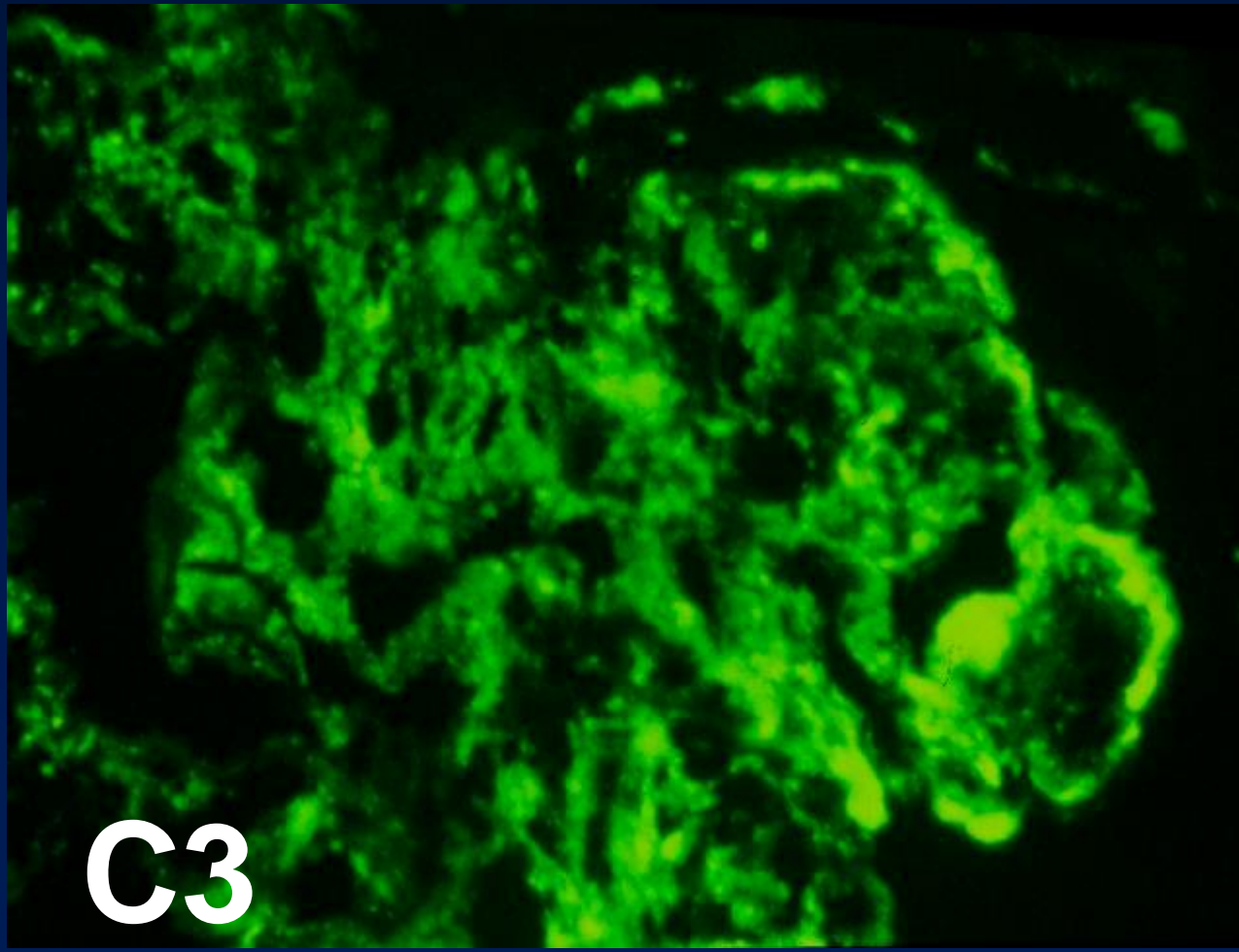
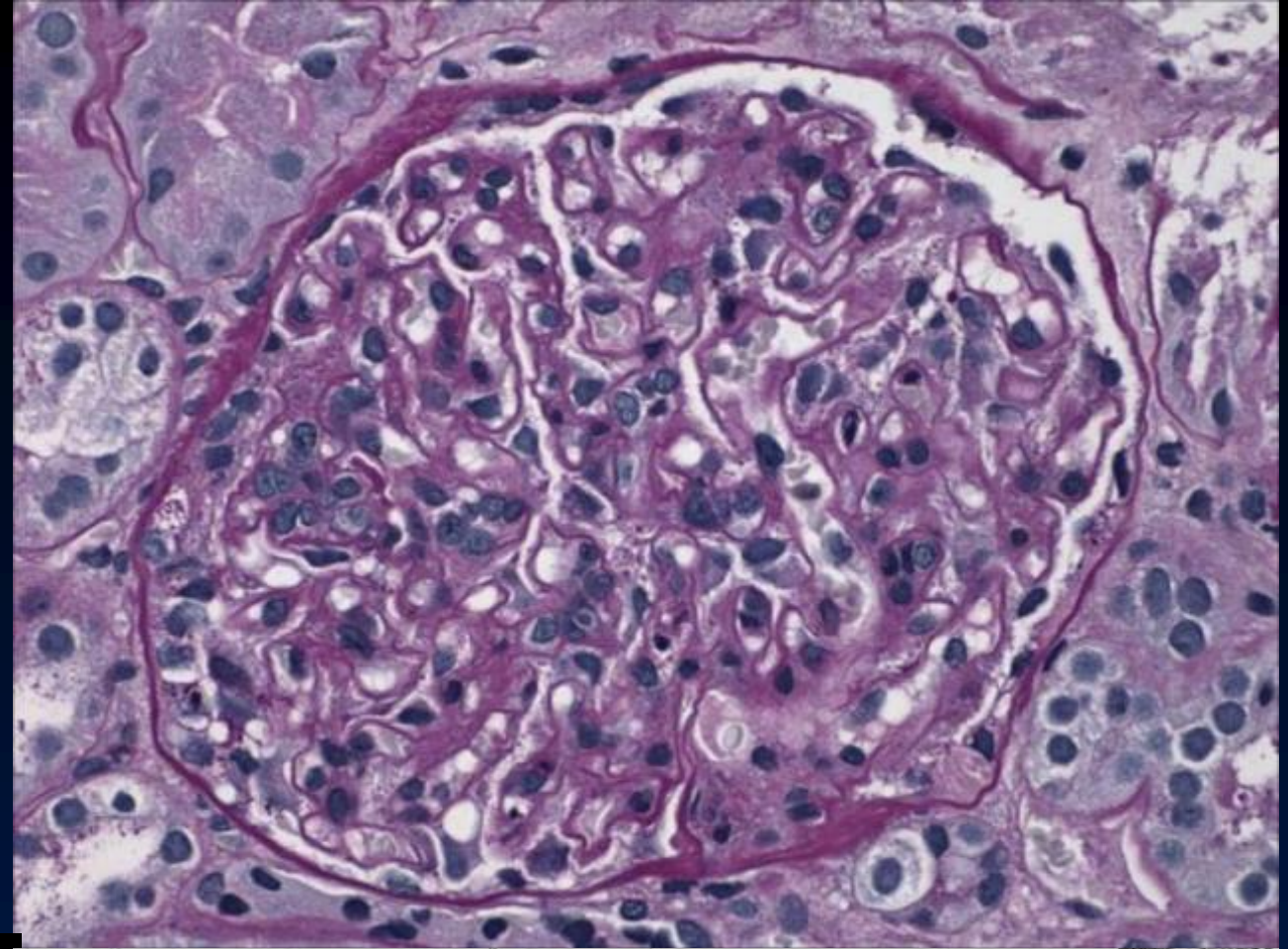




# ACTIVATION OF THE COMPLEMENT SYSTEM



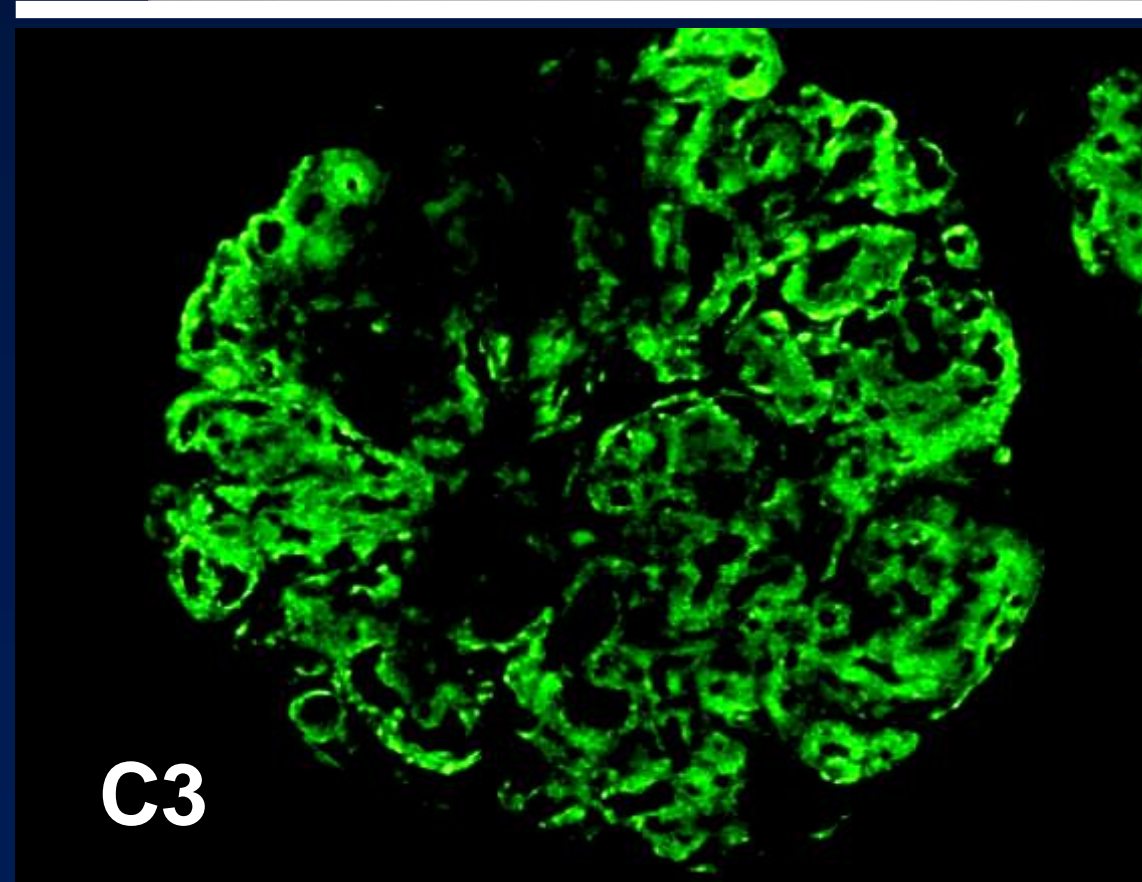
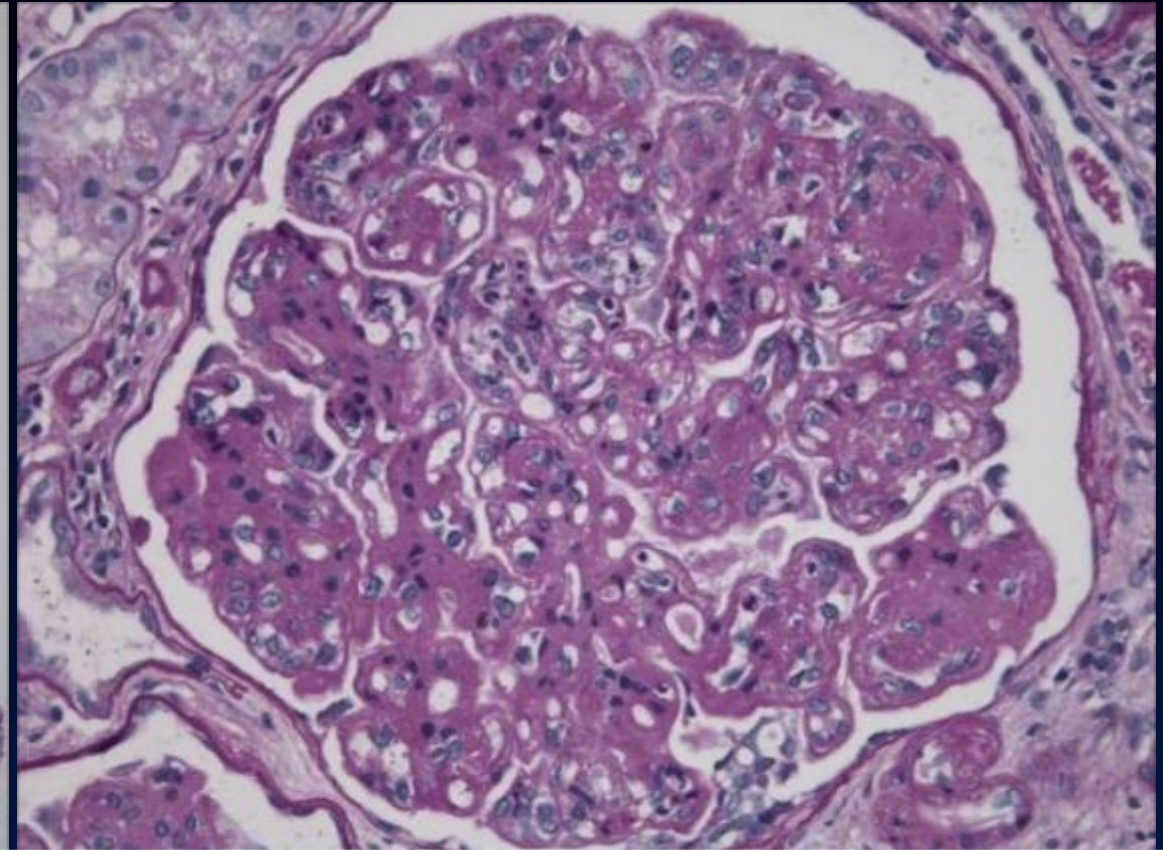
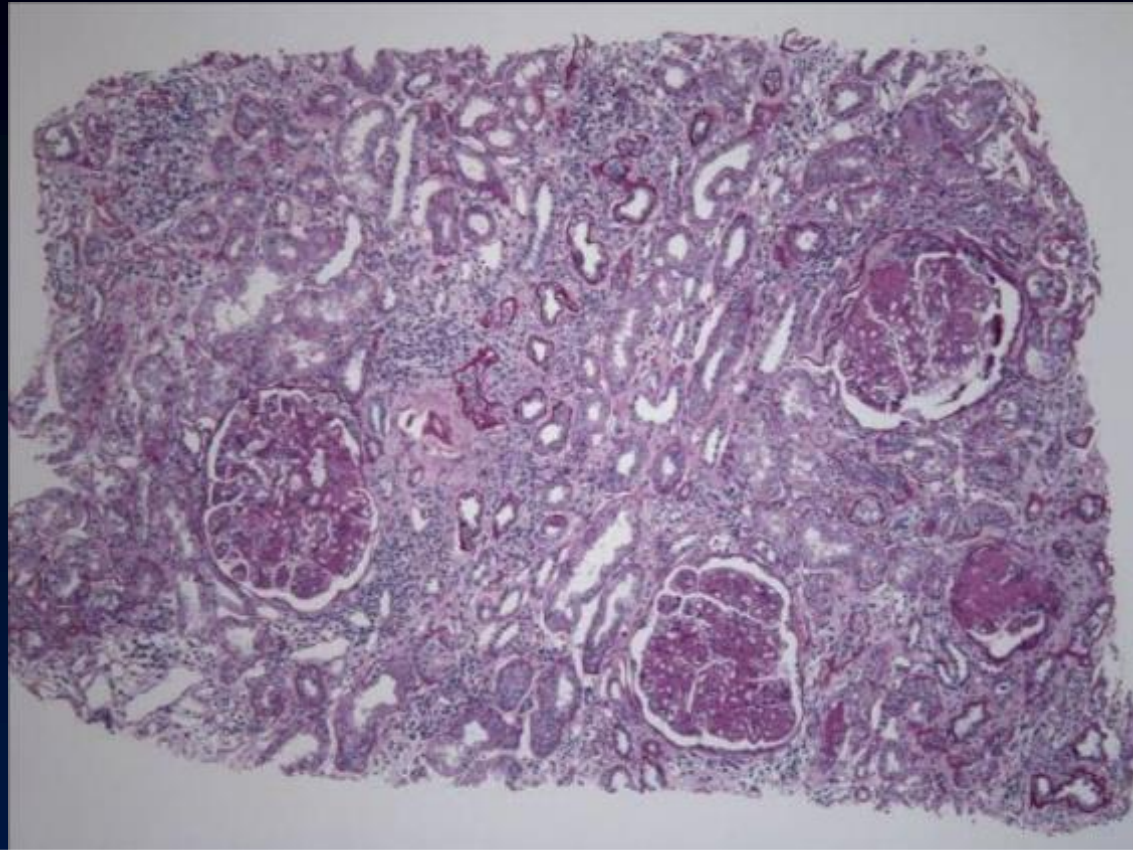
# Dense Deposit Disease



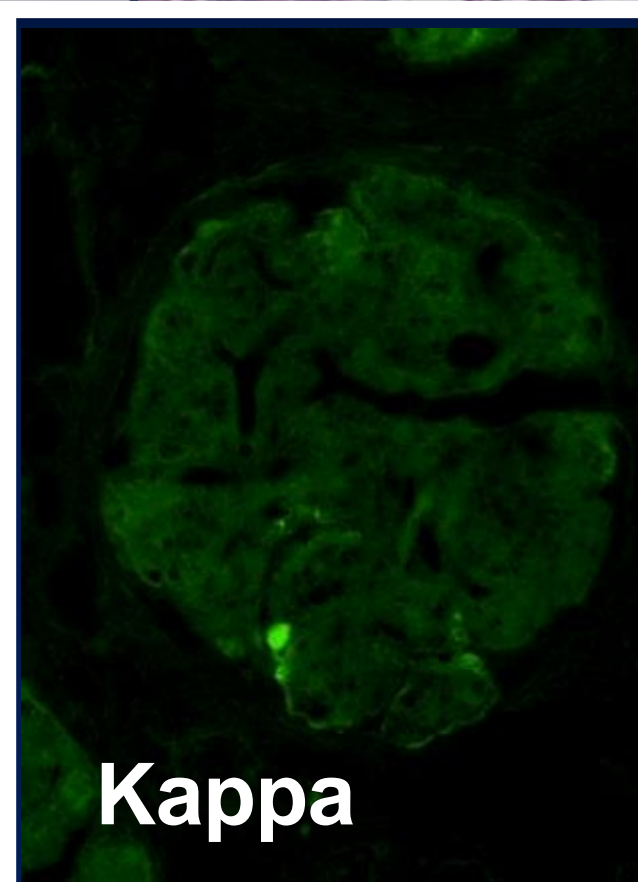


31 y/o woman with h/o hematuria, proteinuria (now ns), hypertension.

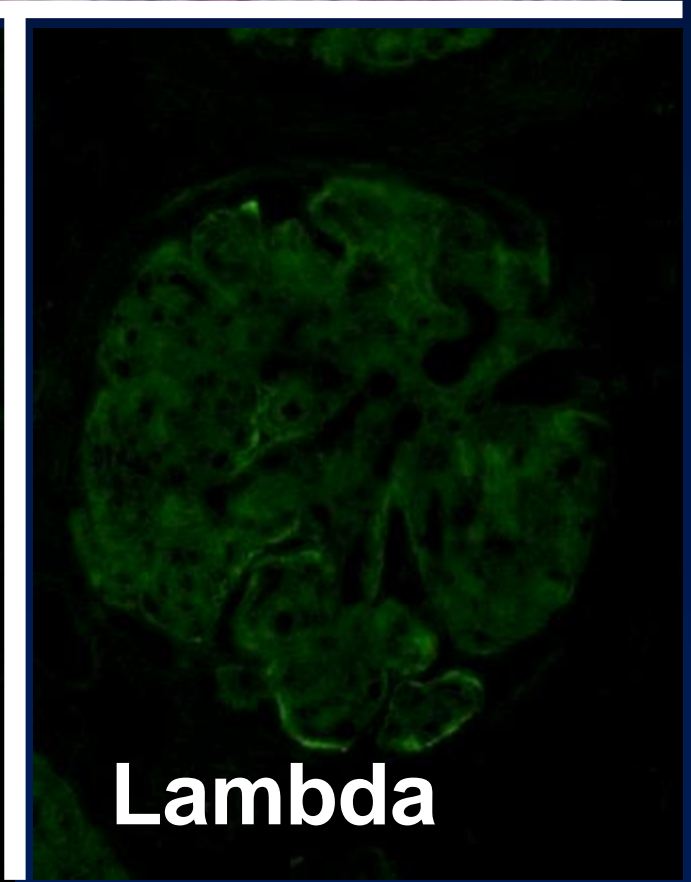
GLOMERULONEPHRITIS C3



C3

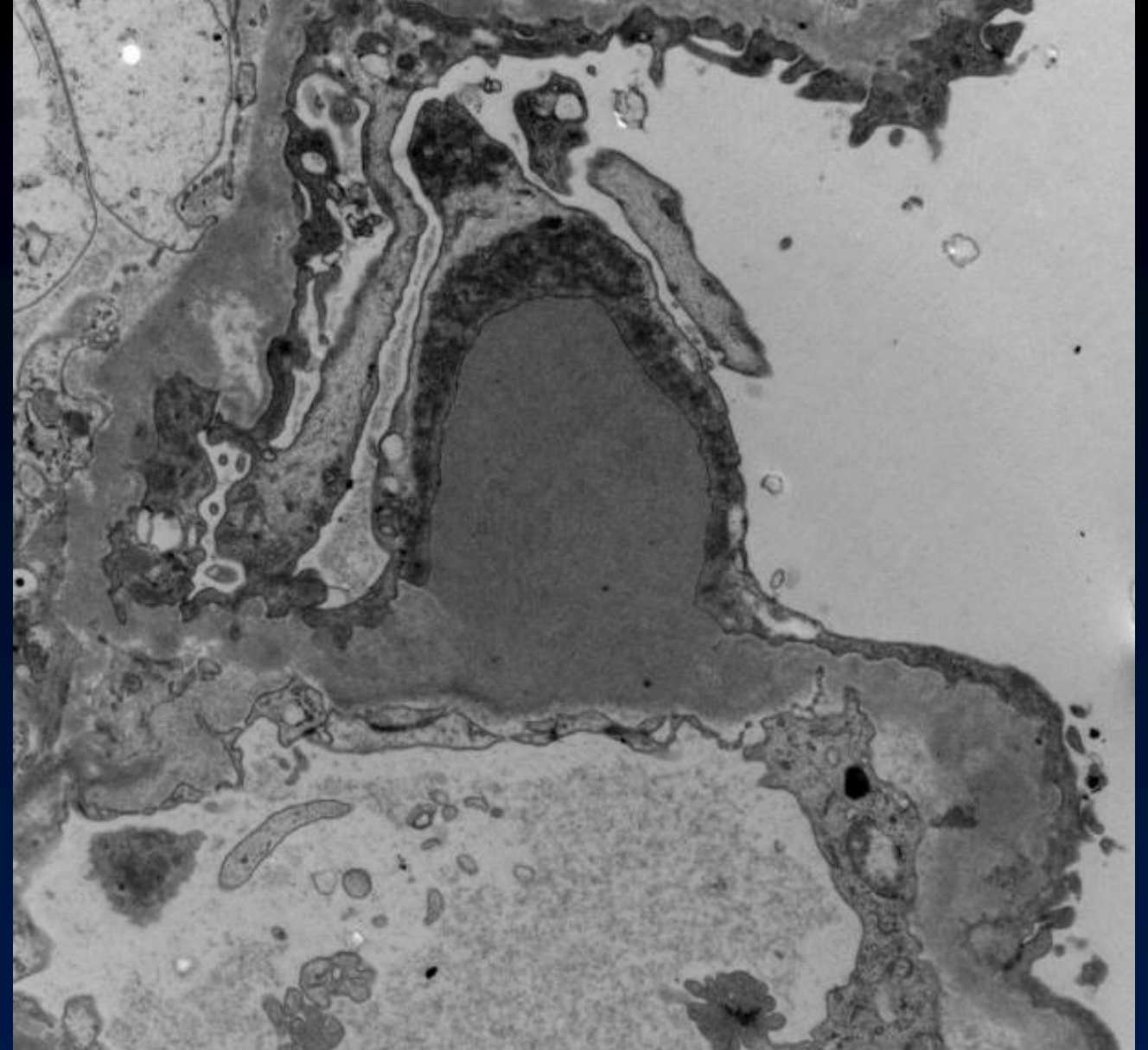
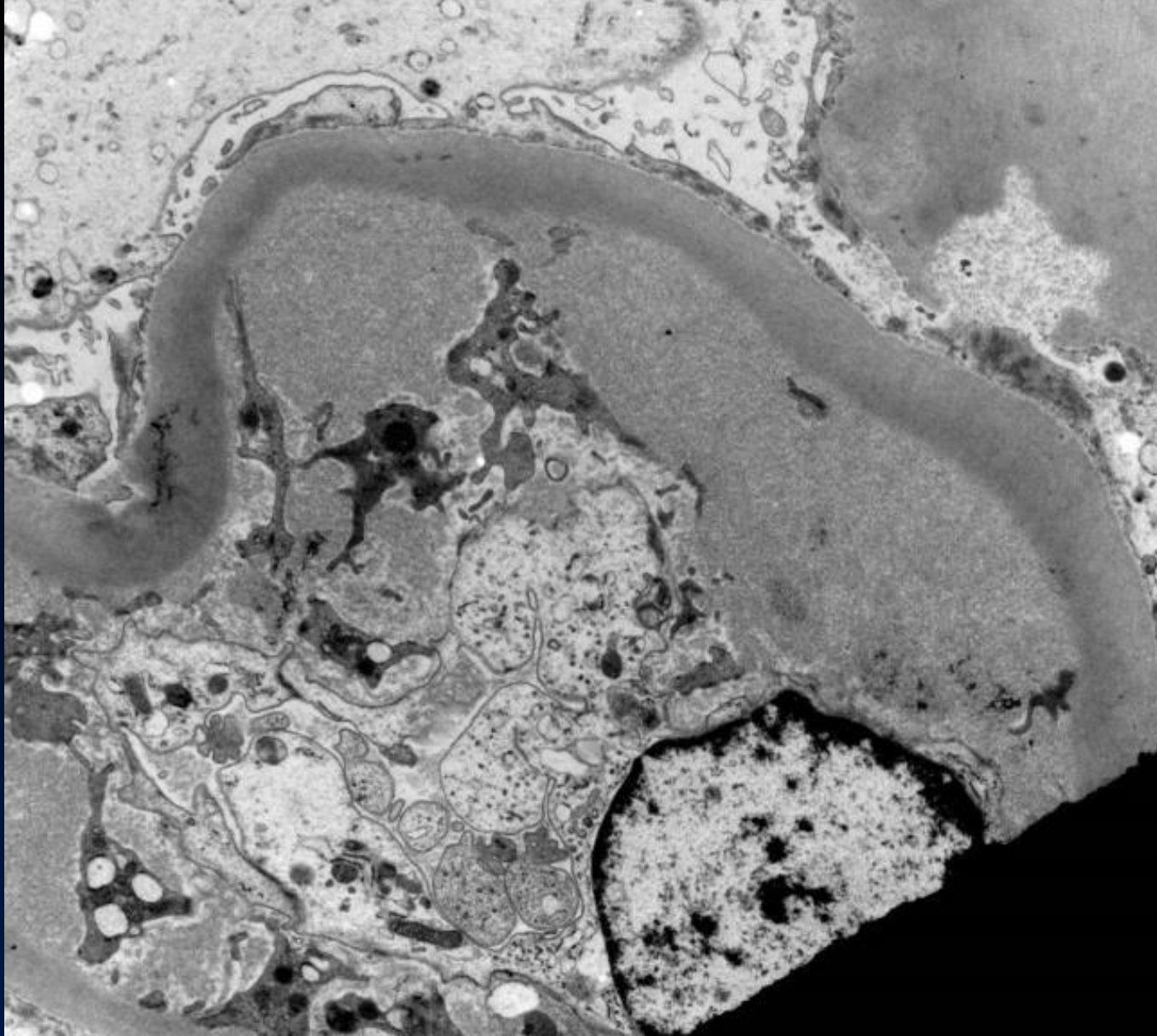


Kappa



Lambda





## CLINICAL RESULTS

### Results: Genetic Tests

Gene	NCBI Reference	Allele 1	Allele 2	Result
CFH	NM_000186	normal allele	normal allele	no pathogenic variants
CFI	NM_000204	normal allele	normal allele	no pathogenic variants
MCP	NM_002389	normal allele	normal allele	no pathogenic variants
CFB	NM_001710	normal allele	normal allele	no pathogenic variants
C3	NM_000064	normal allele	normal allele	no pathogenic variants
CFHR5	NM_030787	normal allele	normal allele	no pathogenic variants
MLPA (CFHR1-CFHR4)	-----	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

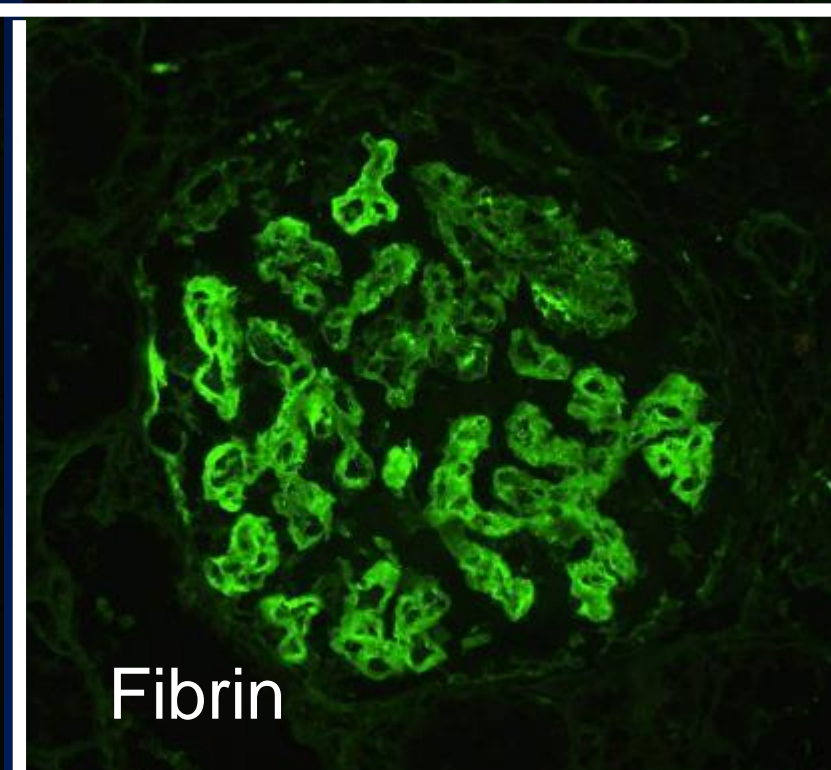
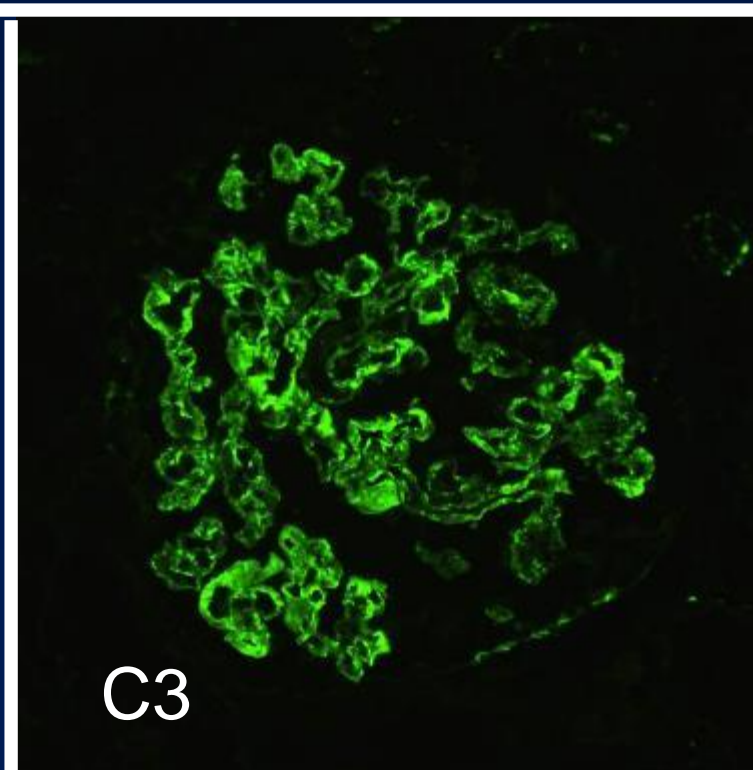
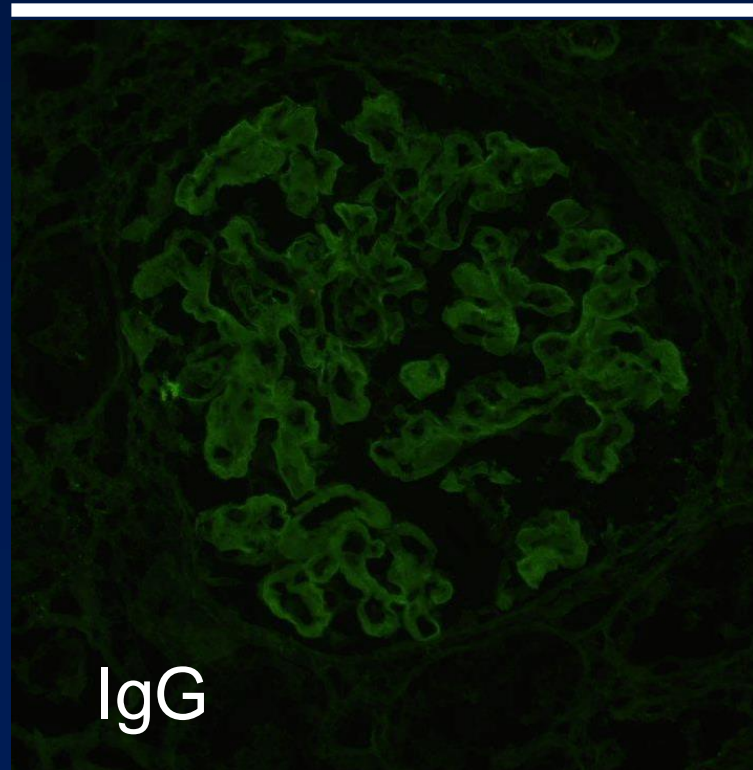
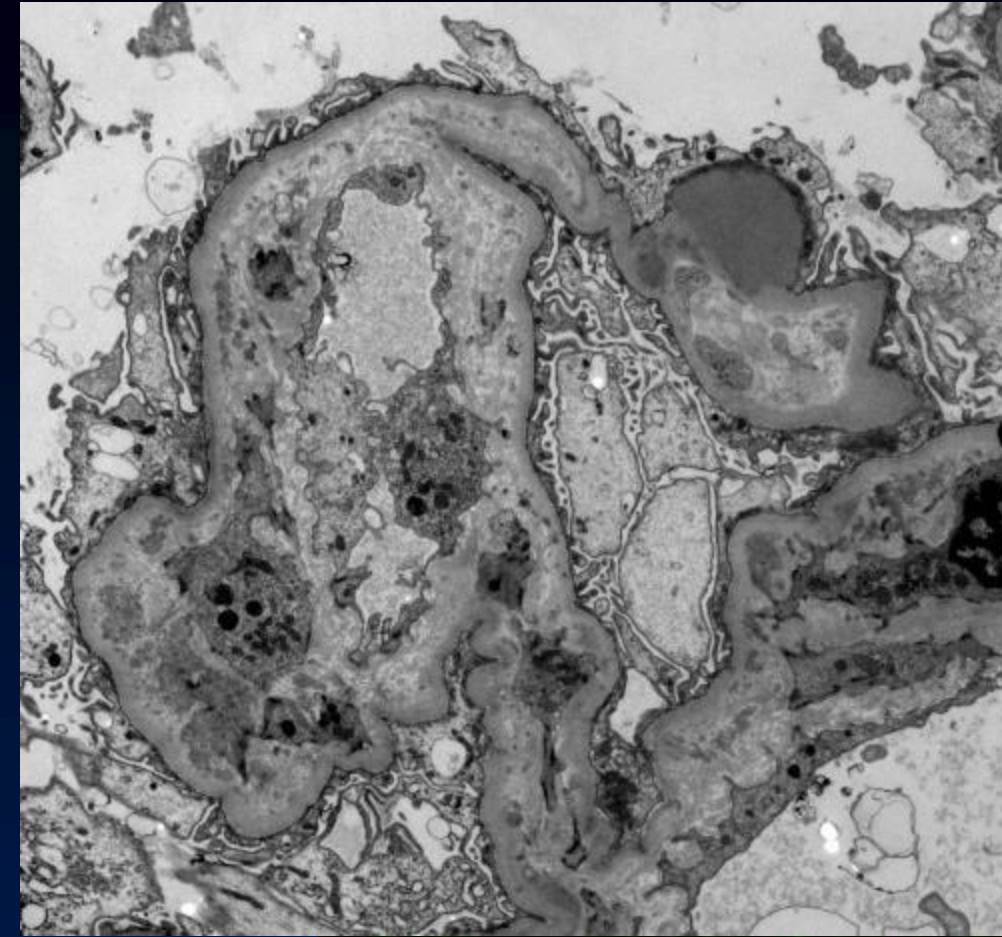
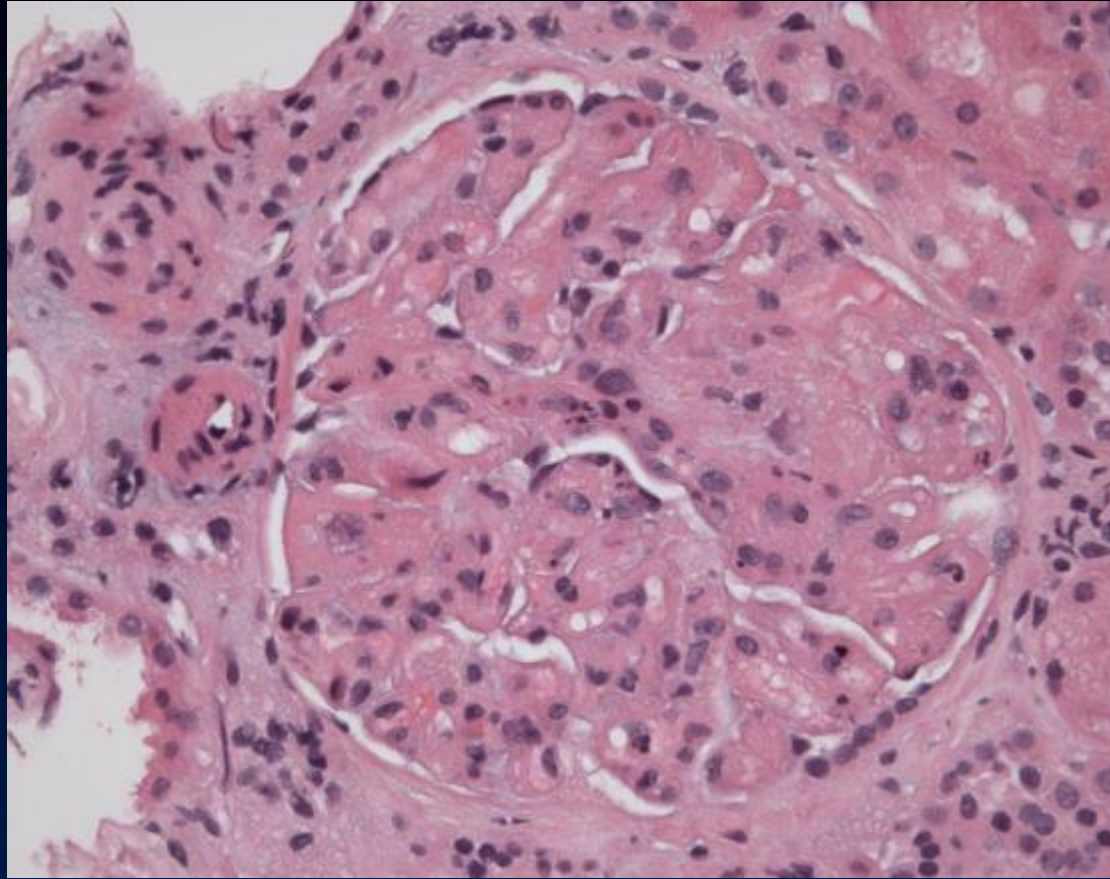
## 2. DEFECTS IN COMPLEMENT-REGULATORY PROTEINS:

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- 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> (titer <200 AU)	<i>FB autoantibody</i> (titer <200 AU)	<i>Hemolytic Assay</i> (<3%)	<i>APFA</i> (50% to 130%)	<i>CH50</i> (30-90 U/mL)	<i>C3Nef – IFE</i> (<7.5%)	<i>C3Nef - C3CSA</i> (<20%)	<i>C3Nef - C3CSAP</i> (<20%)	<i>C4Nef</i> (<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> (0.9 – 1.8 g/L)	<i>C3c Level</i> (<2.0 mg/L)	<i>C4 Level</i> (0.15-0.57 g/L)	<i>Ba Level</i> (<1.2 mg/L)	<i>Bb Level</i> (<2.2 mg/L)	<i>FB Level</i> (22-50 mg/dL)	<i>FH Level</i> (45-80 mg/dL)	<i>FI Level</i> (16-40 mg/L)	<i>C5 Level</i> (10-21 mg/dL)	<i>Properdin Level</i> (10-33 mg/L)	<i>Soluble C5b-9</i> (<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.



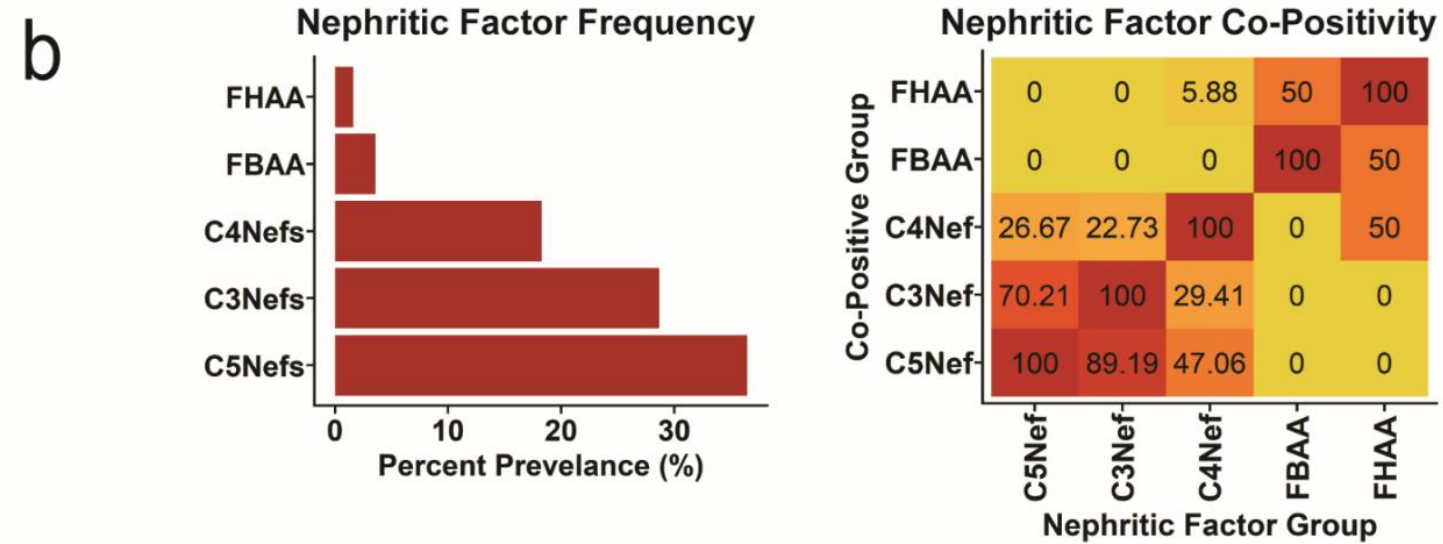
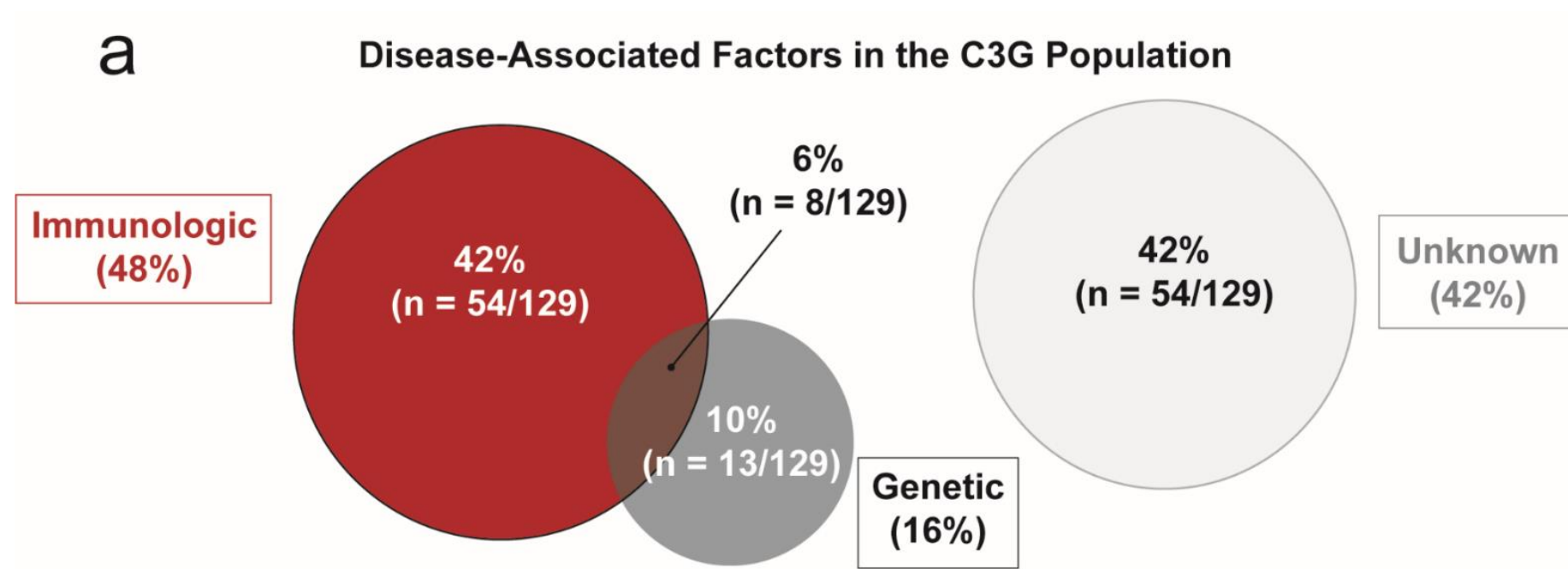
## INTERPRETATION OF RESULTS

- Genetic drivers of disease
  - o Whole blood was not received, and genetic testing was not performed. We would be pleased to perform genetic testing for this patient if you provide 8 – 10 cc of EDTA whole blood (ambient).
- Acquired drivers of disease
  - o Negative for FH autoantibodies and FB autoantibodies.
  - o Positive for C3Nef by IFE but negative for C3Nef by C3CSA and C3CSAP.
- Complement biomarker profiling
  - o C3c, Ba, Bb and soluble C5b-9 levels are high consistent with the dysregulation of the C3 Convertase and C5 convertase.
  - o Properdin level is low suggesting activation of the alternative and terminal pathways of complement.
- Functional assays of complement activity
  - o APFA is low and CH50 is normal, consistent with the consumption of AP proteins.
  - o Hemolytic is normal but this could be a false normal due to the consumption of AP proteins.

## FINAL ASSESSMENT

We suspect your patient has MGRS (not MGUS). The complement biomarkers are consistent with the diagnosis of C3GN (low properdin, high soluble C5b-9). We have not yet attempted to isolate the paraprotein to determine its effect on complement activity. The high levels of soluble C5b-9 suggest that your patient would respond to Eculizumab.



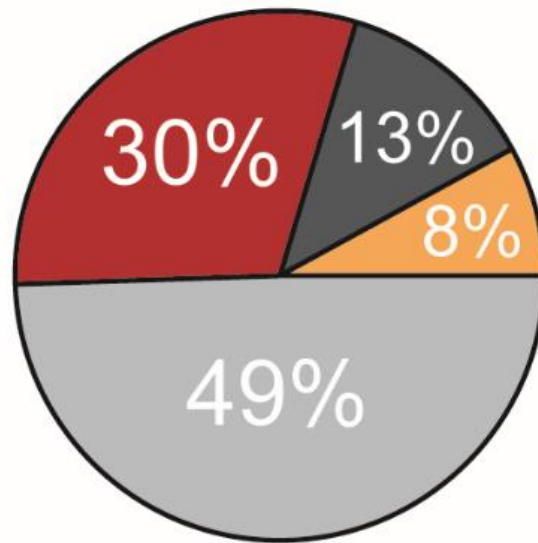


Courtesy Dr. Richard Smith

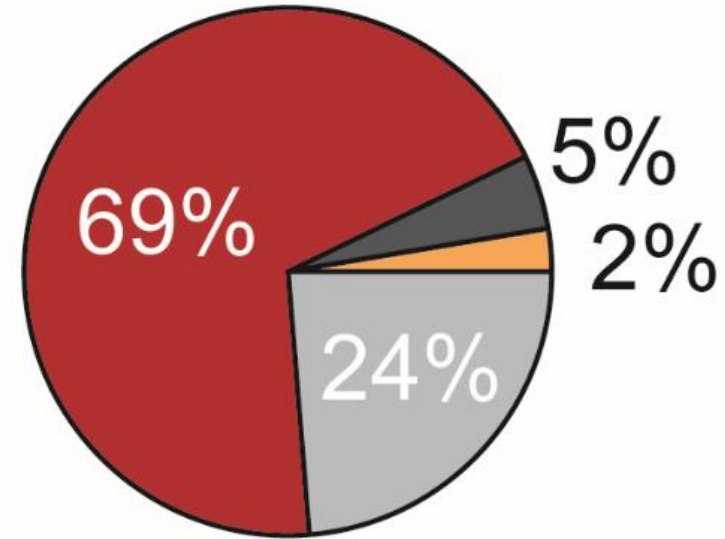


d

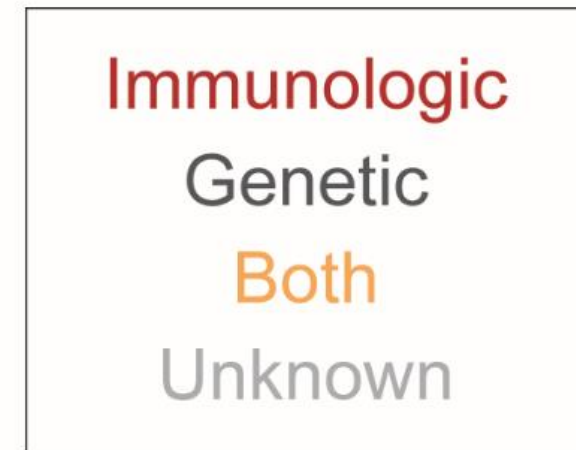
C3GN



DDD



Drivers



# **THE MEMBRANOPROLIFERATIVE PATTERN OF INJURY**

## **STRUCTURAL CHANGES:**

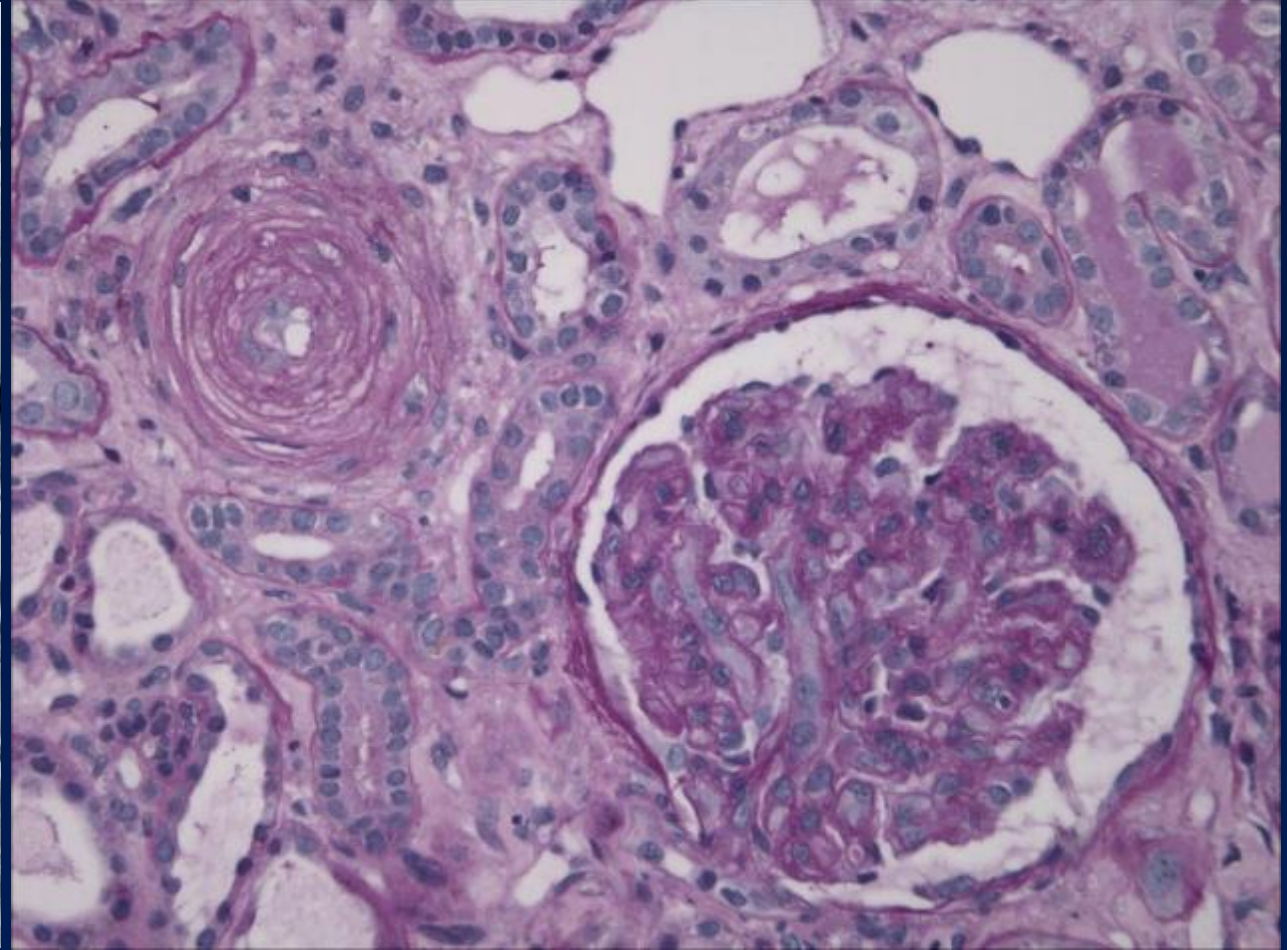
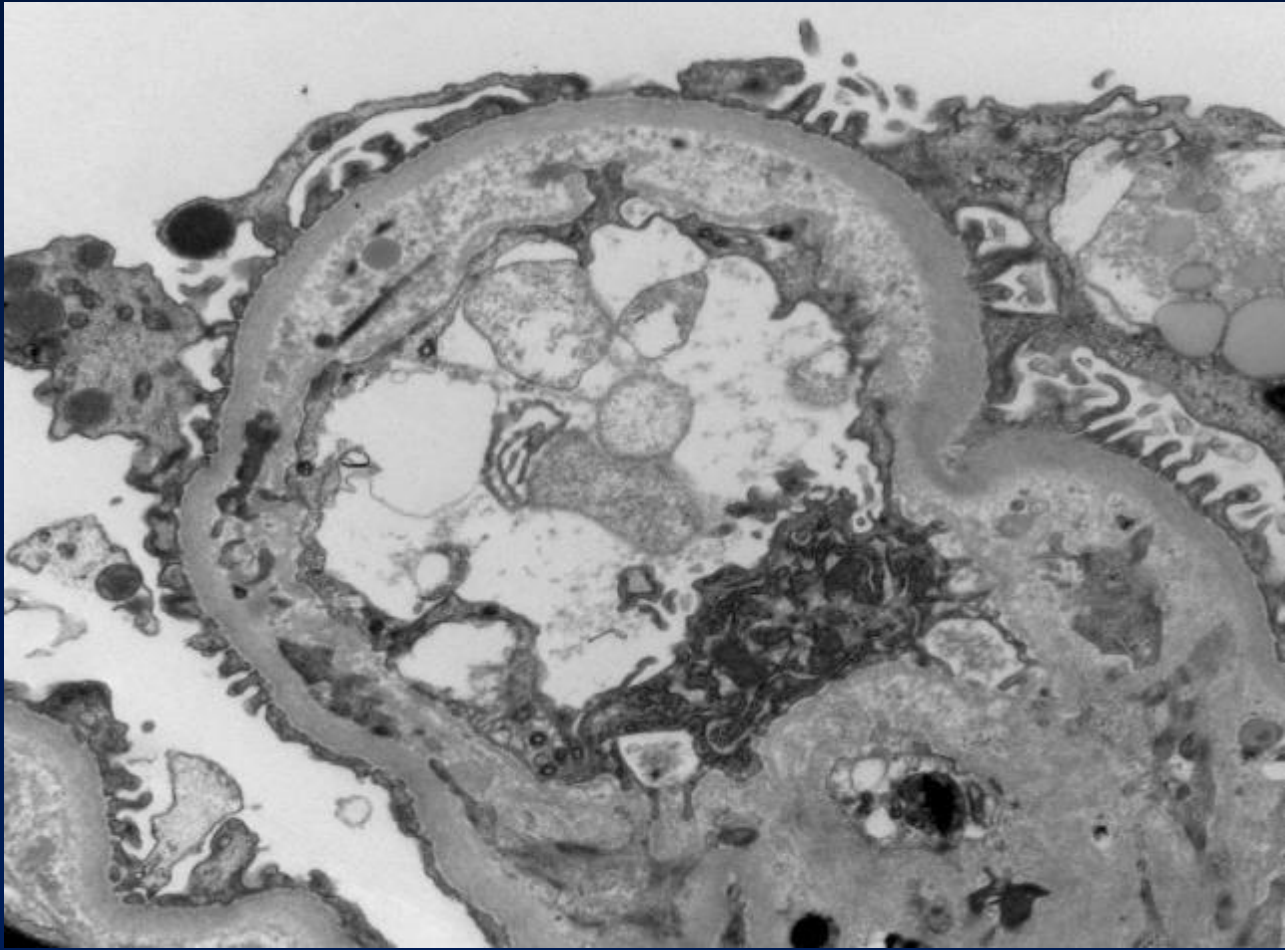
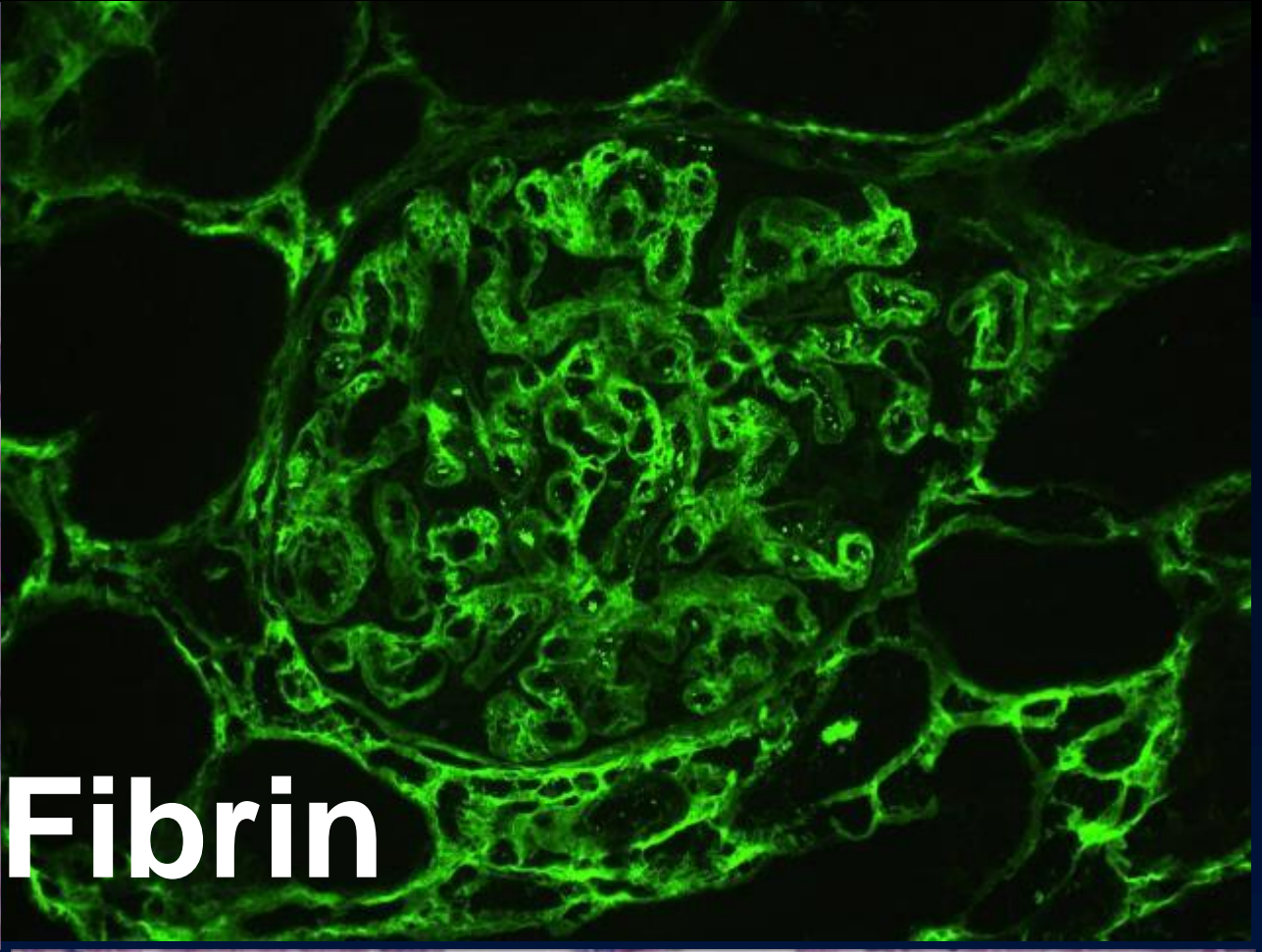
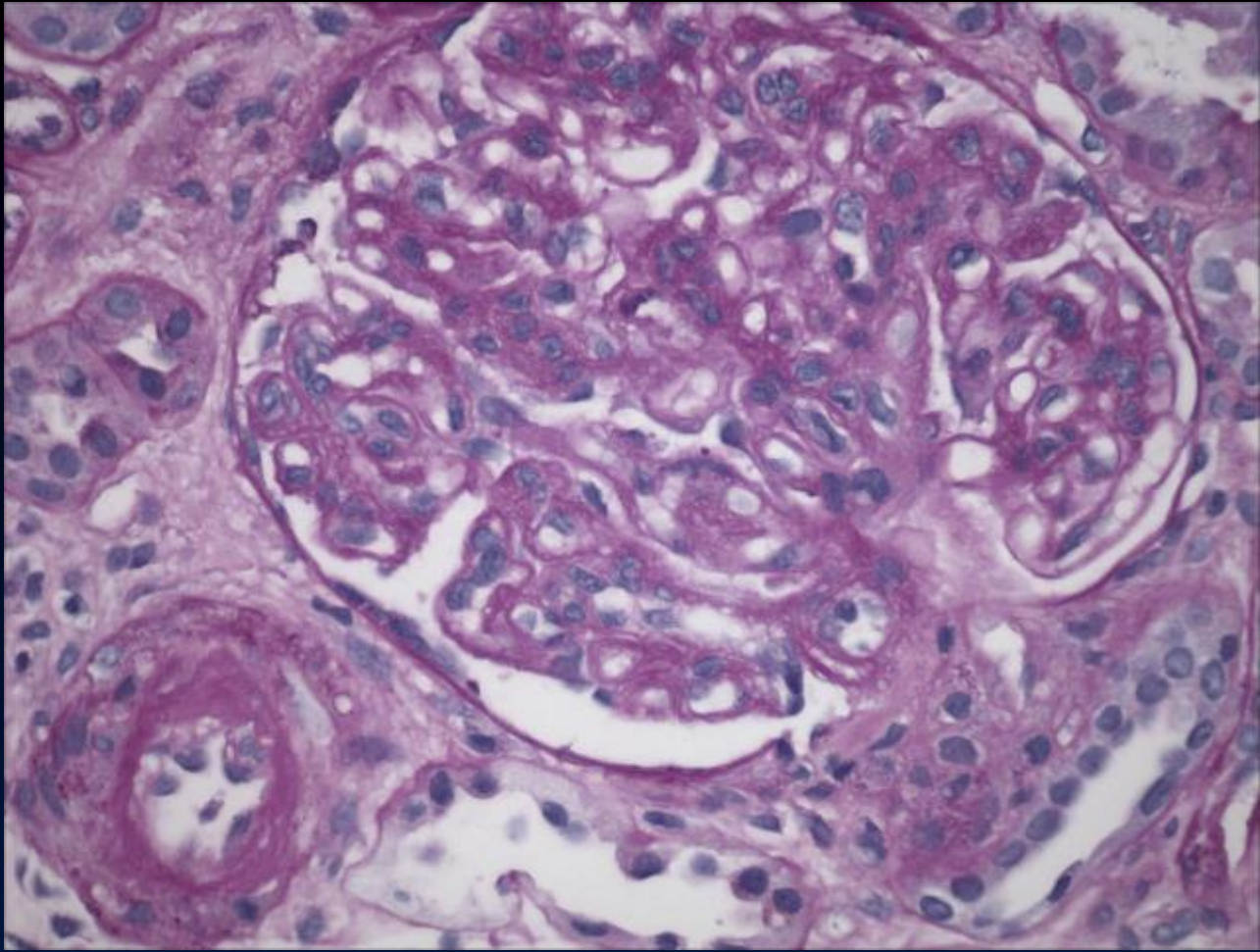
- **HYPERCELLULARITY**
- **CAPILLARY WALL THICKENING (double contours)**

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

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



# THROMBOTIC ANGIOPATHIES





# **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)

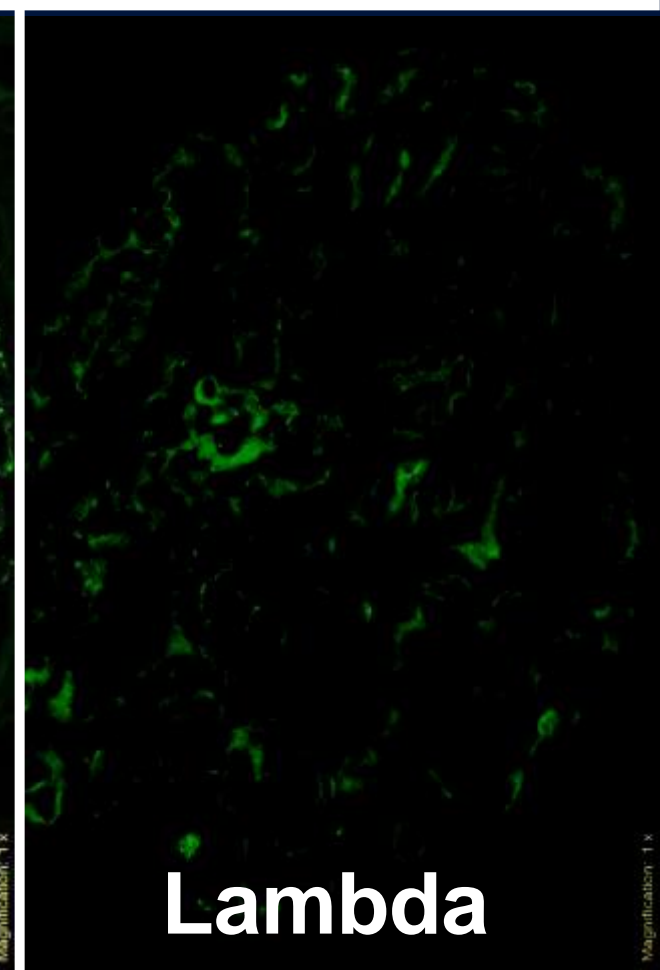
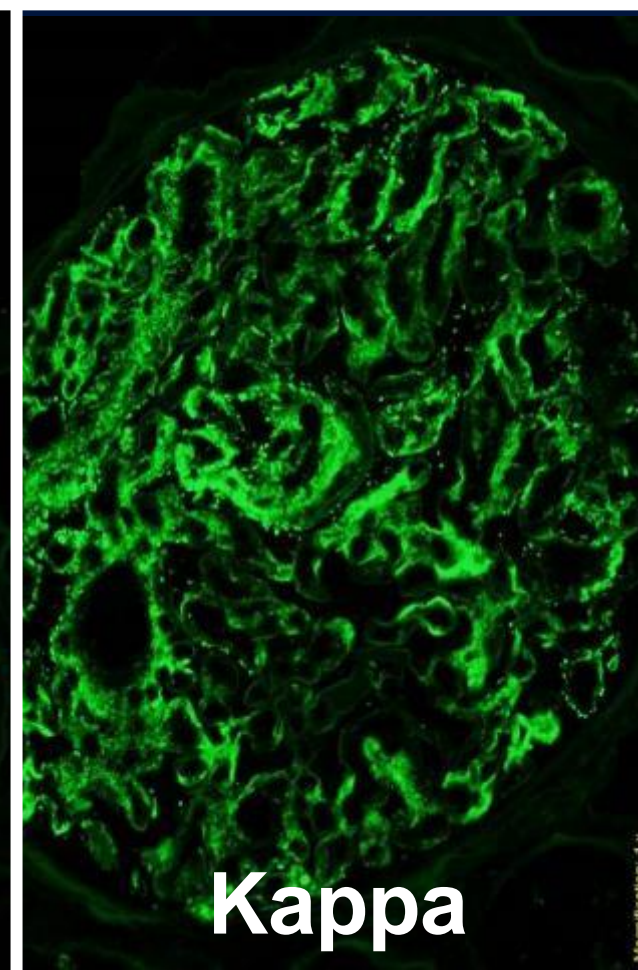
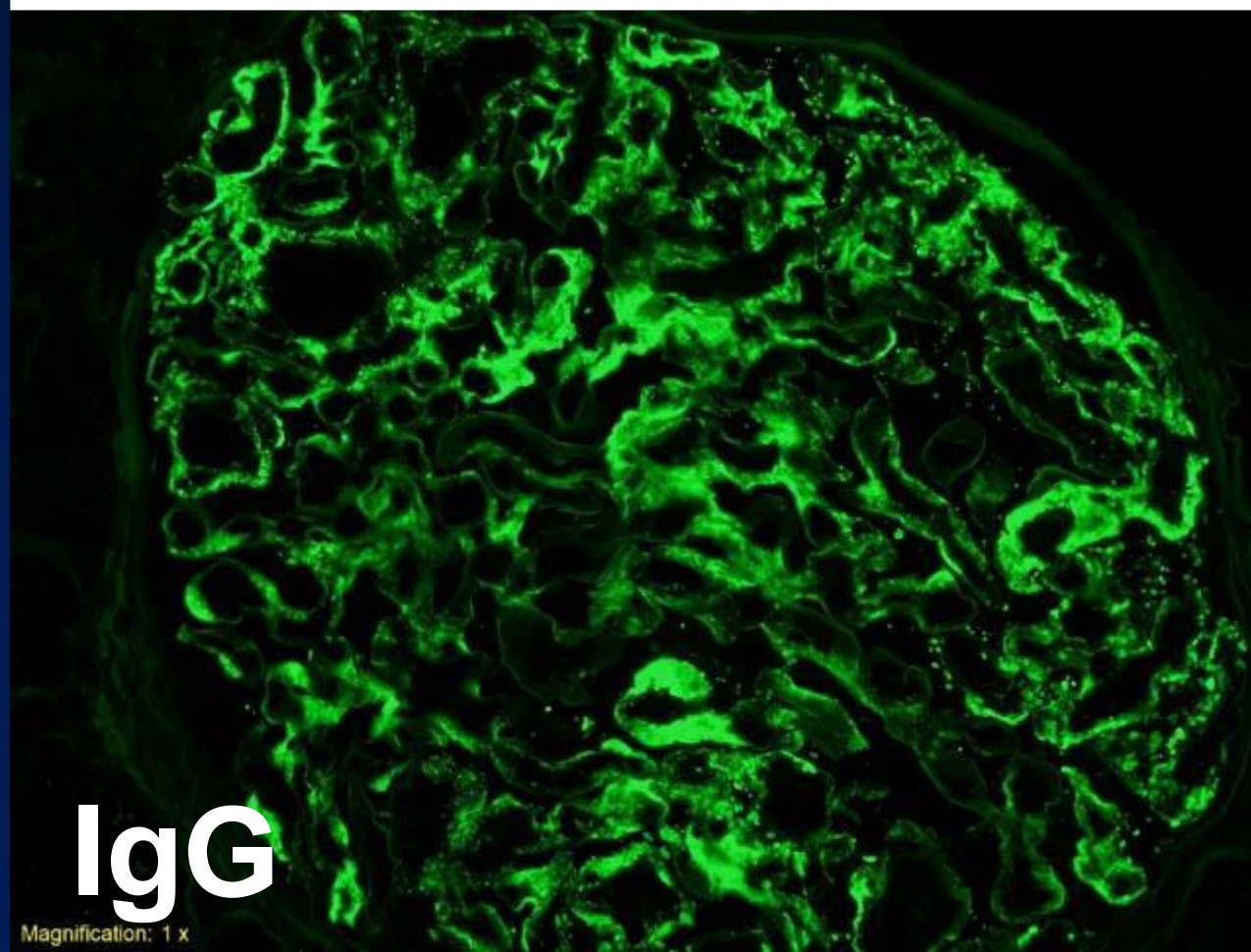
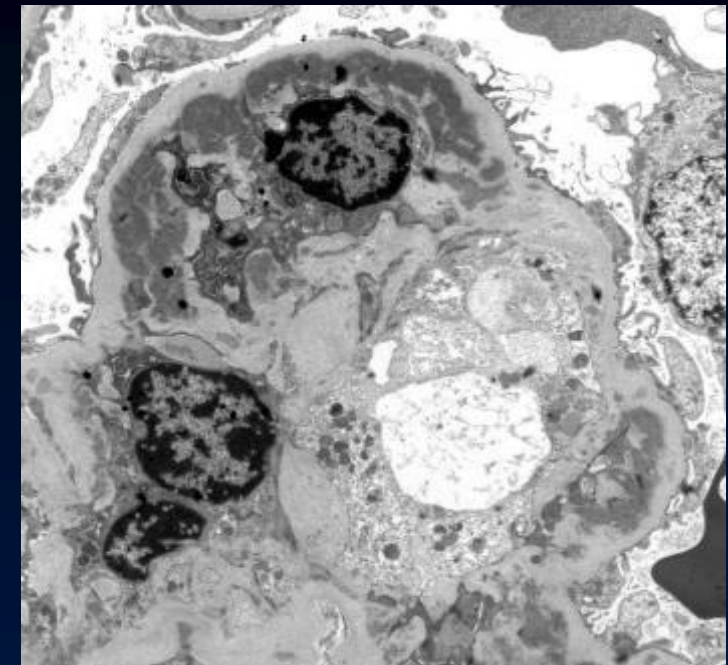
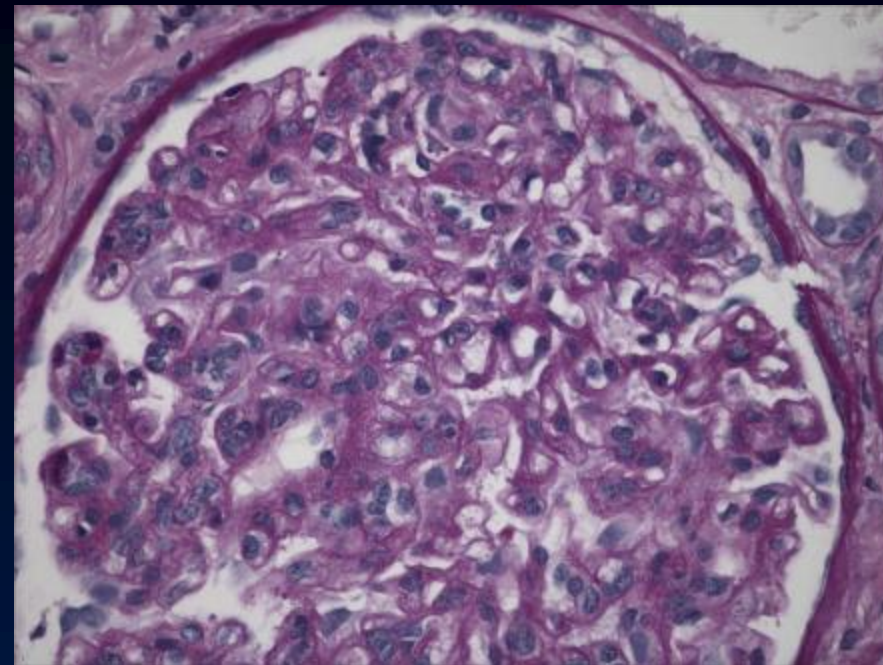
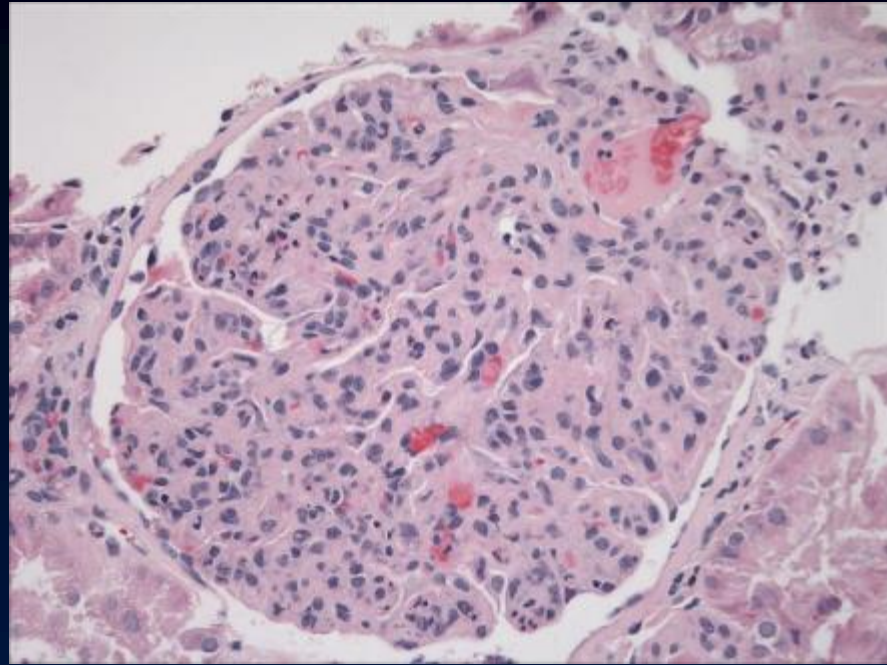
## CONDITIONS ASSOCIATED WITH THE MPGN PATTERN:

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

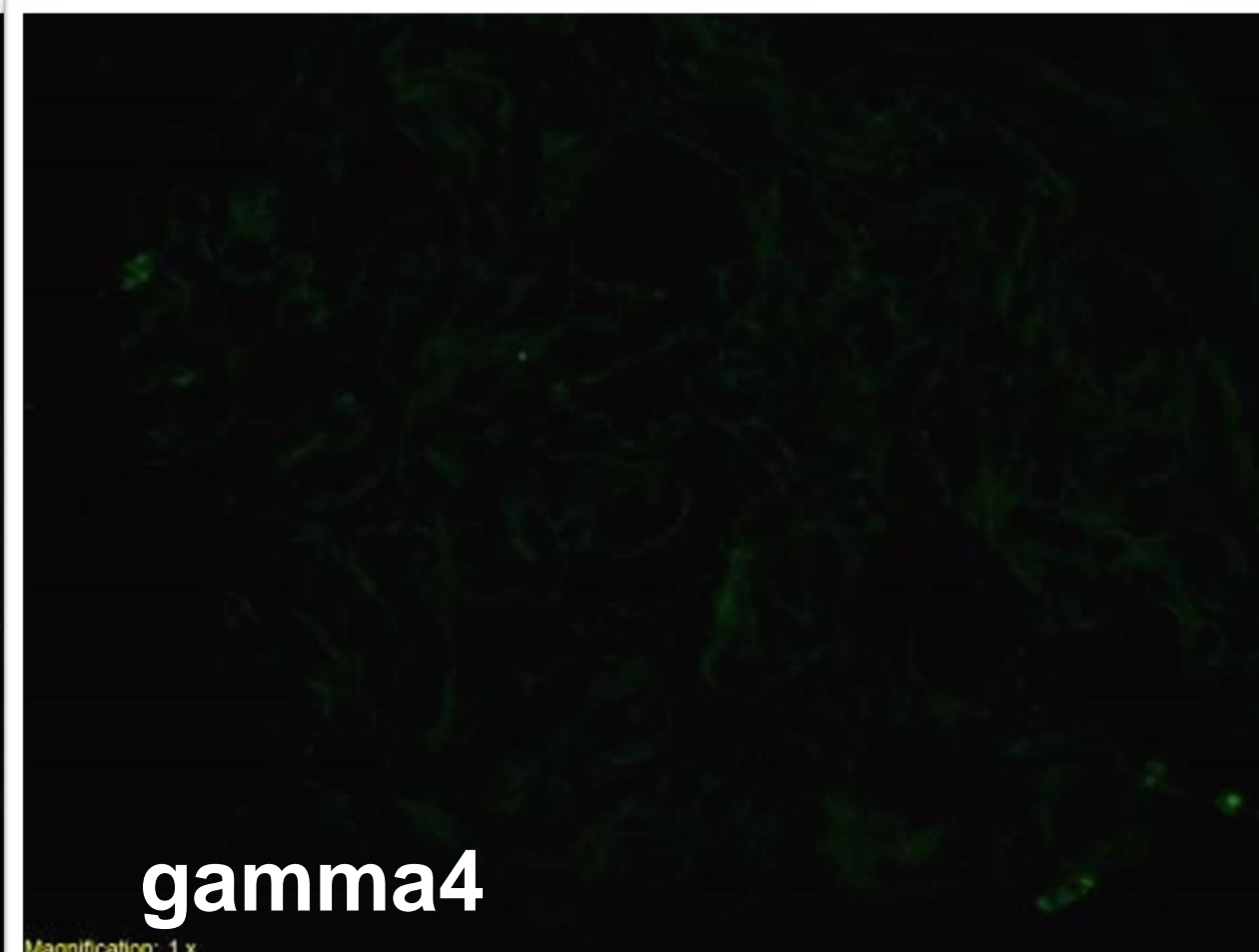
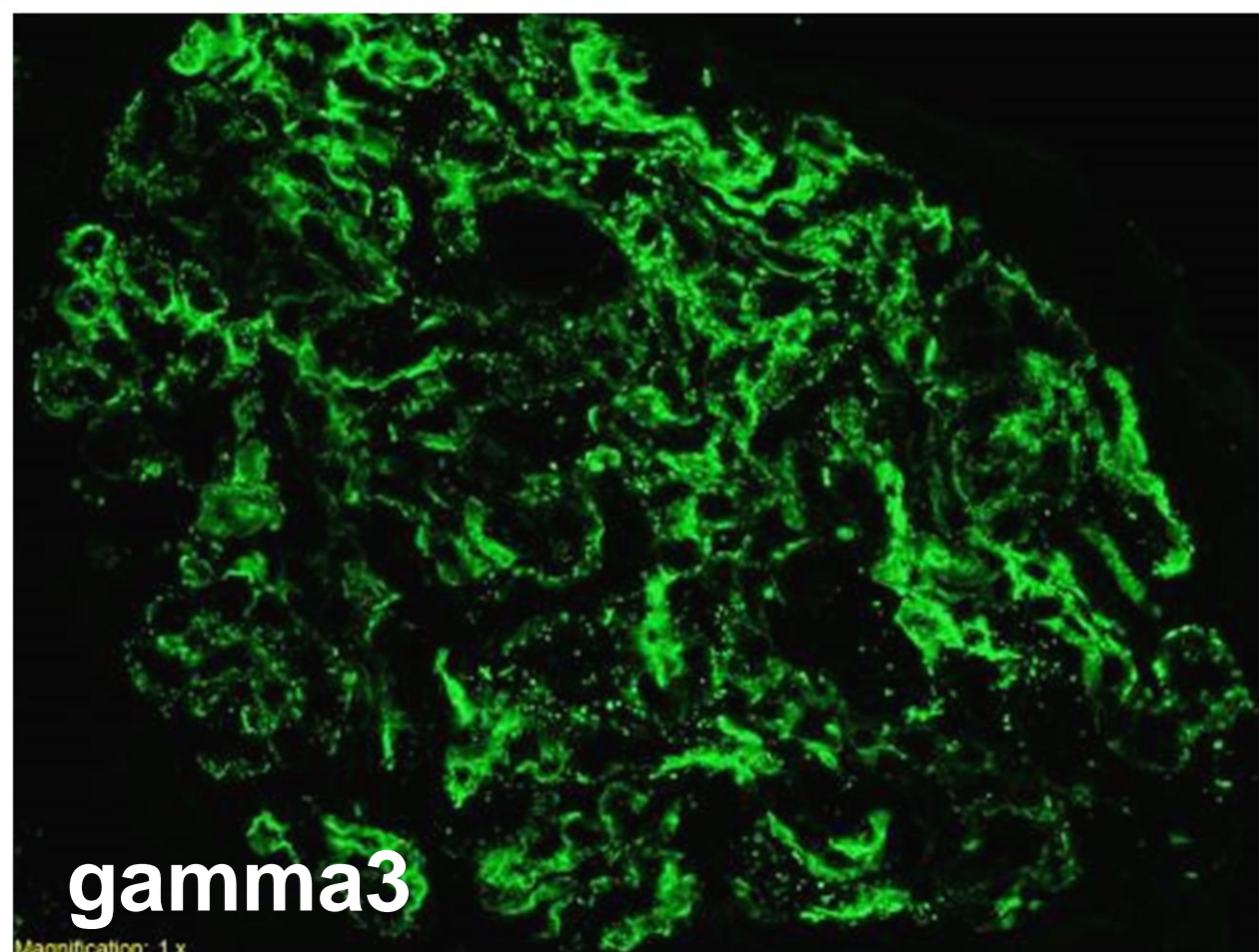
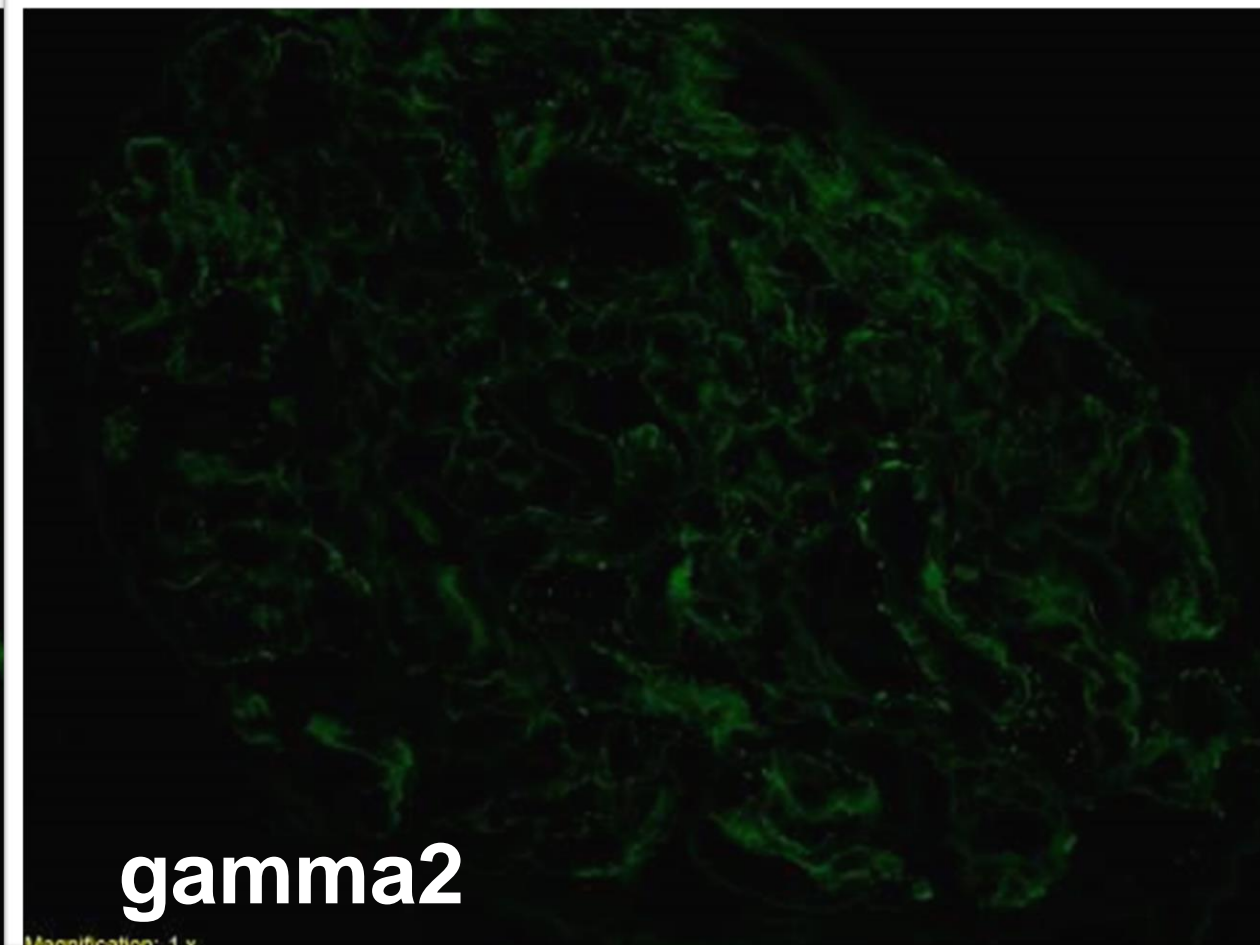
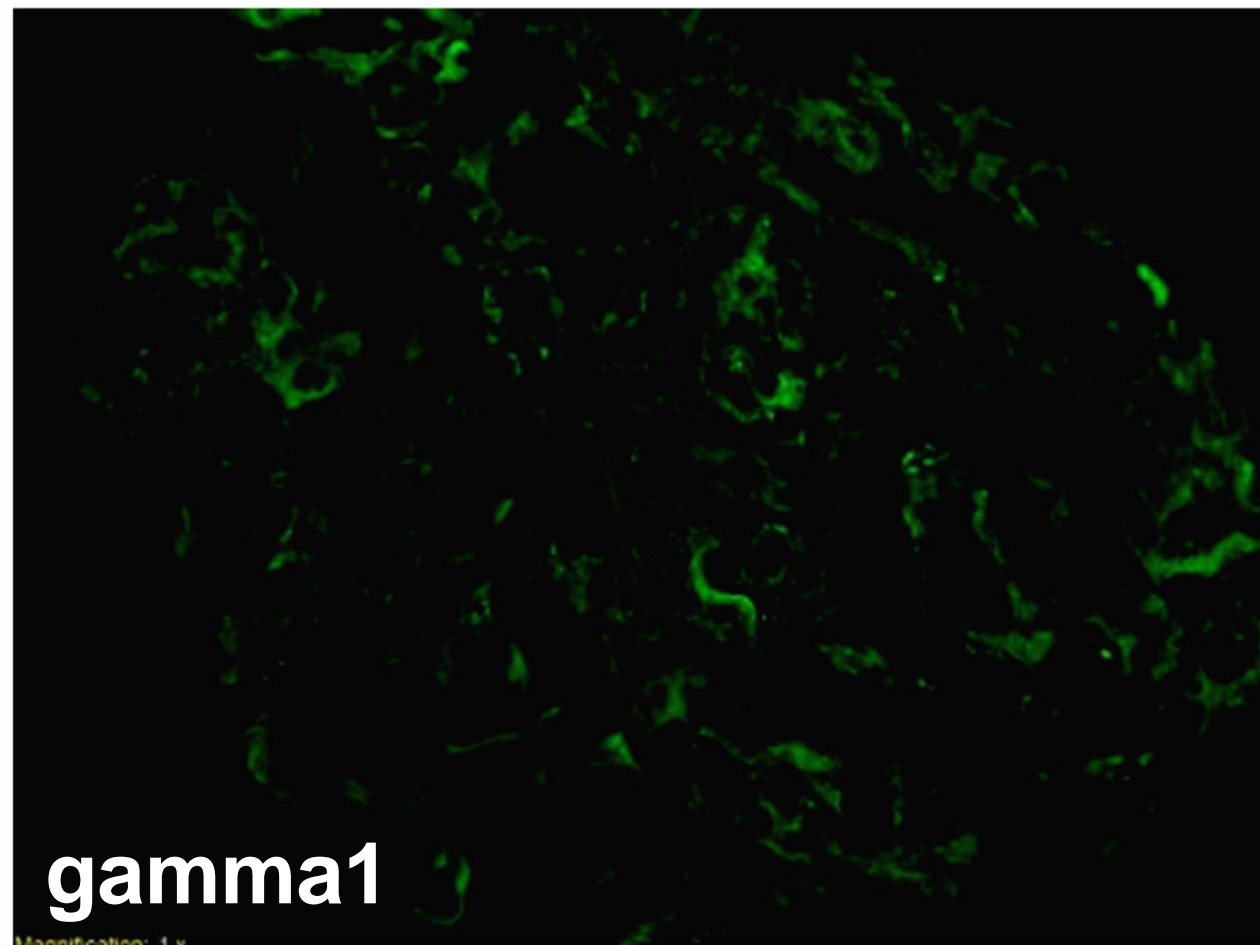


# Monoclonal IgG3/kappa Deposition disease

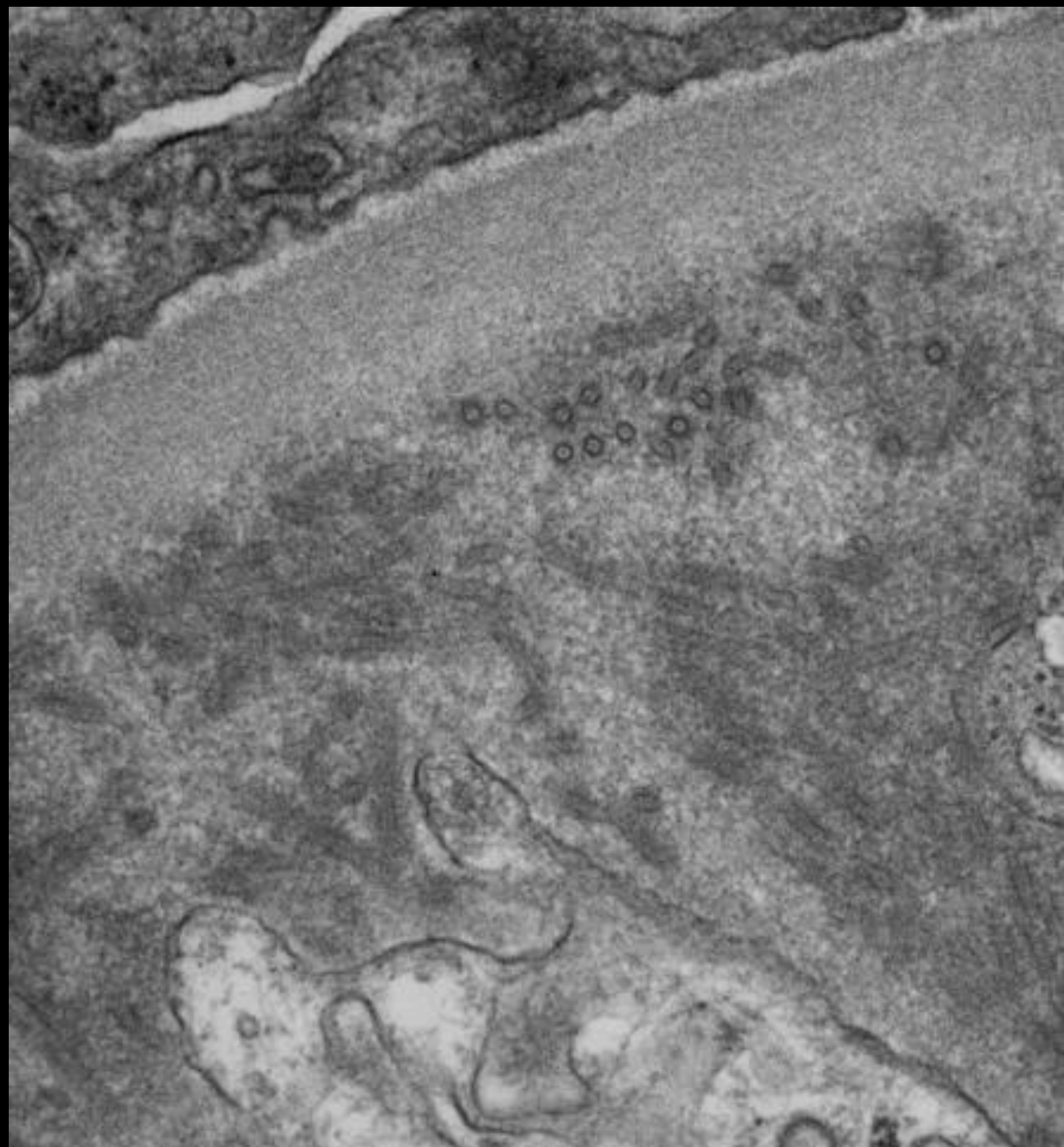
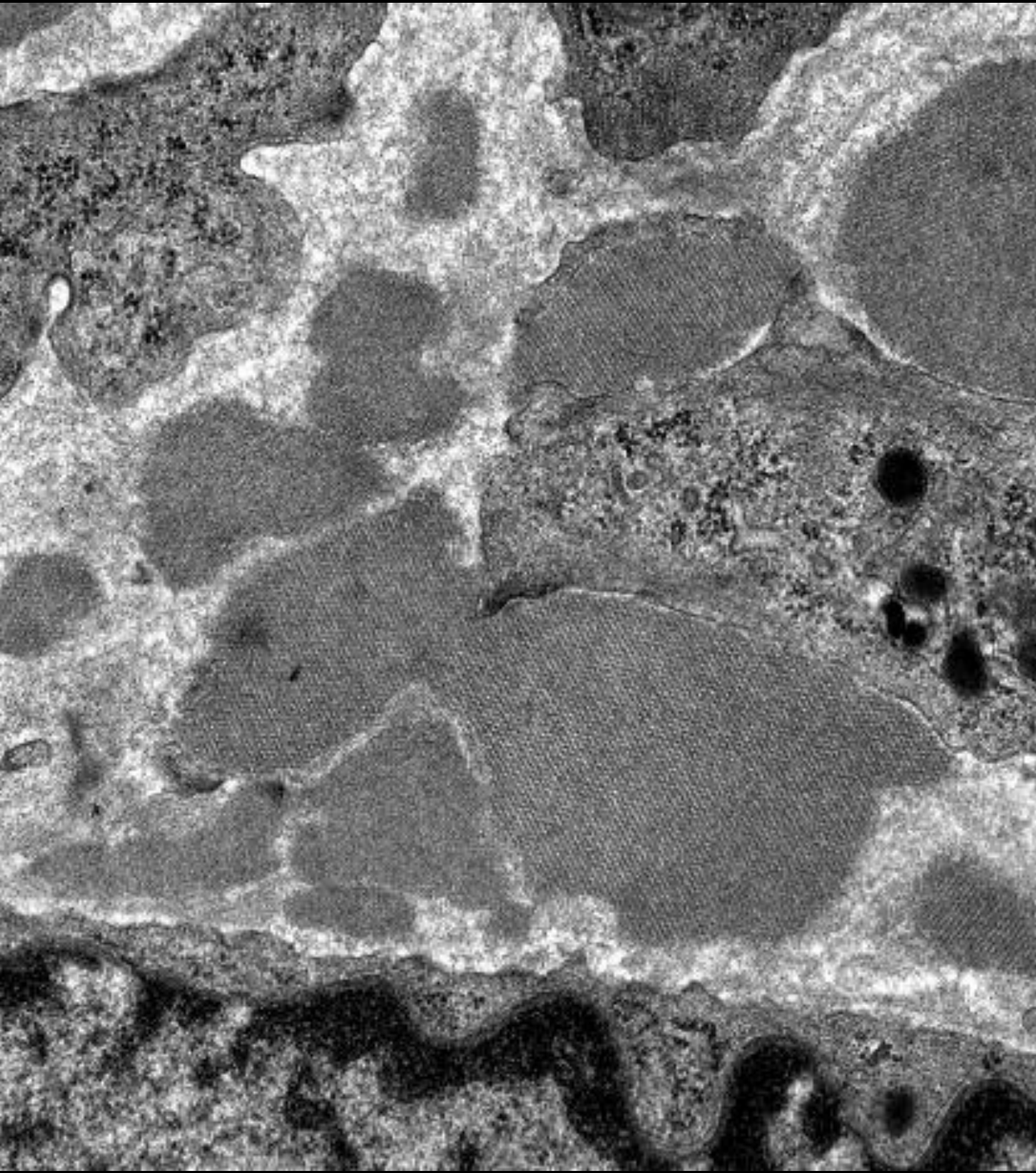
47-year-old woman with HTN and poorly controlled diabetes. The patient presents now with the nephrotic syndrome (proteinuria: 16 grams/24 hours, albumin: 2.5). Recent history of infection treated with amoxicillin for possible UTI. Cr: 2.5 mg/dl and 5-day.











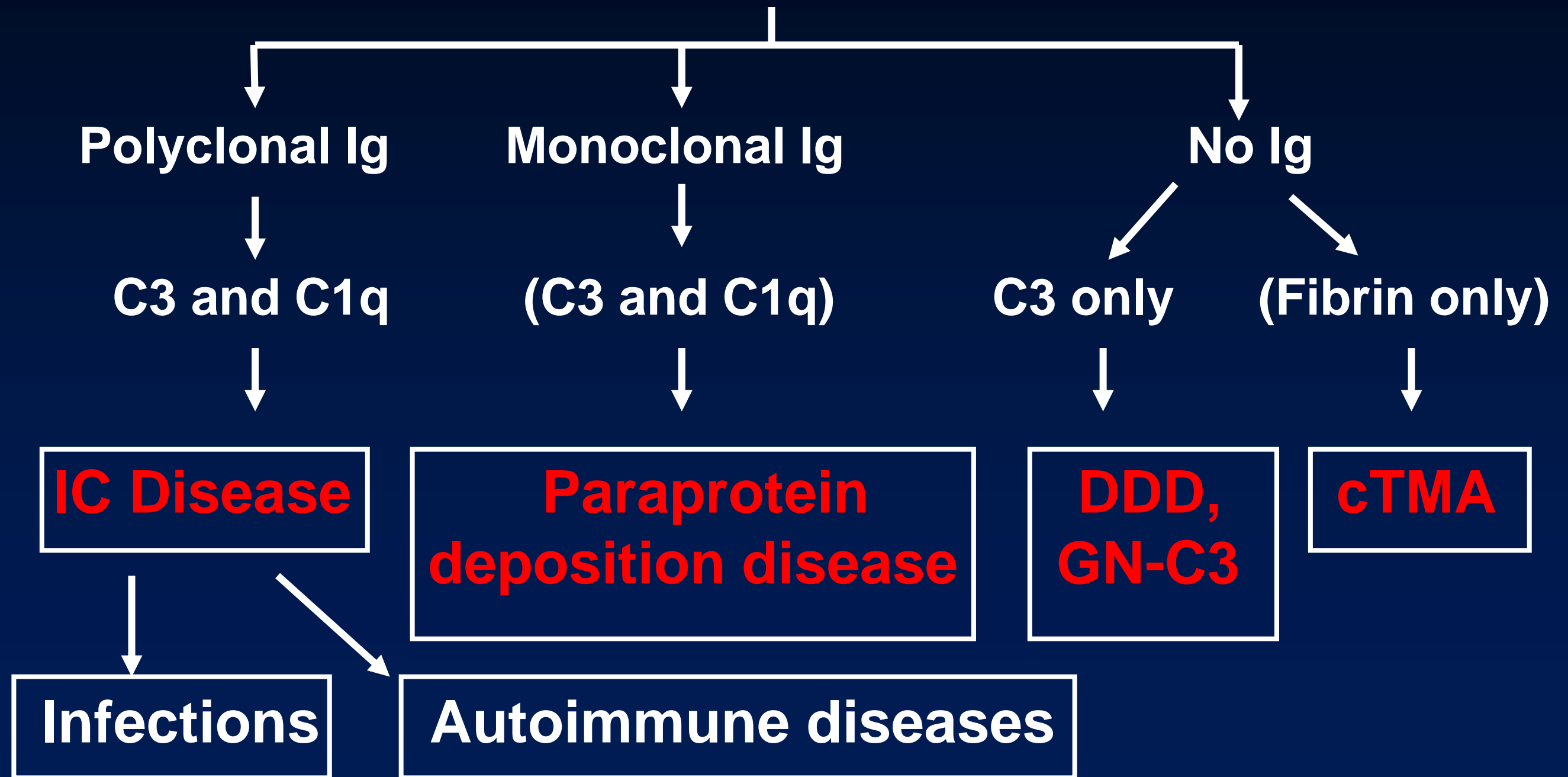


# CONDITIONS ASSOCIATED WITH DYSPROTEINEMIA

- 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

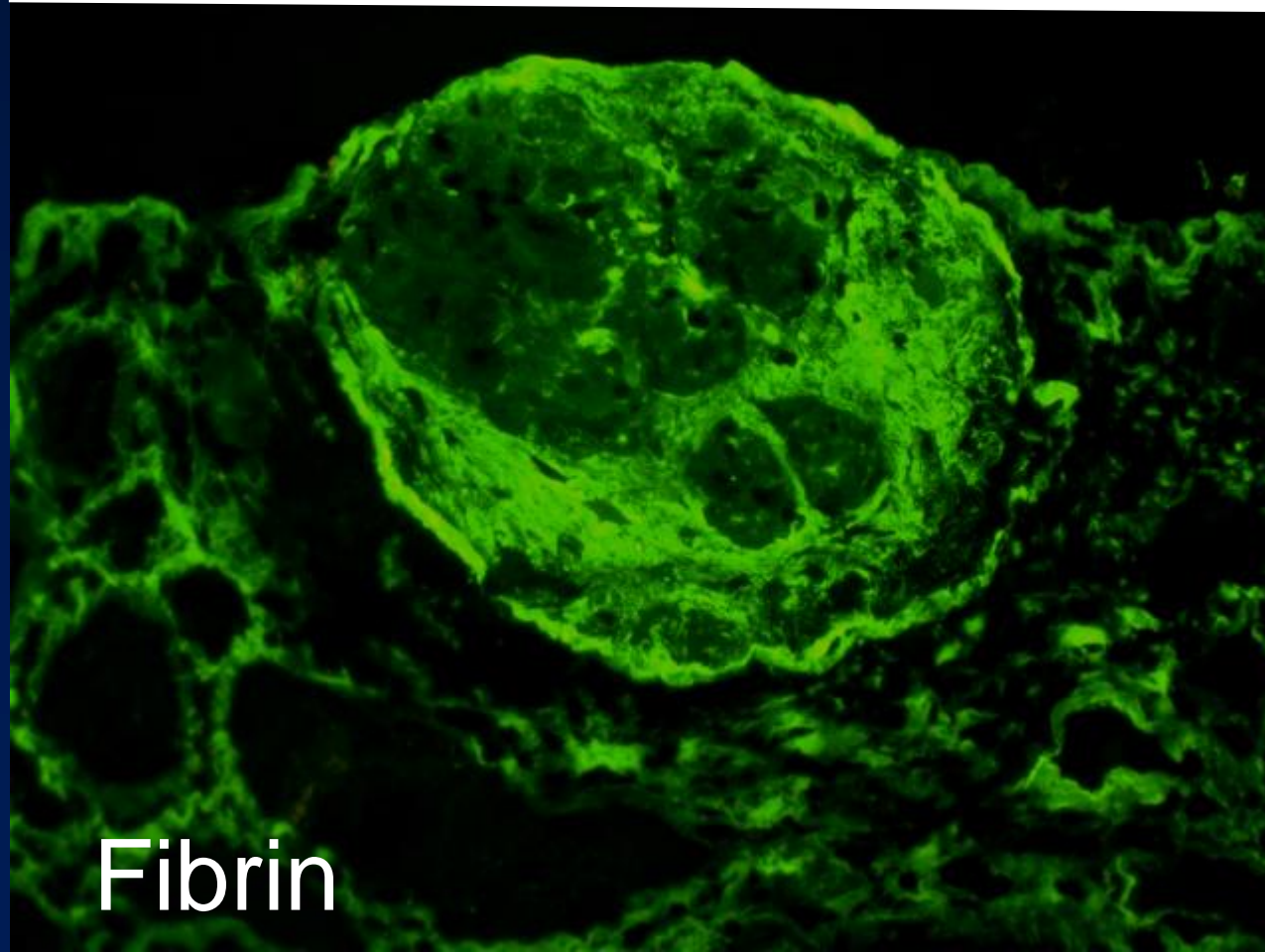
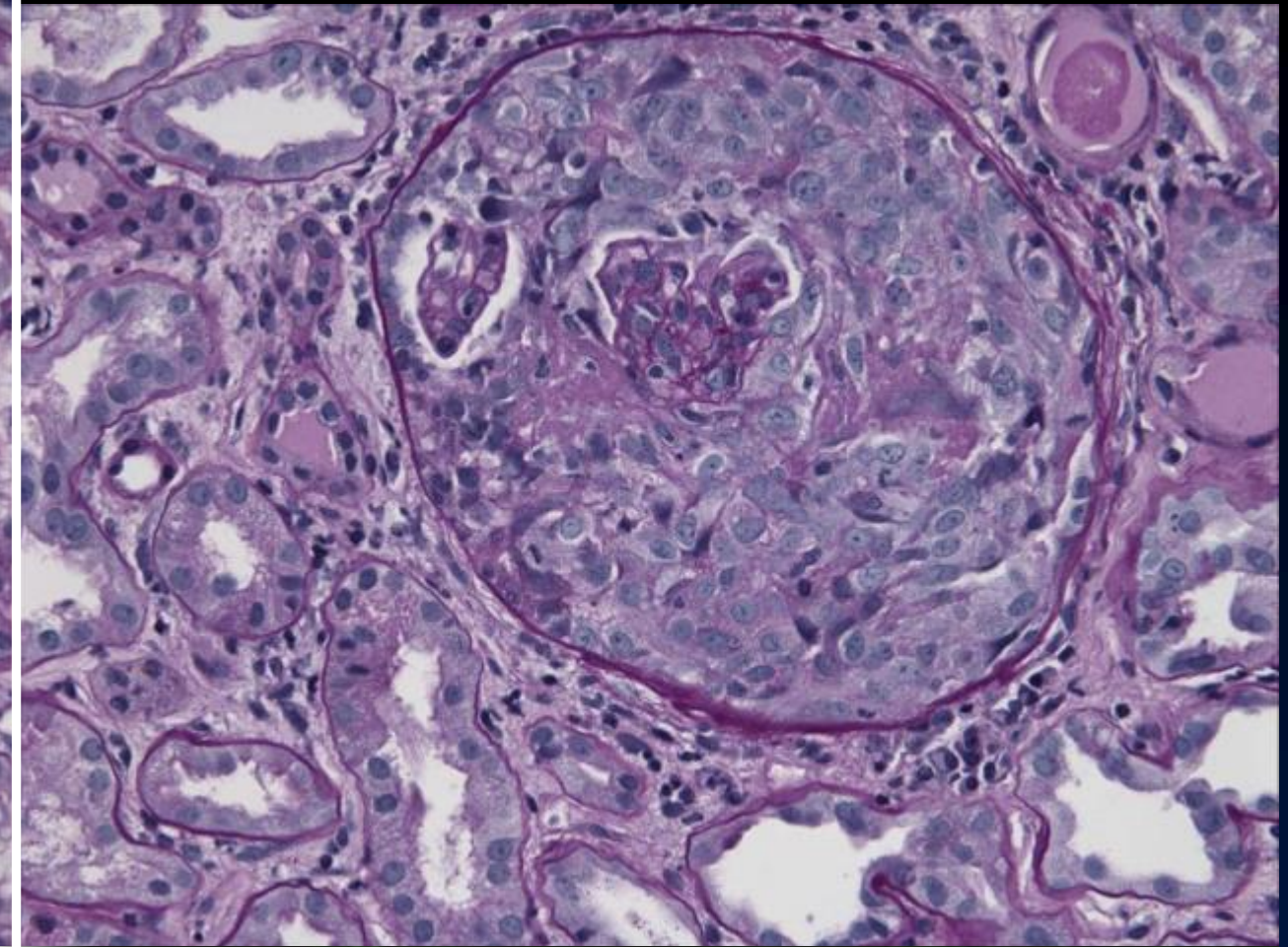
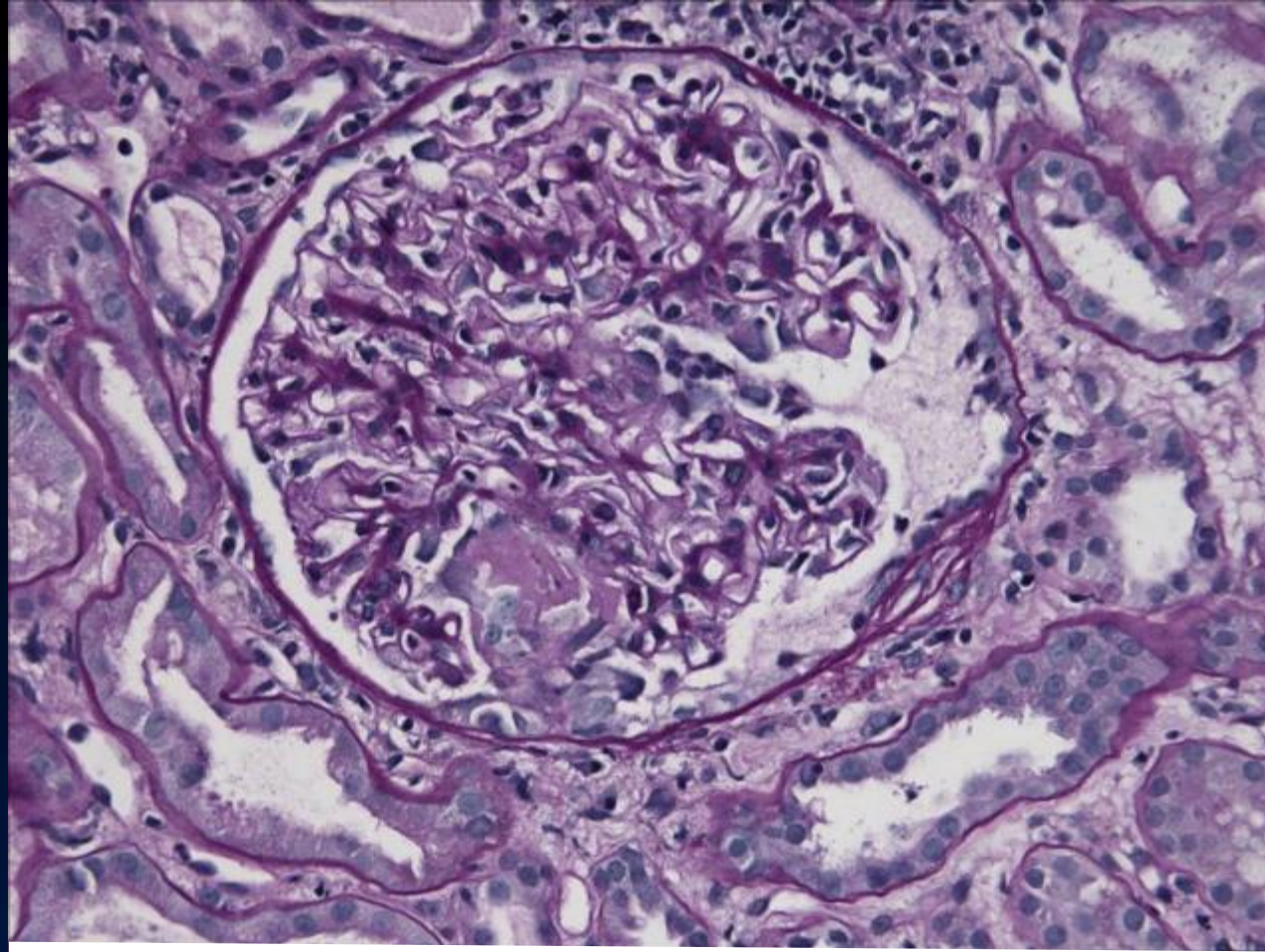


# FOCAL NECROTIZING AND CRESCENTIC GLOMERULONEPHRITIS

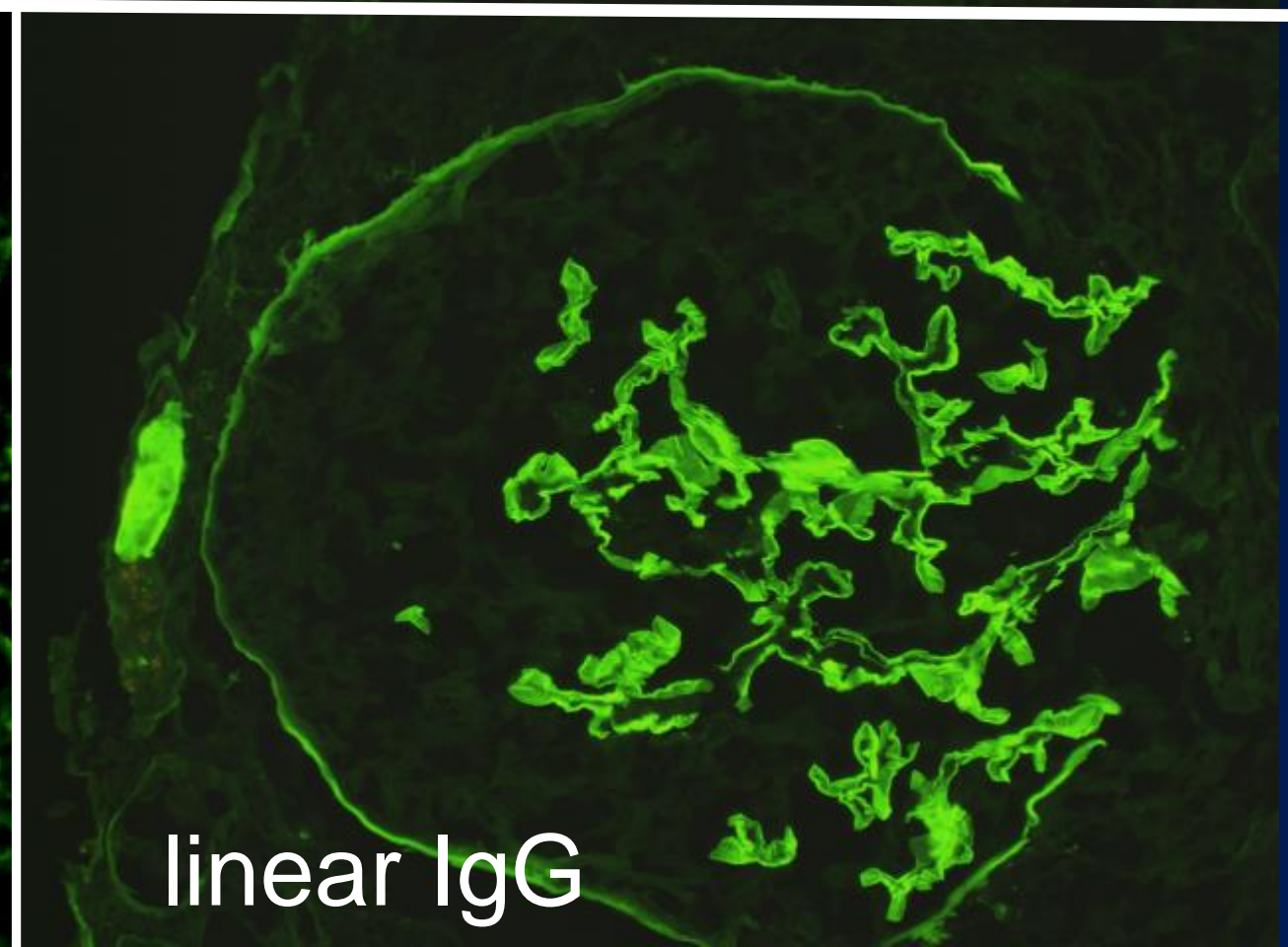
- Idiopathic or primary crescentic glomerulonephritis:
  - Type I, anti-GBM disease
  - Type II, immune complex-mediated
  - Type III, pauci immune polyangiitides (SVV);  
(often ANCA-associated)
    - Microscopic polyangiitis
    - Granulomatosis with polyangiitis
    - Eosinophilic granulomatosis with 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



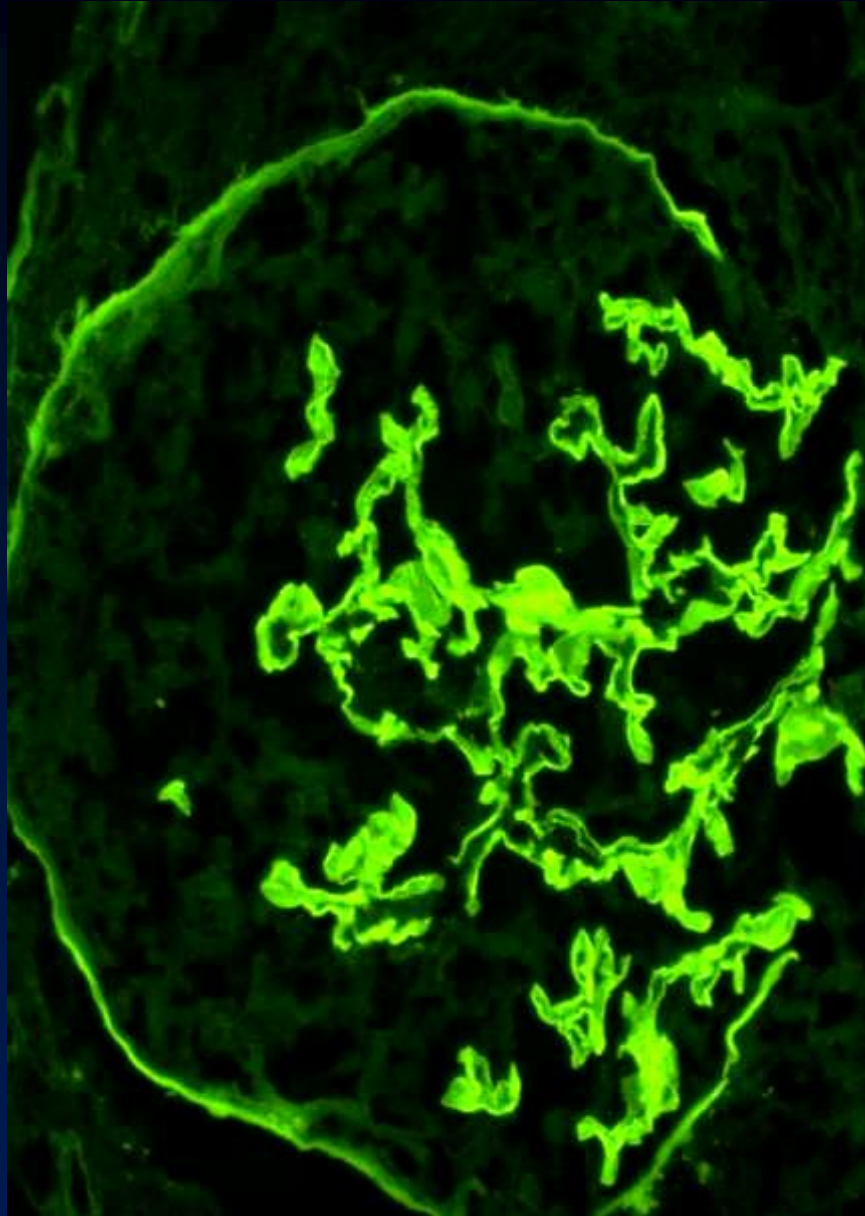
Fibrin



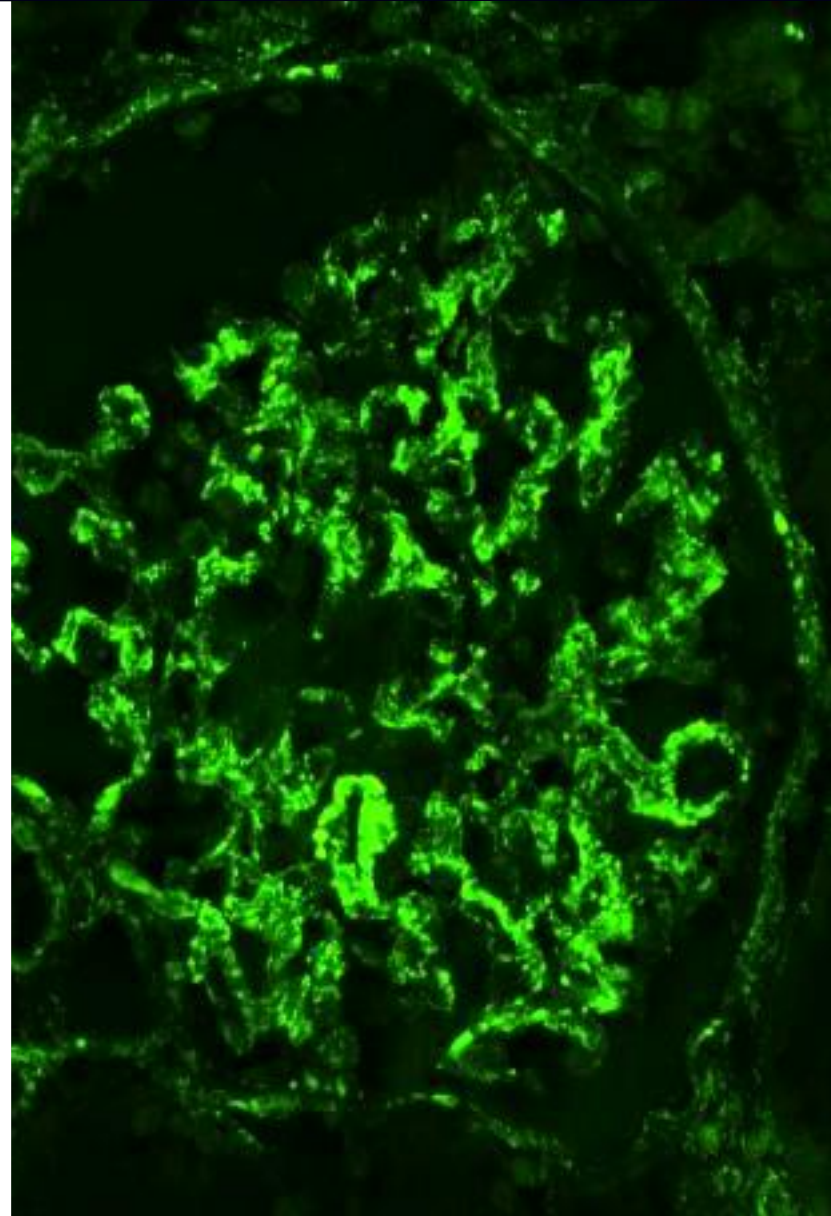
linear IgG



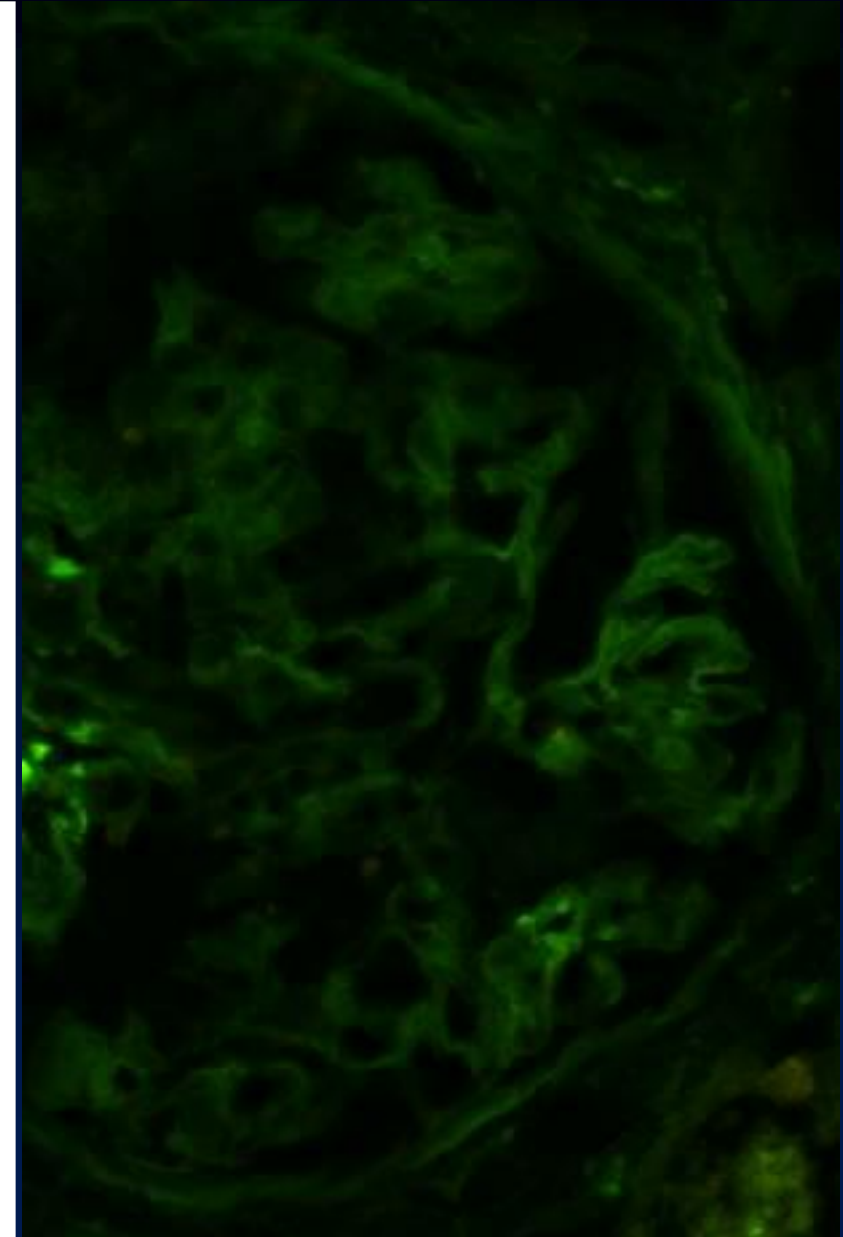
# IMMUNE MECHANISMS OF FOCAL NECROTIZING AND CRESCENT FORMATION



Linear staining for IgG  
Anti-GBM disease  
Goodpasture syndrome



Granular staining for IgG  
Immune-complex  
disease (SLE)

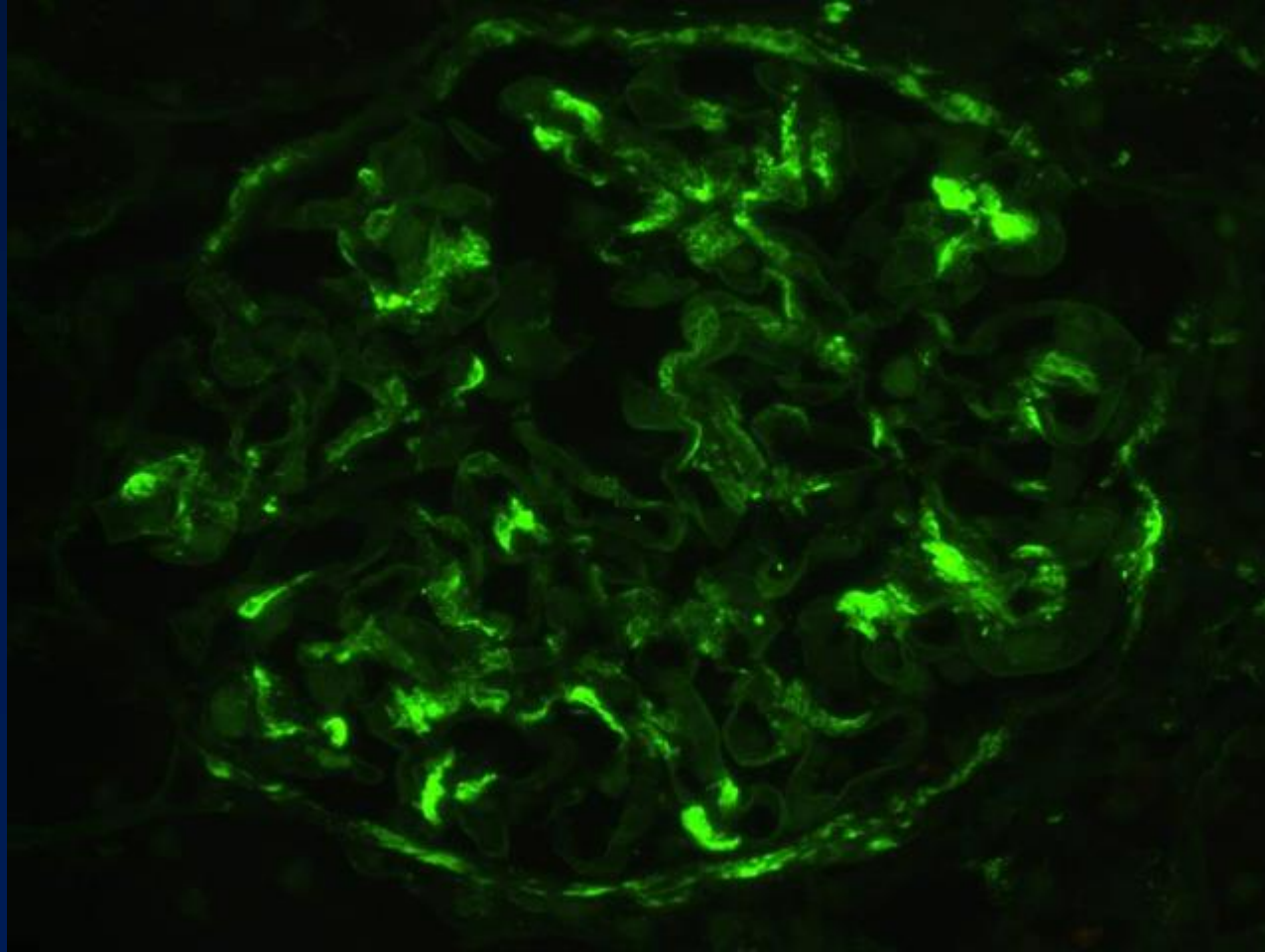
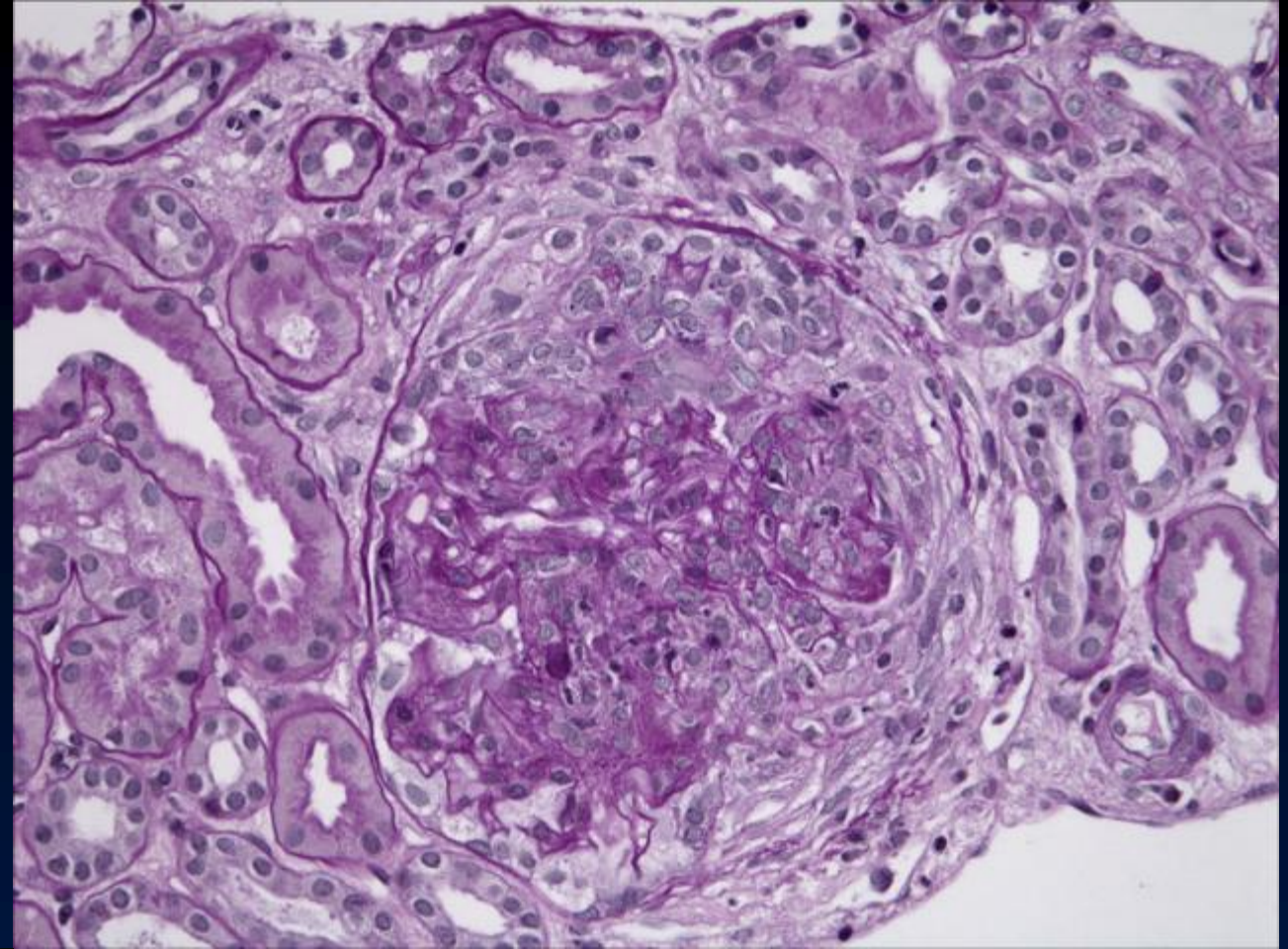


No staining for IgG  
pauci-immune  
disease (usually ANCA)



# Immune complex-mediated crescentic GN

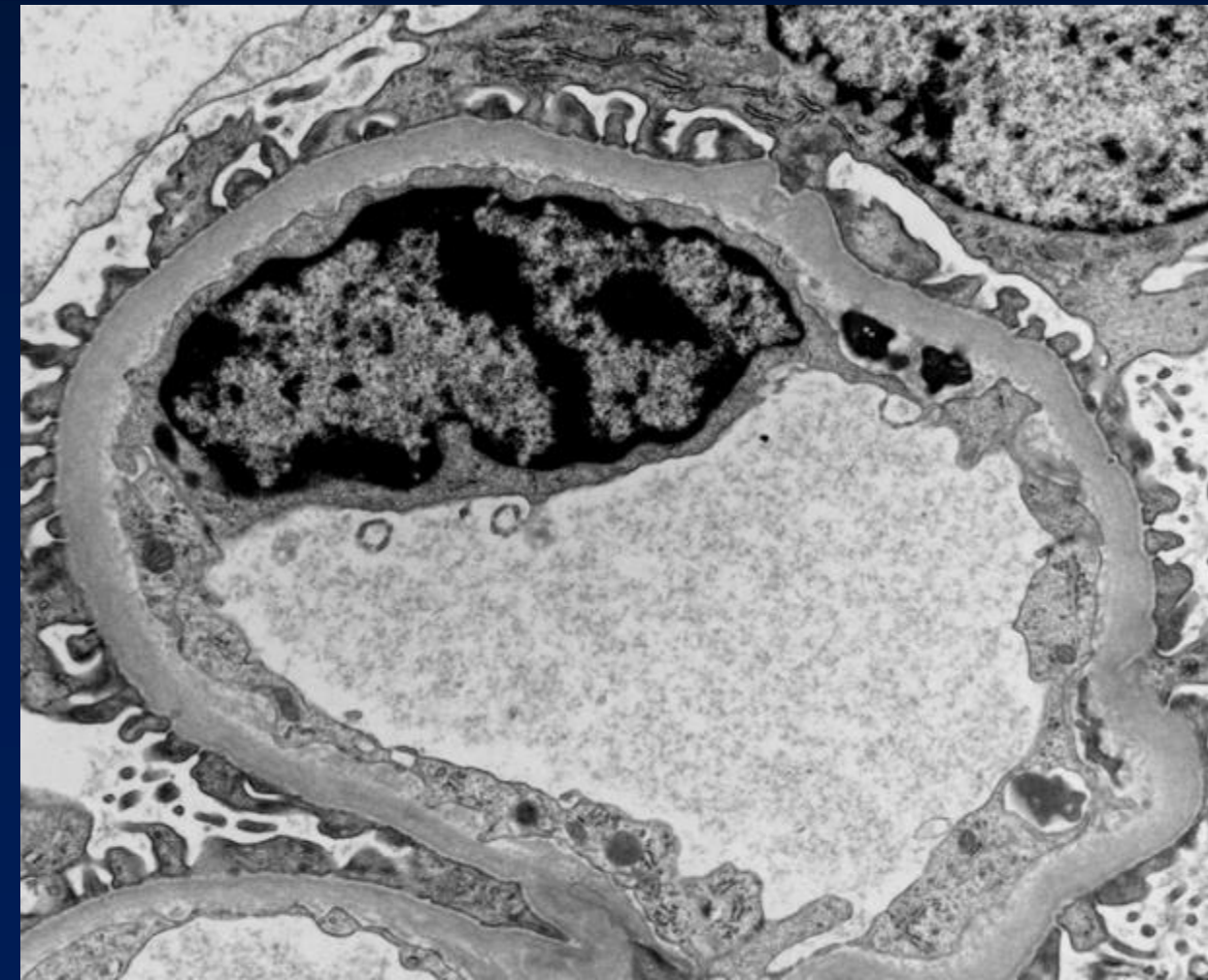
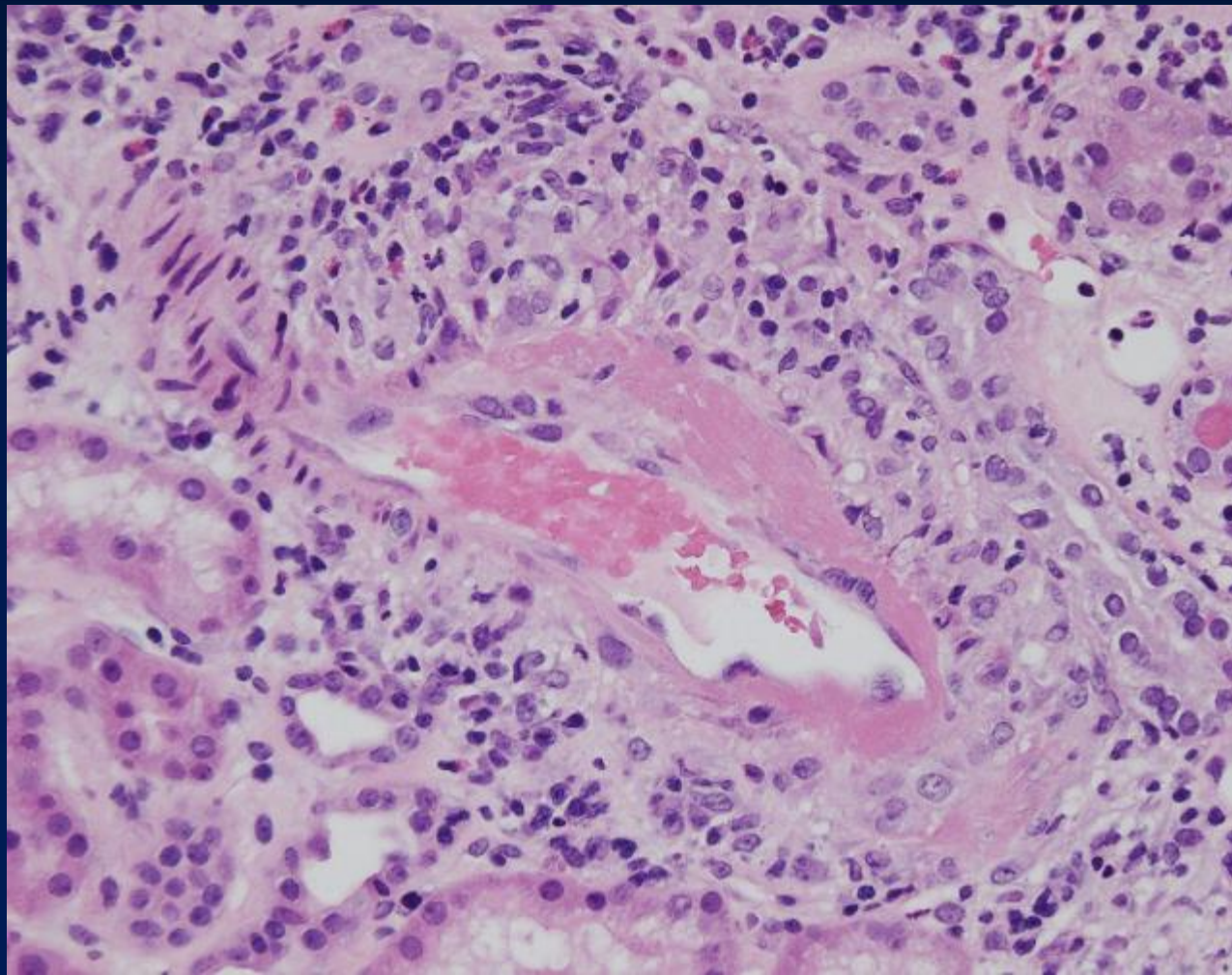
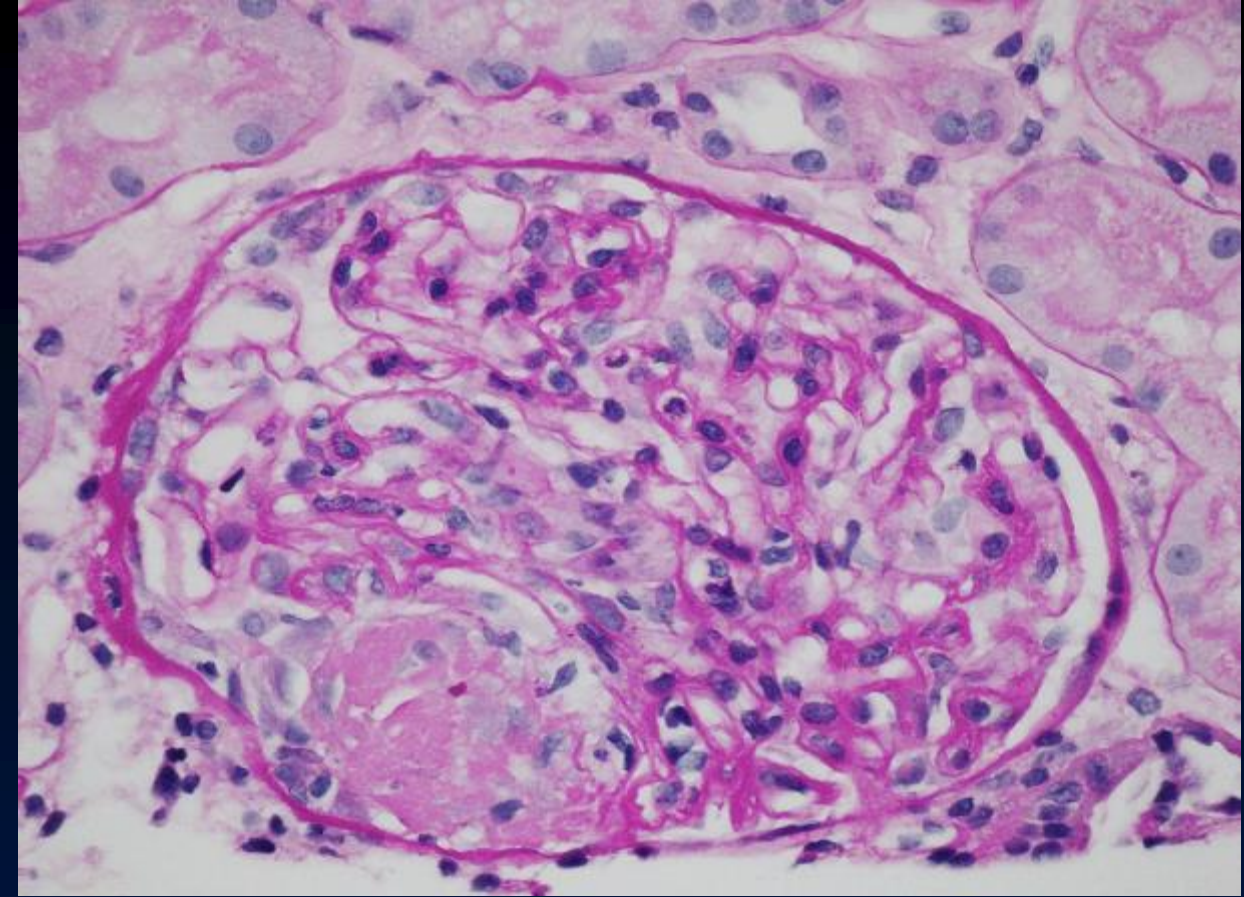
- Lupus nephritis
- IgA nephropathy/HSP
- Infection-associated GN





# Pauci-immune polyangiitis (crescentic GN)

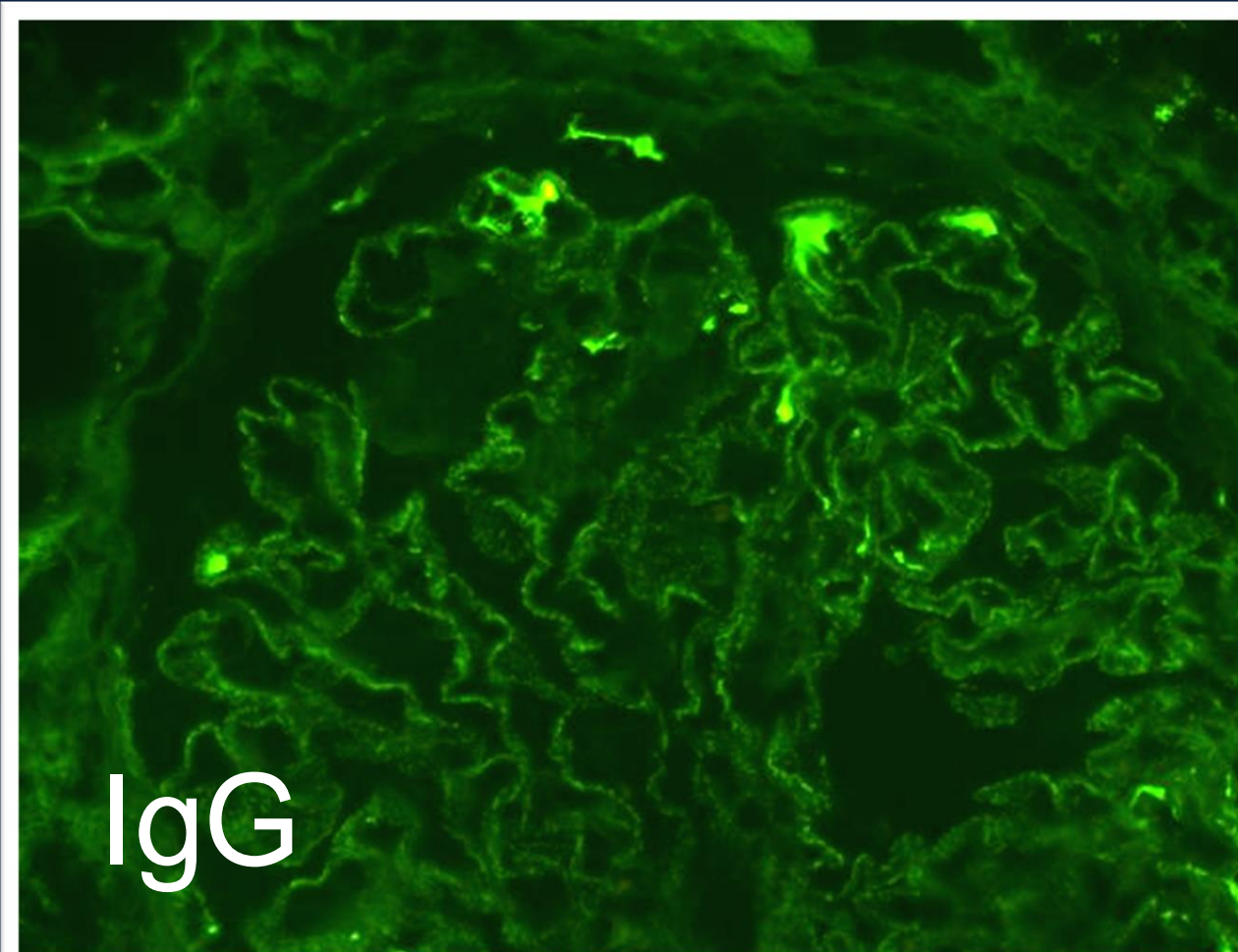
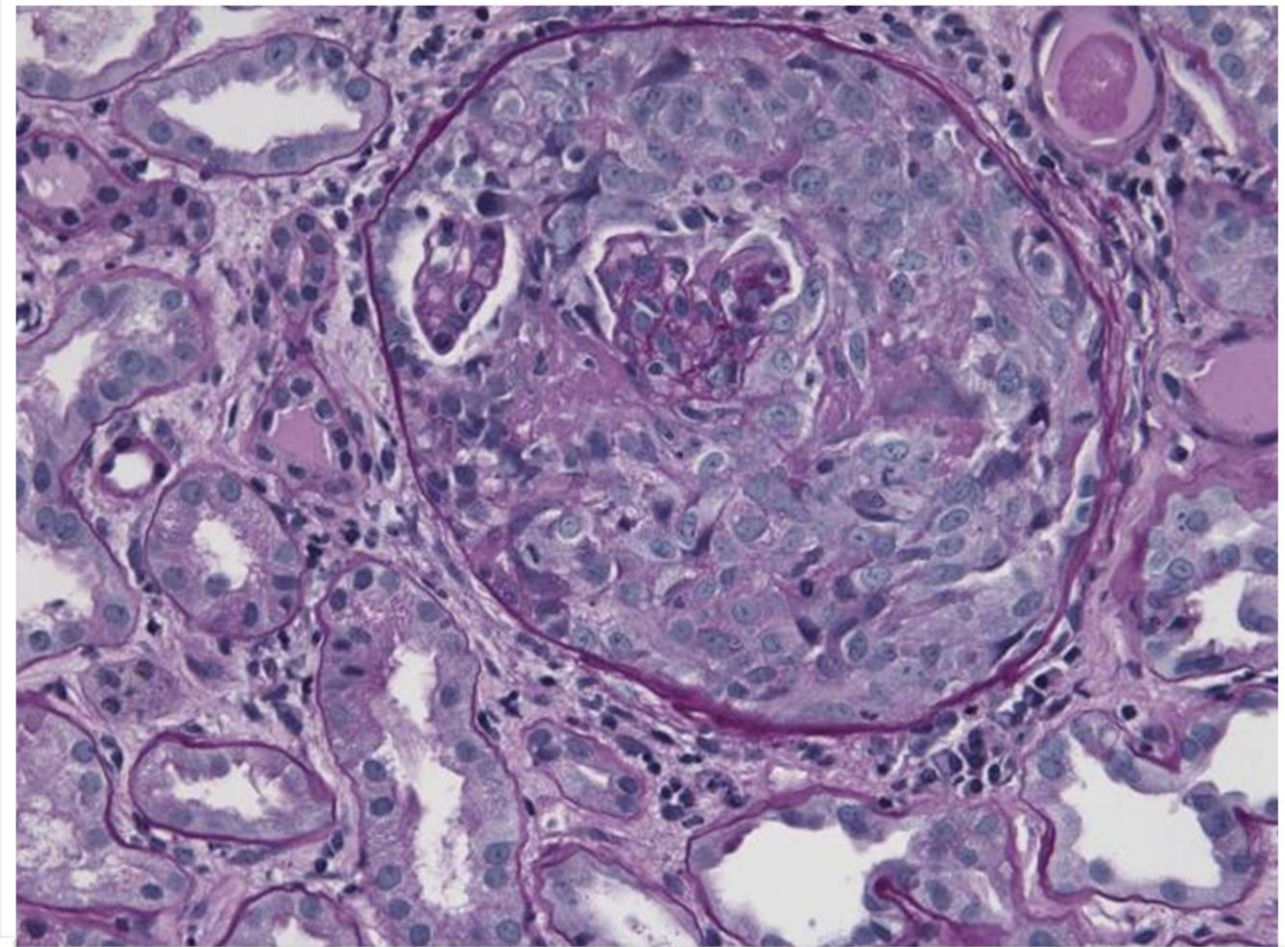
- ANCA-associated microscopic polyangiitis (p-ANCA, MPO)
- Granulomatosis with polyangiitis (c-ANCA, PR3)



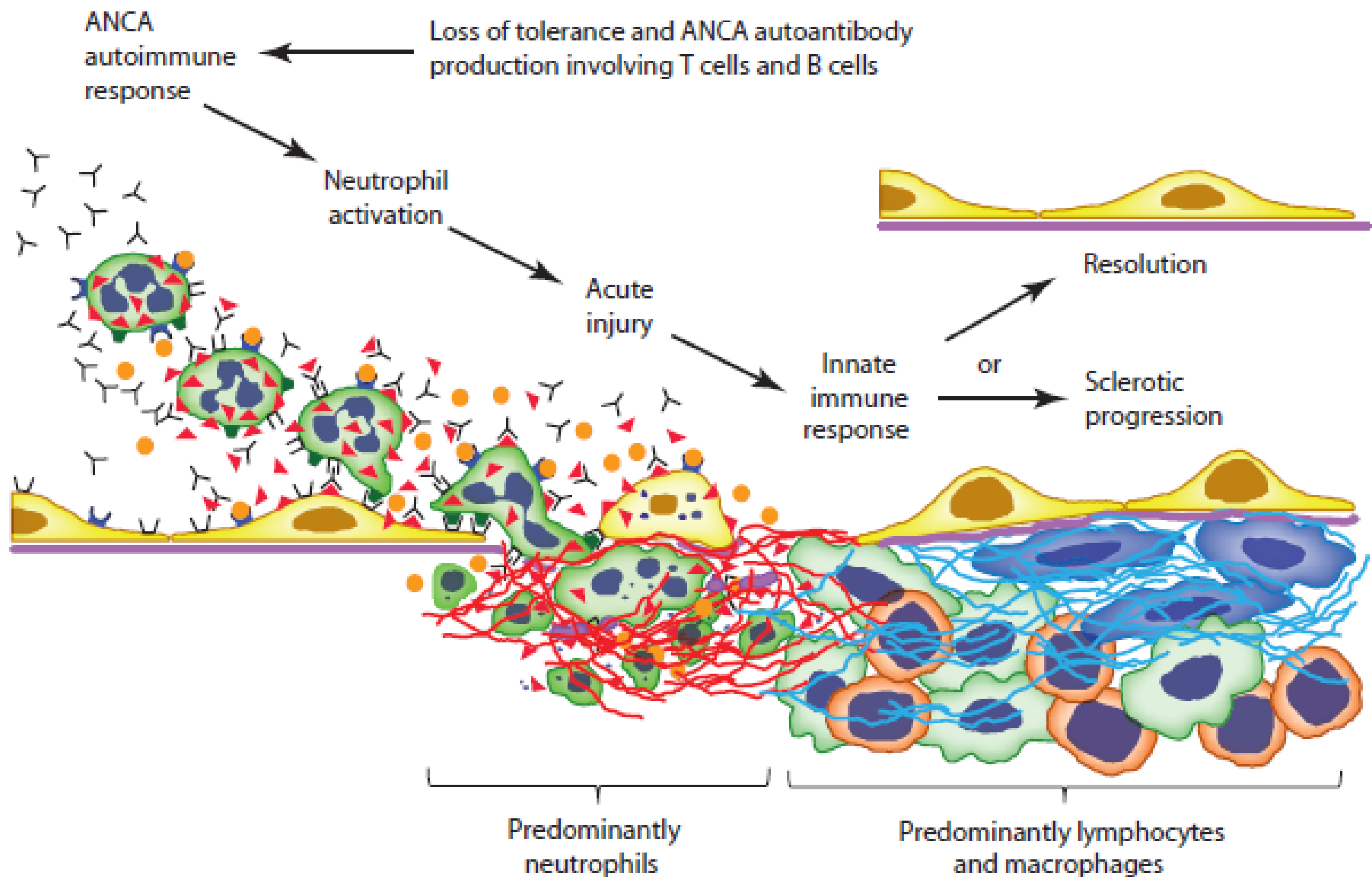


## Drug-induced ANCA crescentic GN:

- 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
- 5.- Membranoproliferative Glomerulonephritis
- 6.- Focal Proliferative and Necrotizing  
Glomerulonephritis
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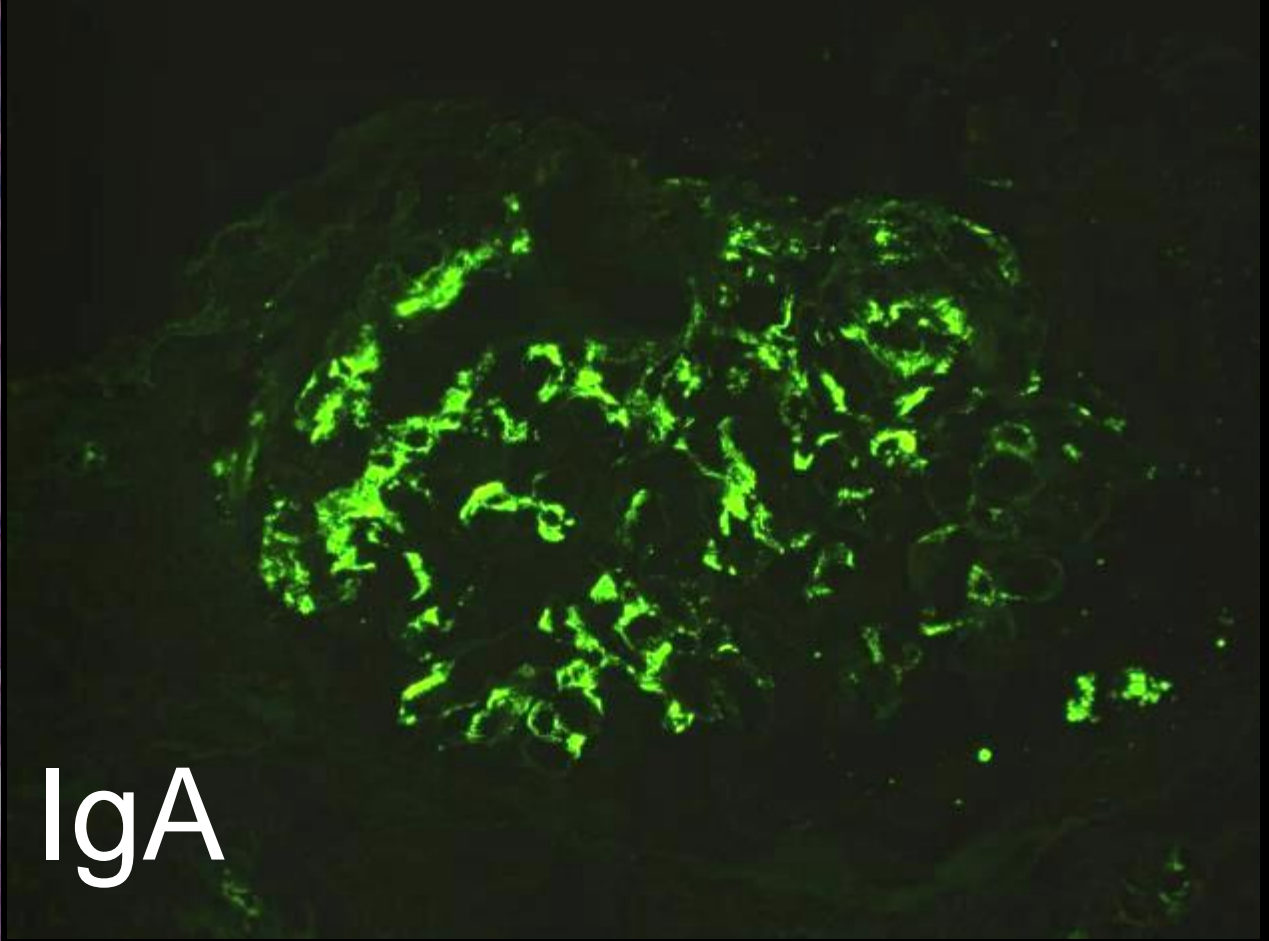
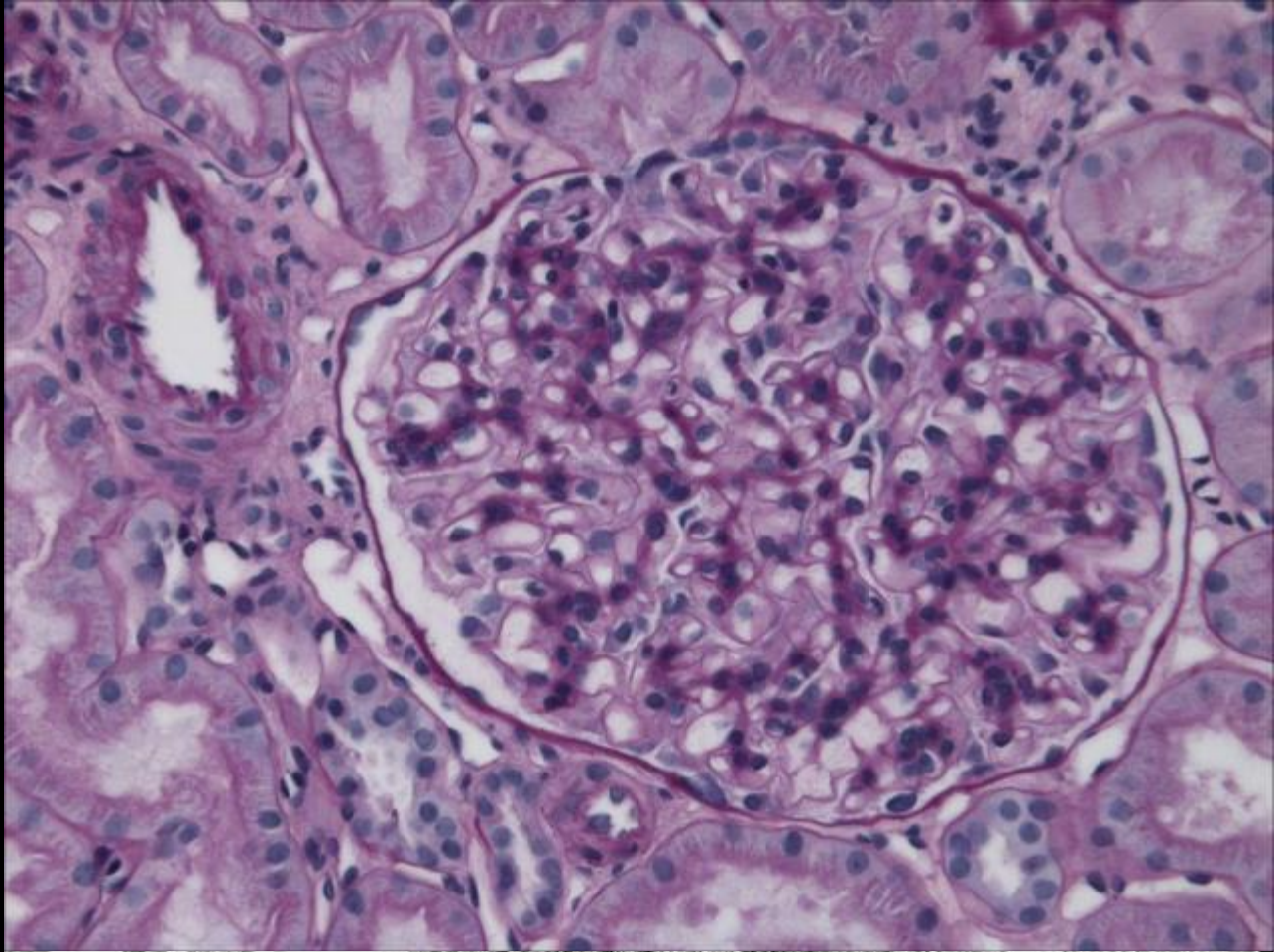
# ASYMPTOMATIC HEMATURIA/PROTEINURIA

## MESANGIOPROLIFERATIVE GLOMERULONEPHRITIS

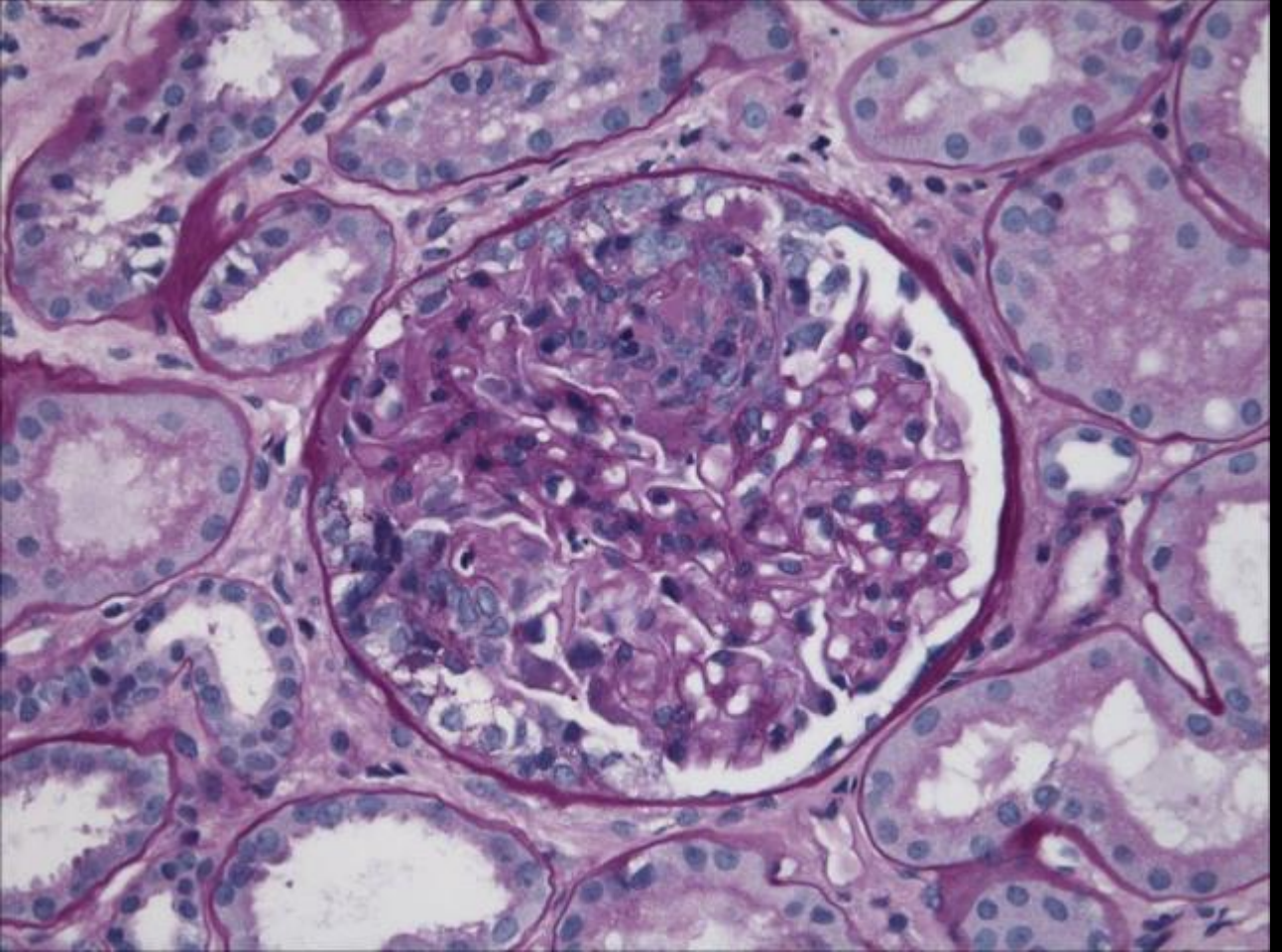
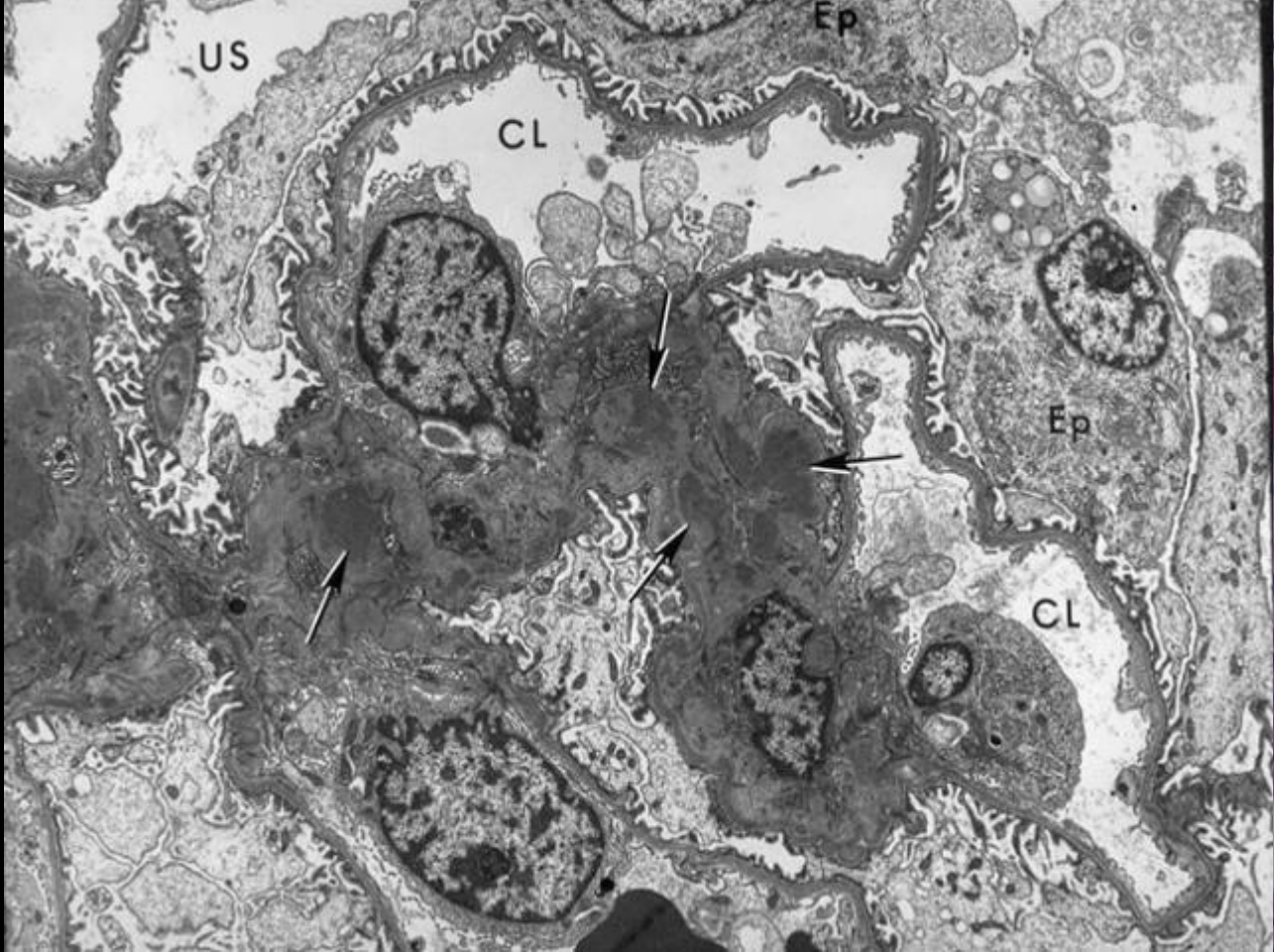
- IgA Nephropathy
- Recovery phase of a postinfectious glomerulonephritis
- Mesangial proliferative lupus nephritis, SLE WHO Class II, and other IC-mediated diseases
- Idiopathic Mesangioproliferative GN
- Some of the deposition diseases



# IgA Nephropathy

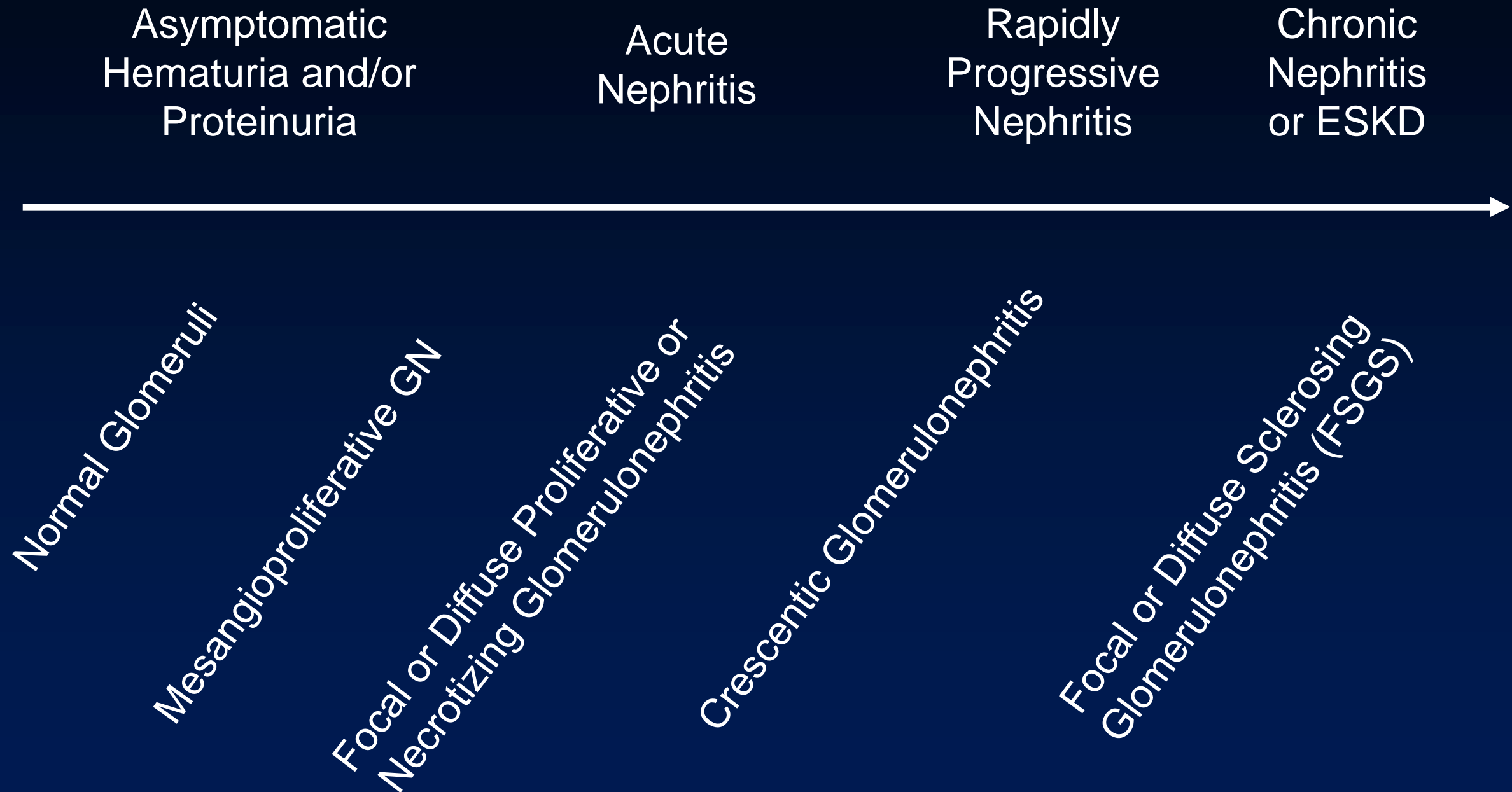


IgA





# 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.)

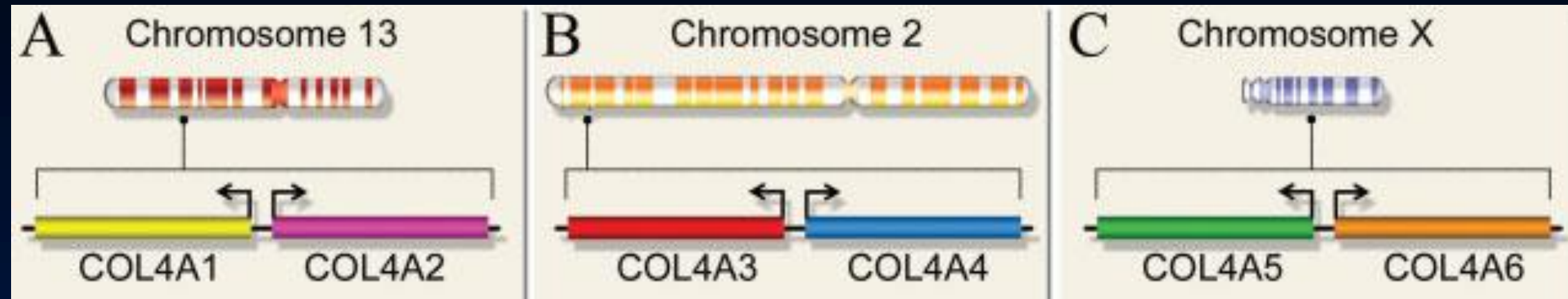
Nail-patella syndrome or hereditary osteo-onychodysplasia (LMX1B, LIM homeodomain transcription factor)

Collagen III glomerulopathy, Fibronectin glomerulopathy

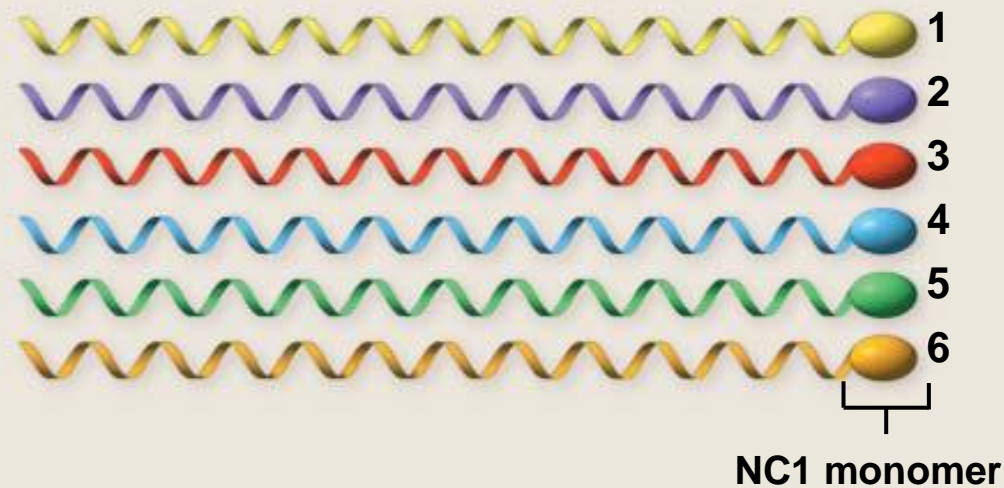
Lecithin-cholesterol acyltransferase deficiency

(Resolving immune complex mediated GN)

# BASEMENT MEMBRANE COLLAGEN GENES AND PROTEINS



## Type IV collagen chains

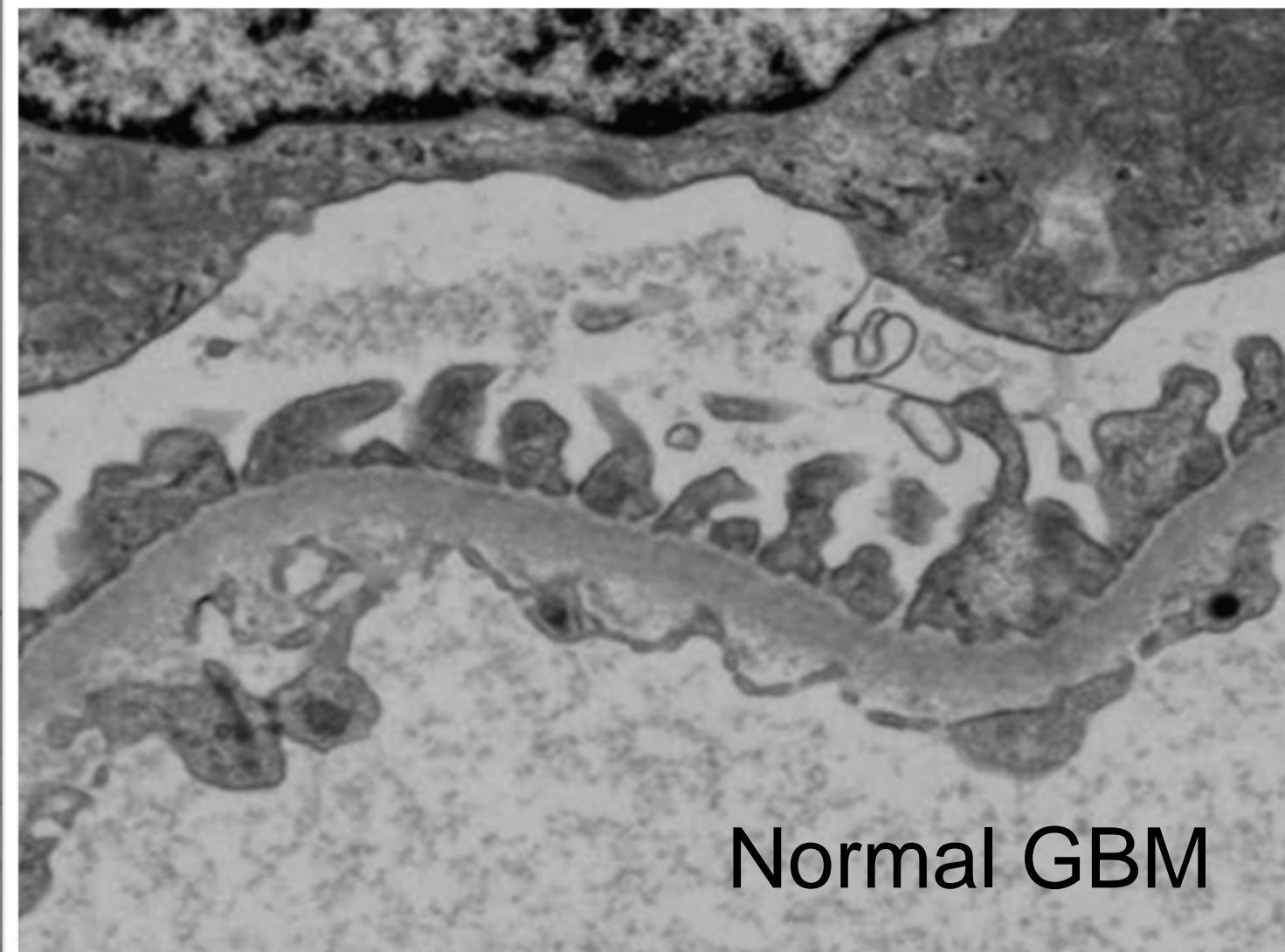
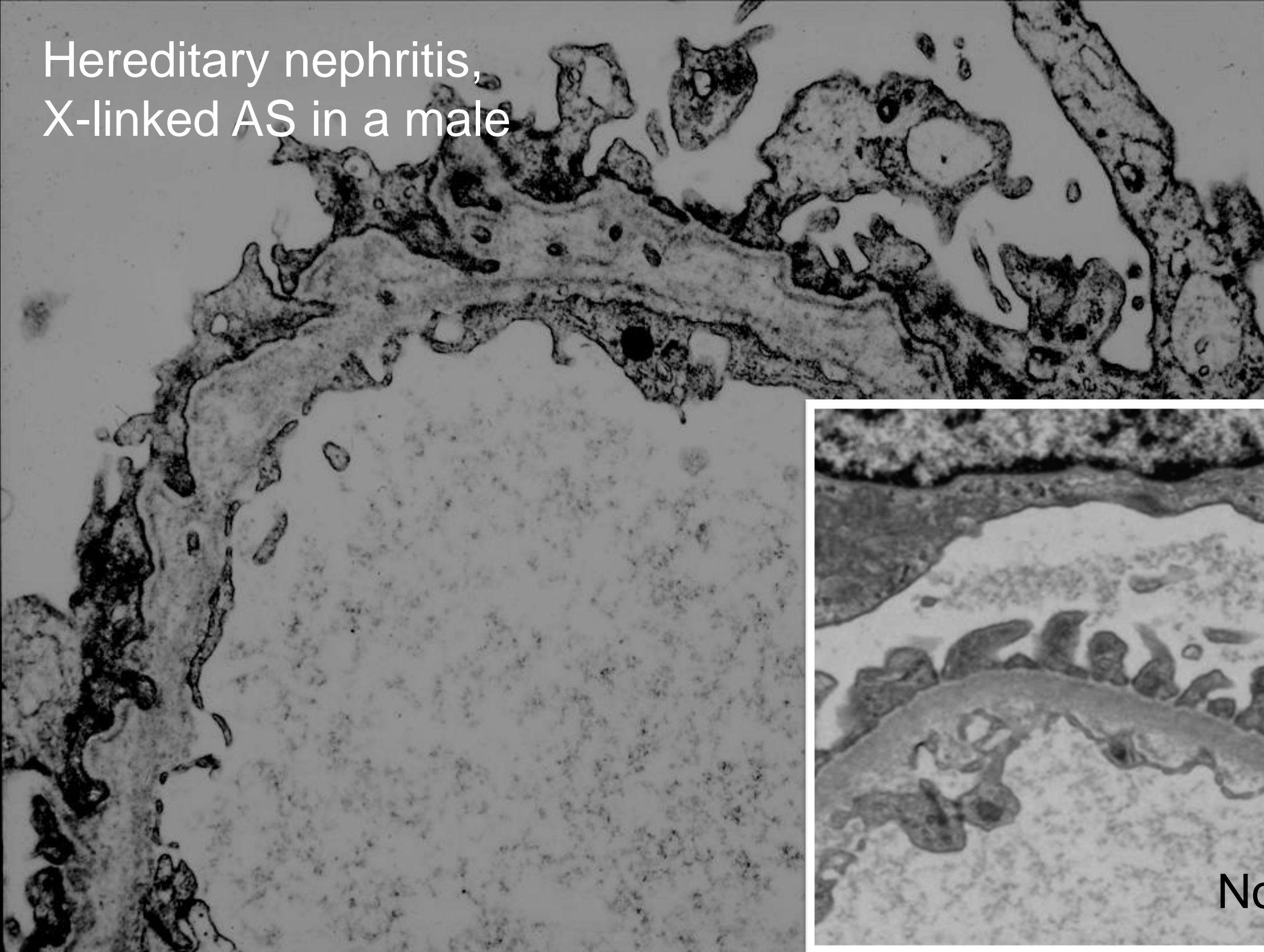


## Protomers

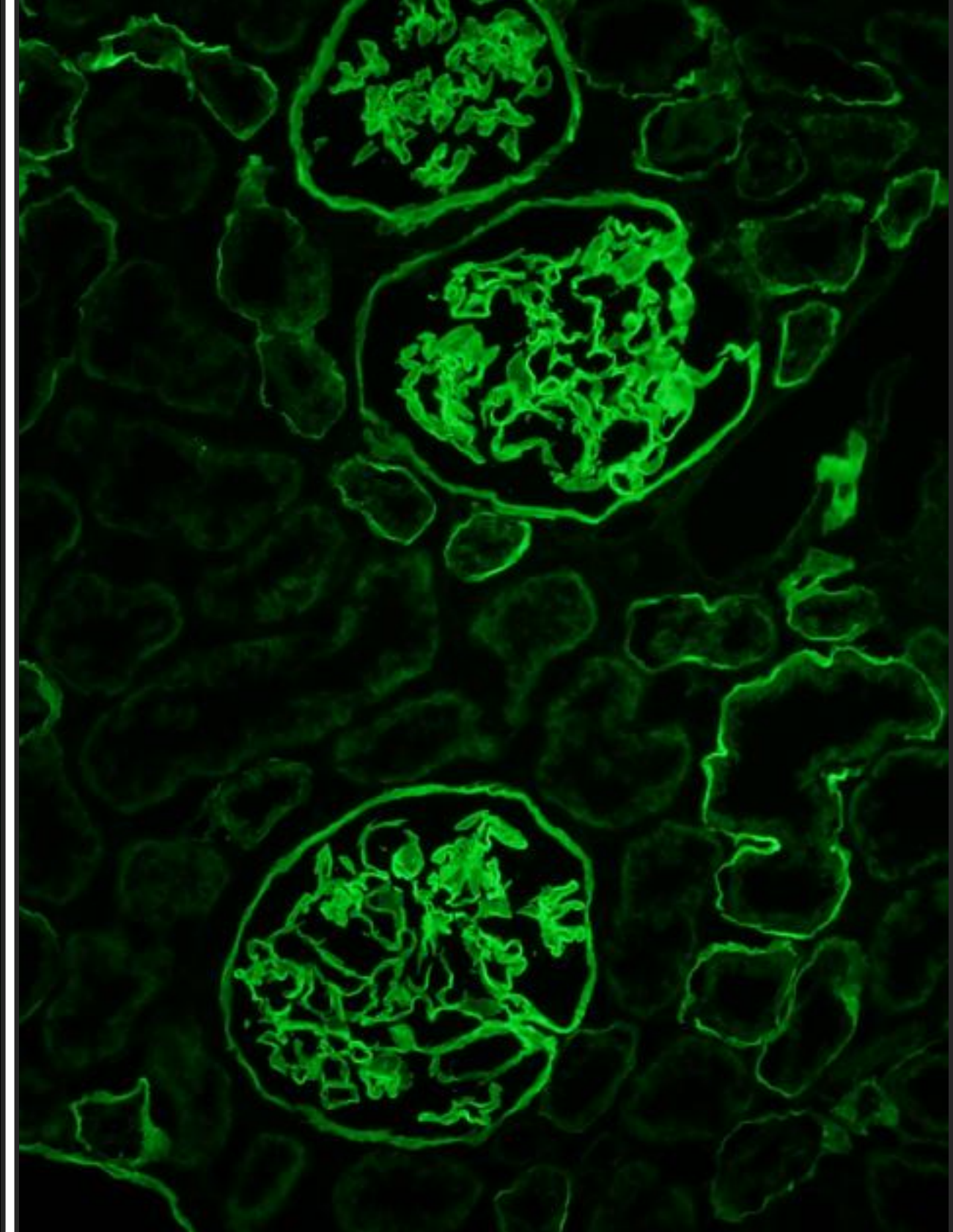
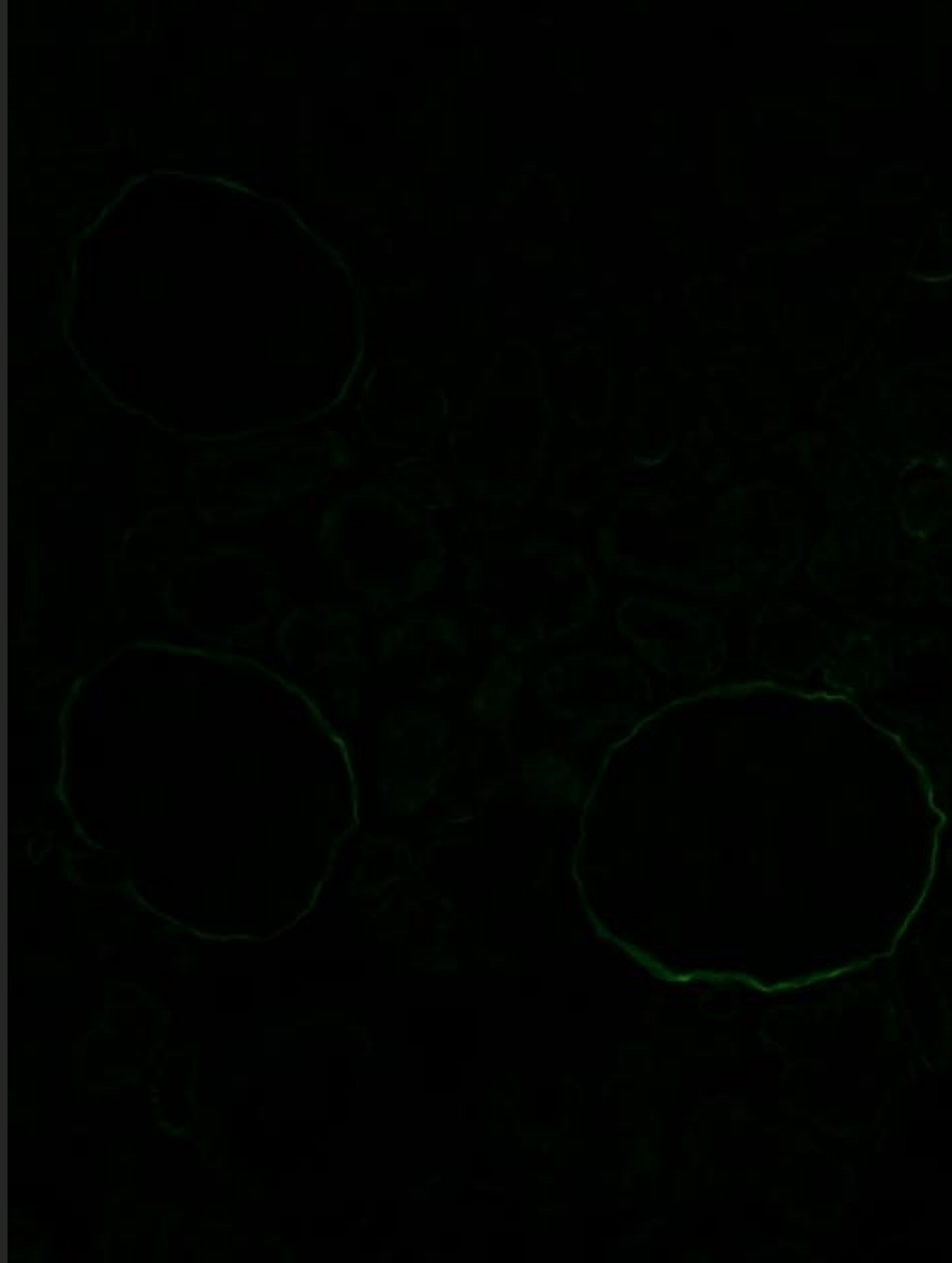




Hereditary nephritis,  
X-linked AS in a male



Normal GBM

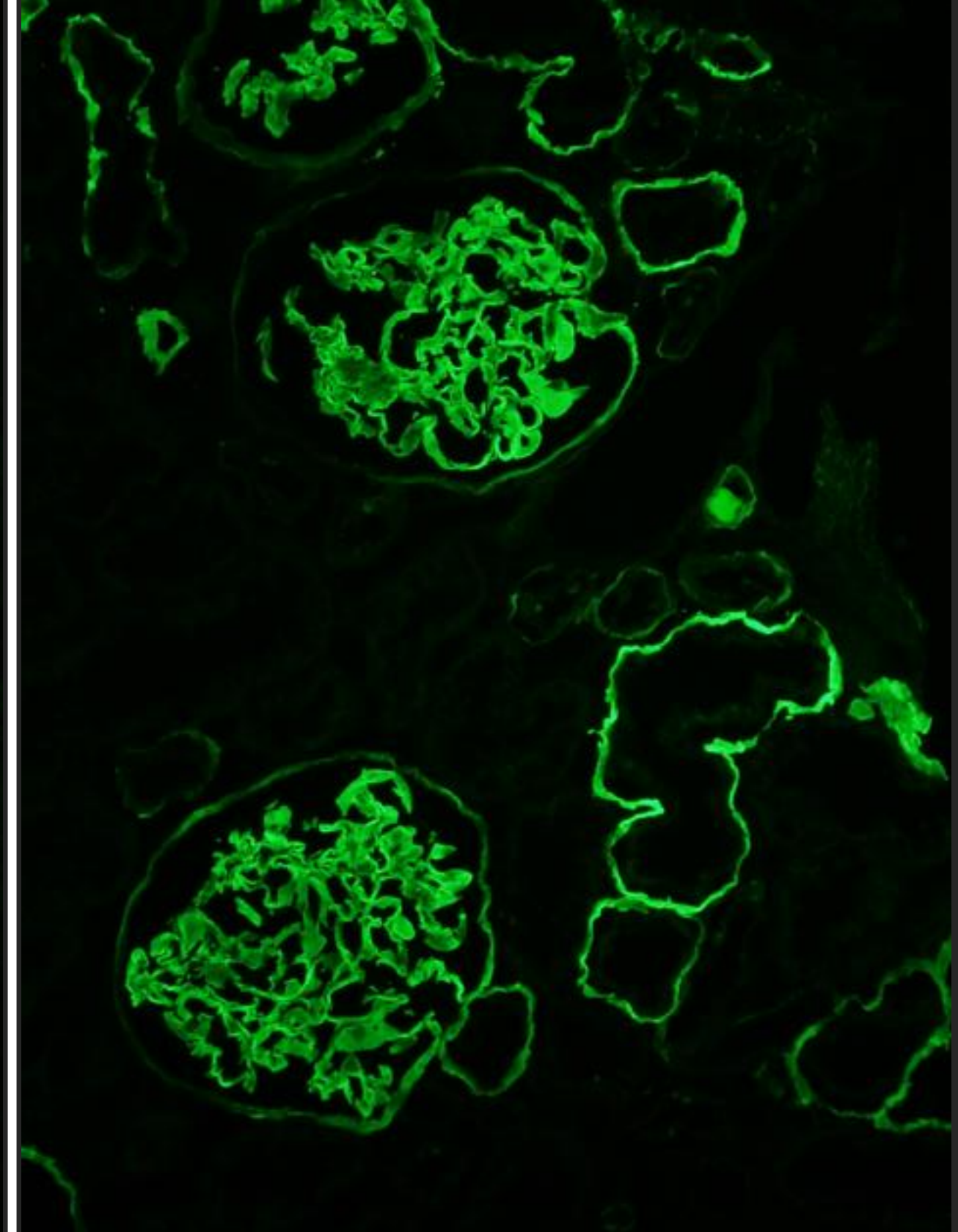


**Patient**

**Alpha5 Collagen IV**

**Normal**





**Patient**

**Alpha3 Collagen IV**

**Normal**

# 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> <i>COL4A4</i>	<i>COL4A3</i> <i>COL4A4</i>	<i>COL4A3</i> <i>COL4A4</i>
Collagen chain	$\alpha 5$	$\alpha 5$	$\alpha 3$ $\alpha 4$	$\alpha 3$ $\alpha 4$	$\alpha 3$ $\alpha 4$
Defective protomer network	$\alpha 3,4,5$ $\alpha 5,5,6$	$\alpha 3,4,5$ $\alpha 5,5,6$ mosaic	$\alpha 3,4,5$	$\alpha 3,4,5$	$\alpha 3,4,5$
Negative stain Kidney	anti- $\alpha 3$ , anti- $\alpha 4$ , anti- $\alpha 5$ , anti- $\alpha 6$	anti- $\alpha 3$ , anti- $\alpha 4$ , anti- $\alpha 5$ , anti- $\alpha 6$ (mosaic)	anti- $\alpha 3$ , anti- $\alpha 4$ , anti- $\alpha 5$	anti- $\alpha 3$ , anti- $\alpha 4$ , anti- $\alpha 5$	normal
Negative stain Skin	anti- $\alpha 5$ , anti- $\alpha 6$	anti- $\alpha 5$ , anti- $\alpha 6$ (mosaic)	normal	normal	normal

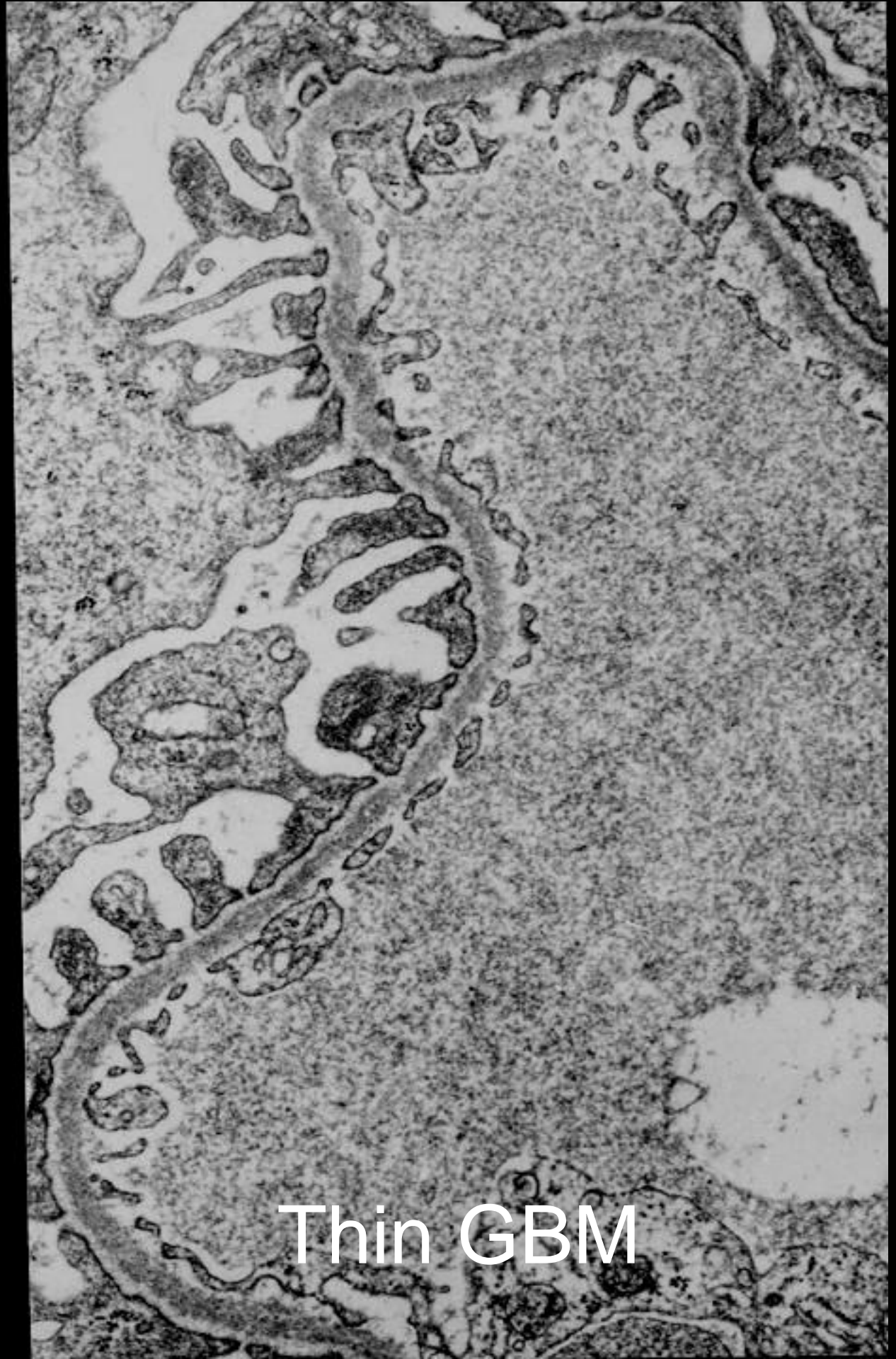


# CLINICAL PRESENTATION OF AS

	<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) 80%(40y) 100%(60y)</b>	<b>12%(45y) 30%(60) 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

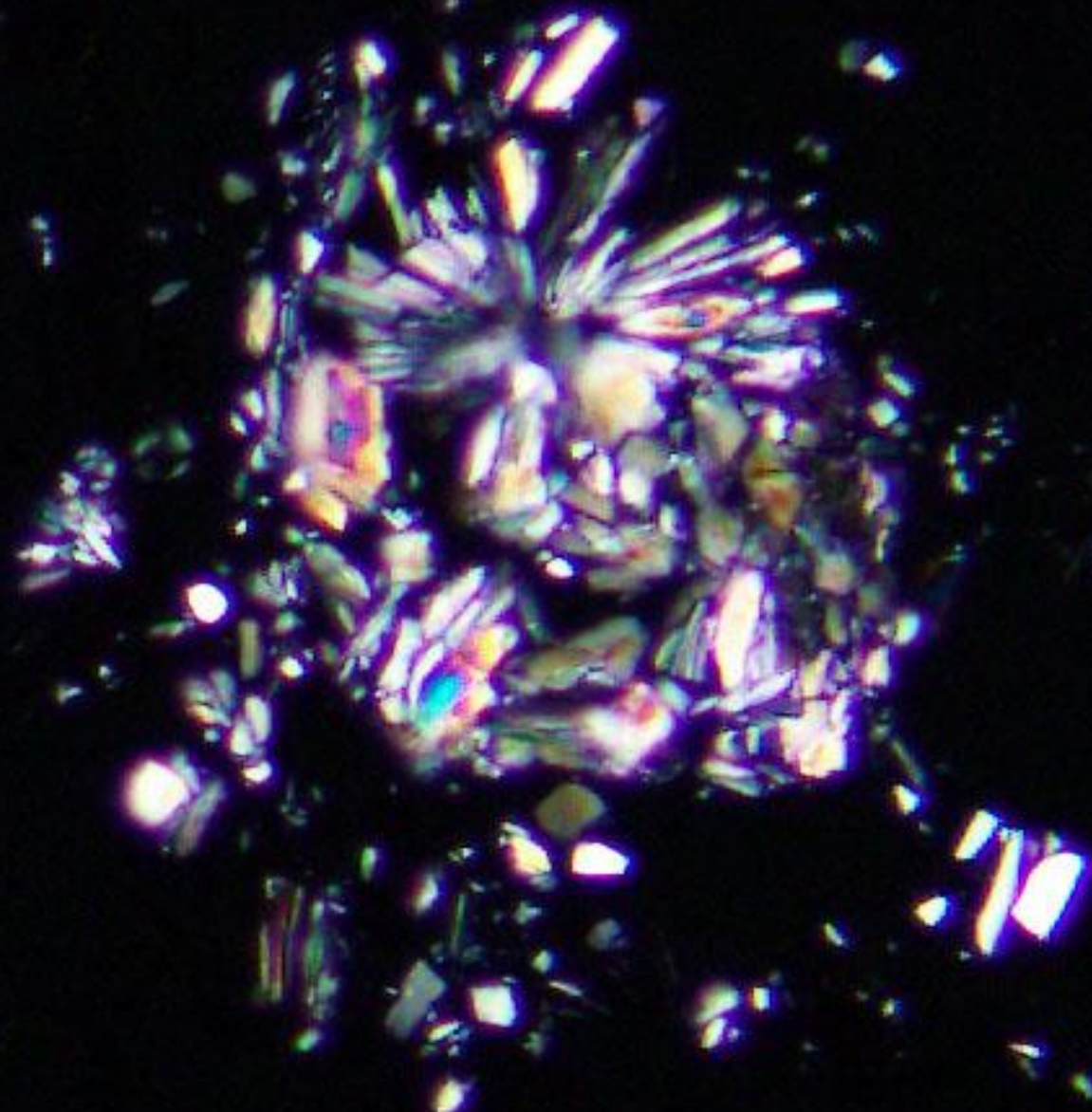
Complement  
abnormalities

Thrombotic  
Angiopathies

Genetic defects  
of the GBM

Rational Therapy





Thank you