Υπέρταση σε ειδικές ομάδες-Νεφρική Βλάβη

Ιωάννης Γ. Γριβέας, *MD, PhD*
Νεφρολόγος

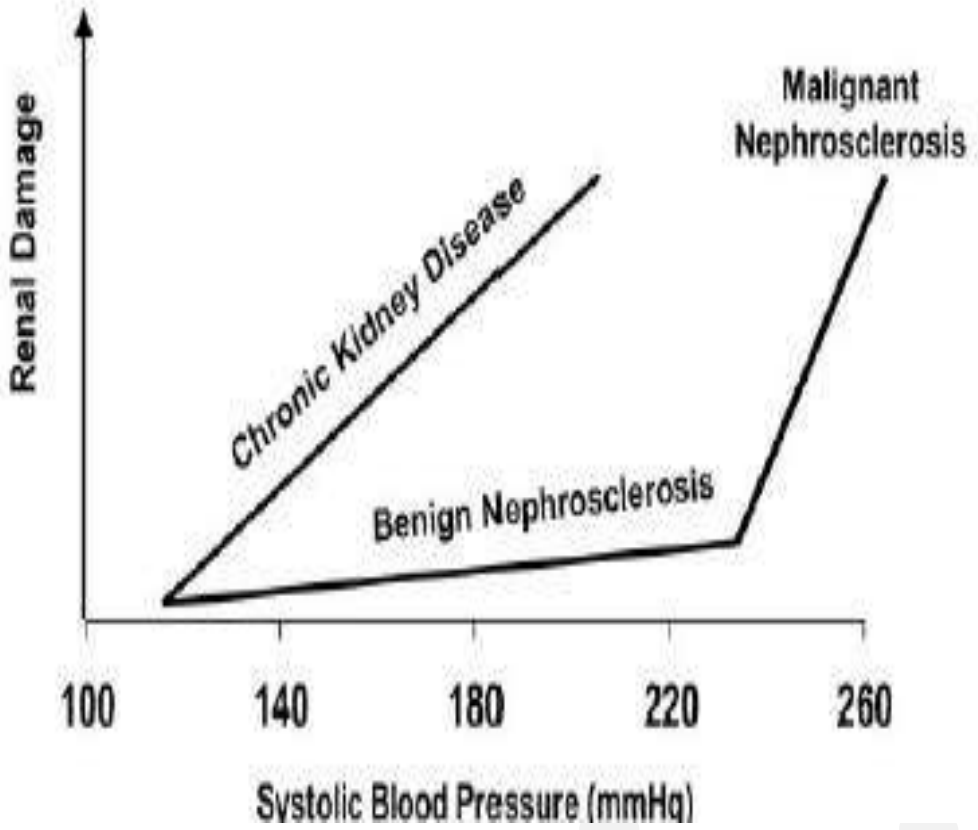
athens-NEPHROLOGY

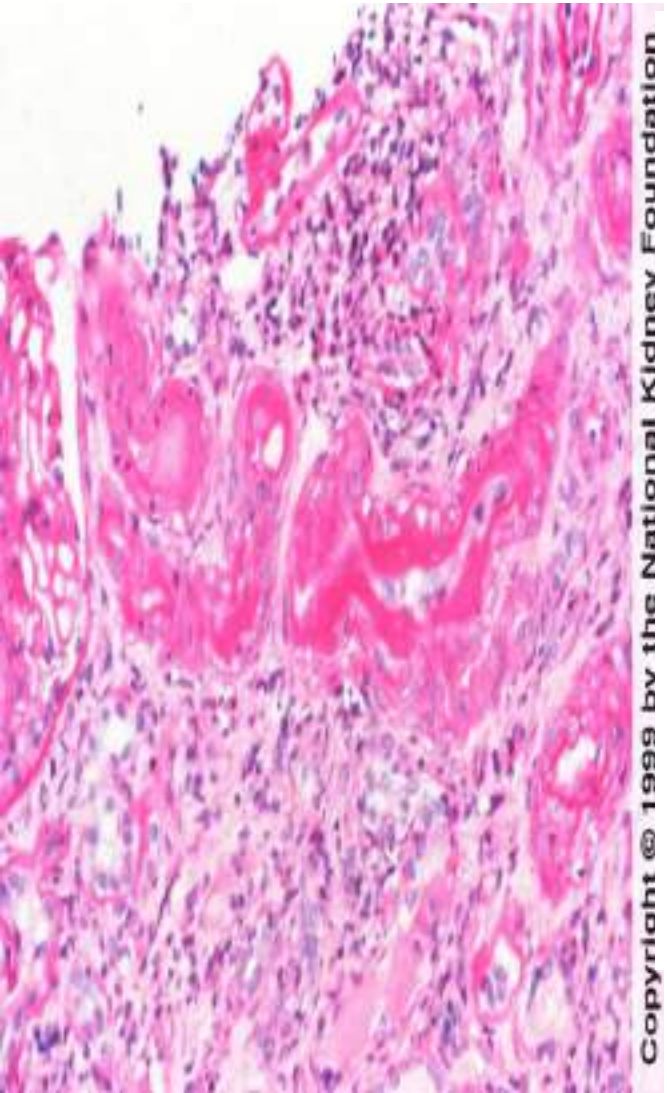
Pathophysiology of Hypertensive Renal Damage

Implications for Therapy

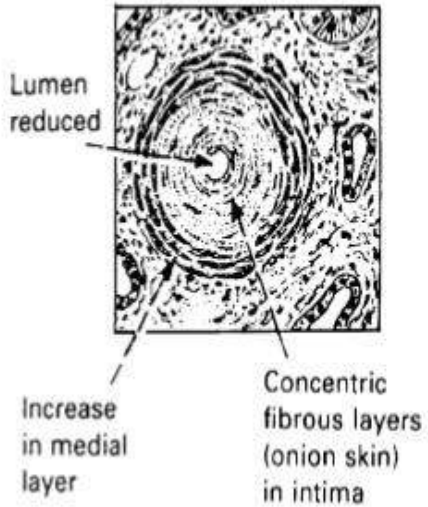
Anil K. Bidani, Karen A. Griffin

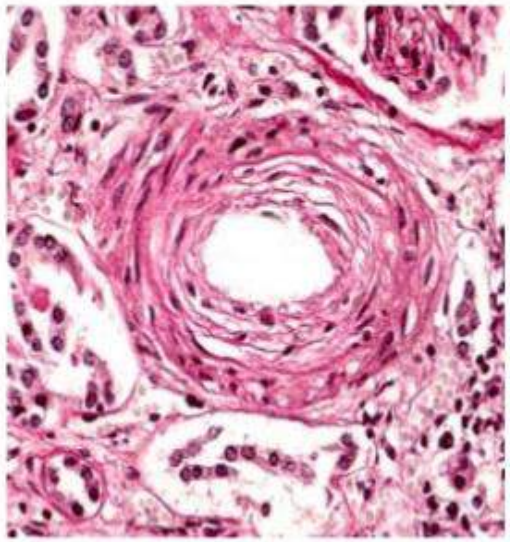
(*Hypertension*. 2004;44:595-601.

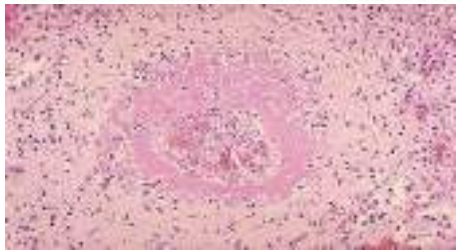


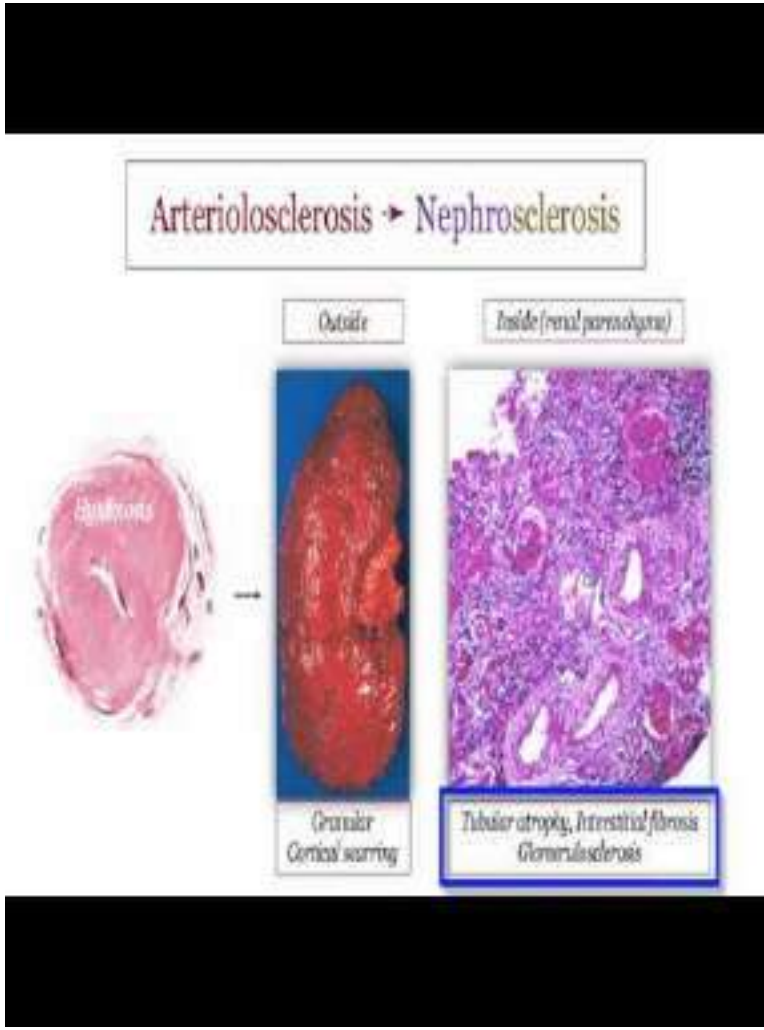


Malignant Nephrosclerosis










Risk Factor

Παράγοντες που επηρεάζουν την έναρξη και την εξέλιξη της ΧΝΝ

- Η ΧΝΝ είναι μία πολυπαραγοντική διαδικασία.
- Οι παράγοντες κινδύνου για ΧΝΝ σχετίζονται με την

  Ευαισθησία (προδιάθεση για ΧΝΝ)

  Έναρξη (πρόκληση απευθείας νεφρικής βλάβης)

  Εξέλιξη (επιδείνωση ήδη εγκατεστημένης νεφρικής βλάβης)

- Οι παράγοντες κινδύνου διακρίνονται σε τροποιήσιμους και μη.
- Από τη στιγμή που εγκατασταθεί νεφρική βλάβη η εξέλιξη της Χρόνιας Νεφρικής Νόσου επηρεάζεται από μία σειρά τροποιήσιμους και μη παράγοντες.

Παράγοντες κινδύνου που σχετίζονται με την έναρξη και την πρόοδο της ΧΝΝ

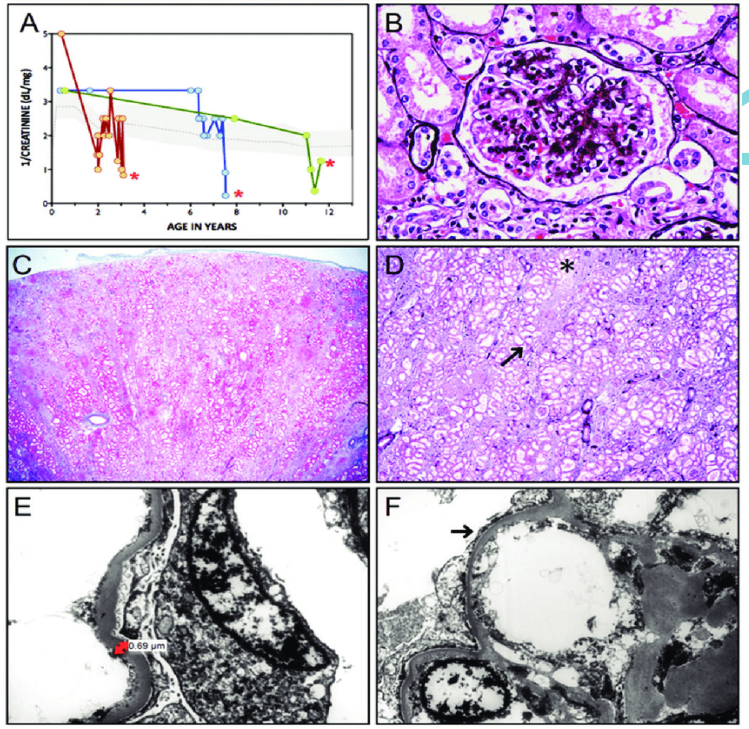
Παράγοντες Έναρξης

- ***Υπέρταση***
- Σακχαρώδης Διαβήτης
- Καρδιαγγειακή Νόσος
- Σπειραματονεφρίτιδες/Αυτοάνοσα νοσήματα
- Δυσλιπιδαιμία
- Παχυσαρκία/Μεταβολικό Σύνδρομο
- Υπερουριχαιμία
- Κάπνισμα
- Χαμηλή κοινωνικοοικονομική θέση
- Νεφροτοξίνες (μη στεροειδή αντιφλεγμονώδη, αναλγητικά, βότανα, βαρέα μέταλλα)

Παράγοντες Προόδου

- Μεγαλύτερη Ηλικία
- Φύλο (άνδρες)
- Φυλή/εθνότητα
- Γενετική Προδιάθεση
- ***Φτωχός έλεγχος αρτηριακής πίεσης***
- Φτωχός έλεγχος γλυκαιμίας
- Πρωτεινουρία
- Καρδιαγγειακή νόσος
- Δυσλιπιδαιμία
- Κάπνισμα
- Παχυσαρκία/Μεταβολικό σύνδρομο
- Υπερουριχαιμία
- Χαμηλή κοινωνικοοικονομική θέση
- Κατανάλωση αλκοόλ
- Οξεία Νεφρική Βλάβη
- Νεφροτοξίνες

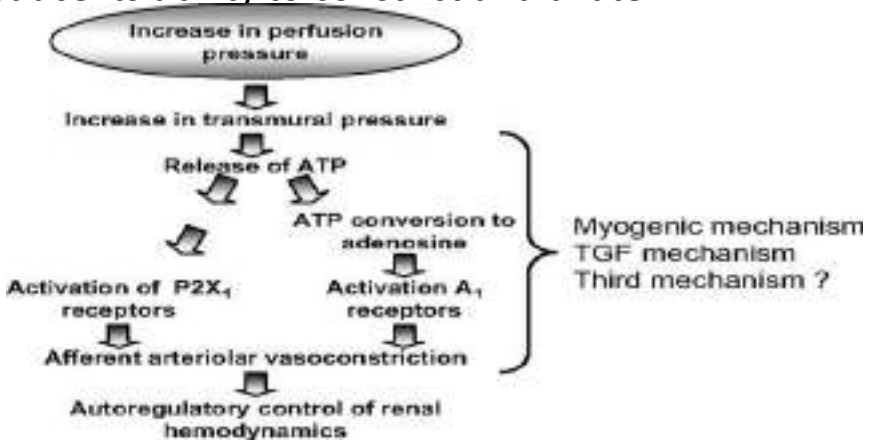
Glomerular hypertension, Nephrosclerosis, and progressive loss of kidney function



1

Normally, the glomerular capillary loops are shielded from elevated systemic arterial pressures by a process called ***autoregulation.***

However, in hypertensive patients, chronically elevated systemic arterial pressures cause remodeling of the afferent arteriole and reduce its ability to constrict and dilate.



02 Content Here

Afferent arteriole caliber changes in response to systemic pressure (myogenic reflex) and sodium chloride delivery to the macula densa (tubuloglomerular feedback) are part of the autoregulatory process that helps maintain intraglomerular pressure and therefore GFR.

Ο παθοφυσιολογικός μηχανισμός νεφρικής βλάβης από υπέρταση συναρτάται από τρείς παραμέτρους

01 το «φορτίο» της υπέρτασης

02 τον βαθμό στον οποίο το φορτίο αυτό μεταφέρεται στο αγγειακό δίκτυο του νεφρού

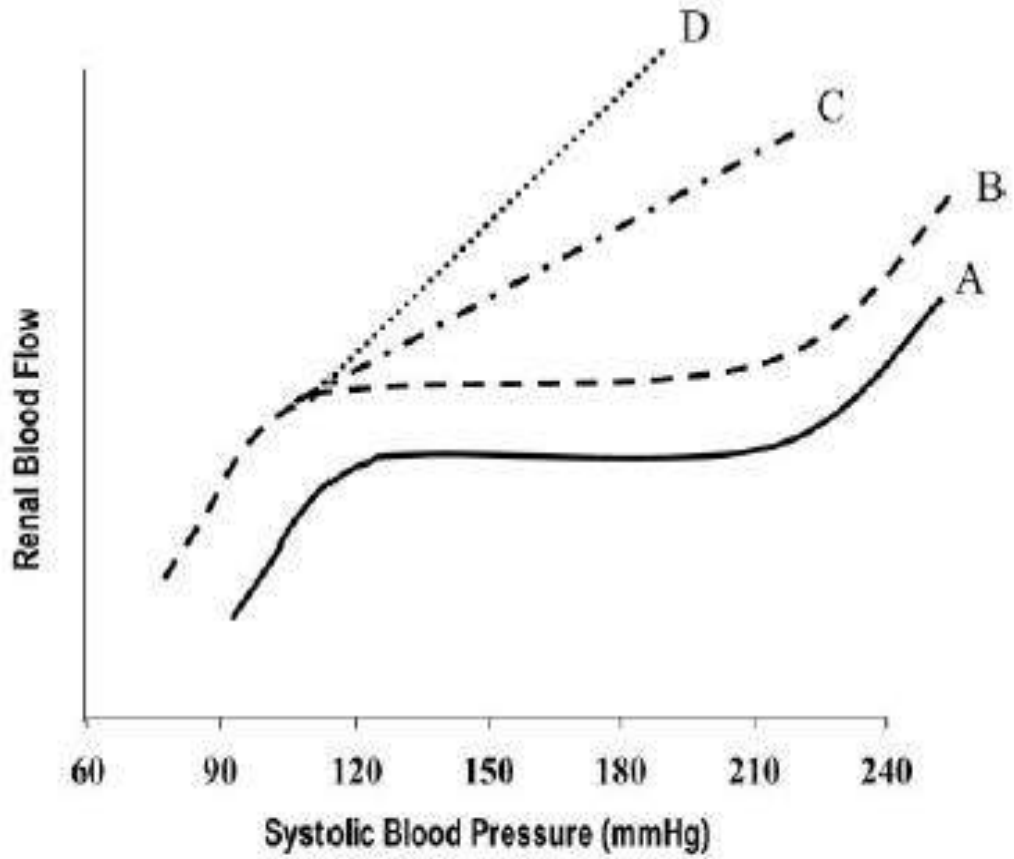
03 την τοπική ευαισθησία του νεφρικού ιστού

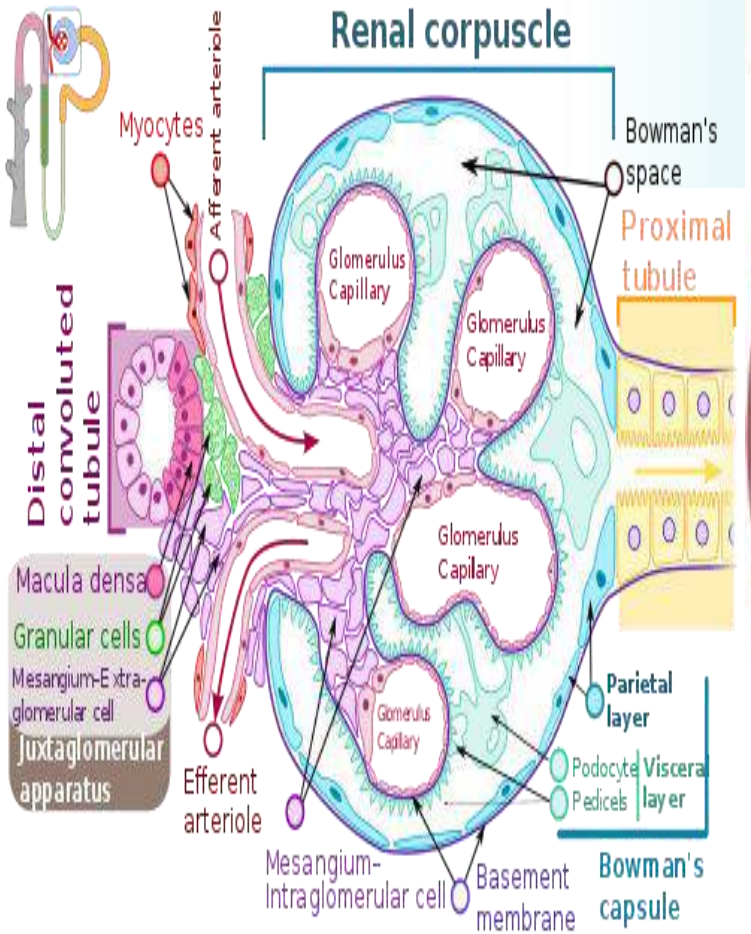
Pathophysiology of Hypertensive Renal Damage

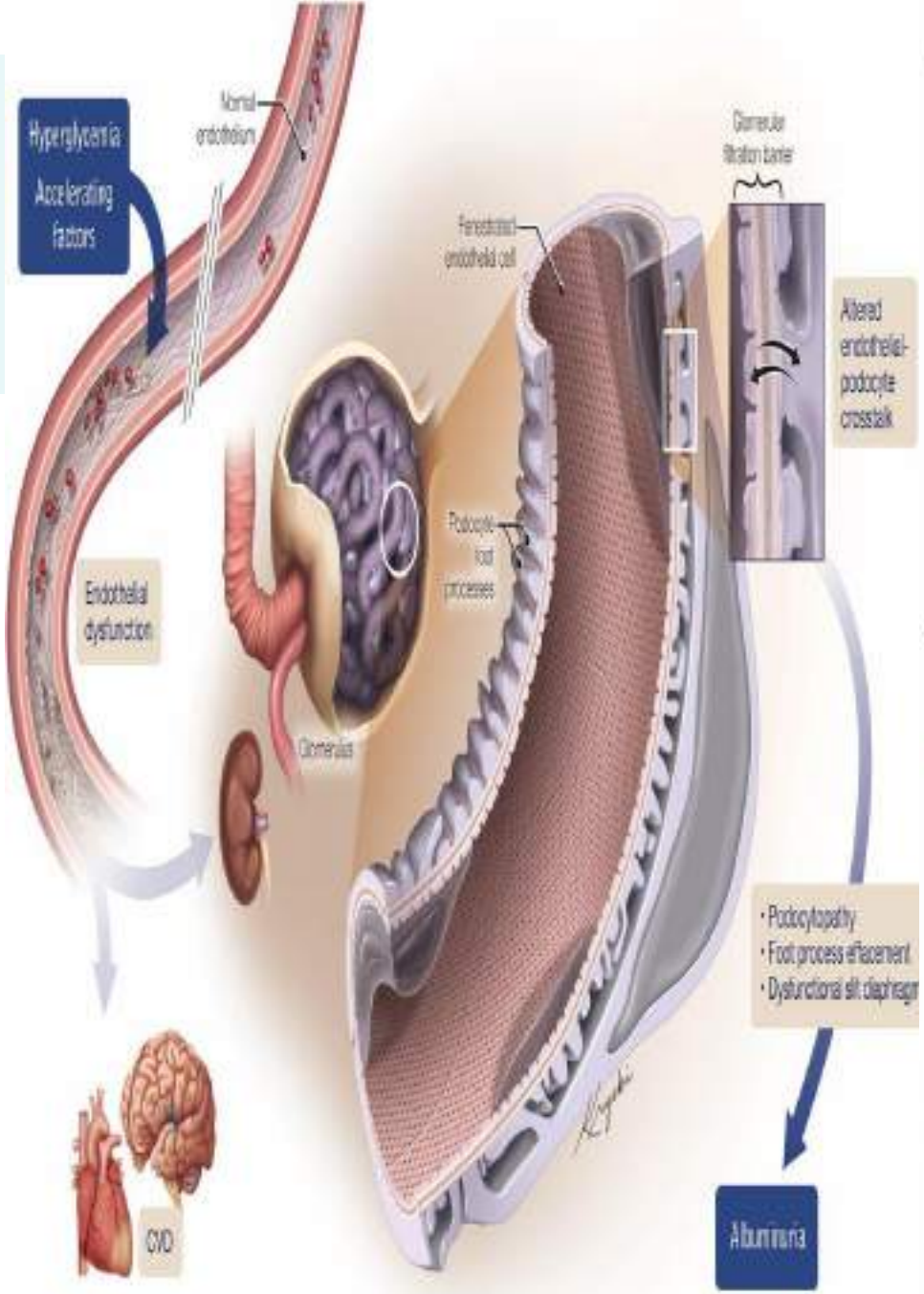
Implications for Therapy

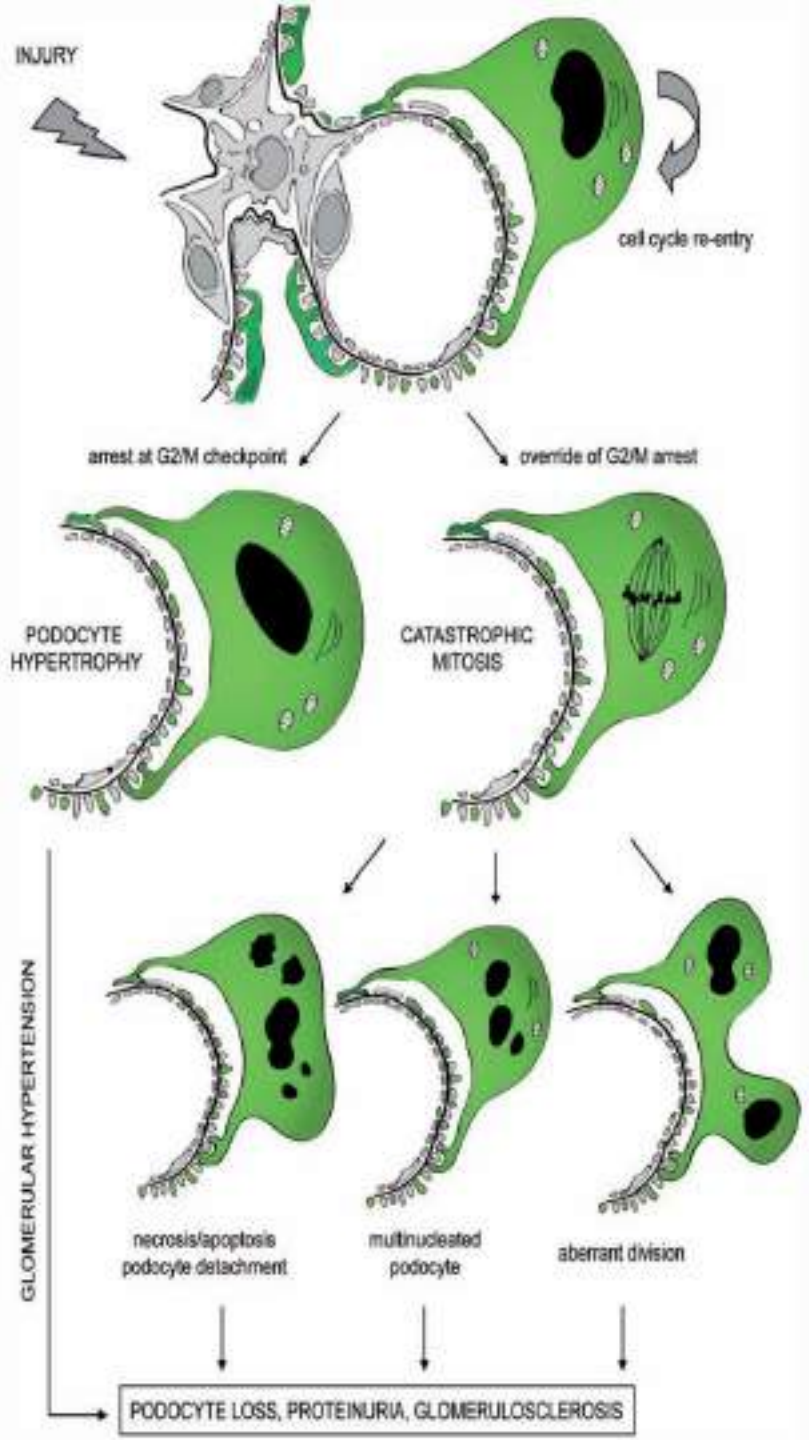
Anil K. Bidani, Karen A. Griffin

(*Hypertension*. 2004;44:595-601.




Renal corpuscle
Myocytes
Afferent arteriole
Bowman's space
Proximal tubule
Glomerulus Capillary
Glomerulus Capillary
Glomerulus Capillary
Distal convoluted tubule
Macula densa
Granular cells
Mesangium-Extra-glomerular cell
Juxtaglomerular apparatus
Efferent arteriole
Glomerulus Capillary
Parietal layer
Podocyte Pedicels
Visceral layer
Mesangium-Intraglomerular cell
Basement membrane
Bowman's capsule

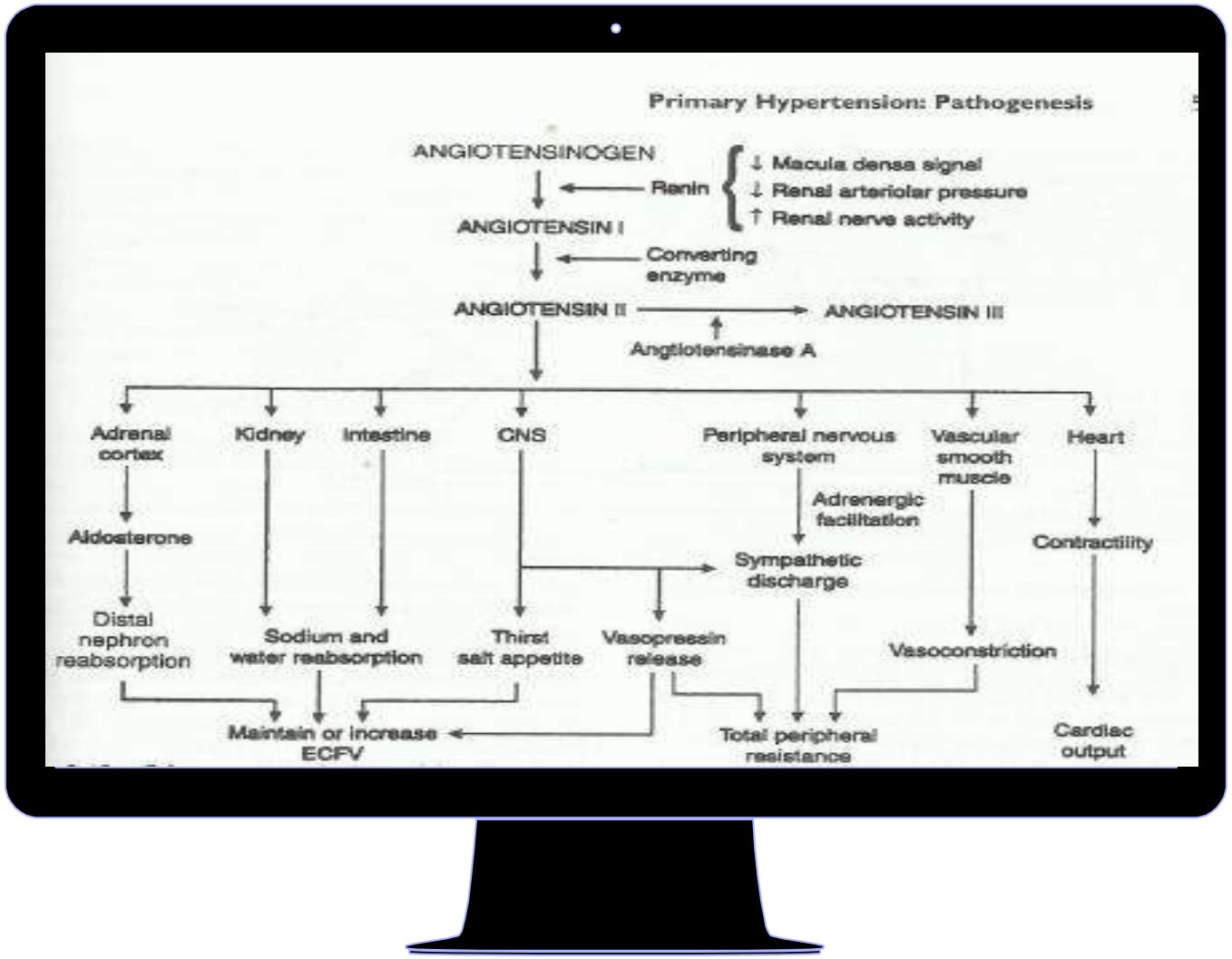

Hyperglycemia
Accelerating factors
Normal endothelium
Endothelial dysfunction
Glomerular filtration barrier
Fenestrated endothelial cell
Podocyte foot processes
Altered endothelial-podocyte crosstalk
Glomerulus
• Podocytopathy
• Foot process effacement
• Dysfunctional slit diaphragm
Albuminuria
CVD


INJURY
cell cycle re-entry
arrest at G2/M checkpoint
override of G2/M arrest
PODOCYTE HYPERTROPHY
CATASTROPHIC MITOSIS
GLOMERULAR HYPERTENSION
necrosis/apoptosis podocyte detachment
multinucleated podocyte
aberrant division
PODOCYTE LOSS, PROTEINURIA, GLOMERULOSCLEROSIS

The inextricable role of the kidney in hypertension

Steven D. Crowley[1] and Thomas M. Coffman[1,2]

The renin-angiotensin system (RAS) is a powerful modulator of blood pressure, and dysregulation of the RAS causes hypertension. Pharmacological blockade of the RAS with renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers effectively lowers blood pressure in a substantial proportion of patients with hypertension (19), reflecting the important role for RAS activation as a cause of human hypertension. Similarly, in rodent models, deletion of RAS genes lowers blood pressure whereas overexpression causes hypertension (20).



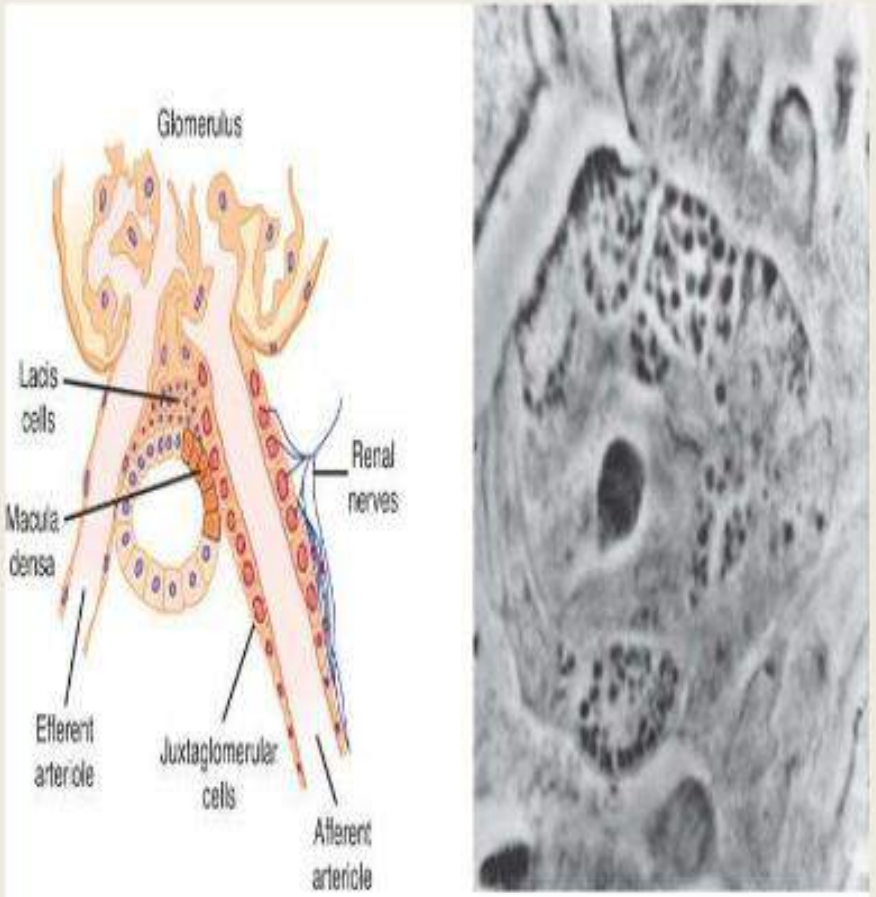
J Clin Invest. 2014;124(6):2341-2347. https://doi.org/10.1172/JCI72274.

...Η Μοριακή βιολογία του συστήματος είναι πιο περίπλοκη από ότι πιστεύαμε...

...Human renin gene...

Renin –
Hormonal peptide-340 AA,an enzyme .
T½ -15 min ,prepared and stored in granular JG cells in kidney and also other tisuue–the main source of plasma Renin (active) and 90% in prorenin (inactive but immune reactive).it is synthesized In both constitutive and rate limiting pathway. It catalyzes the rate limiting step of RAS – attract active future target.

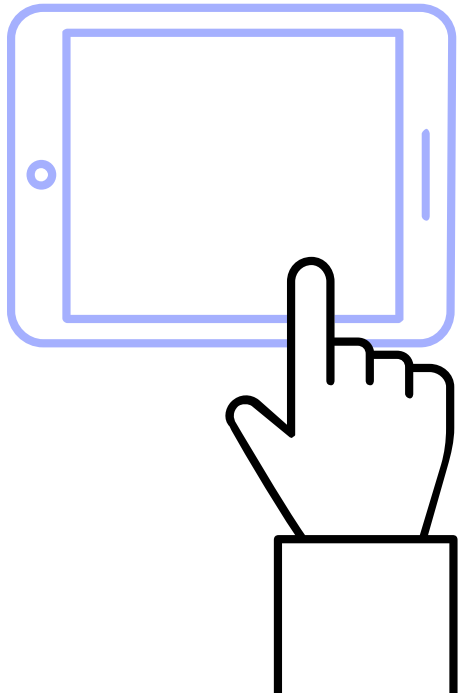
Stretch receptors(pressure sensor) in the afferent arteriole, local SNS , Na content of the tubular fluid reaching the macula Desna cell - release around JGA→Renin .

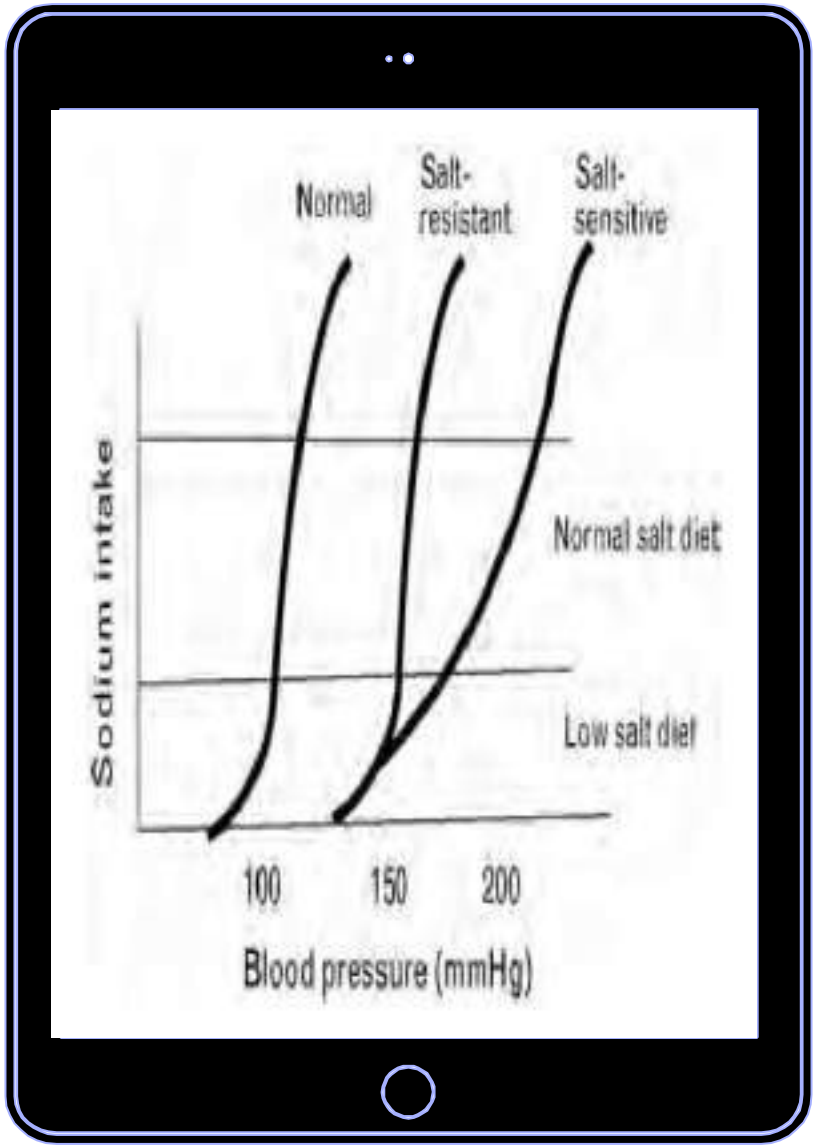


Source: Barrett KE, Barman SM, Boitano S, Brooks HL: Ganong's Review of Medical Physiology, 23rd Edition: http://www.accessmedicine.com

Εξήγηση του φαινομένου

Abnormally regulated and rather fixed local level of tissue AII





LOREM IPSUM
DOLOR SIT AME

LOREM IPSUM DOLOR SIT AMET,
CU USU AGAM INTEGRE IMPEDIT.

Therapeutic Implications

The pathophysiology of hypertensive renal damage discussed suggests 3 broad targets for therapeutic interventions: (1) reduction of BP load; (2) reduction of pressure transmission to the renal microvasculature; and (3) interruption and/or modification of the local cellular/molecular pathways that mediate eventual tissue injury and fibrosis.

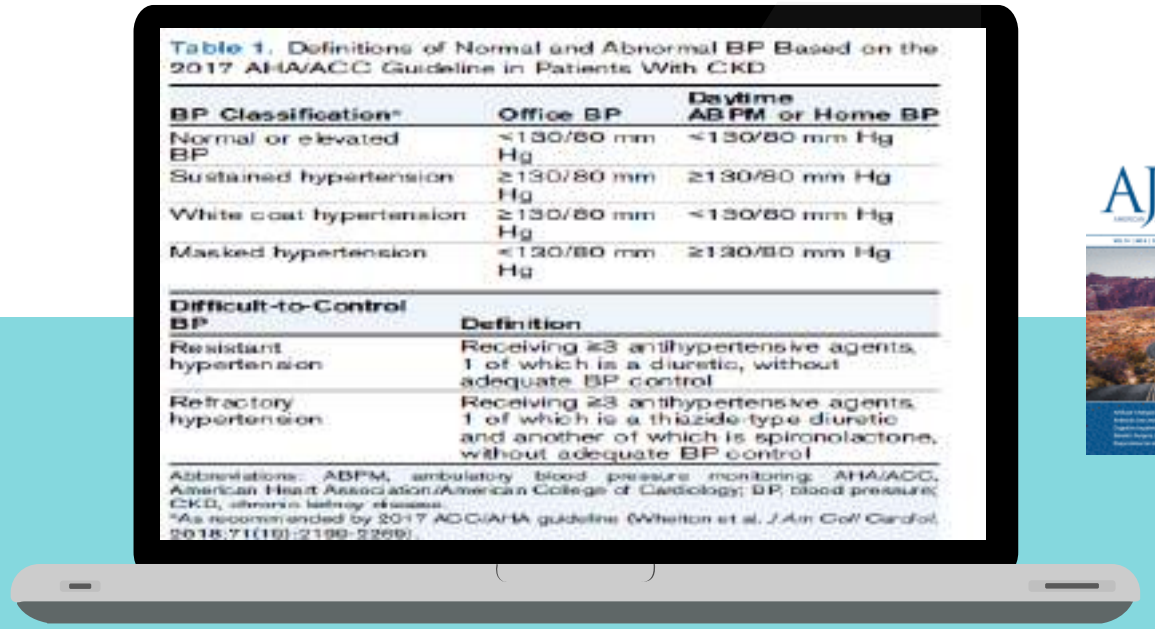


Table 1. Definitions of Normal and Abnormal BP Based on the 2017 AHA/ACC Guideline in Patients With CKD

BP Classification*	Office BP	Daytime ABPM or Home BP
Normal or elevated BP	<130/80 mm Hg	<130/80 mm Hg
Sustained hypertension	≥130/80 mm Hg	≥130/80 mm Hg
White coat hypertension	≥130/80 mm Hg	<130/80 mm Hg
Masked hypertension	<130/80 mm Hg	≥130/80 mm Hg

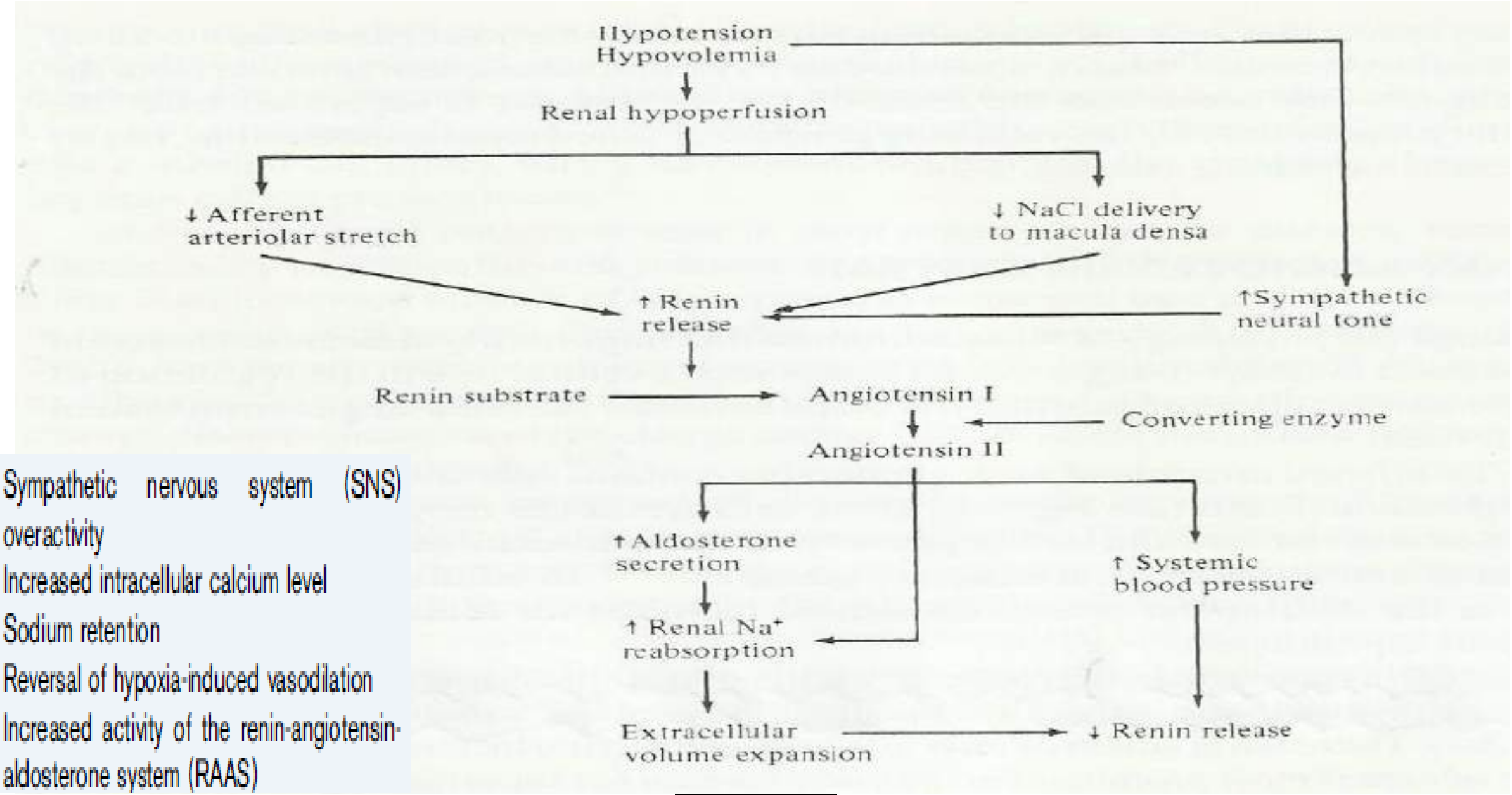
Difficult-to-Control BP	Definition
Resistant hypertension	Receiving ≥3 antihypertensive agents, 1 of which is a diuretic, without adequate BP control
Refractory hypertension	Receiving ≥3 antihypertensive agents, 1 of which is a thiazide-type diuretic and another of which is spironolactone, without adequate BP control

Abbreviations: ABPM, ambulatory blood pressure monitoring; AHA/ACC, American Heart Association/American College of Cardiology; BP, blood pressure; CKD, chronic kidney disease.
*As recommended by 2017 ACC/AHA guideline (Whelton et al. J Am Coll Cardiol. 2018;71(19):2199-2269).

AJKD

Hypertension in CKD: Core Curriculum 2019

Elaine Ku, Benjamin J. Lee, Jenny Wei, and Matthew R. Weir



a) Sympathetic nervous system (SNS) overactivity
b) Increased intracellular calcium level
c) Sodium retention
d) Reversal of hypoxia-induced vasodilation
e) Increased activity of the renin-angiotensin-aldosterone system (RAAS)

[redacted]

AJKD

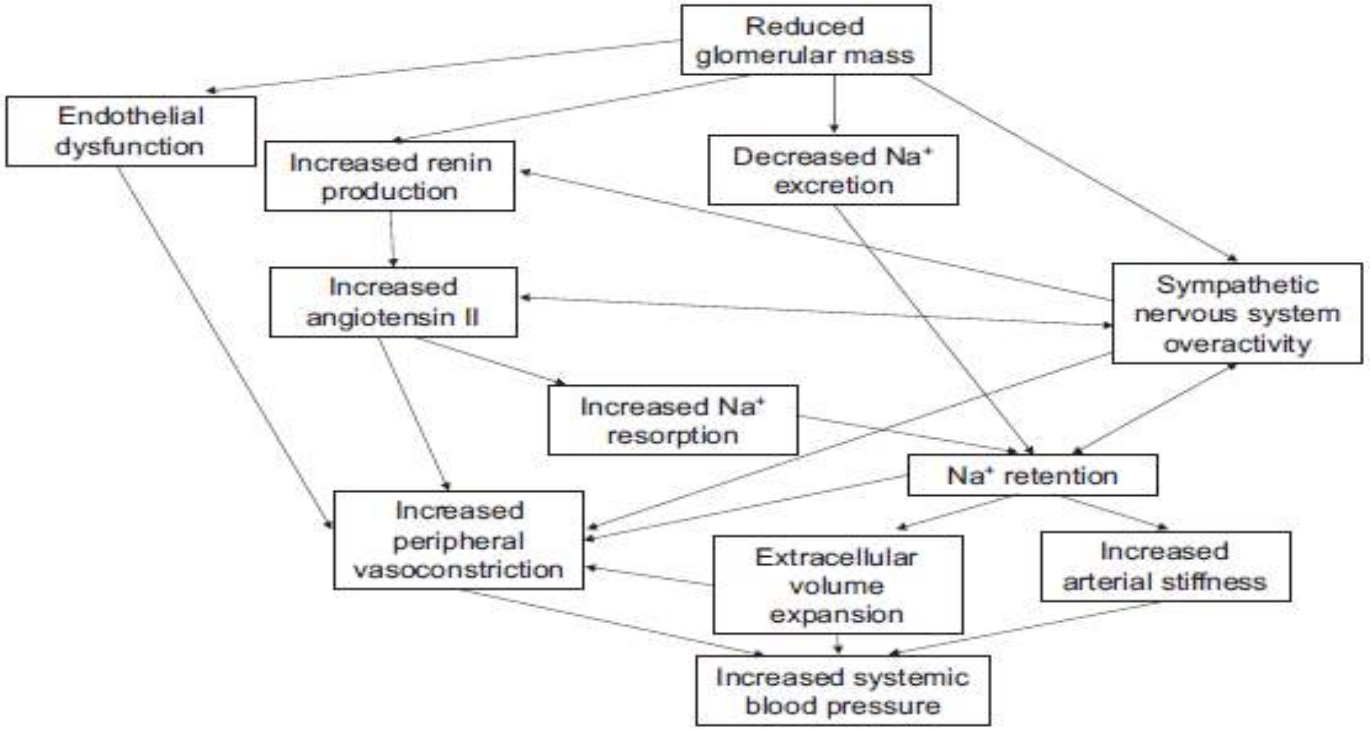


Figure 1. Pathophysiologic mechanisms of hypertension in chronic kidney disease.

AJKD

Hypertension in CKD: Core Curriculum 2019

Elaine Ku, Benjamin J. Lee, Jenny Wei, and Matthew R. Weir

Box 1. Causes of Secondary Hypertension

- Renovascular hypertension (atherosclerosis, fibromuscular dysplasia)
- Coarctation of the aorta
- Primary aldosteronism
- Pheochromocytoma
- Polycystic ovary syndrome
- Cushing syndrome
- Hyperthyroidism, hypothyroidism
- Obstructive sleep apnea
  - Chemical or medication induced
  - Caffeine, coffee
  - Alcohol
  - NSAIDs
  - Oral contraceptives
  - Steroids
  - Calcineurin inhibitors
  - Chemotherapeutic agents (gemcitabine, VEGF receptor inhibitors)
  - Illicit drugs (amphetamines, cocaine)
- Monogenic disorders
  - Liddle syndrome
  - Syndrome of apparent mineralocorticoid excess
  - Glucocorticoid-remediable hypertension (familial hyperaldosteronism type I)
  - Familial hyperaldosteronism type III
  - Gordon syndrome
  - Subtypes of congenital adrenal hyperplasia

Difficult-to-Control BP	Definition
Resistant hypertension	Receiving ≥3 antihypertensive agents, 1 of which is a diuretic, without adequate BP control
Refractory hypertension	Receiving ≥3 antihypertensive agents, 1 of which is a thiazide-type diuretic and another of which is spironolactone, without adequate BP control

AJKD

Hypertension in CKD: Core Curriculum 2019

Elaine Ku, Benjamin J. Lee, Jenny Wei, and Matthew R. Weir

Table 2. Selected Indications and Considerations in the Choice of Antihypertensive Agents for Patients With CKD

Medications	CKD-Related Indications	Other Potential Indications	Common Side Effects	Potential Contraindications	Other Considerations
Diuretics					
Thiazide (eg, hydrochlorothiazide, chlorthalidone, metolazone)	Fluid overload; may improve proteinuria if used in combination with RAS inhibitors	Kidney stone prevention (hypercalciuria); Gordon syndrome; NDI	Hyperuricemia; hypercalcemia; hyponatremia; hypokalemia; hyperglycemia (with long-term use)	Gout; hypercalcemia	May be less effective when eGFR is <30 although some studies have shown these agents remain effective even with low eGFR
Loop (eg, furosemide, bumetanide, torsemide)	Fluid overload	Heart failure; hypercalcemia	Hearing loss; hypokalemia; hypocalcemia; hyponatremia	Gout; sulfonamide-related hypersensitivity	Bumetanide and torsemide have better intestinal absorption than furosemide
Potassium-sparing (triamterene, amiloride)	Fluid overload; hypokalemia	Refractory hypomagnesemia; lithium toxicity/NDI	Hyperkalemia; metabolic acidosis	Pregnancy	
RAS Blockade					
ACEI (first-line agents if proteinuria)	Proteinuria reduction; delays progression of CKD	Heart failure with reduced ejection fraction; post–myocardial infarction	Cough; angioedema; hyperkalemia; leukopenia; anemia	Pregnancy; bilateral renal artery stenosis	
ARBs (first-line agents if proteinuria)	Proteinuria reduction; delays progression of CKD	Uric acid lowering (losartan) or gout; similar to ACEI	Cough (less than with ACEI); angioedema; hyperkalemia	Pregnancy; bilateral renal artery stenosis	
β-Blockers					
Selective (metoprolol, nebivolol)		Heart failure; atrial fibrillation; migraines; essential tremors; anxiety disorders; angina	Bradycardia; hyperkalemia; fatigue; depression; sexual dysfunction	Asthma; COPD; 2nd or 3rd degree heart block	
Combined α-β (carvedilol, labetalol)		Heart failure; atrial fibrillation	Bradycardia; hyperkalemia; fatigue; depression; sexual dysfunction	2nd or 3rd degree heart block	May be better tolerated in lung disease than selective β-blockers
Calcium Channel Blockers					
Dihydropyridine (amlodipine, nifedipine)		Raynaud, esophageal spasms	Lower-extremity edema; gingival hypertrophy		May worsen proteinuria
Nondihydropyridine (diltiazem, verapamil)	Proteinuria reduction	Atrial fibrillation	Constipation; gingival hyperplasia	2nd or 3rd degree heart block	↑ calcineurin and mTOR inhibitor levels
Other					
α-Blockers		Benign prostatic hypertrophy; kidney stone passage	Orthostasis		
Central α-adrenergic agonists (clonidine)			Sedation; bradycardia; dry mouth; rebound hypertension	Depression	
Vasodilators (minoxidil, hydralazine)			Headache; tachycardia; lupus-like syndrome (hydralazine); edema; pericardial effusion	Post–myocardial infarction; heart failure	
Direct renin inhibitors (aliskiren)	Proteinuria reduction; if not tolerating ACEI or ARB			Bilateral renal artery stenosis	Not recommended for use in combination with ACEI or ARBs

(Continued)

was severe and widespread edema. The clinical picture appears in fact to be almost as characteristic as the histological one: the patients are relatively old; hypertension is present, usually of the benign type, and the kidneys frequently show signs of decompensation; there is a history of diabetes usually of long standing; the presenting symptoms may be those of edema of the nephrotic type, renal decompensation or heart failure; the urine contains large amounts of albumin and there is usually impairment of concentrating power with or without nitrogen retention.

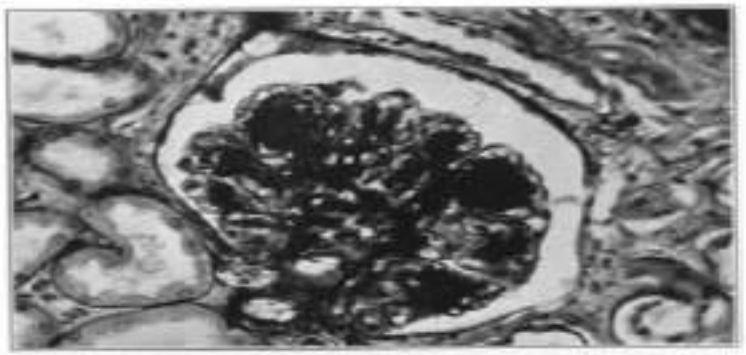
INTERCAPILLARY LESIONS IN THE GLOMERULI OF THE KIDNEY *

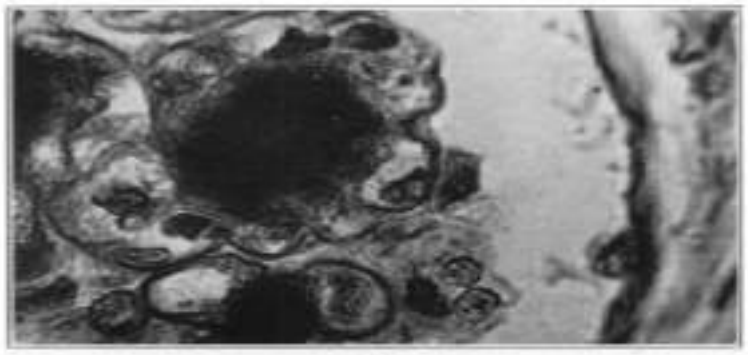
PAUL KIMMELSTIEL, M.D., AND CLIFFORD WILSON, M.B. †

(From the Mallory Institute of Pathology, Boston City Hospital, Boston, Mass.)

was severe and widespread edema. The clinical picture appears in fact to be almost as characteristic as the histological one: the patients are relatively old; hypertension is present, usually of the benign type, and the kidneys frequently show signs of decompensation; there is a history of diabetes usually of long standing; the presenting symptoms may be those of edema of the nephrotic type, renal decompensation or heart failure; the urine contains large amounts of albumin and there is usually impairment of concentrating power with or without nitrogen retention.

* Received for publication August 10, 1935.





1

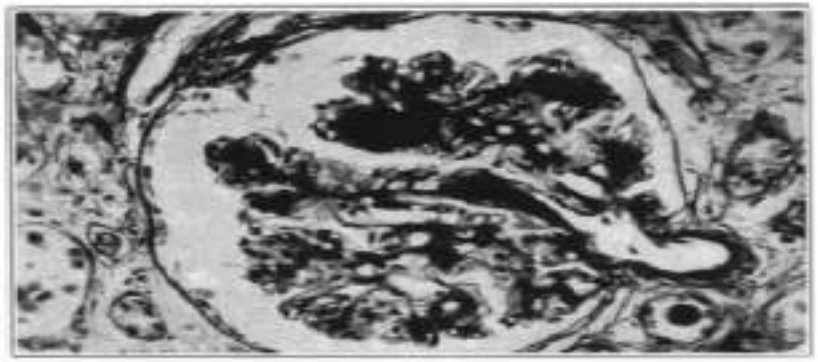
2

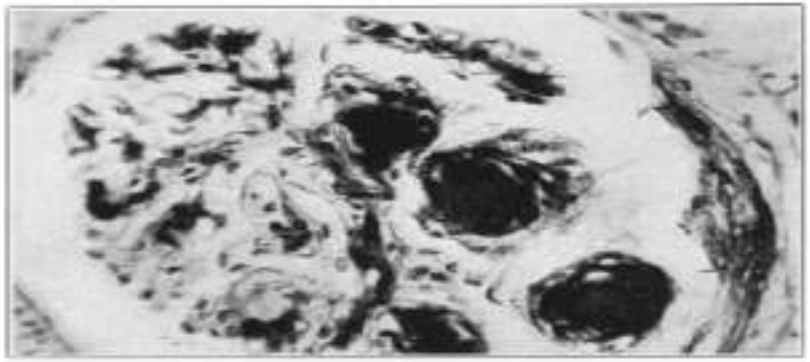
3

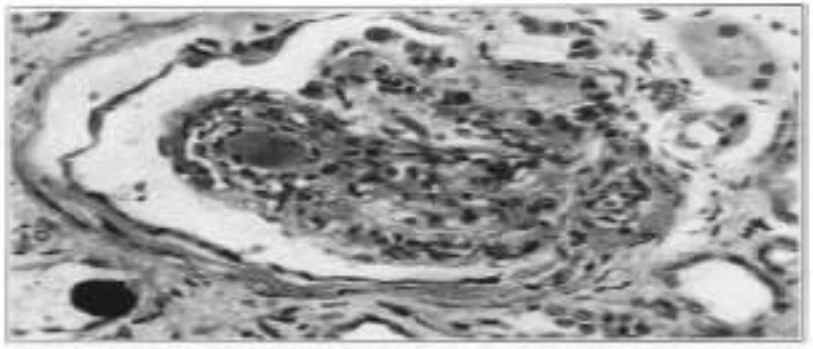
FIG. 1. Intercapillary glomerulosclerosis. Central hyalinization of all glomerular loops. Peripheral capillaries patent. Special basement membrane stain.

FIG. 2. Central hyalinization of peripheral loop. Capillaries wide open and contain red blood cells. Basement membrane clearly delineated and delicate. Special basement membrane stain. High power.

FIG. 3. Intercapillary hyalinization. Peripheral capillaries patent, nuclei of endothelial and epithelial cells clearly recognizable. Capillary basement membrane somewhat thickened. Special basement membrane stain. High power.







4

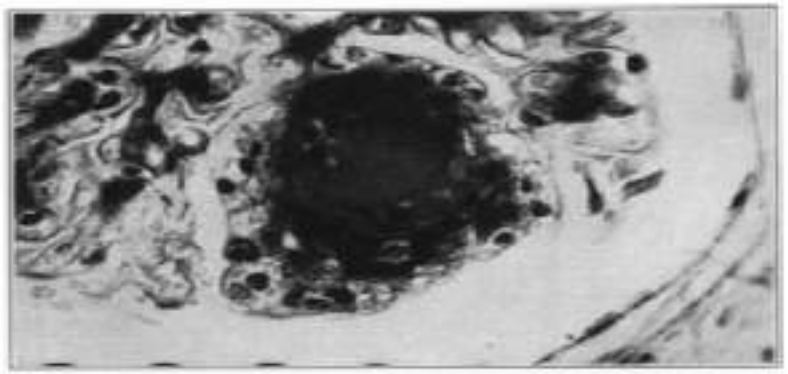
5

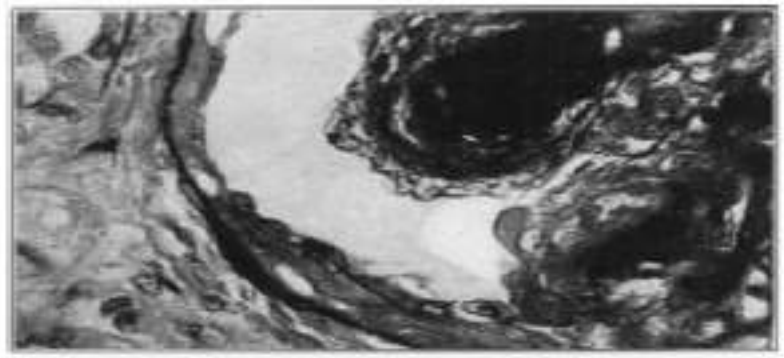
6

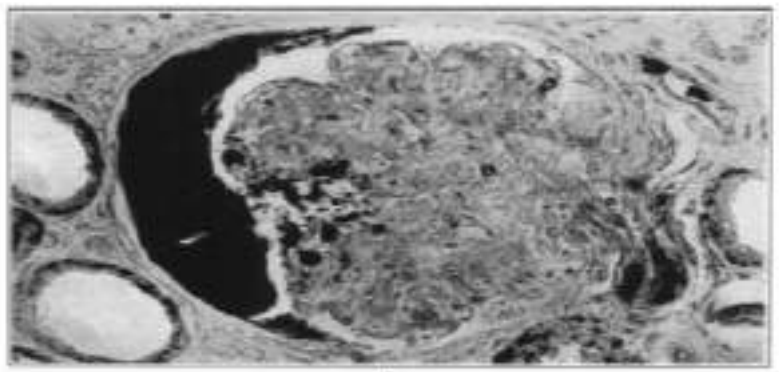
FIG. 4. Hyalinization of intercapillary connective tissue extending into most of the loops, in direct continuity with the hyaline material of the vas afferens. Special basement membrane stain. Medium power.

FIG. 5. Intercapillary hyalinization in several loops; the hyaline material encroaches upon the capillary wall which is homogeneously thickened. The capillaries are collapsed and their lumen reduced to a narrow slit. Special basement membrane stain. Medium power.

FIG. 6. Central hyalinization clearly seen even with eosin-methylene blue stain. Crowding of endothelial nuclei around collapsed capillaries gives appearance of "onion layers." Eosin-methylene blue stain. High power.







7

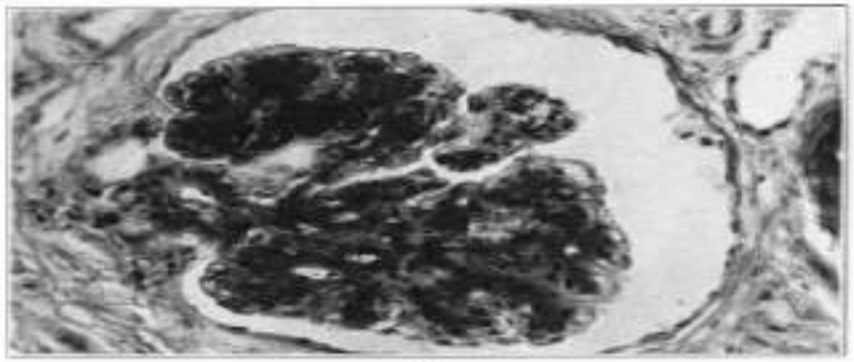
8

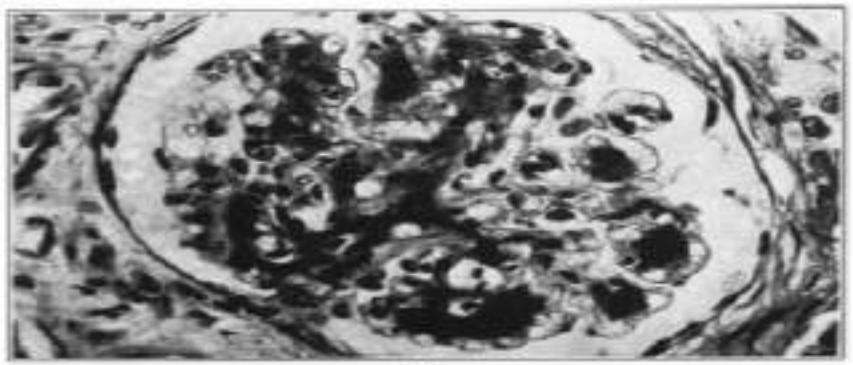
9

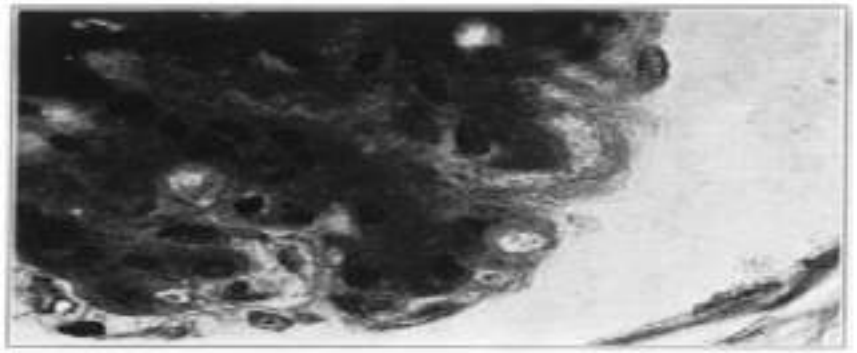
FIG. 7. Well preserved endothelial nuclei are seen embedded in central hyaline mass. Special basement membrane stain.

FIG. 8. Hyaline fatty mass seen between basement membrane and epithelial cells of Bowman's capsule. Special basement membrane stain. High power.

FIG. 9. Sudan III fat stain shows large fatty mass between epithelial cells and basement membrane of Bowman's capsule. The picture also shows fat in the vas afferens, some fatty degeneration of capillary loops and fat in the tubular epithelial cells. Sudan III stain. High power.







10

11

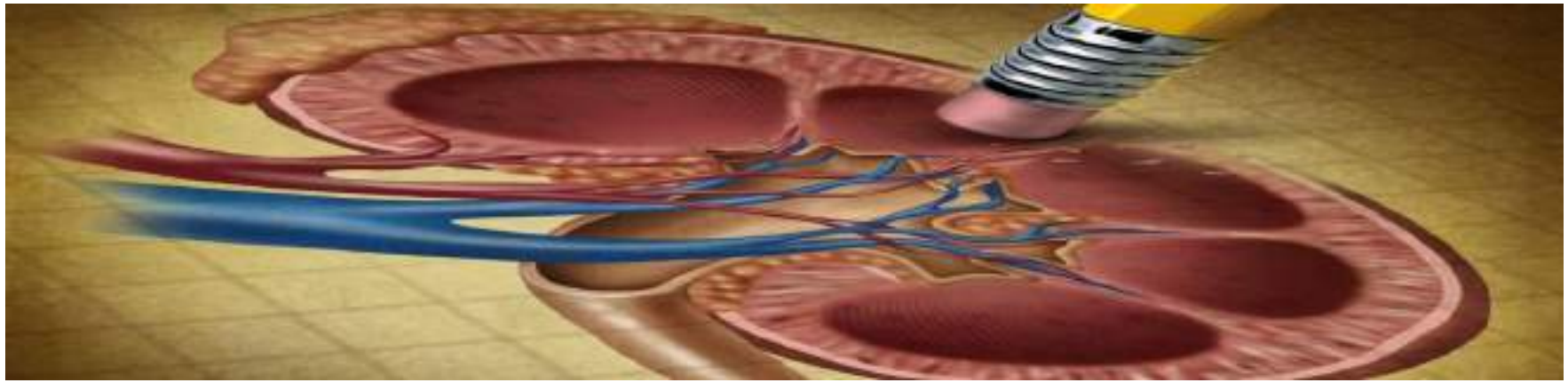
12

FIG. 10. Intracapillary glomerulonephritis. Central hyalinization identical in situation with that of intercapillary glomerulosclerosis (see Fig. 1). Notice open capillaries in the periphery. Special basement membrane stain. High power.

FIG. 11. Single glomerulus in an otherwise diffuse intracapillary glomerulonephritis. There is no other change but a severe central intercapillary hyalinization. Special basement membrane stain. High power.

FIG. 12. Intracapillary glomerulonephritis showing blurred outline of peripheral capillaries. Special basement membrane stain. High power.

Η Χρόνια Νεφρική Νόσος (ΧΝΝ) είναι μια κατάσταση που χαρακτηρίζεται από προοδευτική απώλεια της νεφρικής λειτουργίας με την πάροδο του χρόνου.



ΤΙ ΕΙΝΑΙ Η ΧΡΟΝΙΑ ΝΕΦΡΙΚΗ ΝΟΣΟΣ (ΧΝΝ):

Οι ομάδες υψηλού κινδύνου περιλαμβάνονται τα άτομα με ιστορικό διαβήτη, υπέρτασης και οικογενειακό ιστορικό νεφρικής νόσου.

Τρεις απλές εξετάσεις μπορούν να ανιχνεύσουν την ΧΝΝ:

- **Μέτρηση αρτηριακής πίεσης**
- **Λεύκωμα στα ούρα**
- **Κρεατινίνη ορού**

Thank You

athens-NEPHROLOGY