



Mechanisms of progressive renal injury and renal fibrosis

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คณะแพทยศาสตร์รพ.รามาธิบดี

Renal disease progression

- Mechanisms of kidney injury
- Mechanisms of kidney disease progression
- Glomerular hypertension and Ang II
- Proteinuria and tubulointerstitial fibrosis

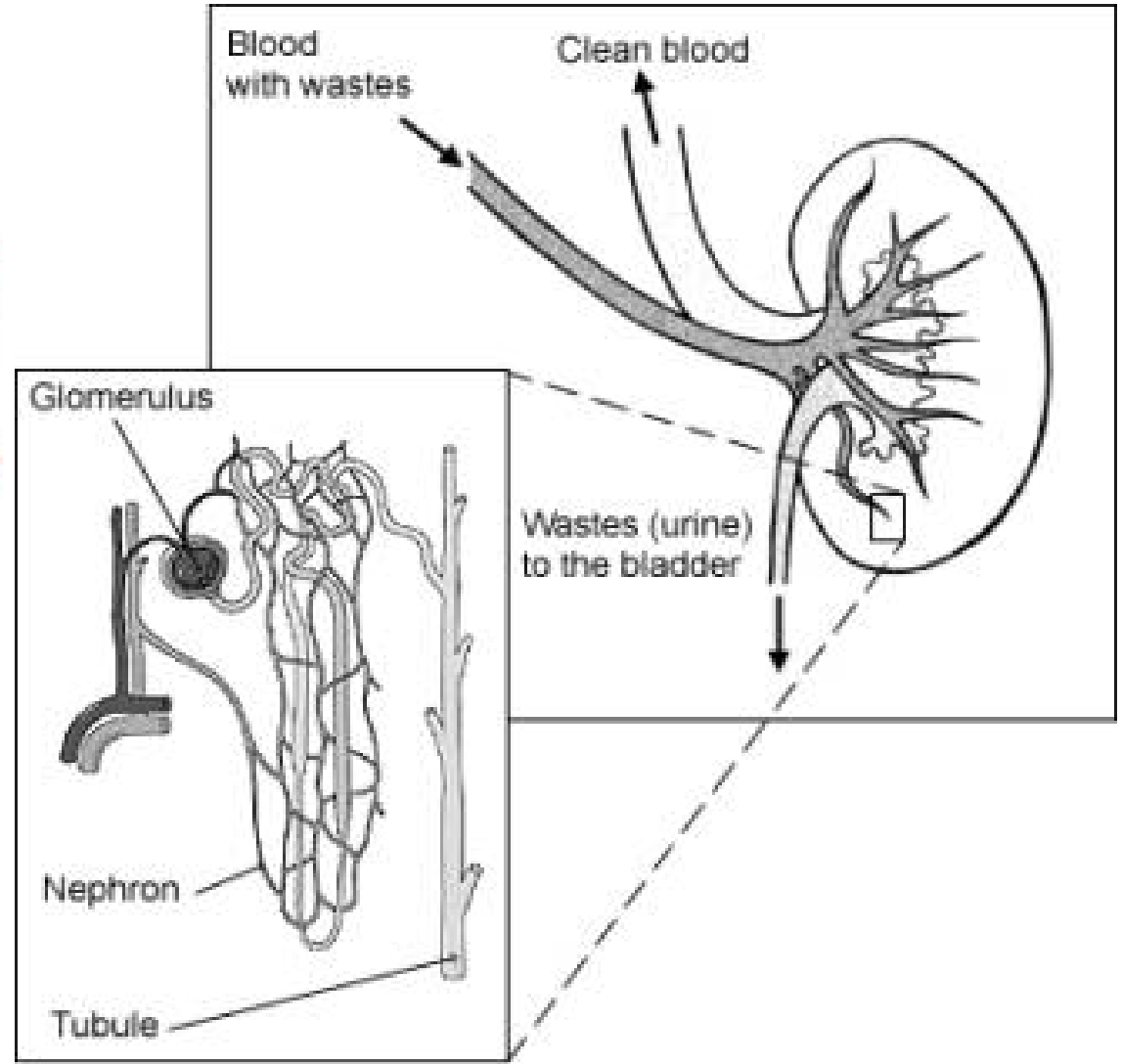
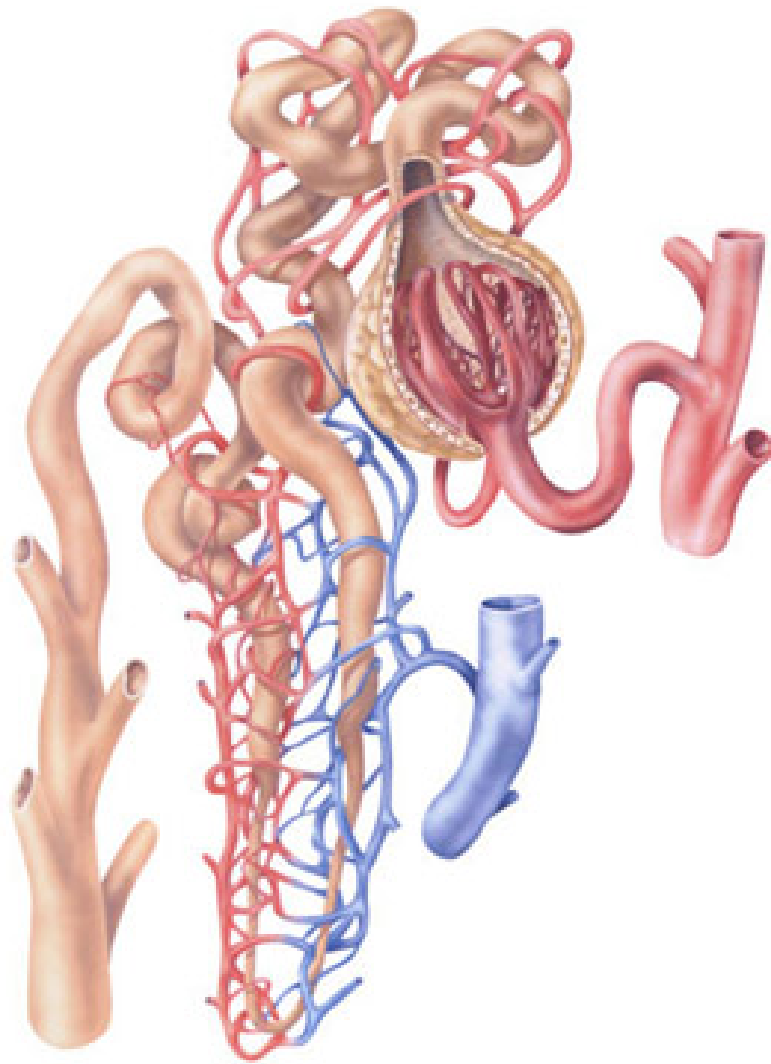
Functions of the kidney

- Selectively filters blood to allow waste excretion but prevent protein into urine
- Modify fluid and salt composition of urine
- Synthesis of hormones eg erythropoietin

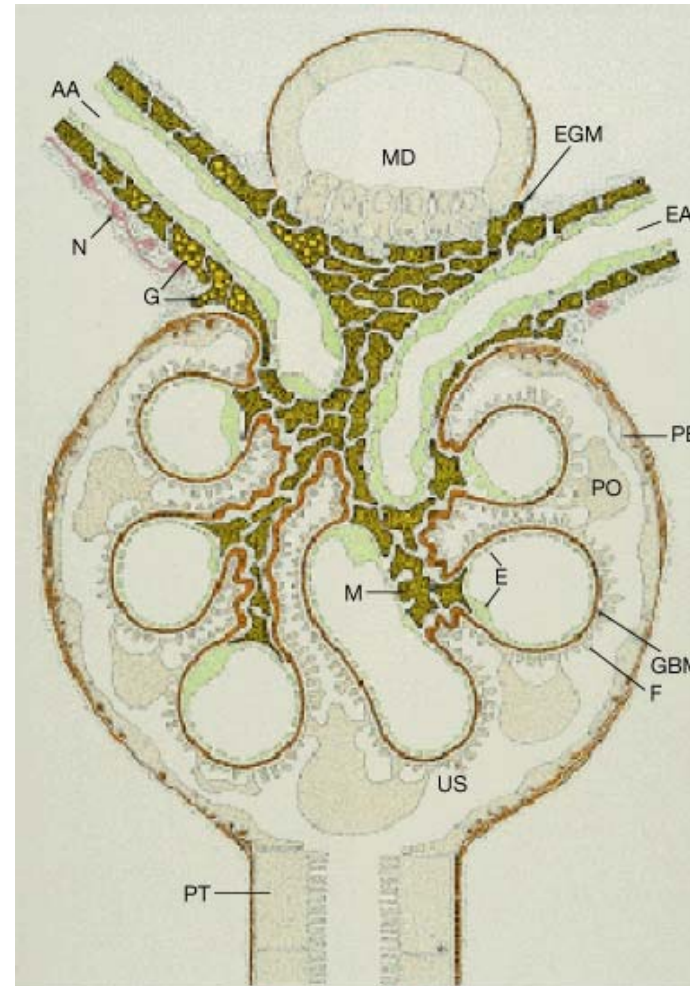
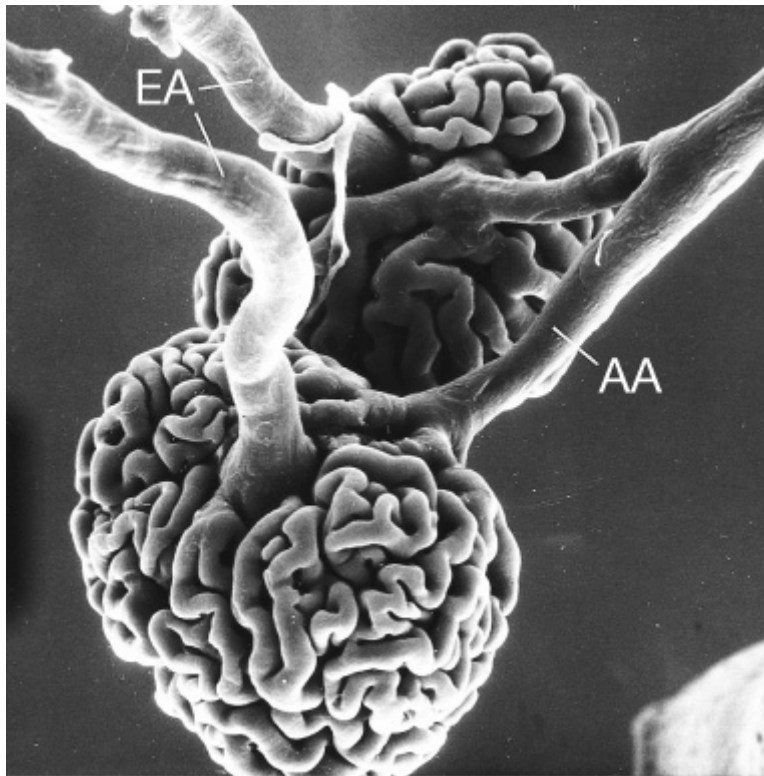
Compartments of the kidney

- Glomerulus: podocytes, mesangial cells, endothelial cells
- Tubules
- Interstitium
- Blood vessels

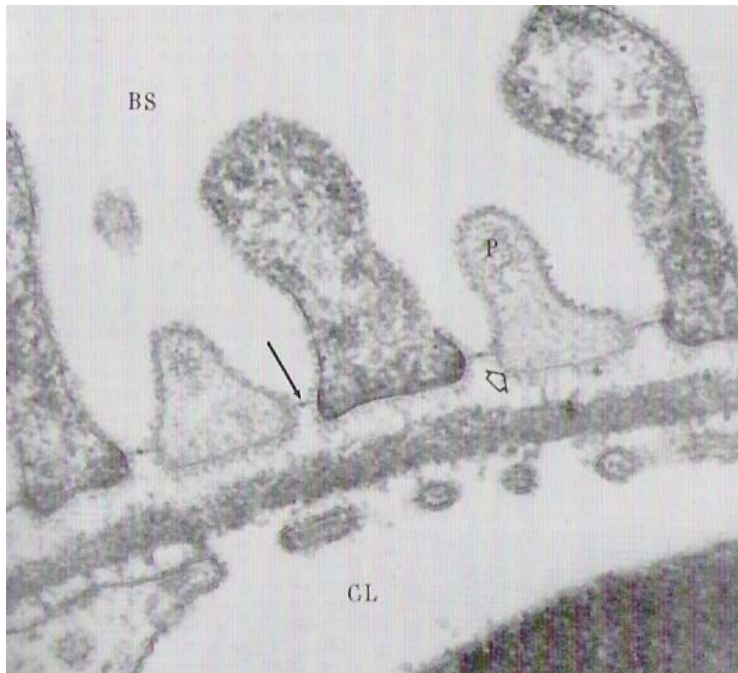
Requires precise arrangement to function



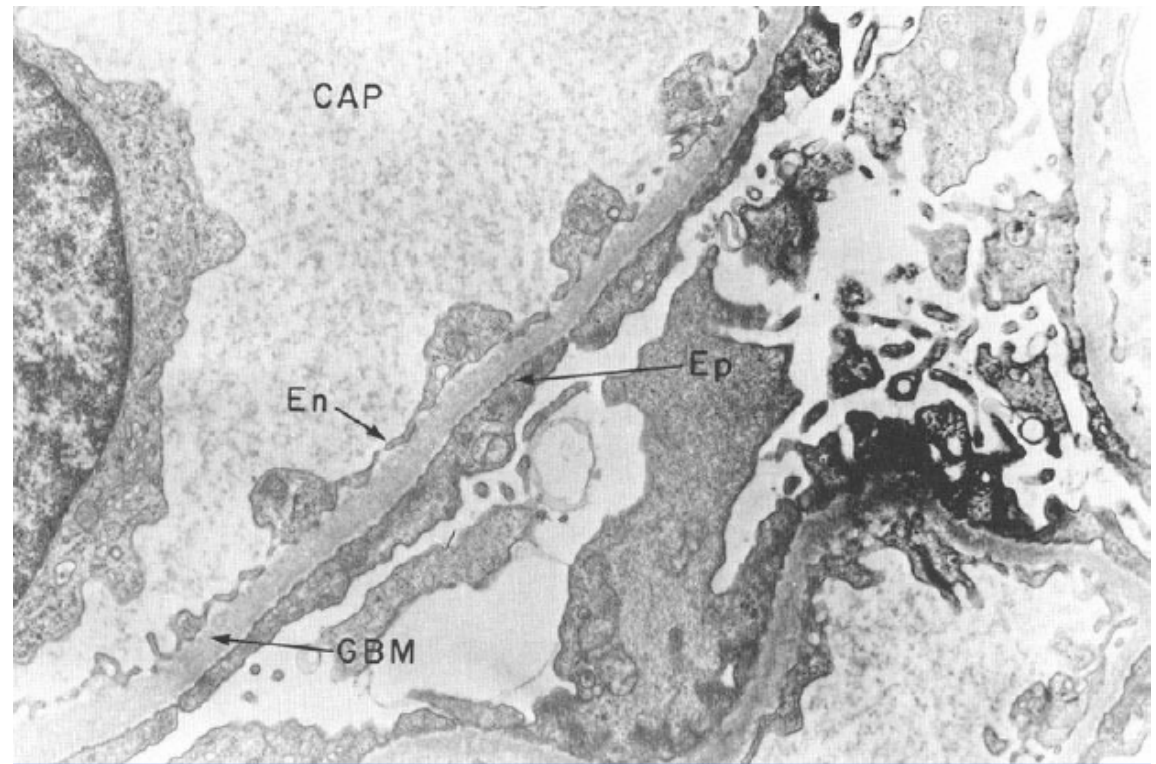
Glomerulus is a complex capillary that functions as a selective filter



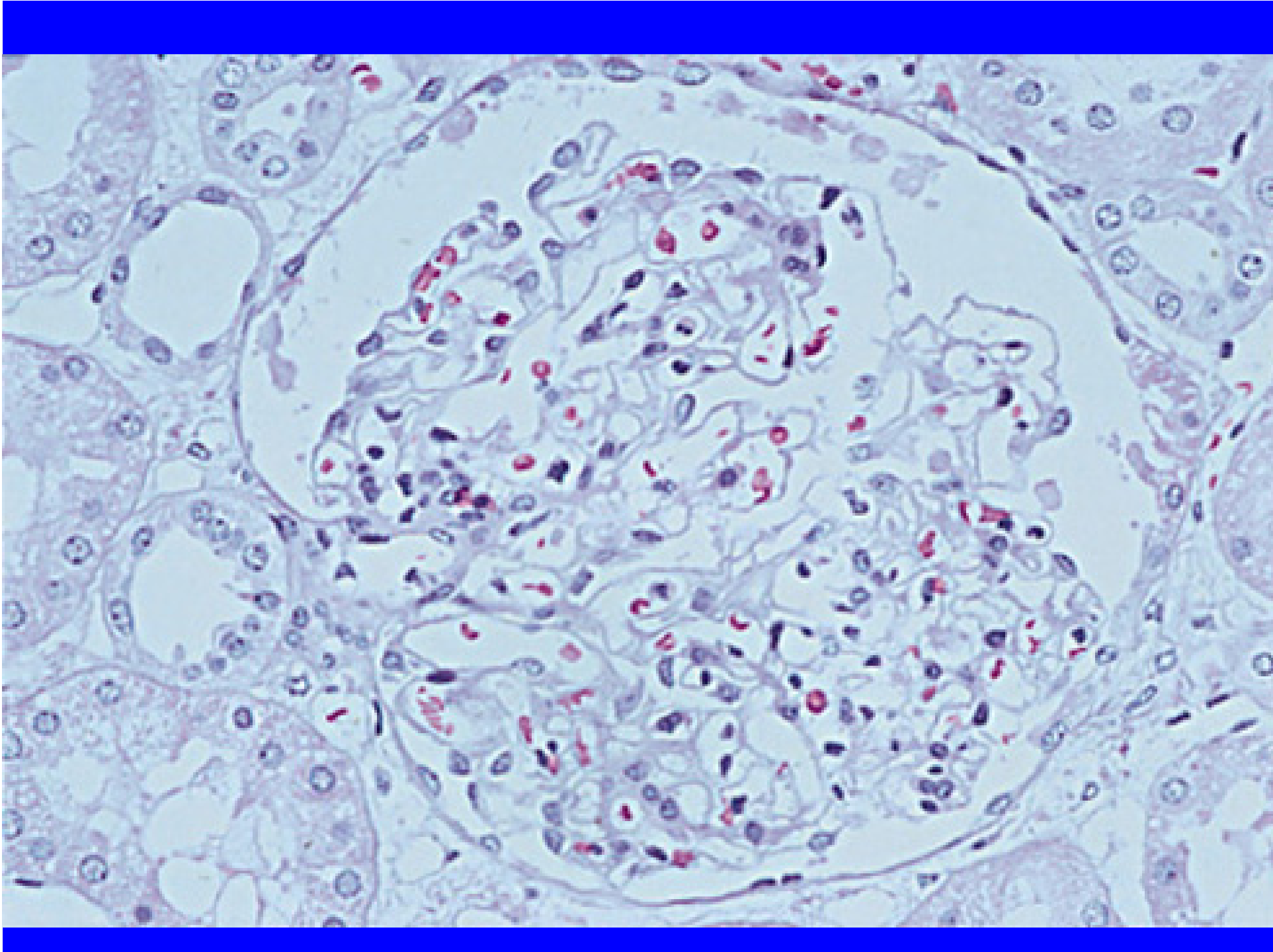
Foot process fusion/effacement in proteinuric kidney disease

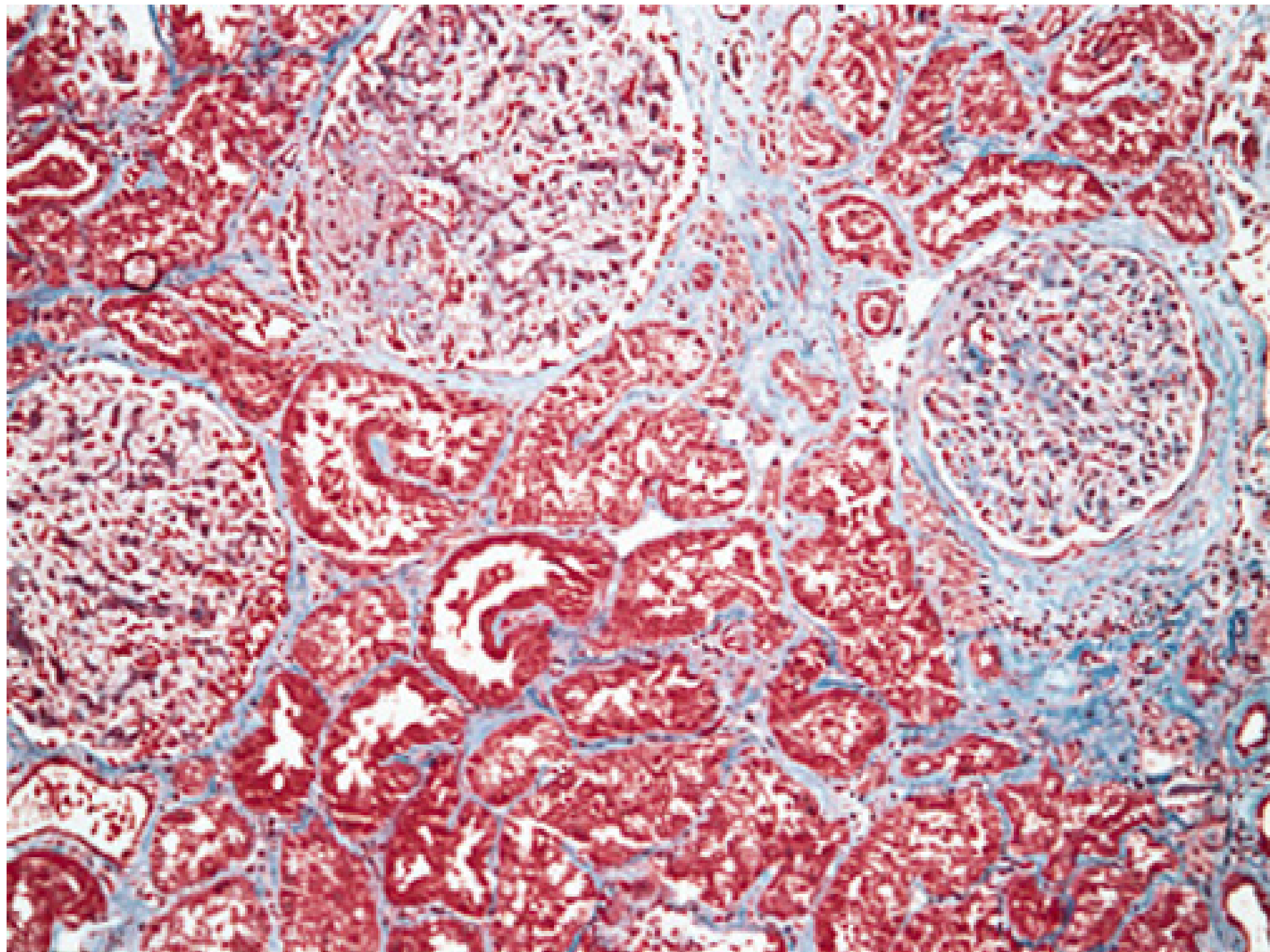


Normal

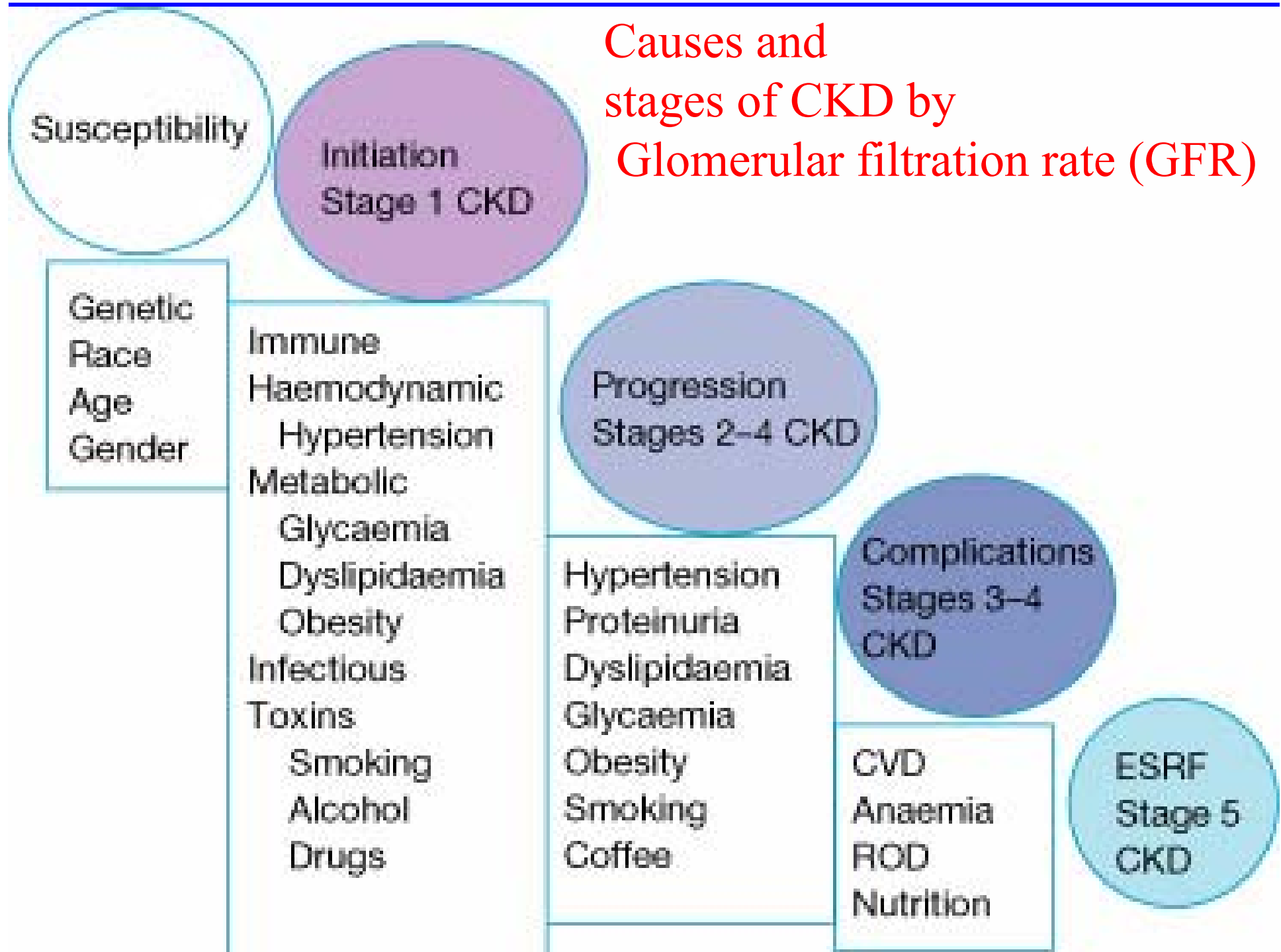


Nephrotic





Causes and stages of CKD by Glomerular filtration rate (GFR)



Susceptibility factors in Thai subjects: EGAT study

- Cohort (n= 2067) followed for 12 years
- New CKD (GFR <60ml/min/1.73 m²) 6.3%

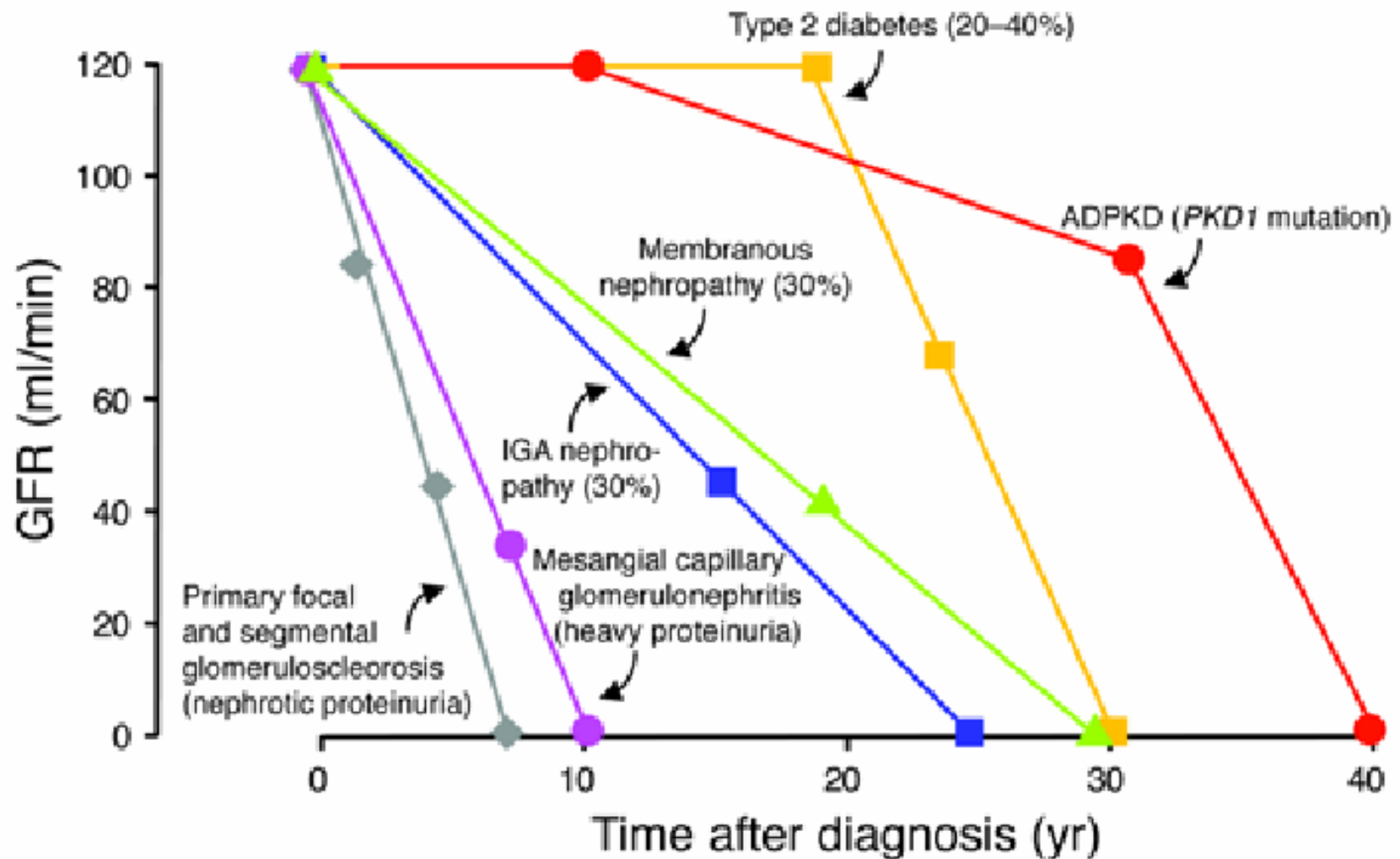
Risk factors	Folds increase
• High BS (>110)	2.7
• High BS + BP>130/85 + High TG	6.3
• High BS + high TG + Obese	7.3

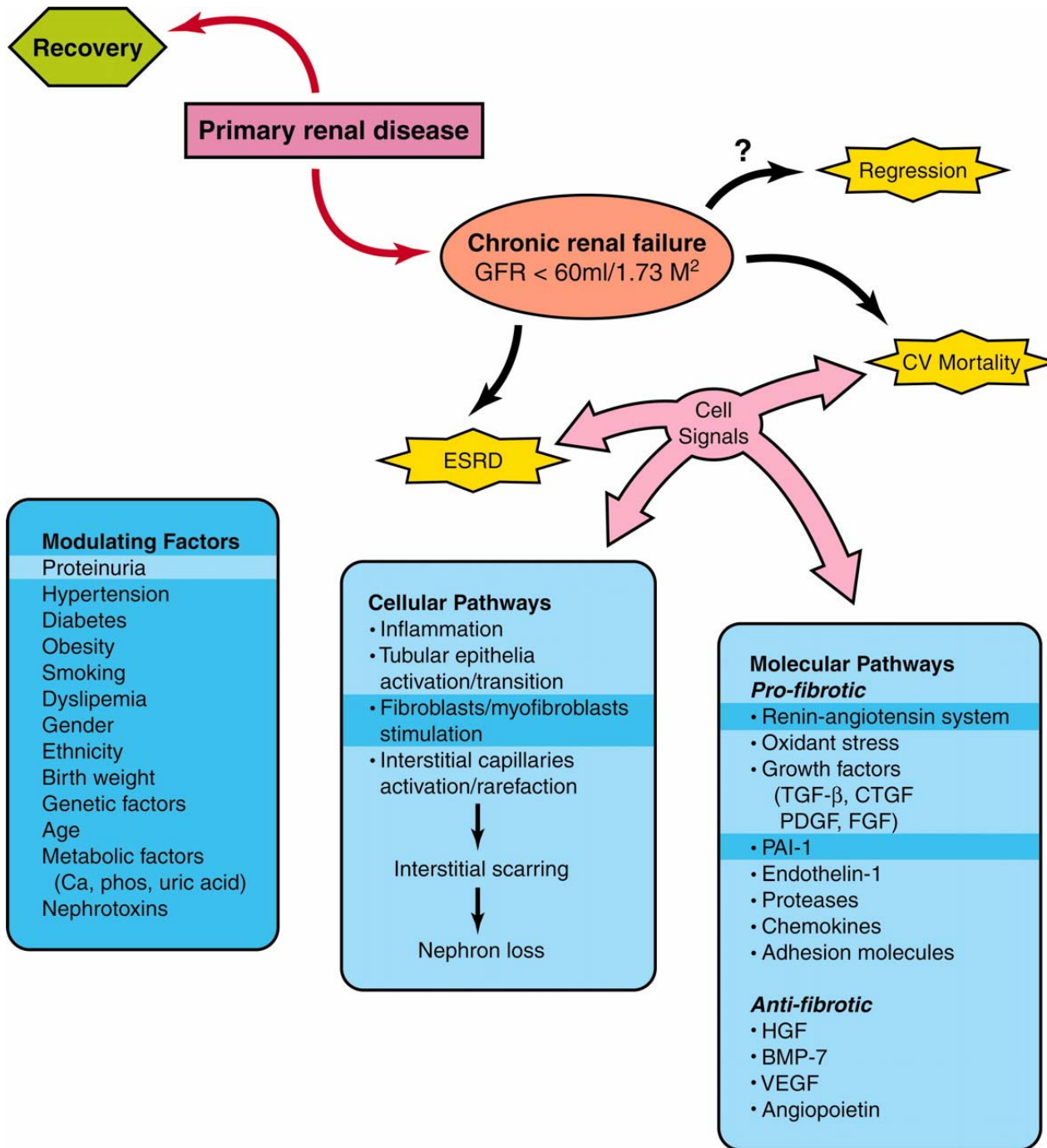
Kitiyakara C, Yamwong S, Sritara P. Kidney Int (in press)

Renal disease progression

- Once established: renal failure is often progressive even after original cause is treated
- Steps to prevent progression essential

Rate of progression depend on disease, genetics, treatment





Factors contributing to progressive renal disease

Primary renal disease:- extent of initial injury

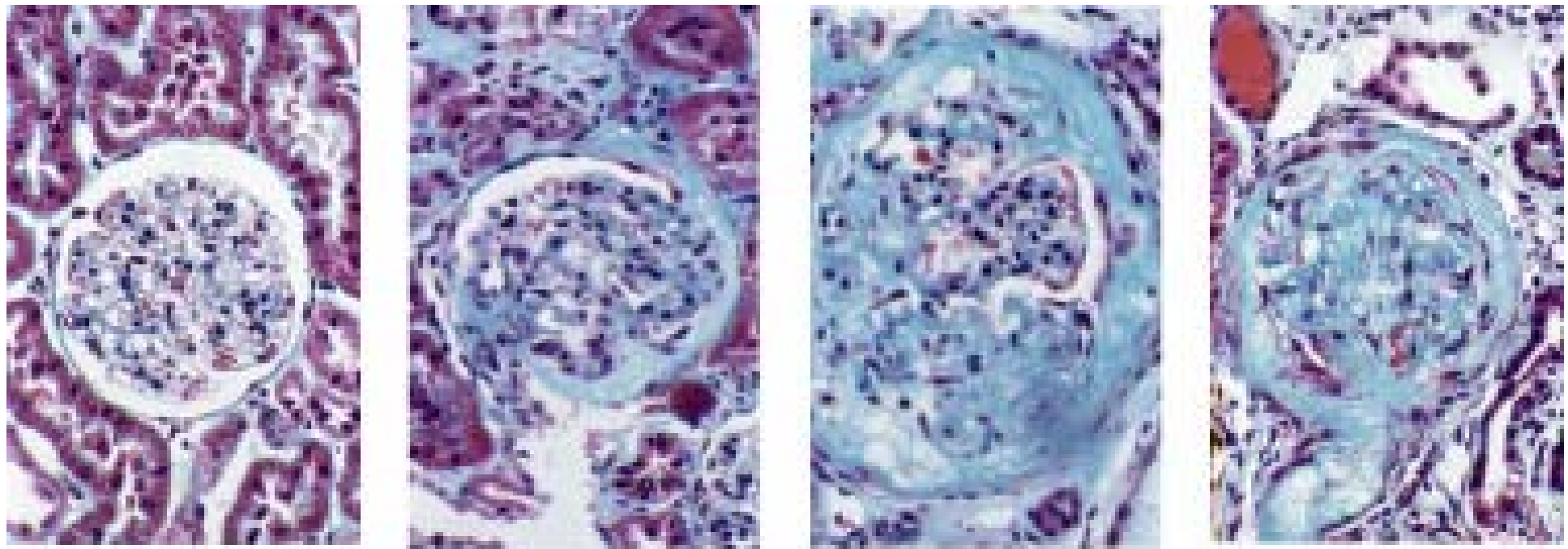
Secondary factors

- Systemic hypertension
- Glomerular hypertension
- Renin-Angiotensin II-Aldosterone
- Proteinuria
- High protein intake
- Hyperlipidemia, obesity
- Smoking
- Anemia
- Race, male gender, genetics, decreased nephron endowment

Cellular pathways of progression

- Persistent glomerular injury and glomerular hypertension
- Heavy glomerular proteinuria
- Immune response and cytokines
- Fibroblast formation and recruitment
- Collagen matrix deposition
- Acellular scar, ischemia, tubular atrophy and interstitial fibrosis

Glomerular sclerosis and glomerular hypertension



Normal



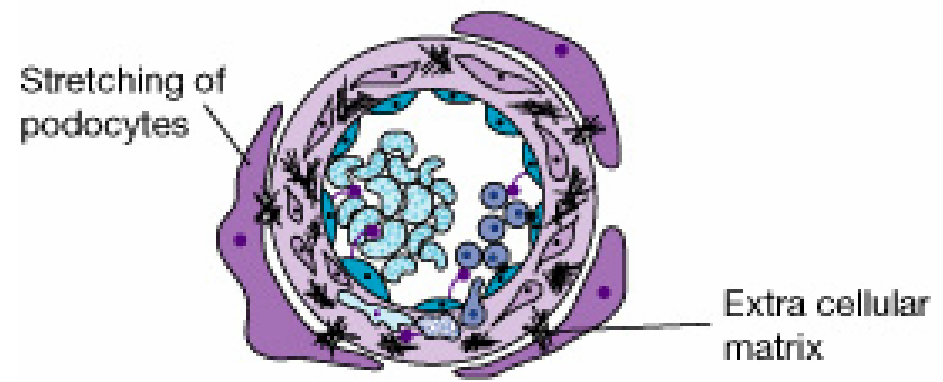
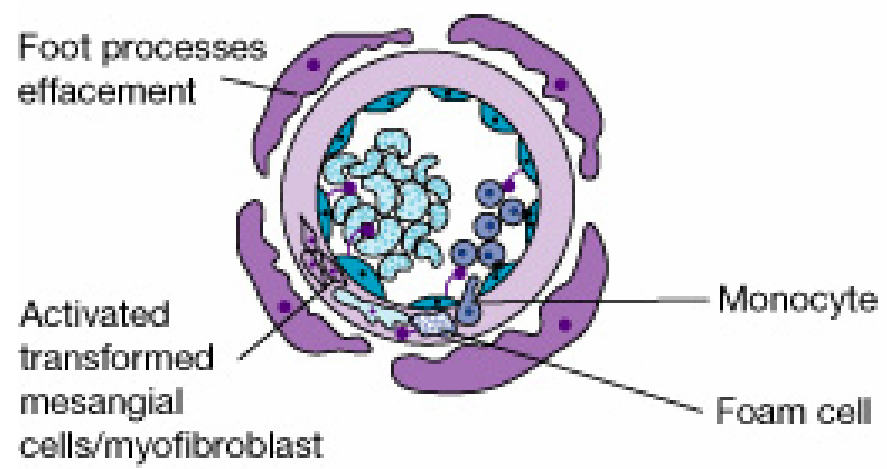
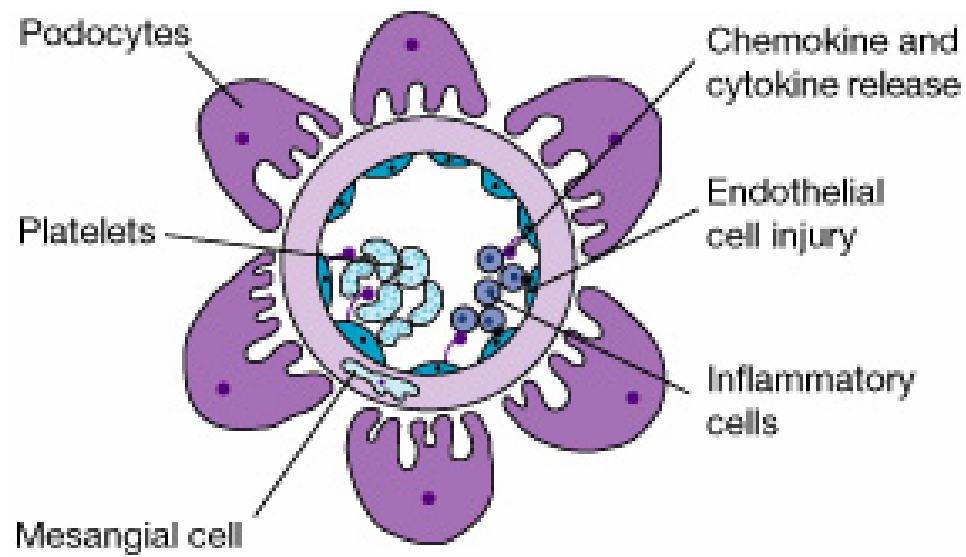
Early GS



Segmental GS



Diffuse GS



Inflammation



Proliferation

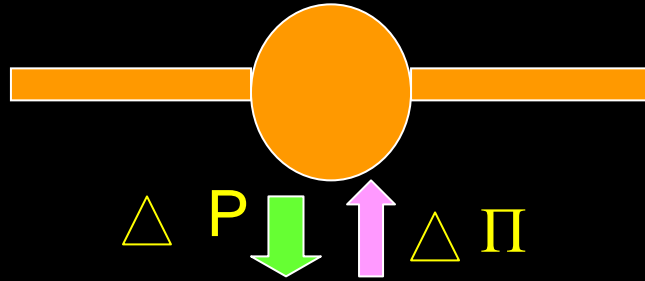


Fibrosis

Glomerular hypertension

- Hyperfiltration hypothesis-Brenner et al
- Decreased nephron mass leads to compensation by other remaining nephrons
- This is mediated by increased glomerular pressure and increased blood pressure and angiotensin II
- Decreasing intraglomerular pressure (eg by ACEi) or protein restriction decreases damage

$$\Delta P = P_{Gc} - P_T$$



↓↓ Whole kidney GFR

↓ Whole Kidney GFR
↑↑ SNGFR

↓↓ R_A ↑ R_E

↑ BP

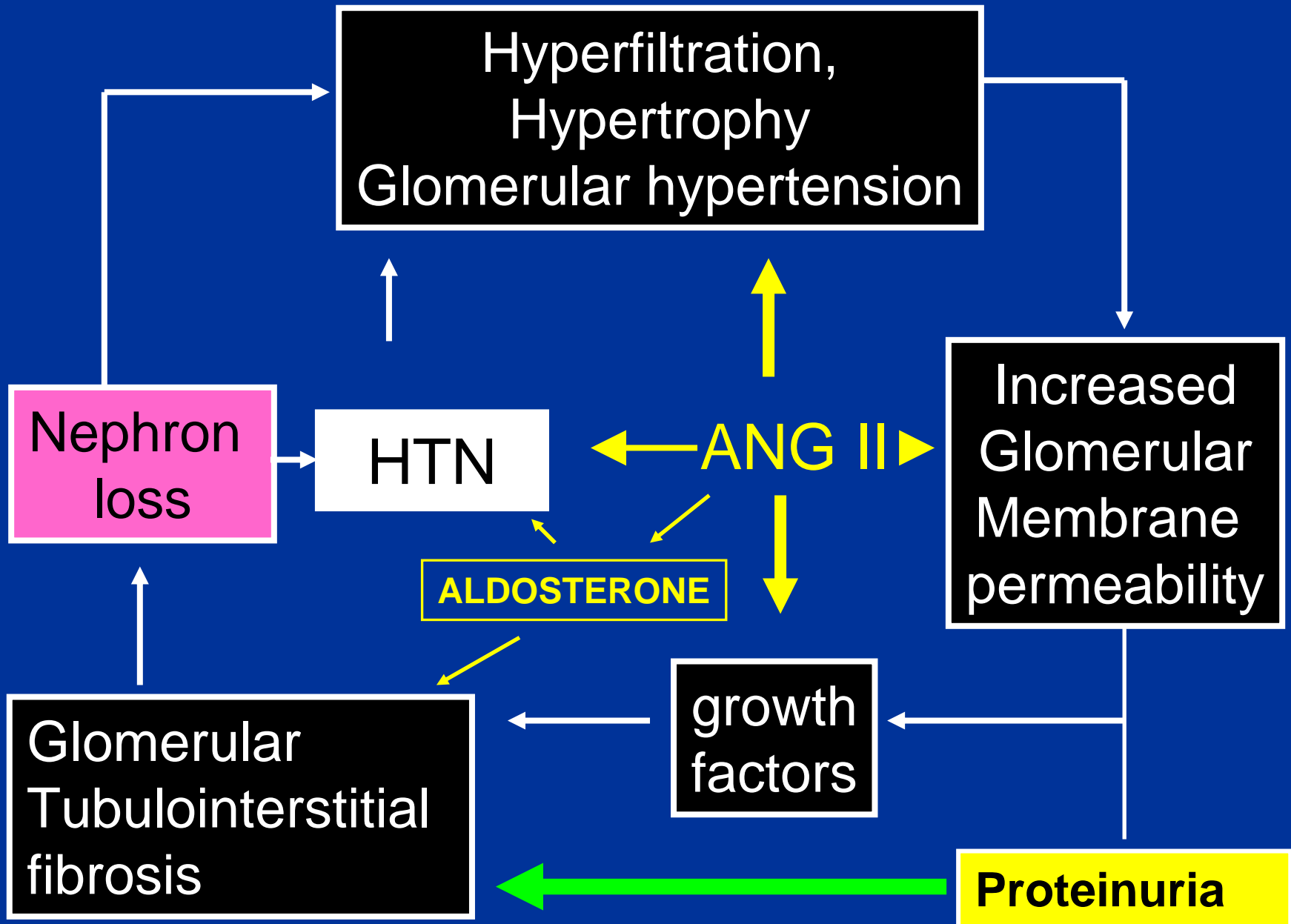
PGI_2

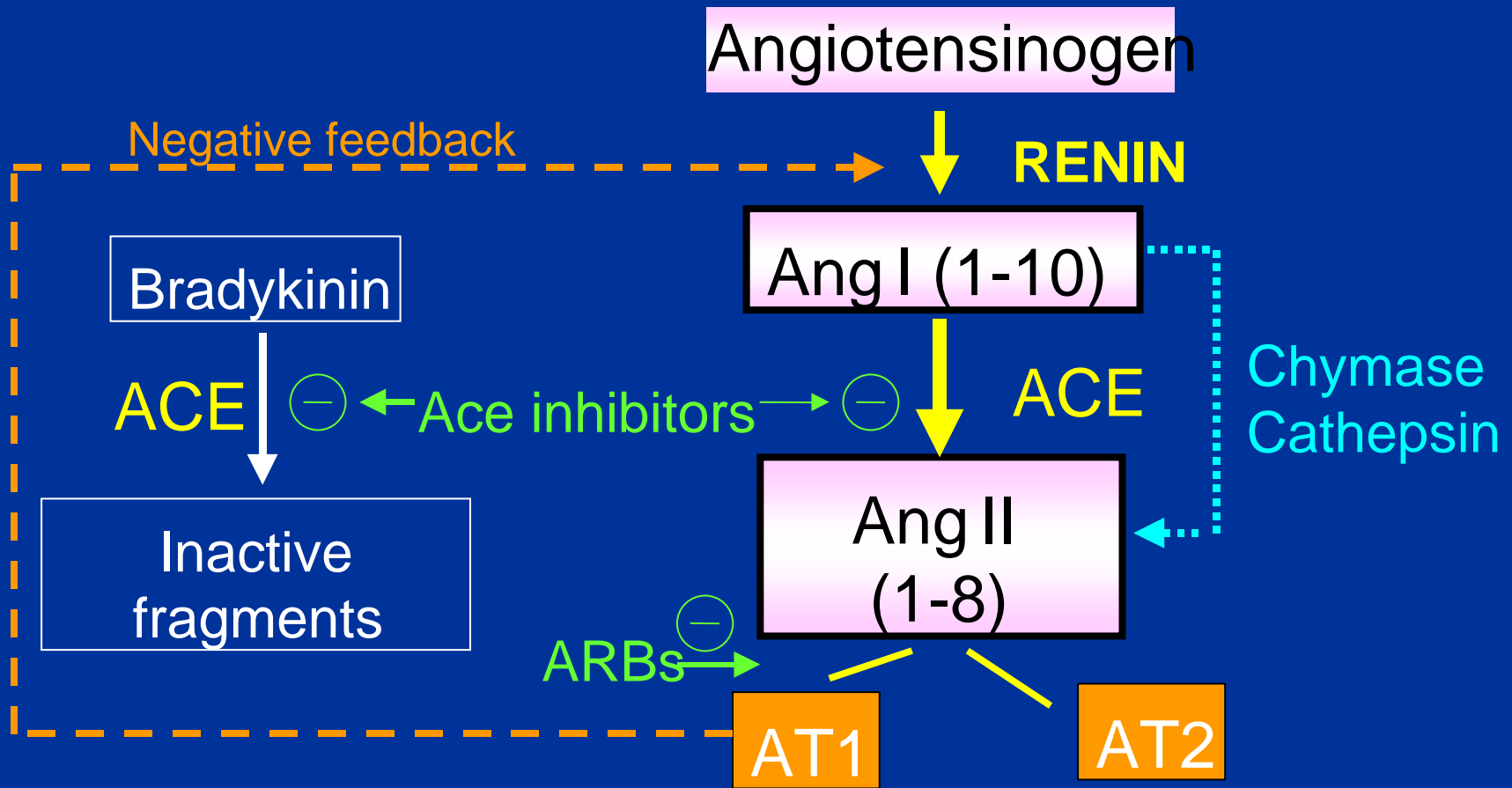
Ang II

vasodilation

↑↑ P_{Gc}

vasoconstriction

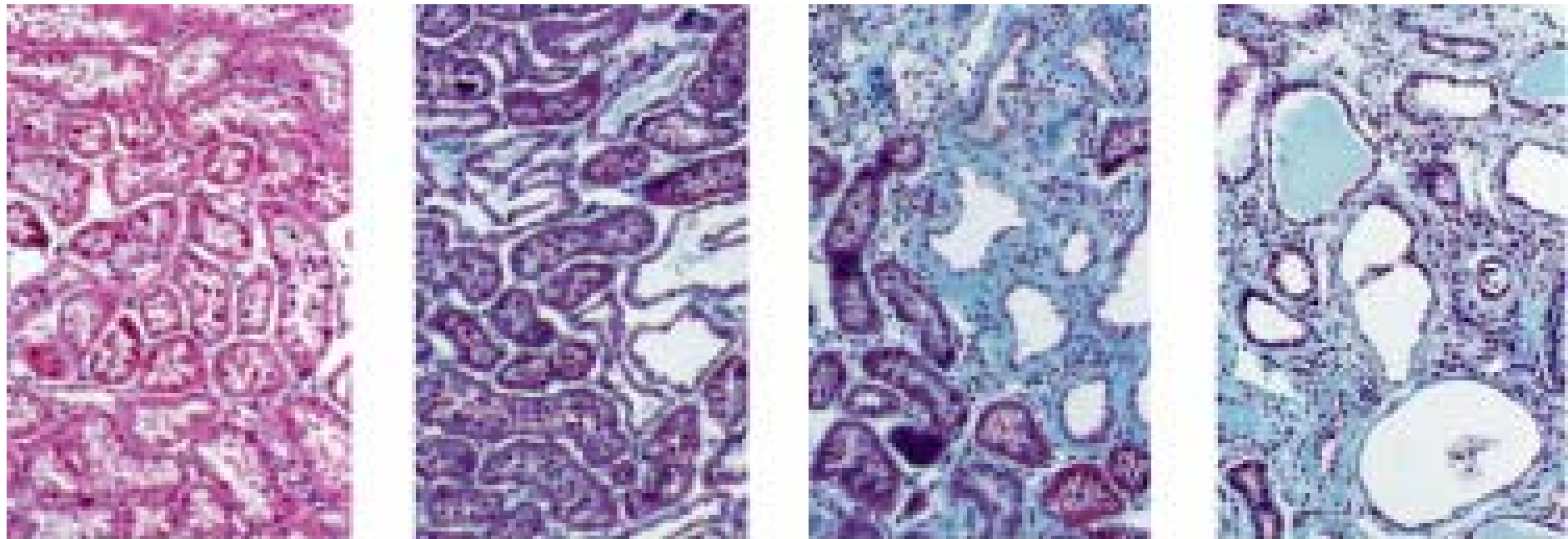




Glomerular hypertension
 Vasoconstriction
 TGF b stimulation
 Fibrosis

Vasodilation

Tubulointerstitial injury and fibrosis



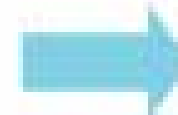
Normal



Mild TIS

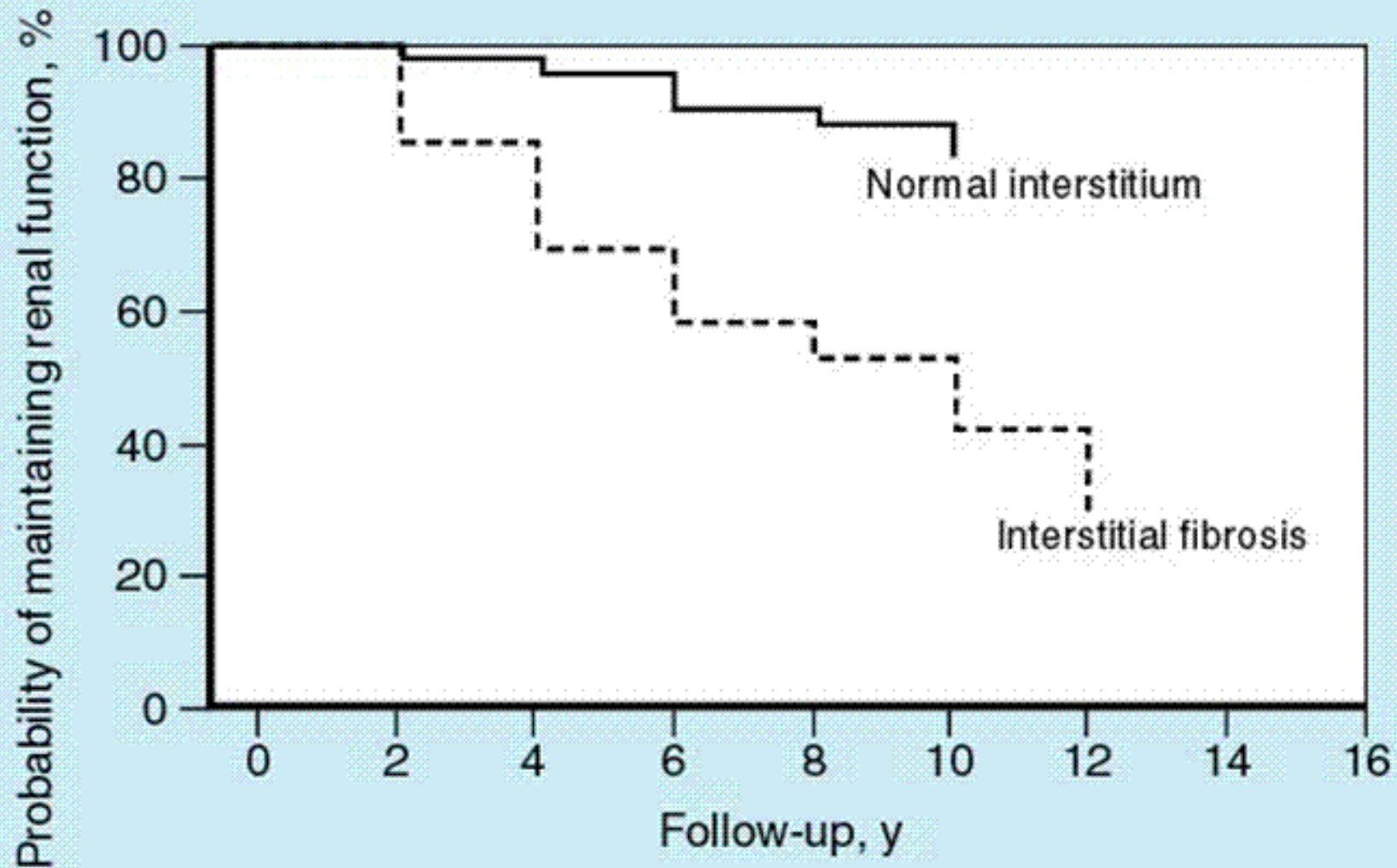


Moderate TIS

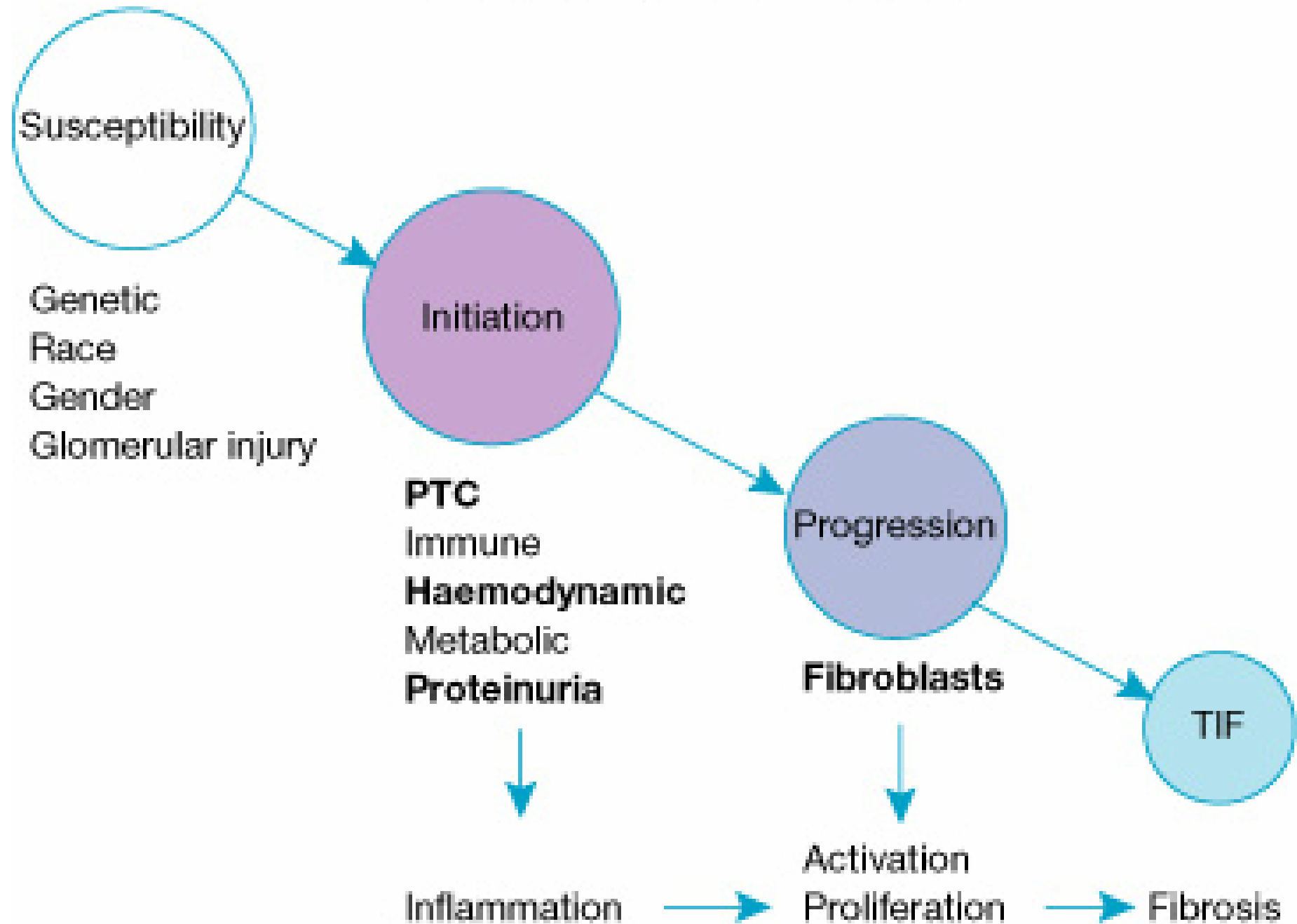


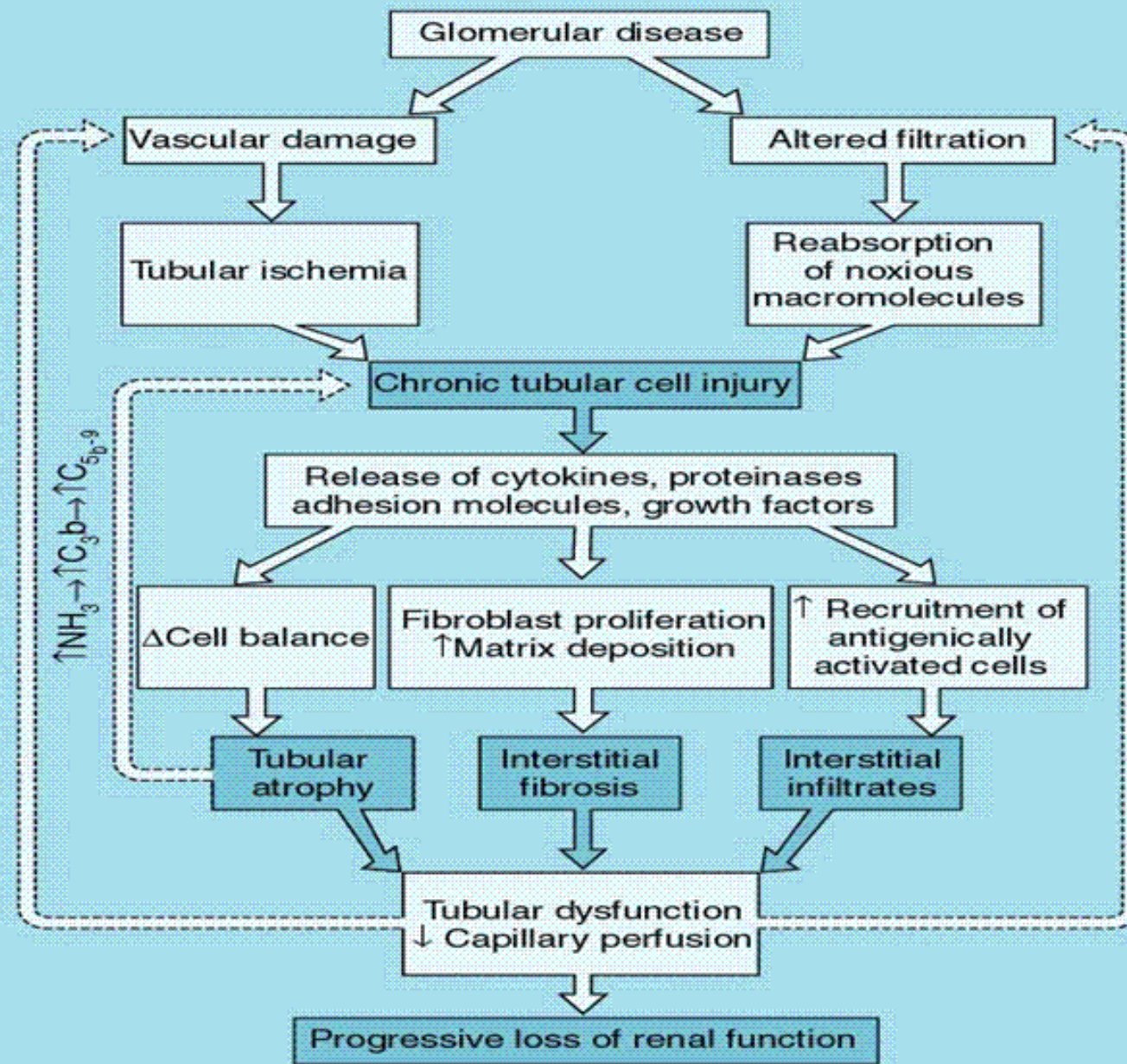
Severe TIS

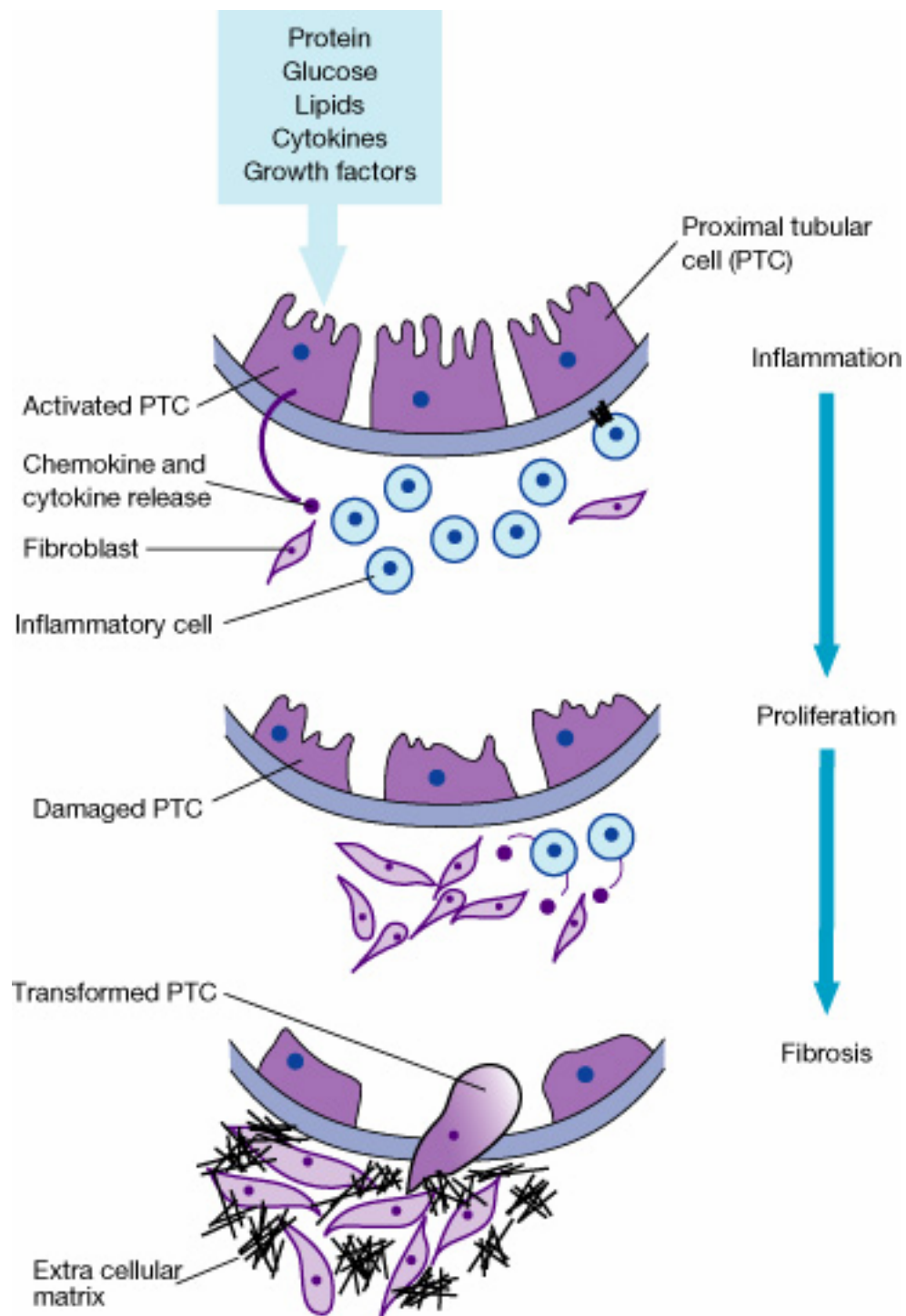
Interstitial fibrosis predicts ESRD

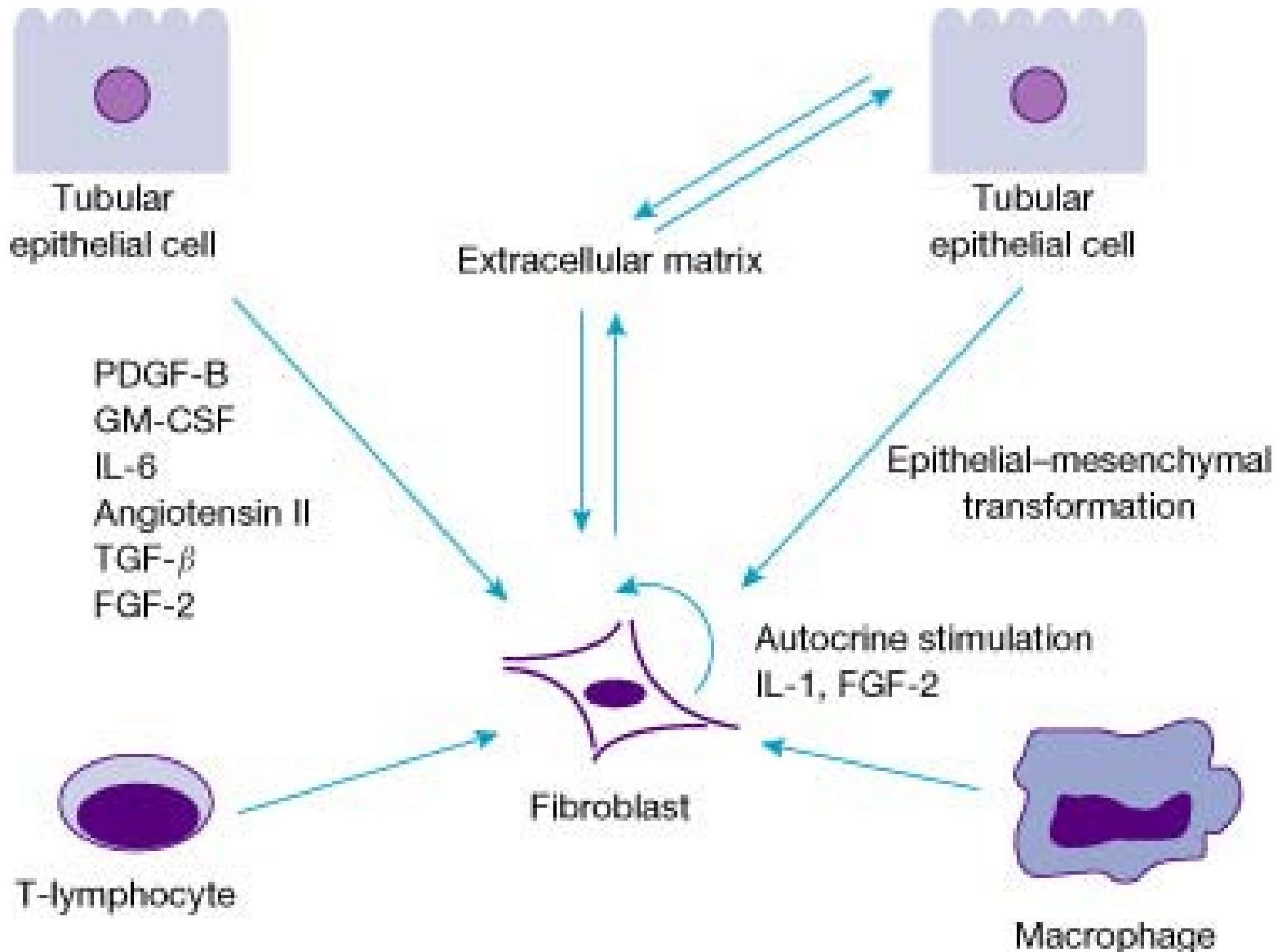


Progression of interstitial fibrosis





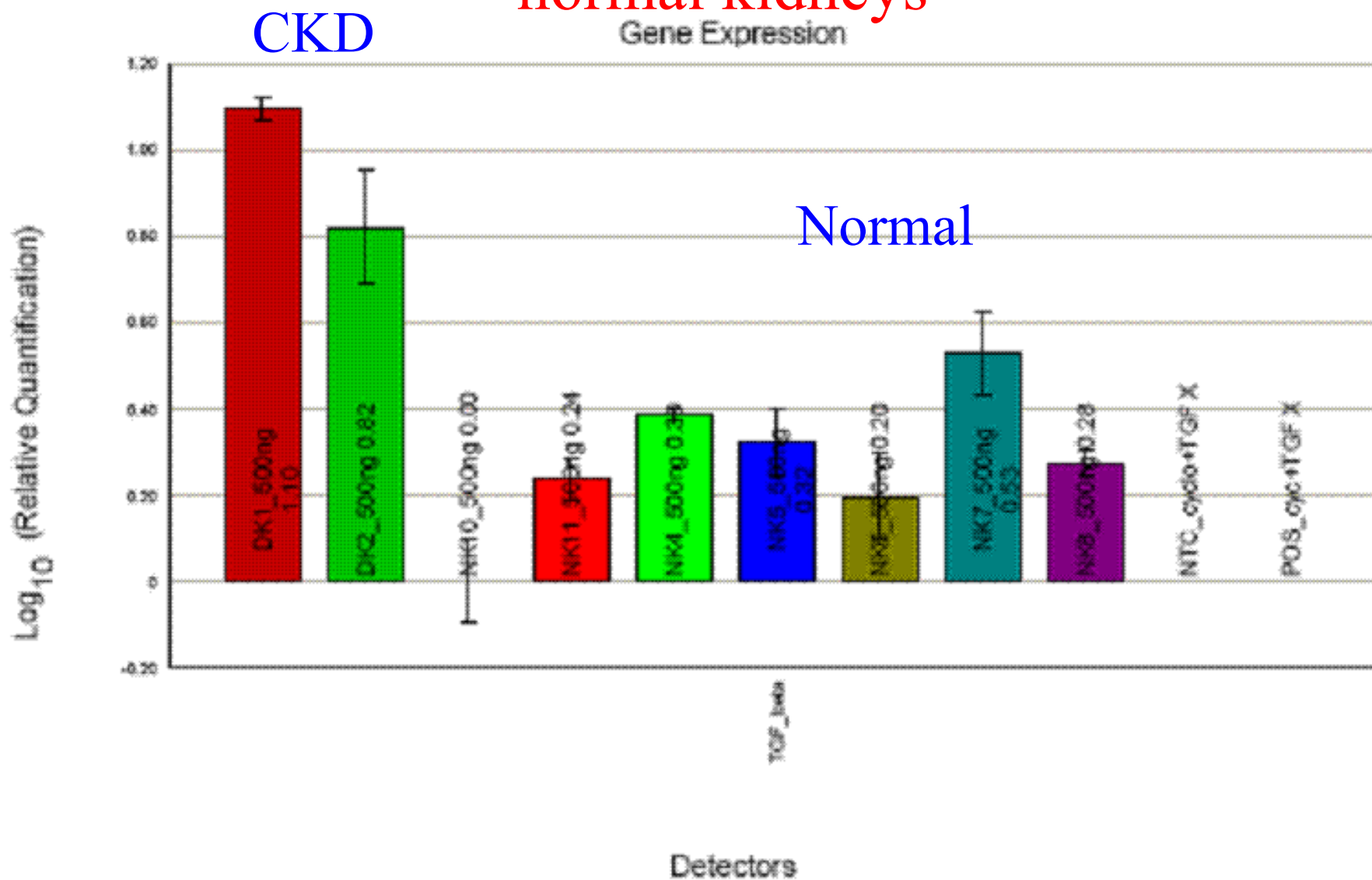




Transforming growth factor beta

- Cytokine that is anti-inflammatory and stimulates fibrosis
- Increased in fibrogenic diseases
- Natural inhibitors (e.g. Bone morphometric protein 7-BMP7) which may decrease kidney disease progression

Relative expression of TGF-beta in disease and normal kidneys

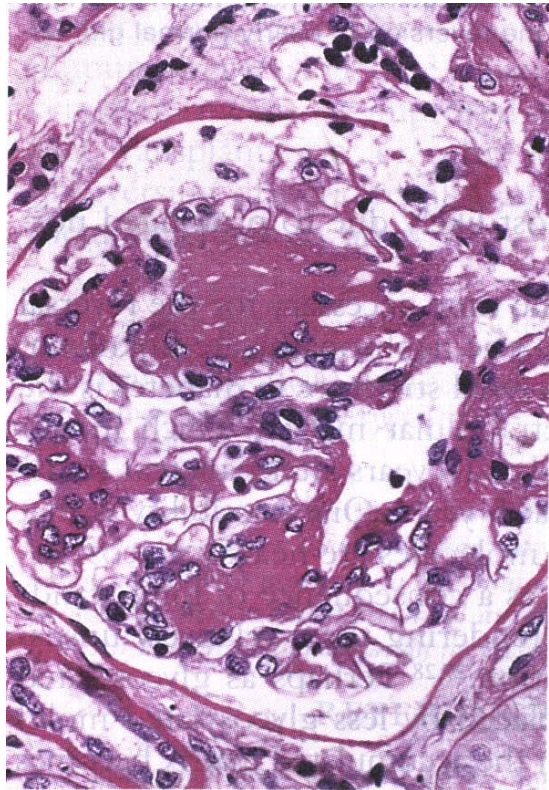


Conclusions:

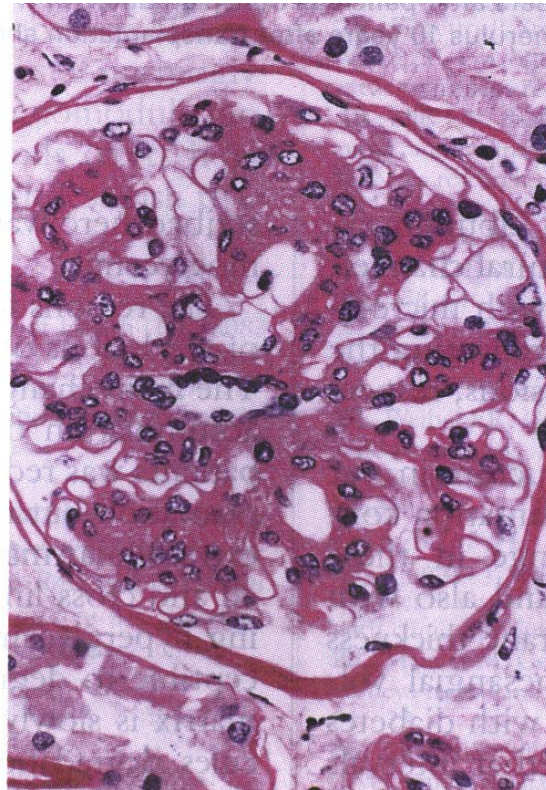
Chronic kidney disease progression

- Occurs even if the primary disease is treated at an individually determined rate
- Injury and scarring of glomeruli, tubulo-interstitium and loss of blood vessels mediated by cells in the kidney, circulating cells and secreted factors
- Strategies to minimize these processes may prevent continued loss of kidney function

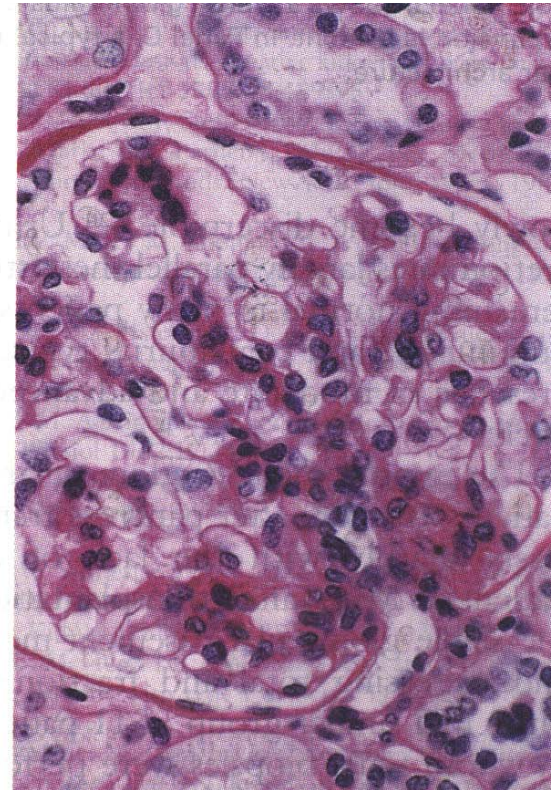
Can Chronic kidney disease be reversed?



Baseline



5 years



10 years

Reversal of diabetic nephropathy
after pancreas transplantation

Fioretto et al NEJM 1998



THANK YOU

