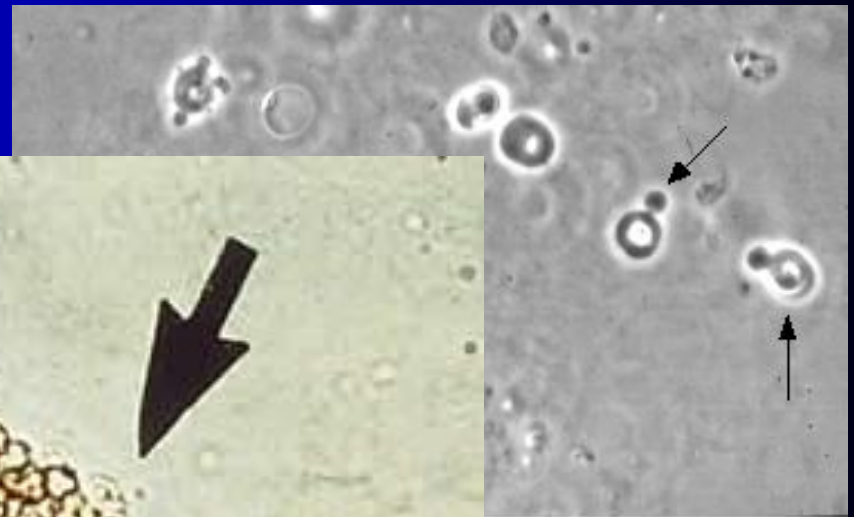


ΠΡΩΤΟΠΑΘΕΙΣ ΚΑΙ ΣΥΣΤΗΜΑΤΙΚΕΣ ΝΟΣΟΙ ΤΩΝ ΝΕΦΡΩΝ

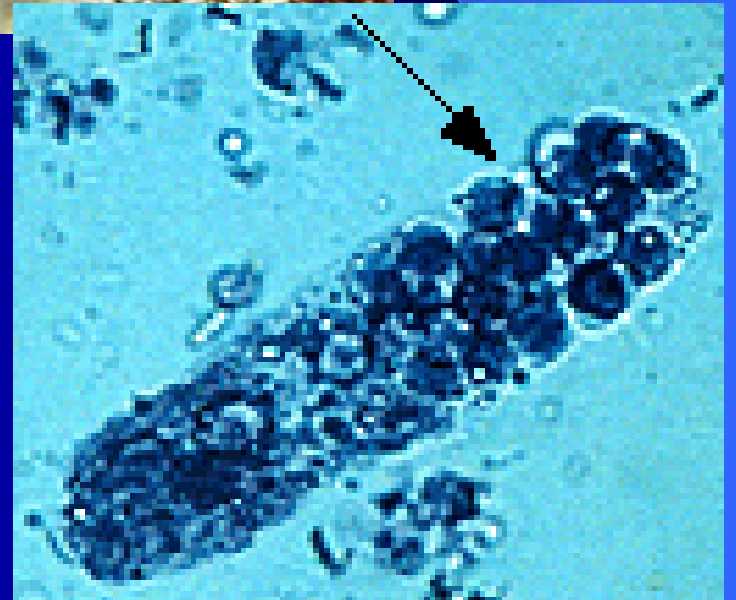
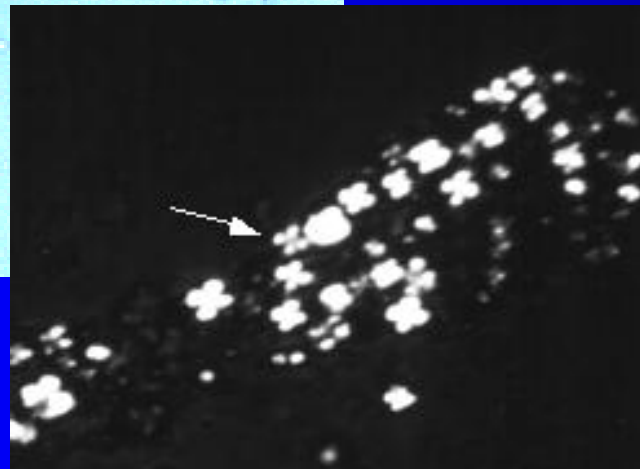
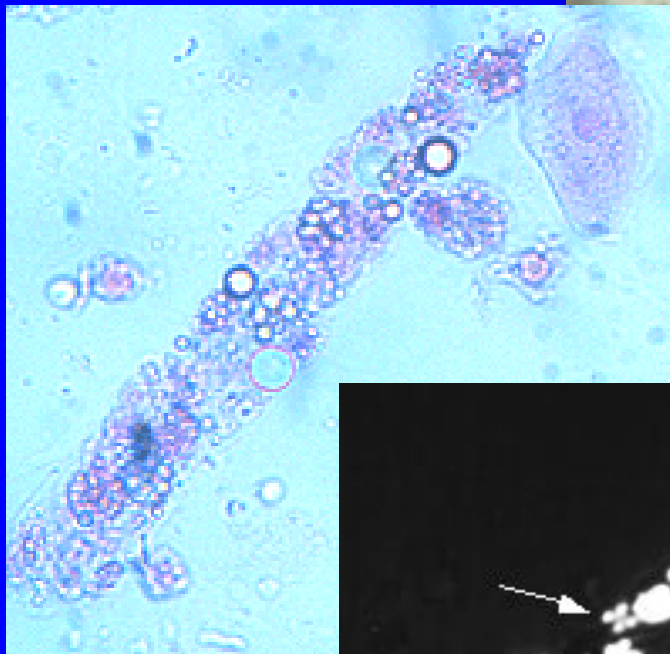
Δημήτριος Β. Βλαχάκος
Καθηγητής Παθολογίας-Νεφρολογίας
Υπεύθυνος Νεφρολογικής Μονάδας
Β΄ Προπαιδευτική Παθολογική Κλινική
Πανεπιστημιακό Γενικό Νοσοκομείο «ΑΤΤΙΚΟΝ»

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



contrast microscopy

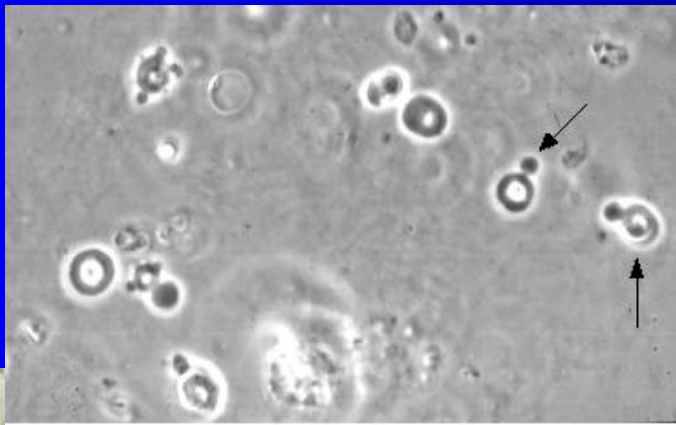


Asymptomatic Proteinuria

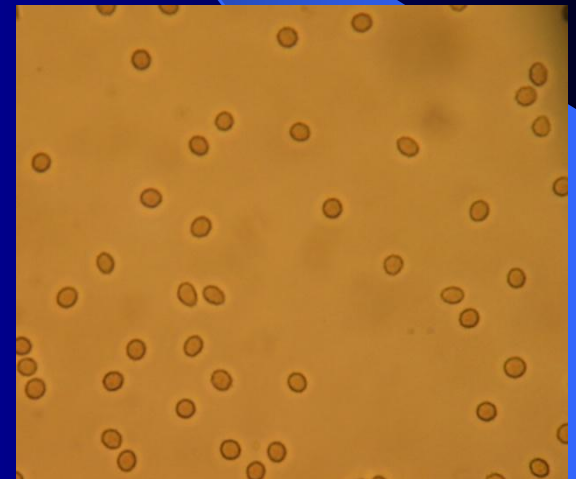
- **Transient Idiopathic:** In children, adolescents, and young adults, otherwise healthy, normal urinalysis. Repeat 2-3 times.
- **Intermittent Idiopathic:** <30 years old and long term prognosis is favorable. Yearly monitoring is recommended.
- **Functional:** Acute illness, fever, CHF, exercise, seizures, 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 $< 3.5 \text{ g}/24\text{h}/1.73 \text{ m}^2$ 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

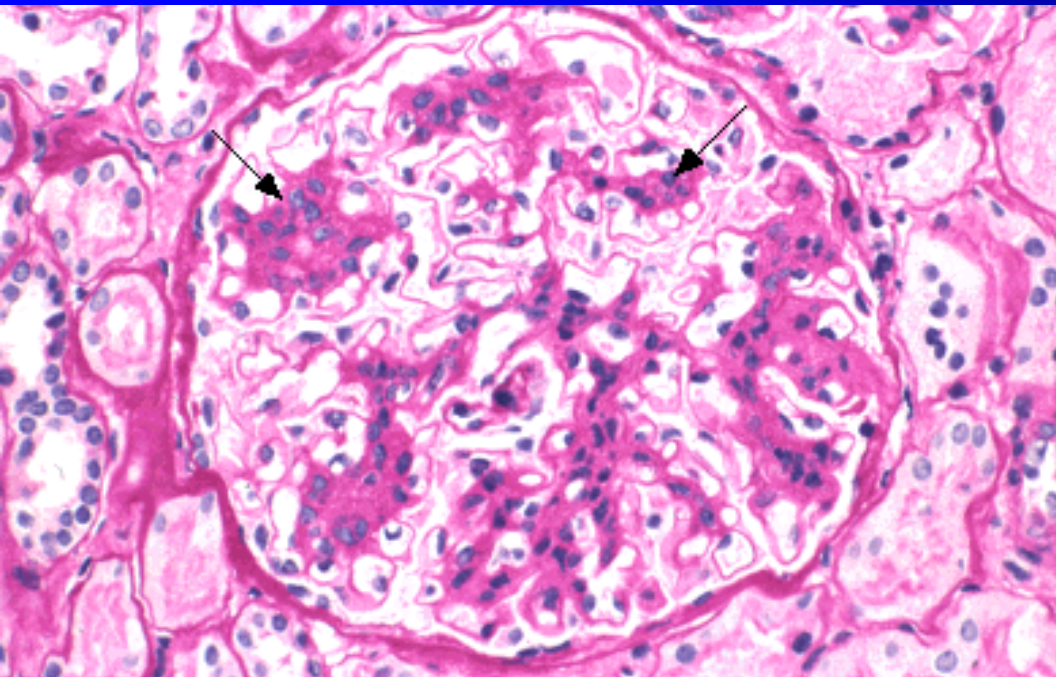
(**IgA**, Νόσος λεπτής μεμβράνης,
Μεσαγγειοϋπερπλαστική ΣΝ,
Alport's syndrome)



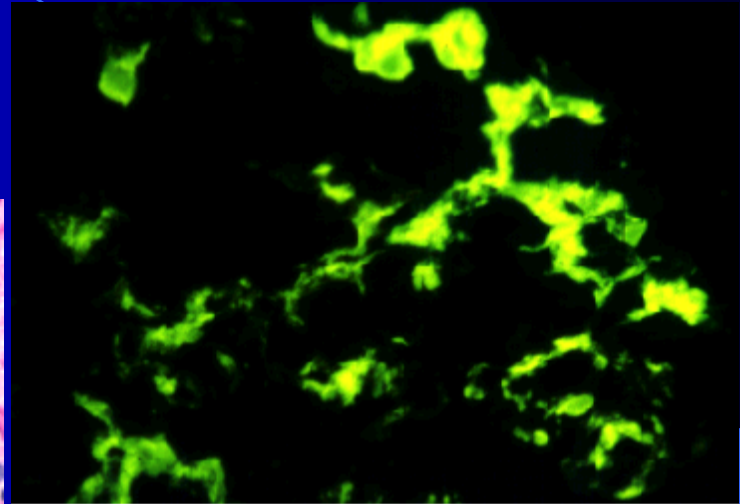
Dysmorphic red cells Phase contrast microscopy



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

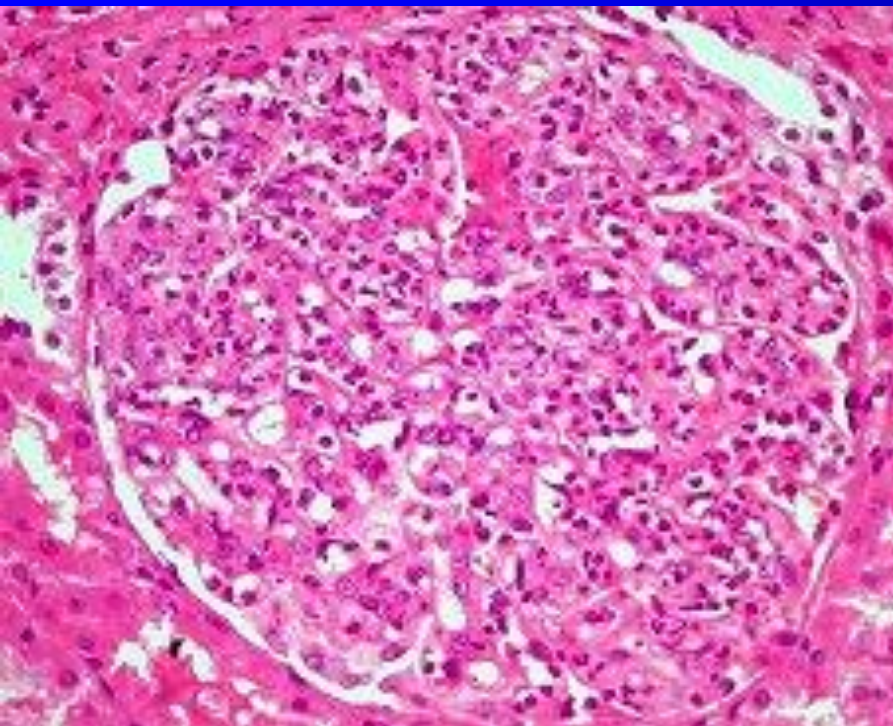
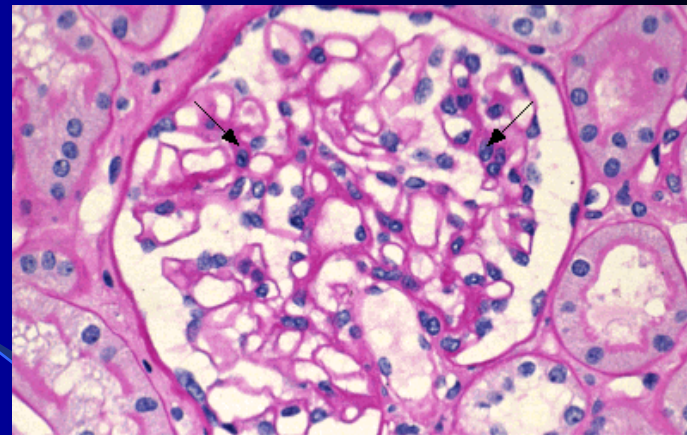
10% nephrotic syndrome

10% renal failure

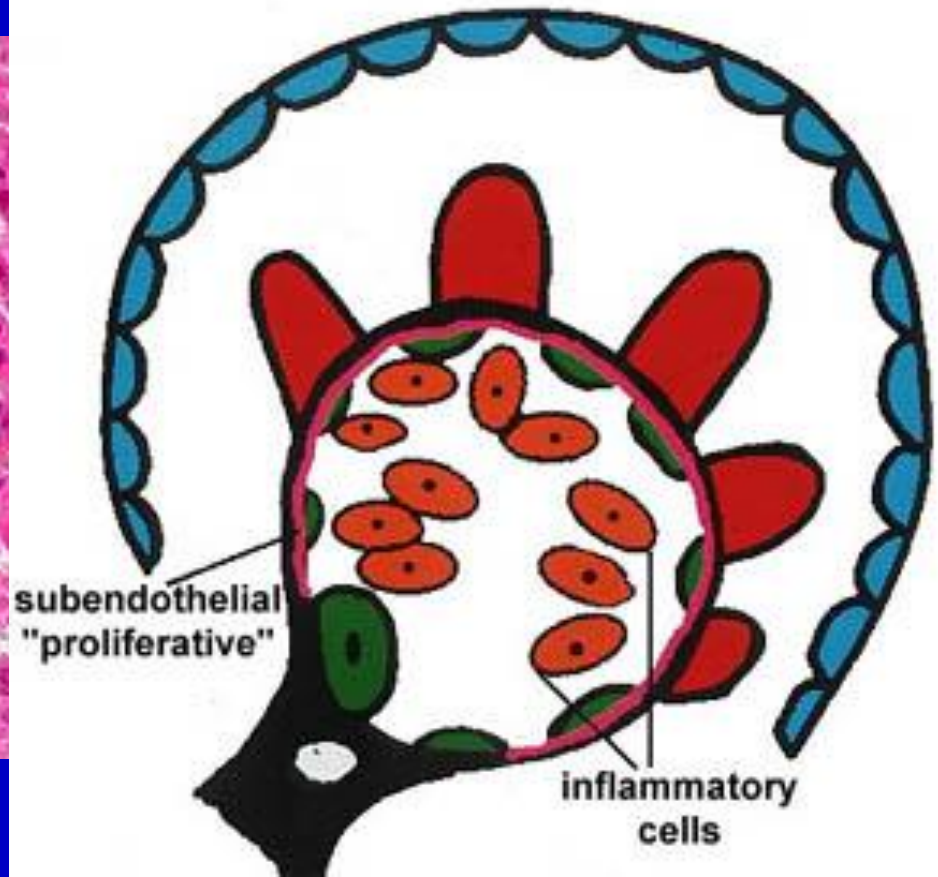
Χαρακτήρες ανοσοσυμπλεγμάτων

- Το μέγεθος εξαρτάται από την σχέση αντιγόνου-αντισώματος
- Πληθώρα αντιγόνου-μικρή ανοσολογική απόκριση => θάνατος
- Ελάχιστο αντιγόνο-μεγάλη ανοσολογική απόκριση => ταχύς καθαρισμός αντιγόνου
- Αντιγόνο – αντίσωμα σε ίδια αναλογία, κατάλληλο μέγεθος ανοσοσυμπλεγμάτων, ελεύθερη κυκλοφορία επί μακρού, σύνδεση και ενεργοποίηση συμπληρώματος, ιστική εναπόθεση και βλάβη

Υπερπλαστική Σπειραματονεφρίτιδα (μεταλοιμώδης ΣΝ)

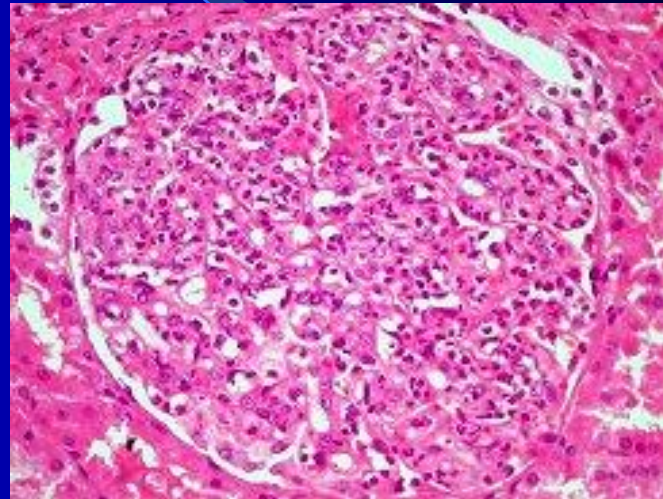


"large" immune complexes >1,000,000 mw



Νεφριτιδικό Σύνδρομο

- **Αιματουρία**
- **Πρωτεϊνουρία**
- **Ολιγουρία**
- **Ουραιμία**
- **Οίδημα**
- **Υπέρταση**
- **Καρδιακή Κάμψη - Πνευμονικό Οίδημα**



ACUTE POSTINFECTIONOUS 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% persistent hematuria/proteinuria

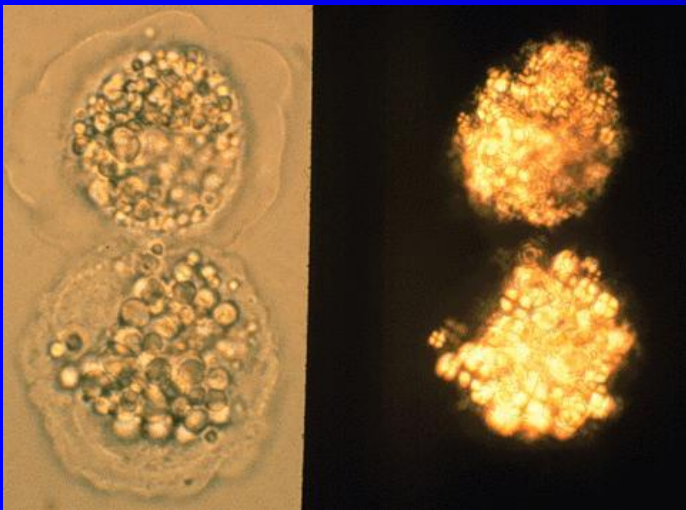
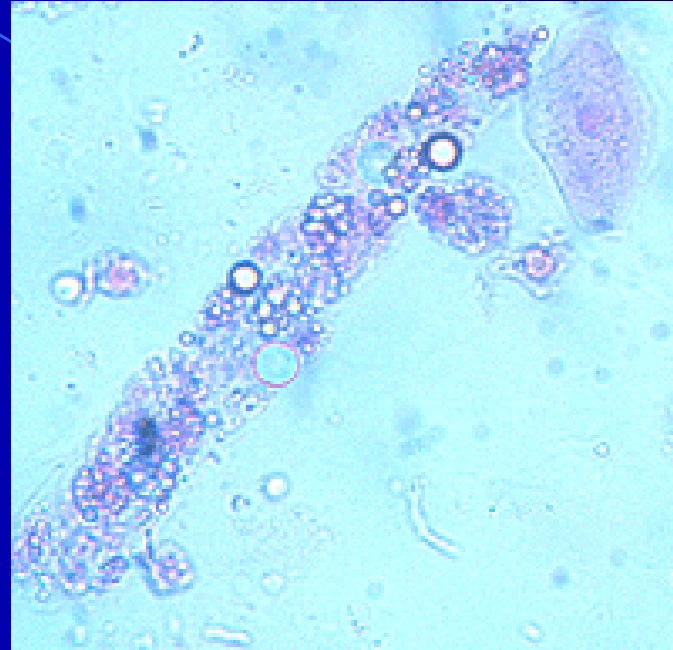
1% chronic renal disease



Νεφρωσικό Σύνδρομο

- Πρωτεϊνουρία $> 3\text{g} / 24\text{ωρο}$
- Υπολευκωματαιμία ($< 3 \text{ g/dl}$)
- Υπερλιπιδαιμία
- Λιπιδουρία
- Οίδημα

ΙΖΗΜΑ ΟΥΡΩΝ ΣΕ ΝΕΦΡΩΣΙΚΟ ΣΥΝΔΡΟΜΟ





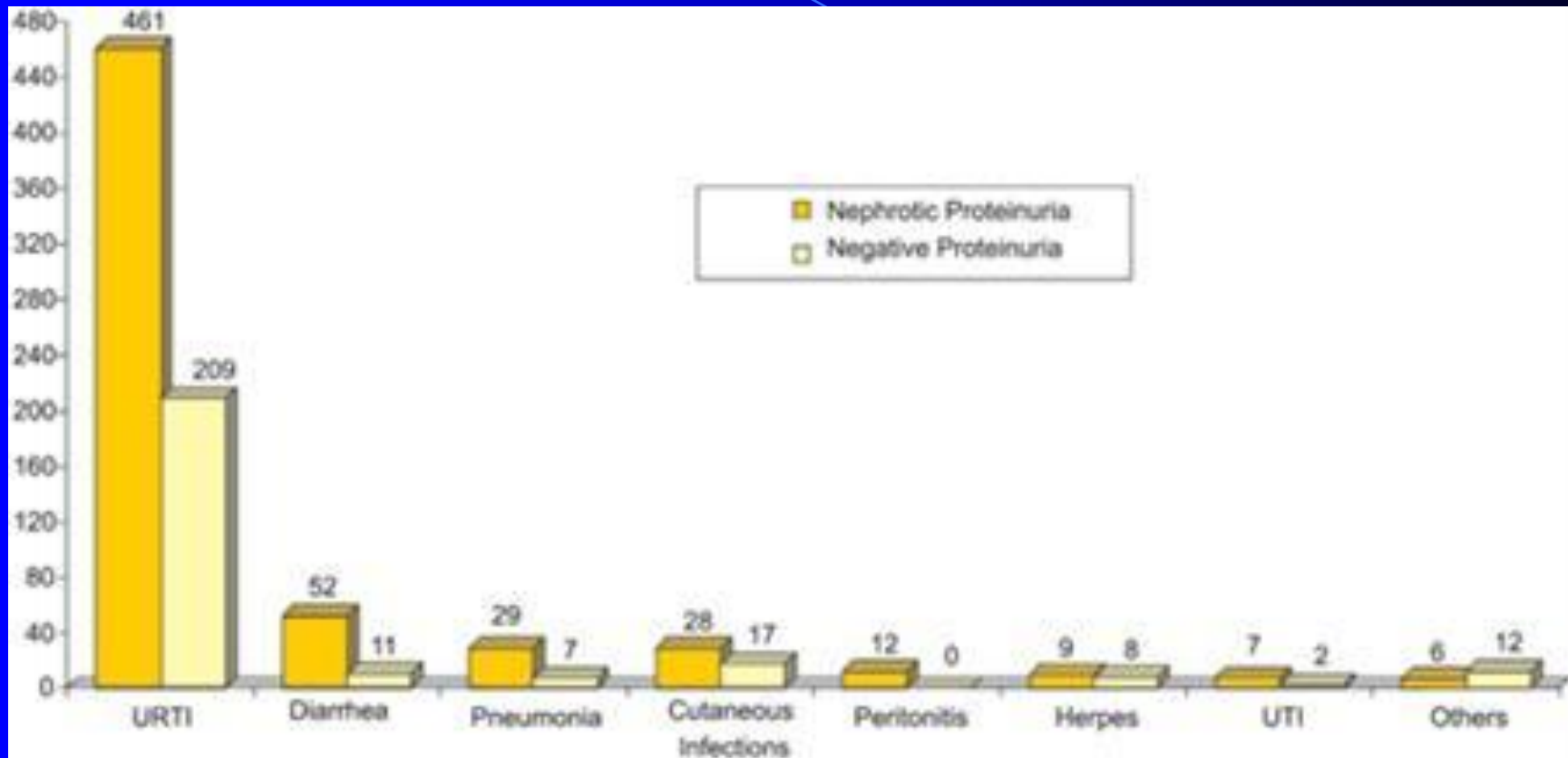


Figure 1 - Number and type of infection of 92 patients during the period with nephrotic proteinuria (604 infections/1140 months) and of the 89 patients during the period with negative proteinuria (266 infections /6822 months).

Hypercoagulation in NS

Low zymogen factors; factors IX, factor XI

Increased procoagulatory cofactors. factor V, factor VIII

Increased fibrinogen levels

Decreased coagulation inhibitors; antithrombin III (but protein C and Protein S increased)

Altered fibrinolytic system (al-antiplasmin increased, plasminogen decreased)

Increased platelet reactivity

Thrombocytosis

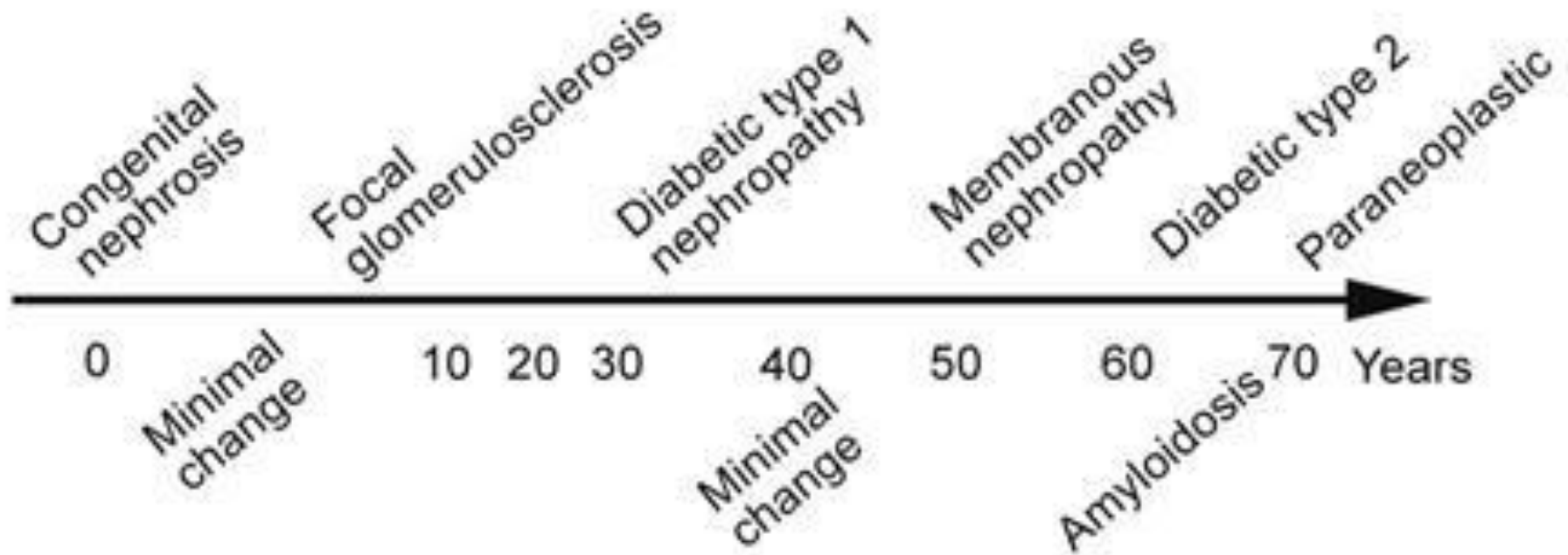
Increased release reaction *in vitro* (adenosine diphosphate; thrombin, collagen, arachidonic acid, epinephrine)

Increased factor IV and b-thromboglobulin *in vivo*

Altered endothelial-cell function

average ages of types of nephrotic syndrome

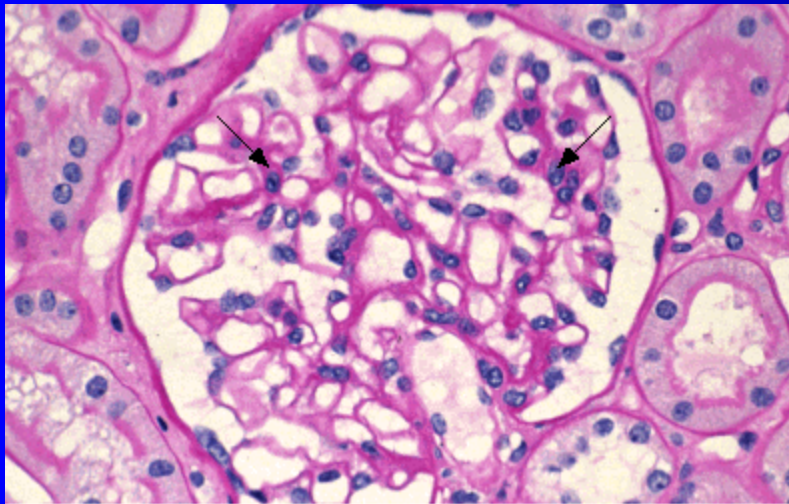
timeline not to scale



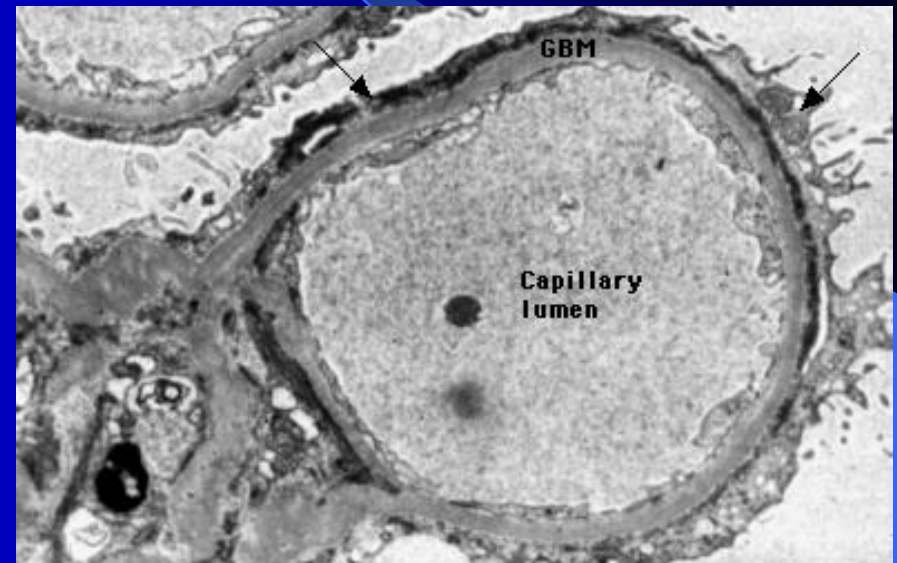
CAUSES OF NEPHROTIC SYNDROME

<u>Disease</u>	<u>Children(%)</u>	<u>Adults(%)</u>
Minimal change GN	75	20
Membranous GN	5	40
Focal Segmental GN	10	15
MPGN I	5	5
Other GN	5	20

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

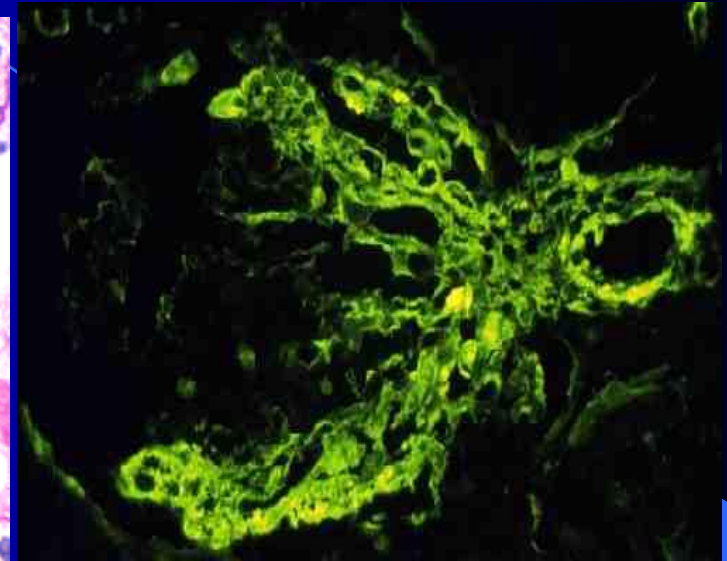
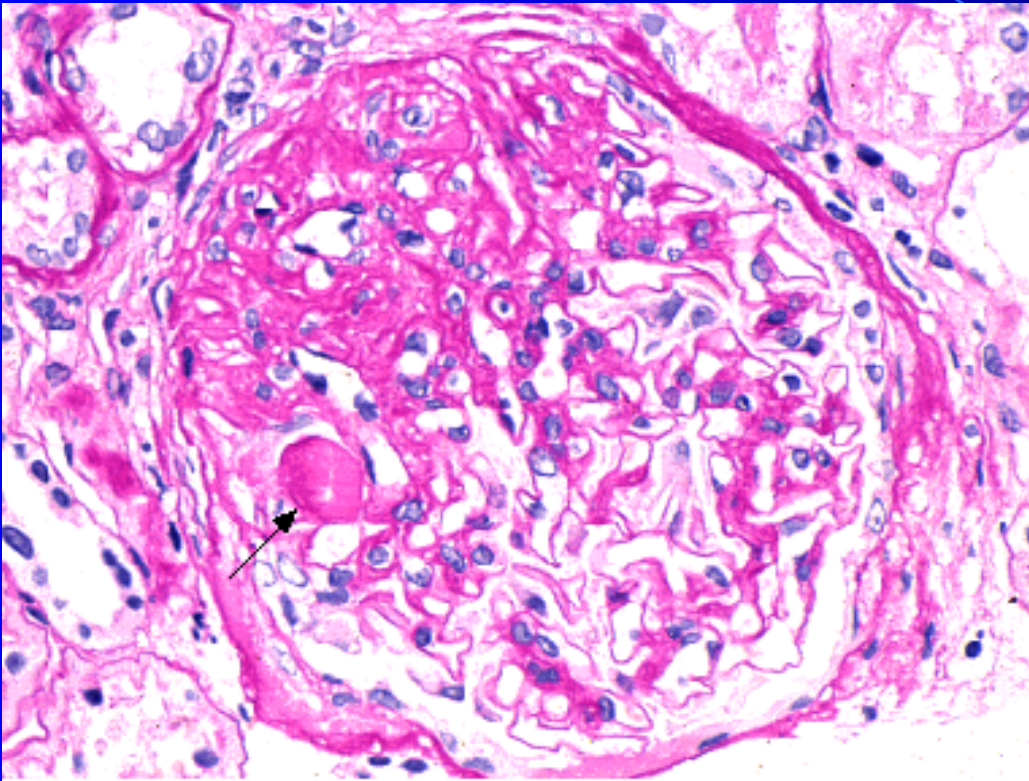
CL: Most common cause of nephrotic syndrome in children

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

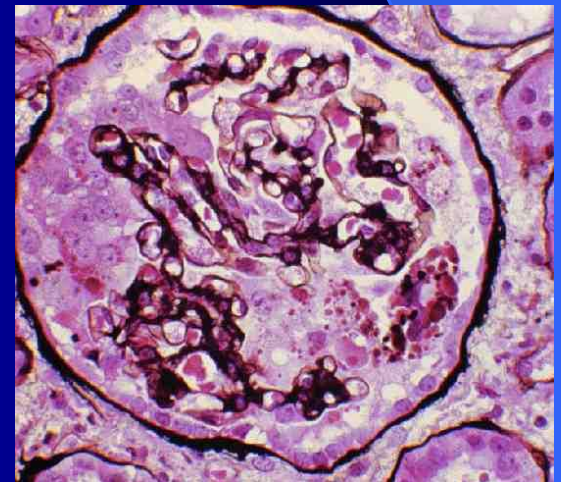
Path: normal by LM and IF

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)

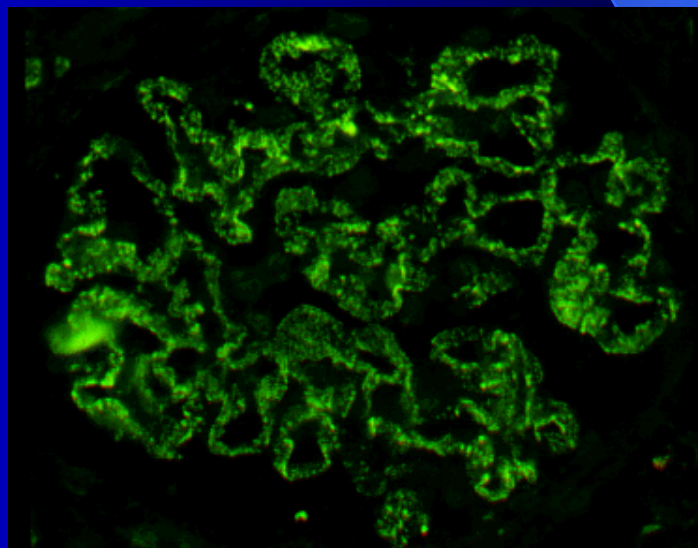
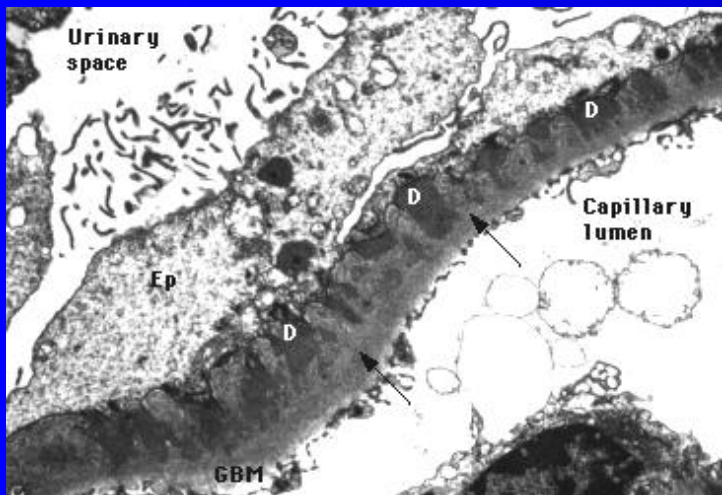
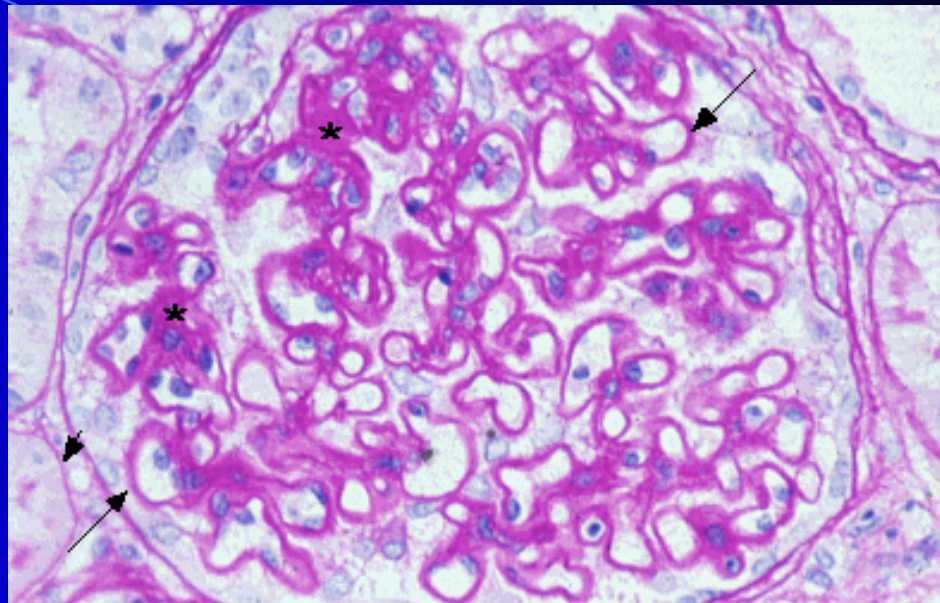
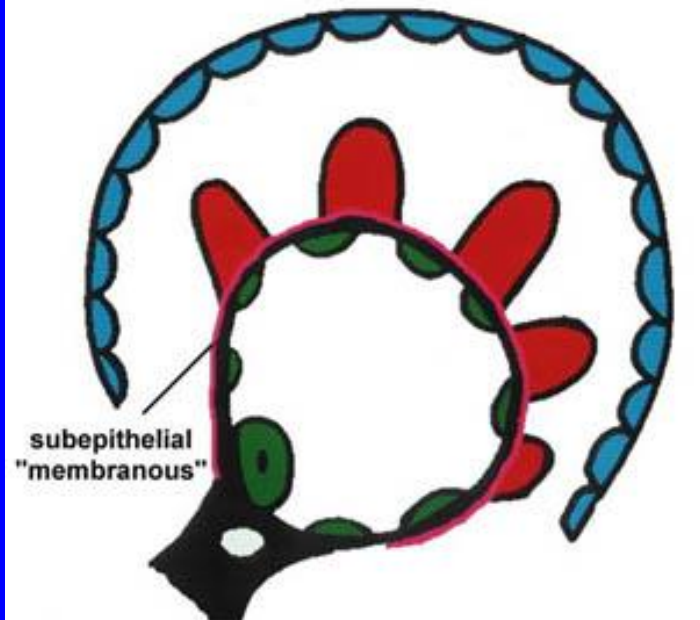
Trapping of serum proteins (IF and EM)

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

Therapy: Glycocorticosteroids +/- calcineurin inhibitors

ΜΕΜΒΡΑΝΩΔΗΣ ΣΠΕΙΡΑΜΑΤΟΝΕΦΡΙΤΙΣ

"small immune complexes 300,000 - 500,000 mw



MEMBRANOUS NEPHROPATHY

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

M-Type **Phospholipase A₂ 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

Crescentic GN
Rapidly Progressive GN
Renal-Pulmonary Syndromes
Rapidly progressive
glomerulonephritis

(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).

Ταχέως Εξελισσόμενη Σπειραματονεφρίτις

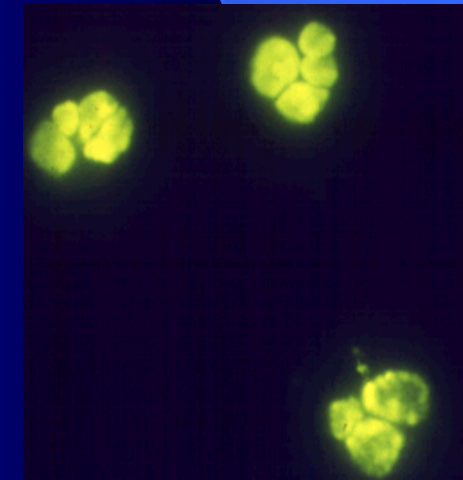
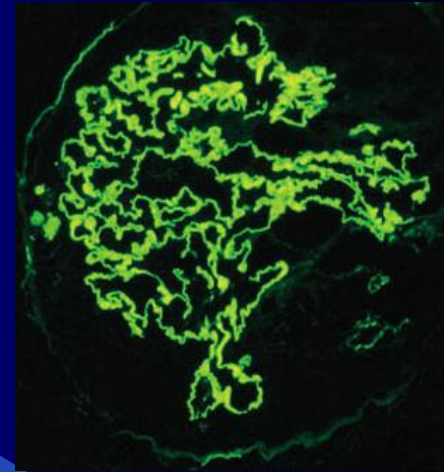
- **Anti-GBM Disease** (Type 1)

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

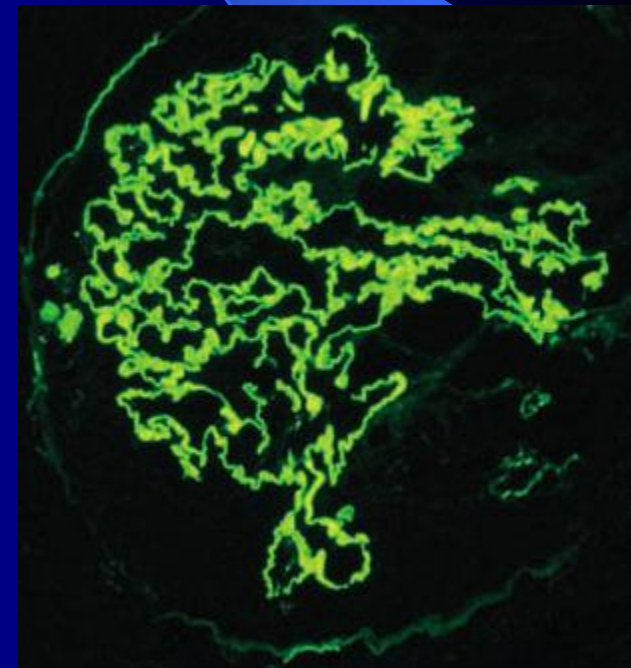
Antibody to collagen IV

Linear IF

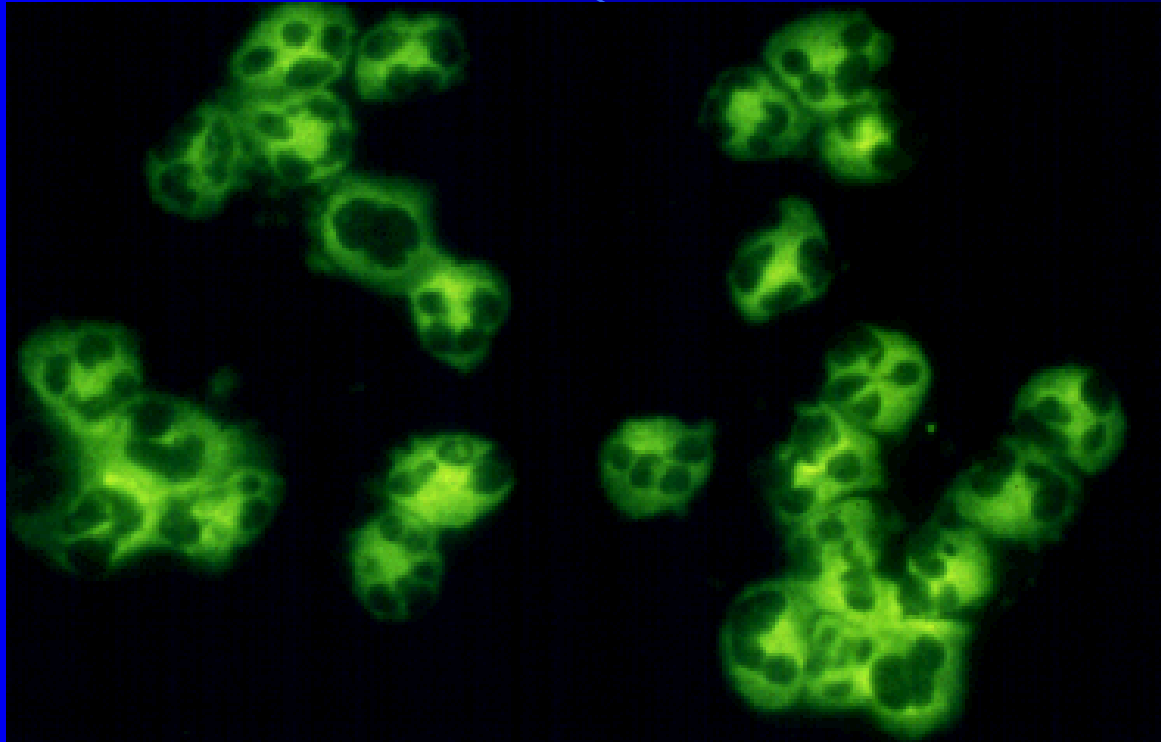
Fibrinoid necrosis of GBM

Crescentic GN

Goodpasture syndrome



Proteinase – 3 ANCA



C-ANCA pattern Demonstration of **cytoplasmic** antineutrophil cytoplasmic antibodies (C-ANCA) by indirect immunofluorescence with normal neutrophils. There is heavy staining in the cytoplasm while the multilobulated nuclei (clear zones) are nonreactive. These antibodies are usually directed against proteinase 3 and most patients have Wegener's granulomatosis. Courtesy of Helmut Rennke, MD.

Wegener's Granulomatosis

Pulmonary

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

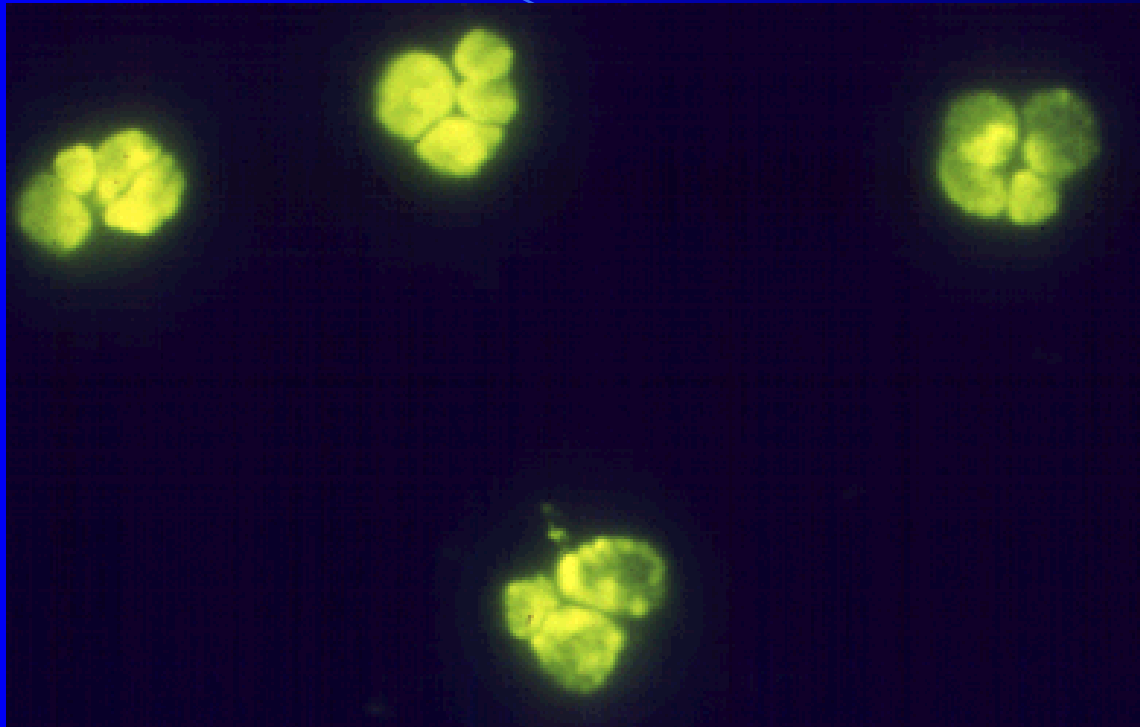
Upper Airway

- Sinusitis
- Epistaxis
- Rhinitis
- Saddle nose deformity

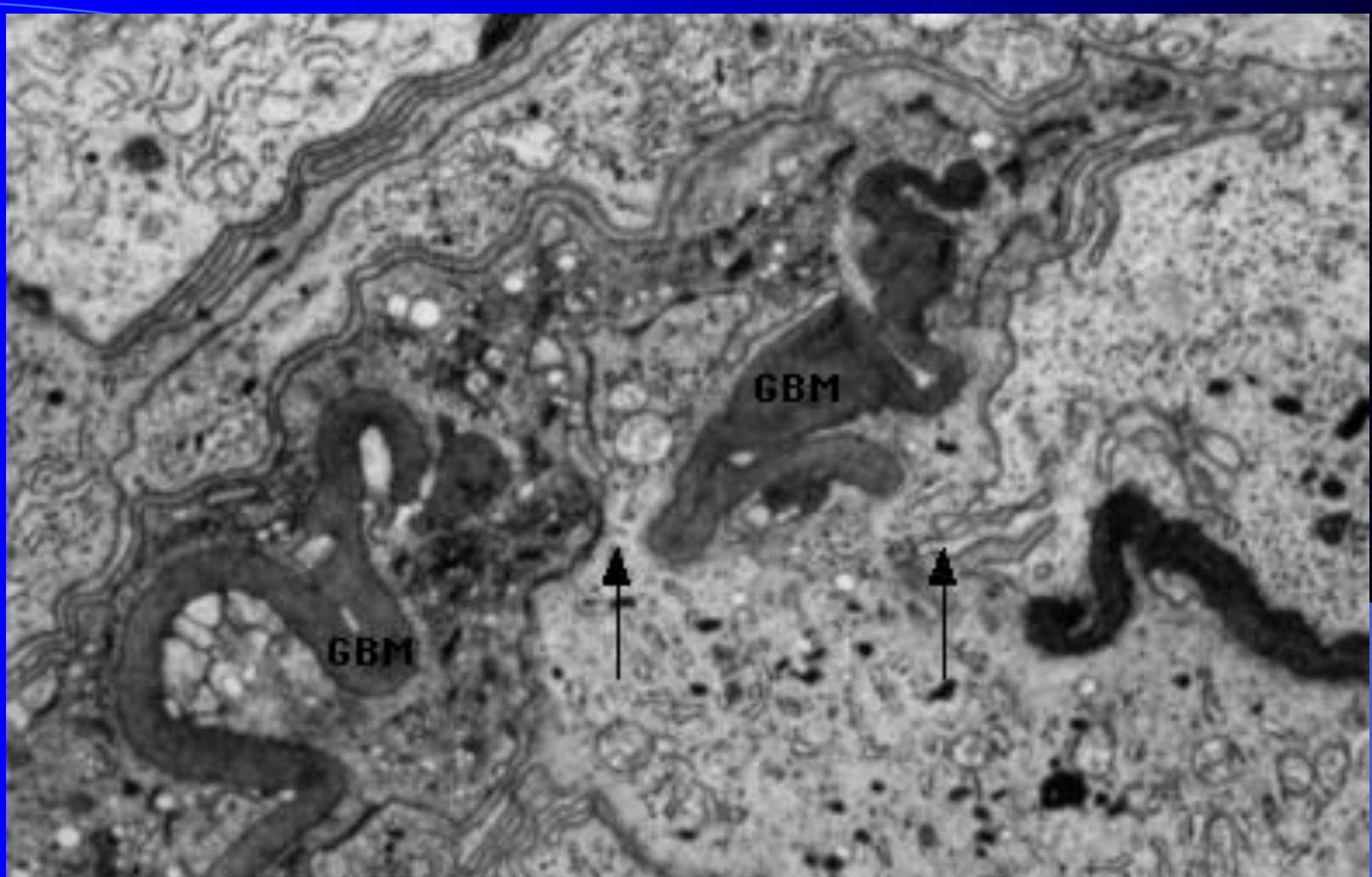
Otologic

- Otitis
- Tinnitus
- Eustachian tube dysfunction

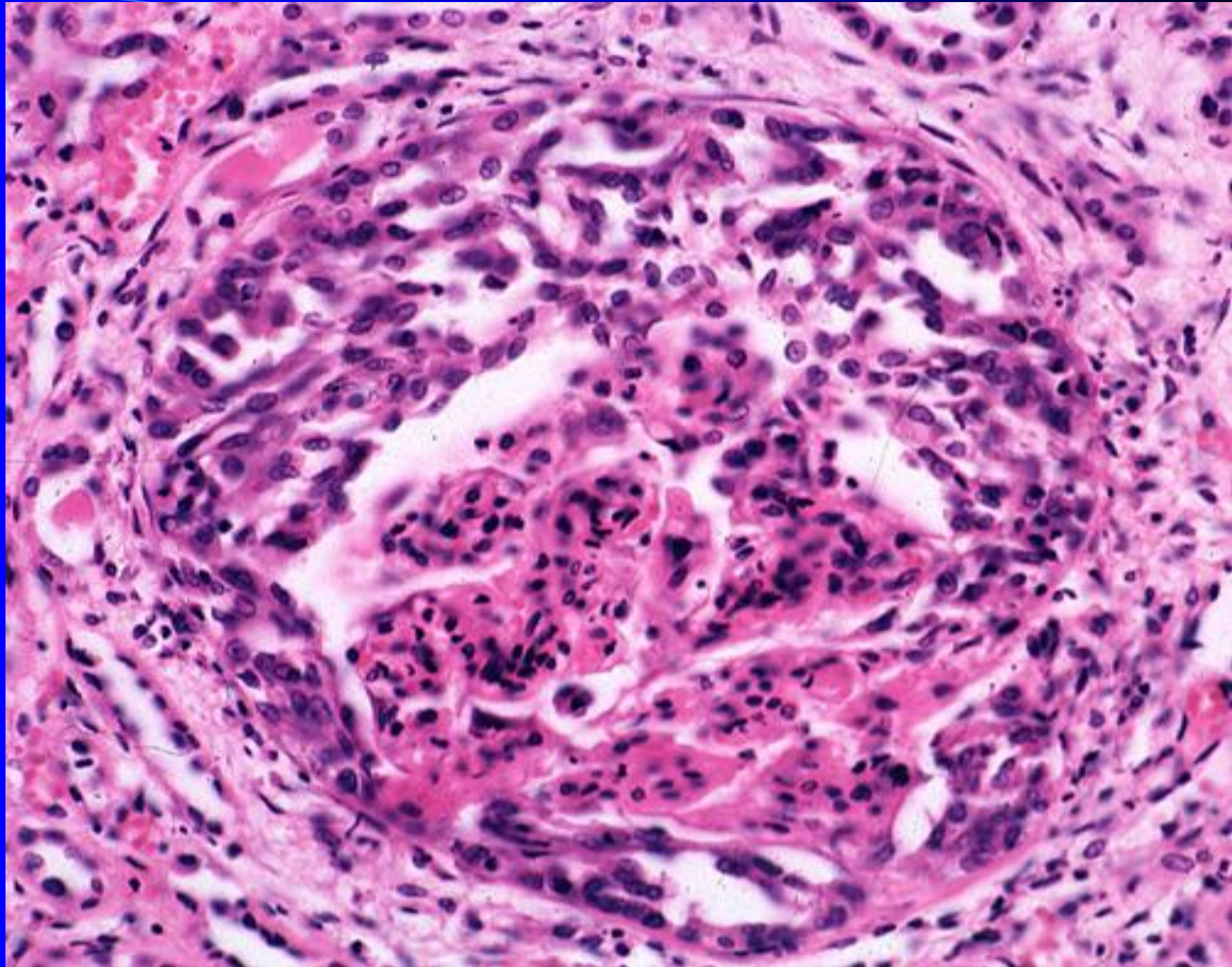
Myeloperoxidase ANCA



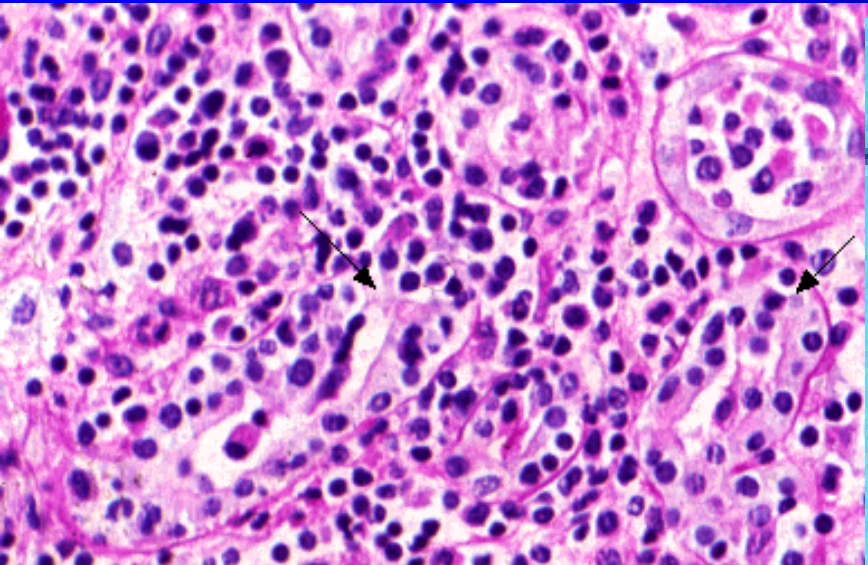
P-ANCA pattern Demonstration of **perinuclear** antineutrophil cytoplasmic antibodies (P-ANCA) by indirect immunofluorescence with normal neutrophils. Staining is limited to the perinuclear region and the cytoplasm is nonreactive. Among patients with vasculitis, the antibodies are usually directed against myeloperoxidase. However, a P-ANCA pattern can also be seen with autoantibodies against a number of other antigens including lactoferrin and elastase. Non-MPO P-ANCA can be seen in a variety of nonvasculitic disorders. Courtesy of Helmut Rennke, MD.



Rapidly progressive glomerulonephritis Electron micrograph in RPGN showing characteristic breaks in the glomerular basement membrane (GBM) (arrows). These rents allow fibrin and cellular elements to enter Bowman's space and initiate crescent formation. Courtesy of Helmut Rennke, MD.



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

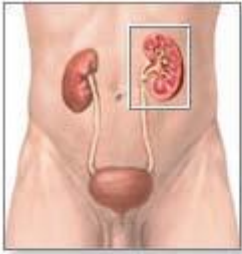
Φάρμακα και Διάμεσος Νεφρίτις

- β-λακτάμες π.χ. μεθικιλίνη, πενικιλίνη, κεφαλοσπορίνες
- Ριφαμπικίνη
- Φάρμακα με σουλφομάδα π.χ. Φουροσεμίδη, Σουλφαμεθοξαζόλη, Σουλφασαλαζίνη
- Σιπροφλοξασίνη
- Μη στερινοειδή αντιφλεγμονώδη π.χ. φενοπροφένη

Λοιμώξεις και Διάμεσος Νεφρίτις

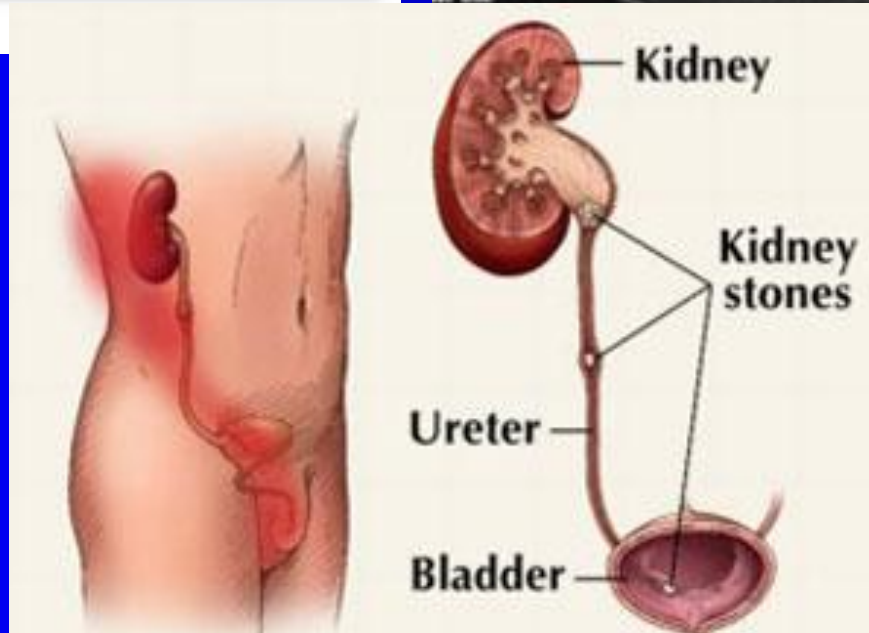
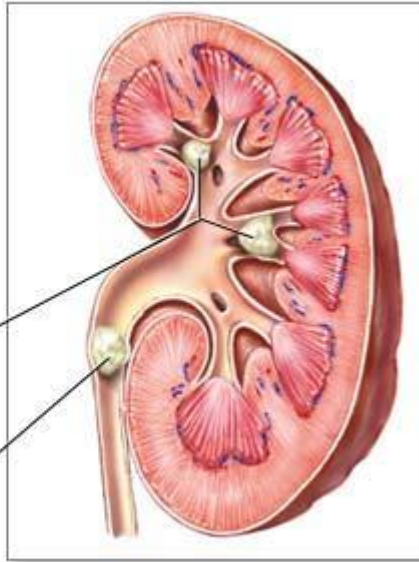
- Legionella
- Leptospirosis
- Streptococcal infections
- Viruses

Nephrolithiasis



Kidney stones in the minor and major calyces of the kidney

Kidney stone in the ureter



Risk Factors for Kidney Stones

- Family History/personal history
- Being over the age of 30 years old
- Male
- Dehydration
- Diet
- Obesity
- Digestive disease
- History of digestive surgeries
- Renal Tubular Acidosis
- Cystinuria
- Hyperparathyroidism
- Urinary Tract Infections

Blood Tests:

Check the function of the kidneys, check for infection, calcium or uric acid levels and can also check for other medical conditions.

Urine Tests:

Urine can be sent for a urinalysis and culture to check for infection within the urinary tract.

Imaging Tests: X-rays are often performed of the abdomen to see if a calcification in the area of the kidneys or ureters can be seen

Analysis of passed stones

Surgical Inventions

- Extracorporeal Shock Wave Lithotripsy
- Percutaneous Nephrolithotomy
- Ureteroscopic Stone Removal
- Open Surgery

ΣΥΣΤΗΜΑΤΙΚΕΣ ΝΟΣΟΙ ΝΕΦΡΩΝ

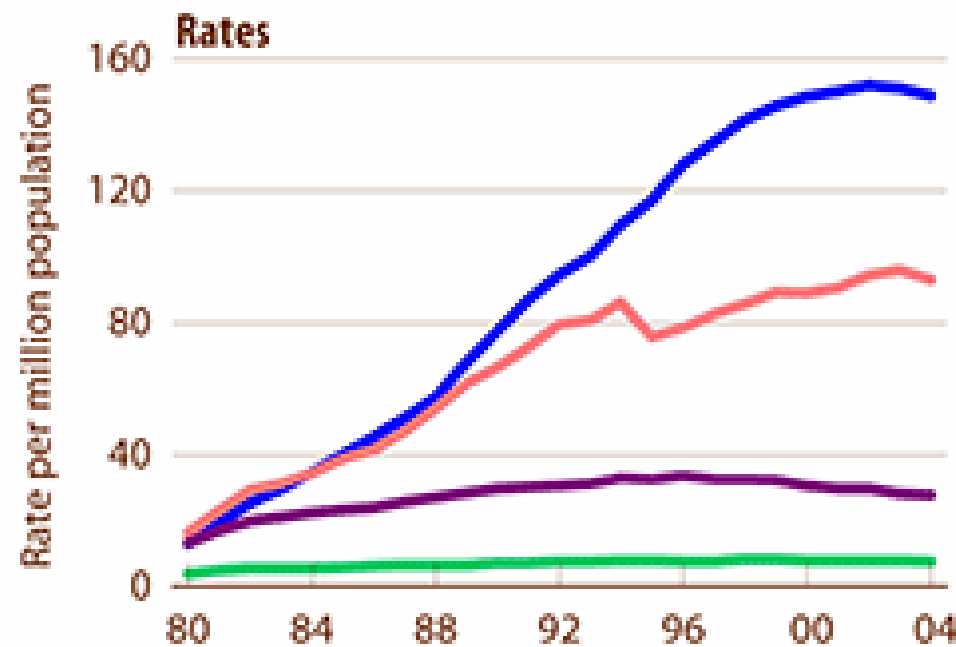
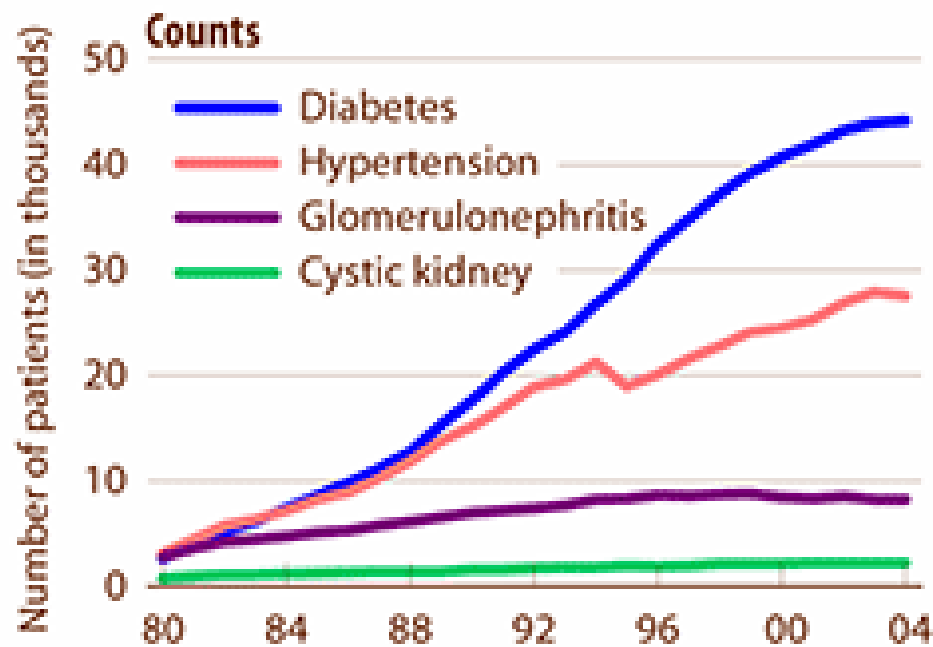
Table 11. Definition of Chronic Kidney Disease

Criteria

- 1. Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by *either*:**
 - Pathological abnormalities; or**
 - Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests**
 - 2. GFR < 60 mL/min/1.73 m² for ≥ 3 months, with or without kidney damage**
-

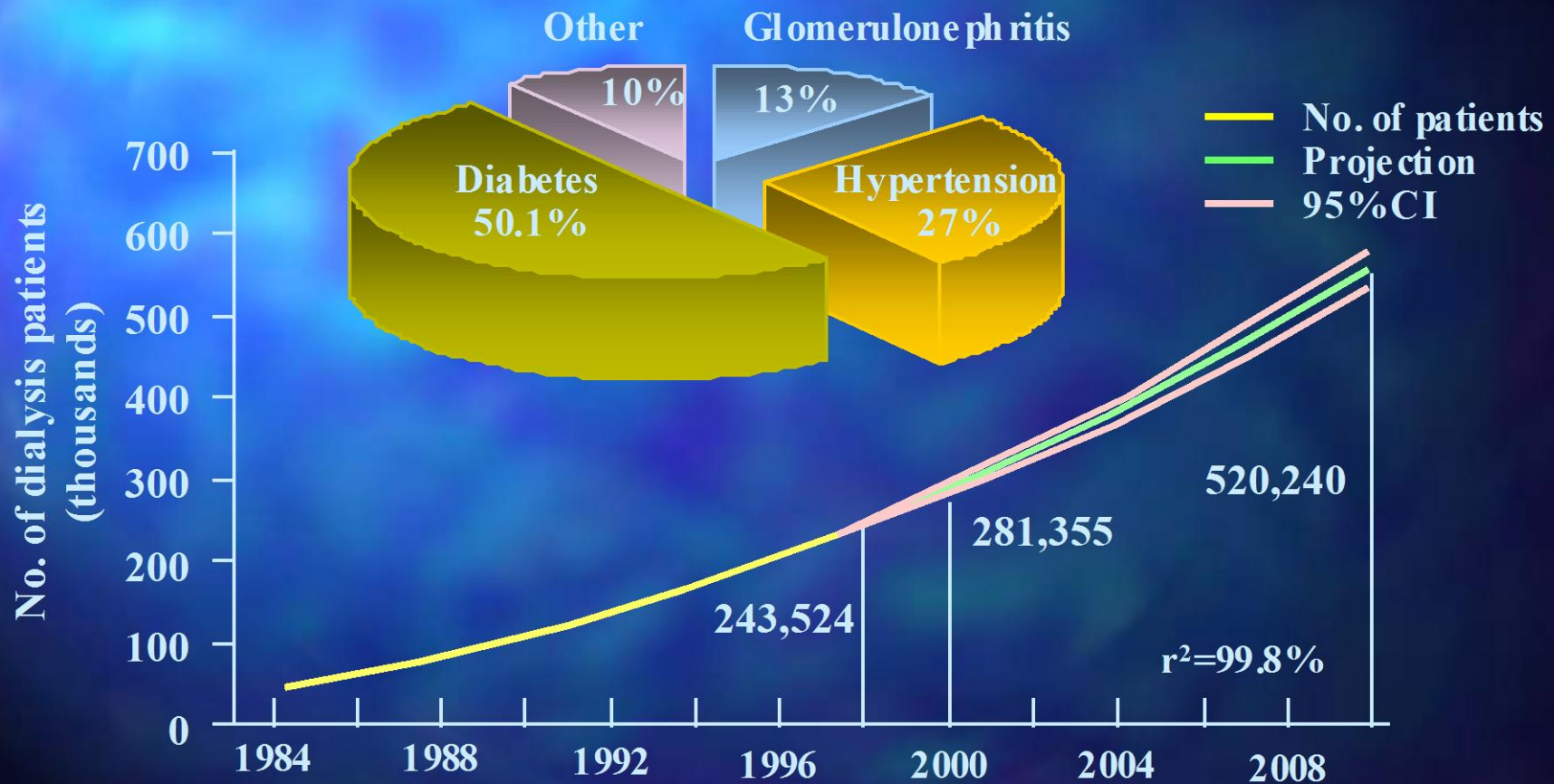
Methods to estimate GFR are discussed in Guideline 4. Markers of kidney damage are discussed in Guidelines 5–6.

Επιπλωλασμός της ΧΝΝ



ΑΙΤΙΑ ΤΣΑΝΑ

Διάγνωση ασθενών που άρχισαν εξωνεφρική υποστήριξη



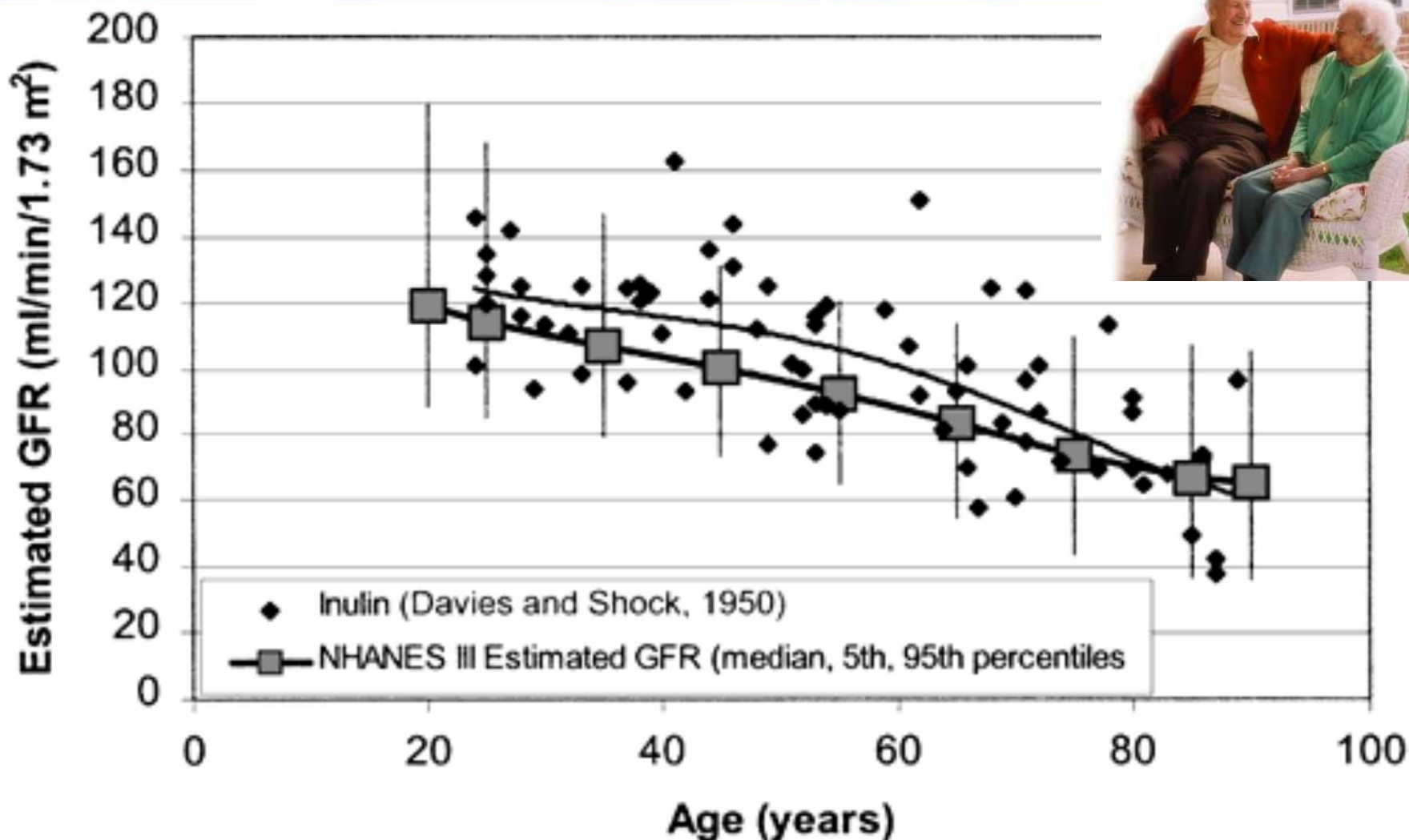
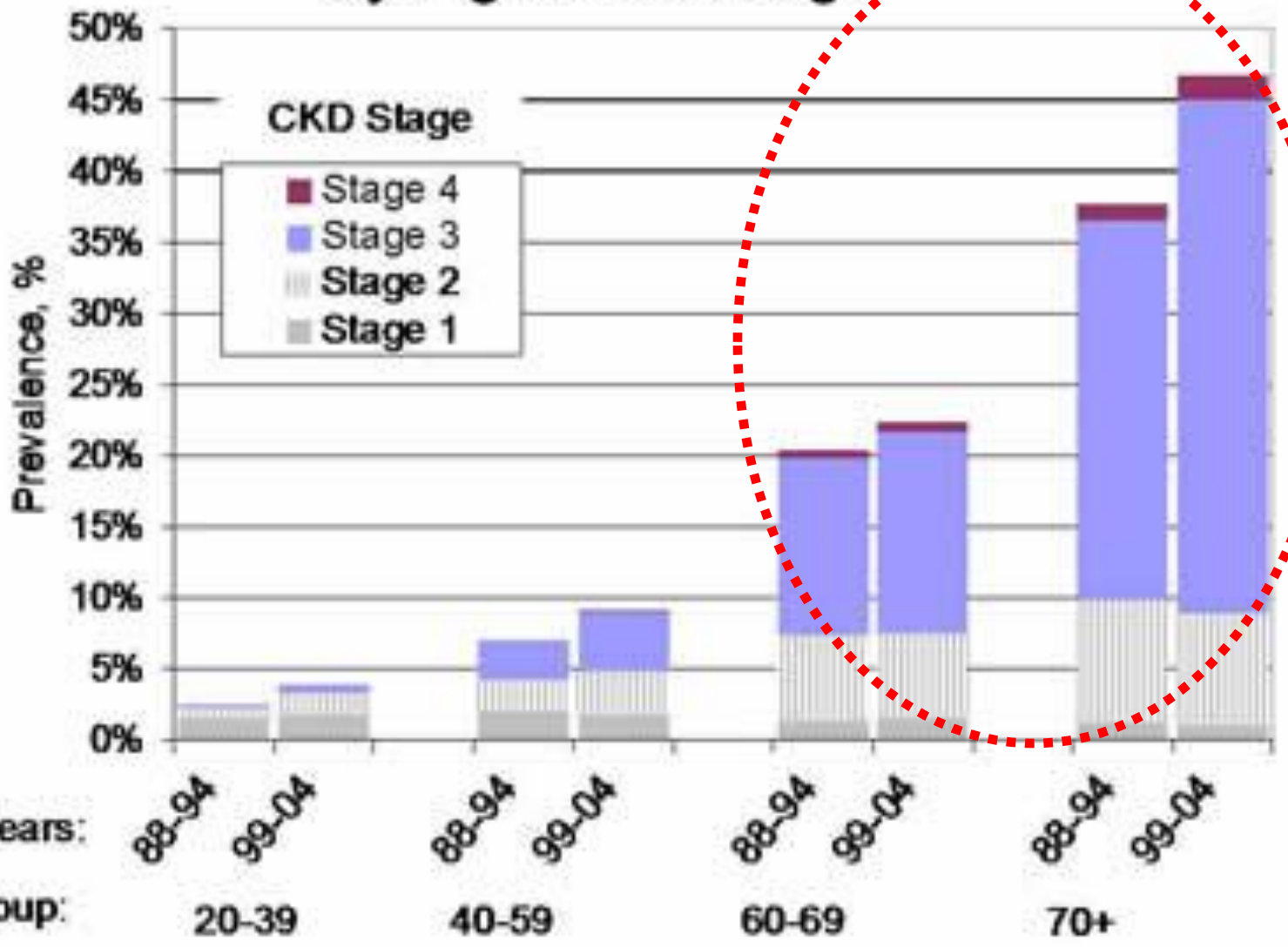


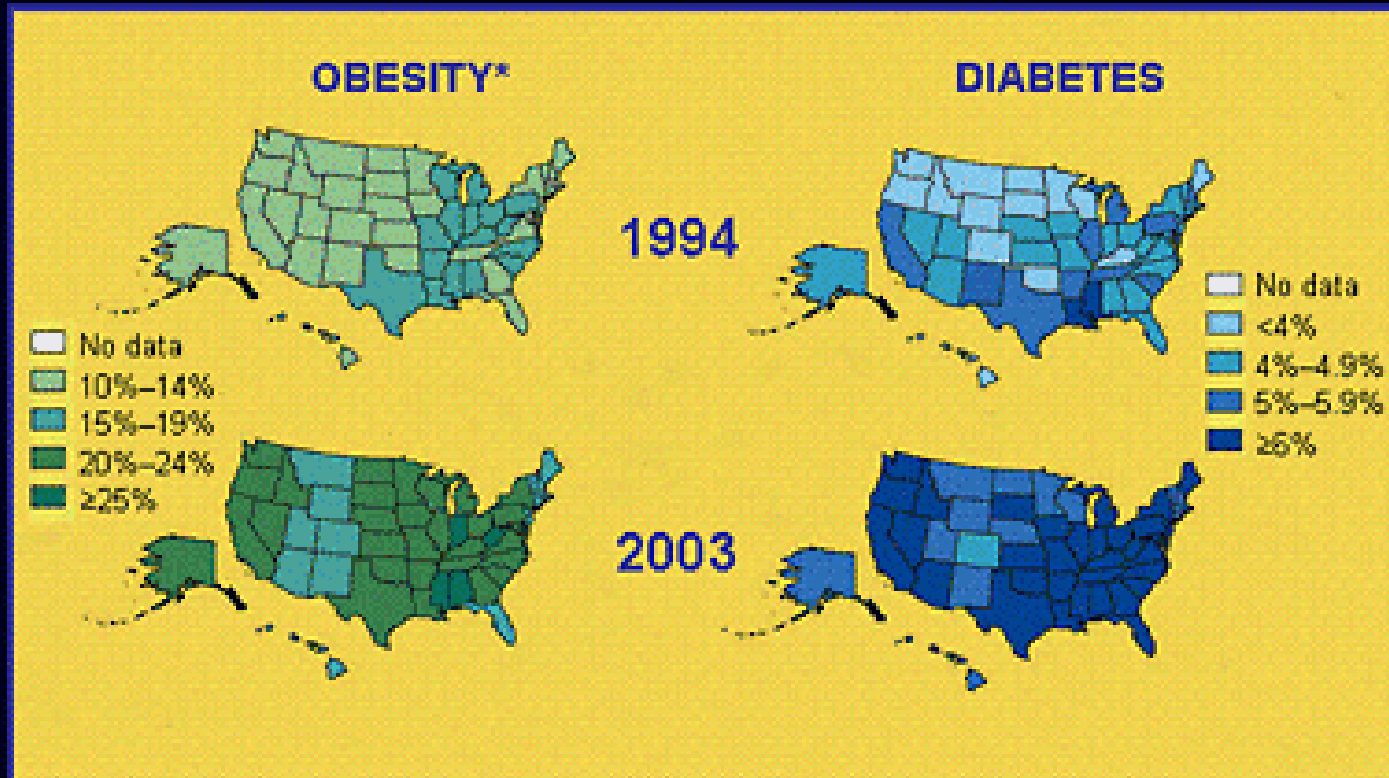
Figure 9 GFR versus age. Estimated GFR percentiles for the US population using NHANES III serum creatinine, age, sex, and race data (see Part 10, Appendix 2) by age compared to a regression of inulin clearance measurement of GFR on age among 70 healthy male participants. (Data abstracted from Davies and Shock [72])

US Trends in the Prevalence of CKD by Age and Stage



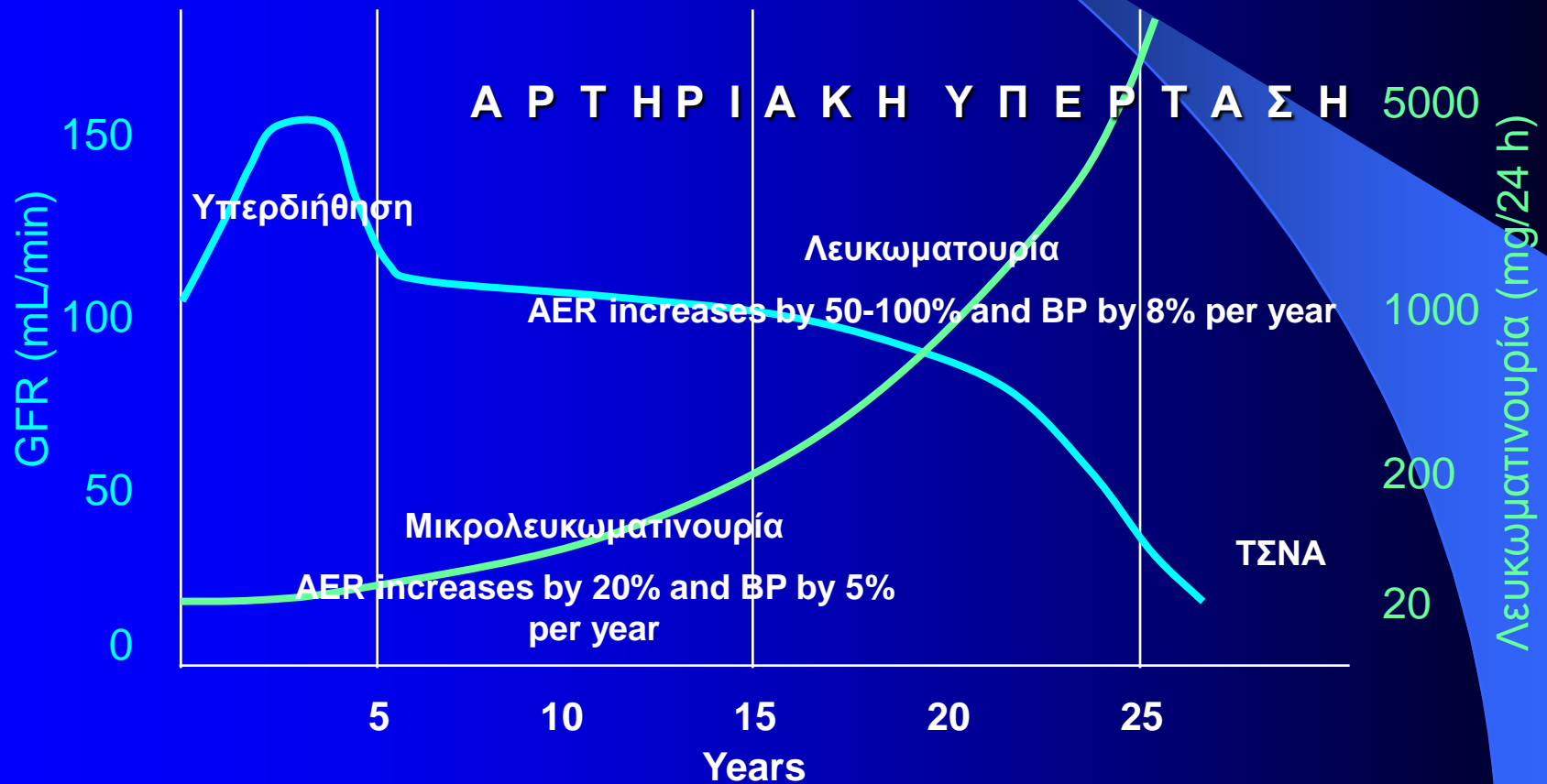
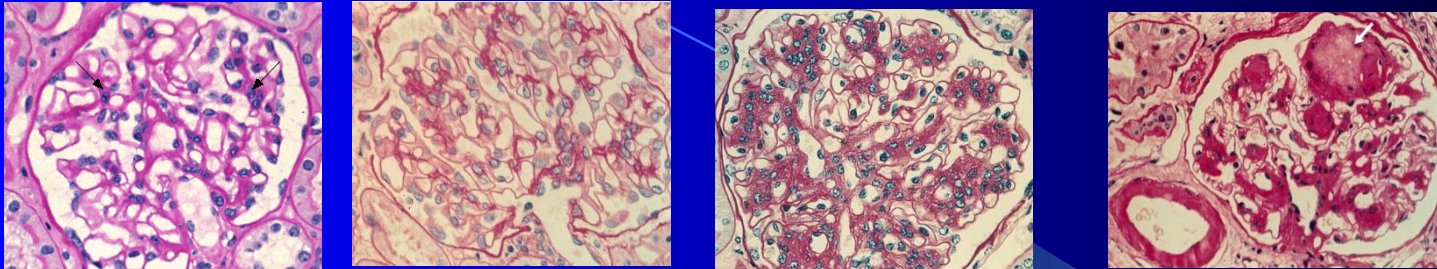


Obesity and Diabetes Epidemics

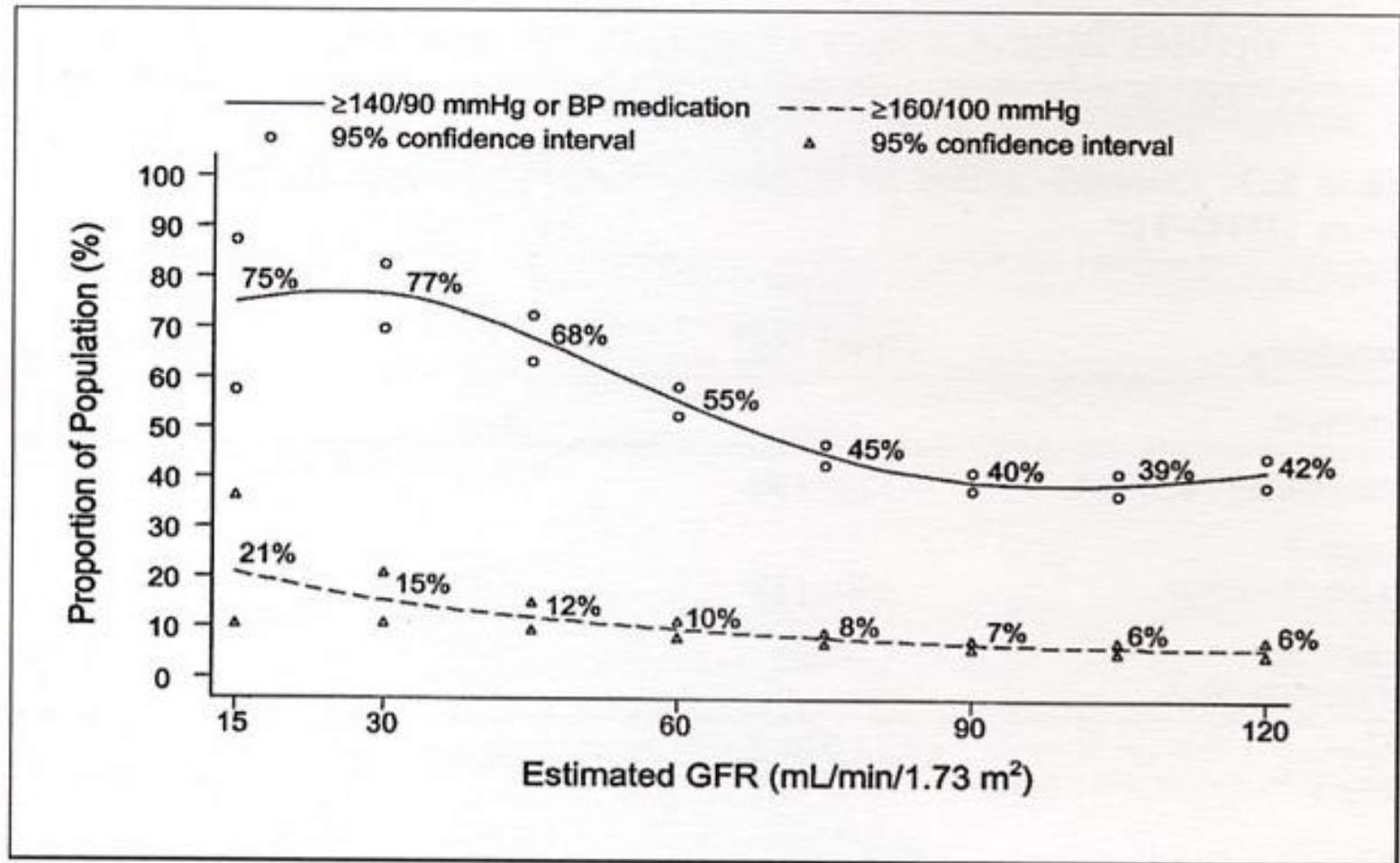


Εξέλιξη της διαβητικής νεφροπάθειας

ΔΝ 10% σε Τύπου II και 30% σε Τύπου I



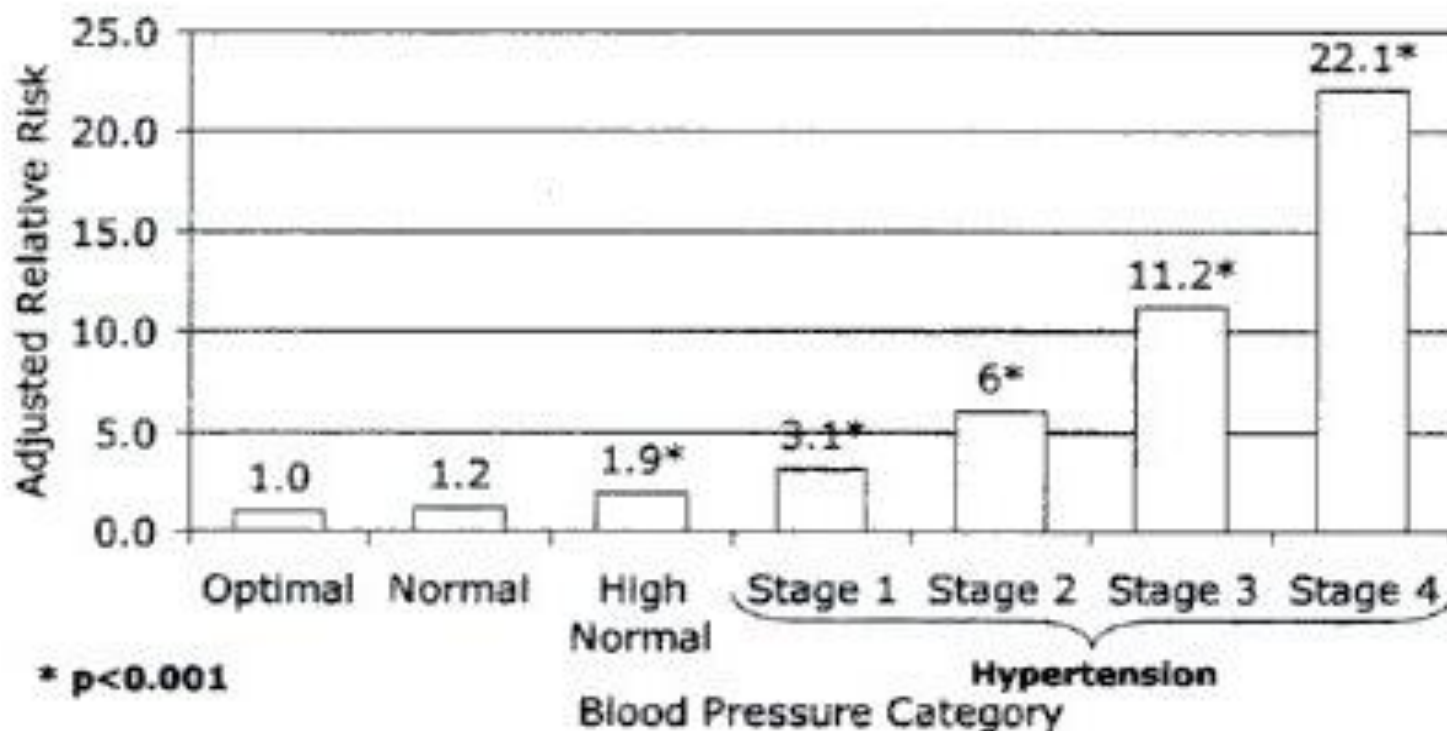
Prevalence of High Blood Pressure by Level of GFR, Adjusted to Age 60 Years (NHANES III)





ESRD Due to Any Cause In 332,544 Men Screened for MRFIT

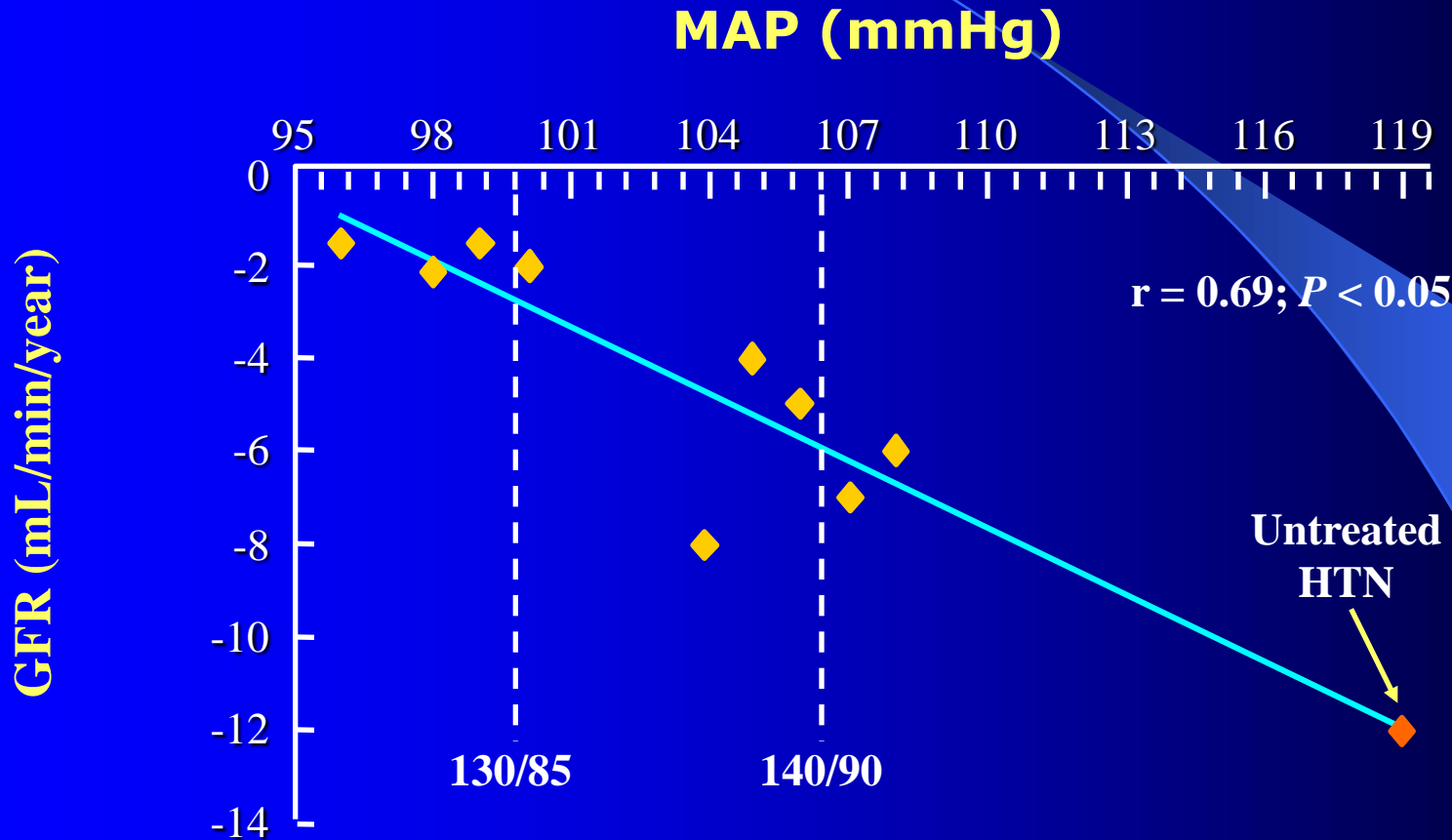
Adjusted Relative Risk[§]



Klag MJ, et al. N Engl J Med. 1996;334(1):13-18.

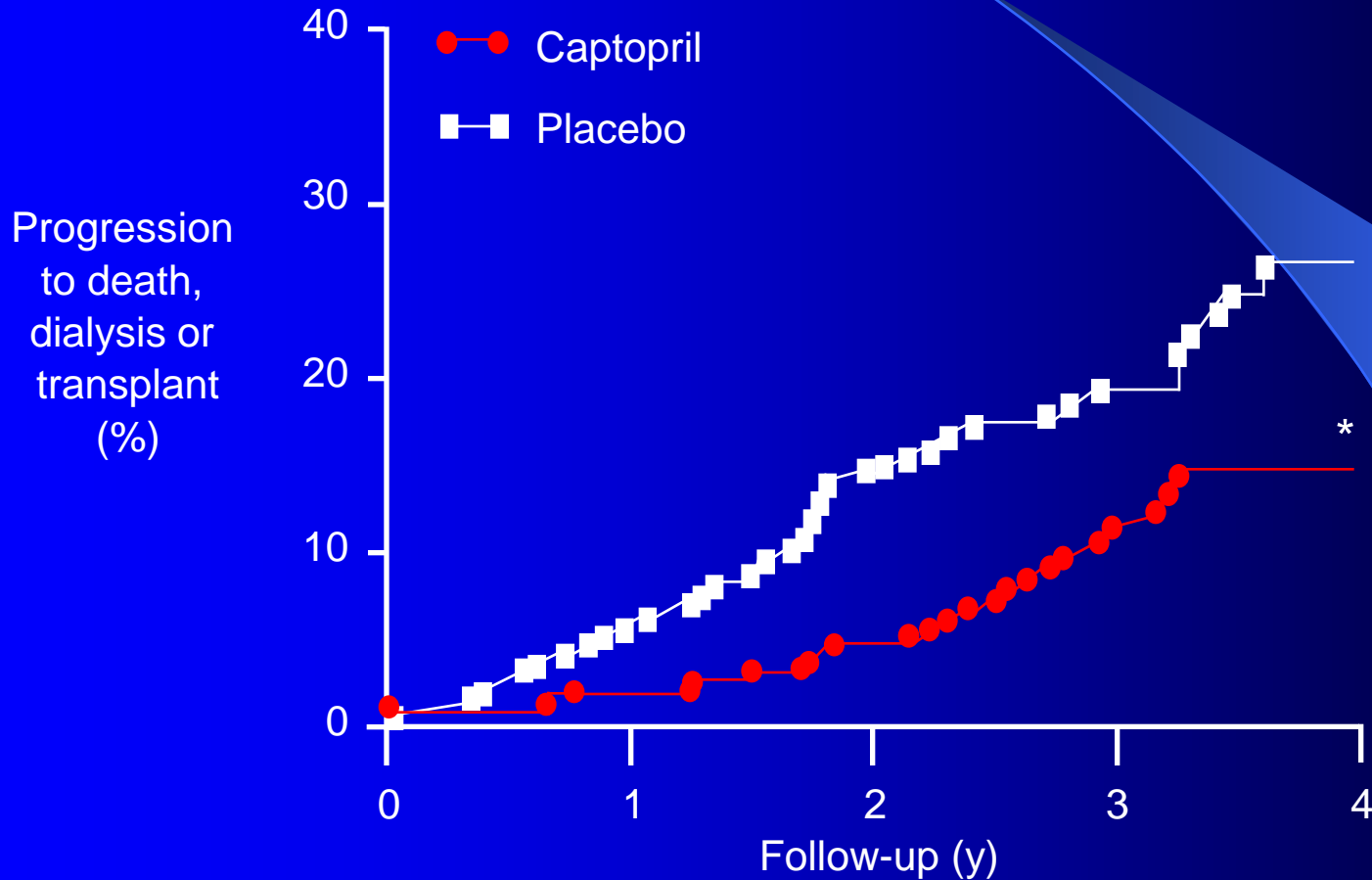


Meta Analysis: Lower Mean BP Results in Slower Rates of Decline in GFR in Diabetics and Non-Diabetics



Bakris GL, et al. Am J Kidney Dis. 2000;36(3):646-661.

Effect of ACE Inhibition on Nephropathy in Patients with Type 1 Diabetes



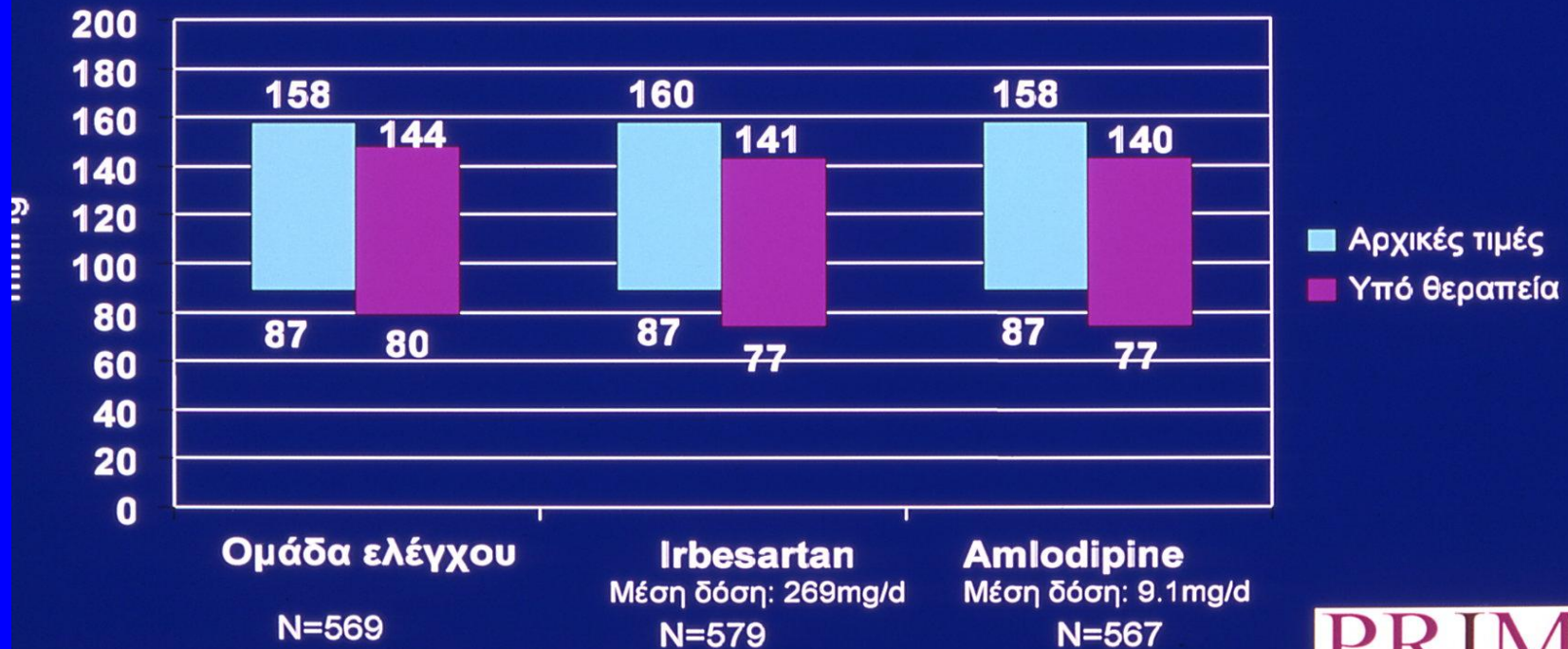
Collaborative Study Group
* $p = 0.006$ vs placebo.

Lewis EJ et al. *N Engl J Med* 1993;329:1456-1462.

Irbesartan vs Amlodipine in AODM

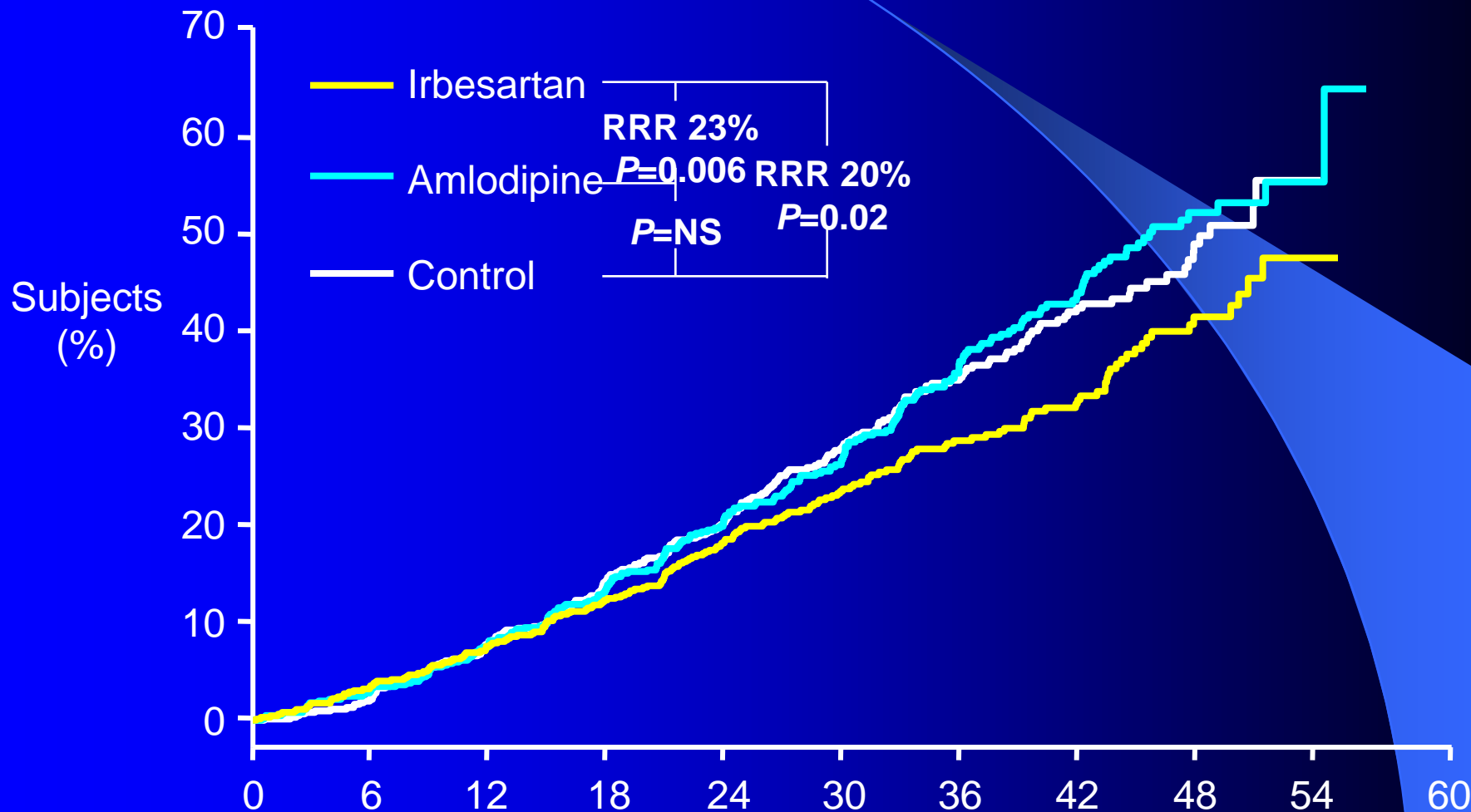
IDNT: Επίδραση στην αρτηριακή πίεση

Παρόμοια μείωση της ΑΠ



IDNT Primary Endpoint

Time to Doubling of Sr Creatinine, ESRD, or Death



Lewis EJ et al. *N Engl J Med* 2001;345:851-860. Follow-up (mo)

ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗΝ
ΠΡΟΣΟΧΗ ΣΑΣ

Ερώτηση 1: Ποια από τις παρακάτω παθήσεις του νεφρού **δεν** σχετίζεται με χαμηλά επίπεδα συμπληρώματος;

1. IgA νεφροπάθεια
2. Κρυσφαιριναιμική σπειραματονεφρίτιδα
3. Μεταλοιμώδης Σπειραματονεφρίτιδα
4. Νεφρίτιδα του Λύκου

Ερώτηση 2: Ποια από τις παρακάτω τιμές ΑΠ αποτελεί την ΑΠ στόχο σε διαβητικούς ασθενείς με σοβαρή πρωτεϊνουρία ;

1. $< 120/70$
2. $< 130/80$
3. $< 145/90$
4. $< 150/85$

Η σωστή απάντηση είναι η 2

Ερώτηση 3: Τί **ΔΕΝ** ισχύει για τη πρωτεϊνουρία:

1. Σε φυσιολογικές συνθήκες το ποσό της μετρούμενης πρωτεΐνης στα ούρα αντιστοιχεί στο ποσό πρωτεΐνης που διηθείται από το σπείραμα
2. Η πρωτεϊνουρία συμβάλλει στην εξέλιξη της ΧΝΝ μέσω της έναρξης της σωληναριακής βλάβης κι εξέλιξης της διαμεσοσωληναριακής ίνωσης
3. Η μείωση της πρωτεϊνουρίας συνδυάζεται με καλύτερη έκβαση της νεφροπάθειας
3. Δεν αποτελεί μηχανισμό ικανό να εξηγήσει από μόνος του την εξέλιξη της ΧΝΝ

Η σωστή απάντηση είναι η 1

Ερώτηση 4: Ποιο από τα παρακάτω είναι σωστό όσον αφορά στη θεραπευτική παρέμβαση στο ΣΔ.

1. Ο καλός γλυκαιμικός έλεγχος σημαίνει επίτευξη επιπέδων HbA1c < 6%
2. Ο καλός γλυκαιμικός έλεγχος έχει ευεργετικά αποτελέσματα στις μικροαγγειακές επιπλοκές του ΣΔ
3. Ο καλός γλυκαιμικός έλεγχος δεν έχει επίδραση στην εμφάνιση και εξέλιξη της λευκωματινουρίας
4. Ο αποκλεισμός του άξονα ΡΑΑ δεν έχει νεφροπροστατευτική δράση

Η σωστή απάντηση είναι η 2

Ερώτηση 5: Με ποια από τις παρακάτω παθήσεις φαίνεται να έχει στενή παθογενετική σχέση η σπειραματονεφρίτιδα με αντισώματα εναντίον της βασικής μεμβράνης

1. Πορφύρα Henoch-Schoenlein
2. Μικροσκοπική πολυαγγειίτιδα
3. Σύνδρομο Goodpasture
4. Κρυσφαιριναιμία

Η σωστή απάντηση είναι η 3