

Glomerulonephritis

Salwa Ibrahim, MD MRCP (UK)

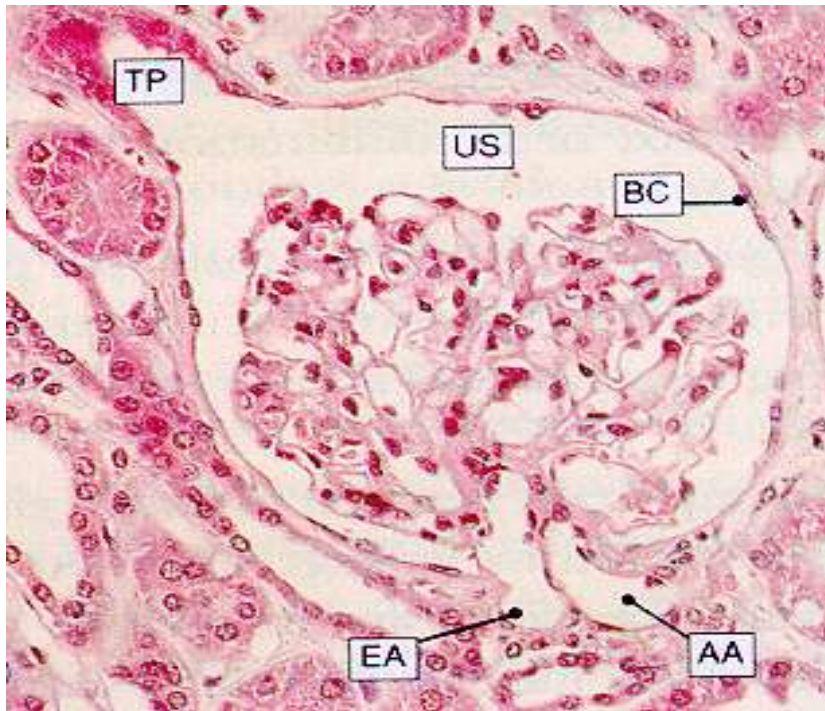
Professor of Nephrology

Objectives

- **Classification of Glomerulopathies**
- **Pathology**
- **Clinical features**
- **Investigations**
- **Management**



Glomerulus



Pathological CLASSIFICATION

► PRIMARY

- Minimal Change Disease
- Membranous GN
- Membranoproliferative GN
- Diffuse Proliferative GN
- Focal Segmental GS
- Rapidly Progressive GN (Anti GBM GN, ANCA associated GN)
- IgA Nephropathy

- **SECONDARY**

Diabetes Mellitus

Hypertensive Nephrosclerosis

SLE, Lymphoma, Solid tumors

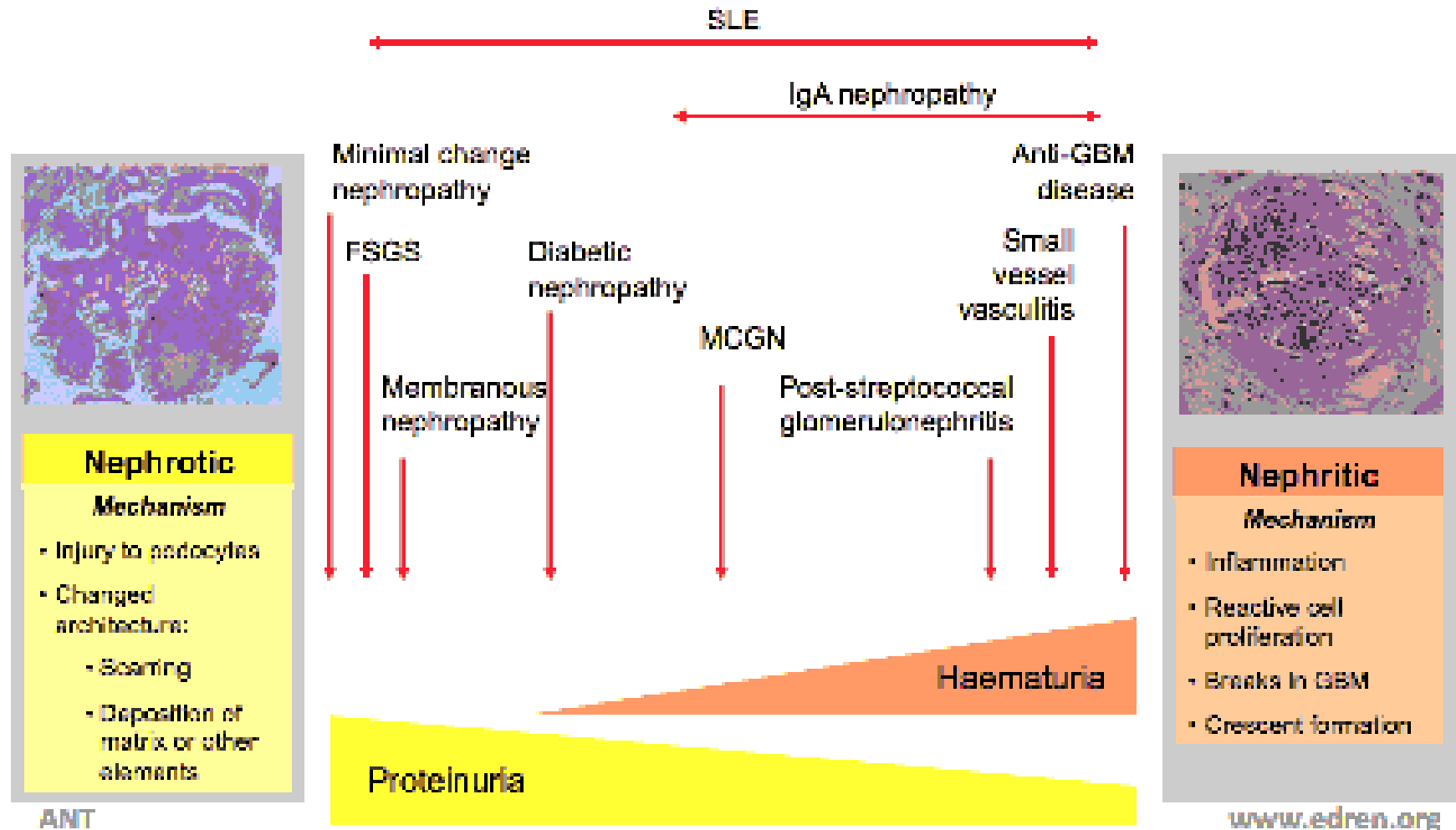
Amyloidosis, MM

Malaria, Endocarditis

Clinical Classification of glomerular disease

- *Nephrotic syndrome*
- *Acute glomerulonephritis (acute nephritic syndrome)*
- *Rapidly progressive glomerulonephritis*
- *Asymptomatic urinary abnormality (Haematuria, proteinuria or both)*

The spectrum of glomerular diseases



Acute nephritic syndrome

Diseases commonly associated with acute GN

- Post streptococcal GN
- Non- streptococcal post-infectious GN
- Infective endocarditis
- Visceral abscess
- SLE
- IgA nephropathy
- Henoch-schonlein syndrome
- Cryoglobulinemia

Etiology

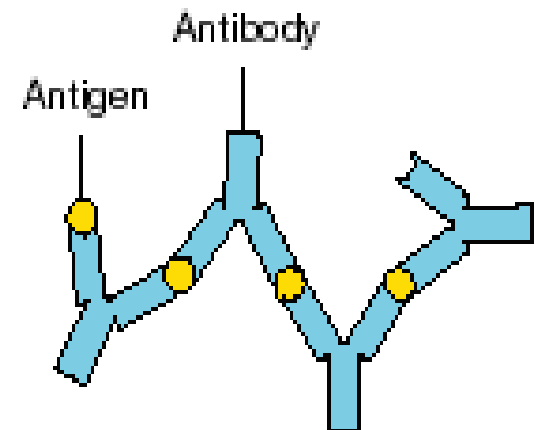
Antigen antibody complex formation Complement-leukocyte- mediated mechanism

➤ Recruitment of neutrophils and monocytes

➤ Neutrophils

Protease	GBM degradation
O ₂ free readicals	cell damage
AA metabolites	↓ GFR

➤ (+) epithelial & mesangial cells to secrete damaging chemical mediators



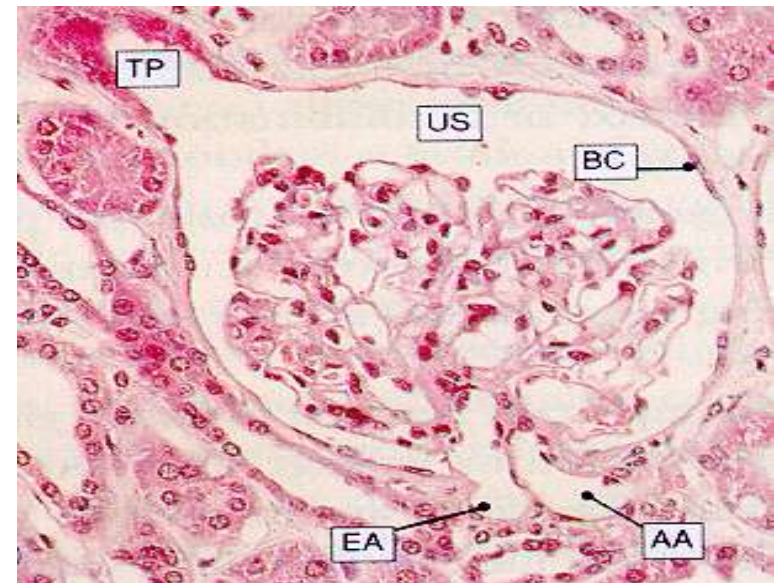
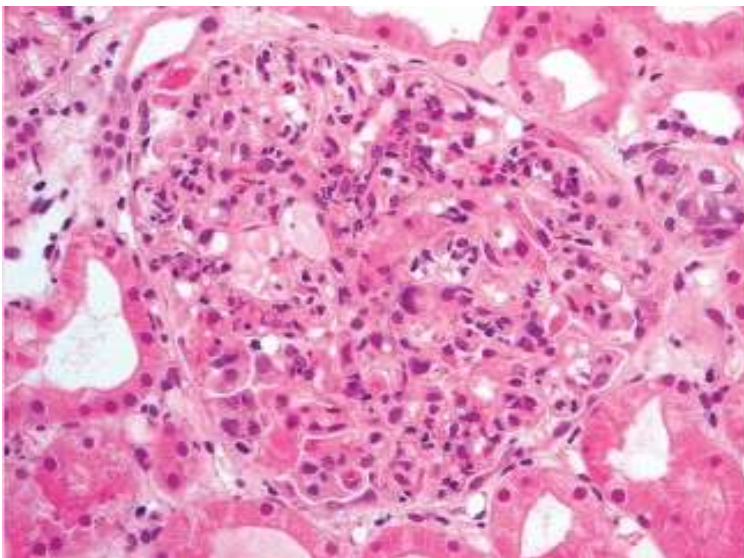
Pathology of Acute Glomerulonephritis

Diffuse proliferative GN (PGN)

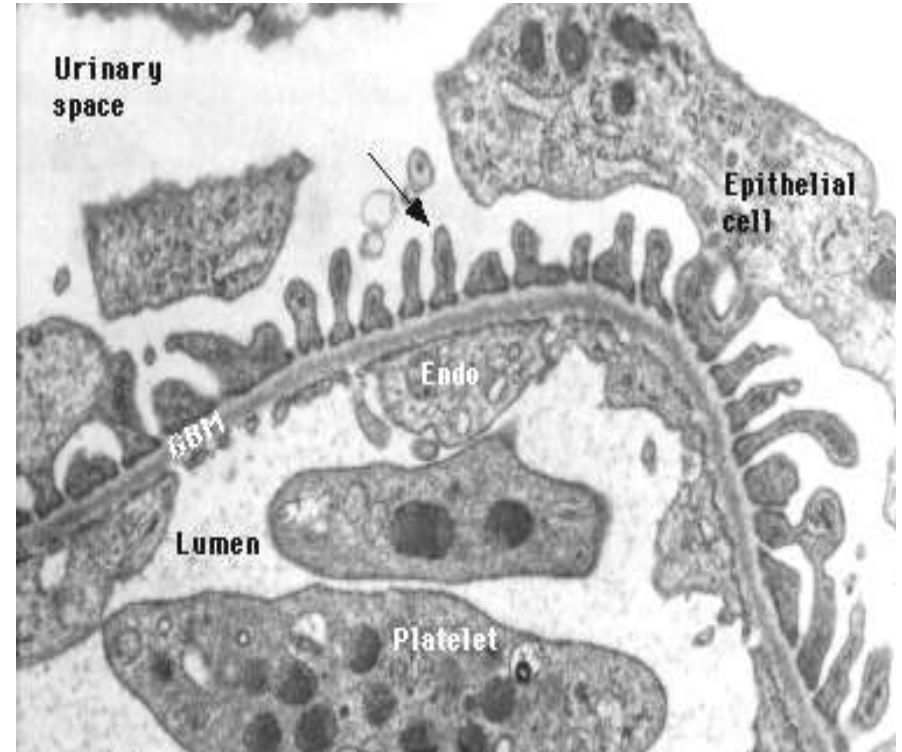
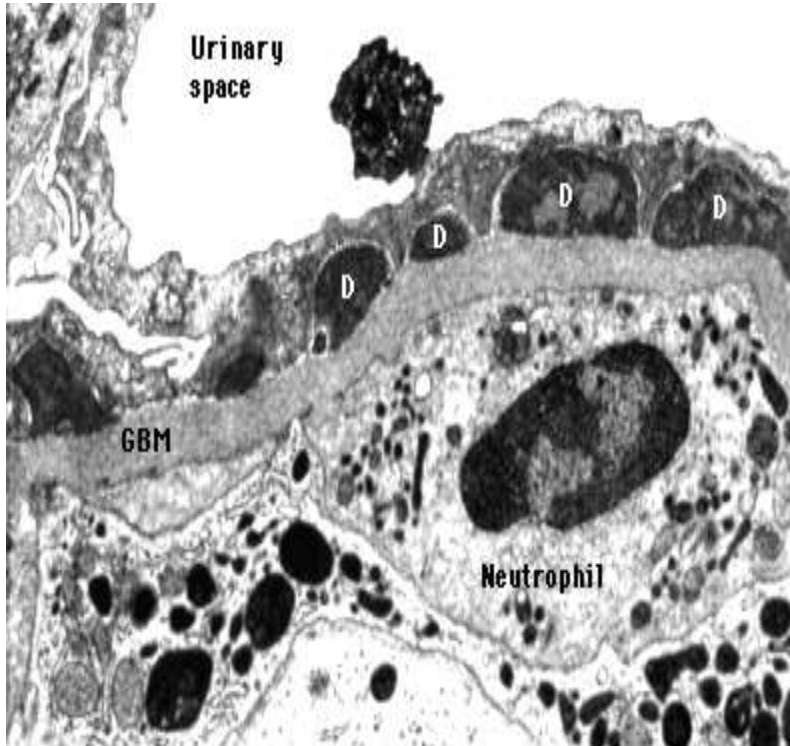
➤ Proliferation of cells within the glomeruli, accompanied by leukocyte filtrate

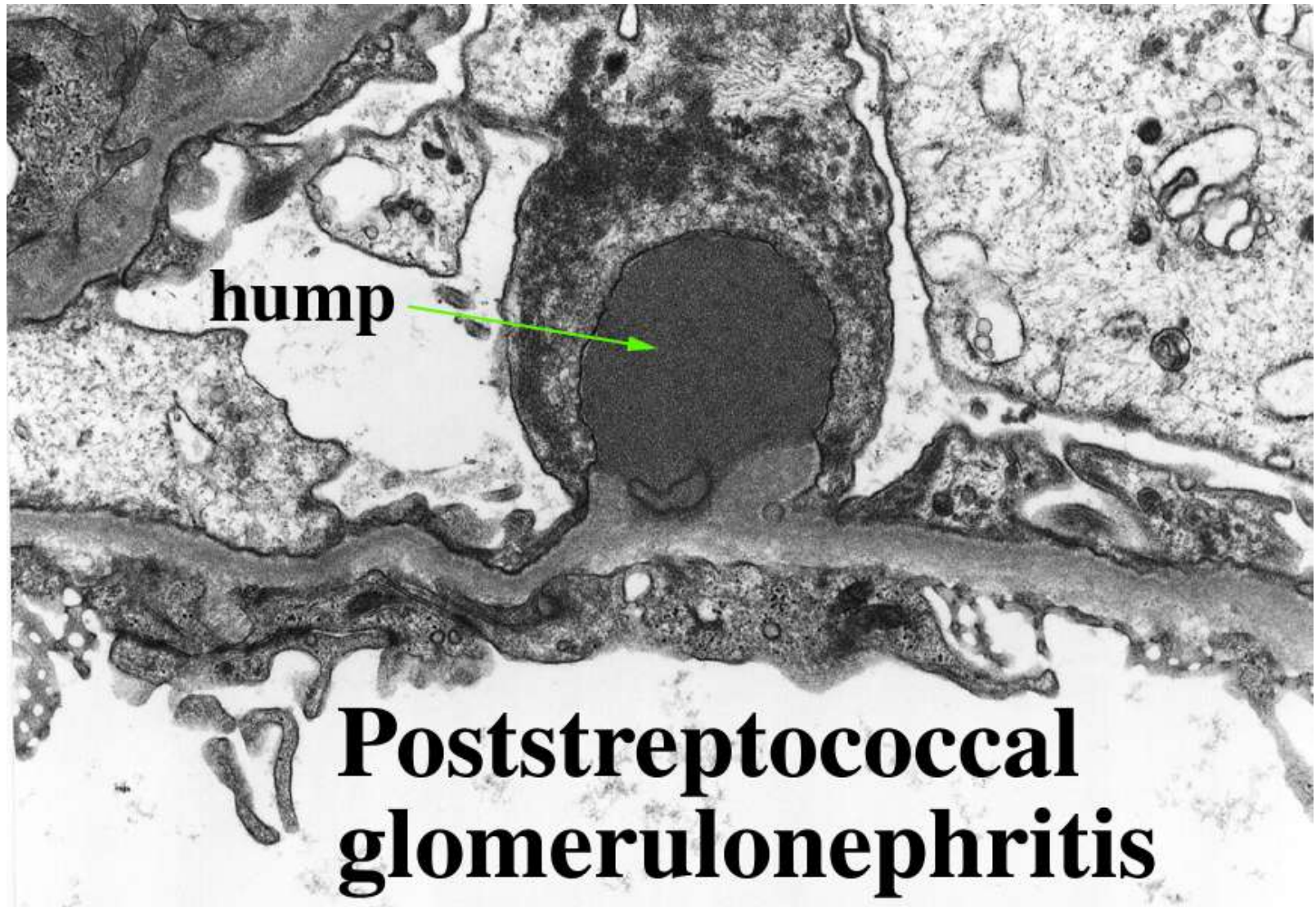
➤ typical features of immune complex disease :

- hypocomplementemia
- granular deposits of IgG & complement on GBM



Electron Microscopic Exam





CLINICAL FEATURES

Abrupt onset of

- ▶ Glomerular haematuria (RBC casts or dysmorphic RBC)
- ▶ Non- nephrotic range proteinuria (< 2 g in 24 hrs)
- ▶ Oedema (periorbital, sacral)
- ▶ Hypertension
- ▶ Transient renal impairment (oliguria, uraemia)



Hematuria specimens will show levels of red blood cells, white blood cells, epithelial cells, casts, bacteria, yeast, crystals, pH, glucose, ketones and more.

INVESTIGATIONS

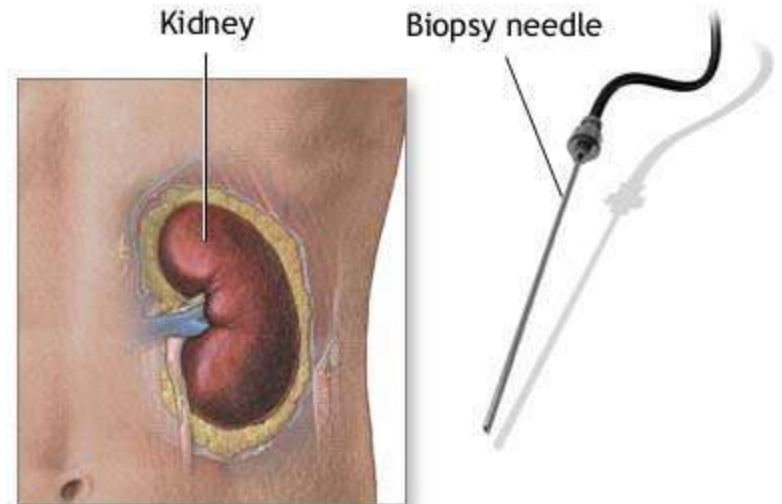
Base line measurements

- ↑ Urea
- ↑ Creatinine
- Urinalysis (MSU) :
 - a) Urine microscopy (red cell cast)
 - b) proteinuria



Diagnostically useful tests :

- Culture (swab from throat or infected skin)
- Serum anti-streptolysin-O titre
- Hepatitis B surface antigen
- Hepatitis C antibody
- anti DNA , ANCA
- ↓C3,4
- Renal biopsy



Management & Prognosis

- It has a good prognosis in children
- Supportive measures until spontaneous recovery
- Control HTN
- Fluid balance, salt restriction, diuretic
- Antibiotic to eradicate infection
- Steroid has no benefit

IgA Nephropathy

▶ IgA deposits in mesangium

▶ Cause

Unknown, exaggerated immune response to viral or bacterial infection (surface infection like tonsillar)

Assoc. Liver cirrhosis, celiac disease, seronegative arthritis

➤ Epidemiology

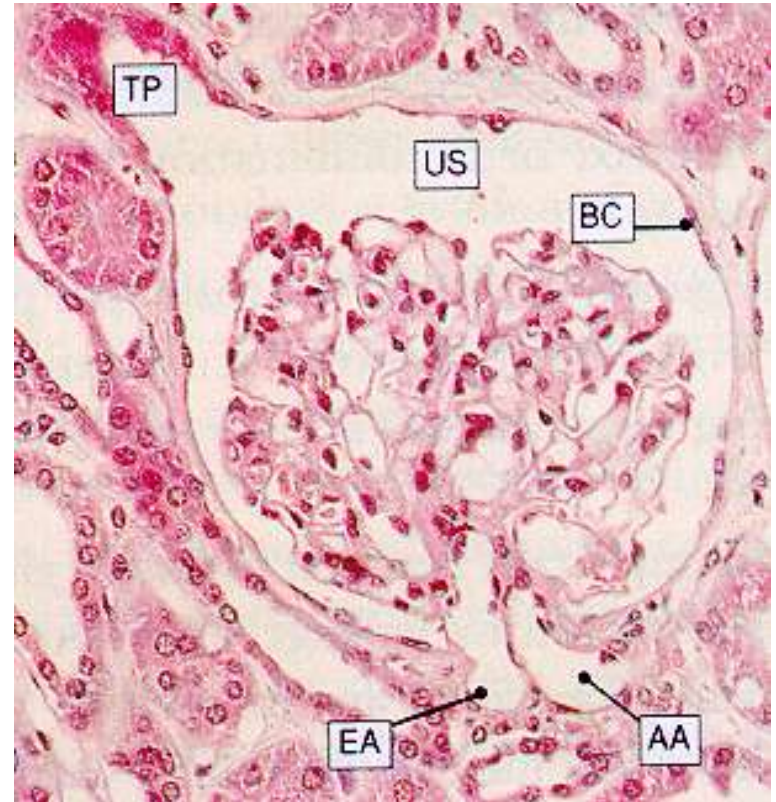
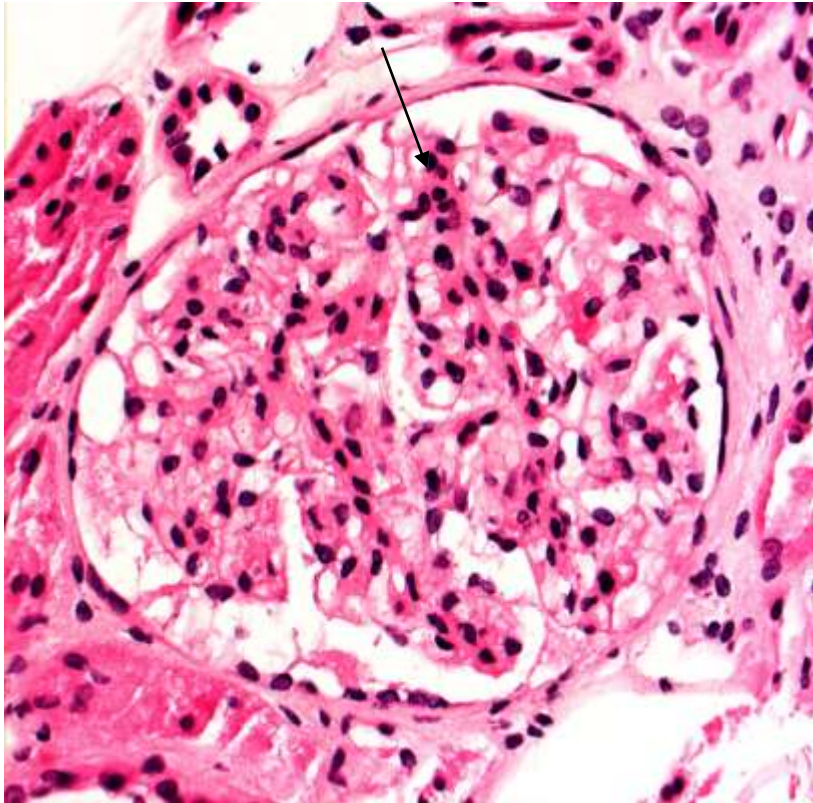
Asia

Children....young.....Male

➤ Features

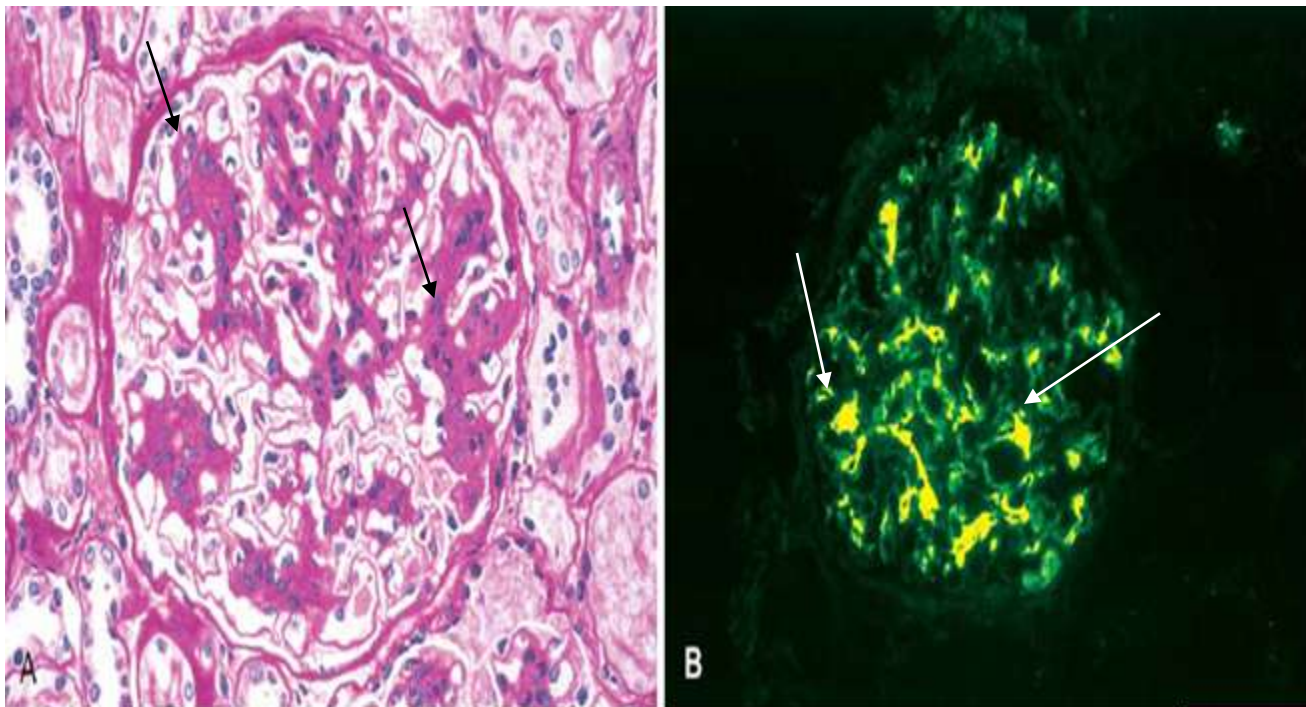
1. Upper respiratory tract infection followed by gross haematuria
2. Microscopic haematuria
3. Nephrotic syndrome

Light microscopy



Mesangial cell proliferation, mesangial matrix expansion
Patent capillary loops

Immunofluorescence



**Mesangial matrix expansion
IgA deposits**

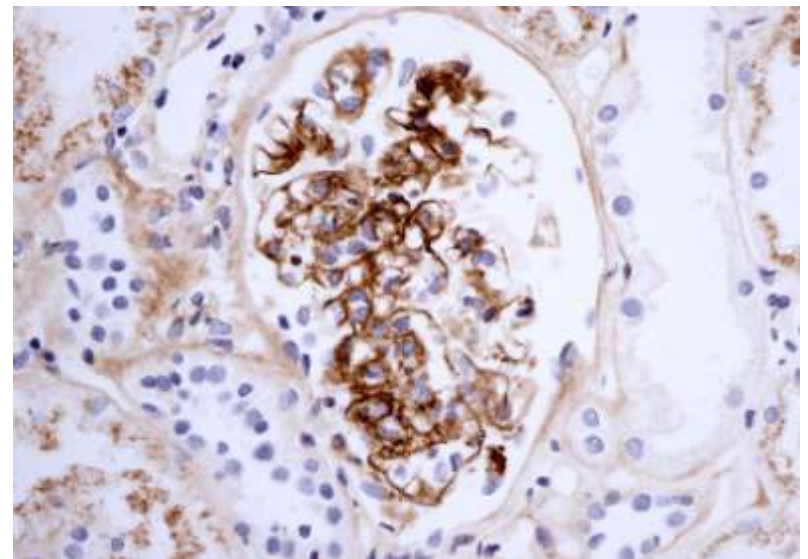
► MANAGEMENT

- ❖ ROTENURIA > 1G/DAY
ACEI/ARB
- ❖ PROTEINURIA 2-3.5G/DAY
ACEI/ARB +
CORTICOSTEROIDS
MP 1G/DAY IV for 3 days
prednisone 0.5 mg/kg alternate day for 6 months
FISH OIL 2-5G/DAY
- ❖ TRANSPLANT good but 30% recurrence

Henoch–Schönlein purpura

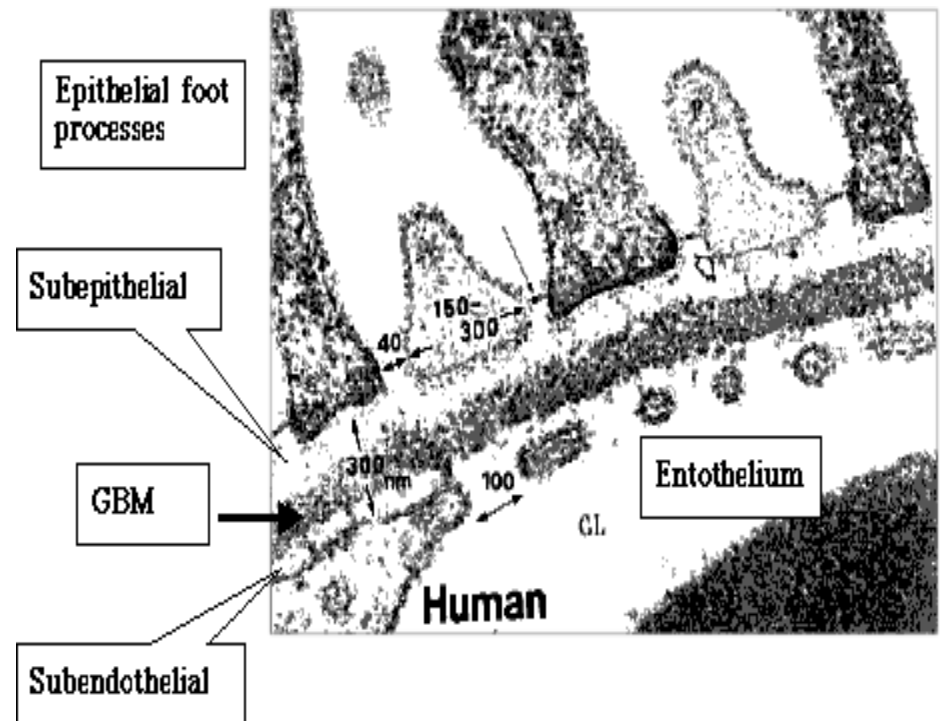
Vasculitis affecting

1. Skin
 2. Joint
 3. Gut
 4. Kidney
- Mesangial IgA deposits
 - Recovery is the role
 - Steroids are avoided unless Renal functions deteriorates



Nephrotic syndrome

1. Hypoalbuminemia
2. Proteinuria > 3.5 g /day
3. Hyperlipidemia
4. edema



Nephrotic syndrome

With normal sediments

- Minimal change disease
- Focal segmental glomerulosclerosis
- Membranous nephropathy
- Diabetic glomerulosclerosis
- Amyloidosis

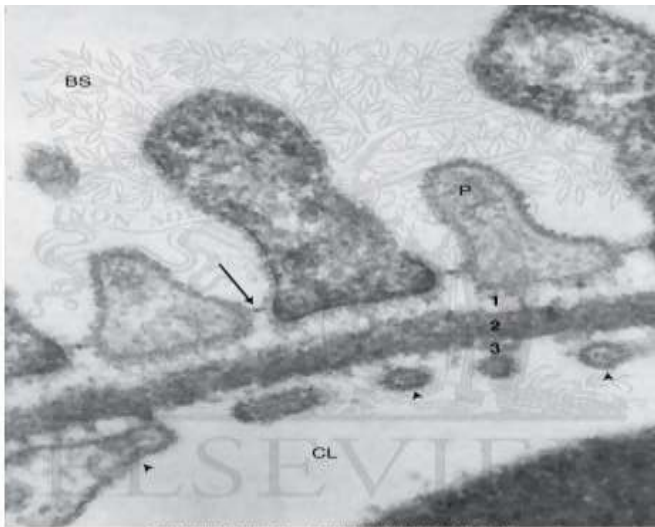
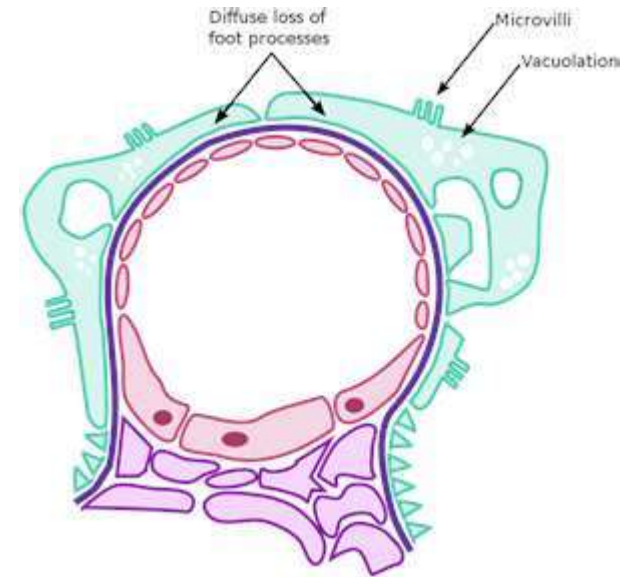
With active sediments

- Membranoproliferative GN

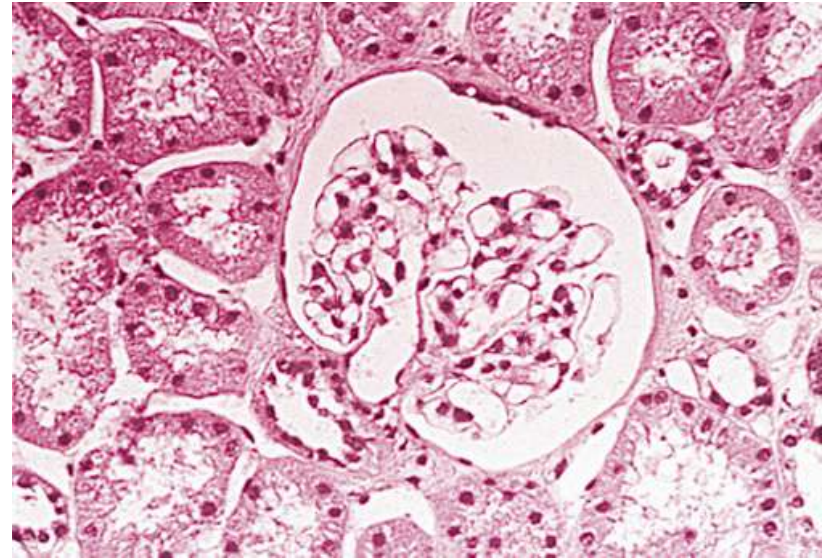
Minimal change disease

Minimal Change Disease

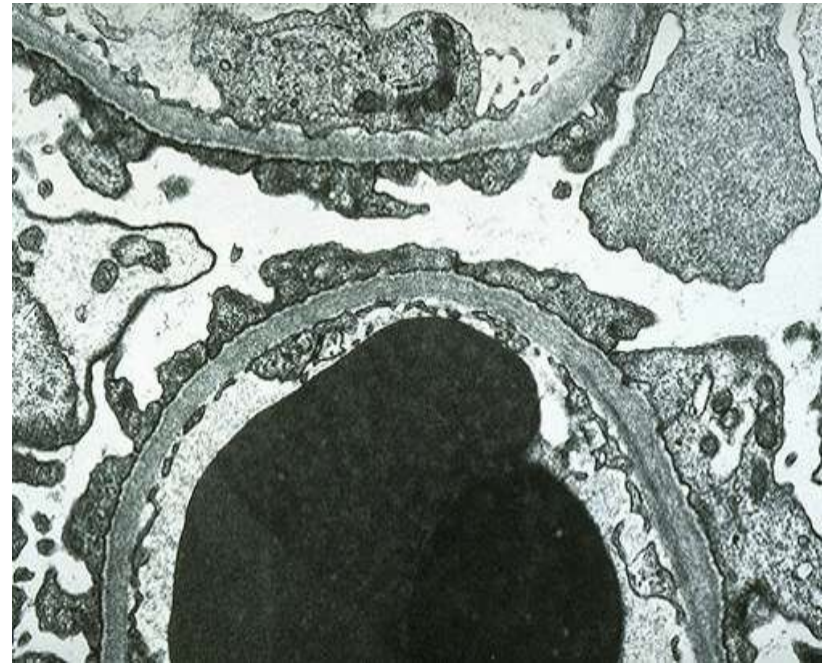
- Usually children
- Nephrotic syndrome with highly selective proteinuria and generalised oedema



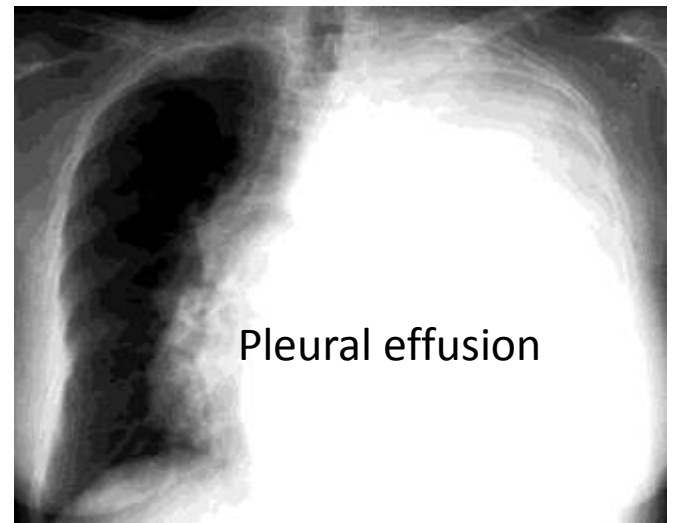
- By light microscopy, glomeruli appears normal



- By E/M, fusion of the epithelial foot processes



Clinical presentation



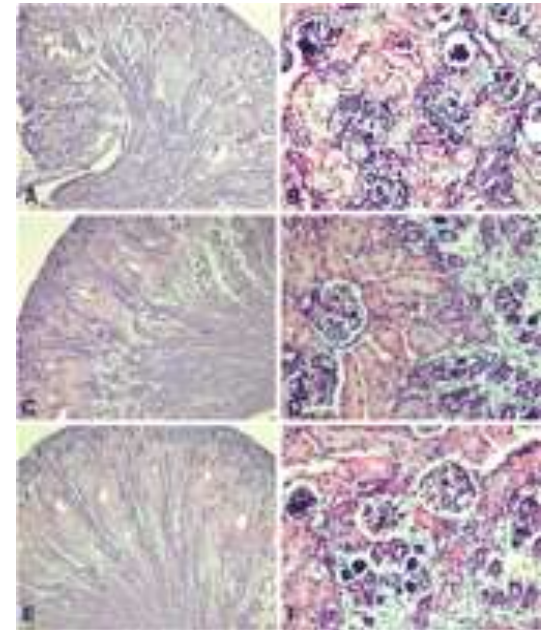
Management

- Dietary salt restriction
- Bed rest
- Diuretic: thiazide, loop diuretic, potassium sparing diuretic
- Normal protein diet
- Albumin infusion
- Statin therapy
- ACEI/ARB



Specific therapy

- High dose steroid therapy 1mg/kg/d for 4-6 weeks
- 40 mg/EOD for another 4-6 weeks
- Cyclophosphamide 1.5-2 mg/kg/d for 8-12 weeks with steroid 7.5-15 mg/day for frequent relapser or steroid resistant cases
- Cyclosporin 3-5 mg/kg/day over 2-3 years to prevent relapse

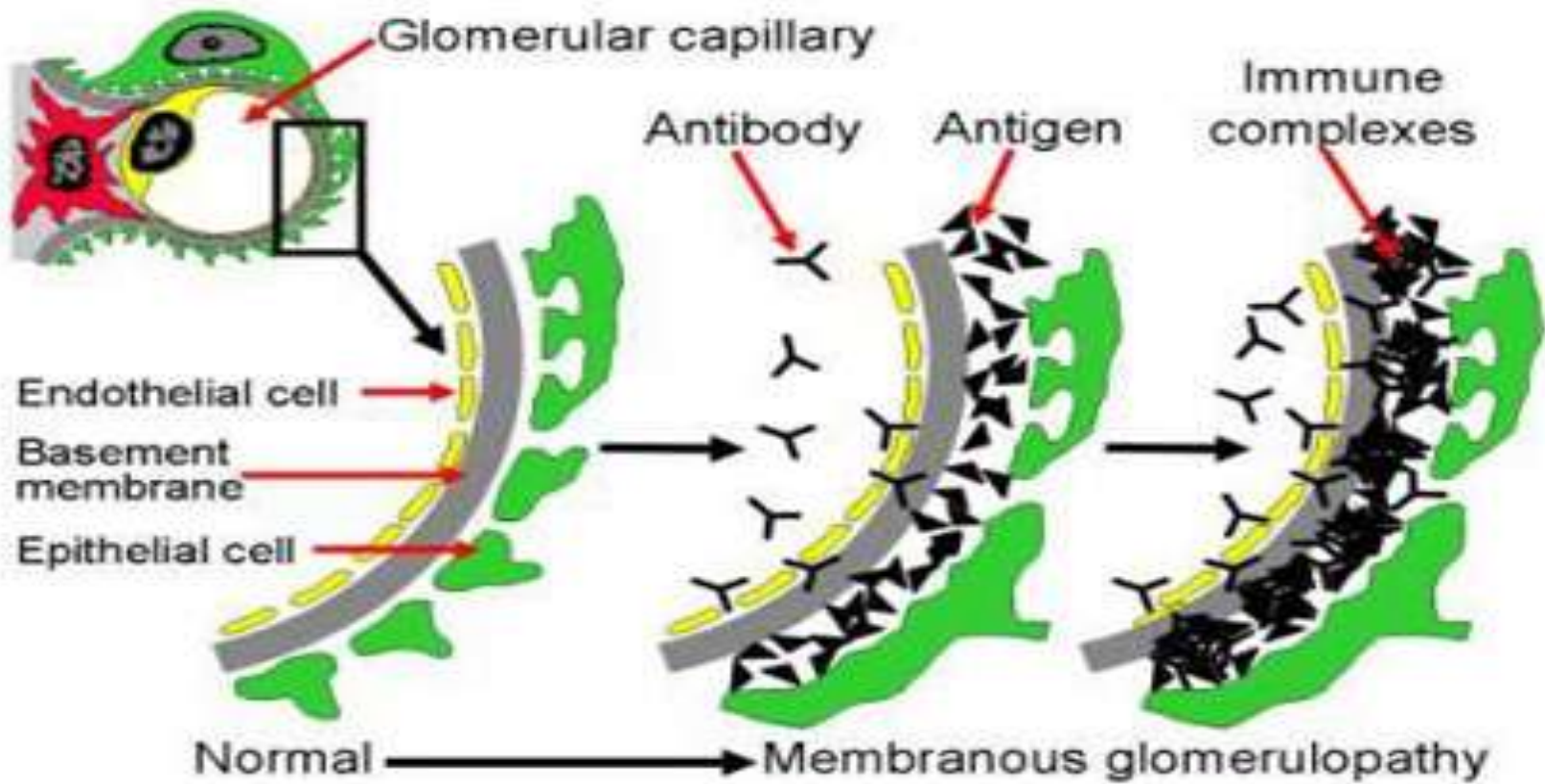


Membranous nephropathy

Etiology

- **Idiopathic**
- **Secondary to**
 1. **Systemic Lupus Erythematosus (Lupus)**
 2. **Hepatitis B and C**
 3. **Cancers (especially of the lung or colon)**
 4. **Secondary MN has also been associated with some drugs, such as penicillamine, gold, and non-steroidal anti-inflammatory drugs.**
 5. **Anyone who is found to have MN, especially those over 50 years old, should be tested for Hepatitis and undergo routine age-appropriate cancer screening**

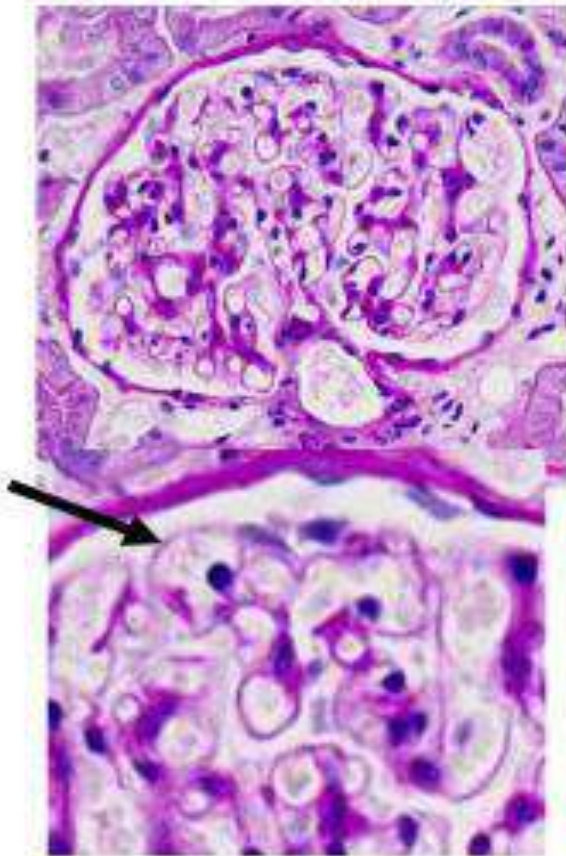
Pathogenesis



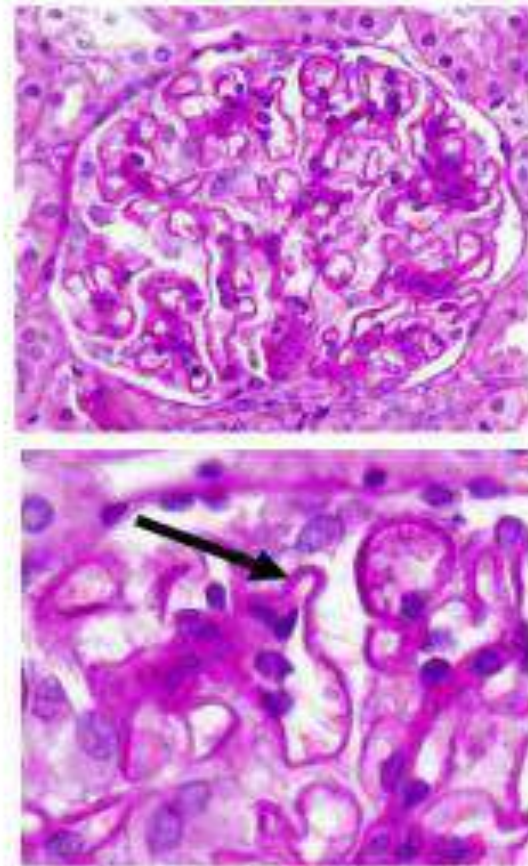
Subepithelial deposits of IgG and C3

Light microscopy

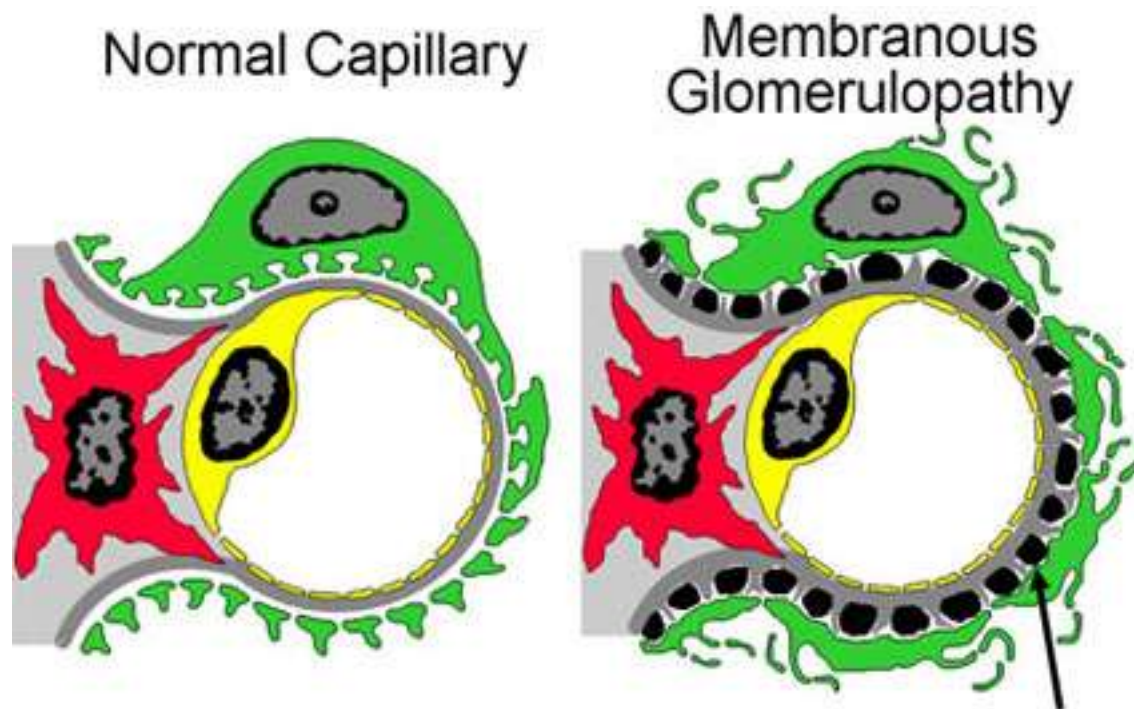
Normal glomerular capillaries with thin walls



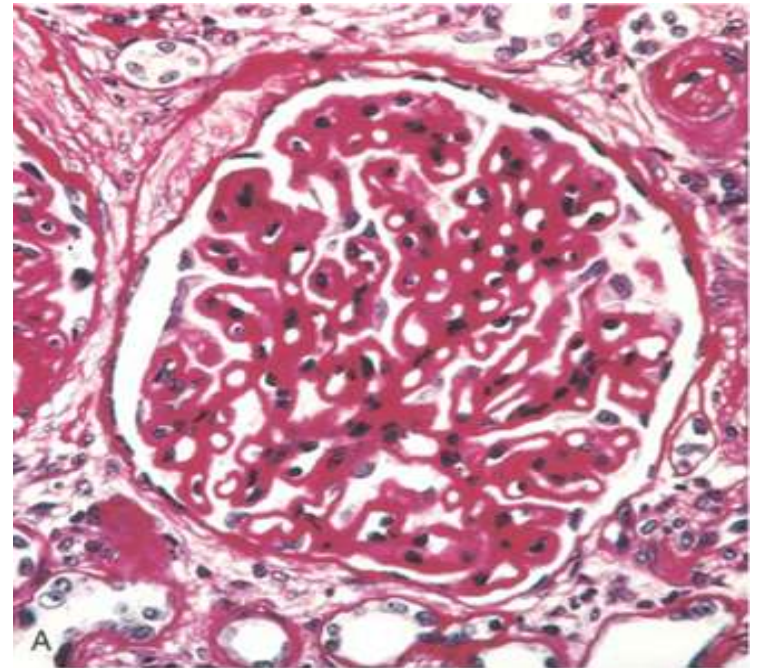
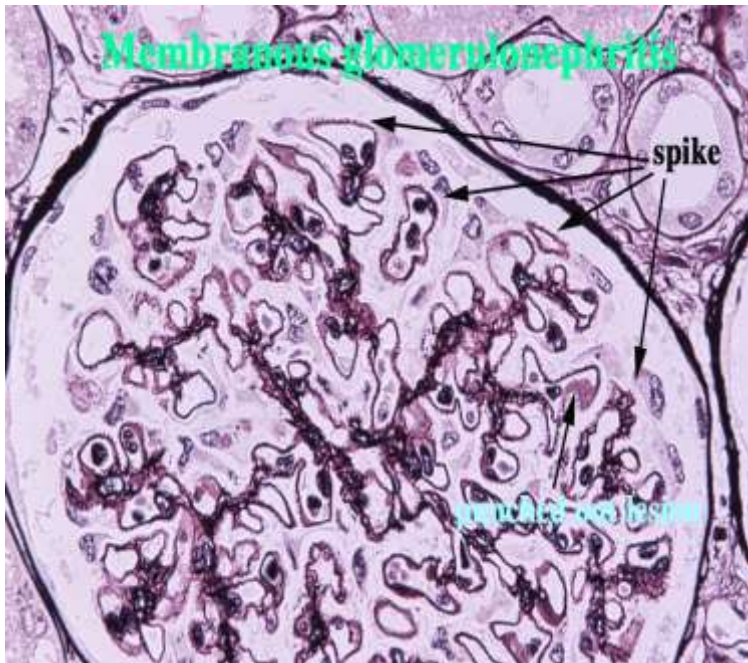
Membranous glomerulopathy with thick capillary walls



In situ immune complex formation with sub-epithelial pattern

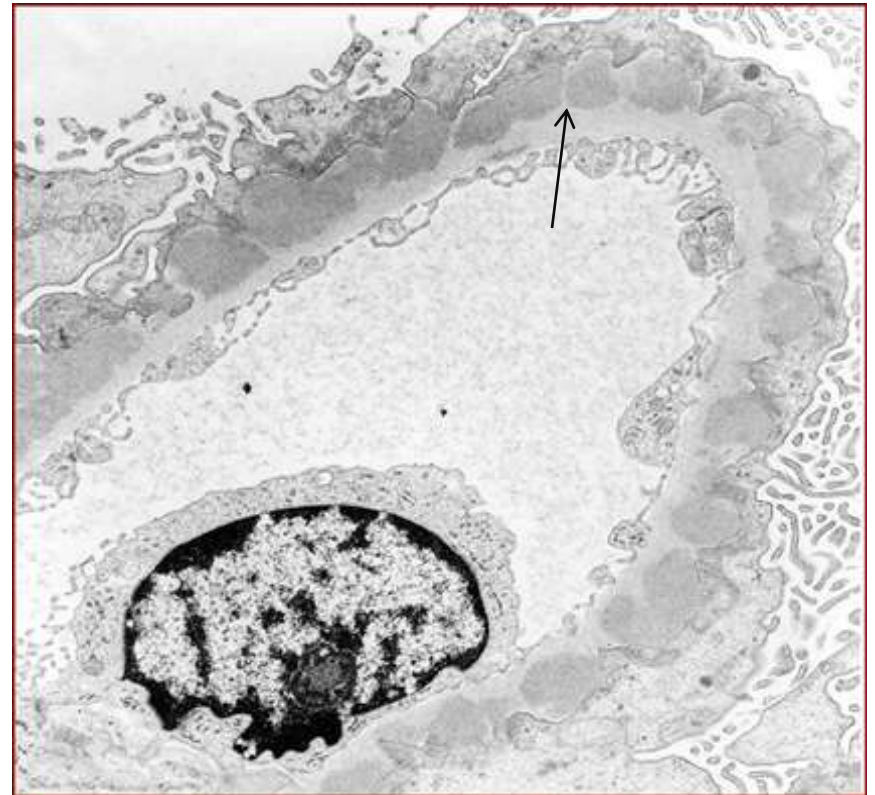
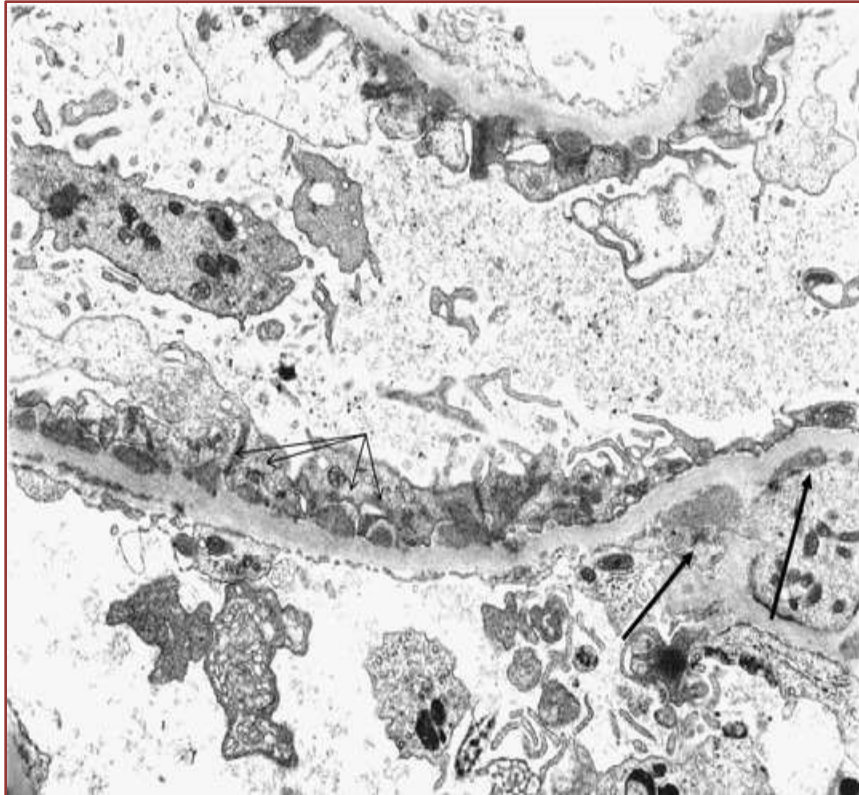


Light microscopy

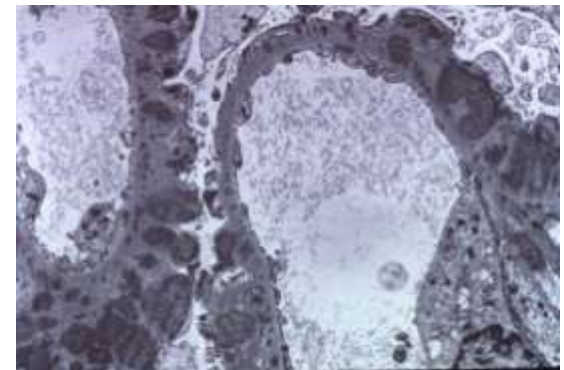
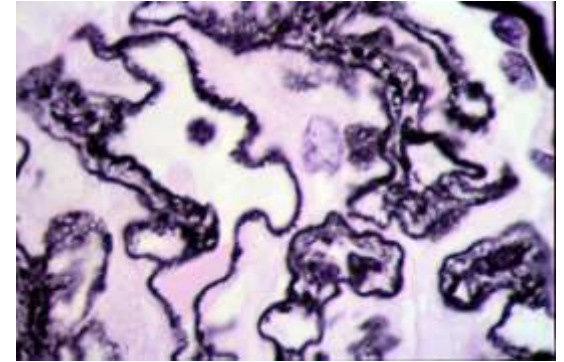


Diffuse thickening of GBM

E/M



- Proteinuria (often nephrotic)
- Hypertension
- Third improve; third stable; third progress
- May be secondary to tumours etc
- Immunosuppression if bad NS / progressive

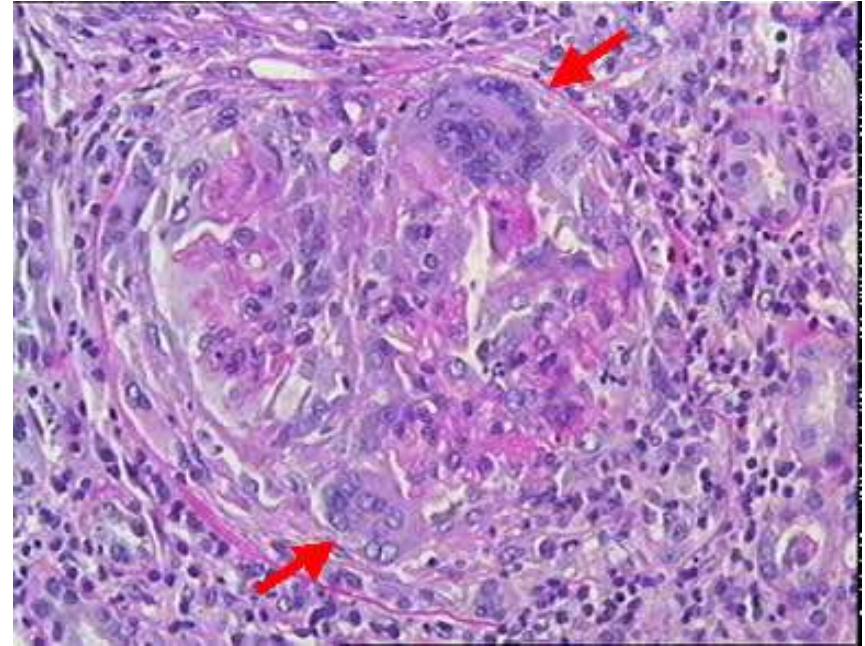


Treatment

- **Steroid alone is ineffective**
- **Cyclophosphamide is effective but reserved for persistent proteinuria, renal insufficiency**
- **Cyclosporine and mycophenolate are alternatives**
- **Anticoagulant if proteinuria heavy and persistent, risk of RVT is high**

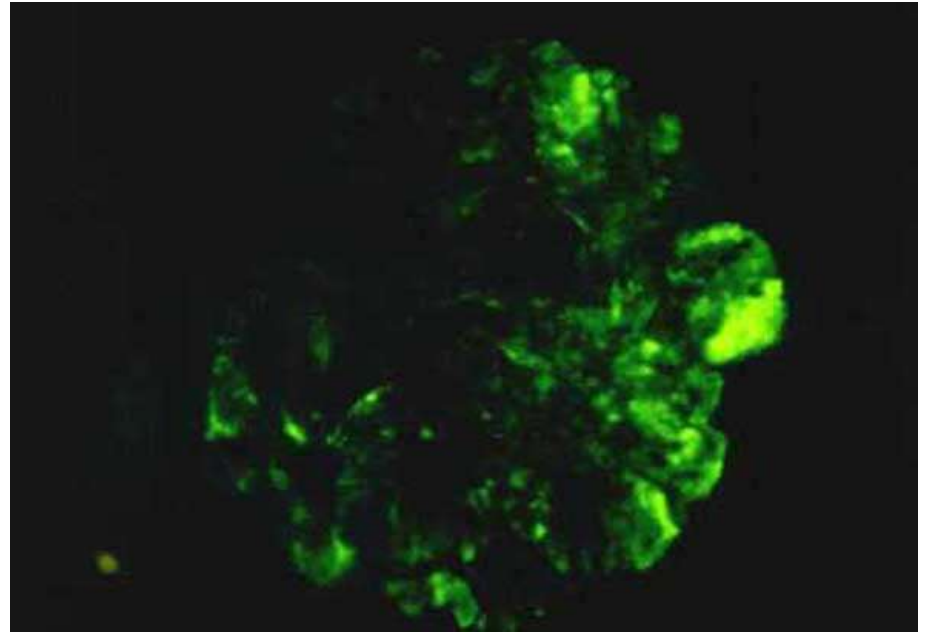
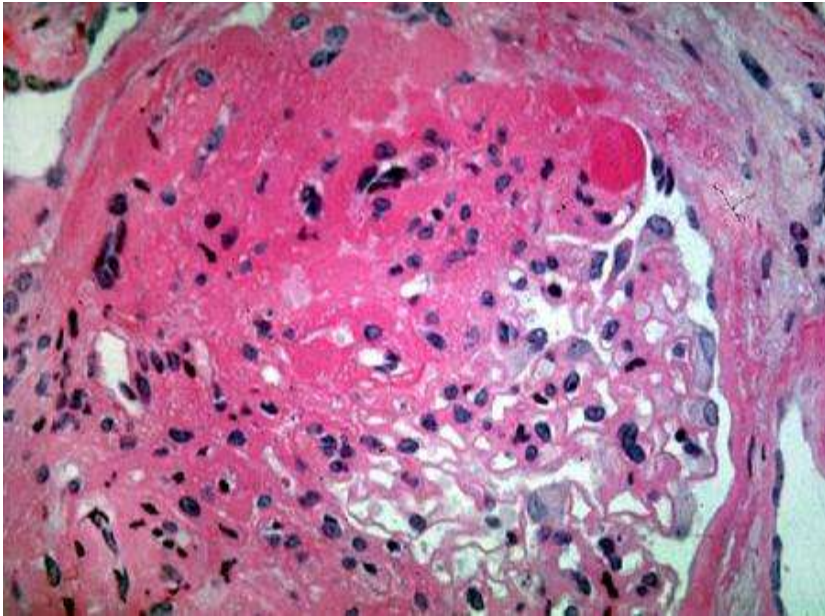
Focal segmental glomerulosclerosis

Focal segmental glomerulosclerosis



Segmental sclerosis that spread globally

Collapsing FSGS



Segmental sclerosis that spread globally causing collapse of capillary loops

Main features

- **Immune mediated**
- **Circulating permeability factor in the serum**
- **Massive selective proteinuria**
- **Renal impairment**
- **Resistance to steroid therapy**
- **Recurrence after renal transplantation**

Non immunological forms

- **Familial**
- **Secondary: obesity, sickle cell anemia, reflux nephropathy**

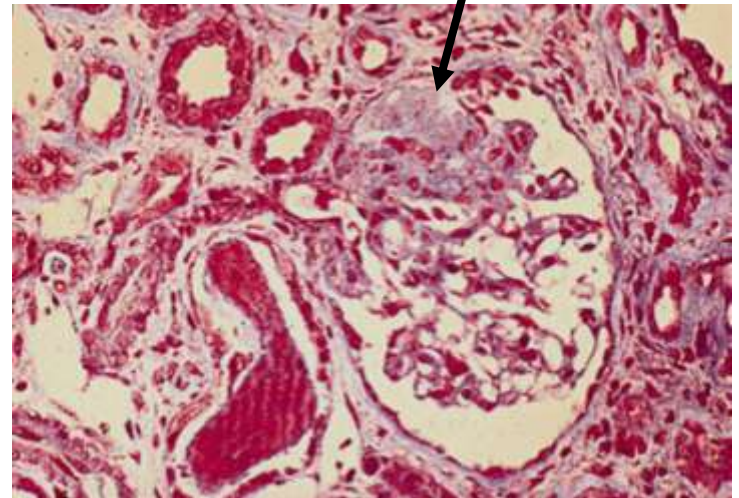
Treatment

1. Steroid 0.5 mg/d for 6 months
2. Cyclosporine 3-5 mg/day/6 months
3. Cylophosphamide 1-1.5 mg/day for 3-6 months



HIV Nephropathy

- HIV associated FSGS is characterized by collapse of capillary loops
- Coarse vacuulations in the cytoplasm
- Affects blacks
- Progression to ESRD
- HAART therapy stabilizes kidney function and proteinuria



Diabetic nephropathy

Diabetic nephropathy

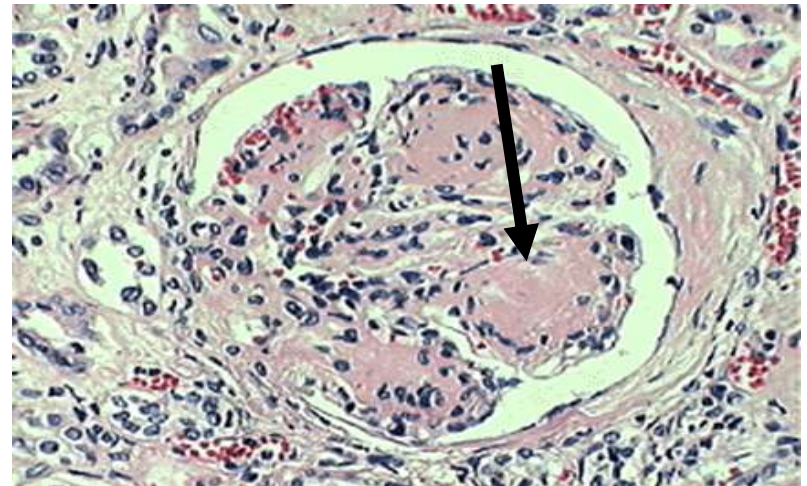
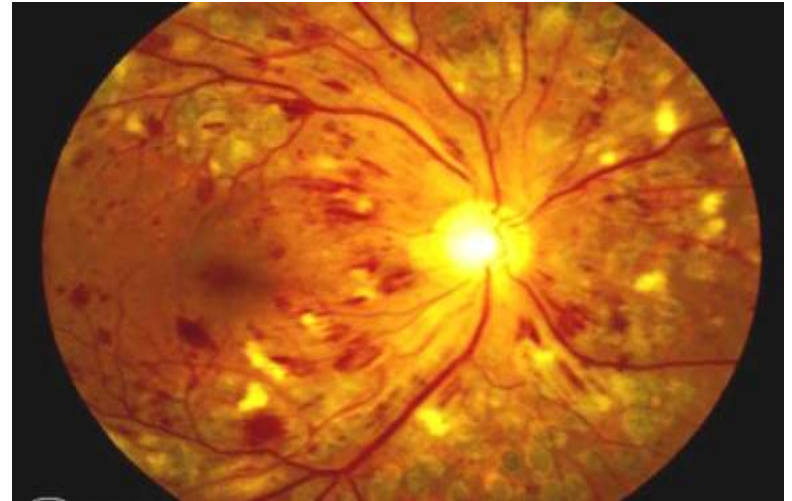
- 15 years after onset of DM in type I and variable onset in type II
- 25-35% of Diabetics will develop DN
- Genetic basis, uncontrolled blood sugar, high blood pressure
- 5 stages (hyperfiltration, micro, macroalbuminuria, NS, Progressive renal failure)



Kimmelstiel -Wilson syndrome
Nodular diabetic glomerulosclerosis

Diabetic glomerulosclerosis

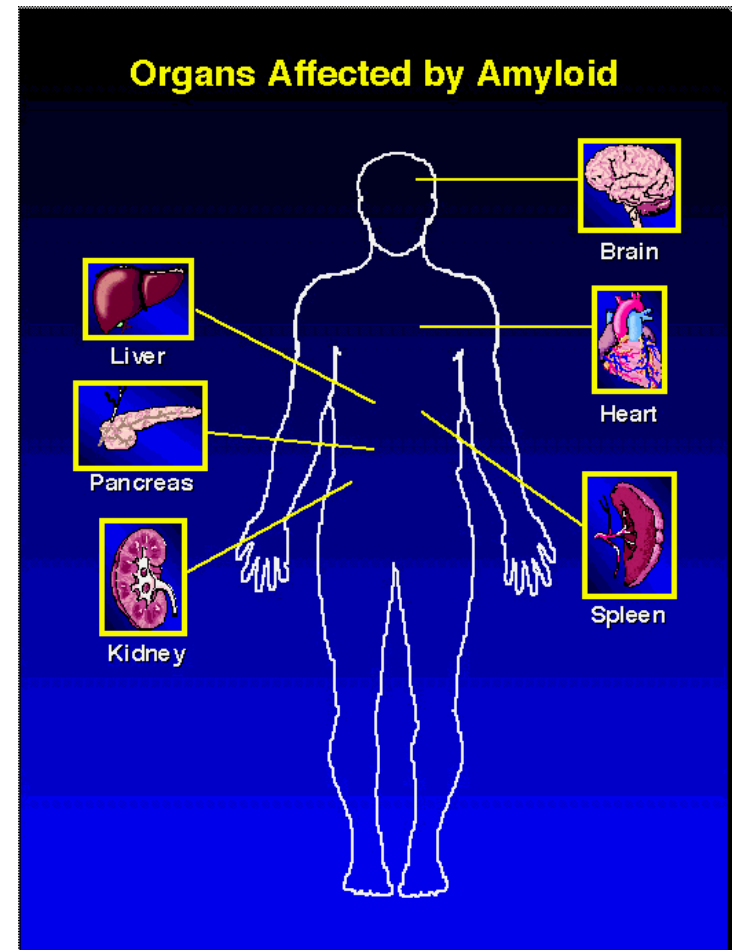
- Retinopathy
- Hypertension
- **Microalbuminuria**
- Strict control of blood glucose and blood pressure stabilize and reverse structural changes
- Renal failure – usually progressive
- Poor prognosis on RRT



Amyloidosis

Amyloidosis

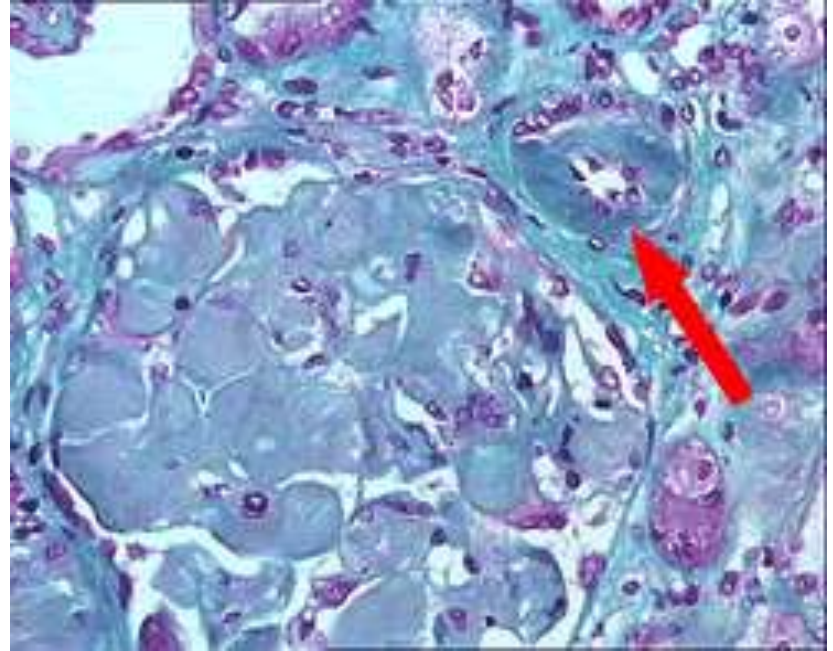
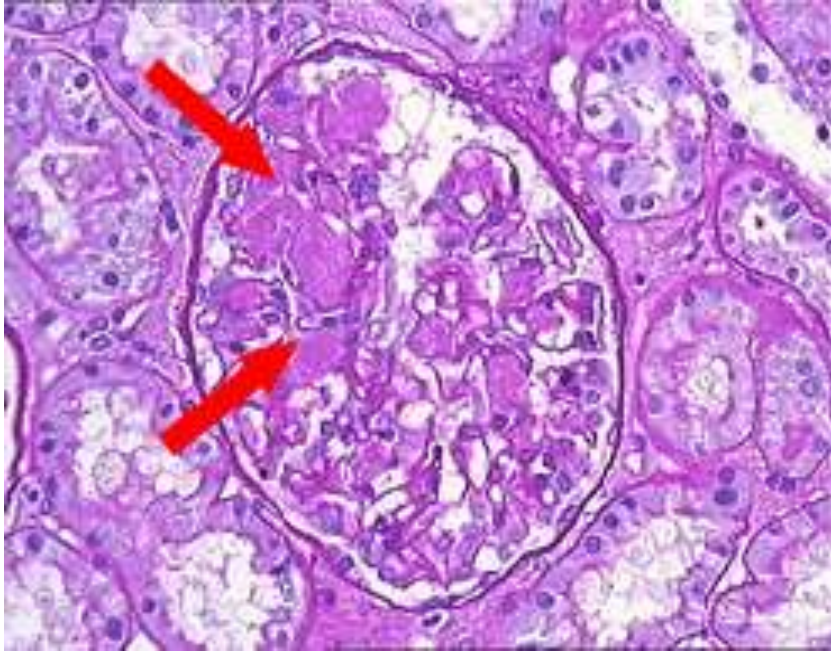
- Amyloid proteins are abnormally deposited in organs and/or tissues
- Over production of immunoglobulin light chains in MM (AL amyloid)
- Overproduction of acute phase proteins in chronic inflammation (AA amyloid)



Primary Amyloidosis

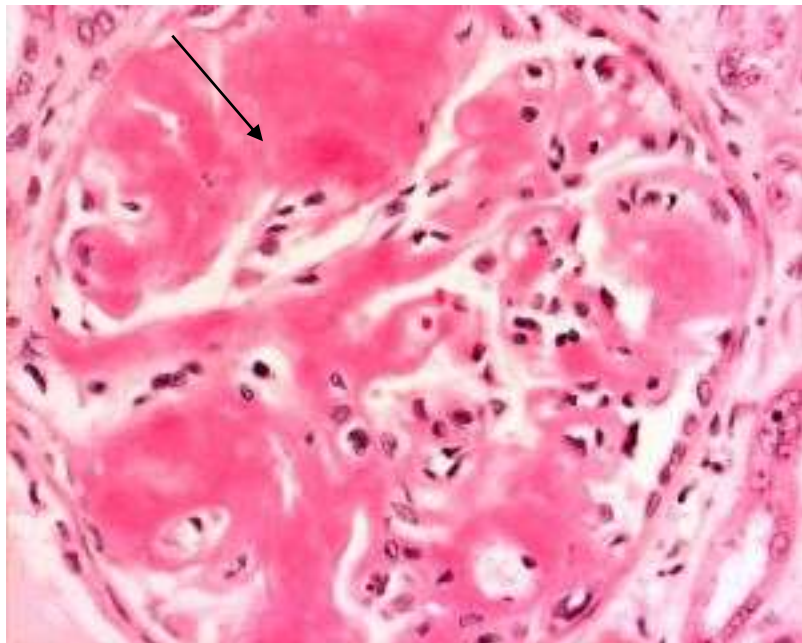
- Carpal tunnel syndrome
- Cardiomyopathy leading to congestive heart failure
- Intestinal malabsorption
- Liver enlargement
- Kidney failure
- Nephrotic syndrome

By light microscopy, amyloid appears as an amorphic, eosinophilic, extracellular substance



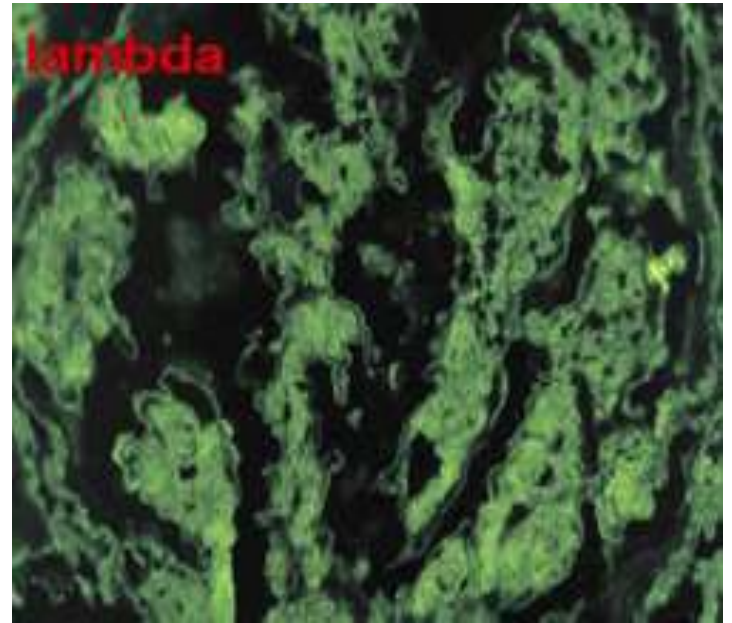
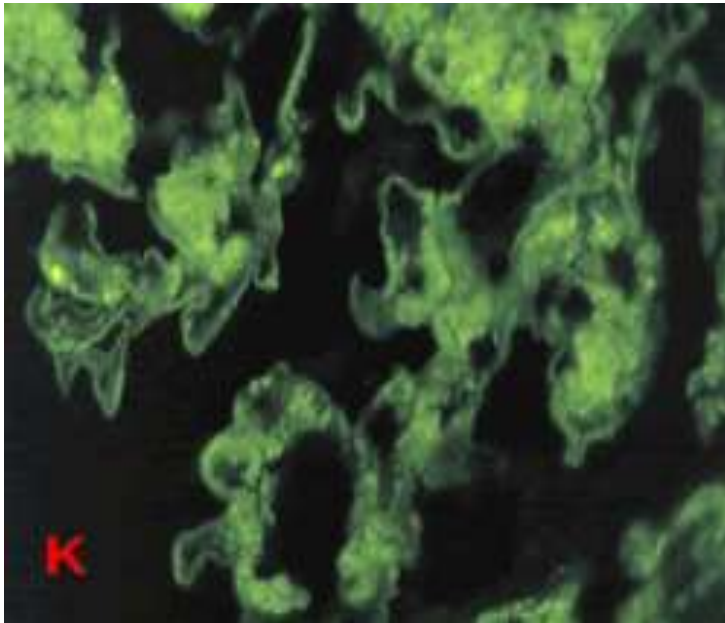
Its deposition is present not only in glomeruli, but also in the wall of arteries and arterioles

Congo Red staining



A typical apple-green birefringence under polarized light

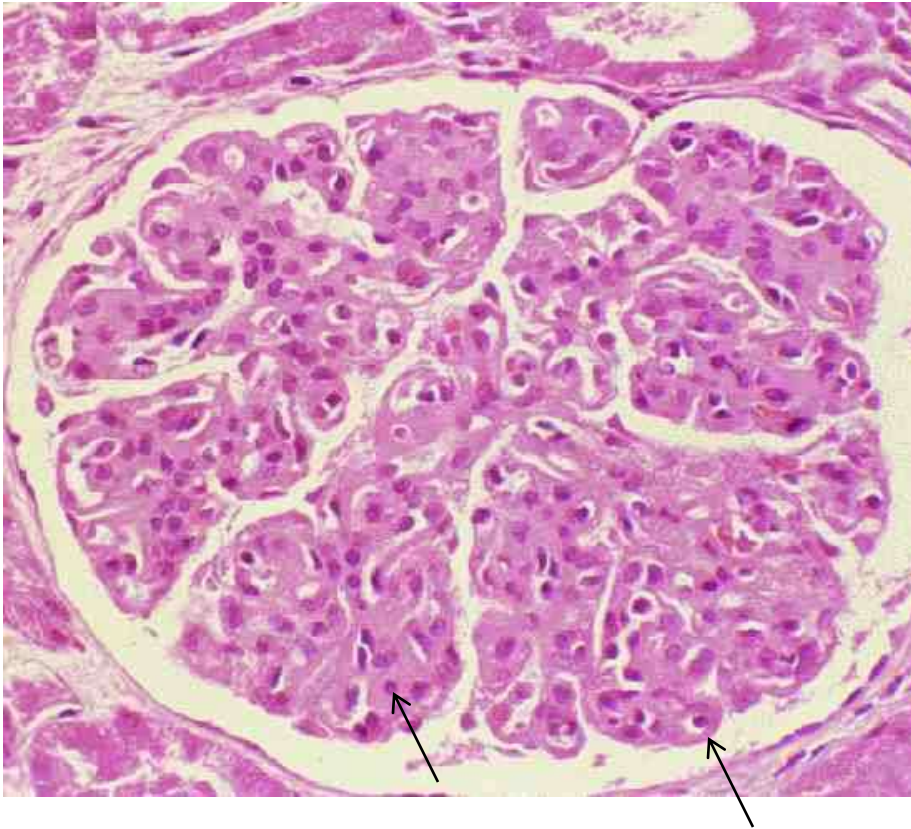
AL Amyloidosis



Anti-immunoglobulin light chains (κ e λ) are useful for amyloid AL diagnosis

Membranoproliferative GN

Membranoproliferative GN



Thickening of capillary walls usually global and diffuse

There is also hypercellularity

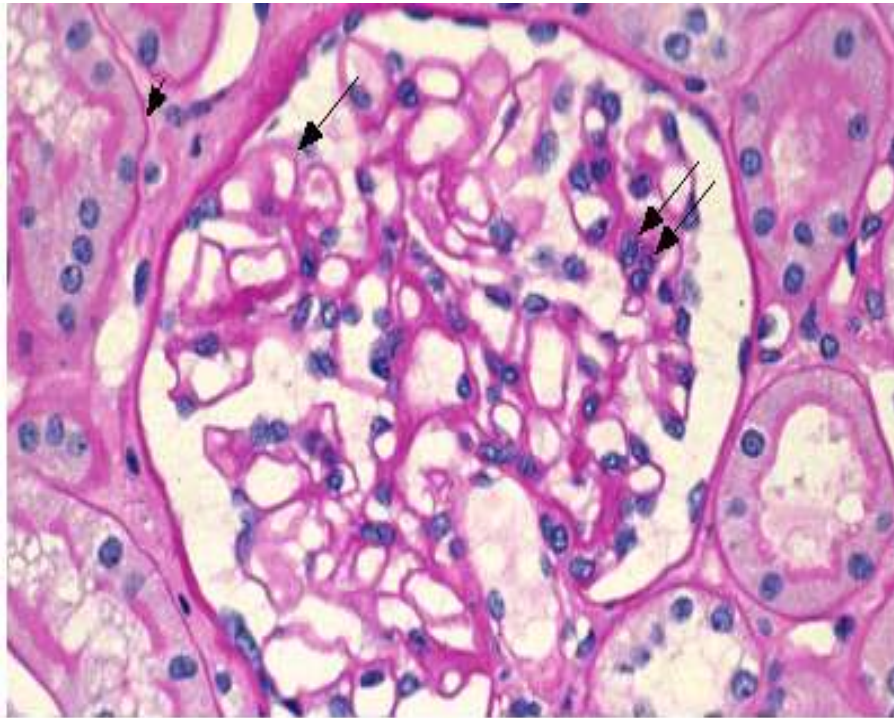
Much of this hypercellularity is mesangial proliferation

And some of the capillary wall thickening is caused by mesangial interposition into the subendothelial zone of the capillary loops

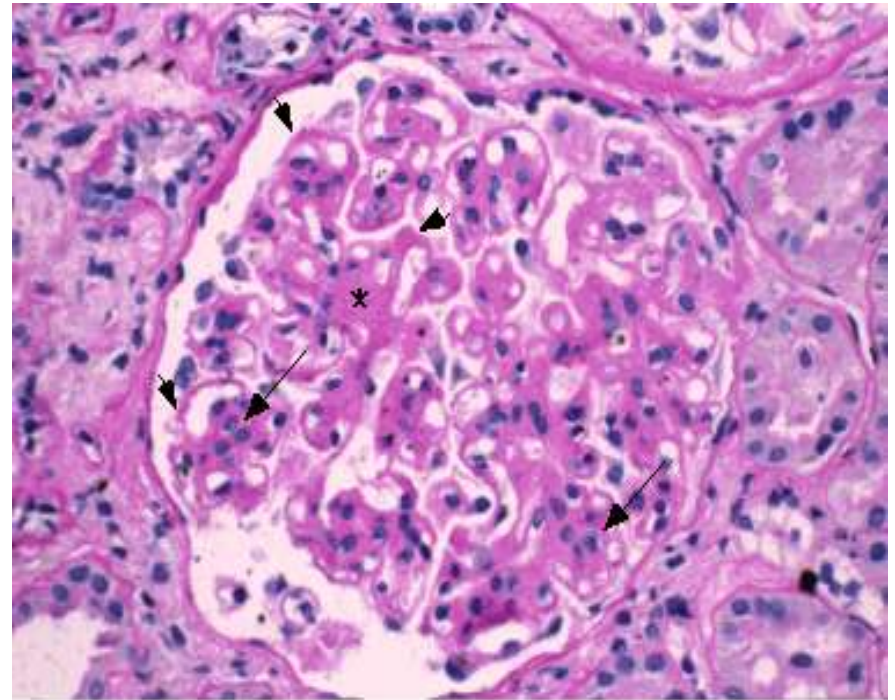
Etiology

- **Primary (idiopathic) vs. Secondary**
- **Autoimmune disorders – SLE, Sjogren's, Rheumatoid arthritis**
- **Infections – chronic infections rather than acute; Hep B, Hep C, SBE, ventriculoatrial shunt infection, chronic visceral abscess, HIV, schistosomiasis, malaria, leprosy**
- **Thrombotic microangiopathies – transplant glomerulopathy, antiphospholipid antibody syndrome, TTP/HUS, scleroderma**

Light microscopy

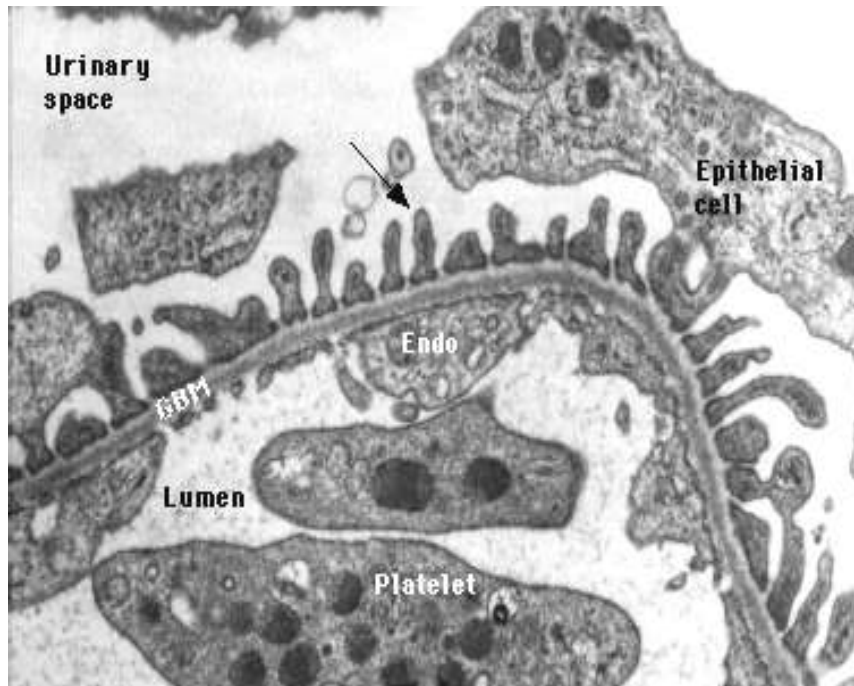


Normal glomerulus Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial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

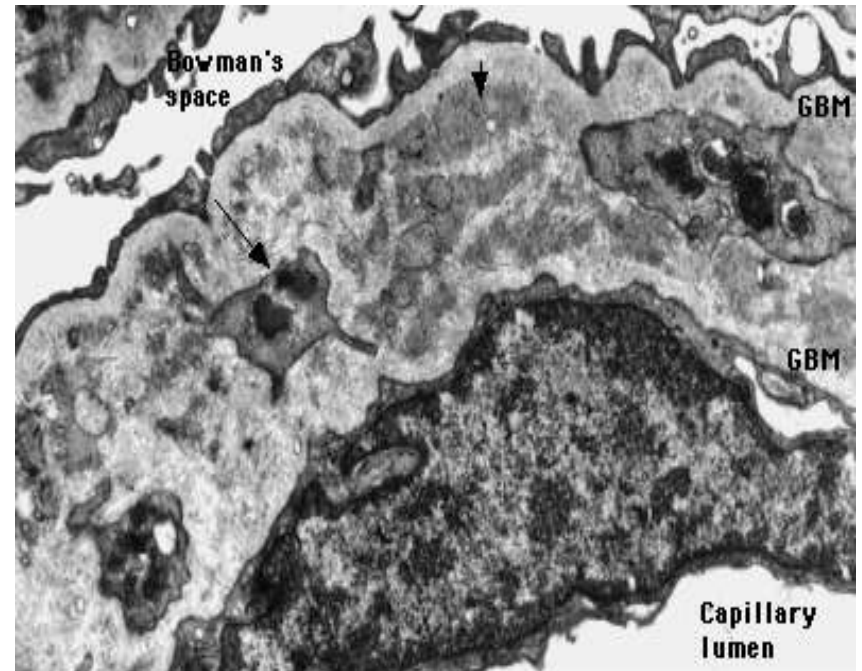


Membranoproliferative glomerulonephritis Light micrograph in membranoproliferative glomerulonephritis showing a lobular appearance of the glomerular tuft with focal areas of increased glomerular cellularity (large arrows), mesangial expansion (*), narrowing of the capillary lumens, and diffuse thickening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

Electron Microscopy-type 1

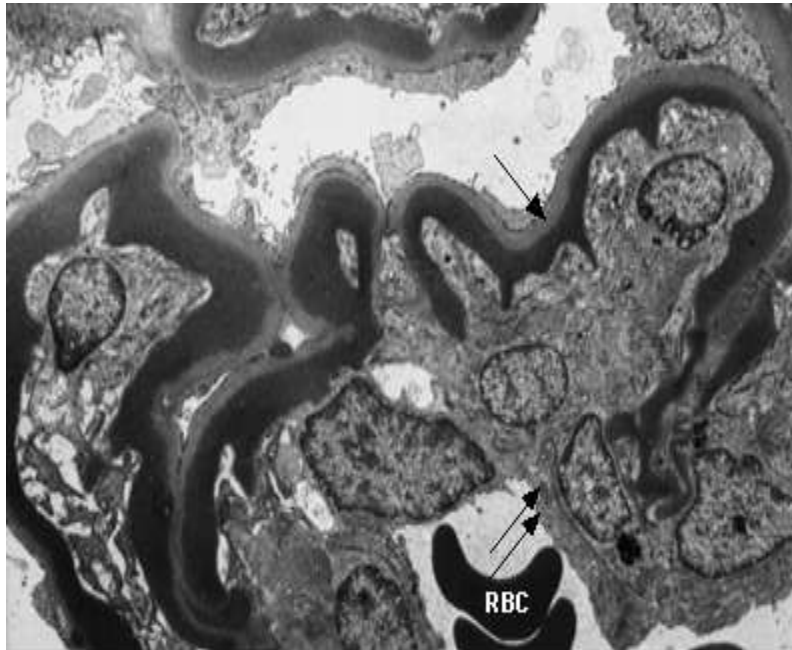


Normal glomerulus Electron micrograph of a normal glomerular capillary loop showing the fenestrated endothelial cell (Endo), the glomerular basement membrane (GBM), and the epithelial cells with its interdigitating foot processes (arrow). The GBM is thin and no electron dense deposits are present. Two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



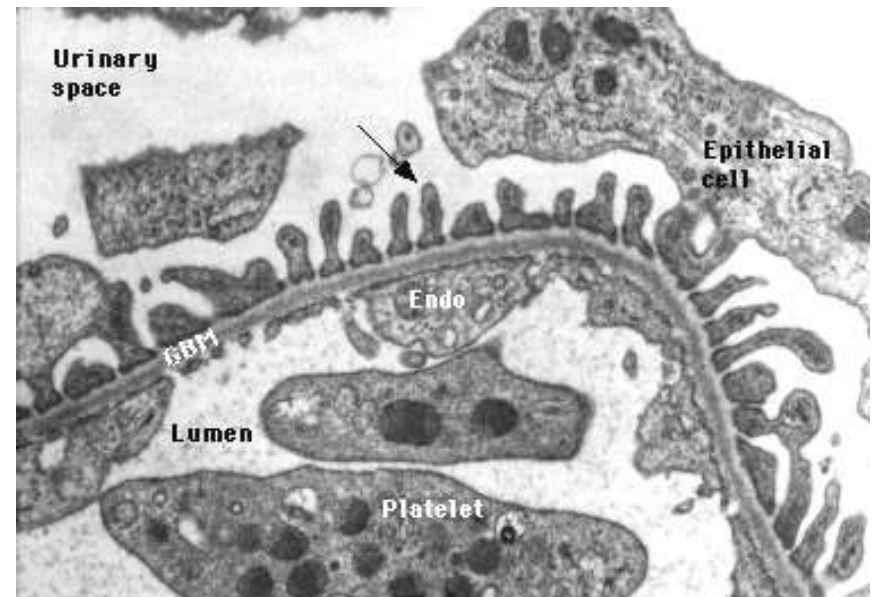
Type 1 MPGN Electron micrograph in type 1 membranoproliferative glomerulonephritis shows marked thickening of the glomerular capillary wall by immune deposits (short arrow) and by interposition of mesangial cell processes (long arrow). There are two layers of the glomerular basement membrane (GBM) surrounding the mesangial interposition that account for the double contour appearance on light microscopy. Courtesy of Helmut Rennke, MD.

E/M Type 2



Type 2 membranoproliferative glomerulonephritis

Electron micrograph in type 2 MPGN (dense-deposit disease) showing dense, ribbon-like appearance of subendothelial and intramembranous material (arrow) and narrowing of the capillary lumen due to proliferation of cells (double arrow). Courtesy of Helmut Rennke, MD.



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 Rennke, MD.

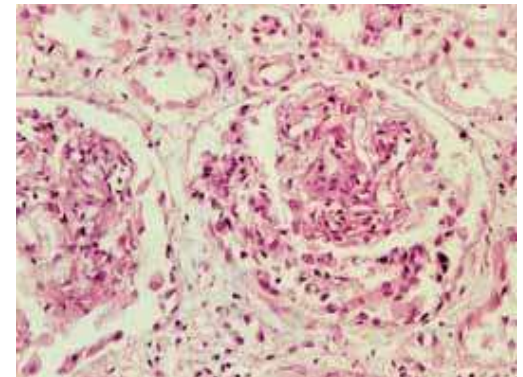
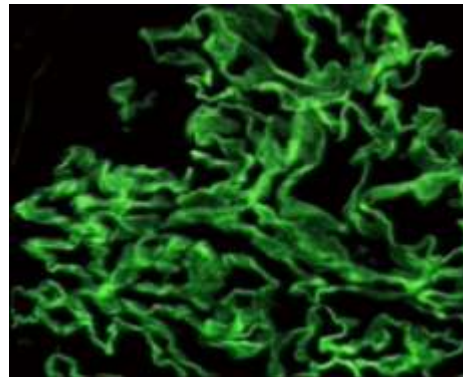
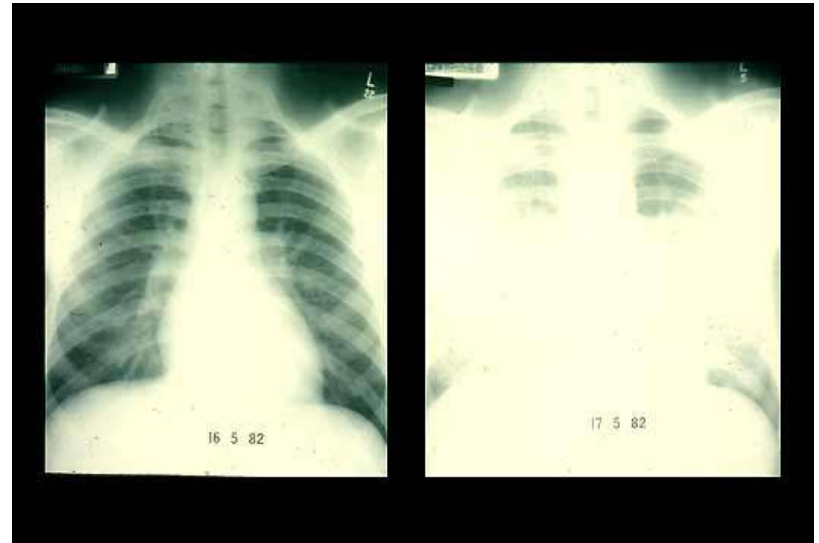
Management

- Idiopathic with normal kidney function and non-nephrotic proteinuria: non specific therapy
- Children with nephrotic syndrome $\pm$ renal impairment: trial of steroid 40 mg/EOD for 6-12 months. If no response DC
- Adults with nephrotic/nephritic syndromes: aspirin and treatment of underlying cause

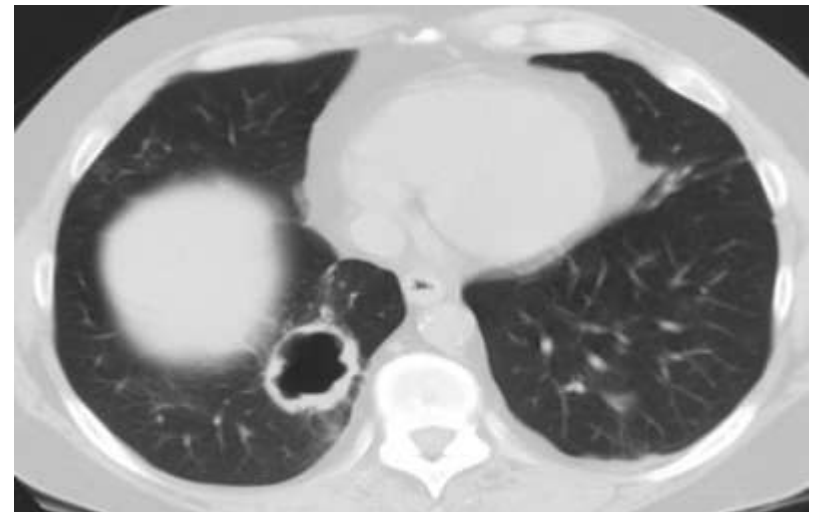
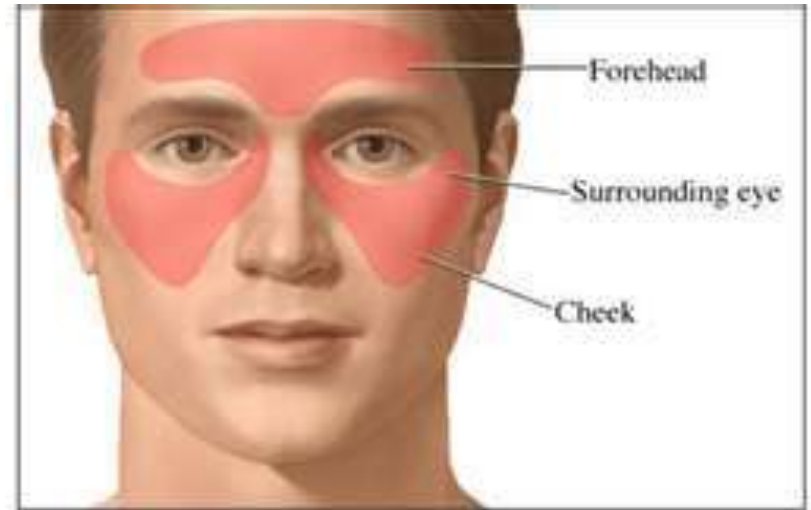
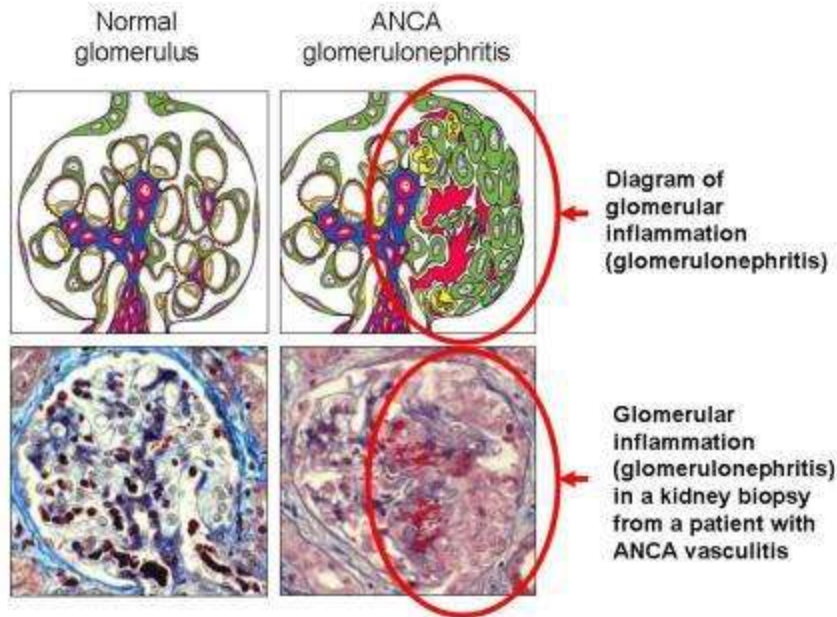
Rapid progressive GN

Anti GBM disease

- RPGN $\pm$ Lung haemorrhage
- Destructive process – medical emergency!
- Antibody-mediated
- High dose immunosuppression
- Plasma exchange

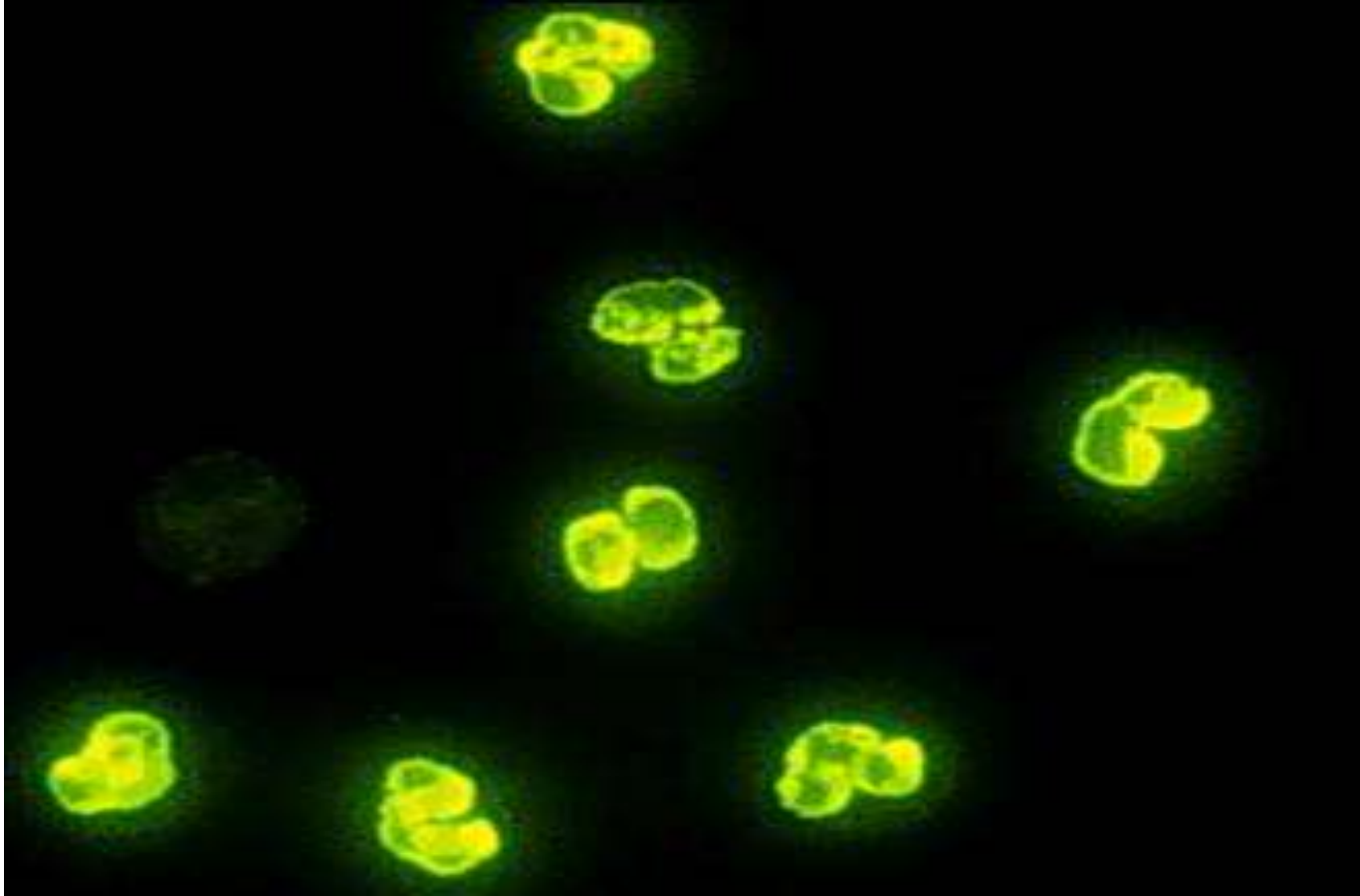


Wegner's granulomatosis



**Vasculitis affecting upper, lower respiratory
Tracts and glomeruli
Focal necrotizing lesions**

ANCA Test



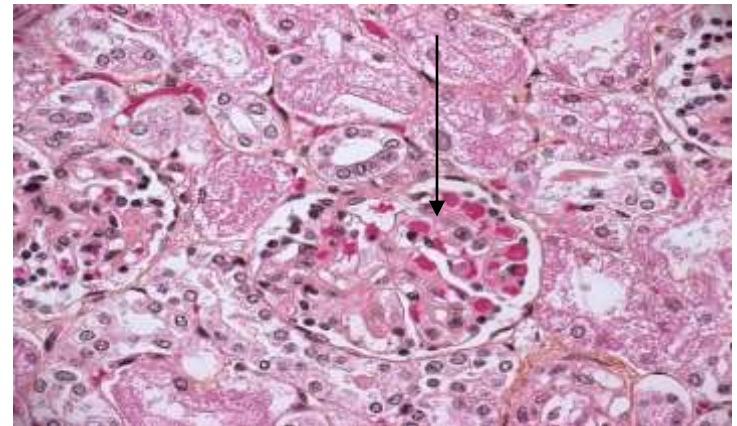
Antibodies against neutrophil cytoplasm

Management

- High dose corticosteroid IV (methylprednisolone 1 g/d/3days)
- Cyclophosphamide 2 mg/kg/day
- Plasma exchange if fulminate disease

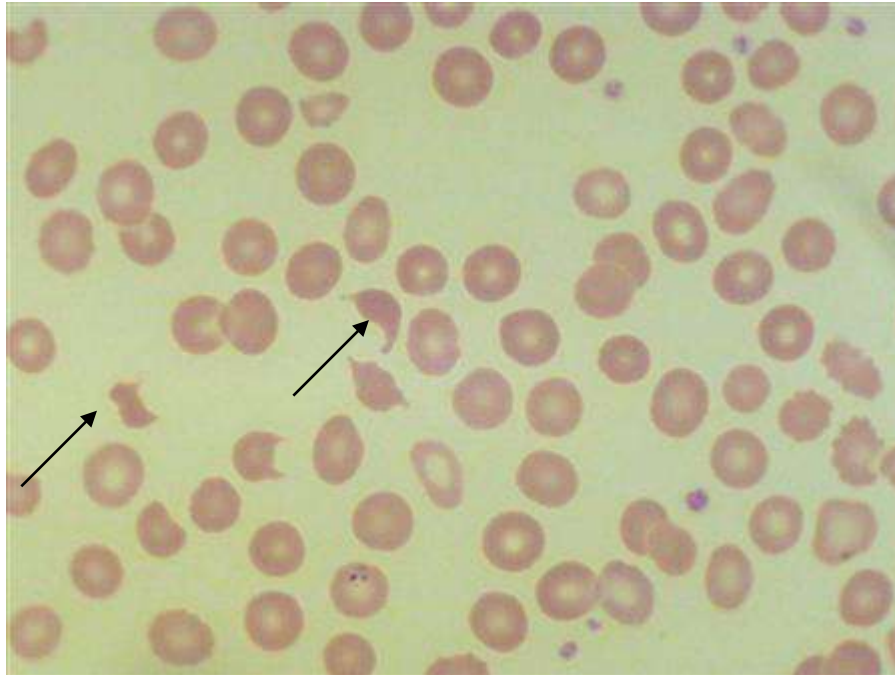
Thrombotic microangiopathy

- **Thrombotic thrombocytopenic purpura (TTP)** is a [rare disorder](#) of the [blood-coagulation](#) system causing extensive microscopic [thromboses](#) to form in small blood vessels throughout the body ([thrombotic microangiopathy](#))



- Most cases of TTP arise from inhibition of the [enzyme ADAMTS13](#), a metalloprotease responsible for cleaving large multimers of [von Willebrand factor](#) (vWF) into smaller units.

TMA



Red blood cells passing the microscopic clots are subjected to [shear stress](#) which damages their membranes leading to intravascular [hemolysis](#) and [schistocyte](#) formation

C/P

- Classically, the following five features ("pentad") are indicative of TTP

1. **Neurologic symptoms**

2. **Fever**

3. **Hemolysis**

4. **Thrombocytopenia**

5. **Renal Failure**

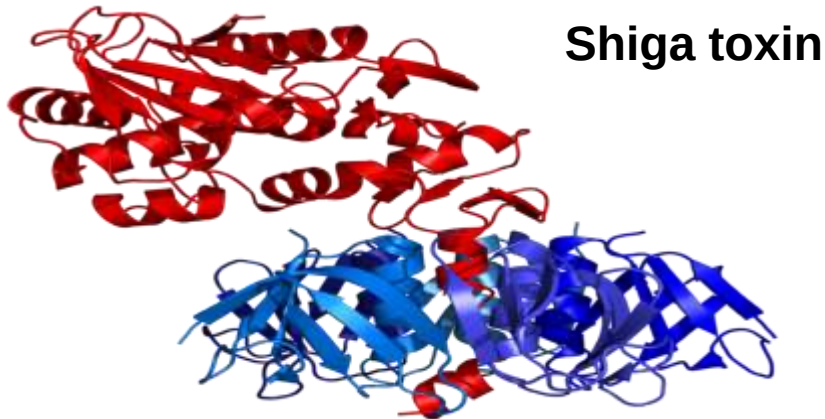
Treatment with plasma exchanges

Immunosuppression in refractory cases

Hemolytic uremic syndrome

A disease characterized by [hemolytic anemia](#), [acute renal failure](#), low [platelet](#) count
It predominantly affects children

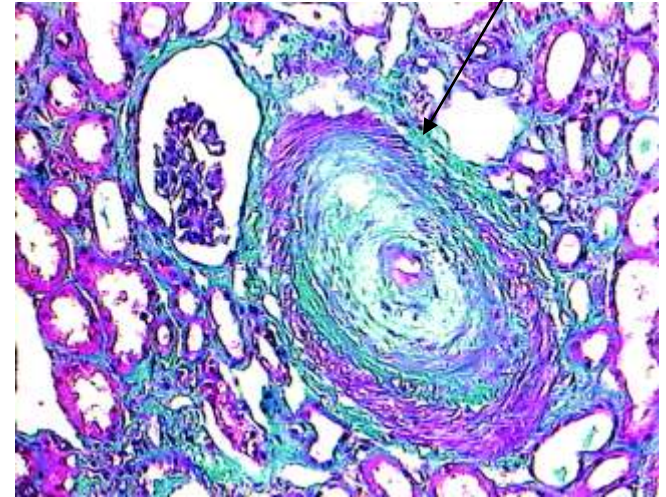
Most cases are preceded by an episode of [diarrhea](#) caused by [E. coli O157:H7](#), which is acquired as a [foodborne illness](#)



Hemolytic uremic syndrome

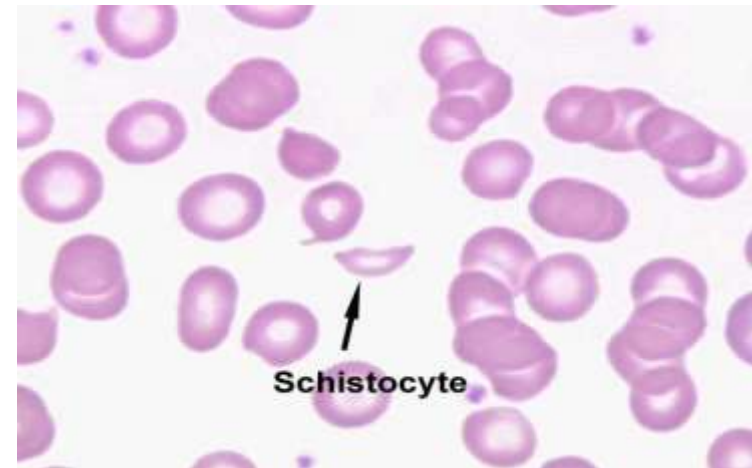
Secondary causes in Adults

[HIV](#); antiphospholipid syndrome; postpartum renal failure
[malignant hypertension](#); [scleroderma](#); and certain drugs
including some [chemotherapy](#) drugs
and other [immunosuppressive](#) agents (cyclosporine, [cisplatin](#))



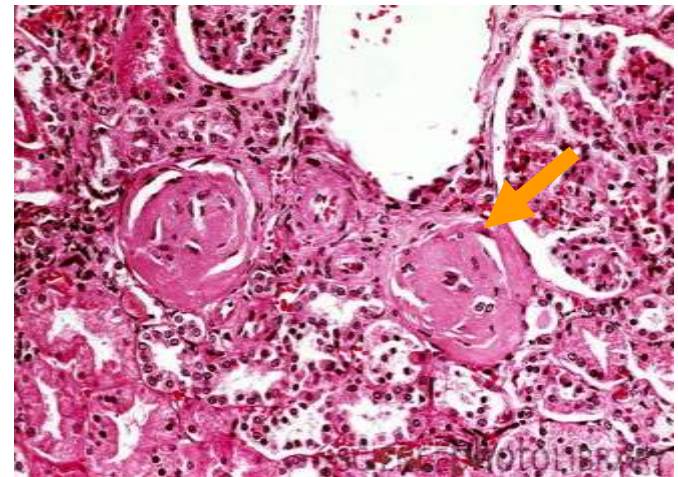
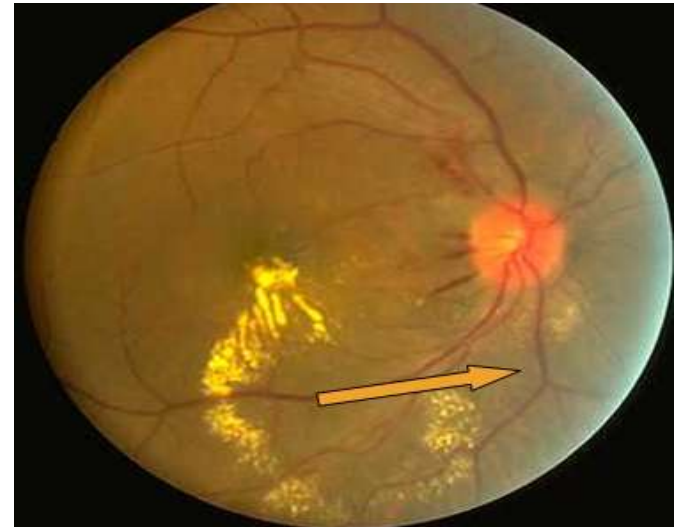
[Hemolytic anemia](#), [thrombocytopenia](#), and [acute renal failure](#)

Most cases recover spontaneously
No role for immunosuppression
PE in adults



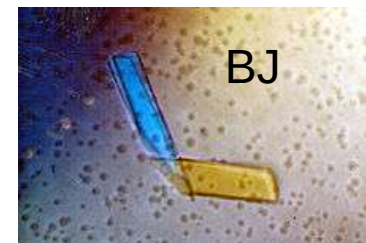
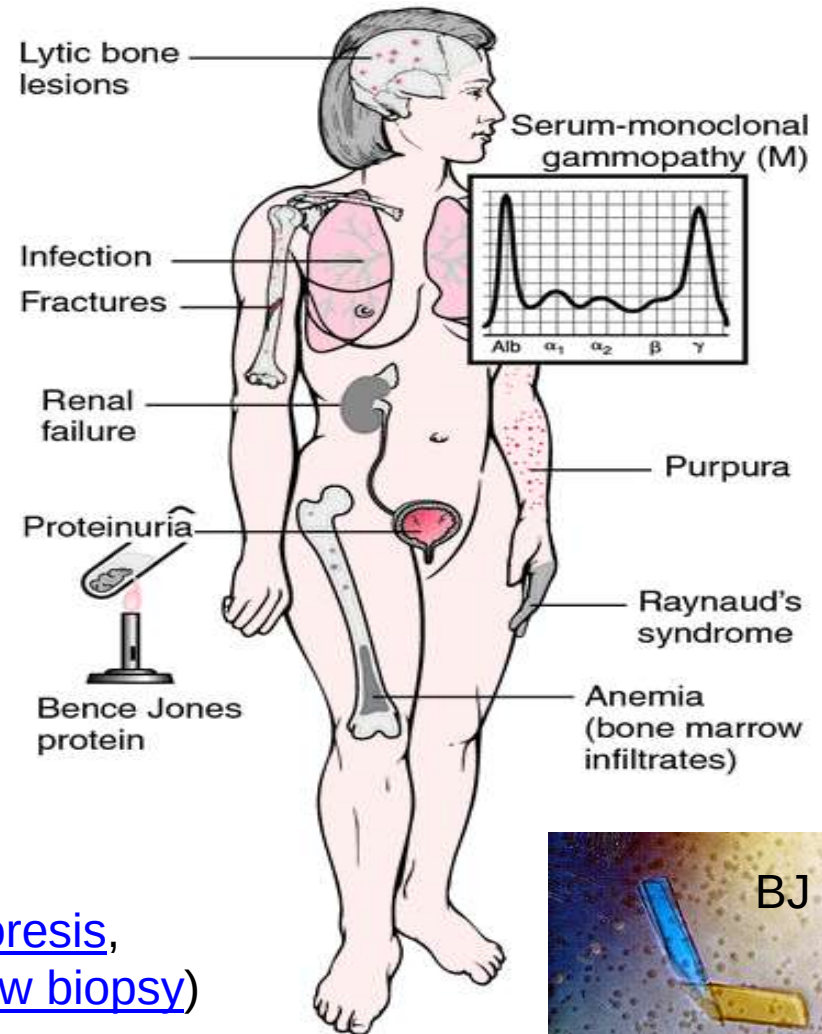
Hypertensive nephrosclerosis

- As a result of *benign* [arterial hypertension](#), [hyaline](#) (pink, amorphous, homogeneous material) accumulates in the wall of small arteries and arterioles, producing the thickening of their walls and the narrowing of the [lumina](#) — hyaline [arteriosclerosis](#)
- Consequent [ischemia](#) will produce [tubular atrophy](#), [interstitial fibrosis](#), glomerular alterations (smaller [glomeruli](#) with different degrees of hyalinization - from mild to sclerosis of glomeruli) and periglomerular fibrosis
- In advanced stages, [renal failure](#) will occur



Paraproteinemia

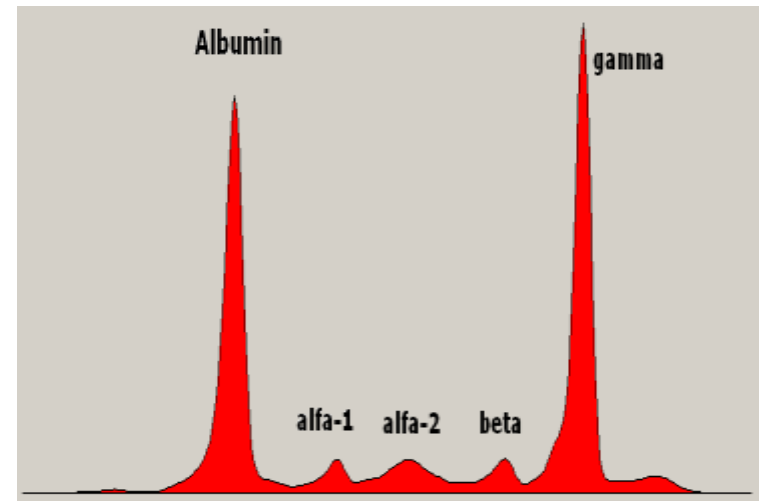
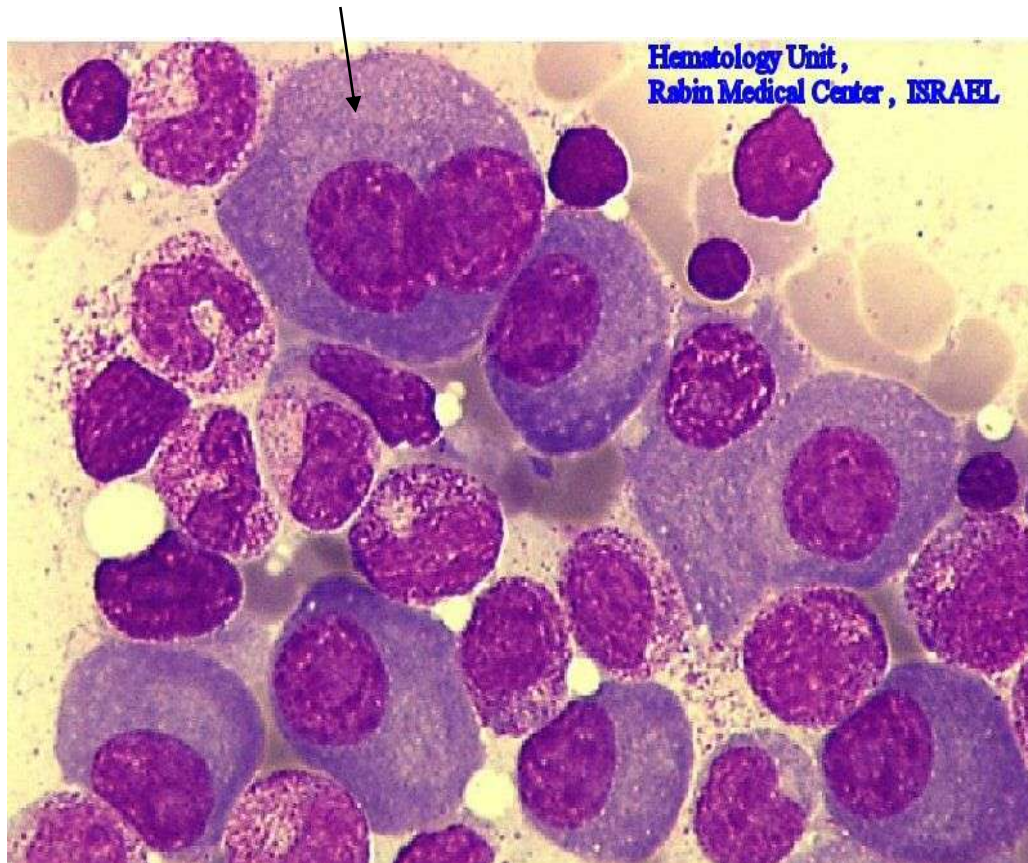
Clinical presentation of MM



Myeloma is diagnosed with [protein electrophoresis](#),
Examination of the bone marrow ([bone marrow biopsy](#))
[Radiographs](#) of commonly involved bones

Bone marrow

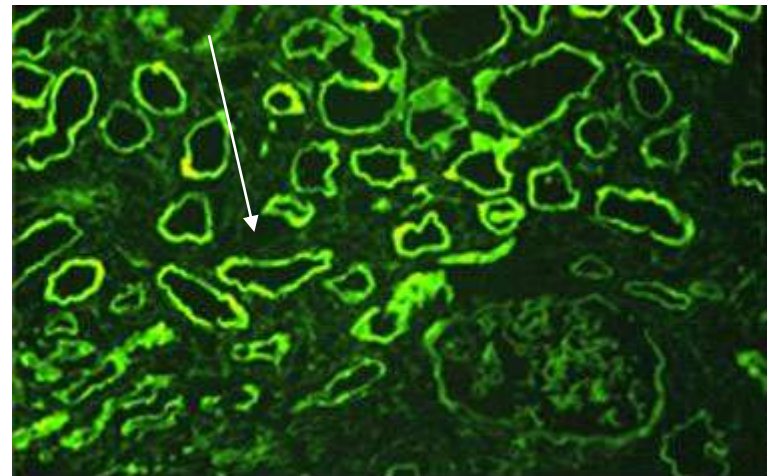
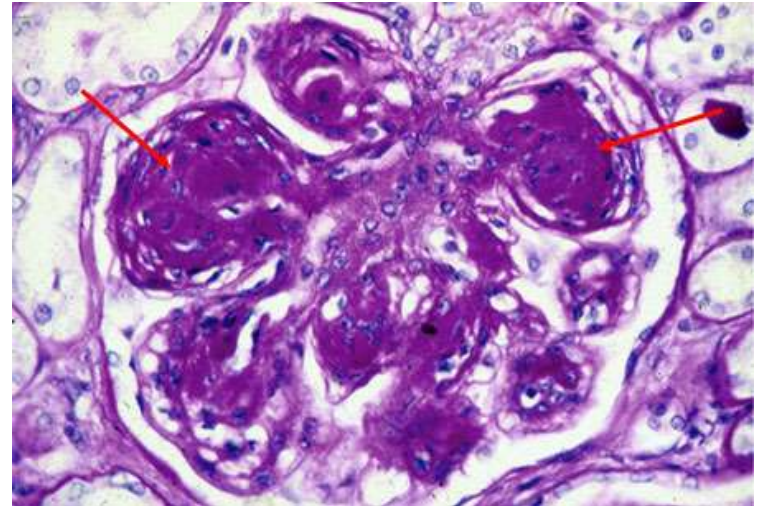
Abnormal plasma cells



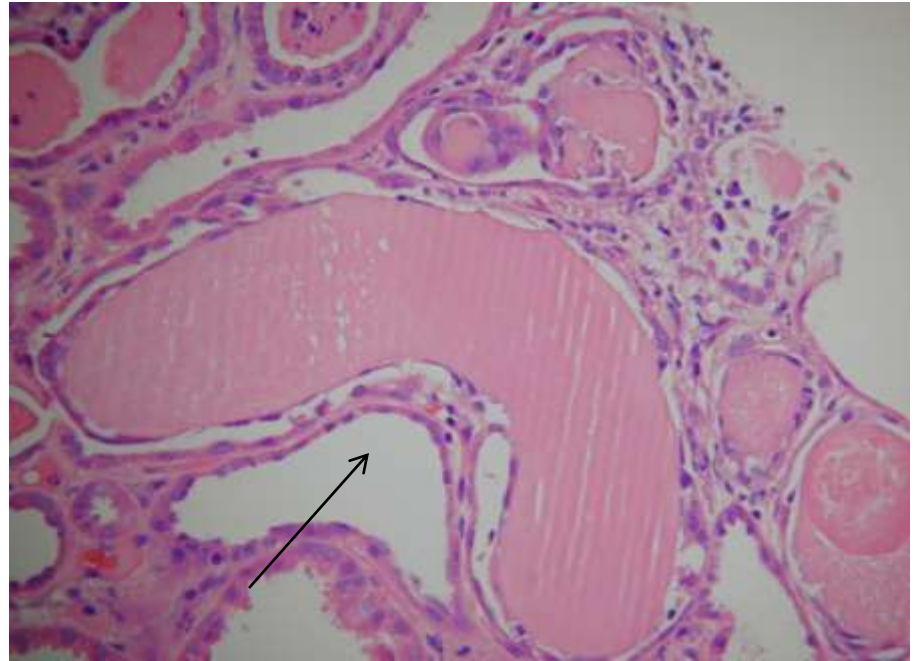
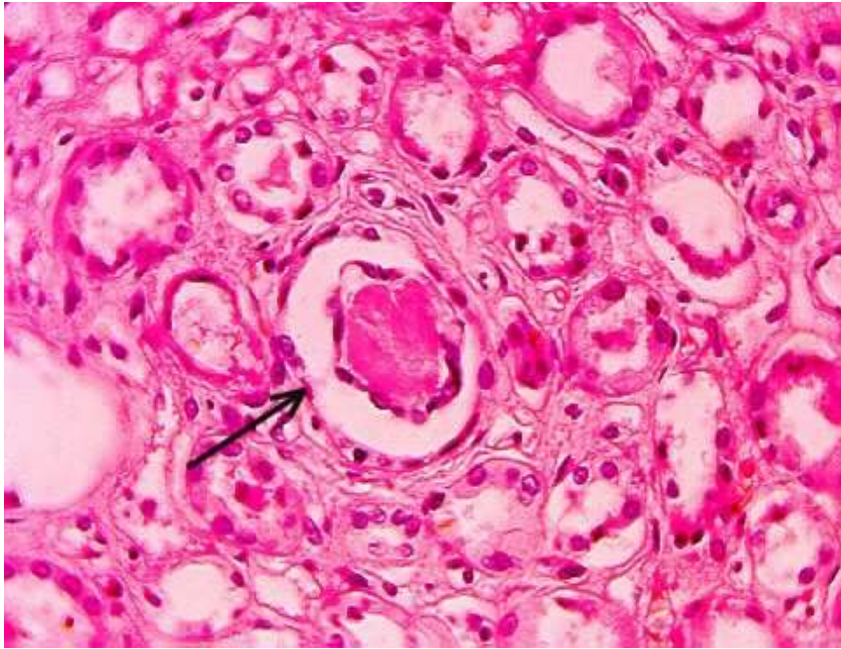
Serum [protein electrophoresis](#) showing a paraprotein (peak in the gamma zone) in a patient with MM

Renal lesions

- Light chain nephropathy
- AL Amylodosis
- Tubular defects (Fanconi's syndrome)
- Hypercalcaemia
- Hyperuricaemia



Multiple Myeloma



Cast Nephropathy (fractured casts of light chain and TH protein)

HCV Related GN

HCV Related GN

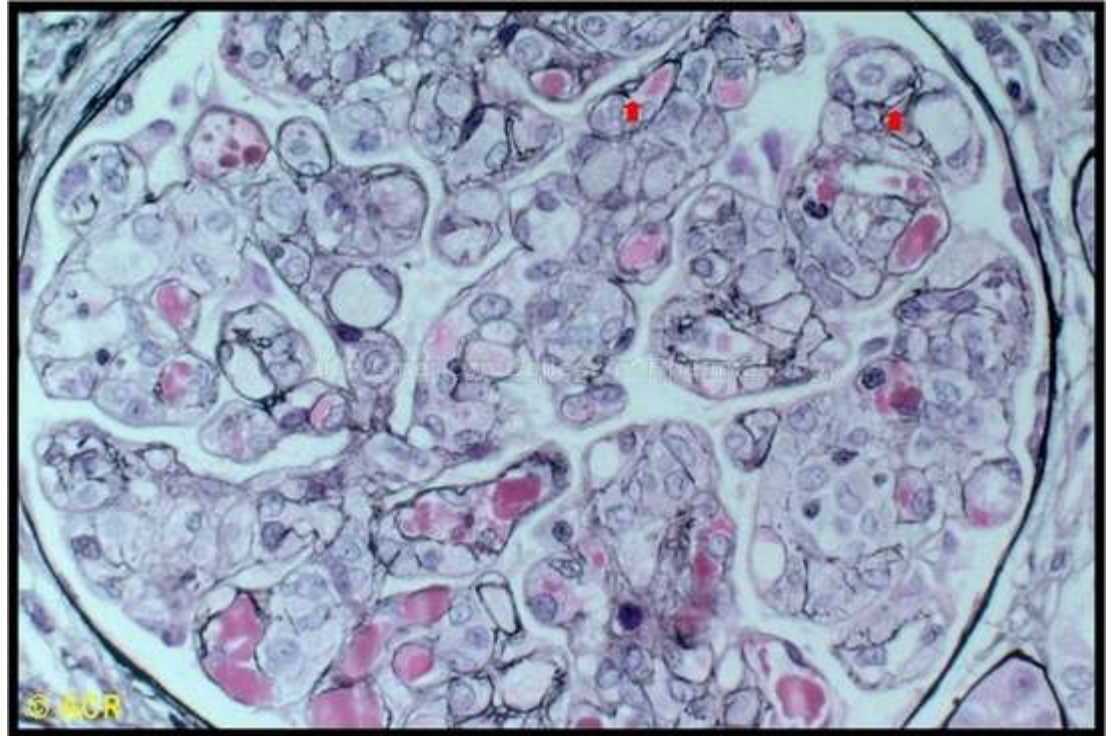
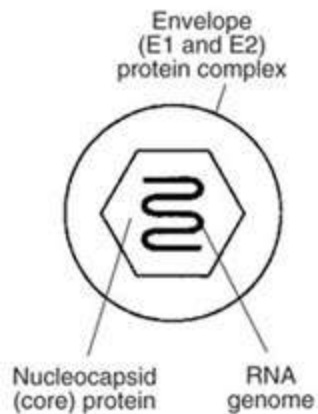
- **HCV RNA is found in the cryo-precipitates in HCV patients strongly suggesting a pathogenic role for HCV in cryoglobulin-related disease**
- **HCV core antigens bound to specific IgG, which was in turn bound to rheumatoid factor (IgM)**
- **Low complement, positive rheumatoid factor, positive cryoglobulin test**

HCV Related GN



CRYOGLOBULIN RASH

HCV Viral Components



**Treatment by steroid, cytotoxic drugs, PE,
Antiviral**

LUPUS NEPHRITIS

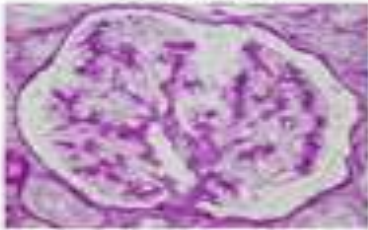
Classification of Lupus Nephritis

Table 2. World Health Organization (WHO) morphologic classification of lupus nephritis (modified in 1982)

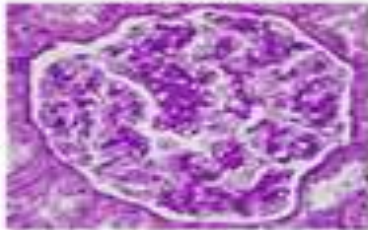
Class I	Normal glomeruli a. Nil (by all techniques) b. Normal by light microscopy, but deposits by electron or immunofluorescence microscopy
Class II	Pure mesangial alterations (mesangiopathy) a. Mesangial widening and/or mild hypercellularity (+) b. Moderate hypercellularity (++)
Class III	Focal segmental glomerulonephritis (associated with mild or moderate mesangial alterations) a. With “active” necrotizing lesions b. With “active” and sclerosing lesions c. With sclerosing lesions
Class IV	Diffuse glomerulonephritis (severe mesangial, endocapillary or mesangio-capillary proliferation and/or extensive subendothelial deposits) a. Without segmental lesions b. With “active” necrotizing lesions c. With “active” and sclerosing lesions d. With sclerosing lesions
Class V	Diffuse membranous glomerulonephritis a. Pure membranous glomerulonephritis b. Associated with lesions of class II c. Associated with lesions of class III d. Associated with lesions of class IV
Class VI	Advanced sclerosing glomerulonephritis

Classification of Lupus Nephritis

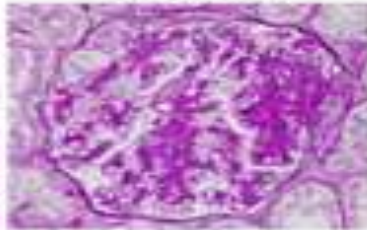
Class I



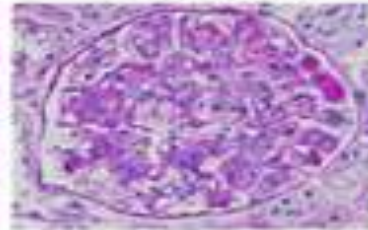
Class II



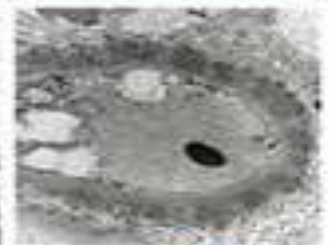
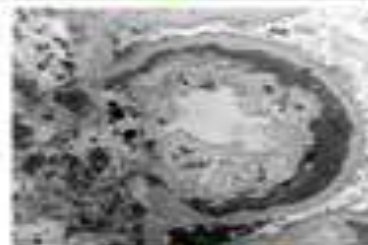
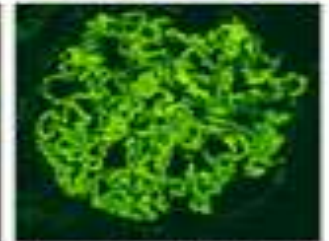
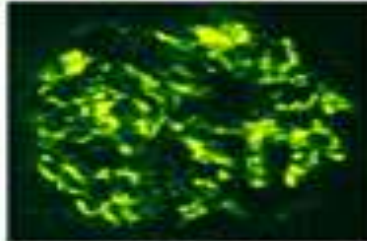
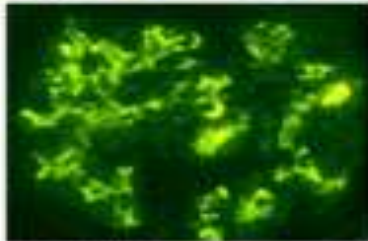
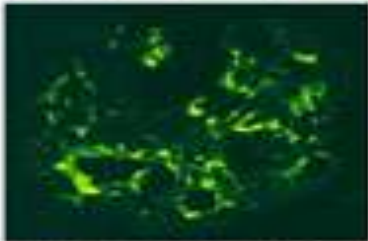
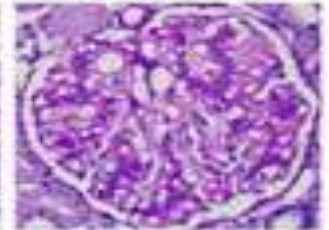
Class III



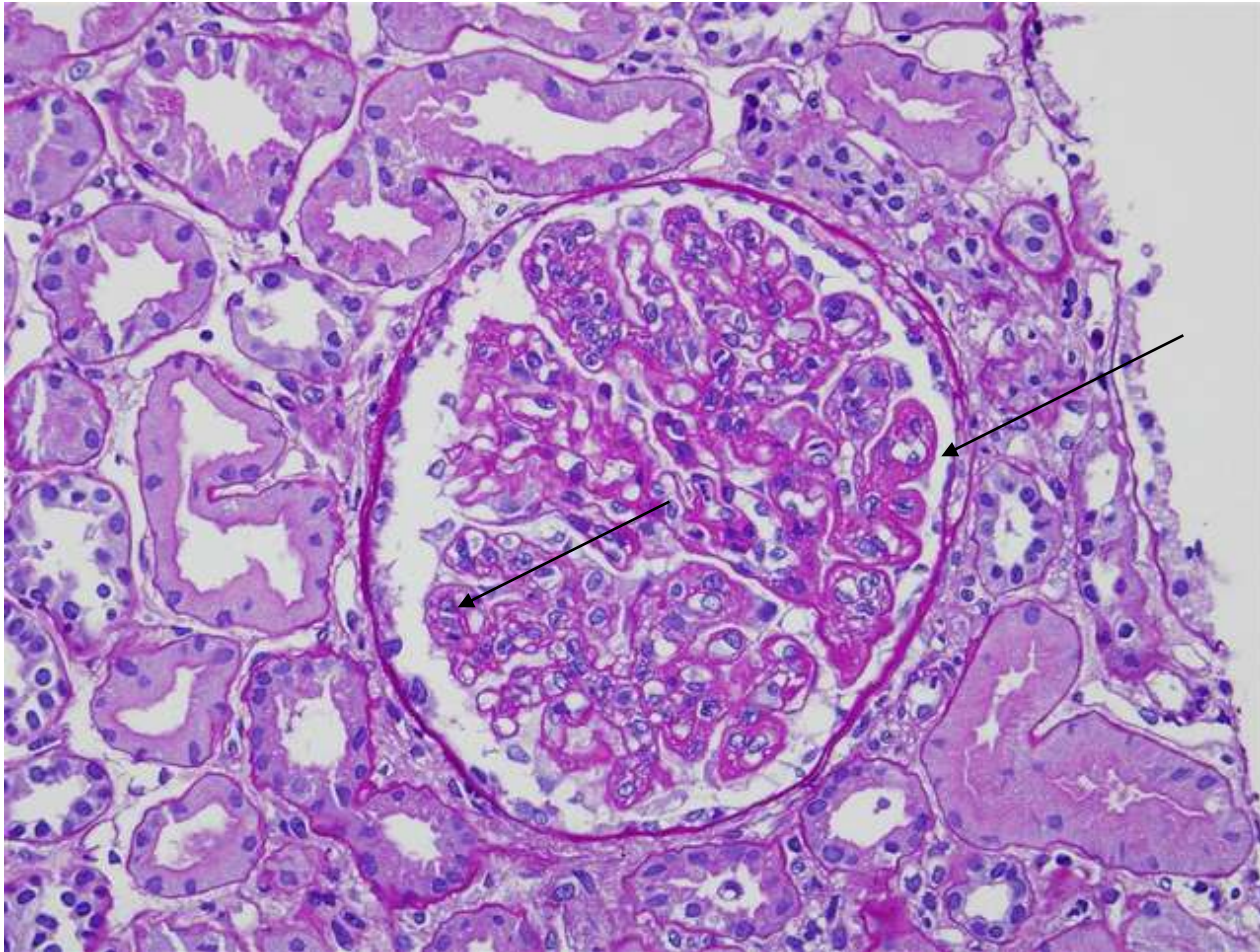
Class IV



Class V

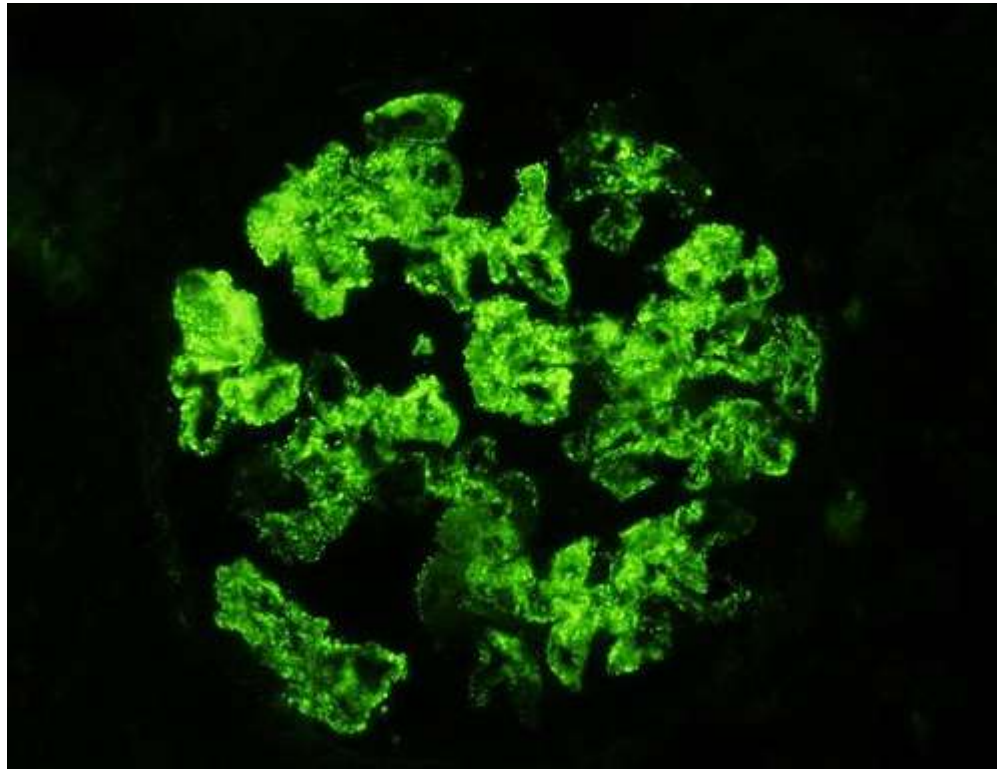


Lupus nephritis class IV-V



Mixed lesions (endocapillary proliferation and BM Thickening)

Immunofluorescence



IgG, IgM and C3 deposition in a granular pattern

Treatment

- Class I is minimal mesangial glomerulonephritis which is histologically normal on light microscopy but with mesangial deposits on electron microscopy. It constitutes about 5% of cases of lupus nephritis. Renal failure is very rare in this form
- Class II is based on a finding of mesangial proliferative lupus nephritis. This form typically responds completely to treatment with corticosteroids. It constitutes about 20% of cases. Renal failure is rare in this form
- Class III is focal proliferative nephritis and often successfully responds to treatment with high doses of corticosteroids. It constitutes about 25% of cases. Renal failure is uncommon in this form
- Class IV is diffuse proliferative nephritis. This form is mainly treated with corticosteroids and immunosuppressant drugs. It constitutes about 40% of cases. Renal failure is common in this form
- Class V is membranous nephritis and is characterized by extreme edema and protein loss. It constitutes about 10% of cases. Renal failure is uncommon in this form

Treatment of class III-IV

- Steroid 1mg/kg/day for 4 weeks and taper slowly
- IV solumedrol in RPGN
- Cyclophosphamide monthly doses for 6 months
- Mycophenolate mofetil (cellcept) maintenance dose of 1 gram BID for 2-3 years to maintain remission



Side effects of cyclo: neutropenia, bladder toxicity
Cellcept: bone marrow suppression, infections



Case history

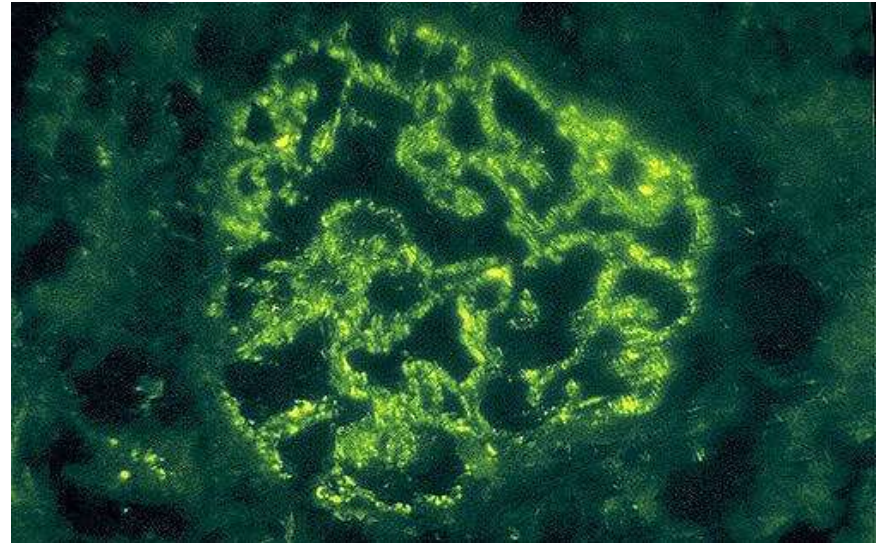
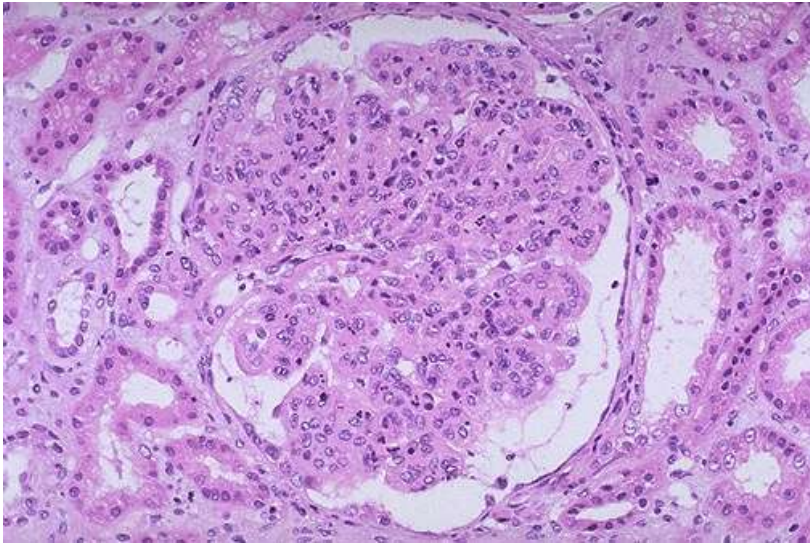


Case -1

Clinical History

- A 10 year old girl was brought by her parents to their family physician
- History revealed that the child had a sore throat for about 10 days prior to the office visit.
- Initial laboratory tests ordered by the family physician revealed an elevated BUN and creatinine
- A urinalysis showed haematuria with dysmorphic RBC's
- A renal biopsy was performed next

Renal Biopsy



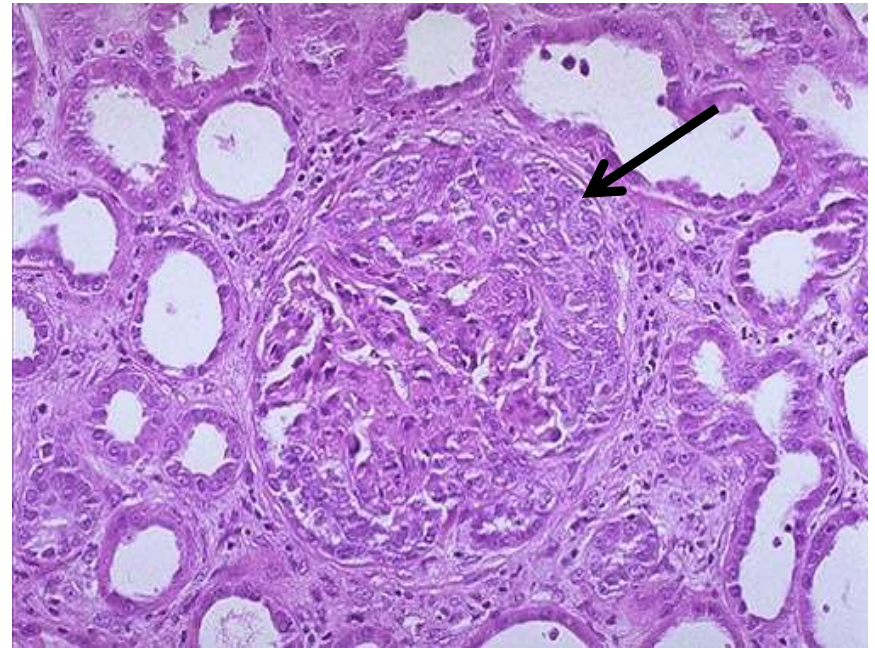
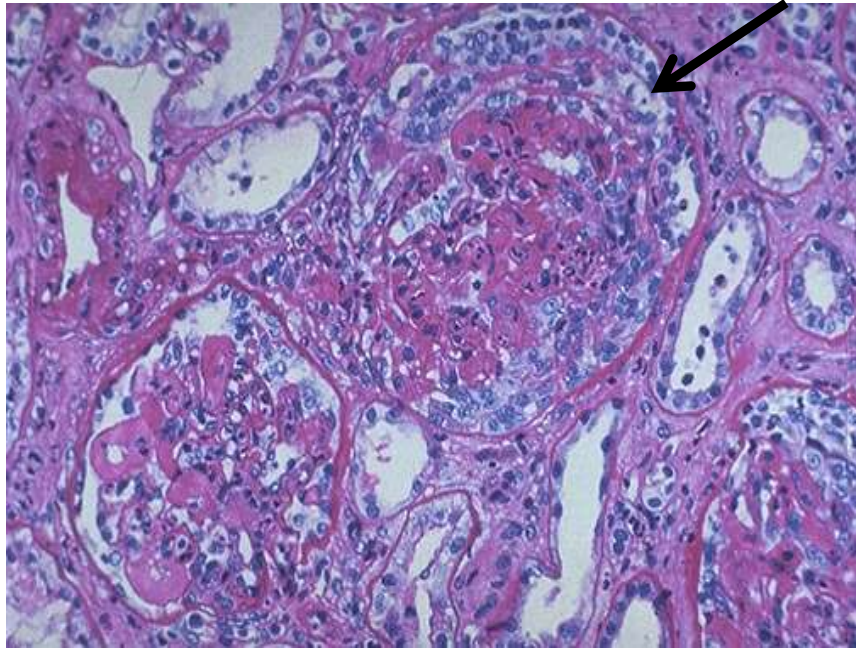
Endocapillary cellular proliferation
granular IgG Deposits

Case- 2

Clinical History

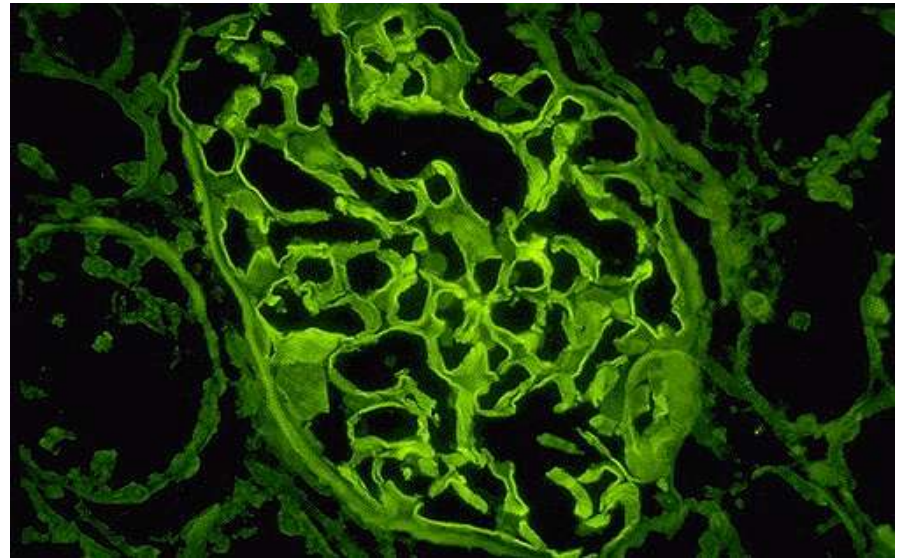
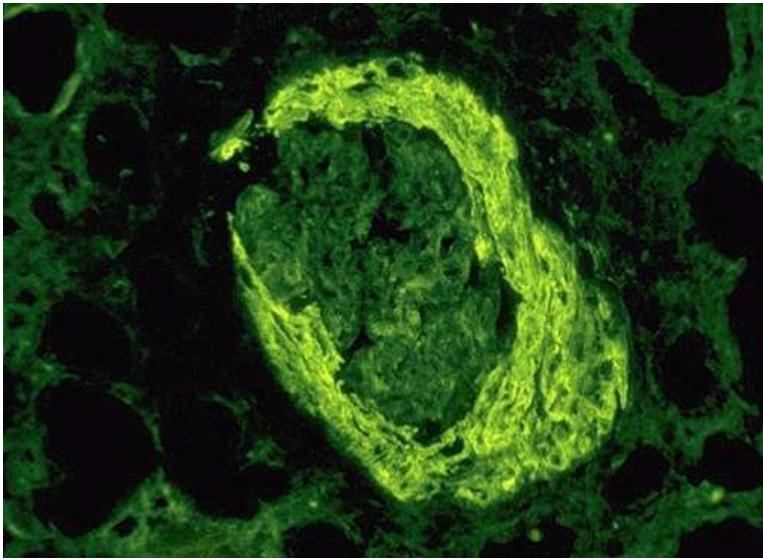
- A 25 year old male works in a military fuel depot
- He began having respiratory difficulty along with red tinged sputum
- He went to see the base physician. The patient then developed very rapid onset of renal failure with haematuria within three days

Light Microscopy



Extracapillary cellular proliferation
cellular crescents

Immunofluorescence

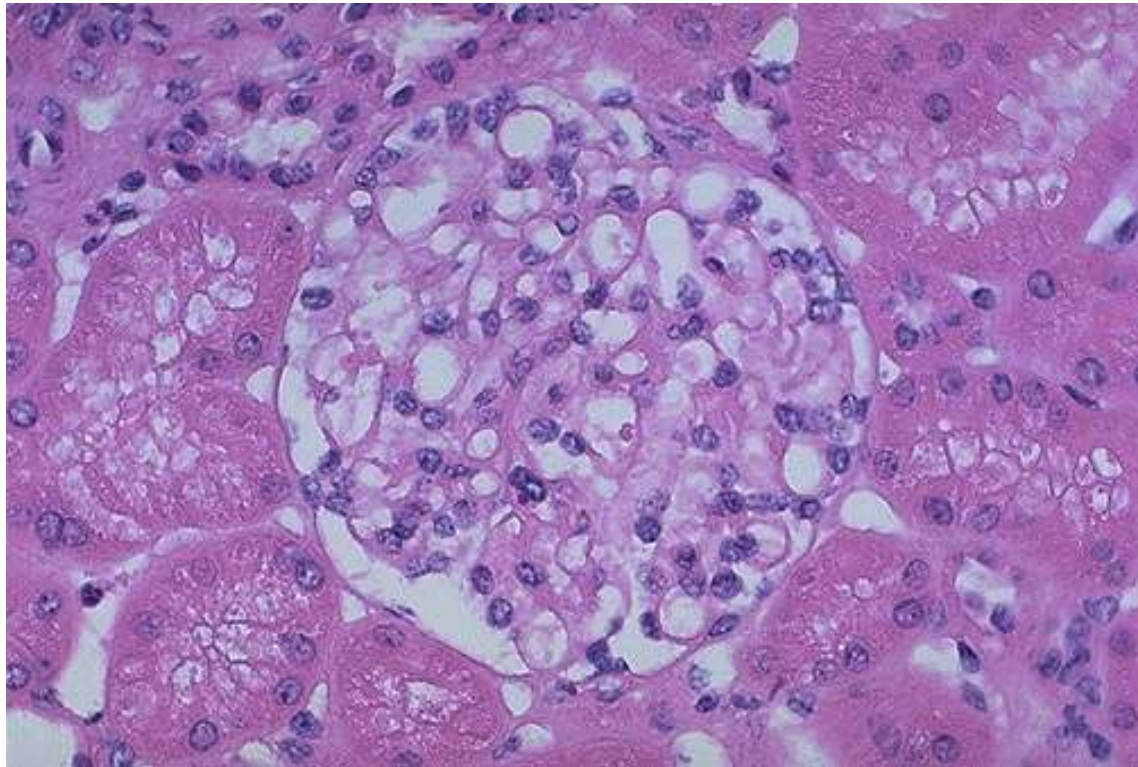


Linear IgG deposits against basement membrane
Crescent stained with fibrinogen

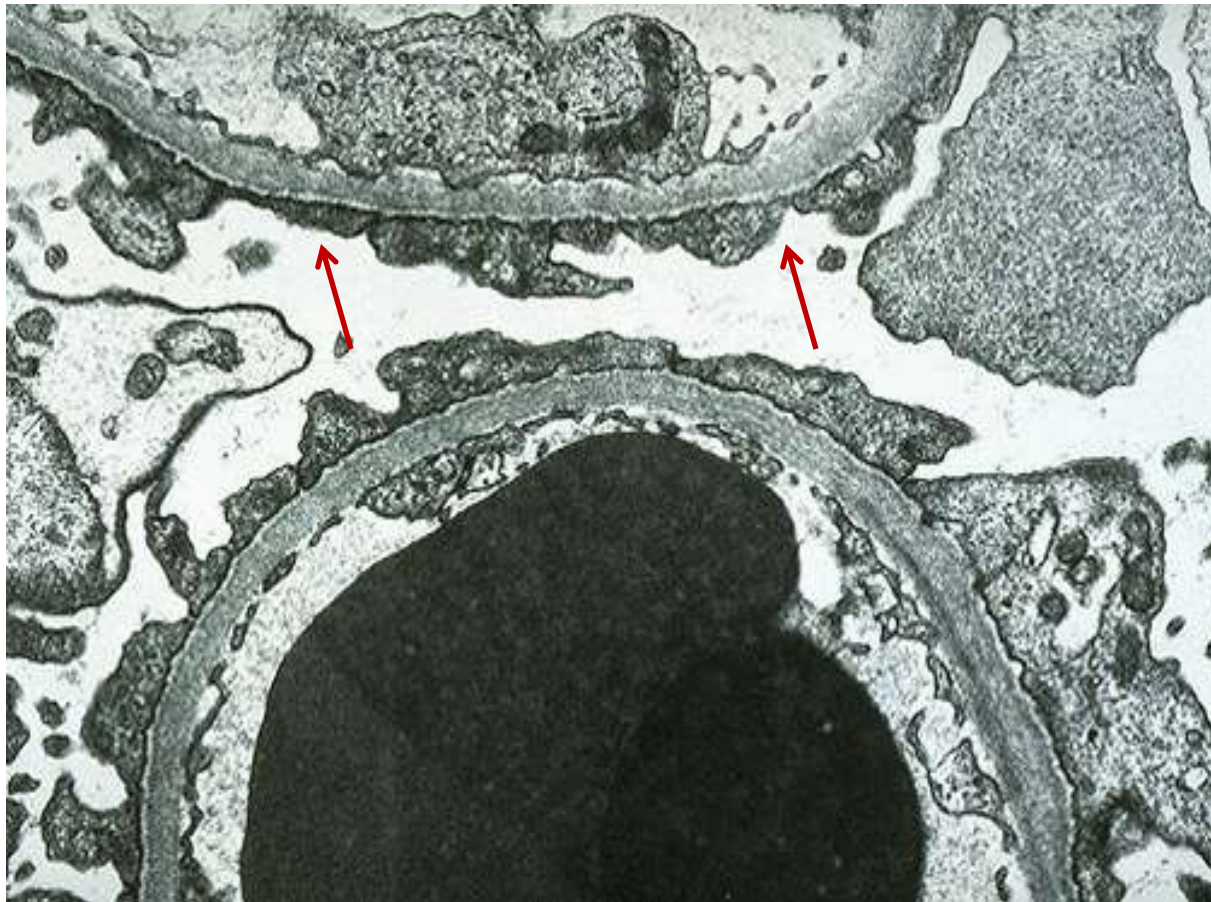
Case 3

- 5 year old male was admitted with bilateral ankle swelling and facial puffiness
- Urine analysis shows no haematuria, ++++ protein

Light microscopy



E/M



FUSION OF THE EPITHELIAL FOOT PROCESSES

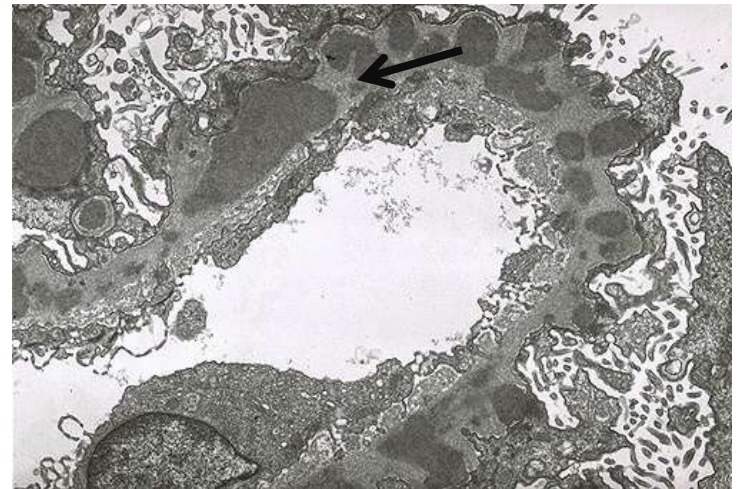
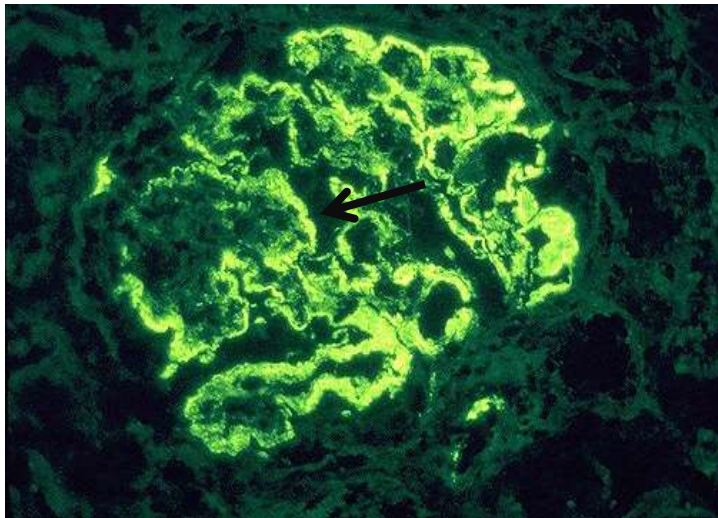
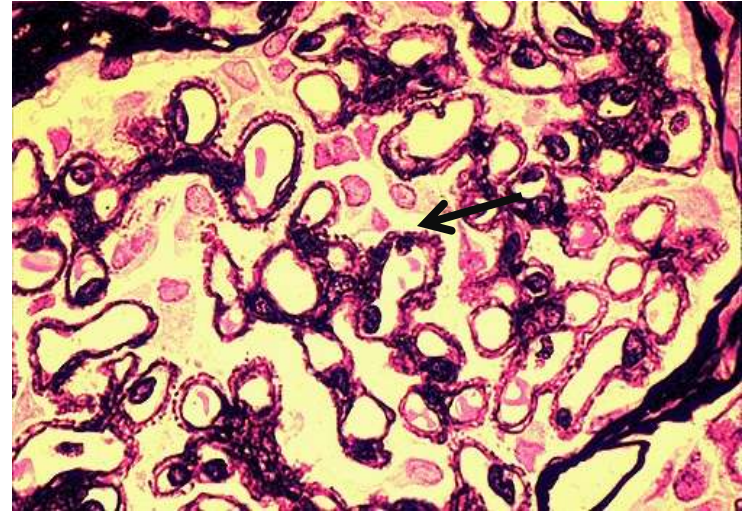
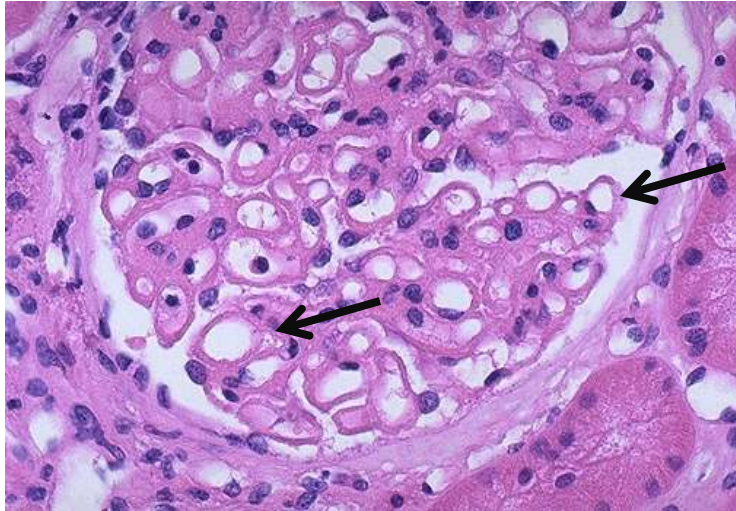
Case 4

A 41 year old male is found to have proteinuria on urinalysis performed as part of a yearly checkup by his physician

The dipstick urinalysis showed no blood, glucose

Physical examination findings include 1+ pitting edema of the lower extremities to the knees. His blood pressure is 130/80

Membranous nephropathy



Case-5

Clinical History

- A 34 year old male is found to have 1+ proteinuria on urinalysis performed as part of a pre-employment physical examination
- The dipstick urinalysis showed glucose was 2+

Diabetic nephropathy

