How to approach Hematuria

How to approach Proteinuria

Glomerulonephritis Overview

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اول ثلاث صفحات هي كتابة لنوتس الدكتور في ملف وورد
منفصل وباقي الصفحات هي السلايدز العادية

Notes by Jumana Alghtani

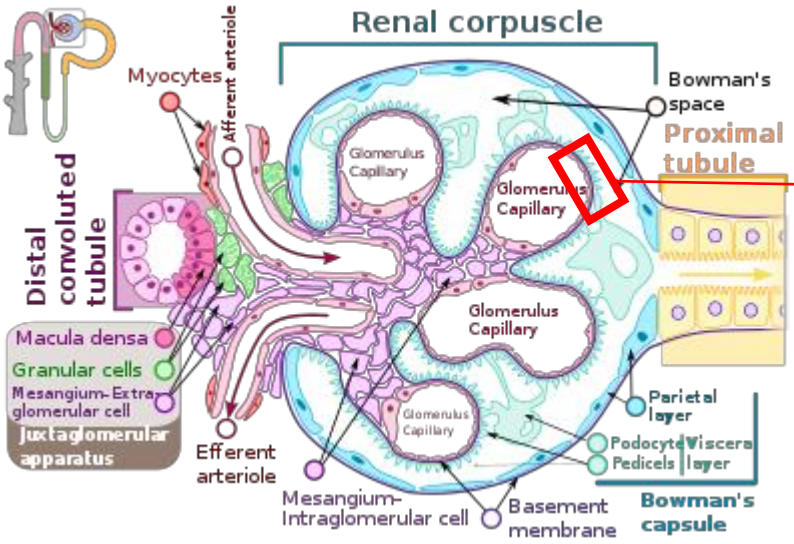
Dr. Alkhowaiter notes

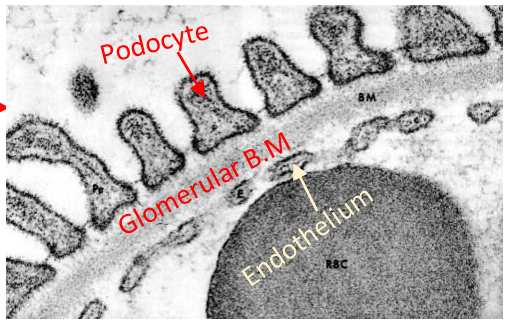
Glomerulonephritis overview:

Objectives:

- To know the basics about the structure and functions of the glomerulus.
- To have an idea how diseases are named in GN.
- To know some of the secondary causes of GN and realize its impact on the clinical management.
- To know the initial screening workup for glomerulonephritis.
- To know the different causes of haematuria and make your approach accordingly.

INTRODUCTION:





- Size, charge, shape and molecular weight effect the passage of molecules in/out of the membrane.
- Slit diaphragm are the spaces between the podocytes , any gene mutations in its structure will cause inborn nephrotic syndrome.
- Mesangial cells maintain the structure and function of the glomerulus.
- Typical feature of active GN include: High creatinine, Hypervolemia, Microscopic haematuria and proteinuria.

Classification of GN according to structure effected:

1. **Podocytes:** a diffuse effacement will lead to Nephrotic syndrome.
   - Causes of Nephrotic syndrome:
     - ✓ Minimal change disease
     - ✓ Focal segmental glomerulosclerosis (FSGS)
     - ✓ Membranous nephropathy
   - Signs: edema, low serum albumin, increased sodium retention, Sx of DVT and PE.
   - Urine-analysis will show: heavy proteinuria more than 3.5g in 24h, Hypoalbuminemia less than 30 g/L, Lipiduria, Hyperlipidaemia.

2. GBM:

Non-immune related	Immune related
1- Alport syndrome: characterized by kidney **disease**, hearing loss, and eye abnormalities. People with Alport syndrome experience progressive loss of kidney function. Almost all affected individuals have blood in their urine (hematuria), which indicates abnormal functioning of the kidneys. Many people with Alport syndrome also develop high levels of protein in their urine (proteinuria), high BP and edema. The kidneys become less able to function as this condition progresses, resulting in end-stage renal disease (ESRD), caused by mutation in type 4 collagen+ Alpha chain. 2- Familial haematuria (thin B.M): Renal function is typically normal, but a few patients develop progressive renal failure for unknown reasons. Recurrent flank pain	1- Anti-GBM disease: Due to autoantibody against (alpha-3 chain) of type IV Collagen that is found in GBM, if there is lung involvement (lung haemorrhage) its called Good Pasture's syndrome 2- Immune complex diseases: cause sub-endothelial deposit. ✓ membranoproliferative GN ✓ Lupus nephritis class 3 and 4 ✓ Post infectious GN ✓ IgA nephropathy

3. Endothelium:

A) ANCA vasculitis: (another name is Pauci immune vasculitis = No I.F finding)
- ✓ Granulomatosis with polyangiitis (Wegner)
- ✓ Microscopic polyangiitis
- ✓ Eosinophilic granulomatosis with polyangiitis

B) thrombotic microangiopathy: TTP , Haemolytic uremic syndrome (a pathology that results in **thrombosis** in capillaries and arterioles, due to an endothelial injury. It may be seen in association with thrombocytopenia, anaemia, purpura and kidney failure)

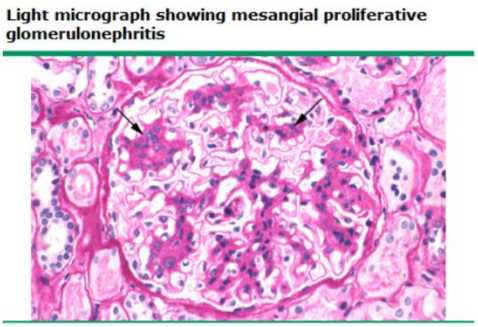
Other Classification of GN diseases:

Proliferative	Non-proliferative (Podocyte diseases)
○ Immune complex diseases ○ Anti-GBM ○ ANCA vasculitis	○ Minimal change disease ○ Focal segmental glomerulosclerosis (FSGS) ○ Membranous nephropathy

To differentiate between 1ry and 2ry causes we order:

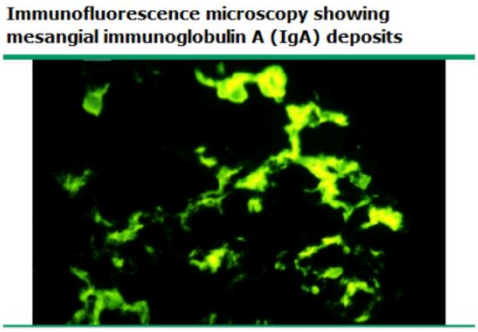
hepatitis B+C , ASO titer, IgA level , complements: C3 and C4 (diseases that give us low complement levels are Lupus, post infectious GN), ANA , Anti-DNA … etc. (from the table in the slides)

Note:



Light micrograph of a mesangial glomerulonephritis showing segmental areas of increased mesangial matrix and cellularity (arrows). This finding alone can be seen in many diseases, including IgA nephropathy and lupus nephritis.
Courtesy of Helmut G Rennke, MD.

This is not a diagnosis
we have to order I.F



Immunofluorescence microscopy demonstrating large, globular mesangial IgA deposits that are diagnostic of IgA nephropathy or Henoch-Schönlein purpura (IgA vasculitis). Note that the capillary walls are not outlined since the deposits are primarily limited to the mesangium.

Cases:

70 y/o gentleman came to the ER complaining of fatiguability, weight loss, chronic sinusitis, Creatinine = 400 , high BP, biopsy showed a lot of crescents. What are DDx:

- A lot of crescents is a typical presentation of ANCA vasculitis (Granulomatosis with polyangiitis, Anti-GBM (not likely due to age group)
- We do Immunofluorescence (I.F) in case of ANCA vasculitis it will be negative.
- Diagnosis is: Granulomatosis with polyangiitis (Wegner) we must ask about Drug Hx, Respiratory symptoms, hearing problems.

22 y/o lay was referred to you for microscopic haematuria, what you must ask about?

- Ask about joint pain, oral ulcers we think of Lupus
- Family Hx (normal BP and urinalysis shows only blood in the urine = isolated haematuria) we think of Thin B.M
- Make sure she is not menstruating

22 y/o gentleman smoker coming with haemoptysis and high creatinine

- due to his age and presentation we think of Good Pasture Syndrome (GN+ Lung haemorrhage)

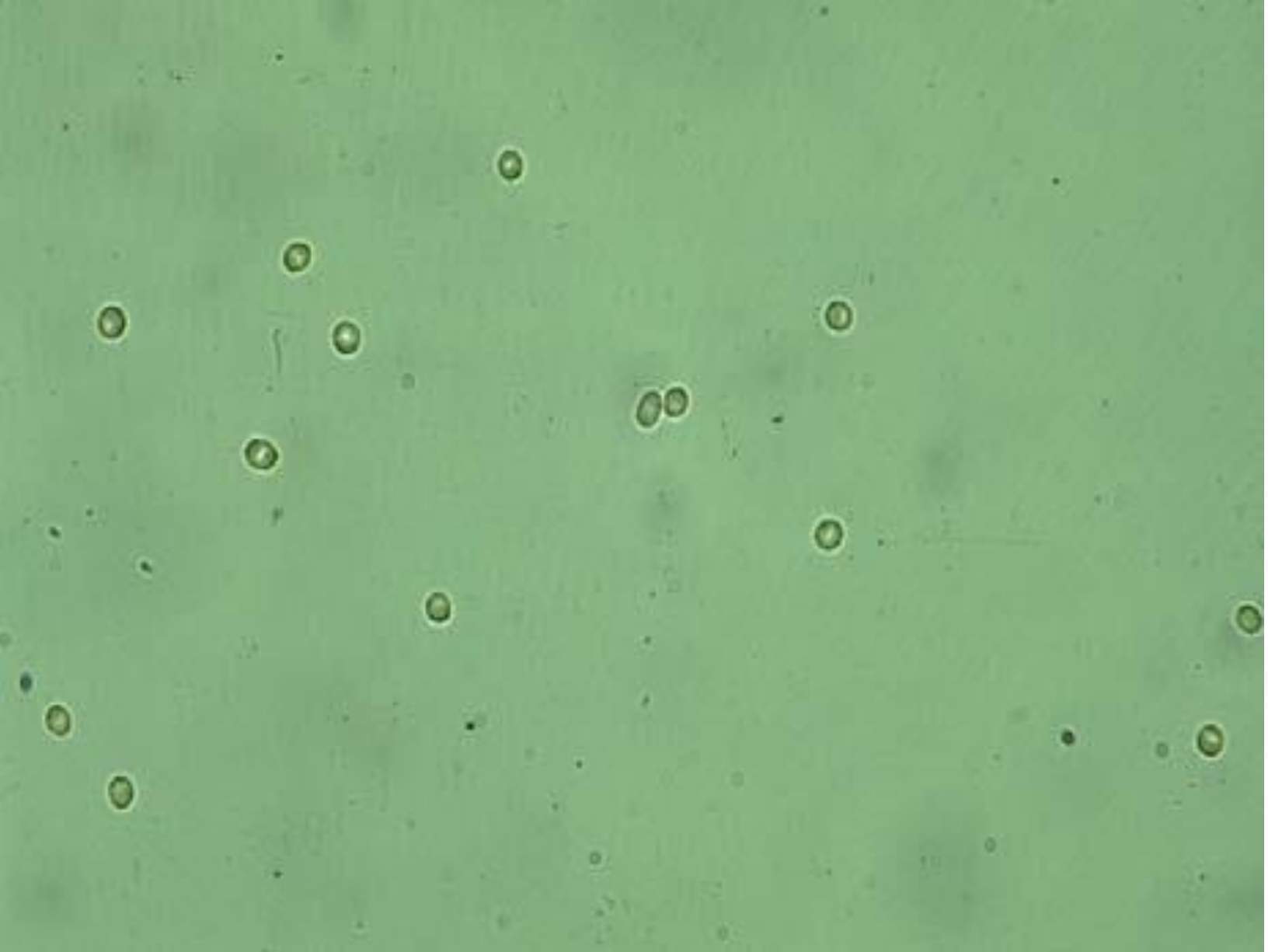
55 y/o man, heavy smoker for the last 20 years referred for 2+ blood and RBCs in the urine, no casts, 1+ protein 400 mg/day. Is this GN? Should we do kidney biopsy for him?

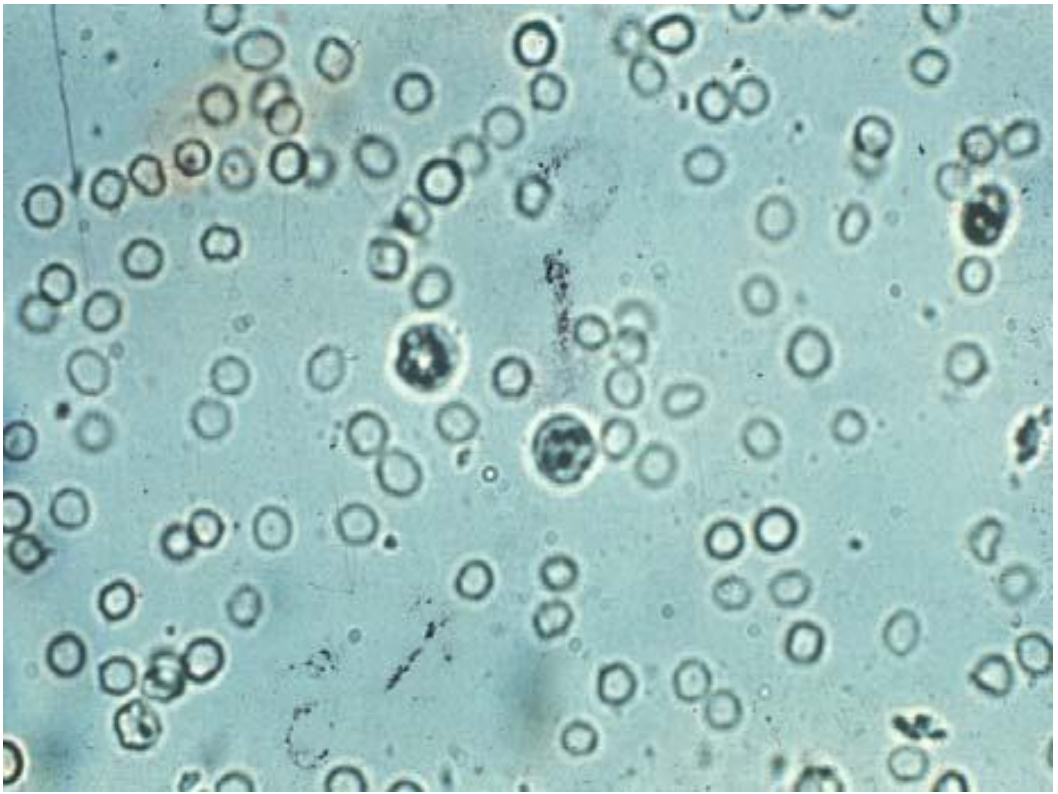
- For this age group and his presentation, we think of malignancy, before we do kidney biopsy for him we have to rule out bladder and prostatic cancer with Cystoscopy

- **Definition of Hematuria**:

Presence of at least 3 RBCs per high power field (HPF) in a spun urine

HPF: 400x magnification level





Microscopic Hematuria: Non-visible, detected by microscopy.

Macroscopic Hematuria = Gross hematuria

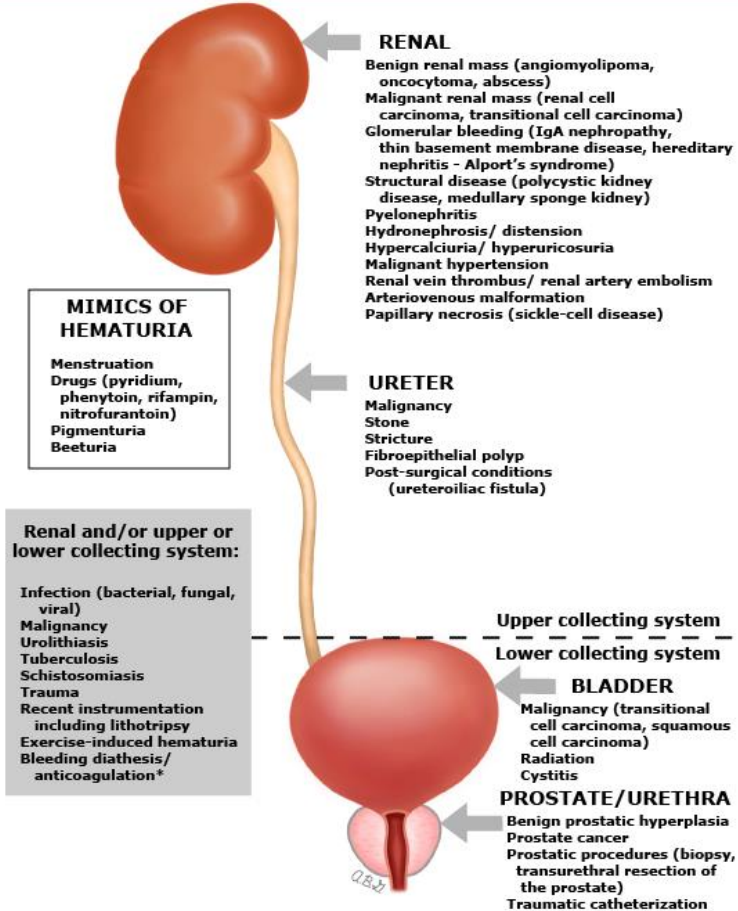
Not every dark urine means Hematuria:

Conditions where the urine becomes dark and positive for heme on dipstick but negative for RBCs on microscopy (+ve dipstick but no hematuria):

- Intravascular hemolysis (Hemoglobin)
- Rhabdomyolysis (Myoglobin).

Negative dipstick exclude hematuria.

Causes of hematuria



* Hematuria may not be attributed solely to alterations in coagulation or platelet function until competing causes have been ruled out.

Courtesy of Michael Kurtz, MD.

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Main causes of Hematuria:

- Glomerular

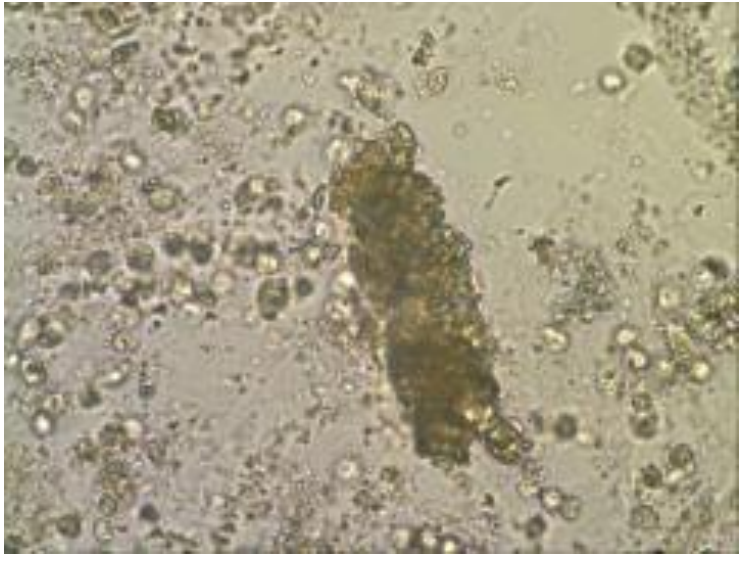
Non- Glomerular:

- Stones
- Tumors
- Infections
- Trauma

- In **Interstitial nephritis**: Urinalysis typically show WBCs, RBCs and WBC casts.

- **Acute tubular necrosis**: Characterized by Heme granular cast (muddy brown cast) on urinalysis.

  Typically there are **no** RBCs however presence of some won't exclude the possibility of ATN.



Gross Hematuria:

Distinguishing extraglomerular from glomerular hematuria

	Extraglomerular	Glomerular
Color (if macroscopic)	Red or pink	Red, smoky brown, or "Coca-Cola"
Clots	May be present	Absent
Proteinuria	<500 mg/day	May be >500 mg/day
RBC morphology	Normal	Some RBCs are dysmorphic
RBC casts	Absent	May be present

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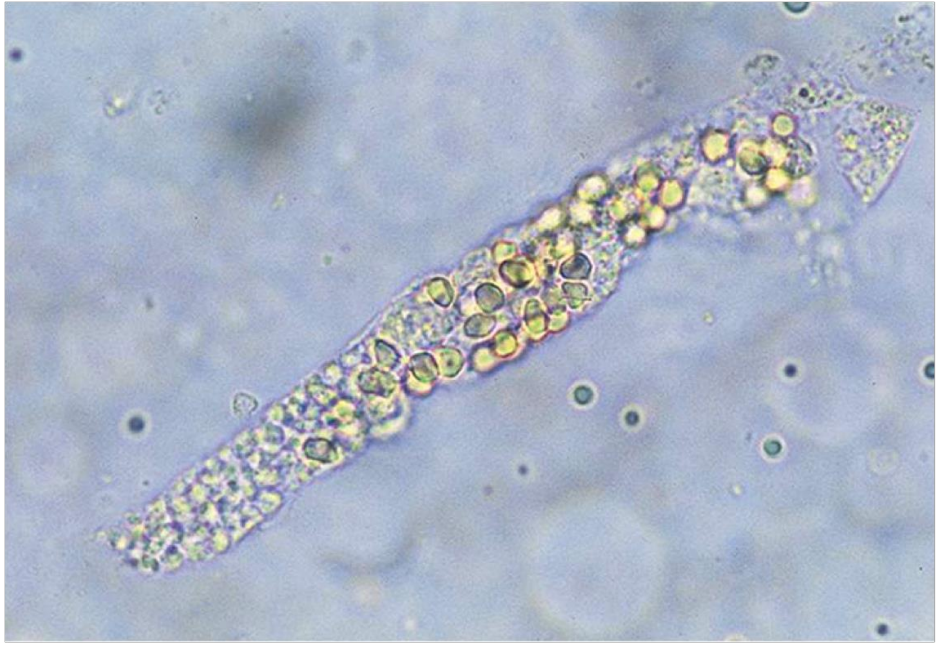
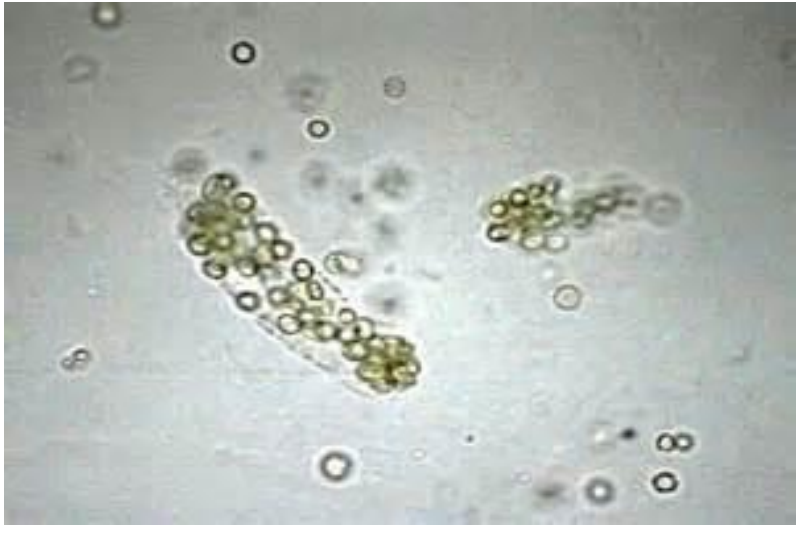
RBC Cast



RBC cast



- Commonest type of glomerulonephritis that can present with gross hematuria:

IgA nephropathy

Post infectious glomerulonephritis

Both can be triggered by URTI

Both can cause nephritis: AKI, HTN

The onset of hematuria in relation to the URTI is important:

In IgA: it is synpharyngitic (within 4days after URTI symptoms) while in post infectious is usually 1 week– 2weeks.

The definitive way of differentiation is renal biopsy.

- **Commonest Causes of Isolated glomerular microscopic hematuria (without proteinuria or renal impairment):**

IgA nephropathy

Thin basement membrane (benign familial hematuria)

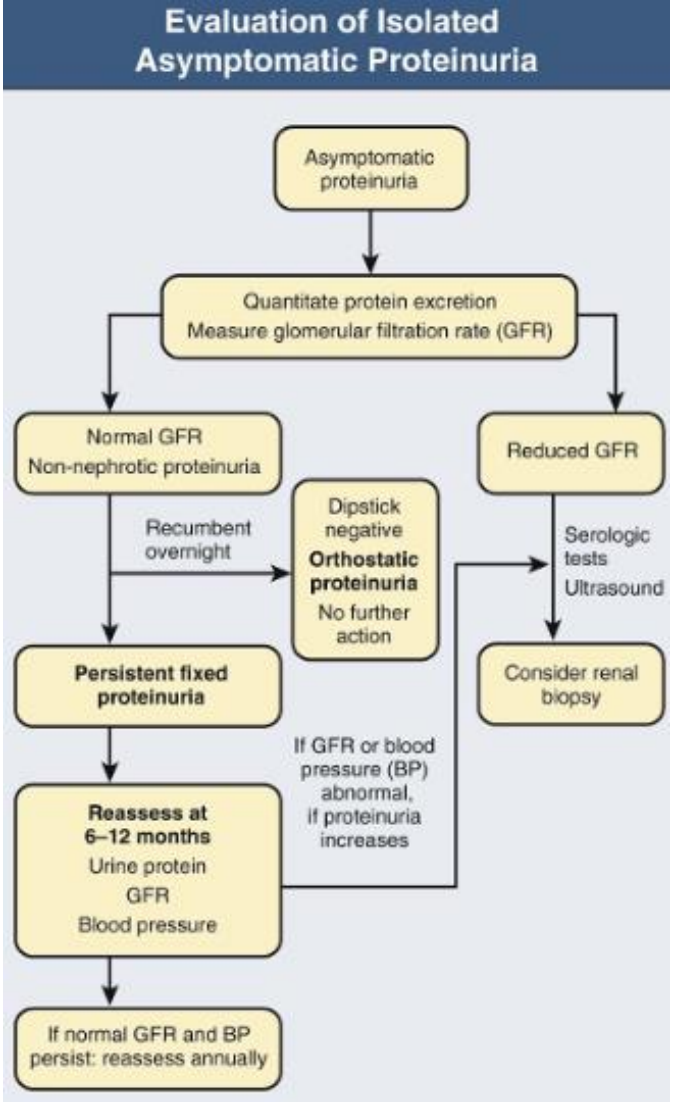
Alport's syndome

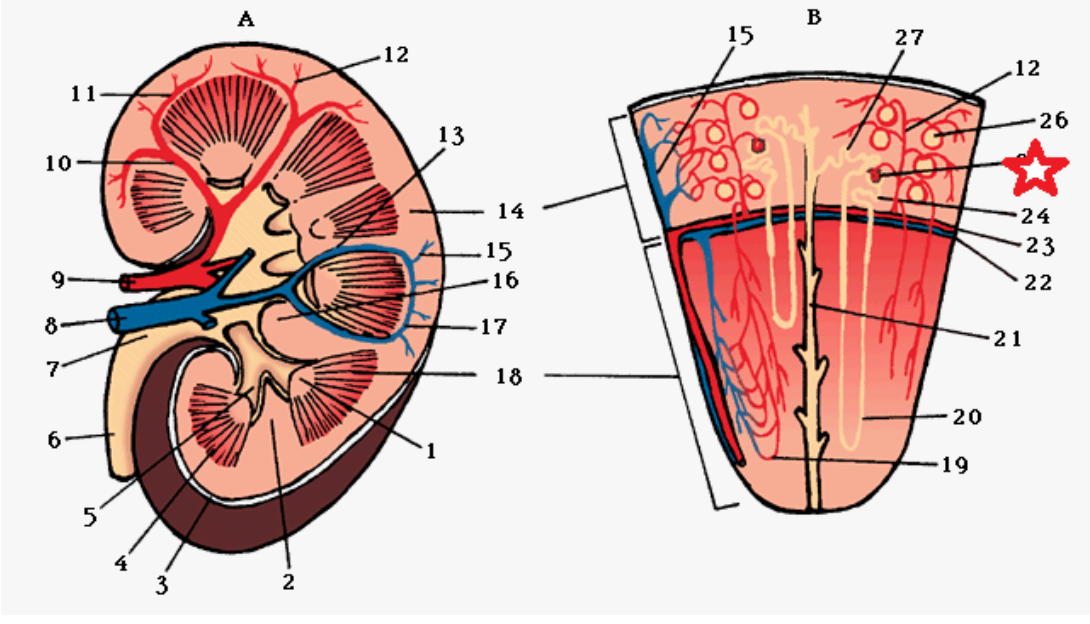
- **Indication for biopsy in microscopic hematuria:**

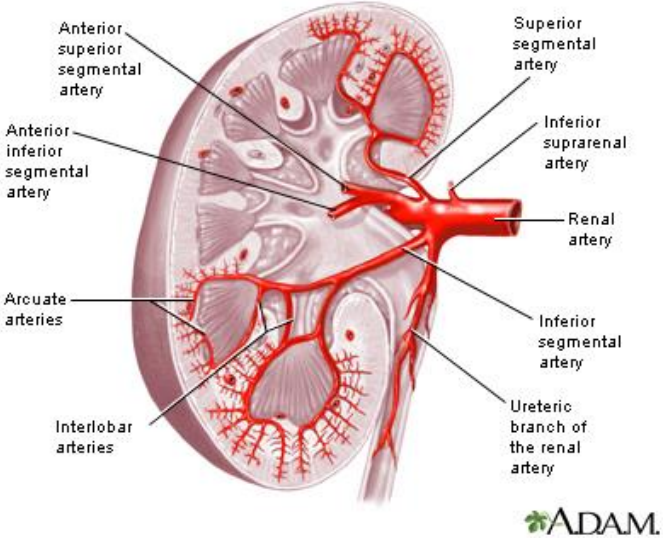
renal impairment or

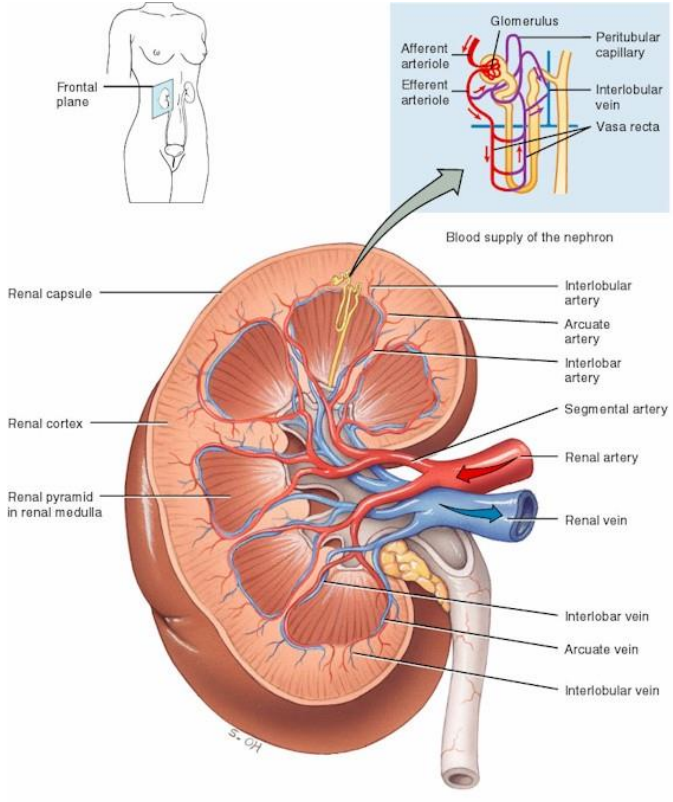
Presence of proteinuria > 1 g/day or

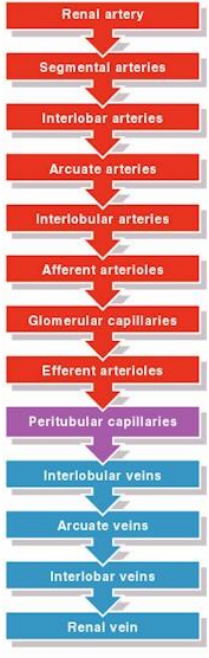
HTN











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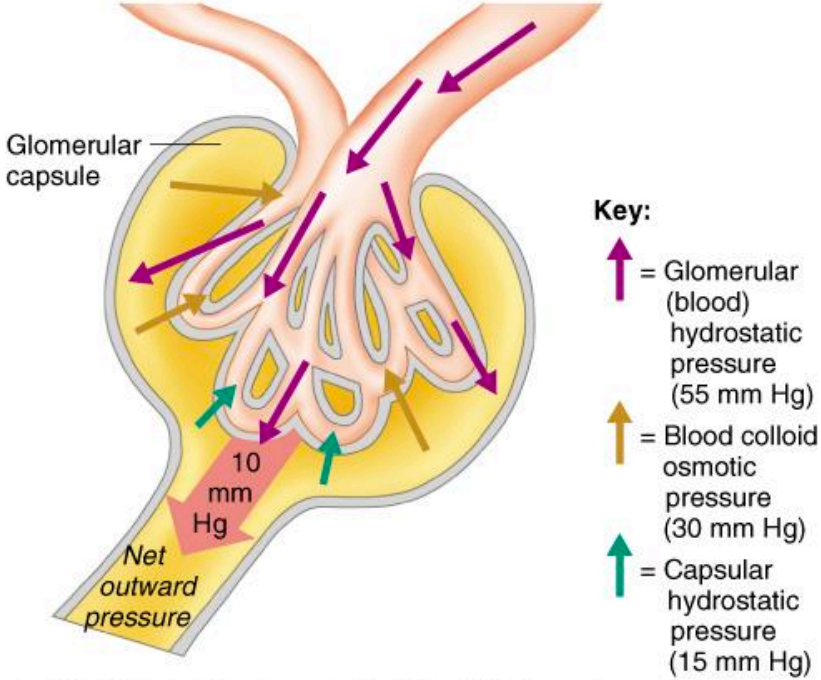
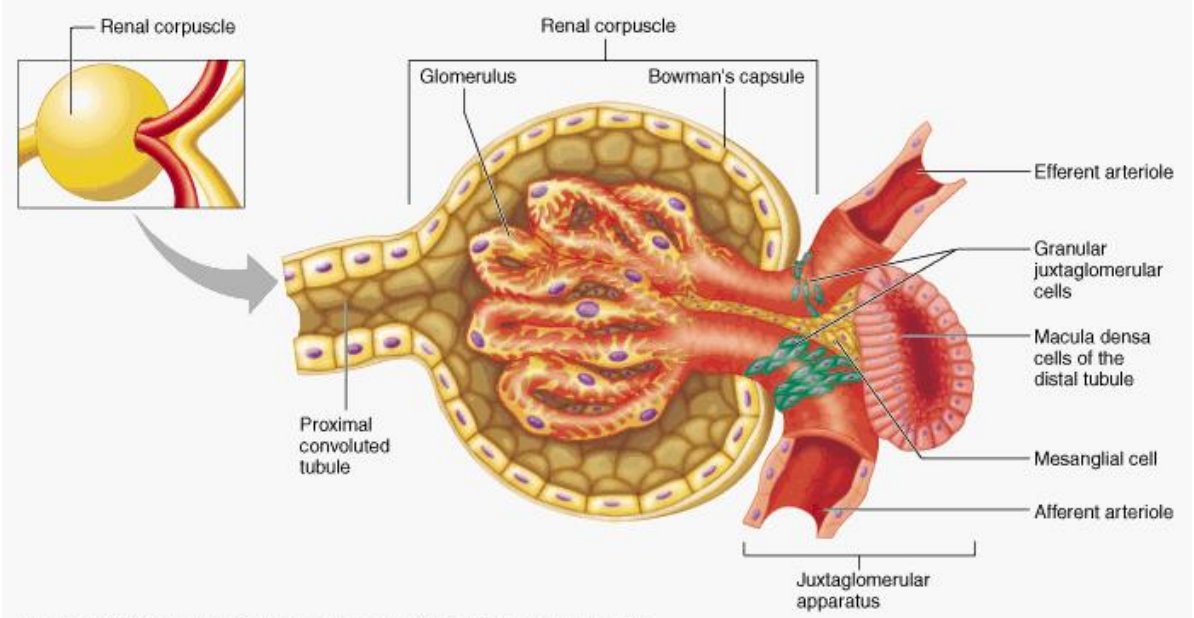
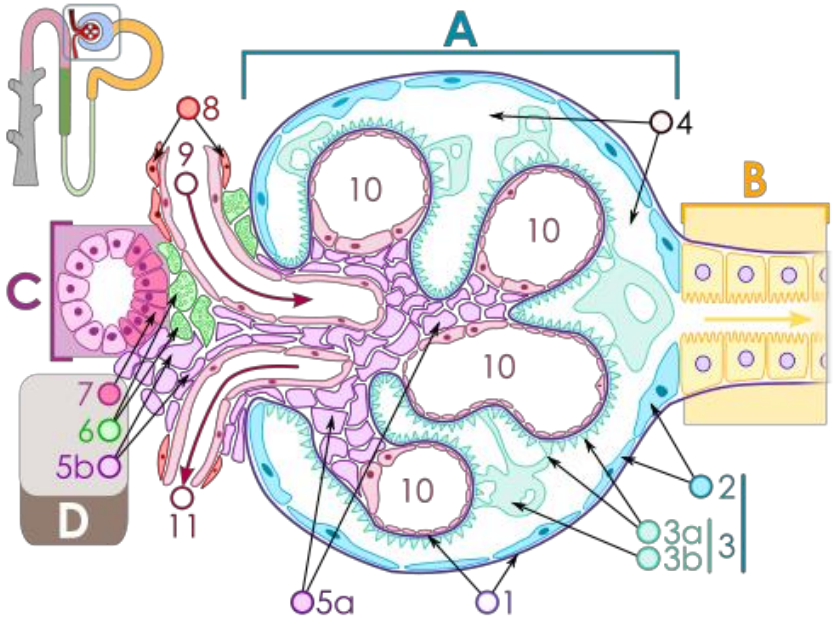
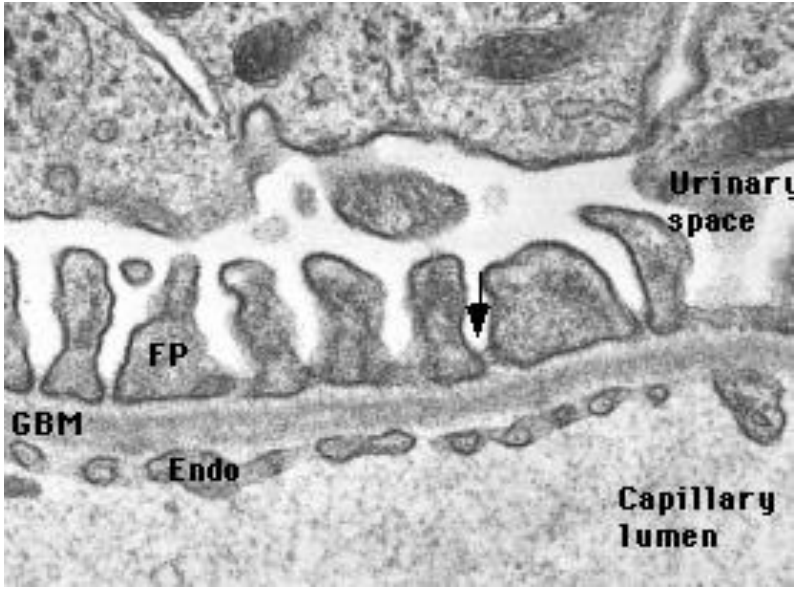
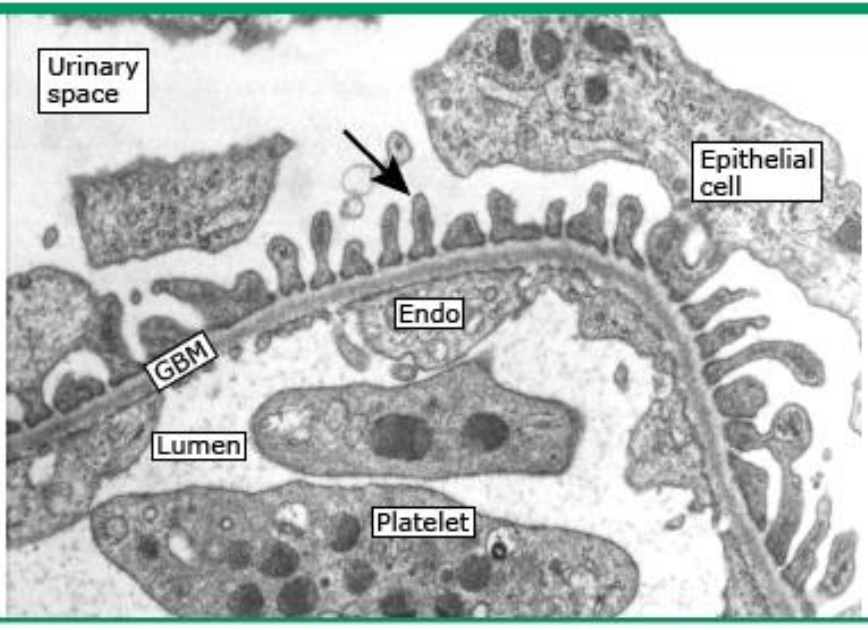








Electron micrograph of a normal glomerulus



Electron micrograph of a normal glomerular capillary loop showing the fenestrated endothelial cell (Endo), the glomerular basement membrane (GBM), and the epithelial cells with its interdigitating foot processes (arrow). The GBM is thin, and no electron-dense deposits are present. Two normal platelets are seen in the capillary lumen.

Courtesy of Helmut G Rennke, MD.

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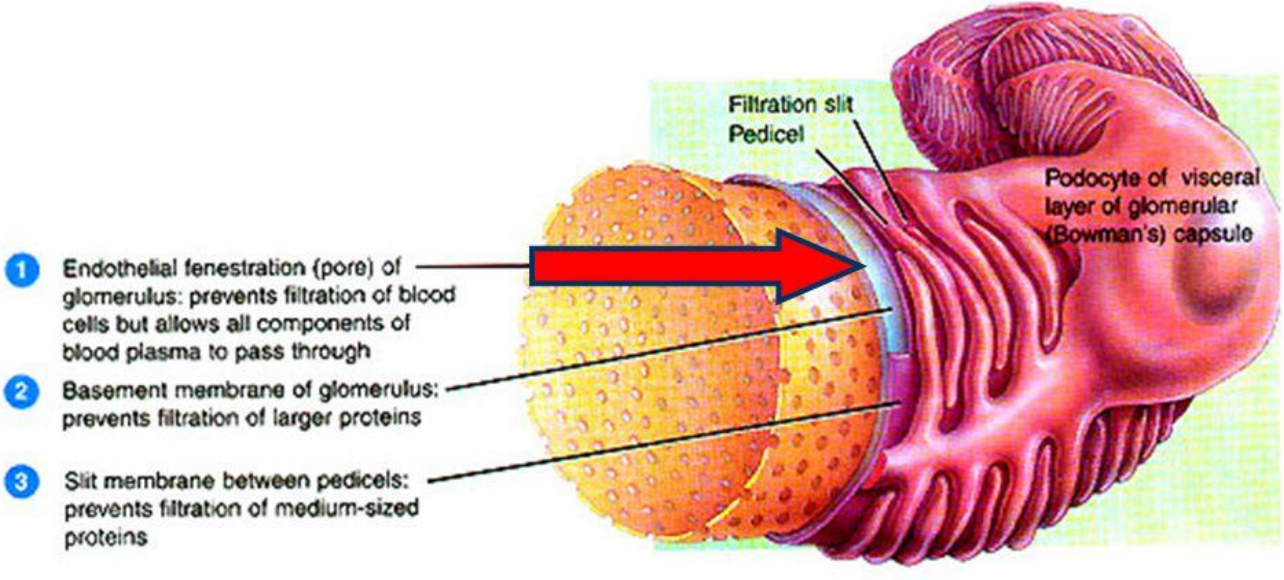
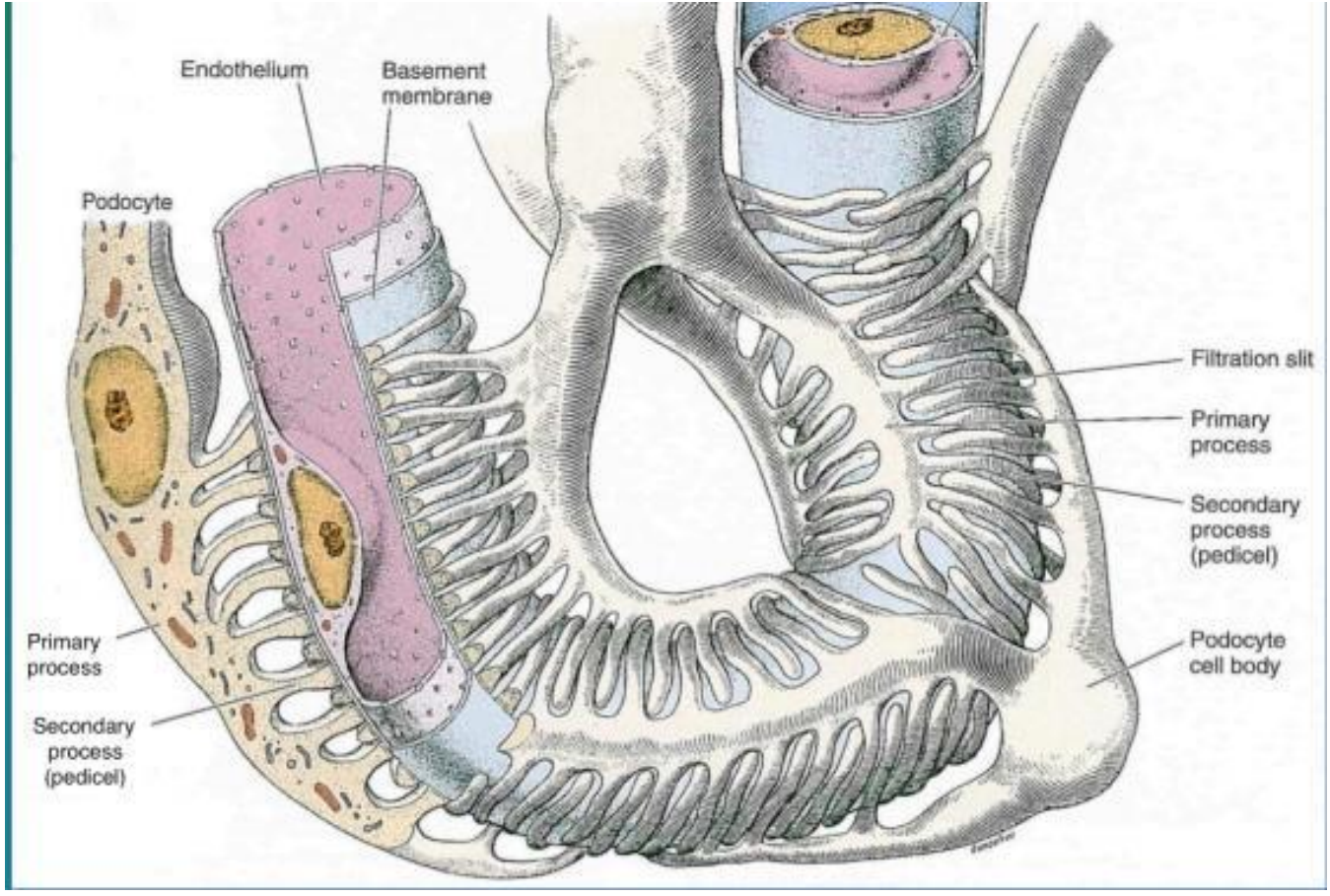
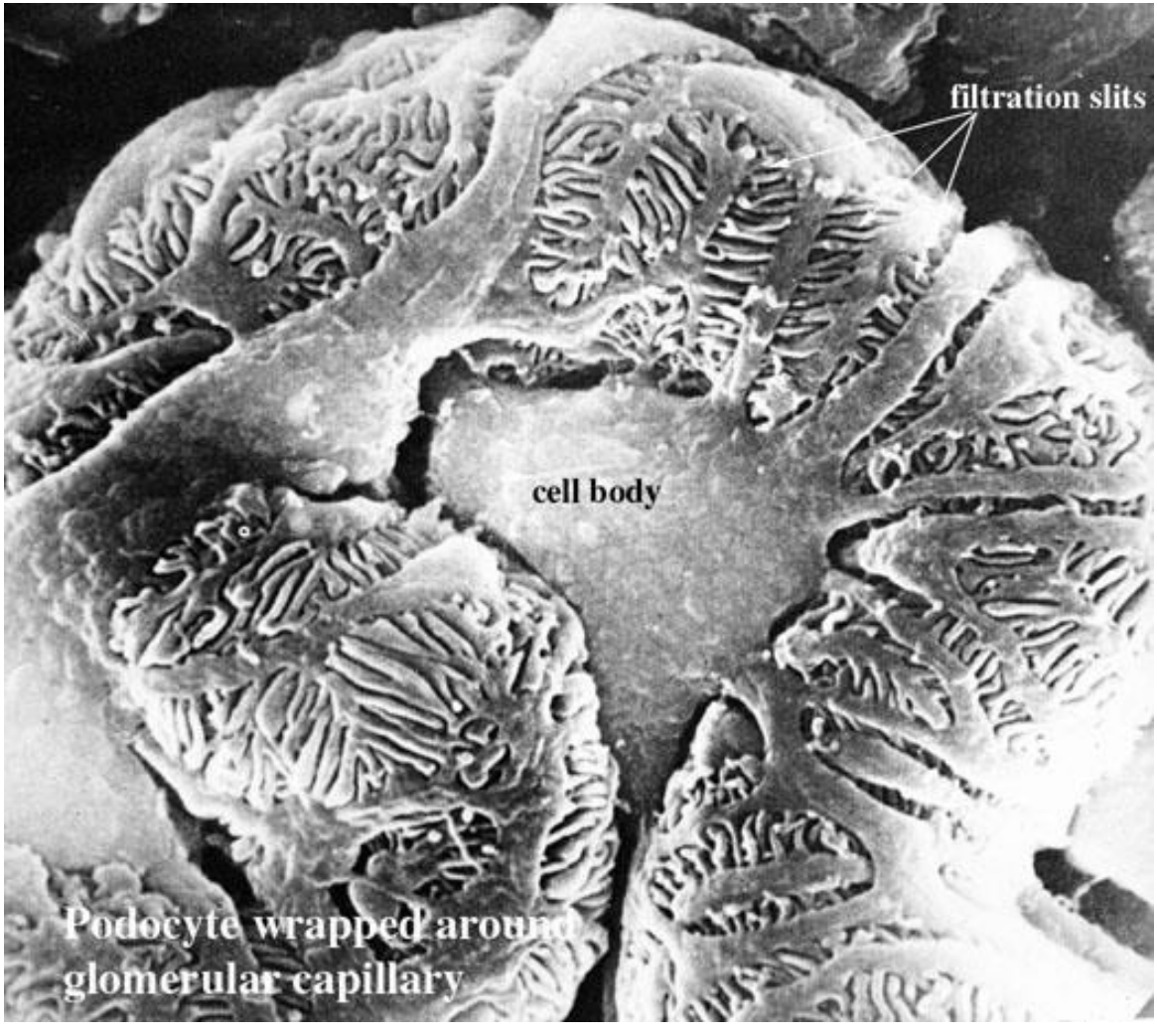
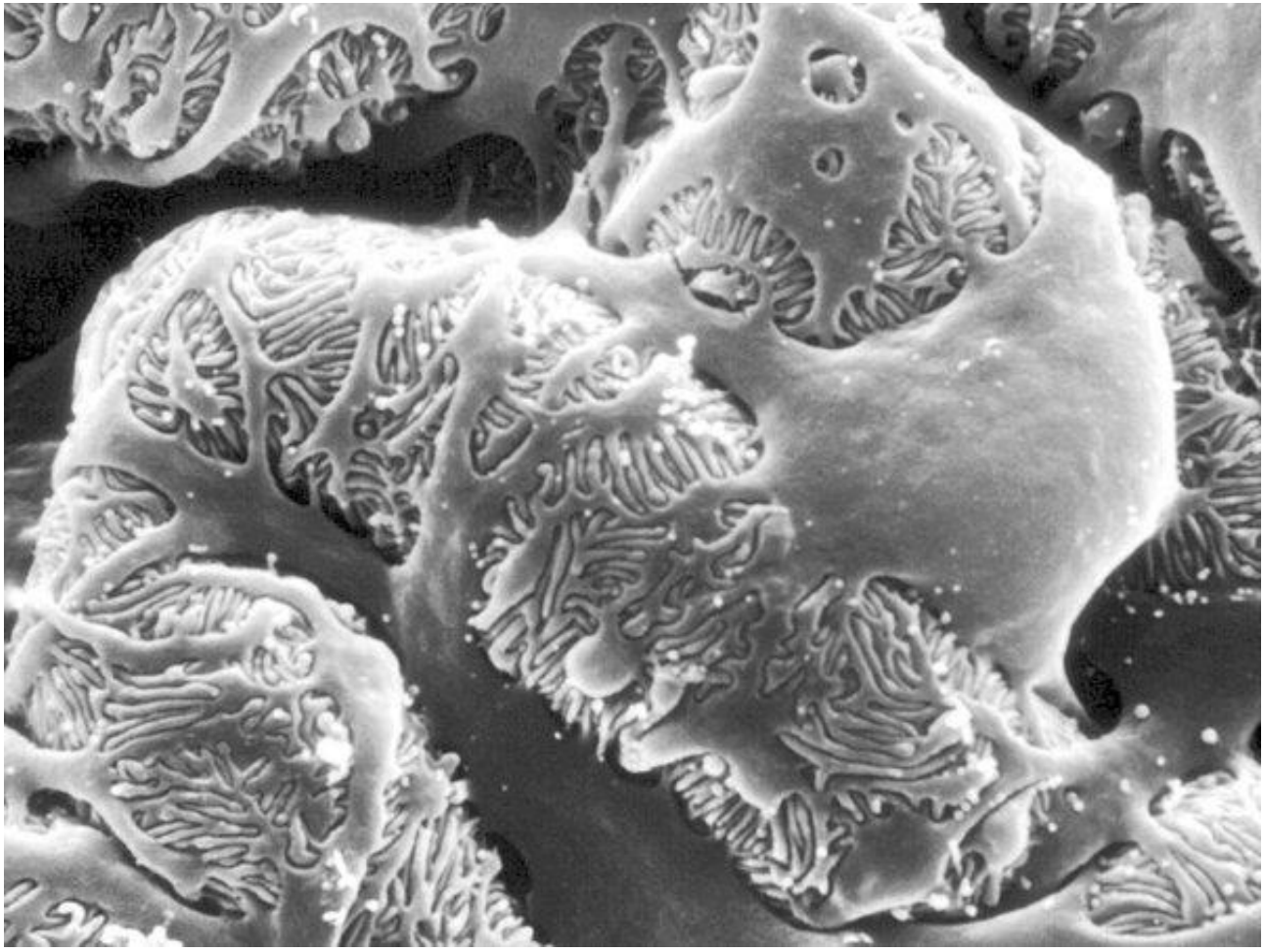
Renal Corpuscle Histology

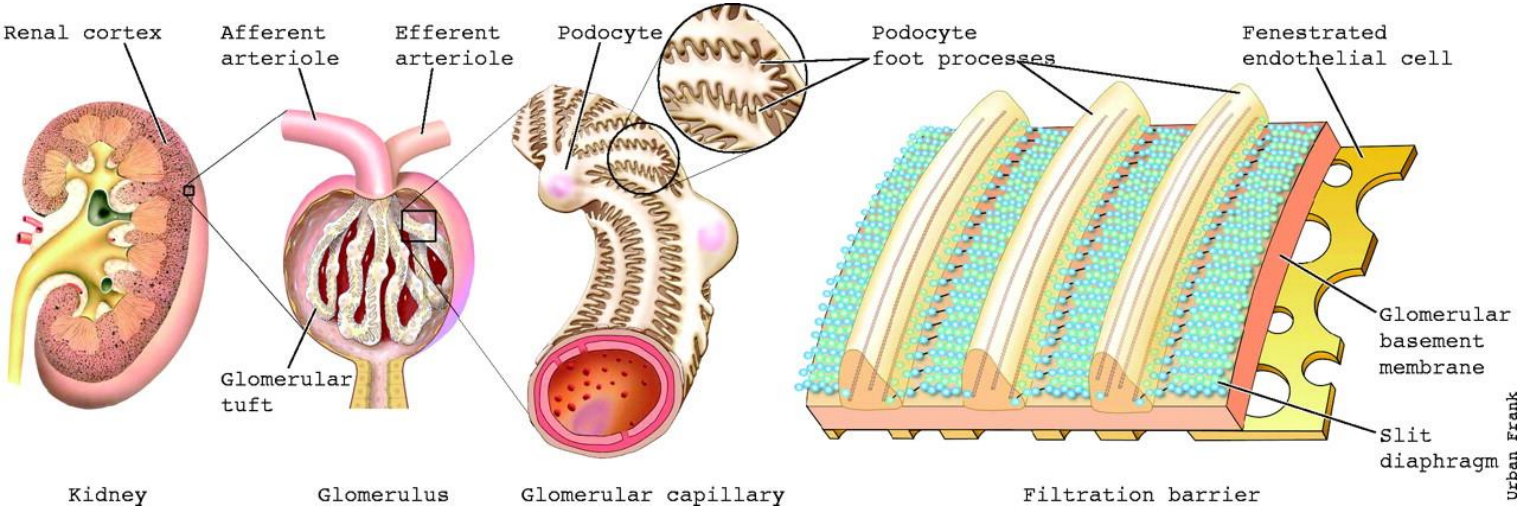
2) Basement membrane of glomerulus
   - Between endothelium and visceral layer of glom capsule
   - Prevents large protein movement

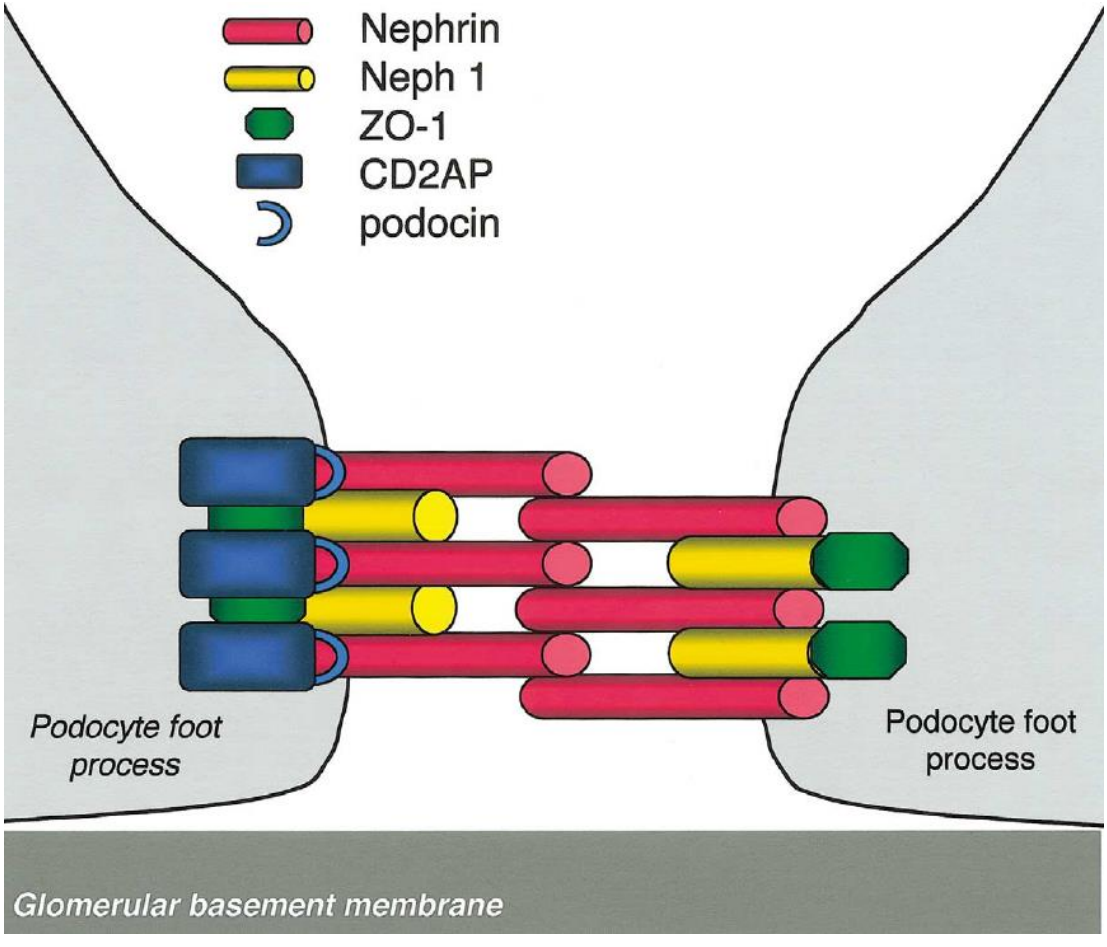












- **Glomerulonephritis Diseases could be primary or secondary to variety of conditions:**

Examples:

- Membranous nephropathy could be primary (idiopathic) or secondary to HBV or to Lupus.
- Minimal change disease could be primary or secondary to Hodgkin lymphoma or NSAID use.

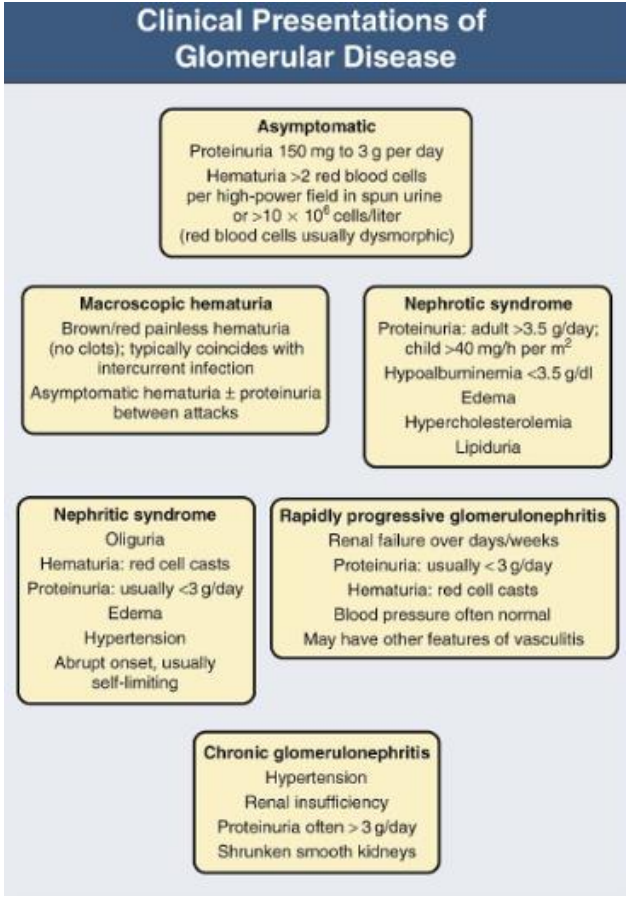
In primary we treat them with immunosupprrssive agents while in secondary we treat the underlying diseases.

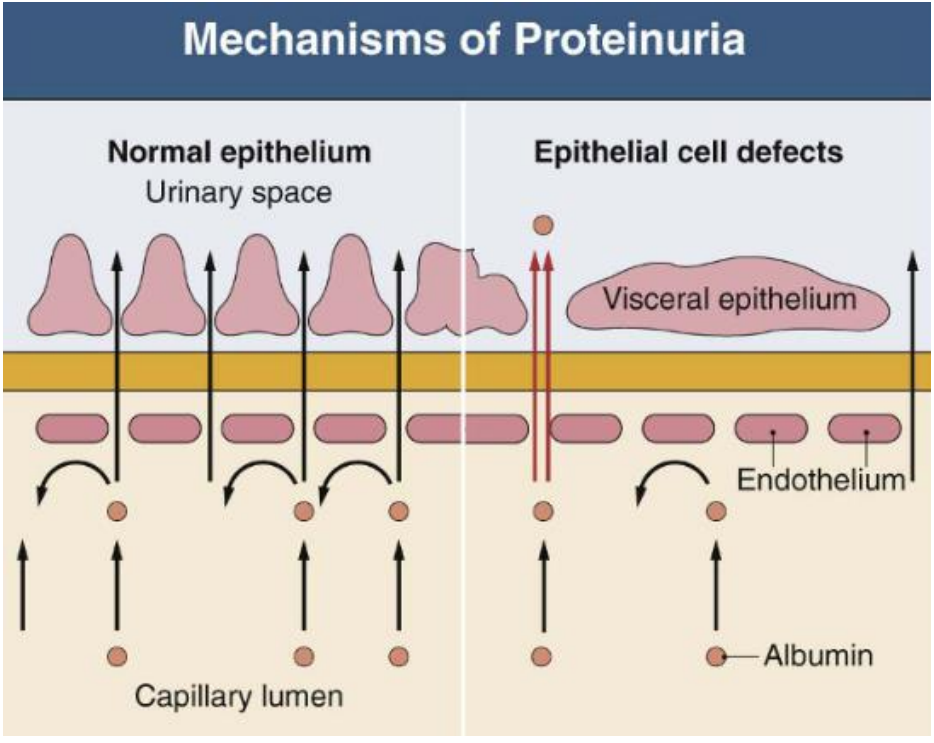
Differentiation Between Nephrotic Syndrome and Nephritic Syndrome

Typical Features	Nephrotic	Nephritic
Onset	Insidious	Abrupt
Edema	++++	++
Blood pressure	Normal	Raised
Jugular venous pressure	Normal/low	Raised
Proteinuria	++++	++
Hematuria	May/may not occur	+++
Red cell casts	Absent	Present
Serum albumin	Low	Normal/slightly reduced

Common Glomerular Diseases Presenting as Nephritic Syndrome

Disease	Associations	Serologic Tests Helpful in Diagnosis
Poststreptococcal glomerulonephritis	Pharyngitis, impetigo	ASO titer, streptozyme antibody
Other postinfectious disease		
Endocarditis	Cardiac murmur	Blood cultures, C3 ↓
Abscess	—	Blood cultures, C3, C4 normal or increased
Shunt	Treated hydrocephalus	Blood cultures, C3 ↓
IgA nephropathy	Upper respiratory or gastrointestinal infection	Serum IgA ↑
Systemic lupus	Other multisystem features of lupus	Antinuclear antibody, anti-double-stranded DNA antibody, C3 ↓, C4 ↓





Common Glomerular Diseases Presenting as Nephrotic Syndrome in Adults

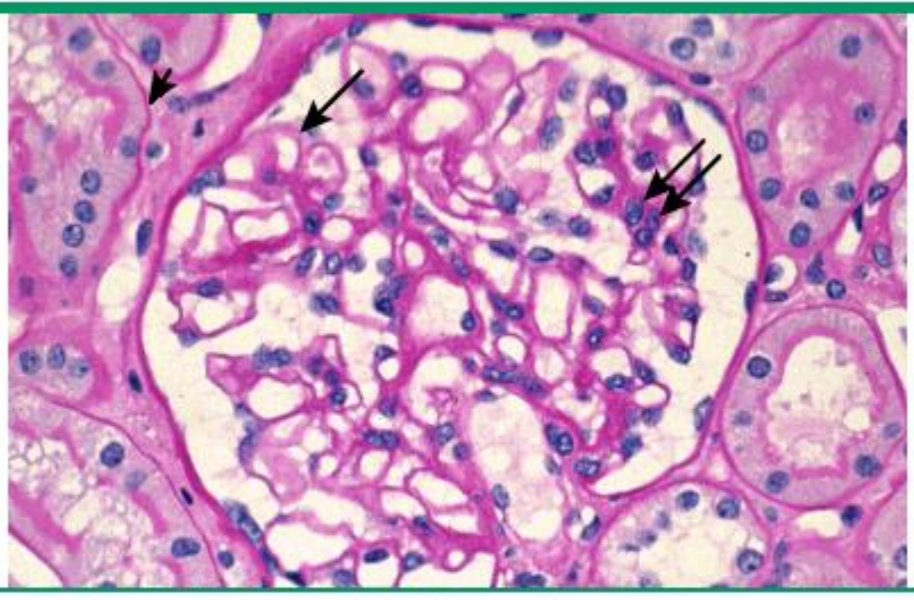
Disease	Associations	Serologic Tests Helpful in Diagnosis
Minimal change disease (MCD)	Allergy, atopy, NSAIDs, Hodgkin's disease	None
Focal segmental glomerulosclerosis (FSGS)	African Americans	—
	HIV infection	HIV antibody
	Heroin, pamidronate	—
Membranous nephropathy (MN)	Drugs: gold, penicillamine, NSAIDs	—
	Infections: hepatitis B, C; malaria	Hepatitis B surface antigen, anti–hepatitis C virus antibody
	Lupus nephritis	Anti-DNA antibody
	Malignancy: breast, lung, gastrointestinal tract	—
Membranoproliferative glomerulonephritis (MPGN) (type I)	C4 nephritic factor	C3 ↓, C4 ↓
Membranoproliferative glomerulonephritis (MPGN) (type II) (Dense deposit disease)	C3 nephritic factor	C3 ↓, C4 normal
Cryoglobulinemic membranoproliferative glomerulonephritis	Hepatitis C	Anti-hepatitis C virus antibody, rheumatoid factor, C3 ↓, C4 ↓, CH50 ↓
Amyloid	Myeloma	Serum protein electrophoresis, urine immunoelectrophoresis
	Rheumatoid arthritis, bronchiectasis, Crohn's disease (and other chronic inflammatory conditions), familial Mediterranean fever	—
Diabetic nephropathy	Other diabetic microangiopathy	None

- Pathological Classification of Glomerulonephritis diseases:

- Proliferative

- Non-proliferative

Normal glomerulus



Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).

Courtesy of Helmut G Rennke, MD.

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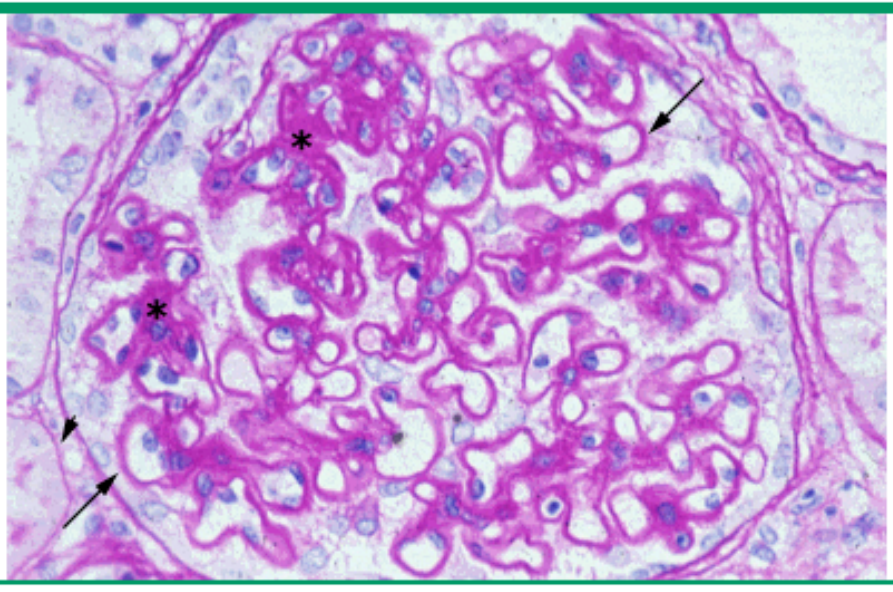
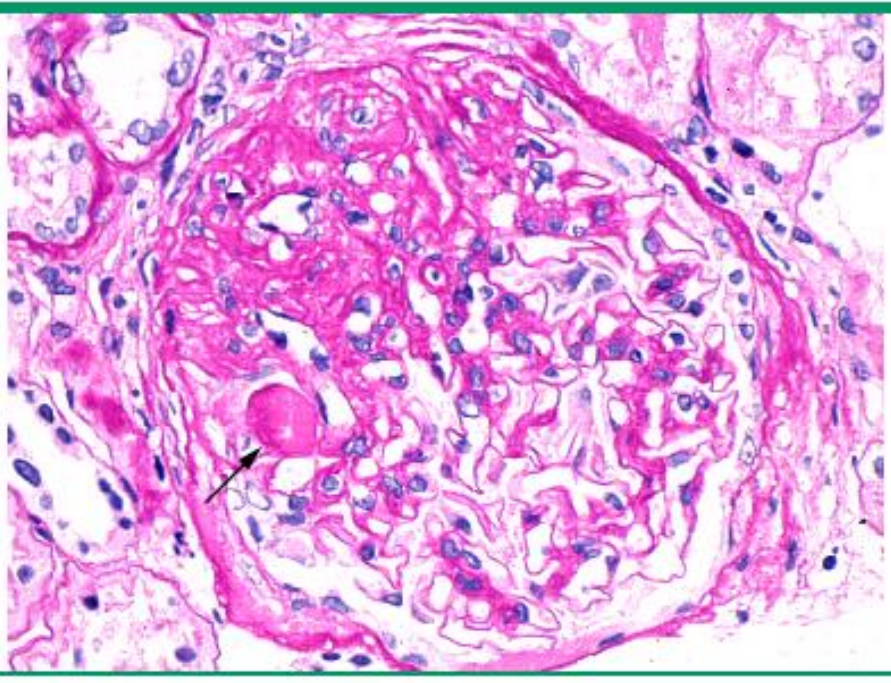
Light micrograph showing membranous nephropathy



Light micrograph of membranous nephropathy, showing diffuse thickening of the glomerular basement membrane (long arrows) with essentially normal cellularity. Note how the thickness of the glomerular capillary walls is much greater than that of the adjacent tubular basement membranes (short arrow). There are also areas of mesangial expansion (asterisks). Immunofluorescence microscopy (showing granular IgG deposition) and electron microscopy (showing subepithelial deposits) are generally required to confirm the diagnosis.

Courtesy of Helmut Rennke, MD.

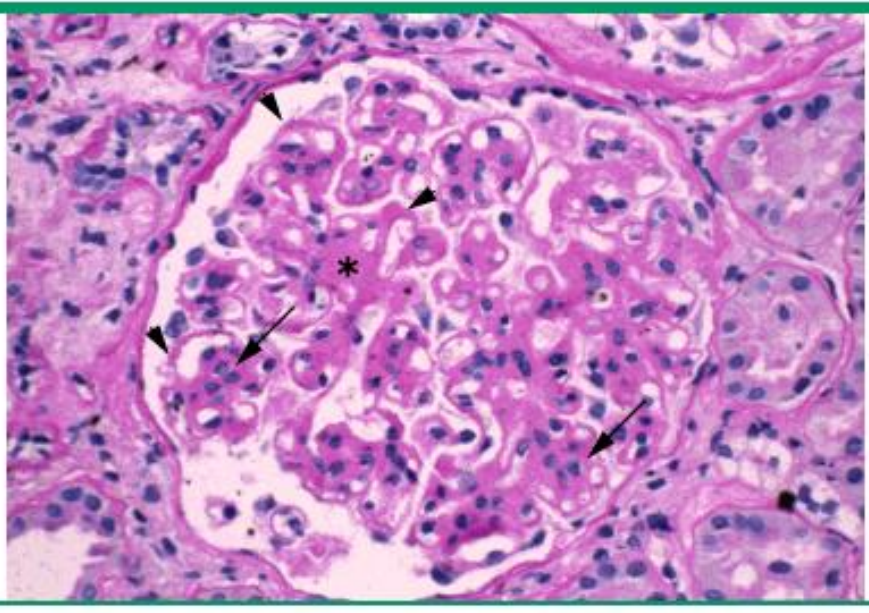
Moderate FGS



Light micrograph in focal segmental glomerulosclerosis shows a moderately large segmental area of sclerosis with capillary collapse on the upper left side of the glomerular tuft; the lower right segment is relatively normal. Focal deposition of hyaline material (arrow) is also seen.

Courtesy of Helmut Rennke, MD.

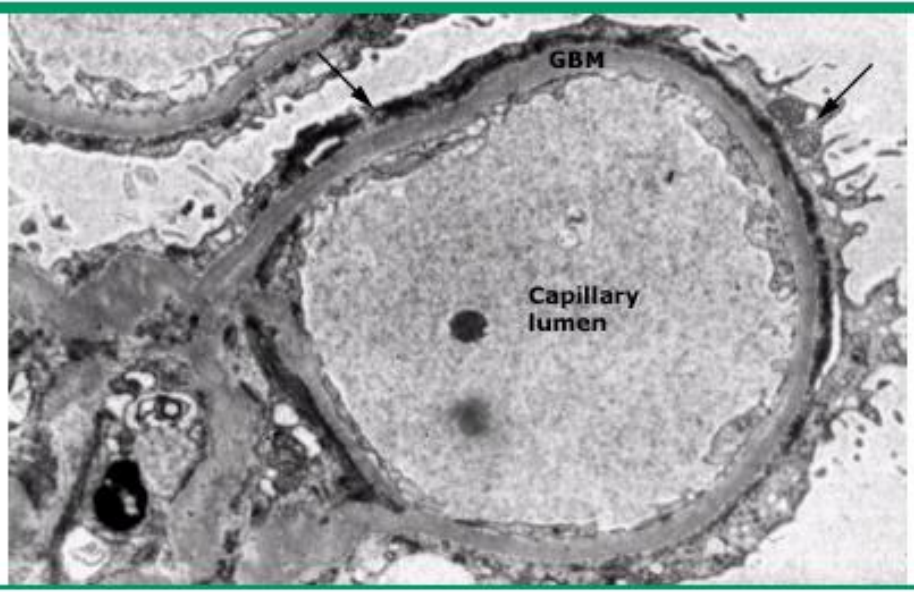
Membranoproliferative glomerulonephritis



Light micrograph in membranoproliferative glomerulonephritis showing a lobular appearance of the glomerular tuft with focal areas of increased glomerular cellularity (large arrows), mesangial expansion (*), narrowing of the capillary lumens, and diffuse thickening of the glomerular capillary walls (small arrows).

Courtesy of Helmut Rennke, MD.

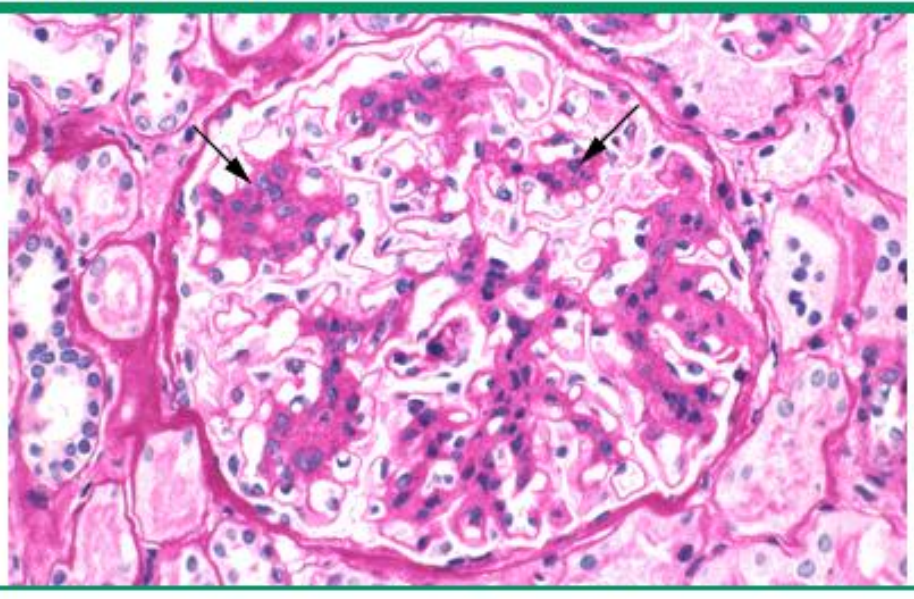
Electron microscopy in minimal change disease



Electron micrograph in minimal change disease showing a normal glomerular basement membrane (GBM), no immune deposits, and the characteristic widespread fusion of the epithelial cell foot processes (arrows).

Courtesy of Helmut Rennke, MD.

Light micrograph showing mesangial proliferative glomerulonephritis



Light micrograph of a mesangial glomerulonephritis showing segmental areas of increased mesangial matrix and cellularity (arrows). This finding alone can be seen in many diseases, including IgA nephropathy and lupus nephritis.

Courtesy of Helmut G Rennke, MD.

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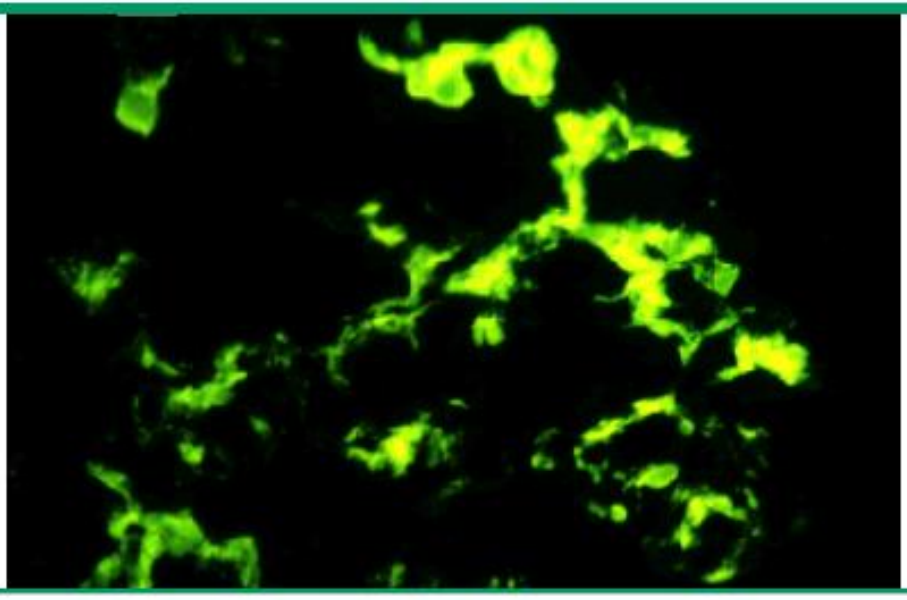
Immunofluorescence microscopy showing mesangial immunoglobulin A (IgA) deposits



Immunofluorescence microscopy demonstrating large, globular mesangial IgA deposits that are diagnostic of IgA nephropathy or Henoch-Schönlein purpura (IgA vasculitis). Note that the capillary walls are not outlined since the deposits are primarily limited to the mesangium.

Courtesy of Helmut Rennke, MD.

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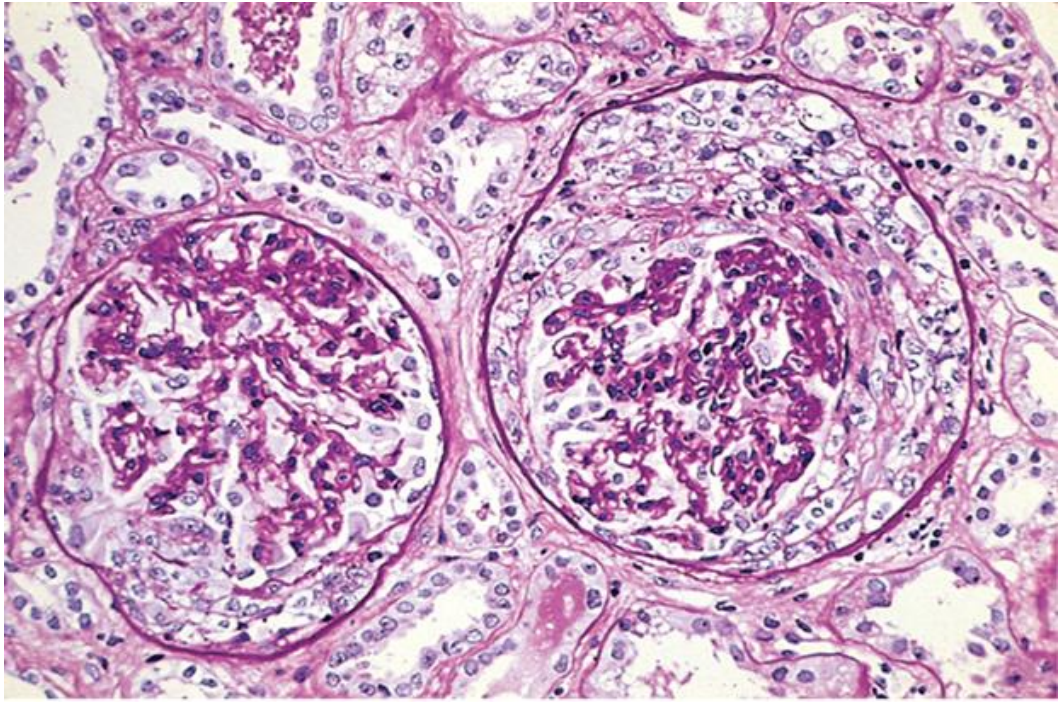

Thank You

For feedback and further questions:

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