Chronic Kidney Disease

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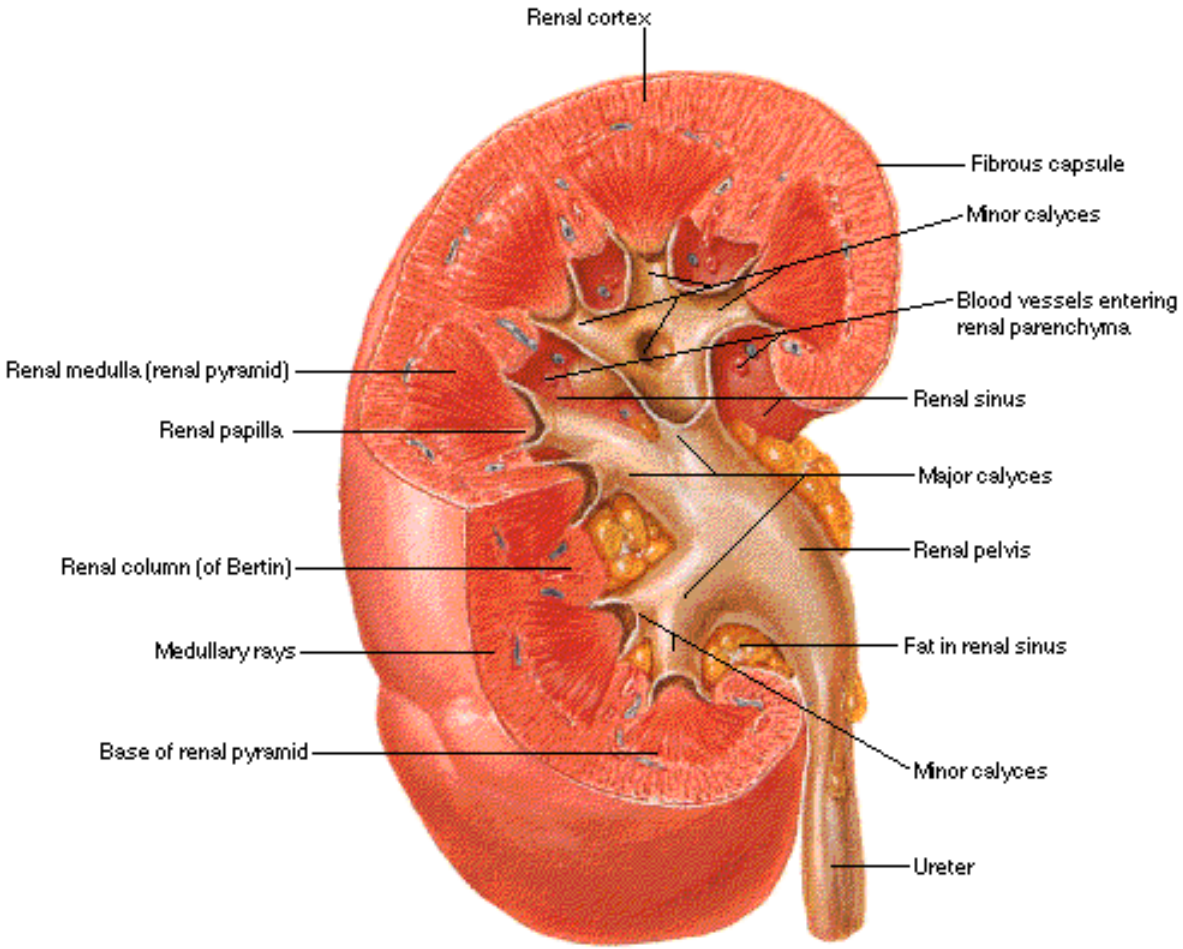
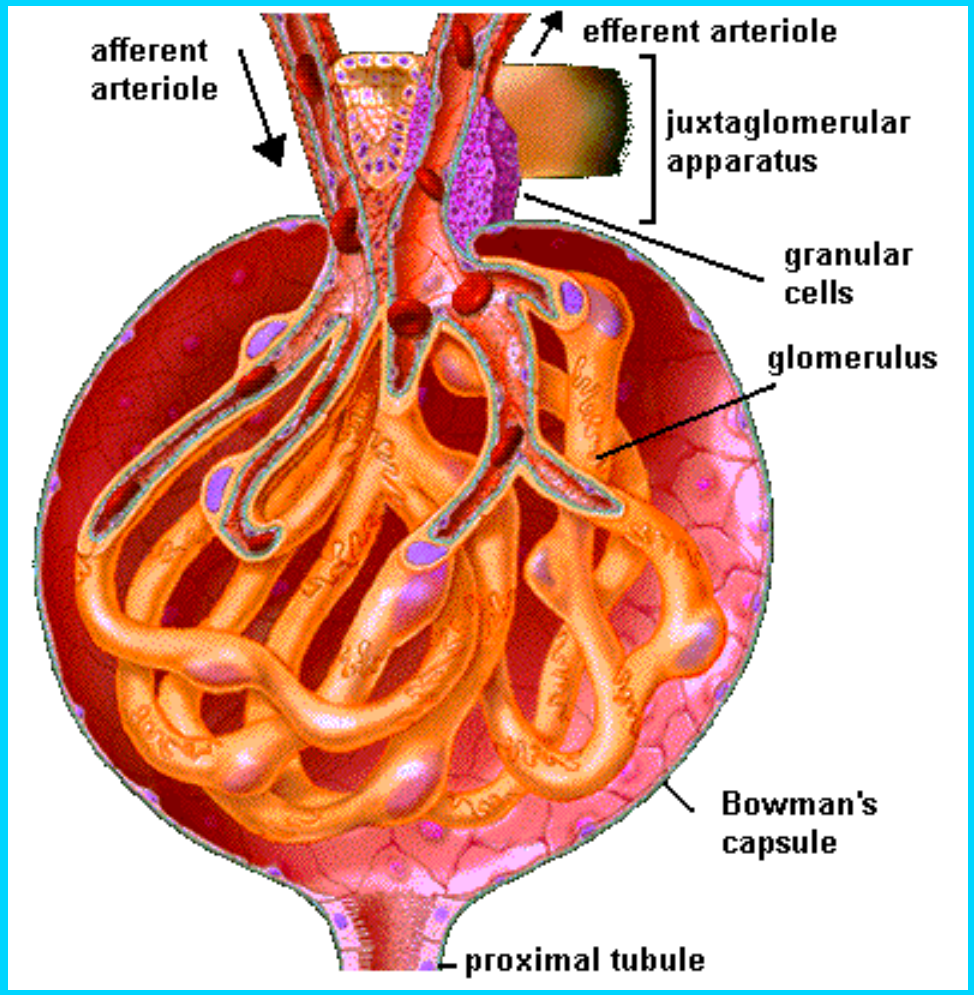
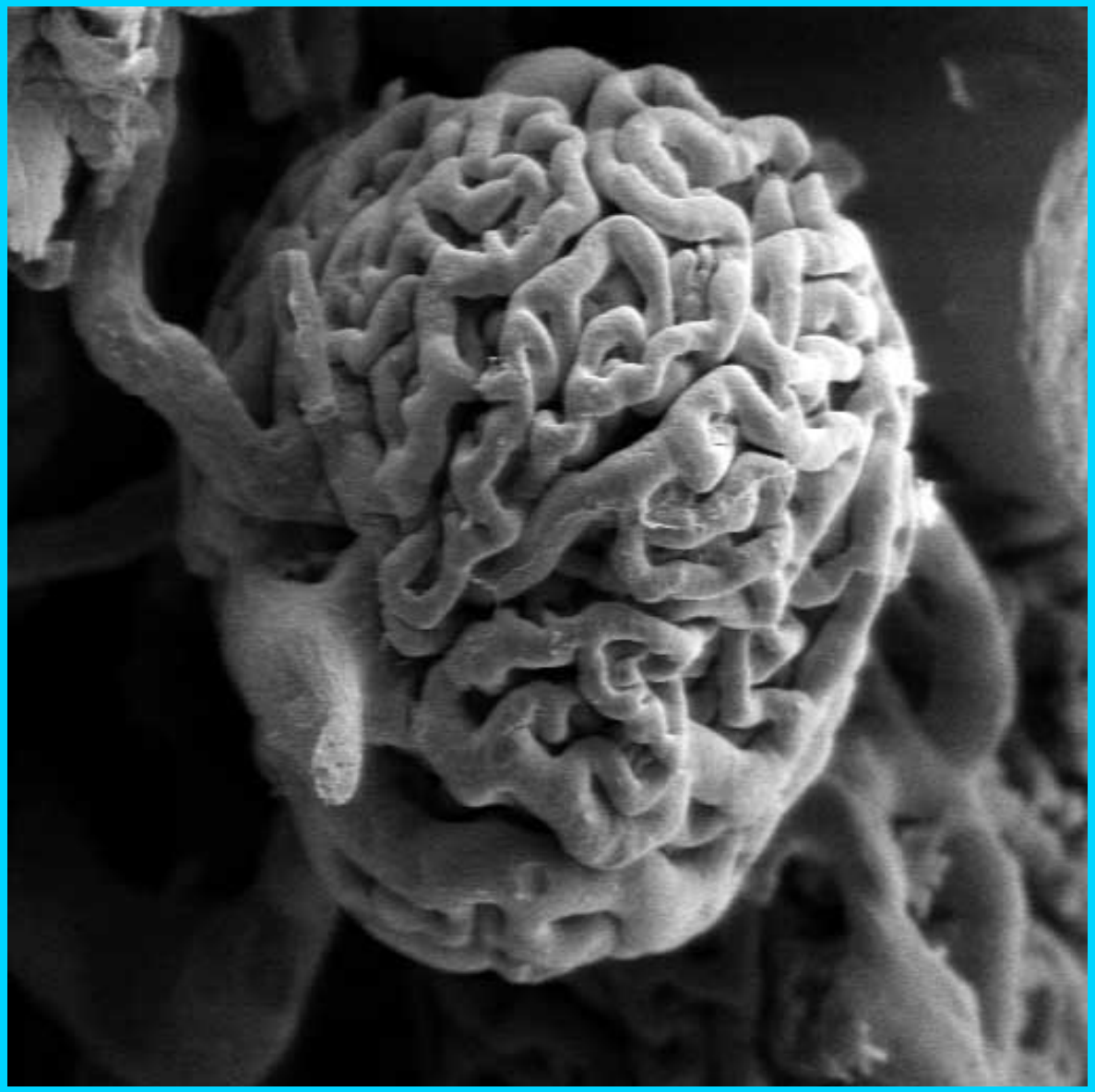
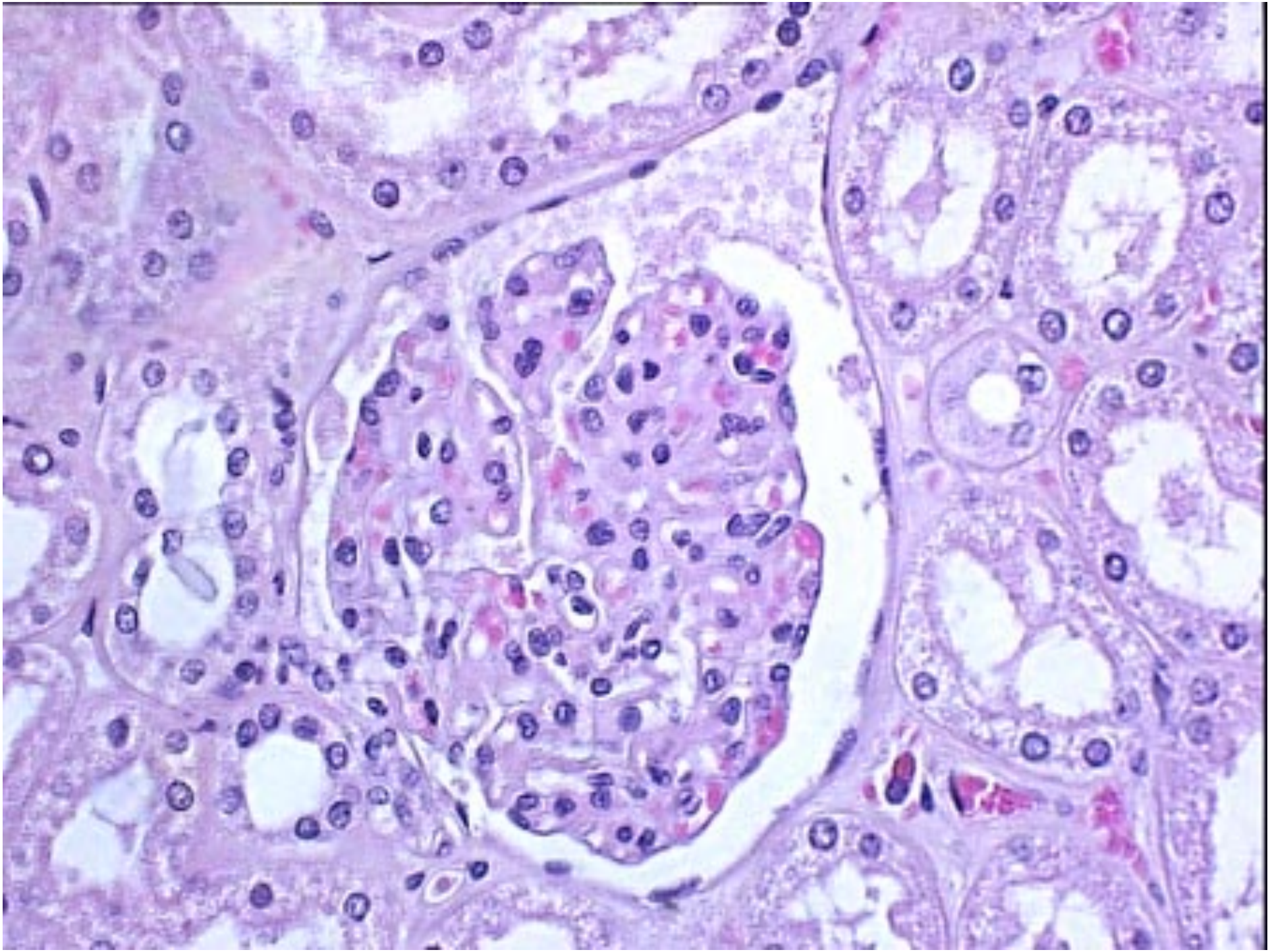
Right Kidney Sectioned in Several Planes

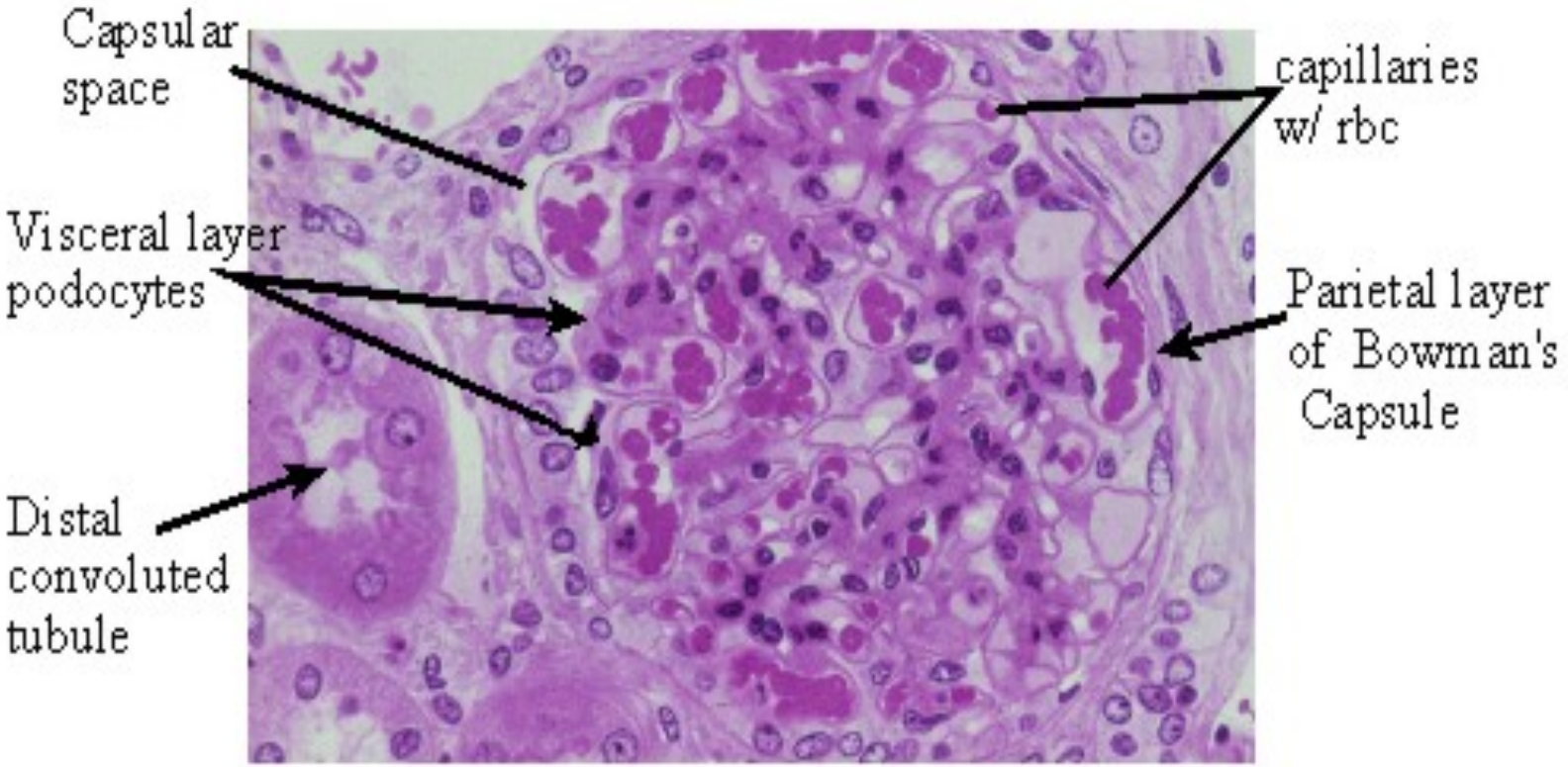


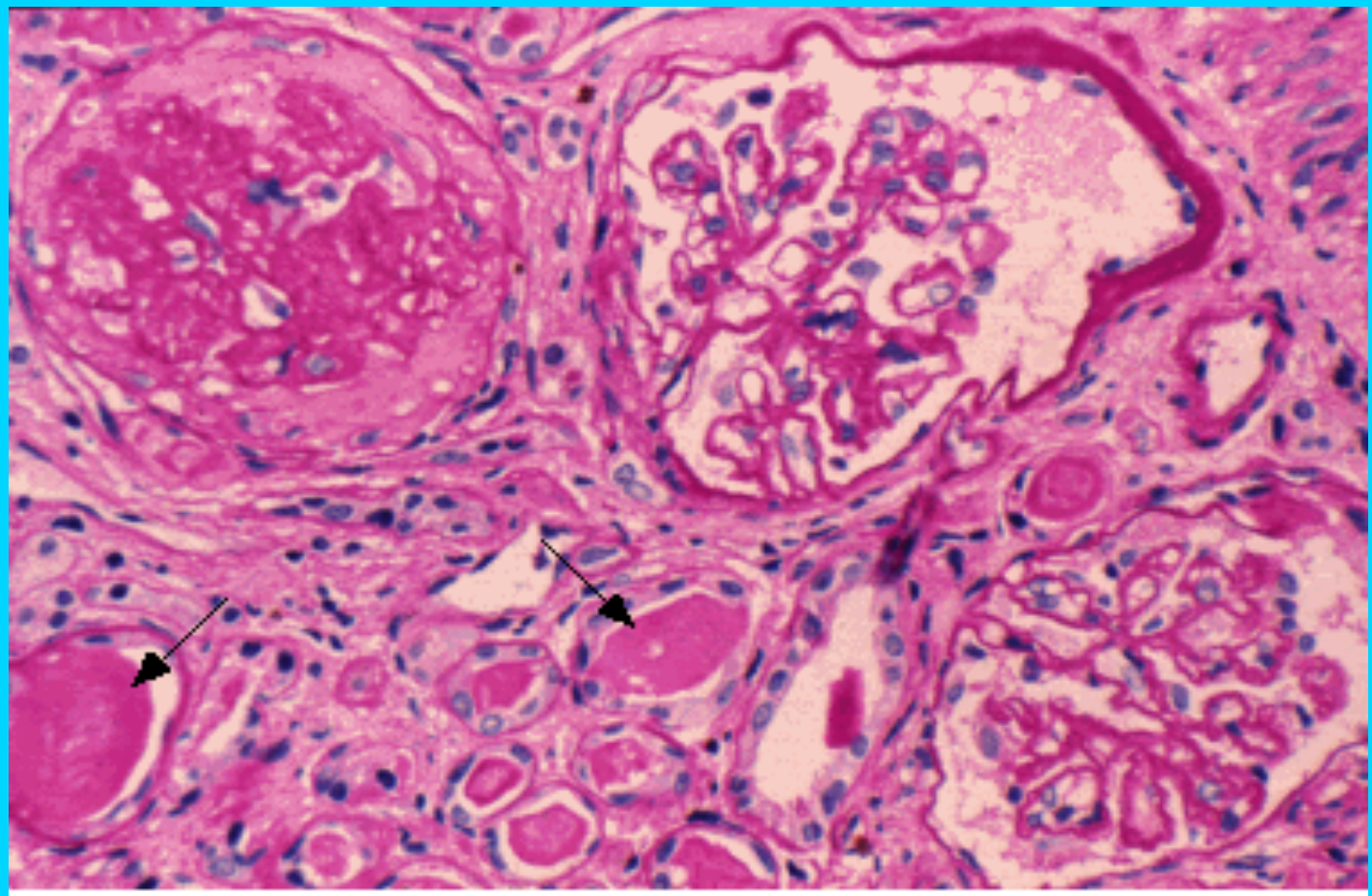

afferent arteriole
efferent arteriole
juxtaglomerular apparatus
granular cells
glomerulus
Bowman's capsule
proximal tubule





Detailed Glomerular Structure





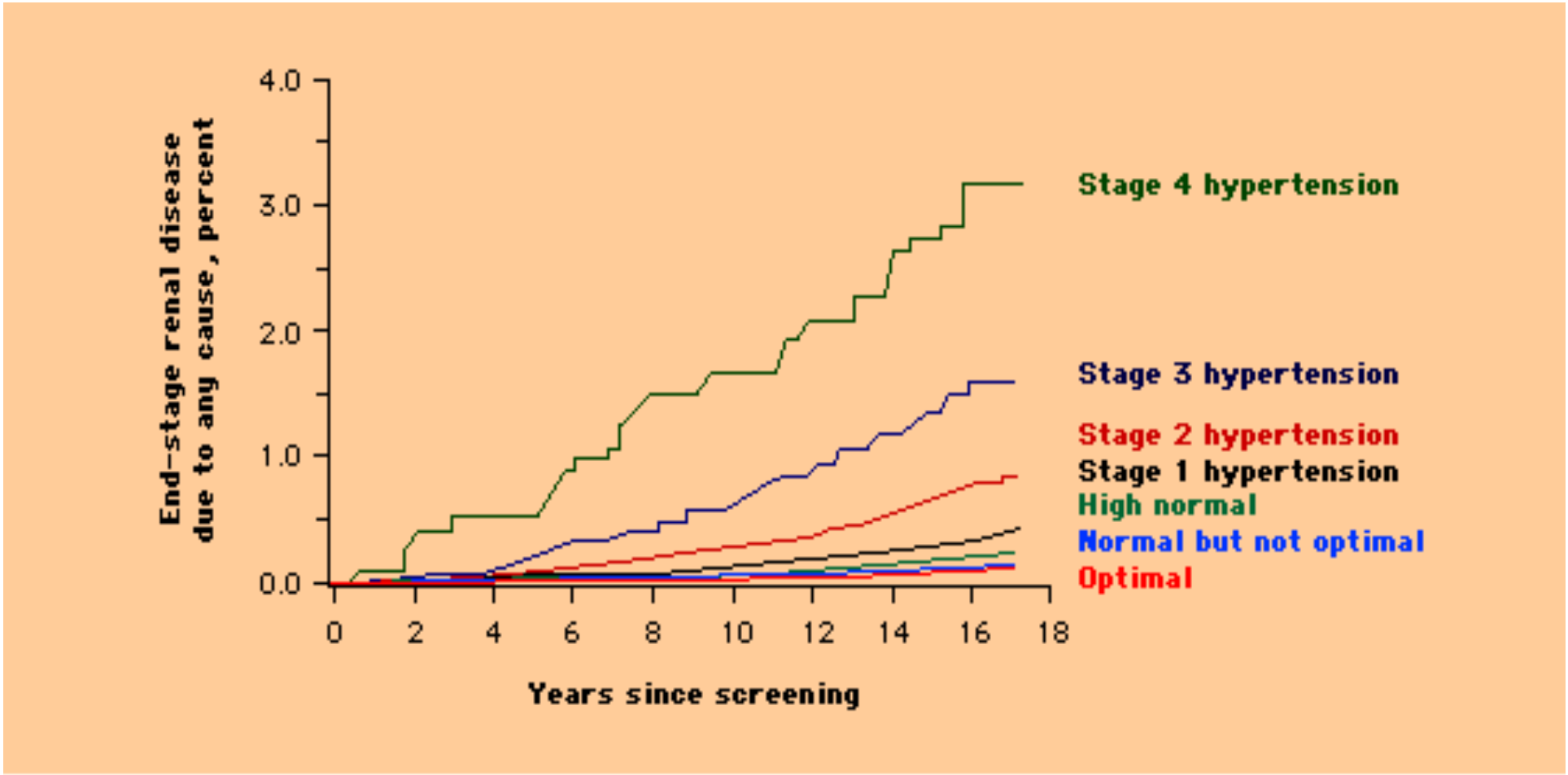
Benign nephrosclerosis Light micrograph in benign nephrosclerosis showing a completely sclerotic glomerulus (upper left) adjacent to two shrunken glomeruli that are still intact. There is also prominent tubular atrophy and dilatation with intratubular hyaline casts (arrows). These changes are induced by ischemia resulting from arterial and arteriolar thickening (not shown). Courtesy of Helmut Rennke, MD.

Nephrosclerosis

- Associated with aging and aggravated by hypertension
- Progression to endstage is 1-2%
- African-Americans, higher BP's, concomitant renal disease (diabetes) associated with a higher risk of progression

Nephrosclerosis

- Benign urinary sediment and usually less than 1 gram proteinuria
- Blood pressure control delays progression
- ACE inhibitors and ARB's are important (diuretics with African-Americans)



Relation between hypertension and development of ESRD Cumulative incidence of end-stage renal disease (ESRD), due to any cause, according to blood pressure category in 332,544 men screened for the MRFIT trial. The adjusted relative risk increased from 1.0 in those with optimal blood pressure (<120/<80) to 1.9 with high normal blood pressure, 3.1 with mild hypertension, 6.0 with moderate hypertension, and 11.2 with severe hypertension. Patients with stage 1 hypertension or lower blood pressure were at very low risk of ESRD at 16 years (≤0.34 percent). (Redrawn from Klag, MJ, Whelton, PK, Randall, BL, et al, N Engl J Med 1996; 334:13.)

Low Nephron Number

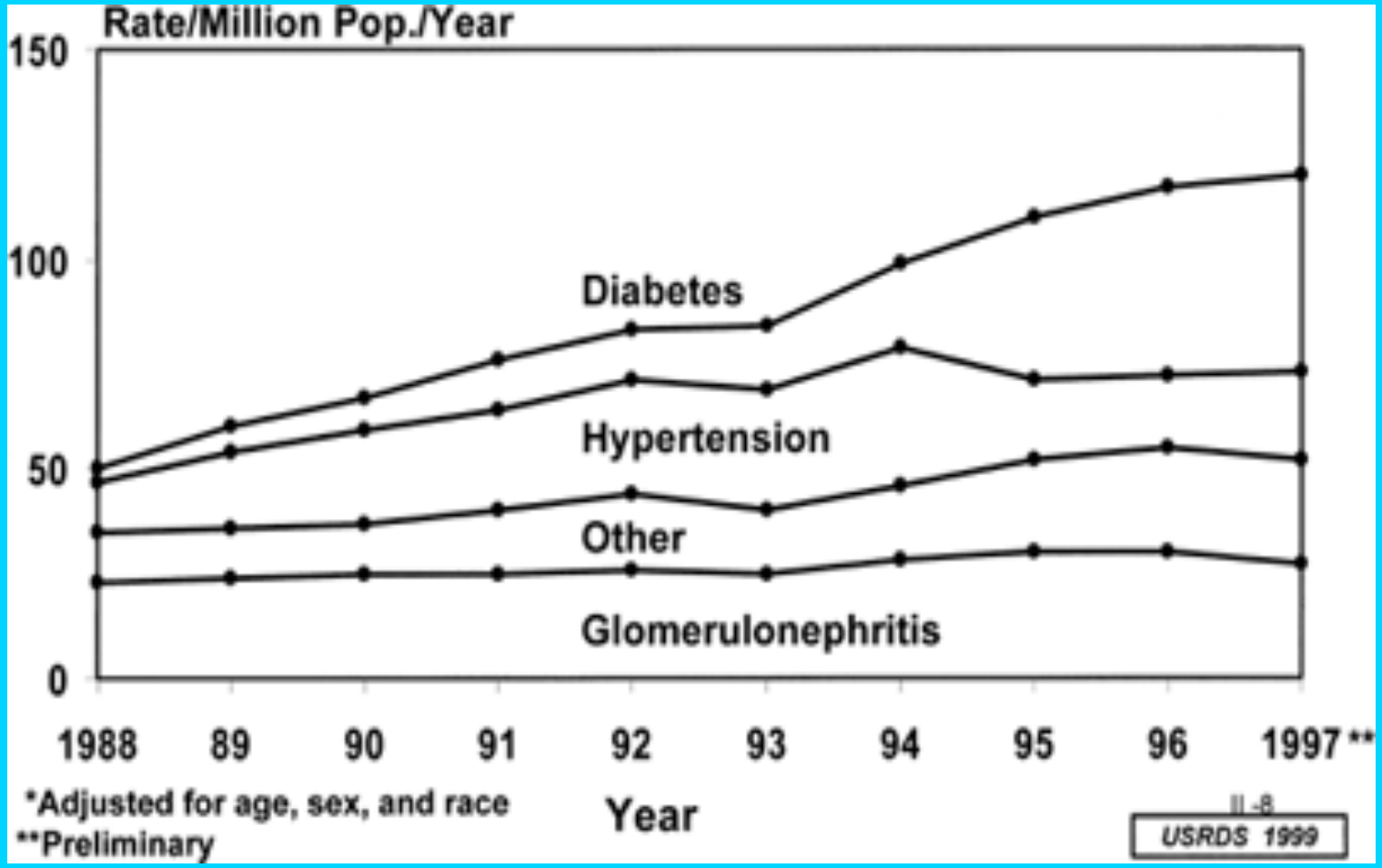
- Low birth weight (less than 5 pounds) is associated with hypertension, diabetes, cardiovascular and kidney disease
- Low birth weight is associated with fewer nephrons and larger glomerular volume
- Compensatory glomerular hypertrophy indicates glomerular hyperfiltration which may hasten glomerular loss

Table 40. Potential Risk Factors for Susceptibility to and Initiation of Chronic Kidney Disease

Clinical Factors	Sociodemographic Factors
Diabetes	Older age
Hypertension	US ethnic minority status: African American, American Indian, Hispanic, Asian or Pacific Islander
Autoimmune diseases	Exposure to certain chemical and environmental conditions
Systemic infections	Low income/education
Urinary tract infections	
Urinary stones	
Lower urinary tract obstruction	
Neoplasia	
Family history of chronic kidney diseases	
Recovery from acute kidney failure	
Reduction in kidney mass	
Exposure to certain drugs	
Low birth weight	

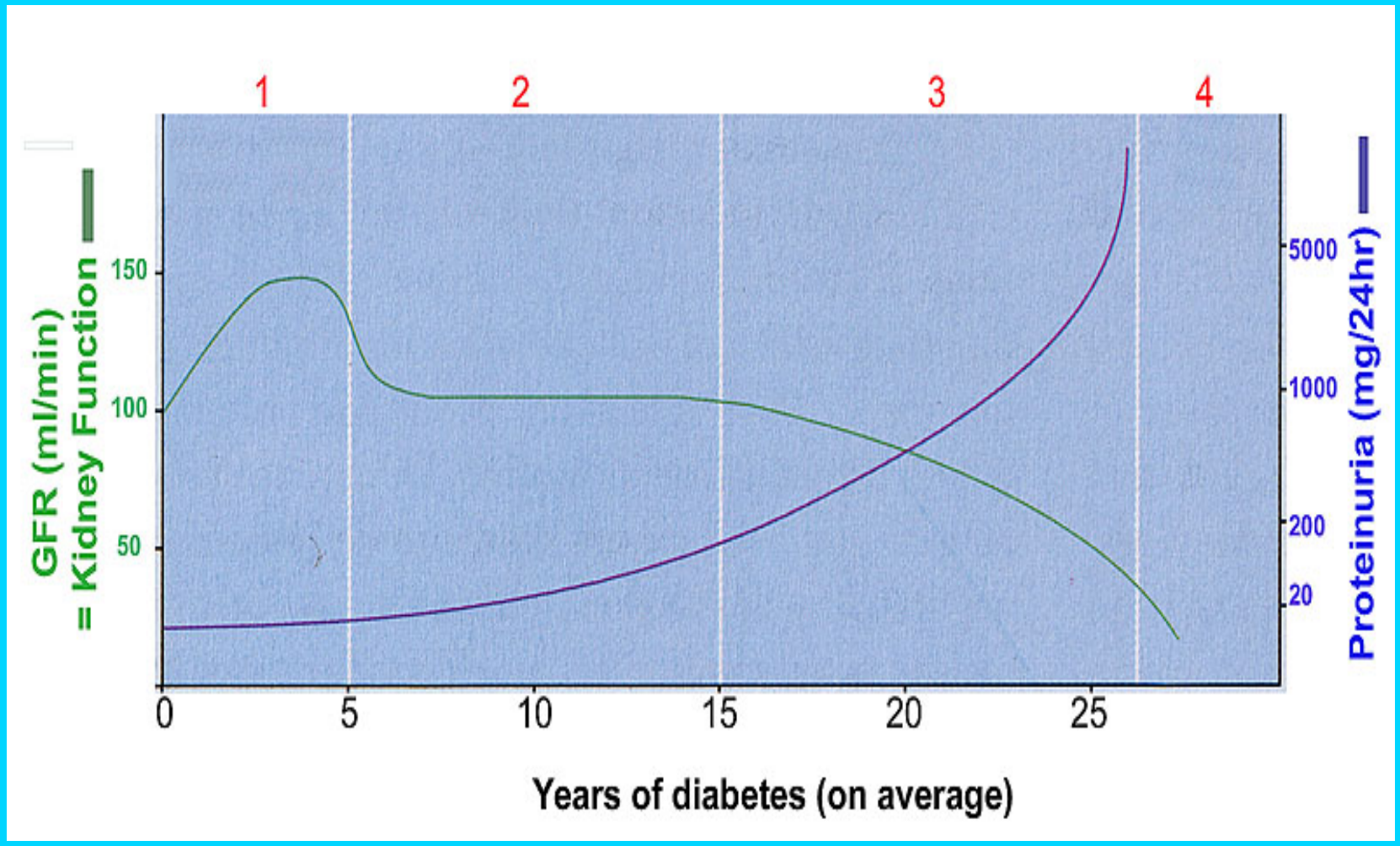
Diabetic Nephropathy

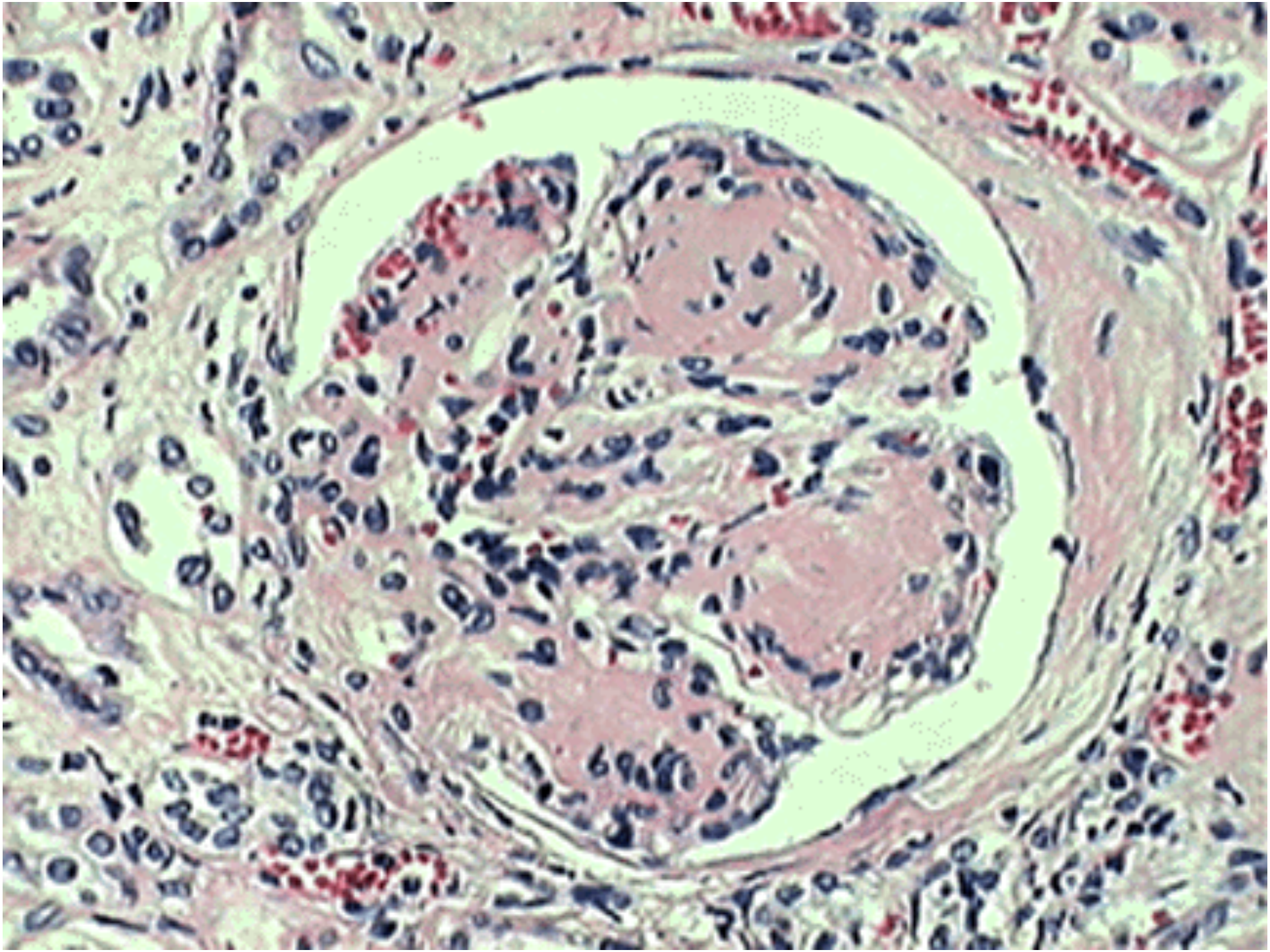
- Diabetes is the most common cause of ESRD, about 40% of new cases
- 20-30% of all diabetics develop nephropathy
- A smaller proportion of type 2 diabetics develop ESRD than type 1
- Because of the greater prevalence of type 2, half of diabetic patients with ESRD are type2


Rate/Million Pop./Year
150
100
50
0
Diabetes
Hypertension
Other
Glomerulonephritis
1988
89
90
91
92
93
94
95
96
1997 **
*Adjusted for age, sex, and race
**Preliminary
Year
II -8
USRDS 1999

Progression to ESRD

- Progression to nephropathy is similar in type 1 and type 2
- Microalbuminuria develops in about 5 years
- Overt proteinuria develops in 5-10 years
- ESRD develops 3-5 years after nephrotic syndrome occurs


1
2
3
4
GFR (ml/min)
= Kidney Function
150
100
50
0
5
10
15
20
25
Years of diabetes (on average)
5000
1000
200
20
Proteinuria (mg/24hr)



Pathophysiology

- Renal lesions are due to accumulation of extracellular matrix in glomerular and tubular basement membranes resulting in mesangial expansion
- Increased activity TGF-beta, GH, IGF, VEGF. EGF
- Cytokine activation eg renin, angiotensin, endothelin, bradykinin
- Reactive oxygen species ROS
- Accumulation of glycation end products
- Altered glomerular proteoglycan metabolism
- Increased aldose reductase activity and sorbitol
- Protein kinase C

Table 14. Prevalence of Stages of Chronic Kidney Disease and Levels of Kidney Function in the US

Stages of CKD			Levels of Kidney Function		
	N (1000's)*	(%)	GFR (mL/min/1.73 m^2)	N (1000's)*	(%)
1	10,500[a] 5,900	5.9[a] 3.3	≥90	114,000	64.3
2	7,100[a] 5,300	4.0[a] 3.0	60–89	55,300	31.2
3	7,600	4.3	30–59	7,600	4.3
4	400	0.2	15–29	400	0.2
5	300	0.2	<15 (or dialysis)	300	0.2

* Data for Stages 1–4 from NHANES III (1988–1994). Population of 177 million with age ≥20 years. Data for Stage 5 from USRDS (1998),[2] includes approximately 230,000 patients treated by dialysis, and assumes 70,000 additional patients not on dialysis. Percentages total >100% because NHANES III may not have included patients on dialysis. GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine.

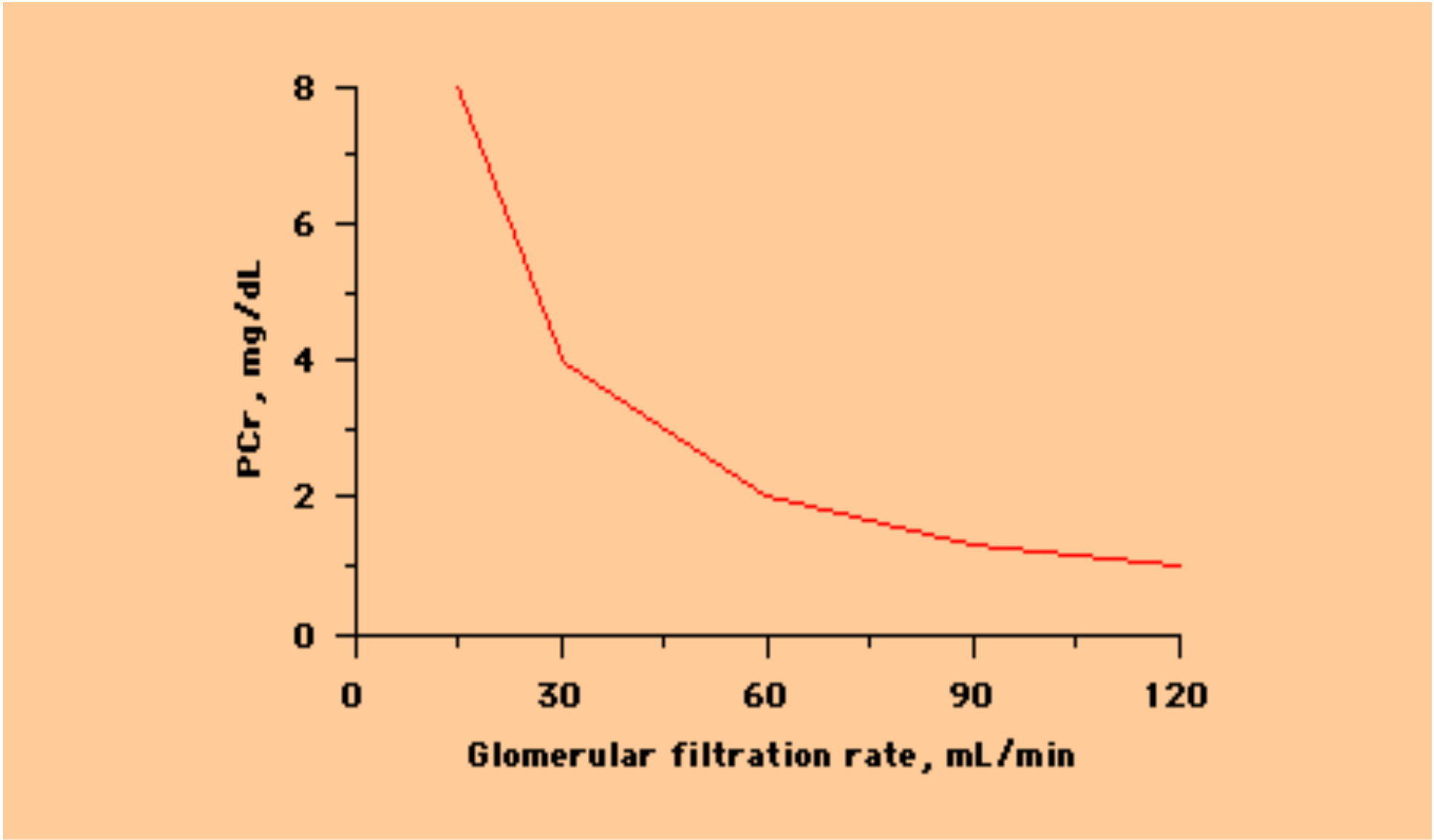
[a] For Stages 1 and 2, kidney damage was assessed by spot albumin-to-creatinine ratio >17 mg/g (men) or >25 mg/g (women) on one occasion (larger prevalence estimate) or on two measurements (smaller prevalence estimate). Albuminuria was persistent in 54% of individuals with GFR ≥90 mL/min/1.73 m^2 (n = 102) and 73% of individuals with GFR 60–89 mL/min/1.73 m^2 (n = 44).

Increased CV Risk With CRF

- About 10% of adults have CRF
- CV risk increases with severity of CRF
- Most patients with CRF die before reaching ESRD
- Associated risk factors include diabetes, hypertension, smoking, age, hyperlipidemia, anemia, LVH, abnormal calcium and phosphorus, inflammation, oxidative stress, thrombosis, uremic toxins

CV Disease

- Less aggressive therapy noted in more advanced renal disease
- 40-60% one year mortality in ESRD patients with AMI
- Troponin-T and troponin-I levels are elevated in renal failure with troponin-I more specific for AMI



Plasma creatinine and GFR. Idealized steady-state relationship between the plasma creatinine concentration (PCr) and the GFR. A fall in GFR decreases creatinine filtration and produces a proportionate rise in the plasma creatinine concentration.

Estimation of GFR

- Cockcroft-Gault equation
- Modification of Diet in Renal Disease equation (MDRD)

Table 1: Methods for estimating creatinine clearance (GFR) in ml/min/1.73 m^2.

Cockcroft-Gault formula:[W4]

$$\text{Creatinine clearance} = \frac{(140\text{-age})(\text{weight in kilograms})}{\text{Serum creatinine } (\mu\text{mol/L}) \times 0.81} \times (0.85 \text{ if female})$$

MDRD equation:[W5]

$$\text{GFR} = 186.3 \times (\text{serum creatinine level (mg/dl)})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

Hypertension and Proteinuria

- ACE inhibitors and ARB's reduce proteinuria and progression to renal failure
- The level of proteinuria correlates with renal disease progression
- Non-dihydropyridine calcium channel blockers reduce proteinuria more than dihydropyridines

Microalbuminuria

- Normal rate of albumin excretion is less than 20 mg per day
- Persistent excretion of 30 mg to 300 mg indicates microalbuminuria
- Albumin/creatinine greater than 30 mg/gm indicates microalbuminuria
- Microalbuminuria indicates increased risk of cardiovascular death and renal failure

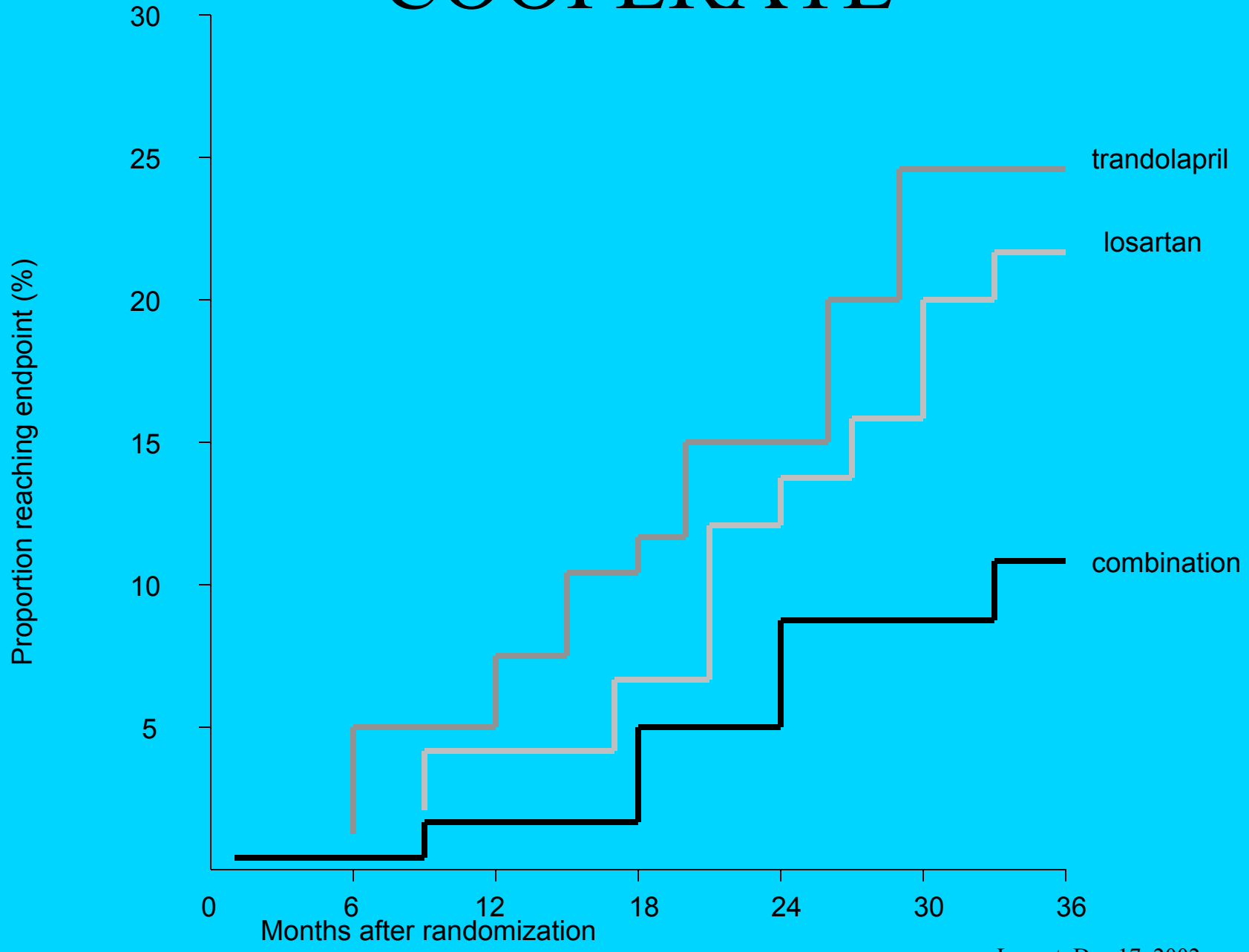
ACE Inhibitors

- Reduce intraglomerular pressure
- Improve the size selective properties of the glomerular basement membrane

ACE-I's and ARB's

- Reduce proteinuria
- Delay progression of renal failure
- Combined use reduces proteinuria and delays renal progression more
- Combined use causes more hyperkalemia and may increase serum creatinine
- Combined use reduces mortality in chronic CHF but not in acute MI

COOPERATE



Lancet, Dec 17, 2002

Protein Restriction

- Animal studies show a delay in renal disease progression with dietary protein restriction
- Human studies are inconsistent in showing any benefit especially when there is good blood pressure control
- 0.8 gm/kg – 1.0 gm/kg could be safely instituted without causing malnutrition

Contrast Nephropathy

- 0.5 mg/dl increase in creatinine or 25%
- Due to renal vasoconstriction or tubular injury due to oxygen free radicals
- Most commonly seen in chronic renal failure (creatinine greater than 1.5), diabetics with renal failure, multiple myeloma, congestive heart failure, hypovolemia

N-Acetylcysteine (Mucomyst)

- Mucomyst plus hydration reduce the incidence of radiocontrast-induced nephropathy
- 600 mg bid for two days
- Acts as an antioxidant and replenishes depleted glutathione levels

Intravenous Sodium Bicarbonate

- 154 mEq/L $NaHCO_3$ in D5W-3ml/kg bolus in one hour prior to the procedure with 1 ml/kg/hr for six hours post procedure (volume of D5W reduced to 850 ml)

Contrast Nephropathy-Prevention

- Avoidance of radiocontrast in high risk patients, or use small doses, or MRI
- Avoidance of volume depletion or NSAID's
- Administer intravenous sodium bicarbonate and oral N-Acetylcysteine (Mucomyst)

Atherosclerotic Renal Artery Stenosis

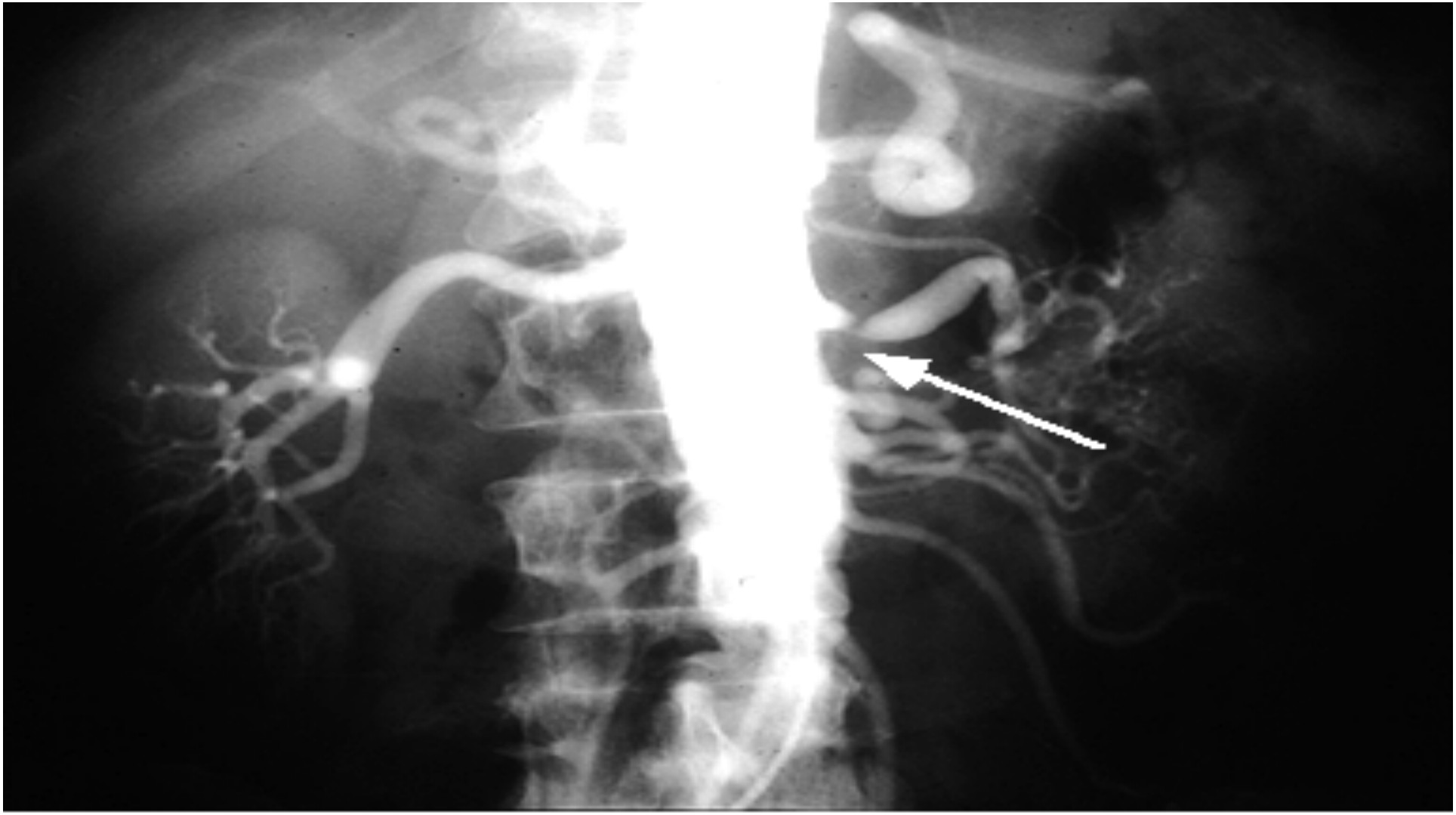
- Prevalence rises with age and presence of vascular disease
- RAS found in 4.3% in 5000 consecutive autopsies, 10.4% in patients with stroke, 14-28% in patients undergoing coronary angiography, 14-42% in patients with vascular disease of the legs or aorta

Clues to RAS

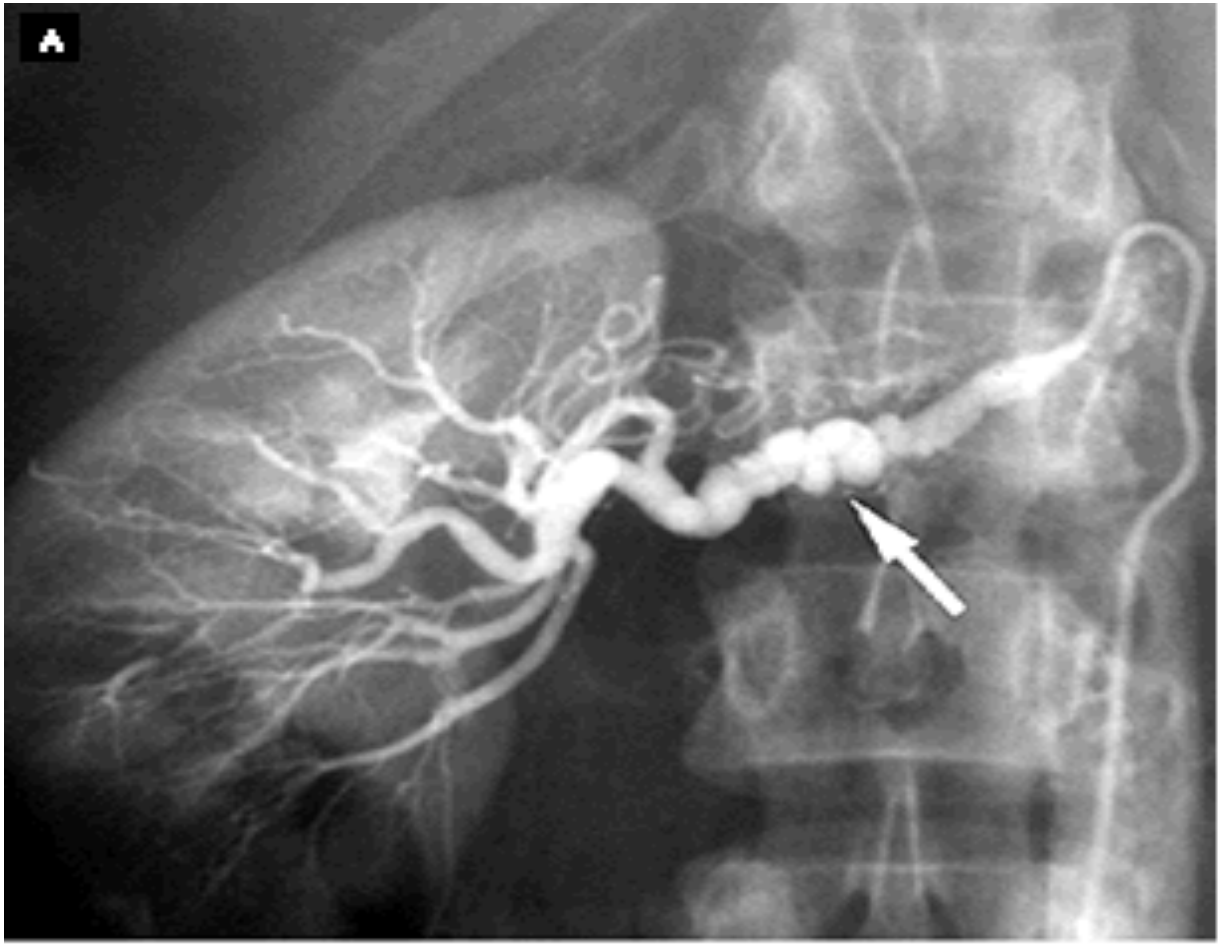
- Uncontrolled hypertension
- Worsened renal function with ACE-I or ARB
- Flash pulmonary edema
- Coexistence of vascular disease

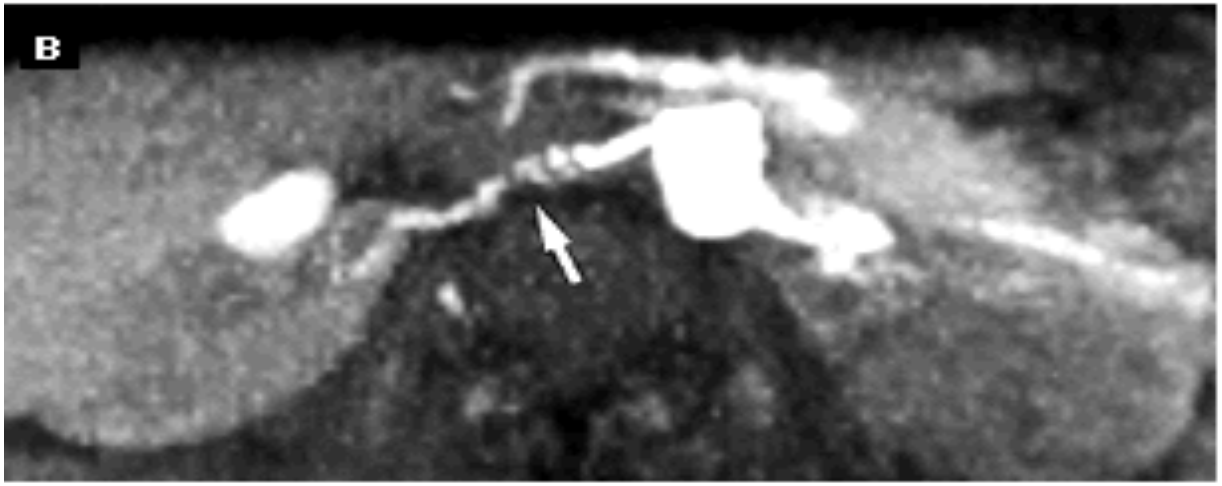
Diagnosis of RAS

- MRA with gadolinium
- CT angiography



Renal artery stenosis Aortogram shows a focal stenosis of the left renal artery with poststenotic dilatation (arrow). The right renal artery has a normal caliber and is delivering contrast to the right kidney well before the left kidney recieves contrast. Courtesy of Jonathan Kruskal, MD.





Fibromuscular hyperplasia Figure A: A conventional angiogram of the right renal artery demonstrates a beaded appearance of the mid-right renal artery (arrow) with multiple focal areas of stenoses. By comparison, the intrarenal arteries have a normal appearance. Figure B: The corresponding flow sensitive magnetic resonance image also demonstrates multiple stenoses in the mid-right renal artery; these features are consistent with the medial form of fibromuscular dysplasia. Courtesy of Jonathan Kruskal, MD, PhD.

Approach to RAS

- Angioplasty and stent, surgery
- Medical therapy if there is renal parenchymal disease (suggested by resistive index greater than 0.8 by doppler ultrasound, increased echogenicity, or creatinine greater than 2.8)

Renal failure and OTC meds – Dietary Supplements

- Aristolochic acid contained in Aristolochia serpentaria (Snakewood)
- Found as a contaminant in Chinese herbal products
- Causes renal failure with interstitial fibrosis and tubular atrophy

RF – Dietary Supplements

- Chromium picolinate can raise chromium levels and cause interstitial nephritis, ARF, anemia, hemolysis, thrombocytopenia
- Arsenic, lead, and mercury have been found as contaminants in many preparations
- Tanacetum parthenium (feverfew), Curcuma longa (turmeric), Zingiber officinale (ginger) inhibit cyclooxygenase COX

RF – Dietary Supplements

- Individual case reports of renal failure have been found with Echinacea, kelp (arsenic), germanium, penny, hydrazine, chaparral, willow bark (salicylate), cat's claw, yohimbe
- Rhabdomyolysis has been observed with Ma-Huang, wormwood, creatine
- Renal stones have been associated with Ma-Huang, yellow dock, cranberry
- St John's wort lowers and grapefruit raises some drug levels (cyclosporine, tacrolimus)

Obesity Related Nephropathy

- Proteinuria is a recognized complication of obesity
- Associated with focal and segmental glomerulosclerosis and glomerulomegaly
- Improved with weight loss
- High incidence of renal failure

Obesity Related Nephropathy

- Caused by hyperfiltration
- Associated with leptin
- Leptin is a protein hormone produced by adipocytes that can cause proteinuria, glomerulosclerosis, and synthesis of transforming growth factor beta and collagen

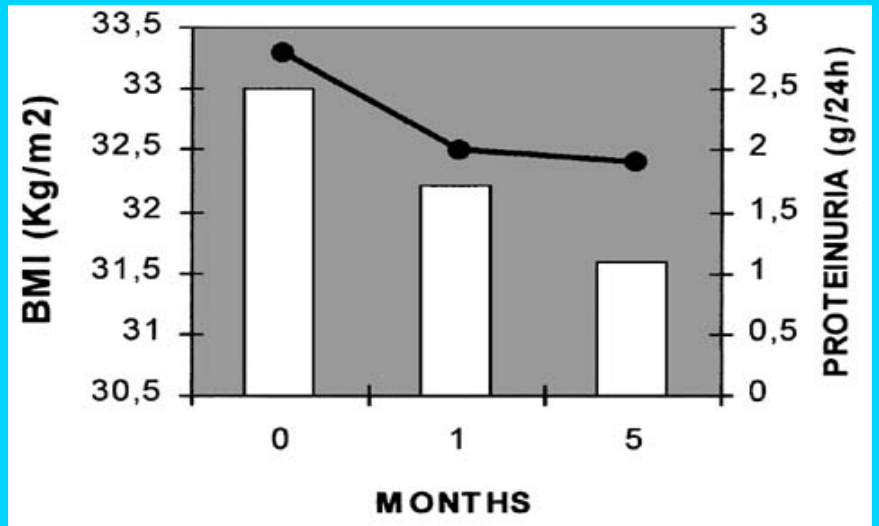
Obesity Related Nephropathy

- 30 overweight (BMI > 27) diabetic and nondiabetic patients with proteinuria randomized to weight loss diet and control
- Moderate weight loss significantly reduced protein excretion similar to ACE-I and ARB

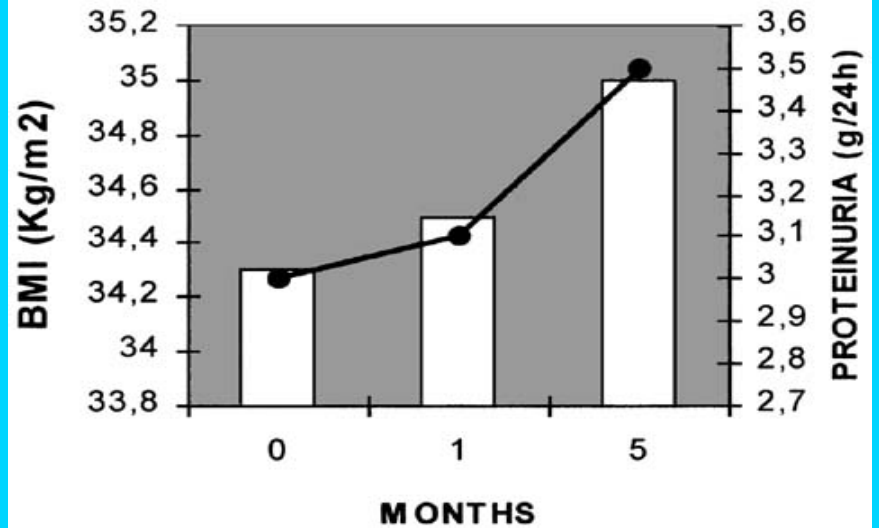
AJKD 2003:319-327

Obesity Related Nephropathy

Diet group



Control group



RENAAL

RENAAL Overview

- Randomized multi-site, double-blind, placebo-controlled study to evaluate the renal protective effects of the angiotensin II receptor antagonist losartan in patients with type 2 diabetes and nephropathy

Population

- 1,513 patients (31 to 70 years old)
  - Diagnosed type 2 diabetes and nephropathy
    - albumin/creatinine ratio ≥300 mg/g
    - serum creatinine between 1.3–3.0 mg/dL (1.5–3.0 mg/dL for men >60 kg)

Brenner BM, et al. N Engl J Med. 2001;345(12):861-869.

RENAAL

- Cr 2.1-3.6 24.6% reduction ESRD
- Cr 1.6-2.0 26.3%
- Cr less 1.6 35.3%
- Losartan reduced the risk of ESRD with lower levels of GRF

JASN 2004 Dec;15(12):3117-25

Conclusion

- CRF is a major public health problem affecting 10% of the adult population
- Most CRF patients die before reaching ESRD
- Significant efforts must be made to identify those at risk so that medical therapy may be begun to reduce renal disease progression and death due to cardiovascular disease