

Glomerular Diseases

Part I

Elise Barney, DO

Nephrologist, Phoenix VA Health Care System

Associate Professor, University of Arizona College of Medicine

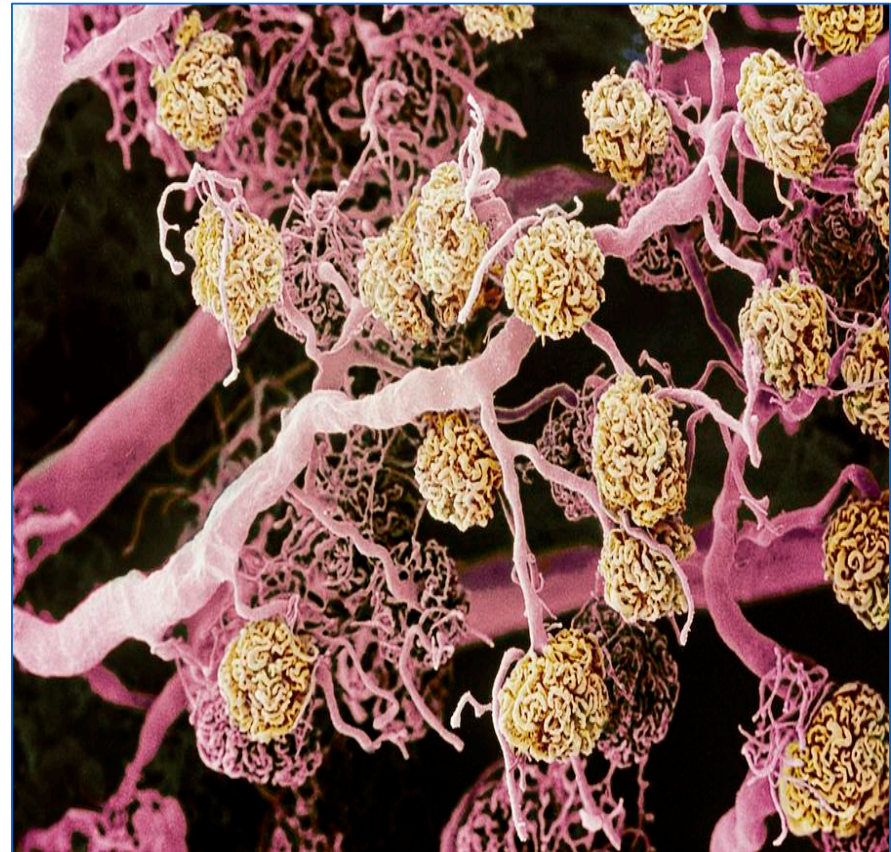
BUMC Internal Medicine Resident Lecture

January 24, 2017

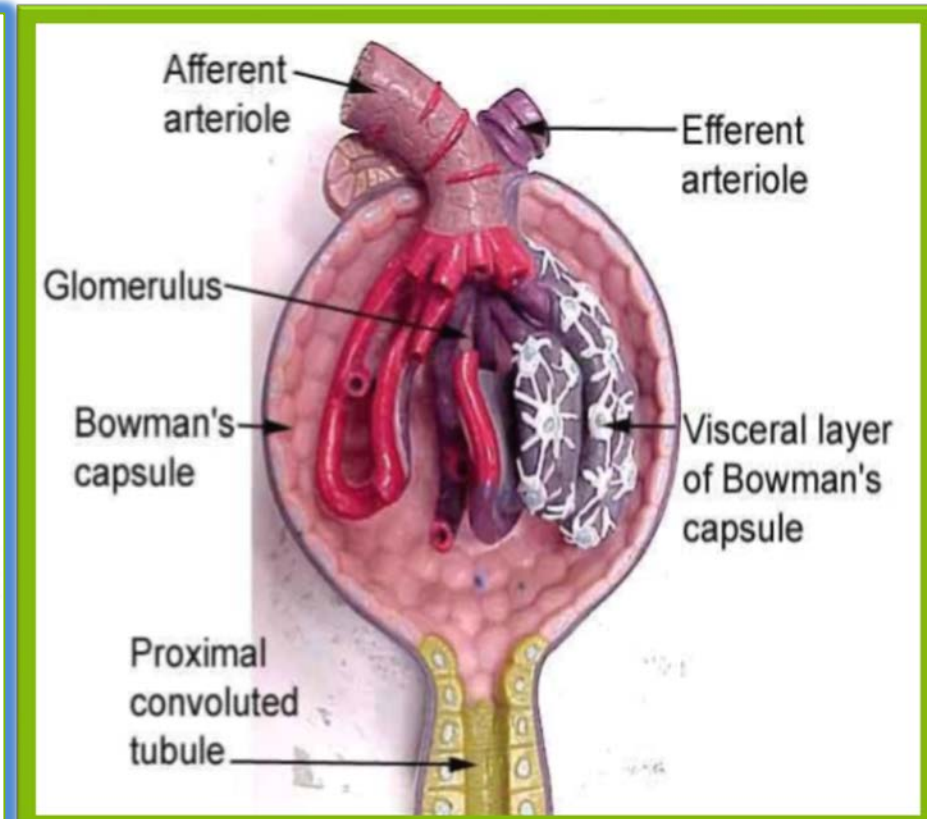
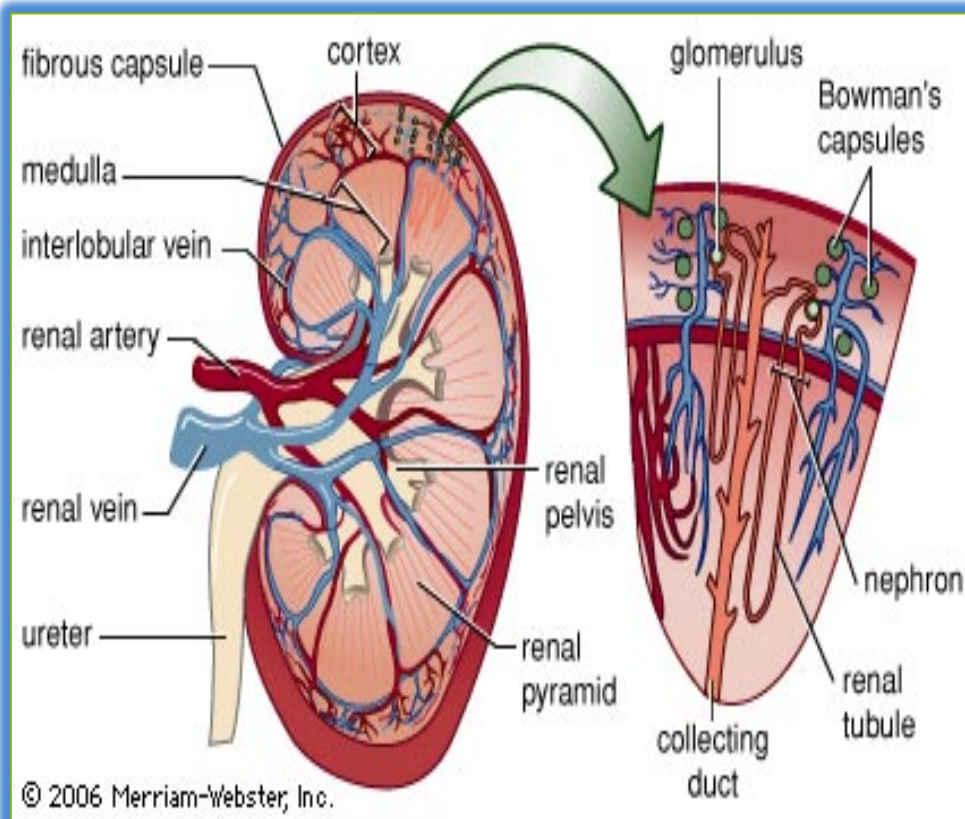


Outline

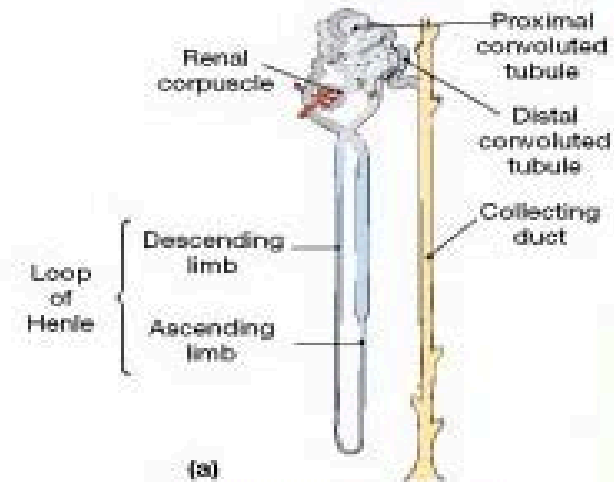
- ◆ Glomerular Architecture
- ◆ Glomerular Hematuria
- ◆ Immune-complex GNs
- ◆ Hereditary Nephritis
- ◆ Anti-GBM Ab Disease
- ◆ Pauci-immune GNs
- ◆ RPGN



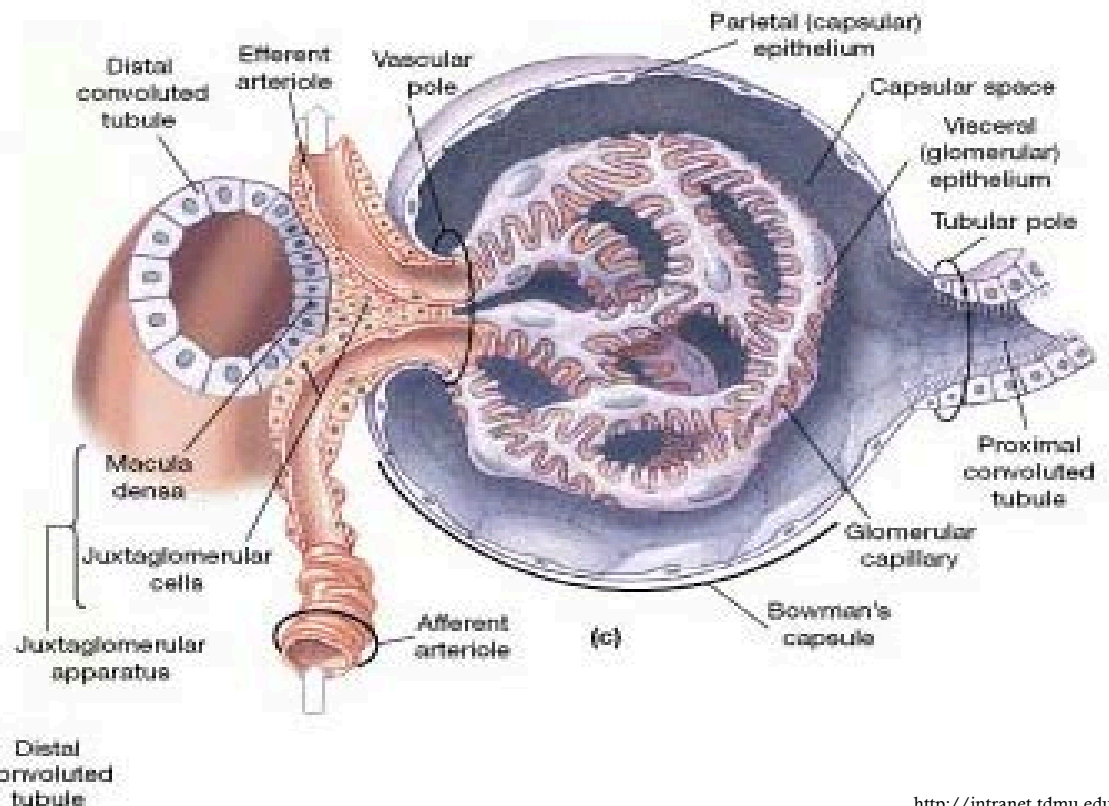
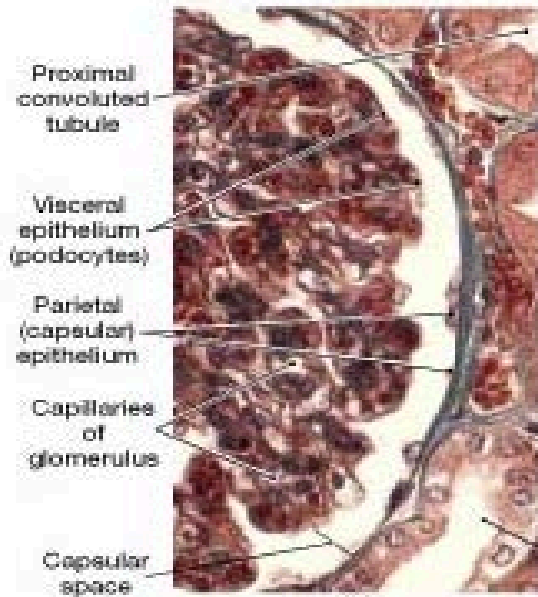
Anatomy: Renal Cortex and Corpuscle



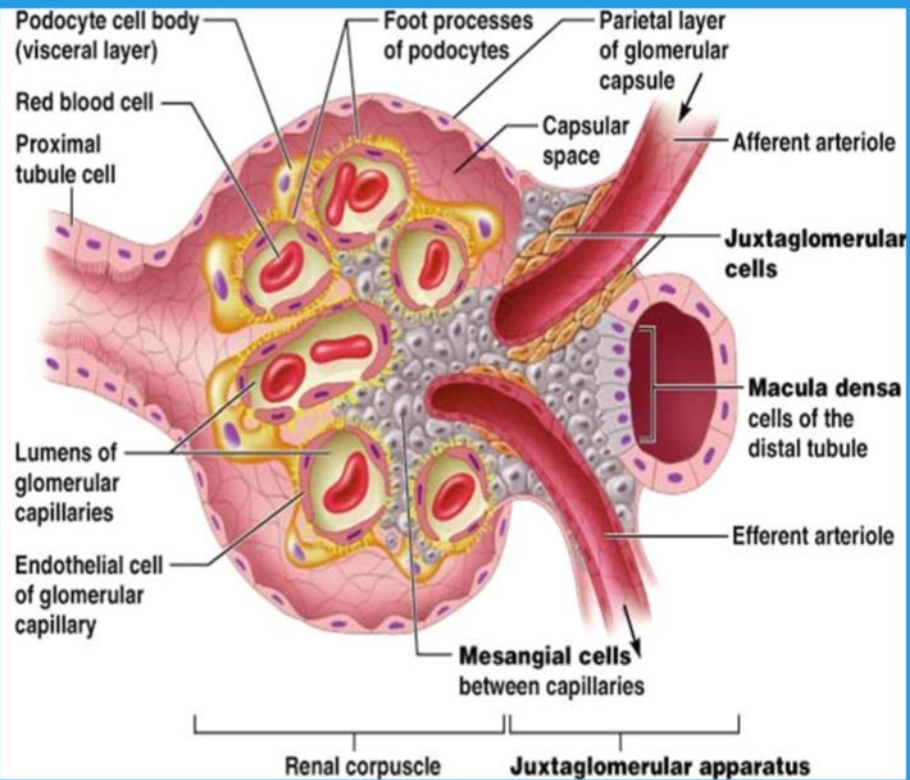
The Renal Corpuscle



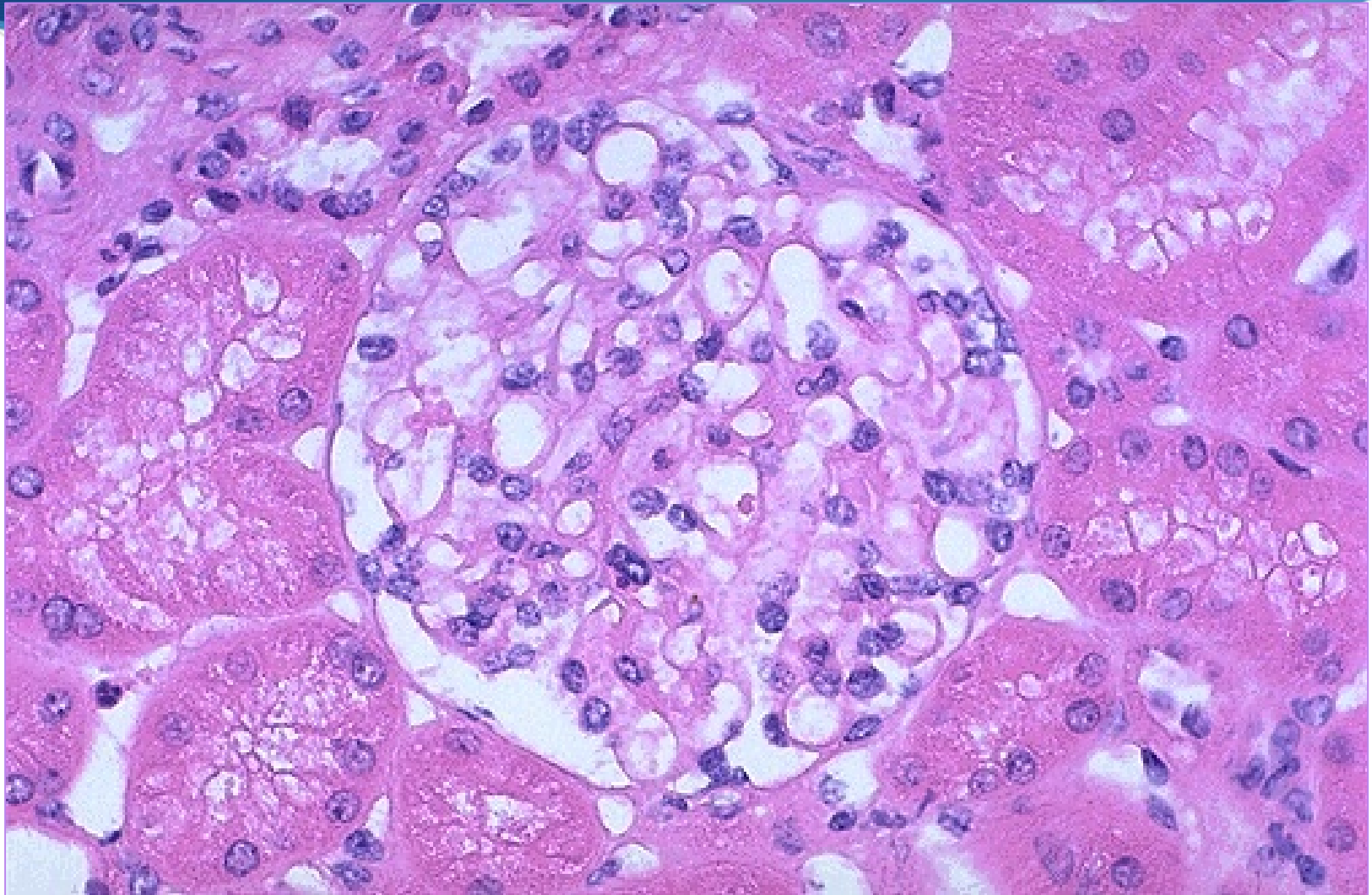
• **FIGURE 26-5 The Renal Corpuscle.** (a) A more realistic view of a juxtamedullary nephron, showing the coiling of the renal tubule. (b) Micrograph of a renal corpuscle, showing a portion of the glomerular capillary network. (LM $\times 1120$) (c) The renal corpuscle, showing important structural features.



Glomerulus: Capillary network latin *“little ball of yarn”*

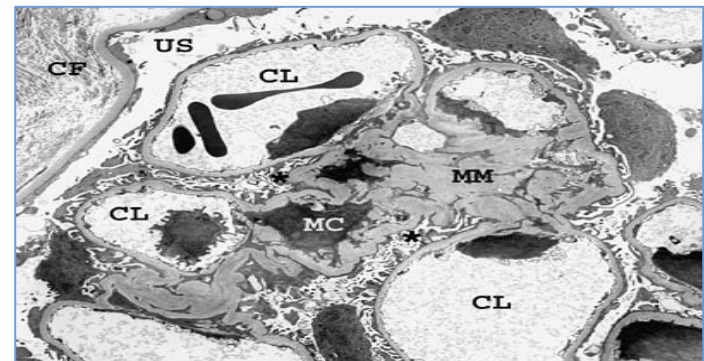
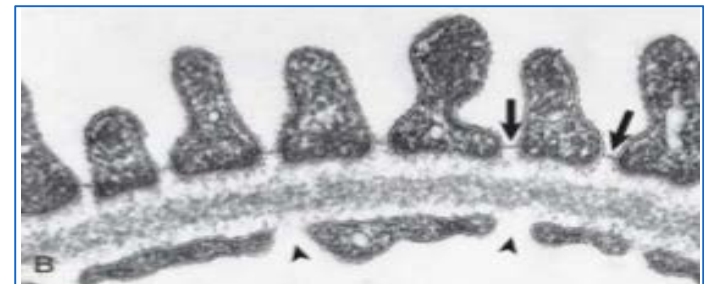
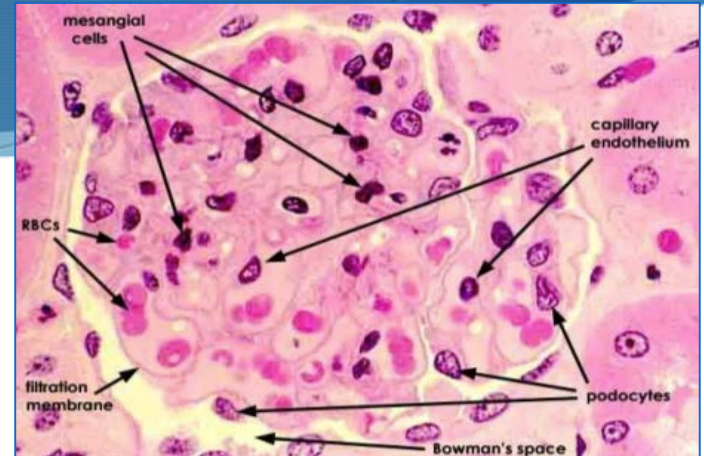


Normal Glomerulus: LM

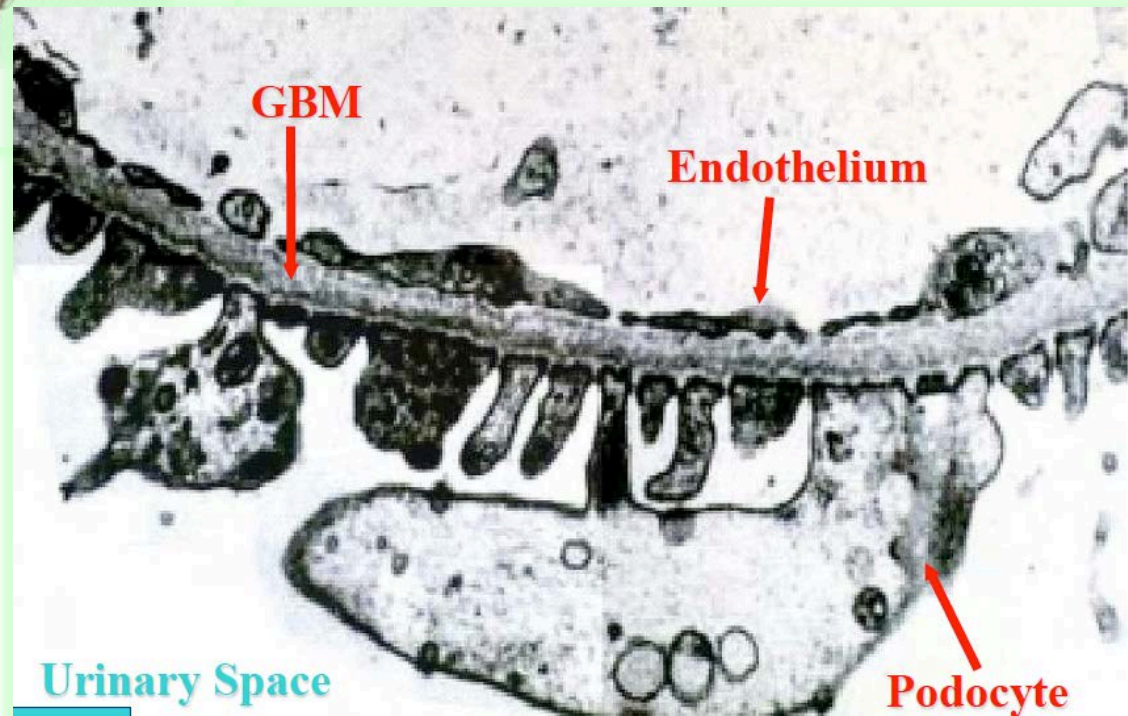
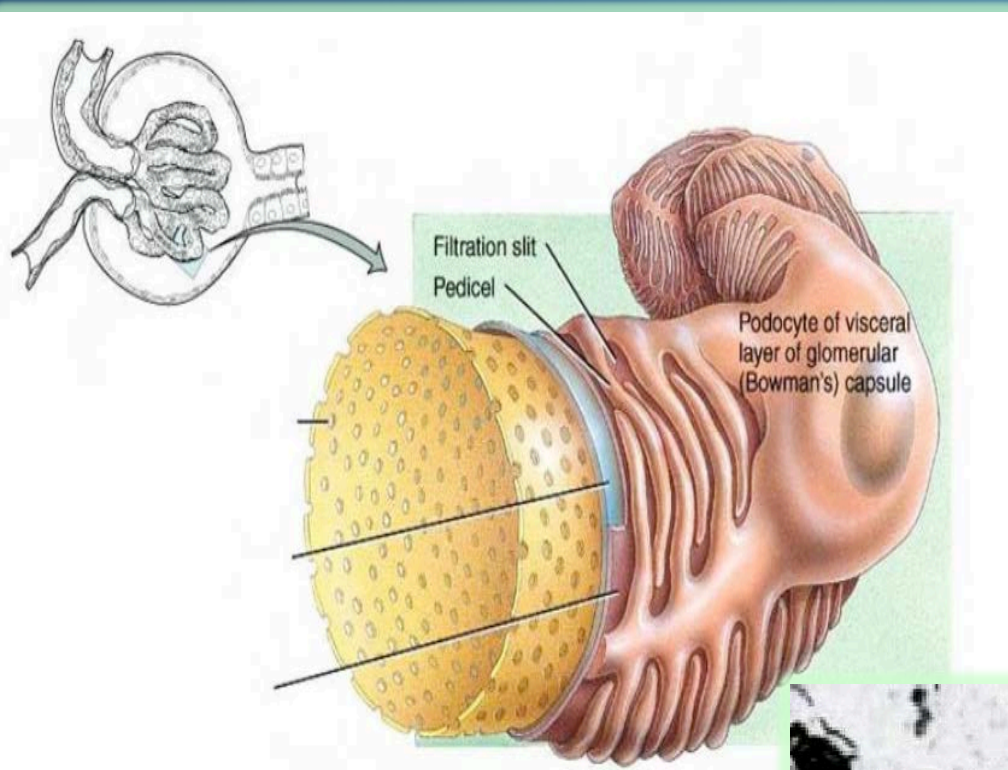


Glomerular Histology

- ◆ **Glomerular capillary wall**
 - ◆ **GBM**
 - ◆ Made of Type IV collagen and laminin
 - ◆ 3 layers on EM
 - ◆ **Podocyte = VEC**
 - ◆ Cytoplasmic foot processes wrap around GBM
 - ◆ Gap b/t podocytes form slit pores
 - ◆ Key proteins: nephrin, CD2AP, podocin
 - ◆ **Endothelial cell**
 - ◆ Initial barrier b/t capillary lumen & Bowman space
 - ◆ VEGF receptors
 - ◆ Synthesize NO & Endothelin-1
- ◆ **Mesangium = matrix + mesangial cells**
 - ◆ ~1-3 cells per capillary
 - ◆ Support, phagocyte properties
 - ◆ Contractile, role in GFR regulation

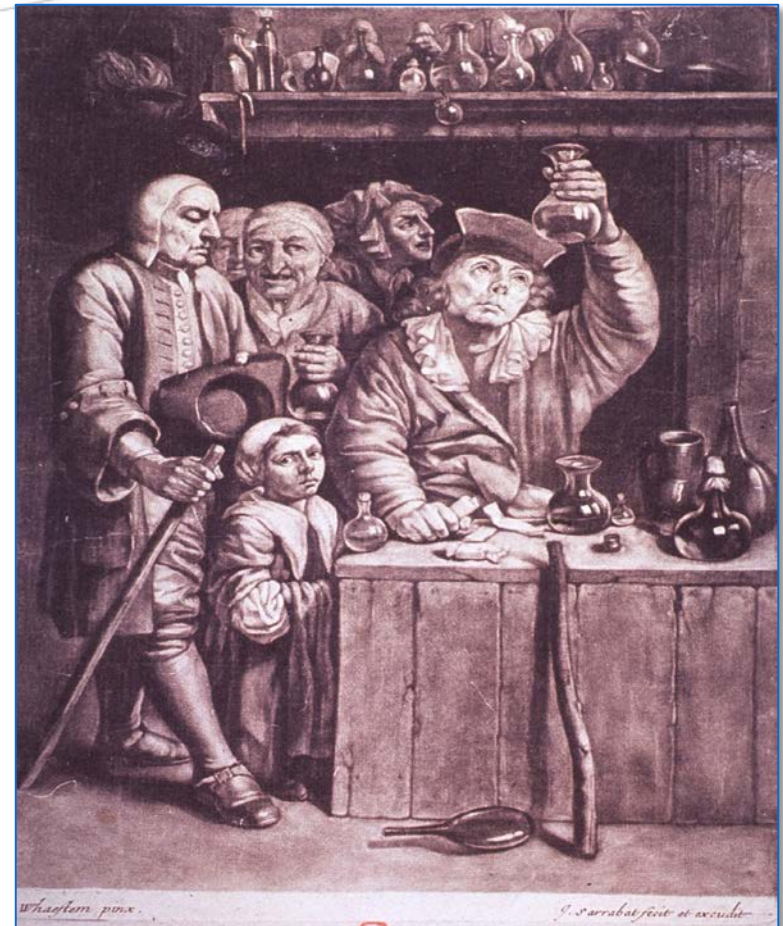


Anatomy of the Podocyte

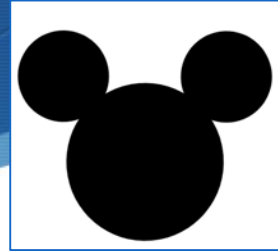


Clinical: Glomerular Hematuria

- ◆ RBC > 3 per HPF on 2 or more separate urinalyses
- ◆ Dysmorphic RBCs
- ◆ RBC casts
- ◆ Proteinuria > +1 on dipstick, >30 on UA or > 500mg/g on UPC
- ◆ Decline in GFR
- ◆ Hypertension
- ◆ Negative urological workup
- ◆ Absence of clots, terminal hematuria



Dysmorphic RBCs



Normal erythrocytes	Glomular erythrocytes
Fresh erythrocytes, no double contour	simple ring shape
Fresh erythrocytes, with double contour	curly ring shape
thorn apple shape	curly ring shape slitted
shadow of erythrocyte without margin	ring shape with surface protrusion
shadow of erythrocyte with margin remnants +/- spikes	ring shape with surface protrusion
deformed shadow of erythrocyte	ring shape with internal bleb
deformed erythrocyte curly double contour	ring shape with internal bleb



στυλ σφαιρική σκιά απειροσμένη περιφέρεια	internal bleb with surface margin
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Dysmorphic RBCs



RBC Cast



Diagnostic Evaluation: Glomerular Disease

- ◆ Urinalysis with microscopy → spin urine!
- ◆ Urine protein / creatinine ratio and 24 hour urine protein
- ◆ Serological workup
 - ◆ Primary vs Secondary (systemic)
- ◆ Renal ultrasound for morphology
- ◆ Renal biopsy

“Nephritic” Syndrome: Challenges in Terminology

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES
OCTOBER, 1926

ORIGINAL ARTICLES.

PROBLEMS IN RENAL PATHOLOGY.*

By ELI MOSCHICOWITZ, M.D.,

ASSOCIATE PHYSICIAN IN MT. SINAI HOSPITAL, NEW YORK.

Classification. Let us analyze some of the reasons for the confusion in current classifications of the nephritides.

1. The classification may be based upon *etiology*. This is obviously fallacious because: (a) We do not know the cause of many of the nephropathies; (b) the same factor or agent (for example, the streptococcus) may result in a variety of lesions; (c) the same lesion (for example, an acute glomerulonephritis) can be produced by different causes.

2. The classification may be *clinical*. Such classifications fail for the following reasons: (a) The clinical manifestations of nephropathies overlap. Almost any symptom or sign may be produced by a number of widely different disorders so that a completely identical clinical picture may be associated with two entirely separate lesions. (b) The clinical manifestations of almost any nephropathy are usually never complete in the sense of an end result. Most nephropathies are characterized by stages, and the final stage is often entirely different from the initial one. This change is usually consequent upon the natural history of the disease, but often upon the result of an extrarenal complication as well. One reason that we know so little of many of the chronic diseases is because we are not aware of what has gone before. We

* Read by Invitation at the University of Michigan, Ann Arbor, Michigan, April 8, 1926.

The “Nephritic” GN picture

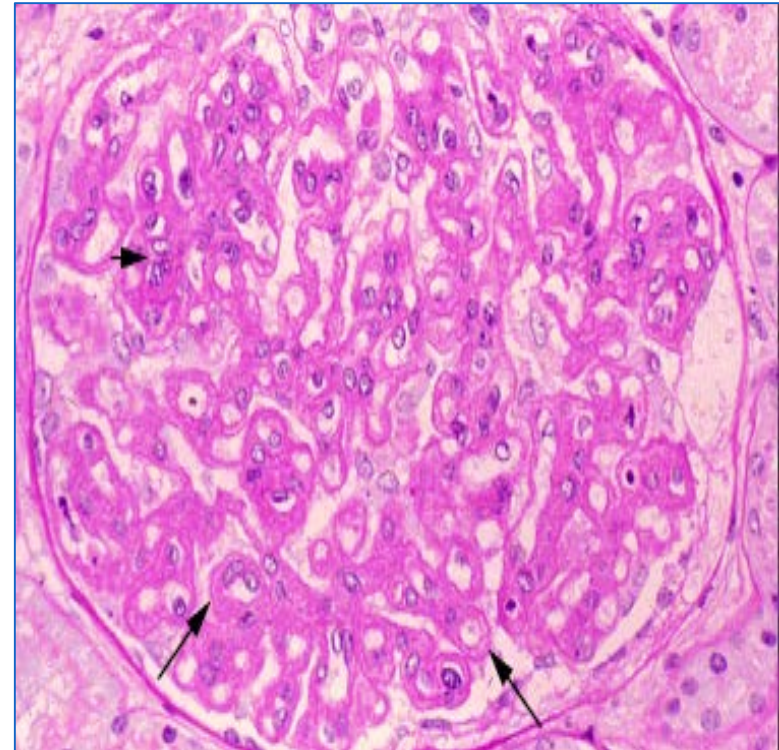
- ◆ Sub-nephrotic proteinuria
- ◆ Glomerular hematuria
 - ◆ Micro
 - ◆ Macro
 - ◆ Active urinary sediment

Immune-Complex GN

- ◆ Membranoproliferative Glomerulonephritis
- ◆ Cryoglobulinemia
- ◆ Infection-Related / Post-Strep Glomerulonephritis
- ◆ IgA Nephropathy

The Membranoproliferative Pattern of Injury

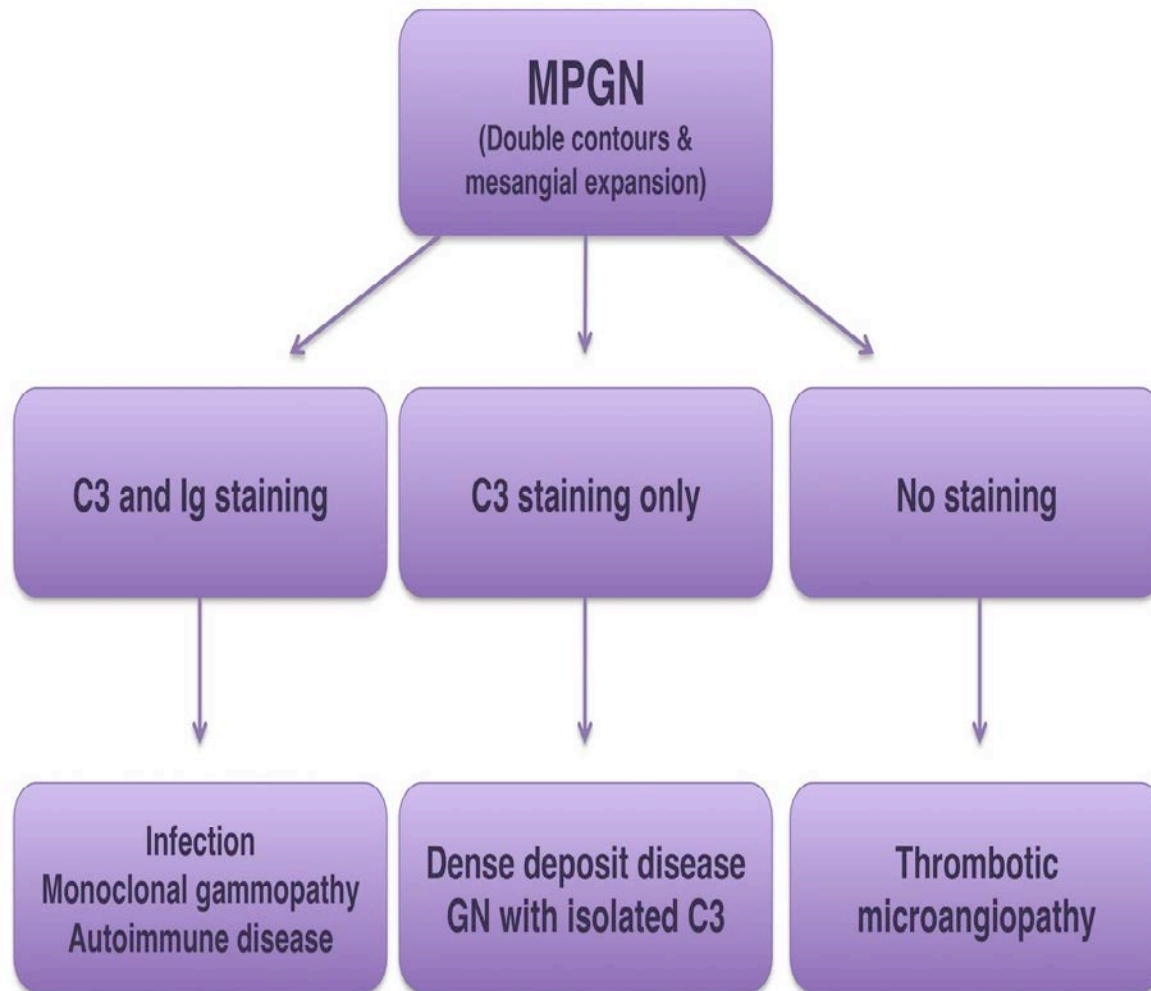
- ◆ AKA MPGN or Mesangiocapillary GN
- ◆ Describes a general pattern of injury of variety of diseases that share common pathogenetic mechanism
- ◆ Typical LM features mesangial hypercellularity, endocapillary proliferation & **capillary wall remodeling**
- ◆ Deposition of immunoglobulins, complement or both in mesangium & capillary walls



Membranoproliferative GN (MPGN)

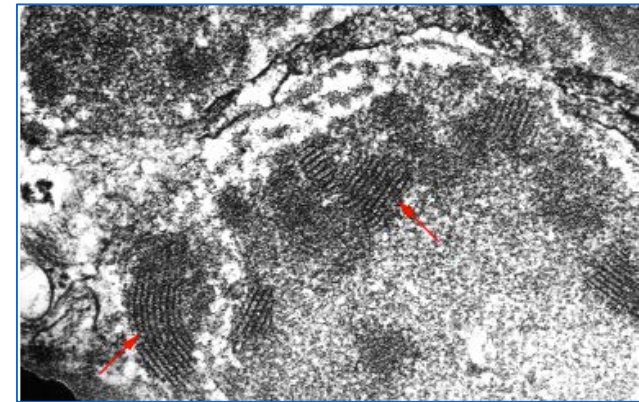
- ◆ Clinical: may be nephrotic or **sub-nephrotic**
- ◆ Low serum C3
- ◆ Causes
 - ◆ Infections: HBV, HCV, IE, chronic bacterial or parasitic infxns
 - ◆ Auto-immune dz: SLE, Sjogrens, RA
 - ◆ Dysproteinemias, inherited mutations in complement-regulating proteins

MPGN Classification



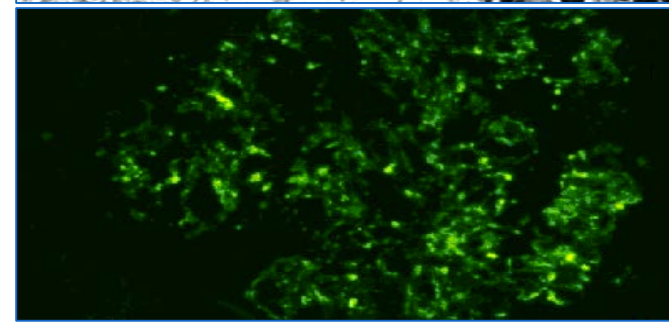
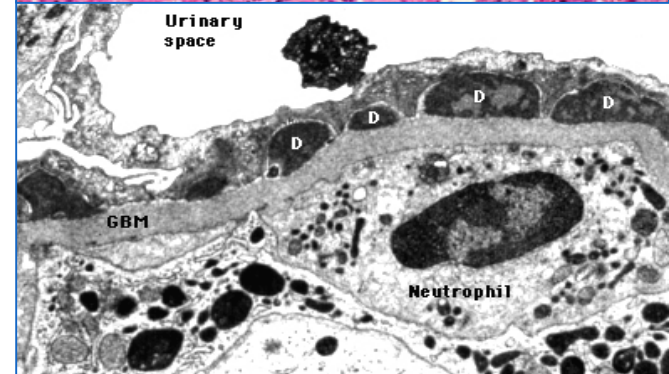
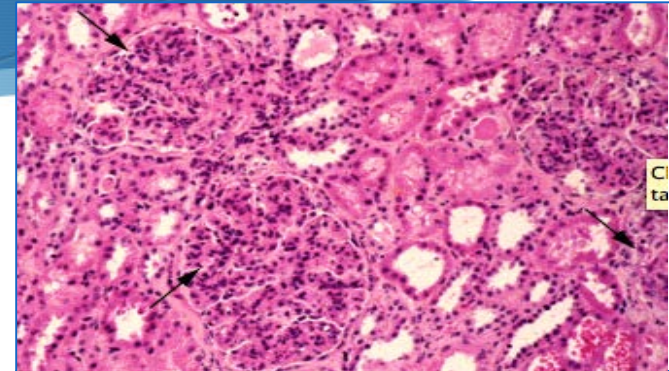
Mixed Cryoglobulinemia

- ◆ Production of circulating IG that precipitate on cooling
- ◆ IG complexes deposit in glomeruli + arterioles → bind complement → proliferative response
 - ◆ Sub-endothelial deposits on electron microscopy= “fingerprinting”
- ◆ Renal disease occurs in ~ 40 %
- ◆ Low serum C4 > C3 and (+) RF
- ◆ Associations
 - ◆ Type I: Myeloma, Waldenstrom macroglobulinemia
 - ◆ Type II: Infections such as HCV, HBV
 - ◆ Type III: Collagen-vascular diseases, lymphoproliferative diseases, HCV



Infection-Related / PSGN

- PSGN on decline in developed countries
 - 97 % cases occur in regions of the world with poor socioeconomic status
 - In developed countries, no longer a strong association with pharyngitis, rather skin-related
 - Mainly affects children, older adults
 - ~ 10 days post-infection
- Staph, gram (-) bact, viral infections now more common and without renal latent period
- Low C3
- Pathology: LM: hypercellularity, EM: hump-like dense sub-epi deposits, IF: granular capillary and mesangial staining +IgG and C3

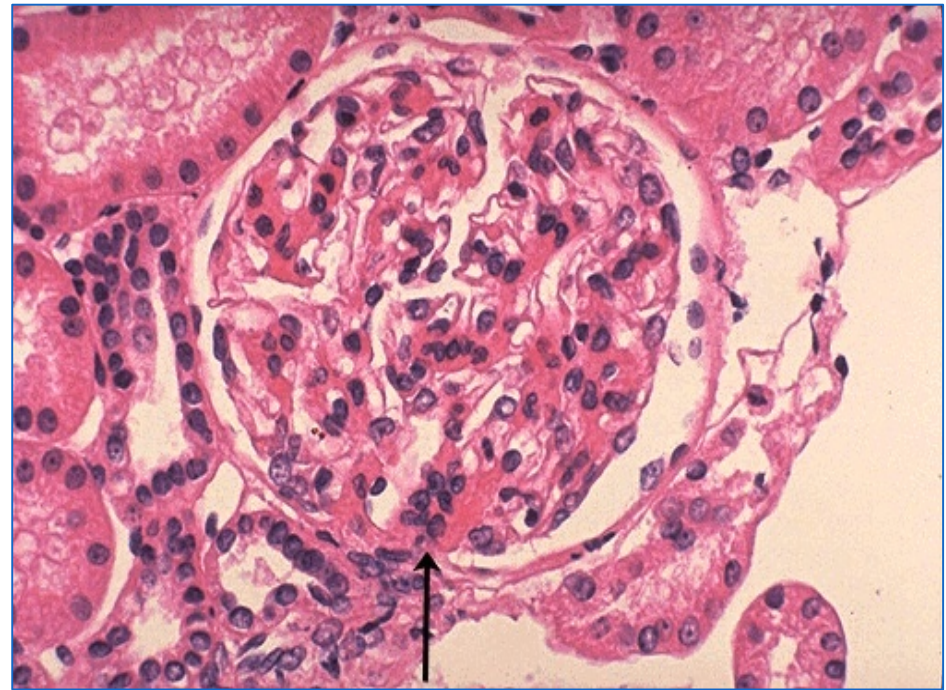


IgA Nephropathy

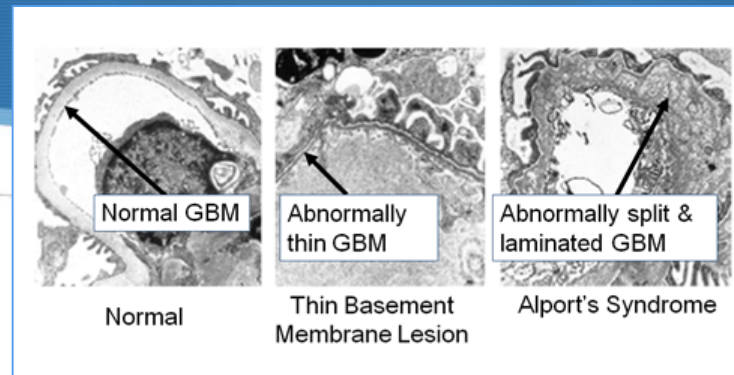
- ◆ Most common GN **in the world**
- ◆ Male > female, 2nd to 3rd decade of life
- ◆ Clinical presentations are varied and progression typically slow.
 - ◆ Temporal relationship with URI/tonsillitis
 - ◆ 50 % Macrohematuria
- ◆ Pathogenesis : multi-hit hypothesis – galactose deficient IgA1 + anti-glycan IgA and IgG → immune complexes
- ◆ Associations / Secondary Causes
 - ◆ Liver disease
 - ◆ Celiac disease
 - ◆ Crohn's disease
 - ◆ Reiter syndrome, Ankylosing spondylitis
 - ◆ HSP = systemic vasculitis + IgA, children
- ◆ Treatment limited to ACE/ARB

IgA Nephropathy Path

- ◆ Mesangial proliferation and matrix expansion on LM
- ◆ Deposits of IgA (often accompanied by C3 and IgG) in the mesangium on IF
- ◆ Oxford Classification
 - ◆ Mesangial and endocapillary hypercellularity, TI fibrosis & segmental glomerulosclerosis



Hereditary Nephritis



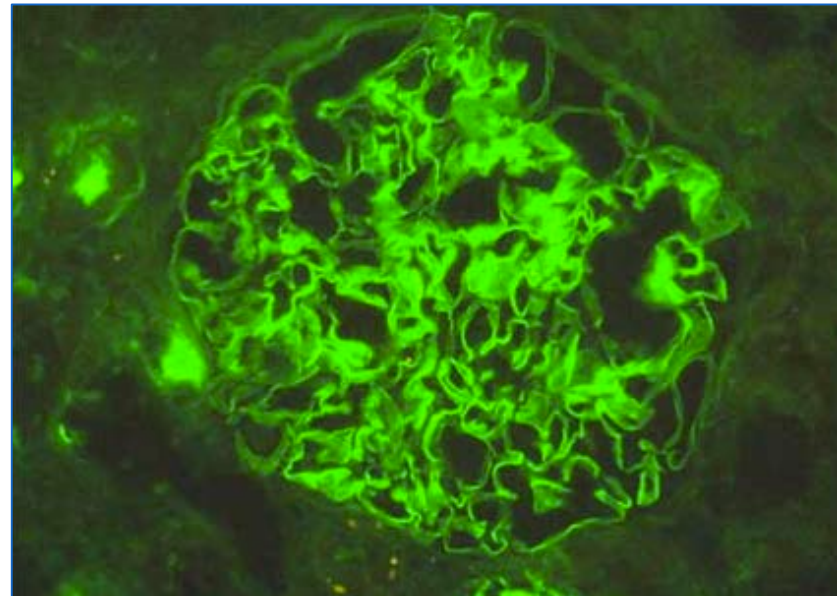
- ◆ AKA Alport Syndrome
- ◆ X-linked, either AR or AD
- ◆ Mutation in COL4A5 gene on X chromosome encoding α -5 chain of type IV collagen found in GBM
- ◆ Clinical presentation: young man with asymptomatic persistent microhematuria
- ◆ Progression to ESRD typically by age 35

Thin BM Nephropathy vs Alport Syndrome

Thin BM Nephropathy	Alport / Hereditary Nephritis
Persistent hematuria	Persistent hematuria
Minimal proteinuria	Proteinuria (< 1-2 g/d)
Normal GFR, benign course	Progressive renal failure
No extra-renal manifestations	Sensorineural deafness, lenticonus, retinopathy, leiomyomatosis
	+/- mental retardation
May represent carrier state of Alports	Wide clinical variability among kindreds

Anti-GBM Disease

- ◆ Circulating antibodies to GBM with IgG deposits
- ◆ Renal disease + pulmonary hemorrhage = Goodpasture Syndrome (30-40% pts)
- ◆ Age/Gender predilection
 - ◆ 20-30 yo men > women
 - ◆ 60-70 yo women > men
- ◆ Diagnosis
 - ◆ Renal bx: Linear IgG staining on IF
 - ◆ (+) Anti-GBM Ab
- ◆ Treatment
 - ◆ Plasmapheresis, steroids, Cytoxan

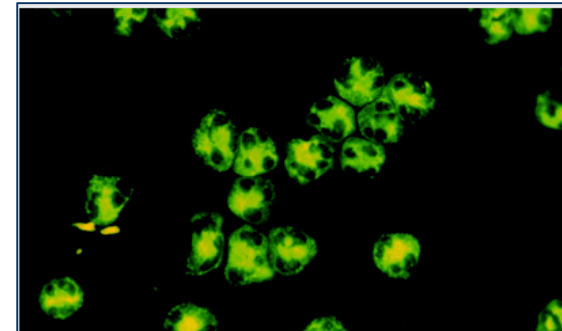


Pauci-Immune GN

- ◆ Misnomer – classic renal autoimmune disease
- ◆ Most common cause of RPGN
- ◆ Usually a component of systemic small-vessel vasculitis
- ◆ Distinct histological pattern on IF
 - ◆ < 2+ glomerular Ig and complement staining
 - ◆ 1 year mortality ~ 80% without treatment
- ◆ ANCA (+) vasculitis ~ 90 %
 - ◆ Granulomatosis with Polyangiitis (GPA)
 - ◆ Microscopic Polyangiitis (MPA)
 - ◆ Renal-limited ANCA (+) vasculitis – 80% are MPO-ANCA (+)
 - ◆ Eosinophilic Granulomatosis with Polyangiitis (EGPA or Churg-Strauss)
- ◆ ANCA (-) vasculitis ~ 10 %

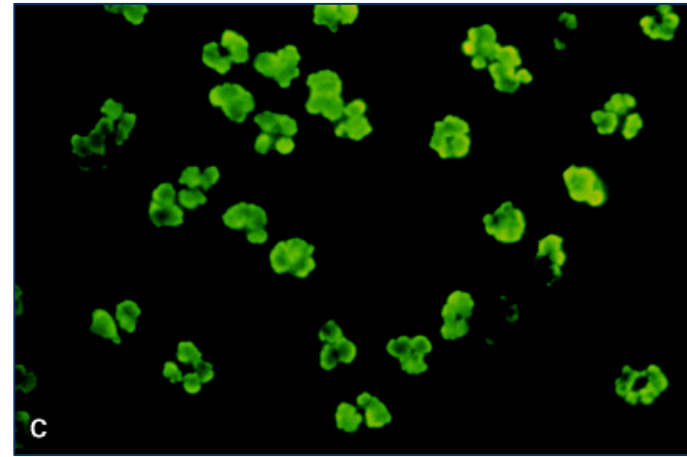
Granulomatosis with Polyangiitis (GPA)

- ◆ cANCA cytoplasm staining for PR3 antibodies → neutrophil activation → release of ROS and lytic enzymes + alternative complement path activation
- ◆ Granulomatous inflammation and extensive extra-renal involvement → upper respiratory tract, ENT, & lung (oral ulcers, nasal discharge, uveitis, sinusitis, pulm infiltrates)
- ◆ Higher relapse rate than pANCA phenotype
- ◆ Microbial factors implicated – + *S aureus* nares
- ◆ ? Genetic factors – more common in whites, older



Microscopic Polyangiitis (MPA)

- ◆ pANCA perinuclear staining for MPO-antibodies
- ◆ Worse renal prognosis than cANCA phenotype
- ◆ Similar clinical picture to GPA but without significant respiratory tract involvement
- ◆ Non-specific sx fatigue, fever, anorexia, weight loss
- ◆ ~ 50% patients: Leukocytoclastic angiitis
urticaria, livedo reticularis & other skin lesions



Eosinophilic Granulomatosis with Polyangiitis

- ◆ pANCA (+) > cANCA
- ◆ Eosinophilia, asthma, and atopy
- ◆ +/- elevated serum IgE levels
- ◆ Episodic cough and and pulm infiltrates years prior to systemic disease
- ◆ Tender subcutaneous nodules (granulomas) on the extensor surfaces of the arm (50-67%)
- ◆ Peripheral neuropathy, usually mononeuritis multiplex (75%)
- ◆ Milder than GPA and MPA



ANCA Vasculitis: Treatment

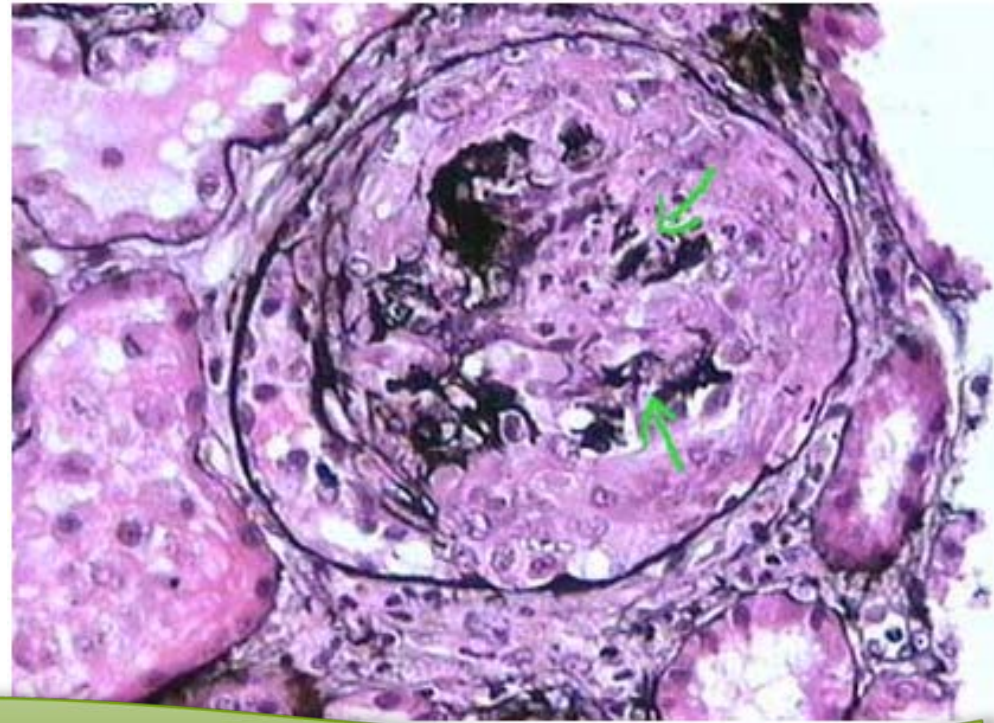
- ◆ Steroids
- ◆ Cyclophosphamide
- ◆ Rituxan
- ◆ Plasmapheresis in severe / dialysis-dependent AKI

Rapidly Progressive GN (RPGN)

- ◆ NOT a specific disease
 - ◆ Clinical & histological entity indicating severe glomerular damage
- ◆ Clinical definition: rapidly progressive renal failure (weeks to months) secondary to acute glomerulonephritis
- ◆ Pathological definition: glomerular extracapillary proliferation
 - ◆ Hallmark: “Crescents” typically $\geq 50\%$ gloms
 - ◆ AKA “Crescentic GN”

Glomerular Crescent

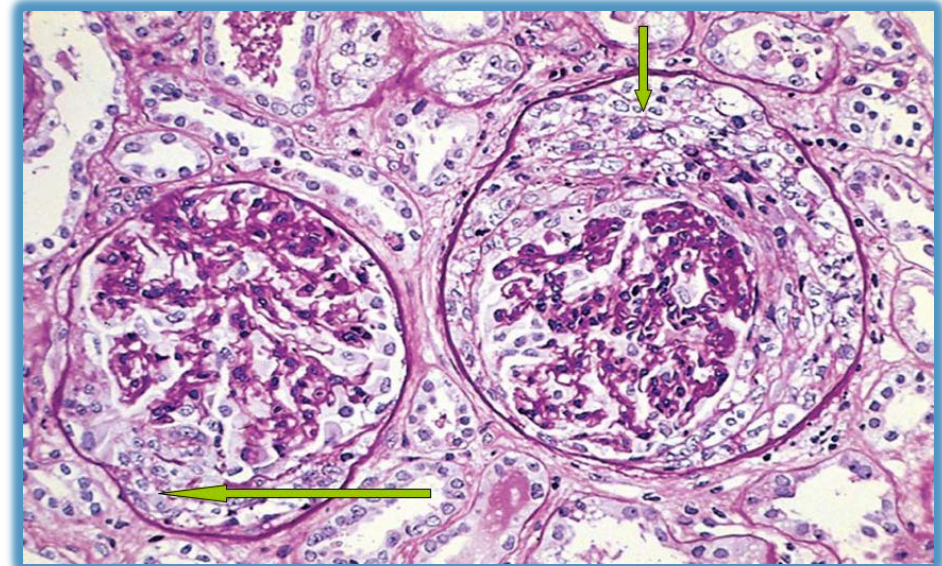
- ◆ Either partially or completely filling up Bowman's space
- ◆ Composed of proliferating parietal epithelial cells, podocytes, macrophages, and fibroblasts
- ◆ Stimulated by entry of fibrin and other plasma proteins from the capillary lumens following the rupture of the GBM



Extracapillary proliferation within a glomerulus

RPGN Causes

- ◆ Pauci-immune GN (80%) = #1 Cause
 - ◆ 96 % are ANCA (+)
- ◆ Anti-GBM Ab disease
- ◆ Immune-complex GNs



Questions?

References

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