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Differential Diagnosis of Glomerular Disease

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Disclosures

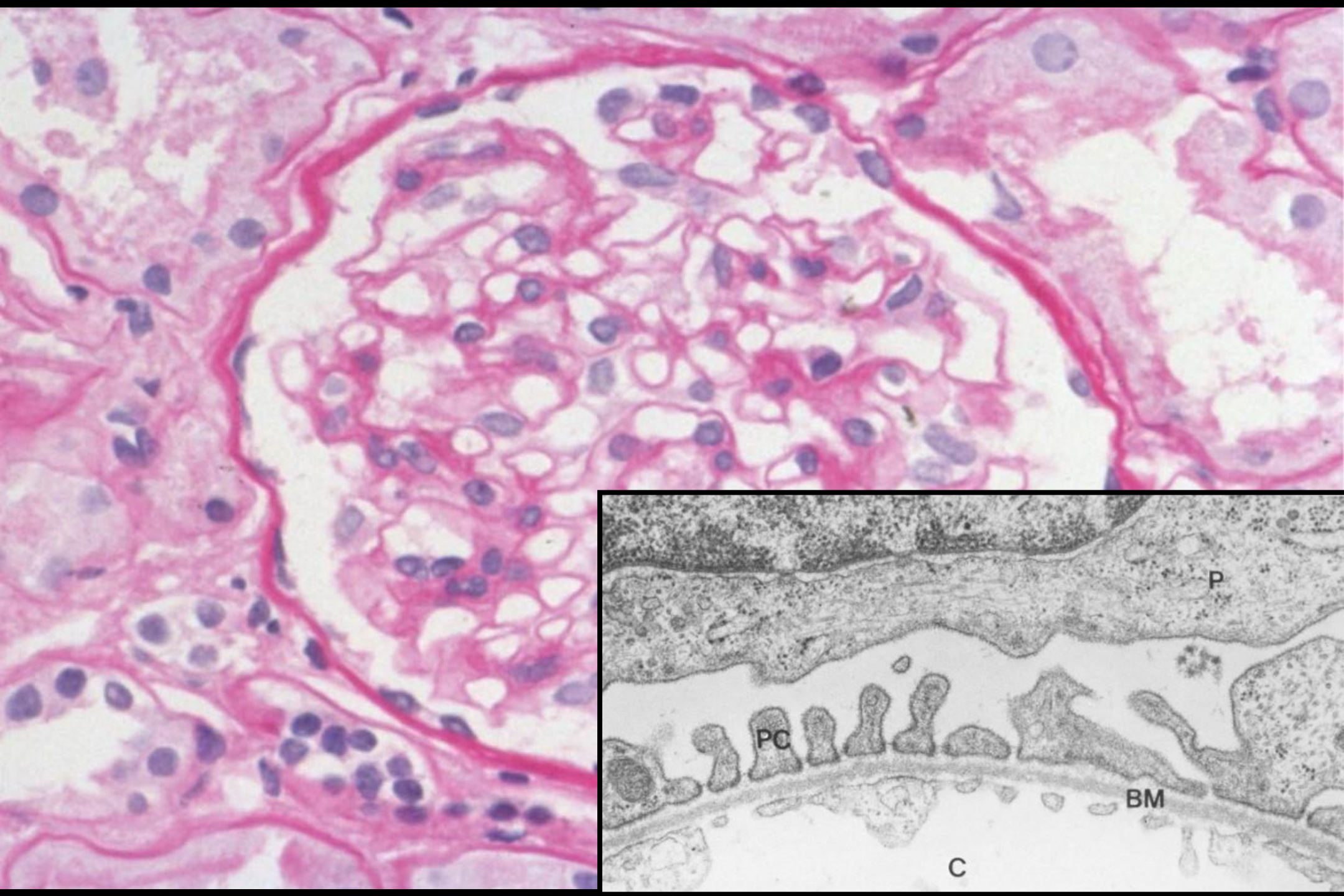
Nothing to disclose

Overview

- Pathologic features of glomerular diseases
- Classification of glomerular diseases
- Clinical patterns of glomerular diseases
- Diagnostic evaluation of glomerular disease
- Examples of glomerular diseases

Classification of glomerular diseases

- Primary versus secondary glomerular disease
- Morphologic classification
- Immunohistologic classification
- Classification according to serum complement levels
- Etiologic classification
- Classification based on clinical features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Classification of glomerular diseases

Type of disorder	Proliferative changes	No proliferative changes
Primary disorder	IgA nephropathy Membranoproliferative glomerulonephritis Idiopathic crescentic glomerulonephritis Anti-GBM nephritis	Focal segmental glomerulosclerosis Membranous glomerulopathy Minimal change disease Thin basement membrane nephropathy
Secondary disorder	Lupus nephritis Infection-related glomerulonephritis Henoch-Schönlein purpura ANCA-associated vasculitis	Diabetic nephropathy Amyloidosis Light-chain nephropathy HIV nephropathy

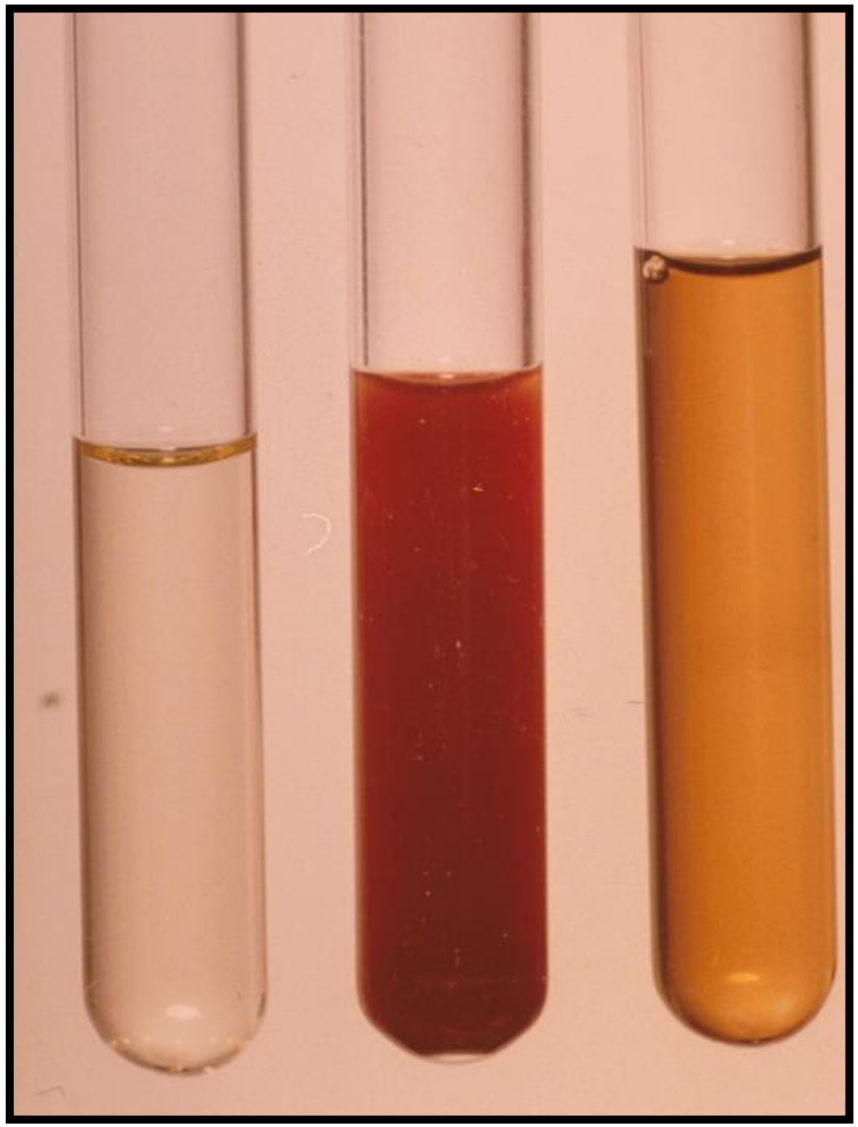
Clinical patterns of glomerular disease

- Isolated proteinuria and/or hematuria
- Nephrotic syndrome
- Nephritic syndrome
- Rapidly progressive glomerulonephritis

Proteinuria

- **Urine dipstick (semiquantitative)**
  - 1+ ~300 mg/L; 2+ ~1 g/L; 3+ ~3 g/L
- **24-hour urine collection**
  - >150 mg/24 hours (albumin 10-30 mg)
- **Urine protein/creatinine ratio (PCR)**
  - >15 mg/mmol
- **Urine albumin/creatinine ratio (ACR)**
  - Men >2.5 mg/mmol
  - Women >3.5 mg/mmol
- **Isolated asymptomatic proteinuria**
  - Usually 1-3 g protein per 24 hours
  - PCR of 100 mg/mmol and ACR of 70 mg/mmol ≈ 1 g of protein per 24 hours
- **Nephrotic-range proteinuria**
  - >3.5 g protein per 24 hours
  - PCR >300 mg/mmol
  - ACR >250 mg/mmol

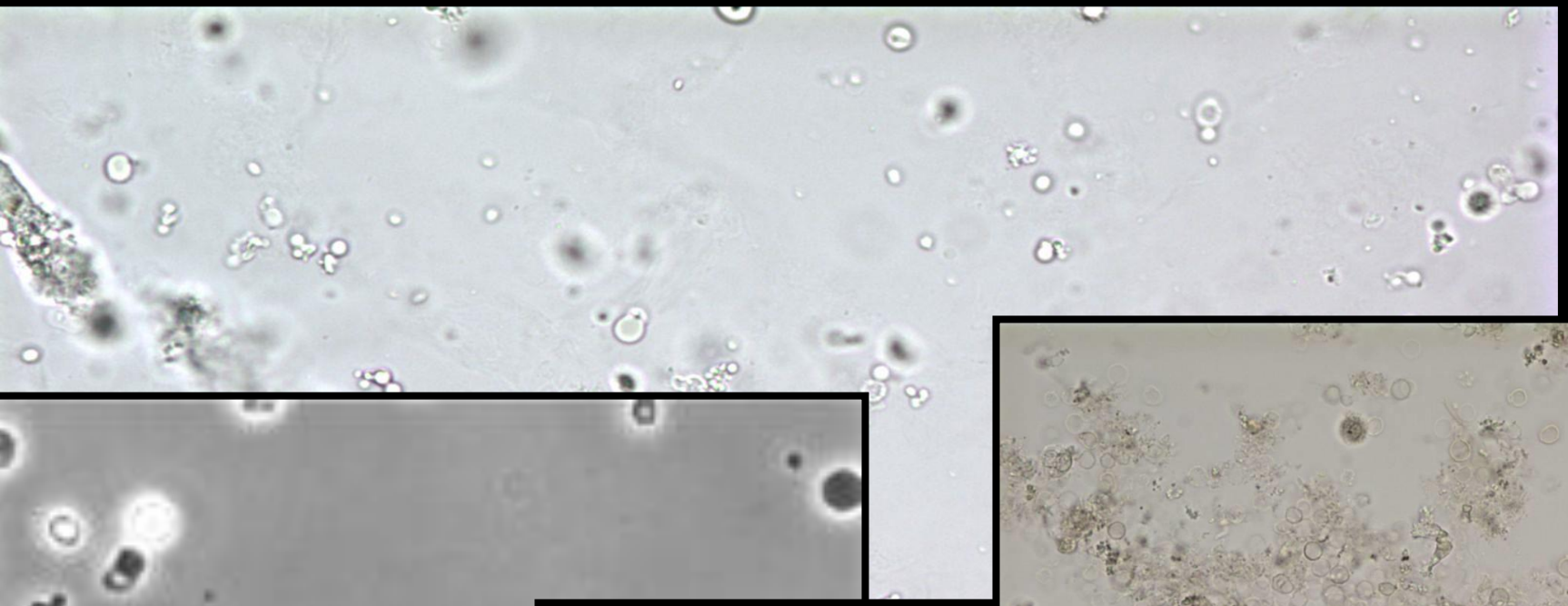
Hematuria

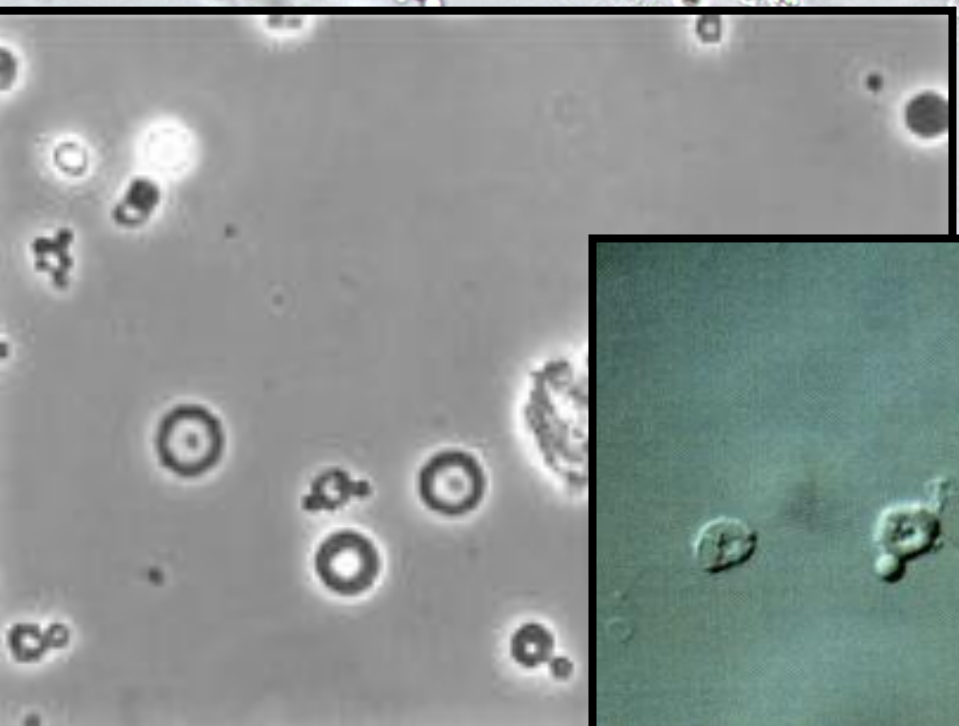


- Urine dipstick detects heme pigments
- The dipstick cannot differentiate between RBCs, hemoglobin and myoglobin
- Persistently >3 RBC/HPF is considered abnormal

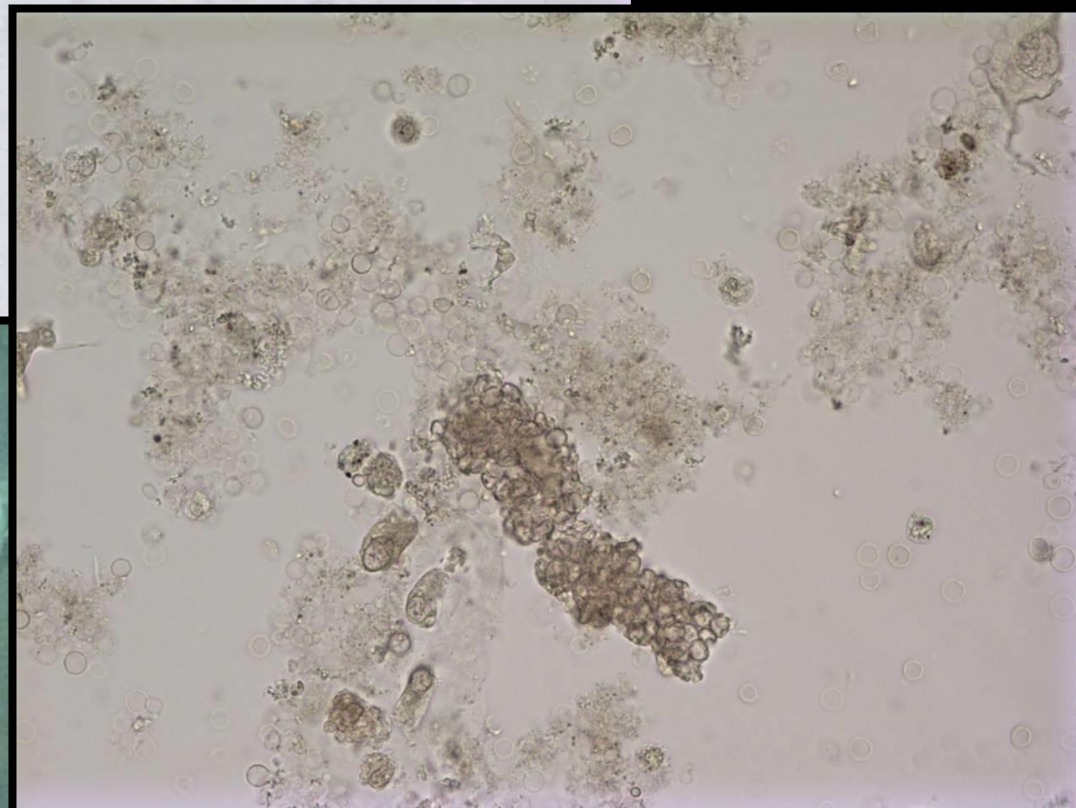
Glomerular hematuria

Dysmorphic red blood cells





Red blood cell cast



Diagnostic evaluation of glomerular disease

- Clinical features
  - Age
  - Race
  - Family history
  - Systemic manifestations
- Urinalysis
- Serum creatinine/eGFR
- Serologic tests
- Kidney biopsy

Integration of clinical and histological features

GFR estimating equations

Abbreviation	GFR equation
Cockcroft and Gault [4]	$[((140 - age) \times weight) \times 1.23]/(SCr) \times 0.85$ (if female)
MDRD (ID-MS traceable) [5]	$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.210 (if black)
CKD-EPI$_{creat}$ [6]	$141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) $\times$ 1.159 (if black), in which SCr is serum creatinine, κ is 0.7 for women and 0.9 for men, α is –0.329 for women and –0.411 for men, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1
CKD-EPI$_{cys}$ [7▪▪]	$133 \times \min(Scys/0.8, 1)^{-0.499} \times \max(Scys/0.8, 1)^{-1.328} \times 0.996^{Age} \times 0.932$ (if female), in which Scys is serum cystatin C, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1
CKD-EPI$_{creat-cys}$ [7▪▪]	$135 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-0.601} \times \min(Scys/0.8, 1)^{-0.375} \times \max(Scys/0.8, 1)^{-0.711} \times 0.995^{Age} \times 0.969$ (if female) $\times$ 1.08 (if black), in which SCr is serum creatinine, Scys is serum cystatin C, κ is 0.7 for women and 0.9 for men, α is –0.248 for women and –0.207 for men, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1
BIS1 [8▪▪]	$3736 \times (SCr \times 88.4)^{-0.87} \times age^{-0.95} \times 0.82$ (if female)
BIS2 [8▪▪]	$767 \times Scys^{-0.61} \times SCr^{-0.40} \times age^{-0.57} \times 0.87$ (if female)

Age is given in years, serum creatinine (SCr) in µmol/l, serum cystatin C (Scys) in mg/l, and weight in kg.
BIS, Berlin Initiative Study; CKD-EPI, Chronic Kidney Disease-Epidemiology Consortium; ID-MS, isotope dilution-mass spectrometry; MDRD, Modification of Diet in Renal Disease.

Lamb & Stevens, Curr Opin Nephrol Hypertens 2014;23:258-66

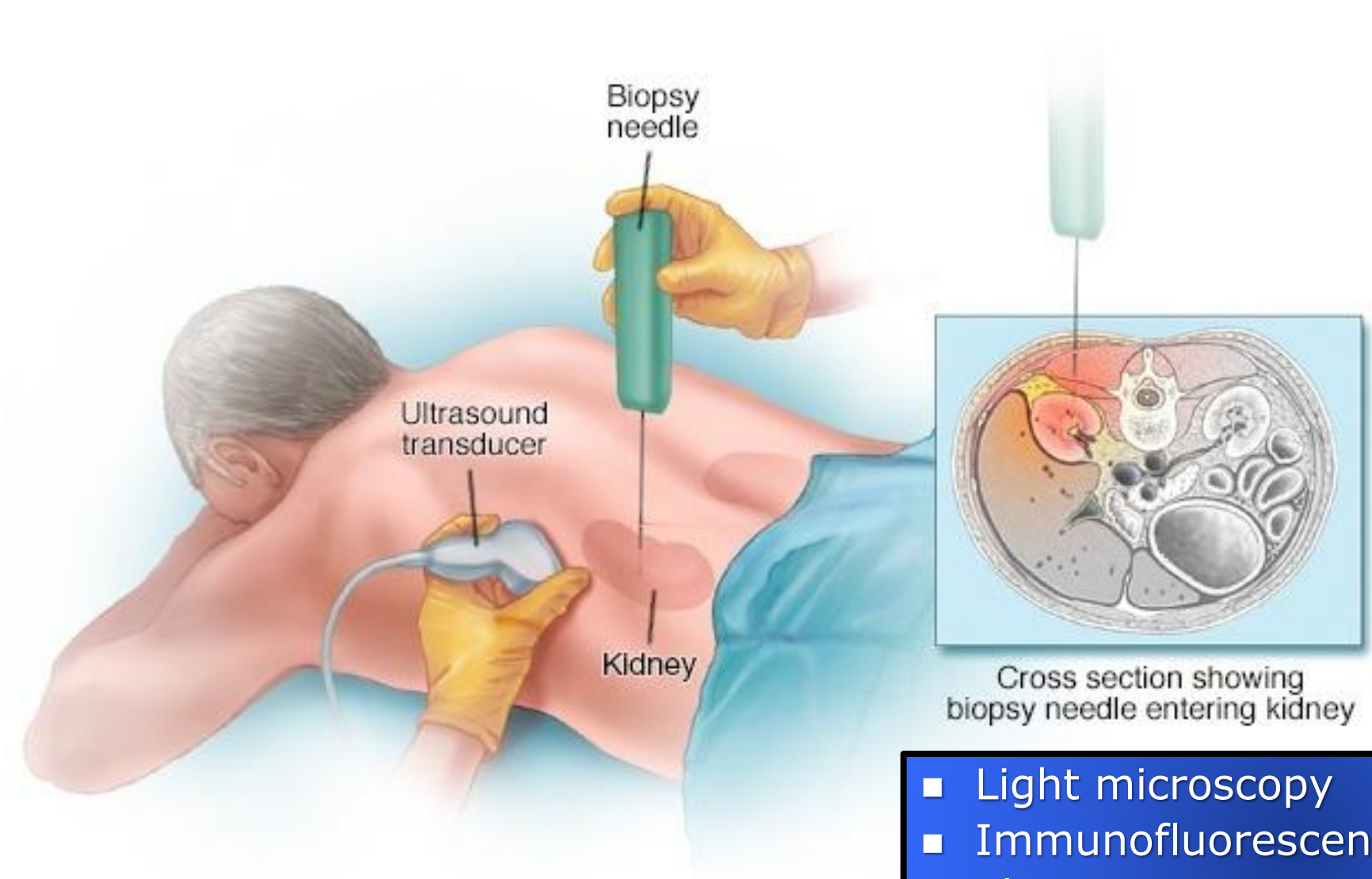
Serologic tests

- Anti-streptolysin O, anti-DNAse B
- ANA, anti-dsDNA
- Anti-GBM
- ANCA
- Cryoglobulin
- Anti-HCV
- C3 nephritic factor
- Anti-PLA_2R
- Complement levels

Hypocomplementemia

- Infection-related glomerulonephritis
  - Low CH50 and C3
- Membranoproliferative glomerulonephritis
  - Low CH50, C3 and/or C4
- Lupus nephritis
  - Low CH50, C3 and C4
- Cryoglobulinemic glomerulonephritis
  - Low CH50, C3 and C4

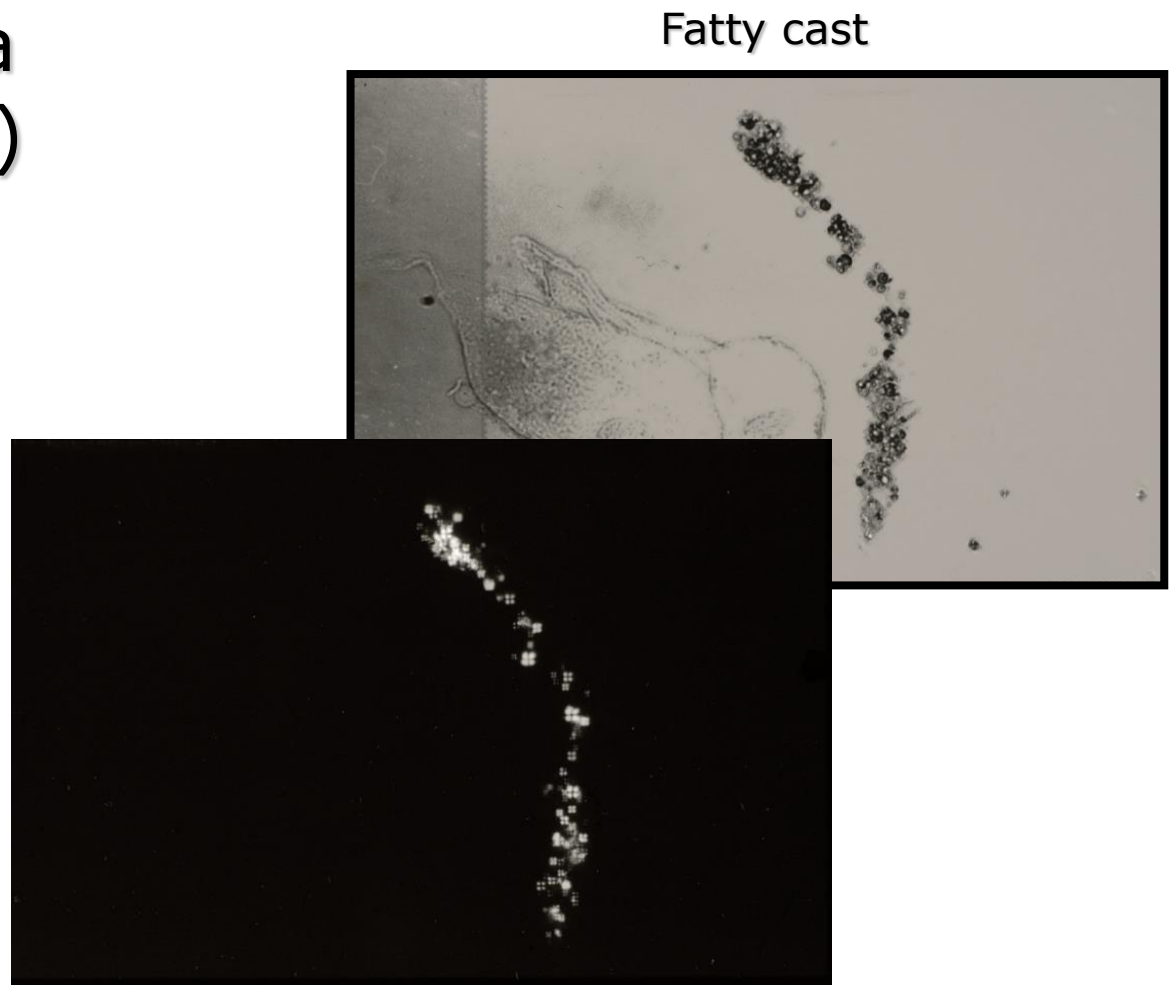
Percutaneous kidney biopsy



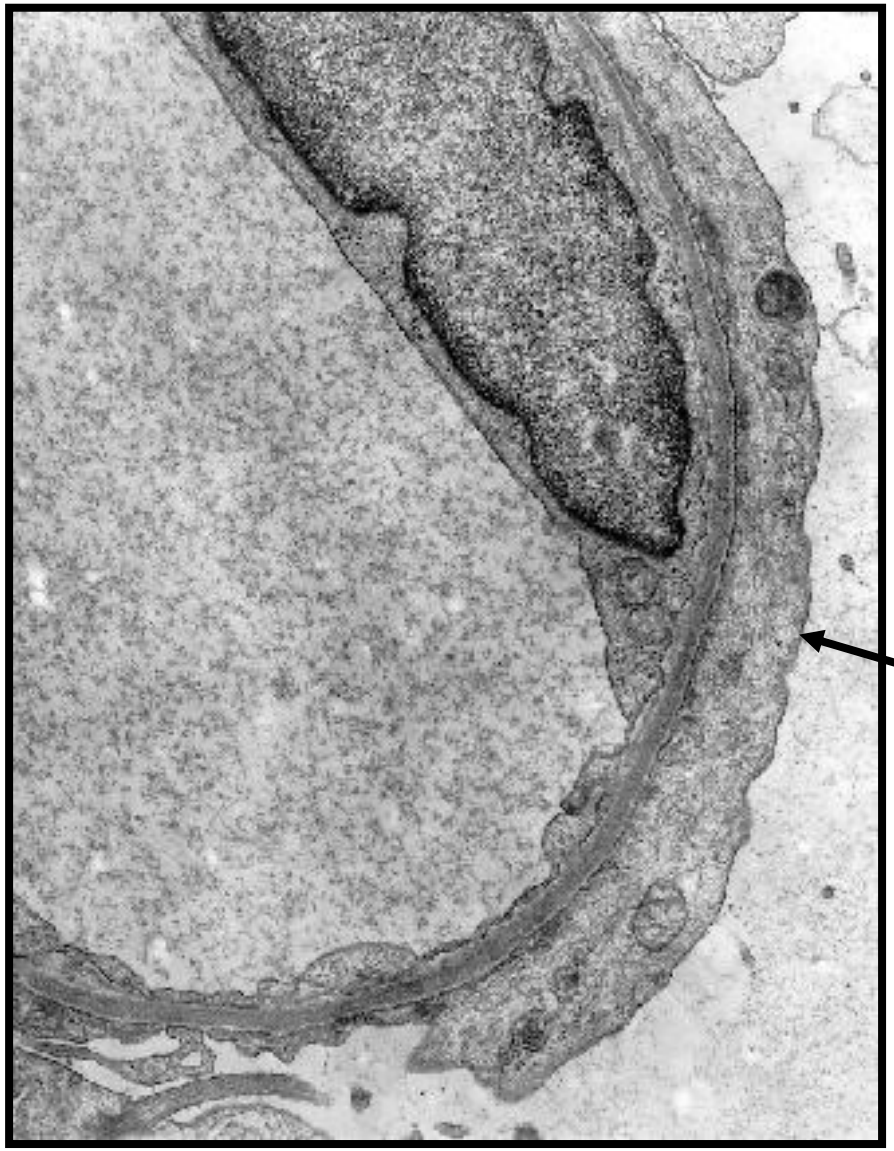
- Light microscopy
- Immunofluorescence microscopy
- Electron microscopy

Nephrotic syndrome

- Massive proteinuria (>3.5 g per 24 hrs)
- Hypoalbuminemia
- Edema
- Hyperlipidemia
- Lipiduria

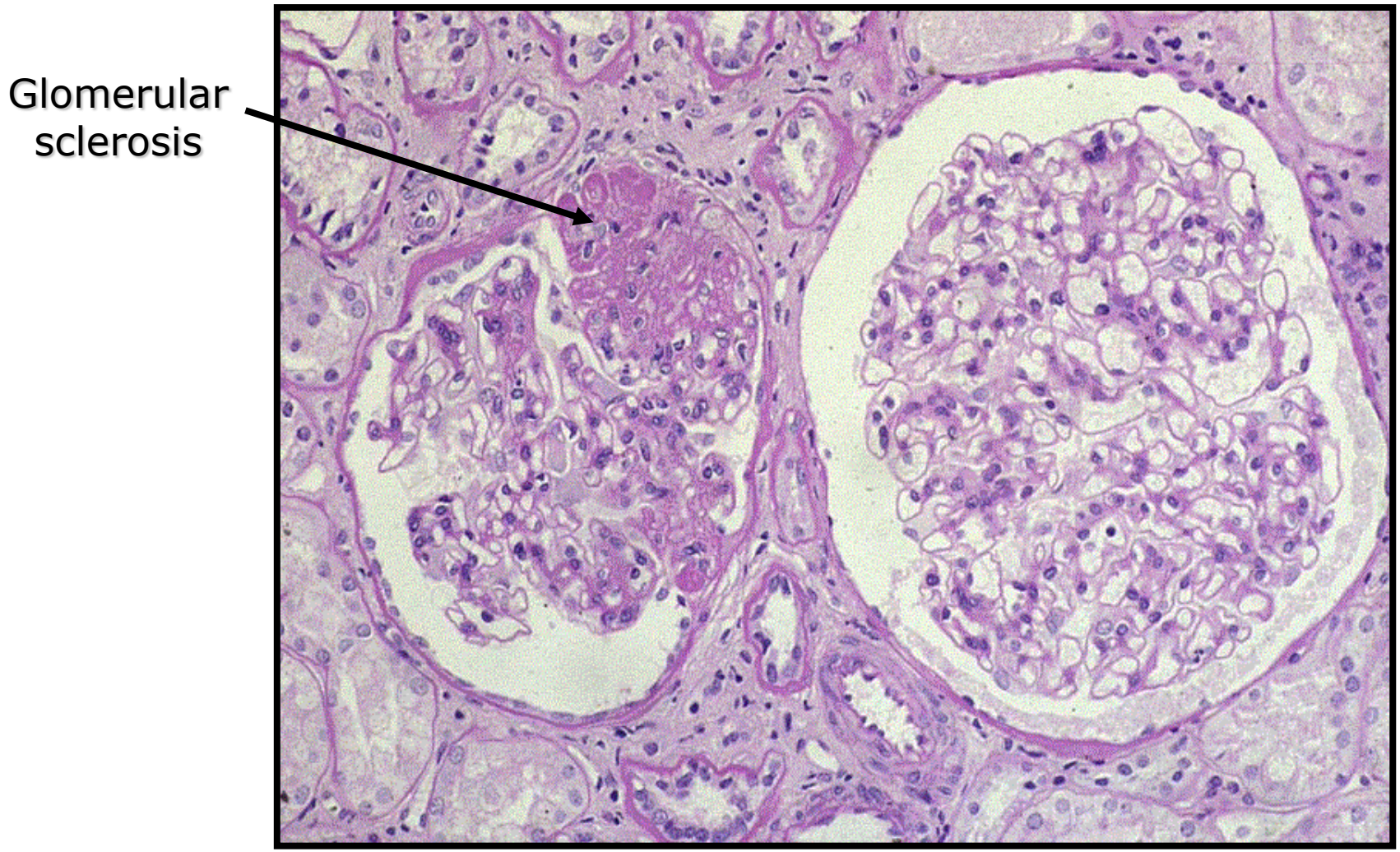


Minimal change disease

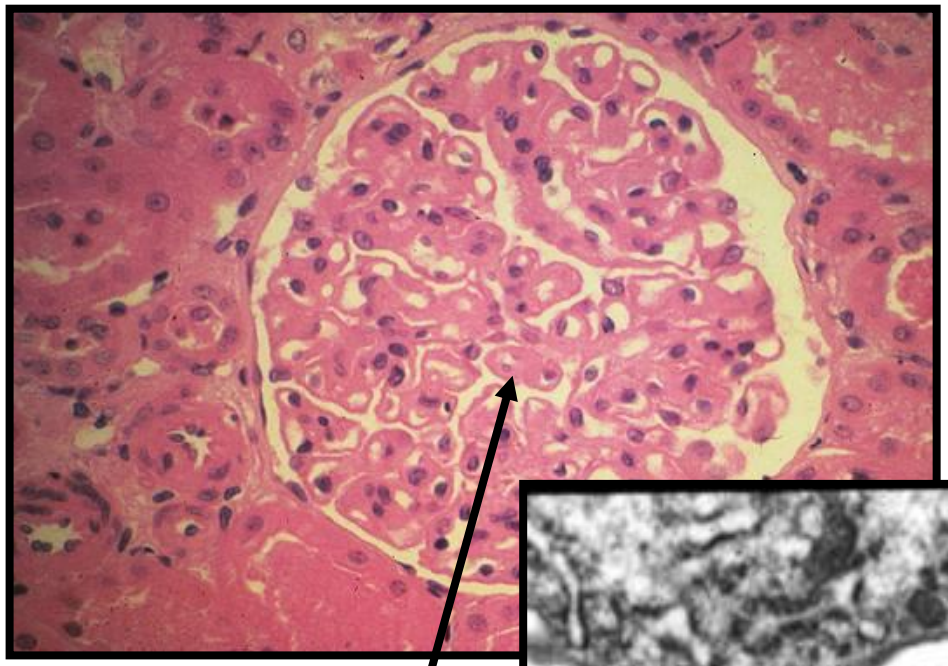


Effacement of podocyte
foot processes

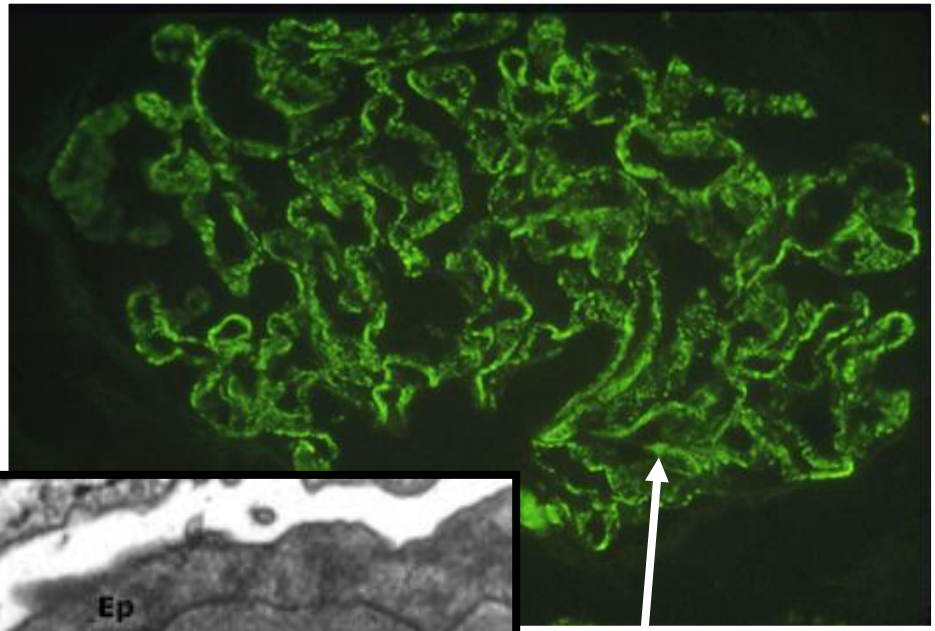
Focal segmental glomerulosclerosis



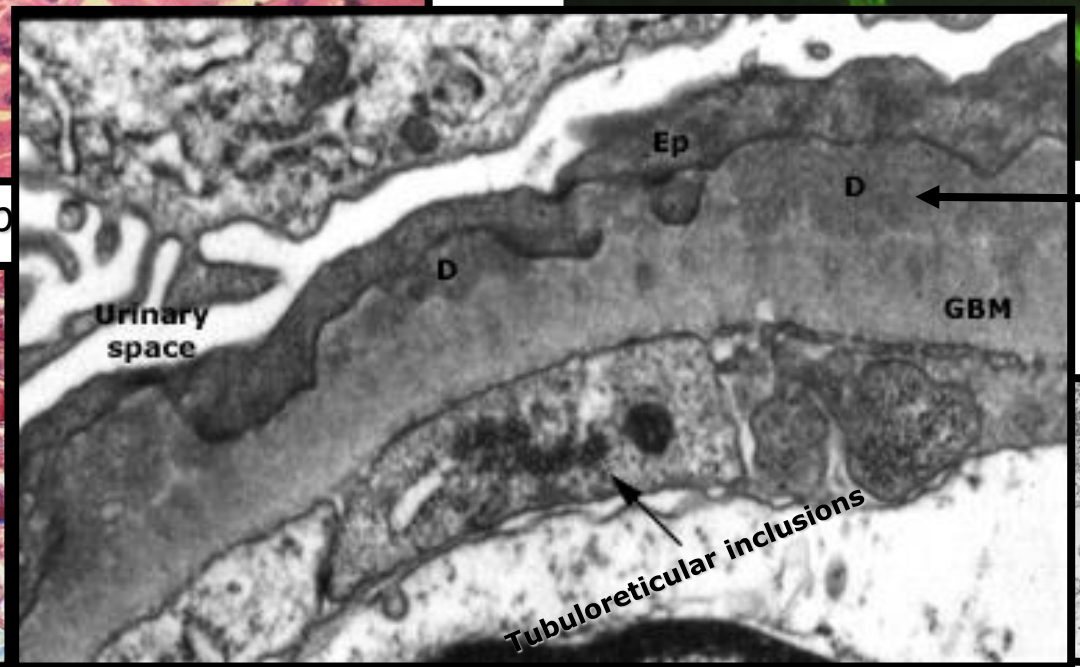
Membranous nephropathy



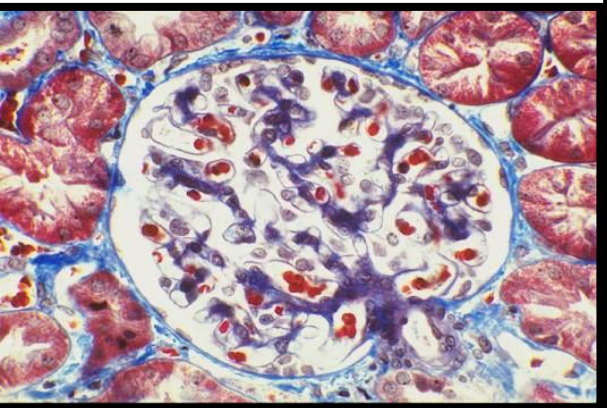
Thickened cap

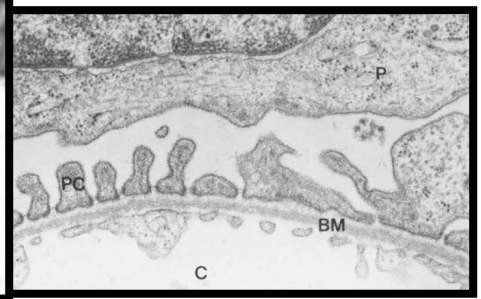


Immune deposits

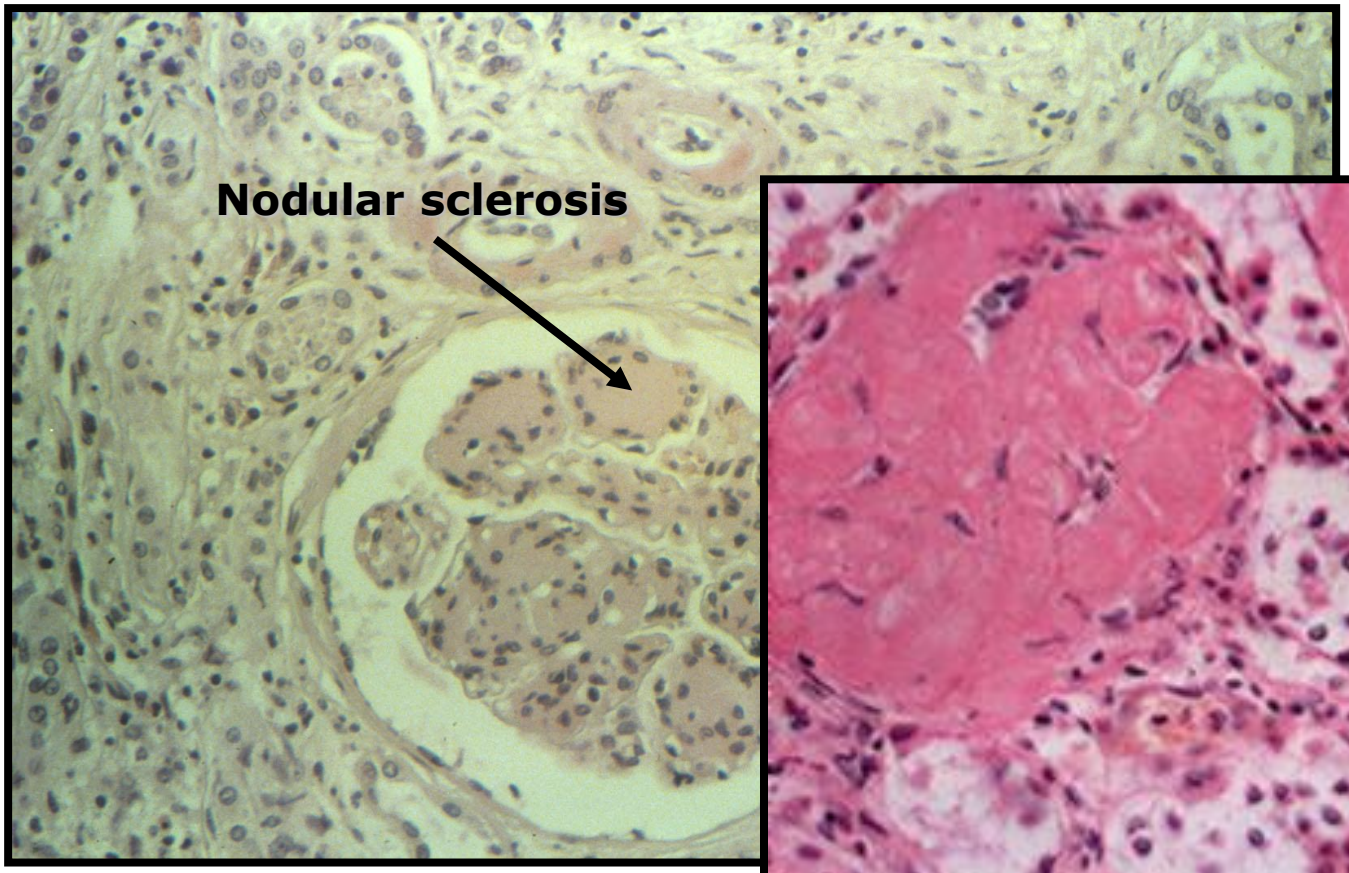


Normal glomerular capillary wall

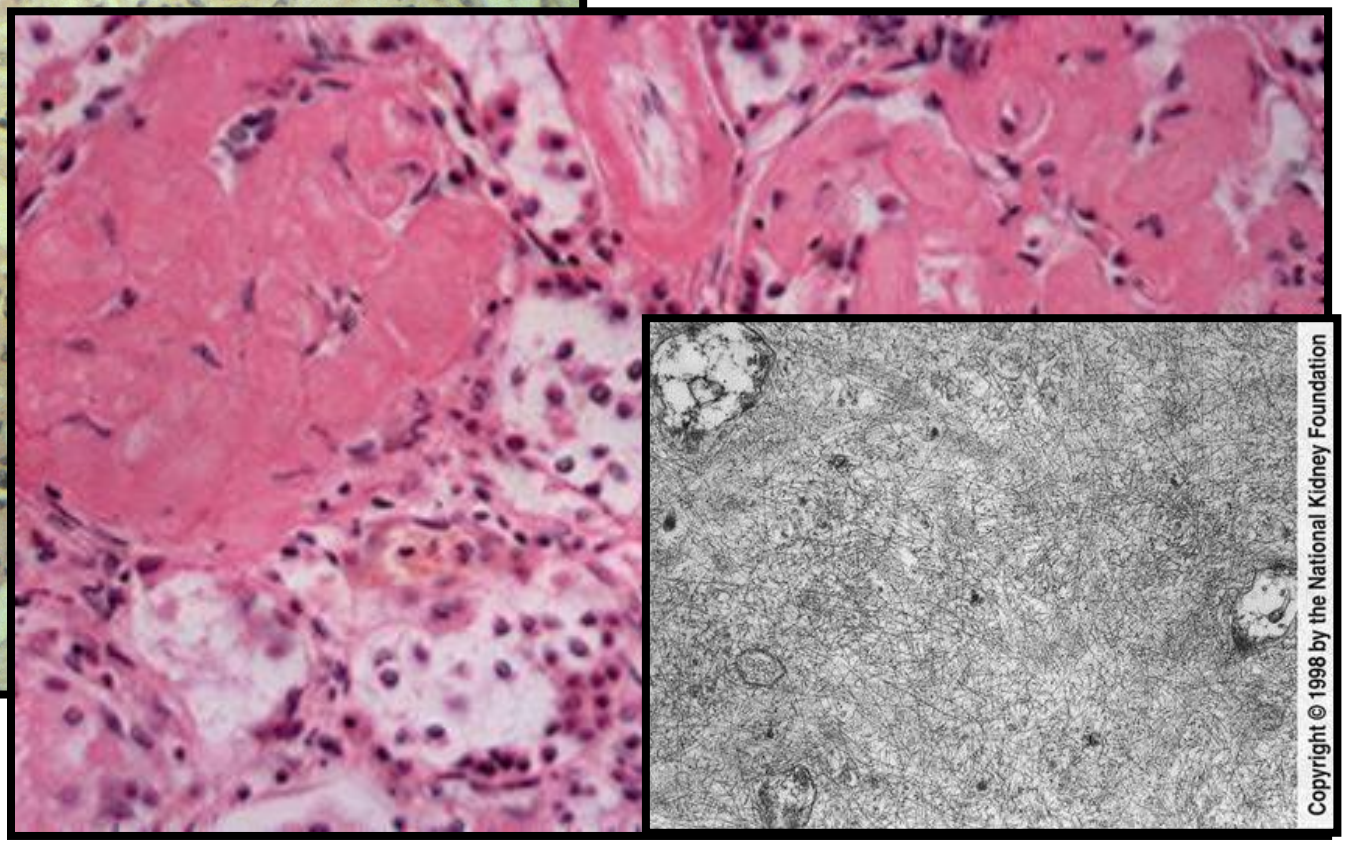




Secondary causes of the nephrotic syndrome



Diabetic nephropathy

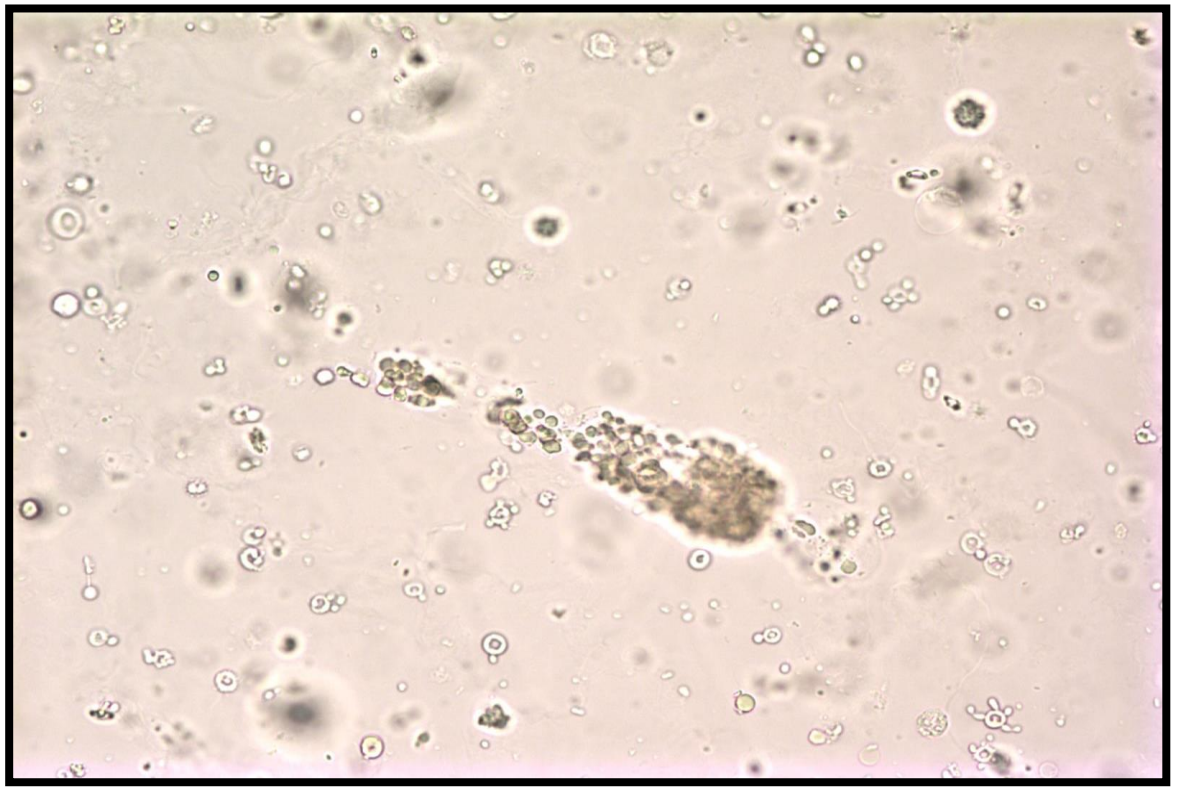


Renal amyloidosis

Nephritic syndrome

- Glomerular hematuria
- Azotemia
- Oliguria
- Edema
- Hypertension
- Variable degree of proteinuria

Red cell cast

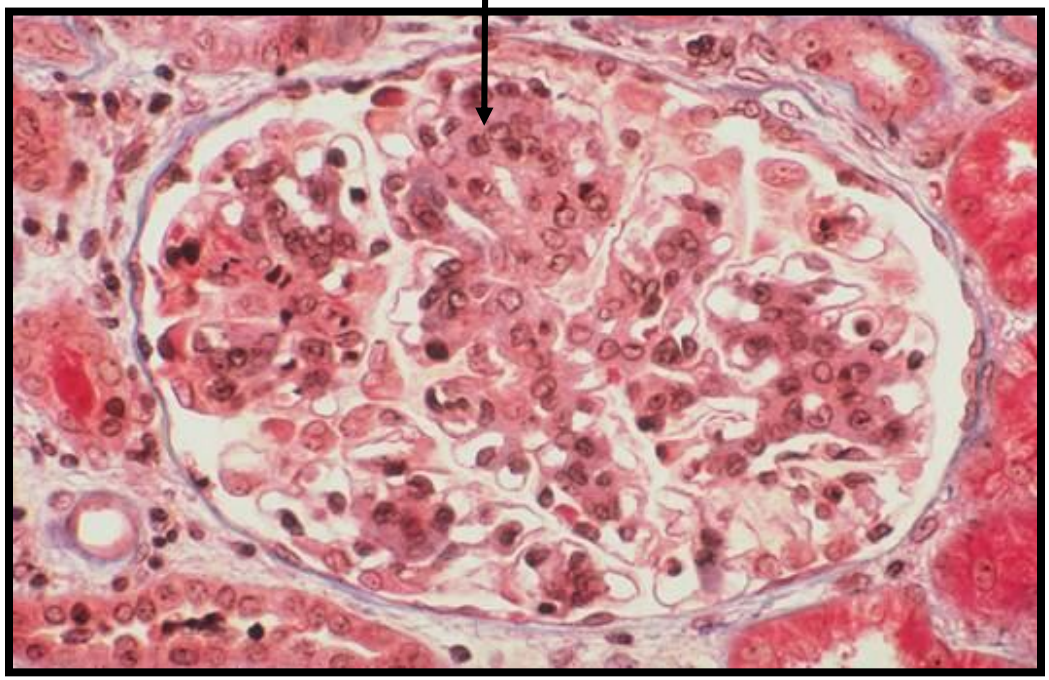


Isolated microscopic hematuria

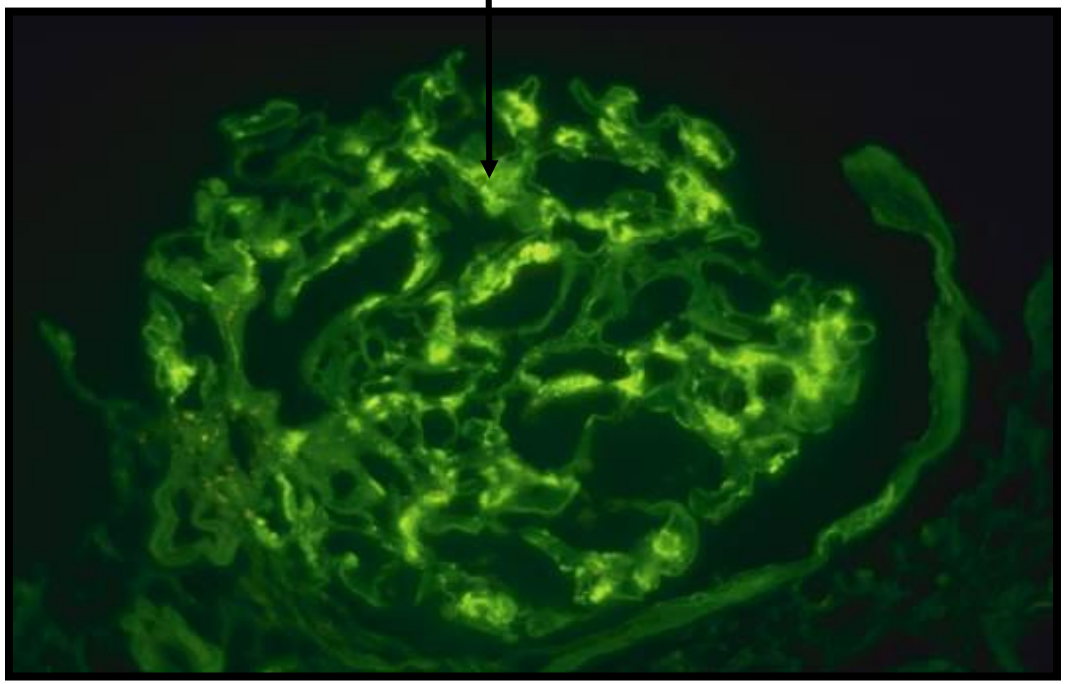
- More frequent than macroscopic hematuria following upper respiratory infection
- Usually not detected
- Most common causes of persistent microscopic hematuria are IgA nephropathy and thin basement membrane nephropathy

IgA nephropathy

Mesangial proliferation



Mesangial IgA deposits

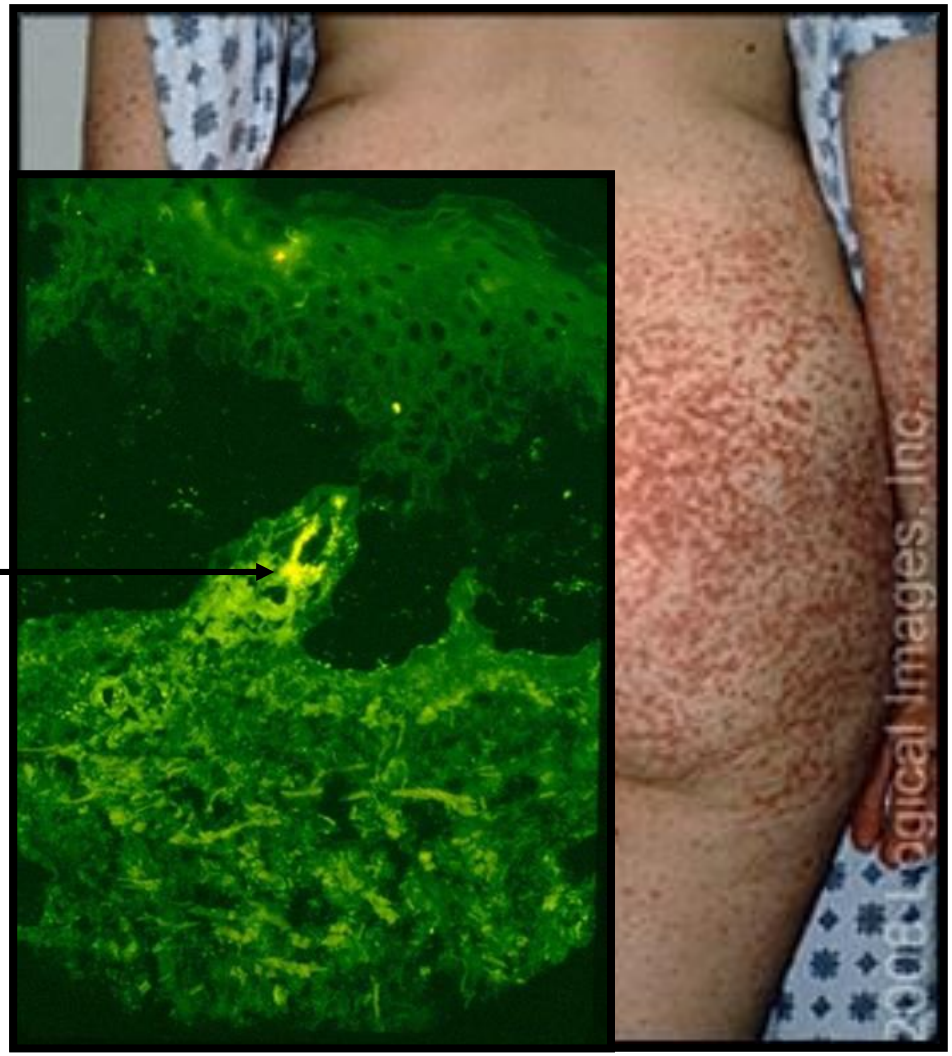


IgA nephropathy (Berger disease)

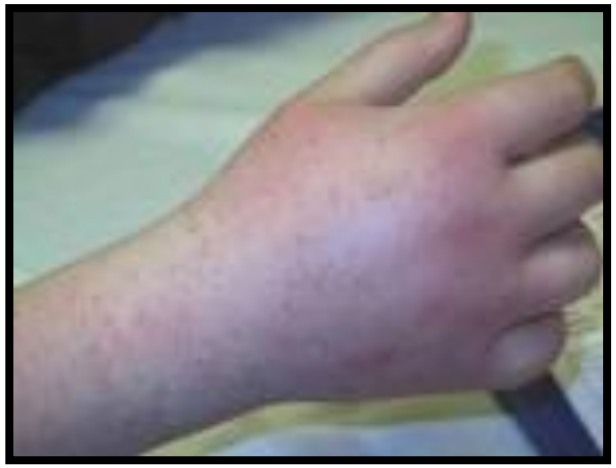
- Most common type of primary glomerular disease worldwide
- Variable clinical features
  - Episodes of gross hematuria most common
  - Persistent microscopic hematuria
  - Nephritic or nephrotic syndrome
  - Low back or loin pain
- Usually idiopathic

Henoch-Schönlein purpura

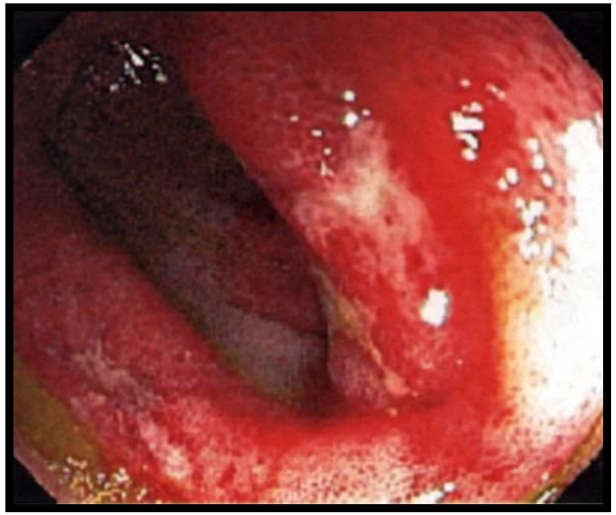
Palpable purpura



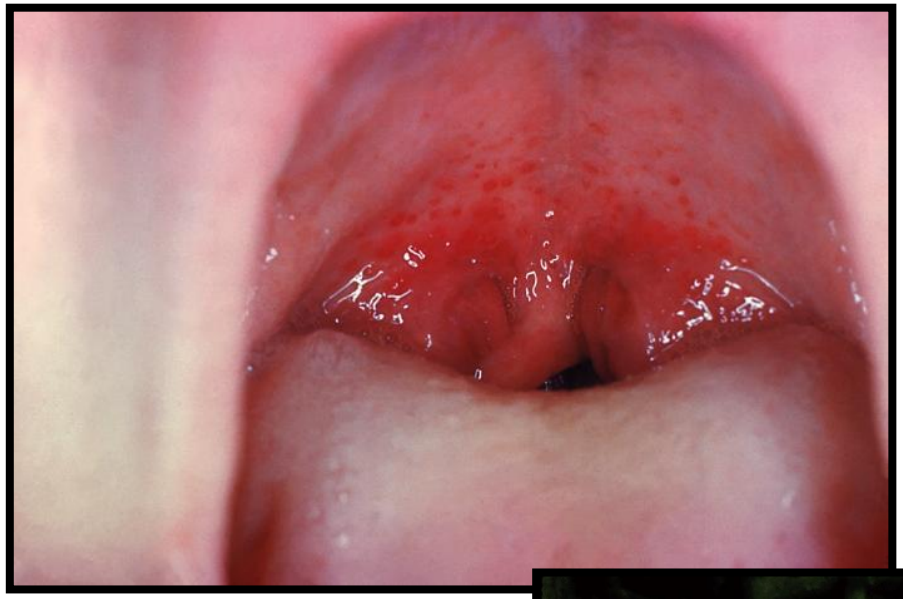
Arthritis



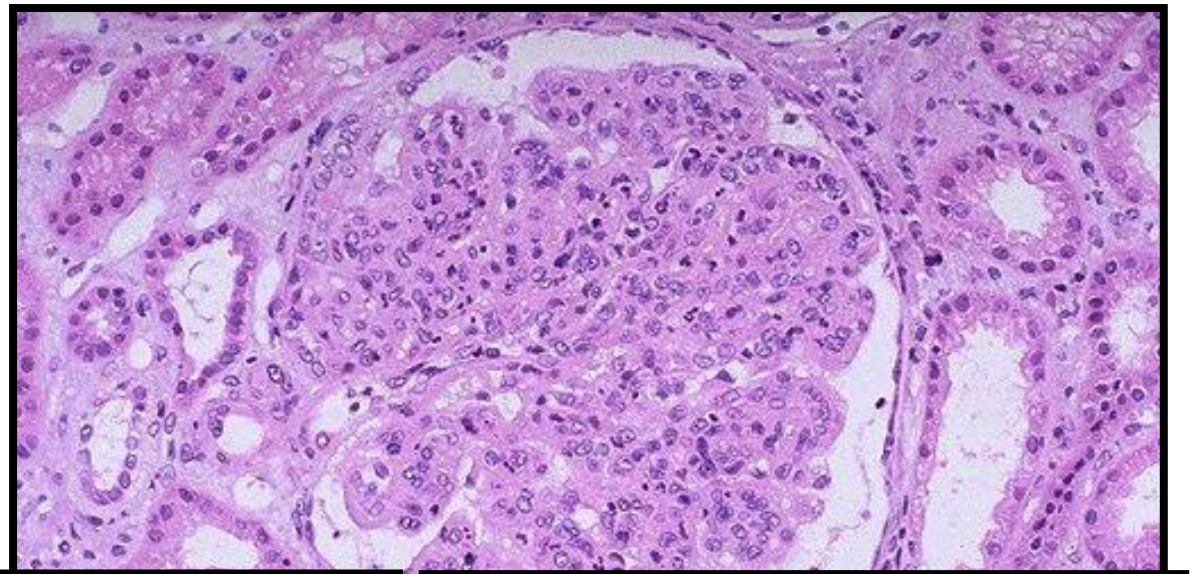
Colitis

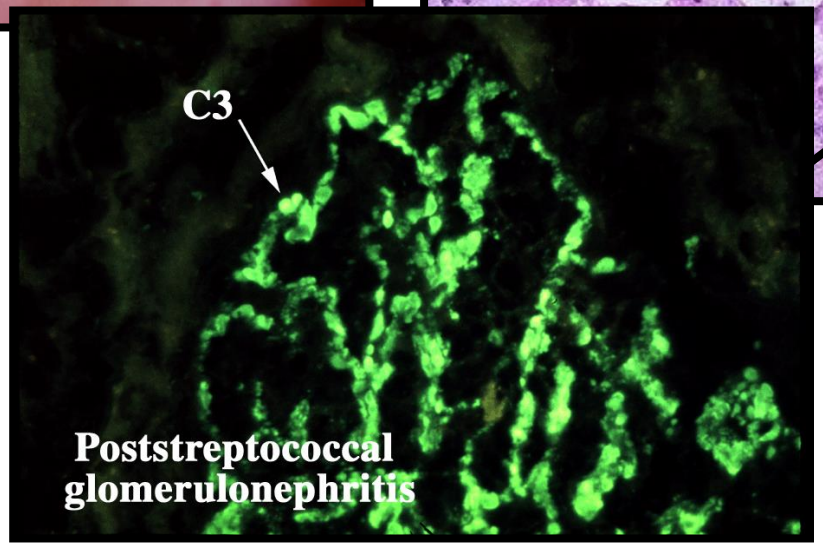


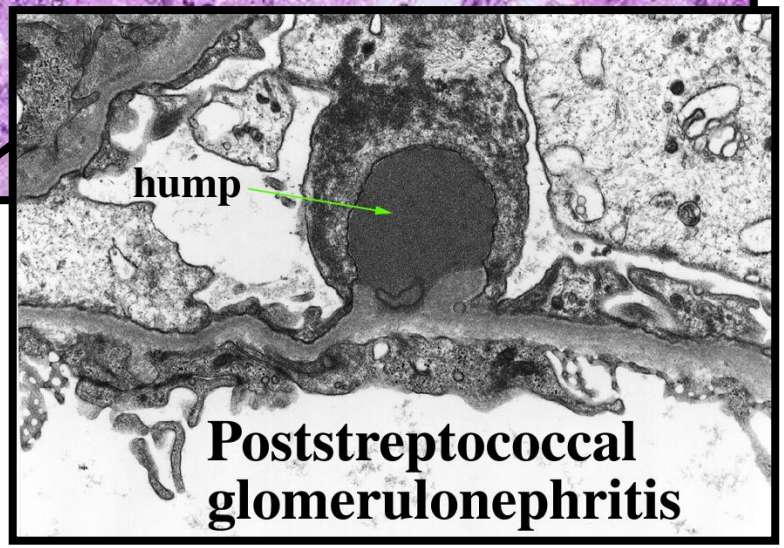
Poststreptococcal glomerulonephritis



Pharyngotonsillitis







IgA nephropathy versus poststreptococcal glomerulonephritis

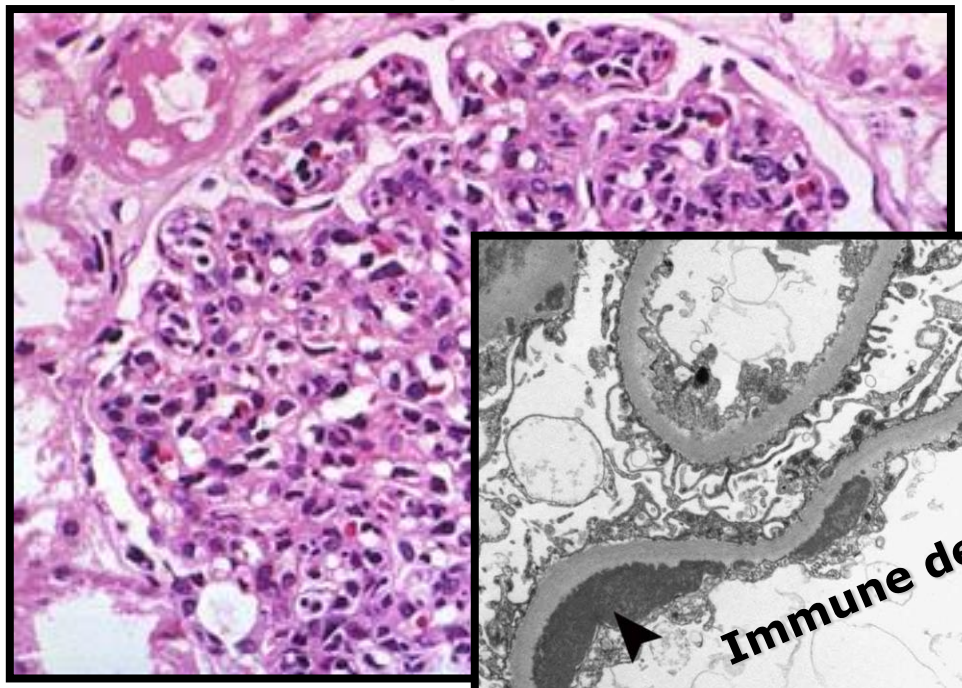
- In IgA nephropathy, an episode of gross hematuria usually occurs 1-3 days after onset of upper respiratory infection
- PSGN occurs 1-3 weeks following the initial clinical manifestations of pharyngitis or impetigo
- Throat culture and tests for anti-streptococcal antibodies should be positive in PSGN
- Decreased levels of CH50 og C3 (>90%) in PSGN
- PSGN gradually resolves, while IgA nephropathy is generally a chronic disease
- Recurrent episopes of gross hematuria common in IgA nephropathy

Lupus nephritis

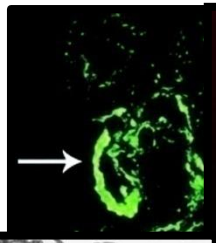
- ANA
- Anti-dsDNA
- Anti-Smith
- Low CH50, C3, C4

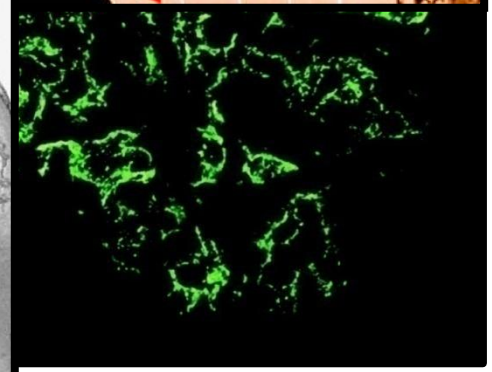
Diffuse proliferative glomerulonephritis (Class IV)

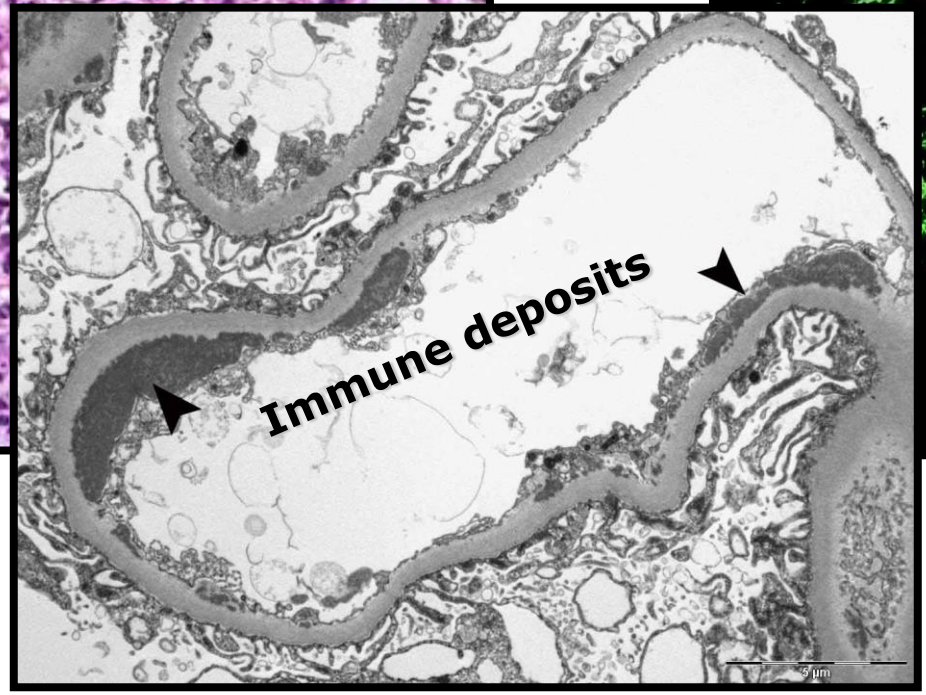
Cellular proliferation



IgG

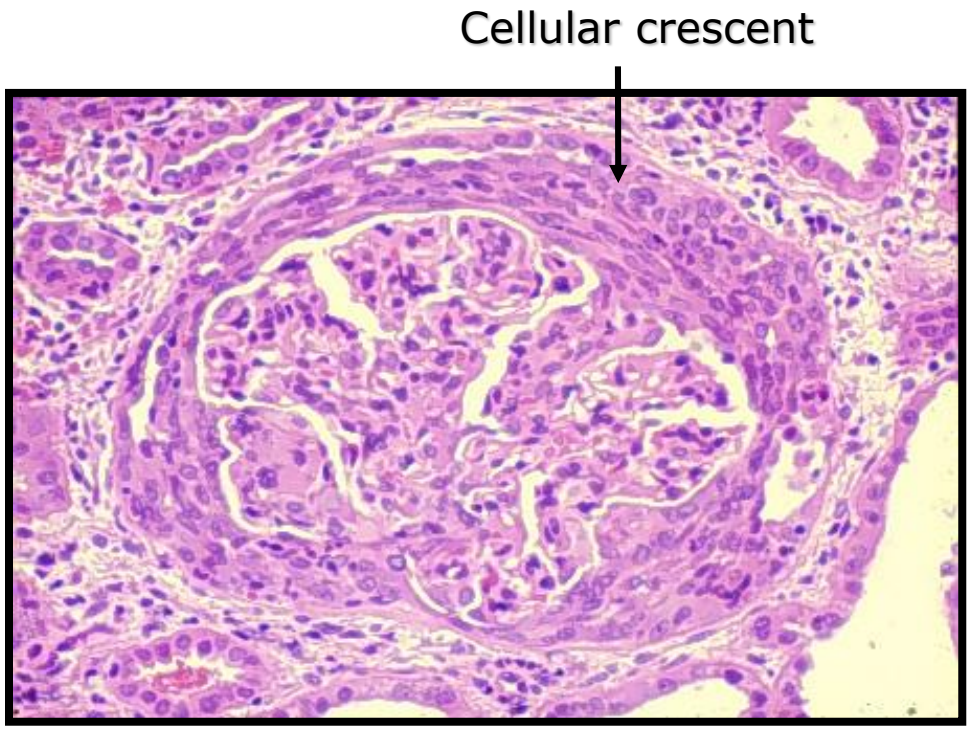




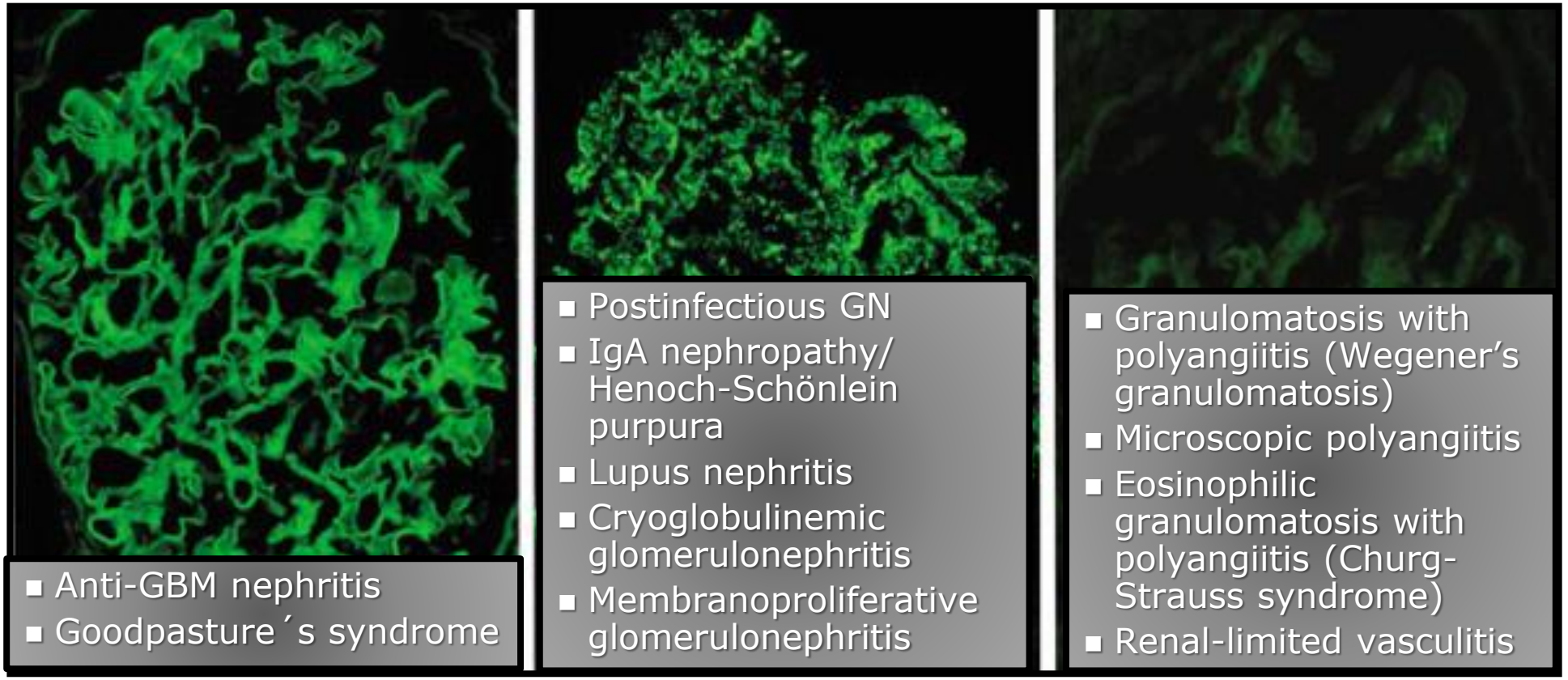


Rapidly progressive glomerulonephritis

- Clinical syndrome
- Rapid deterioration of kidney function, over days, weeks or months
- Urine microscopy shows signs of glomerulonephritis
- Kidney biopsy usually reveals diffuse crescents (>50% of glomeruli)



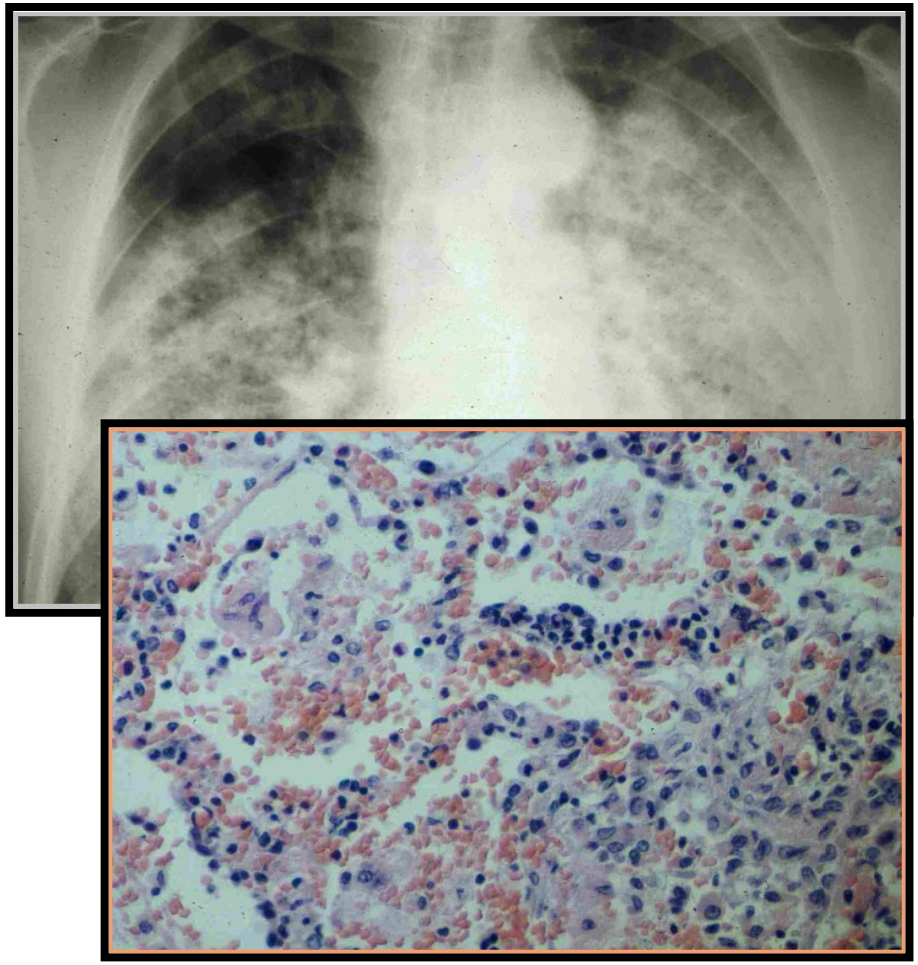
Patterns of immunostaining in crescentic glomerulonephritis



Jennette JC & Nickeleit V, Hepinstall's Pathology of the Kidney, 6th Ed., 2007

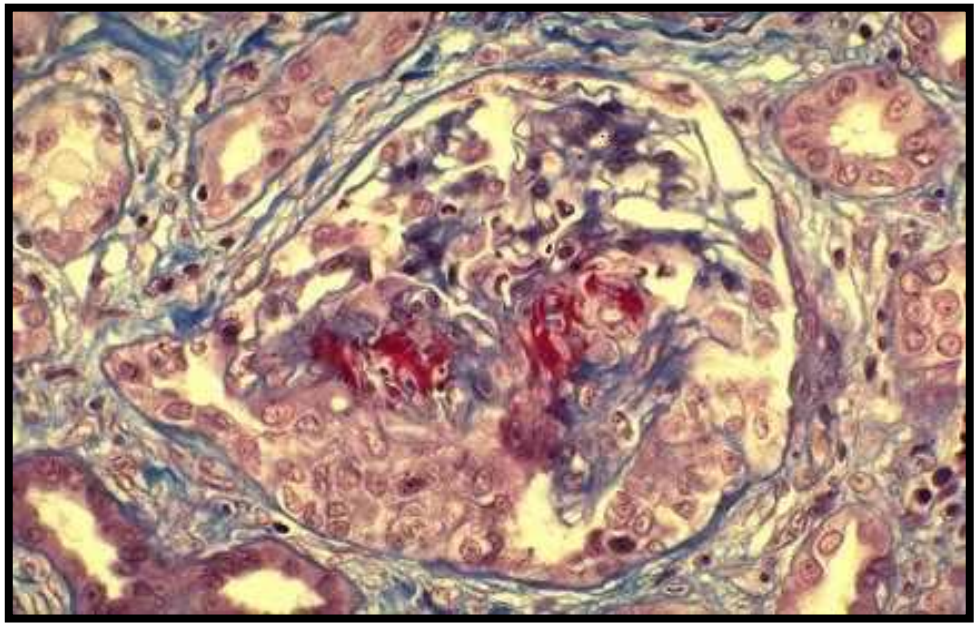
Pulmonary-renal syndrome

Diffuse pulmonary opacities



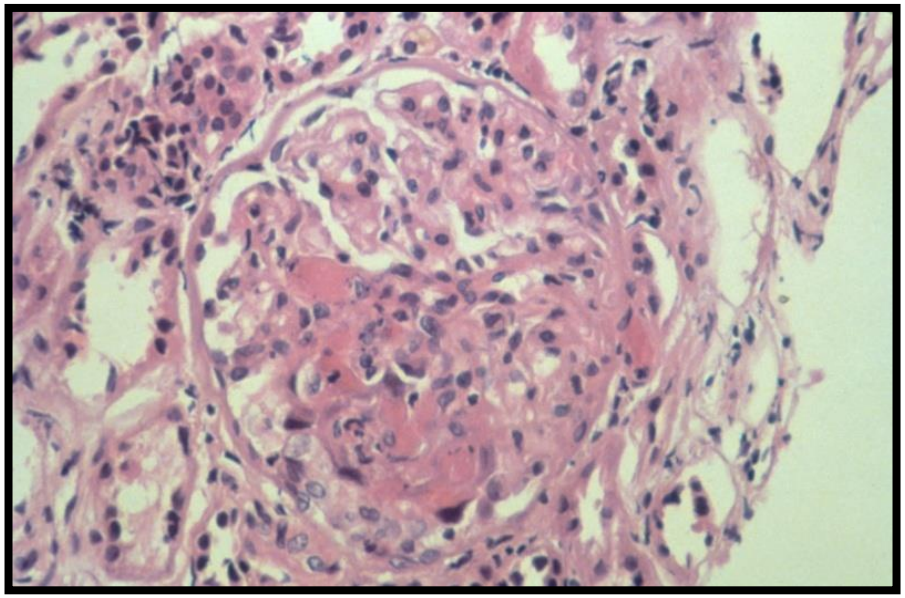
Alveolar capillaritis and hemorrhage

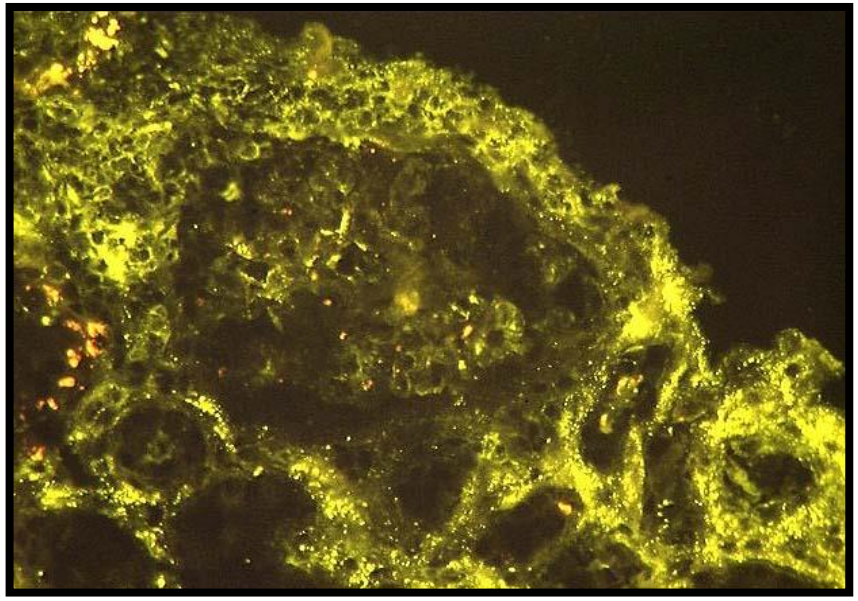
Necrotizing and crescentic glomerulonephritis



~60% ANCA-associated vasculitis
~20% Goodpasture´s syndrome

Pauci-immune necrotizing and crescentic GN

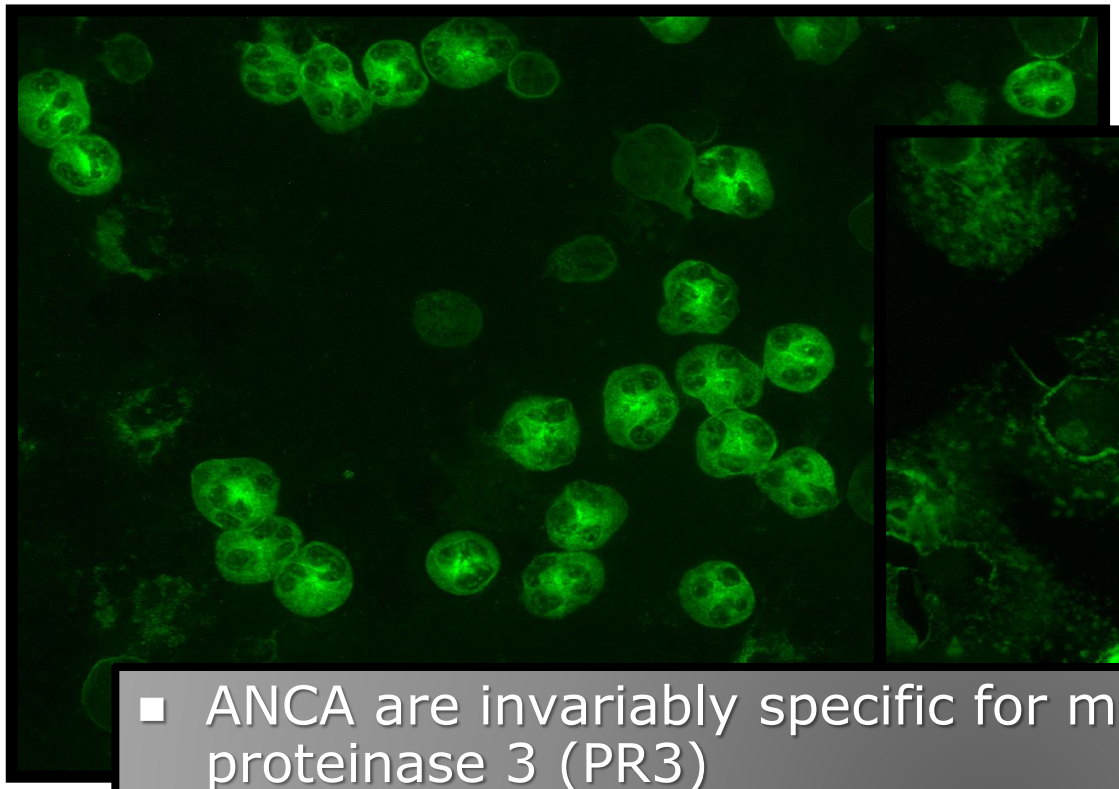




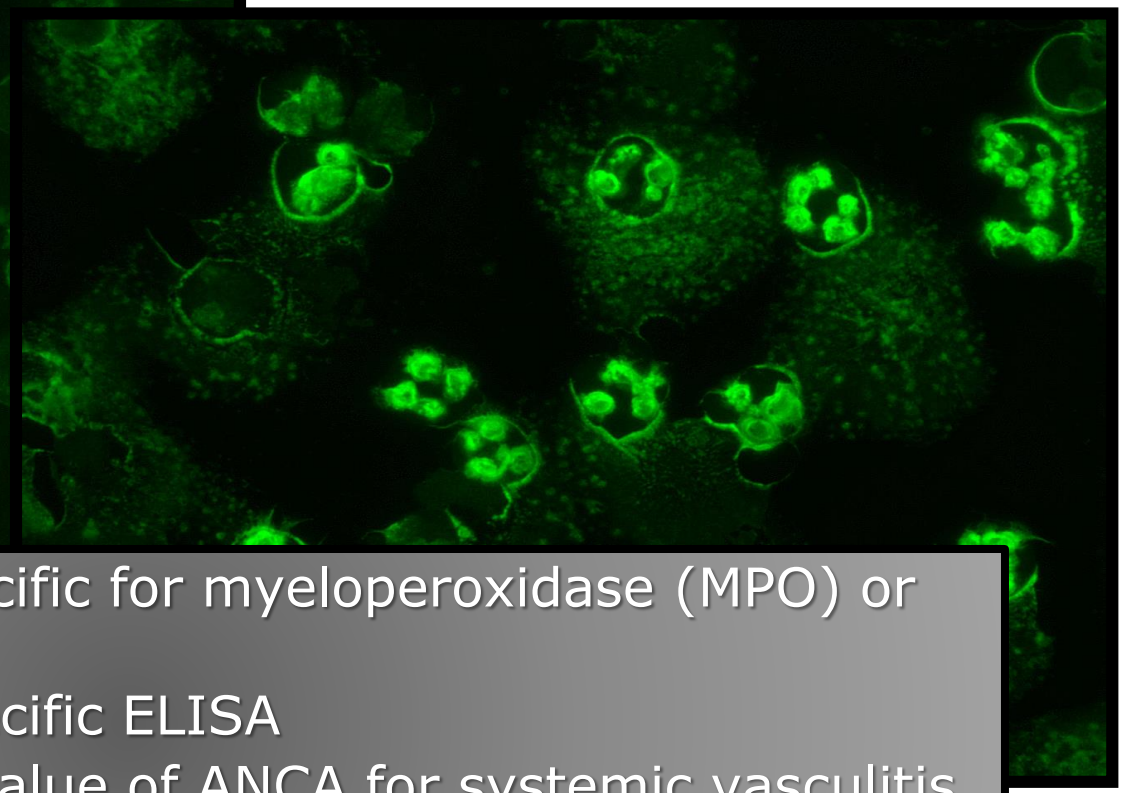
- Close to 90% are ANCA positive
- ANCA is a highly specific marker of systemic small-vessel vasculitides associated with pauci-immune necrotizing and crescentic GN
- ANCA-negative cases share the same features

Anti-neutrophil cytoplasmic antibodies (ANCA)

C-ANCA

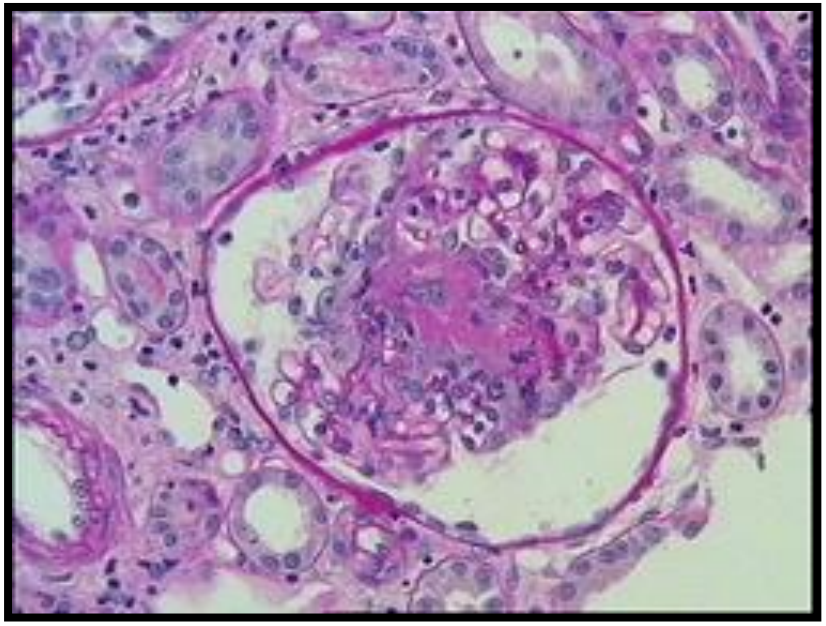


P-ANCA

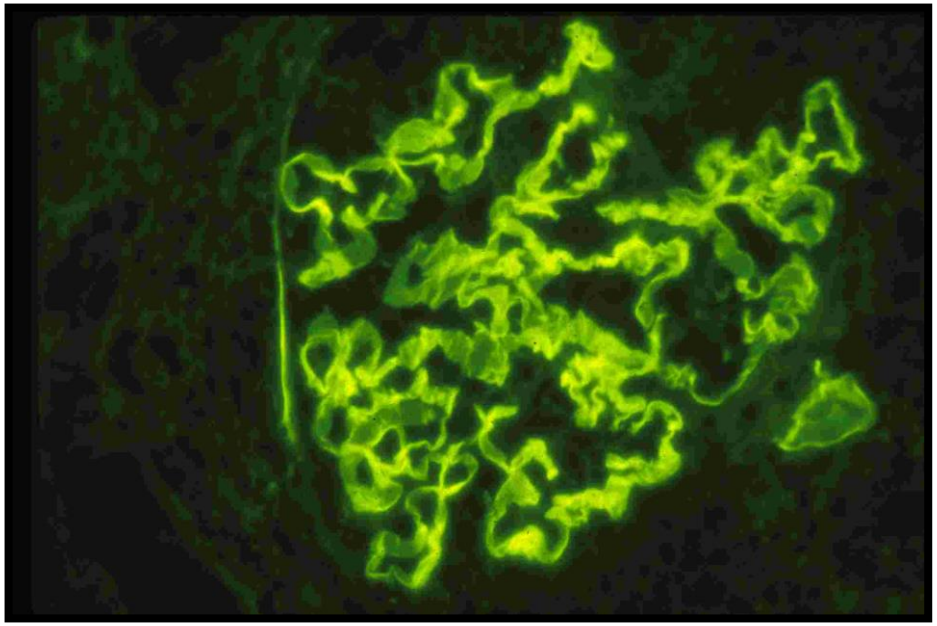


- ANCA are invariably specific for myeloperoxidase (MPO) or proteinase 3 (PR3)
- Detected by antigen-specific ELISA
- The positive predictive value of ANCA for systemic vasculitis is 98% in the setting of RPGN or pulmonary hemorrhage

Anti-GBM glomerulonephritis



Necrotizing and crescentic glomerulonephritis



Linear IgG deposits along the GBM

- Anti-GBM antibodies detected in the serum of nearly all patients
- Directly pathogenic
- Anti-GBM nephritis (60%)
- Goodpasture´s syndrome (40%)

Urgent and accurate diagnosis is key to successful outcome of RPGN

Early diagnosis is dependent on:

- Recognition of clinical features
- Appropriate use of serologic testing
  - ANCA, anti-GBM and C3 and C4
- Kidney biopsy
  - Confirm the diagnosis
  - Assess disease activity and chronic (irreversible) damage
  - Evaluate likelihood of response to therapy

Take home messages

- The nephrotic and nephritic syndromes are distinct clinical patterns of glomerular disease
- Serologic testing can provide important clues
- Kidney biopsy is necessary in most cases
- The diagnosis is based on integration of clinical and histological features
- In RPGN, urgent diagnosis is essential and is facilitated by serologic testing

Thank you!

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