Histopathological patterns of glomerular disease

George Liapis

Pathologist, Director NHS

1st Department of Pathology, National and Kapodistrian University of Athens,

Laiko General Hospital

Benefit of kidney biopsy in native kindeys

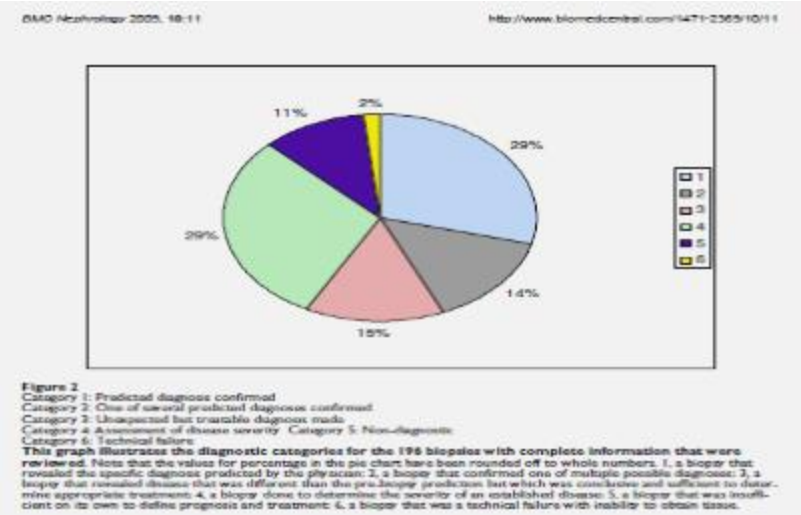


Figure 2
Category 1: Predicted diagnosis confirmed
Category 2: One of several predicted diagnoses confirmed
Category 3: Unexpected but treatable diagnosis made
Category 4: Assessment of disease severity Category 5: Non-diagnostic
Category 6: Technical failure
This graph illustrates the diagnostic categories for the 198 biopsies with complete information that were reviewed. Note that the values for percentage in the pie chart have been rounded off to whole numbers. 1, a biopsy that revealed the specific diagnosis predicted by the physician; 2, a biopsy that confirmed one of multiple possible diagnoses; 3, a biopsy that revealed disease that was different than the pre-biopsy prediction but which was conclusive and sufficient to determine appropriate treatment; 4, a biopsy done to determine the severity of an established disease; 5, a biopsy that was insufficient on its own to define prognosis and treatment; 6, a biopsy that was a technical failure with inability to obtain tissue.

- Diagnosis without biopsy ~50%.
- Unexpected findings ~15%.

BMC Nephrology 2009 May 21; ***10:11***

Benefit of kidney biopsy in transplants

- *36% diagnosis is changed,*
- *~60% therapy is changed,*
- *22% unnecessary immunosuppression is avoided.*

No. of biopsies	Changed clinical diagnosis	Changed therapy	Avoided immunosuppression	References
		1289		
Heptinstall Pathology of the Kidney 7th Edition				
89	46%			(55)
35	46%	46%		(54)
64	42%	42%	30%	(53)
240		83%		(56)
95	30%	38%	18%	(57)
263		55%		(58)
100	27%			(60)
82		42%	19%	(59)
Total 968	**36%**	**59%**	**22%**	
THE RENAL ALLOGRAFT BIOPSY				

Heptinstall's Pathology of the kidney

Two classifications: two different approaches/views for the same purpose

1. From clinical findings to histology.

- Based on clinical findings, what is the expected histology?

2. From histology to clinical image.

- Based on histology, what are the expected clinical symptoms?

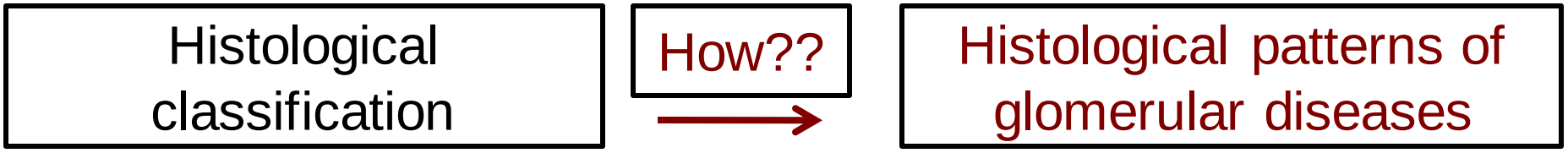
- Two classifications:
  - Based on clinical syndromes
  - Based on histology
  - Histological findings without relative clinical finding
  - Clinical finding without relative histological finding

One goal: Diagnosis, therapy

Discussion!

From histology to clinical syndromes

- Biopsy: “gold standard” for diagnosis.



- **Ideal:** one histological pattern, one disease. Not in real life!
- **Different histological patterns** can be seen **in the same disease.**
- **The same histological pattern**, can be seen in **different diseases.**

Variety of histology in the same disease

- Heterogeneity in the natural course, morphological diversity in some diseases (lupus nephritis, IgA nephropathy).
- Time of biopsy, disease progression (acute vs chronic, early vs late GN).
  - Post infectious GN.
  - Membranoproliferative GN.
  - Transplant glomerulopathy
  - Membranous Glomerulopathy (four stages)
  - Vasculitis (necrosis vs sclerosis)
- Lesions after treatment.
  - Therapy before biopsy.
  - Repeat biopsy
- Inflammation or a second disease on the ground of the main disease (IgA nephropathy on the ground of Diabetic nephropathy).
- Primary vs Secondary GN, implicating different pathogenetic mechanism
  - Membranous Primary vs Secondary (different causes).
  - IgA nephropathy (IgA nephropathy vs post infectious IgA staphylococcal GN, vs other secondary IgA like cirrhosis associated, etc).

Common histological patterns in different diseases

- Inflammation, no inflammation (glomerulus has no many ways to "react" in damage).
  - **Glomerulonephritis (intraglomerular inflammation).**
  - **Glomerulopathy (no glomerular inflammation).**
- Different diseases can affect the same glomerular segments.
  - SLE vs IgA nephropathy, Immunoflourescence allows the distinction (both can result in mesangial and/or endocapillary changes).
  - Cryoglobulinemic GN vs C3 GN vs SLE (all can have membranoproliferative pattern, again Immunofluorescence allows the distinction).

Final stage of glomerular diseases

- In the final stage global and segmental glomerulosclerosis appears; at this stage is not feasible the distinction among diseases. Defining original disease can be a difficult task, however, in some cases can be achieved.
- At chronic stage, biopsy shows findings of “Focal Segmental Glomerulosclerosis” (FSGS), meaning **not the original disease, but the pattern of injury** (including immune complex diseases, such as IgA nephropathy, C3 GN, Lupus nephritis etc).

Heptinstall Pathology of the Kidney 7th Edition

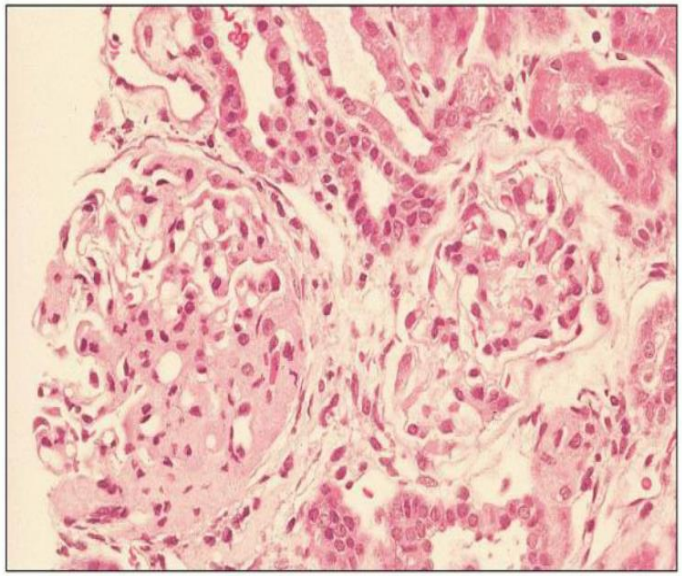


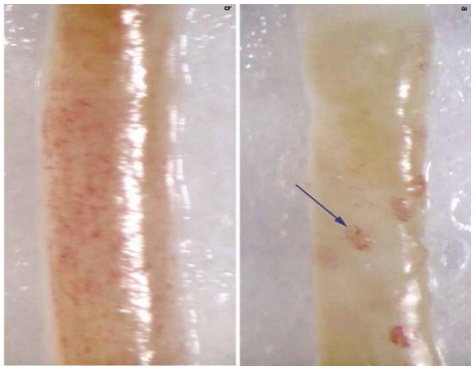
FIGURE 12.8 IgA nephropathy resembling focal segmental glomerulosclerosis (M0 E0 S1 T0). The glomerulus at left shows perihilar segmental sclerosis with associated hyalinosis as well as an increase in mesangial matrix; however, neither glomerulus shows mesangial or endocapillary hypercellularity. A small number of red blood cells are seen within a tubular lumen above the segmentally sclerotic glomerulus. (H&E, ×400.)

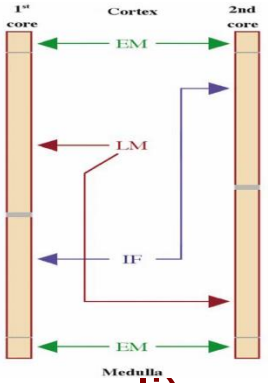
Do we need morphological patterns/histology?
Knowing causes isn't enough?

- **One cause may result in different diseases.**
  - Hematological diseases can affect with different ways the parenchyma, amyloidosis vs others (myeloma cast nephropathy, Light chain DD etc), prognosis and therapy can be different, according to the pattern of injury.
- **One cause may result in different types of injury, clinical manifestations, variable degree of severity and prognosis, therapy.**
  - mesangial vs endocapillary GN (endocapillary GN has a different presentation, required more aggressive therapy).
  - membranoproliferative vs mesangial vs endocapillary.
  - GN with many crescents vs GN without, or with minimal crescents.
- **Defining Chronicity** (chronic changes can change therapy, in severe chronicity aggressive therapy is avoided – there is no benefit).

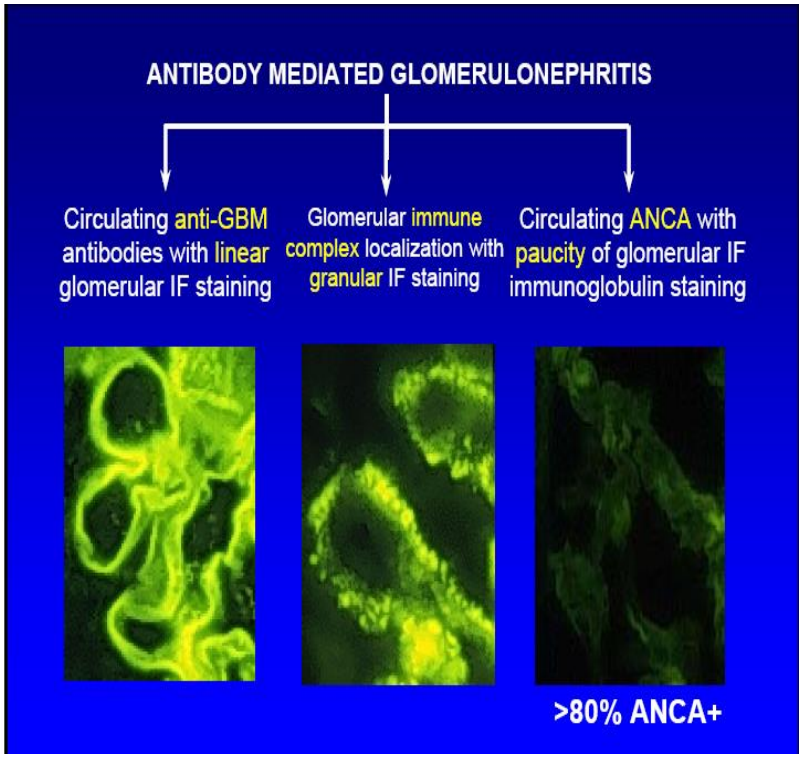
Final diagnosis is a combination of histological patterns + causes.

Important for pathological examination:



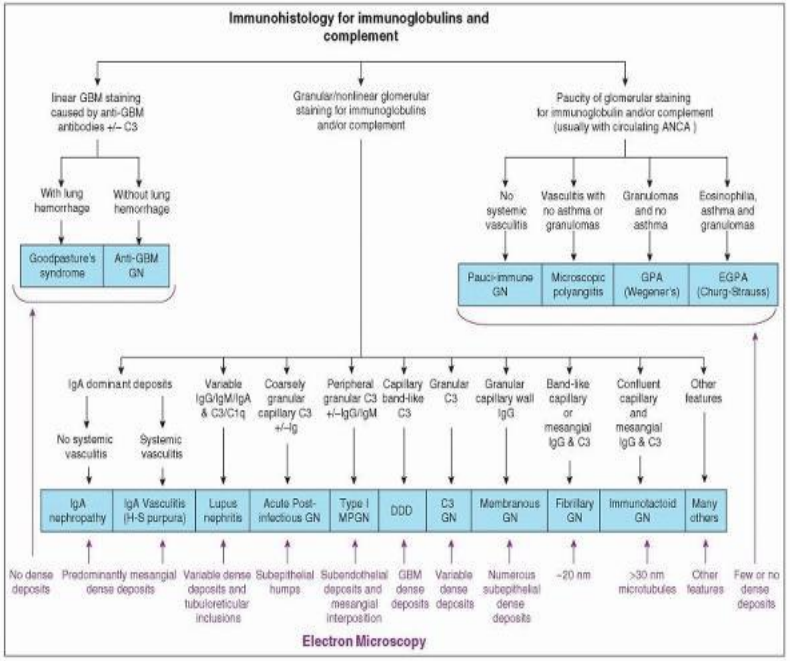


- Clinical history (detailed), adequate sample (at least 10 glomeruli).
- Light Microscopy: H&E, levels are important.
- Special Histochemical Stains (PAS, Silver, Masson).
- Other special stains (Congo-Red, von Kossa etc).
- Immunofluorescence – Immunohistochemistry for the detection of Immunoglobulins, Complement components and light chains (IgG, IgA, IgM, C3, C1q, Fibrinogen, k and l light chains). Other markers cal also be useful in Transplantation (C4d, HSV40 - BK).
- Electron Microscopy.
- Combination of the methods.



Distinction of different diseases is fascilitated by Immunofluorescence examination

Linear pattern: Strong - anti-GBM disease, Weak -DM.
Granular: granules/grains in GBM and/or Mesangium: Membranous, IgA nephrop. etc
Paucity/Absence of staining: ANCA vasculitis, Minimal change disease etc.



Main distinction – Immunofluorescence

- Classical Immune Complex diseases, Ig + Complement

IF is positive, for Immunoglobulins + Complement

  - IgG (SLE, Membranous, Fibrillary GN)
  - IgA (IgA Nephropathy)

- Dominant Complement expression (over Ig).

IF is positive mainly for Complement

  - Post infectious GN (C3)
  - C3 GN (C3)
  - C1q nephropathy(C1q)

- Non Immune Complex disease

IF is negative.

  - Minimal change disease
  - FSGS.
  - Thin basement membrane d.–Alport
  - Pauci immune vasculitis

Patterns

PATTERNS OF GLOMERULAR INJURY OBSERVED BY LIGHT MICROSCOPY AND SOME BUT NOT ALL OF THE DISEASES THAT CAN CAUSE EACH PATTERN OF INJURY

No abnormality by light microscopy
No glomerular disease
Glomerular disease with no light microscopic changes (e.g., minimal change glomerulopathy, thin basement membrane nephropathy)
Mild or early glomerular disease (e.g., lupus nephritis, IgA nephropathy, C1q nephropathy, membranous glomerulopathy, amyloidosis, Alport's syndrome, etc.)

Thick capillary walls without hypercellularity or mesangial expansion
Membranous glomerulopathy (primary or secondary) with thick GBM
Thrombotic microangiopathy with expanded subendothelial zone
Pre-eclampsia/eclampsia with endothelial swelling
Fibrillary glomerulonephritis with predominance of capillary wall deposits

Thick walls with mesangial expansion but little or no hypercellularity
Diabetic glomerulosclerosis with diffuse rather than nodular sclerosis
Secondary membranous glomerulopathy with mesangial immune deposits
Amyloidosis
Monoclonal immunoglobulin deposition disease
Fibrillary glomerulonephritis
Dense-deposit disease (type II membranoproliferative glomerulonephritis)

Focal segmental glomerular sclerosis without hypercellularity
Focal segmental glomerulosclerosis (primary or secondary)
Chronic sclerotic phase of a focal glomerulonephritis
Hereditary nephritis (Alport's syndrome)

Mesangial or endocapillary hypercellularity
Focal or diffuse mesangioproliferative glomerulonephritis[a]
Focal or diffuse (endocapillary) proliferative glomerulonephritis[a]
Acute diffuse proliferative postinfectious glomerulonephritis
Membranoproliferative glomerulonephritis (type I, II, or III)

Extracapillary hypercellularity
ANCA crescentic glomerulonephritis (paucity of immunoglobulin by IFM)
Immune complex crescentic glomerulonephritis (granular immunoglobulin by IFM)
Anti-GBM crescentic glomerulonephritis (linear immunoglobulin by IFM)
Collapsing variant of focal segmental glomerulosclerosis (including HIV nephropathy)

Membranoproliferative, lobular, or nodular pattern
Membranoproliferative glomerulonephritis (type I, II, or III)
Diabetic glomerulosclerosis with nodular mesangial expansion (KW nodules)
Monoclonal immunoglobulin deposition disease with nodular sclerosis
Thrombotic microangiopathy
Fibrillary glomerulonephritis
Immunotactoid glomerulopathy

Advanced diffuse global glomerular sclerosis
End-stage glomerular disease
End-stage vascular disease
End-stage tubulointerstitial disease

A specific disease (e.g., lupus nephritis) can cause more than one pattern of injury.
[a]Each pattern could be caused by IgA nephropathy, lupus nephritis, postinfectious glomerulonephritis, and so forth.

Focal	Involving <50% of glomeruli
Diffuse	Involving ≥50% of glomeruli
Segmental	Involving part of a glomerular tuft
Global	Involving all of a glomerular tuft
Mesangial hypercellularity	Four or more nuclei in the contiguous matrix of a peripheral mesangial segment
Endocapillary hypercellularity	Increased cellularity internal to the GBM composed of leukocytes, endothelial cells, and mesangial cells
Lobular	Consolidated expansion of glomerular segments representing major anatomic subunits (lobules) of the glomerular tuft formed by dichotomous branchings of the afferent arteriole. (hypersegmentation)
Extracapillary hypercellularity	Increased cellularity in Bowman space or more than one layer of parietal or visceral epithelial cells
Crescent	Extracapillary hypercellularity other than the epithelial hyperplasia of the collapsing variant of FSGS, often accompanied by fibrin extravasation into Bowman space.
Fibrinoid necrosis	Lytic destruction of cells and matrix with deposition of acidophilic fibrin-rich material and often accompanied by GBM rupture and apoptosis of infiltrating leukocytes
Mesangiolysis	Detachment of the paramesangial GBM from the mesangial matrix resulting in a capillary aneurysm, or lytic dissolution of the mesangial matrix
Sclerosis	Increased collagenous extracellular matrix that is expanding the mesangium, obliterating capillary lumens, or forming adhesions to Bowman capsule
Hyaline	Glassy acidophilic extracellular material

Because each light microscopic pattern of glomerulonephritis can have many different causes with very different prognoses, recognition of the specific cause of the injury in a given specimen is as important as, if not more important

Causes

Glomerulonephritis

Acute glomerulonephritis

Sanjeev Sethi, An S De Vriese, Fernando C Fervenza

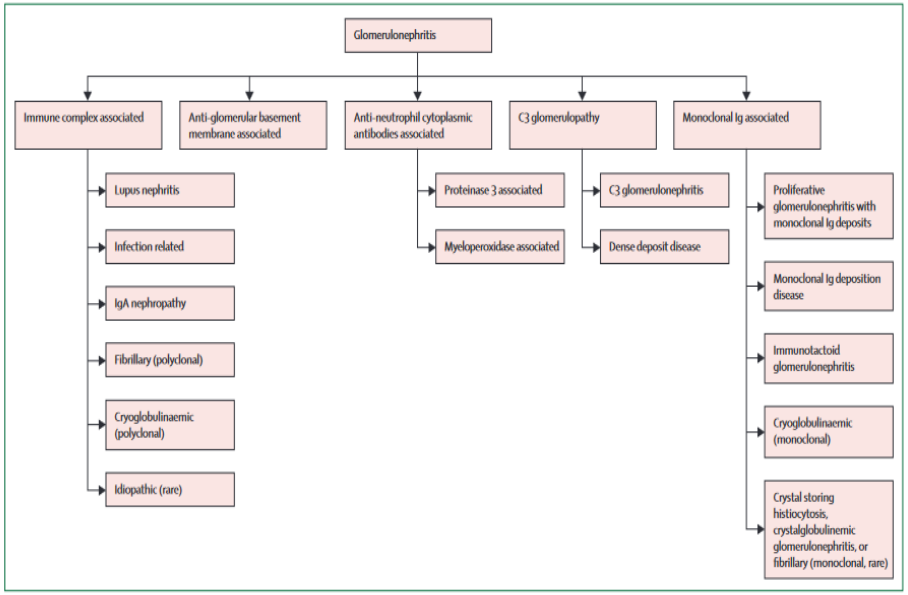


Figure 1: Classification of glomerulonephritis based on cause

1st Classification (Patterns of injury)

- Proliferation (membranoproliferative including).
- «Nodular» mesangial increase/expansion with GBM thickening.
- FSGS.
- Lesions of Glomerular basement membranes.
- No lesions on Light Microscopy (or with minimal changes), important IF, EM.
- Glomerulosclerosis/chronic changes

<u>Special (additional) findings</u>

- Diseases with deposition of “material” in LM.
- Diseases with lesions in LM, but EM is necessary for classification.

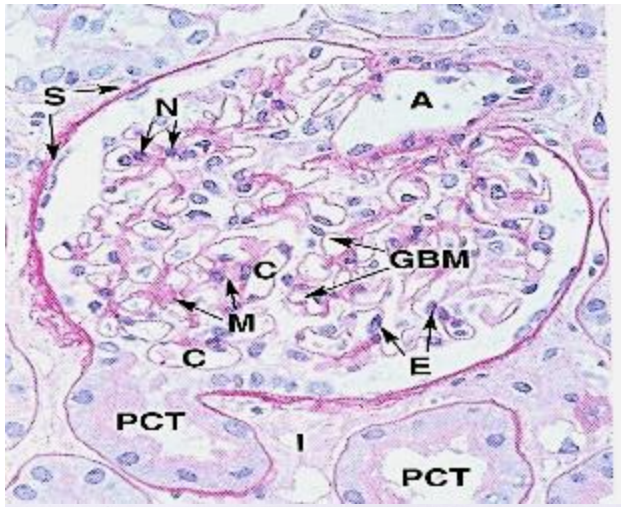
Patterns of Proliferation

- Proliferation.
  - Mesangial (αύξηση του υποστρώματος, υπερπλασία των μεσαγγειακών κυττάρων).
  - Endocapillary (intraglomerular inflammation, endothelial cell proliferation, segmental GBM thickening, lumen occlusion).
    - Special: Membranoproliferative –Lobular pattern.
      - Membranoproliferative GN
      - C3 GN

      Mimics:
      - Chronic TMA- endothelial damage.
      - Transplant Glomerulopathy
  - Extracapillary (crescents)

Glomerulus, normal

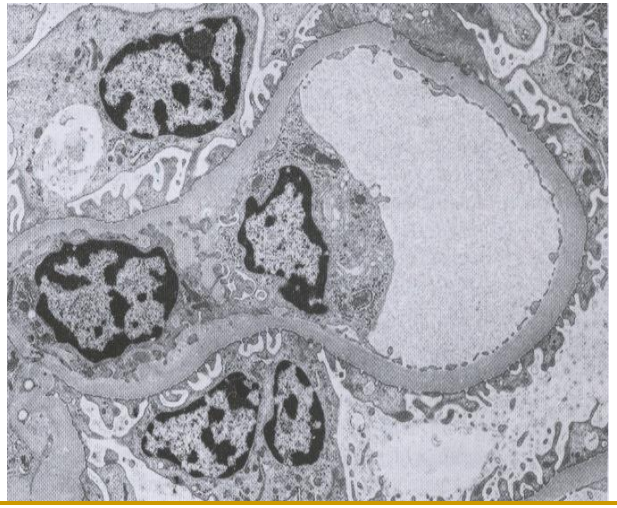
- Spherical or elipsoidal collections of specialized capillaries, supported by mesangial matrix.

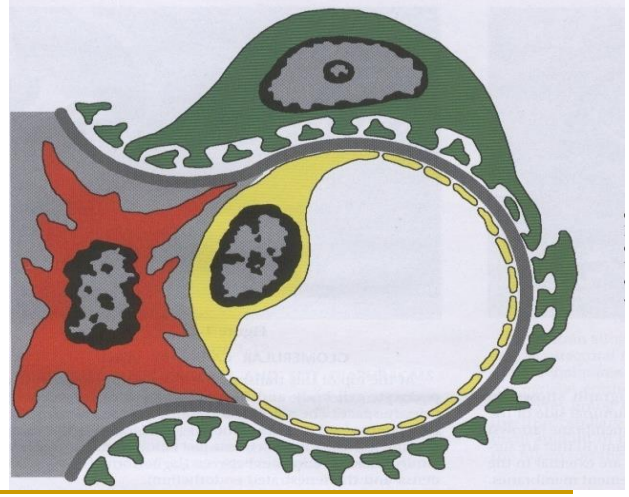


- Specialized vascular structure.
- Role: blood infiltration.

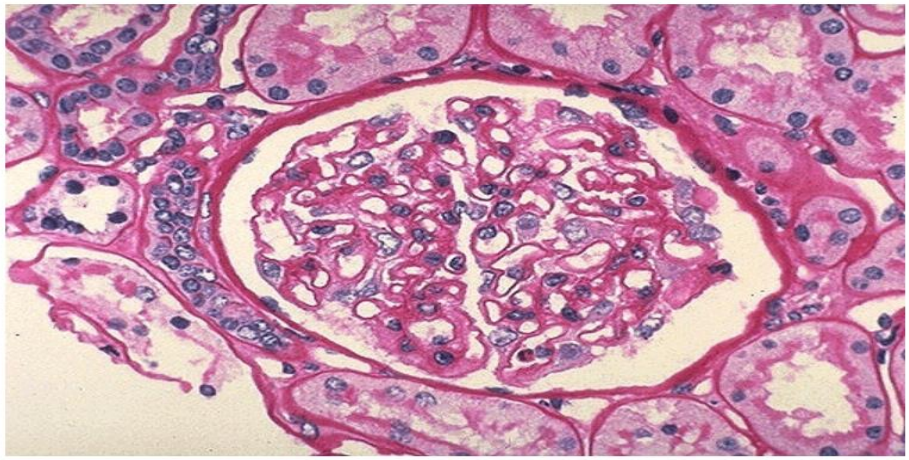
Types of cells:

- Mesangial
- Endothelial
- Podocytes
- Parietal cells (Bowman's capsule)

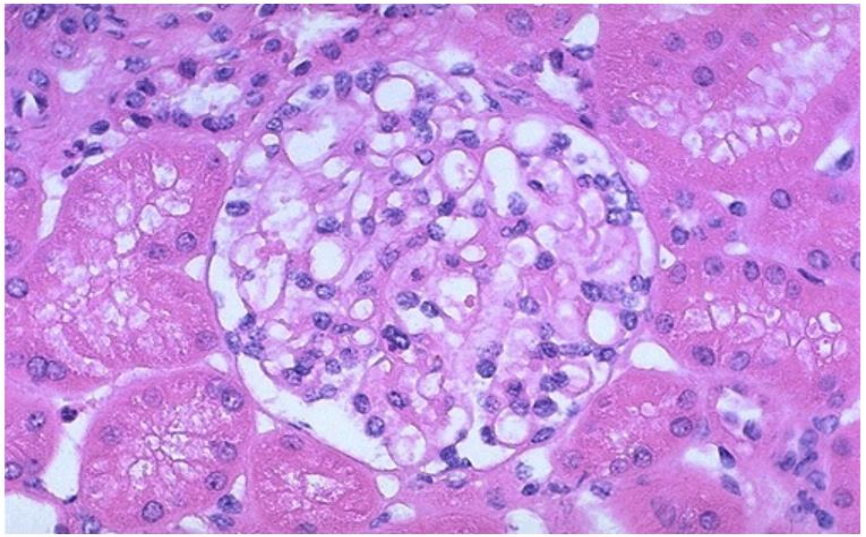




Wheater's histology

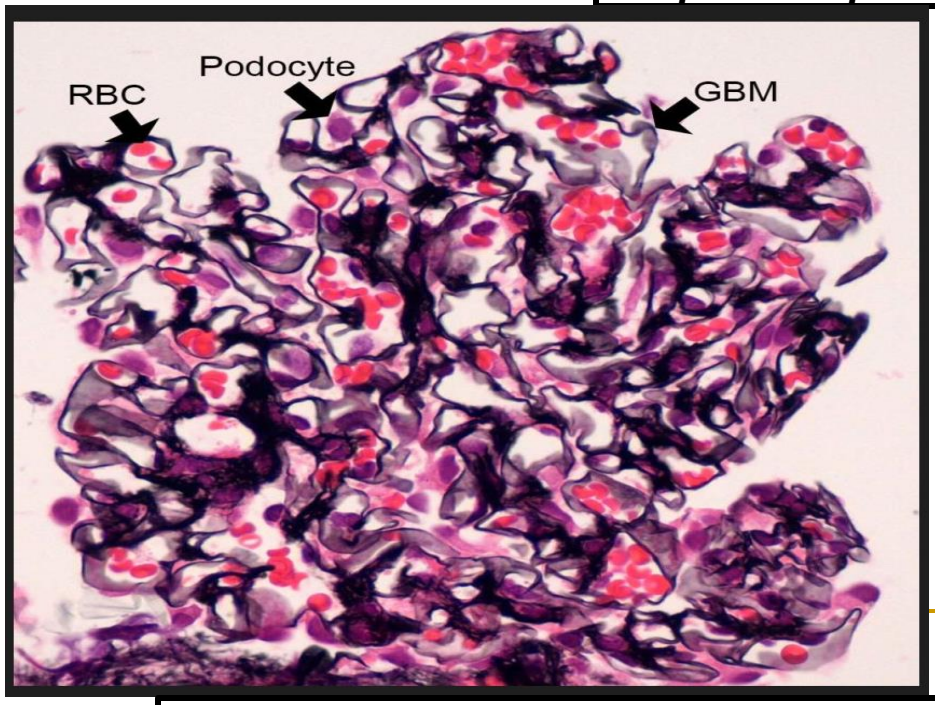


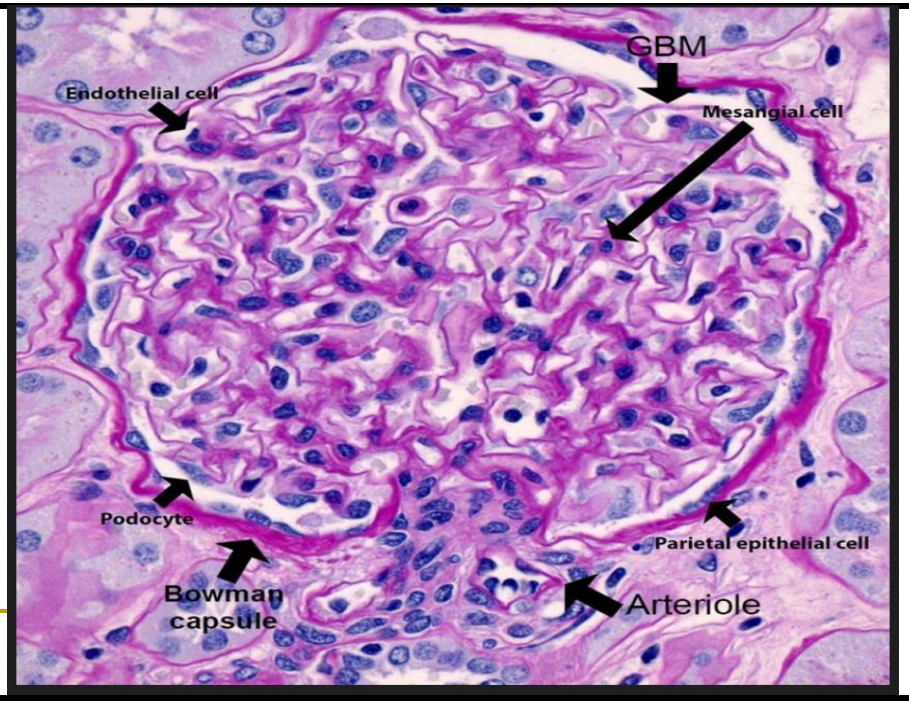
This normal glomerulus is stained with PAS to highlight basement membranes of glomerular capillary loops and tubular epithelium. The capillary loops of this normal glomerulus are well-defined and thin. The **endothelial cells** are seen in capillary loops. The **mesangial regions** are of normal size. **Podocytes** are present and forming the visceral epithelial surface. **Bowman's space** is seen along with **parietal epithelial cells**.



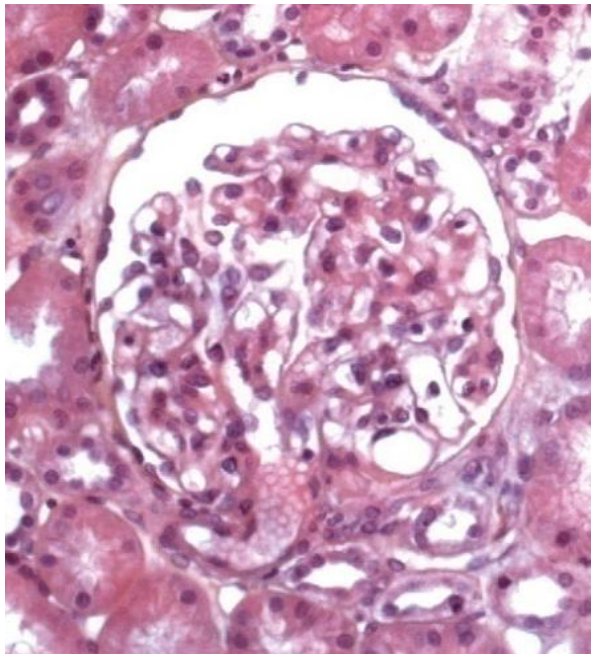
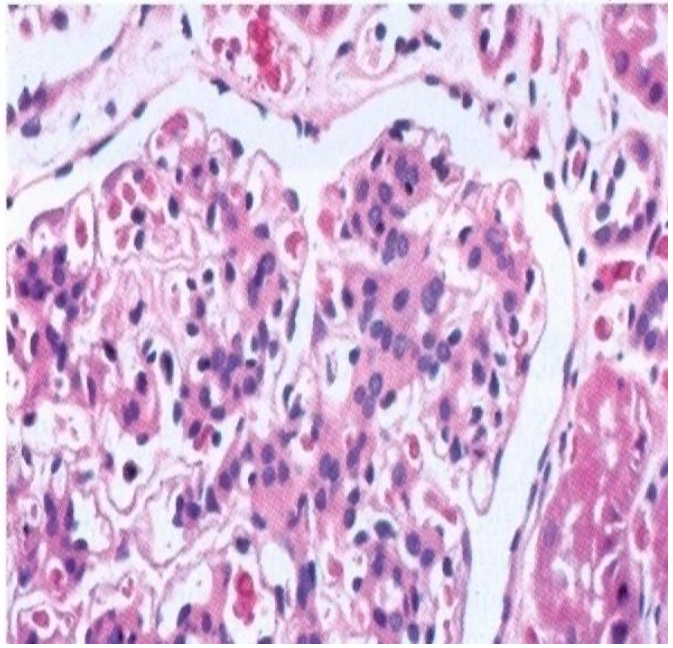
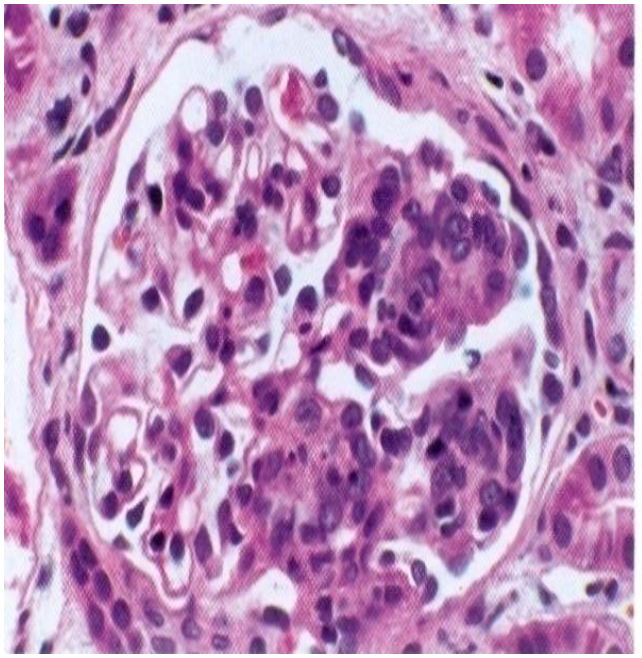
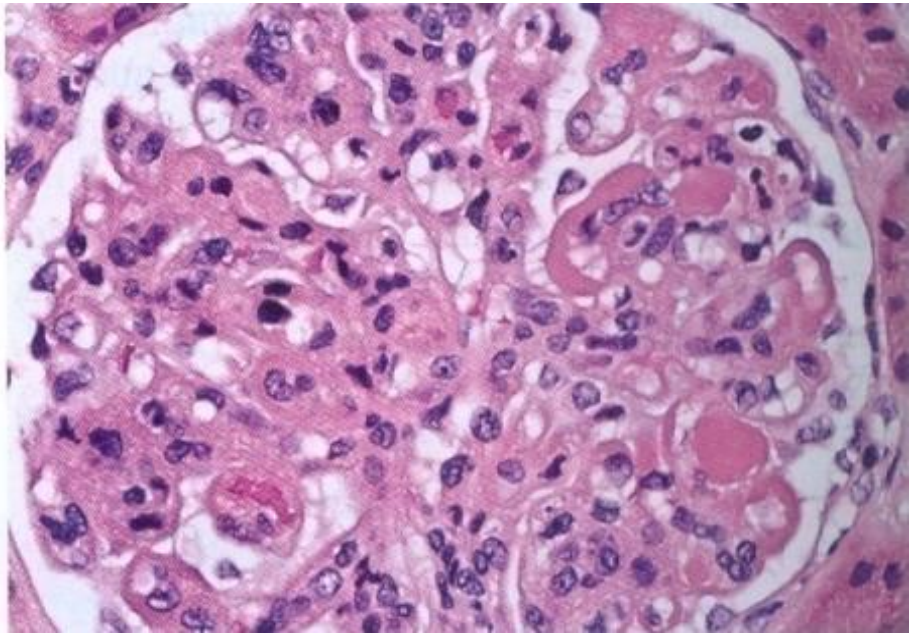
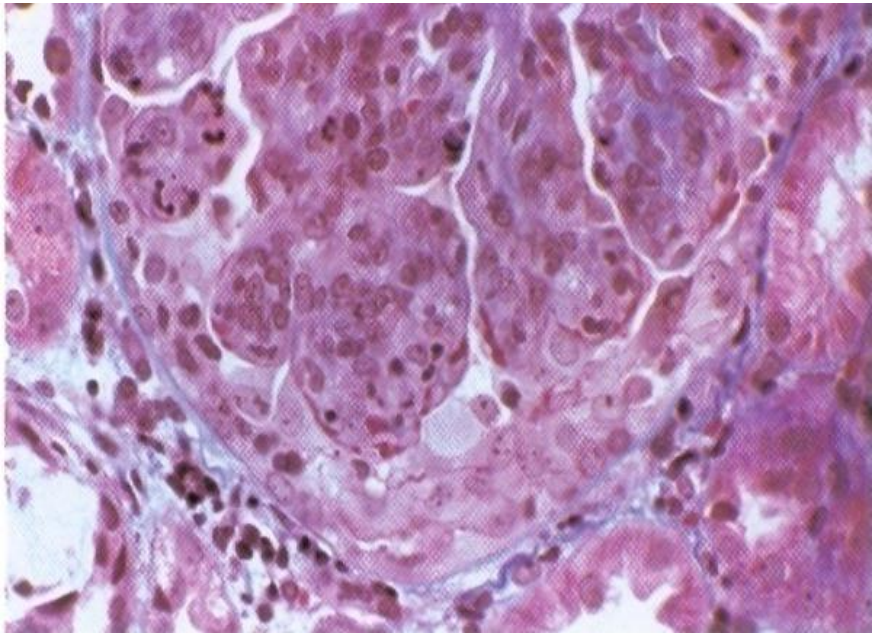
This is a normal glomerulus by light microscopy. The glomerular capillary loops are thin and delicate. Endothelial and mesangial cells are normal in number. The surrounding tubules are normal. Life is

https://webpath.med.utah.edu/RENAHTML/RENALIDX.html#8



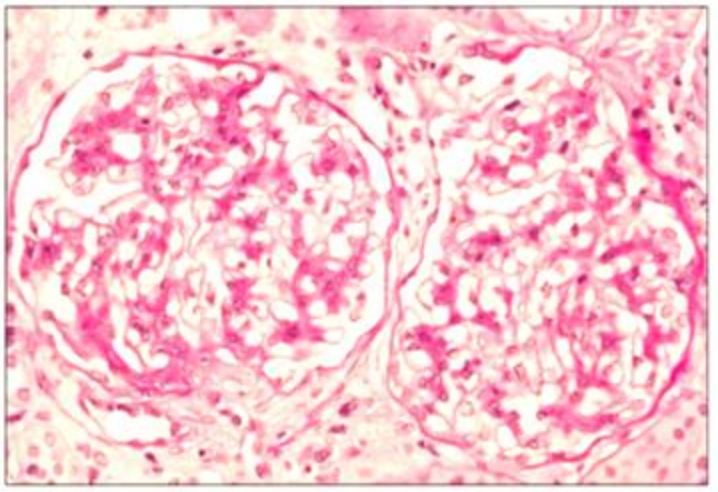


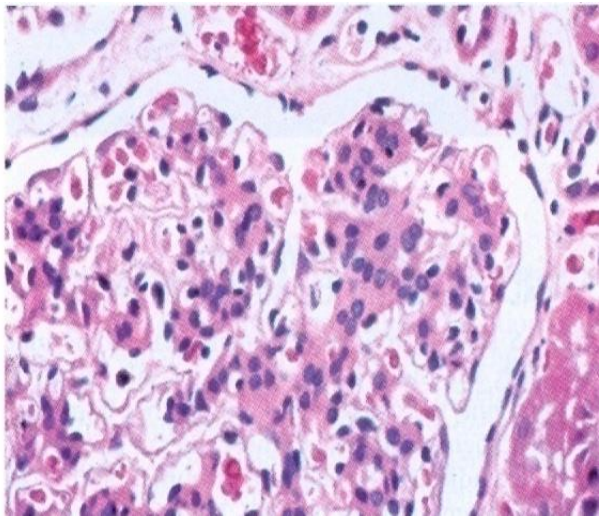
https://www.renalfellow.org/2019/01/04/kidney-biopsy-of-the-month-what-is-normal/

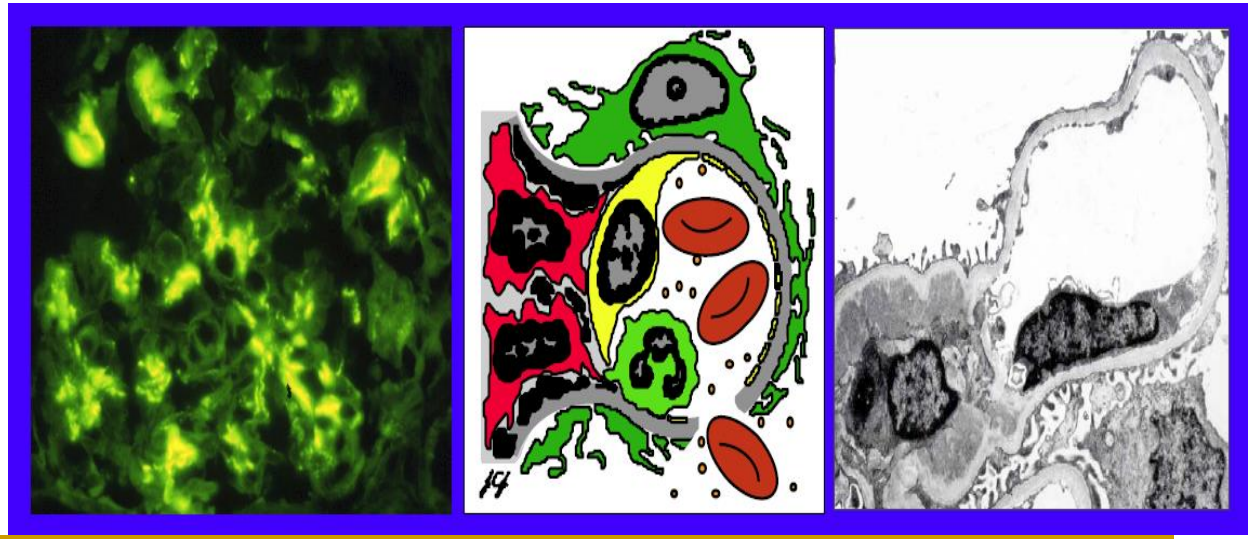






Mesangial proliferation (Clinical hematuria +/- mild proteinuria)

- > 3 mesangial cells in areas away from the vascular pole, increase of the mesangial matrix, IF+.
- Focal or Diffuse (or finger -like) mesangial increase in association with cellularity (IgA, SLE, Fibrillary GN etc).





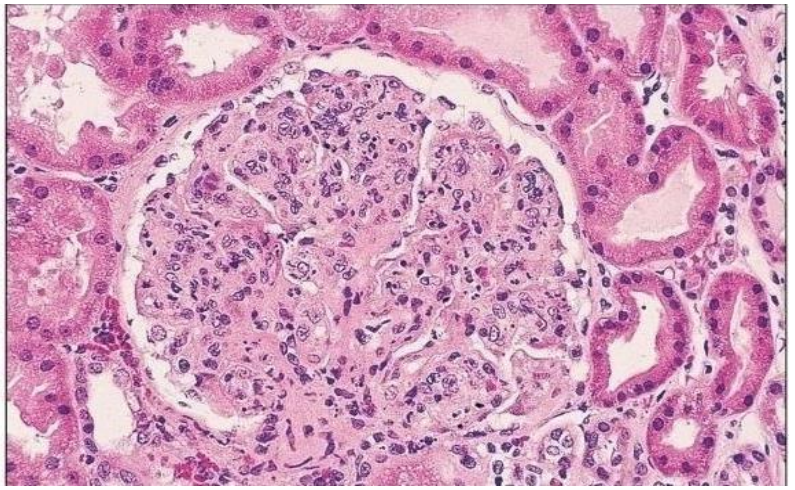


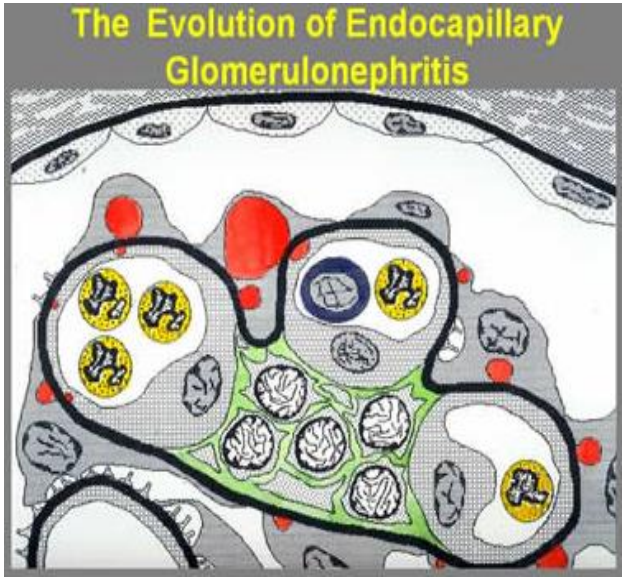
Jennette JC. UNC, Tutorial 2010

IgA nephropathy

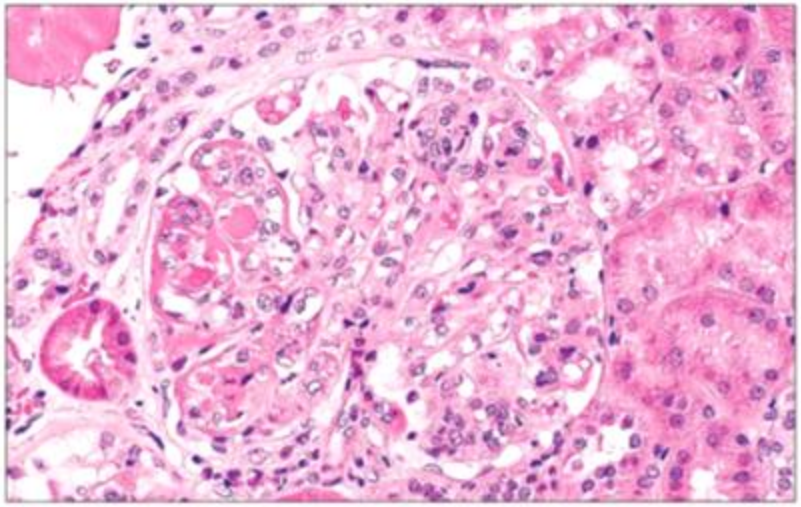
Endocapillary Proliferation (hematuria, proteinuria, deteriorating renal function –Cr/EGFR)

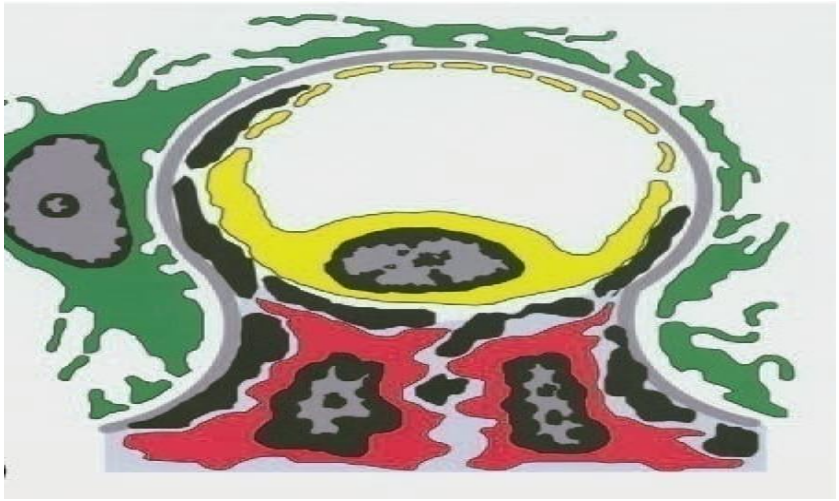
- Inflammation into capillary lumens, (neutrophils, lymphocytes, monocytes), endothelial cells proliferation, GBM thickening, occlusion/stenosis of lumens.
- Mesangial proliferation usually coexists.
- In acute phase, increased cellularity, neutrophils can be more > monocytes, the opposite in chronic phase (less neutrophils).
- IgA, SLE, Post infectious GN etc.

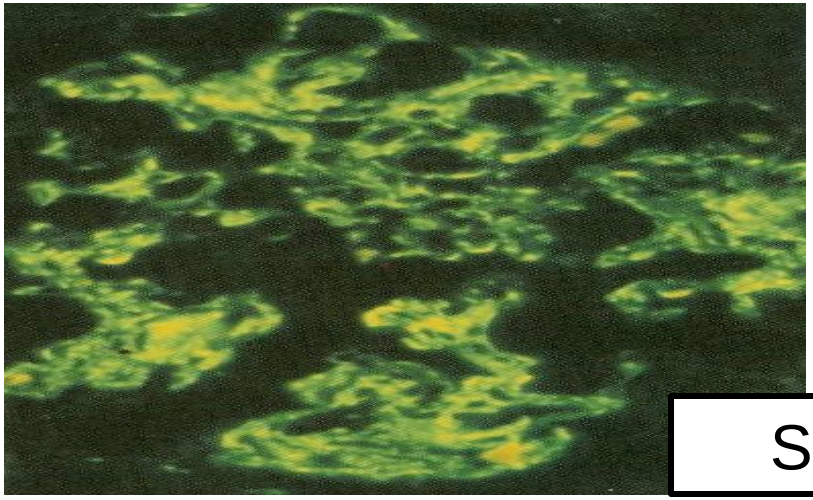


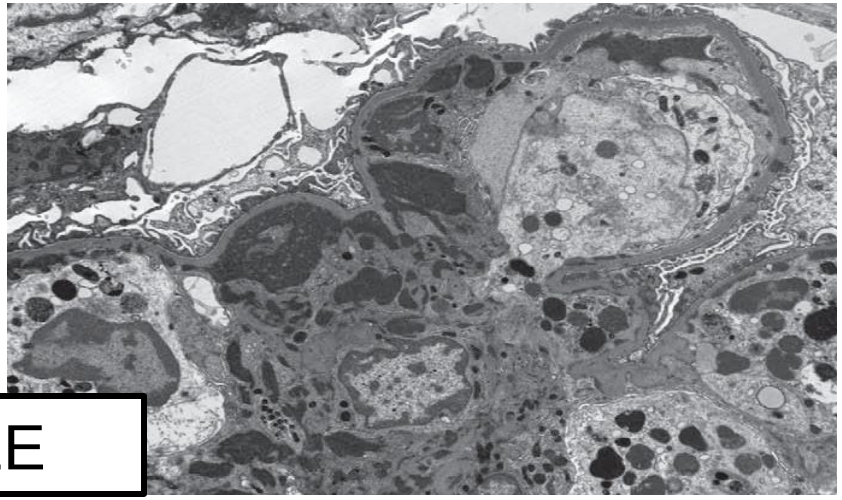


Endocapillary Proliferation





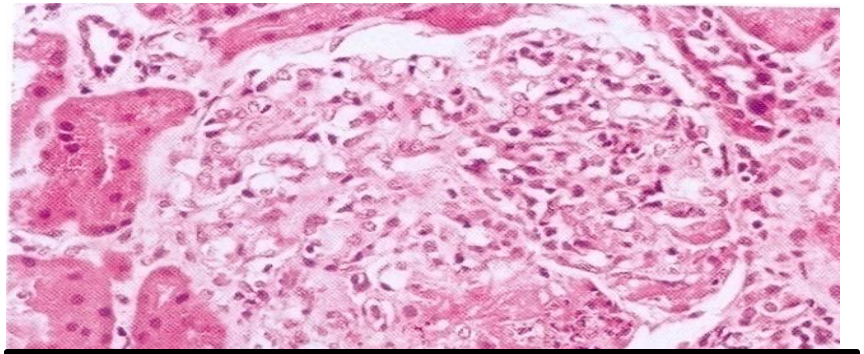




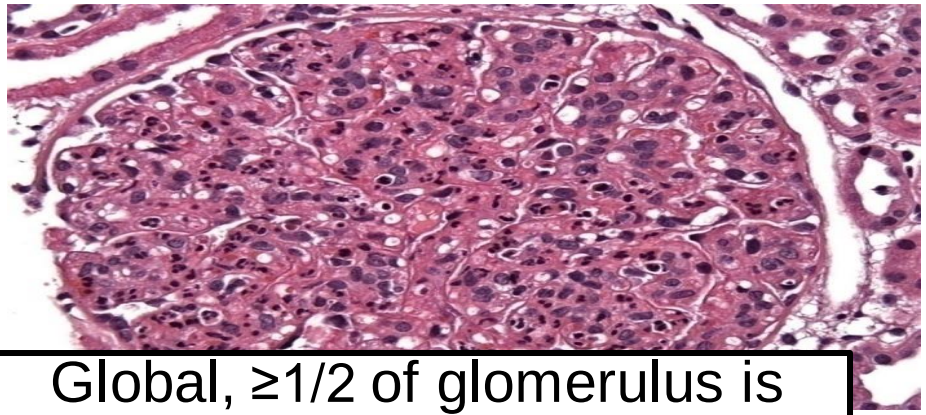
SLE

Quantification of lesions (how much?)

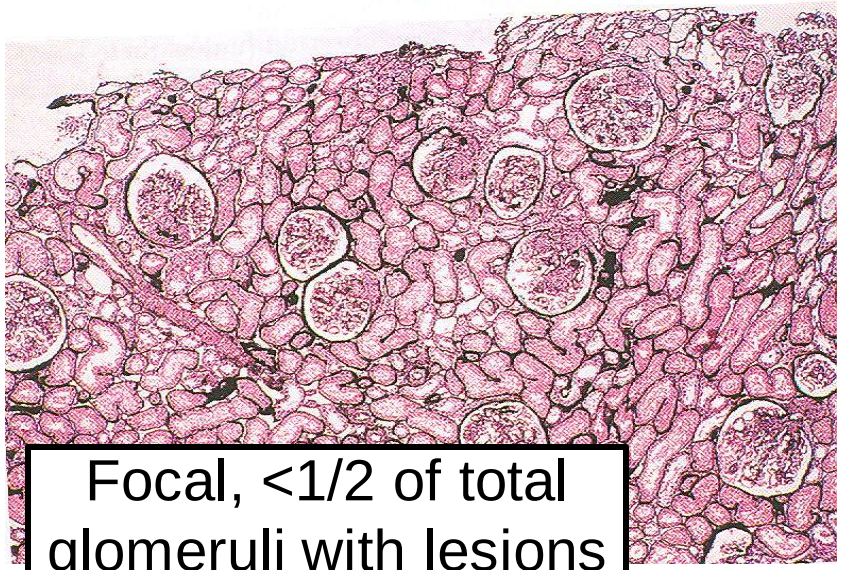
- Segmental - Global (<1/2 glomerulus, ≥ 1/2 of glomerulus)
- Focal - Diffuse (<1/2, ≥ 1/2 of glomeruli in total)



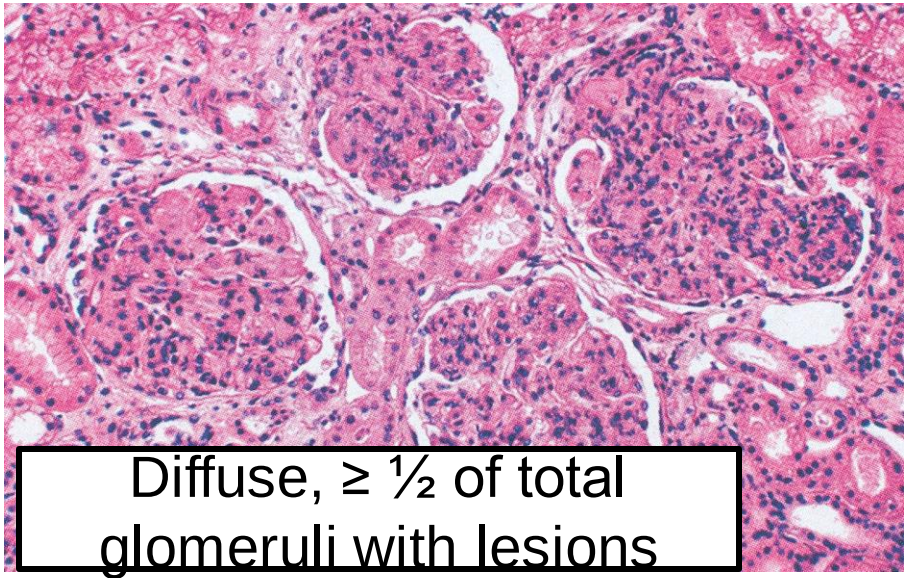
Segmental, <1/2 of glomerulus is affected by disease



Global, ≥1/2 of glomerulus is affected by disease

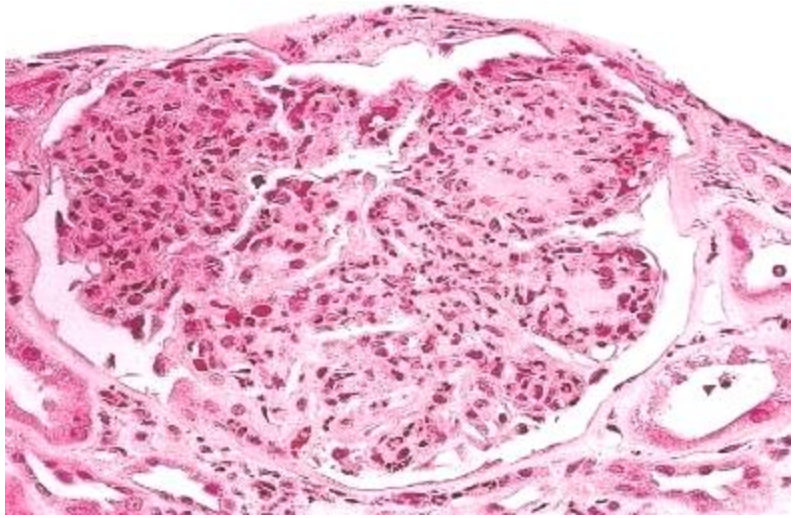


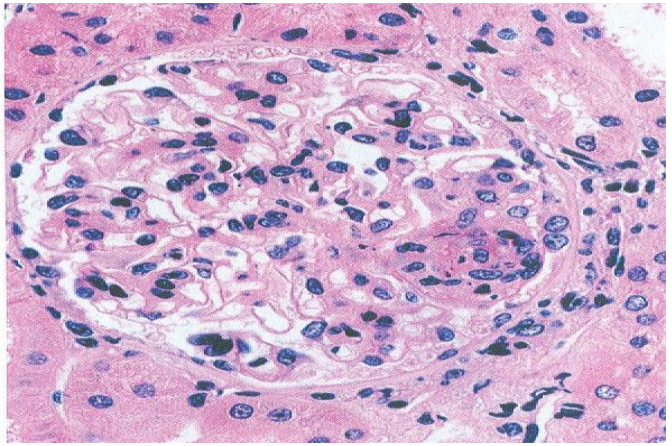
Focal, <1/2 of total glomeruli with lesions



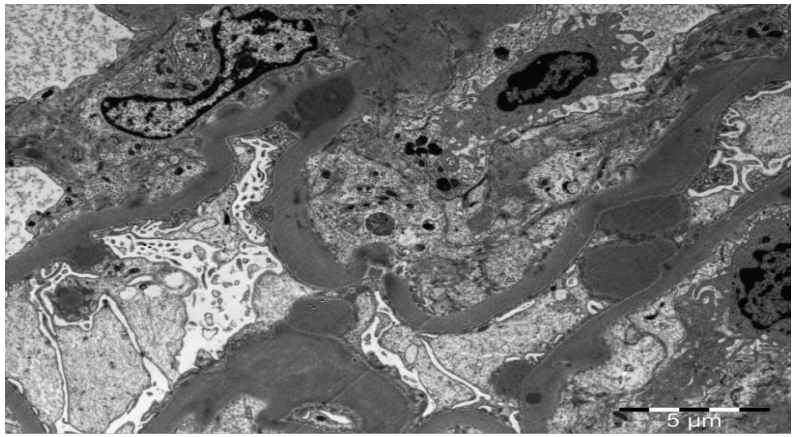
Diffuse, ≥ ½ of total glomeruli with lesions

Subtypes of Endocapillary proliferation

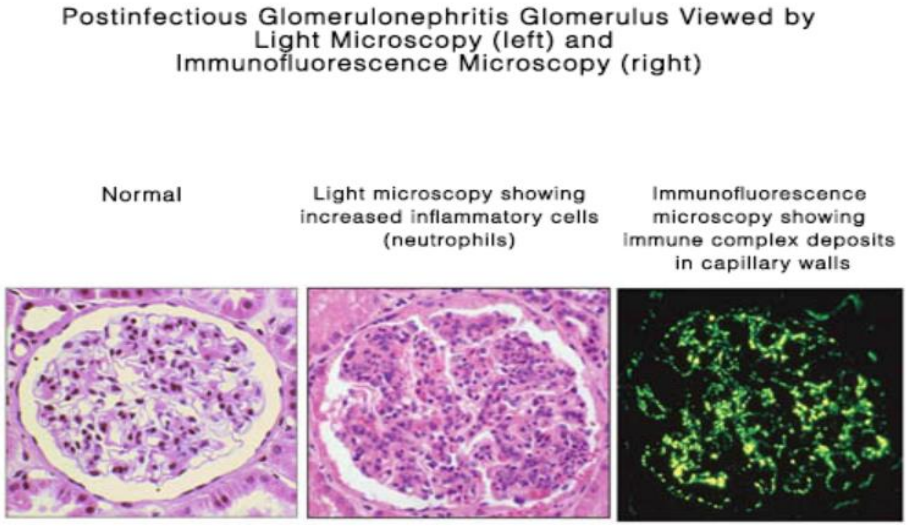




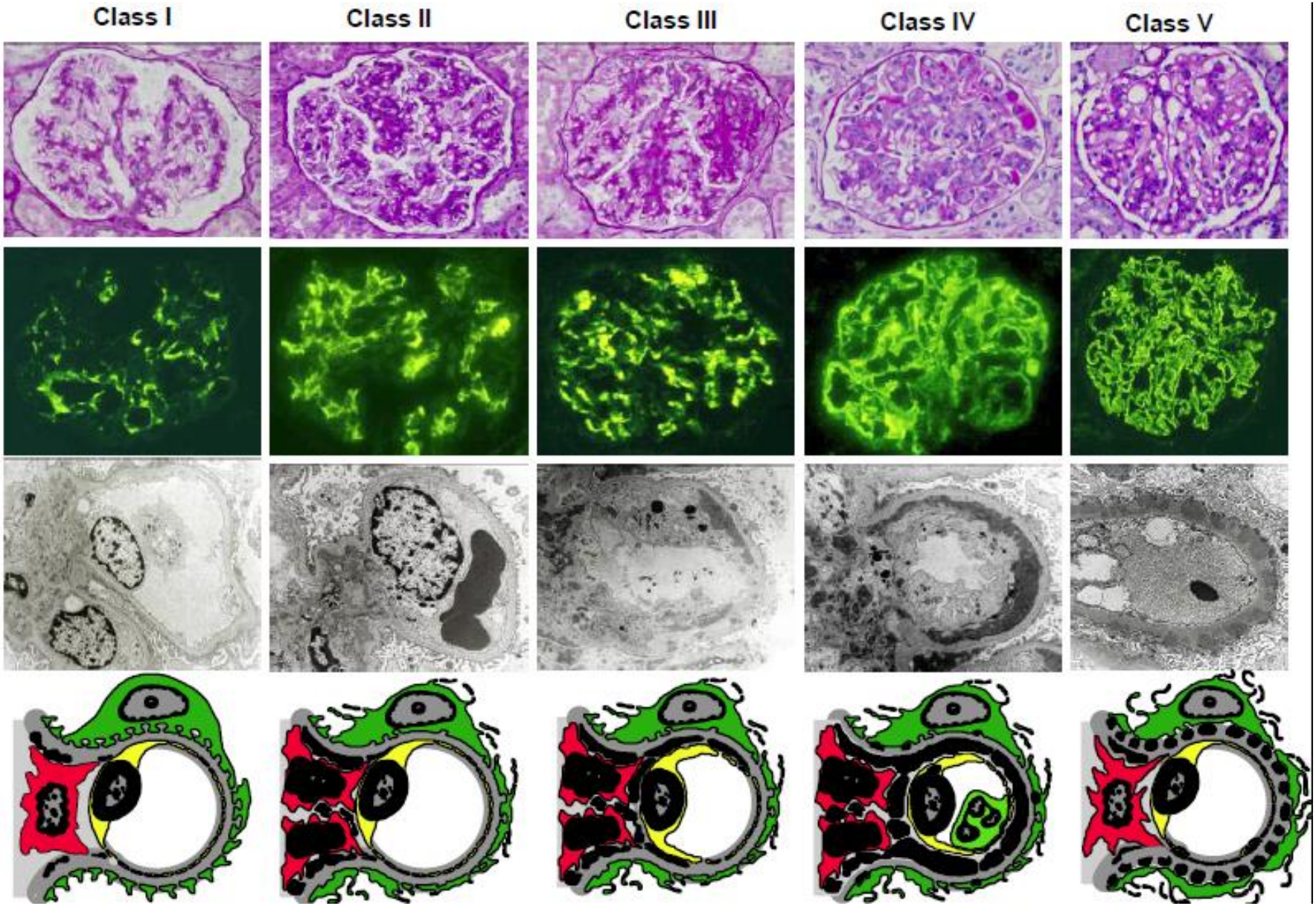
SLE with nuclear “dust”/debris



Post infectious GN superimposed on DM



- “What is the diagnosis” (Acute Post Infectious Glomerulonephritis: Not always a benign condition) Sophia Lionaki, Maria Pappa, John N Boletis, Liapis G. CJASN, 4/2020 Vol 15.



- SLE can have many "faces", mesangioproliferative, endocapillary proliferation, membranoproliferative, membranous, sclerosing.

Jennette JC, UNC

Membranoproliferative Pattern (hematuria, proteinuria, increase of Cr)

Lobular architecture, “double contour” of GBM.

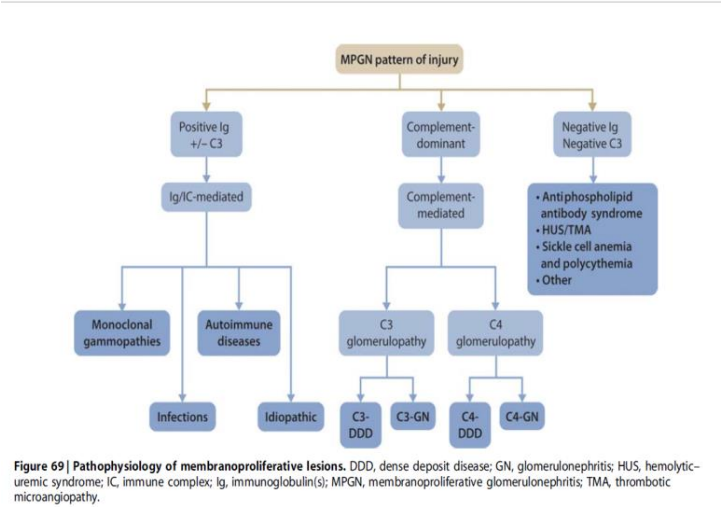


Figure 69 | Pathophysiology of membranoproliferative lesions. DDD, dense deposit disease; GN, glomerulonephritis; HUS, hemolytic–uremic syndrome; IC, immune complex; Ig, immunoglobulin(s); MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy.

- New basement membrane formation, with mesangial interposition (“double contor”, subendothelial deposits).

Ig+ AND C3+/-

- Monoclonal Gammopathy
- Autoimmunity SLE, Cryoglobulinemia
- Infections

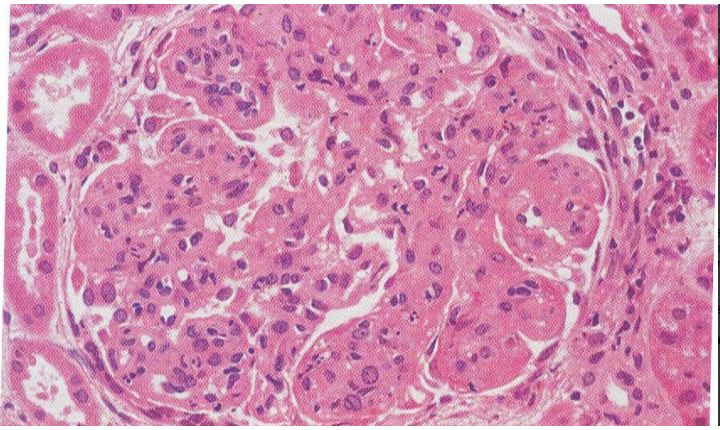
C3 dominant

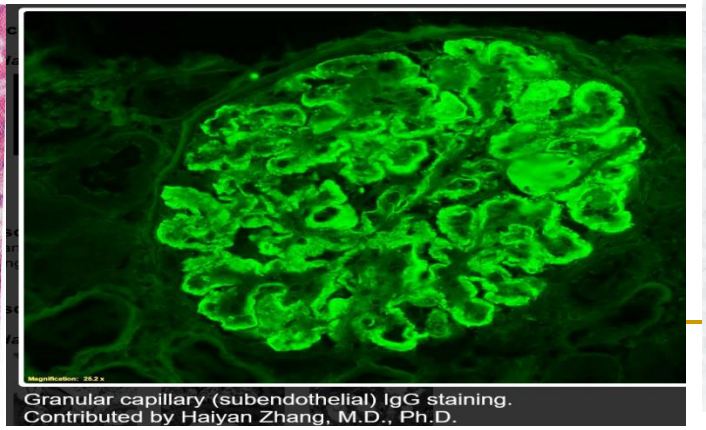
- C3GN /Glomerulopathy

Ig-, C3-

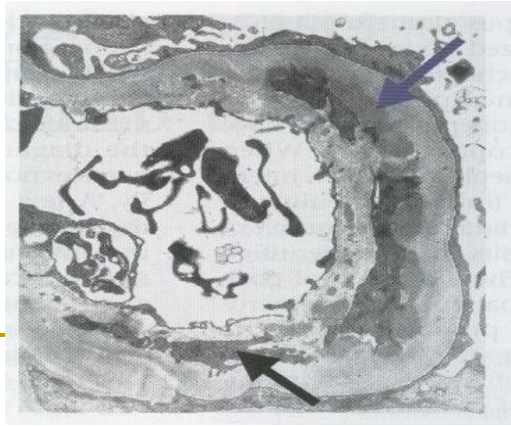
- TMA
- Others

Immune complex mediated - Complement mediated





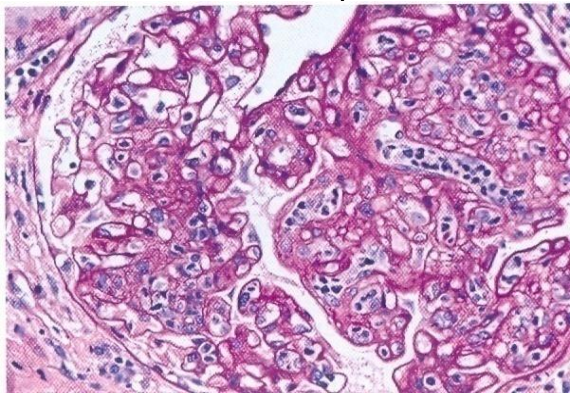
Granular capillary (subendothelial) IgG staining.
Contributed by Haiyan Zhang, M.D., Ph.D.

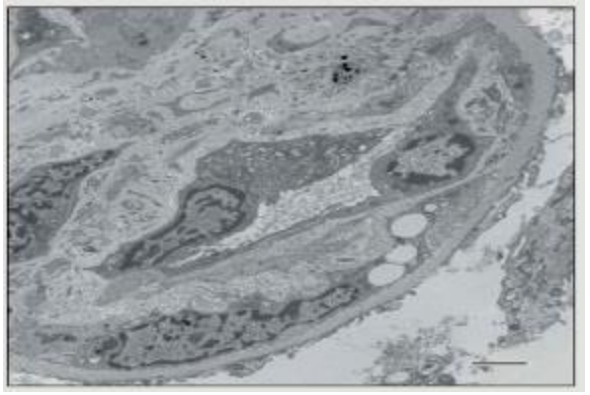


Mimics of MPGN

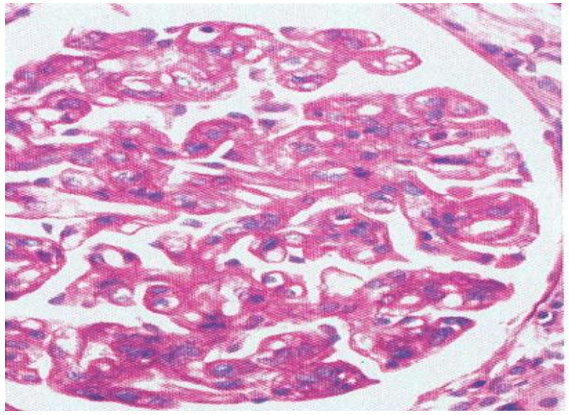
Chronic active antibody mediated rejection

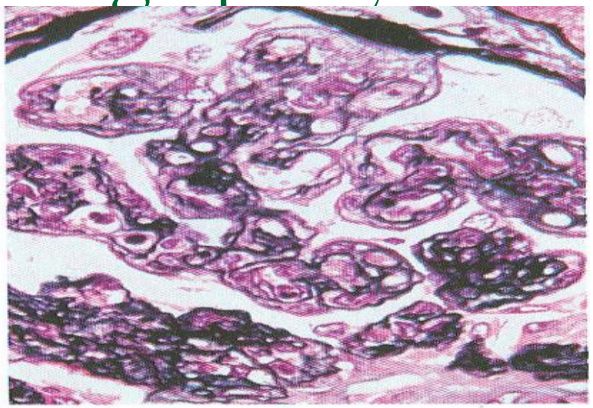
- GBM reduplications.
- Saubendothelial edema, inflammatory cells into the lumens.

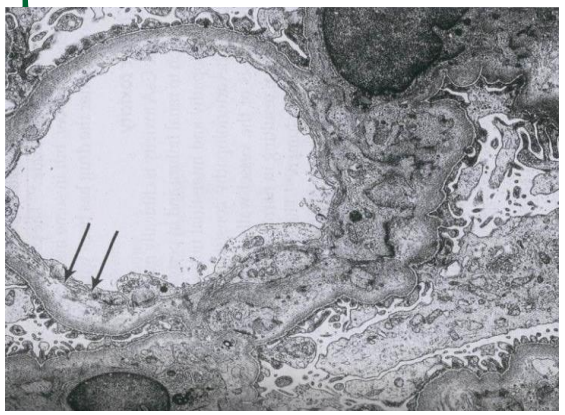




Thrombotic Microangiopathy chronic phase



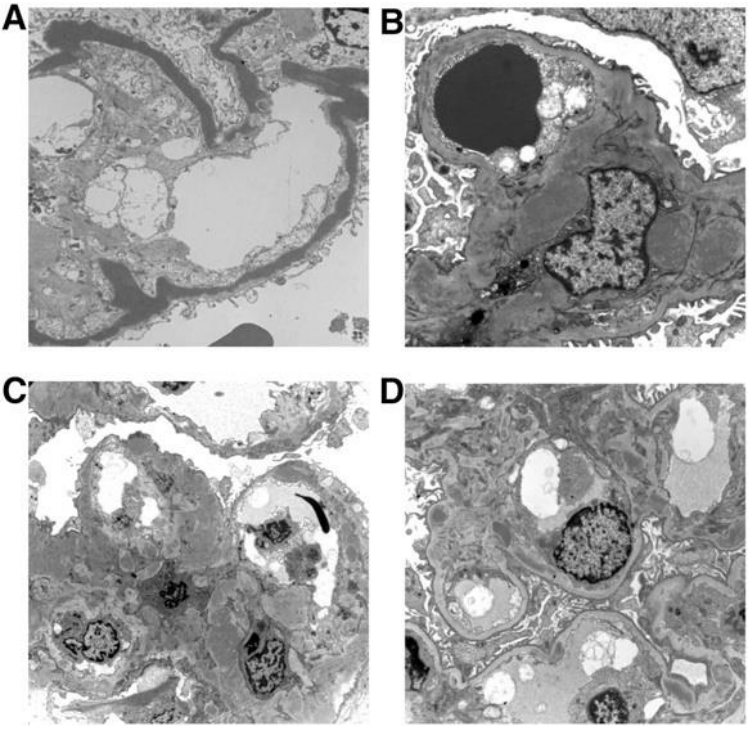




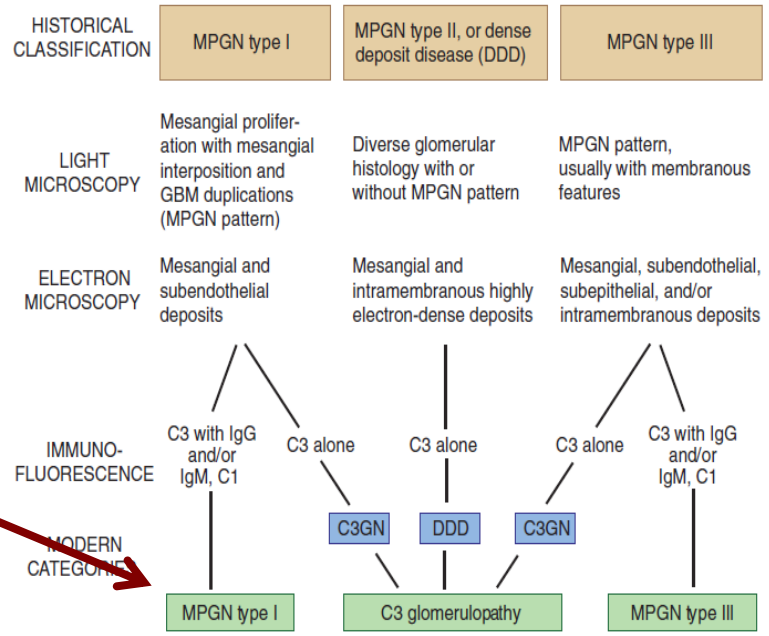
- Subendothelial edema, new basement membrane formation, GBM reduplications, IF -.

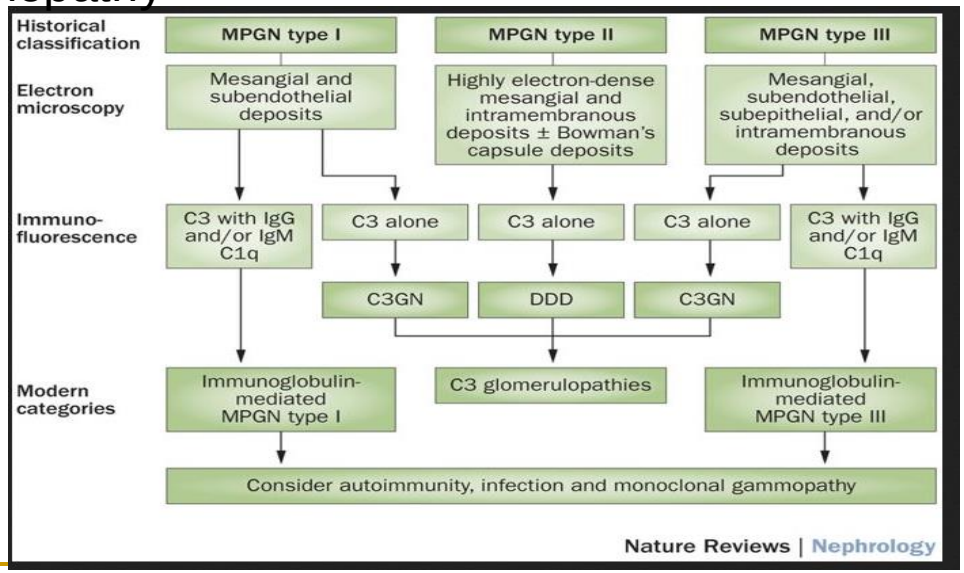
C3 GN

- Dominant C3 expression.
- CFHR5 nephropathy
- C3 GN
- Dense Deposits Disease.



- Autoimmunity
- Infections,
- Monoclonal Gammopathy





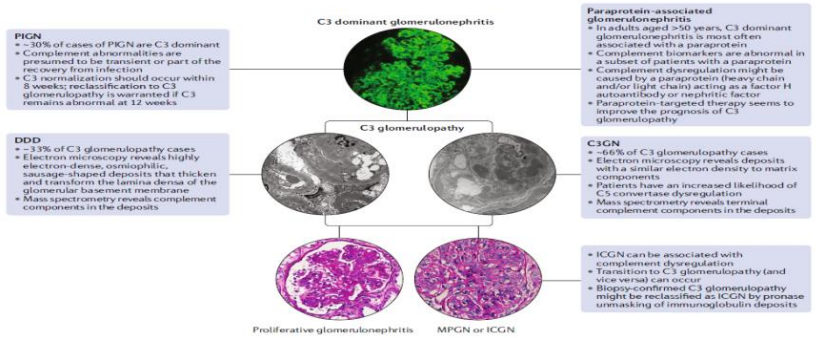
Agati V, Kidney International (2012) 82, 379 – 381.

Cook T. Reviews Nephrology volume 11, pages 14–22 (2015)

TABLE 9.1 Pathologic classification of C3 glomerulopathy

C3 glomerulopathy
Dense deposit disease (DDD) (formerly membranoproliferative GN type II)
Membranoproliferative GN pattern (type II)
Mesangioproliferative or proliferative GN pattern
C3 glomerulonephritis (C3GN)
Membranoproliferative GN pattern (types I and III)[a]
Mesangioproliferative or proliferative GN pattern

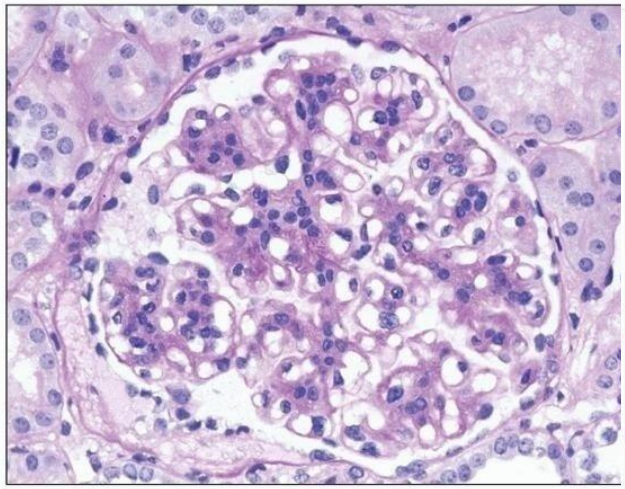
[a]Note that membranoproliferative GN types I and III may be either the result of a C3 glomerulopathy or an immune complex-mediated glomerulonephritis (see Chapter 8).

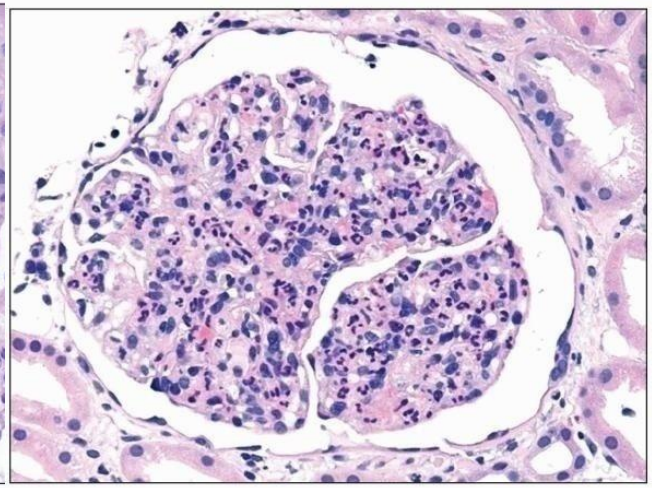


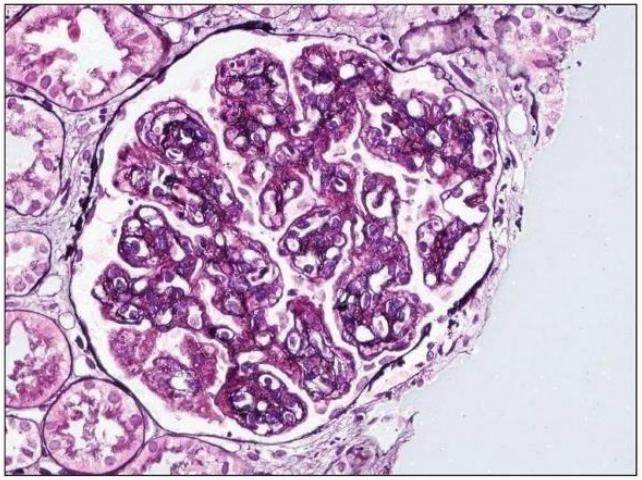
- Low C3 in the serum (40%-80).
- Previous infectious of Upper respiratory system.
- Nephrotic syndrome: 27% C3 GN, 38%DDD, 65% MPGN.

Servais et al. Kidney Int 2012;82:454-464

>50 years, high suspicious for MGRS, Immunofluorescence in paraffin sections.







Heptinstall's Pathology of the kidney

Extracapillary proliferation (hematuria, proteinuria, severe increase in Cr)

- Parietal cell proliferation of Bowman's capsule, fibrin, macrophages, inflammatory cells («crescents»). Usually GBM disruptions.
  - Crescentic GN >50% of glomeruli with crescents,
  - GN with crescents <50% of glomeruli with crescents.
- Mimics (Collapsing FSGS).
- Immune complex GN, IF+.
  - SLE.
  - IgA Nephropathy.
  - Fibrillary GN
  - Membranoproliferative GN
- Anti-GBM *
- Pauci immune GN, IF- (ANCA vasc.)*

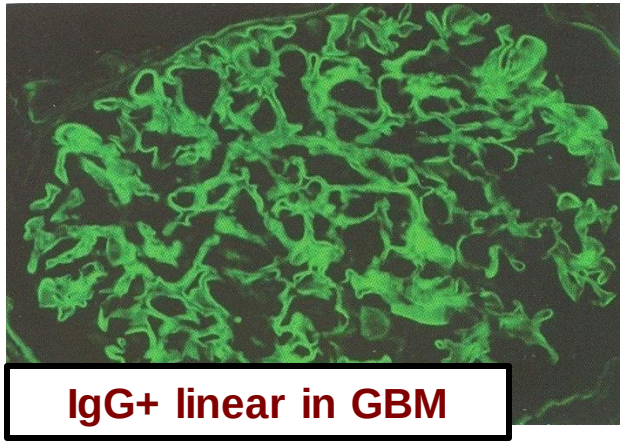
* No proliferation.

TABLE 15.2 Frequency of glomerular crescents, necrosis, and endocapillary hypercellularity in different types of glomerular disease evaluated by the University of North Carolina Nephropathology Laboratory

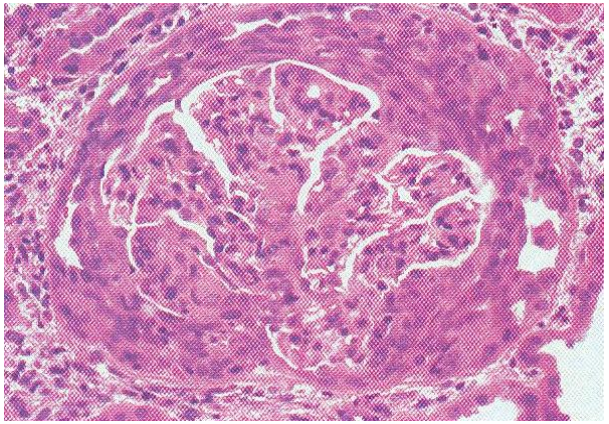
Type of glomerular disease	% With any [illegible]	% With >50% [illegible]	Average % glomerular crescents[a]	Glomerular necrosis (0–4+)	Glomerular hypercellularity (0–4+)
Anti-GBM glomerulonephritis	97.1	84.8	77	1.7+	0.8+
ANCA glomerulonephritis	89.5	50.3	49	1.2+	0.8+
Lupus glomerulonephritis (III and IV)	56.5	12.9	31	1.7+	2.2+
Henoch-Schönlein purpura glomerulonephritis	61.3	9.7	27	0.4+	1.5+
IgA nephropathy	32.5	4.0	21	0.1+	1.4+
Postinfectious glomerulonephritis	33.3	3.3	19	0.3+	2.7+
Type I membranoproliferative glomerulonephritis	23.8	4.6	25	0.2+	2.8+
DDD/C3 glomerulopathy	43.8	18.8	48	0.2+	1.8+
Fibrillary glomerulonephritis	22.8	5.0	26	0+	0.6+
Monoclonal immunoglobulin deposition disease	5.6	0	13	0+	0.3+
Thrombotic microangiopathy	5.6	0.9	26	0.4+	0.3+
Diabetic glomerulosclerosis	3.2	0.3	20	0+	0.3+
Nonlupus membranous glomerulopathy	3.2	0.1	15	0+	0.1+

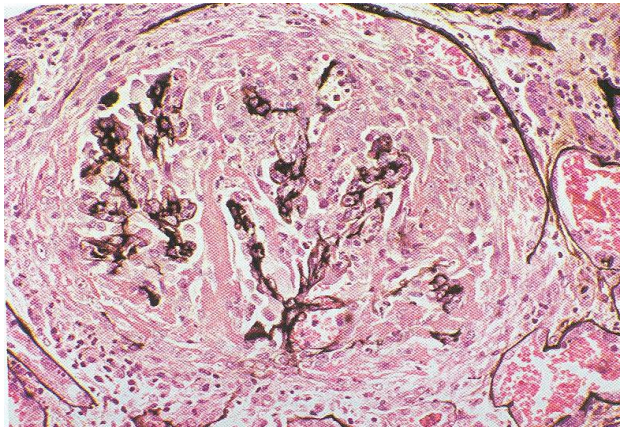
Anti-GBM disease

Necrosis, fibrin → GBM disruptions/breaks → proliferation of parietal cells of Bowman's capsule, along with podocytes (crescents).

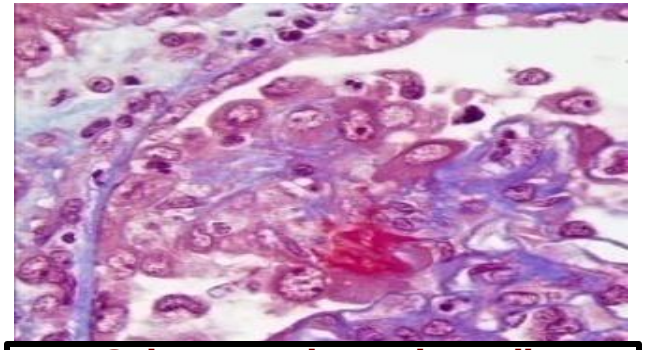


IgG+ linear in GBM

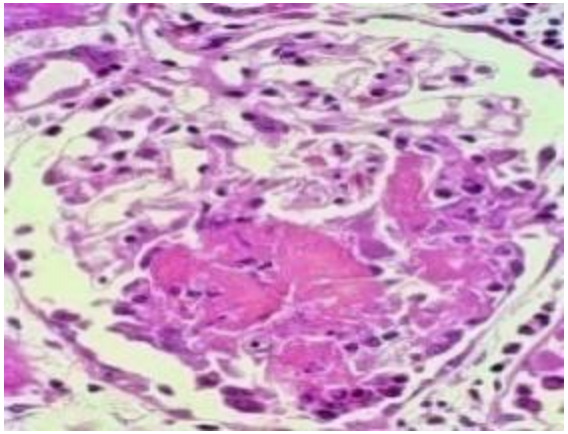


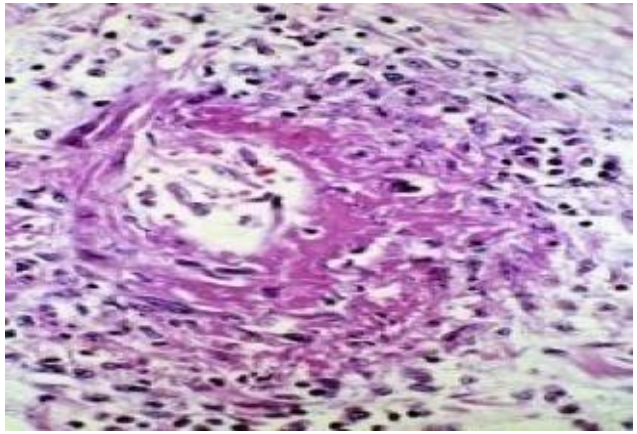


Pauci immune GN (ANCA vasculitis)



IgG is negative, also all IF markers are negative





Absence of mesangial proliferation, paucity of immune complexes.

Evolution of glomerular cellular crescents

Cellular crescent:>10% cellular components
Fibrous crescent: >90% extracellular matrix

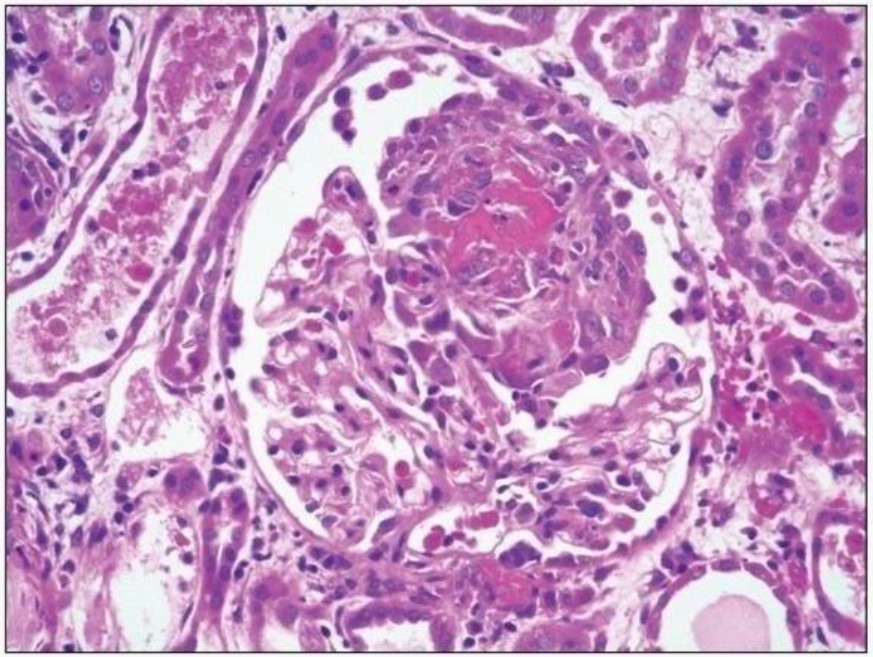
ANCA J Am Soc Nephrol 21: 1628–1636, 2010

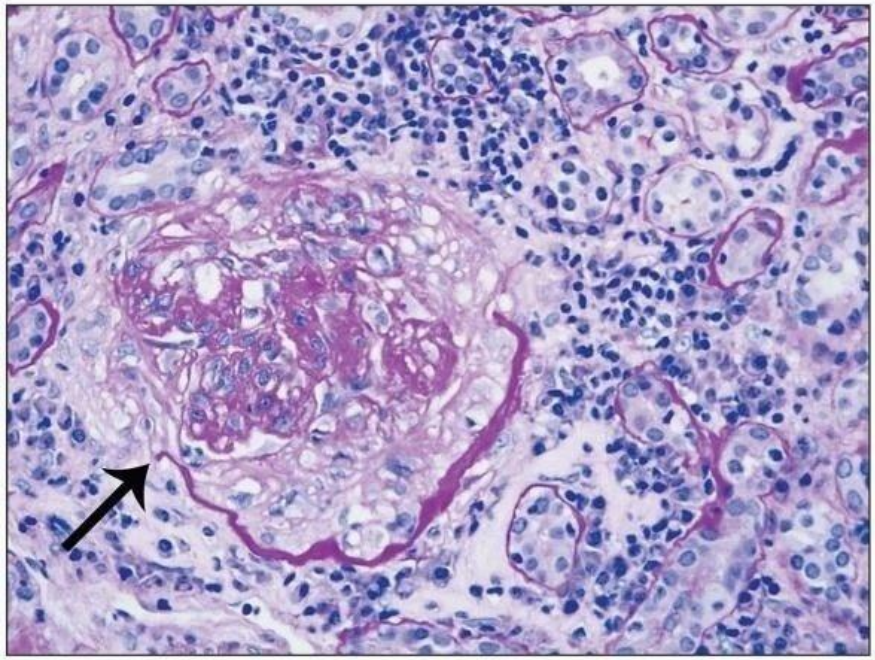
Cellular crescent: more than 75% cells and fibrin and less than 25% fibrous matrix (C)

Fibrous crescent: more than 75% fibrous matrix and less than 25% cells and fibrin (D)

Fibrocellular crescent: 25-75% cells and fibrin and the remainder fibrous matrix (E)

SLE Kidney Int. Apr;93(4):789-796 , 2018

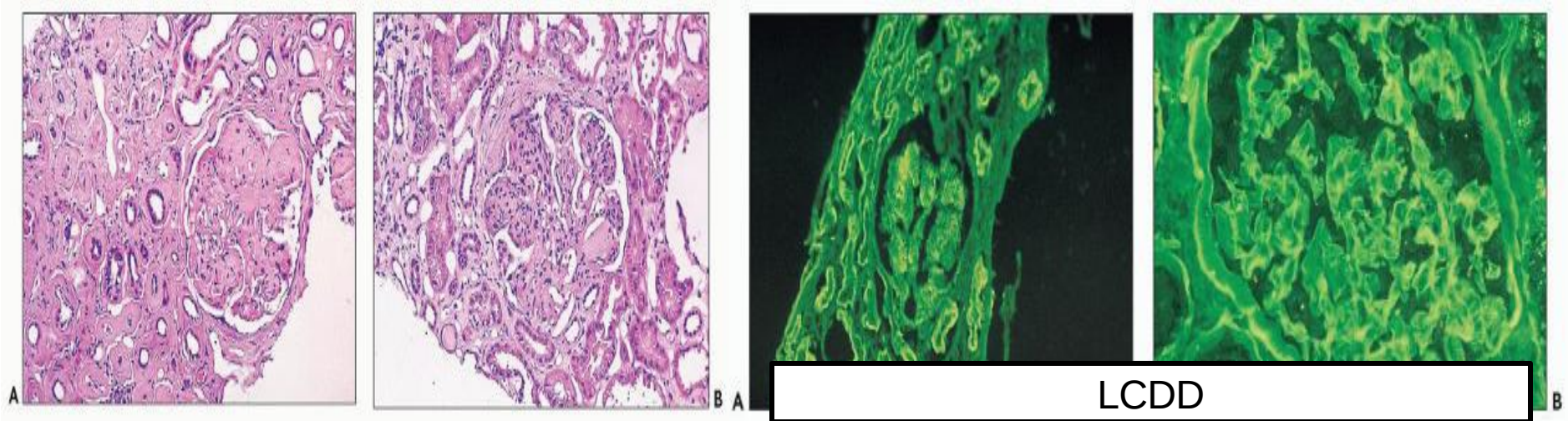




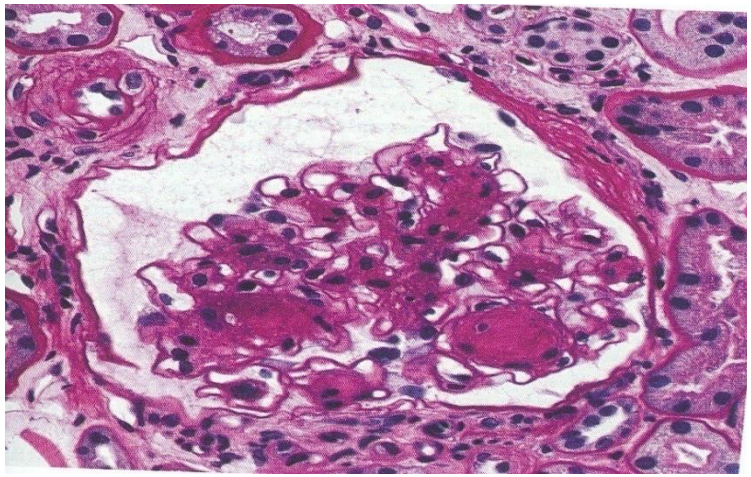
In chronic/final stage, necrosis is absent. Cellular crescents transform to fibrocellular /fibrotic and finally to sclerosed glomeruli.

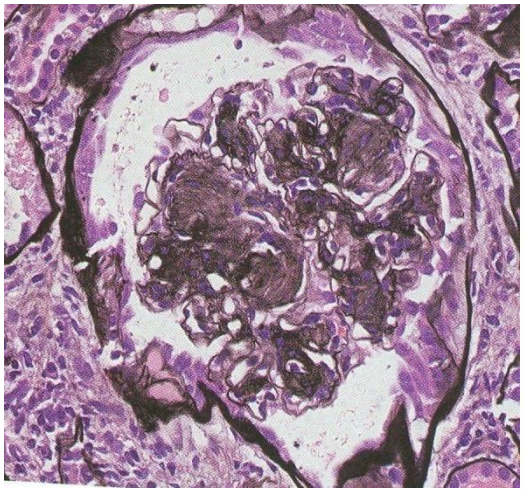
Nodular pattern of mesangial growth, with no cellularity, GBM thickening (severe proteinuria/ nephrotic syndrome)

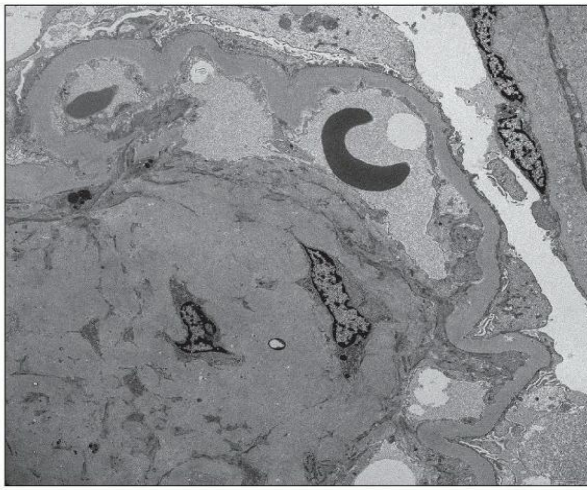
- Nodular glomerulosclerosis pattern of injury.
  - Metabolic: Diabetes Mellitus
  - Deposition of material
    - Light chain deposition disease (LCDD).
    - Amyloidosis
    - Membranoproliferative pattern in chronic stages.
    - Rare disease



Nodules in mesangium, GBM thickening, Diabetes Mellitus

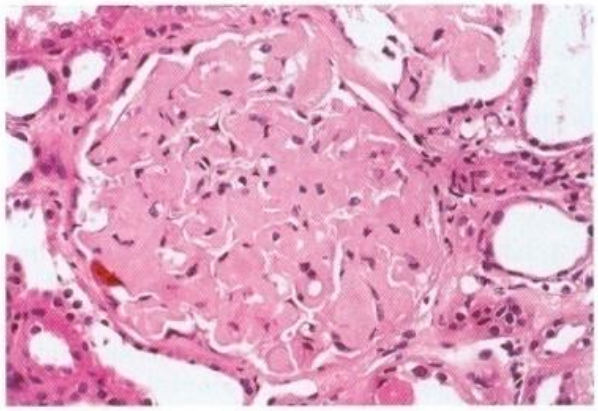






Heptinstall's pathology of the kidney

Amyloidosis (Congo Red+)



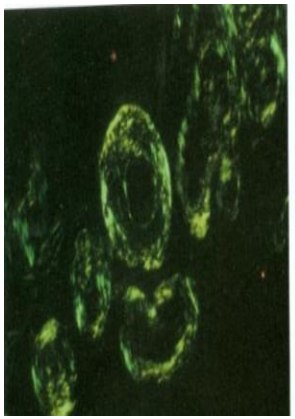
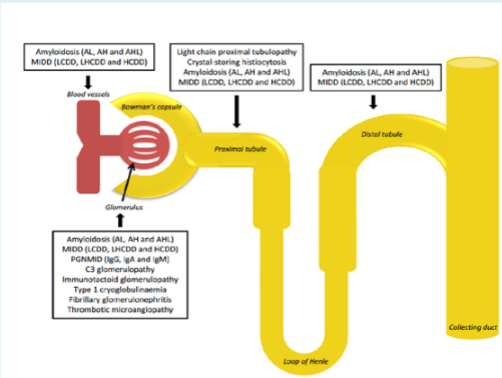


Figure 1. *Spectrum of monoclonal gammopathy of renal significance by localisation*



Monoclonal gammopathy of renal significance (MGRS): histopathologic classification, diagnostic workup, and therapeutic options

K. Amaador[1], H. Peeters[2], M.C. Minnema[3], T.Q. Nguyen[4], A. Dendooven[5,6,7], J.M.I. Vos[8], A.J. Croockewit[9], N.W.C.J. van de Donk[10], J.F.M. Jacobs[11], J.F.M. Wetzels[12], B. Sprangers[2,13], A.C. Abrahams[1]*

Focal segmental glomerulosclerosis-FSGS

(severe proteinuria, nephrotic syndrome)

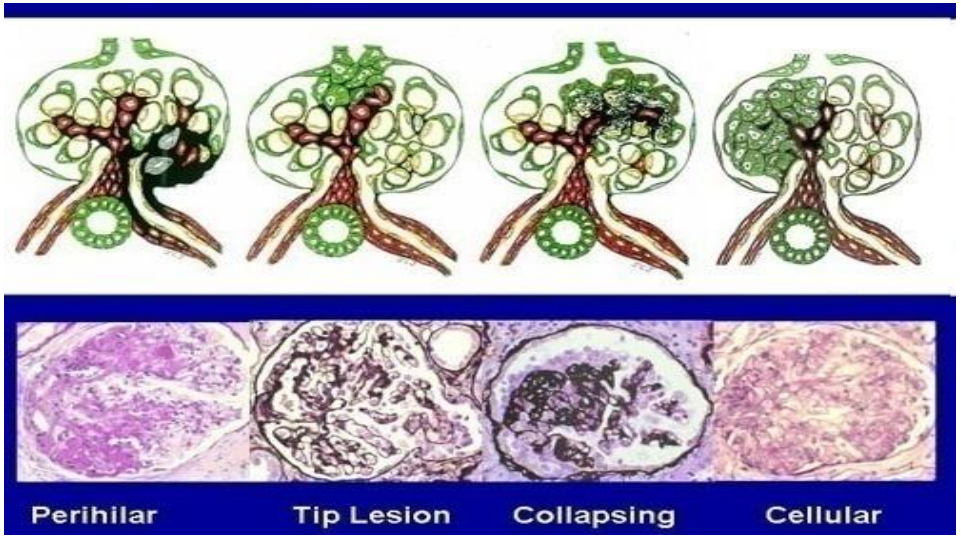
Laboratory Investigation 28:533, 1973

Focal Sclerosing Glomerulonephropathy with Segmental Hyalinosis

A Clinicopathologic Analysis

Lawrence R. Hyman, M.D., and Peter M. Burkholder, M.D.

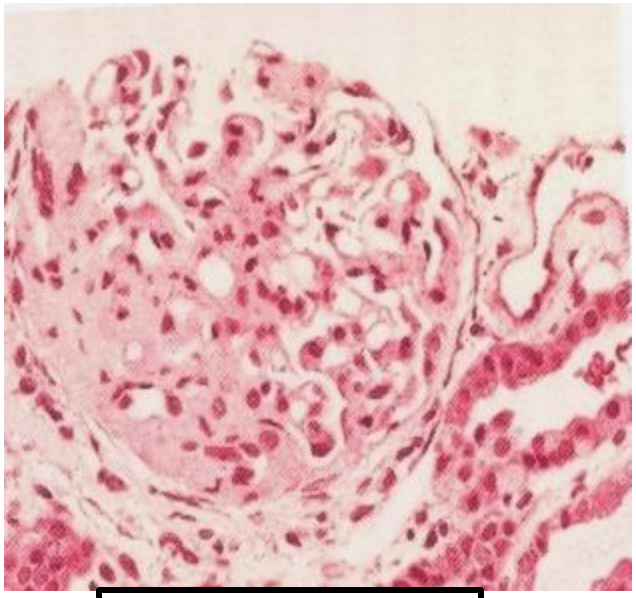
- IF-, Histological types:
  - Classic
  - Perihilar
  - "Tip" lesion
  - Cellular
  - Collapsing
  - "NOS"



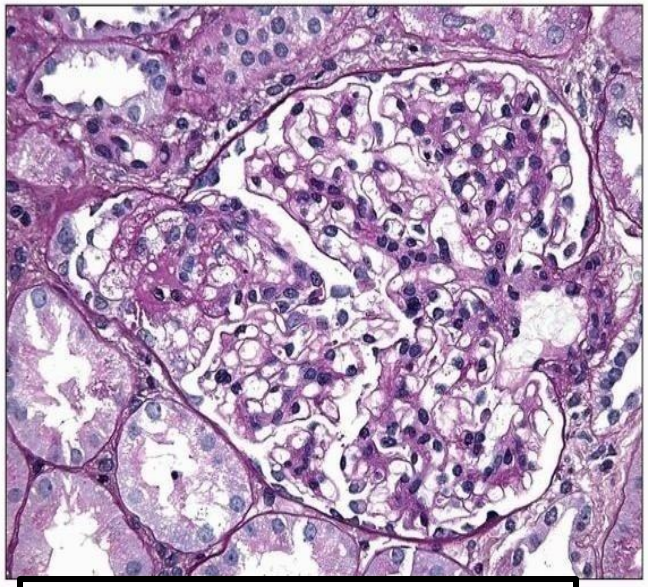
- **Forms: Primary, Genetic (>50 genes), secondary** (hyperfiltration injury, Hypertension, obesity, drugs, infections, etc).
- For chronic glomerulonephritides, FSGS can be a pattern of injury, not the disease entity; can be **the end morphological point of every disease, immune complex diseases including.**

American Journal of Kidney Diseases, Vol 43, No 2 (February), 2004: pp 368-382

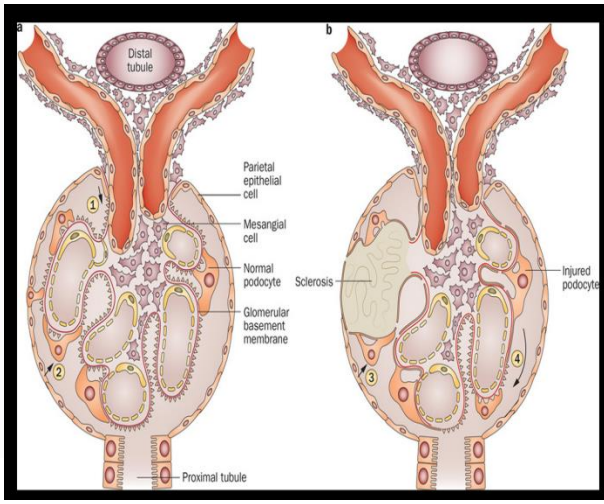
FSGS

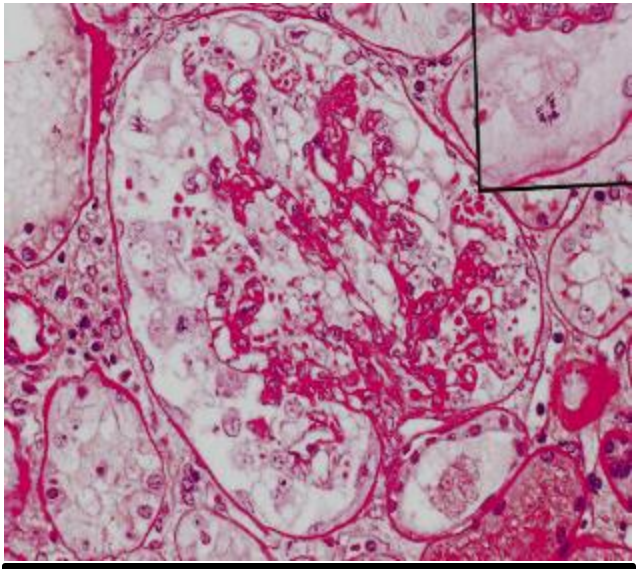


Classical FSGS

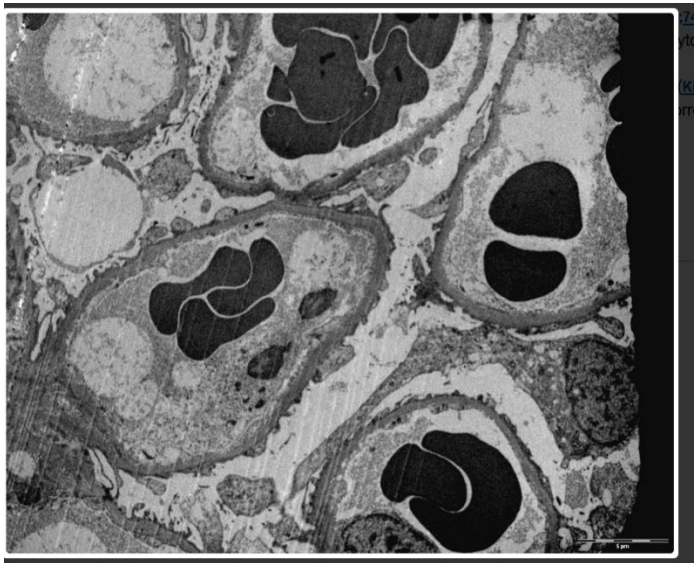


“Tip” lesion





Collapsing FSGS



Extensive foot process effacement involving > 80% of the capillary walls, suggestive of a primary FSGS form (transmission electron microscopy, 1,100x).

	SARS-COV-2 (with *APOL1* risk genotype)
Drug-induced	Direct-acting antiviral therapy mTOR inhibitors, CNIs Anthracyclines Heroin (adulterants) Lithium Interferon Anabolic steroids NSAIDs
Secondary to adaptive changes with glomerular hypertension	
Reduced nephron number	Reflux nephropathy Renal dysplasia Oligomeganephronia Sickle cell disease Age-related FSGS
Normal nephron number	Obesity-related glomerulopathy Primary glomerular diseases Systemic conditions, e.g., diabetic nephropathy, hypertensive nephrosclerosis

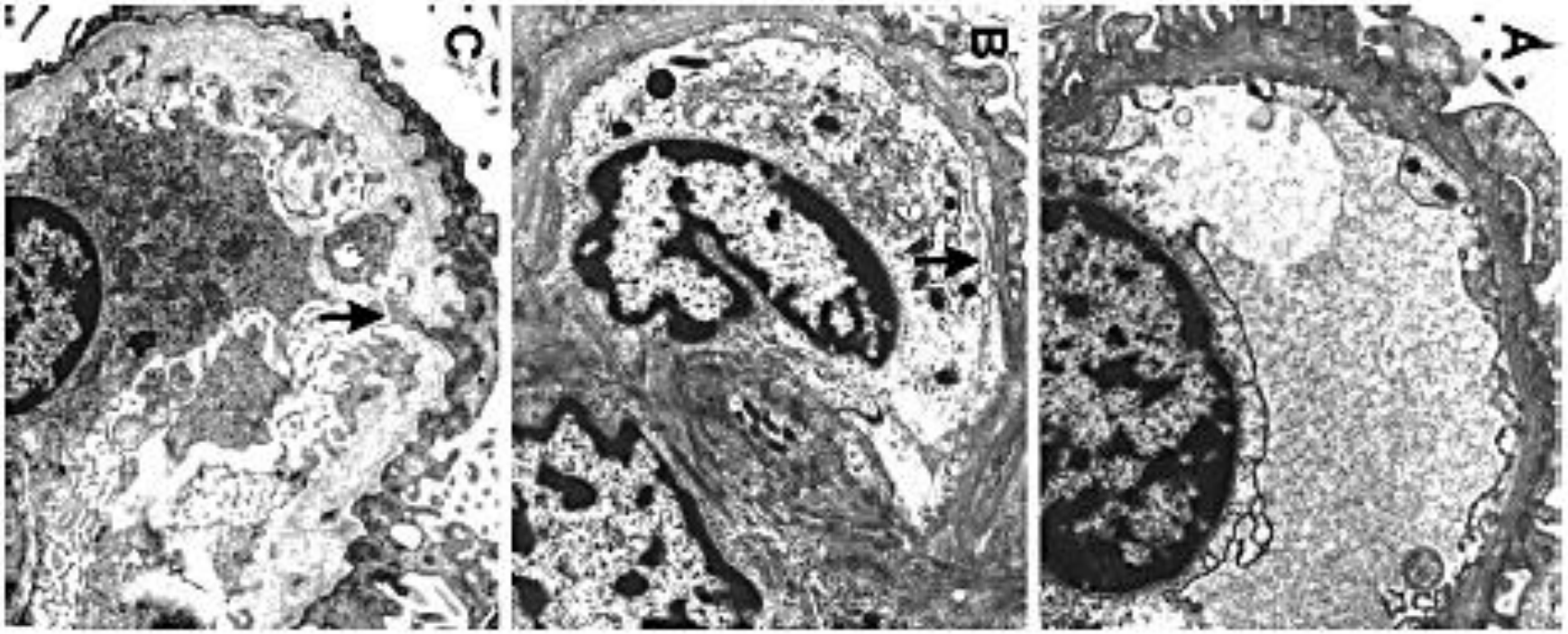
FSGS. *APOL1*, apolipoprotein L1; CMV, cytomegalovirus; CNI, calcineurin in
clerosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; mTOR,
atory drug; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

GBM abnormalities (proteinuria, nephrotic syndrome)

- Thickening of GBM , in association with increase in mesangial matrix (Diabetes Mellitus).
- Reduplications of GBM (TMA, MPGN, transplant glomerulopathy).
- GBM alterations, splitting, disruptions, reduplications (Alport syndrome, usually begins with hematuria).
- GBM thinning diffusely (thin basement membrane disease).
- Thickening of GBM, no alterations in mesangium (membranous glomerulopathy).

Alport syndrome

Thinning or abnormal thickening of GBM, alterations of GBM. GBM splitting, disruptions, reduplications of GBM, laminations, “basket wave”.



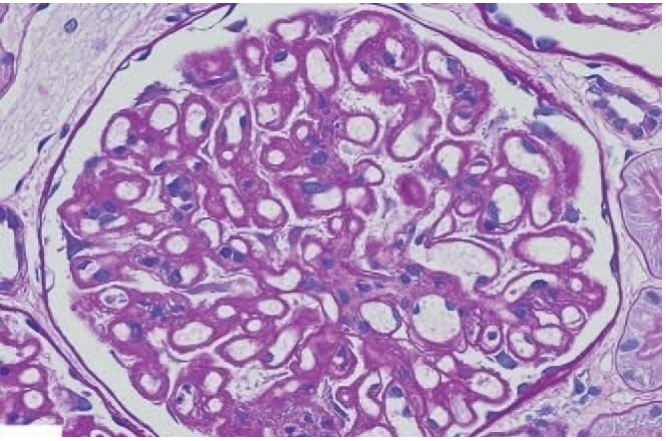
Final stage: pattern of non specific FSGS.

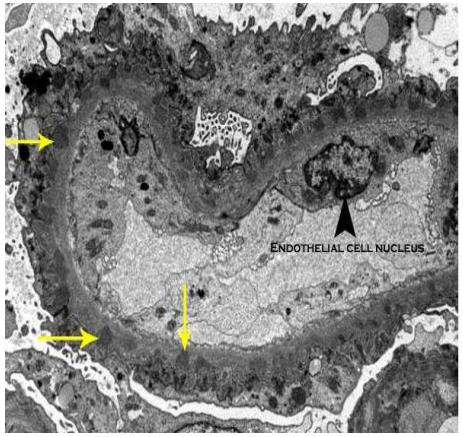
Arch Pathol Lab Med. **2009;133:224–232**

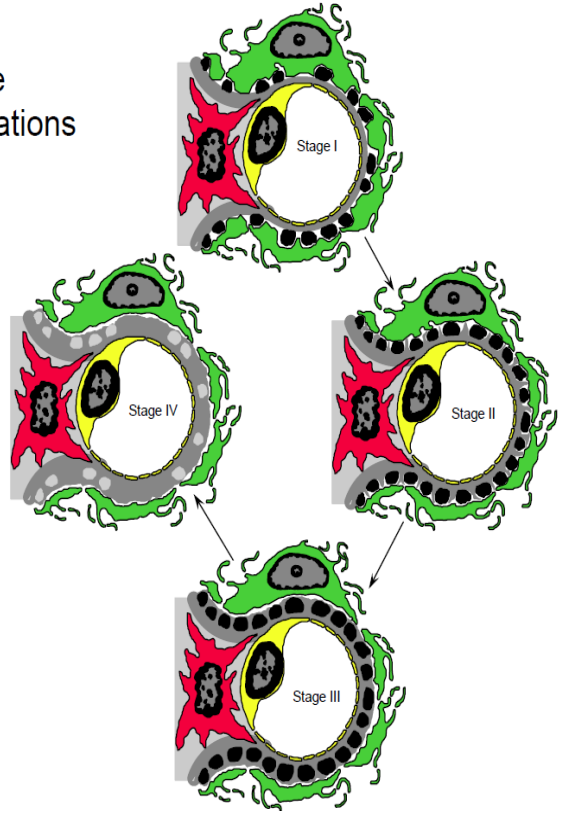
Membranous glomerulopathy

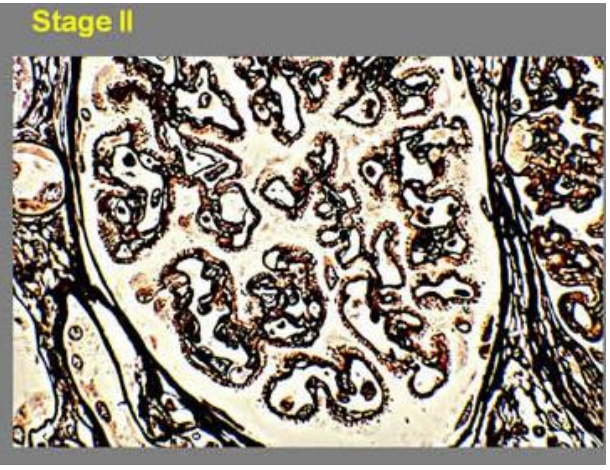
- A glomerulus is enough for the diagnosis, disease involves all gloms!

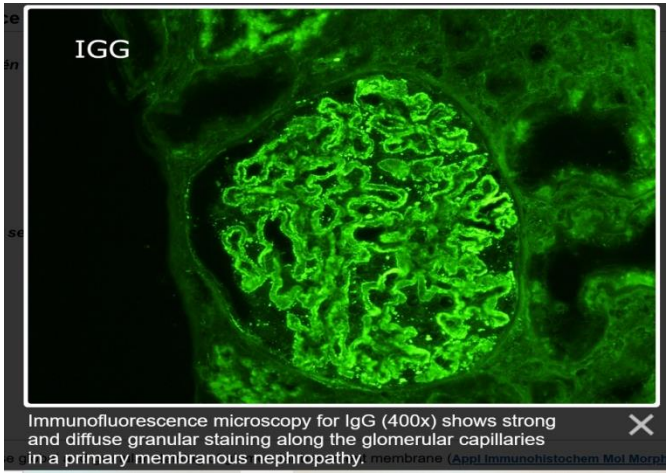
- "Spikes" in Silver stain.
- **Thickening of GBM or double contour in advanced stages**.
- Can be primary (usually PLA2-R+) or secondary (in autoimmune diseases like SLE, malignancies, infections etc).







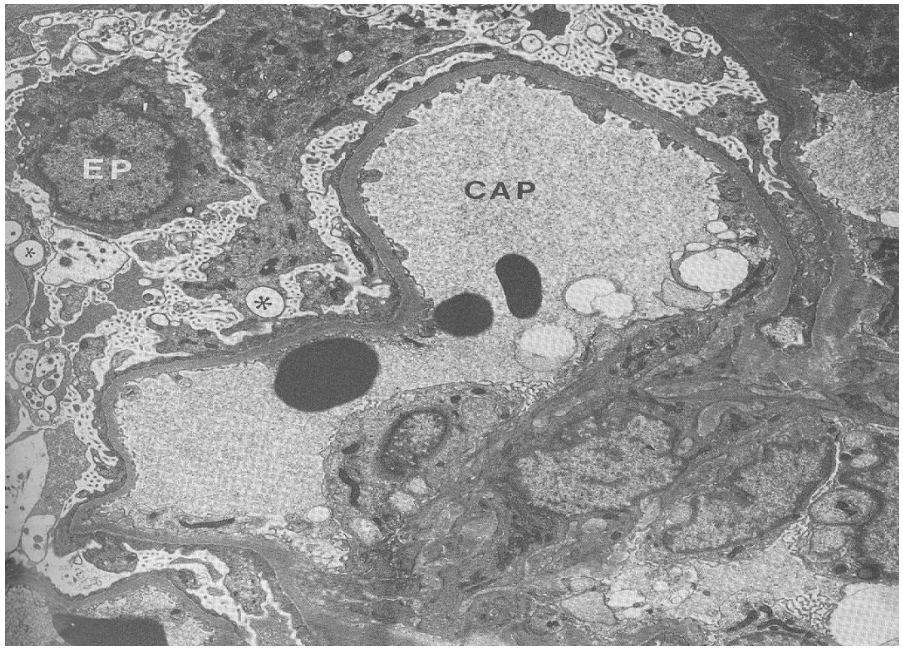




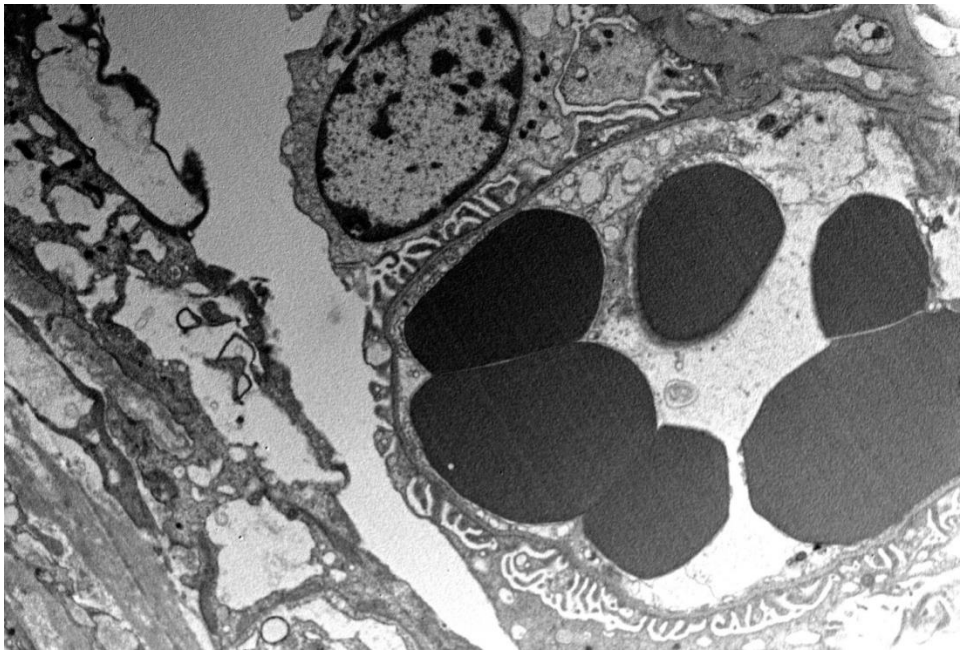
Από Jennette JC. UNC, Tutorial 2010

Minimal or no changes in Light Microscopy.

- IF- : Thin basement membrane disease, minimal change disease.
- IF+: Mild mesangial expansion in IgA nephropathy, SLE etc.



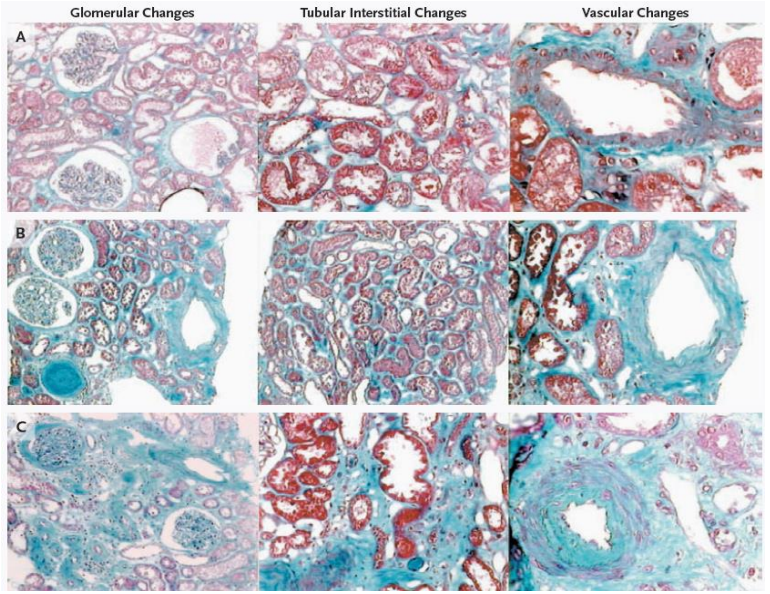
Minimal change disease

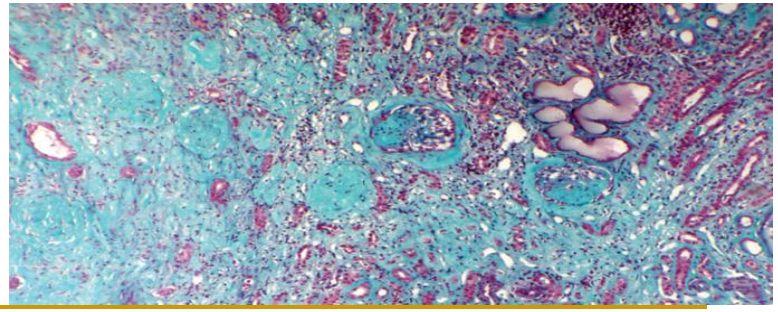


Thin besement membrane (TBM) disease

Global glomerulosclerosis/chronic GN (proteinuria, sediment can be inactive, gradually increased Creatinine)

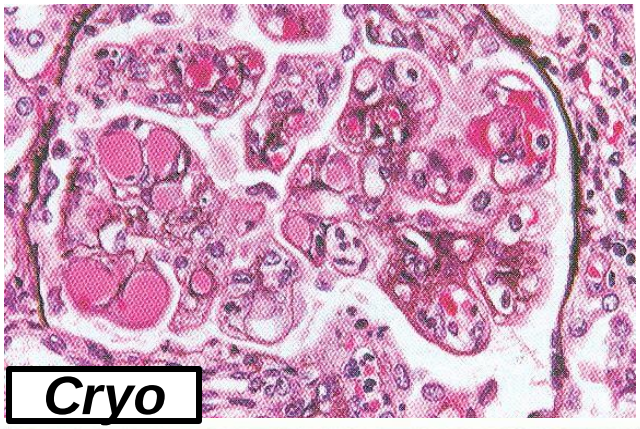
- Chronic GN is characterized by:
  - Interstitial fibrosis
  - Tubular atrophy
  - Vessels damage worsening glomerular damage.
  - No treatment response
  - Prognosis is ominous.
- In the final stage, determination of cause can be difficult.

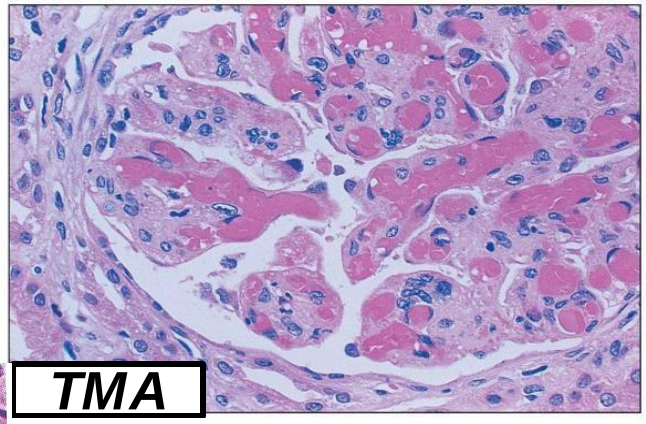


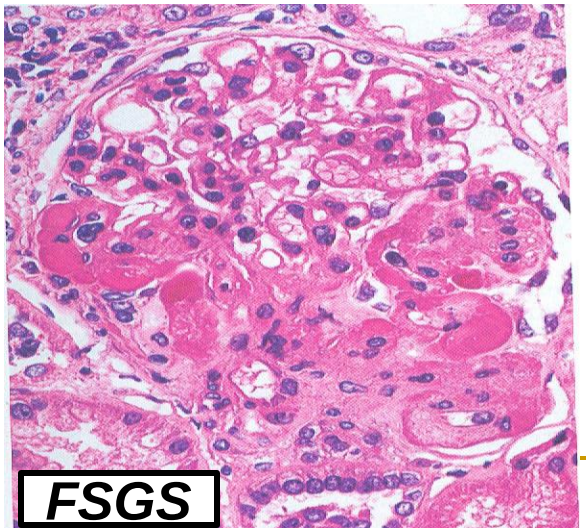


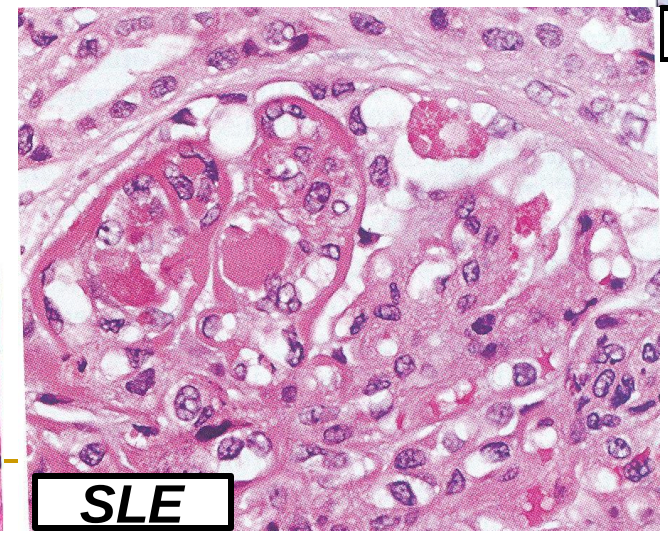
Deposition of amorphous material

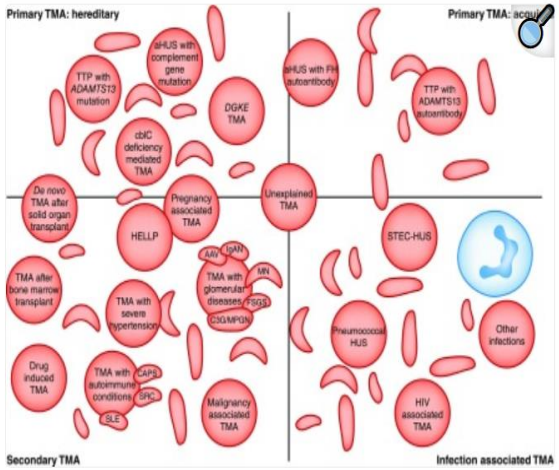
- Hyalinosis (FSGS, DM).
- Thrombi/fibrin (TMA).
- Necrosis (vasculitis).
- Cryoglobulins (Cryoglobulinemia).
- Large immune complexes (SLE).
- Amyloidosis Congo – Red +.











Electron Microscopy is necessary for certain diseases

- EM highlights: organoid deposits, GBM alterations, podocytes.
- Necessary for:
  - **Congo-Red negative diseases, with organoid deposits** (Fibrillary GN etc).
  - **No lesions in Light Microscopy diseases** (Minimal change disease, TBM disease).
  - **Rare genetic syndromes** (Alport, Fabry, LCAT etc).
- Important contribution in other diseases, for additional confirmation, or for more information.
- In ~2% of cases, diagnosis based on Light Microscopy and IF, is changed!

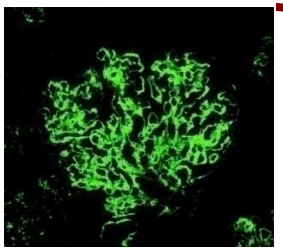
Table 1 Renal biopsy diagnosis requires LM, IF and EM

Diagnoses overlooked without IHC
Light chain-associated diseases
AL amyloid
Monoclonal immunoglobulin deposition disease
Light chain cast nephropathy
IgA nephropathy/Henoch–Shonlein purpura
IgM nephropathy
C1q nephropathy
Antiglomerular basement membrane disease
Humoral (C4d) transplant rejection
Fibronectin glomerulopathy

Diagnoses overlooked without EM
Fibrillary glomerulopathy/immunotactoid glomerulopathy
Nail–patella syndrome
Lipoprotein glomerulopathy
Dense deposit disease
Alport's syndrome
Thin glomerular basement membrane nephropathy
Collagenofibrotic glomerulopathy

Diseases with organoid deposits, classification by Congo- Red

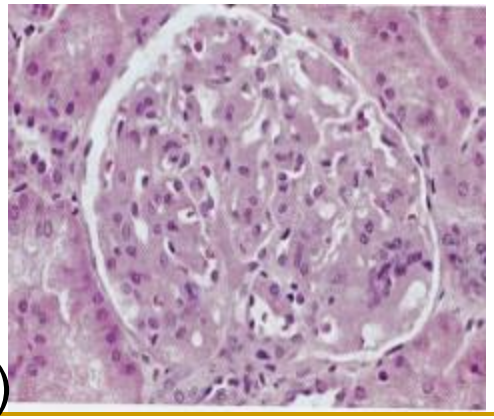
- Congo red positive diseases, with organoid deposits (Amyloidosis).
- **Congo red negative diseases with organoid deposits derived from immunoglobulins**, IF+ (Fibrillary GN, Immunotactoid GN).
- **Congo red negative diseases**, **with organoid deposits, that do not derive from immunoglobulins,** IF- (Fibronectin nephropathy).

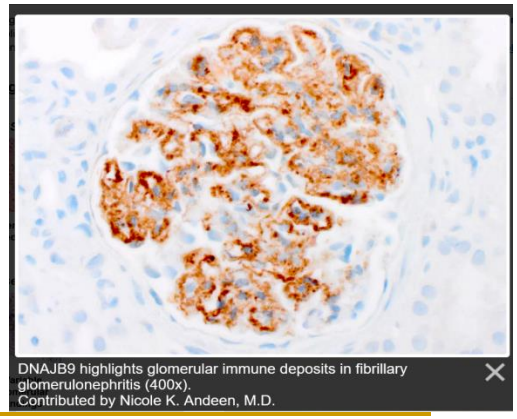


- EM

Congo-Red negative

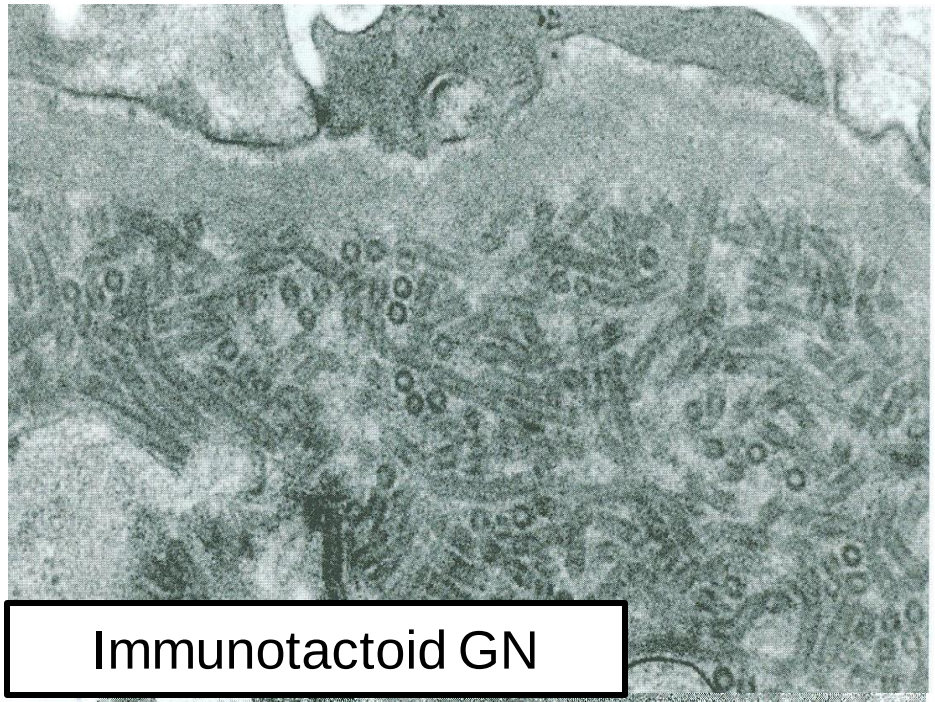
- Usually proliferative GNs.
- Can be associated with plasma cells dyscrasias (Immunotactoid GN), or autoimmunity/malignancies and/or “idiopathic” (Fibrillary GN)



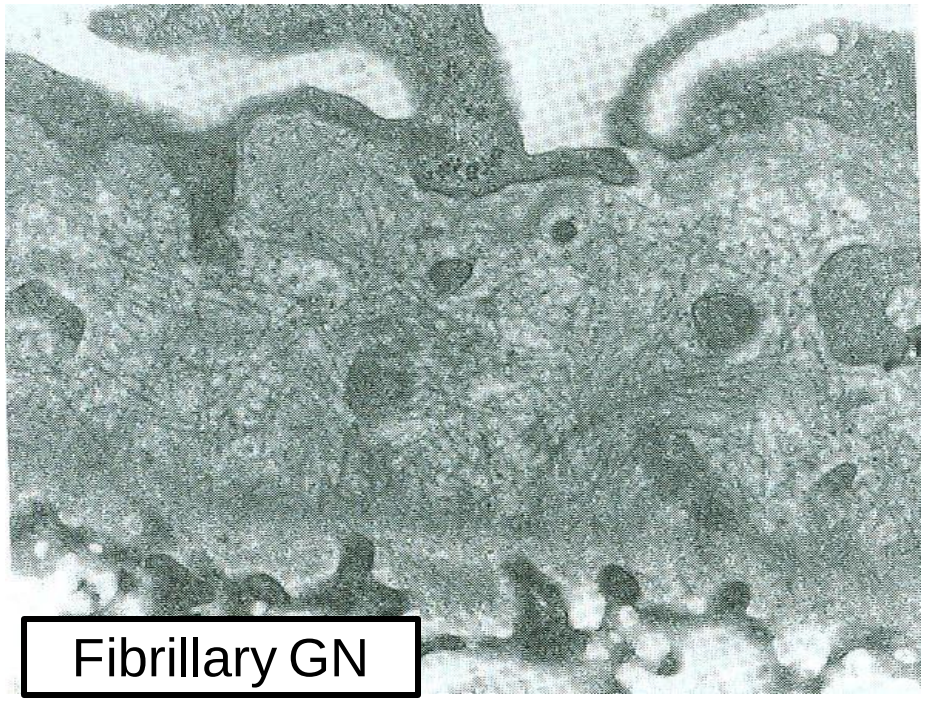


Nasr S.H. et al. Clin J Am Soc Nephrol. 2011 April; 6(4): 775–784.

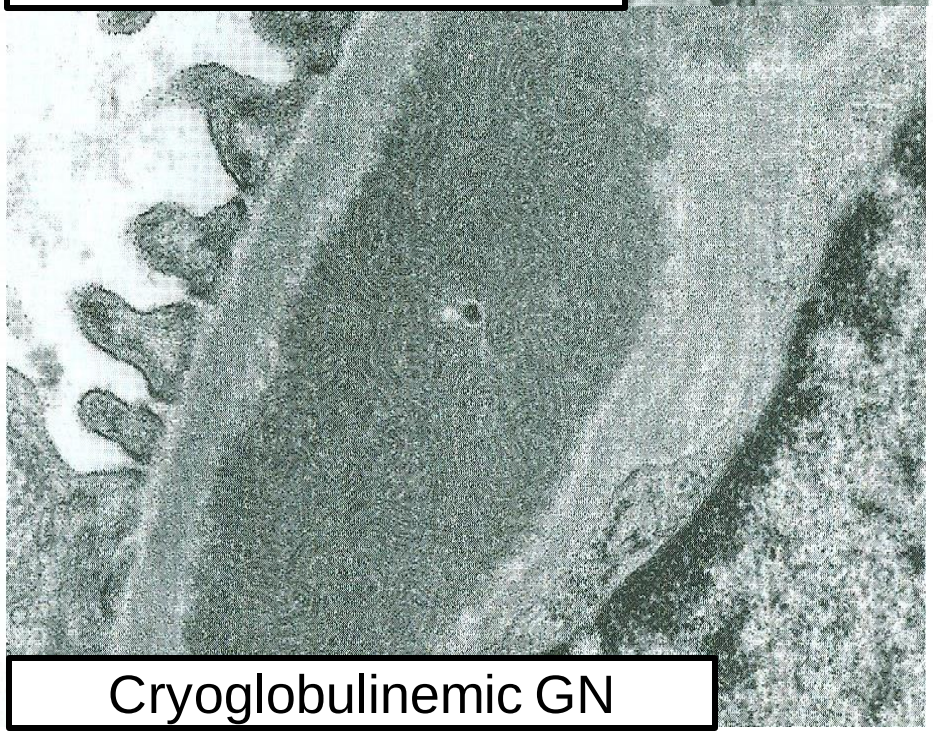
Fibrillary GN
IHC: DNAJB9+



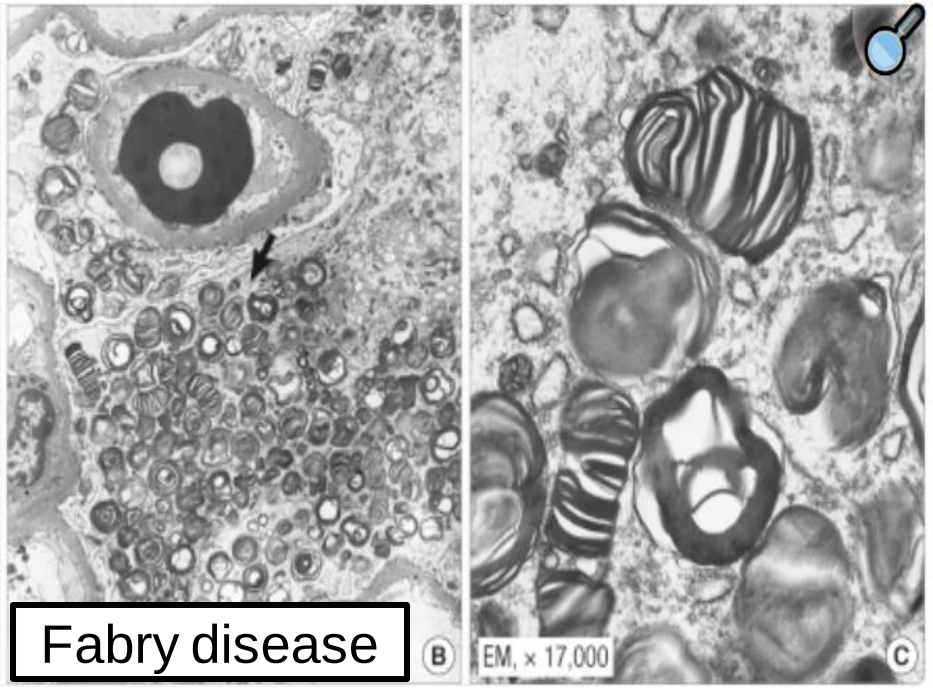
Immunotactoid GN



Fibrillary GN



Cryoglobulinemic GN



Fabry disease

Other indirect findings can also be of value

- Focal vs Diifuse

  ANCA vasculitis vs anti-GBM disease.

  Membranous diffuse (only 1 glom can provide diagnosis!)

  SLE (can be focal), MPGN (usually diffuse).

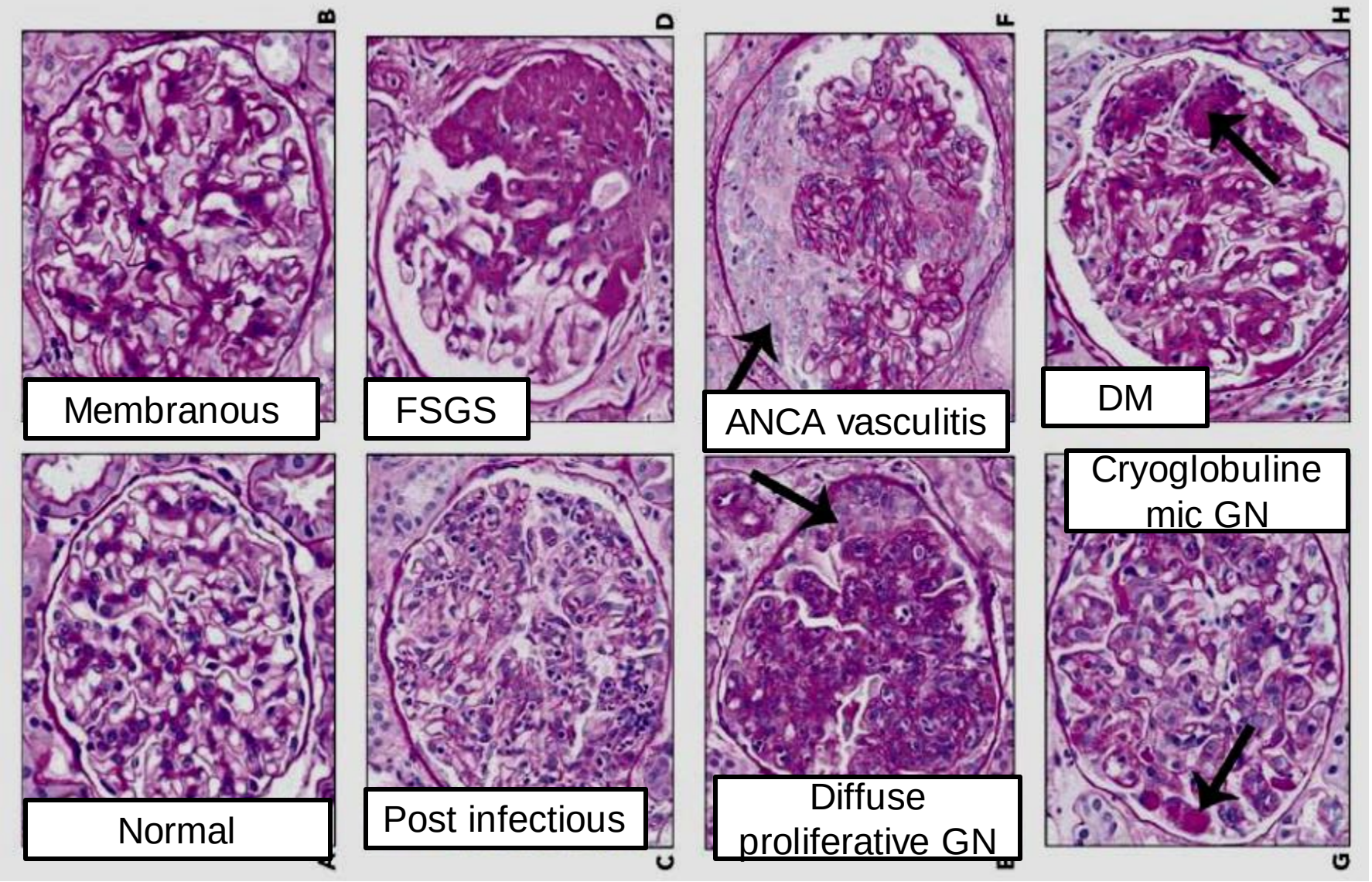
- Acute vs chronic

  Wegener usually active, MPA usually coexist active and chronic lesions.

- Special histological findings ("nuclear dust/debris" in SLE, Cryo-plugs in Cryoglobulinemic GN etc).

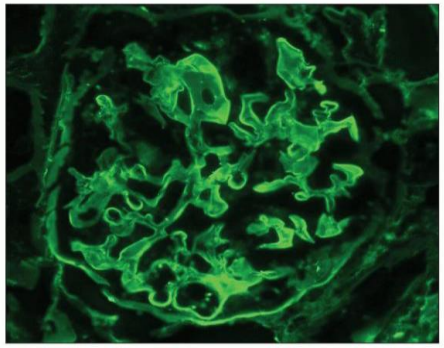
- Glomerular size (DM large gloms, vs Arterial Hypertention /ischemia small gloms).

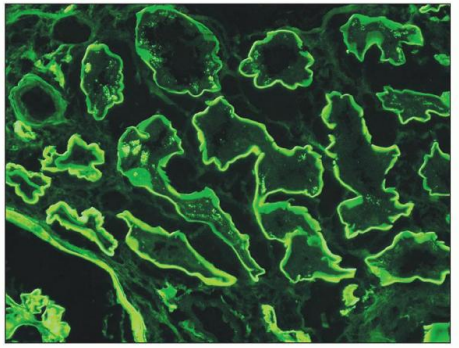
Patterns of injury, Light Microscopy

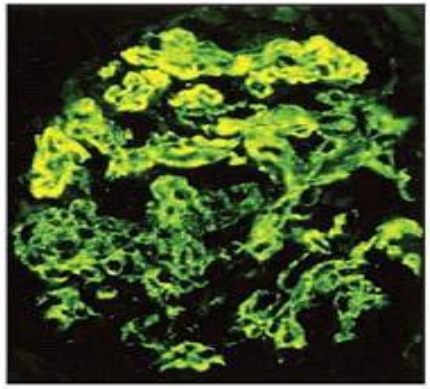


Patterns of injury, Immunofluorescence

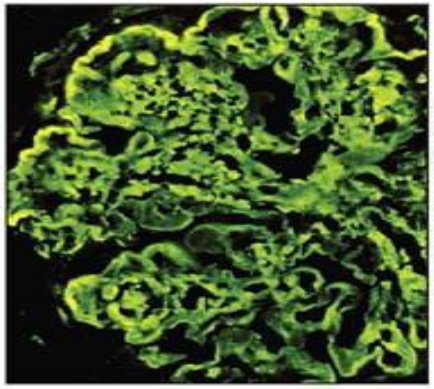
- Mild linear expression of IgG in DM.



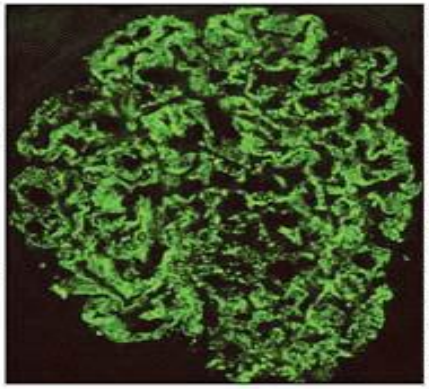




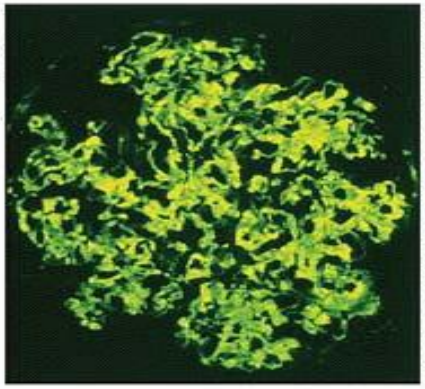
Proliferative GN (IgG)



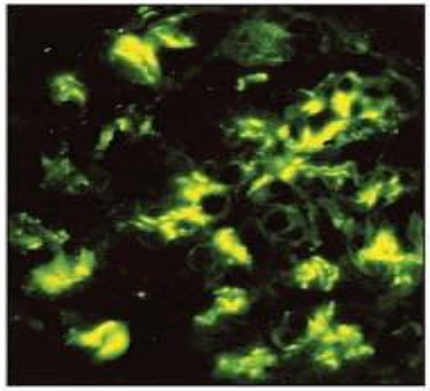
Type II MPGN (C3)



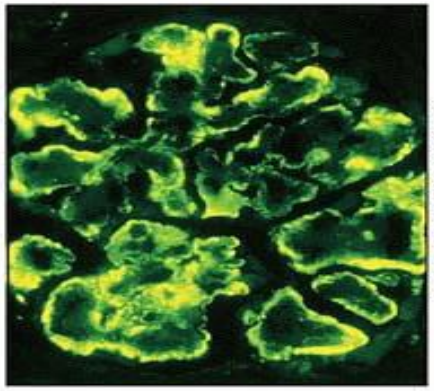
Membranous Glomerulopathy (IgG)



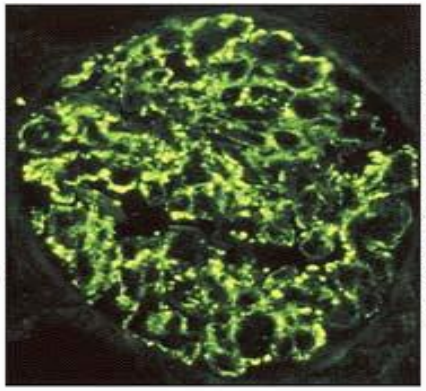
Fibrillary Glomerulonephritis (IgG)



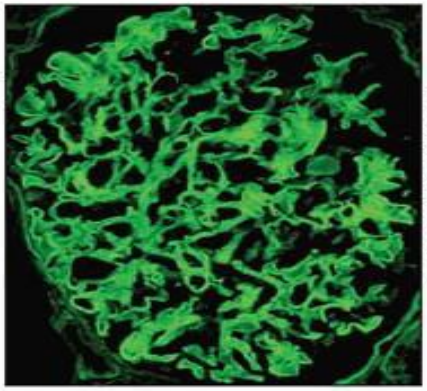
Mesangioproliferative GN (IgA)



Type I MPGN (C3)



Post-infectious GN (C3)



Anti-GBM GN(IgG)

2η Classification, from Clinical syndromes to Histology

A certain clinical syndrome may have different causes.

A certain disease may cause different symptoms/syndromes.

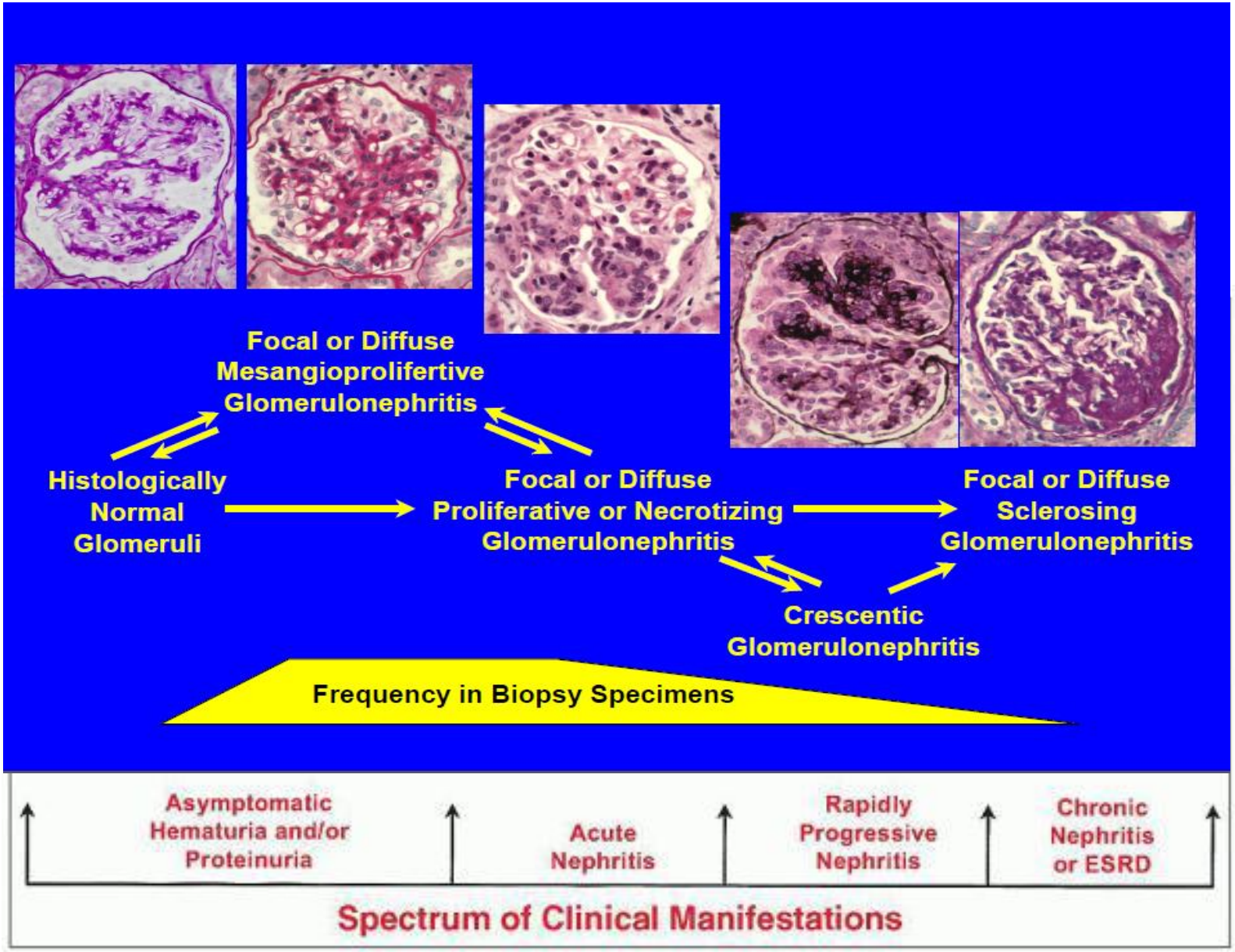
- Non symptomatic proteinuria (non nephrotic range)
- Nephrotic syndrome
- Non symptomatic hematuria.
- Acute nephritic syndrome (acute GN)
- Rapidly progressive GN.
- Chronic GN.

Heptinstall Pathology of the Kidney 7th Edition

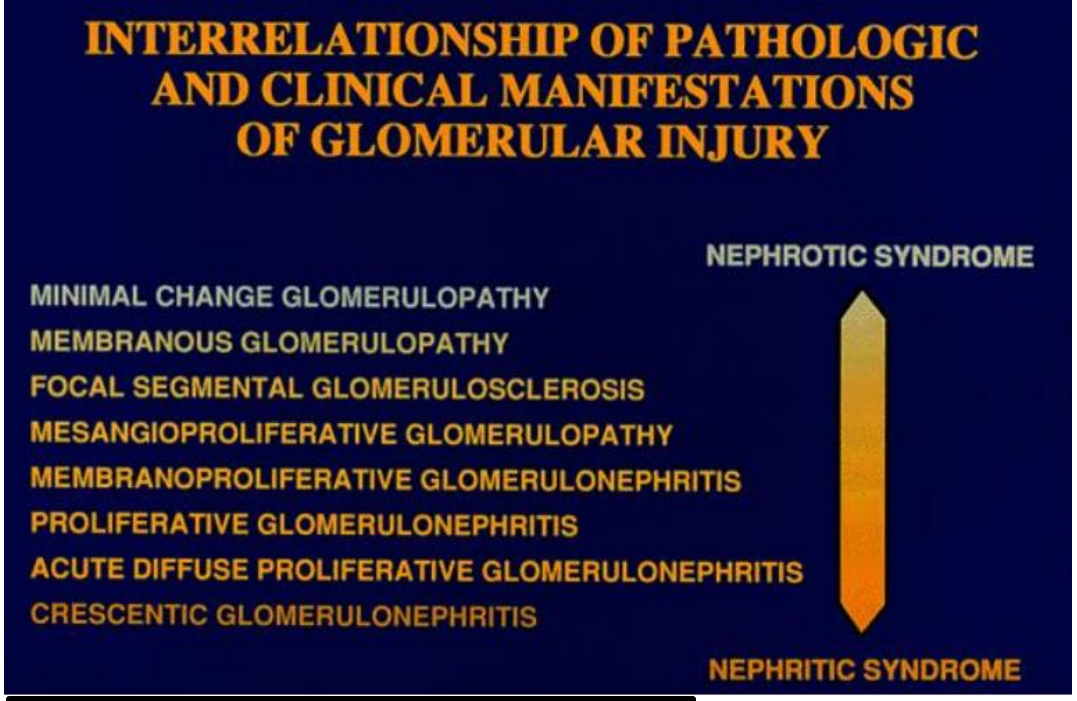
TABLE 3.1 Clinical manifestations of renal disease

Microalbuminuria
Subnephrotic proteinuria
Nephrotic-range proteinuria
Nephrotic syndrome
Asymptomatic hematuria
Microhematuria
Macrohematuria (gross hematuria)
Acute nephritis
Rapidly progressive glomerulonephritis
Hypertension
Thrombotic microangiopathy
Acute kidney injury
Chronic renal failure
Urinary tract infection
Urinary tract obstruction
Nephrolithiasis
Renal malformation/cysts
Renal tumor
Renal transplant dysfunction

TABLE 3.2 Native kidney diseases encountered in renal biopsy specimens from patients with medical renal native kidney disease

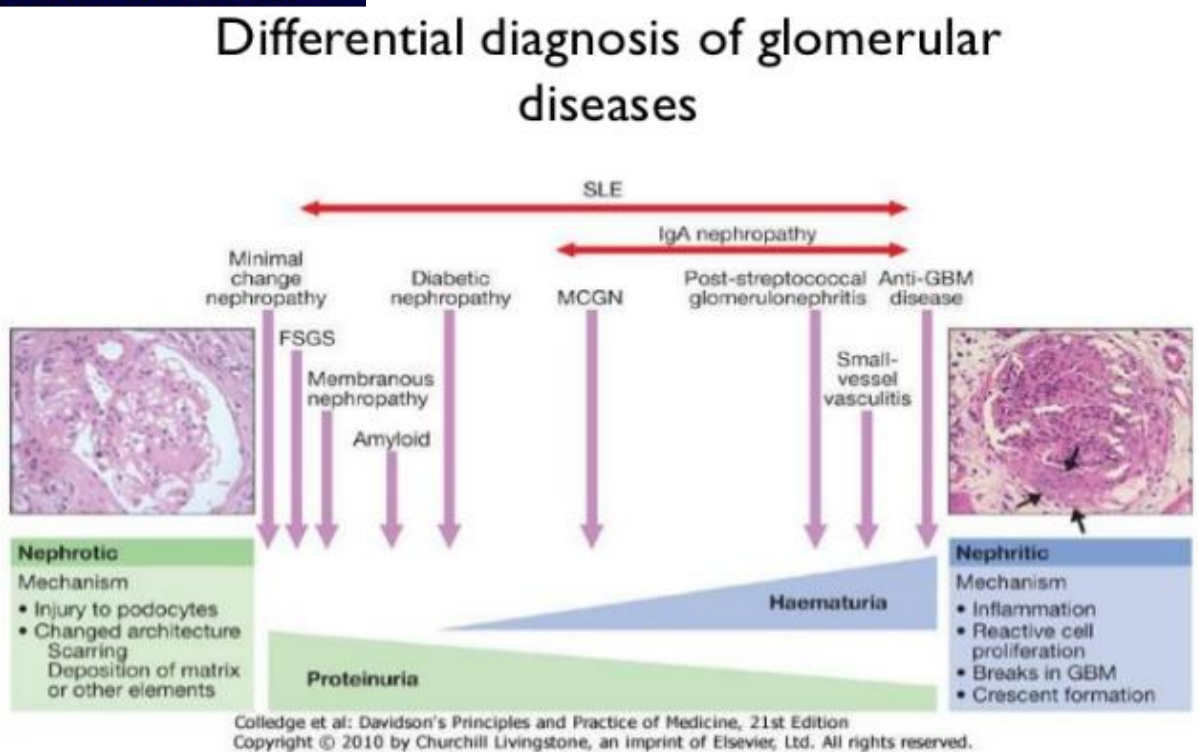


Jennette JC. UNC, Tutorial 2010



Jennette, UNC Neprhropatholgy, Tutorial 2010

- Some glomerular disease may be mainly hematuric or mainly proteinuric, but there are diseases than can be both, covering the whole spectrum of manifestations.



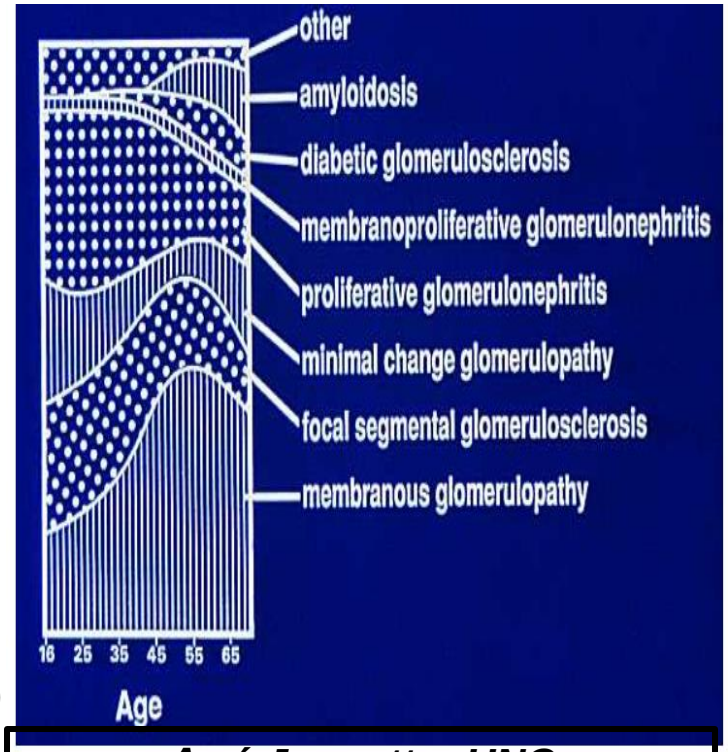
Asymptomatic Proteinuria (subnephrotic range)

- >200mg/24h, no hematuria.
- Focal Segmental Glomerulosclerosis
  - Can present with low proteinuria gradually increased, especially in secondary forms (AH, obesity etc).
- Mesangial Proliferative GN (microscopic hematuria can also be seen)
- Membranous glomerulopathy (unusual, membranous usually manifests with nephrotic range proteinuria).

Nephrotic syndrome

Proteinuria >3,5g/24h, edema, hypoalbuminemia.

- Minimal change disease (usually no hematuria).
- Focal segmental glomerulosclerosis (hematuria can coexist).
- Membranous Glomerulopathy -PLA2R+.
- Amyloidosis (lambda light chains in urine).
- MPGN (low complement, active sediment)
- Fibrillary GN
- Light chain depoition disease (palsma cell dyscrasia).
- Diabetic nephropathy (retinal involvement).



Από Jennette, UNC Neprhropatholgy, Tutorial 2010

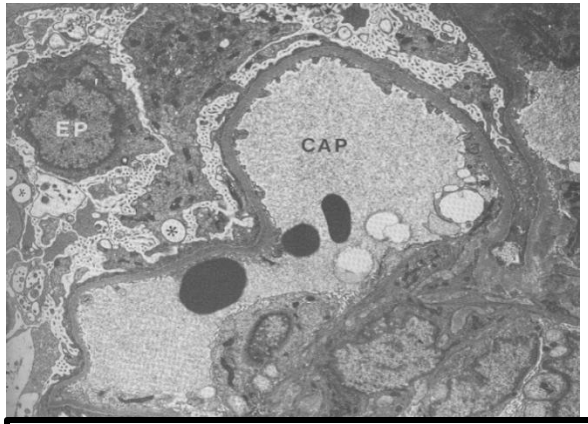
- **Age of patient is helpful for the differential diagnosis.**

Nephrotic syndrome, variety of diseases, variety of patterns

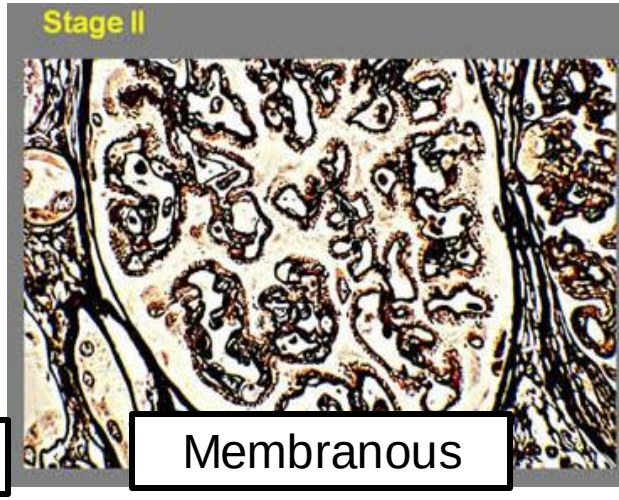
- **Heterogeneity.**

Causes:

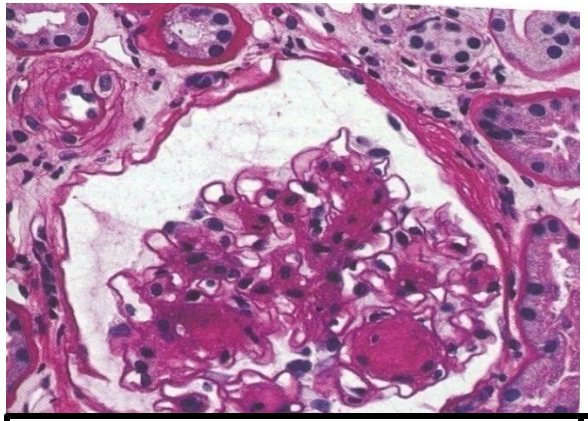
1) «Podocytopathy».
2) Alterations in GBM (thickening etc),and/or nodules in mesangium.
3) Intraglomerular inflammation (in this case, usually microscopic hematuria coexists).



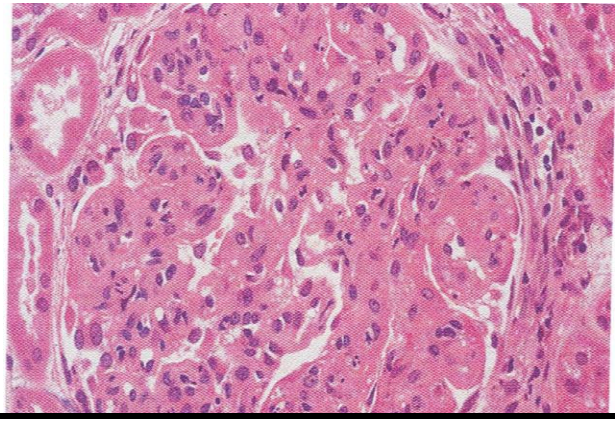
Minimal change disease



Membranous



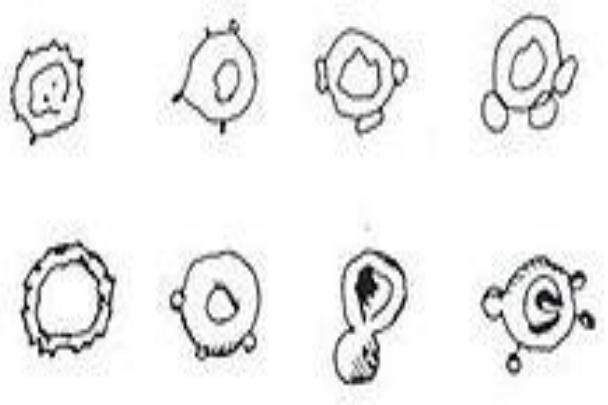
Diabetic nephropathy



Membranoproliferative GN

Microscopic hematuria (or reccurent hematuria), no proteinuria (asymptomatic)

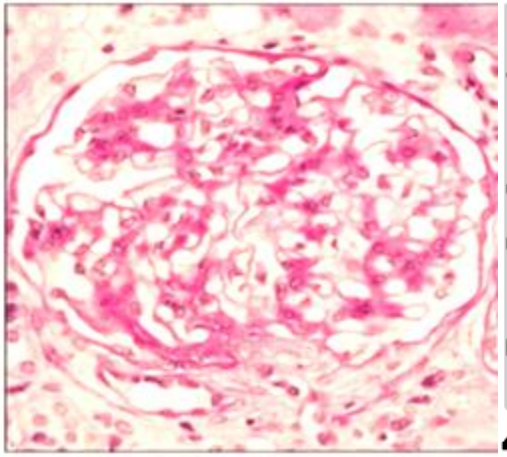
- Red blood cells, can be different in terms of morphology, size, hemoglobulin content)



Dysmorphic

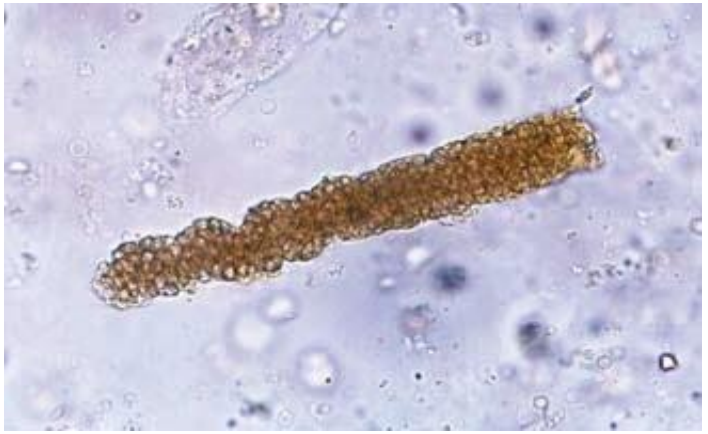
Acanthocytes

- Microscopic (>3 RBC per HPF)
- Macroscopic
- Thin basement membrane disease - **Normal glomeruli.**
- IgA nephropathy – **Mesangial GN.**



Nephritic syndrome

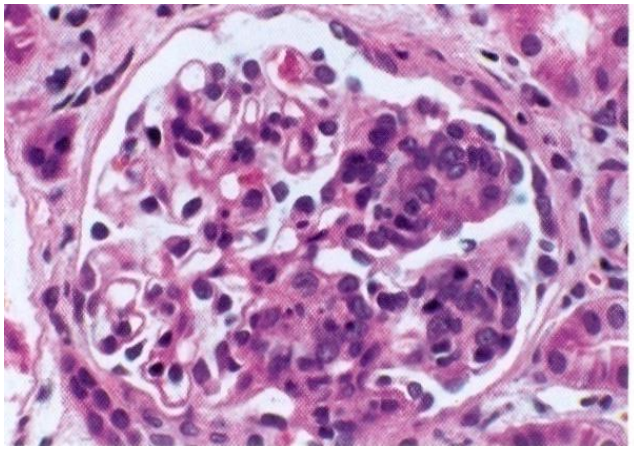
- Hematuria of glomerular origin, Red blood casts.
- Proteinuria
- eGFR reduction, oligoanuria
- Hypertension
- Edema



Types:

- Acute glomerulonephritis
- Rapidly progressive glomerulonephritis

Acute Glomerulonephritis

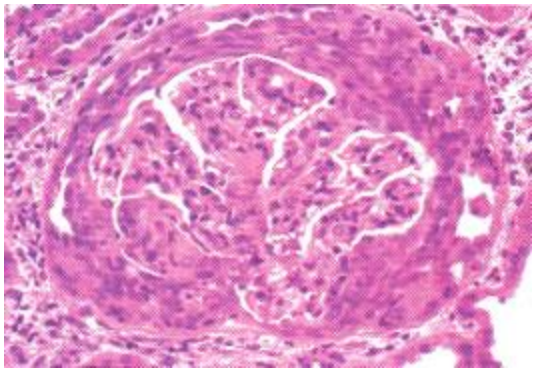


- Characterized by Endocapillary proliferation and/or glomerular crescents/fibrinoid necrosis.

- Proliferative IgA nephropathy

  (↑ IgA in the serum, previous infection of the upper Respiratory Tract).
- Proliferative classes of SLE (positive immunology, other organs are affected, like skin, serosa etc).
- Acute post infectious GN (antibodies against streptococcus, Complement normalization into trimester).
- C3 glomerulopathy/glomerulonephritis.
- Membranoproliferative GN(↓C3, C4).
- Fibrillary GN
- ANCA vasculitis

Rapidly progressive GN



- Rapid deterioration of renal function, in a few days or weeks, double of baseline Cr.
- Crescents, and/or fibrinoid necrosis, Red Blood cell casts.
  - **Pauci immune vasculitis (ANCA+, «pauci immune» IF).**
  - **Anti-GBM disease, IgG+ linear in GBM.**
  - Immune complex GN, with granular IF, SLE, IgA, MPGN etc.

- Red blood cells casts, even if not associated with glomerular crescents or necrosis, can result in rapid deterioration of renal function and mimic clinically vasculitis, while there are no glomerular crescents or necrosis, biopsy is essential for determining the cause and therapy.
- Anticoagulant drugs can deteriorating more an IgA nephropathy.

Int Urol Nephrol (2017) 49:1401–1407
DOI 10.1007/s11255-017-1527-9

NEPHROLOGY – REVIEW

Anticoagulant-related nephropathy: a case report and review of the literature of an increasingly recognized entity

Rigas G. Kalaitzidis[1] · Anila Duni[1] · Georgios Liapis[3] · Olga Balafa[1] · Sofia Xiromeriti[1] · Paulos Karolos Rapsomanikis[1] · Moses S. Elisaf[1,2]

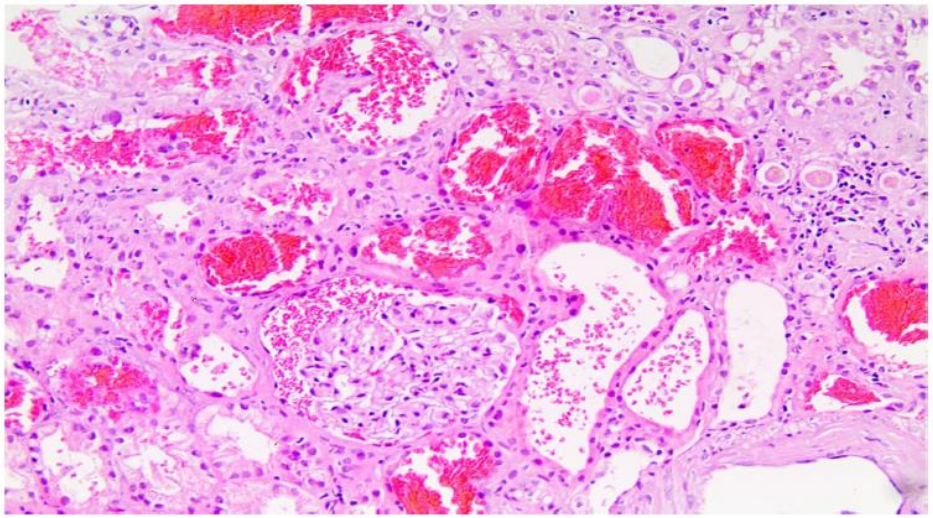
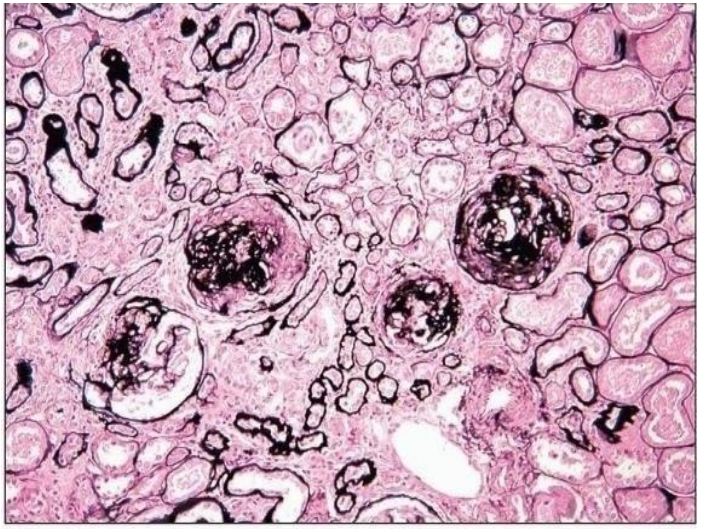
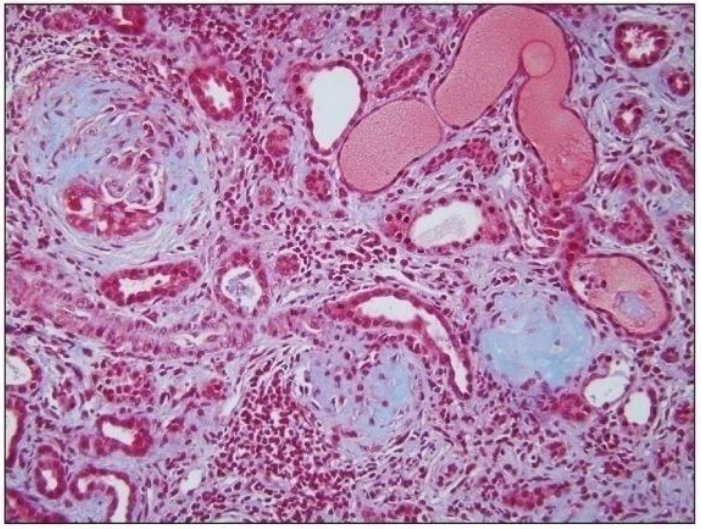


Fig. 1 Occlusion of tubular lumens by red blood cell casts. Red blood cells have entered the Bowman's capsule of a glomerulus (H&E X 200)

- Red blood cell casts in a case of IgA nephropathy, d.d.from ANCA vasculitis.

Chronic glomerulonephritis





- Hematuria +/-, proteinuria, increased Cr (CKD).
- Cause detection can be difficult.
- Global and segmental glomerular scarring, “FSGS” pattern of injury (not the disease entity), fibrotic remnants of crescents can coexist.
- For Proliferative GNs, sometimes, but not always, some proliferation can be noticed.

Conclusions

- Importance of morphological classification of glomerular patterns of injury – correlation with clinical syndromes.
- Disease distinction/diagnosis is made by IF (presence or absence of Immune complex deposits, types etc) in association with morphological patterns (Light Microscopy +EM).
  - Proliferation (types, subtypes, special patterns like MPGN)
  - Nodular glomerulosclerosis,
  - FSGS,
  - Lesions in GBM,
  - Special characteristics.
- Diagnosis: Combination of histology and clinical findings.
- It is mandatory for the Pathologist to think like Clinician and for Clinician to think like the Pathologist ("double" view) for a thorough full examination.

Thank you