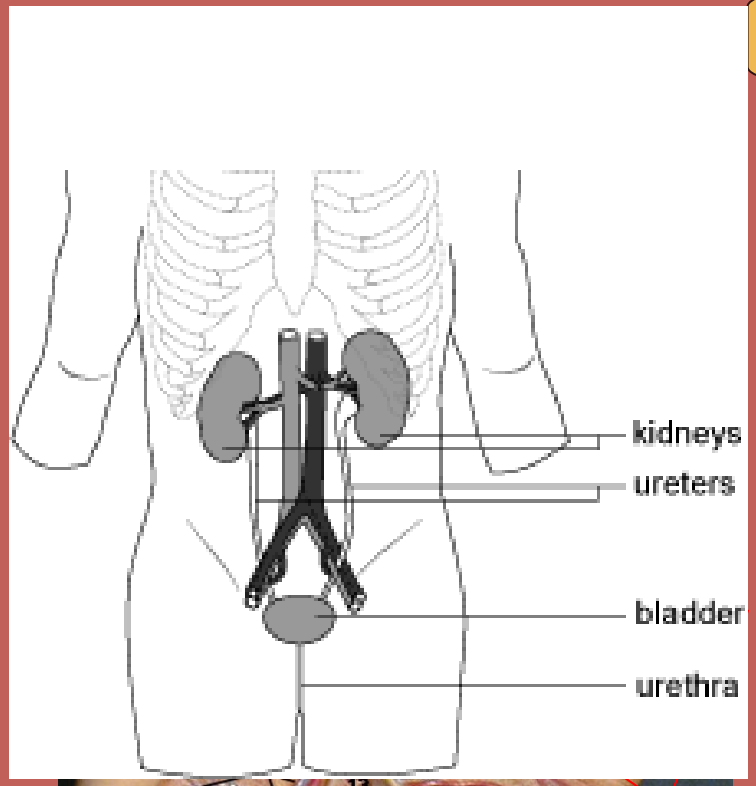
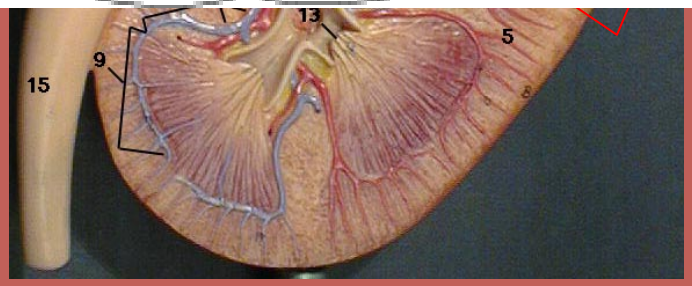
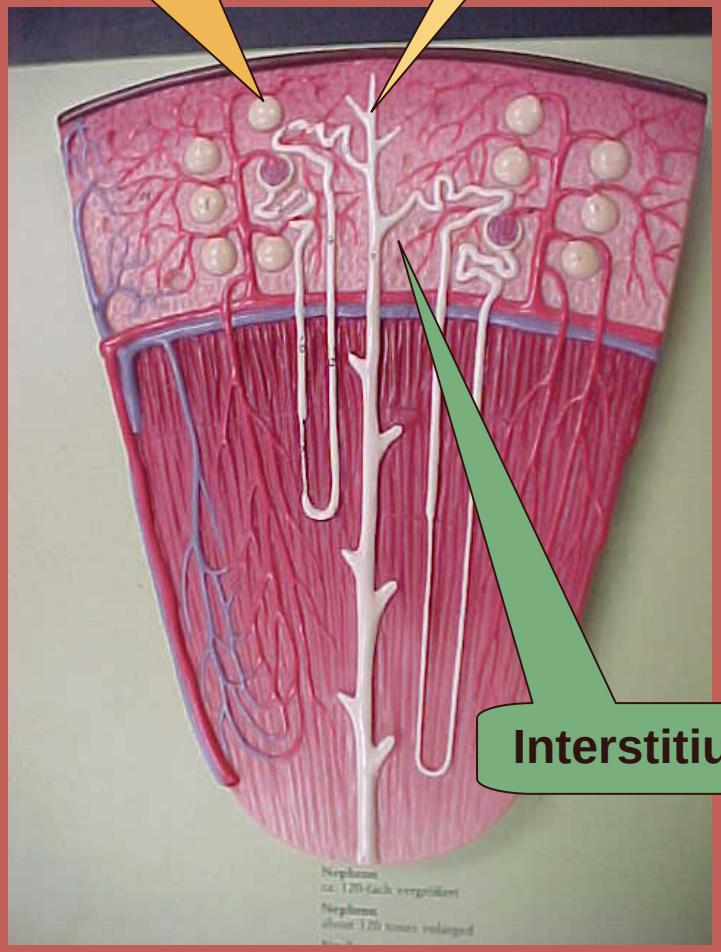
How kidney is vulnerable to injury





Glomerulus

Tubule

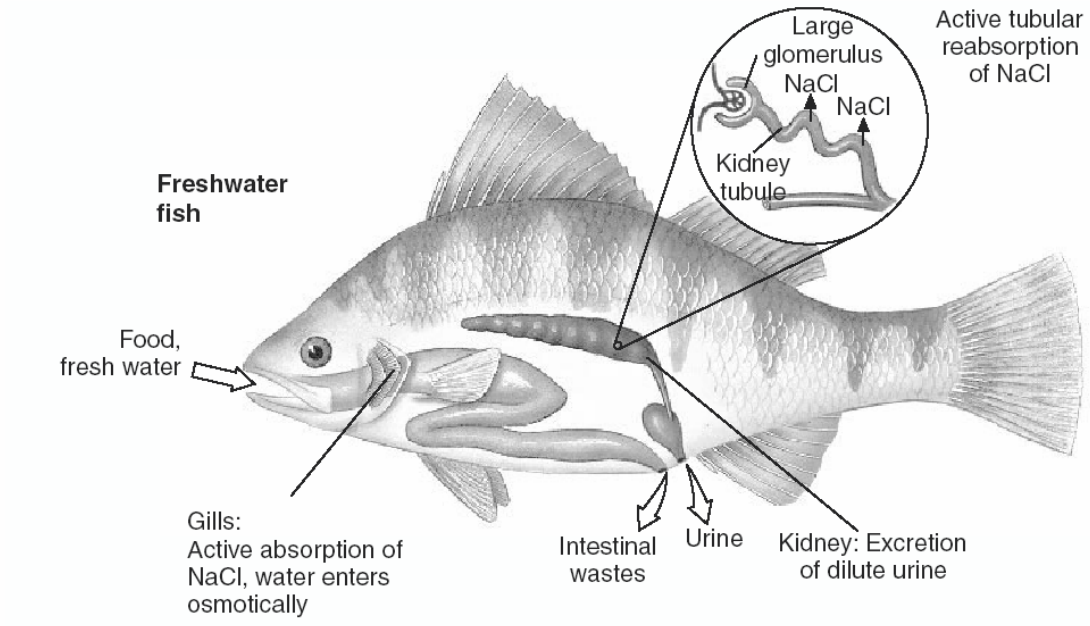


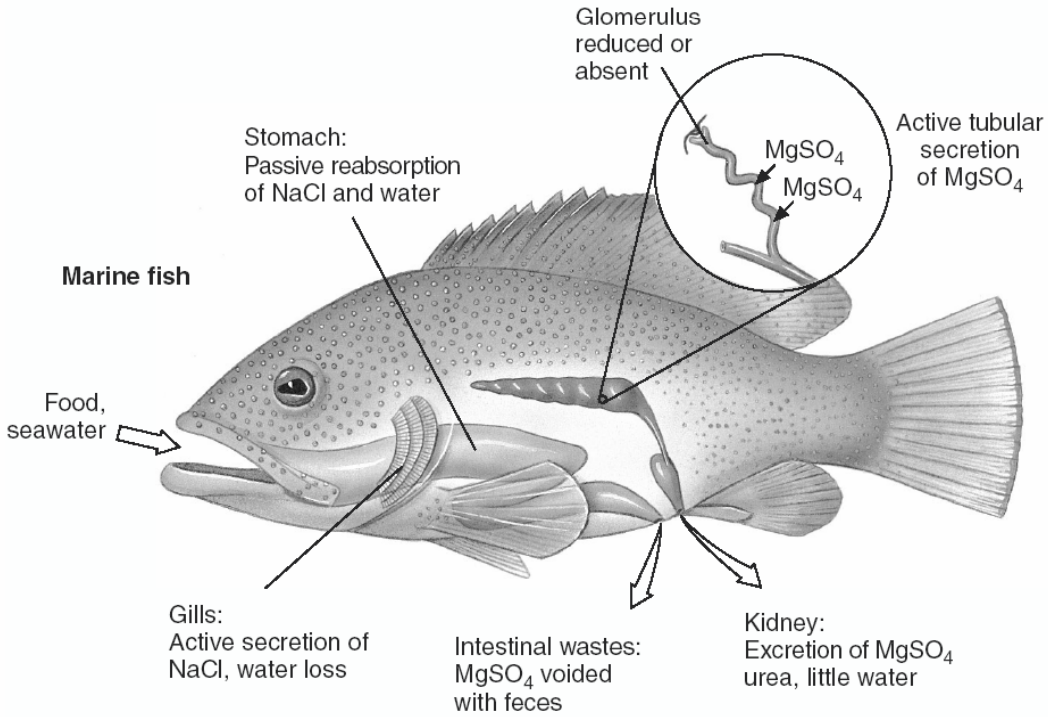
Interstitium

Tubule+Interstitium = Tubulointerstitium

Circulat
syster

Ancient excretory system

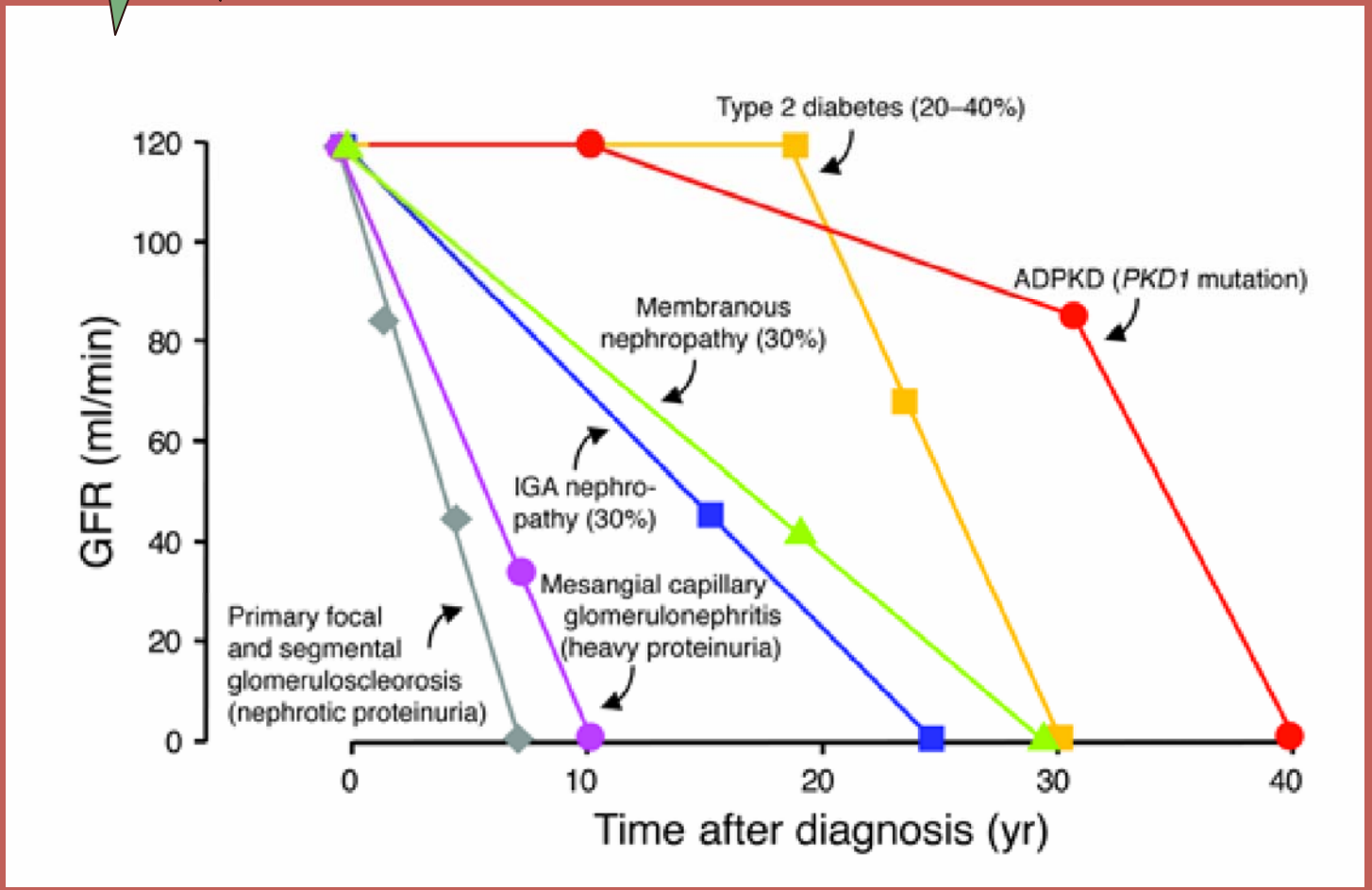




Primary Renal Disease

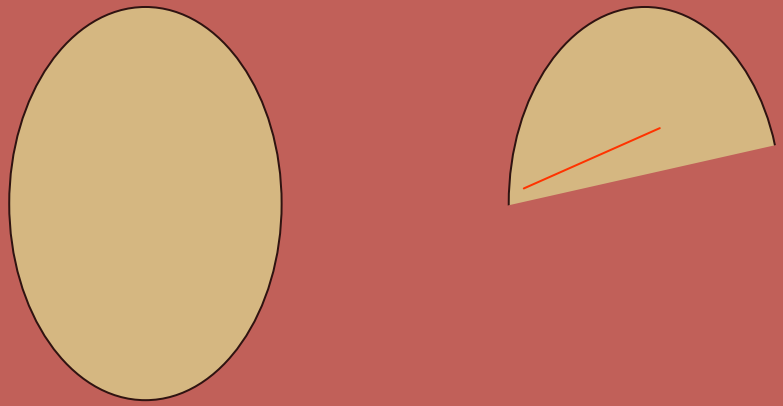
Secondary Progression

ESRD



Secondary Progression

ESRD



Remnant kidney model

Chanutin A 1932

Arch. Intern. Med. 49:767–787.

Glomerular hyperfiltration lead to glomerulosclerosis and (ESRD)

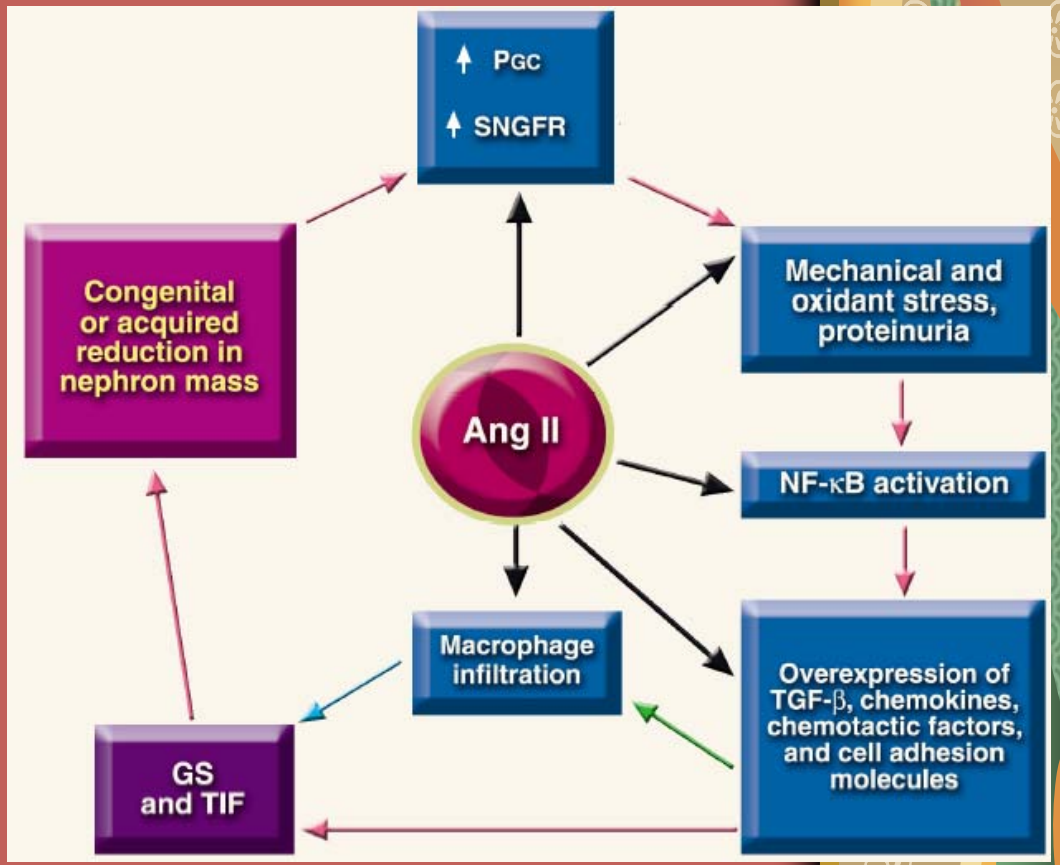
Protein restriction diet
ACEI (ARB) treatment
Model in kidney diseases (e.g. DN)

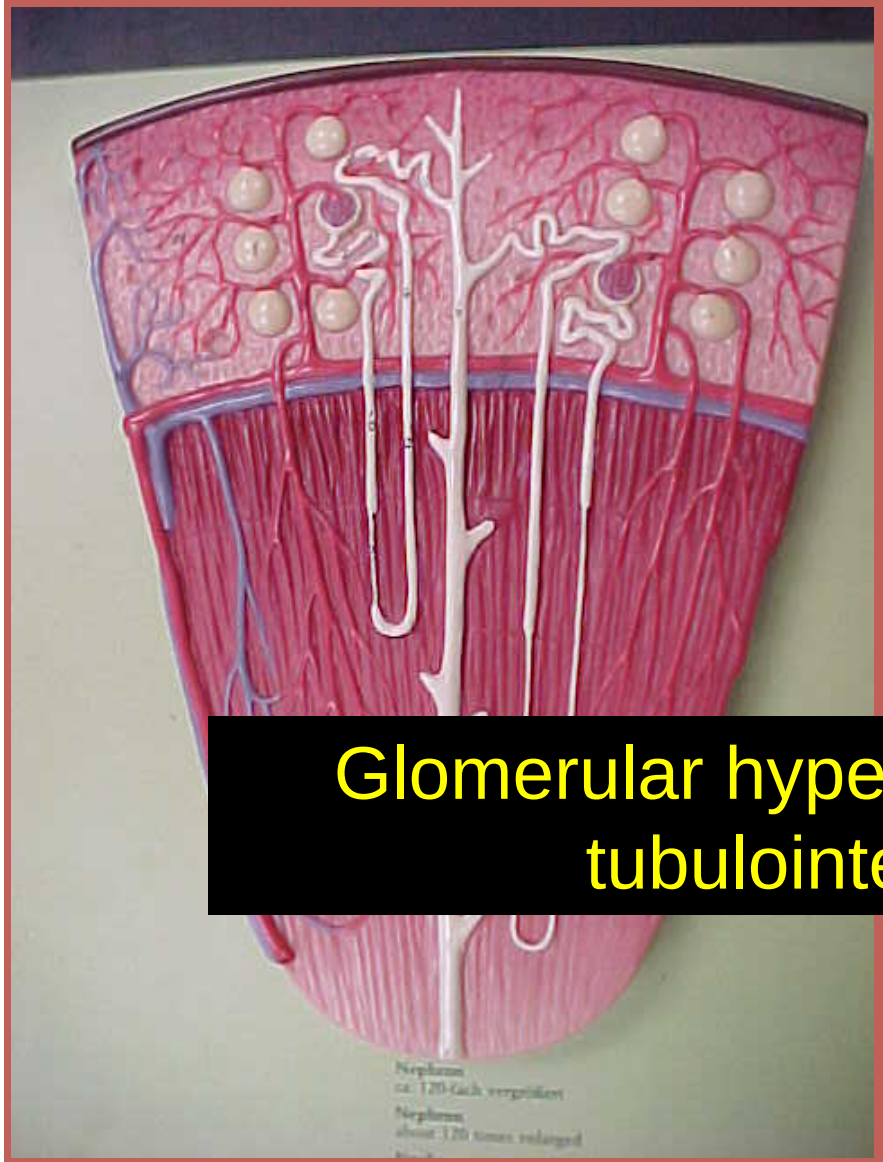
All textbooks

Glomerular hyperfiltration +hypertension

- Renal mass reduction
- Afferent a. dilate >>> Eff.
- Glomerular pressure
- Glomeruloscelrosis

RAS plays Central Role



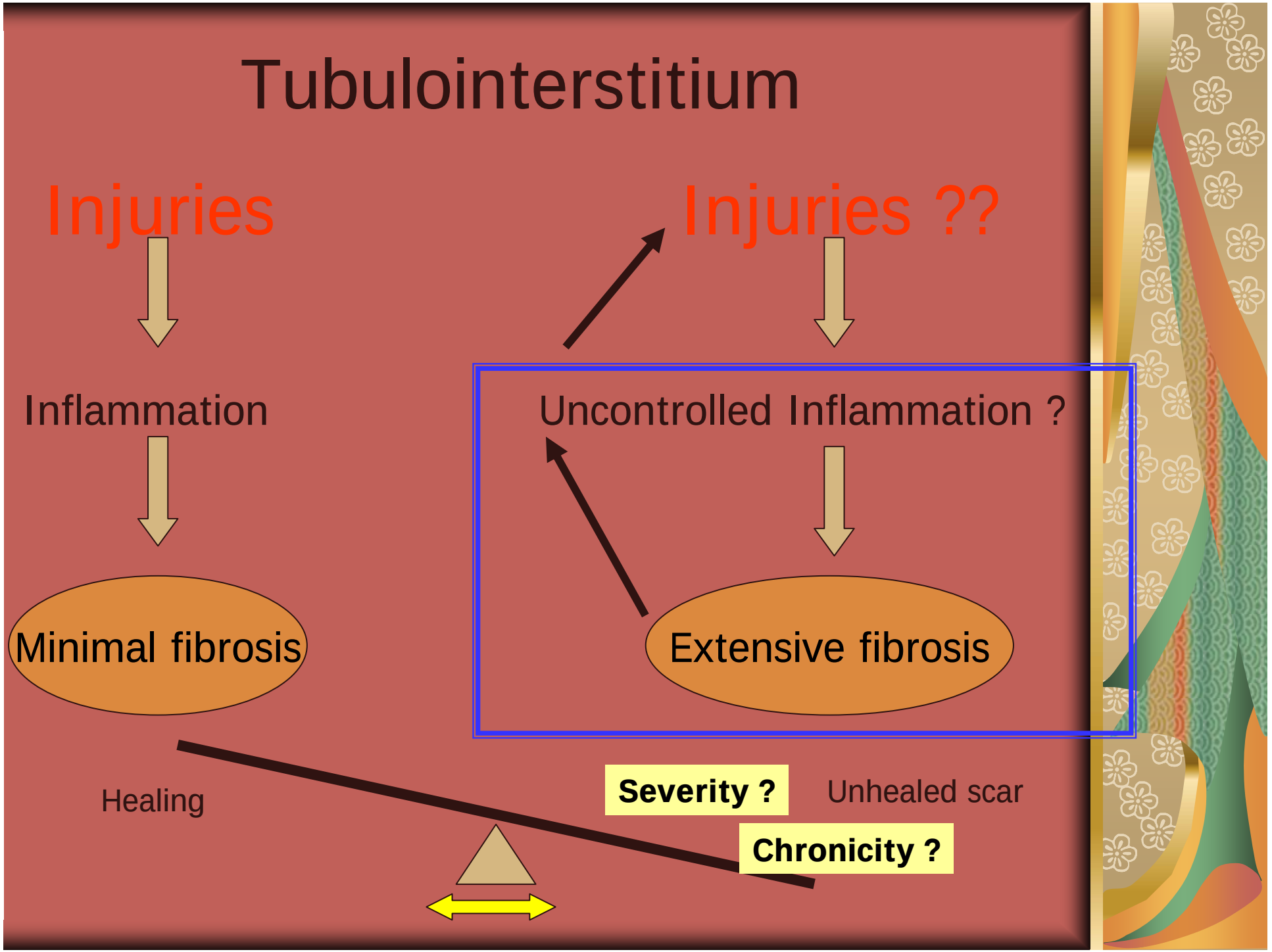


Early 90s many groups

Tubulointerstitium damage
(inflammation, fibrosis)
relate to progression

NOT glomerular damage

Glomerular hyperfiltration damage
tubulointerstitium ?


Tubulointerstitium
Injuries
Injuries ??
Inflammation
Uncontrolled Inflammation ?
Minimal fibrosis
Extensive fibrosis
Healing
Severity ?
Unhealed scar
Chronicity ?

Key insults ?

1. Leakage macromolecule (proteinuria, not albumin)
2. Intrarenal hypoxia (Vascular Derangement)
3. Oxidative damage
4. Atubular Glomeruli

The New England Journal of Medicine

Review Article

Mechanisms of Disease

FRANKLIN H. EPSTEIN, M.D., *Editor*

PATHOPHYSIOLOGY OF PROGRESSIVE NEPHROPATHIES

GIUSEPPE REMUZZI, M.D., AND TULLIO BERTANI, M.D.

IN patients with renal diseases characterized by proteinuria, the initial insult to the kidney is usually followed by a progressive decline in the glomerular filtration rate. This decline has been thought to be due to changes in renal hemodynamics initiated by the loss of nephrons.[1] When renal mass is reduced in rats, the remaining nephrons undergo sudden hypertrophy, with a concomitant lowering of arteriolar resistance and an increase in glomerular plasma flow.[2,3] Afferent arteriolar tone decreases more than efferent arteriolar tone, and therefore, the hydraulic pressure in glomerular capillaries rises[4] and the amount of filtrate formed by each nephron increases. These changes increase the filtration capacity of the remaining nephrons, thus minimizing the functional consequences of nephron loss, but they are ultimately detrimental.[5] Therapies that attenuate these adaptive changes limit the decline in the glomerular filtration rate and minimize structural damage. For example, angiotensin-converting–enzyme (ACE) inhibitors, which reduce intraglomerular capillary pressure more effectively than other antihypertensive drugs, consistently protected rats with reduced renal mass[6,7] or diabetes mellitus[8,9] from progressive renal injury.

Why should hemodynamic changes — specifically, glomerular hypertension — lead to progressive renal injury? One possible explanation is that the high glomerular capillary pressure enlarges the radius of the pores in the glomerular membrane by a mechanism that is mediated at least in part by angiotensin

1998 Remuzzi G

Glomerular hyperfiltration

↓

Proteinuria

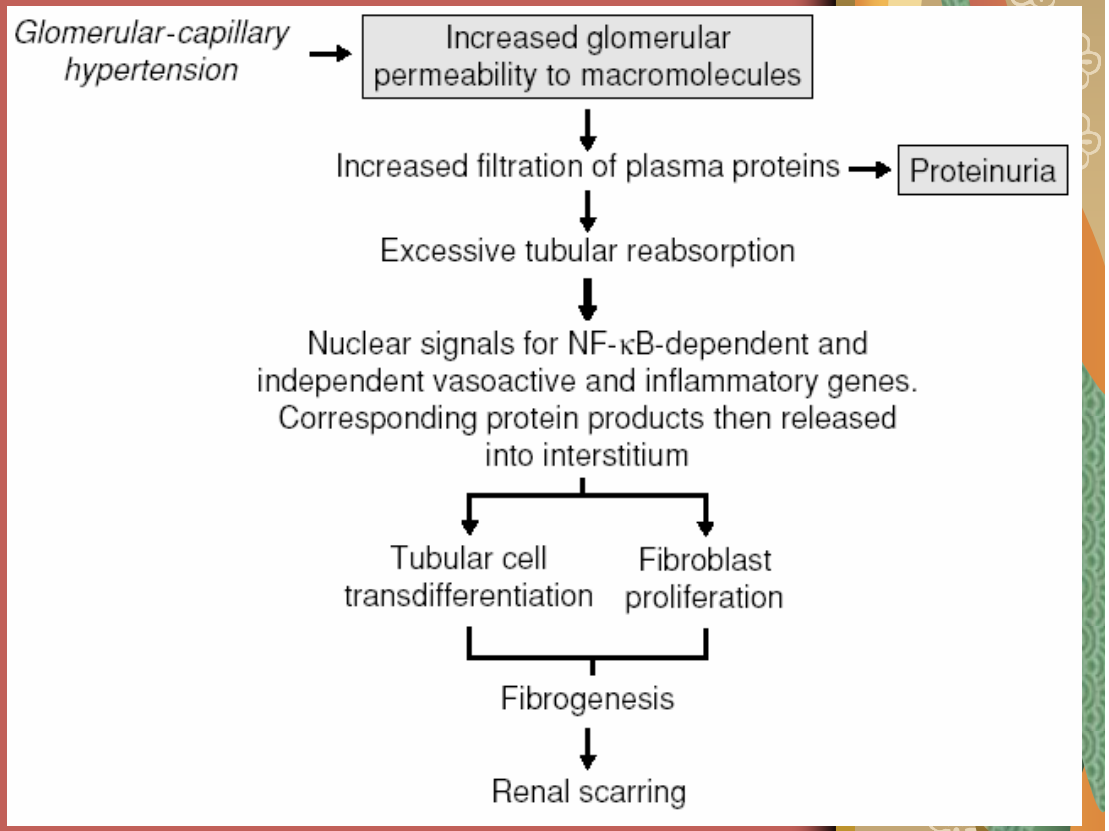
↓

Interstitial damage

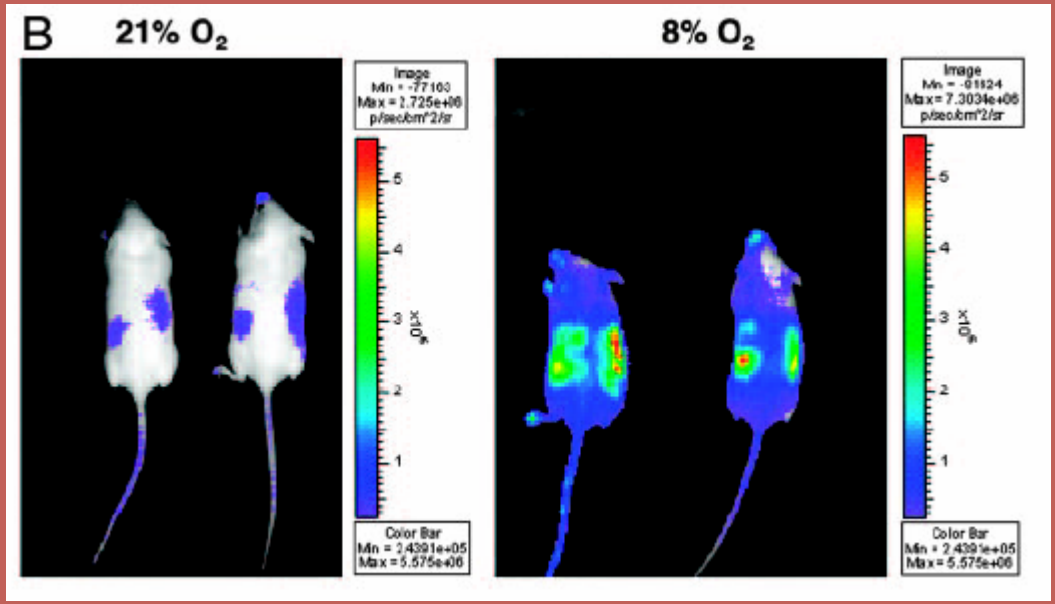
Why should hemodynamic changes — specifically, glomerular hypertension — lead to progressive renal injury? One possible explanation is that the high glomerular capillary pressure enlarges the radius of the pores in the glomerular membrane by a mechanism that is mediated at least in part by angiotensin II.[10,11] This enlargement impairs the size-selective function of the membrane so that the protein content of the glomerular filtrate increases, which in

Toxicity of Leakage Macromolecules

- Filtration barrier < 16,000 KD
- Many endocytosis machineries at tubular cell
- Proteinuria, albuminuria, transferin, Fatty acid bounded albumin.



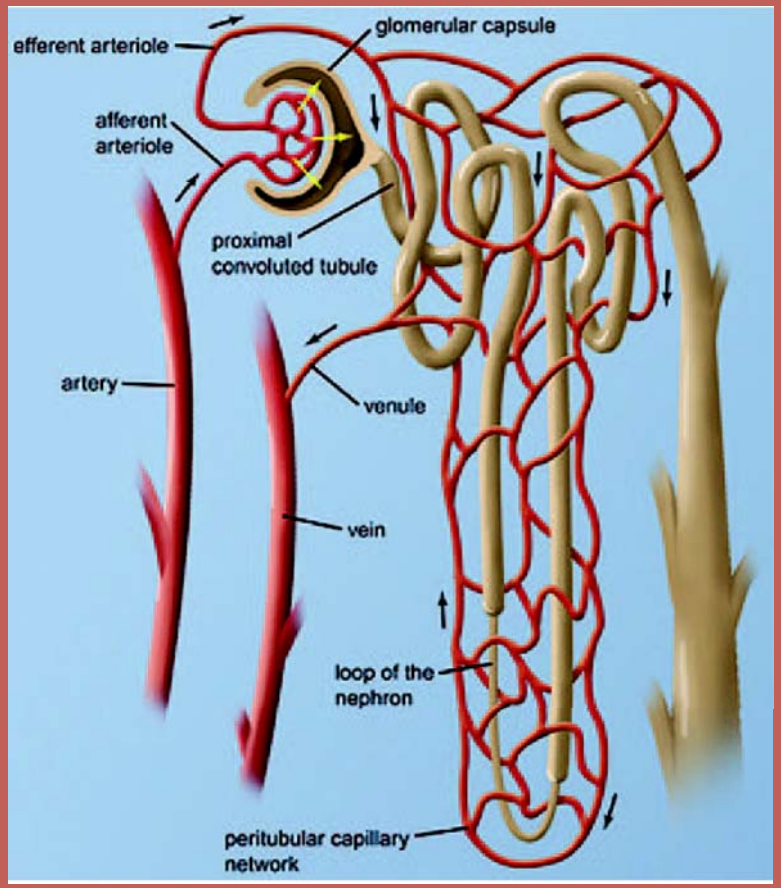
Dana-Faber hypoxia reporting mice



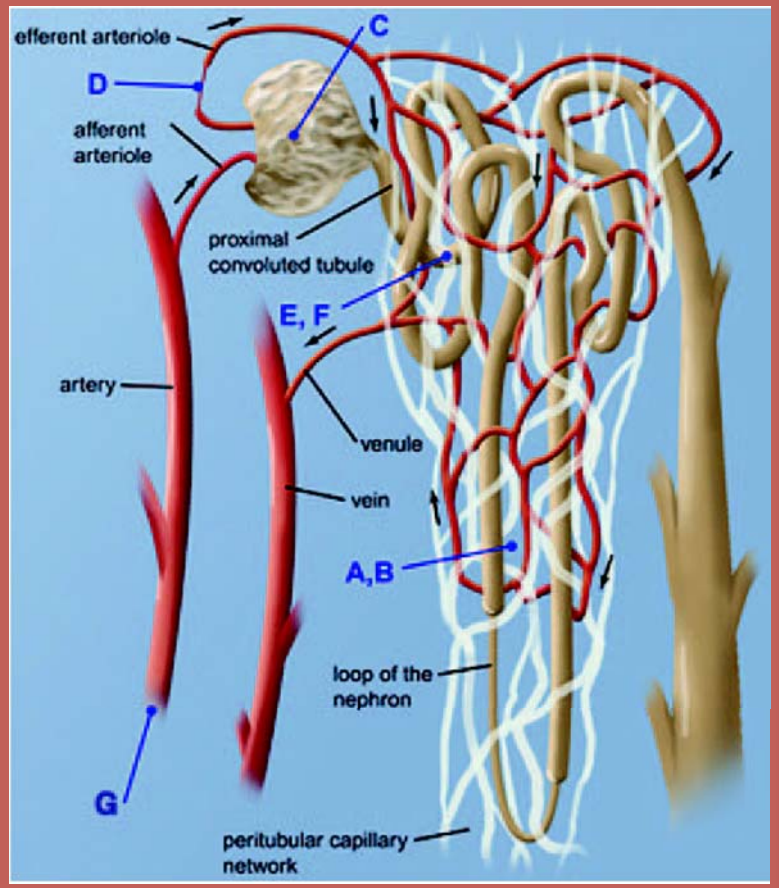
Safran M, PNAS 103, Jan 2006

Peritubular Capillary derangement

Normal

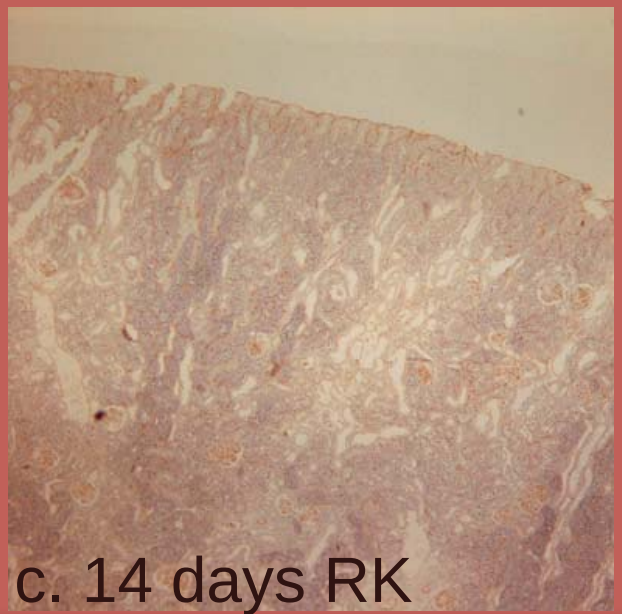


Chronic renal failure

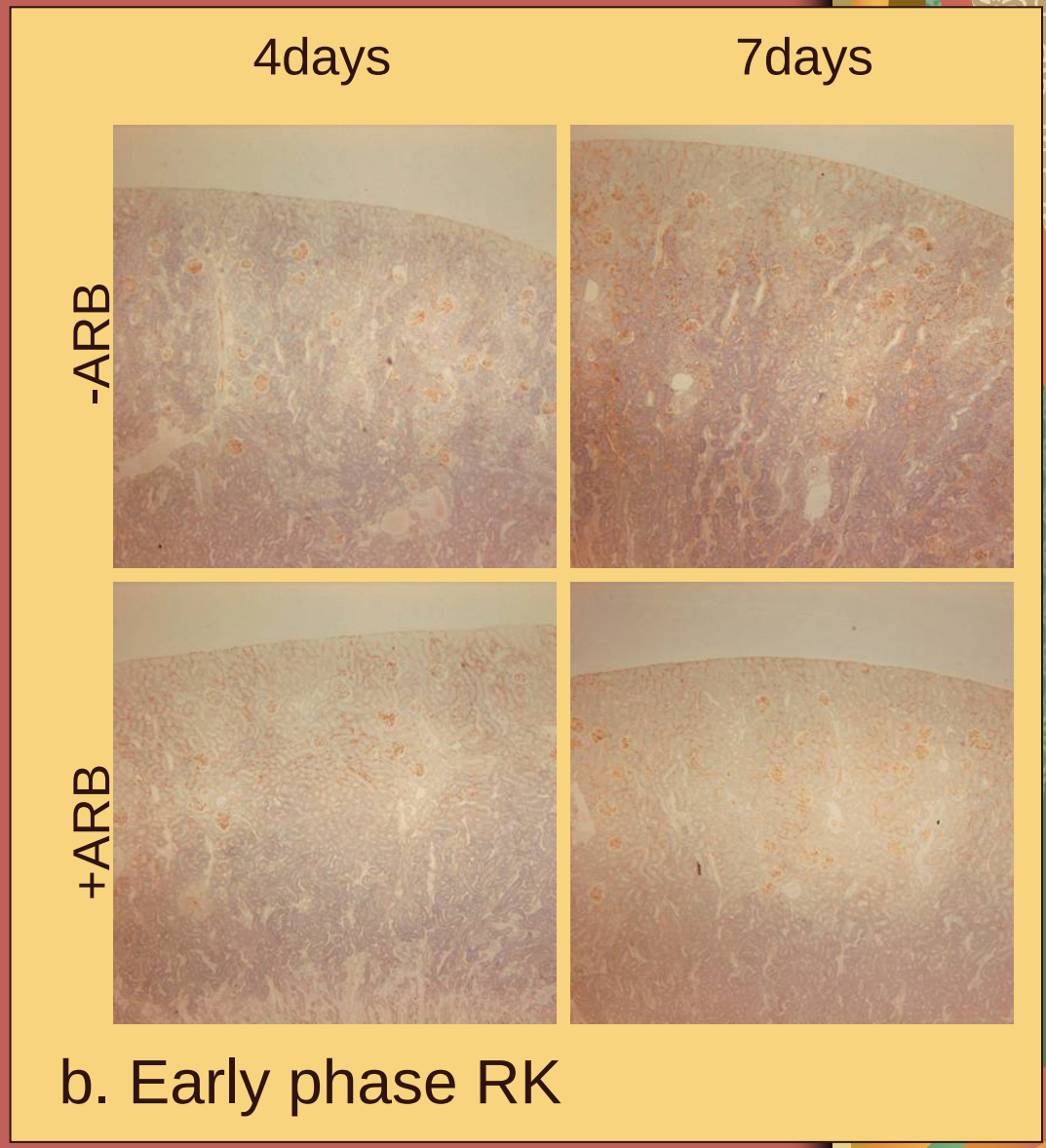


Tubulointerstitial hypoxia occurred at the early onset

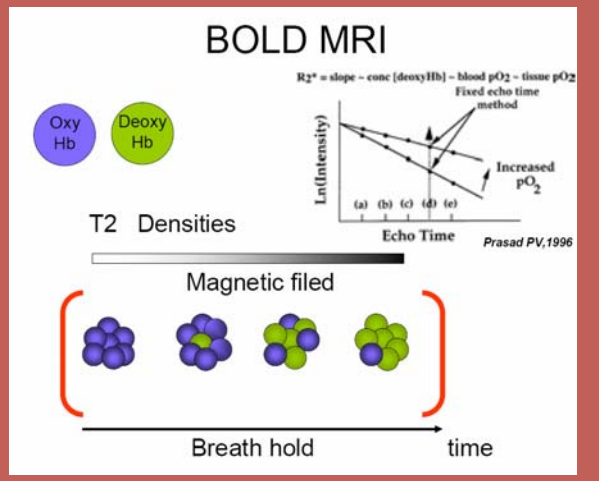
a.Sham

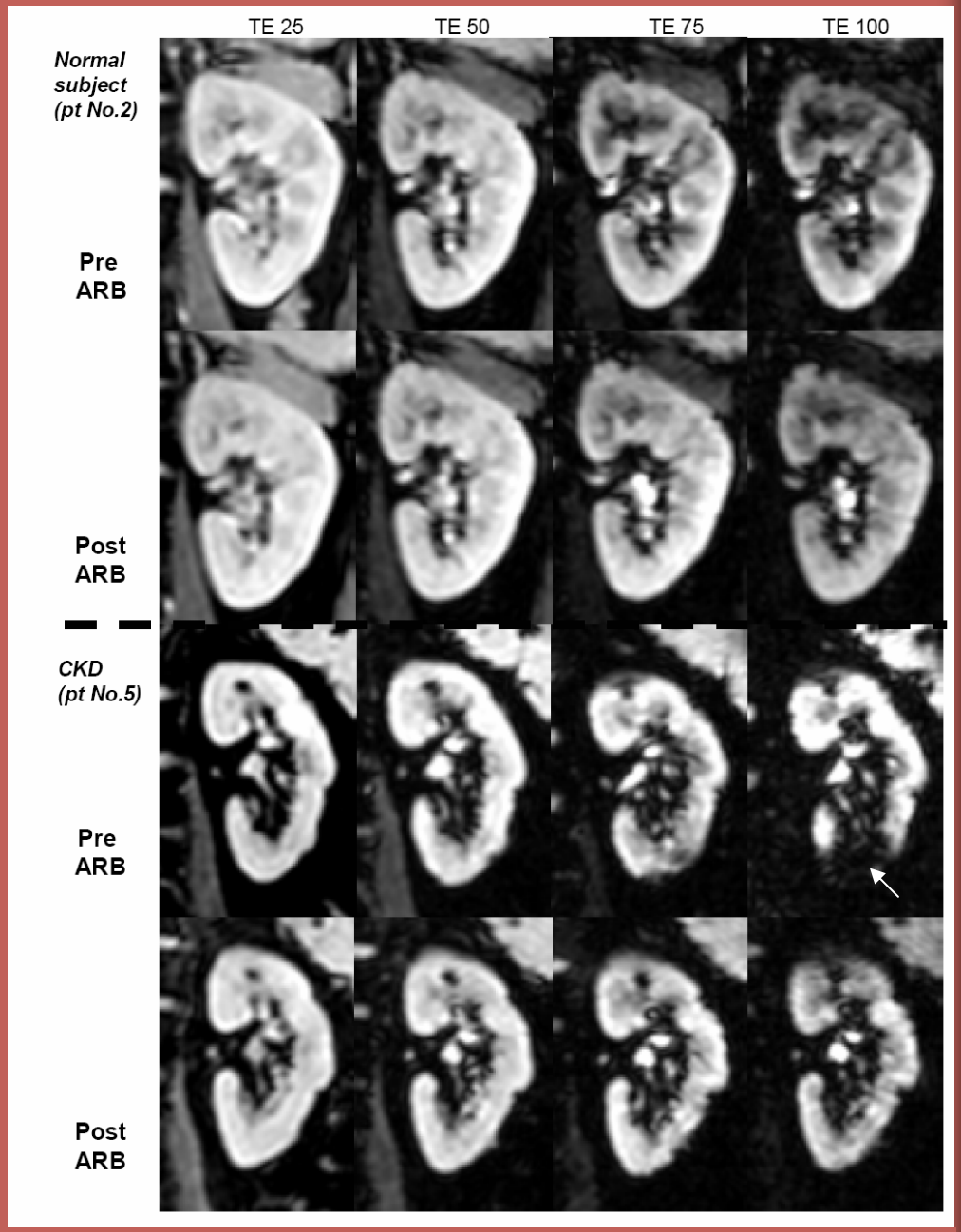


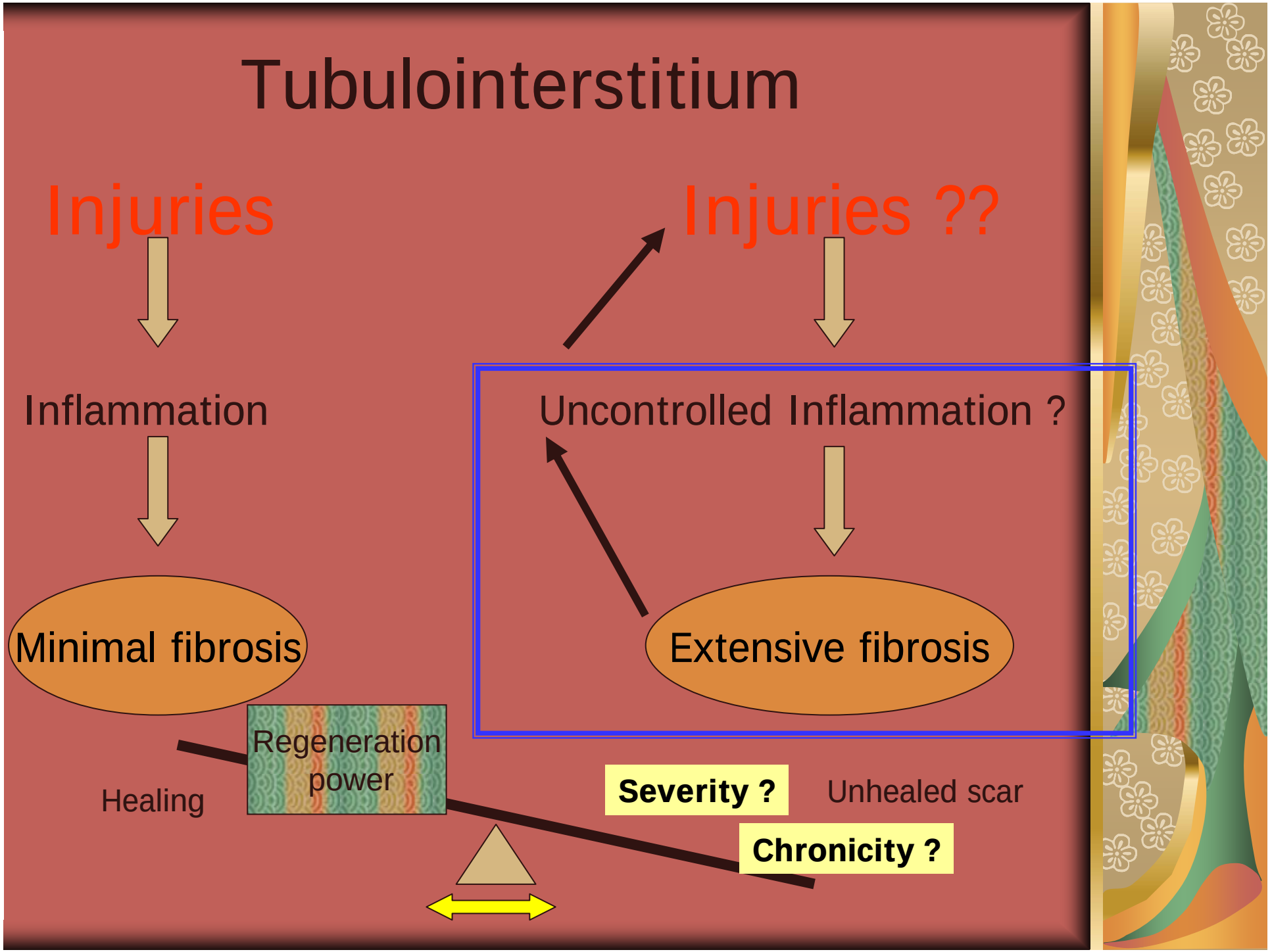
c. 14 days RK



b. Early phase RK


BOLD MRI
Oxy Hb
Deoxy Hb
T2 Densities
Magnetic filed
Breath hold
time
Fixed echo time method
Increased pO2
Ln(Intensity)
Echo Time
Prasad PV,1996


TE 25
TE 50
TE 75
TE 100
Normal subject (pt No.2)
Pre ARB
Post ARB
CKD (pt No.5)
Pre ARB
Post ARB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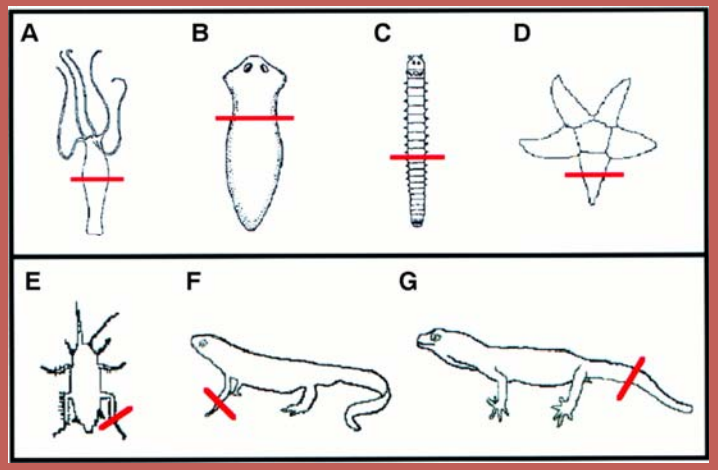
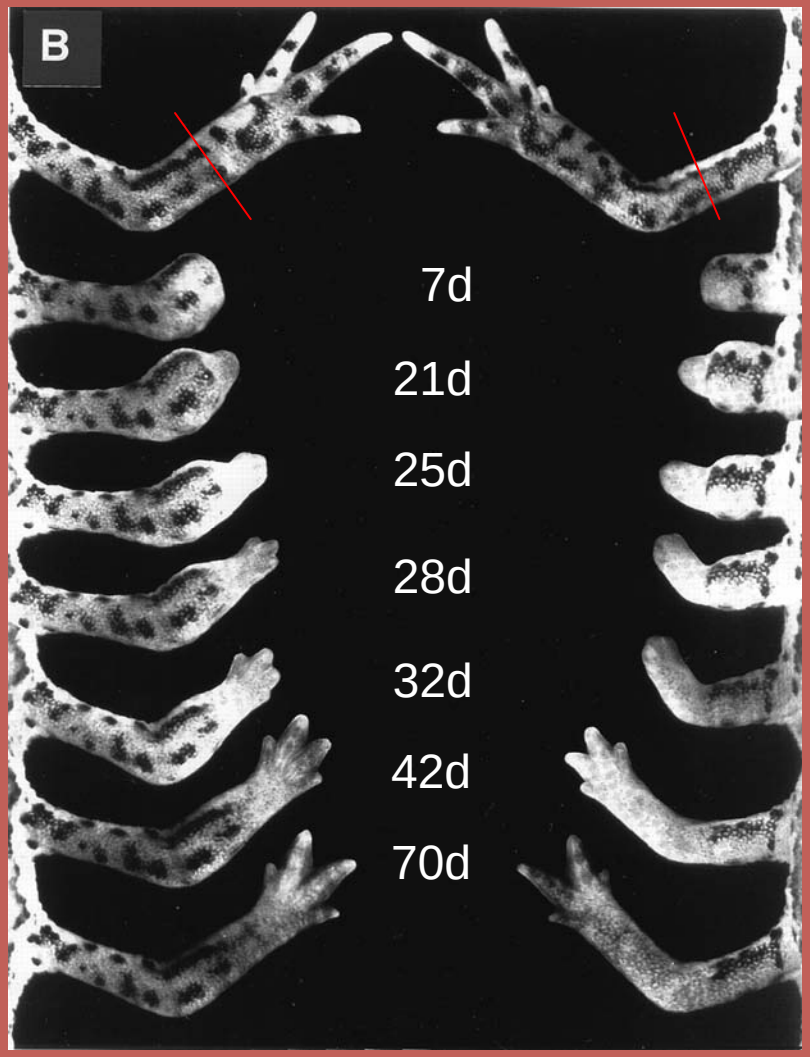
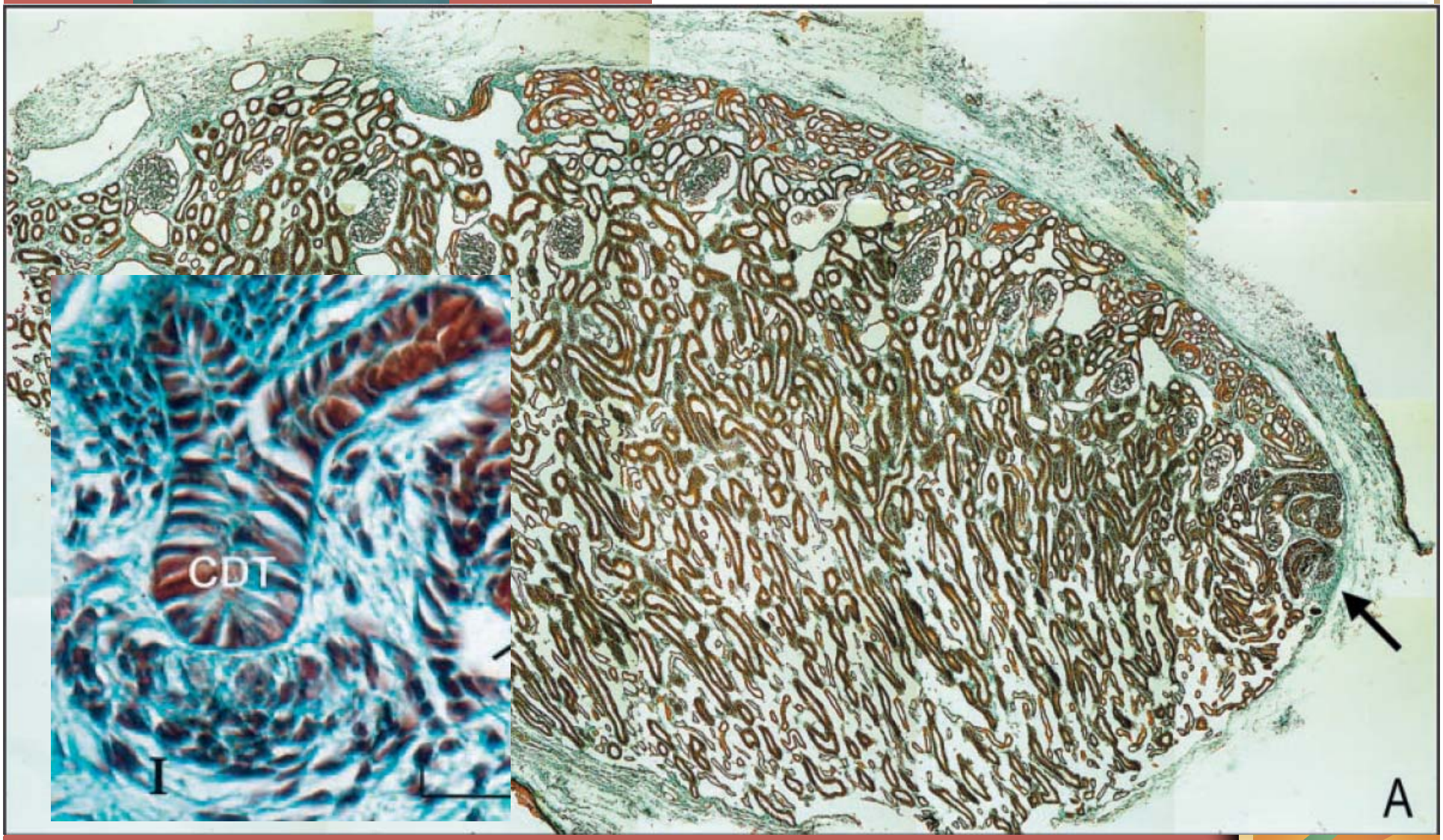
Minimal fibrosis
Extensive fibrosis
Regeneration power
Healing
Severity ?
Unhealed scar
Chronicity ?

Superpower of Healing

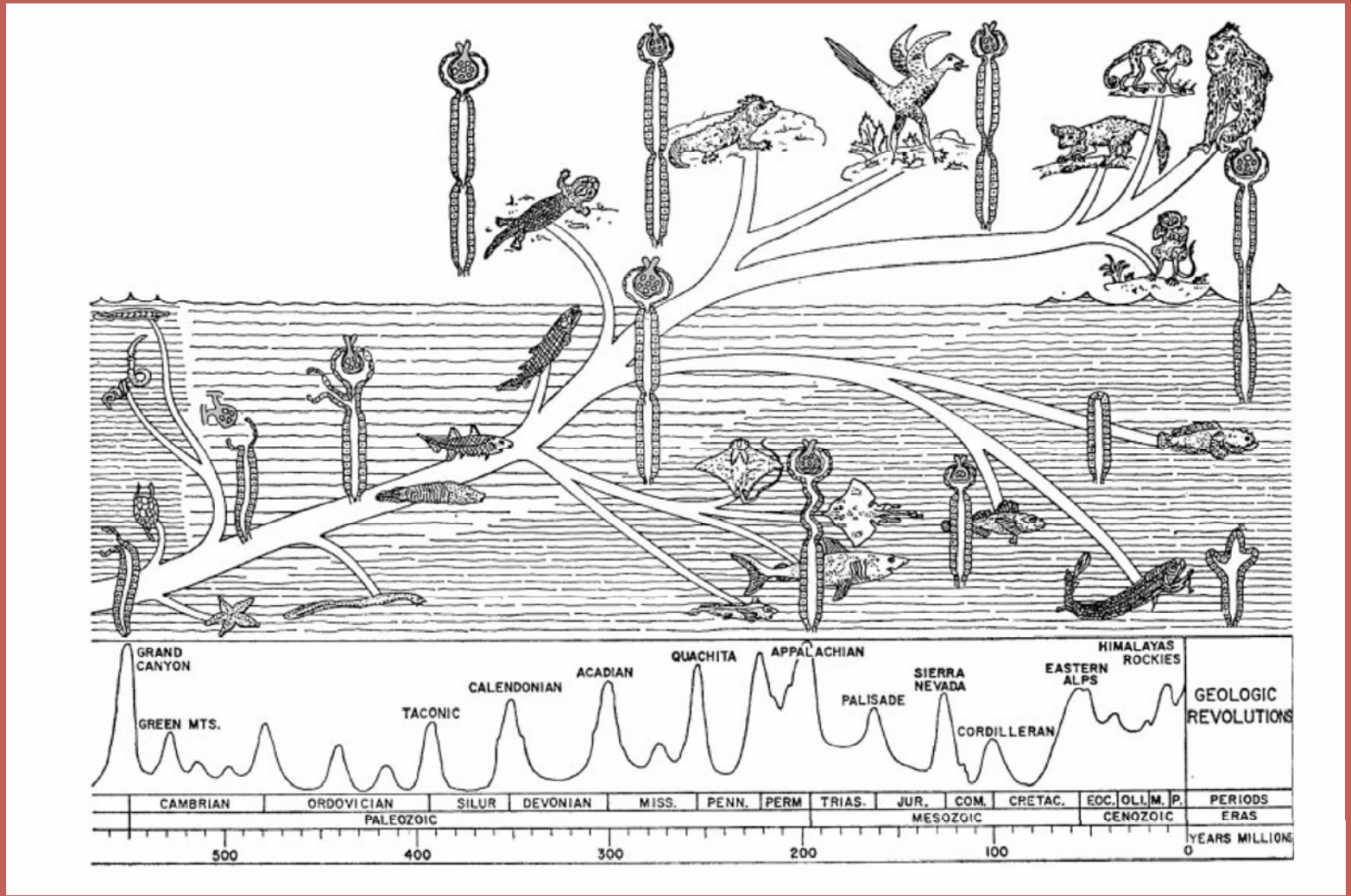




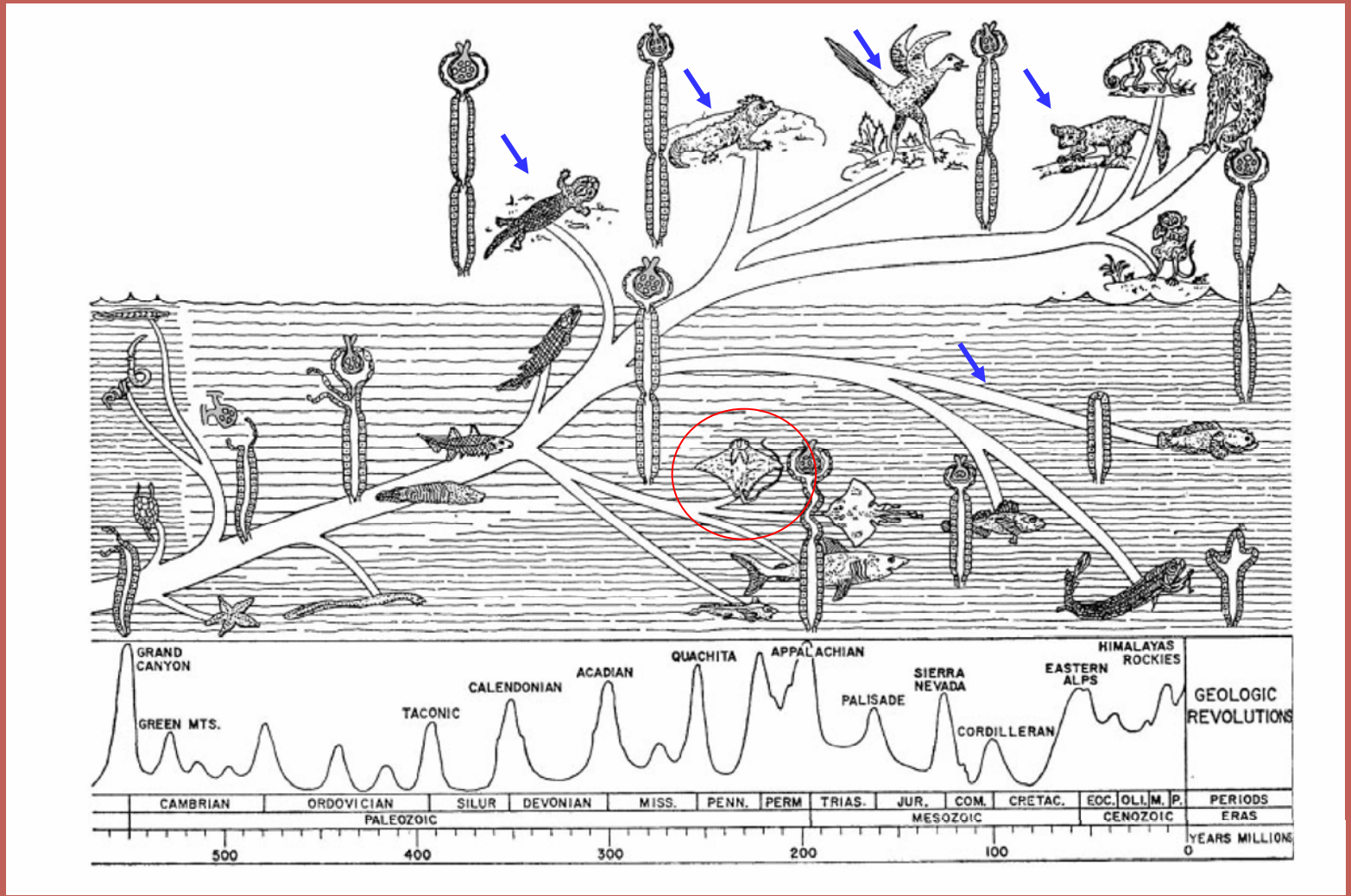
Skate fish

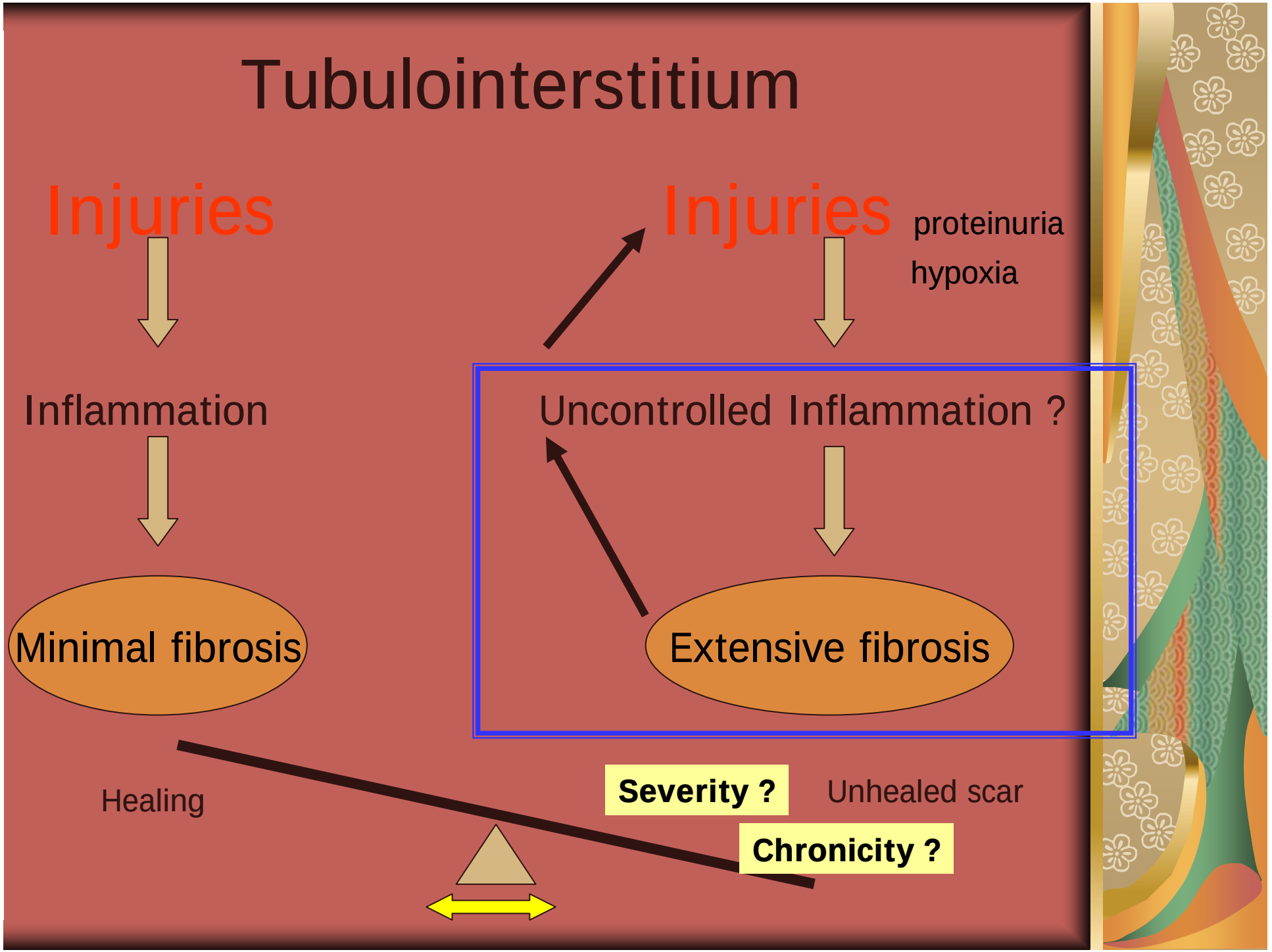


The Evolution of Kidney



The Evolution of Kidney

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Injuries
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The Evolution of Kidney