ΠΡΩΤΟΠΑΘΕΙΣ Ή ΙΔΙΟΠΑΘΕΙΣ ΝΟΣΟΙ ΤΩΝ ΝΕΦΡΩΝ

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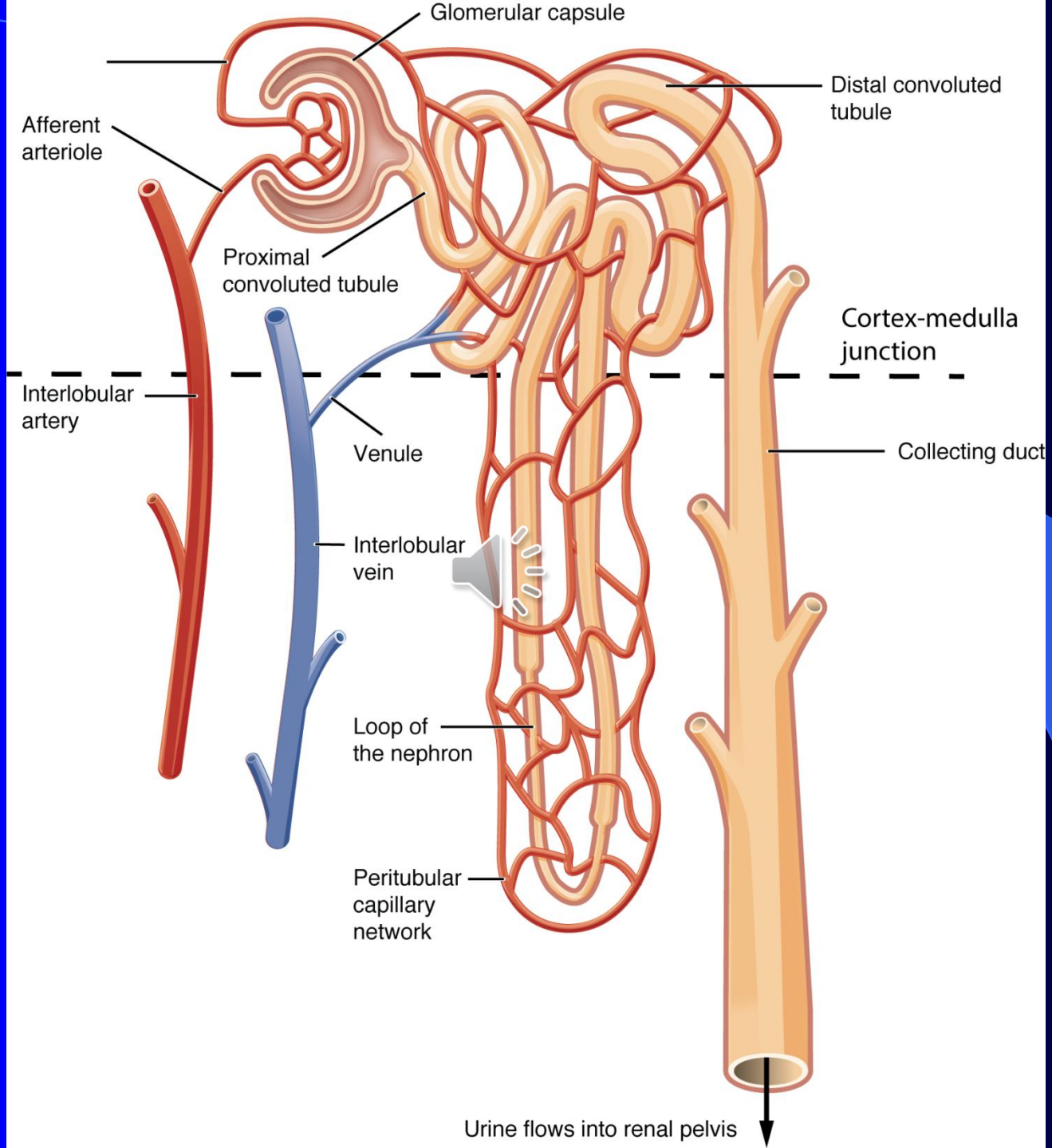
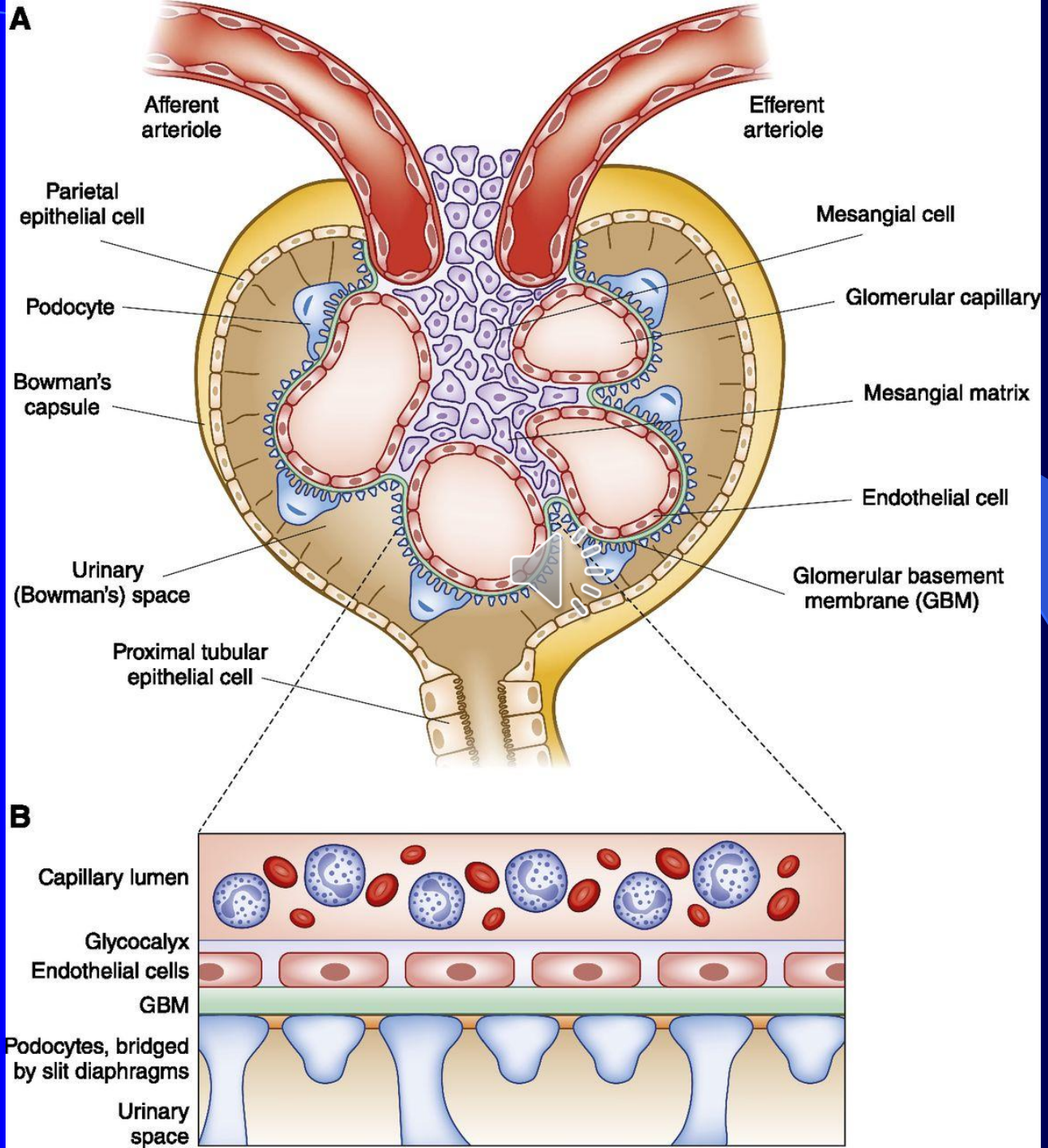
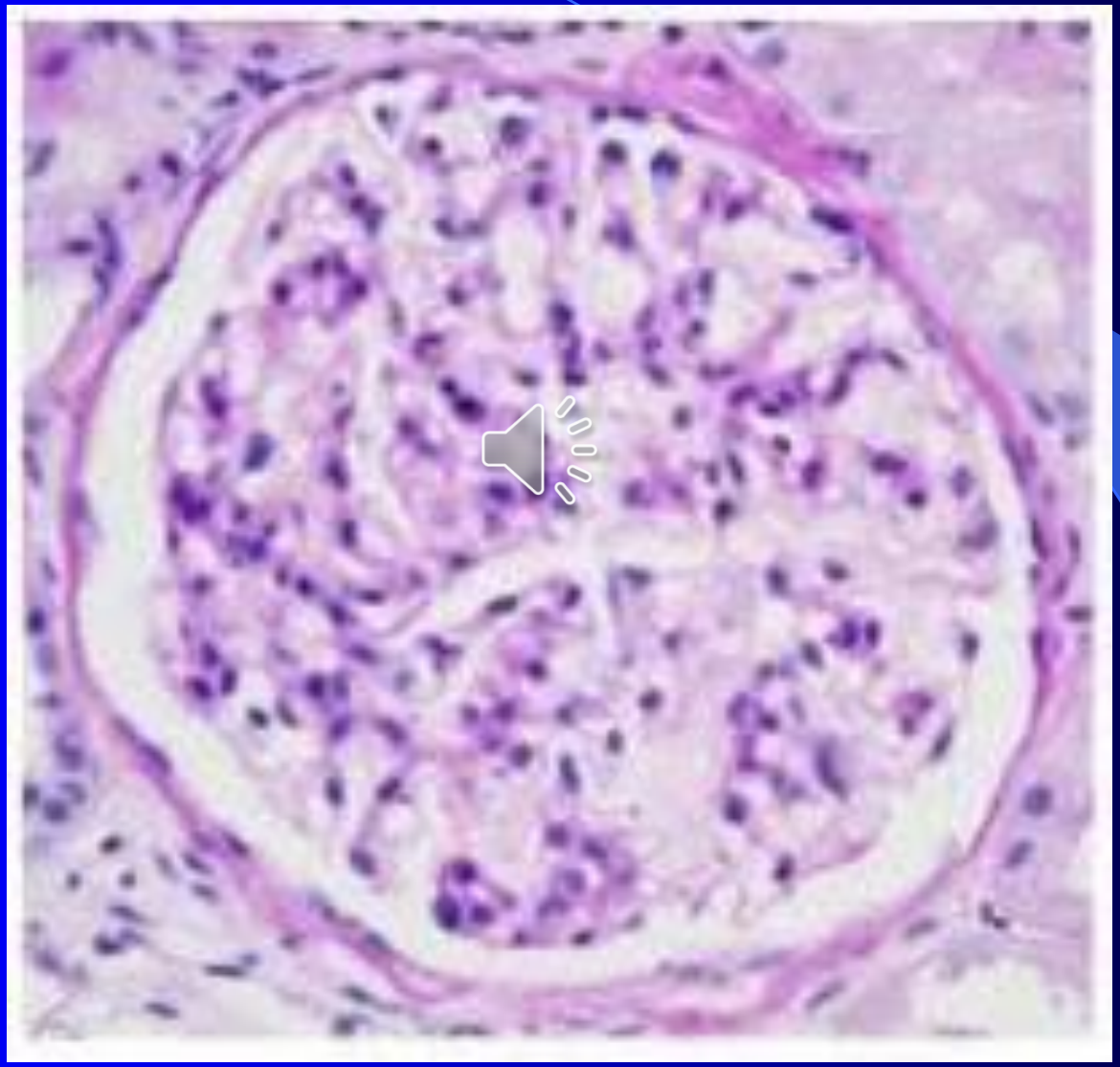
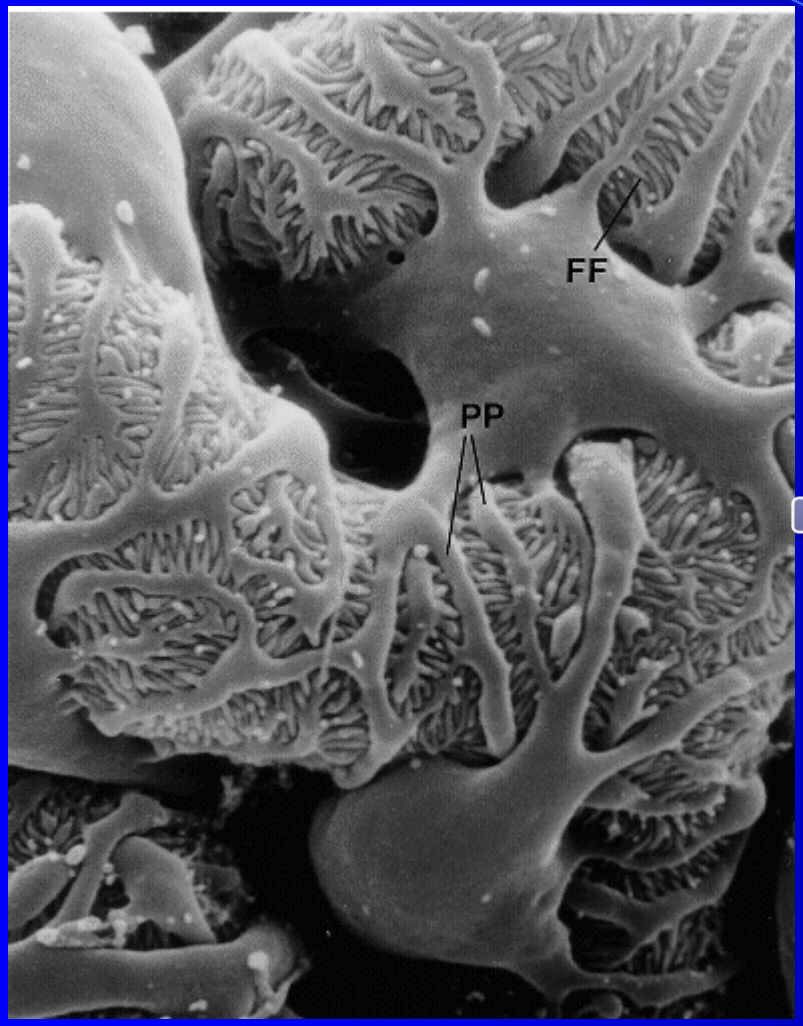
Πανεπιστημιακό Γενικό Νοσοκομείο «ΑΤΤΙΚΟΝ»

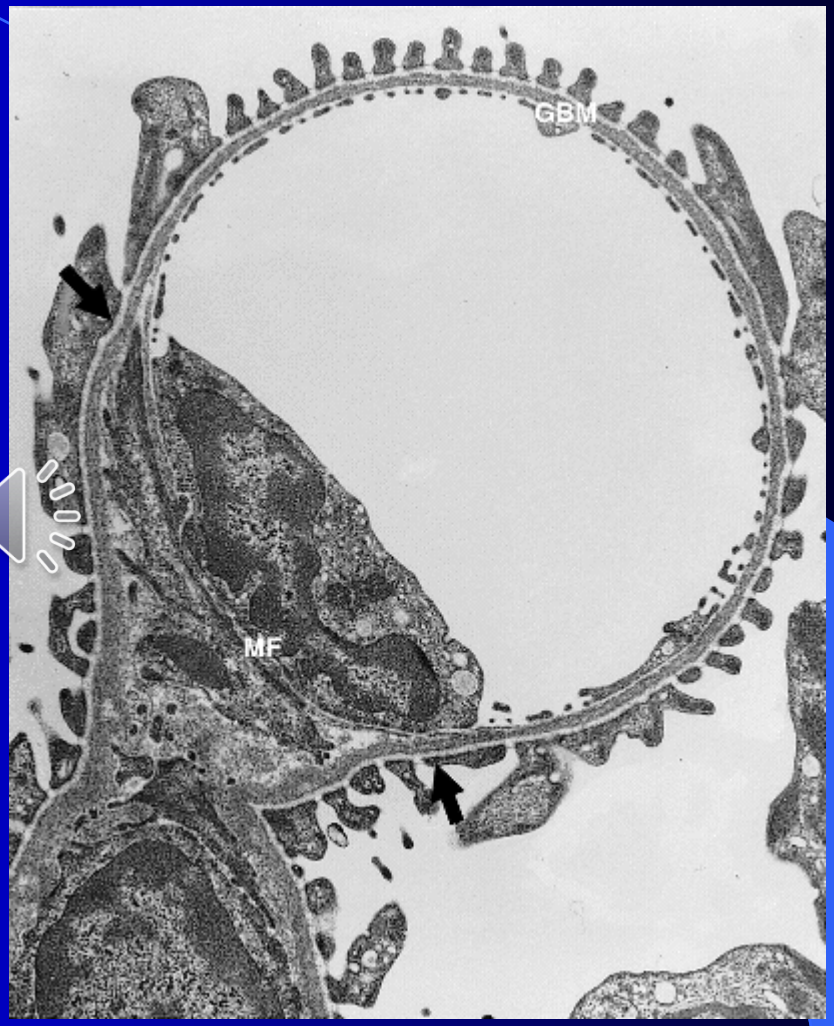

Glomerular capsule
Distal convoluted tubule
Afferent arteriole
Proximal convoluted tubule
Cortex-medulla junction
Interlobular artery
Venule
Collecting duct
Interlobular vein
Loop of the nephron
Peritubular capillary network
Urine flows into renal pelvis

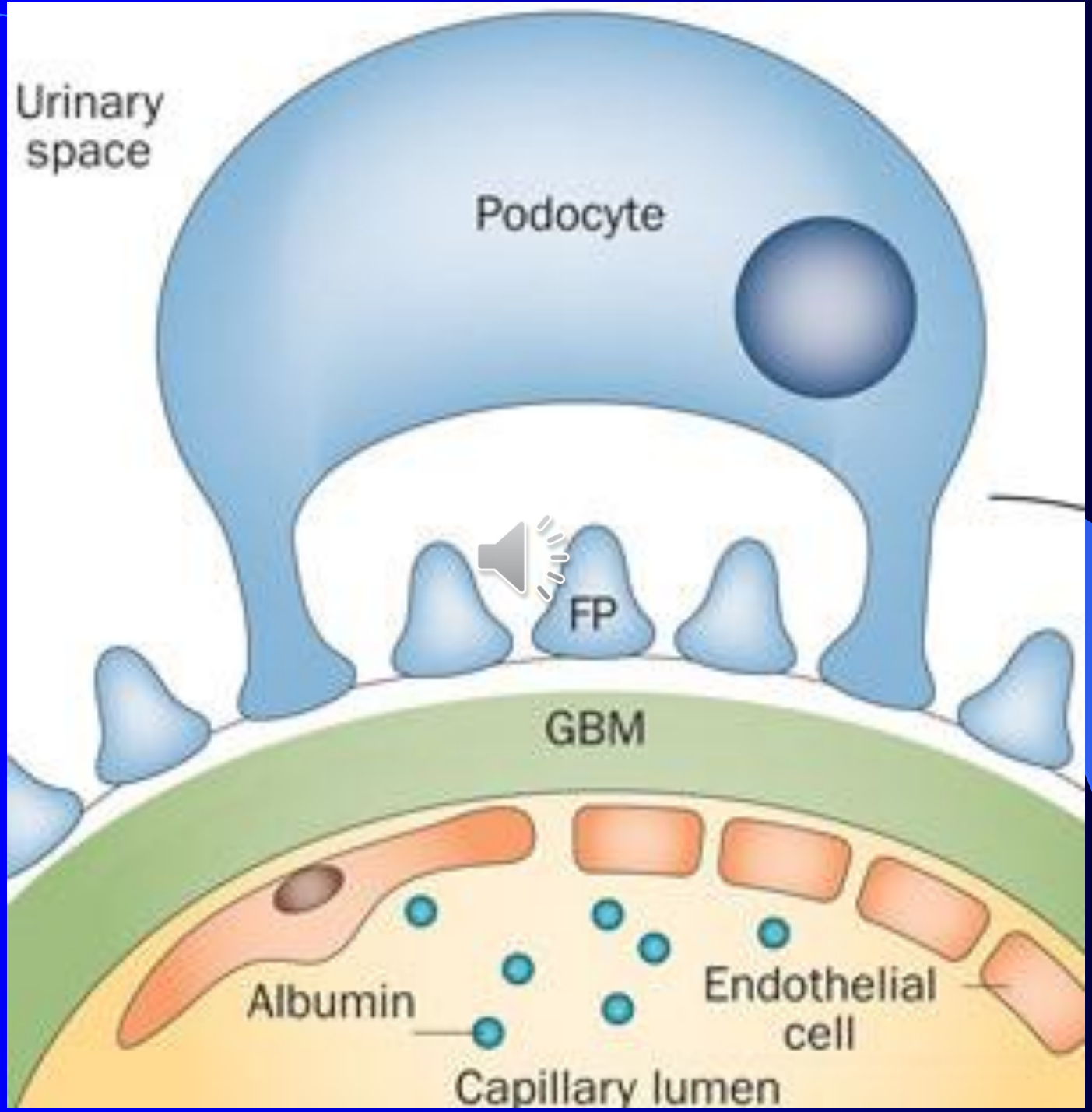

A
Afferent arteriole
Efferent arteriole
Parietal epithelial cell
Podocyte
Bowman's capsule
Urinary (Bowman's) space
Proximal tubular epithelial cell
Mesangial cell
Glomerular capillary
Mesangial matrix
Endothelial cell
Glomerular basement membrane (GBM)
B
Capillary lumen
Glycocalyx
Endothelial cells
GBM
Podocytes, bridged by slit diaphragms
Urinary space

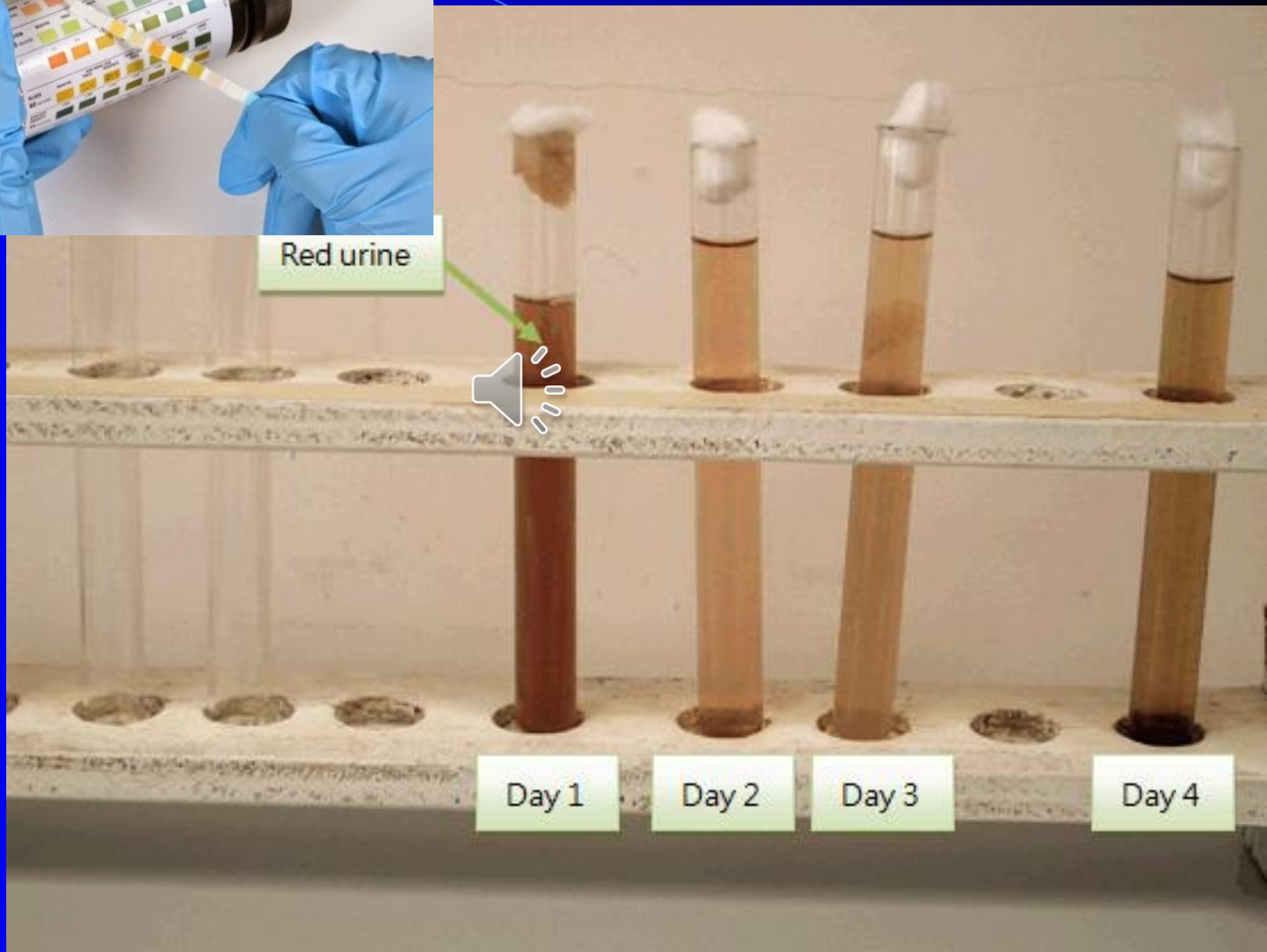
Φυσιολογικό σπείραμα

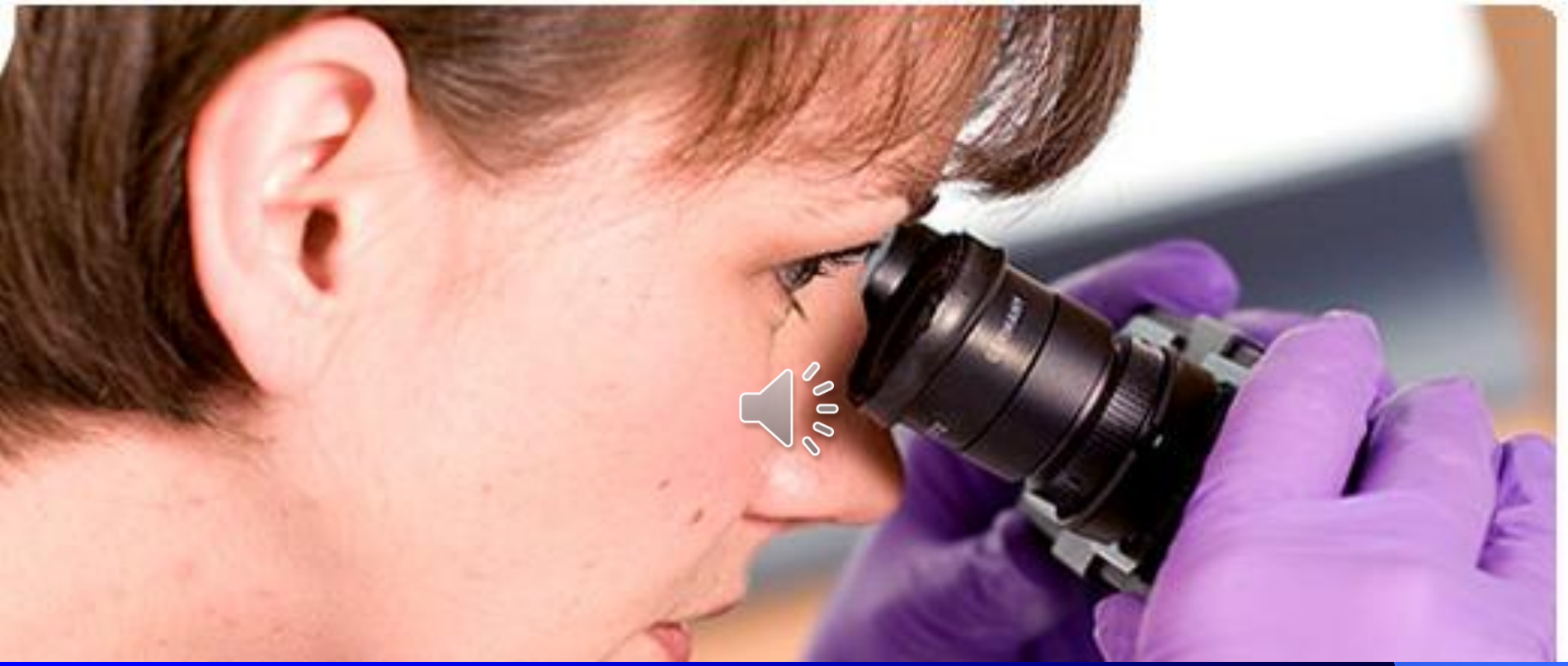



FF
PP

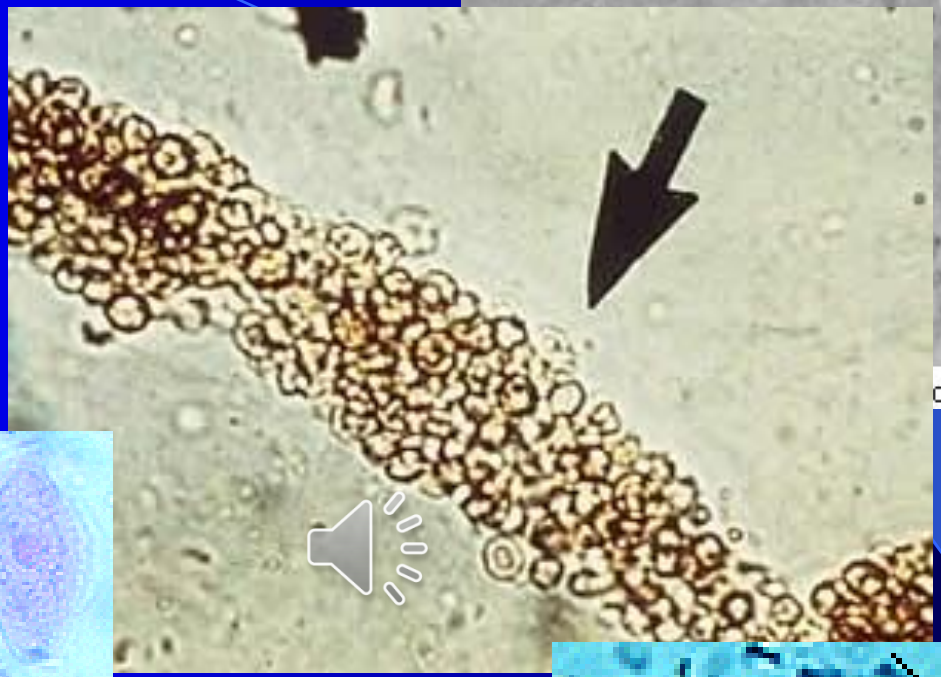

GBM
MF

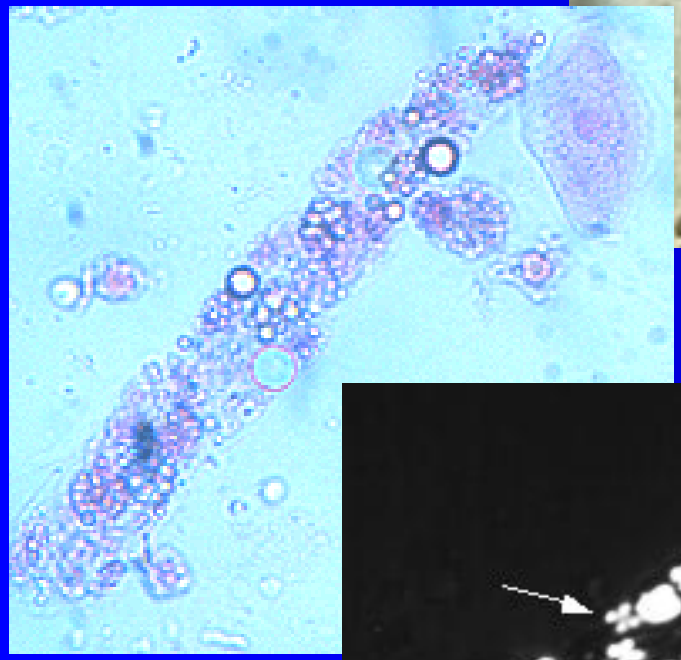

Urinary space
Podocyte
FP
GBM
Albumin
Endothelial cell
Capillary lumen

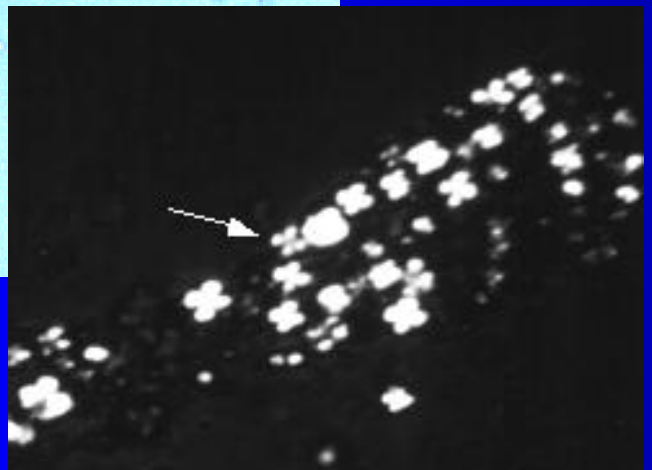

Red urine
Day 1
Day 2
Day 3
Day 4

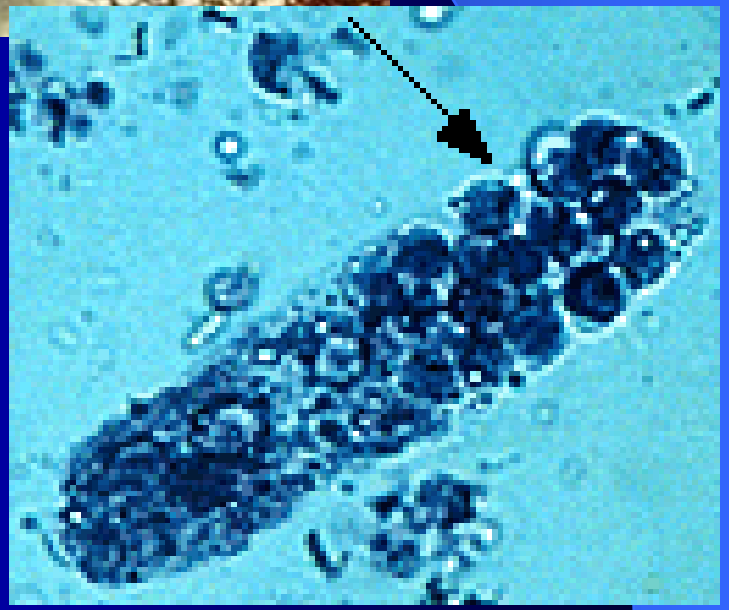


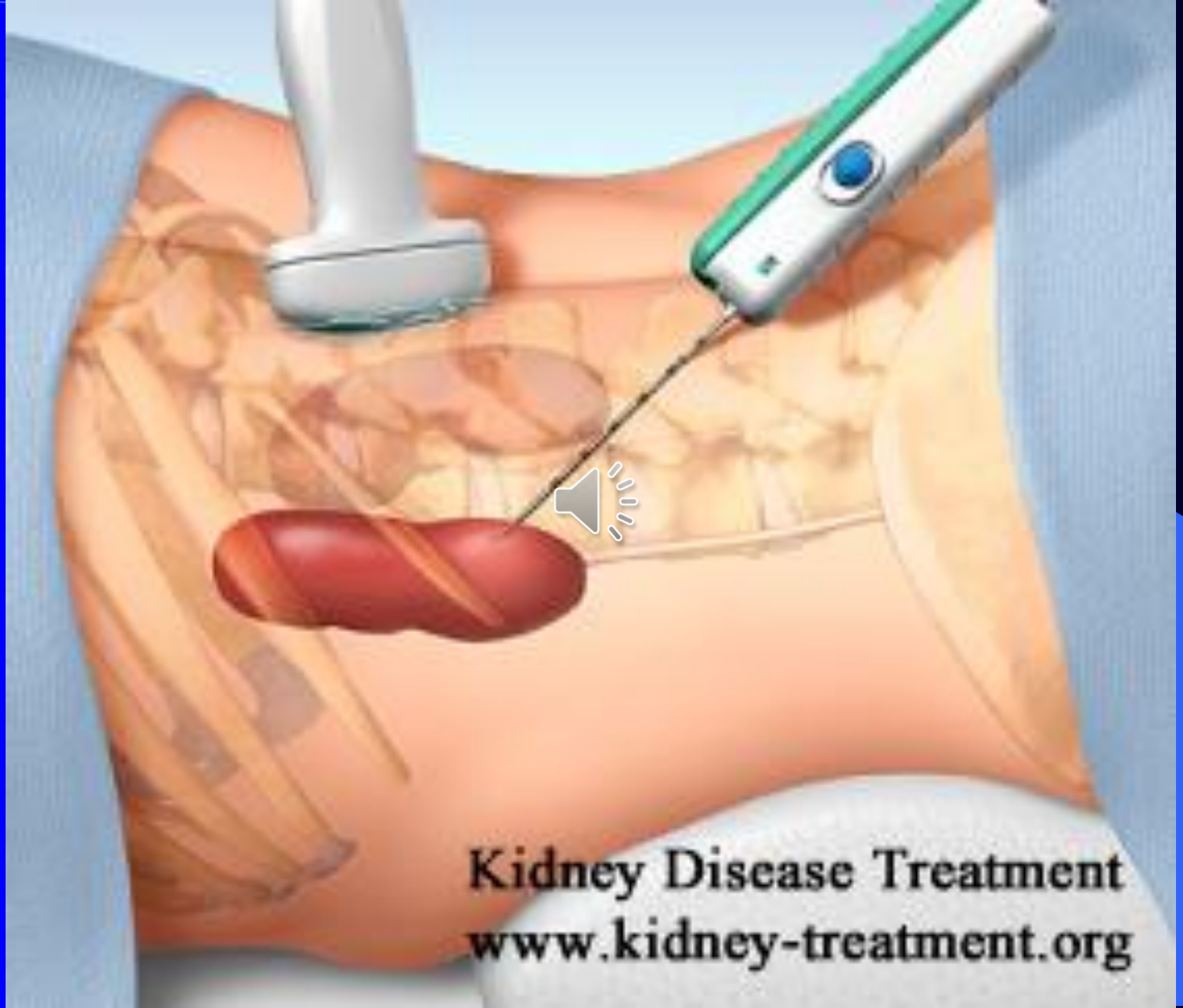

ontrast microscopy










Kidney Disease Treatment
www.kidney-treatment.org

MNEMONIC “ANNURIC”)

A	Asymptomatic hematuria/proteinuria
N	Nephrotic syndrome
N	Nephritic syndrome
U	Urolithiasis
R	Rapidly progressive glomerulonephritis
I	Interstitial and tubular diseases
C	Chronic renal disease

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Asymptomatic Proteinuria

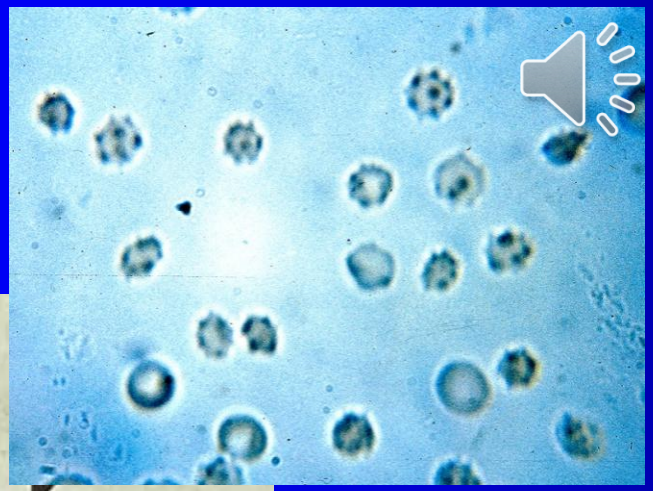
- **Transient Idiopathic**: In children, adolescents, and young adults, otherwise healthy, normal urinalysis. Repeat 2-3 times.
- **Intermittent Idiopathic**: <30 years old and long term prognosis is favorable. Yearly monitoring is recommended.
- **Functional**: Acute illness, fever, CHF, exercise, seizures, pregnancy.

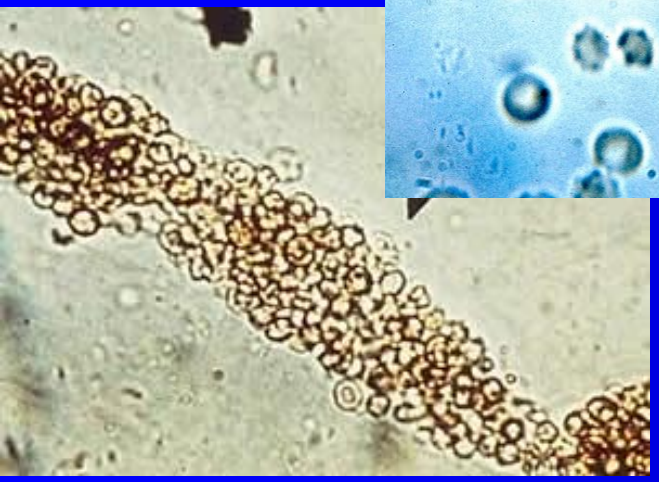
- **Orthostatic** In up to 3-5 % of adolescents and young men; uncommon in patients >30 years old. Do split 24 hour urine collection to diagnose.
- **Persistent Isolated**: Proteinuria that persists at < 3.5 g/24h/1.73 m2 in the absence of other renal or systemic disease. Patients should be followed closely and referred to nephrologist for any change in urinary sediment, worsening proteinuria, or onset of renal insufficiency. Renal biopsy probably indicated.

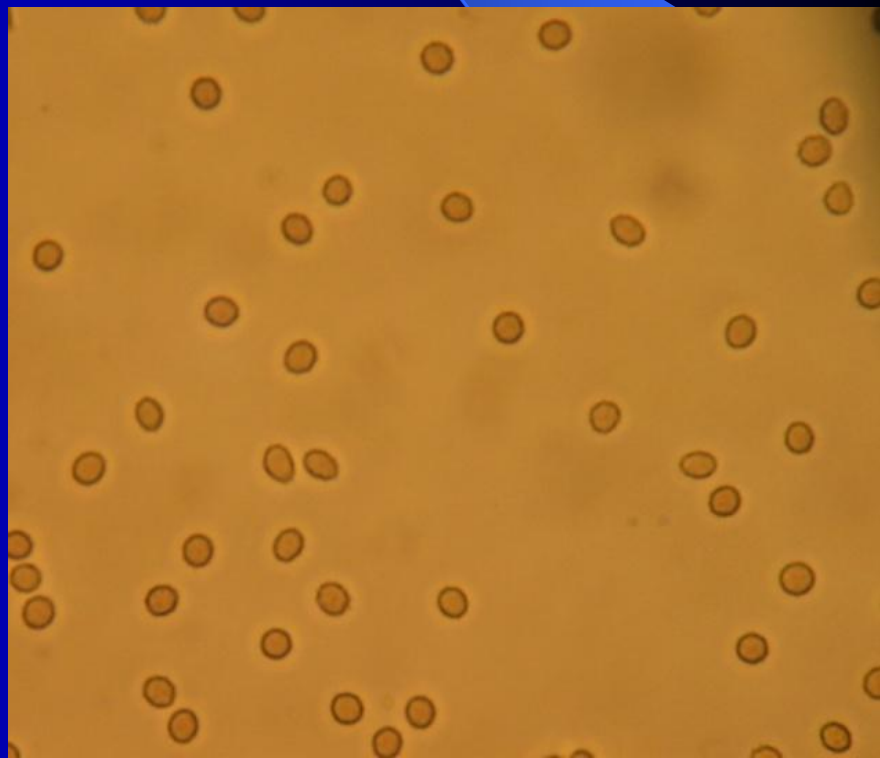
Isolated Microhematuria

<u>Κληρονομικές παθήσεις</u> πχ νόσος λεπτής μεμβράνης, σύνδρομο Alport

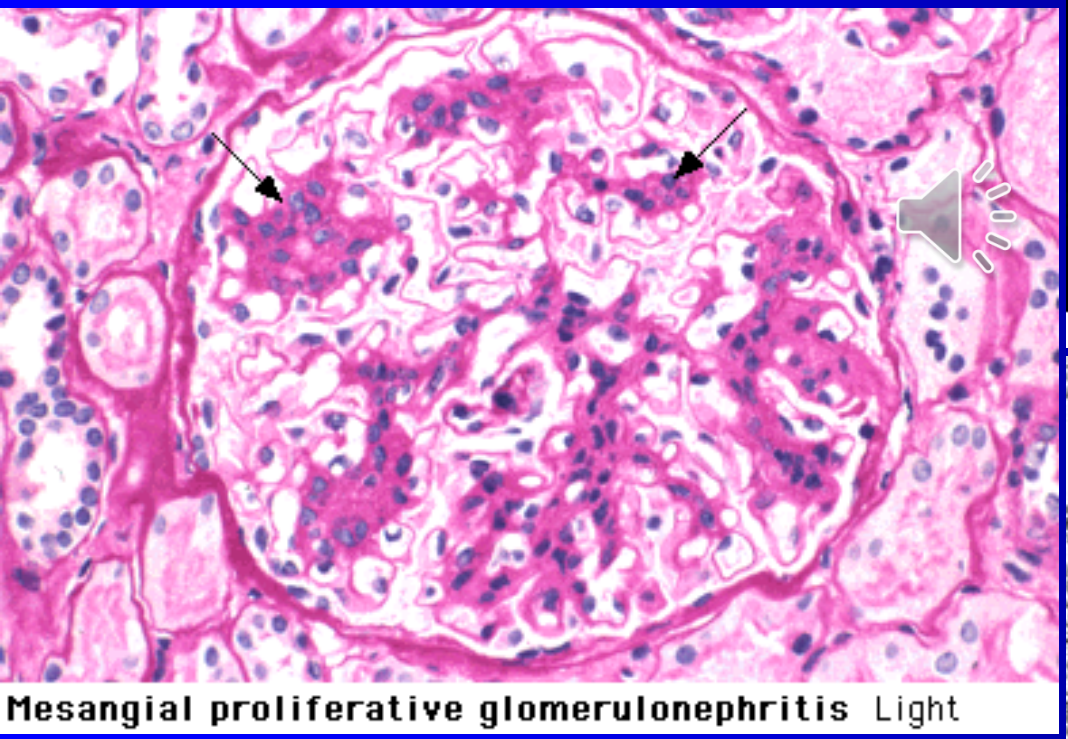
<u>Επίκτητες παθήσεις</u> πχ IgA, Μεσαγγειοϋπερπλαστική ΣΝ,



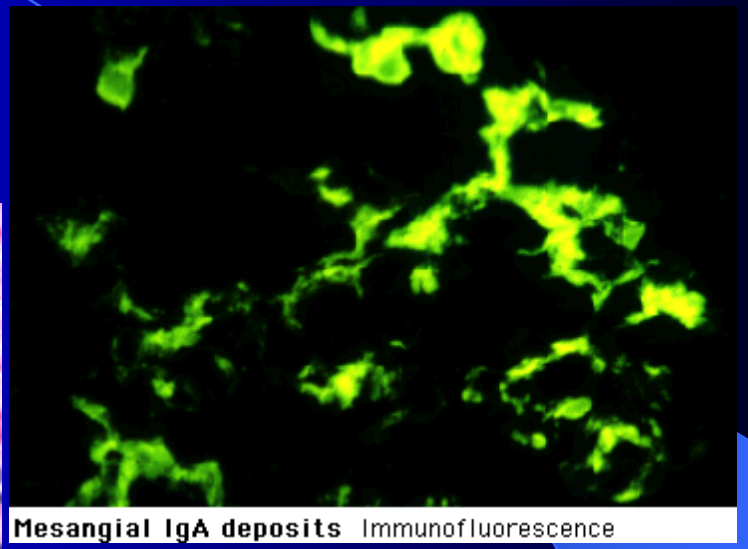




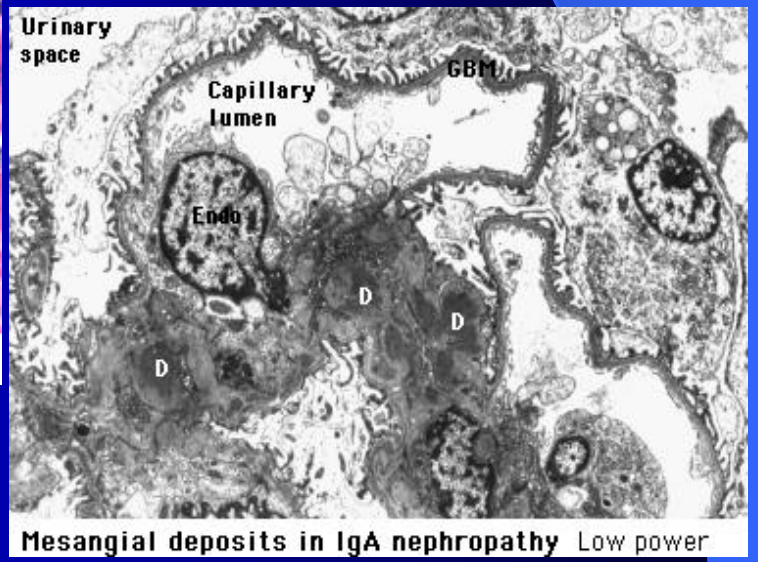
IgA Nephropathy - Berger's Disease



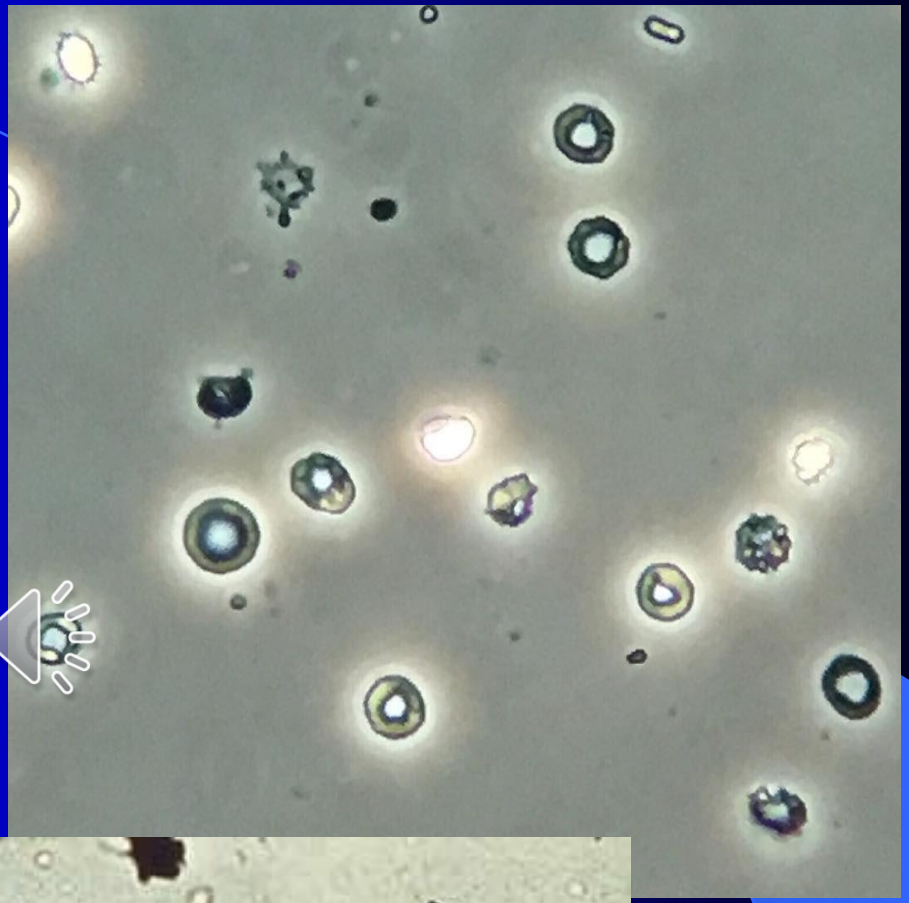
Mesangial proliferative glomerulonephritis Light

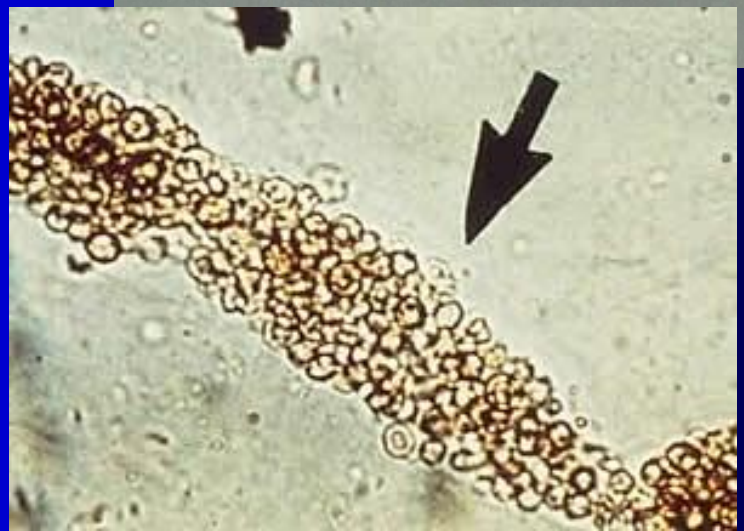


Mesangial IgA deposits Immunofluorescence



Mesangial deposits in IgA nephropathy Low power





IgA NEPHROPATHY (BERGER)

Most common form of GN in young adults (15-30 years)

Pathology: -IgA deposits in mesangium
-varied severity
-IgA is anionic and polymeric IgA,
-poorly O-galactosylated IgA1,
-alterations in IgA1 sialylation.

Protean manifestations

40% asymptomatic microscopic hematuria

40% bouts of macro hematuria

10% nephrotic syndrome

10% renal failure

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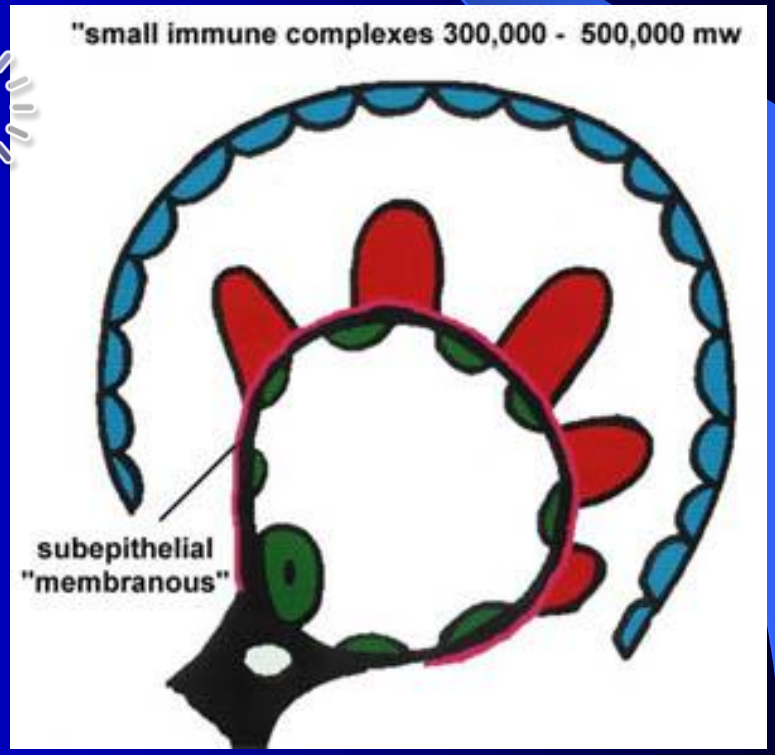
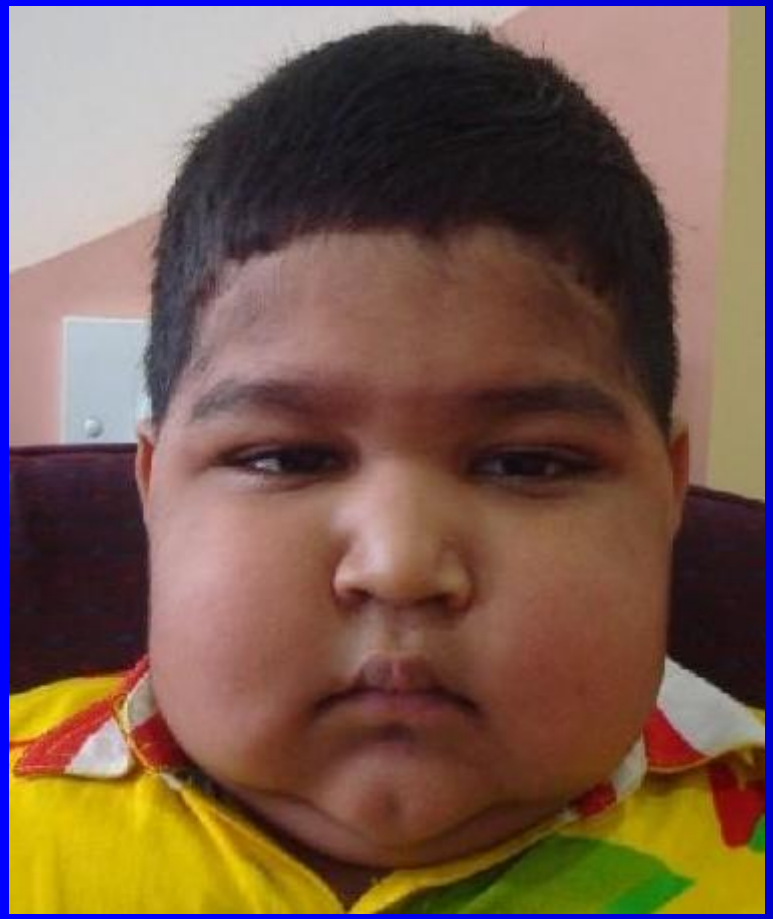
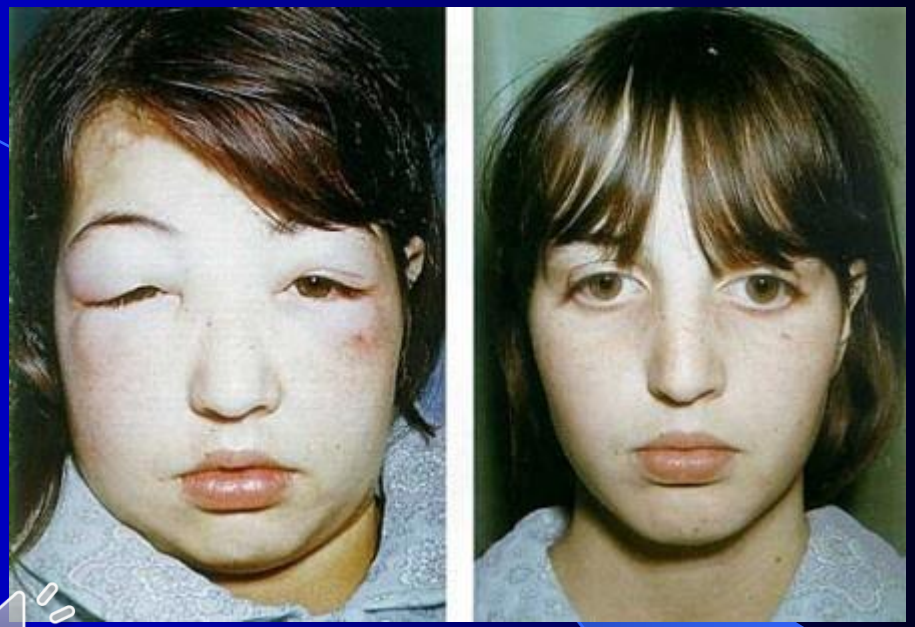
Νεφρωσικό Σύνδρομο

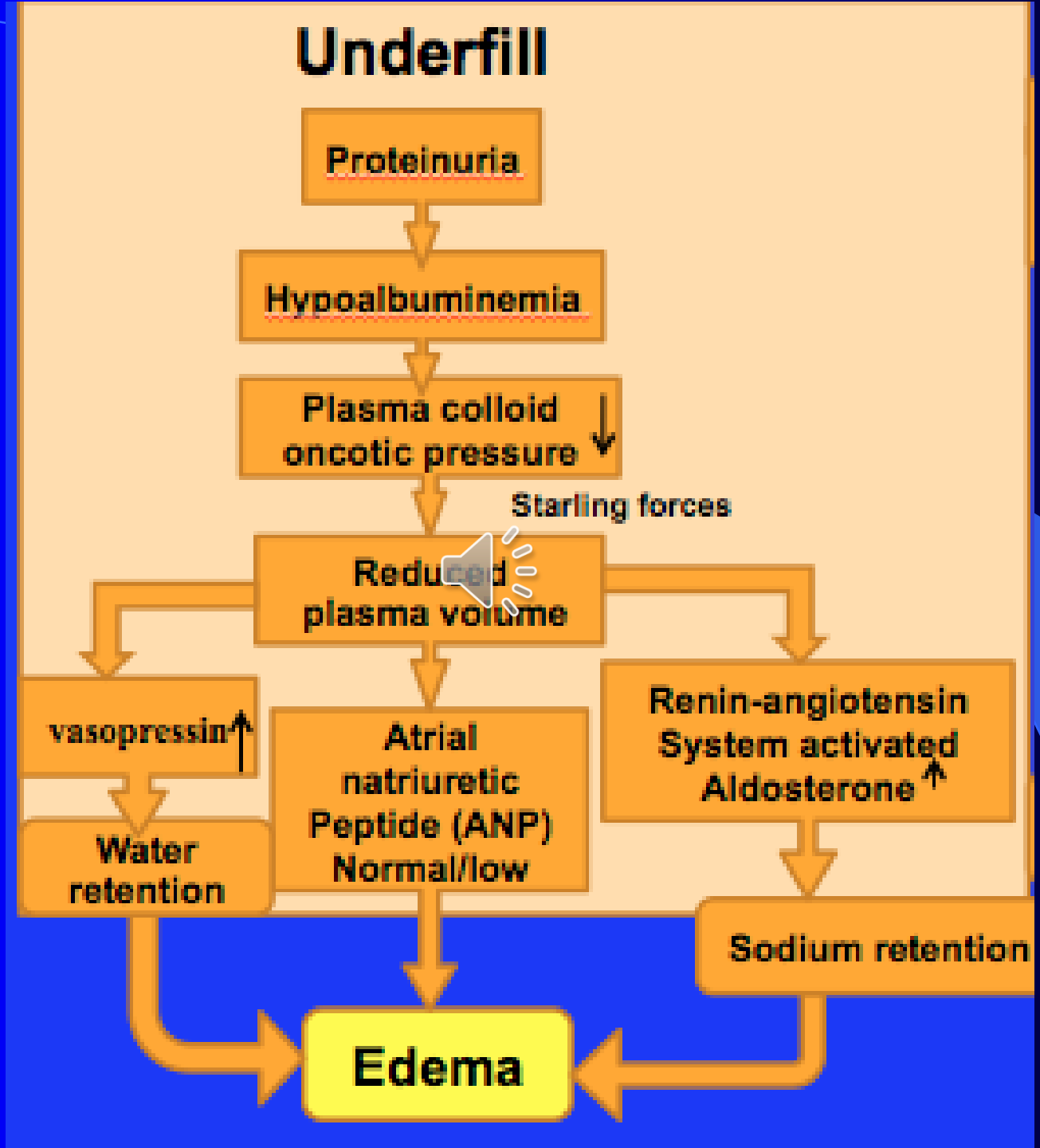
- **Πρωτεϊνουρία > 3g / 24ωρο**
- **Υπολευκωματιναιμία (< 3 g/dl)**
- **Υπερλιπιδαιμία**
- **Λιπιδουρία**
- **Οίδημα**

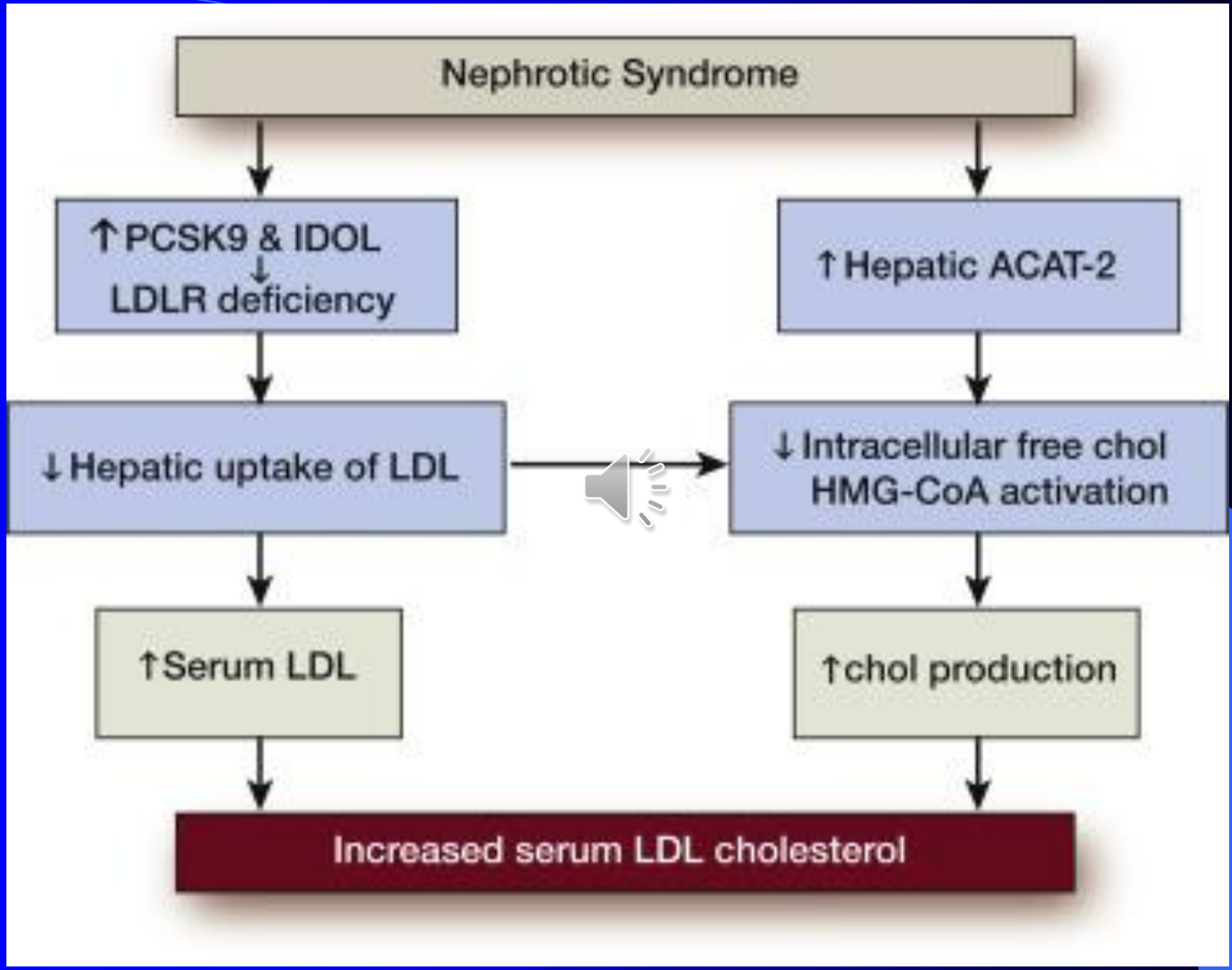




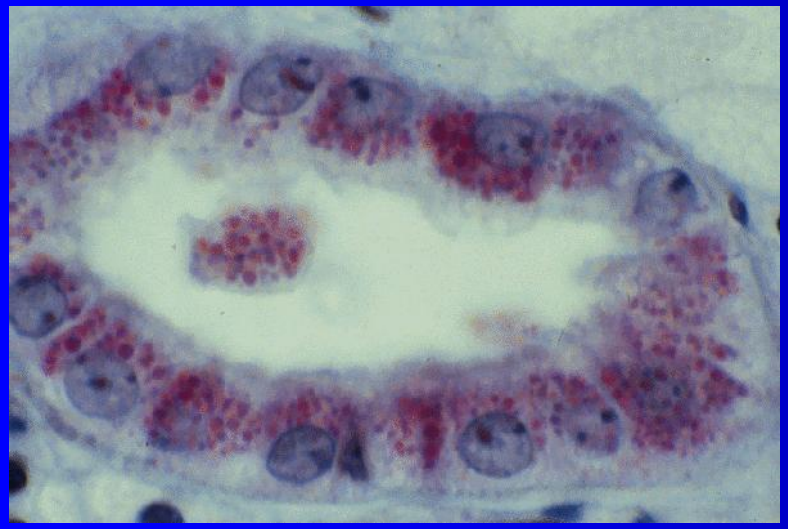


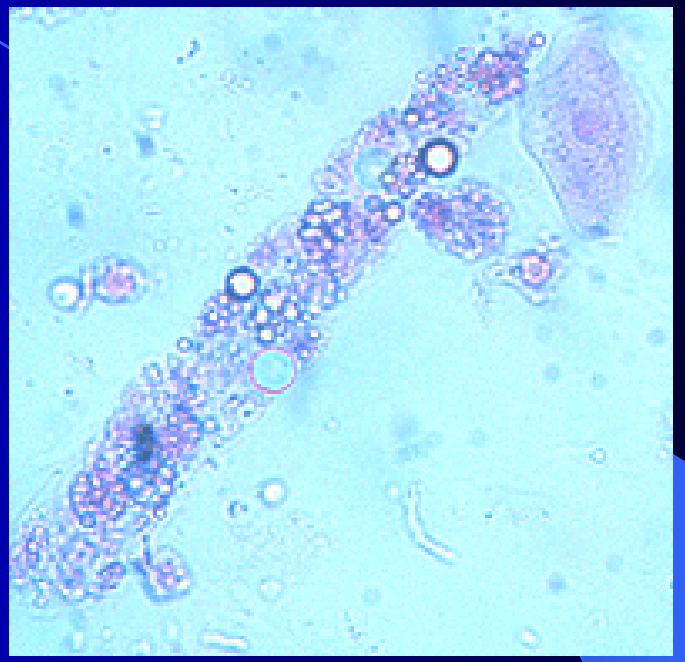
Edema (swelling) of the ankles and feet

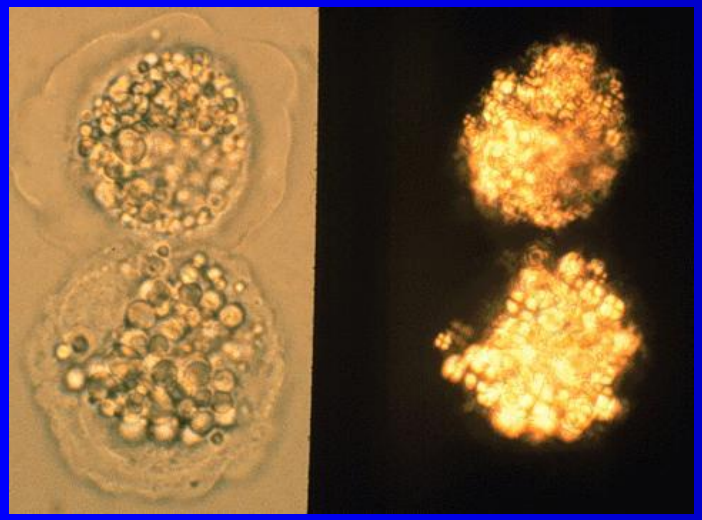

Underfill
Proteinuria
Hypoalbuminemia
Plasma colloid oncotic pressure
Starling forces
Reduced plasma volume
vasopressin
Atrial natriuretic Peptide (ANP) Normal/low
Renin-angiotensin System activated Aldosterone
Water retention
Sodium retention
Edema

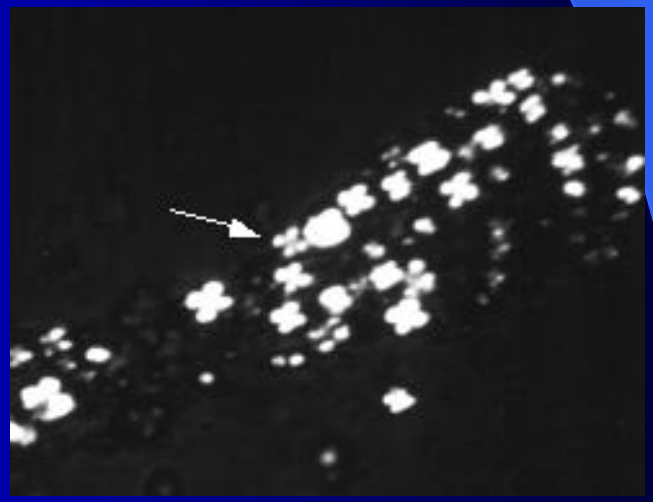

Nephrotic Syndrome
↑PCSK9 & IDOL
↓
LDLR deficiency
↑Hepatic ACAT-2
↓Hepatic uptake of LDL
↓Intracellular free chol
HMG-CoA activation
↑Serum LDL
↑chol production
Increased serum LDL cholesterol

ΙΖΗΜΑ ΟΥΡΩΝ ΣΕ ΝΕΦΡΩΣΙΚΟ ΣΥΝΔΡΟΜΟ









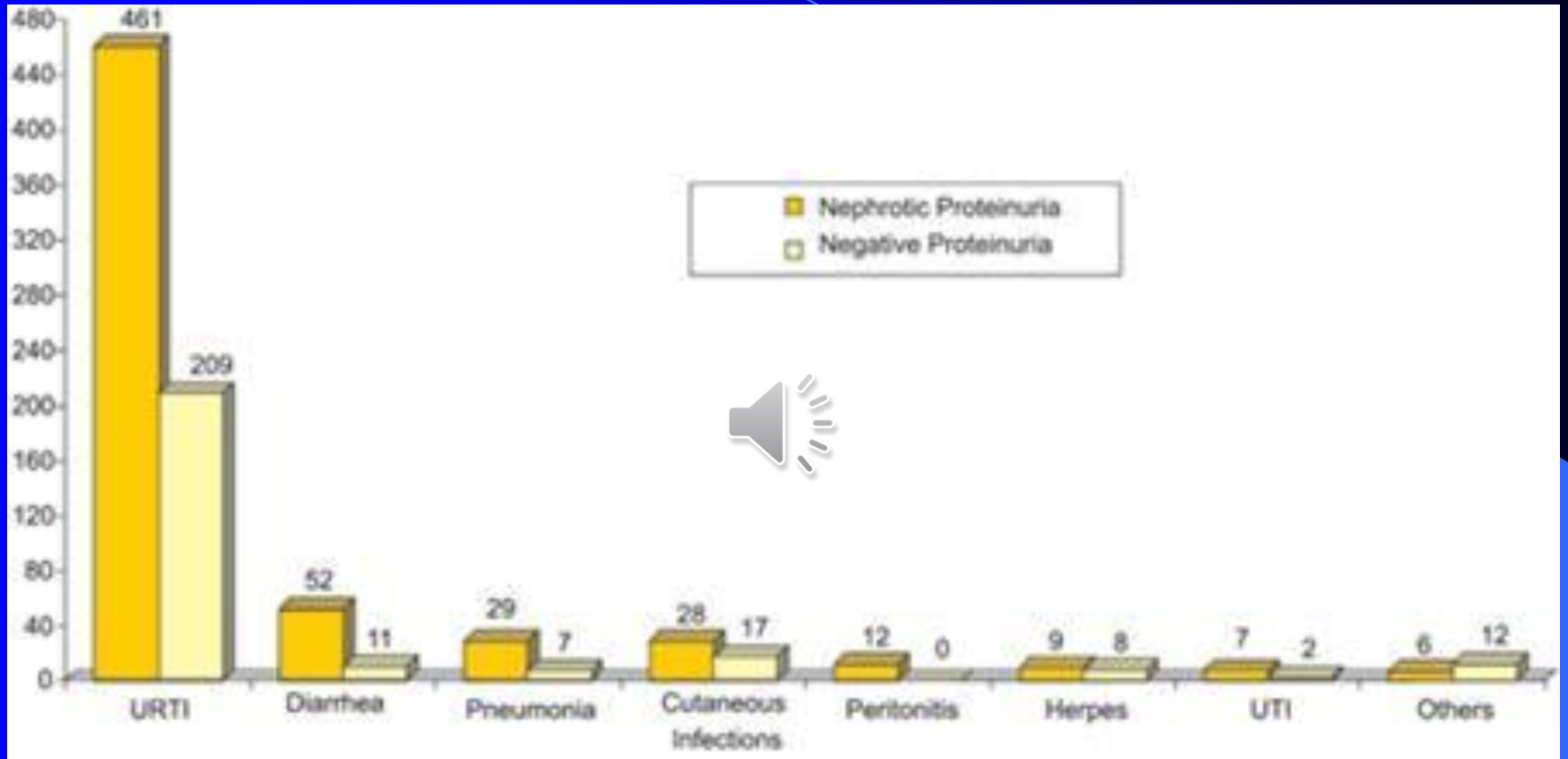
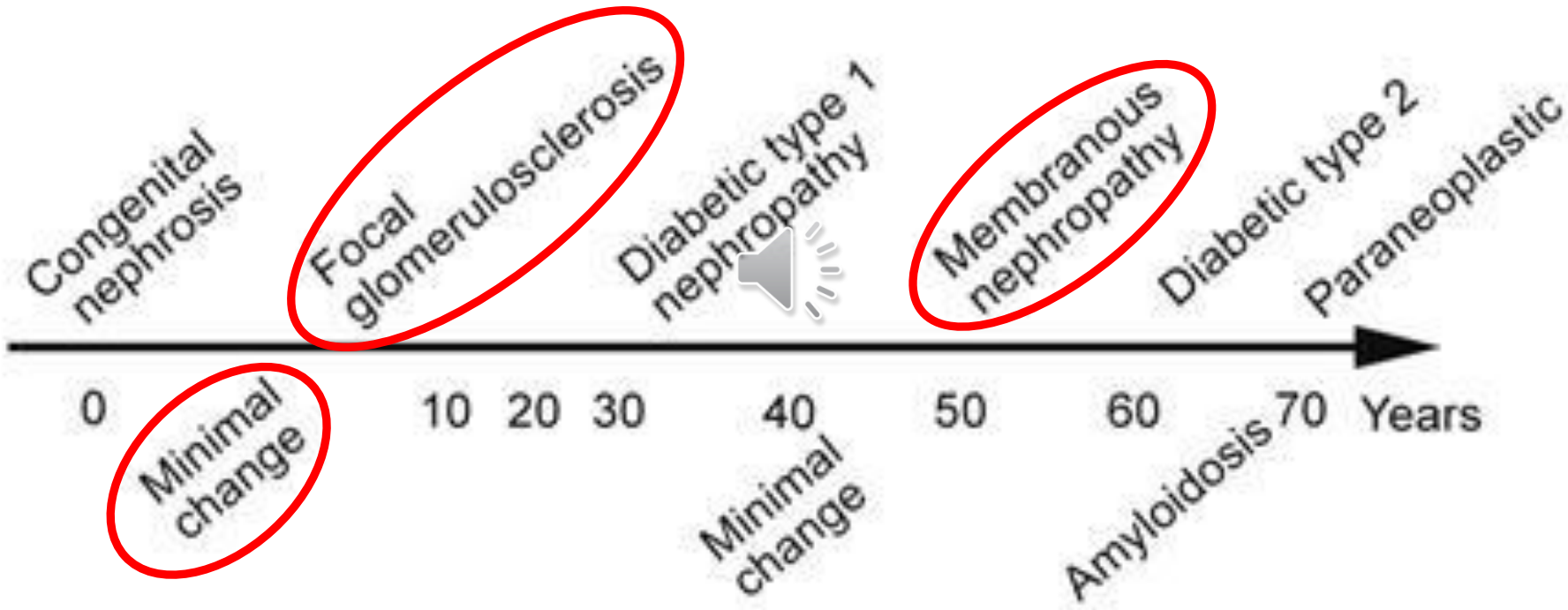


Figure 1 - Number and type of infection of 92 patients during the period with nephrotic proteinuria (604 infections/1140 months) and of the 89 patients during the period with negative proteinuria (266 infections /6822 months).

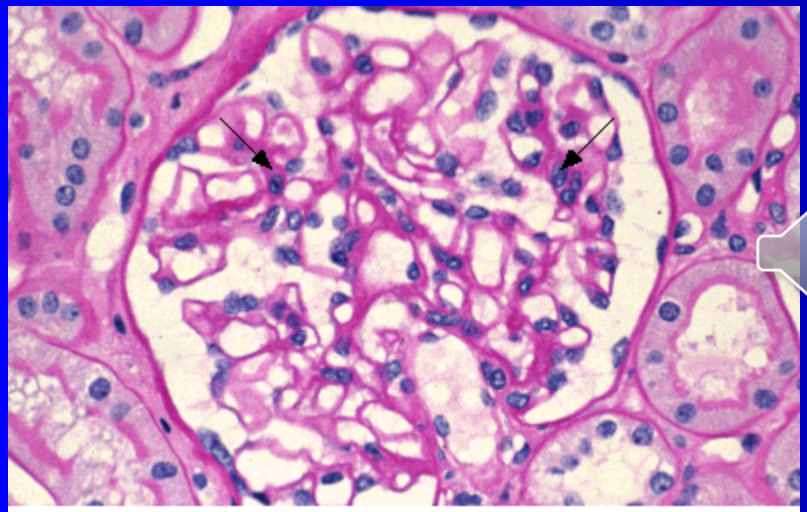
Hypercoagulation in NS

Low zymogen factos: factos Ⅸ, factor Ⅺ
Increased procoagulatory cofactors. factor Ⅴ, factor Ⅷ
Increased fibrinogen levels
Decreased coagularion inhibitors: antithrombin Ⅲ (bur protein C and Protein S increased)
Altered fibrinolytic system (a2-antipiasmin increased, plasmingoen decreased)
Increased platelet reactivity
Thrombocytosis
Increased release reaction *in vitro* (adenosine diphosphate: thrombin, collagen, arachidonic acid, epinephrine)
Increased factor Ⅳ and b-thromboglobulin *in vivo*
Altered endothelial-cell function

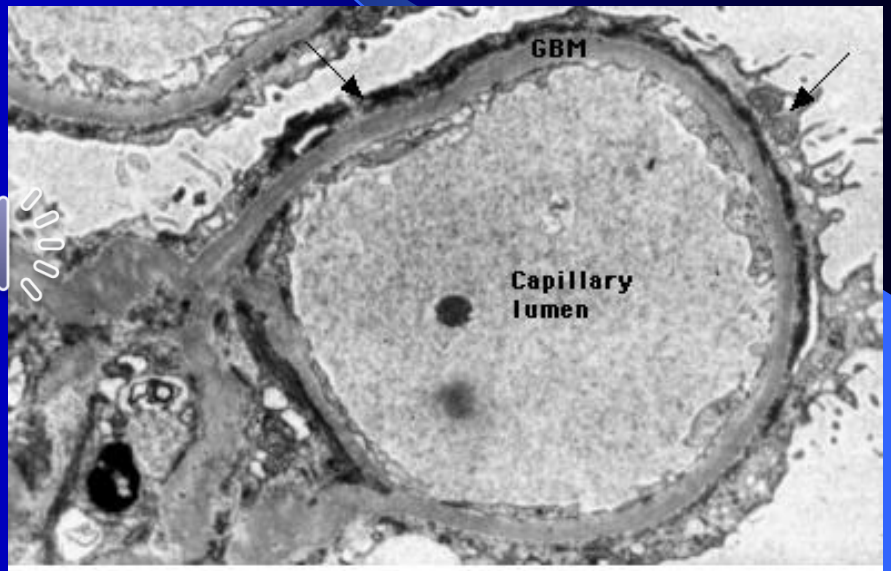
average ages of types of nephrotic syndrome



Νόσος Ελαχίστων Αλλοιώσεων



Minimal change disease Light micrograph of an essentially normal glomerulus in minimal change disease. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary walls is normal, and there is neither expansion nor hypercellularity in the mesangial areas in the central or stalk regions of the tuft (arrows). Courtesy of Helmut G Rennke.



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

MINIMAL CHANGE GLOMERULOPATHY

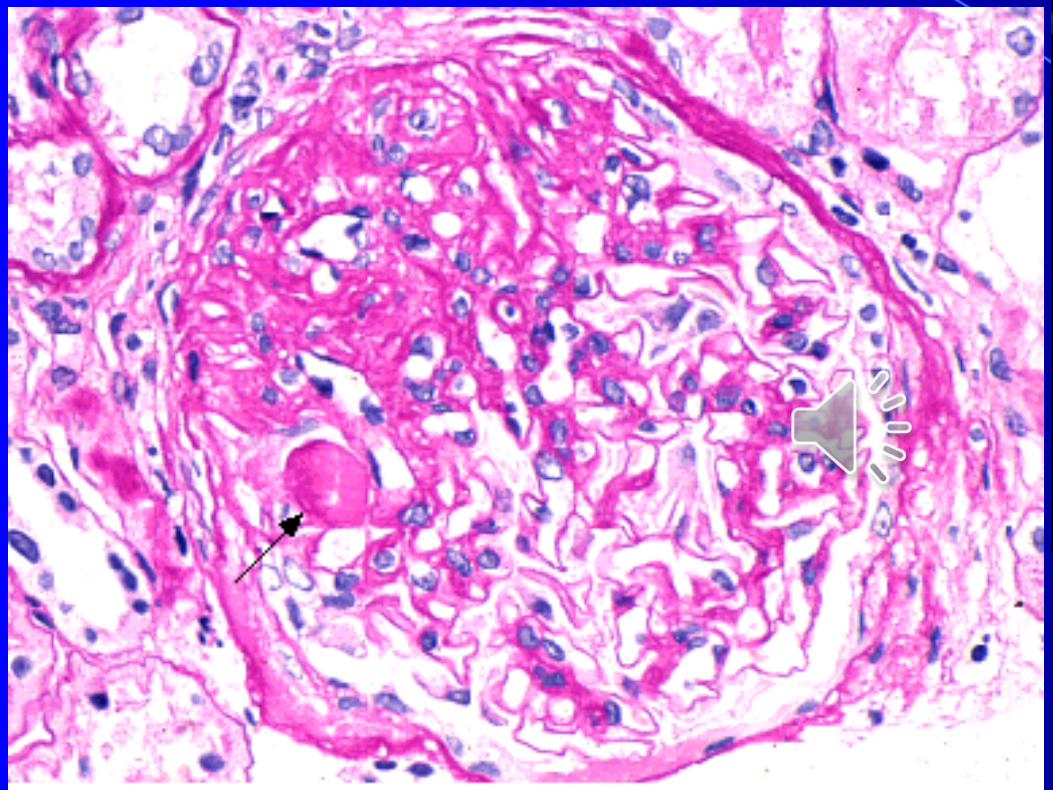
CL: Most common cause of nephrotic syndrome in children

E/P: Remission can be induced by measles, occurs more frequently in Hodgkin lymphoma, cured by glucocorticoids, cyclophosphamide or retuximab, the permeability factor seems to be **IL-13**.

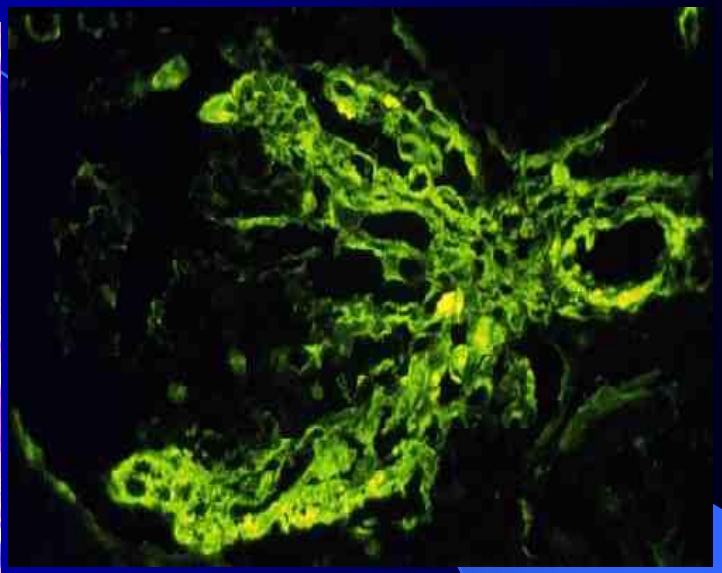
Path: normal by LM and IF

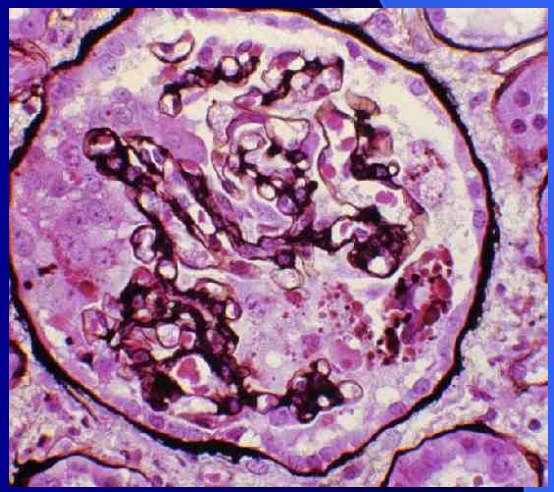
EM: fusion of foot processes

ΕΣΤΙΑΚΗ ΣΠΕΙΡΑΜΑΤΟΣΚΛΗΡΥΝΣΗ



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





FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Def: 15% of all nephrotic syndromes; heterogenous group of diseases (primary vs secondary)

E/P: Increased circulating levels of soluble urokinase receptor (**suPAR**). In HIV, IV drug abuse, CHD, obesity, sickle-cell disease

Path: focal and segmental glomerular hyalinosis

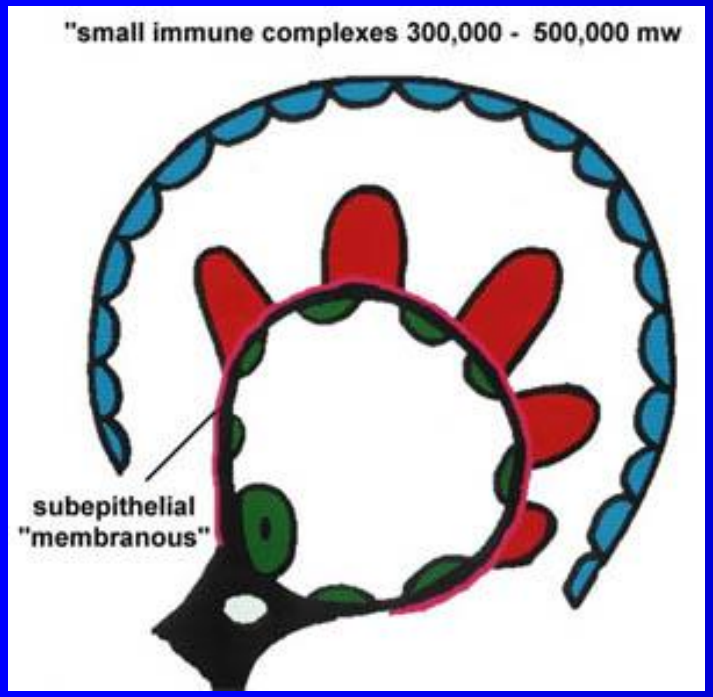
"Collapsing" pattern (e.g. HIV)

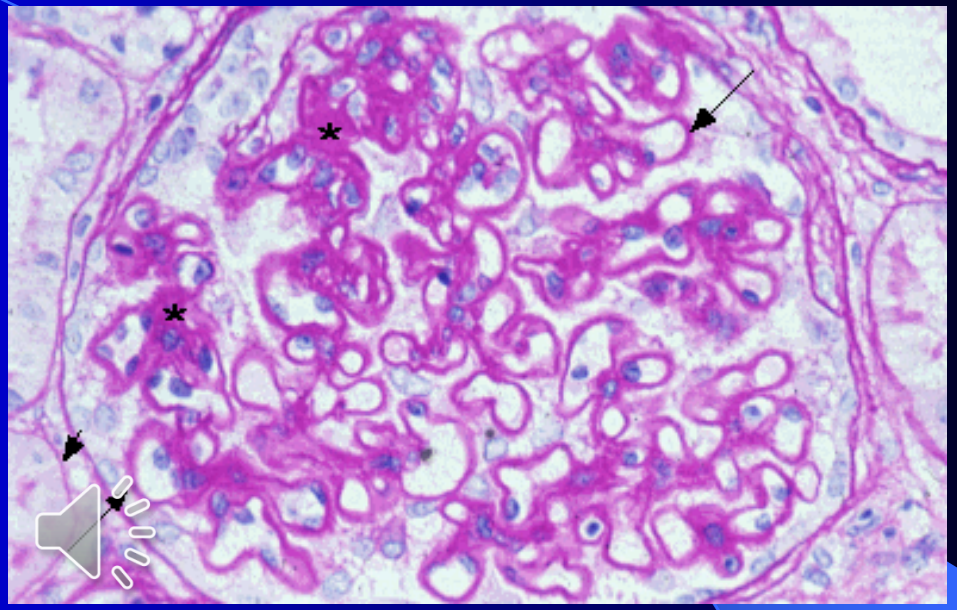
Trapping of serum proteins (IF and EM)

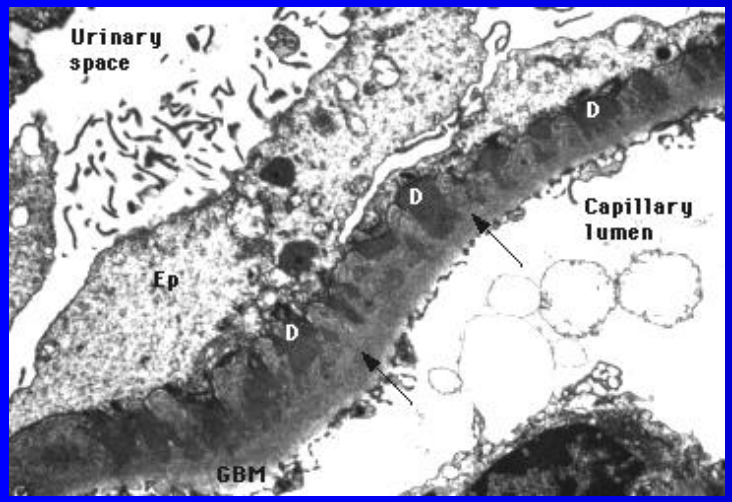
Clin: Nephrotic syndrome→ESRD (5-20y); In HIV related FSGS → ESRD (1 year)

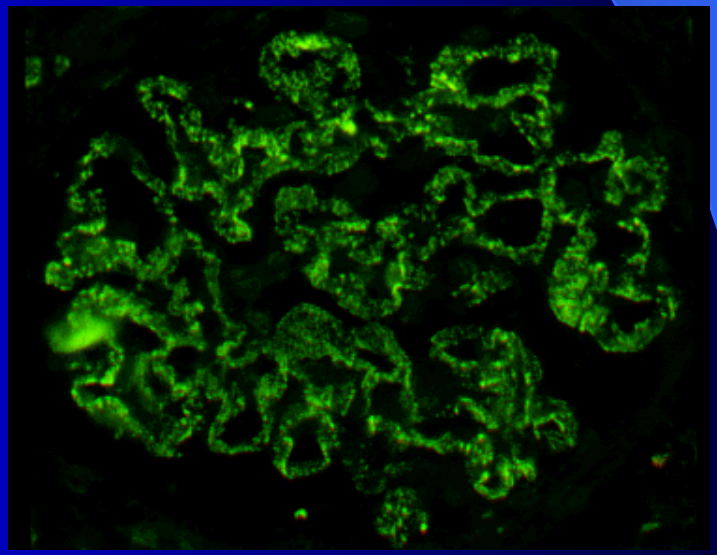
Therapy: Glycocorticosteroids +/- calcineurin inhibitors

ΜΕΜΒΡΑΝΩΔΗΣ ΣΠΕΙΡΑΜΑΤΟΠΑΘΕΙΑ









MEMBRANOUS NEPHROPATHY

Def: Most common cause of nephrotic syndrome in adults (40%)

M-Type **Phospholipase A_2 Receptor** as Target Antigen in Idiopathic Membranous Nephropathy -> Immune complex→BM thickening

E/P: Primary

Secondary (SLE, HBV, drugs, cancer)

Path: Subepithelial deposits of immune complex

CL: Nephrotic syndrome

(25% recover, 50% persist, 25% progress)

Therapy: Glycocorticoids and cytotoxic therapy

Αίτια Μεμβρανώδους Σπειραματοπάθειας

Major Causes of Membranous Nephropathy

Idiopathic, may represent autoantibody against glomerular epithelial cell antigens
Malignancy, primarily solid tumors
Systemic lupus erythematosus
Rheumatoid arthritis
Drugs:
- Penicillamine
- Gold
- Tiopronin

Hepatitis B virus
Syphilis – congenital and secondary
Chronic renal transplant rejection
Hepatitis C virus
Hepatosplenic schistosomiasis
Other glomerular diseases
Rare:
- Sarcoidosis
- Captopril
- Formaldehyde

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N	Nephritic syndrome
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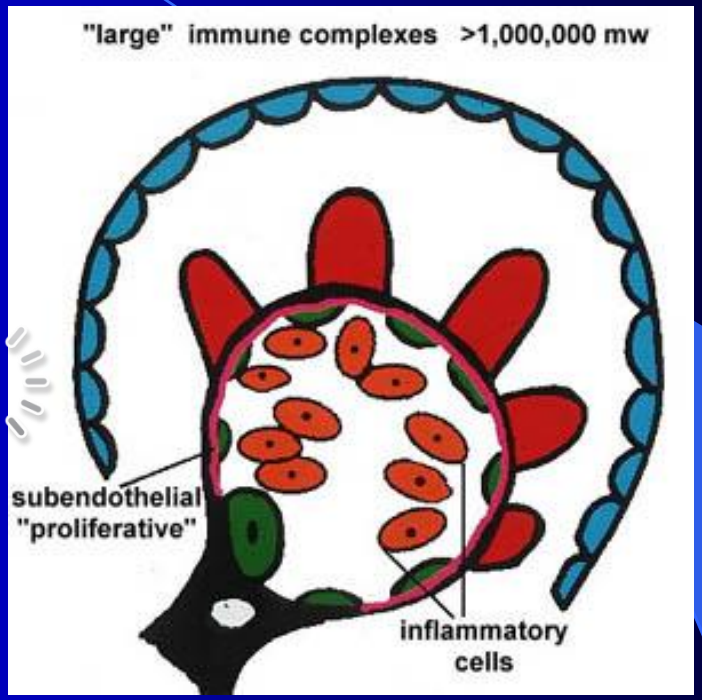
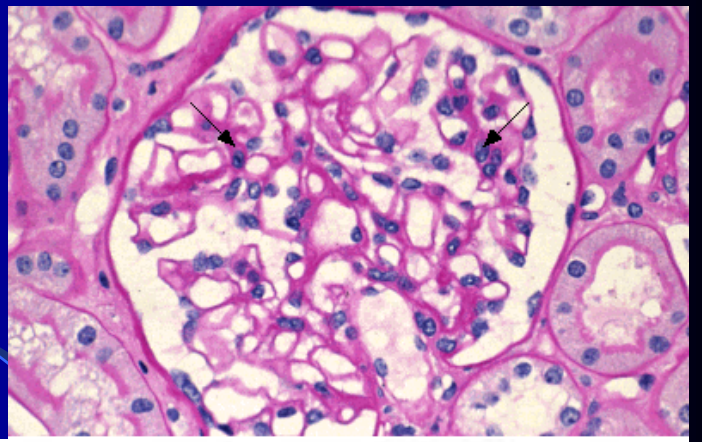
I	Interstitial and tubular diseases
C	Chronic renal disease

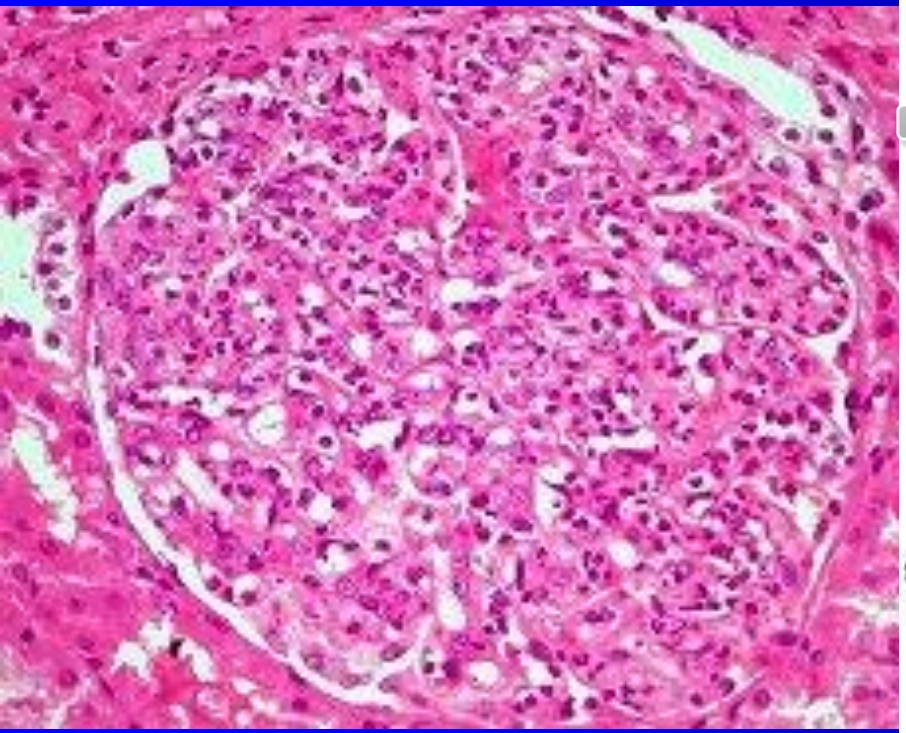
Νεφριτιδικό Σύνδρομο

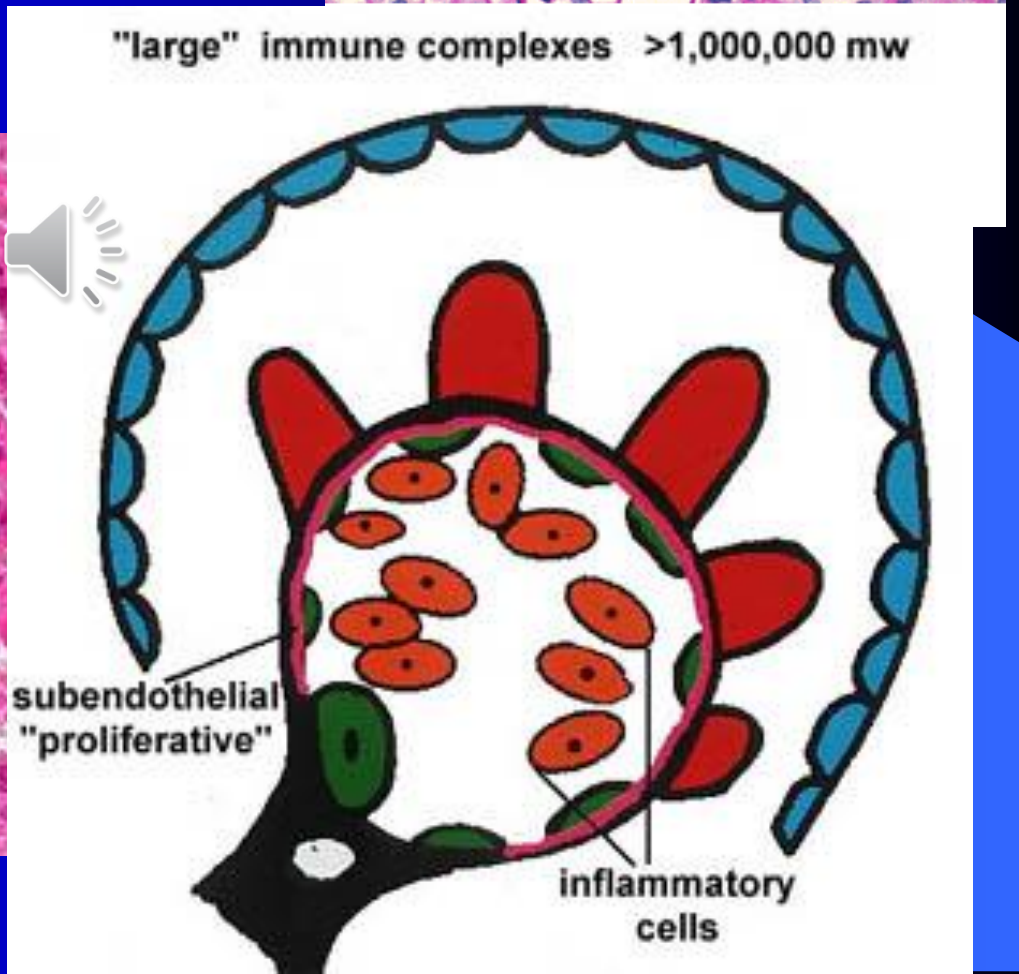
- Αιματουρία
- Πρωτεϊνουρία
- Ολιγοανουρία
- Ουραιμία
- Οίδημα
- Υπέρταση
- Καρδιακή Κάμψη - Πνευμονικό Οίδημα



Υπερπλαστική Σπειραματονεφρίτιδα (μεταλοιμώδης ΣΝ)







ACUTE POSTINFECTIOUS GN

Def: Acute nephritic syndrome 1-2 weeks after infection

E/P: immune response to A β-hemolytic streptococci

(other infections Staph, malaria, HBV less common)

Path: Acute glomerulonephritis

Clin: Childhood nephritic syndrome

90% recover

9% presistent hematuria/proteiru

1% chronic renal disease

MNEMONIC “ANNURIC”)

A Asymptomatic hematuria/proteinuria

N Nephrotic syndrome

N Nephritic syndrome

U Urolithiasis

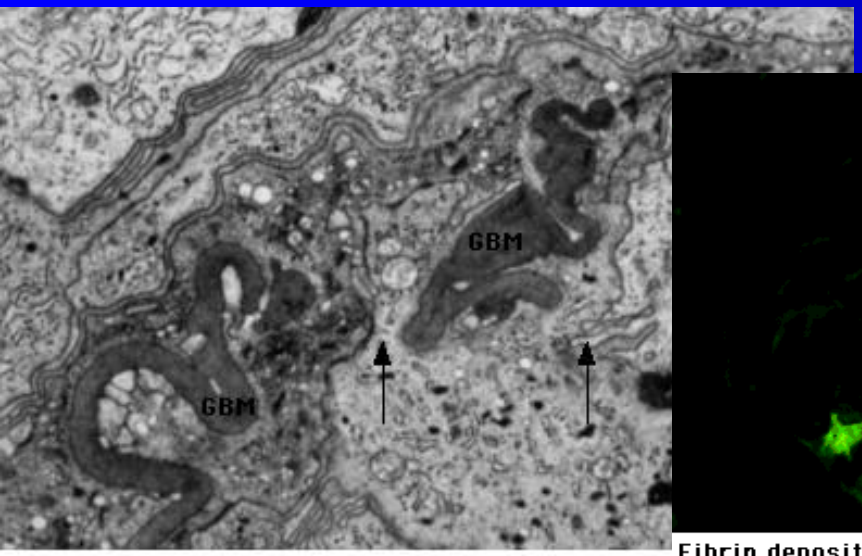
R Rapidly progressive glomerulonephritis

I Interstitial and tubular diseases

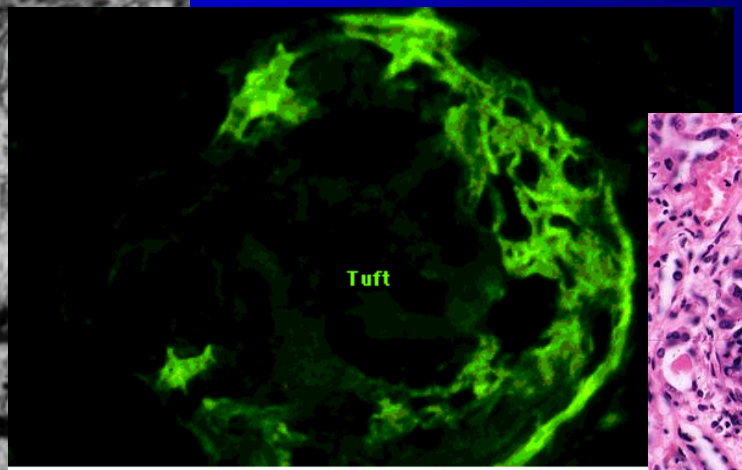
C Chronic renal disease

Ταχέως εξελεισσόμενη ΣΝ
Rapidly Progressive GN

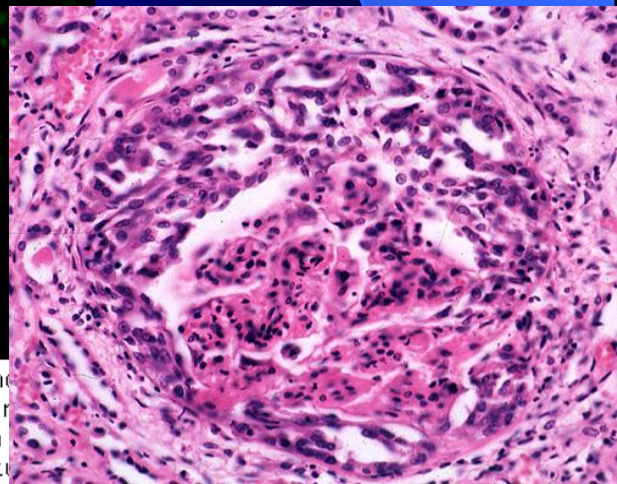
(RPGN) is a clinical syndrome manifested by features of glomerular disease in the urine and by progressive loss of renal function over a comparatively short period of time (days, weeks or months).



Rapidly progressive glomerulonephritis El
micrograph in RPGN showing characteristic brea
glomerular basement membrane (GBM) (arrows).



Fibrin deposition in crescents Immunofluorescen
microscopy showing intense deposition (bright areas i
upper right portion of the glomerulus) of fibrin within
circumferential crescent surrounding the glomerular t



Ταχέως Εξελισσόμενη Σπειραματονεφρίτις

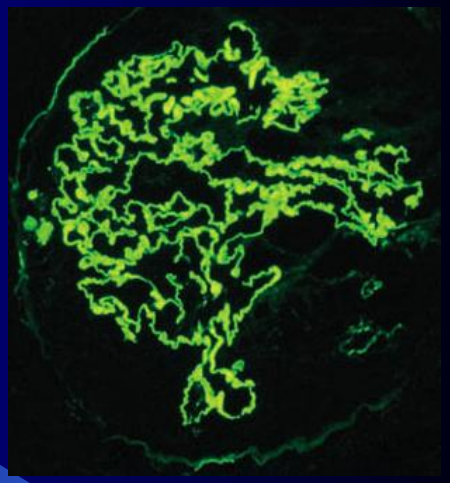
- ***Anti-GBM Disease*** (Type 1)

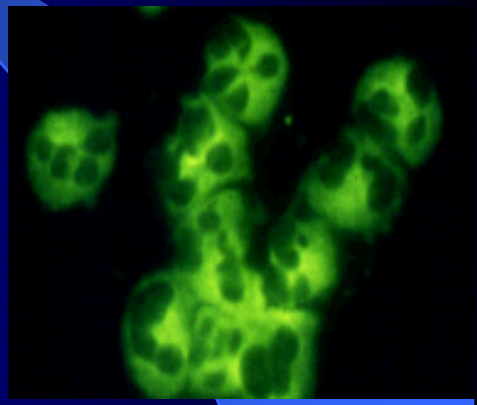
Immune Complex diseases *(Type 2)*

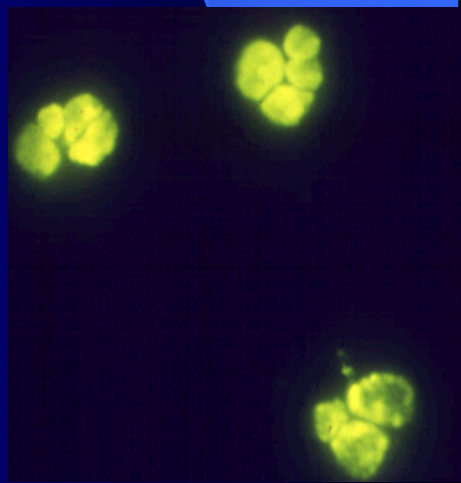
- Systemic Lupus Erythematosus (WHO Class III and IV)
- Infectious Endocarditis
- HCV-associated cryoglobulinemia

Pauci-immune complex diseases (Type 3)

- ANCA related (Microscopic polyarteritis, Wegener's Granulomatosis),
- Henoch Schoenlein Purpura
- Thrombotic Thrombocytopenic Purpura /Hemolytic Uremic Syndrome







ANTI-GBM ANTIBODY GN

RPGN mediated by antibody

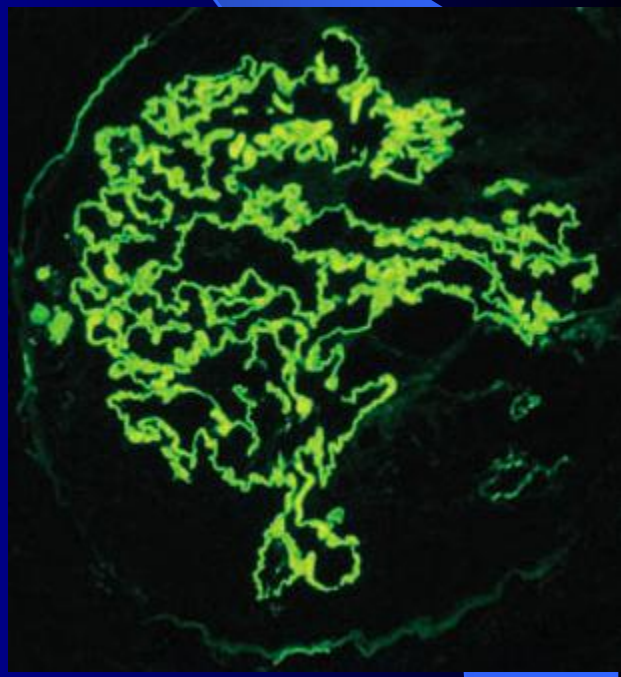
Antibody to collagen IV

Linear IF

Fibrinoid necrosis of GBM

Crescentic GN

Goodpasture syndrome

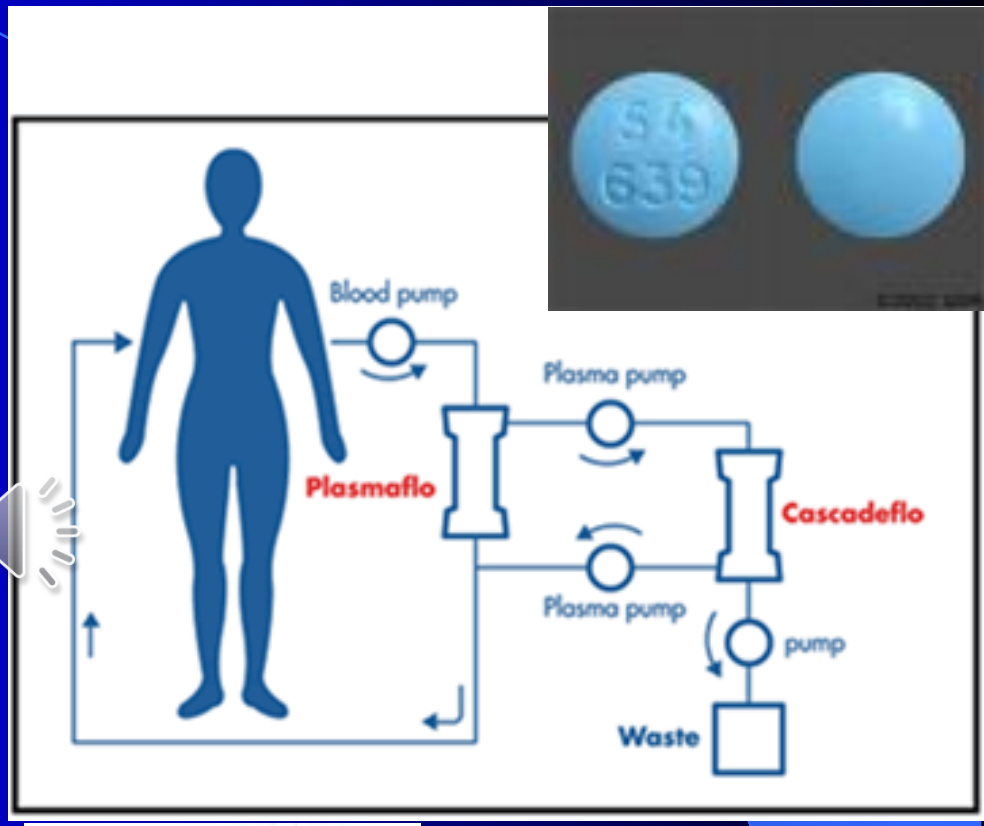


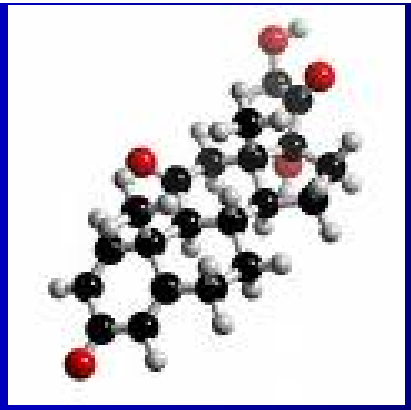
Pulmonary Involvement

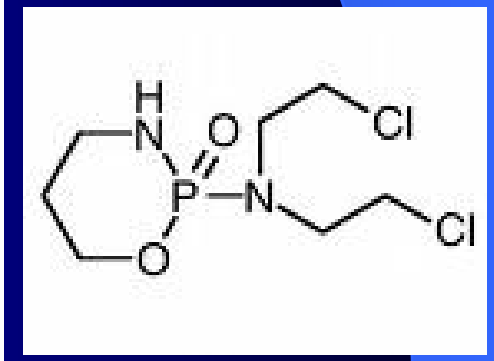
- Circulating anti-GBM antibodies must have access to the alveolar basement membrane to do damage.
- Underlying pulmonary injury:
- Smoking
- Infection
- Cocaine inhalation
- Hydrocarbon exposure

Treatment of Choice

- Early diagnosis and treatment
- Plasmapheresis + Prednisone + Cyclophosphamide
  - Plasmapheresis removes circulating anti-GBM antibodies and other mediators of inflammation (such as complement),
  - immunosuppressive agents minimize new antibody formation.





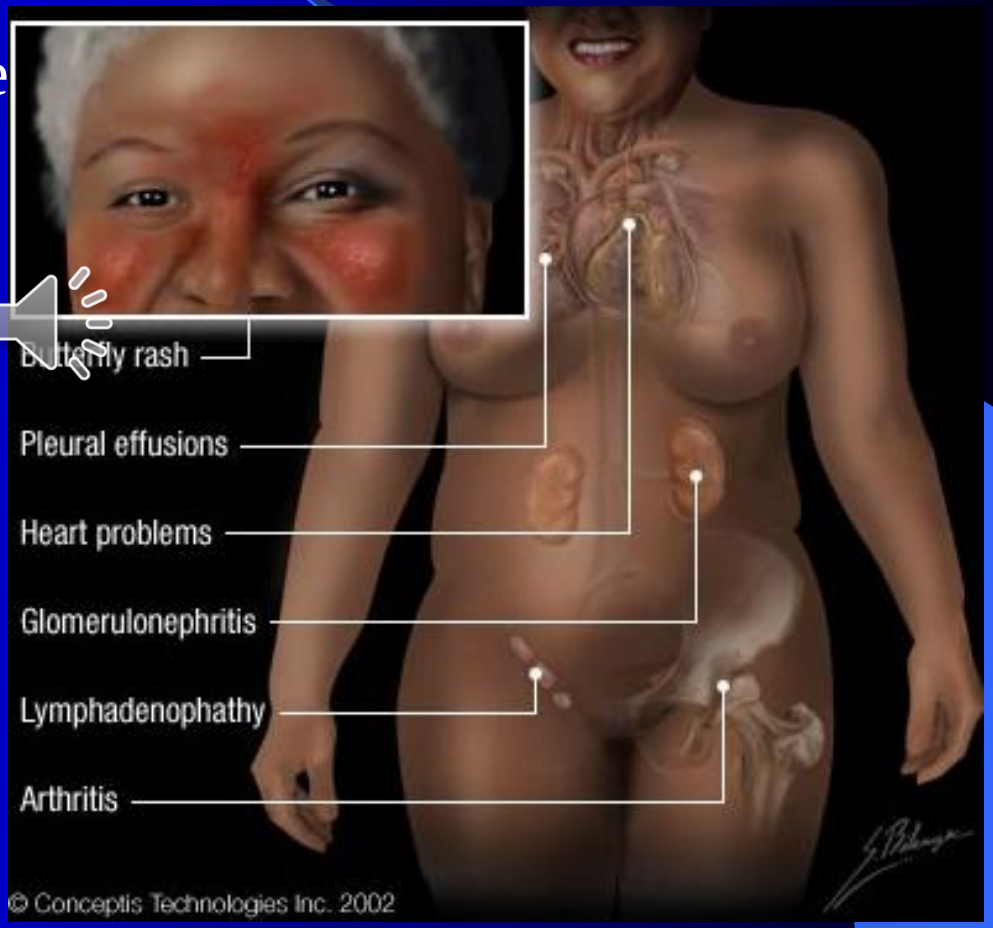


Prognosis

- If treated:
  - ~40 to 45 percent of patients will benefit by not progressing to end-stage renal disease or death
  - Recovery is more likely when treatment begins before oliguria.
- However, in those who require dialysis or who have 75 - 100 percent crescents on biopsy, recovery is rare regardless of treatment.

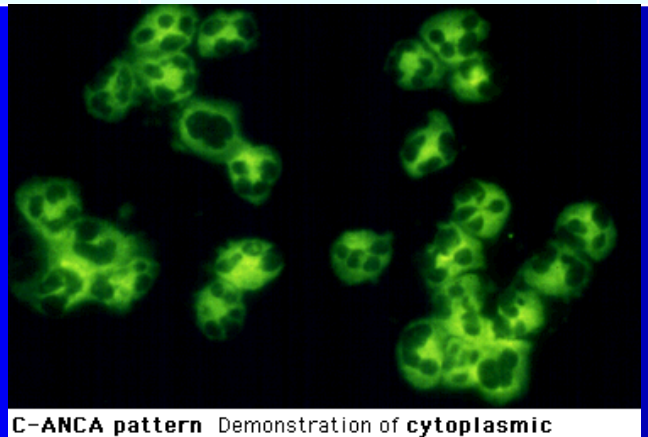
Clinical manifestations of SLE

- Variable: from mild to life threatening
- Onset: gradual (more common) or acute
- Remitting-relapsing course
- Kidney is the most common major organ involved (lupus nephritis)

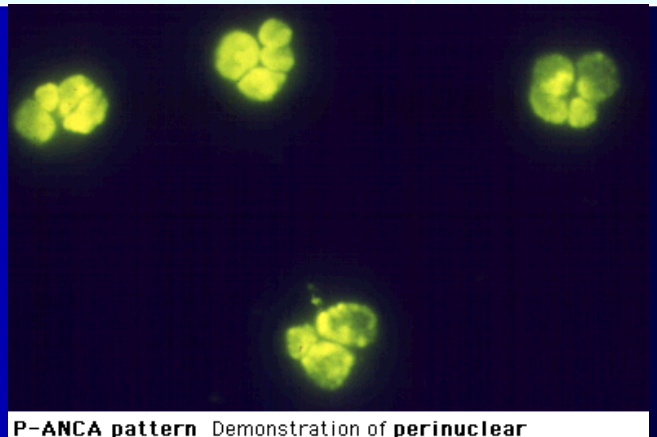


Anti-neutrophil cytoplasmic autoantibodies

	Proteinase 3 (PR3/c-Anca)	Myeloperoxidase (MPO/p-ANCA)	Negative
Wegener's granulomatosis	70%	25%	5%
Microscopic polyangiitis	40%	50%	10%
Churg-Strauss syndrome	10%	60%	30%
Pauci-immune glomerulonephritis	20%	70%	10%



C-ANCA pattern Demonstration of cytoplasmic



P-ANCA pattern Demonstration of perinuclear

Wegener's Granulomatosis

Pulmonary

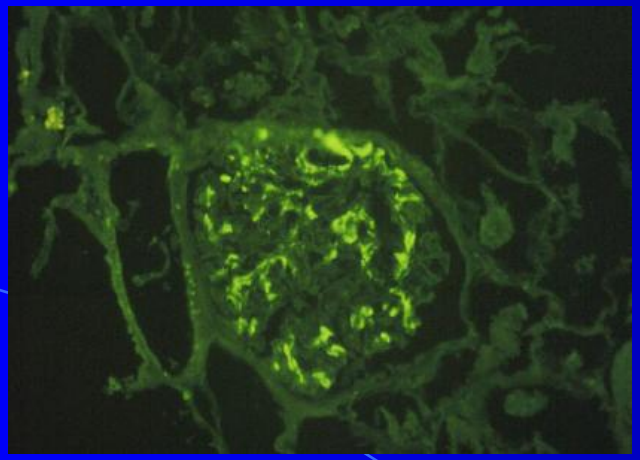
- Interstitial infiltrates
- Hemoptysis
- Cavitating lesions
- Pleural effusion
- Subglottic stenosis
- Cough
- Shortness of breath

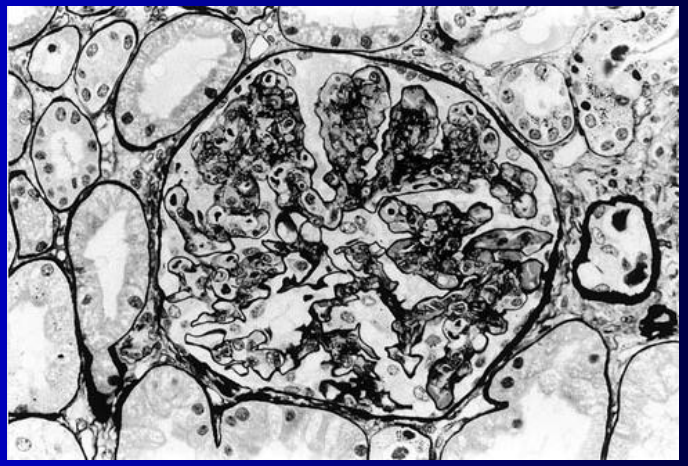
Upper Airway

- Sinusitis
- Epistaxis
- Rhinitis
- Saddle nose deformity

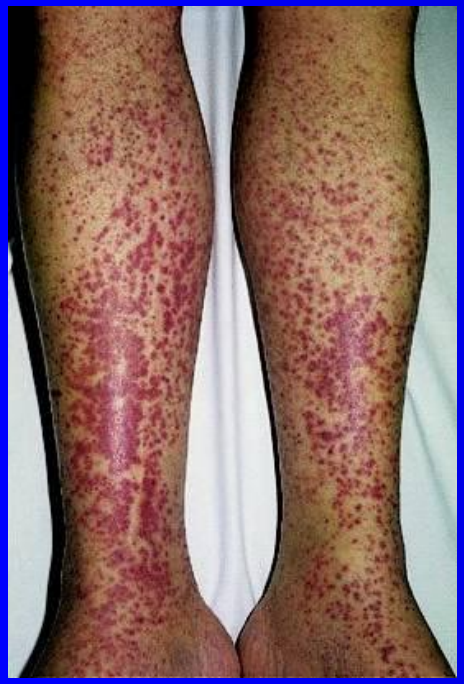
Otologic

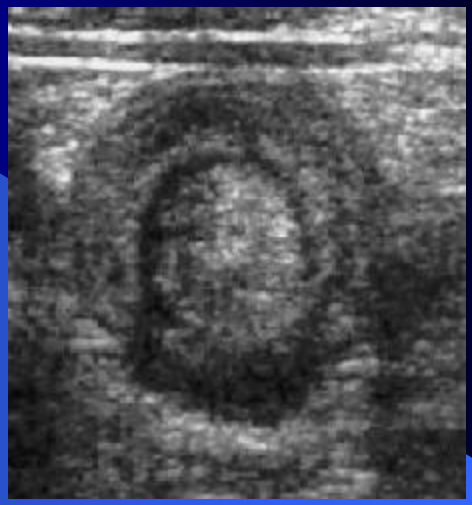
- Ottitis
- Tinnitus
- Eustachian tube dysfunction





HENOCH-SCHÖNLEIN PURPURA





EPIDEMIOLOGY

- 90% of cases reported in children
  - Peak in children aged 4-7
- Male:Female (1.5:1)
- 50% follow a URI
- Renal disease is more severe in adults

MANAGEMENT

- Usually self-limiting (1-6 weeks)
- Steroids:
  - may decrease tissue edema, may aid in arthralgias and some abdominal pain
  - Has not been shown to be beneficial in kidney disease or dermal manifestations
  - Does not lessen chance of recurrence
  - Does not shorten duration of disease

Post-Diarrheal Hemolytic Uremic Syndrome (D+HUS)

- The syndrome includes:
  - **Acute kidney failure**
  - **Hemolytic anemia**
  - **Thrombocytopenia (low platelet count)**

- Most common cause of acute renal (kidney) failure in young children; also occurs in older children and adults

How did these otherwise harmless E. coli become such killers?

- DNA from a Stx producing bacterium (Shigella dysenteriae type 1) transferred by bacteriophage to E. coli

- This provided E. coli with genes to produce Shiga toxin (Stx), one of the most potent toxins known to man

Signs and Symptoms

- diarrhea (usually bloody) with severe pain; can be mistaken for appendicitis
- pallor
- bruises
- seizures and/or coma (occasionally)
- little (oliguria) or no (anuria) urine
- high blood pressure
- pancreatic damage (diabetes)

Outcomes

- Death in 3-5%, due to:
  - brain damage (stroke and/or brain swelling)
  - bowel necrosis and perforation
  - heart damage
  - lung injury
  - multiorgan injury (seen in most fatal cases)

Thrombotic Thrombocytopenic Purpura

- In 1924, Dr.Eli Moschcowitz described a 16- year old girl with abrupt onset of petechiae, pallor, followed by paralysis, coma, and death.
- Autopsy showed ‘hyaline’ thrombi occluding terminal arterioles and capillaries.

British J of Hematology 2000

Definition

- Syndrome of Coomb's negative microangiopathic hemolysis and thrombocytopenia in the absence of an alternative explanation for these manifestations.
- Presence of Fever, Neurological and renal abnormalities : classic Pentad.

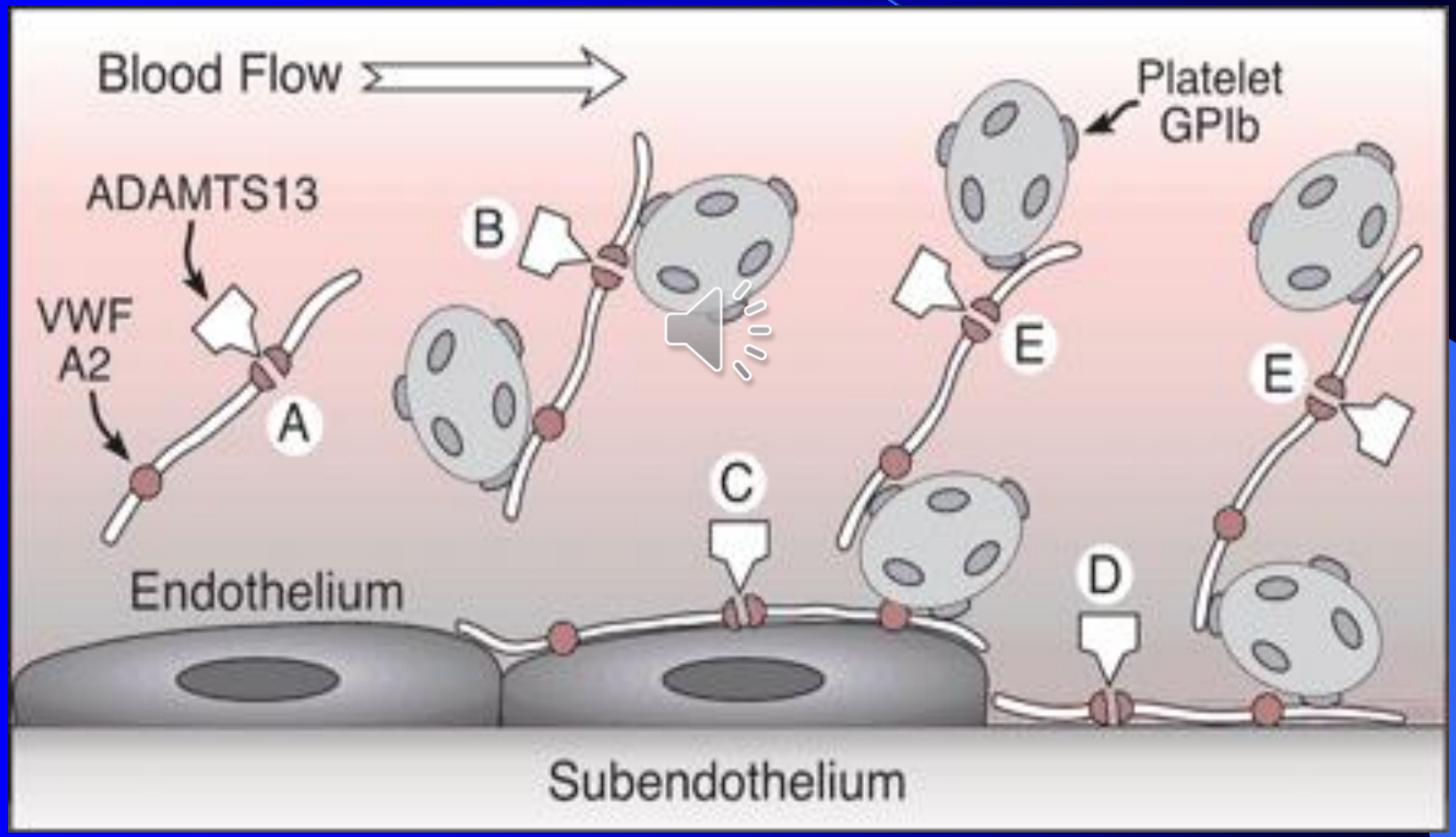
Rock GA, Br J Hematology 2000

Clinical Presentation

- Approximately 1000 new cases occur each year
- Common in middle aged group,median age-40
- Female:male (2:1).
- Acute onset and fulminant course
- Mortality rate >90% in pre-pheresis era.
- Relapse rates, 10-40% ranging from months to years have been reported.

Shumak KH, Ann Intern Med 1995

ULVWF Model


Blood Flow
Platelet GPIb
ADAMTS13
VWF A2
A
B
C
D
E
E
Endothelium
Subendothelium

Diagnosis

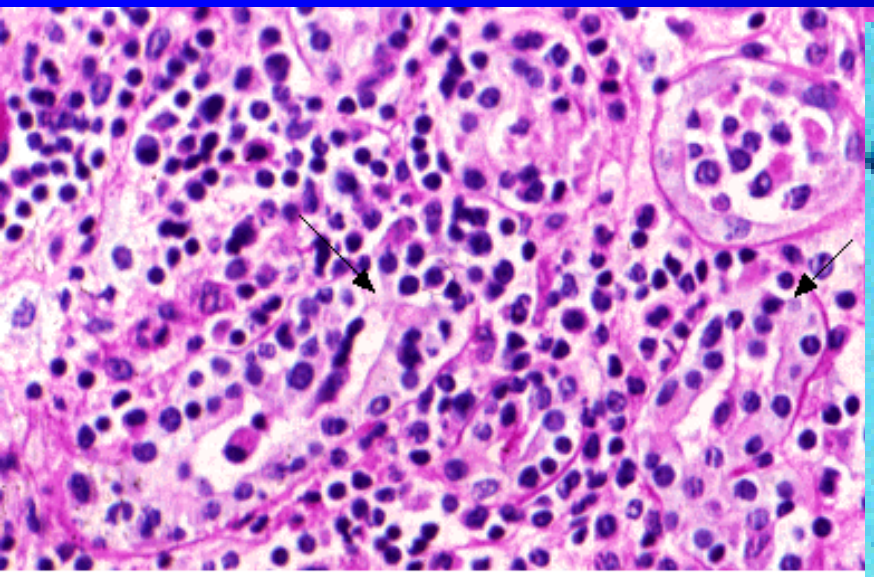
- Primary diagnostic criteria
  - Thrombocytopenia (often below <20,000)
  - Microangiopathic hemolytic anemia
    - Negative Coomb's test.
    - Fragmented red cells (schistocytes) on peripheral smear
    - LDH elevation is the hallmark of RBC destruction and tissue injury related to ischemia.
- Presence of above criteria is sufficient to establish presumptive diagnosis & begin PE

George,Blood Aug 2000

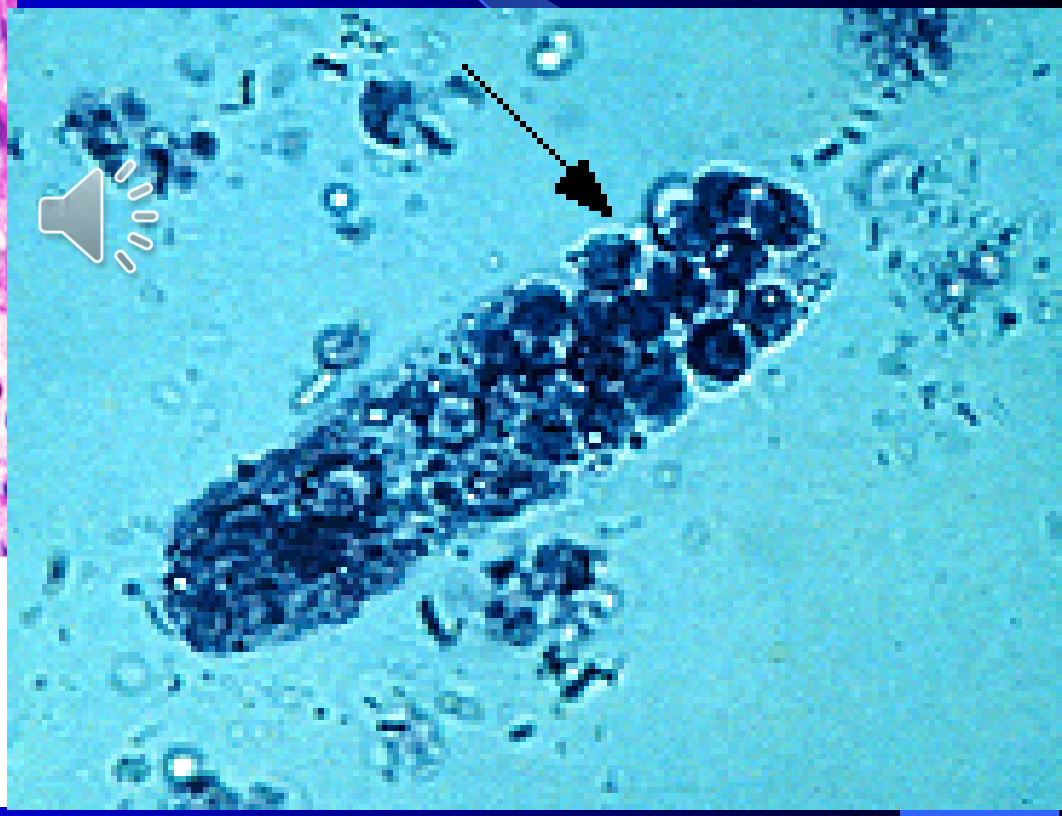
Treatment

- Plasma exchange:
  - Untreated TTP has 80-90% mortality.
  - Removes ULvWF multimers, autoantibody and replaces metalloproteinase.
  - Randomized controlled trial (Rock et al, 1991)
  - FFP as the replacement fluid is most widely used and cost effective.

ΒΙΟΨΙΑ ΣΕ ΑΣΘΕΝΗ ΜΕ ΔΙΑΜΕΣΟ ΝΕΦΡΙΤΙΔΑ



Tubulitis in acute interstitial nephritis High power light micrograph of interstitial nephritis showing diffuse interstitial infiltrate of mononuclear cells, many of which are actively invading the tubules leading to disruption of the tubular basement membranes (arrows). A white cell cast is present in the tubule in the upper right corner. Courtesy of Helmut Rennke, MD.



Αίτια Διαμέσου Νεφρίτιδας

- Φάρμακα
- Λοιμώξεις
- Σαρκοείδωση
- Sjogren's syndrome
- Ενδημική Νεφροπάθεια των Βαλκανίων
- Chinese Herb Nephritis

Φάρμακα και Διάμεσος Νεφρίτις

- β-λακτάμες π.χ. μεθικιλλίνη, πενικιλλίνη, κεφαλοσπορίνες
- Ριφαμπικίνη
- Φάρμακα με σουλφομιάδα π.χ. Φουροσεμίδη, Σουλφαμεθοξαζόλη, Σουλφασαλαζίνη
- Σιπροφλοξασίνη
- Μη στερινοειδή αντιφλεγμονώδη π.χ. φενοπροφένη

Λοιμώξεις και Διάμεσος Νεφρίτις

- Legionella
- Leptospirosis
- Streptococcal infections
- Viruses

ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ