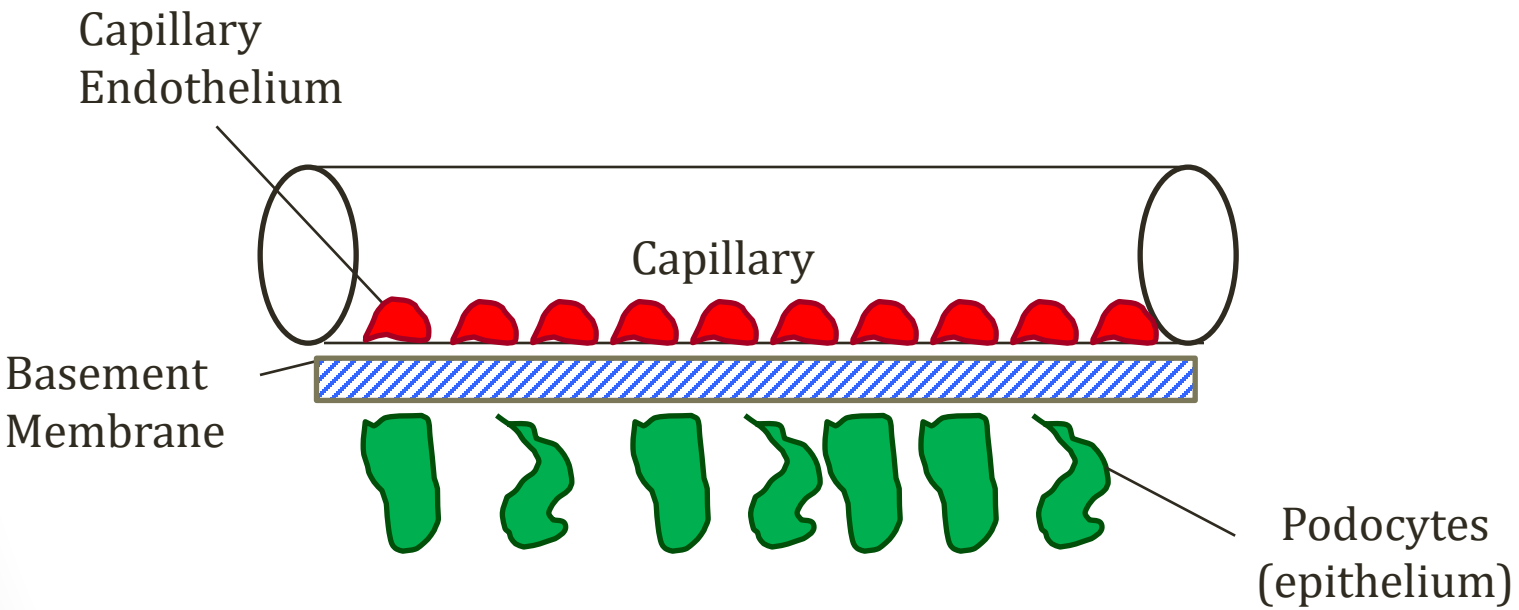
Glomerular Disease Principles

Jason Ryan, MD, MPH

Glomerulus Functions

- Allow “ultrafiltrate” into Bowman’s space
  - Water, electrolytes, glucose, amino acids
- Prevent filtration of most proteins
- Prevent filtration of red blood cells
- Glomerular pathology
  - **Proteinuria**
  - **Hematuria**

Glomerular Filtration Barrier



Capillary Endothelium

- Fenestrated (i.e. has openings)
- Only small (~40nm) molecules pass through
- Repels red cells, white cells, platelets
- First barrier to filtration
- Capillary damage → RBC in urine → **hematuria**
- Capillary damage → inflammation → **nephritis**

Basement Membrane

- Negatively charged molecules
  - Type IV collagen
  - Heparan sulfate
- Repels (-) molecules like albumin
- Also size barrier

Podocytes

- Also called **epithelial cells**
- Long “processes” called “foot processes”
- Wrap capillaries
- Slits between foot processes filter blood
- Further size barrier small molecules
- Damage → loss of protein barrier

Albumin

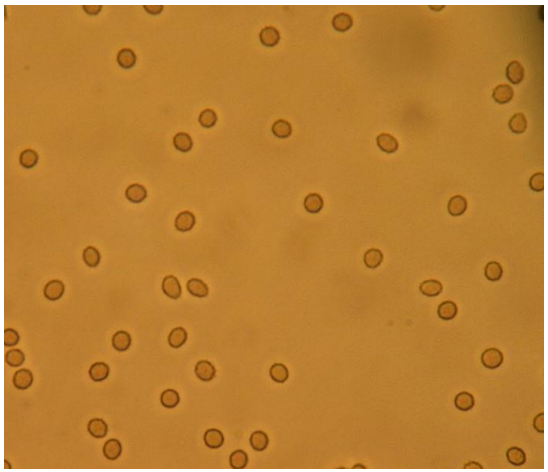
- Small (~3.6nm)
- Can fit through all size barriers
- Negatively charged
- Repelled by GBM charge barrier
- Podocyte/GBM disease → albumin in urine

Glomerular Diseases

- Breakdown of components of filtration barrier
- Things in urine that shouldn't be there:
  - Red blood cells
  - Protein (especially albumin)

Hematuria

- Urinalysis
- Dipstick: tests for the presence of heme
  - Heme has peroxidase activity → reacts with strip
  - Heme positive: hemoglobin or myoglobin
- Microscopy: red cells visualized



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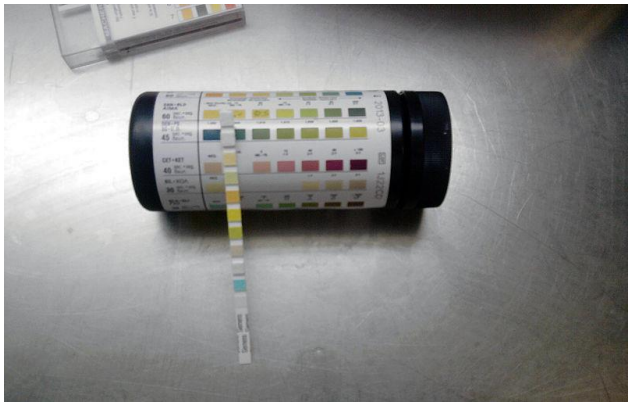

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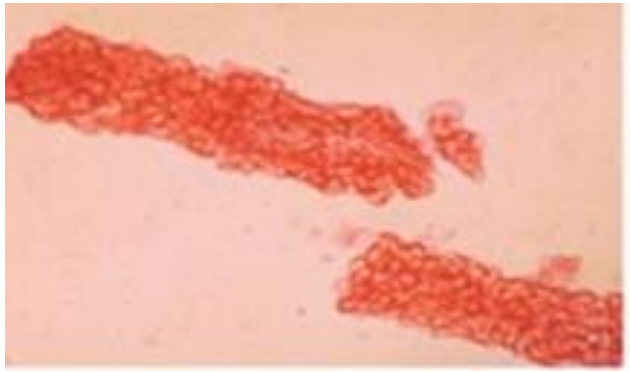
Hematuria

- Many, many causes
- Gross: abnormal color to urine from blood
- Microscopic: Incidental finding on urinalysis
- Can occur after exercise
- Common causes:
  - UTI
  - Kidney stones
- Feared cause: bladder cancer
- Glomerular disease is rare cause

Glomerular Bleeding

- Red cell casts
- Dysmorphic red blood cells
- Acanthocytes
- Proteinuria
- Red, smoky brown or ""coca cola""
- Clots generally not seen



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Proteinuria

- Urine dipstick
  - Color change indicates amount of protein
  - Primarily detects albumin (good for glomerular disease!)
  - 1+, 2+, 3+, 4+
  - Affected by urine concentration

Proteinuria

- Urine protein-to-creatinine ratio
  - "Spot urine"
  - 1st or 2nd morning urine sample after avoiding exercise
  - Normal ratio less than 0.2 mg/mg

Proteinuria

- 24-hour urine collection
  - Gold standard for protein evaluation
  - Gives you grams/day of protein excretion
  - Normal is less than 150 mg/day
  - Cumbersome for patients
  - Errors in collection common

Glomerular Diseases

Spectrum

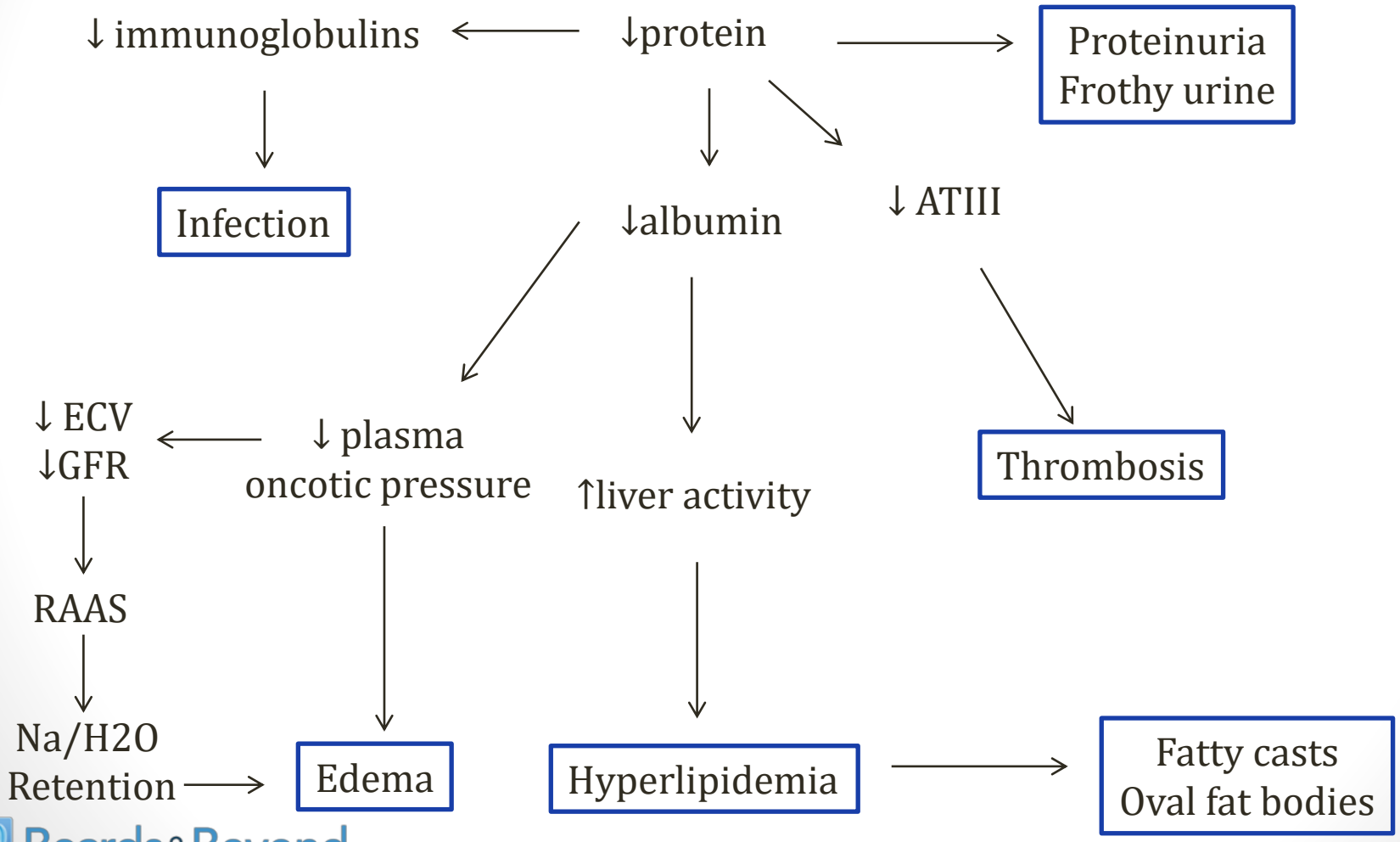
Nephritic Syndrome
RBC casts
Mild proteinuria
Renal Failure

Nephrotic Syndrome
Massive proteinuria
Hyperlipidemia

Nephrotic Syndrome

- Filtration barrier to protein is lost
- RBC filtration barrier remains intact
- Massive proteinuria
  - 4+ on dipstick
  - >3.5g/day
- Triggers cascade of pathology

Nephrotic Syndrome



Urine in Nephrotic Syndrome

- Urinary lipid may be present
- Trapped in casts (fatty casts)
- Enclosed by plasma membrane of degenerative epithelial cells (oval fat bodies)
- Under polarized light fat droplets have appearance of Maltese cross

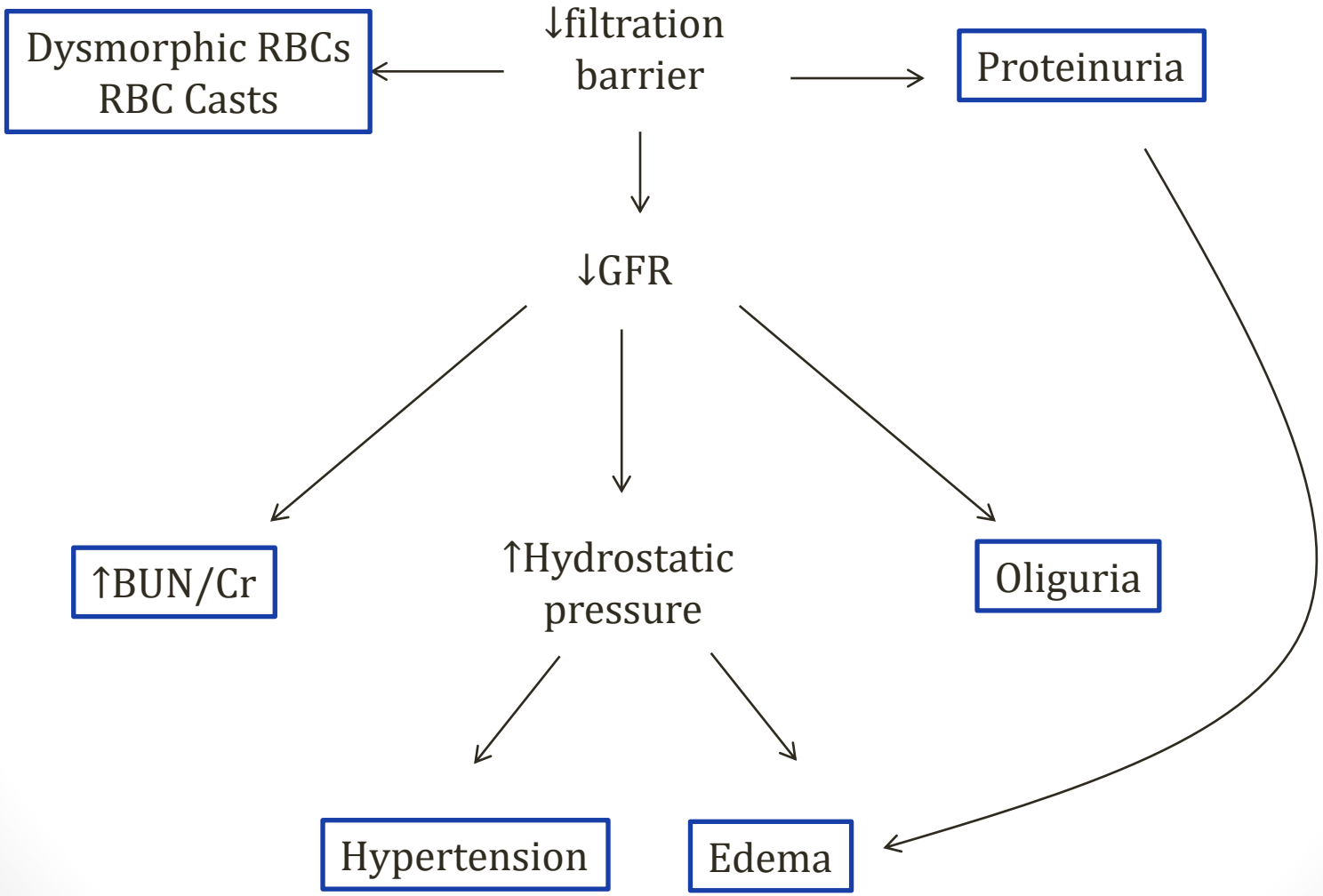
Nephrotic Syndrome

- Classic presentation
  - Frothy urine
  - Swelling of ankles
  - Swelling around eyes (periorbital)
  - Often mistaken for allergic reaction
  - Serum total cholesterol >300mg/dl
  - Proteinuria (>3.5g/day)

Nephritic Syndrome

- Inflammatory process damages entire glomeruli
- Filtration barrier to RBCs and protein lost
- Glomerular damage: ↓GFR
- RBC in urine
  - Dysmorphic
  - RBC Casts
- Protein in urine
  - Less than nephrotic syndrome due to lower GFR
  - <3.5g/day

Nephritic Syndrome

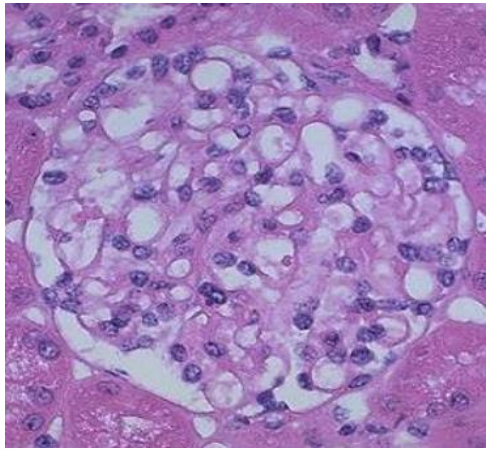


Nephritic Syndrome

- Classic presentation
  - Dark urine (RBCs)
  - Swelling
  - Fatigue (uremia)
  - Proteinuria (<3.5g/day)

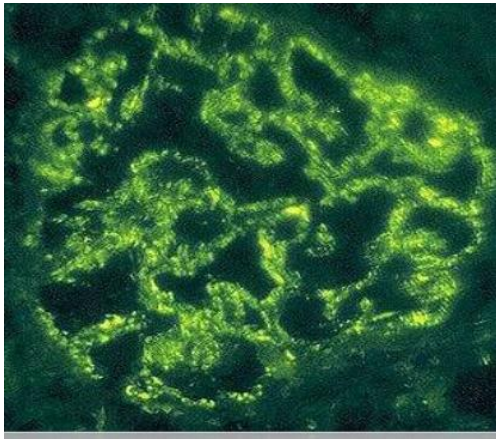
Microscopy

Light Microscopy



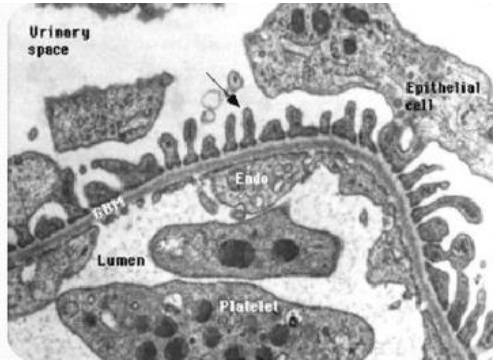
Up to 2000x

Immunofluorescence



Immunostaining

Electron Microscopy



Up to 10,000,000x

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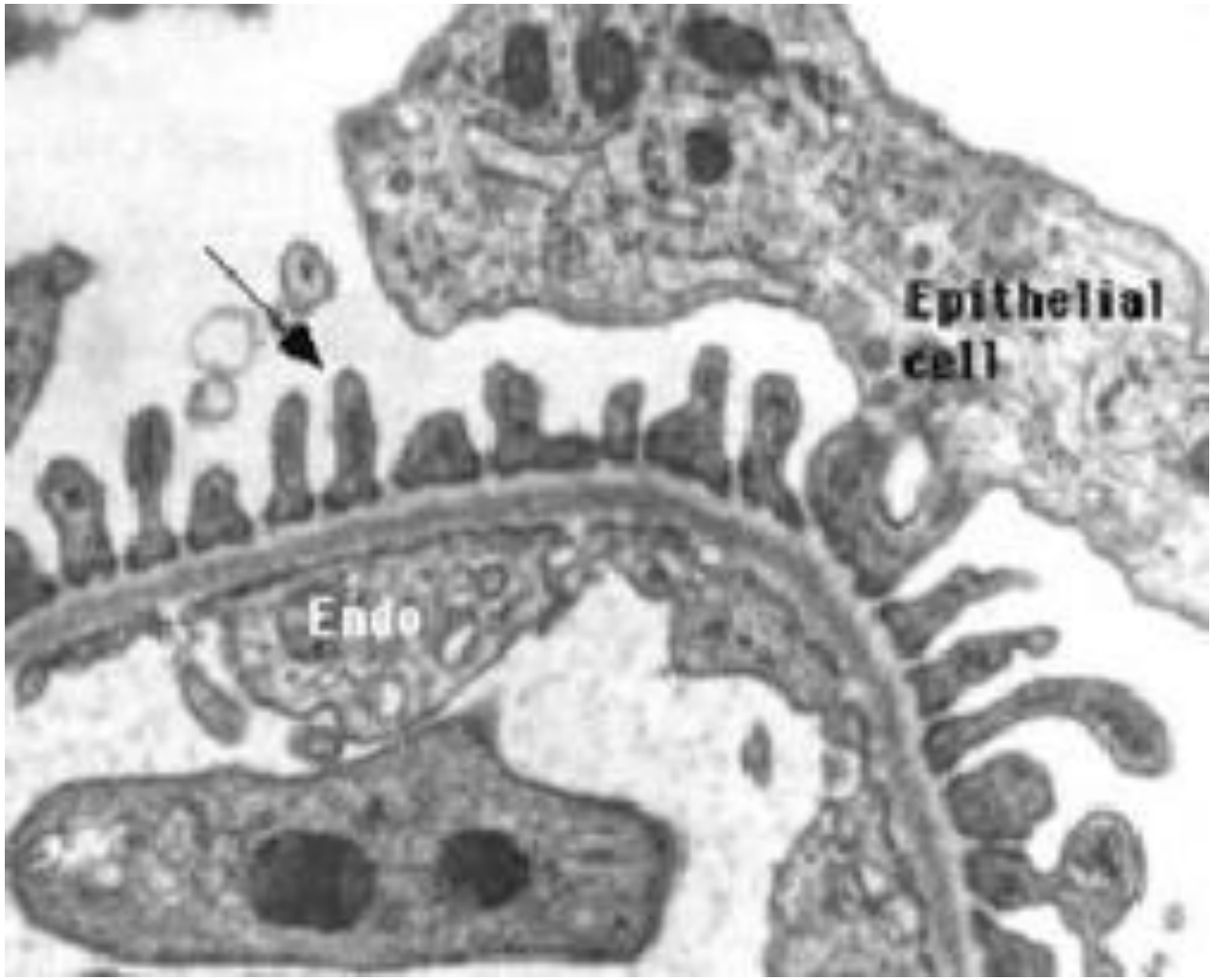
Microscopy



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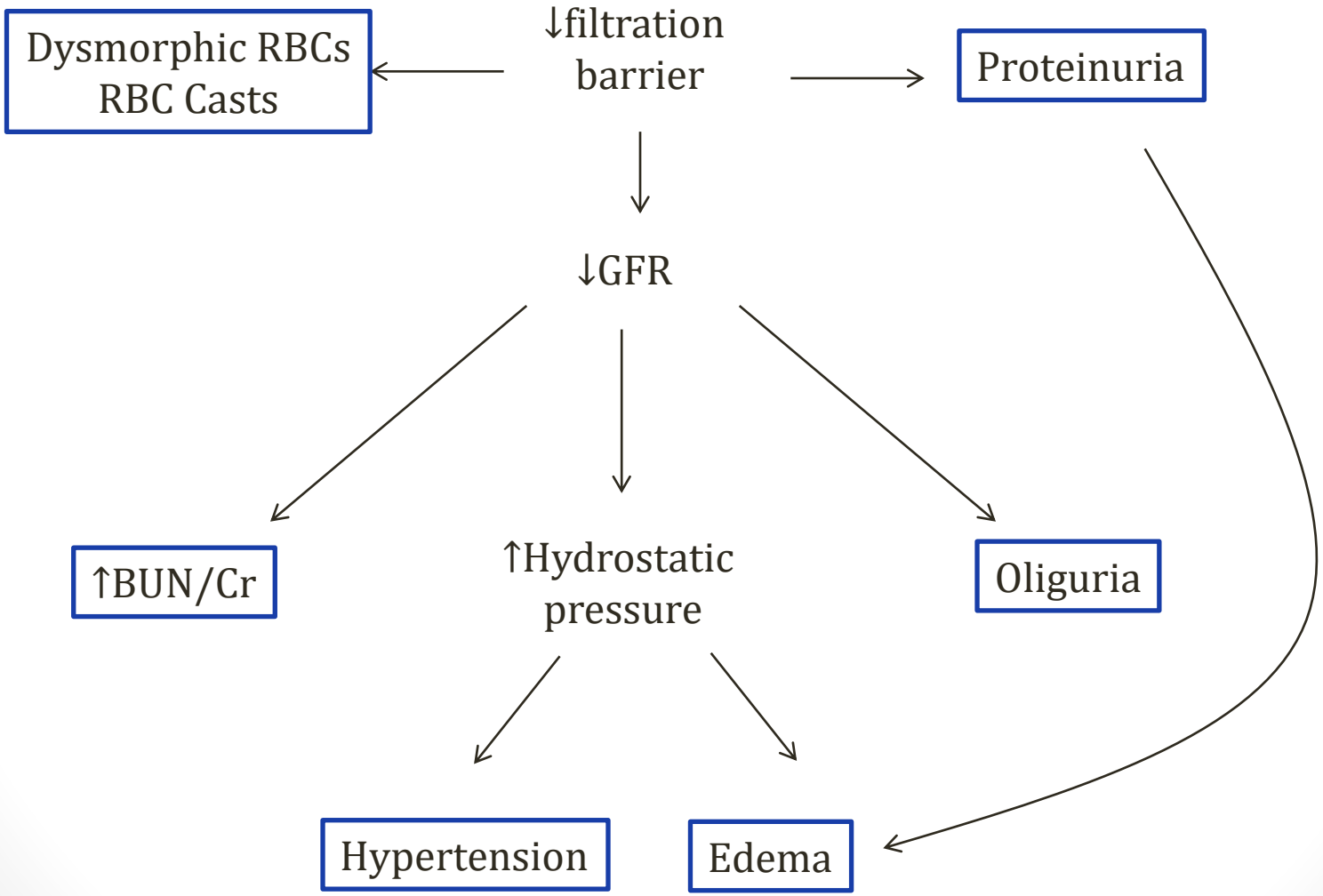
Nephritic Syndrome

Jason Ryan, MD, MPH

Nephritic Syndrome



Nephritic Syndrome

- Classic presentation
  - Dark urine (RBCs)
  - Swelling/edema
  - Fatigue (uremia)
  - Proteinuria (<3.5g/day)

Nephritic/Nephrotic

Sites of Glomerular Injury

- Major determinant of whether a disease process leads to nephritic or nephrotic syndrome is the **site of glomerular injury**

Nephritic/Nephrotic

Sites of Glomerular Injury

- Podocyte injury → protein loss only → nephrotic
- **Endothelial and mesangial cells**
  - Exposed to blood elements
  - Injury lead to inflammation (nephritis)
  - Loss of red blood cells and protein in urine
- Most causes of nephritic syndrome related to **endothelial/mesangial injury** with influx of inflammatory cells

Nephritic Syndrome

Major Causes

1. Post-streptococcal
2. Berger's (IgA) nephropathy
3. Diffuse proliferative glomerulonephritis
4. Rapidly progressive glomerulonephritis (RPGN)
5. Alport syndrome
6. Membranoproliferative glomerulonephritis

Post-streptococcal GN

- Follows **group A β-hemolytic strep infection**
  - Impetigo (skin)
  - Pharyngitis
- Nephritogenic strains
  - Carry specific subtypes of M protein virulence factor

Post-streptococcal GN

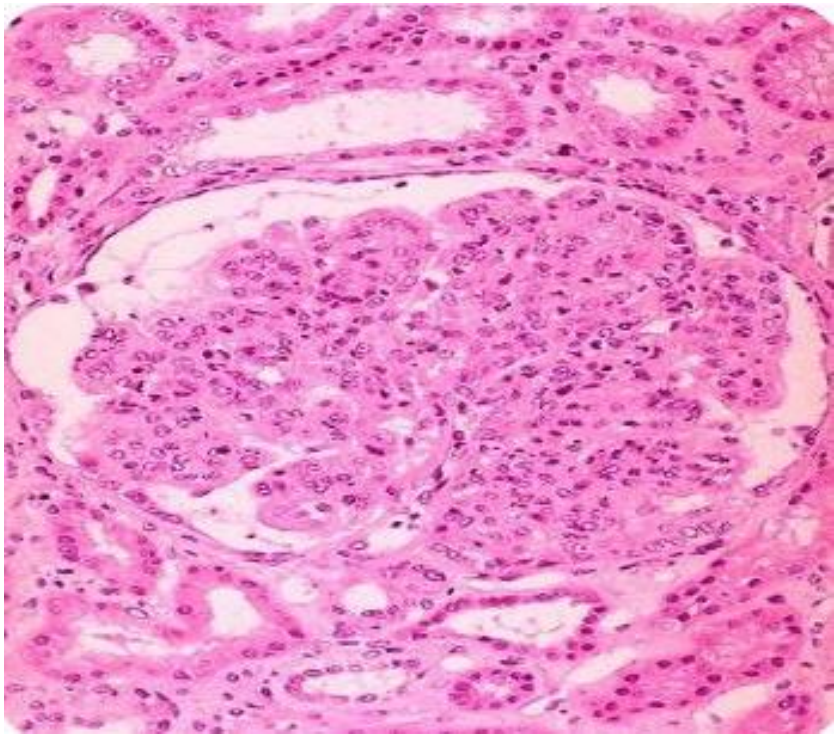
- Immune complexes deposit in kidney
  - Circulating antigen-antibodies complexes
  - In situ formation in kidney
- Fix complement
- Attract PMNs
- **Hypocomplementemia** (also lupus, MPGN)

Post-streptococcal GN

- Common in children (can also occur in adults)
- Classic case
  - Child
  - 2-3 weeks following strep throat infection
  - Nephritic syndrome

Post-streptococcal GN

- Glomeruli: Enlarged, hypercellular



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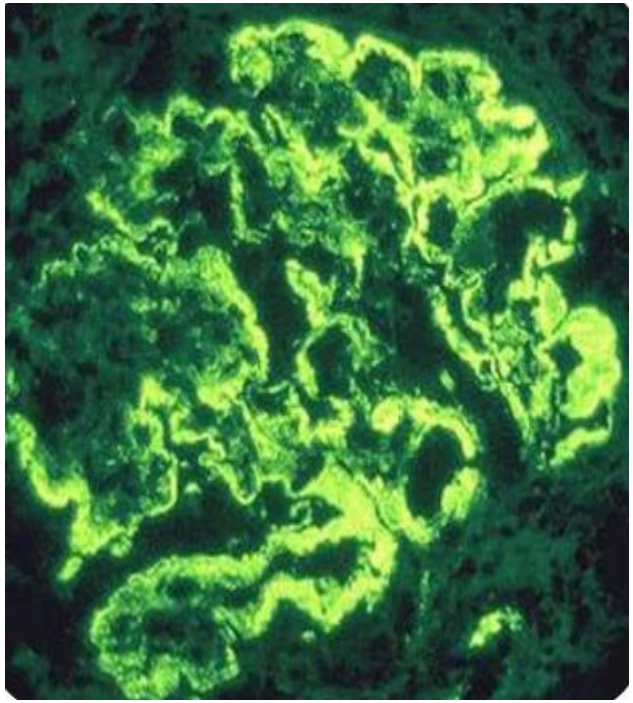
Post-streptococcal GN

- Subendothelial antibodies/complexes
- Granular IF (IgG, C3)



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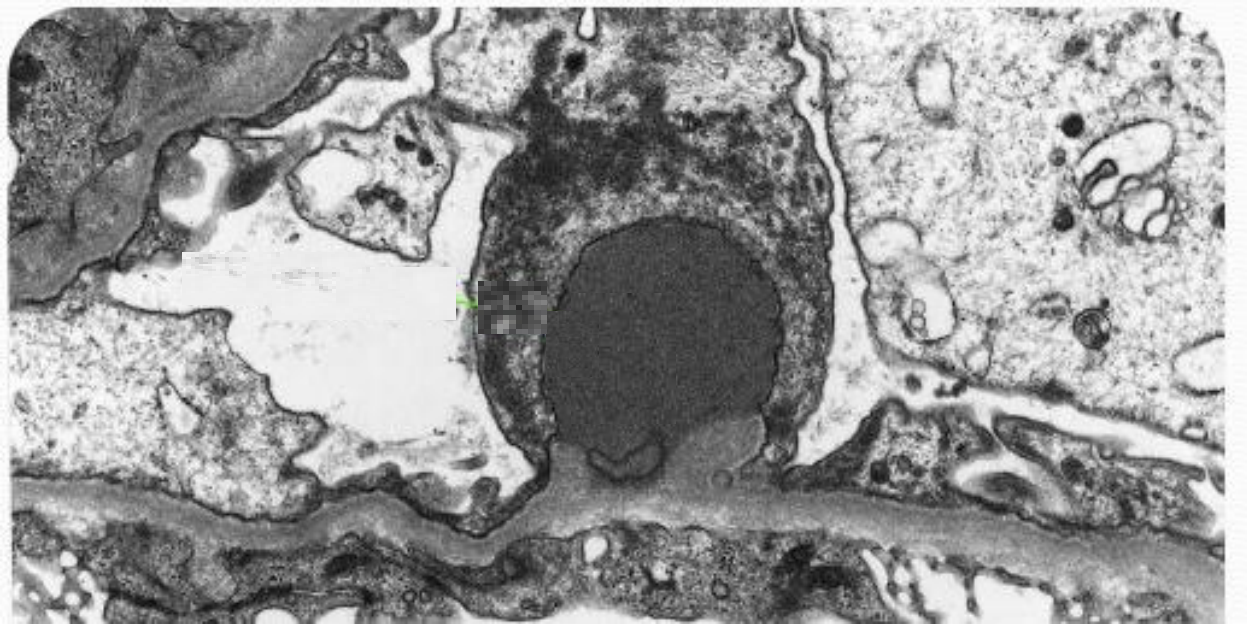
Post-streptococcal GN

- Electron microscopy: **Subepithelial** "humps"
  - Immune complexes



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Post-streptococcal GN

- Good prognosis in children
  - 95% recover completely
- Adults have worse prognosis
  - About 60% recover
  - Many develop renal insufficiency
  - Can be late: 10 to 40 years after initial illness
  - Can develop RPGN

Post-streptococcal GN

- No specific therapy (supportive)
- Spontaneous resolution

IgA Nephropathy

Berger's Disease

- Most common form glomerulonephritis worldwide
- Repeated episodes of hematuria (nephritic)
- Over time leads to ESRD and HD (50% patients)

IgA Nephropathy

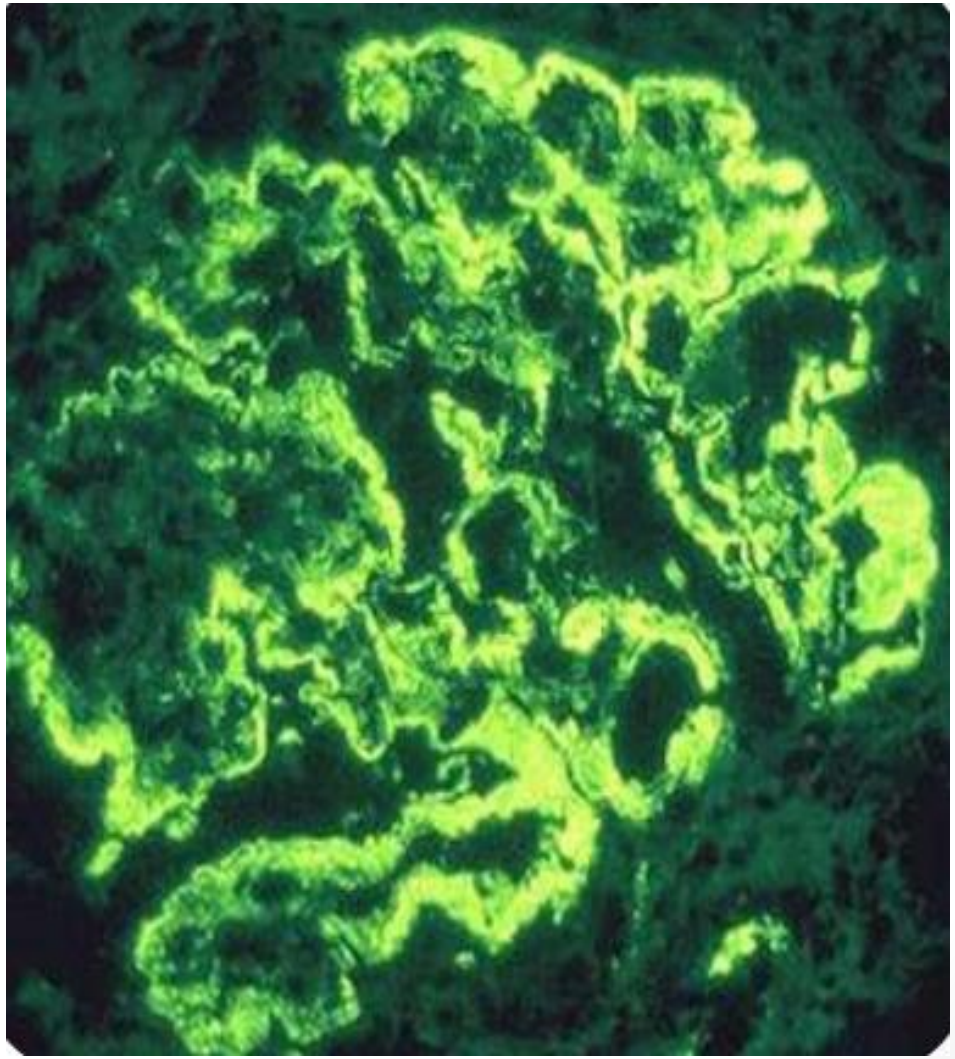
Berger's Disease

- Overactive immune system
- ↑IgA synthesis in response to triggers
  - Respiratory infection
  - GI infection
- IgA immune complexes → **mesangium**
- Activate complement
  - Alternative and lectin pathways
  - No hypocomplementemia
- Glomerular injury occurs

IgA Nephropathy

Berger's Disease

- Granular IF
- Stained for IgA



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IgA Nephropathy

Berger's Disease

- Classic case
  - Recurrent episodes hematuria since childhood
  - Episodes follow URI or diarrheal illness
  - Slowly worsening renal function (BUN/Cr) over time
  - Possible progression to ESRD and HD (20yrs+)
- Don't confuse with other glomerular disorders
  - Post-strep GN: weeks after infection
  - IgA GN: days after infection
  - Minimal change: nephrotic syndrome after URI

Henoch-Schonlein Purpura

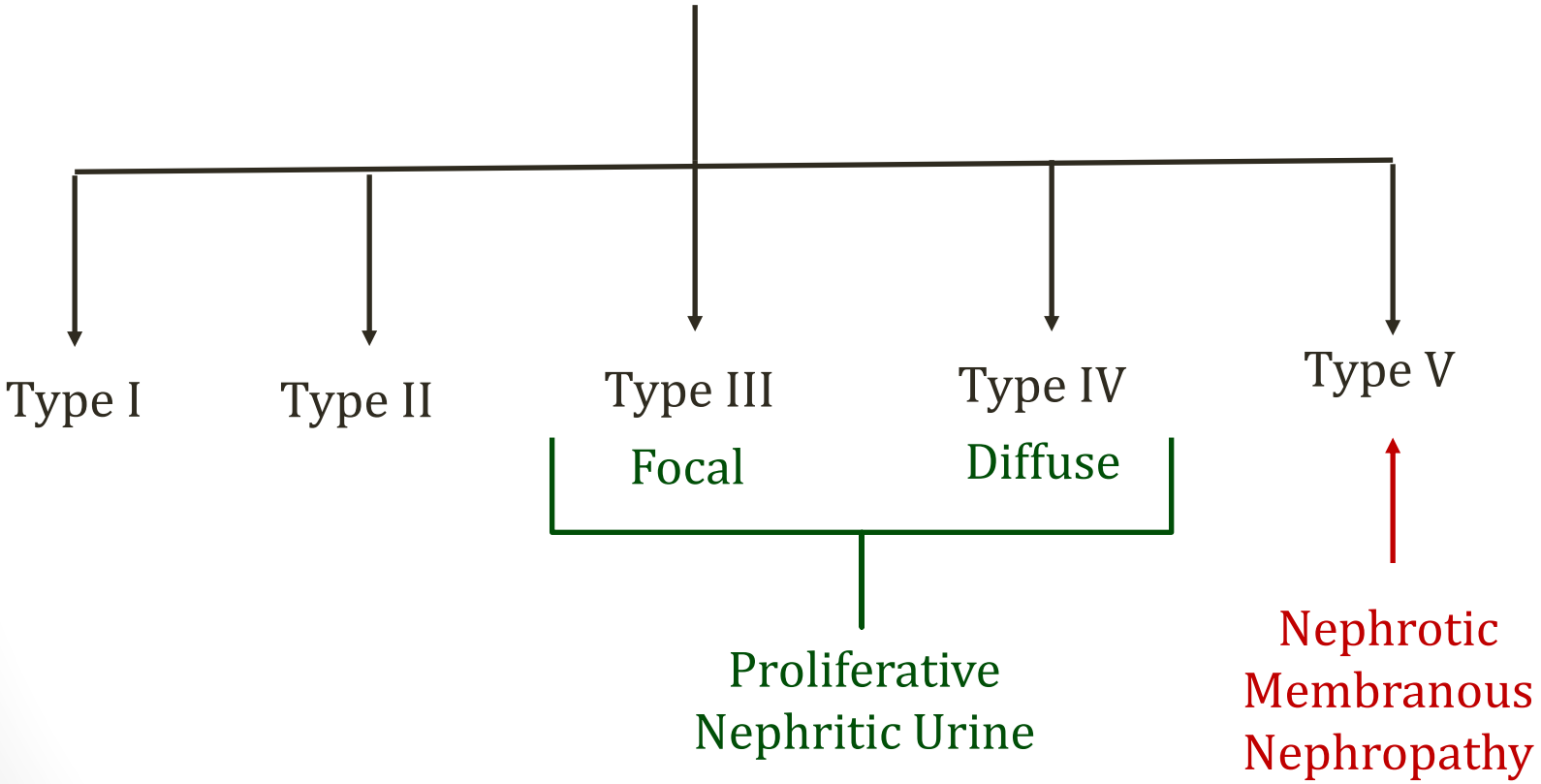
- IgA nephropathy with extra-renal involvement
- Most common **childhood** systemic vasculitis
- Skin: palpable purpura on buttocks/legs
- GI: abdominal pain, melena
- Joint pains
- **Diffuse IgA deposition**
- Tissue biopsy: demonstrates IgA

DPGN

Diffuse proliferative glomerulonephritis

- Systemic lupus erythematosus (SLE)
  - Most common subtype of SLE renal disease
  - "Type IV Lupus Nephritis"
  - Often presents with other SLE features: fever, rash, arthritis
- **Immune complex deposition** in glomeruli
  - IC → inflammatory response

Lupus Nephritis



DPGN

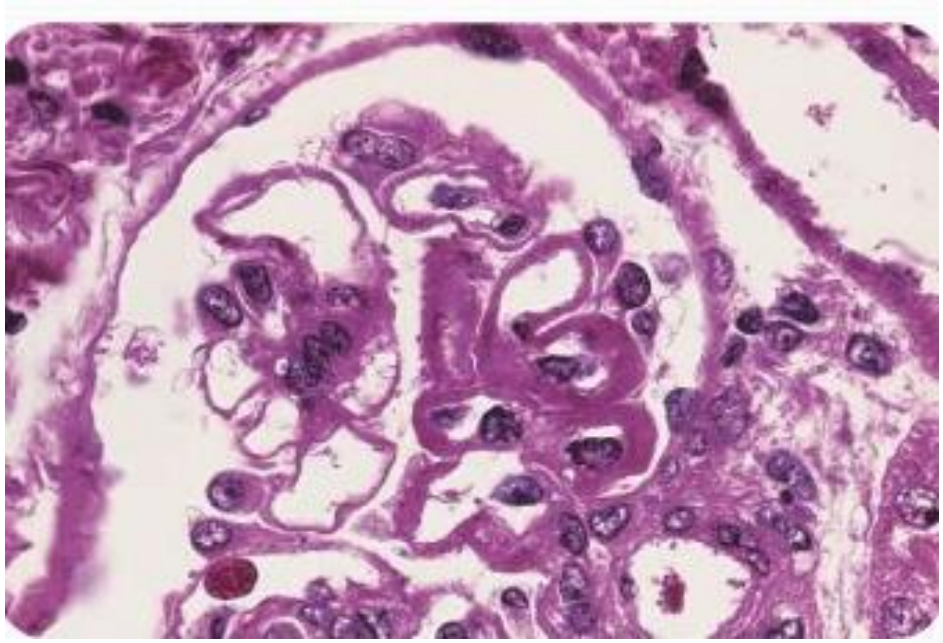
Diffuse proliferative glomerulonephritis

- Diffuse: More than 50% glomeruli affected
- Proliferative:
  - Increase in cellularity of glomeruli
  - Mesangial cells
  - Endothelial cells
  - Monocyte/neutrophil infiltration

DPGN

Diffuse proliferative glomerulonephritis

- **Subendothelial deposits** drive immune response
  - Anti-dsDNA
  - Hypocomplementemia (also post-strep, MPGN)
- Classic finding: **capillary loops thickened**
  - "Wire looping"



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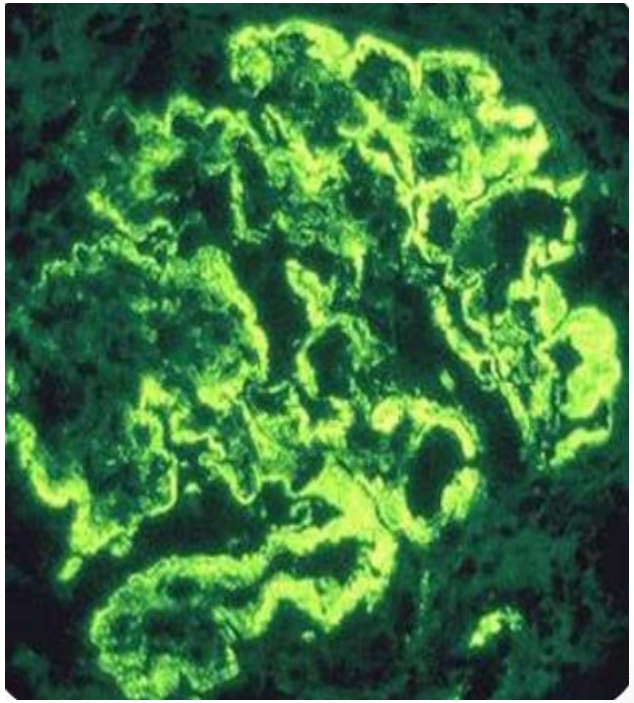
DPGN

Diffuse proliferative glomerulonephritis

- **Granular IF**
- "Full house" immunofluorescence
  - IgG, IgA, IgM, C3, C1q



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DPGN

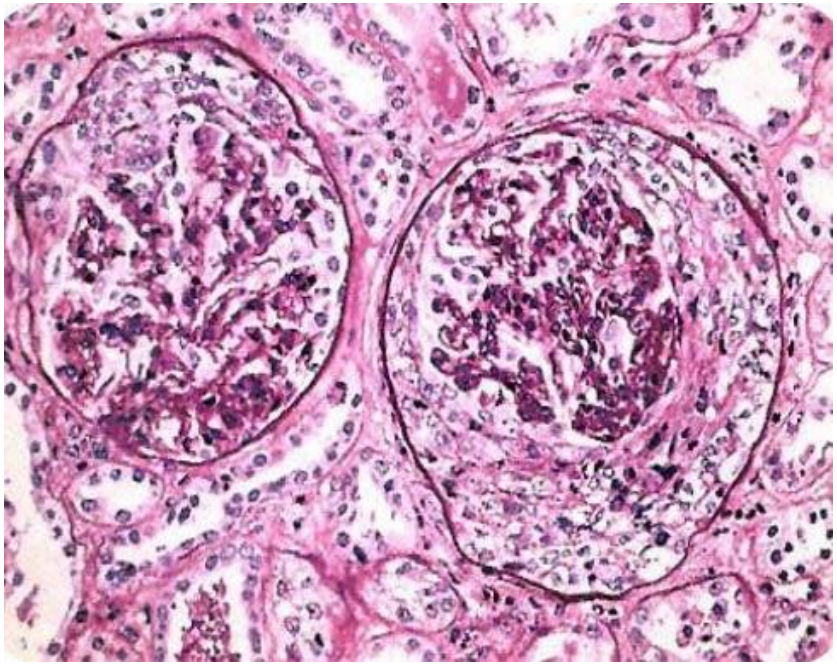
Diffuse proliferative glomerulonephritis

- Mixed clinical presentation
  - Proteinuria (sometimes nephrotic)
  - Hematuria
  - Reduced GFR
- Severe, often leads to ESRD and HD

RPGN

Rapidly progressive glomerulonephritis

- Also called “crescentic” glomerulonephritis
- Pathologic description: Many causes
  - Many diseases lead to this condition



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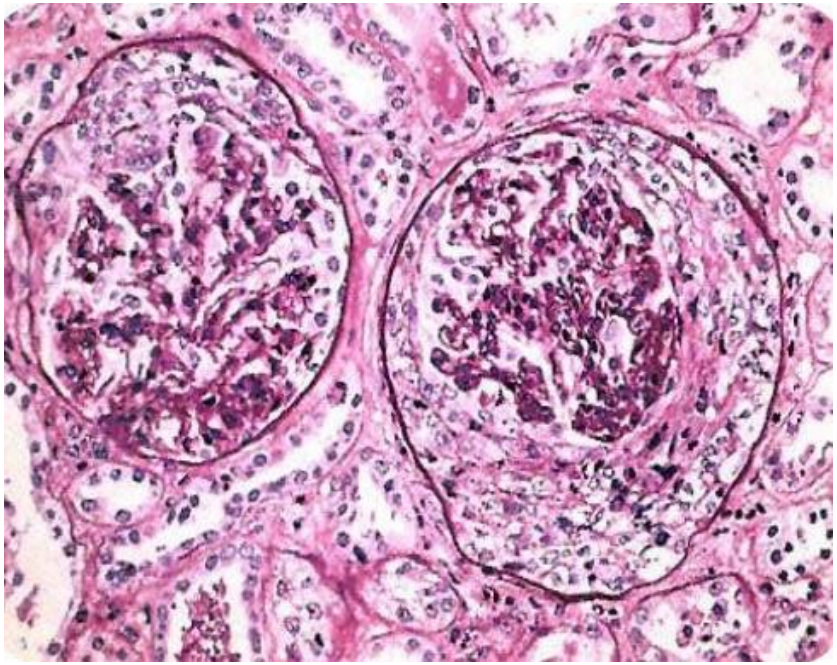
RPGN

Rapidly progressive glomerulonephritis

- Crescents formed by **inflammation**:
  - Monocytes/macrophages
  - Fibrin



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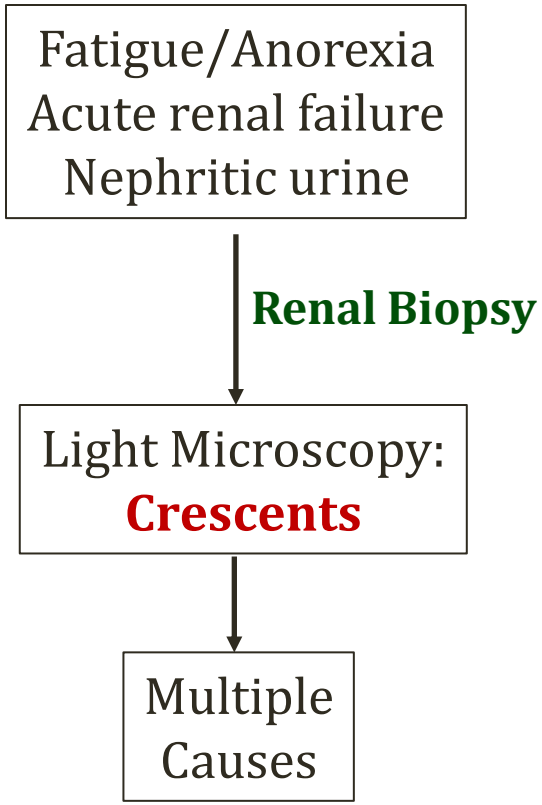
RPGN

Rapidly progressive glomerulonephritis

- Severe form of glomerulonephritis
- Progressive loss of renal function
- Rapid onset
- Often presents as acute renal failure
- Generalized symptoms: fatigue, anorexia

RPGN

Rapidly progressive glomerulonephritis



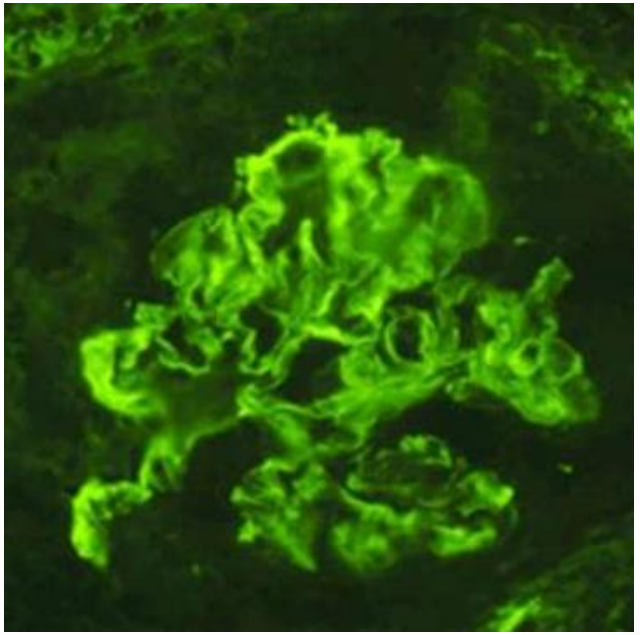
RPGN

Rapidly progressive glomerulonephritis

- Causes distinguished based on immunofluorescence
- Type I: Linear IF
- Type II: Granular IF
- Type III: Negative IF

RPGN Type I

- Anti-glomerular basement membrane antibodies
  - "Anti-GBM antibodies"
- Antibodies against GBM antigens
  - Unknown stimulus
  - Type II hypersensitivity
- **Linear IF**
  - IgG antibodies
  - Linear pattern



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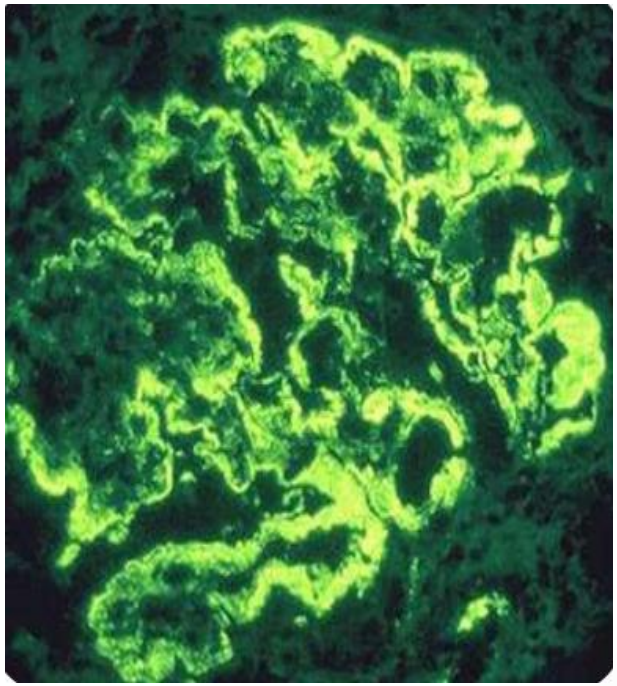
Goodpasture's Syndrome

- Antibody to collagen
- Antibodies to **alpha-3 chain** of type IV collagen
  - Found in GBM and alveoli
- Hemoptysis and nephritic syndrome
- Classic case
  - Young adult
  - Male
  - Hemoptysis
  - Hematuria

RPGN Type II

- Immune complex deposition
  - Type III hypersensitivity
- Granular IF



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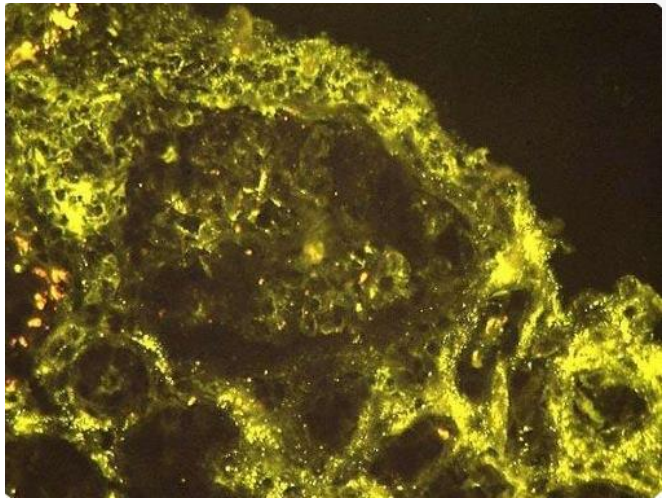
RPGN Type II

- **Post-streptococcal glomerulonephritis**
  - Can progress to RPGN
  - Most common cause RPGN
- **Systemic lupus erythematosus (SLE)**
  - Diffuse proliferative glomerulonephritis
  - Can progress to RPGN

RPGN Type III



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- Negative IF
  - No staining for IgG, IgA, etc.
- "Pauci-immune"
- Most patients **ANCA positive**
  - c-ANCA or p-ANCA
- Most patients have a **vasculitis syndrome**

ANCA Diseases

Anti-neutrophil cytoplasmic antibodies

- Wegener's Granulomatosis (c-ANCA)
- Microscopic Polyangiitis (p-ANCA)
- Churg-Strauss syndrome (p-ANCA)
- All can lead to pauci-immune nephritis

RPGN

Rapidly progressive glomerulonephritis