# 3. Pathology Anatomy of Urinary Tract

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# KIDNEY

I. Congenital / developmental disorders

II. Renal calculi

III. Urinary obstruction

IV. Glomerular disease

V. Pyelonephritis (tubulointerstitial nephritis)

VI. Hypertension

VII. Acute renal failure (ARF)

VIII. Chronic renal failure (CRF)

IX. Neoplasms

X. Renal manifestations of systemic disease

# IV. Glomerular disease

- Injury to the glomerulus → damaged filter → hematuria & proteinuria

**A. Mechanisms of glomerular damage**

**B. Glomerular response to injury**

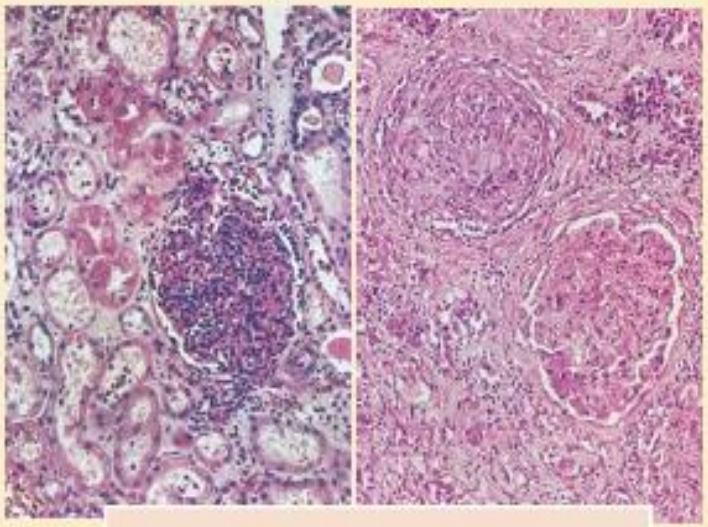
**C. Nephritic syndrome**

**D. Nephrotic syndrome**

## B. Glomerular Diseases

Antigen-antibody complex → Immune complex nephritis

Autoantibodies → Masugi's nephritis



**Glomerulonephritis**

e.g. Multiple mycloma → Protein concentration in plasma ↑ → Glomerular deposition of protein

e.g. Renal vein thrombosis, venous congestion → Hydrostatic pressure ↑ → Abnormalities of glomerular perfusion

Renal perfusion ↓ → Renin angiotensin ↑ → **Renal hypertension**

Renal perfusion ↓ → GFR ↓ → Hyperhydration → **Renal hypertension**

Abnormal permselectivity of the glomerular filter → **Proteinuria, edema**

Death of erythropoietin-forming cells → **Anemia**

Photos from: Doerr, W. ed. Organpathologie. Stuttgart: Thieme; 1974

# GLOMERULAR DISEASES (1)

**Primary Glomerulonephritis (GN)**

- Acute diffuse proliferative GN
- Rapidly progressive (crescentic) GN
- Membraneous GN
- Lipoid nephrosis (minimal change disease)
- Focal segmental GN
- Membranoproliferative GN
- IgA nephropathy
- Chronic GN

# GLOMERULAR DISEASES (2)

**Secondary (Systemic) Diseases**

- SLE
- DM
- Amyloidosis
- Goodpasture's syndrome
- Polyarteritis nodosa
- Wegener's granulomatosis
- Henoch-Schönlein purpura
- Bacterial endocarditis

**Hereditary Disorders**

- Alport's syndrome,
- Fabry's disease

# IV. A. Mechanisms of glomerular damage

1. Loss of GBM polyanions → allows increased filtration of anionic compounds such as albumin

2. Hyperfiltration: functioning nephrons decreased in number → increased demand of the functional → increased GFR → increased glomerular blood flow and capillary pressure → increased permeability to plasma protein, accumulate in urine and mesangium → mesangial proliferation and sclerosis of glomeruli

3. Immunologic …….

# IV. A. ..... 3. Immunologic

a. Native "fixed" antigens

On the GBM (diffuse, IF linear staining) or associated with podocyte (granular, subepithelial staining in IF)

b. Non-glomerular antigens

May become attached to, and incorporated within the glomerular structure (i.e. DNA, lectins, cationic proteins bound to anioninc GBM, etc.) → attacked by antibody → granular appearance IF

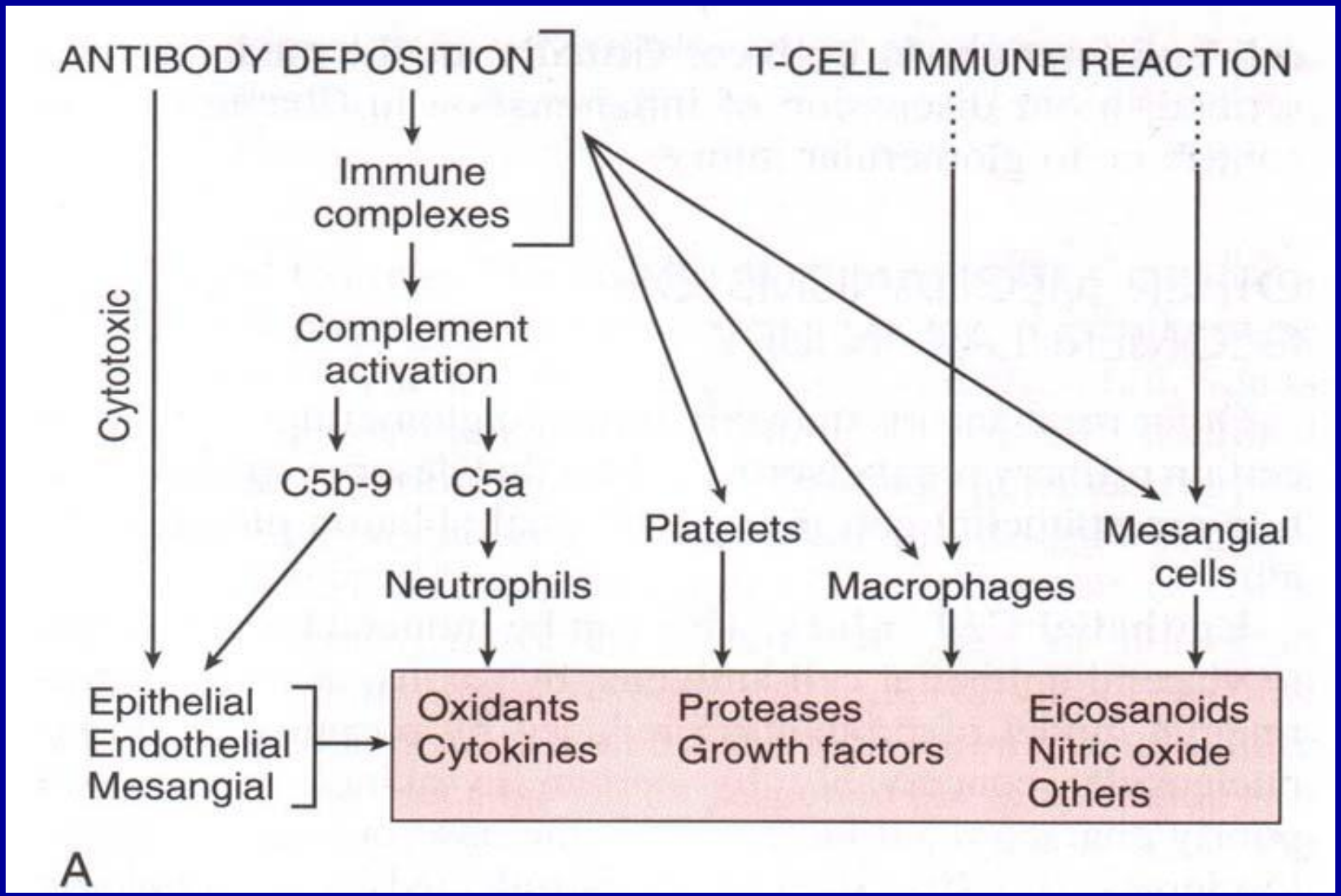
c. Circulating antigen-antibody complexes

Filtered and trapped in the glomeruli → activate complement and attract neutrophil & monocyte → liberate digestive enzymes → glomerular damage.....

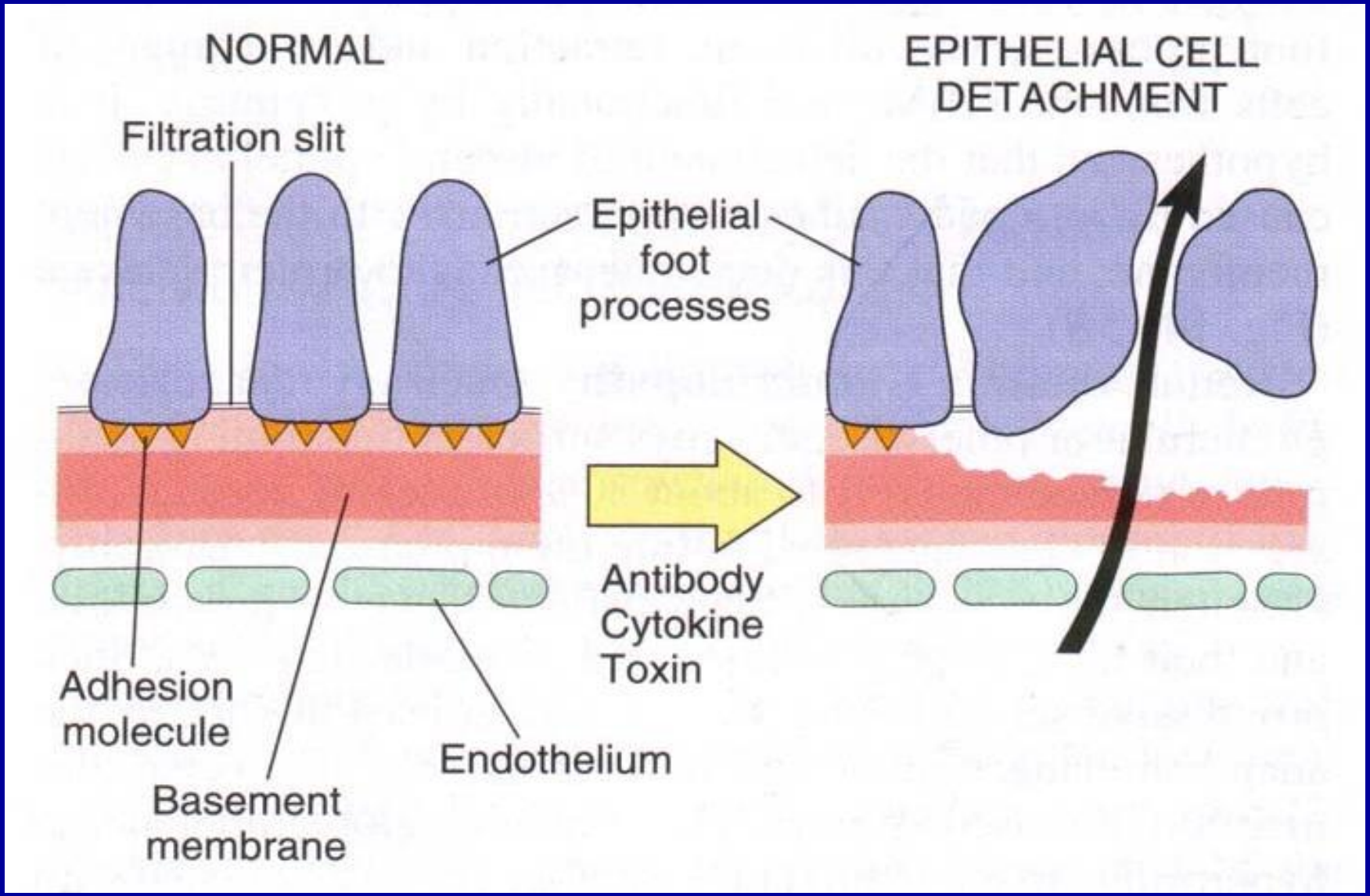
# IV. A. 3. Immunologic :
## ……c. Circulating antigen-antibody complexes

1. Excess production of antibodies → Ag-Ab complexes are large → picked up by RES
2. Small production of antibodies → Ag-Ab complexes are usually soluble and do not become trapped
3. Moderate Ab production → the insoluble complexes may be filtered out
4. High cationic compound tend to traverse the GBM → trapped in subepithelial region
5. Anionic compound trapped in subendothelial region
6. Neutral compound tend to be trapped in mesangium

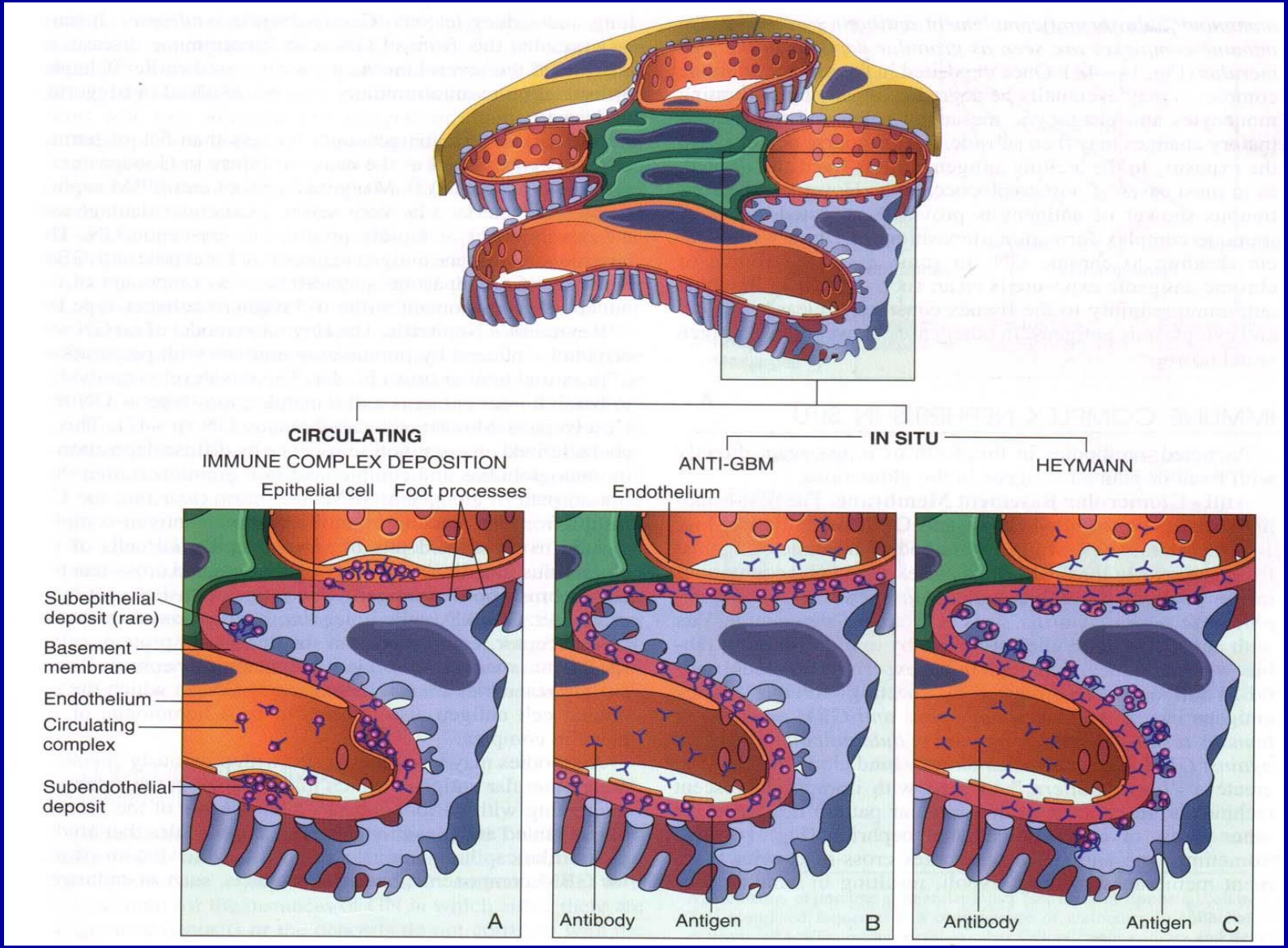
# Mediators of immune glomerular injury



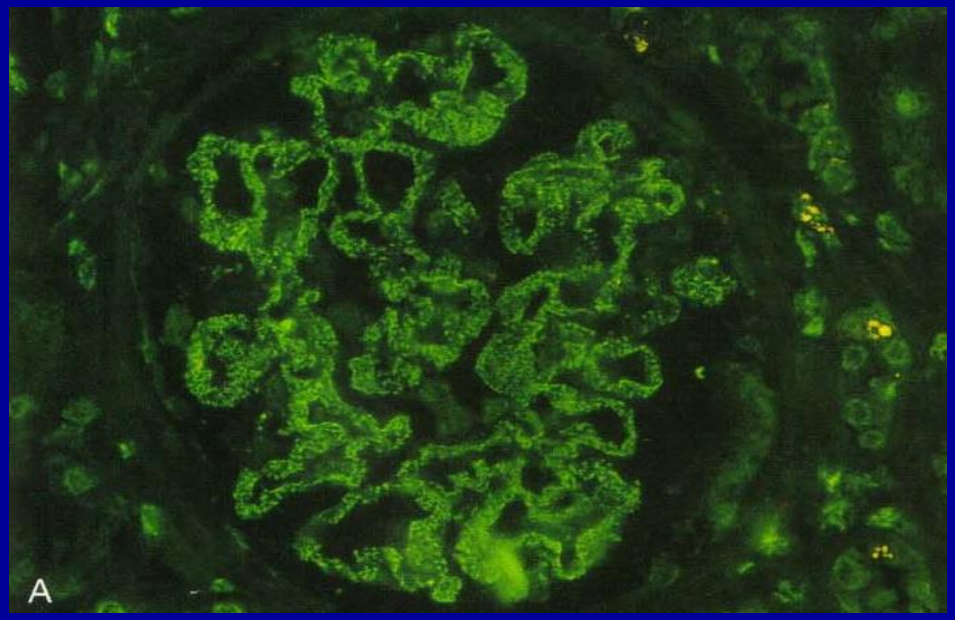
# Epithelial cell injury



# Antibody-mediated glomerular disease

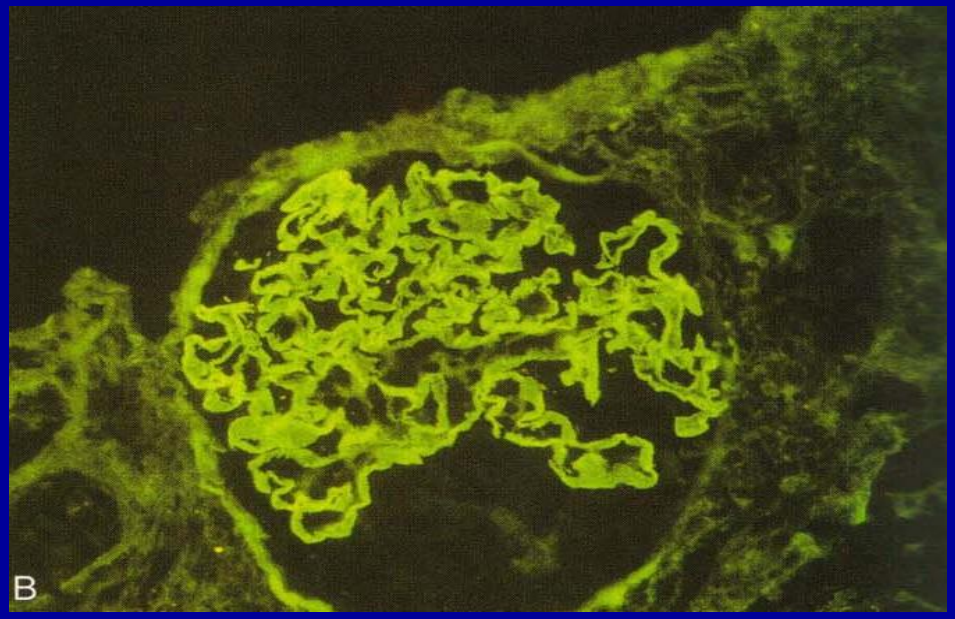


# Patterns of deposition of immune complexes




- **Granular**

  characteristic of circulating and in situ immune complex nephritis

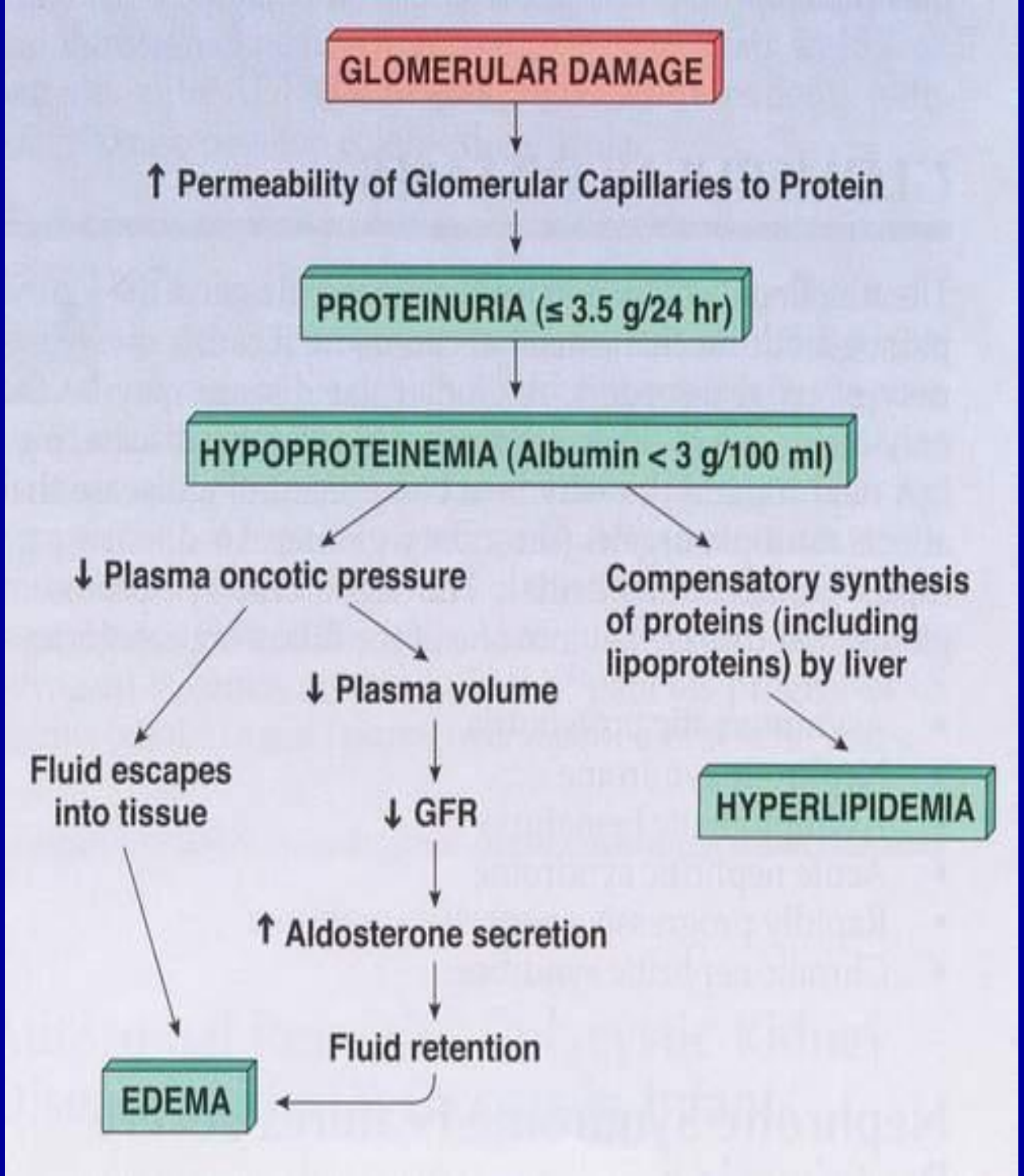



- **Linear**

  characteristic of classic anti-GBM disease

# IV. B. Glomerular response to injury

- Cellular proliferation
  - can involve endothelial, epithelial, mesangial cells
- Inflammatory response
  - manifested primarily by neutrophils → monocyte/macrophage
- Glomerular basement membrane (GBM) thickening
  - true thickening or by deposition of electron dense deposits
- Hyalinization & sclerosis
  - IgA of plasma protein, basement membrane material, mesangial matrix → destroy glomerular architecture


GLOMERULAR DAMAGE
↑ Permeability of Glomerular Capillaries to Protein
PROTEINURIA (≤ 3.5 g/24 hr)
HYPOPROTEINEMIA (Albumin < 3 g/100 ml)
↓ Plasma oncotic pressure
Compensatory synthesis of proteins (including lipoproteins) by liver
↓ Plasma volume
Fluid escapes into tissue
↓ GFR
HYPERLIPIDEMIA
↑ Aldosterone secretion
Fluid retention
EDEMA

# IV. C. Nephritic syndrome

Constellation of signs characterized acutely by:
hematuria, erythrocyte casts, azotemia, hypertension, and oliguria

Types:

1. Acute Proliferative (Diffuse Proliferative, Post-infectious) Glomerulonephritis
2. Membranoproliferative Glomerulonephritis (MPGN)
3. Crescentic / Rapidly Progressive Glomerulonephritis (RPGN)
4. IgA Nephropathy *(Berger's disease)*

# IV. C. 1. Acute Proliferative Glomerulonephritis

(Diffuse Proliferative, Post-infectious GN)

- Mostly results from trapping of immune complexes involving exogenous antigens
- Less frequently may be due to endogenous antigens
- Most frequently seen in children, 1-3 weeks after infection by β-hemolytic streptococcal Group A
- Malaise, fever, oliguria, hematuria, nausea, periorbital edema, mild – moderate hypertension
- In children 95% recover clinically within 2 months of onset, and morphologically within 3 years
- Prognosis: in children a few → chronic GN or RPGN; in adult is a little poorer …….

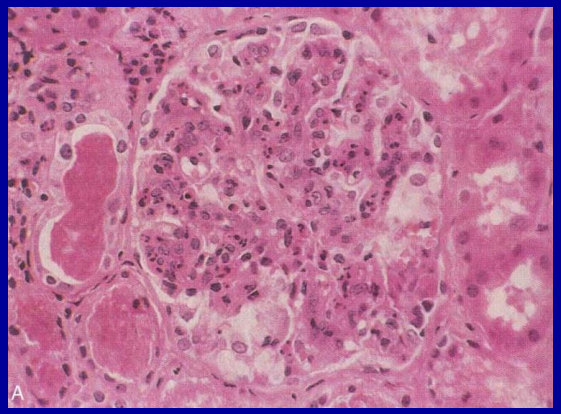
# IV. C. 1. Acute Proliferative Glomerulonephritis

(Diffuse Proliferative, Post-infectious GN)

.....

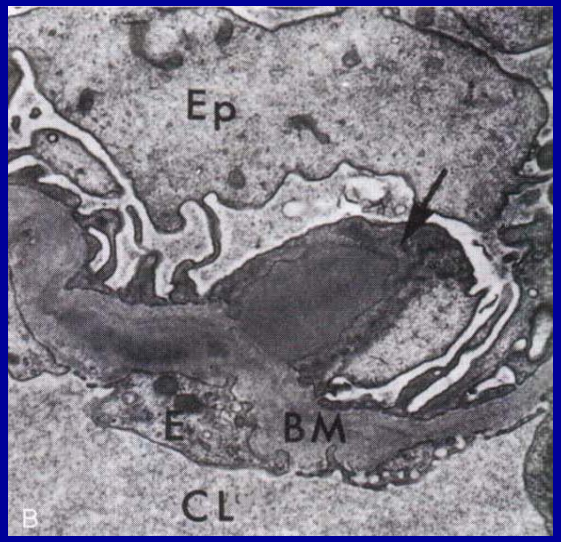
- Acute phase: elevated ASO titers, decreased C3, positive cyoglobulins, elevated Erythrocyte Sedimentation Rate (ESR)
- The kidney may be swollen and "flea bitten"
- Microscopically the kidney is hypercellular (proliferation of mesangial, endothelial, and less epithelial cells)
- **IF** (immunofluorscence)**:** granular deposition of IgG & C3 in subepithelial region

# Acute proliferative (postinfectious) GN



Glomerular hypercellularity

- intracapillary leukocytes
- proliferation of intrinsic glomerular cell

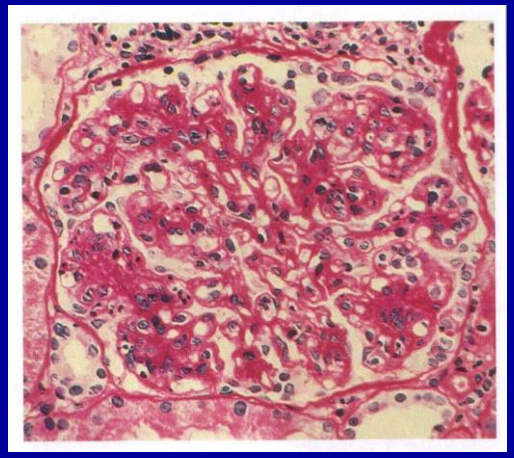


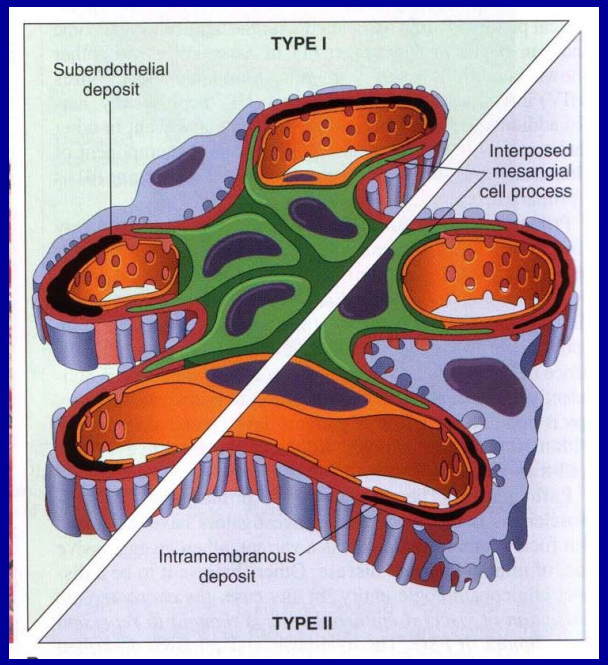

Typical electron-dense subepithelial “hump” and intra-membranous deposits

# IV. C. 2. Membranoproliferative Glomerulonephritis (MPGN)

- **Affects children and young adults**
- **Light microscopy**:
  - hypercellular glomeruli (endothelial & mesangial) → centri-lobular accentuation
  - "tram-track" appearance to the basement membrane (mesangial matrix & cellular cytoplasm is forced between endotehlial cells and GBM)
- **EM**: - electron dense deposits found in subendothelial
  - (Type I), - subendothelial and subepithelial
  - (Type II – intramembranous dense deposit disease),
- Most cases slowly progress to CRF, some to RPGN

# Membranoproliferative glomerulonephritis



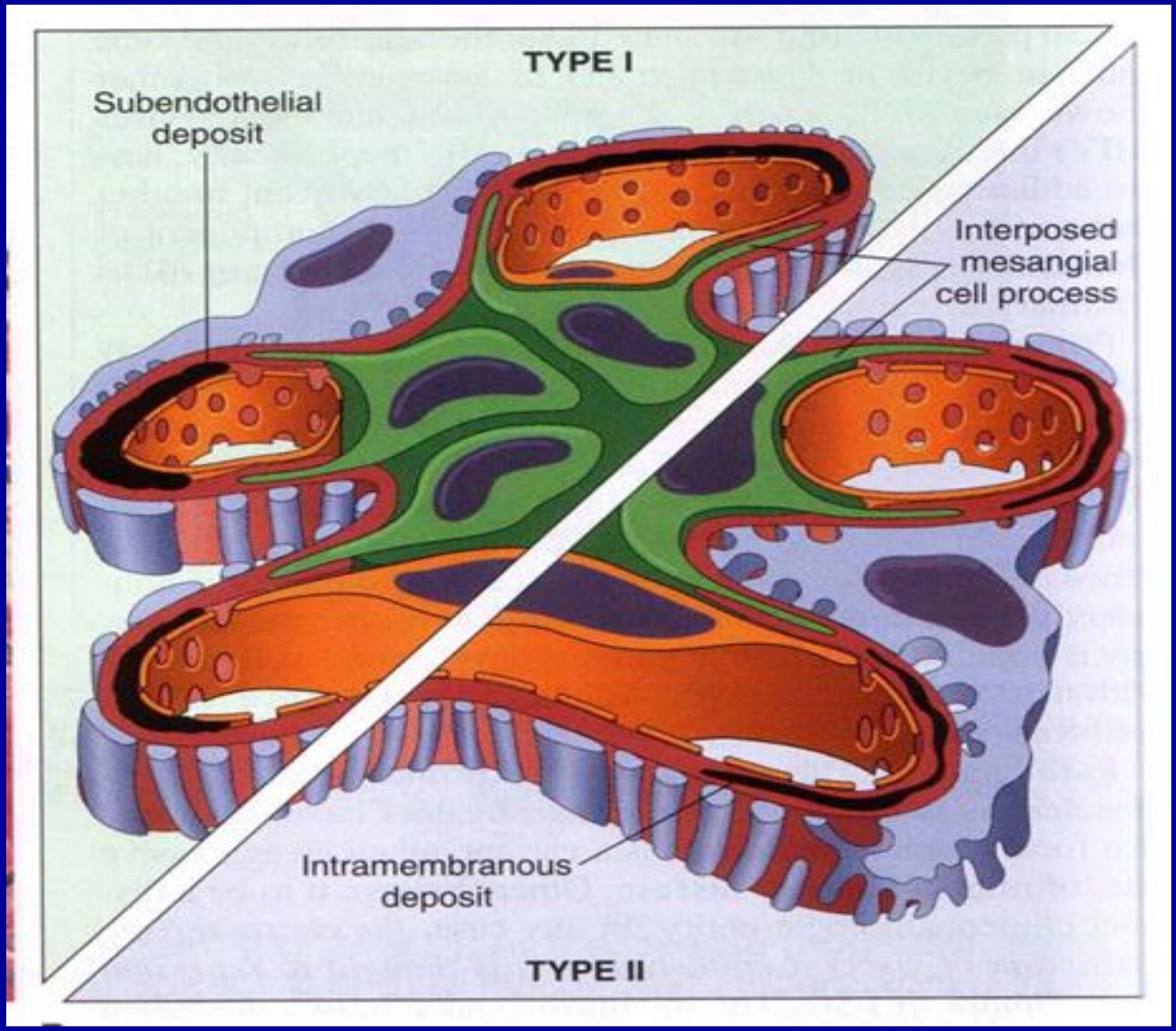



Mesangial cell proliferation, basement membrane thickening, leukocyte infiltration, and accentuation of lobular architecture

Type I: subendothelial deposits

Type II: intramembranous deposits (dense deposit disease)

Mesangial interposition → appearance of split basement membranes (by light microscope)


TYPE I
Subendothelial deposit
Interposed mesangial cell process
Intramembranous deposit
TYPE II

# IV. C. 3. Crescentic / Rapidly Progressive Glomerulonephritis (RPGN)

A clinicopathologic syndrome (not a specific etiologic form of)

→ rapid progression to renal failure (RF) in patient with glomerular "crescent" formation (proliferating parietal epithelial cells, and infiltration by monocyte & macrophages, and fibrin deposit)

→ indicator of severe underlying glomerular disease, may be associated with severe oliguria → death within weeks to months

Pathogenetically there are 3 types of RPGN ……..

# IV. C. 3. Crescentic (RP) GN / Rapidly Progressive Glomerulonephritis :

## Type I RPGN/ (Anti-GBM)

- Young adult males who develop an anti-GBM antibody (may cross-react with pulmonary alveolar BM) → focal & segmental to diffuse fibrinoid necrosis in the capillary tuft, epithelial & endothelial degeneration with disruption of GBM, fibrin deposition
- IF: linear deposits of IgG / C3 on GBM
- Idiopathic
- Goodpature's disease

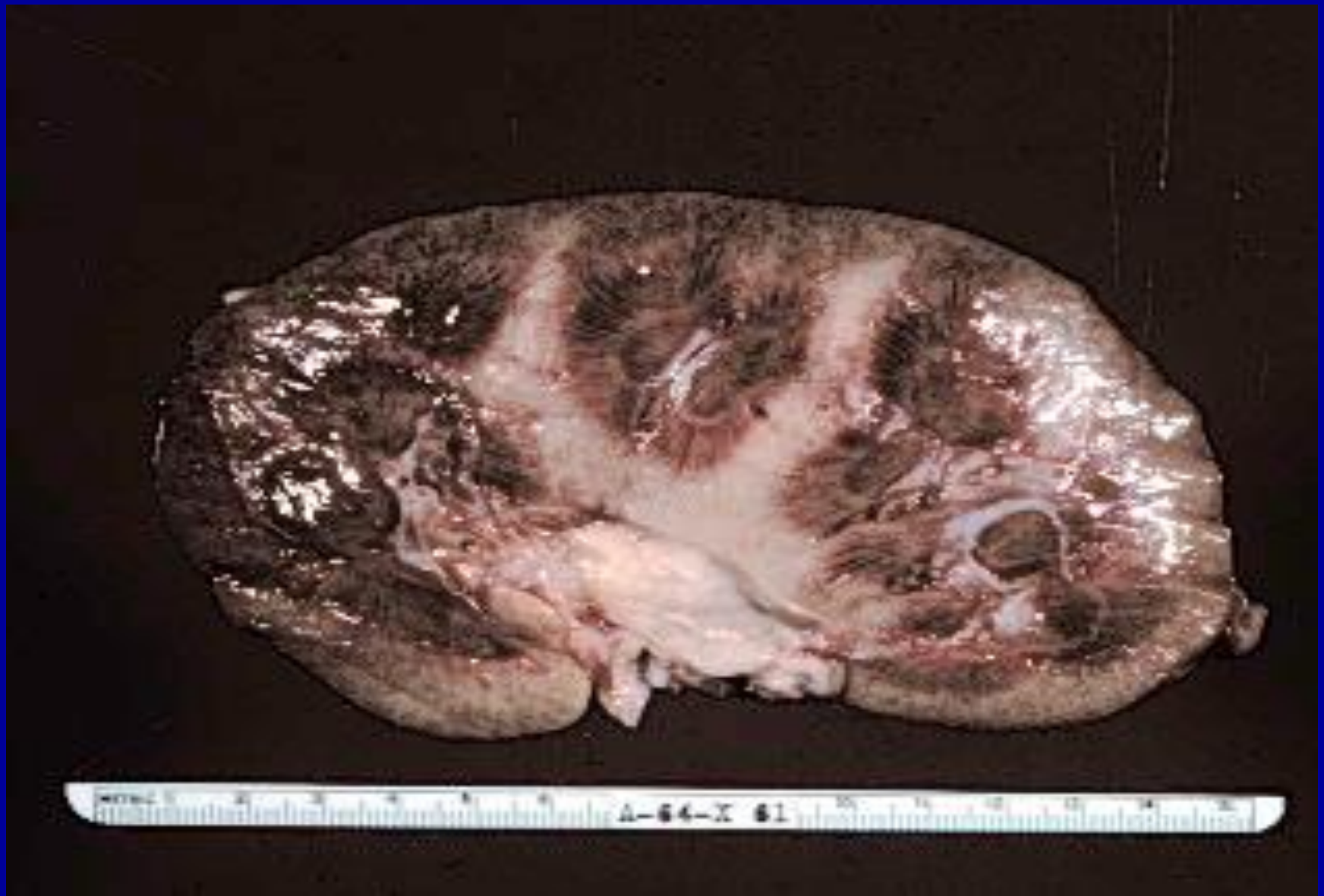
## Type II RPGN (Immune complex / Post-infectious GN)

- Idiopathic
- SLE
- Post infectious
- Henoch-Schönlein purpura
- More commonly adult patient → oliguria → anuria

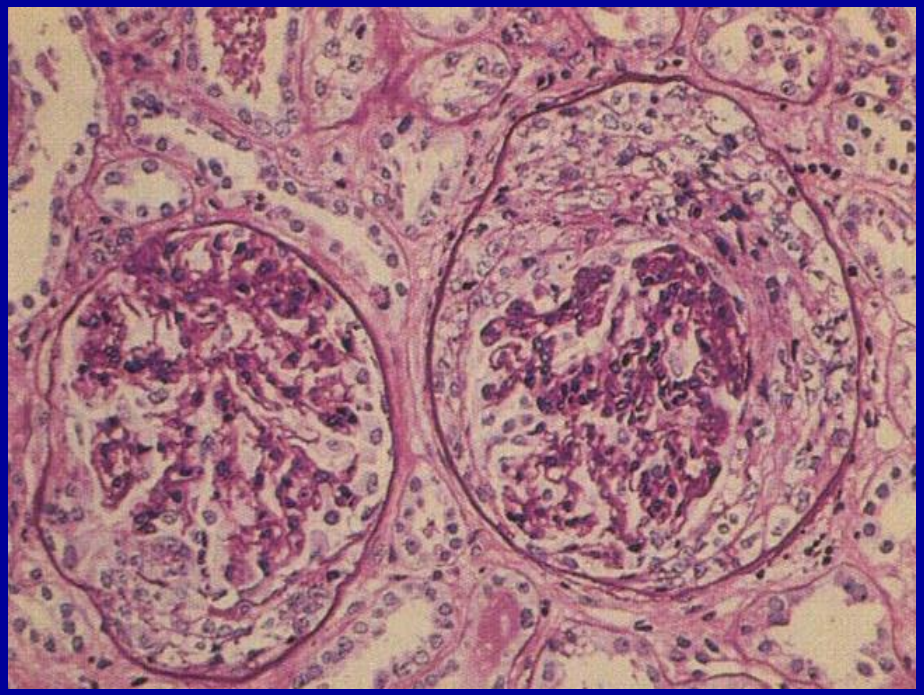
## Type III RPGN (no immune deposit disease / Pauci-immune)

- Idiopathic
- Wegener's granulomatosis
- Polyarteritis

Here is a cross-section of a kidney with **rapidly progressive glomerulonephritis**. Again, the cortex is pale is swollen. This is the kidney which is characterized by epithelial crescents around the glomeruli.



# Crescentic Glomerulonephritis



Collapsed glomerular tufts & crescent-shaped mass of proliferating cells and leukocytes internal to Bowman's capsule

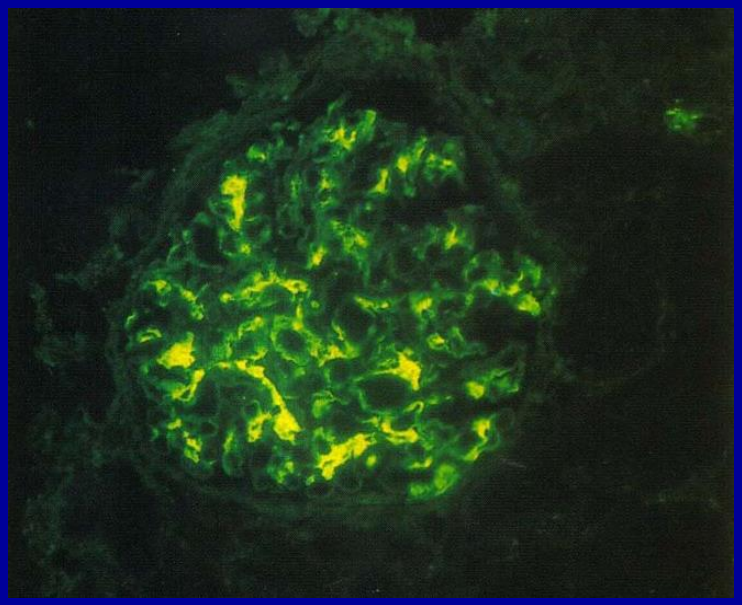
(PAS stain)

# IV. C. 4. IgA Nephropathy *(Berger's disease)*

- A form of focal GN, in children or young adult males
- May be a genetic abnormality → overproduction of IgA, or excessive exposure to antigens eliciting IgA response
- Slowly progressive → 20% CRF
- Characteristics:

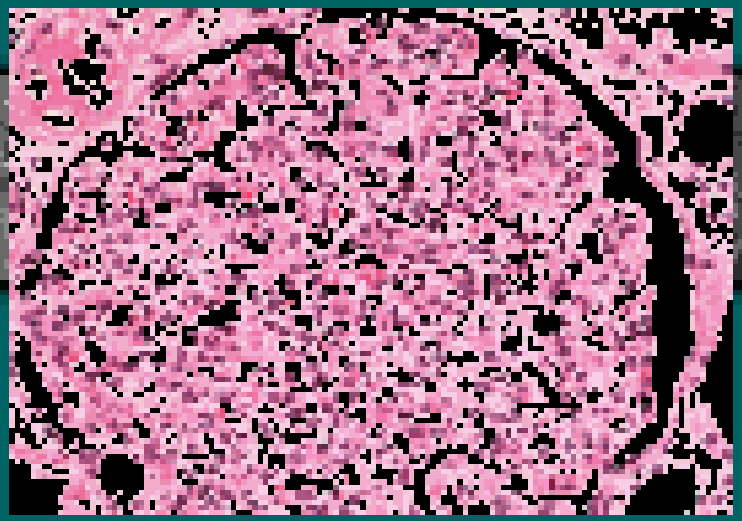
  recurrent self limiting episodes of hematuria often following an upper respiratory tract infection
- Histology:
  - varies from focal GN with segmental mesangial proliferation → diffuse mesangioproliferative GN → RPGN (crescentic)
  - **IF:** deposits of IgA, properdin, C3 diffusely throughout the mesangium

# IgA nephropathy



Characteristic immunofluor-escence deposition of IgA principally in mesangial region

# Pathology of Nephritic Syndrome



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Associate professor and Head
Dept of Pathology
University Sains Malaysia

# What is Nephritic Syndrome?

It is a clinical manifestation in which several different renal diseases giving rise to a group of specific symptoms:

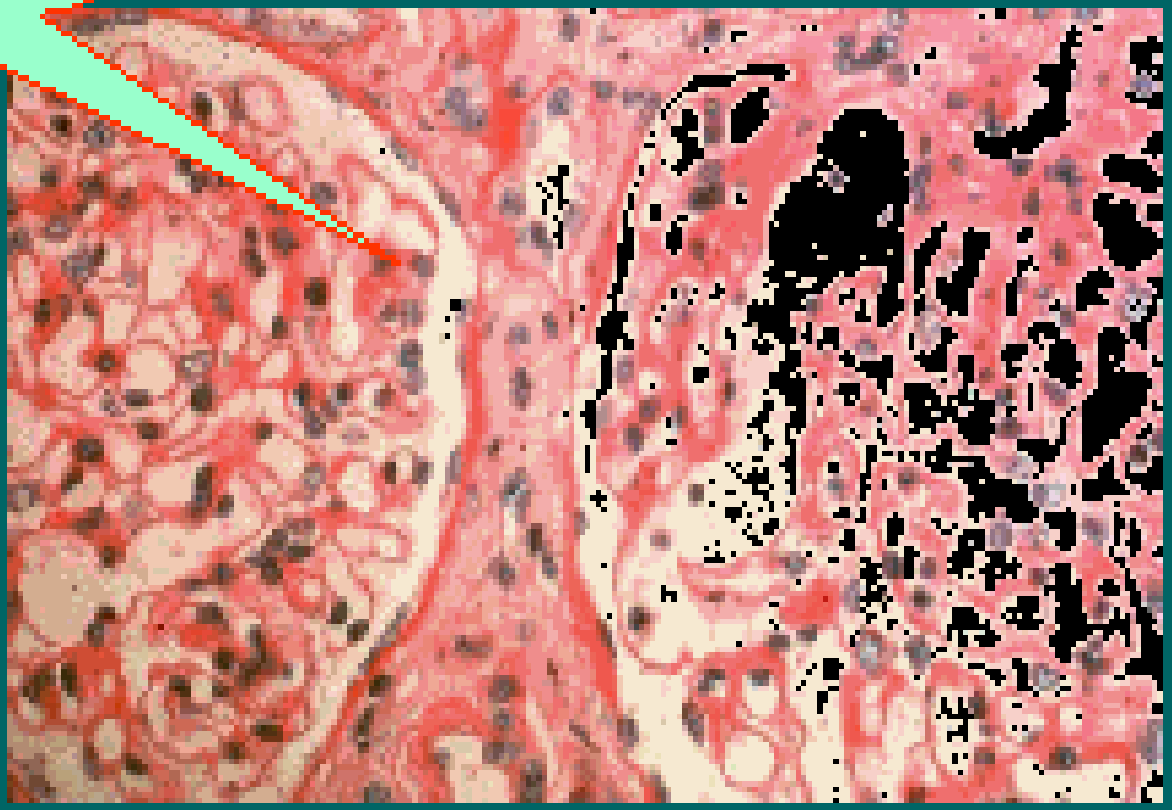
**Poststreptococcal GN**
**Crescentic GN**

Primary GN/secondary to systemic causes

- **Hematuria**
- **Azotemia**
- **Proteinuria**
- **Oliguria**
- **Edema**
- **Hypertension**

# Normal histology

One capillary loop



# Pathologic reaction to injury 1

- **Proliferation of cells in the glomerulus**
  - Mesangial cells ( normal less than 3-4) - macrophages of the kidney
  - Endothelial cells - reduces capillary lumen
  - Epithelial cells -
    - crescent formation when severe
    - decrease Bowman's space
    - usually stimulated by fibrin

# Pathologic reaction to injury 2

- Infiltration by inflammatory cells
  - neutrophils
  - lymphocytes
  - macrophages

Seen in Acute proliferative glomerulonephritis

# Pathologic reaction to injury 3

- **Capillary Basement membrane thickening**
  - deposition of immune complexes , Ig , complements
  - deposition can be
    - subepithelial
    - subendothelial
    - intramembranous

    Alteration in BM thickness disturb capp permeability

# Pathologic reaction to injury 4

- Increase mesangial matrix - due to deposition of Ig and complements
- Epithelial foot process fusion - results when leakage of protein from glomerular capp
- Hyalinisation and sclerosis - accumulation/ precipitation of extracellular material (protein)
  - end stage disease

# Immune mechanism of glomerular injury

- In situ immune complex deposition
  - fixed intrinsic tissue antigen ( eg anti GBM nephritis)
  - planted antigens
    - exogenous - drugs , infectious agents
    - endogenous
- Circulating immune complex deposition ( type III hypersensitivity)
  - Ag-Ab complexes

# What antigens?

- Endogenous
  - SLE nephritis
- Exogenous
  - Poststreptococcal nephritis
  - Hepatitis B virus (HBsAg) infection
  - Treponema pallidum
  - Plasmodium falciparum

# How does the Ag cause renal damage?

- Ag-Ab complexes are formed in the circulation
  - trapped in the glomeruli
  - binds complements in most case
  - get deposited - mesangium , subendothelial , subepithelial region

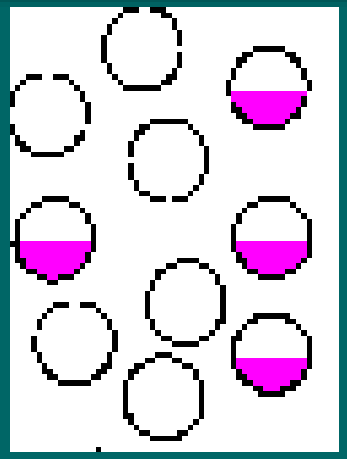

- Stimulate an acute inflammatory reaction

# Circulating Immune complex Nephritis

Why does Ag-Ab get trapped in the glomeruli

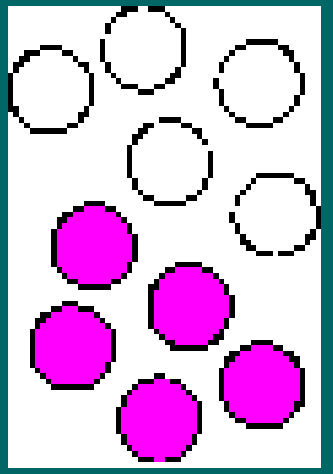
- Their physicochemical properties - the charge of the immune complex
- Hemodynamic factors of the glomerulus
- Permeability of the endothelial cells

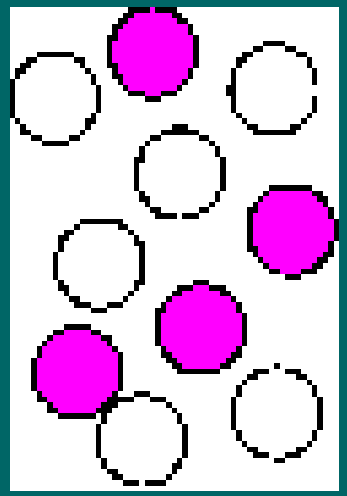
# Terminology of renal pathology



Segmental

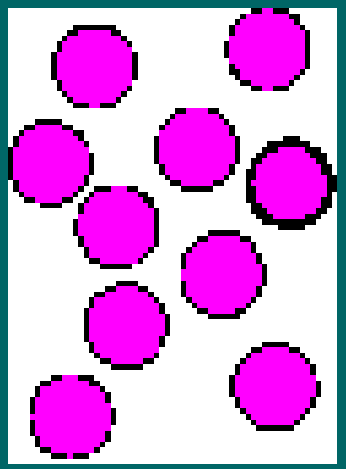
focal





global

diffuse



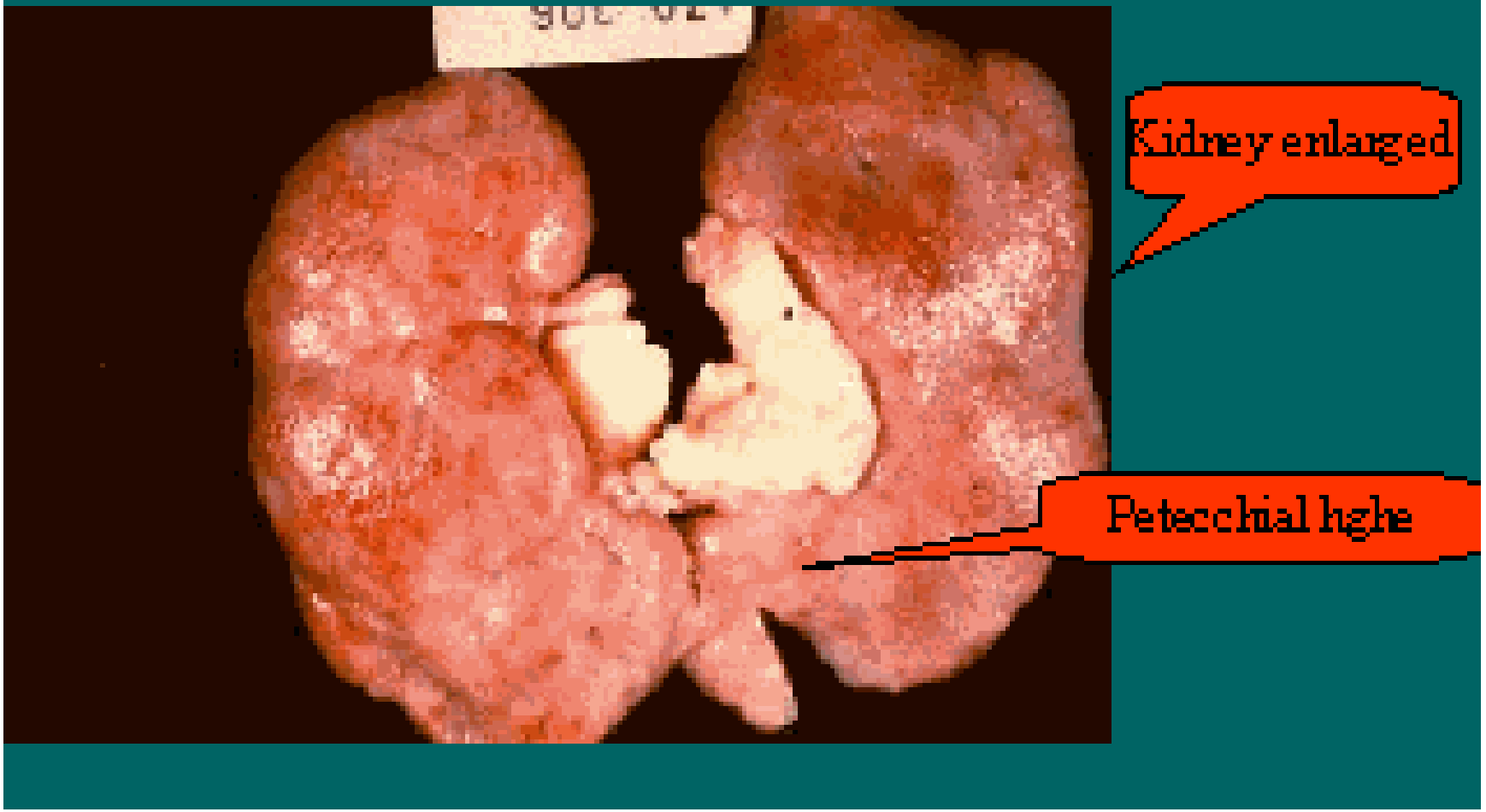
mesangial

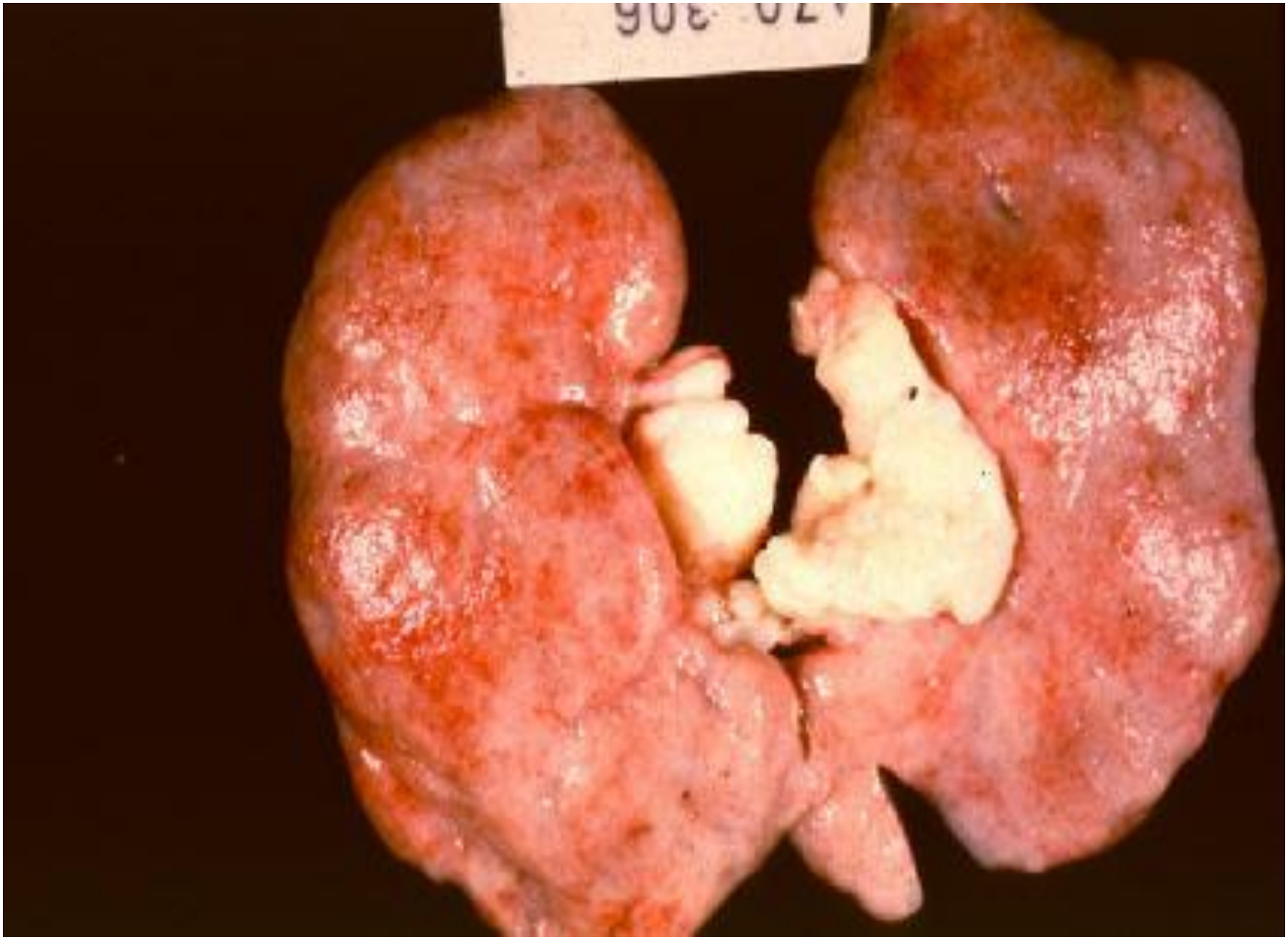
# Poststreptococcal GN ( Diffuse Pfoliferative GN)

- Most common renal ds in childhood
- Infection of skin/throat preceeds 1-3 wks before renal symptoms
- Organisms - us Group A beta hemolytic streptococci*

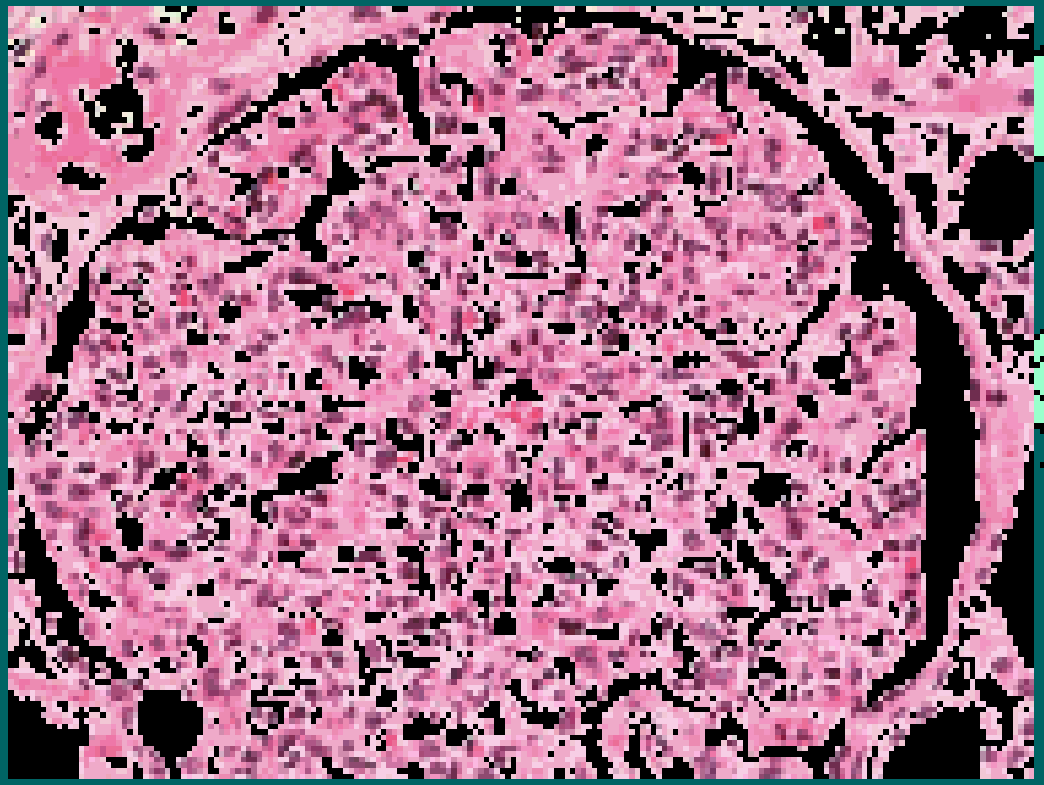
- Immune complexes formed between AG in organism and host AB in glom filtration membrane

# Gross appearance





# Microscopic appearance

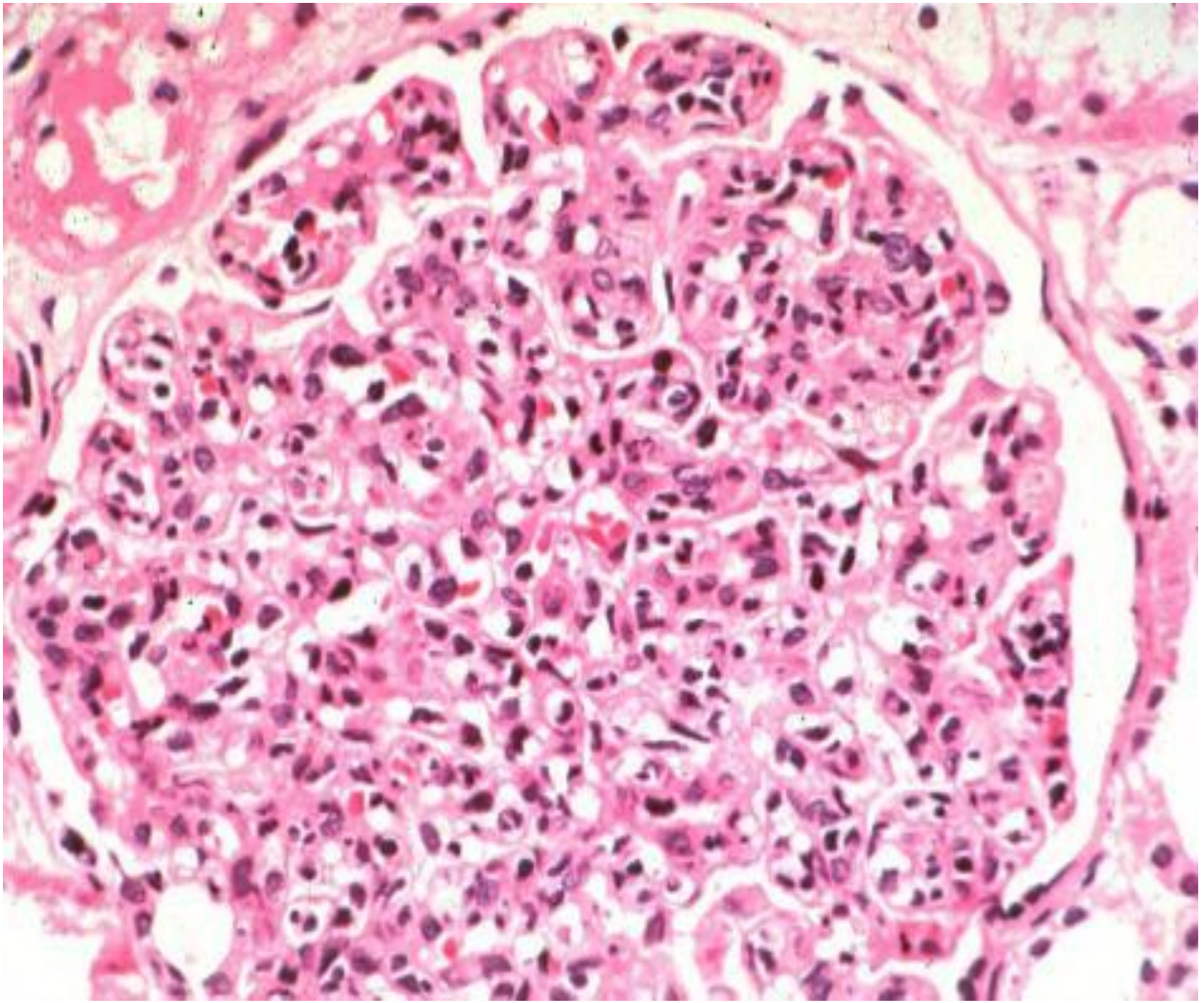


Diffuse involvement

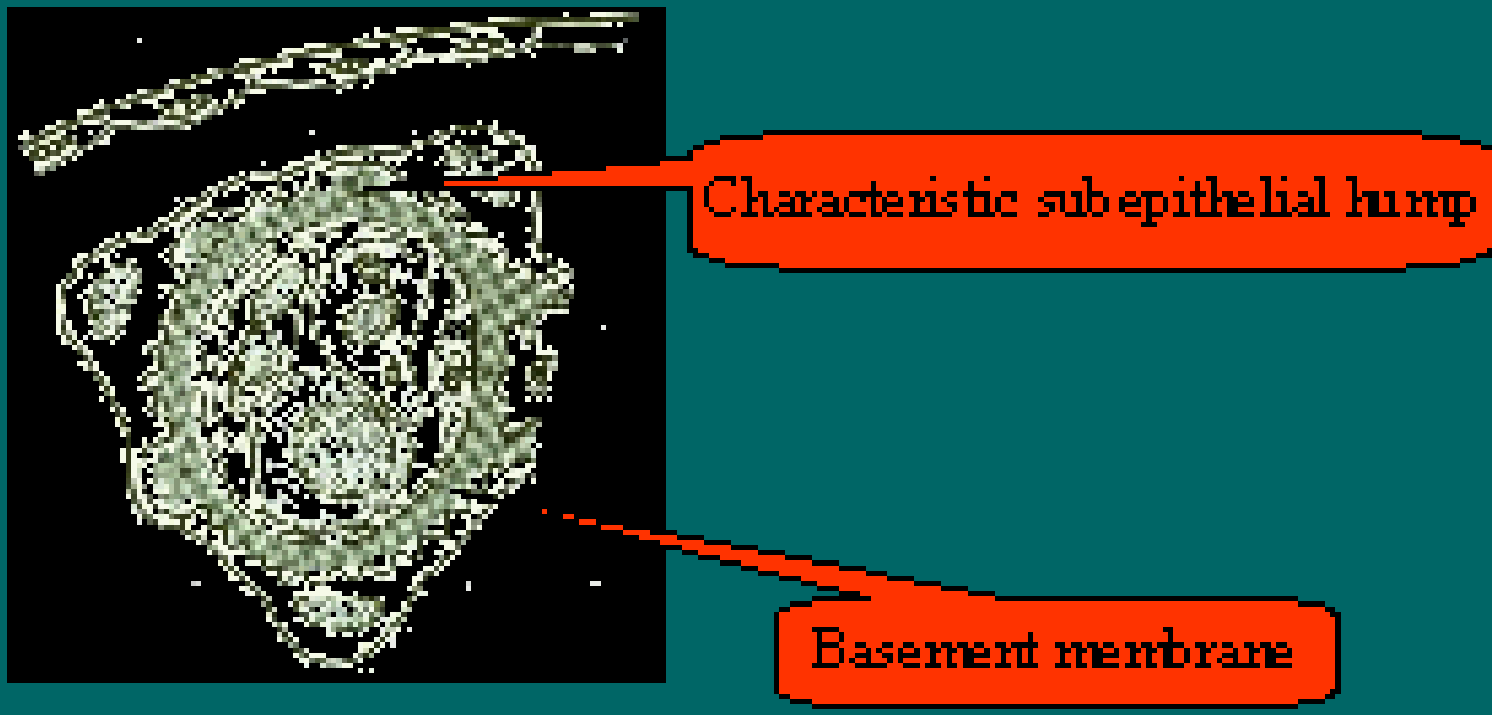
Glom enlarged , edematous

Increased cellularity

Do you remember which cell?



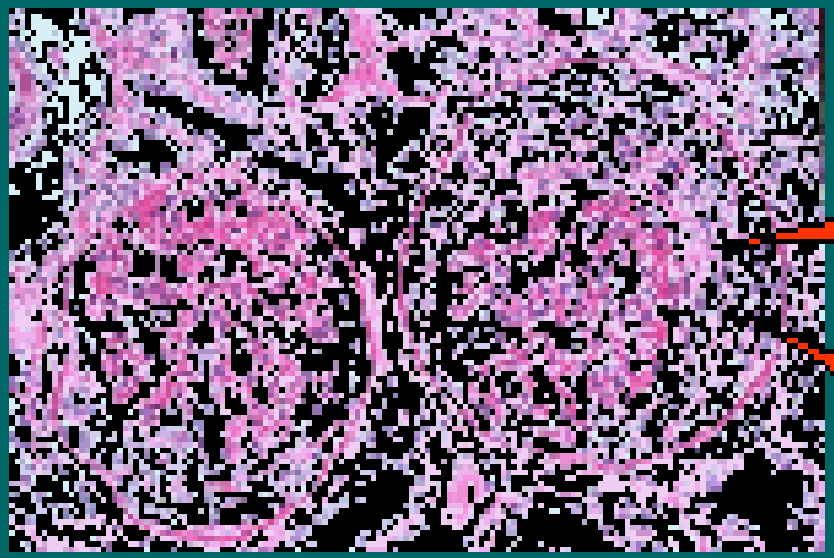
# Electron microscopy



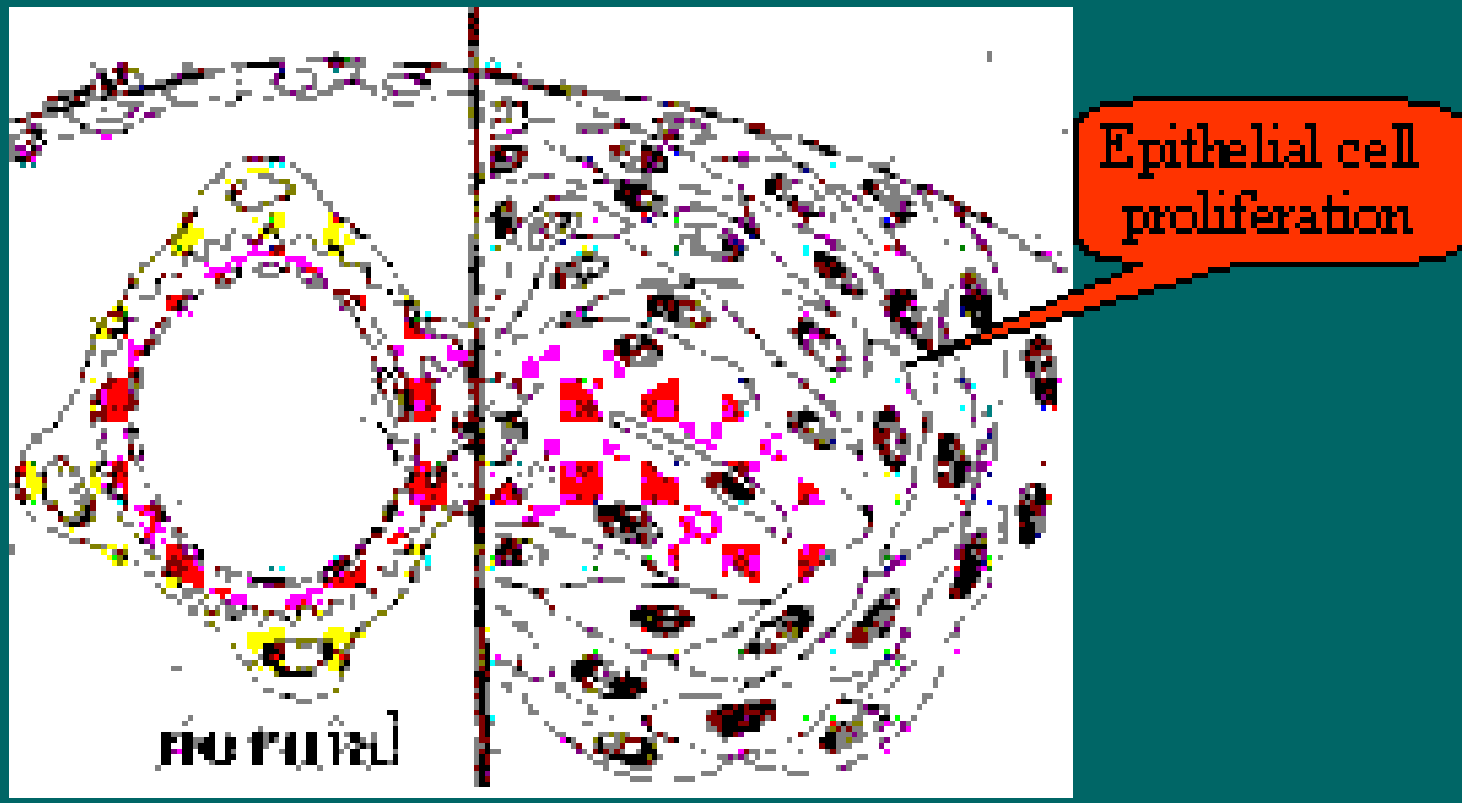
# Crescentic GN (Rapidly progressive GN)

- Causes
  - SLE
  - Goodpasture Syndrome
  - PAN
  - Wegeners Ds
  - HSP
  - Idiopathic

# Crescentic GN (Rapidly progressive GN)

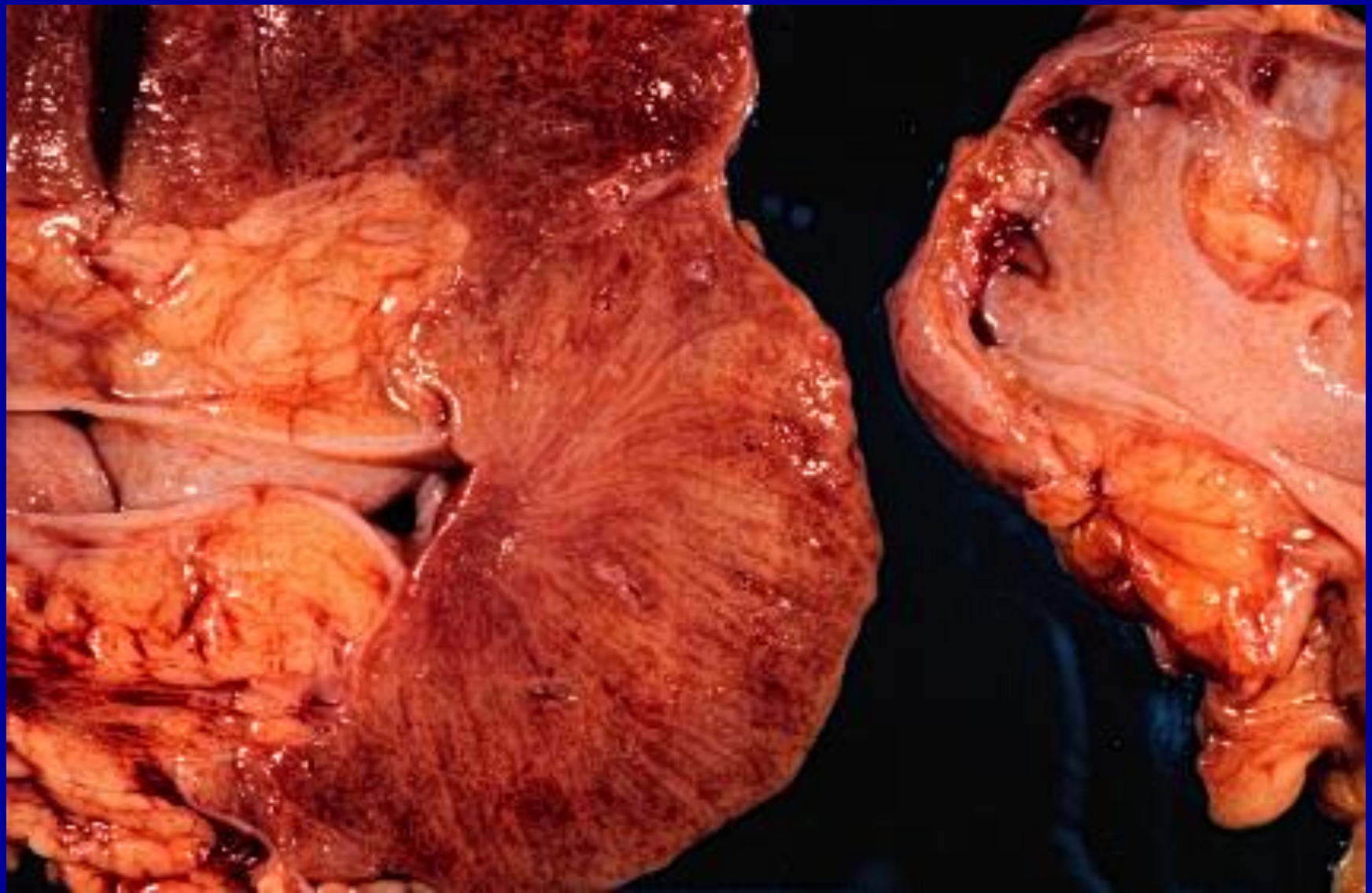


# Crescentic GN (Rapidly progressive GN)

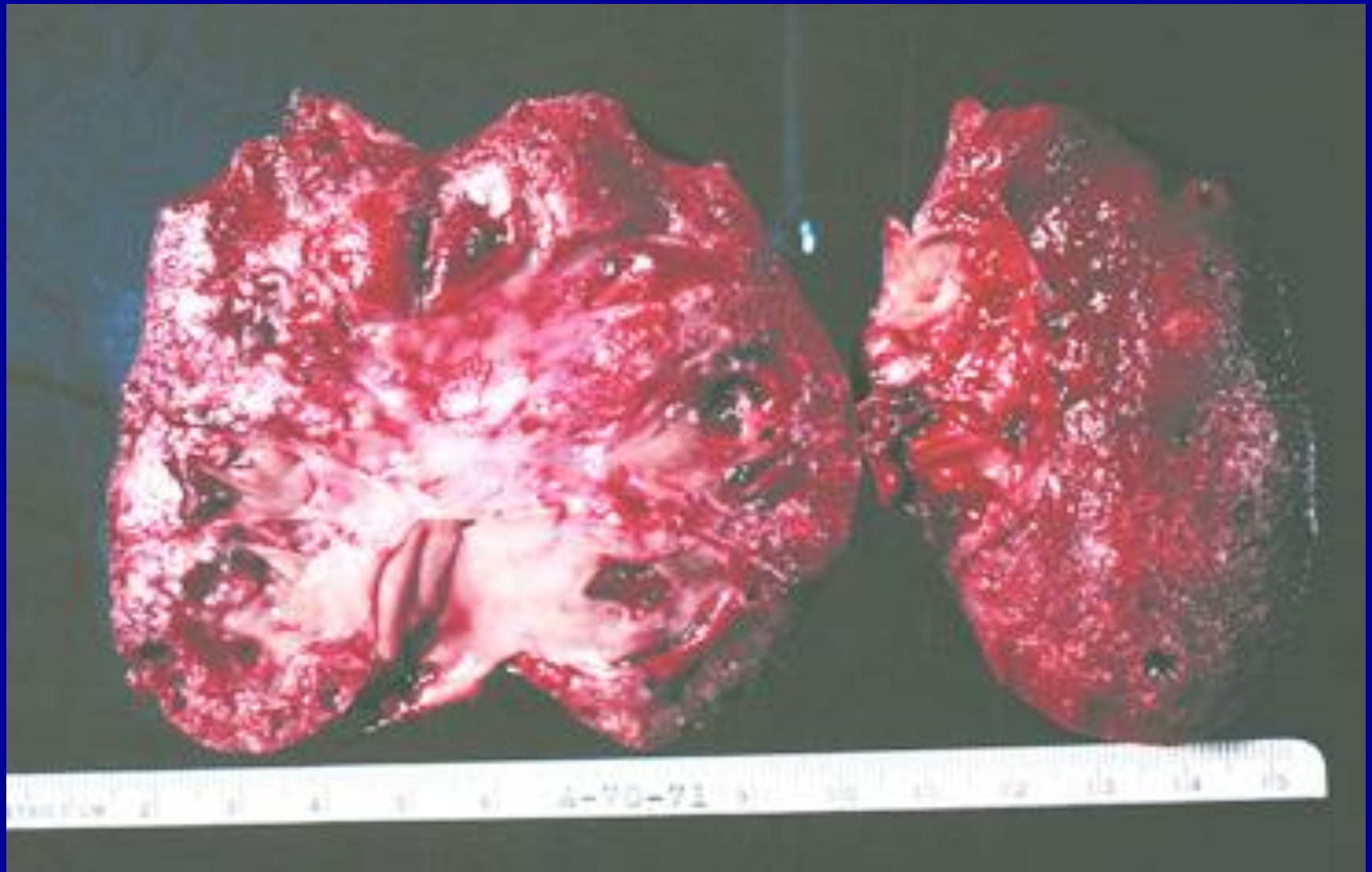


# Chronic Glomerulonephritis

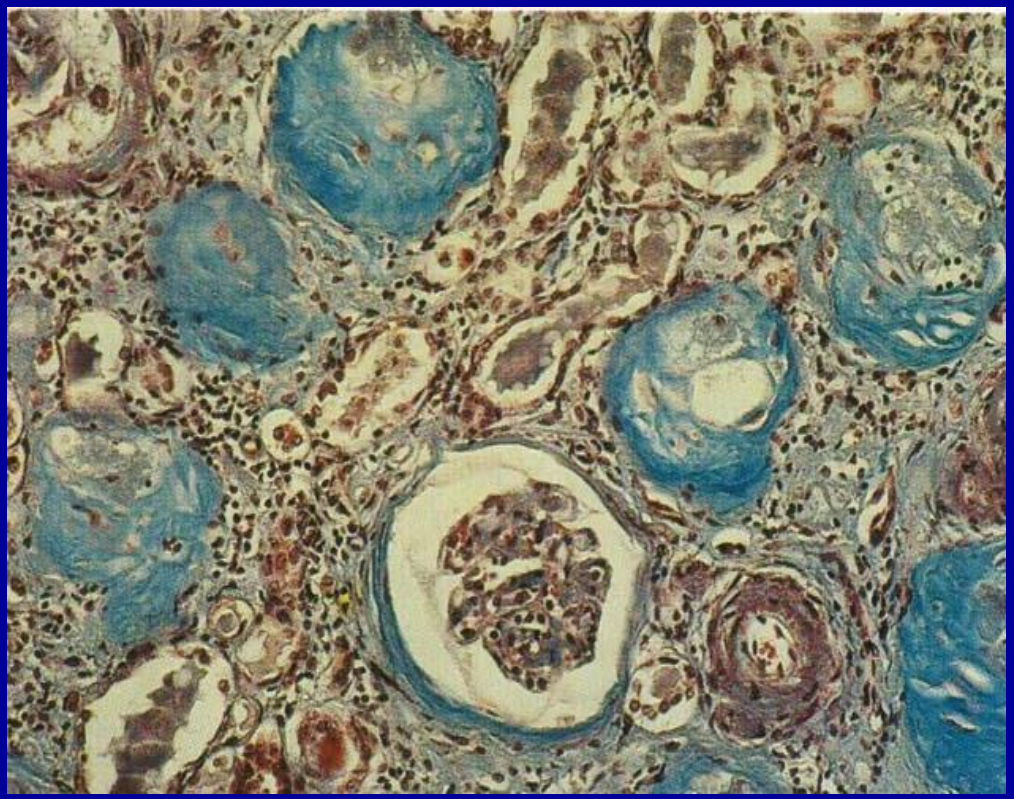
This is a close-up photograph of a cross-section of a kidney with **chronic glomerulonephritis.** The cortex has largely turned to scar tissue and there is a poor demarcation between cortex and medulla due to the glomerular scarring.



This is another example of **chronic glomerulonephritis**. Again, notice the small size of these kidneys about 2 x 3", the small amount of parenchyma in the cross-section, and the finely granular surface in the external view. Such kidneys are incompatible with life.



# Chronic Glomerulonephritis



Complete replacement of virtually all glomeruli by blue-staining collagen (Masson-trichrome)

# IV. D. Nephrotic syndrome

- Proteinuria (>3.5 gm/day)
- Hypoalbuminemia (reversed albumin/globulin ratio)
- Hyperlipidemia (increased LDL)
- Lipiduria (free fat and oval fat bodies in urine)
- Edema (pitting edema most marked in periorbital soft tissue, due to hypoalbuminemia and salt and water retention)

Complications:

- Infections (due to loss of Ig and complement)
- Thrombosis (due to loss of anticoagulant factors)

Three types:

1. Minimal change disease *(lipoid nephrosis)*
2. Focal Segmental Glomerulosclerosis (Focal Sclerosis)
3. Membraneous glomerulonephropathy

# CAUSES OF NEPHROTIC SYNDROME

| Primary Glomerular Diseases | Prevalence (%) Children | Adults |
|---|---|---|
| • Membranous GN | 5 | 40 |
| • Lipoid nephrosis | 65 | 15 |
| • Focal segmental GN | 10 | 15 |
| • Membranoproliferative GN | 10 | 7 |
| • Other proliferative GN (focal, pure mesangial, IgA nephropathy) | 10 | 23 |

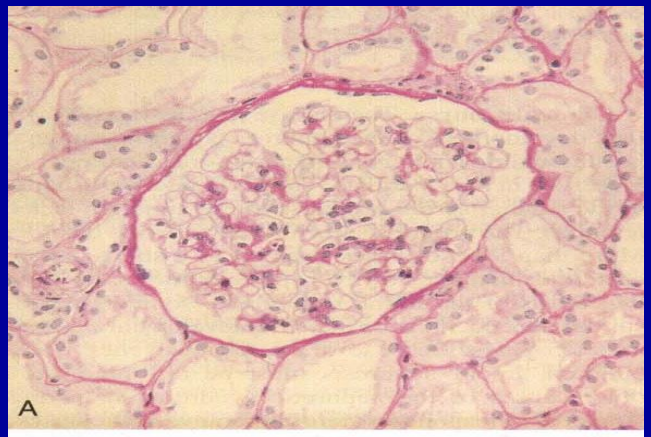
## Systemic diseases

- DM
- Amyloidosis: Most common systemic causes
- SLE
- Drugs (gold, penicillamine, “street heroin”)
- Infections (malaria, syphilis hepatitis, Bhepatitis, AIDS)
- Malignancy (carcinoma, melanoma)
- Miscellaneous (bee-sting allergy, hereditary nephritis)

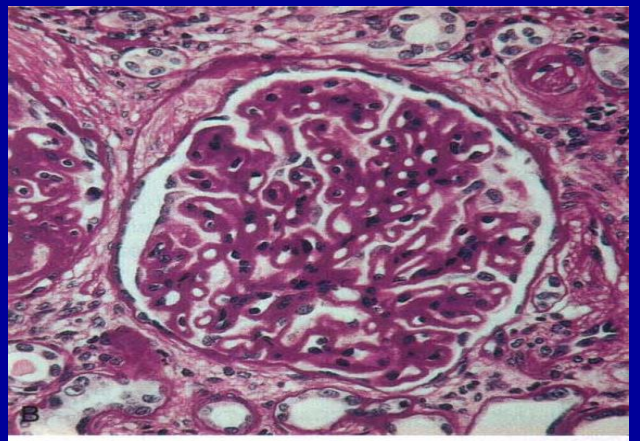
# IV. D. 1. Minimal change disease

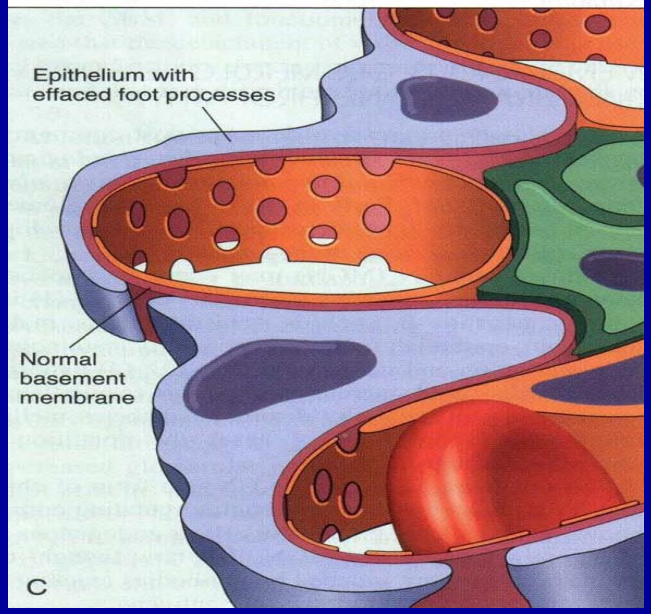
- Most common cause of nephrotic syndrome in children, and 15 – 20 % of adult cases
- Pathogenesis is uncertain → selective proteinuria to low molecular weight protein
- Microscopy is normal, **IF**: no consistent evidence of Ig, C', or electron dense deposits in glomeruli
- EM: visceral epithelial distortion with vacuolization, swelling and retraction of foot processes, flattening of the epithelial cells against capillary BM
- Response to corticosteroid is dramatic, withdrawal → periodic relapses
- No progression to chronic renal diseases

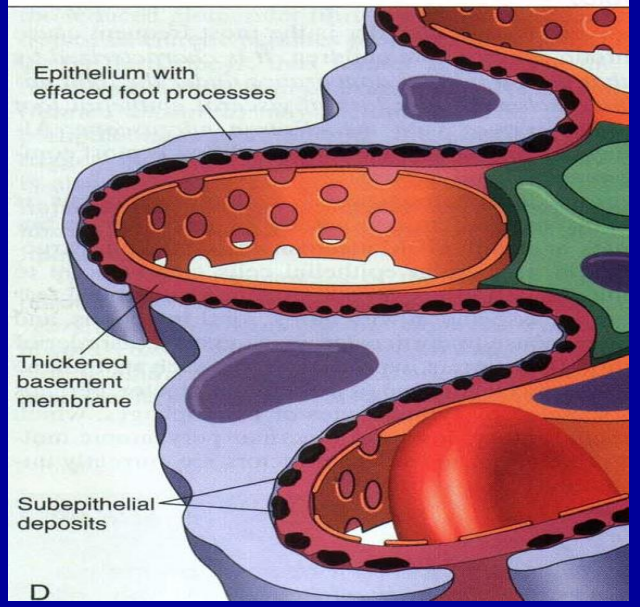
# LIPOID NEPHROSIS & MEMBRANOUS GN




PAS stained



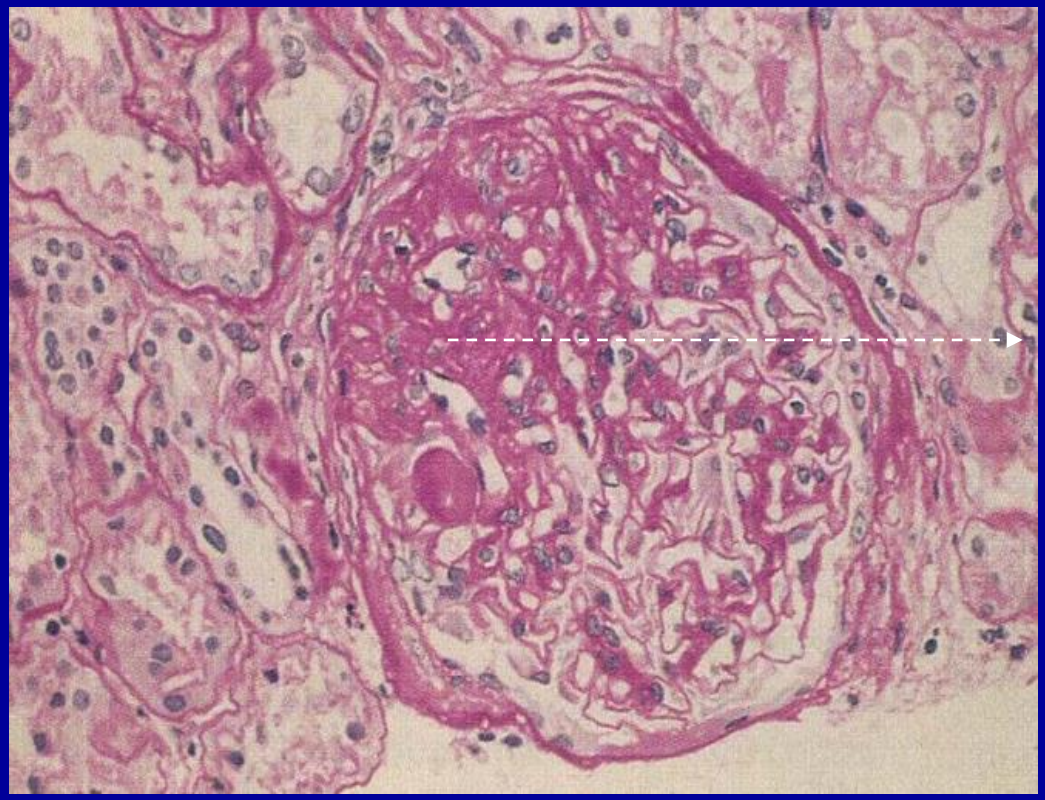



# IV. D. 2. Focal Segmental Glomerulosclerosis (Focal Sclerosis)

- May represent non-specific glomerular changes
- May develop incidious onset of nephrotic syndrom with micro-hematuria, hypertension, non-selective proteinuria, deposit IgM & C3 in sclerotic mesangium, poor response to steroids, and high (50%) progression to Chronic Renal Failure
- The lesions begin in juxtamedullary glomeruli, initially consist of focal and segfmental colaps of capillary structure with adhesion to Bowman's caps.
- **EM:** focal loss of epithelial cells and thickening of the capillary BM → pre-sumably protein is able to enter the mesangium → mesangial reaction with sclerosis and accumulation of PAS positive material (hyalinosis).

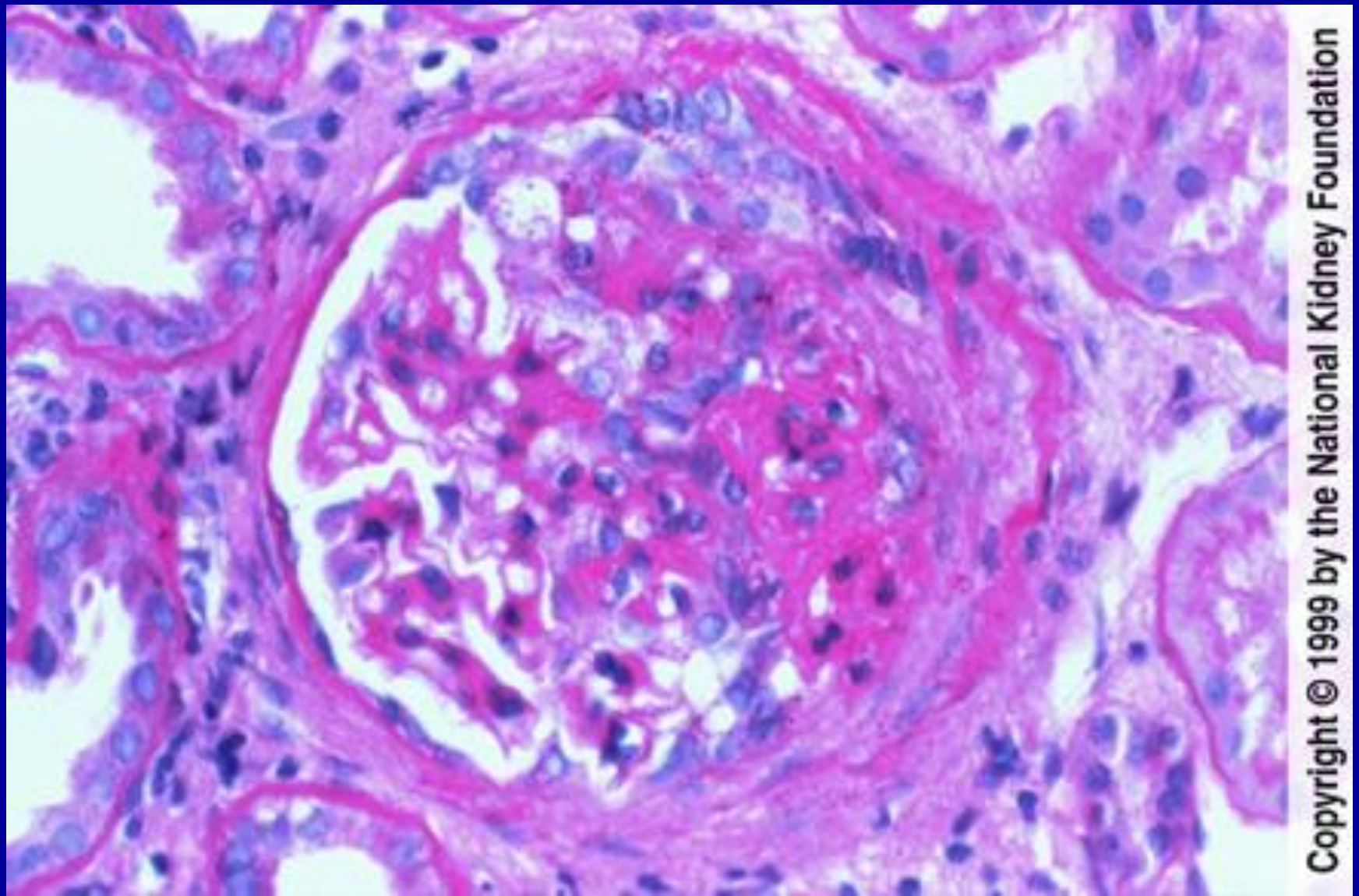
# Focal Segmental Glomerulosclerosis



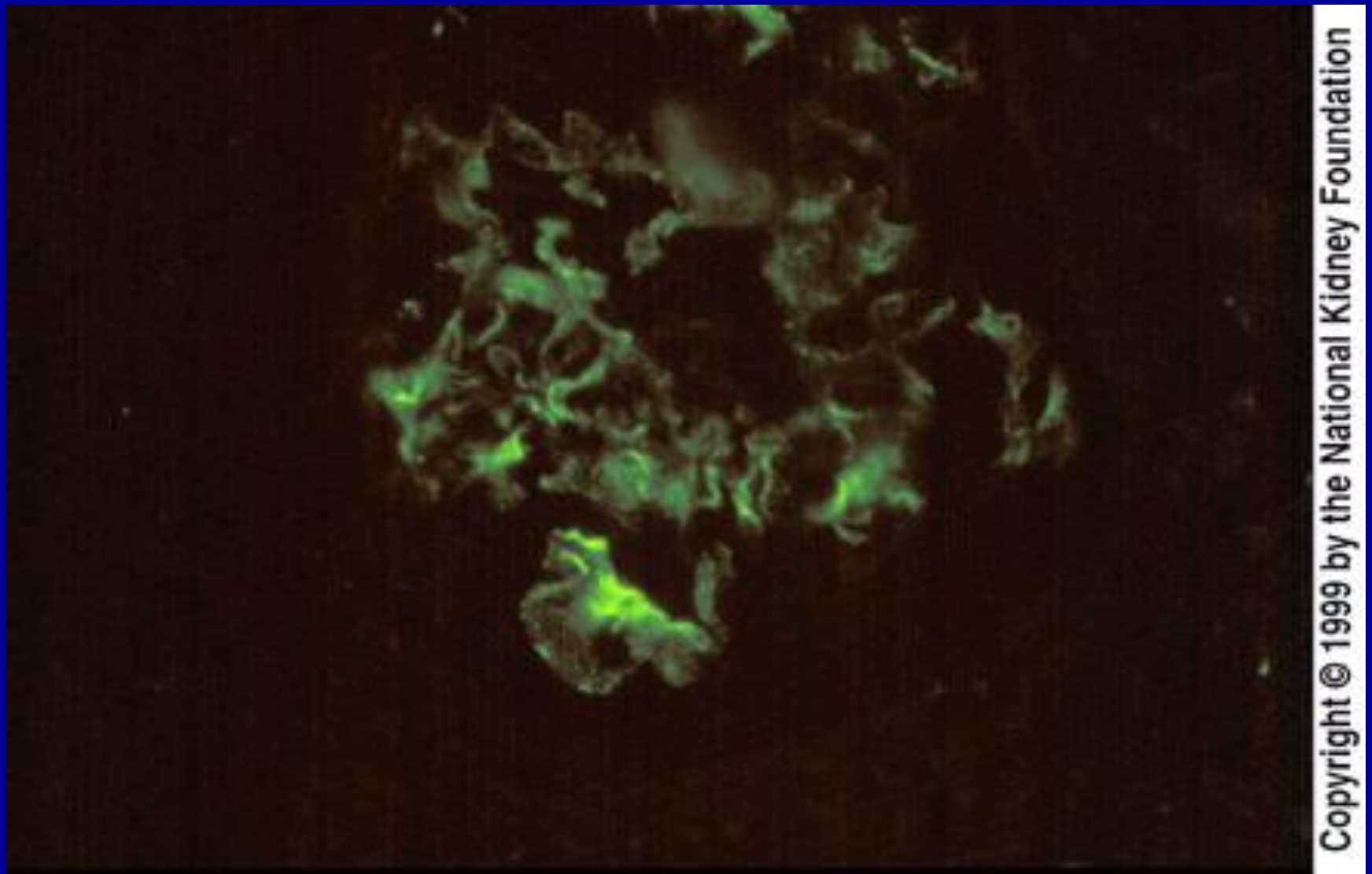
PAS stained (high power)

- Hyaline mass replaced a portion of the glomerulus

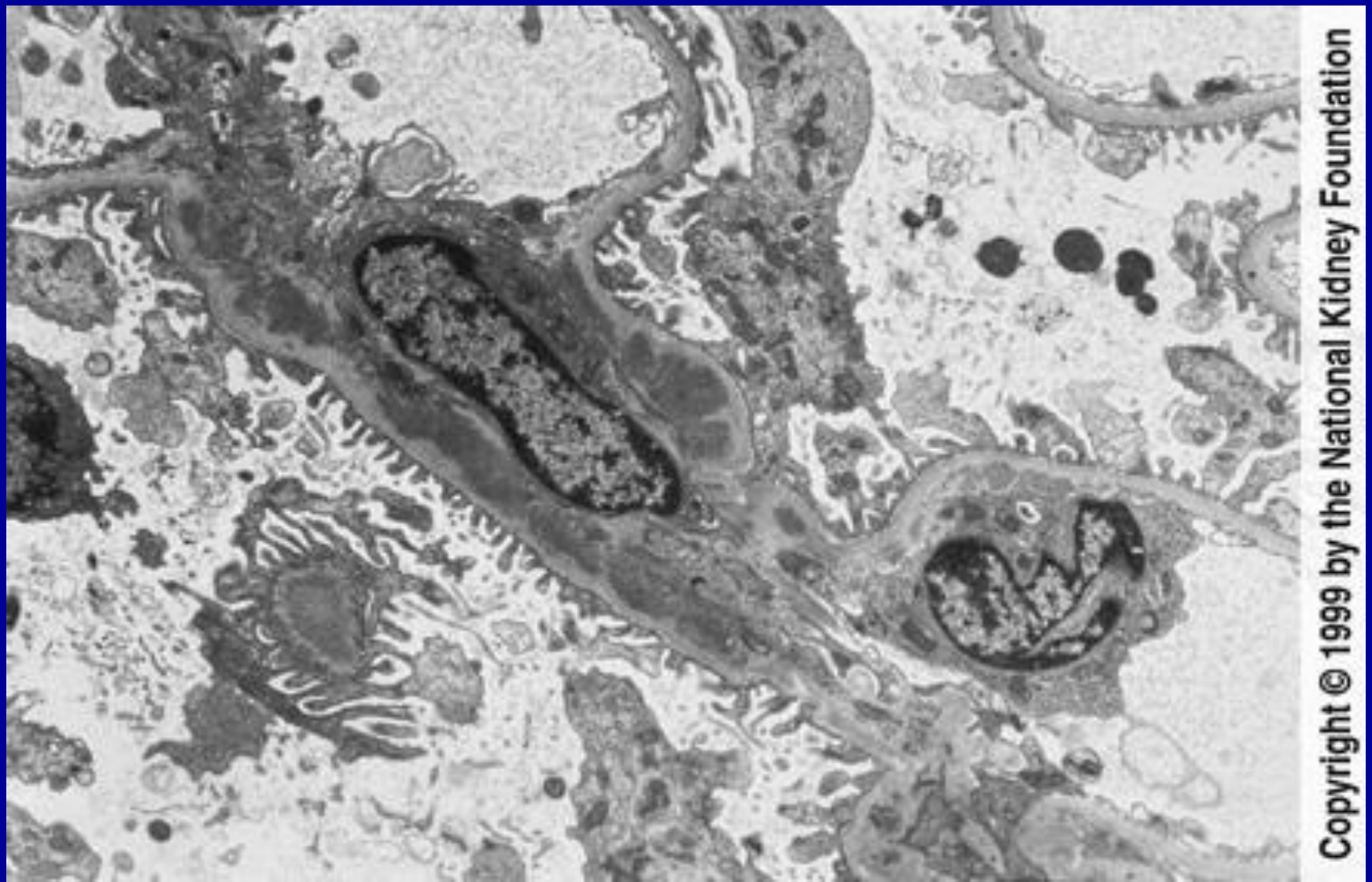
In this case of C1q nephropathy, well-defined segmental sclerotic lesions with increased matrix and obliteration of capillary lumens and adhesion to Bowman's capsule were present. The uninvolved portion of the glomerular tuft shows a mild to moderate increase in mesangial matrix and a minimal increase in mesangial cellularity. There is mild interstitial fibrosis. (Periodic acid-Schiff, X200).



Immunofluorescence shows mesangial or even paramesangial staining for C1q in C1q nephropathy, typically with lesser intensity staining for immunoglobulin (Ig) and C3. The immunofluorescence findings in C1q nephropathy are crucial in making the diagnosis and ruling out possible IgA nephropathy. In this glomerulus, sharply defined mesangial C1q was present, corresponding to electron-dense immune complex-type deposits seen by electron microscopy (see Fig 4). (Immunofluorescence with anti-C1q, X200).



Electron microscopic studies in C1q nephropathy confirm mesangial deposits underlying the basement membrane as it traverses over the mesangial area. There are no reticular aggregates present, a feature useful in distinguishing this from possible lupus nephritis. (Transmission electron microscopy, X3,000).



# IV. D. 3. Membranous Glomerulonephropathy

- Most common causae of nephrotic syndrome in adults
- Grossly: kidneys are large, swollen, and pale
- Mic: normal glomerular cellularity, but uniform diffuse thickening of the capillary wall → EM due to:

  Stage I: irregular subepithelial deposit of electron dense materials

  Stage II: granular deposits of IgG and C'…….. GBM material accumulates between deposits → forming "*spikes*"

  Stage III: *spikes* eventually surround the deposits

  Stage IV: incorporate them into the GBM, additionally there is loss of epithelial foot processes
- 15% associated with known antigen, the rest are idiopathic