

# **RENAL PATHOLOGY**

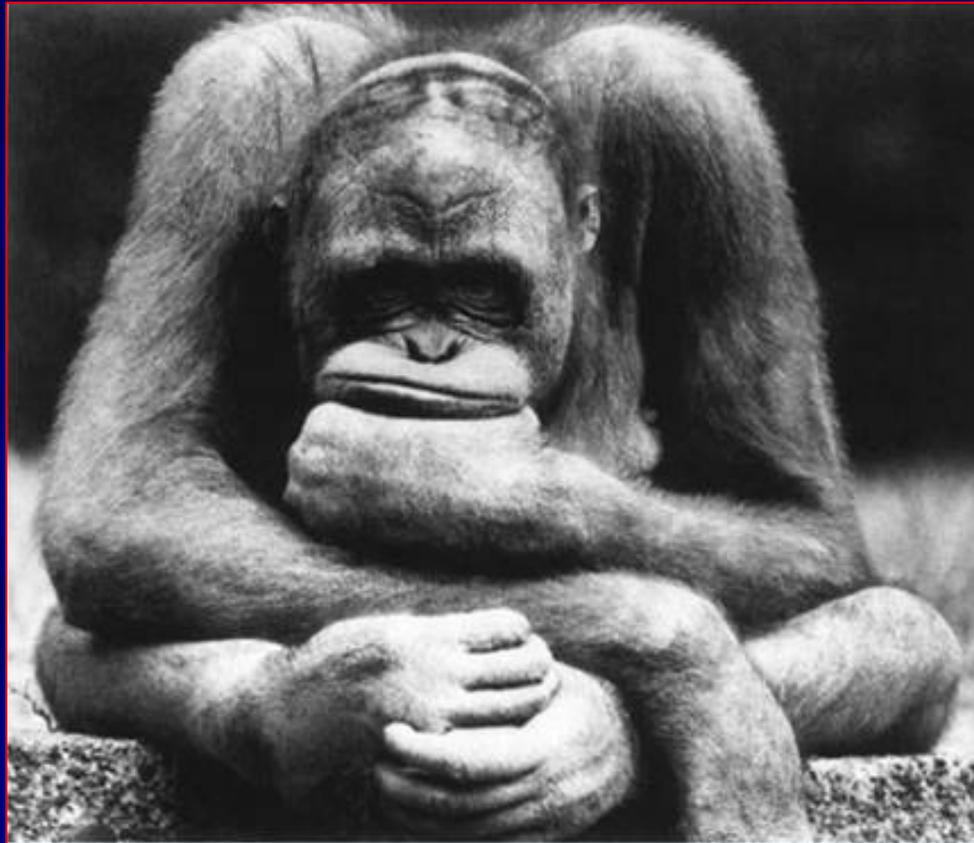
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**Department of Cellular Pathology  
Southmead Hospital  
Bristol, UK**

# Renal biopsy

The renal biopsy has been used to identify pathogenetic mechanisms and to establish clinicopathologic correlations between pathologic findings and clinical symptoms.

Different glomerulopathies with same clinical symptoms



Same glomerulopathies with different clinical symptoms

# Practice guidelines for the renal biopsy

Patrick D Walker et al.

*Modern Pathology* (2004) 17, 1555–1563

- Native kidney biopsies require examination by light microscopy, immunohistochemistry and electron microscopy.
- The processing of the renal biopsy is complex and requires the support of a fully equipped anatomic pathology laboratory.
- Technical expertise is required to process the small fragments of tissue and to produce sections of highest quality.
- The correct diagnosis requires a well-trained renal pathologist with thorough knowledge of not only renal pathology but also renal medicine in order to correlate intricate tissue-derived information with detailed clinical data.

# Interpretation of the renal biopsy

## Categorisation of

glomerulonephritis,  
glomerulopathies

(*eg* diabetes mellitus, amyloid, hereditary renal disease),

interstitial nephritis,  
renal vascular disease.

**Monitoring and measuring activity and chronicity**

**Monitoring transplant rejection.**

Analysing prognostic information

**Diagnosis of**

drug toxicity

systemic disease affecting the kidneys (*eg* vasculitis).



# Renal biopsy



Electronmicroscopy

Electronmicroscopy

Light microscopy

Immune microscopy



- HxE
- PAS
- PAAG
- Congo red
- E v Gieson
- MSB

- IgA
- IgG
- IgM
- C3
- C1q
- Kappa
- Lambda



- The next slides show special stains that often and world-wide are used in evaluating renal biopsy specimens

Many laboratories use a battery of stains for evaluating renal disease, e.g., H&E, PAS, trichrome, and silver stains.

# Routine stains

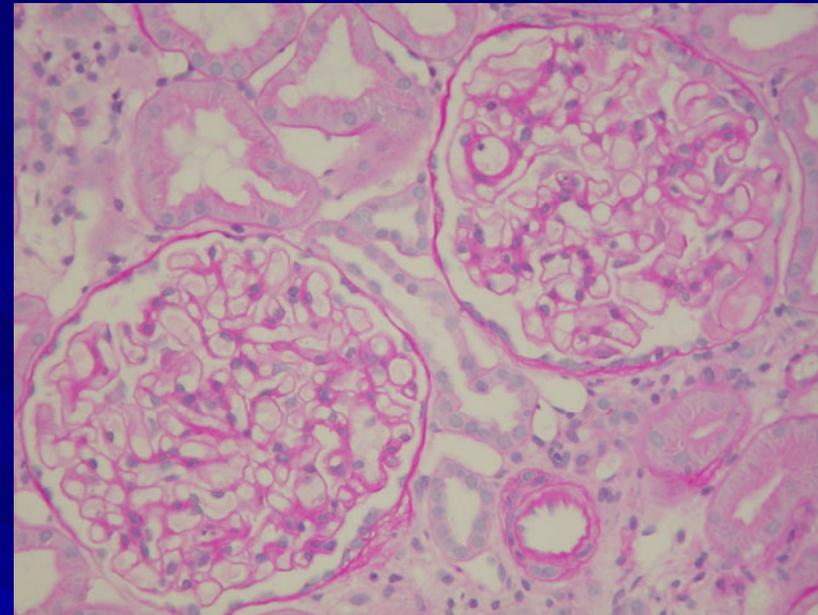
## HE-stain (*hematoxylin-eosin*)

### **composition of tissue:**

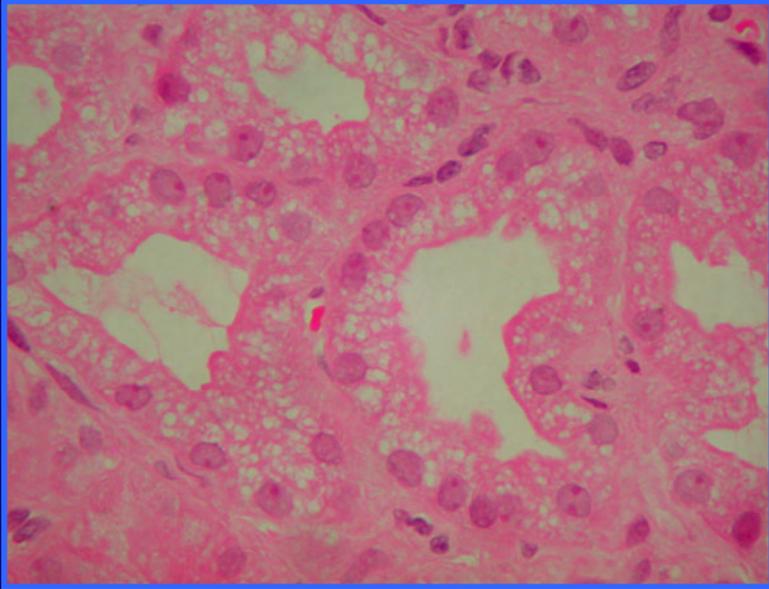
cortex vs medulla,  
number of glomeruli  
cellular infiltrates ..

### **analysis of glomerulus and vessels:**

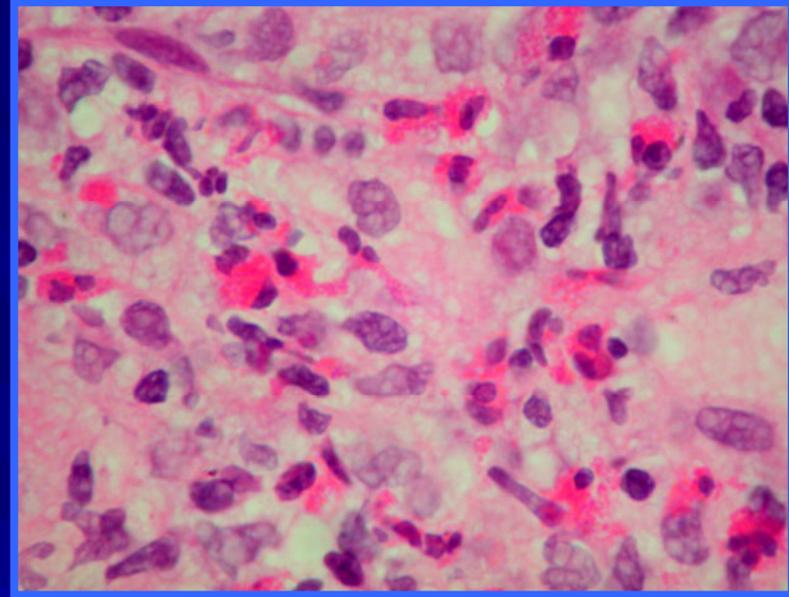
glomerular cells,  
mesangial matrix  
glomerular capillaries,  
glomerular basement membrane  
glomerular space



# HE-stain (*hematoxylin-eosin*)

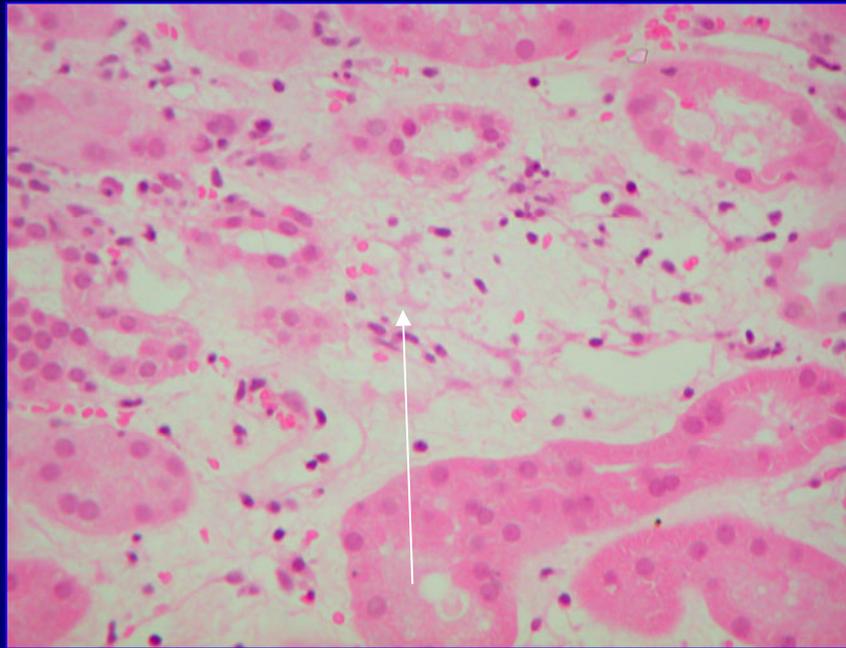


Tubular isometric  
vascuolisation in  
calcineurin-inhibitor-  
nephropathy

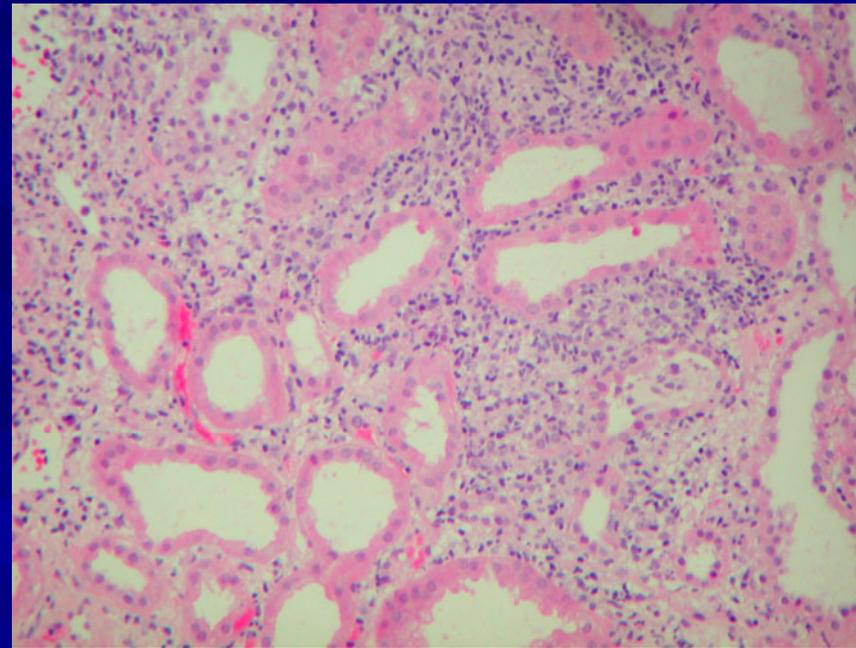


Eosinophils in pauci  
immune glomerulonephritis  
(Churg-Strauss syndrome)-

# HE-stain (*hematoxylin-eosin*)



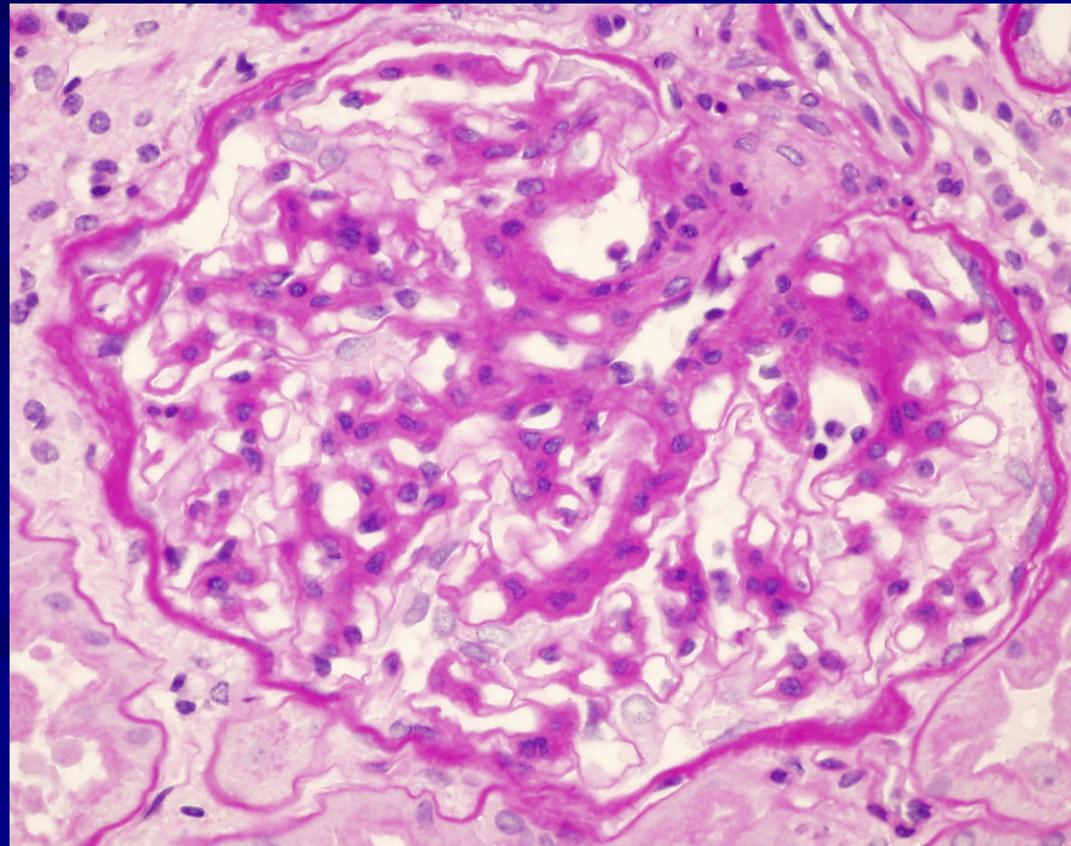
■ Interstitial oedema



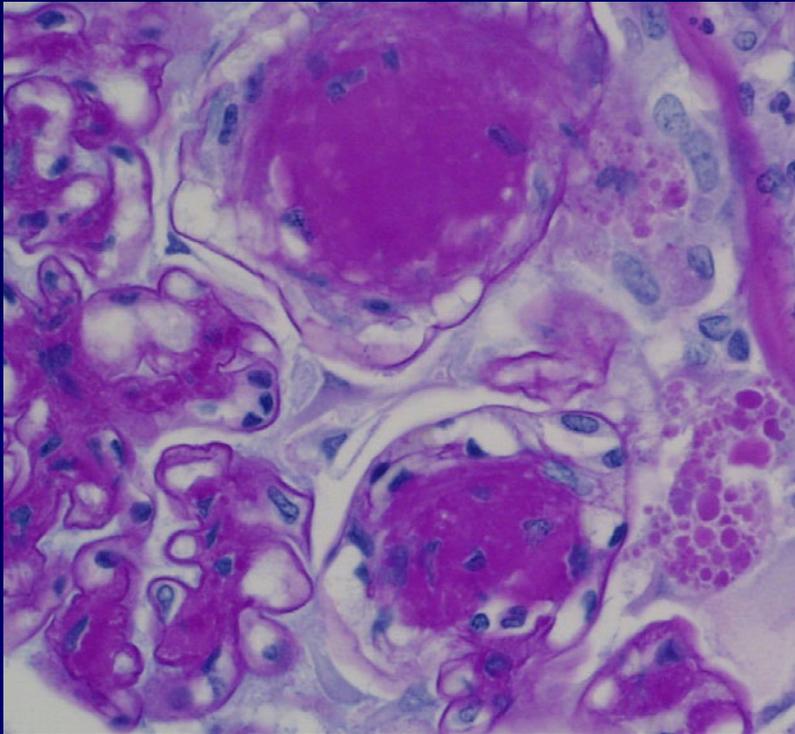
■ Interstitial inflammatory cell infiltration

## PAS (*Periodic acid-Schiff's base*) staining

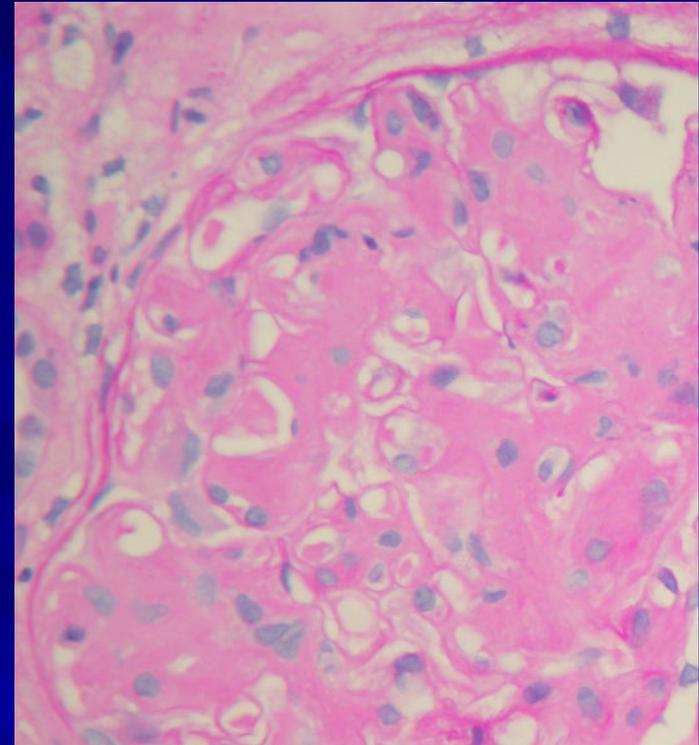
The PAS stain accentuates matrix and basement membrane constituents, protein droplets, arteriolar hyaline etc.



## PAS (*Periodic acid-Schiff's base*) staining



K-W nodules in DM nephropathy  
always PAS +ve



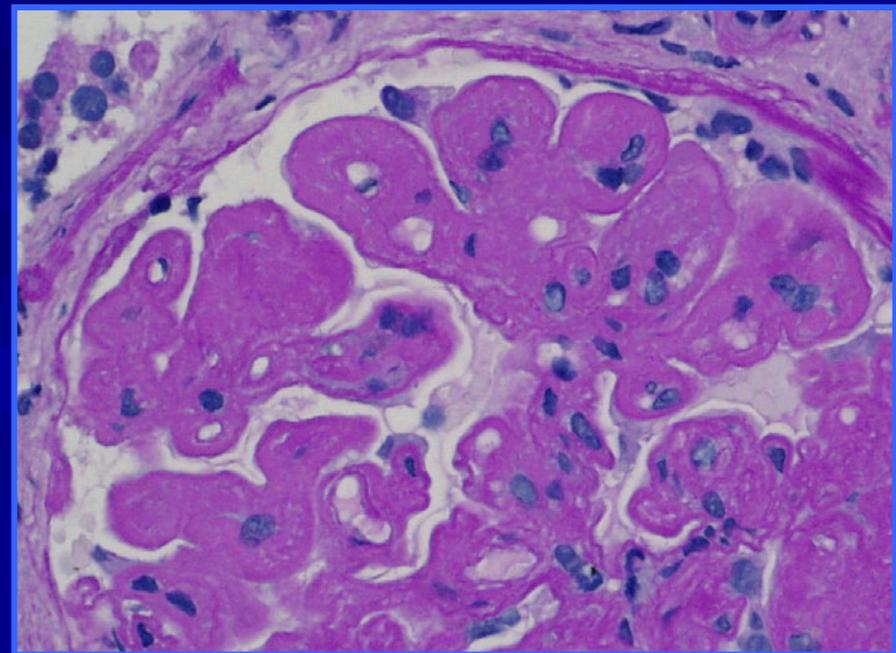
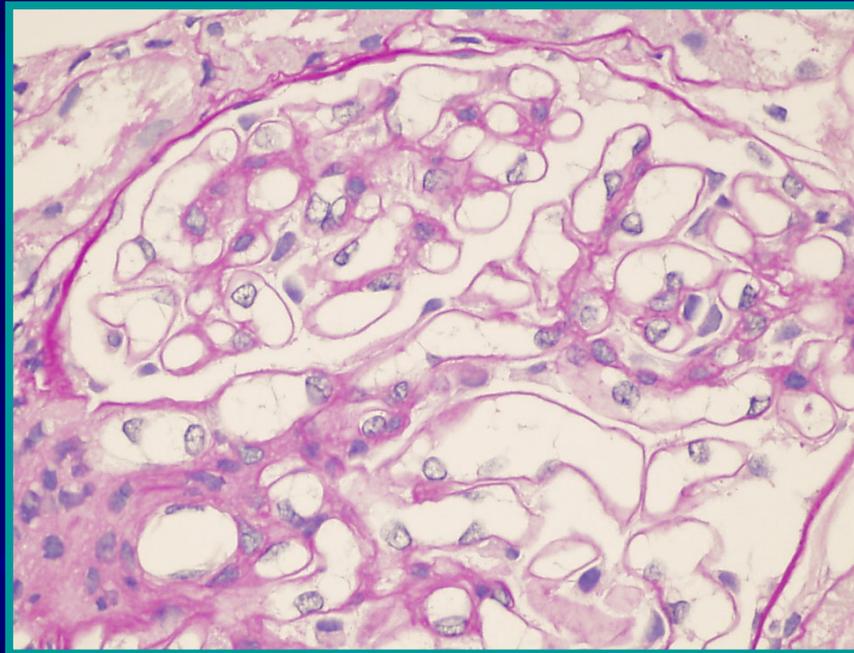
Amyloidosis  
Very weak PAS reaction

# PAS (*Periodic acid-Schiff's base*) staining

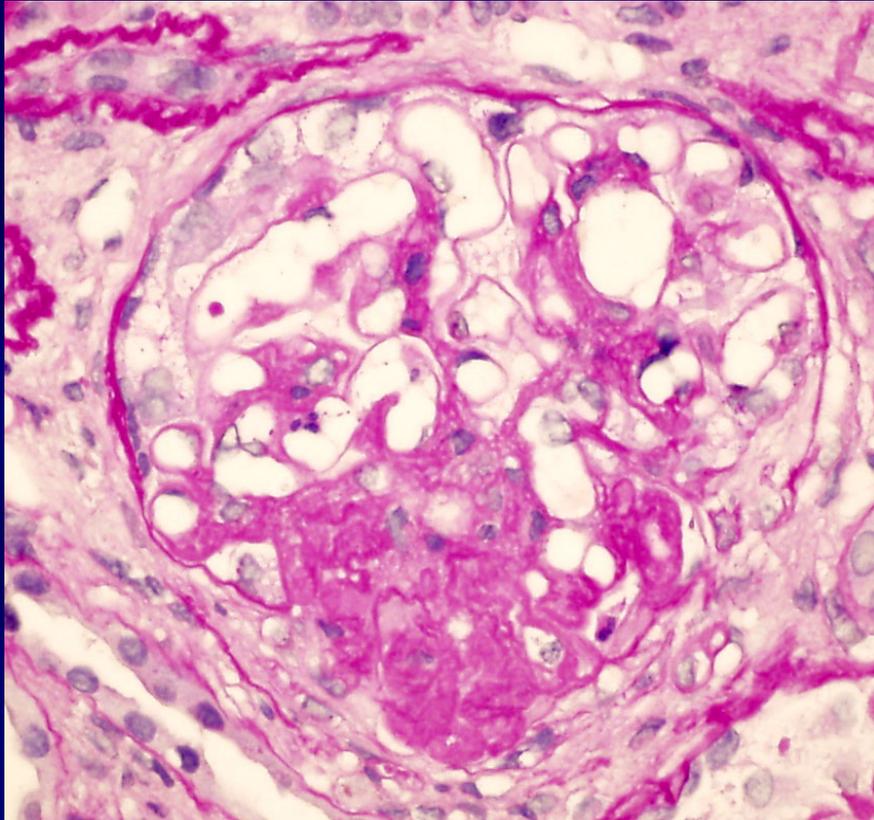
GBM-thickening



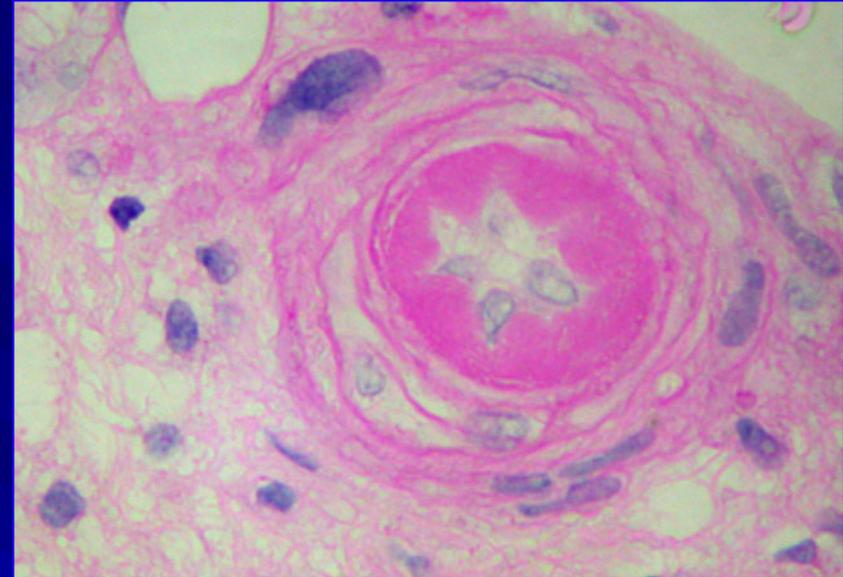
Normal capillary walls



## PAS (*Periodic acid-Schiff's base*) staining

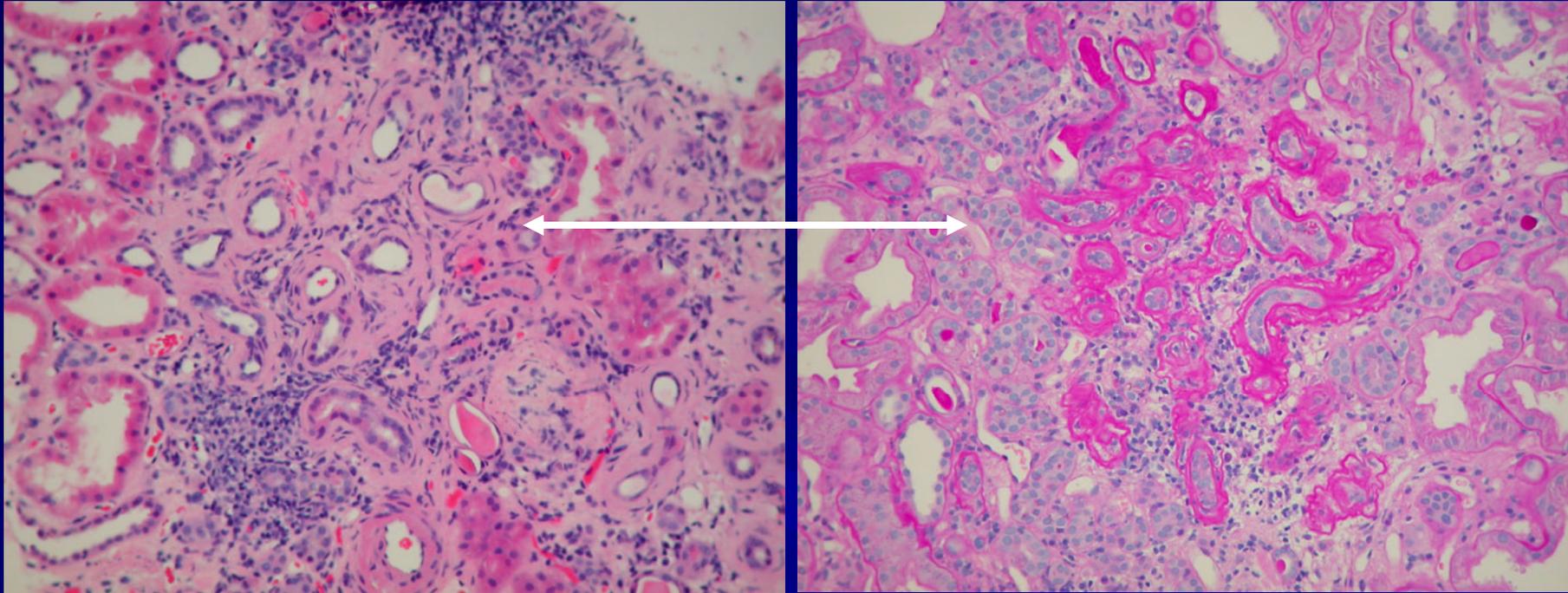


Hyalinosis with  
peripheral adhesion



Arteriolar hyaline deposit

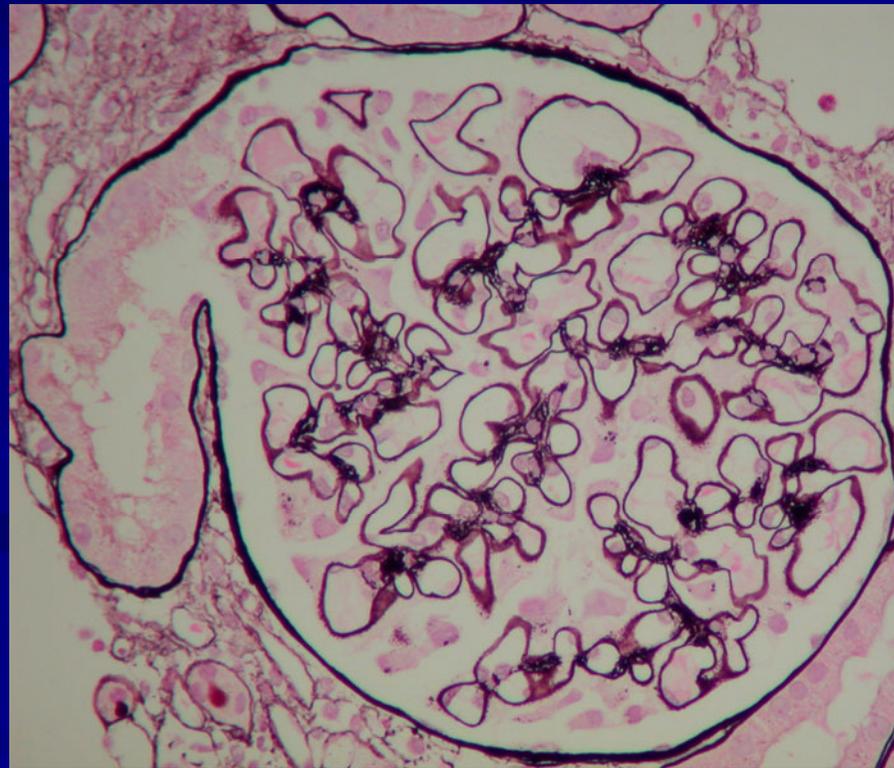
# PAS (*Periodic acid-Schiff's base*) staining



Tubular atrophy

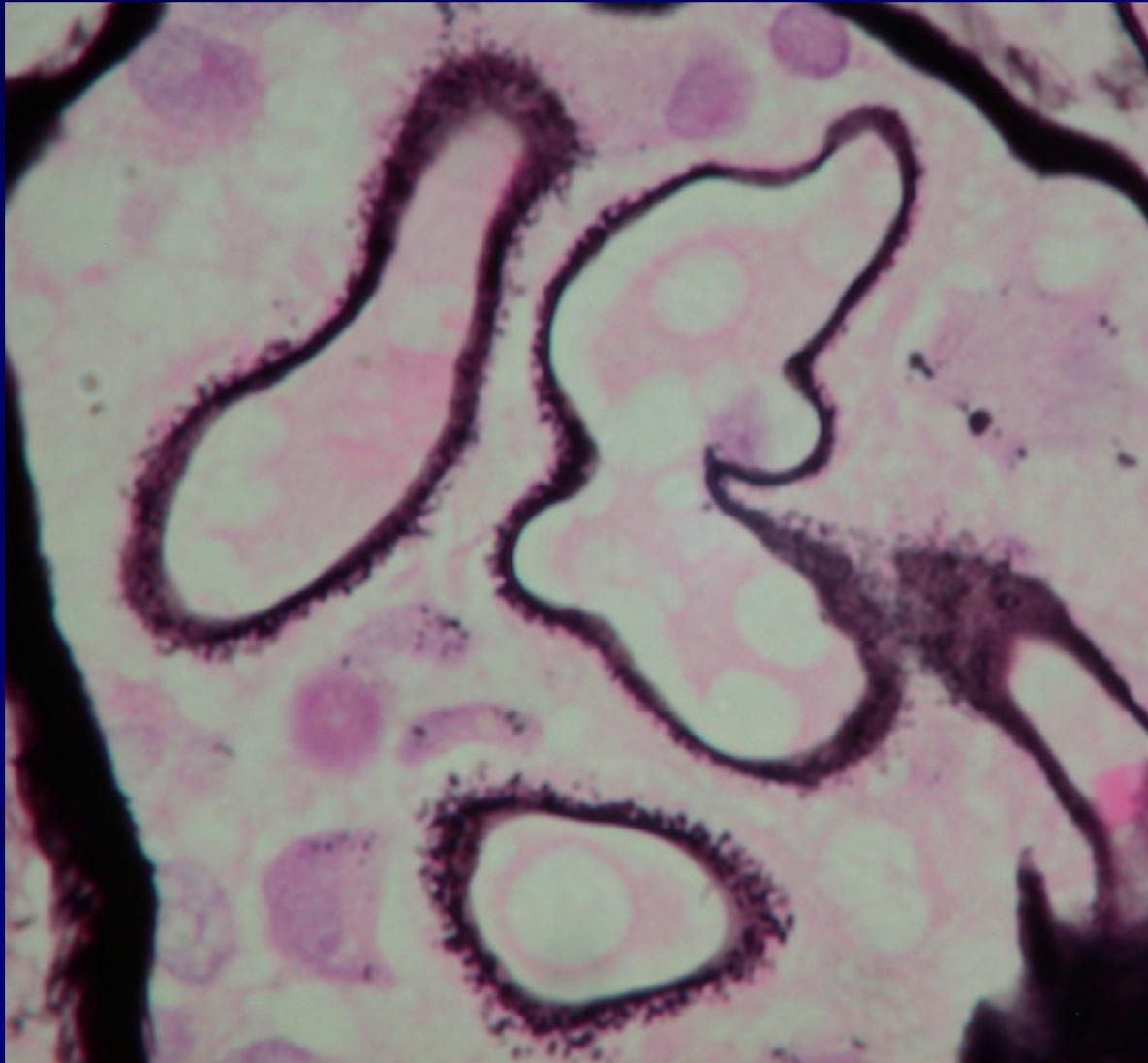
## PAAg (*Periodic acid-silver methenamine*) staining

The silver stain accentuates argyrophilic substances, collagenous structures, e.g., in the glomerulus, the mesangial matrix and the glomerular basement membrane and detect (visualizes) GBM lesions. ie. (spike formation, spicules, double contour, rupture etc.)



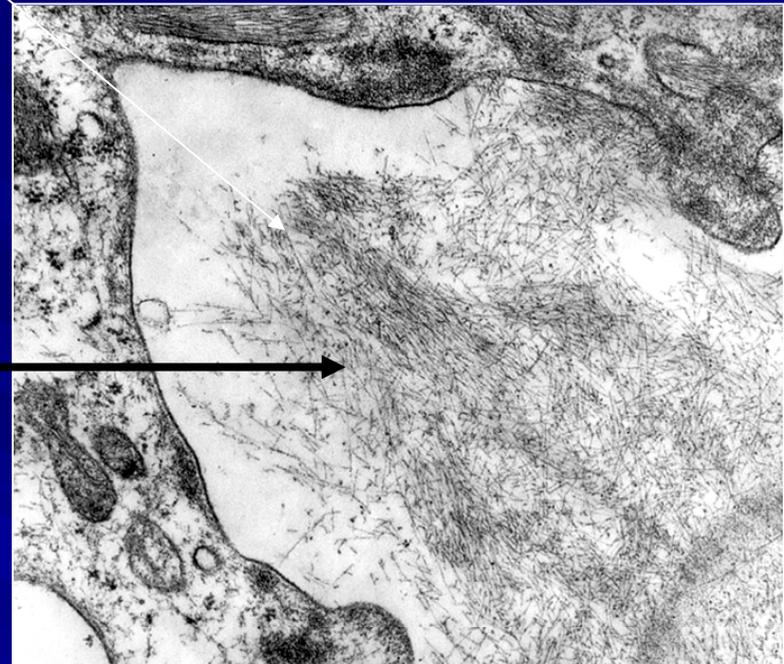
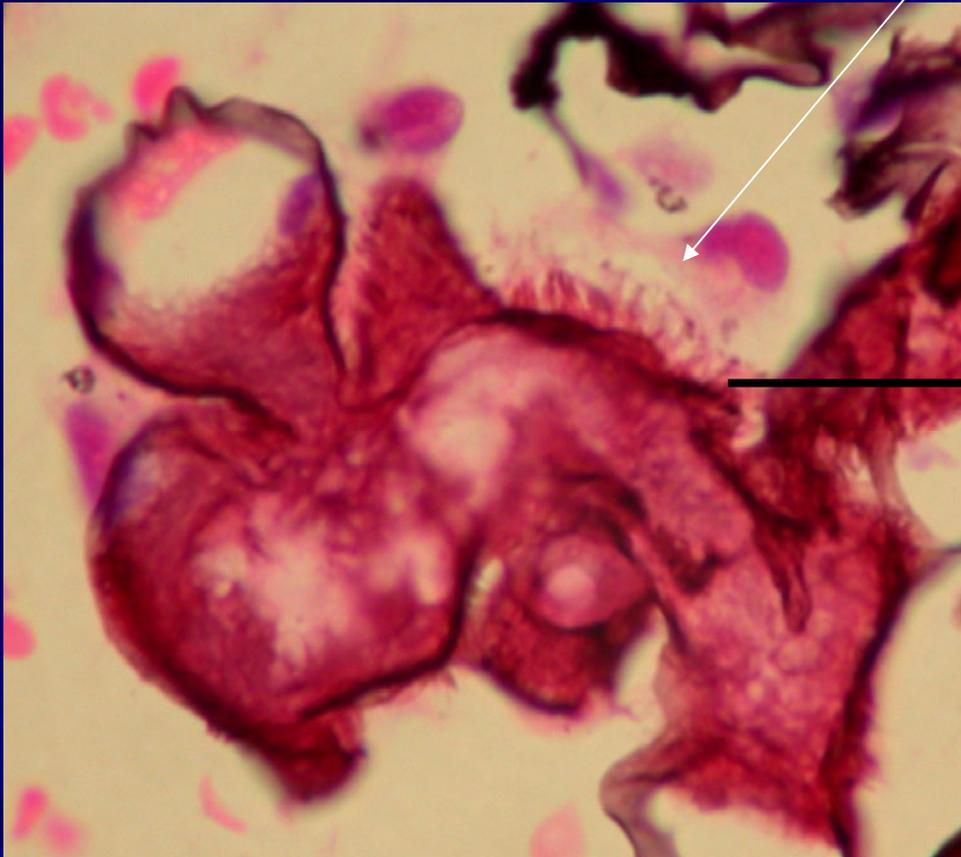
**PAAg** (*Periodic acid-silver methenamine*) **staining**

GBM spikes



# PAAg (*Periodic acid-silver methenamine*) staining

GBM spicules

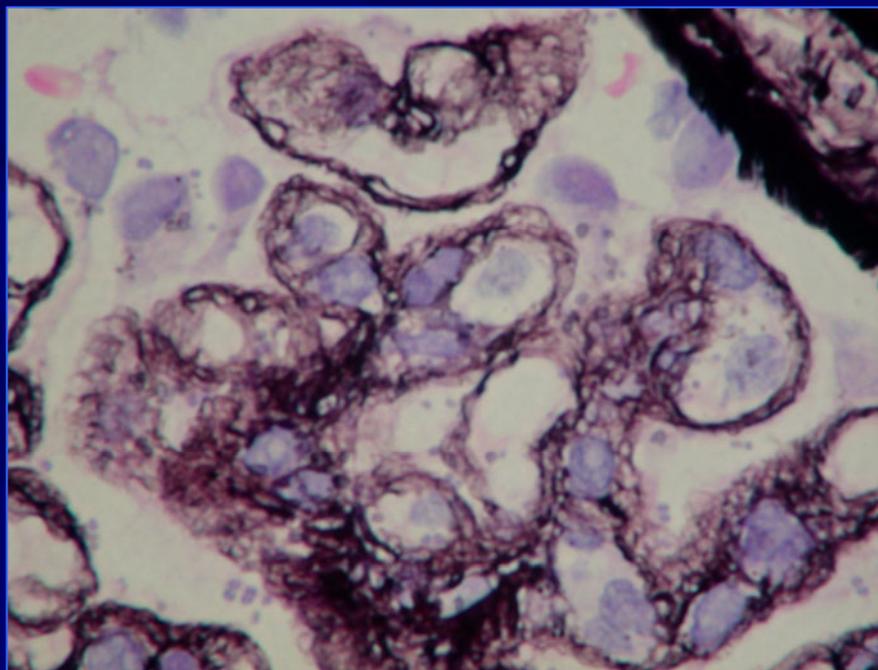


Parallel arranged  
microfibrils

Am,yloidosis  
Fibrillary glomerulopathy

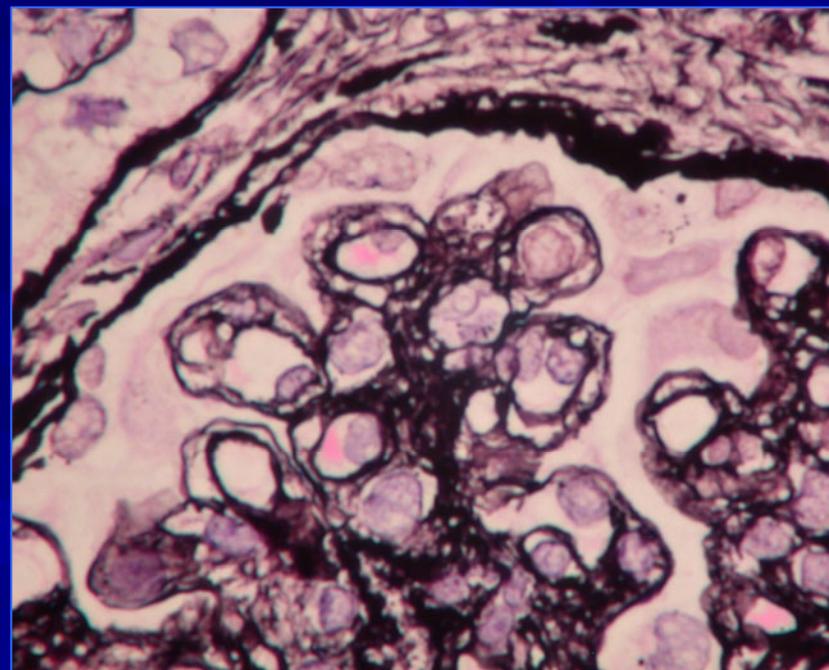
# PAAg (*Periodic acid-silver methenamine*) staining

## Double contour



Bubble-formation

Membranous GN

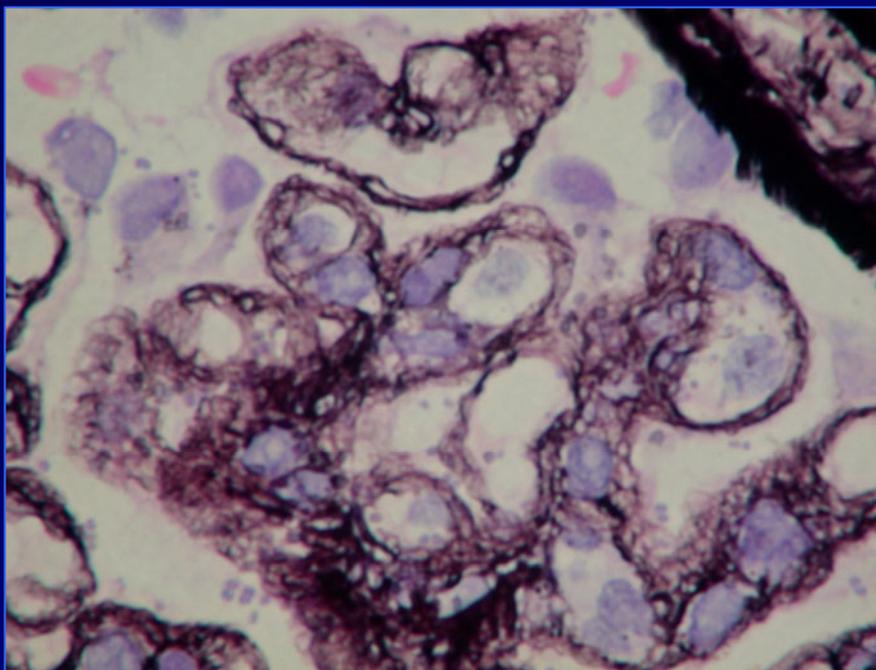


Tram-track lesion

Membranoproliferative GN  
Chronic allograft glomerulopathy

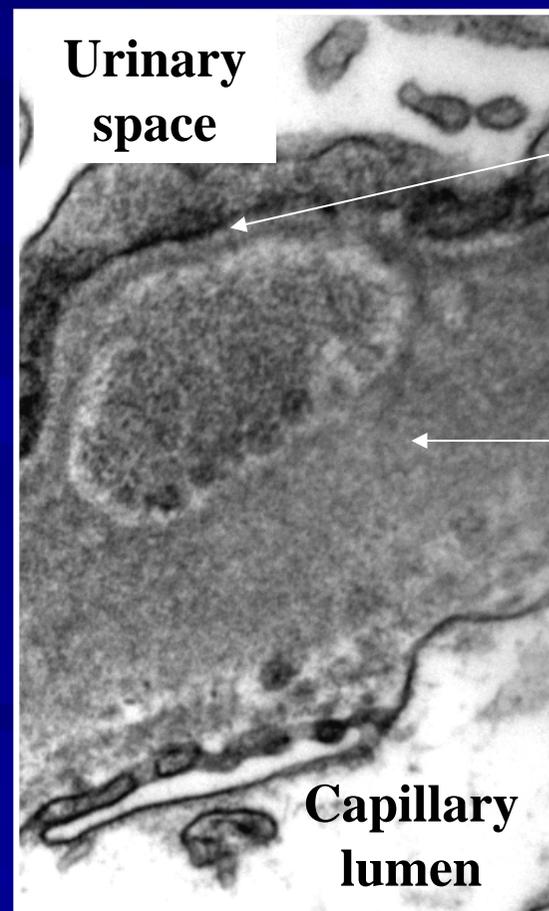
# PAAg (*Periodic acid-silver methenamine*) staining

Double contour



Bubble-formation

Membranous GN



Urinary space

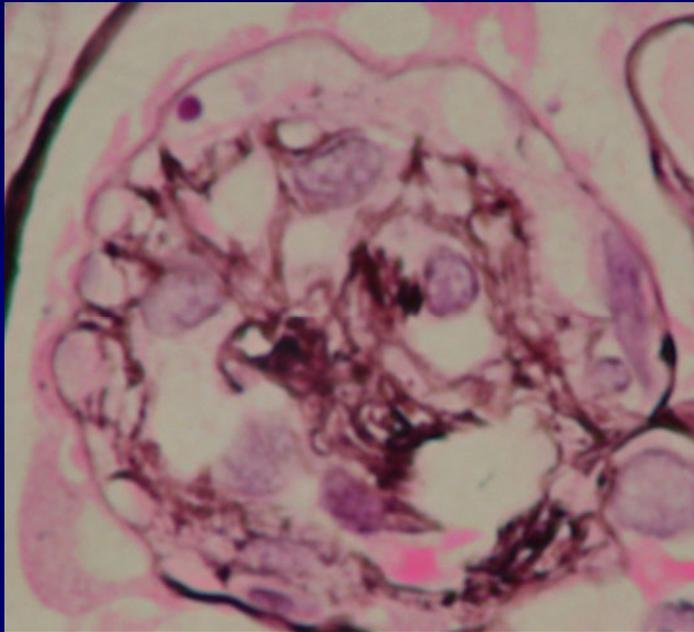
New GBM layer

Original GBM

Capillary lumen

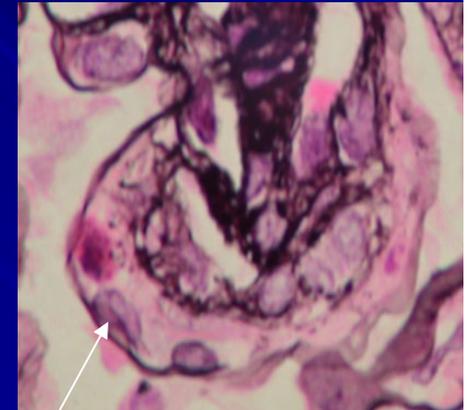
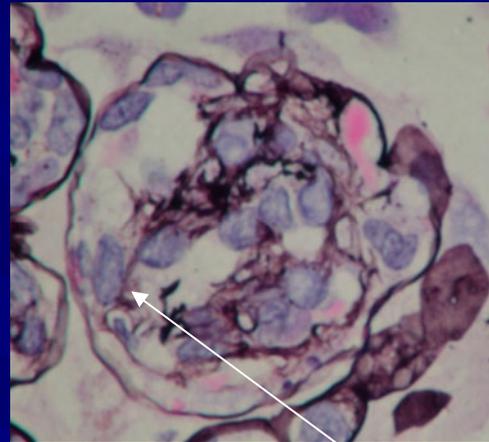
# PAAg (*Periodic acid-silver methenamine*) staining

Double contour



Tram-track lesion

Membranoproliferative GN

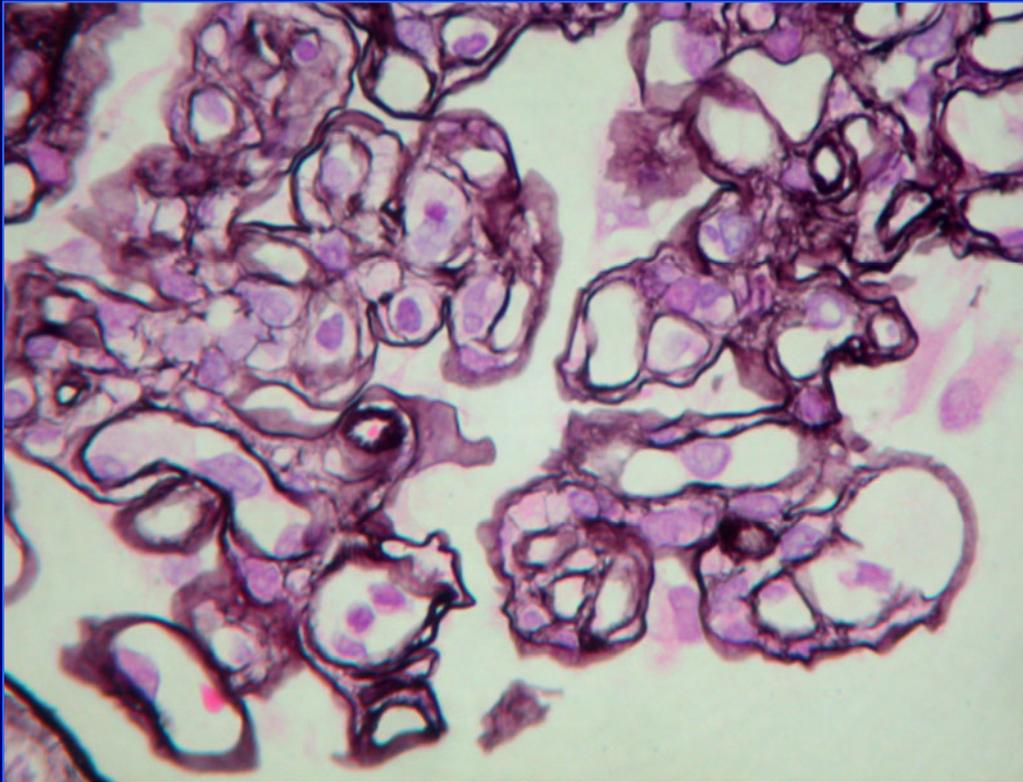


**Mesangial cell interposition**

Mesangial cell migrate to the periphery between the endothelial cell and glomerular basement membrane. Producing GBM material forms new GBM layer.

# PAAg (*Periodic acid-silver methenamine*) staining

Double contour



Chronic allograft  
glomerulopathy

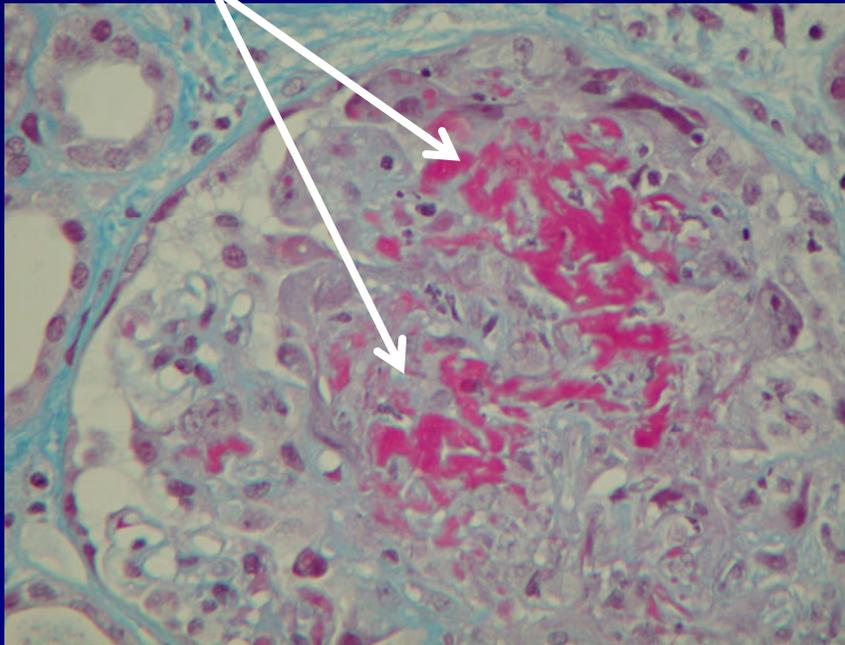
Ischaemic origin

# Trichrome staining

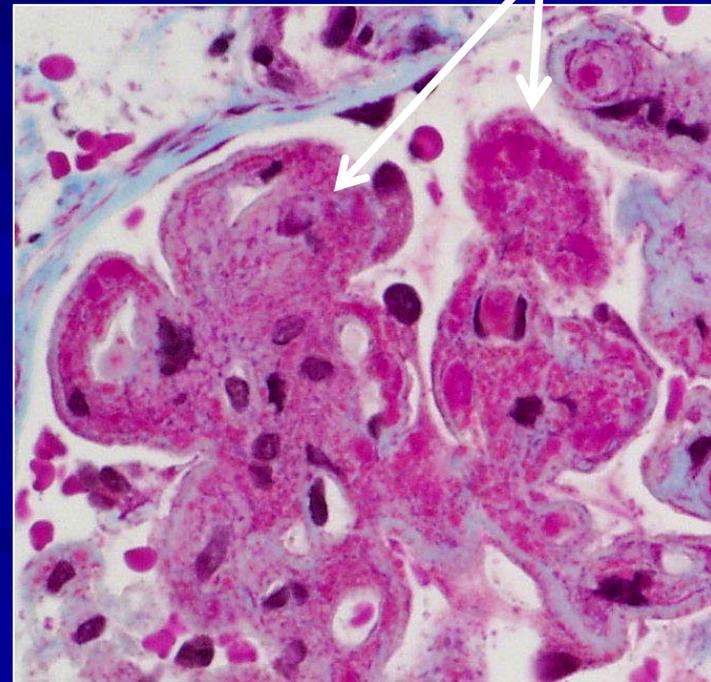
(Martius-Scarlat-blue)

to detect fibrin (thrombus, necrosis) In certain circumstances the trichrome stain demonstrates immune deposits as fuchsinophilic (red) structures.

Fibrin



Immune deposit

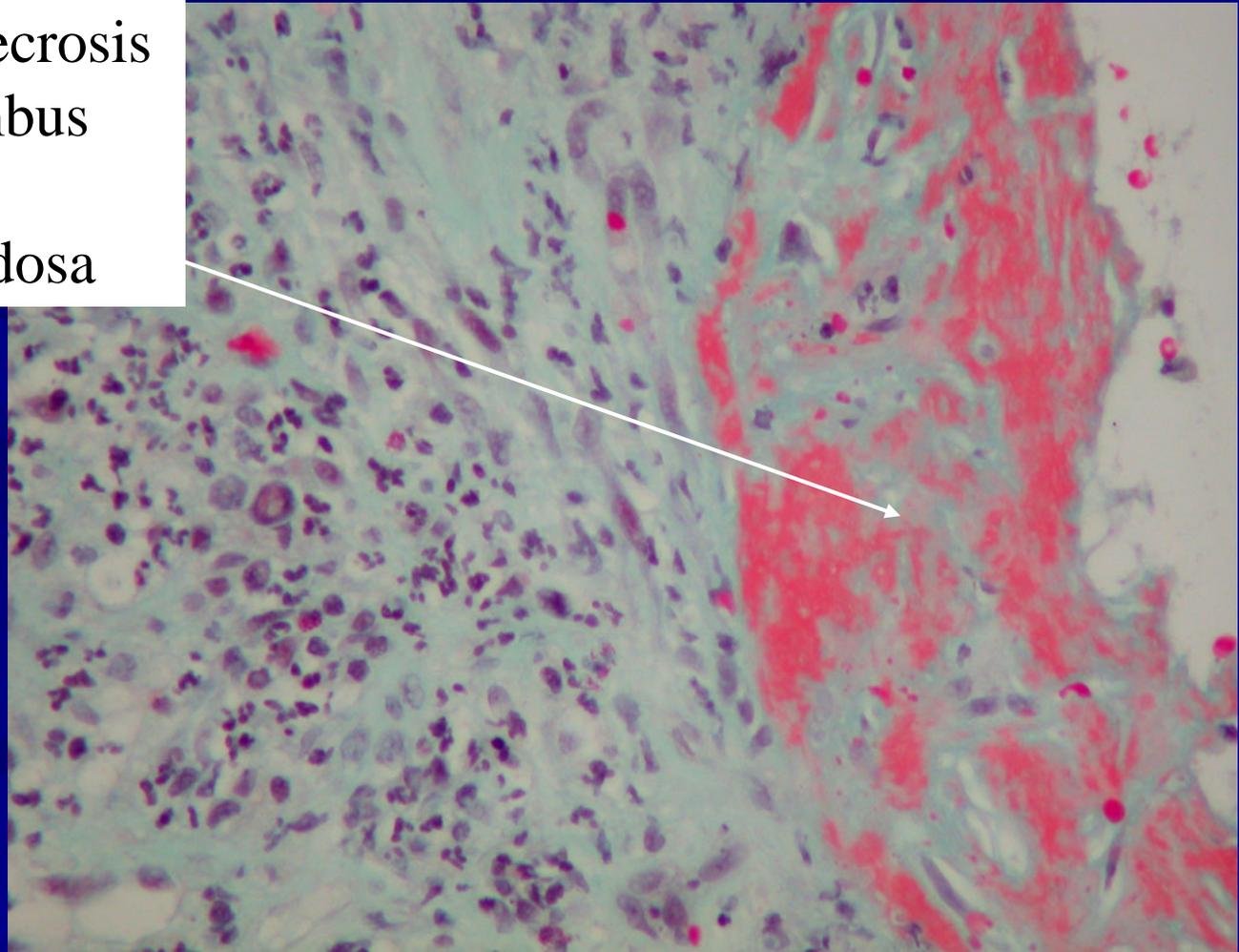


# Trichrome staining

to detect fibrin (thrombus, necrosis)

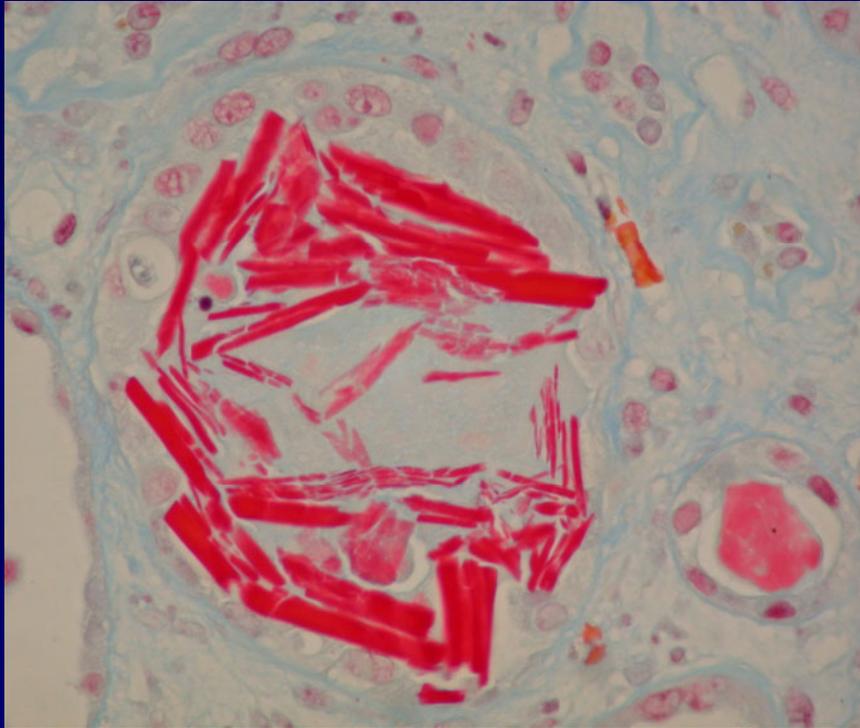
Fibrinoid arterial necrosis  
and fibrin-thrombus

Polyarteriitis nodosa

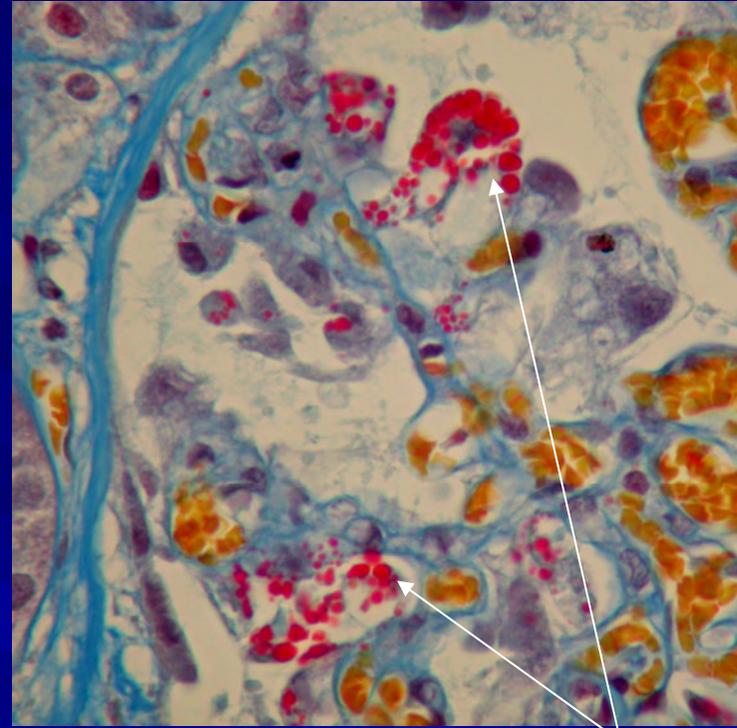


# Trichrome staining

(Martius-Scarlat-blue)



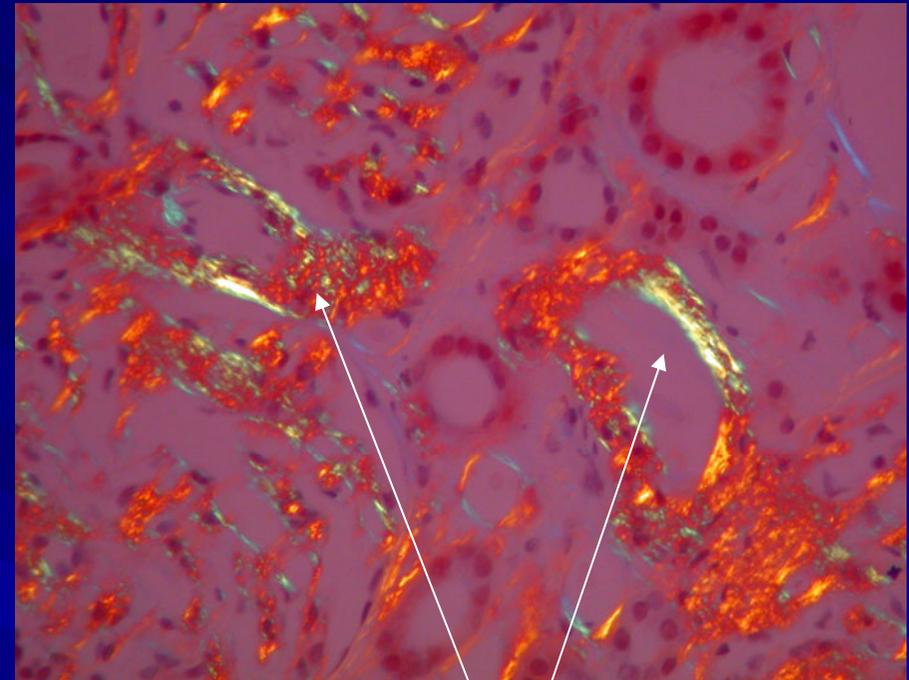
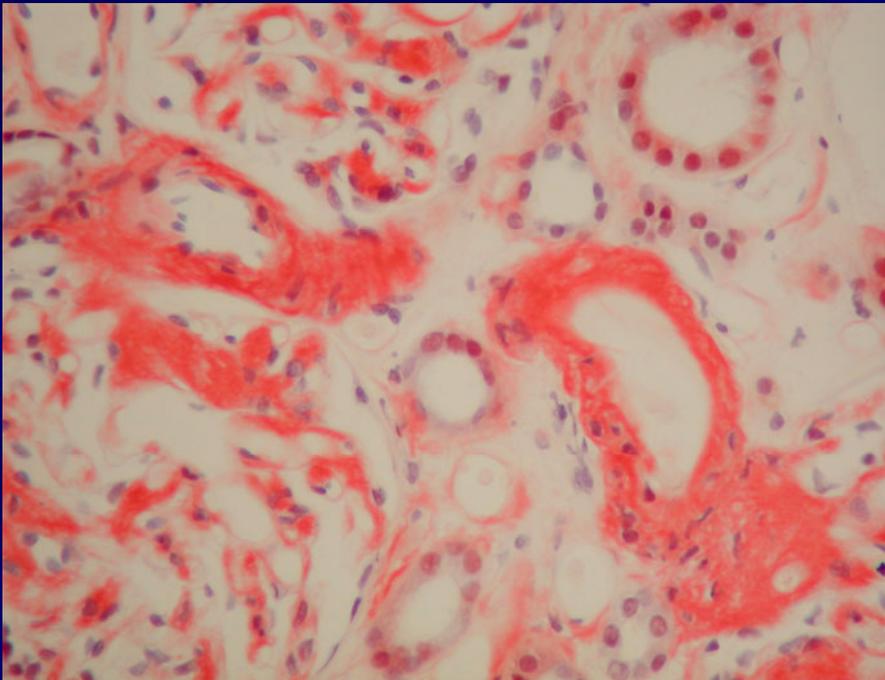
Protein crystals  
in Myeloma kidney



Intracytoplasmic  
protein droplets

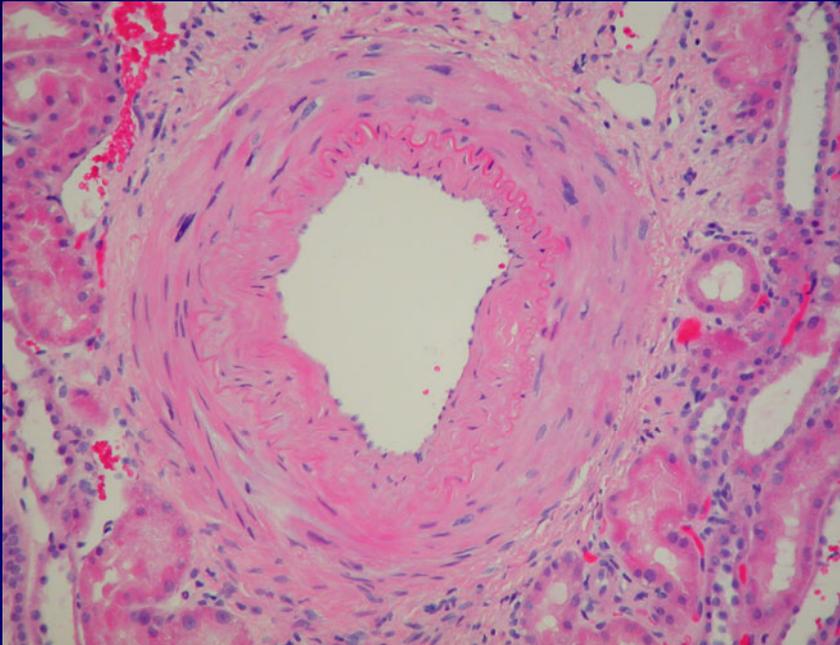
# Congo red staining

to detect amyloid and exclude fibrillary GP

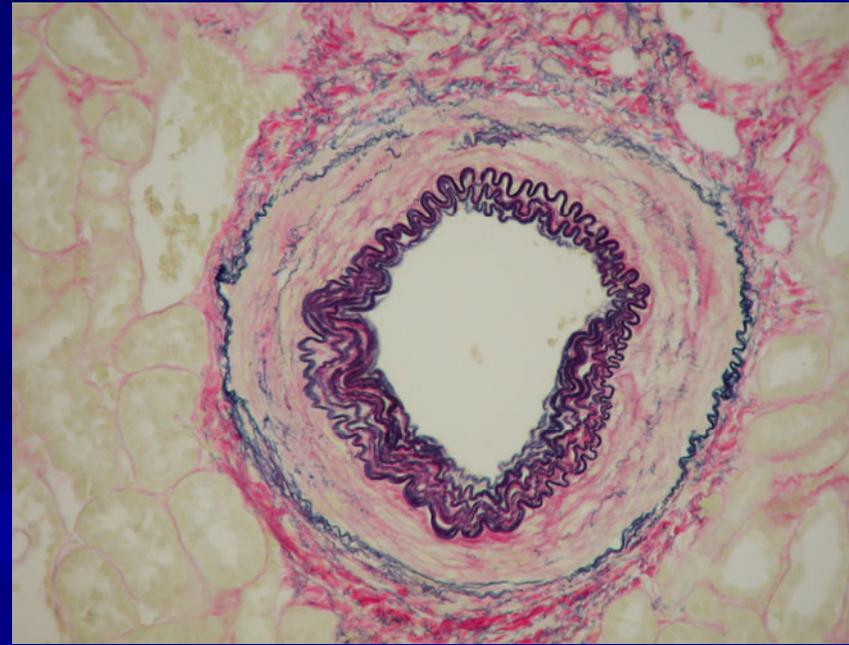


Under polarizing light  
Apple-green birefringence  
is diagnostic for amyloid

## Elastica-van Gieson (EvG)



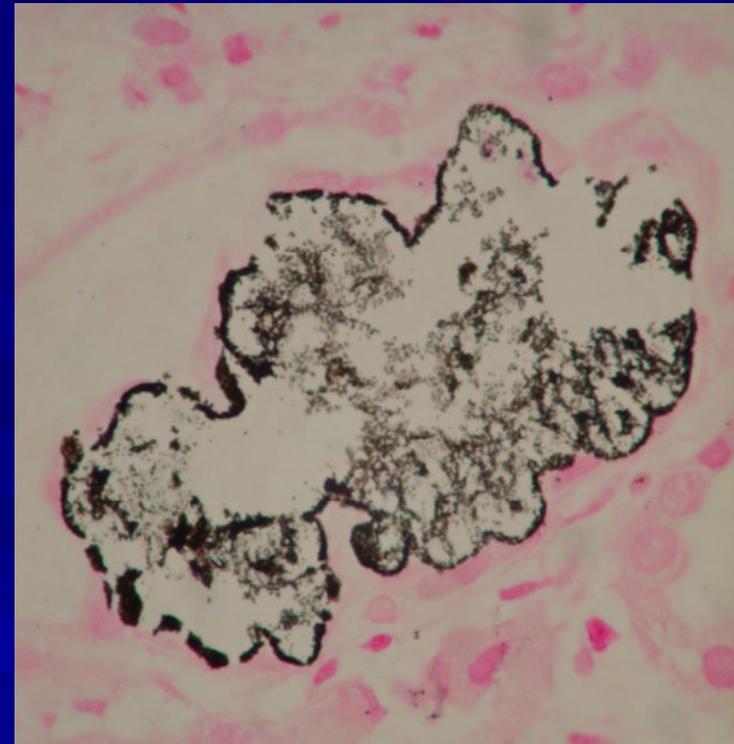
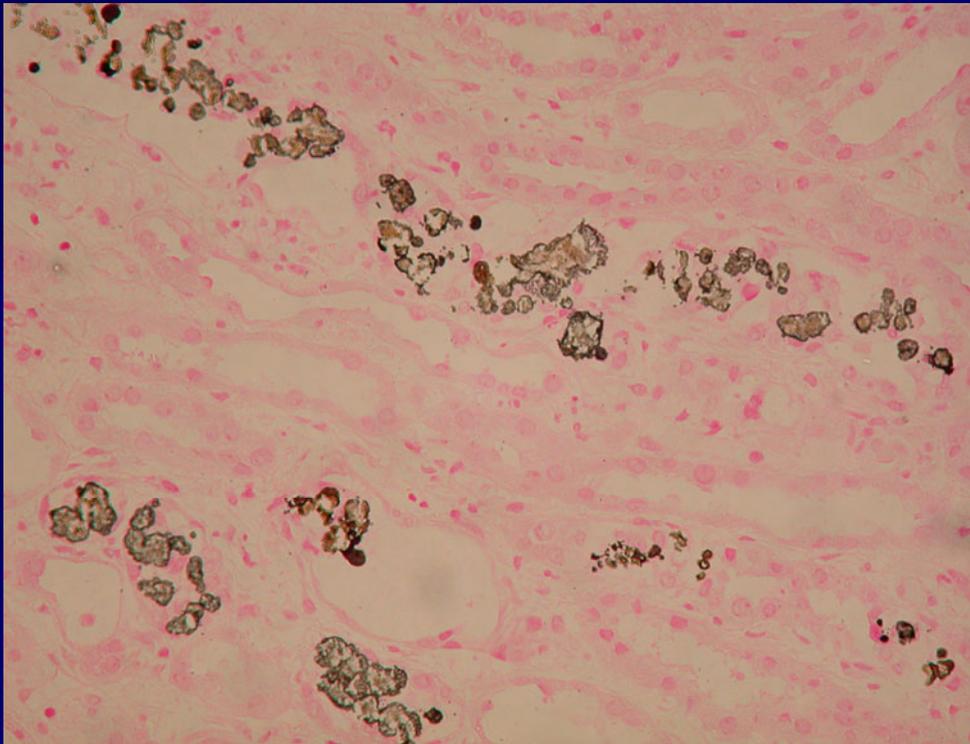
H&E staining



EvG stain

Reduplication of elastic lamina cannot be detected by H&E or PAS

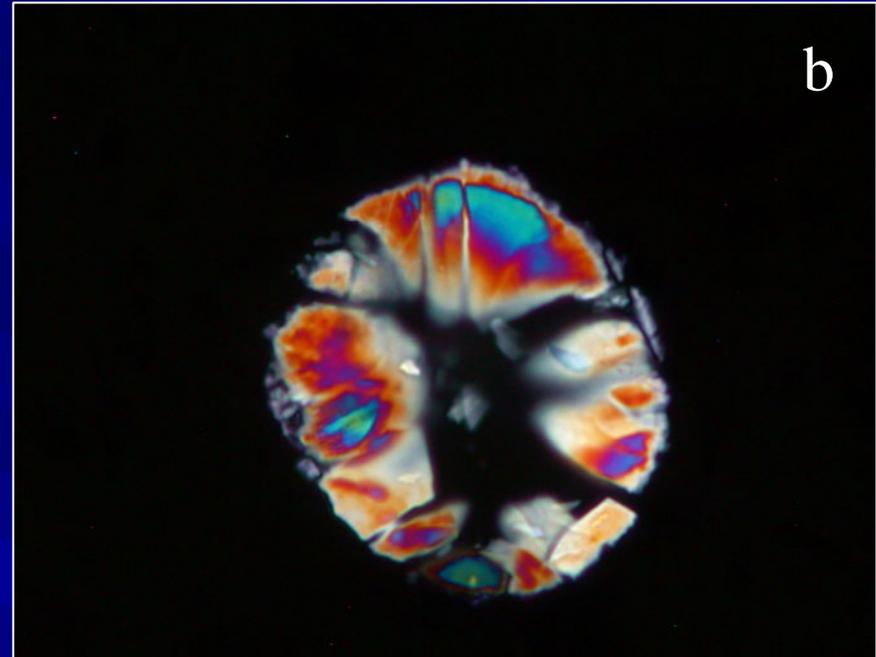
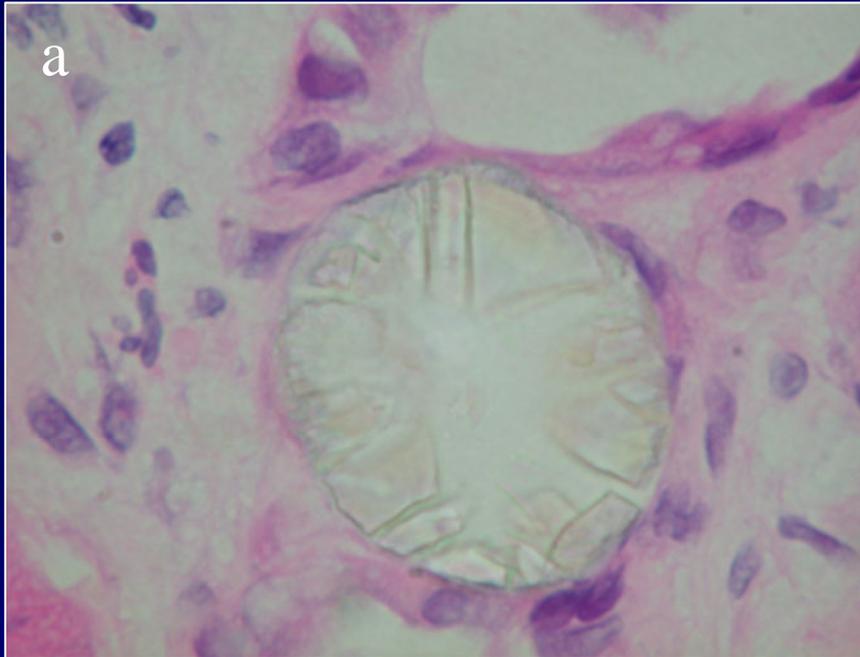
# von Kossa reaction



Tissue sections are treated with silver nitrate solution, the calcium is reduced by the strong light and replaced with silver deposits, visualized as metallic silver.

**Nephrocalcinosis**

# Polarizing light



**Ca-oxalate crystal (a)  
under polarizing light (b)**

# Terminology

Light microscopy

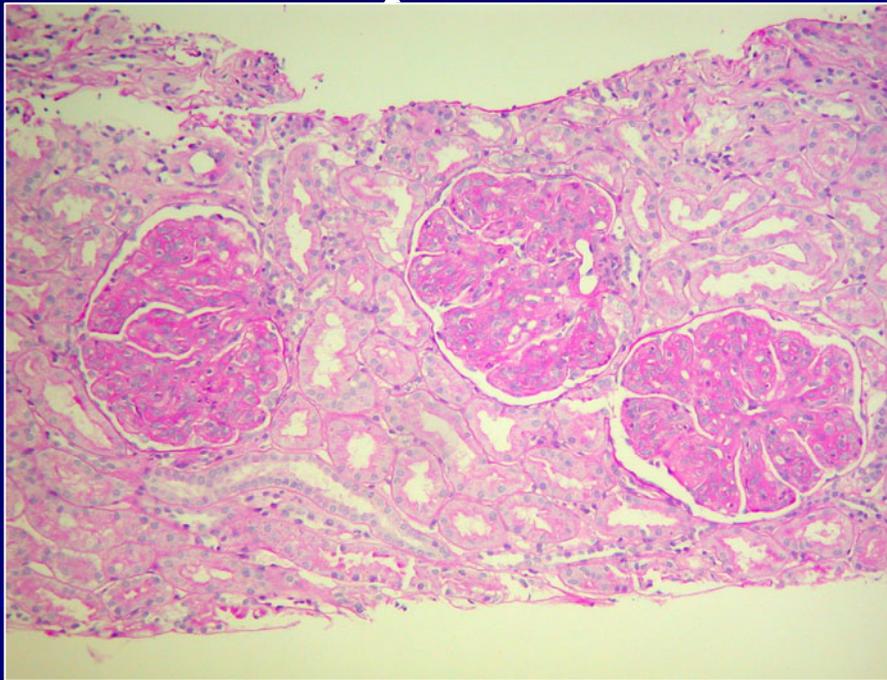
# Glomeruli

What is the distribution of the changes?

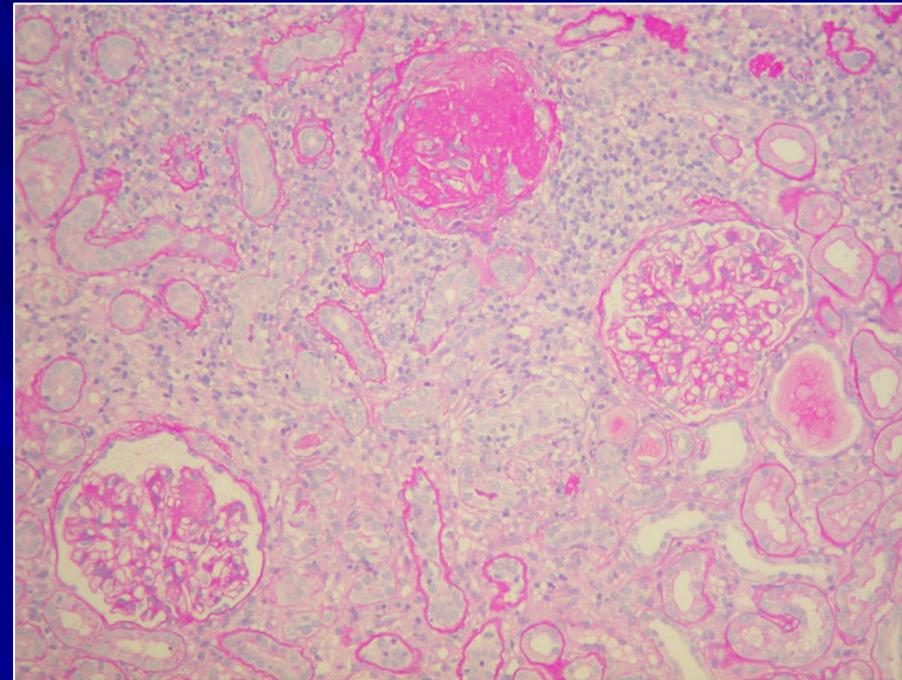
Diffuse

or

focal



Involving >50% of glomeruli

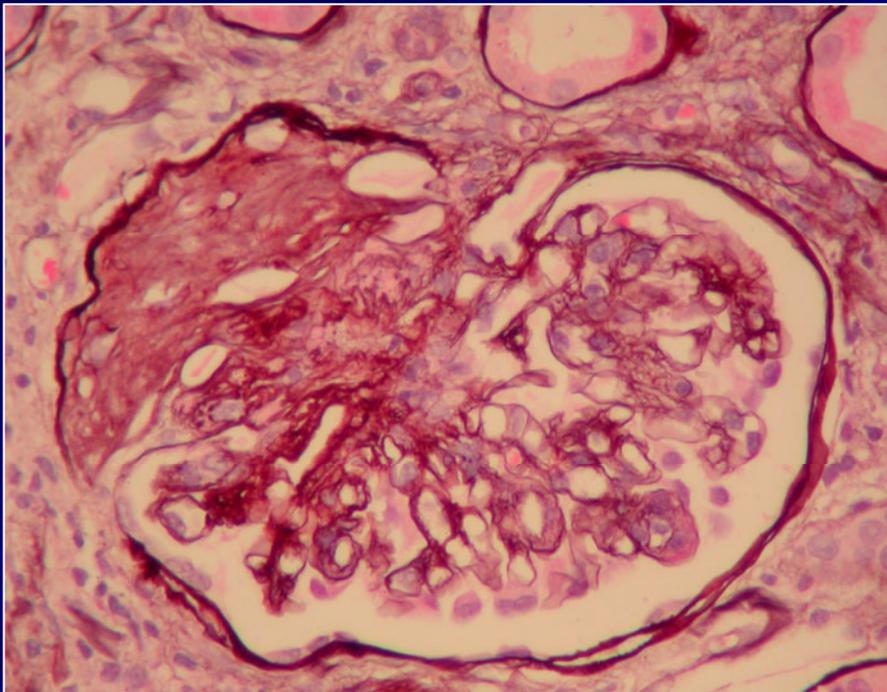


Involving <50% of glomeruli

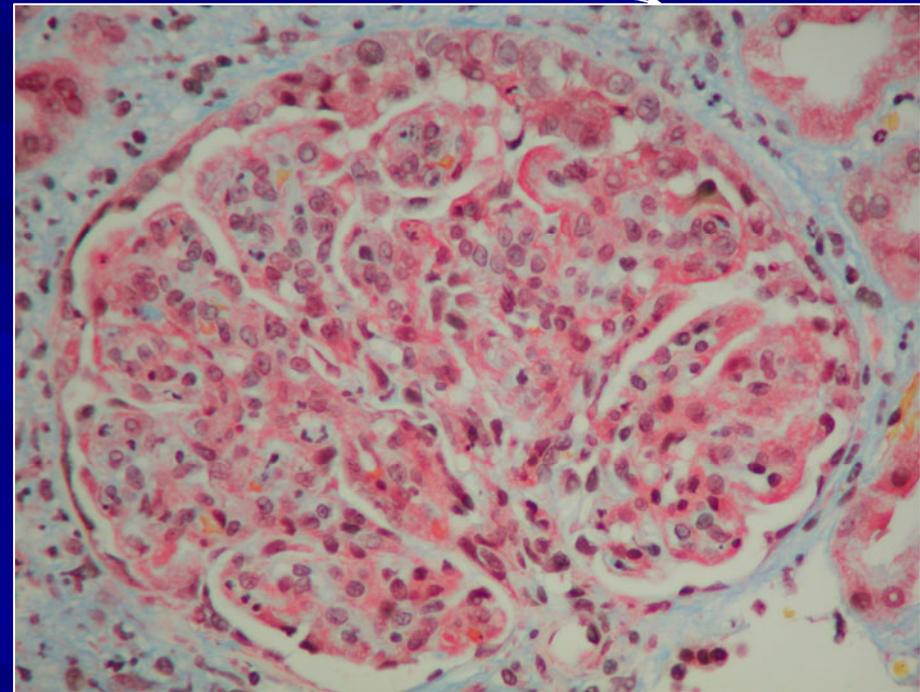
# Glomerulus

What is the distribution of the changes?

segmental or global



Involving **part** of a glomerular tuft



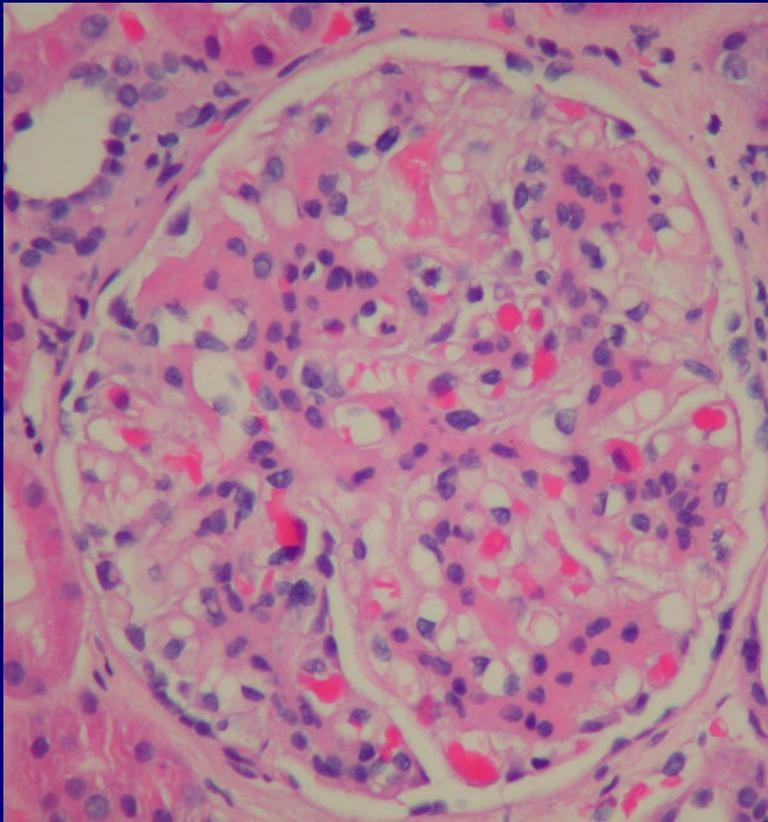
Involving **all** of a glomerular tuft

# Glomerular hypercellularity

More cells than normal in glomerulus.

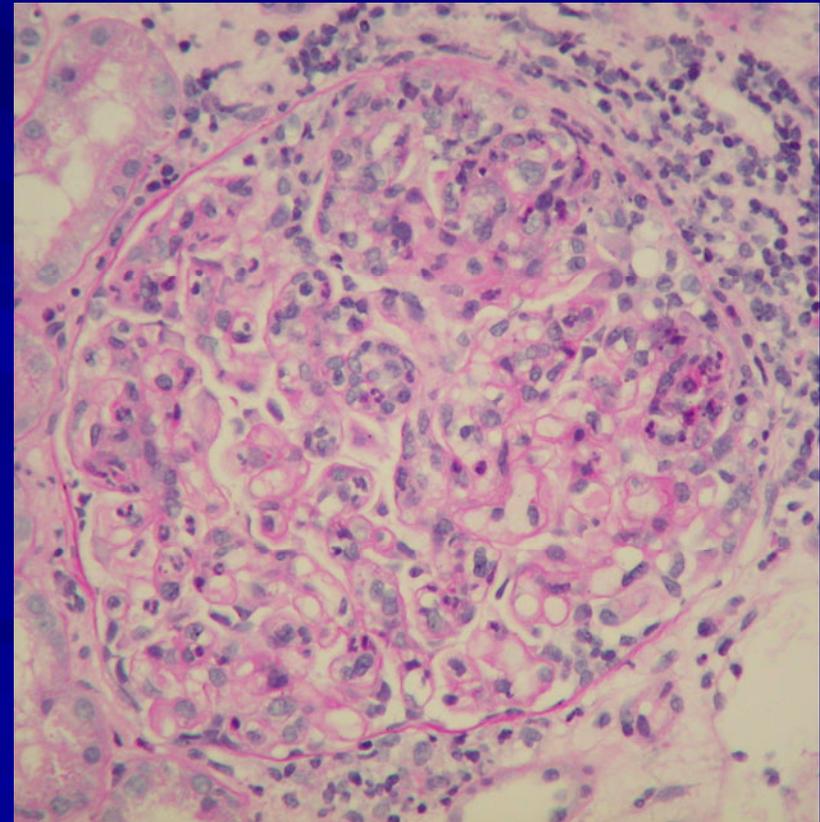
## Proliferative:

Implies multiplication in loco resident glomerular cells.



## Exudative:

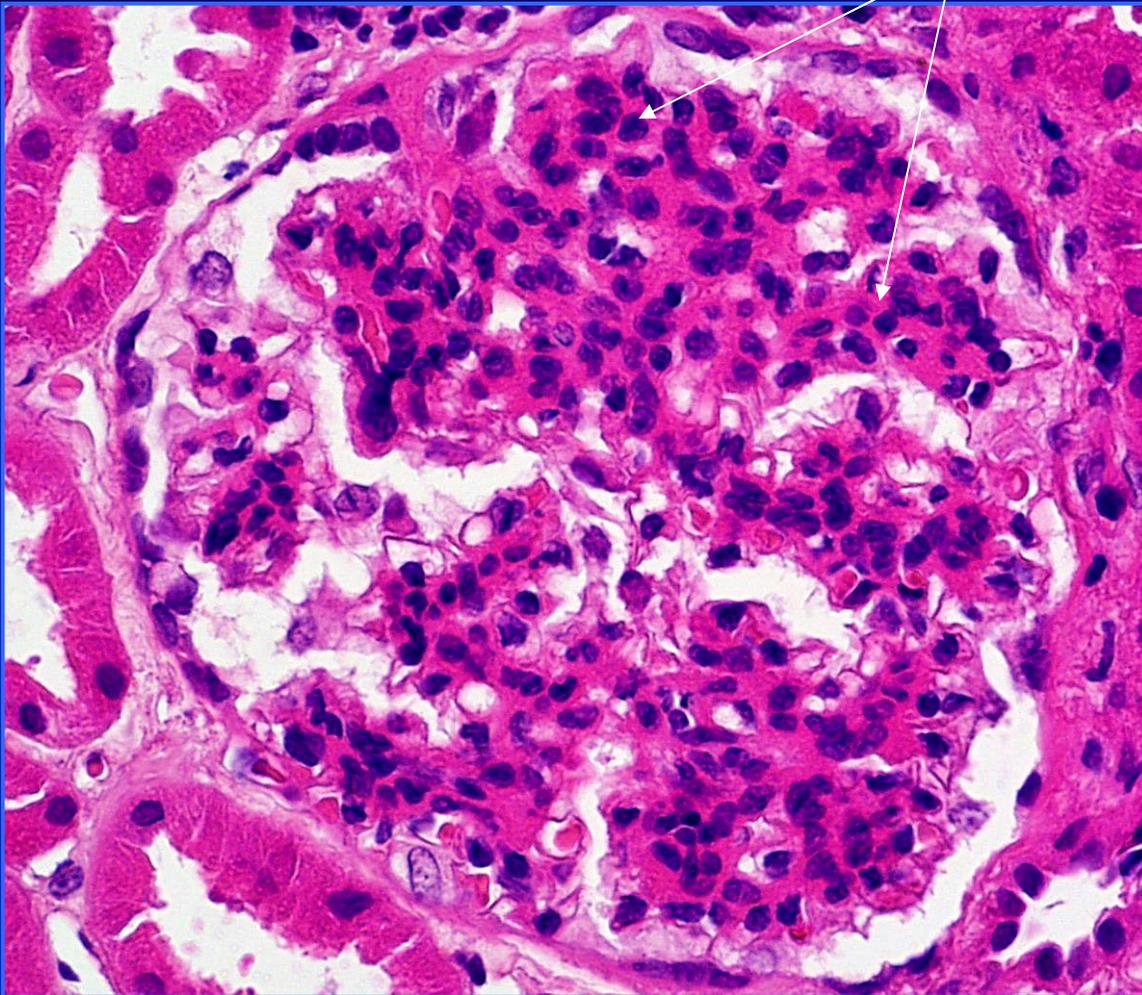
Implies inflammatory cells neutrophils and monocytes



# Glomerulus

**Proliferation:**

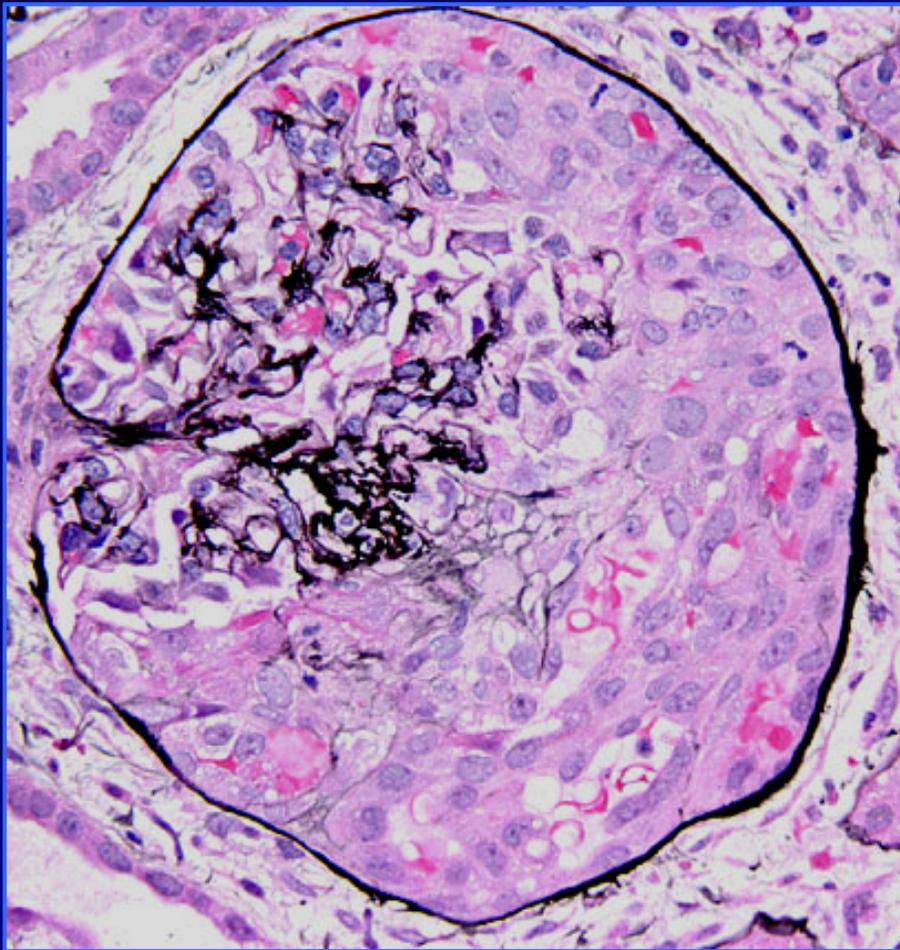
mesangial,



More than 3 nuclei  
in the contiguous  
matrix of a peripheral  
mesangial segment.

# Glomerulus

**Proliferation:** extracapillary-I = **CRESCENT**

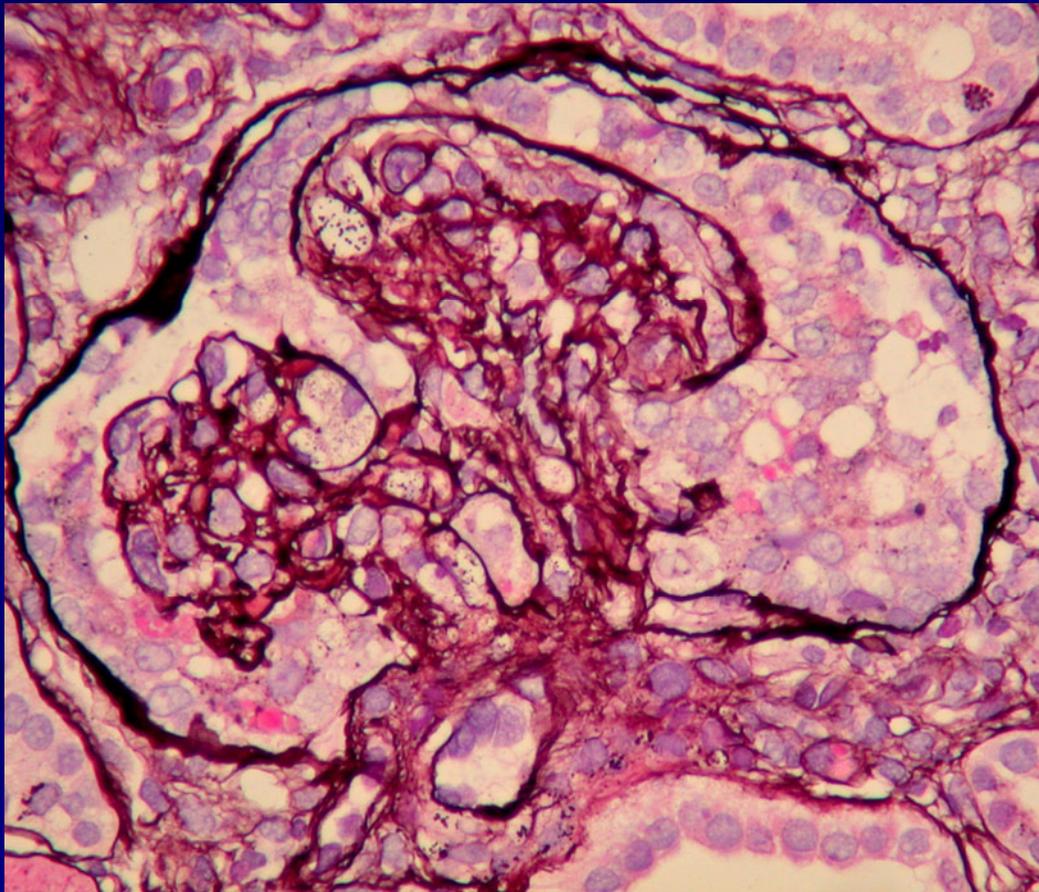


Extracapillary hypercellularity  
other than the epithelial  
hyperplasia of collapsing  
variant  
of FSGS

The cellular crescent is  
composed by epithelial cell(s),  
macrophages and fibrin

# Glomerulus

**Proliferation:**  
extracapillary - II

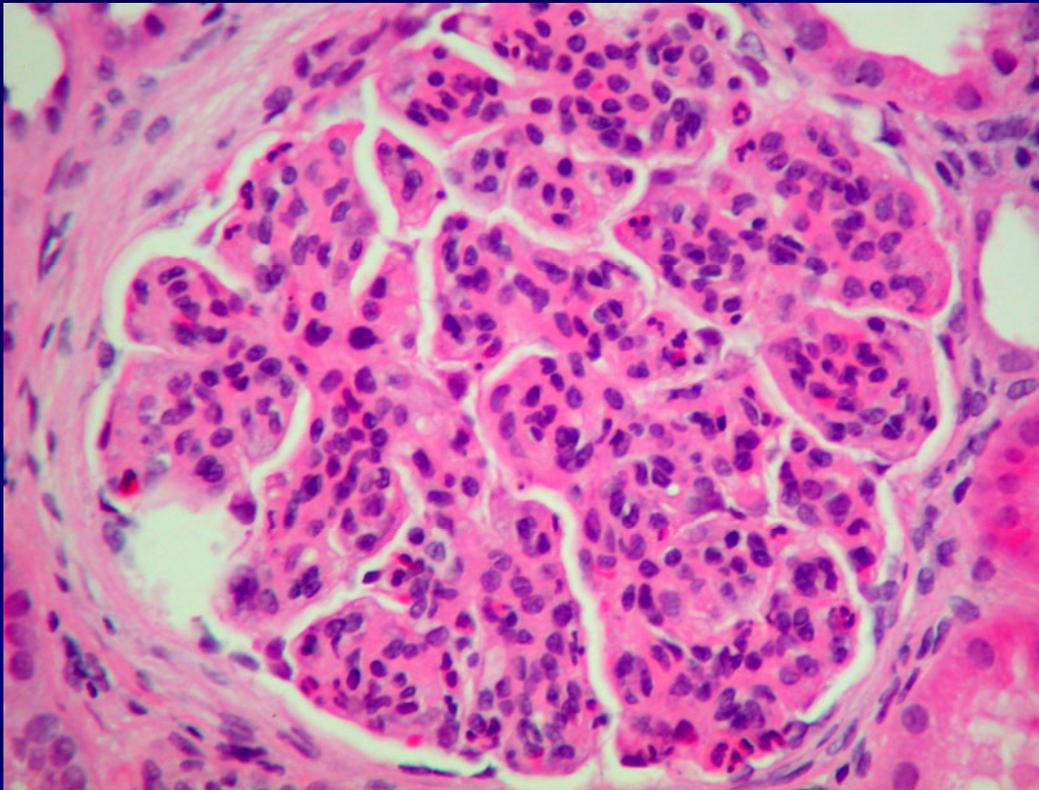


Increased cellularity in  
Bowman's space or more  
than one layer of parietal  
and visceral epithelial cells

No fibrin  
No macrophages

# Glomerulus

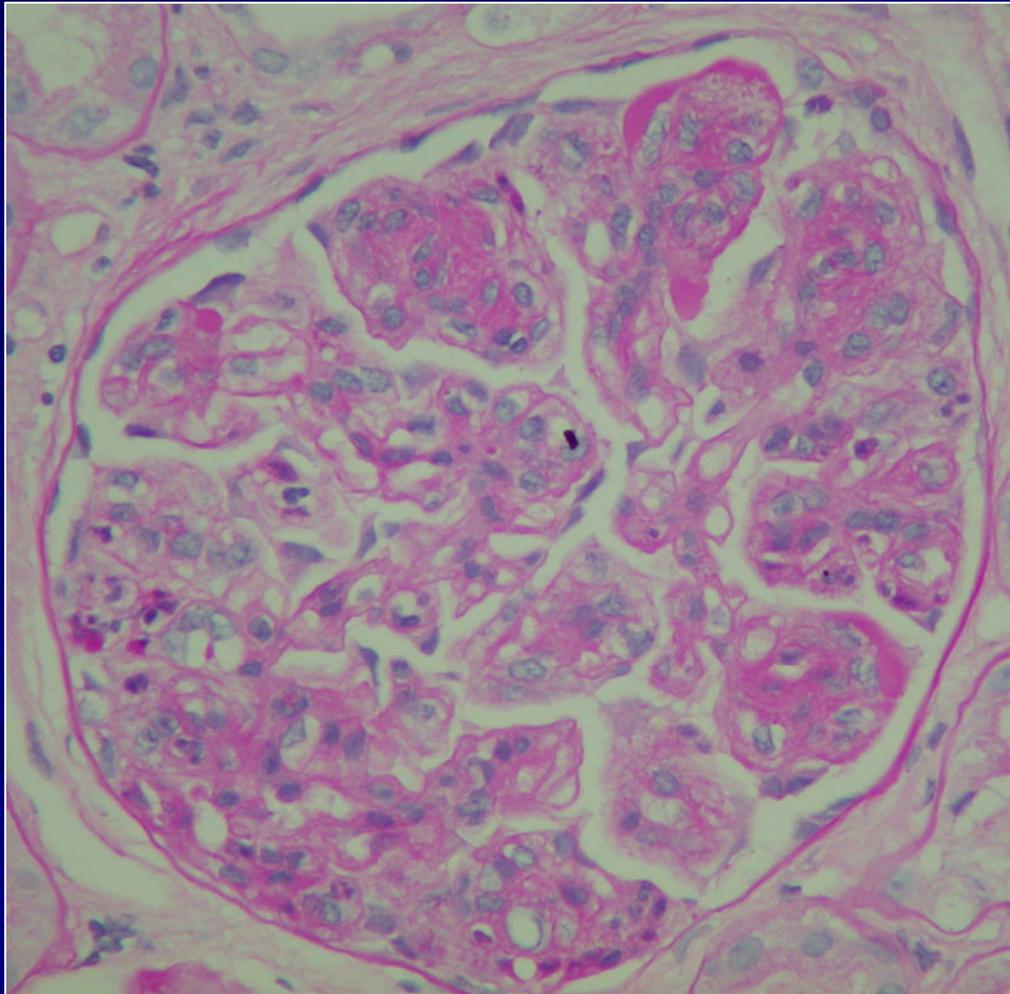
## Membranoproliferative pattern



Combined capillary wall thickening and mesangial or endocapillary proliferation

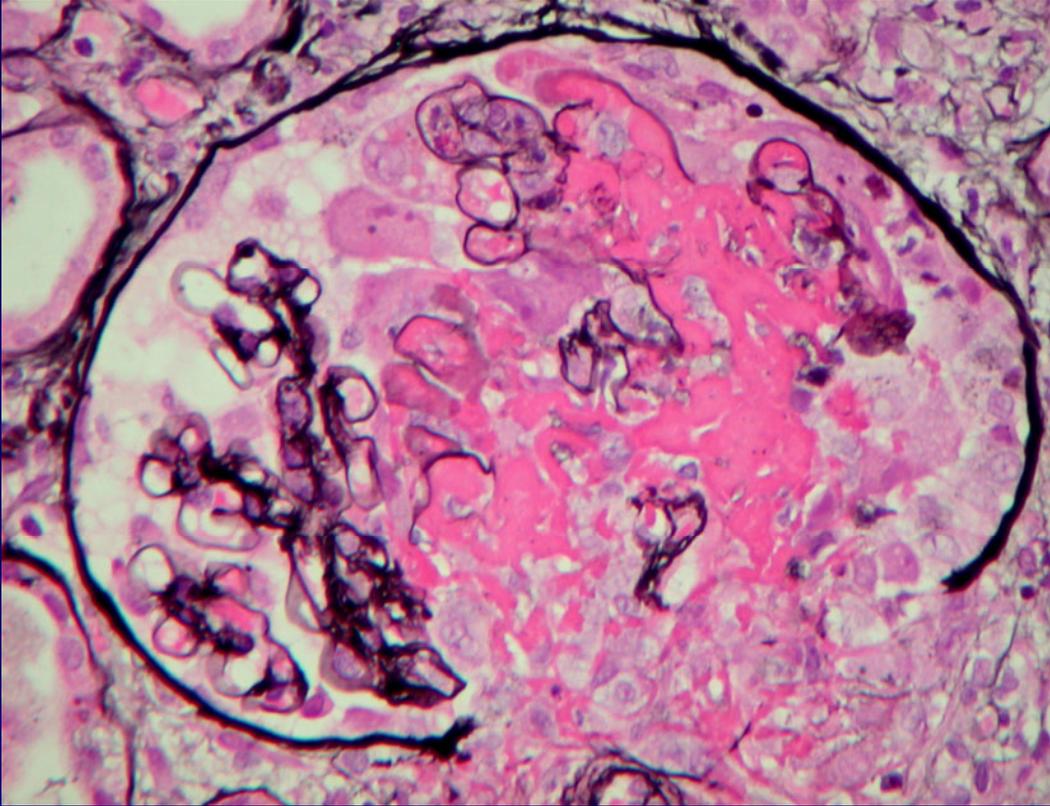
# Glomerulus

## Lobular pattern



Consolidated expansion  
of segments that are  
demarcated by intervening  
urinary space

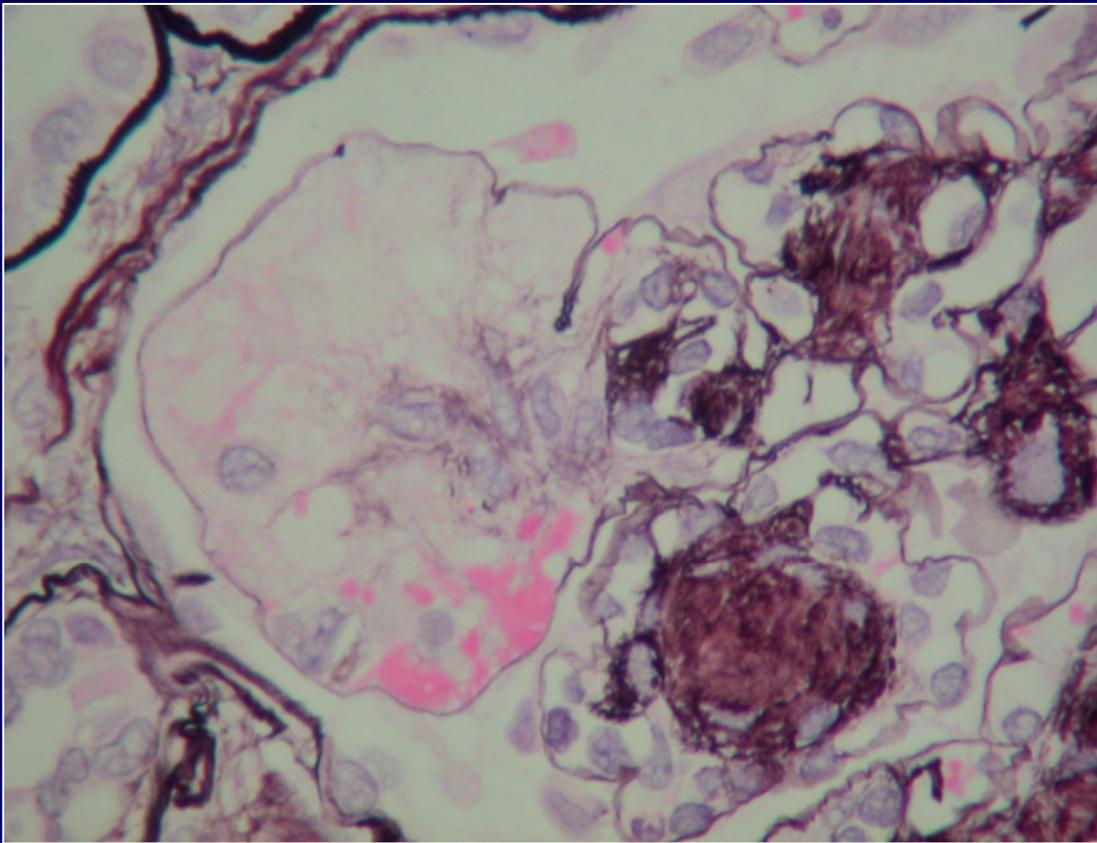
# Necrosis



... due to any acute process, including vascular disease.

# Glomerulus

## Mesangiolytic

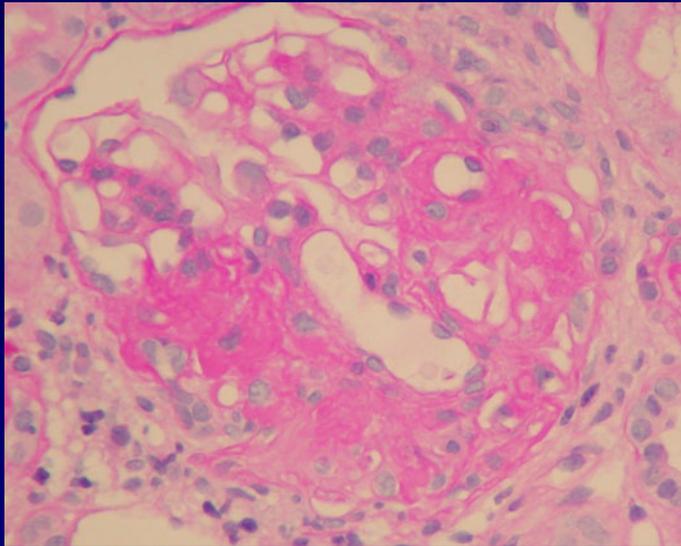


Detachment of the paramesangial GBM from the mesangial matrix resulting in a capillary aneurysm

# Glomerulus

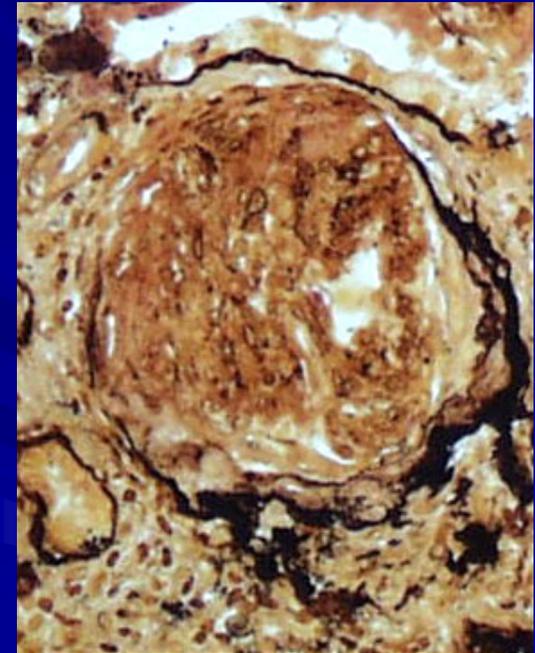
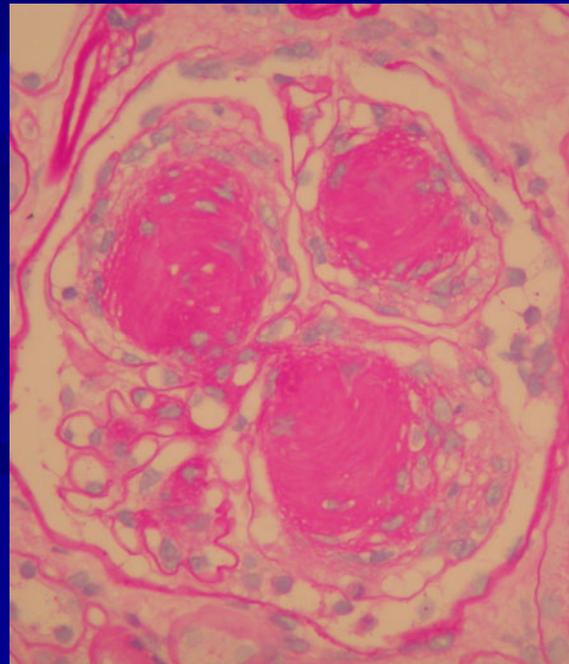
## sclerosis

Scarring of a glomerulus due to any chronic process.



segmental

mesangial

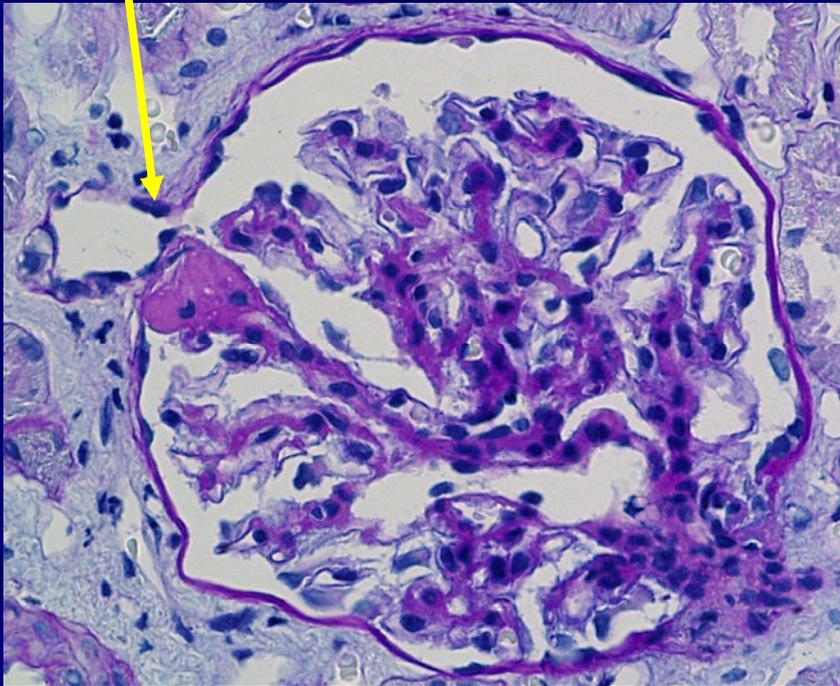


global

# Glomerulus

## tip lesion

Adhesion between the Bowman's capsule and the peripheral glomerular-segment  
at the urinary pole of the glomerulus

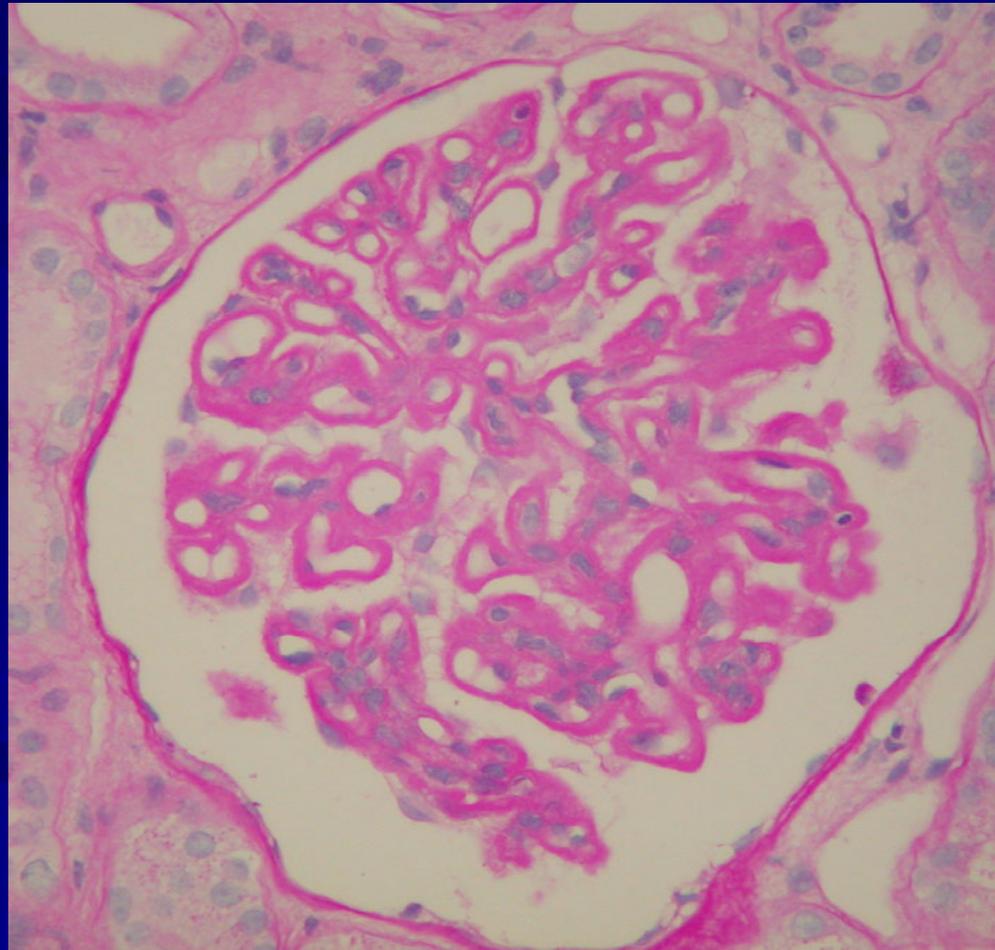


Tip lesion, non-specific may develop in any glomerulonephritis

# Glomerulus

Capillary walls:

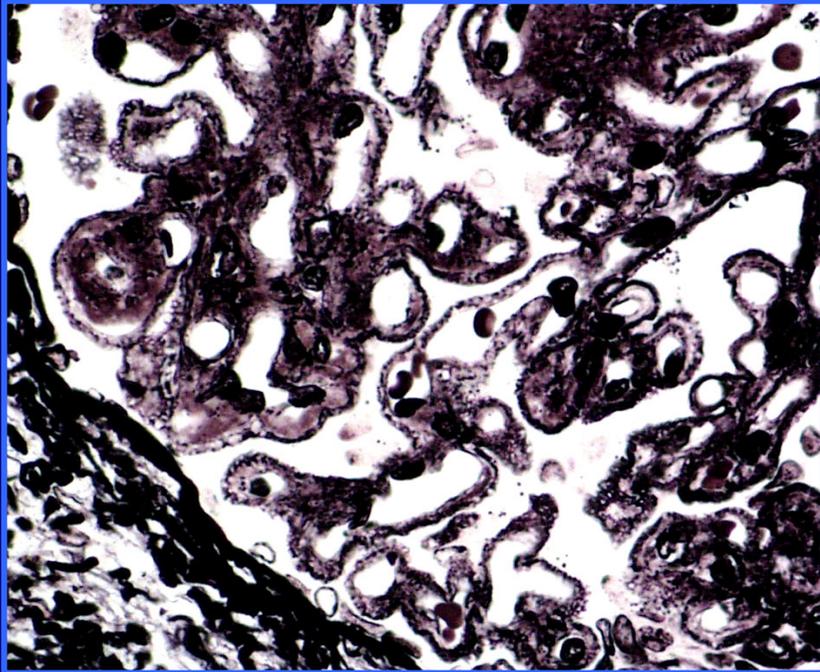
Thickening



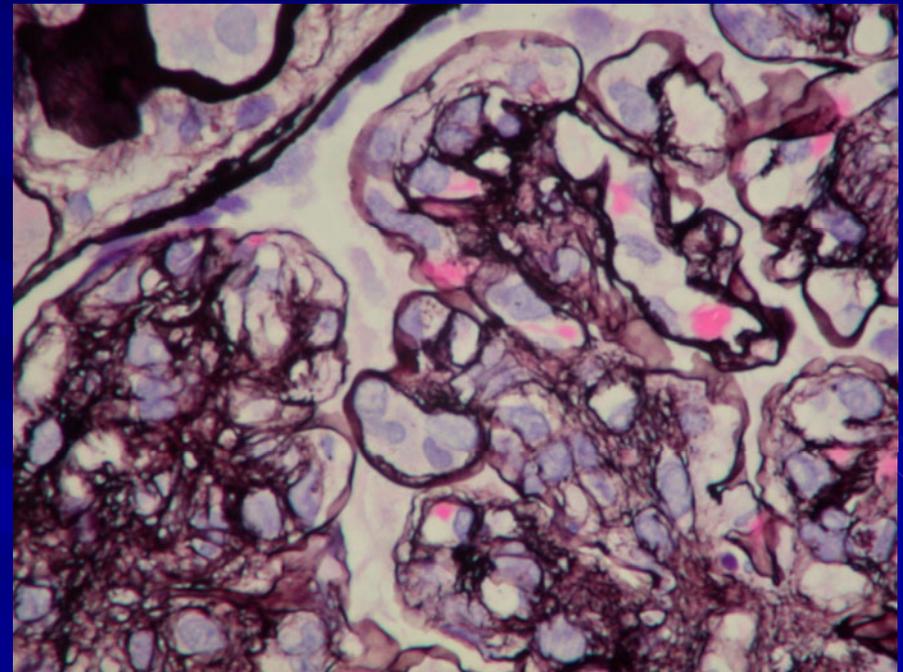
# Glomerulus

Capillary walls:

spikes



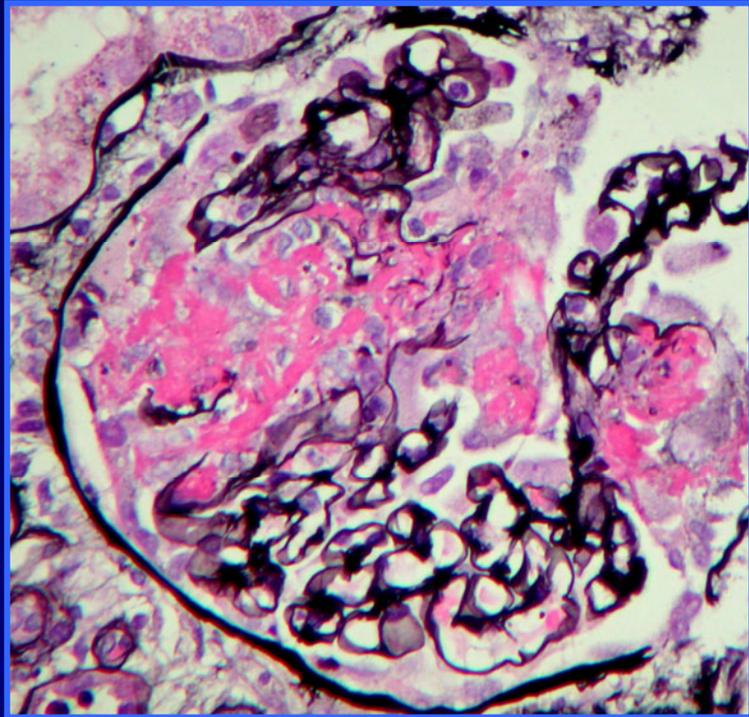
reduplication



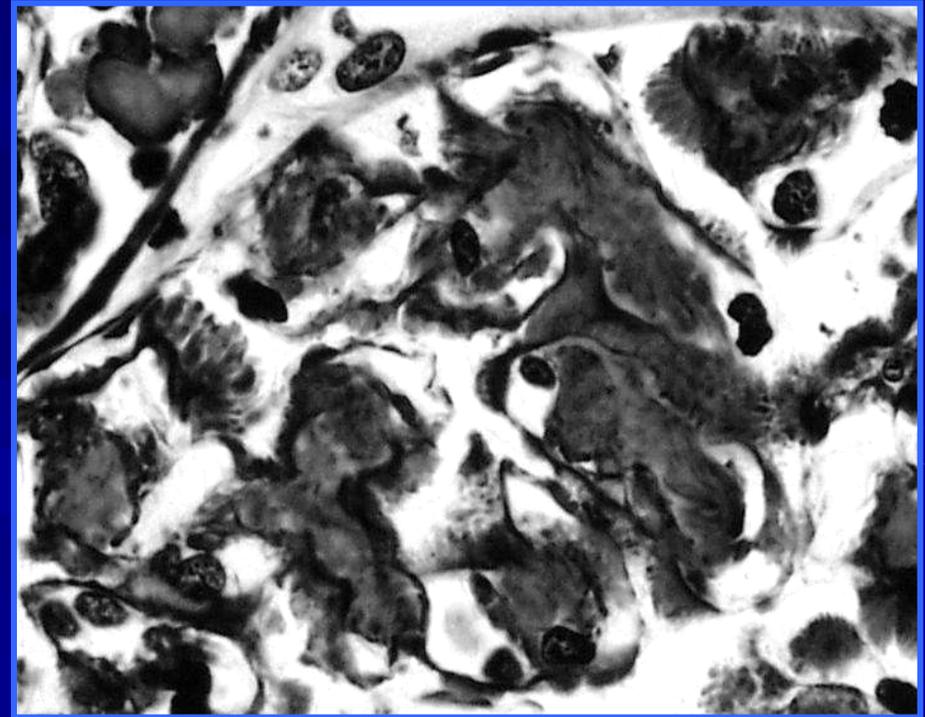
# Glomerulus

Capillary walls:

Rupture

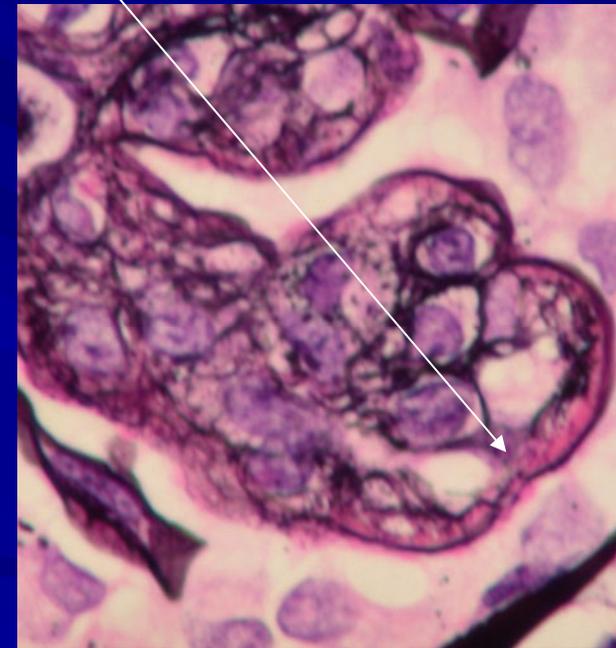
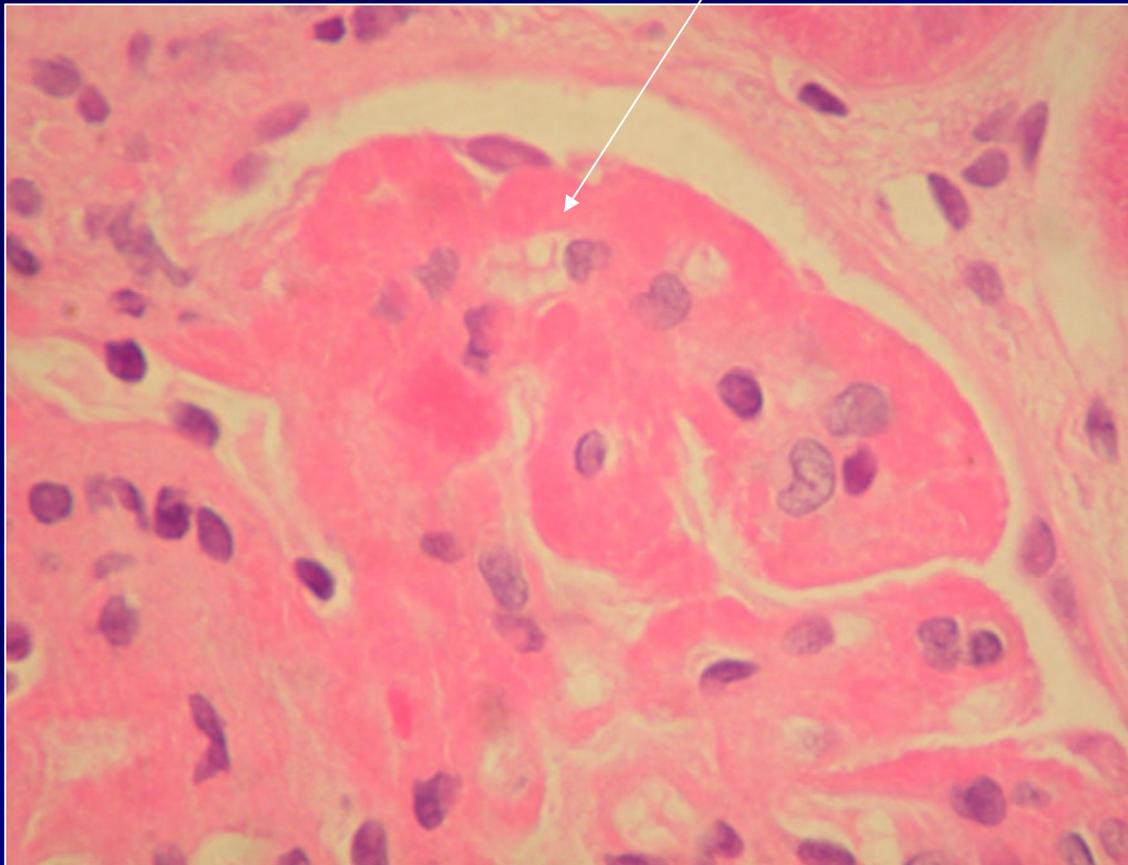


spicule



# Glomerulus

**Capillary wall:** Wire-loop lesion, due to massive subendothelial protein (immune complex) deposits

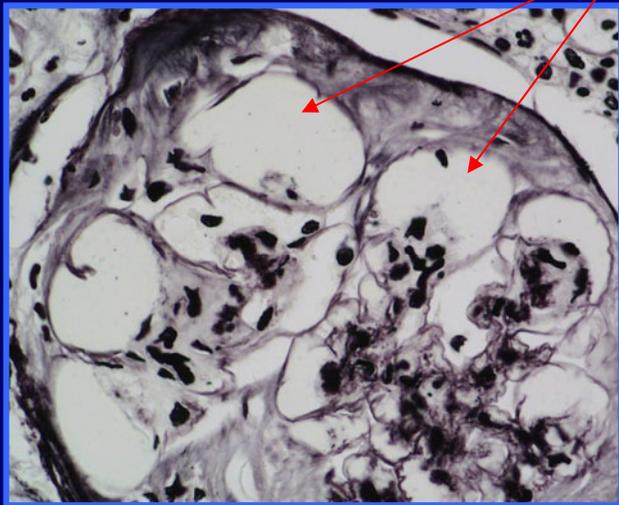


# Glomerulus

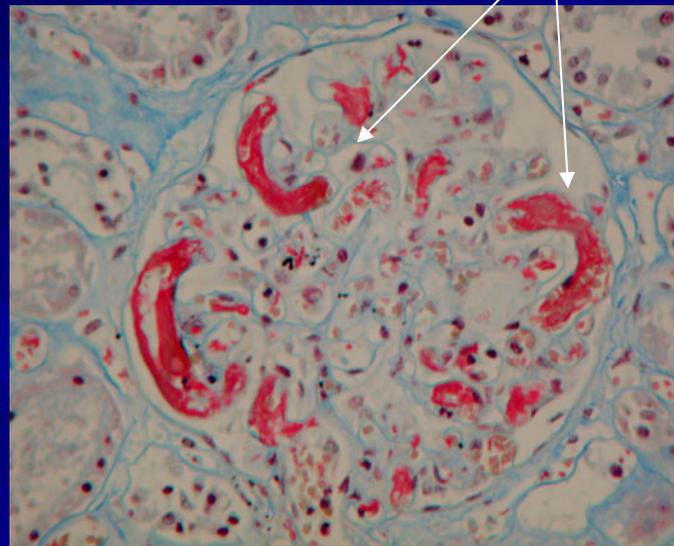
## Capillary lumen:

microaneurysm,

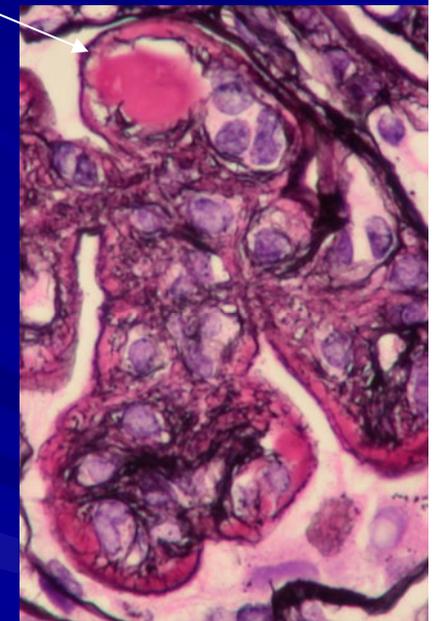
thrombi



DM nephropathy



Fibrin thrombus in DIC



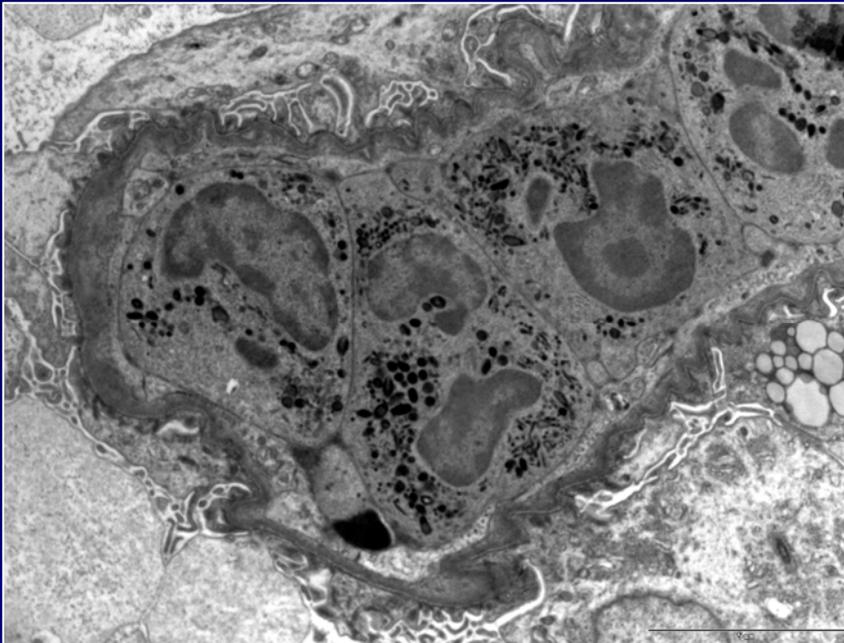
Hyaline thrombus  
in SLE

# Glomerulus

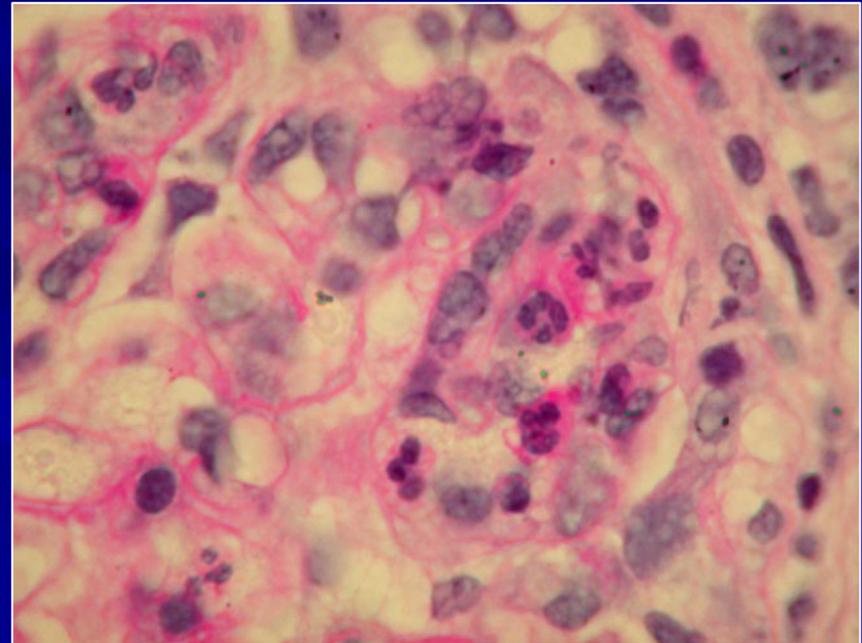
## Capillary lumen:

Lymphocyte aggregate

intracapillary neutrophils



EM picture



# Immunohistology

# IMMUNOHISTOLOGY

## **Distribution**

diffuse or focal  
segmental or global

## **Glomerular location**

mesangial  
capillary wall  
mesangial and capillary wall

## **Extraglomerular location**

tubular BM  
vessel  
interstitium

**Pattern:** granular or linear

**Intensity**

**Composition**

IgG

IgA

IgM

C3

C1q

Kappa light chain

Lambda light chain

Fibrinogen/fibrin

CD8

C4D

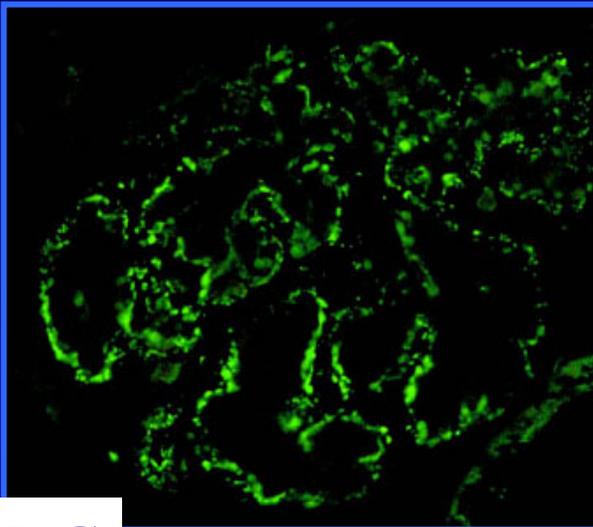
## Immunofluorescence versus Immunoperoxidase

“For half a century, immunofluorescence (IF) on frozen sections has been the gold standard for immunohistochemical evaluation of renal biopsy specimens. In routine diagnostic immunohistopathologic evaluation, traditional IF has been replaced to a large extent by immunoperoxidase (IP) methods applied to paraffin sections of formaldehyde-fixed tissue. This is caused in part by the practical disadvantages inherent in the IF method, eg, separate tissue specimen and handling, UV microscopy, fading and impermanence of the label-making archiving, and difficult later investigation. “

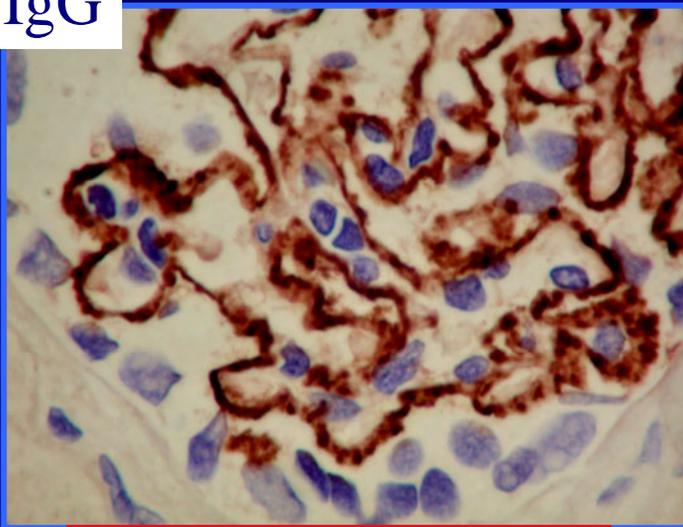
- \_MÖLNE, Johan et al. Am. J. Kidney Dis. 2005 45: 674

# IMMUNOHISTOLOGY

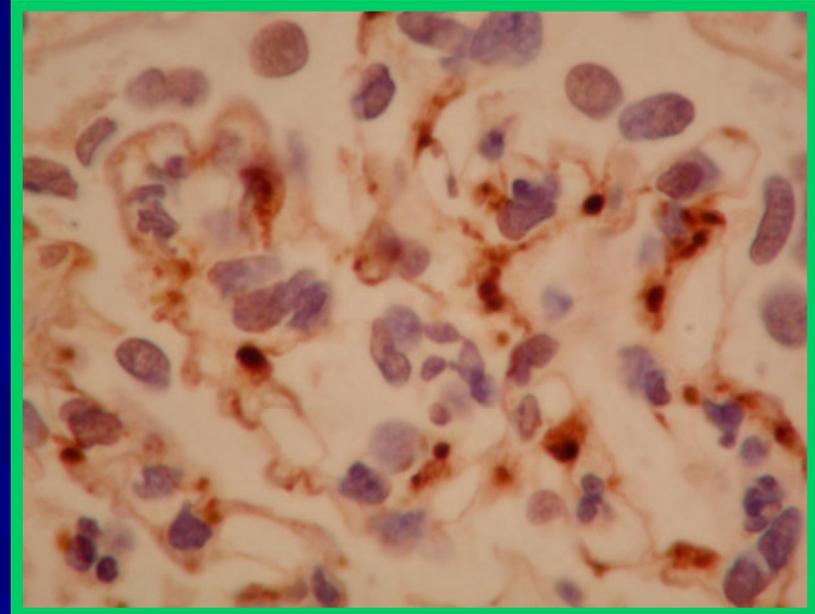
granular



IgG



Membranous GN



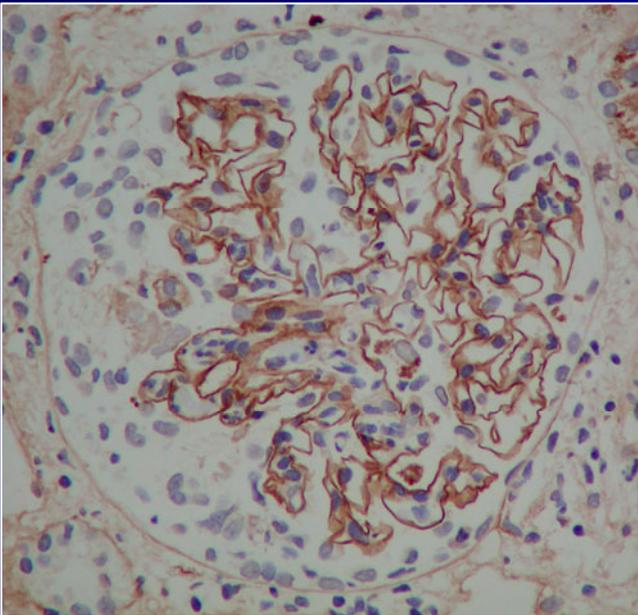
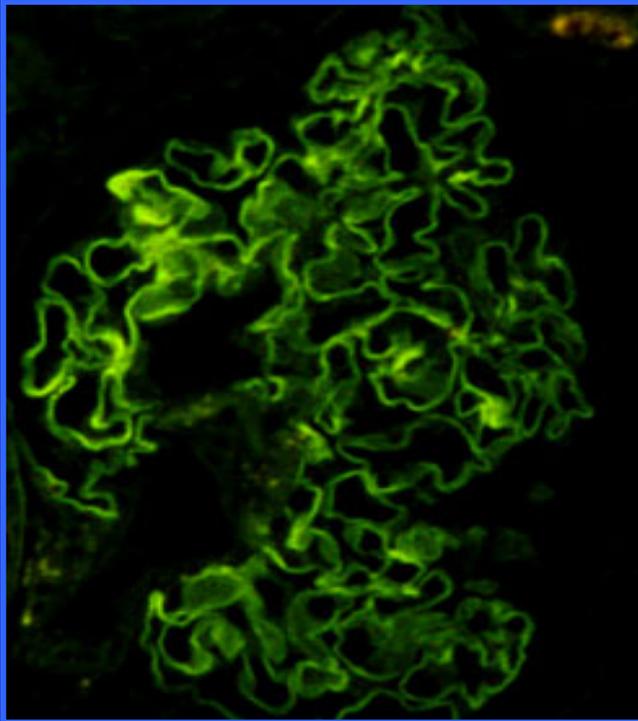
Postinfectious GN

Starry-sky pattern of  
IgG deposits

# IMMUNOHISTOLOGY

Linear (IgG)

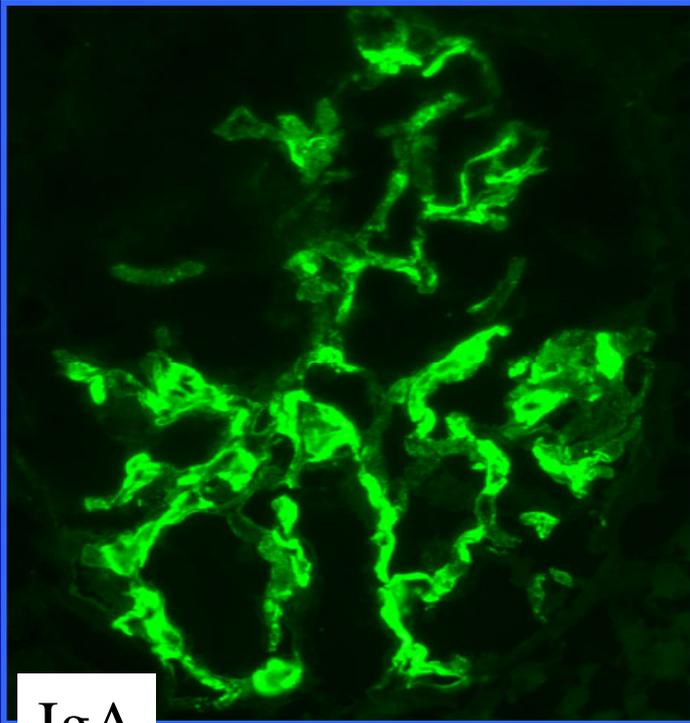
Anti-GBM-GN  
can only be diagnosed by IH



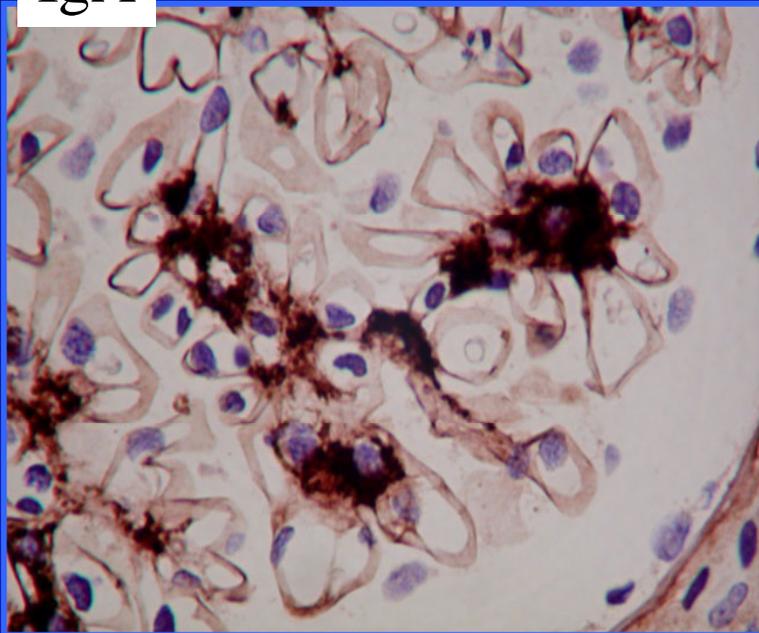
# IMMUNOHISTOLOGY

## Mesangial

IgA-mesangioproliferative GN  
and  
Henoch-Schonlein purpura GN  
can only be diagnosed by IH

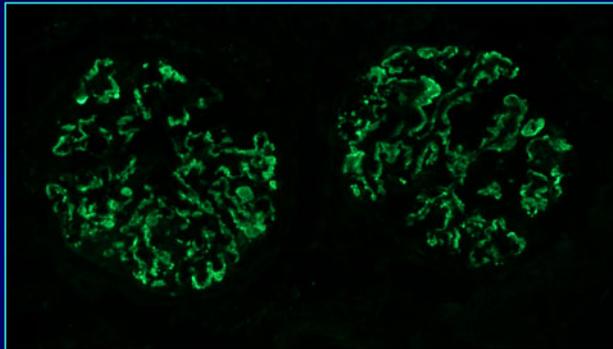


IgA

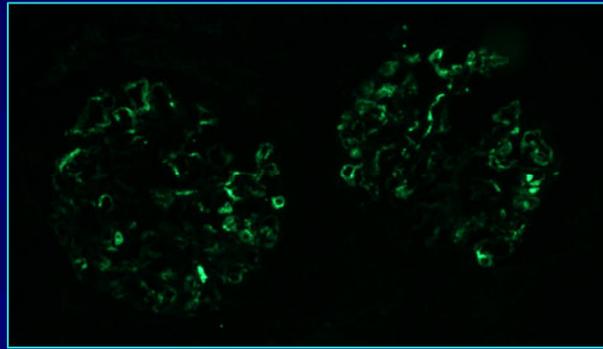


## Lupus nephritis characteristic lesions:

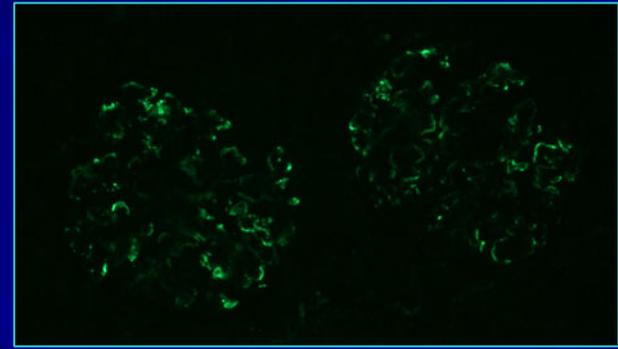
„full house” intensive immune reaction (IgG, IgM, IgA, C3 and **C1q** deposition on various and/or same location



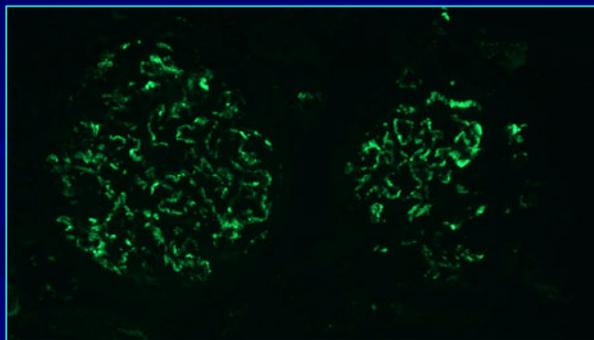
**IgG**



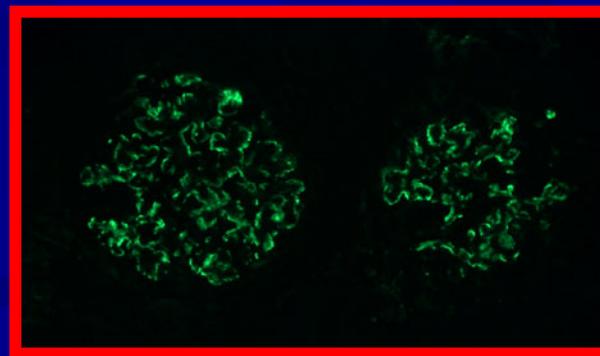
**IgA**



**IgM**



**C3**



**C1q**

**+C1q N**

# ELECTRONMICROSCOPY

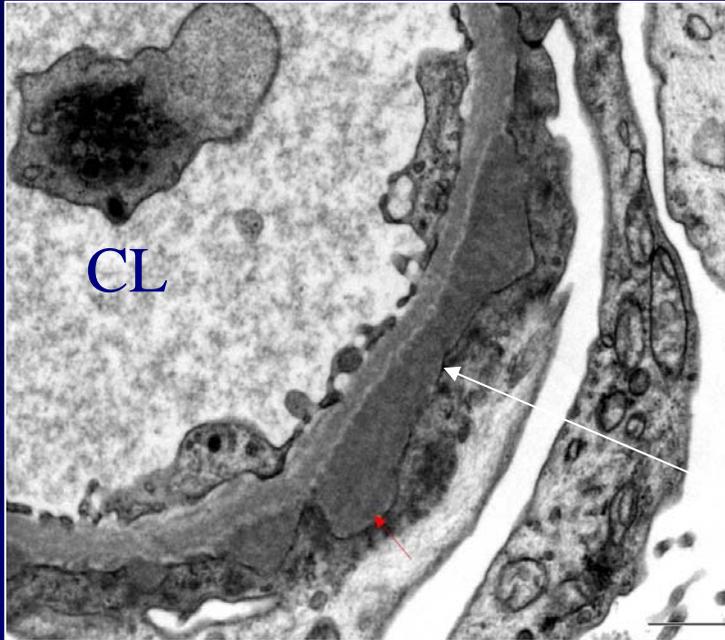
## *Crucial diagnostic method in*

- **Alport's disease (basement membrane structural damage)**
- **thin basement membrane disease**
- **immunotactoid disease**
- **minimal change nephropathy (*foot process fusion*)**
- **amyloidosis, L-chain deposit disease...**
- **lupus (*fingerprints; tubuloreticular structures..*)**
- **location of the deposits (subepithelial subendothelial, mesangial etc.)**
- **deposits are fresh or aging (moth-eaten typed or electron lucent)**

# Glomerulus

Electron dense  
deposits:

subepithelial



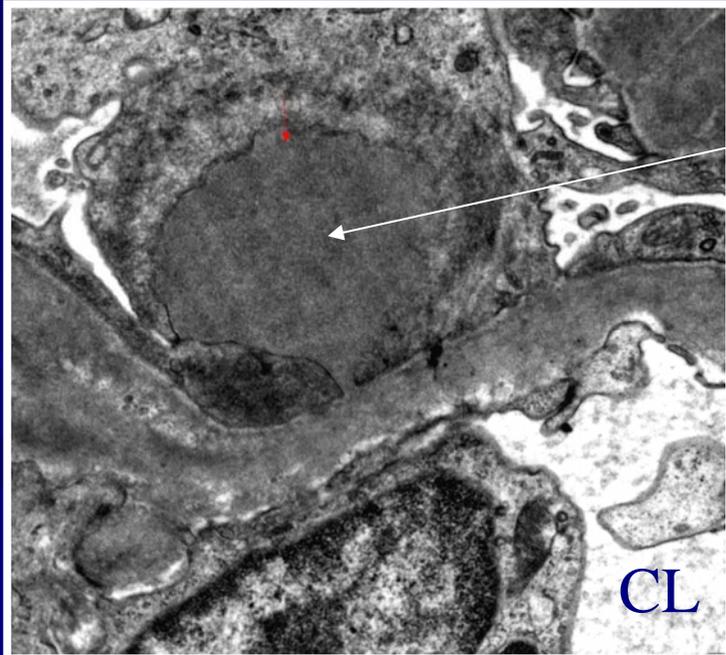
Membranous GN Stage I and II

MPGN

Postinfectious GN

Lupus nephritis

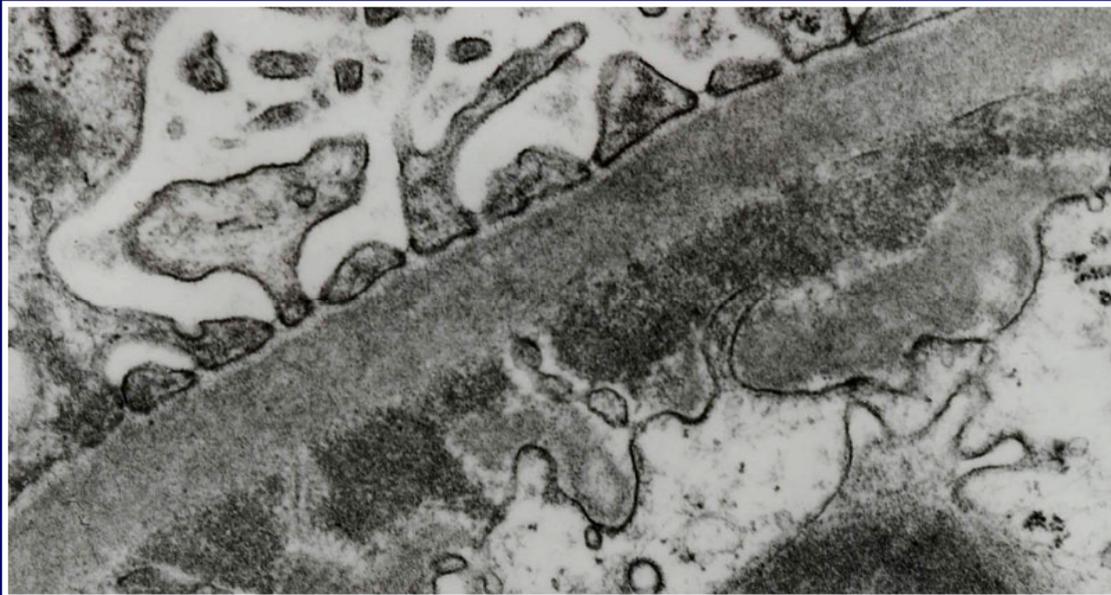
IgAN



# Glomerulus

Electron dense  
deposits:

subendothelial



Lupus nephritis

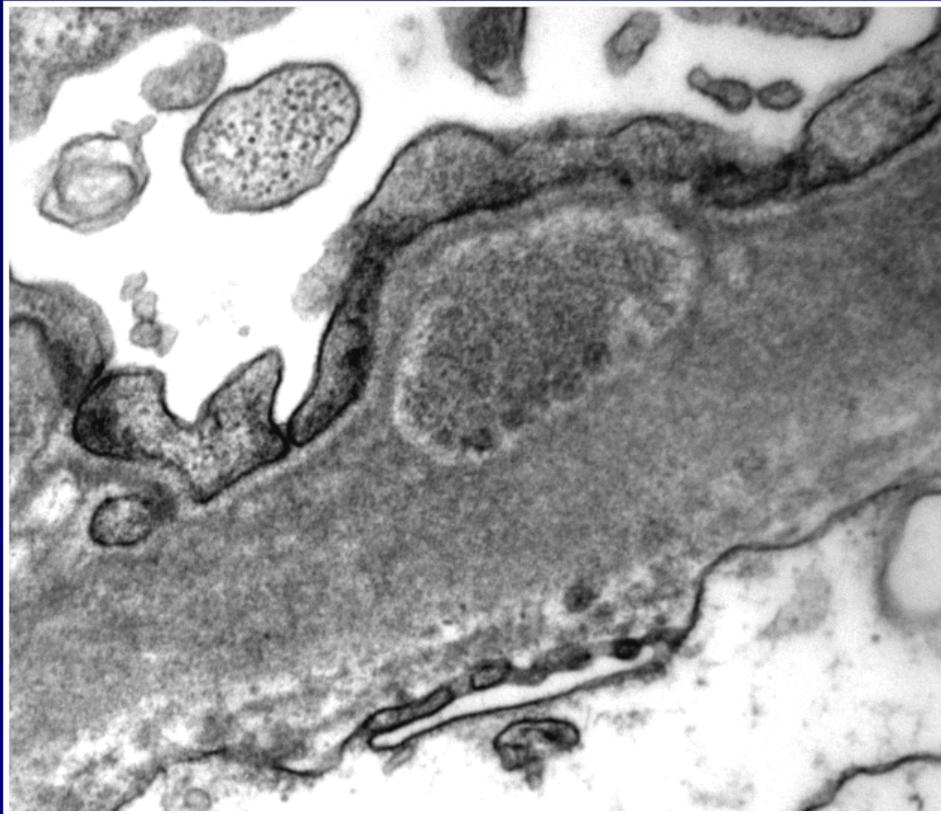
MPGN

Secondary MGN

# Glomerulus

Electron dense  
deposits:

intramembranous



**Membranous GN Stage III**

Lupus N Class IV and/or V

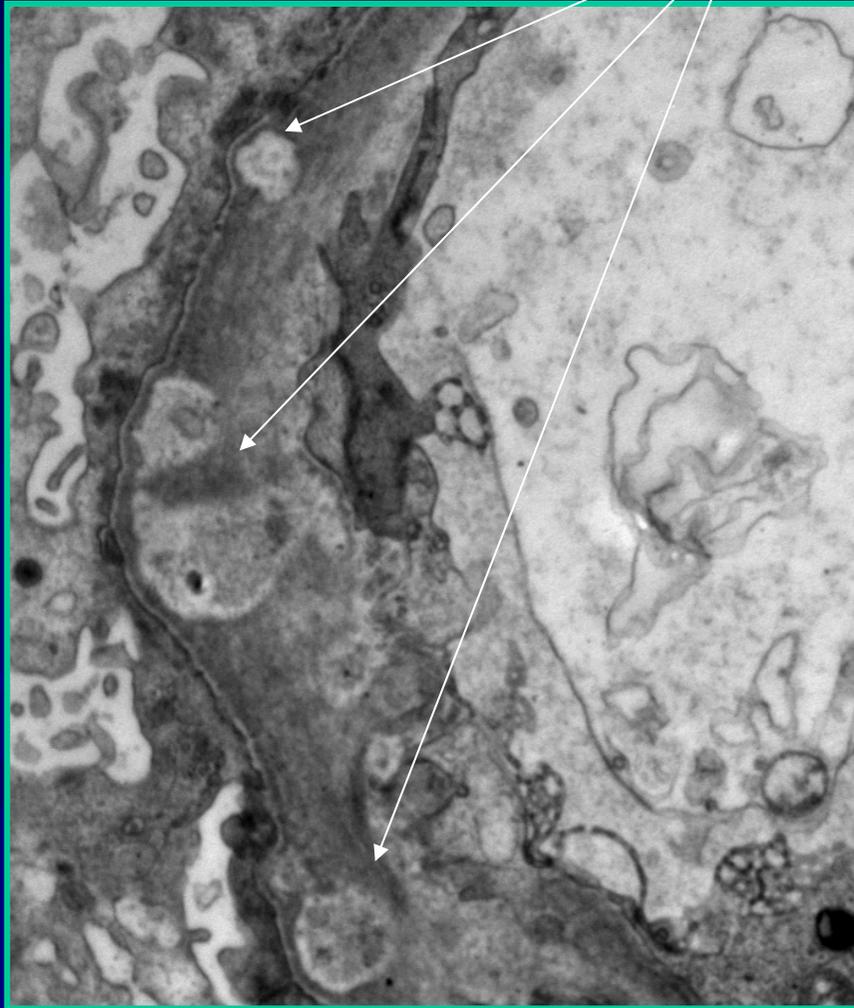
IgAN (rare)

MPGN (rare)

# Glomerulus

Electron dense  
deposits:

intramembranous

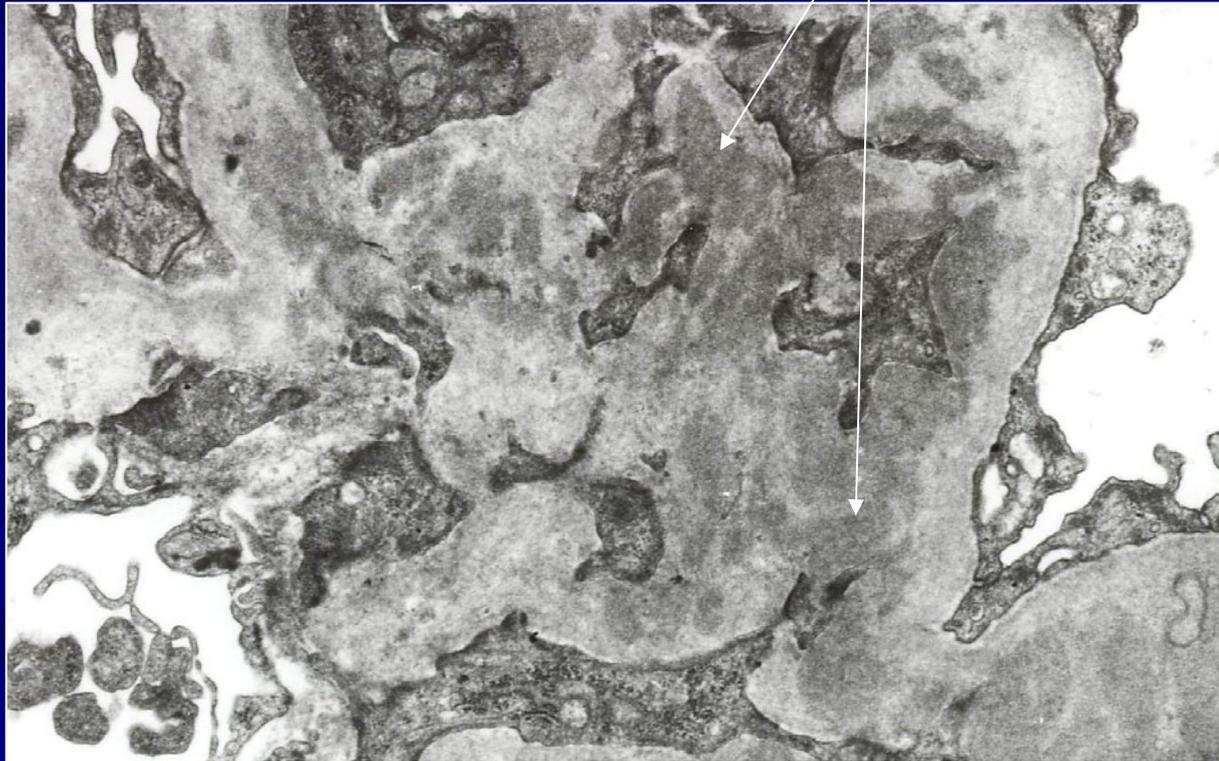


**Membranous GN Stage III**  
Lupus N Class IV and/or V  
IgAN (rare)  
MPGN (rare)

# Glomerulus

Electron dense  
deposits:

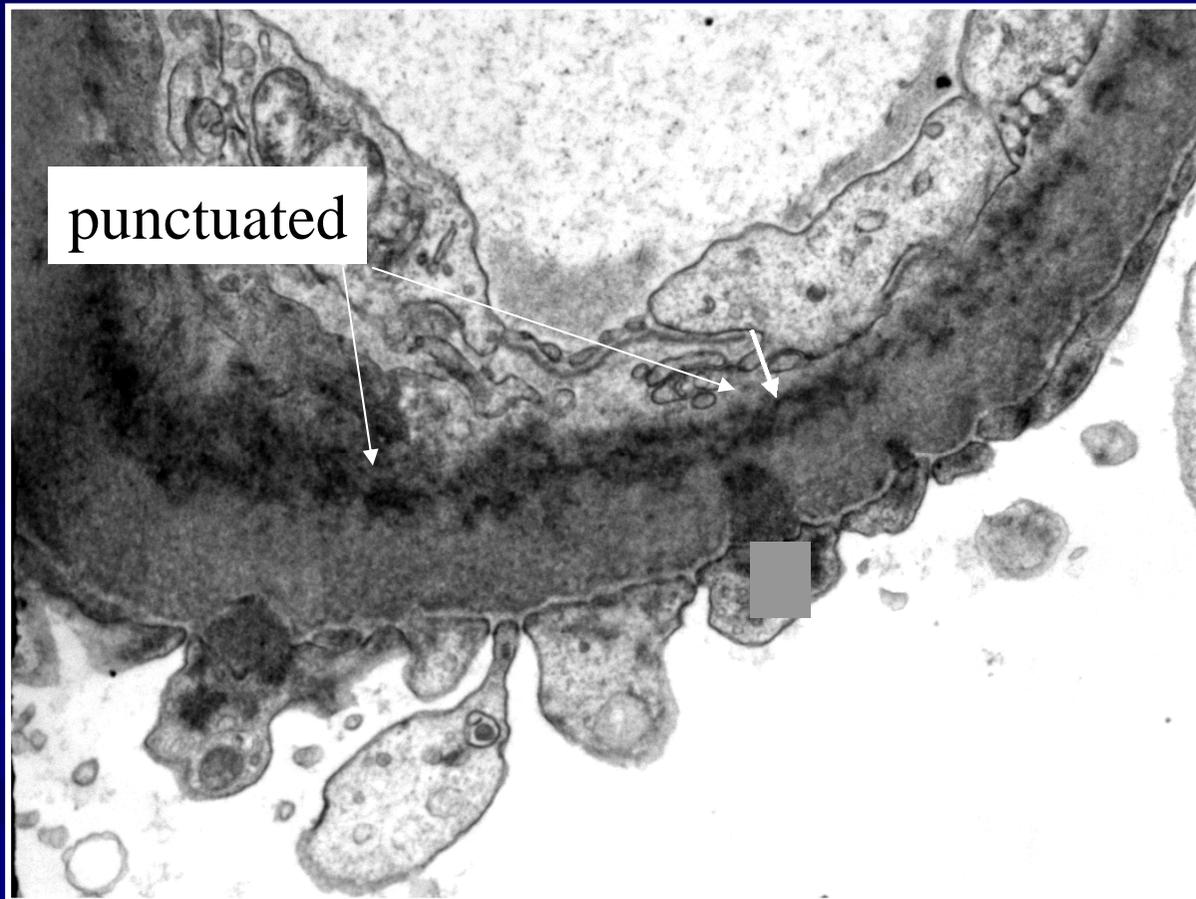
mesangial



IgAN  
Henoch-Schonlein N  
MPGN  
Postinfectious GN

# Glomerulus

Electron dense  
deposits:

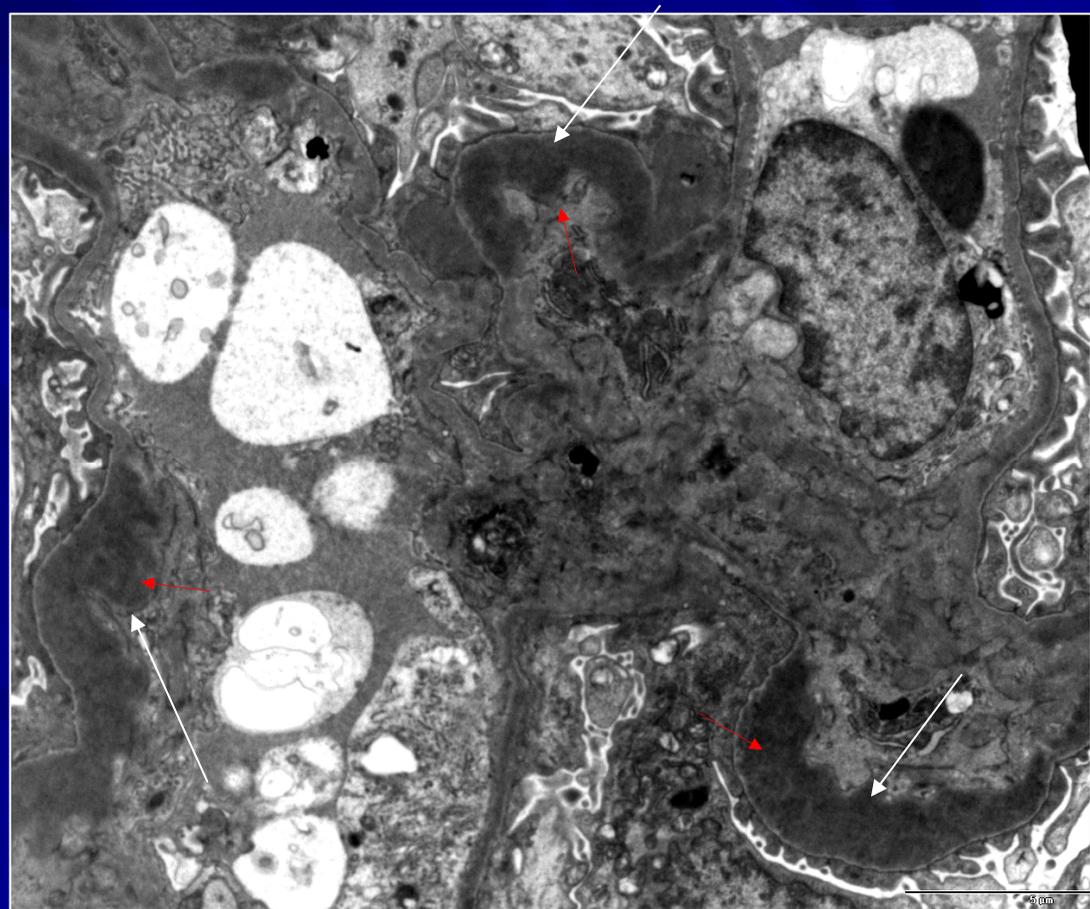
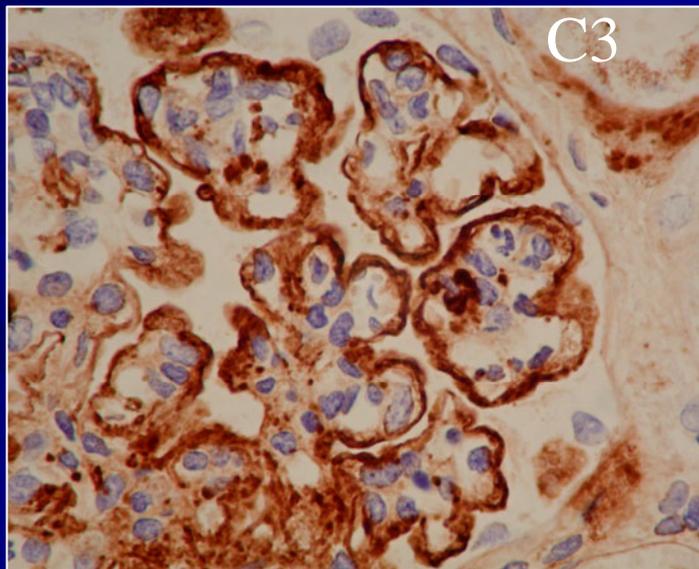


Light chain/heavy chain nephropathy

# C3 Glomerulus

Electron dense deposit-like  
GBM, mesangial-BM lesion:

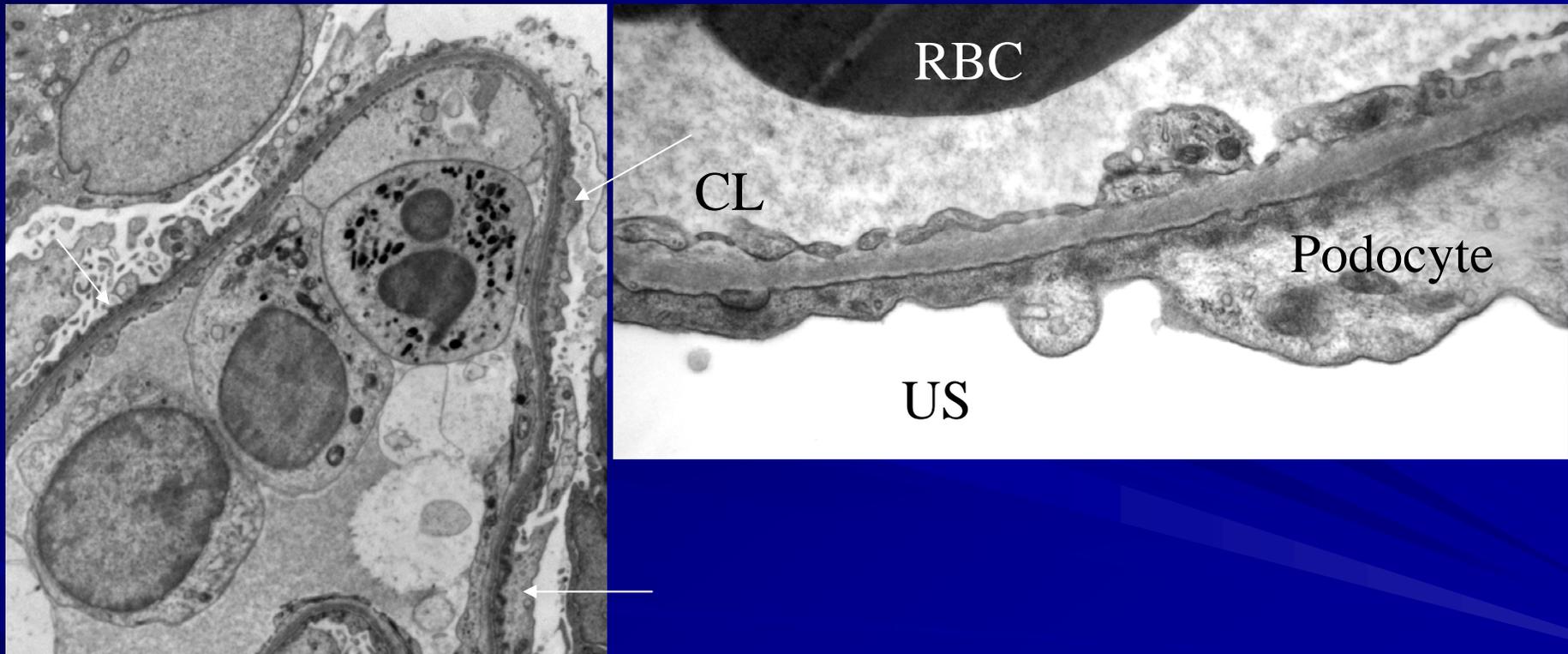
dense deposit disease



# Glomerulus

Podocyte lesion:

foot process fusion



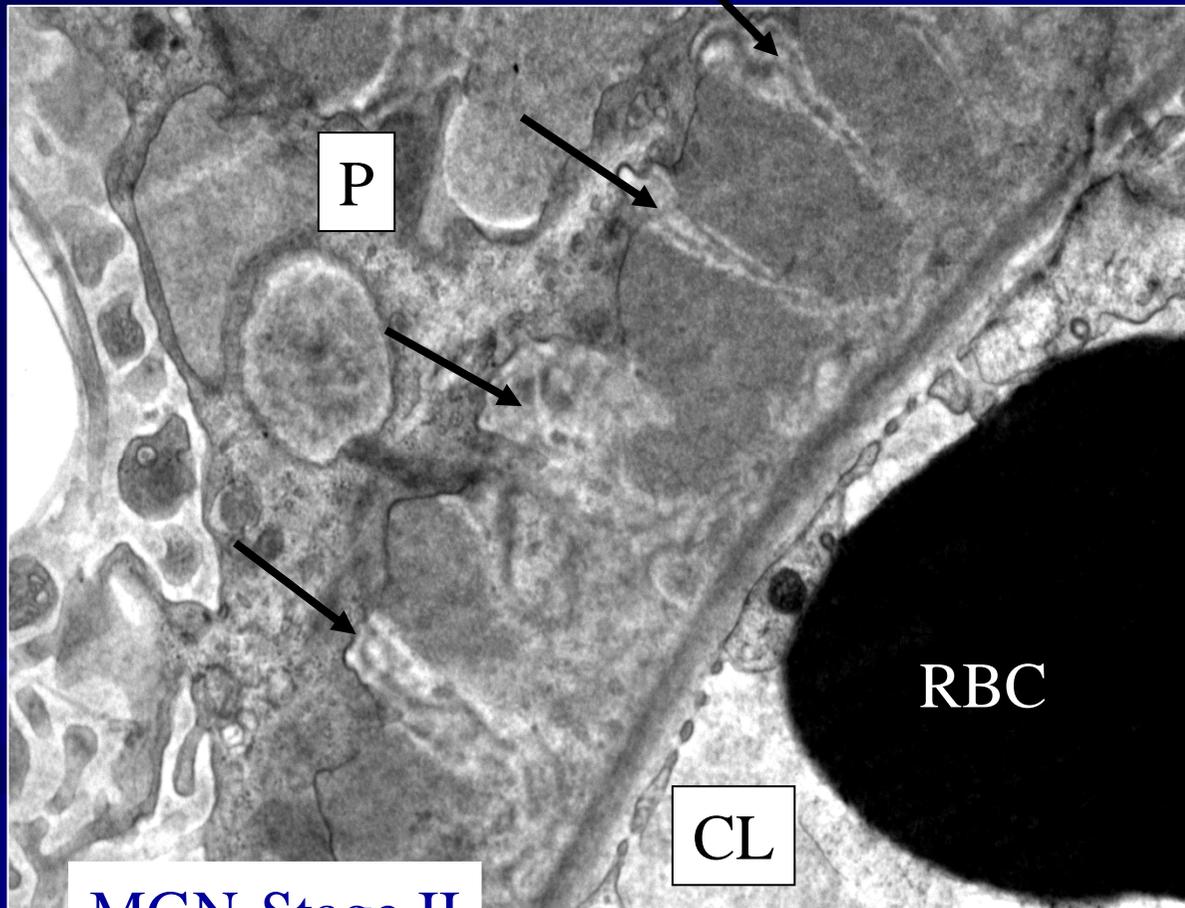
Diagnostic and diffuse in Minimal change Nephropathy

Characteristic and non-specific in all proteinuric case

# Glomerulus

GBM-lesion:

Spike formation



MGN-Stage II

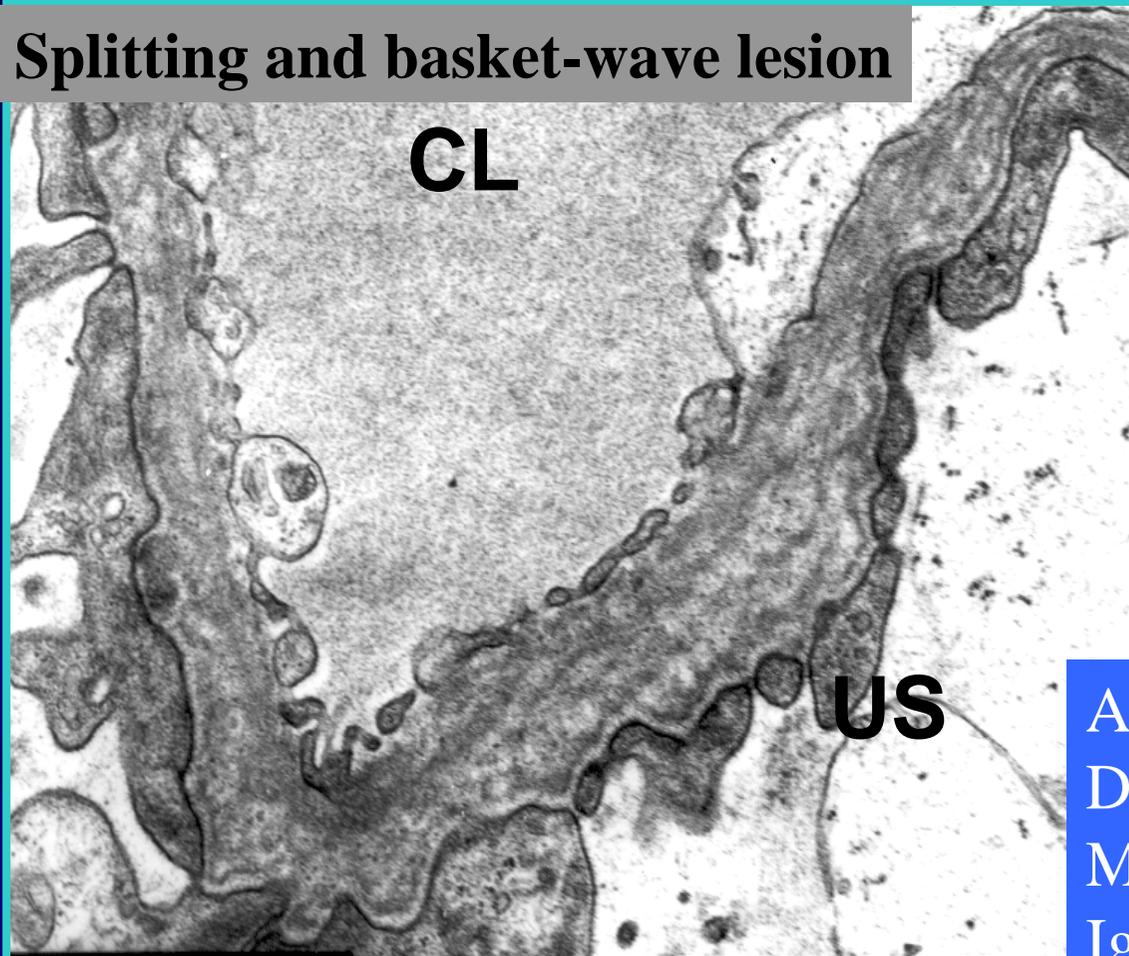
Characteristic in  
MGN,  
Lupus nephritis Class V

# Glomerulus

GBM-lesion:

Irregularity

Splitting and basket-wave lesion



**Alport's  
syndrome**

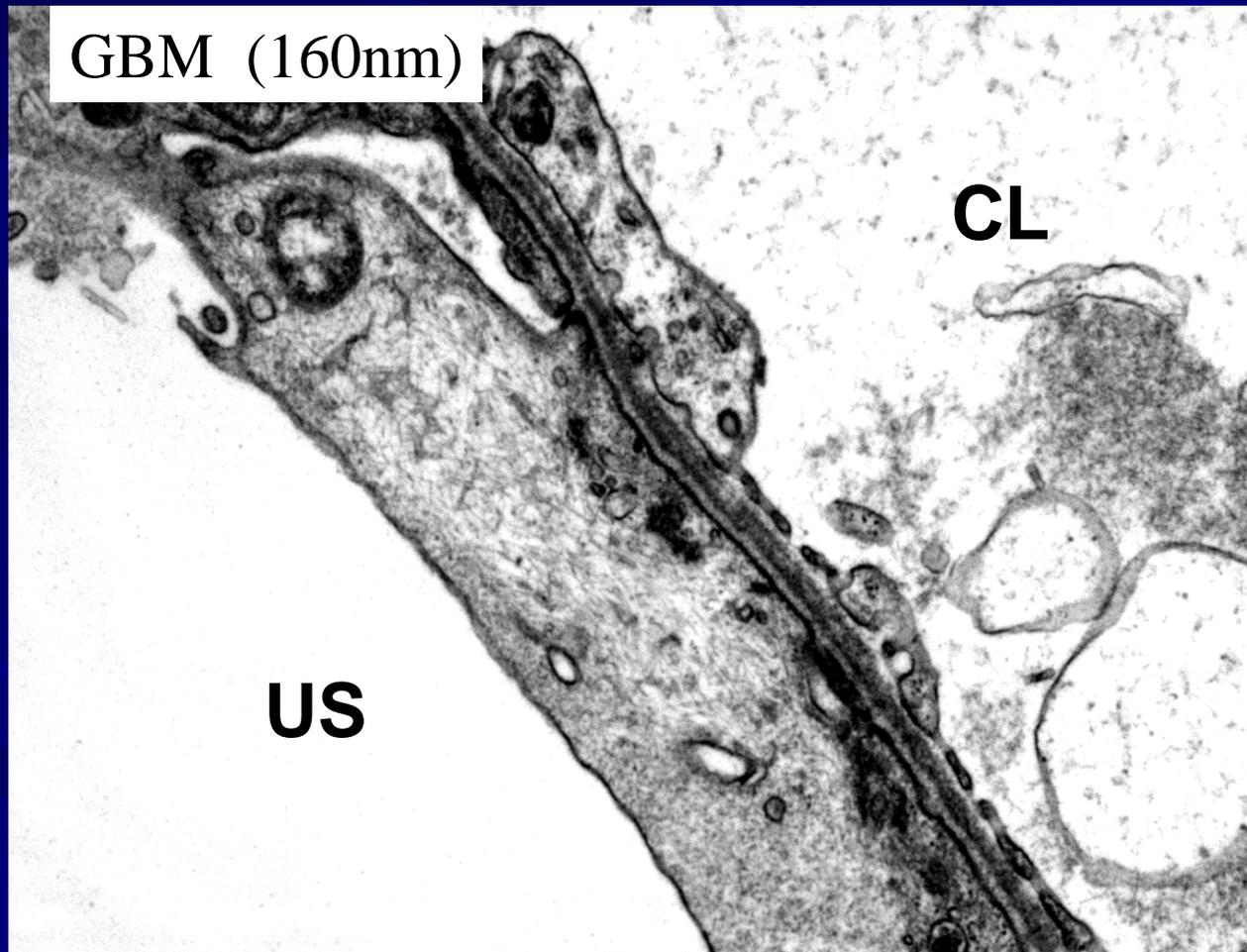
**But not  
specific!**

Alport's sy  
Diabetes GP  
MGN stage III and/or IV  
IgAN-peripheral lesion

# Glomerulus

GBM-lesion:

Thining (less than 200nm)

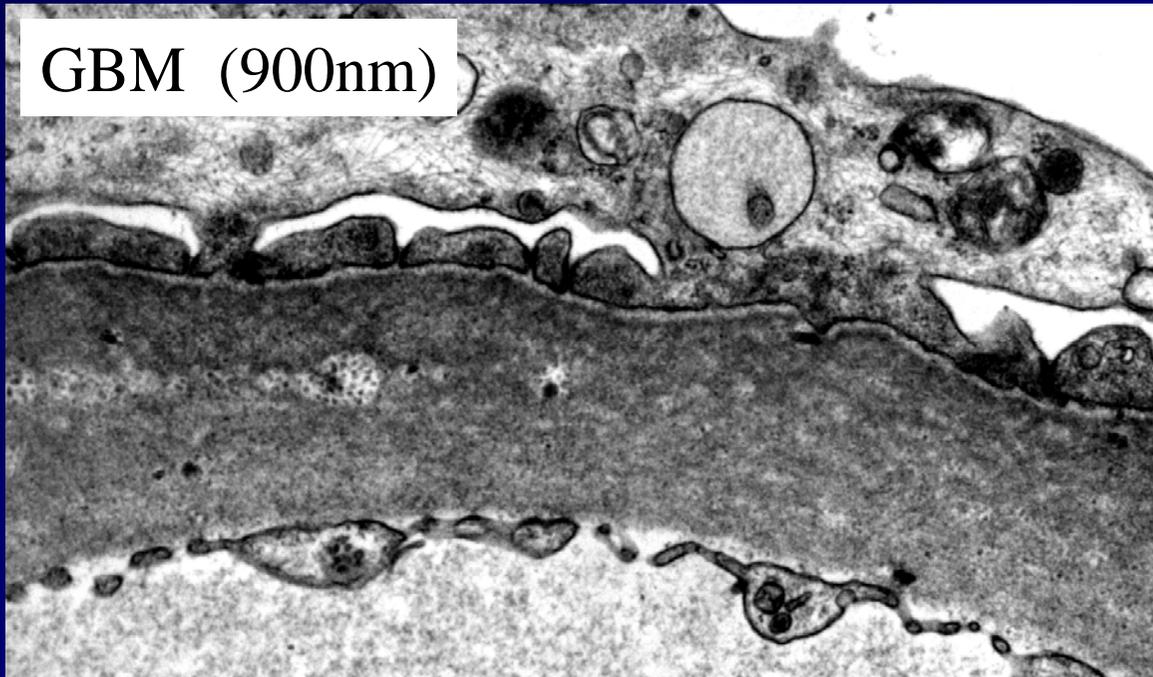


Extremely thinned  
GBM (especially  
the lamina densa)  
with podocyte  
effacement

# Glomerulus

GBM-lesion:

Thickening



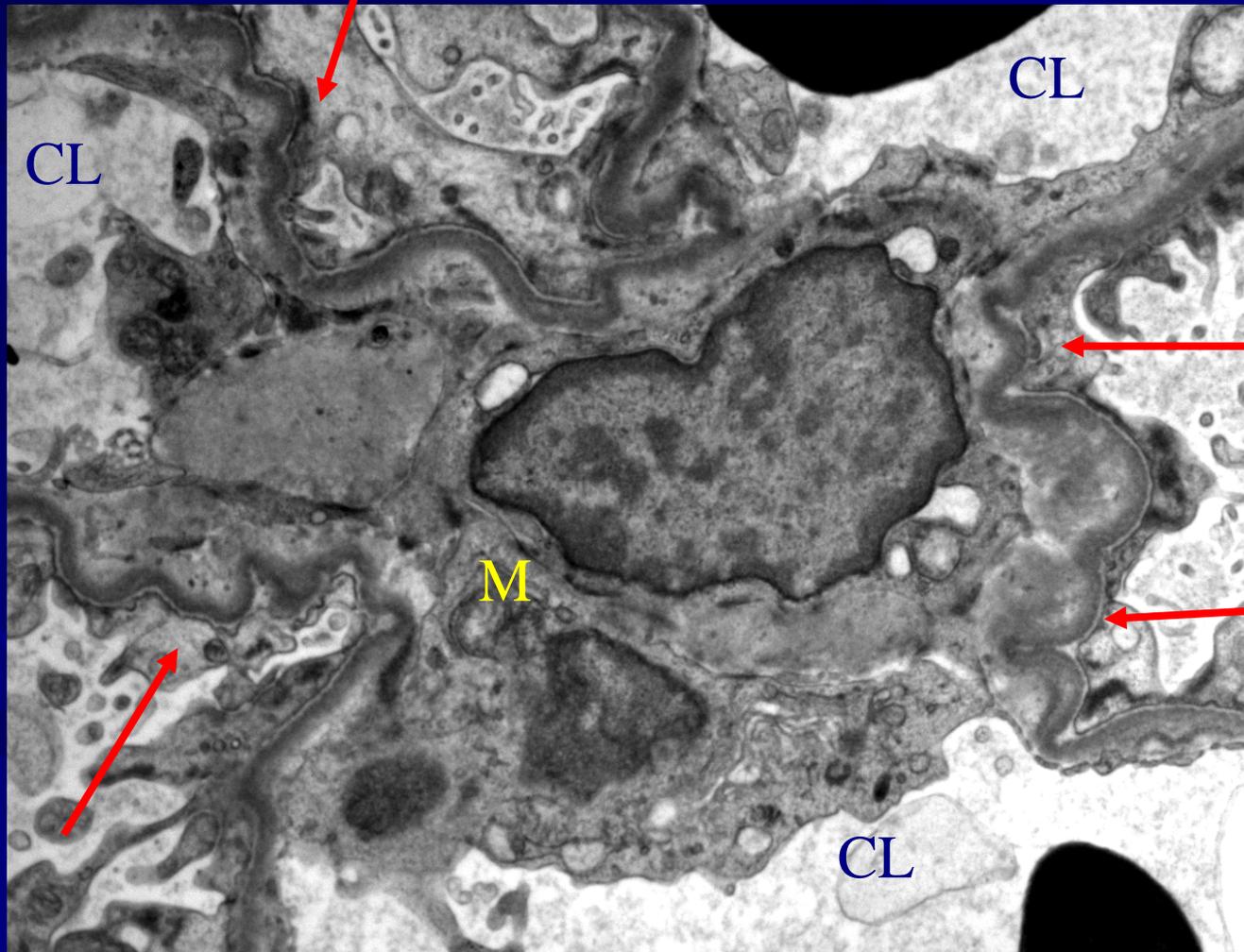
Severe diffuse thickening of the lamina densa is typical for diabetic glomerulopathy,

**but not specific!**

# Glomerulus

GBM-lesion:

Wrinkling



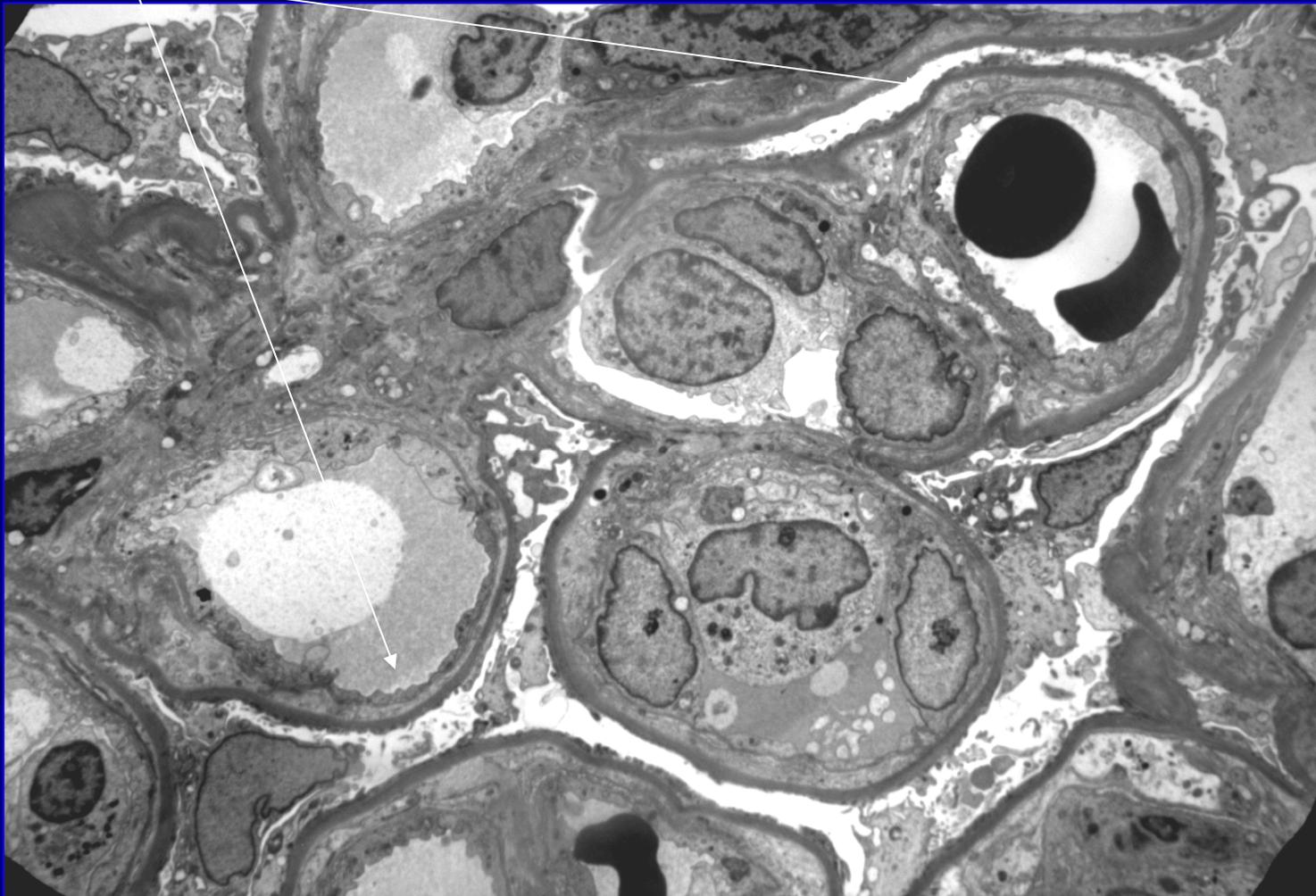
Glomerular  
ischaemic  
change

Non-specific

# Glomerulus

GBM-lesion:

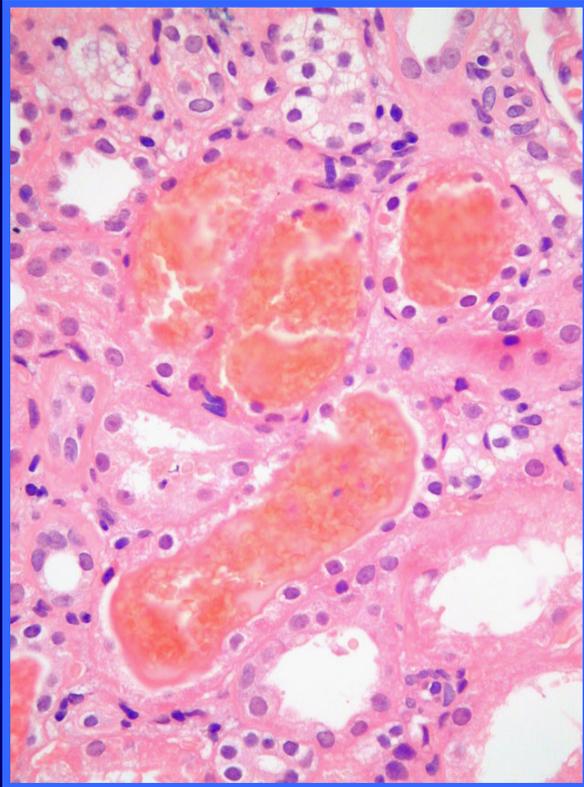
Double contour in chronic allograft glomerulopathy



# TUBULES

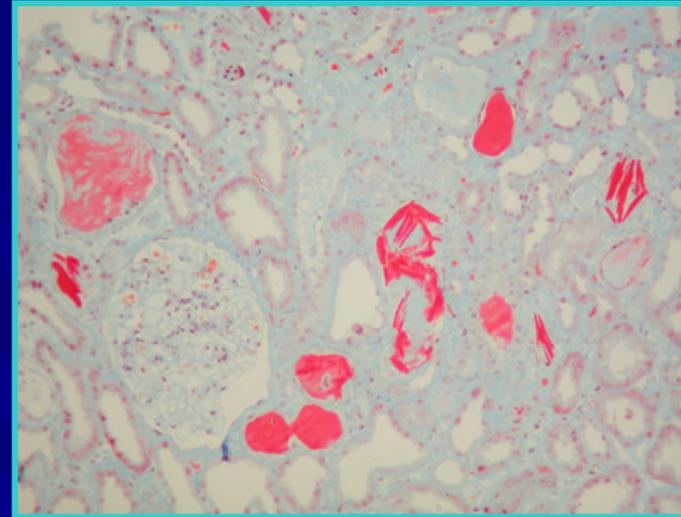
# Tubules

**Casts - red blood cell**

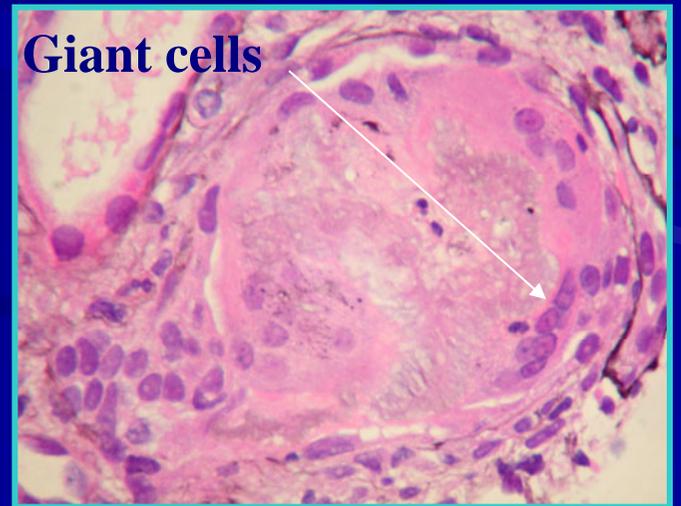


in haematuria

**Myeloma cast**

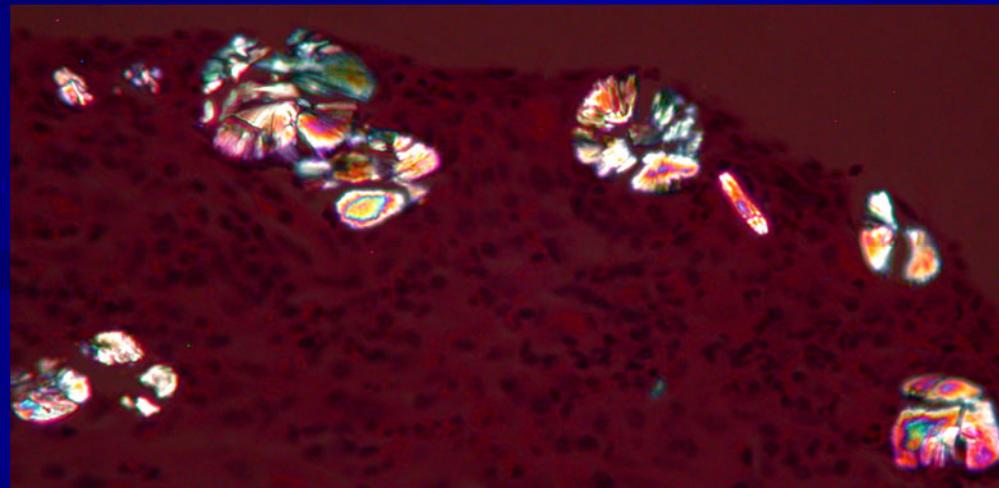
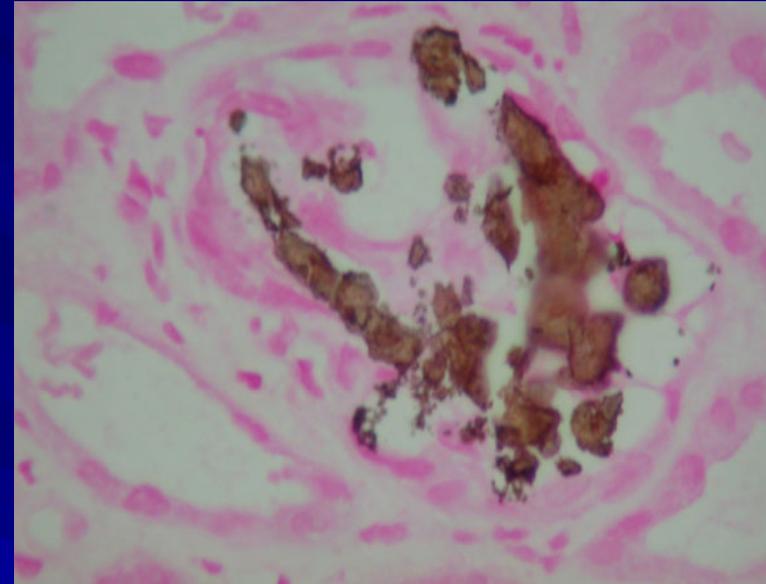
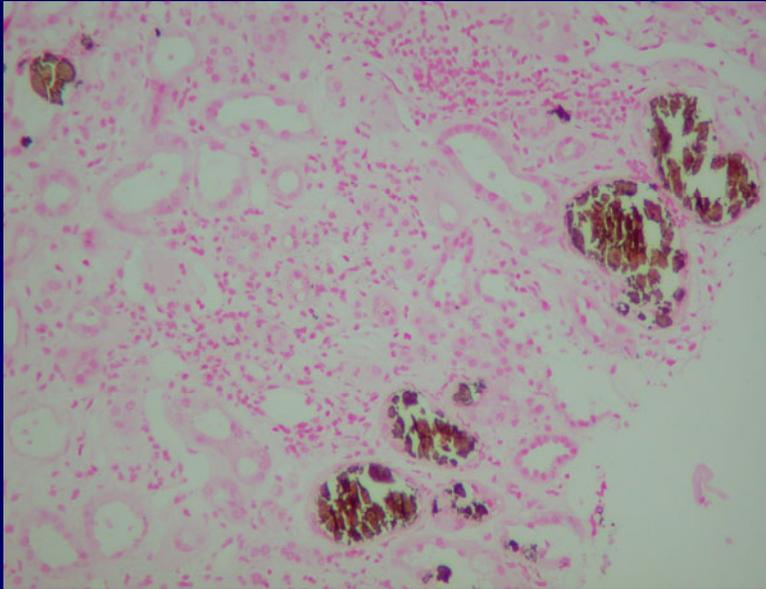


**Giant cells**



# Tubules

Oxalosis (Ca-oxalate crystals)



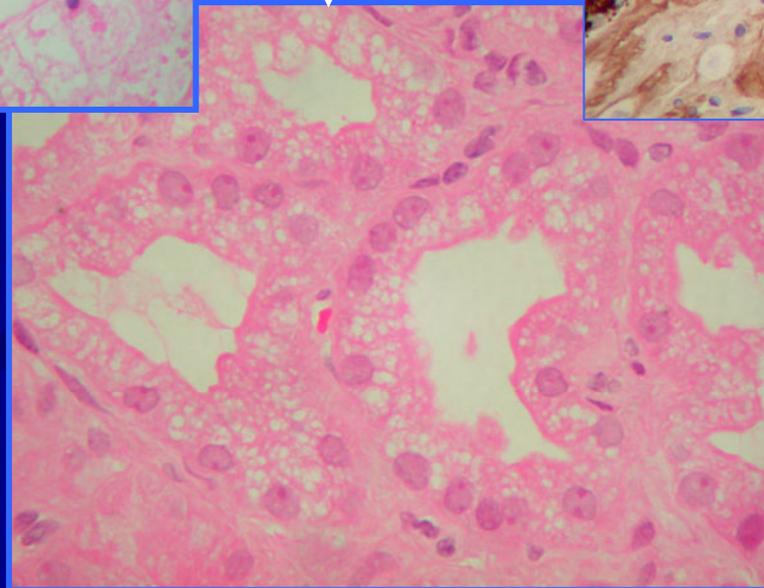
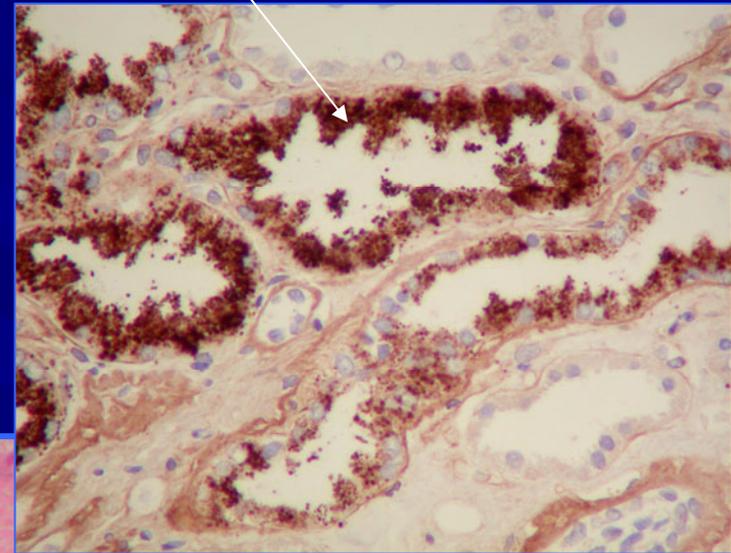
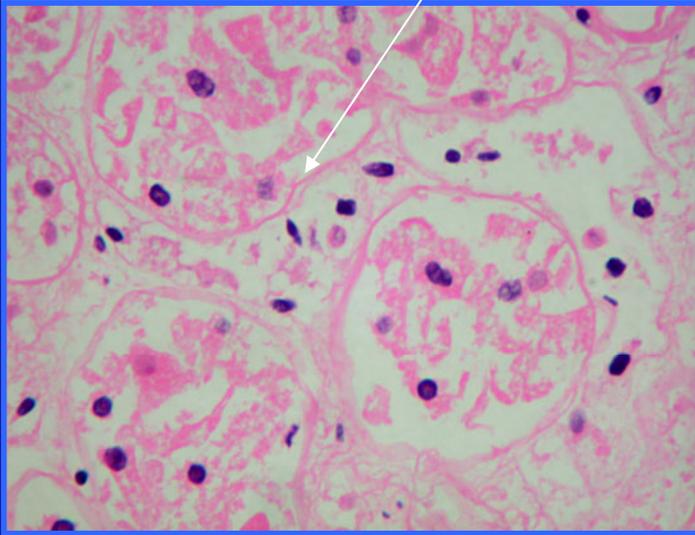
# Tubules

## Epithelium

necrosis,

vacuolation,

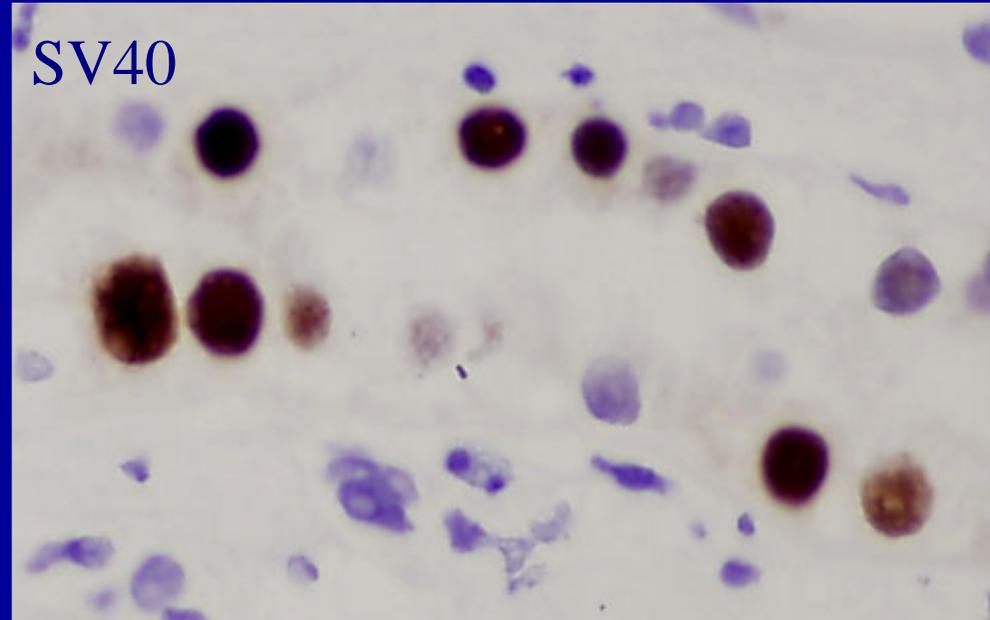
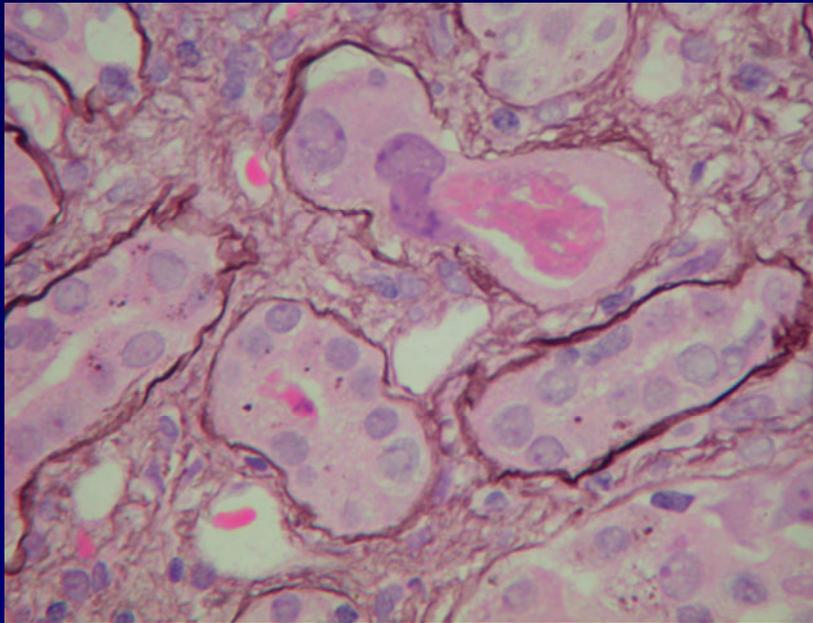
re-absorbed material



# Tubules

Epithelium

Viral inclusion



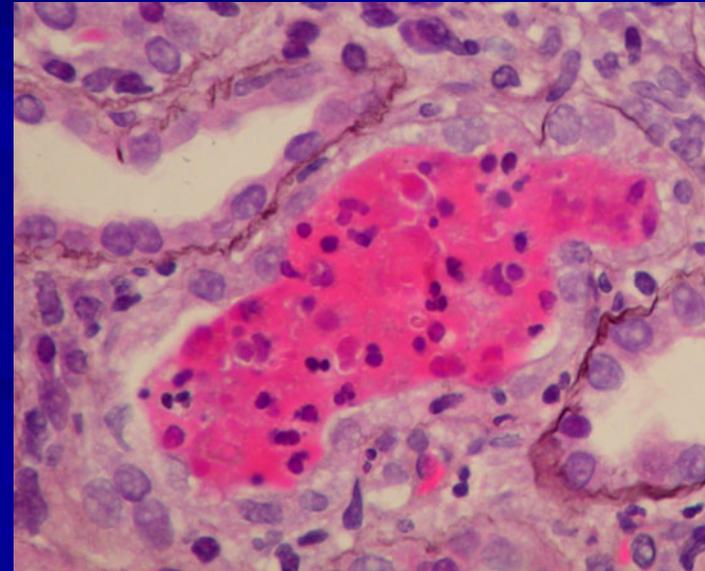
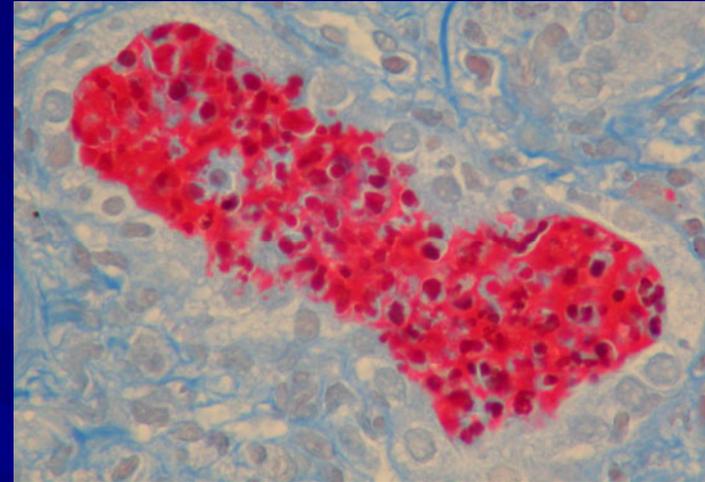
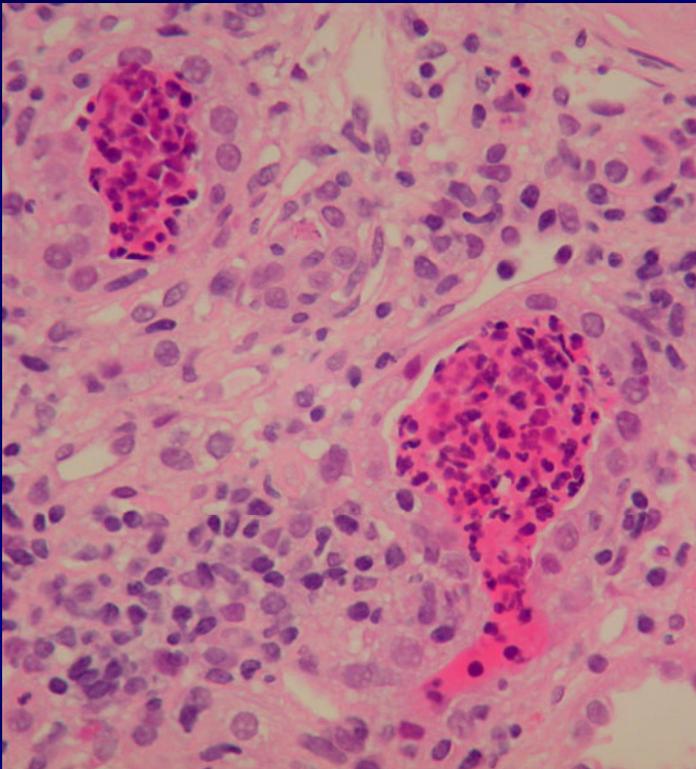
## Human polyomavirus- associated tubulo-interstitial nephritis (PVN) in the allograft kidney

PVN (BK-N) is a transplant complication occurring in 1% to 8% of kidney transplant recipients.

# Tubules

## Inflammation

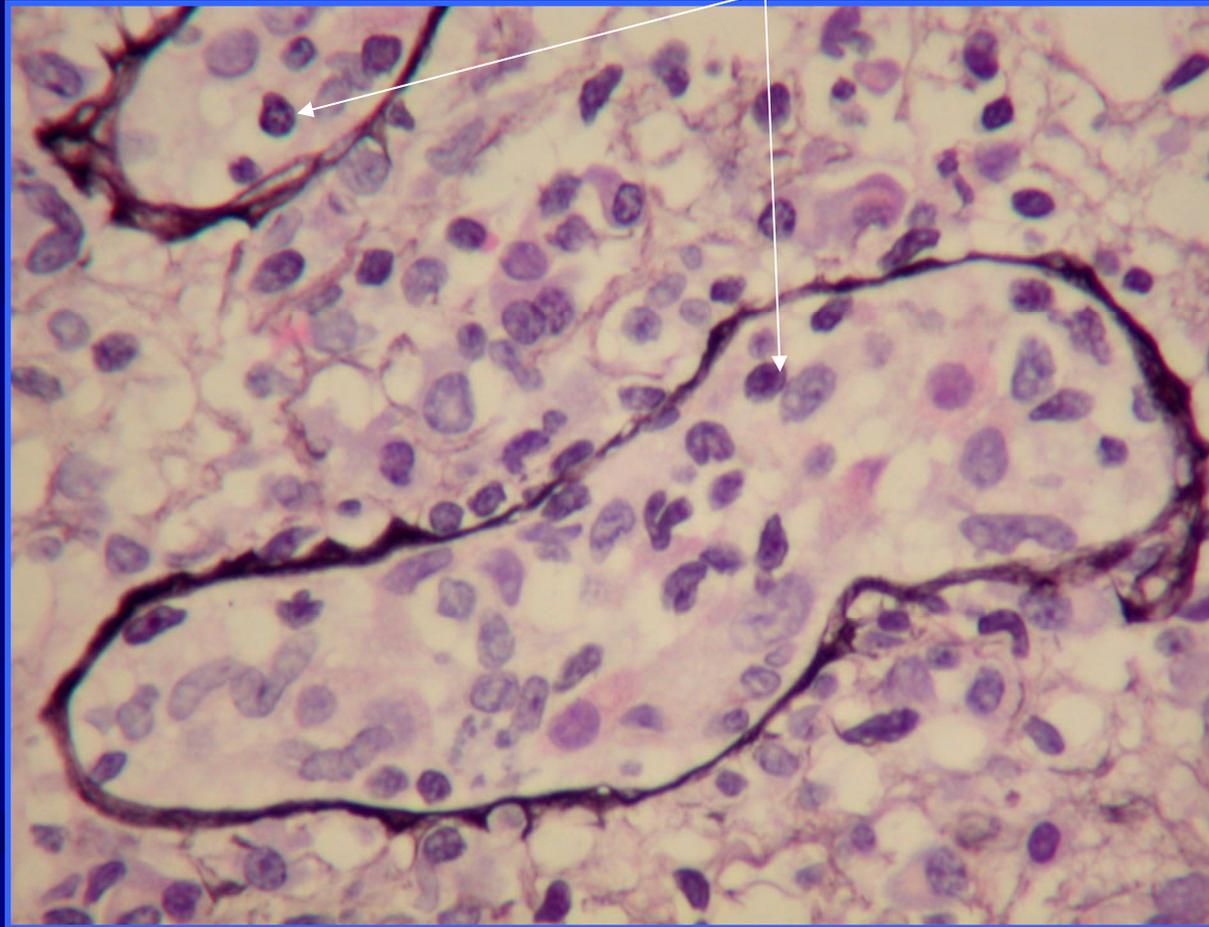
(Intratubular inflammatory cells)



Ascending urinary tract infection

# Tubules

lymphocytic tubulitis,



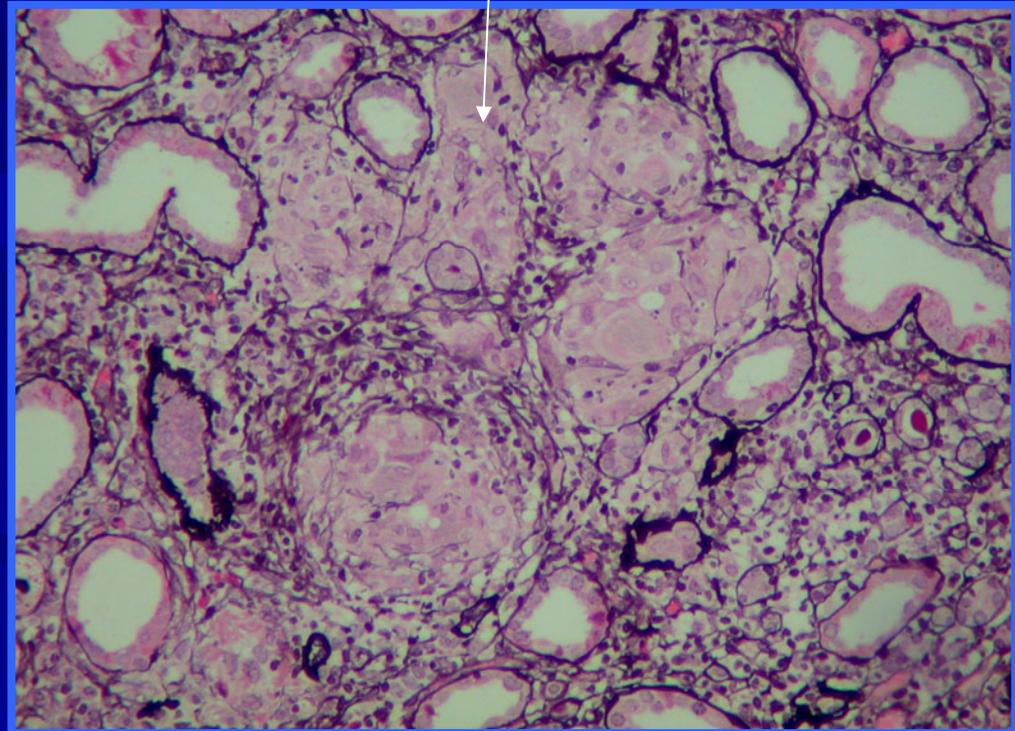
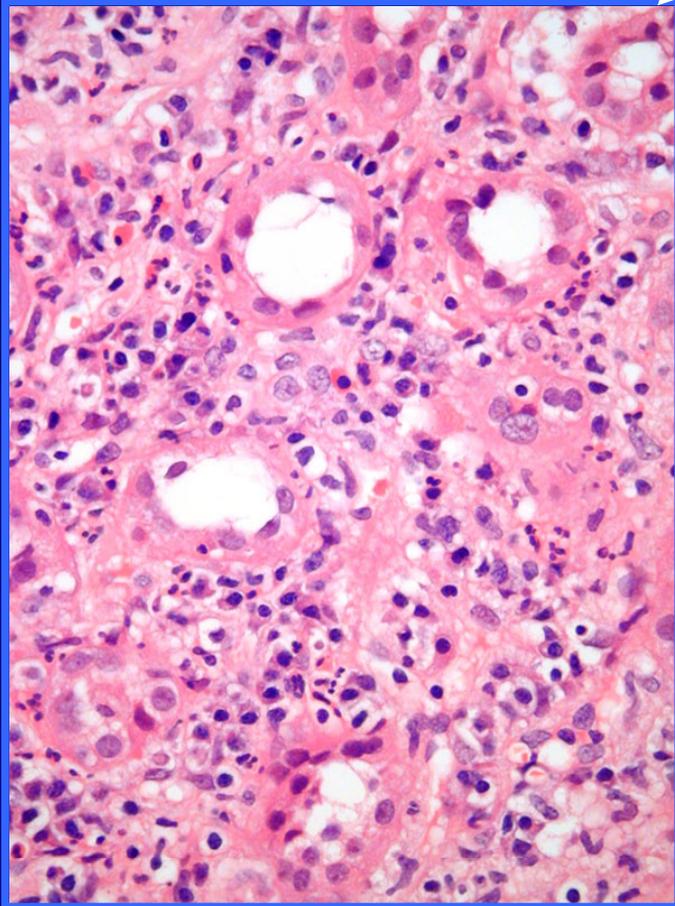
in cellular rejection

# INTERSTITIUM

# Interstitial

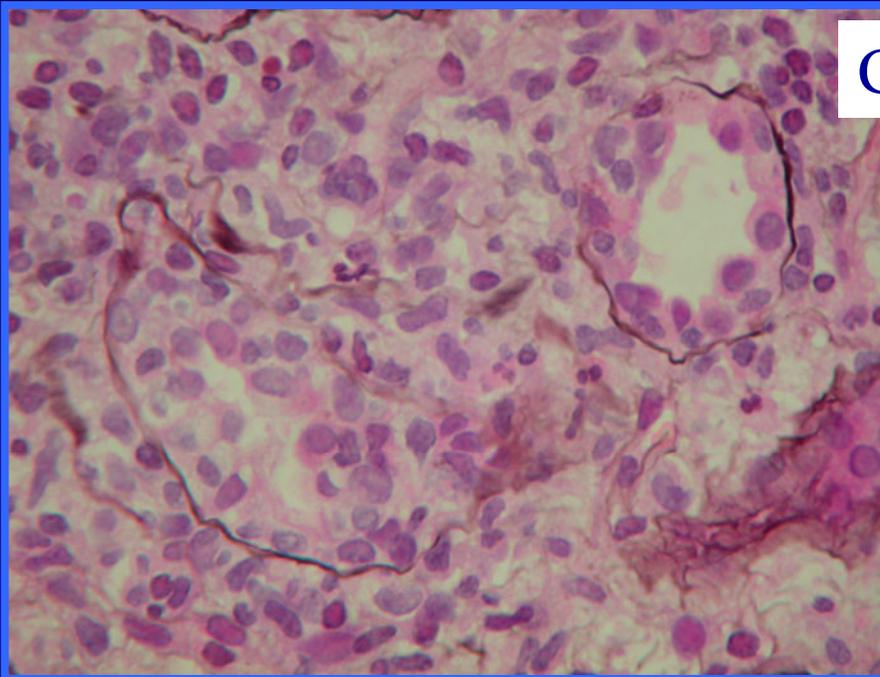
## Inflammation:

chronic with mixed cells and granulomatous

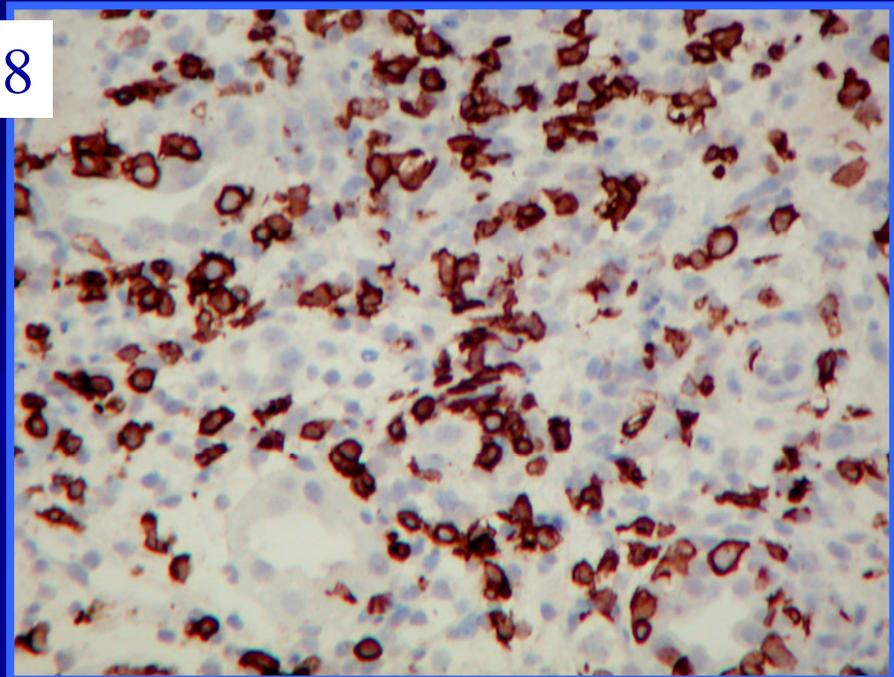


# Interstitium

T-lymphocyte infiltration within the interstitium and within the tubular epithelium



CD8

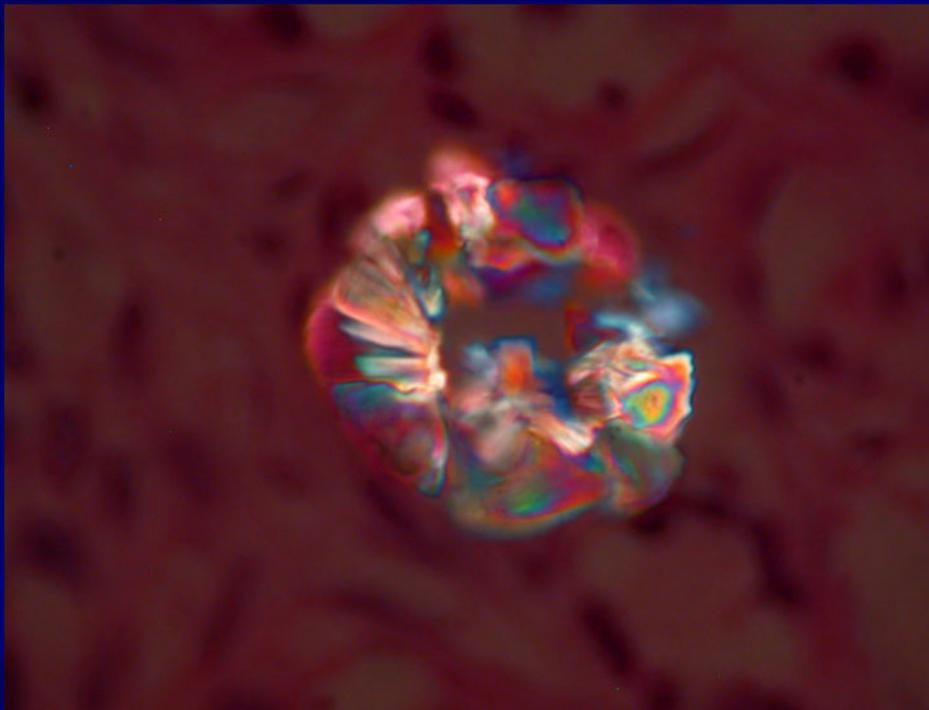


Acute cellular rejection

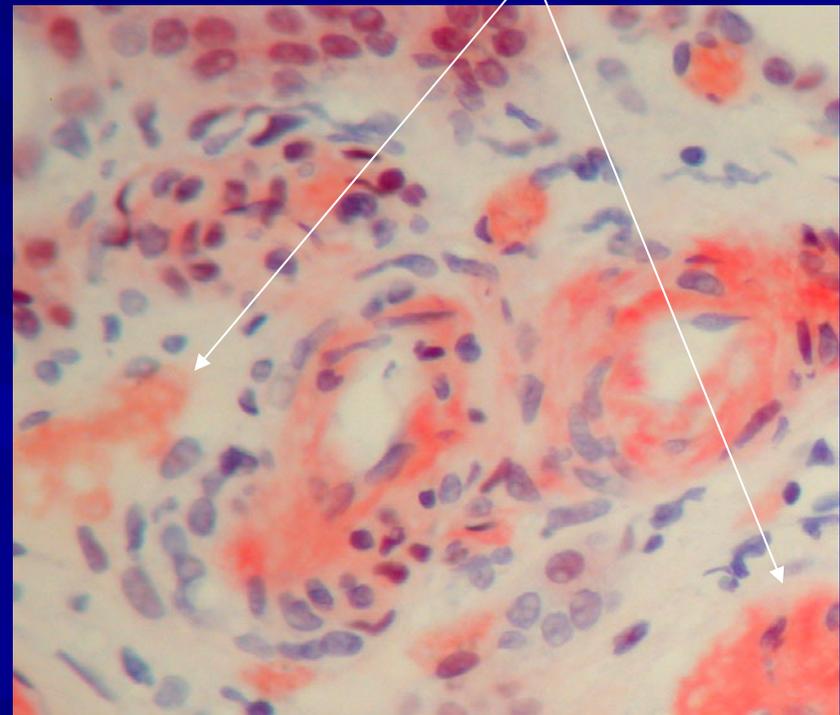
# Interstitium

## Deposits

Crystals (Ca-oxalate),



amyloid



# Interstitial

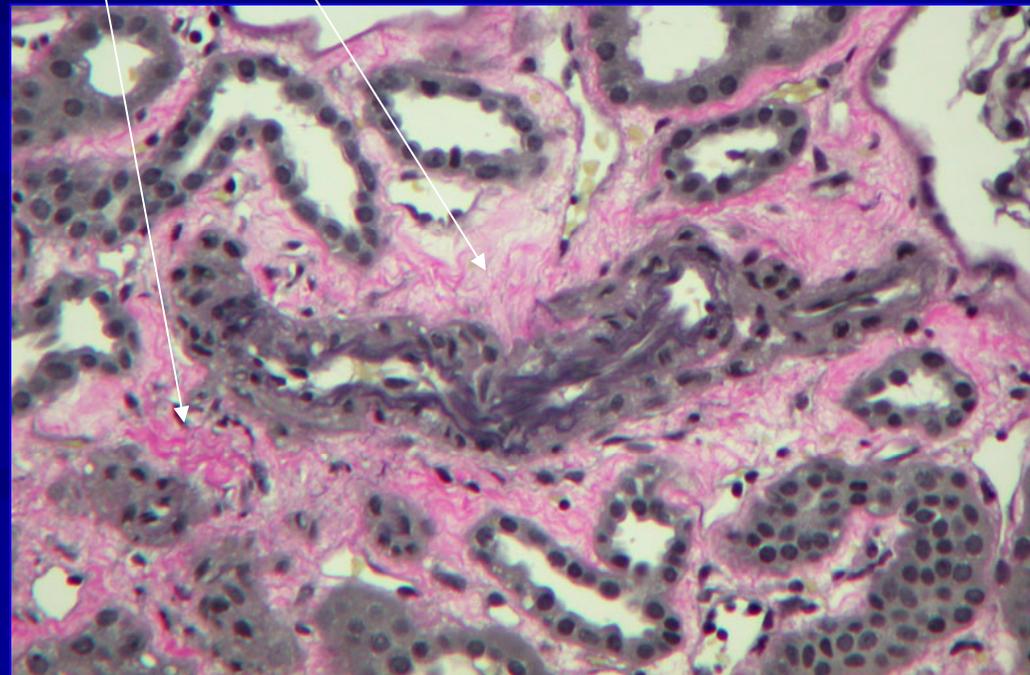
## Fibrosis- patterns

striped

segmental

subcapsular

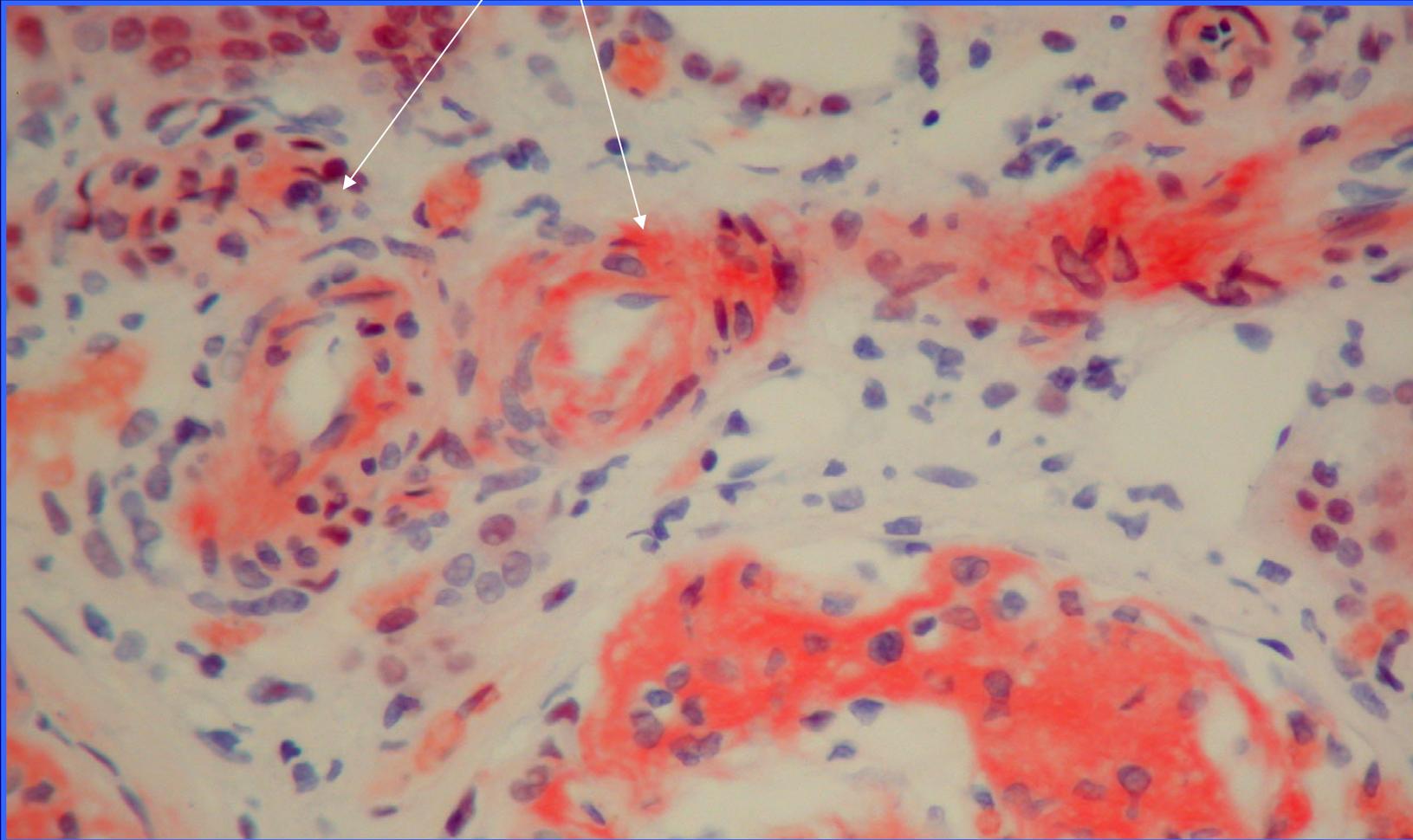
diffuse peritubular



# Vessels

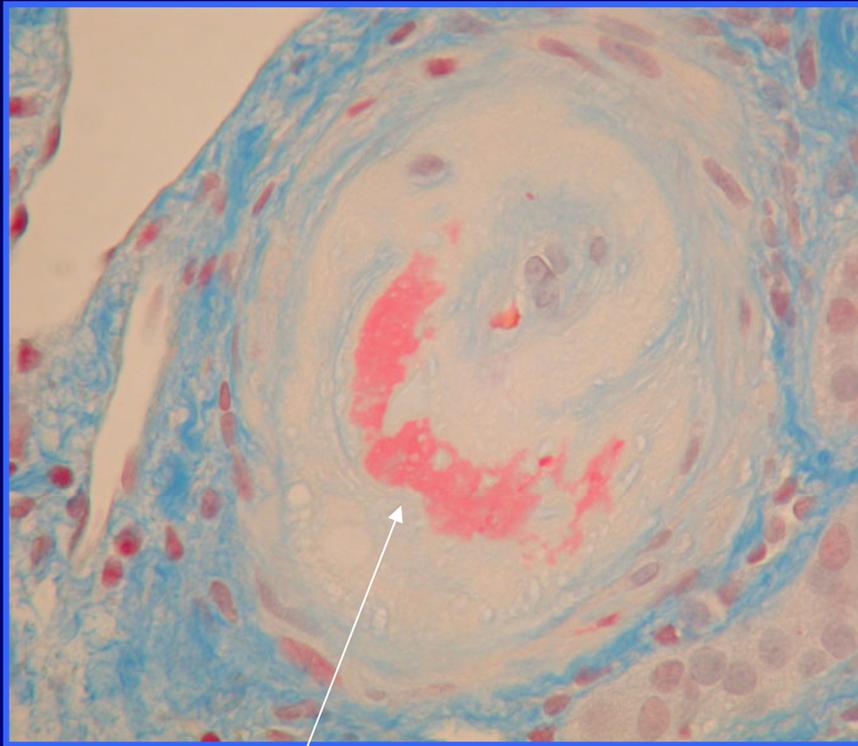
# Vessels

Amyloid deposits in renal vasculature

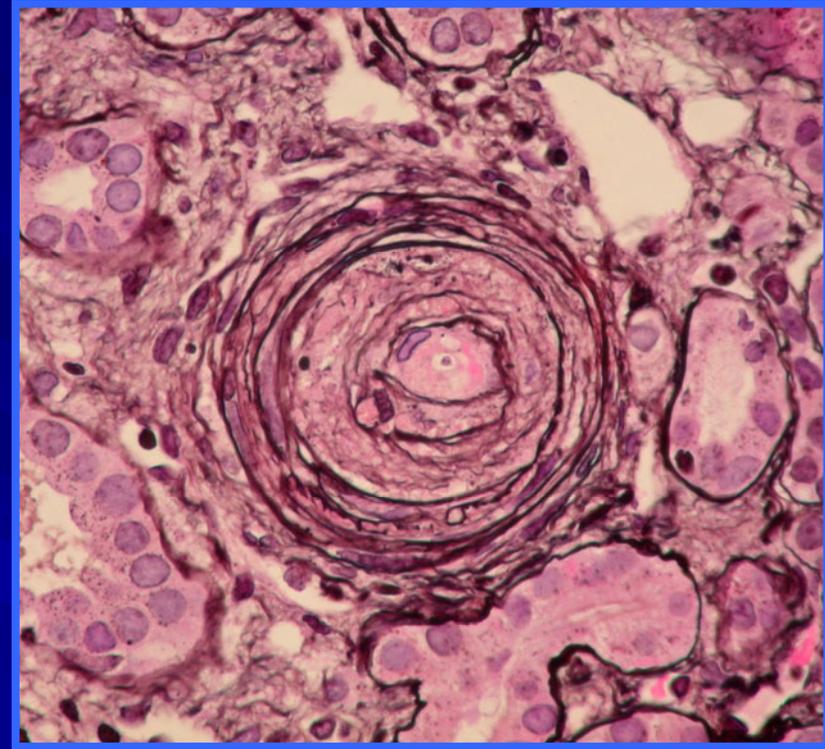


# Vessels

Malignant hypertension

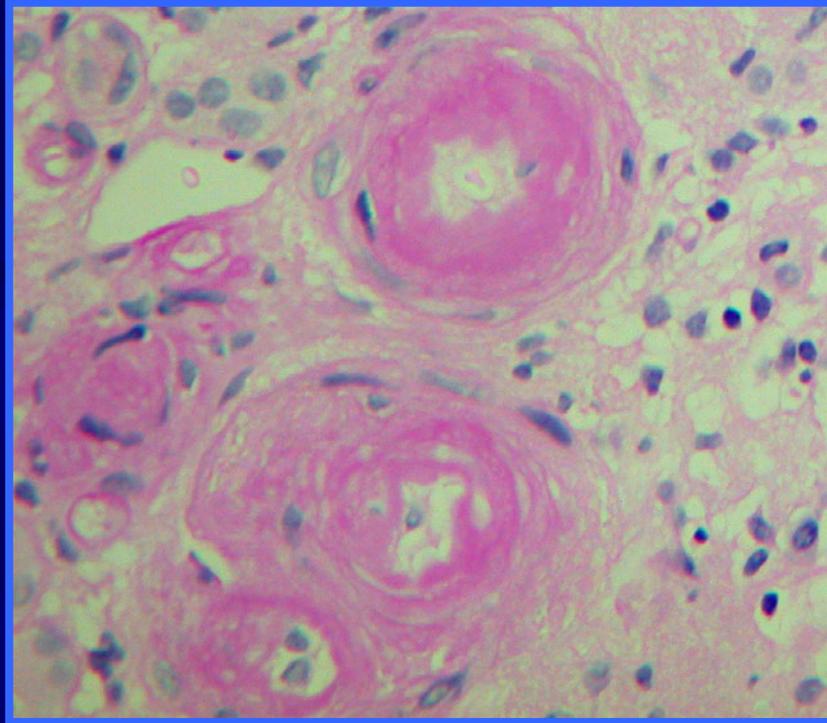


Occlusion,  
mucoid lesion  
intramural fibrin

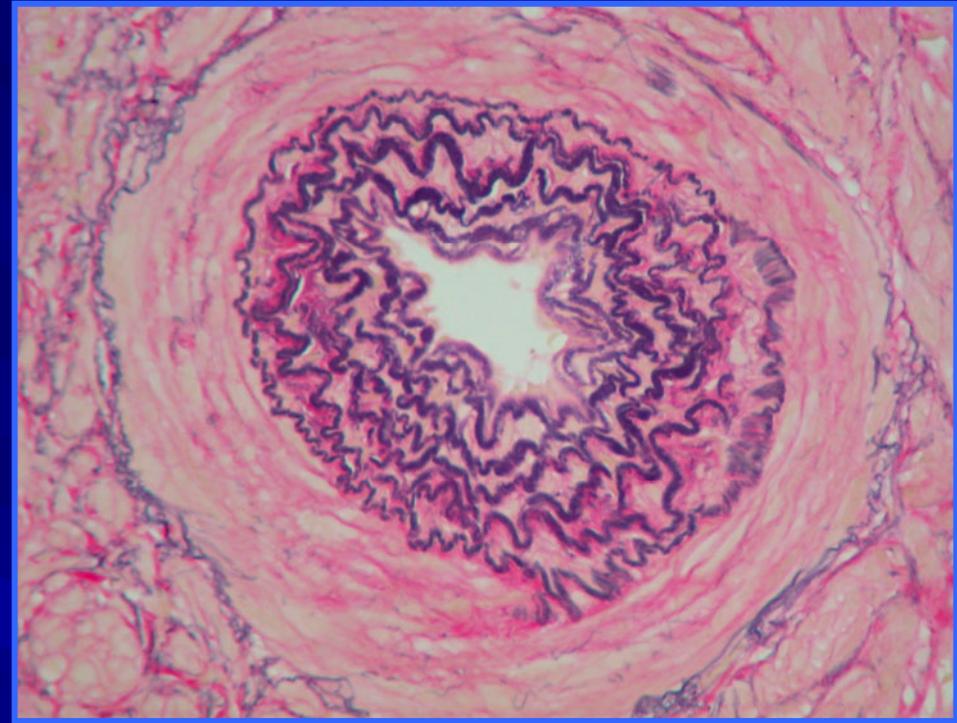


Onion-skin lesion

# Vessels



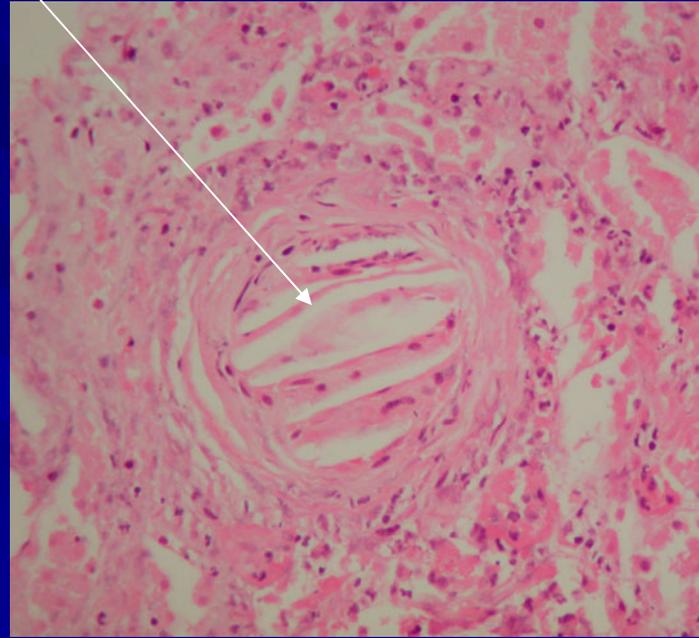
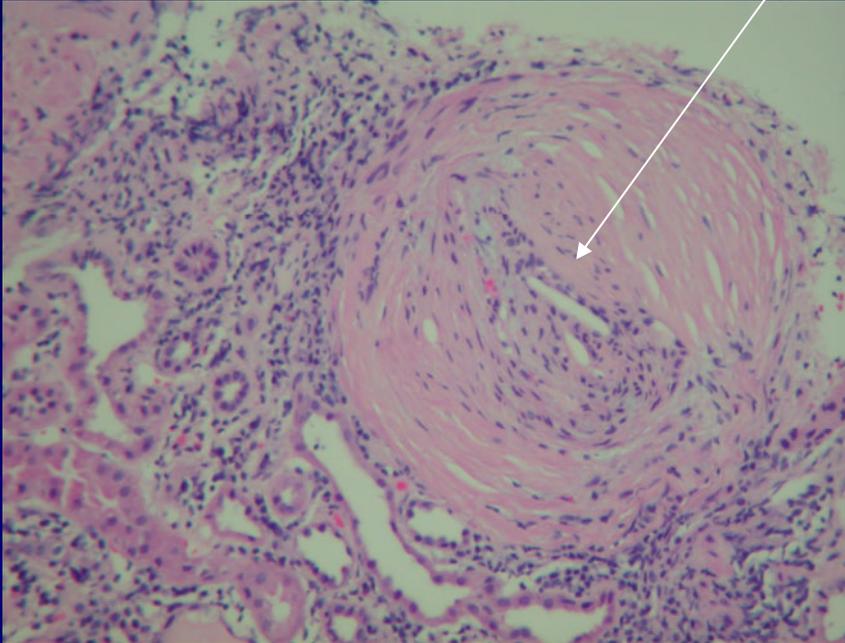
Arteriolar hyalinosis  
in  
Arteriosclerosis  
CNI-nephrotoxicity



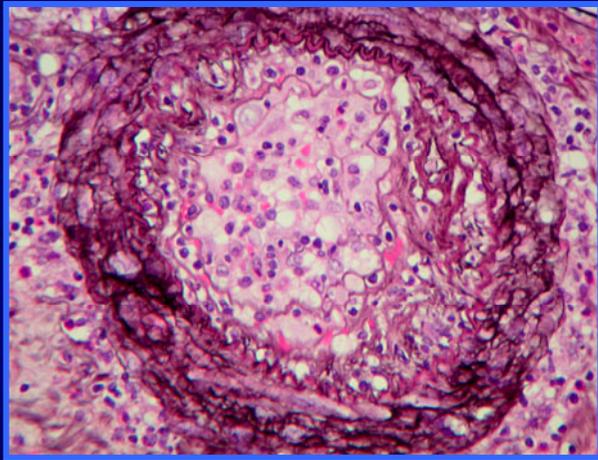
Arteriosclerosis  
with multiplication  
and lamellar appearance  
of the elastic lamina

# Vessels

Cholesterol emboli



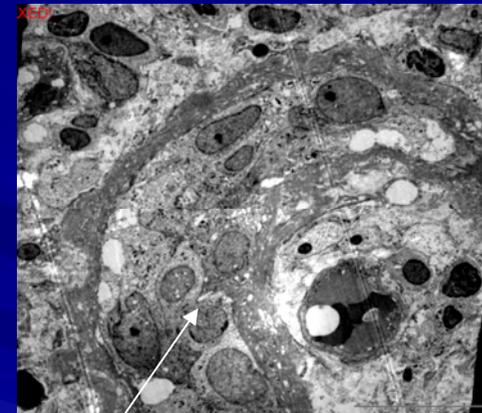
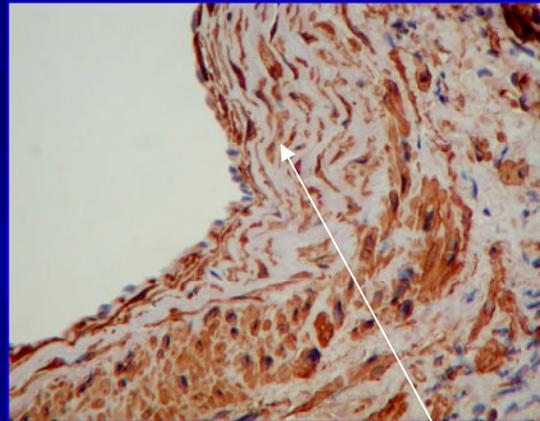
# Vessels



Lymphocytic  
endothelialitis,  
Endarteritis

in acute cellular rejection

Myofibroblast  
proliferation and migration  
into the neo-intima  
in chronic allograft  
vasculopathy



alpha-smooth muscle actin  
positive myofibroblast  
appear within the inner  
arterial layer

# RENAL BIOPSY

Glomerulonephritis presents in many different ways and an accurate diagnosis cannot be made clinically.

P D Mason et al. *BMJ* 1994;309:1557-1563

# Patterns of glomerular injury observed by light microscopy (LM)

## ■ No abnormality by LM

1. No glomerular disease
2. Minimal change nephropathy
3. Thin basement membrane nephropathy
4. Mild or early glomerular diseases
  - Membranous GN stage I.
  - IgA GN-Class I.
  - Lupus N-Class I.
  - Alport's syndrome

# Patterns of glomerular injury observed by light microscopy (LM)

## ■ **GBM-thickening without mesangial lesion by LM**

1. MGN Stage II, III.
2. DMN, pure diffuse form (rare)
3. Thrombotic microangiopathy
4. Fibrillary glomerulopathy
5. Preeclampsia associated glomerulopathy

# Patterns of glomerular injury observed by light microscopy (LM)

## ■ GBM-thickening without mesangial lesion by LM

1. MGN Stage II, III.
2. DMN, pure diffuse form (rare)
3. Thrombotic microangiopathy
4. Fibrillary glomerulopathy
5. Preeclampsia associated glomerulopathy

# Patterns of glomerular injury observed by light microscopy (LM)

## ■ Mesangial hypercellularity by LM

1. IgA nephritis
2. Henoch-Schonlein glomerulonephritis
3. Lupus N, focal or diffuse proliferative form
4. Membranoproliferative GN (Type I, II, III)
5. Postinfectious GN, late-phase

# Patterns of glomerular injury observed by light microscopy (LM)

## ■ Endocapillary hypercellularity by LM

1. IgA nephritis, acute, florid form
2. Henoch-Schonlein GN
3. Lupus N, focal or diffuse proliferative form
4. Postinfectious GN, acute phase

# Patterns of glomerular injury observed by light microscopy (LM)

## ■ Crescentic glomerular lesion by LM

1. Small vessel vasculitis related GN
2. Anti-GBM-Ab crescentic GN
3. Crescentic Immune complex GN
4. IgA nephritis
5. Henoch-Schonlein GN
6. Lupus N,
7. Membranoproliferative GN (Type I, II, III)
8. Postinfectious GN,
9. Secondary MGN

# Patterns of glomerular injury observed by light microscopy (LM)

## ■ Lobularity, nodularity (MPGN-like) by LM

1. Membranoproliferative GN (Type I, II, III)
2. Lupus N, focal or diffuse proliferative form
3. Monoclonal Ig deposition disease
4. Diabetic glomerulosclerosis, nodular form
5. Amyloidosis
6. Thrombotic microangiopathy
7. Fibrillary GN
8. Immunotactoid GP

# Patterns of glomerular injury observed by light microscopy (LM)

## ■ Focal glomerulosclerosis (GS) by LM

1. Focal segmental GS, idiopathic
2. Lupus N, any form, except Class I
3. Membranous GN
4. IgA nephritis and Sc-H nephritis
5. Alport's syndrome
6. IgM nephropathy
7. Benign nephrosclerosis

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