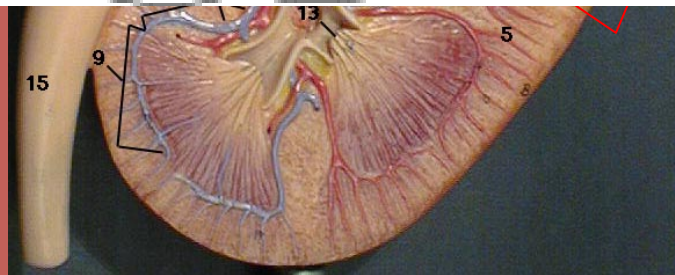
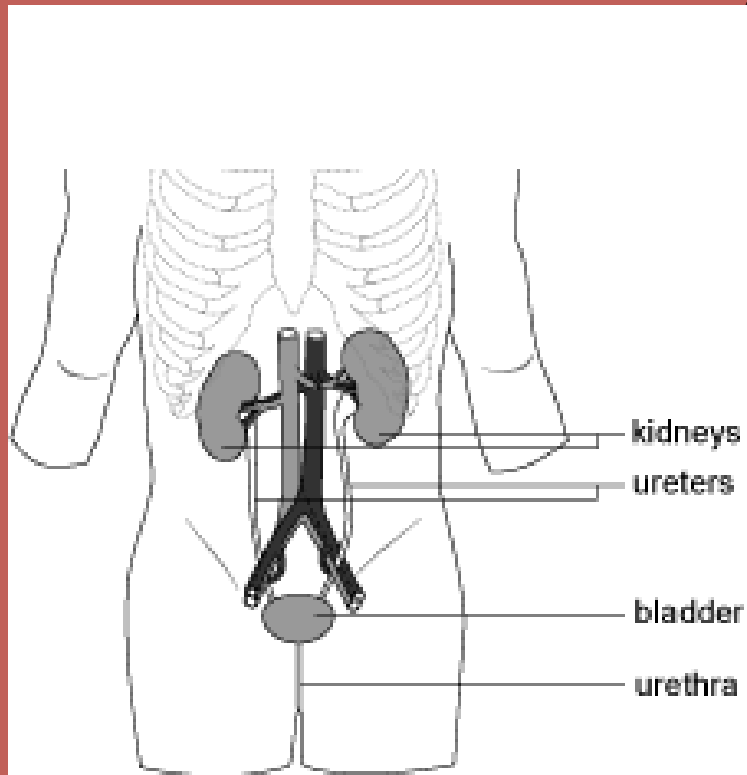


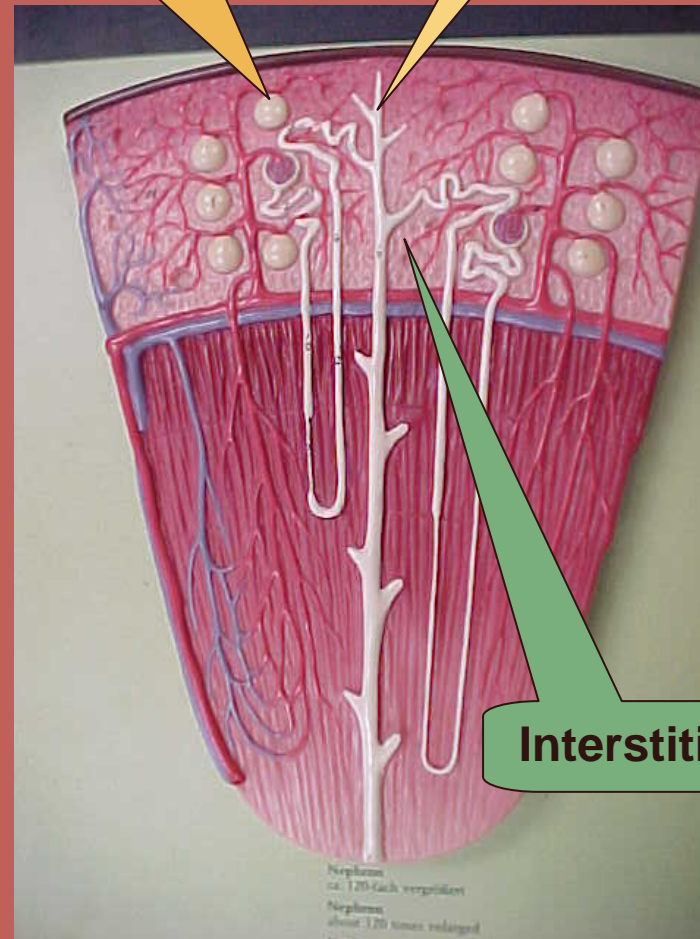
# How kidney is vulnerable to injury





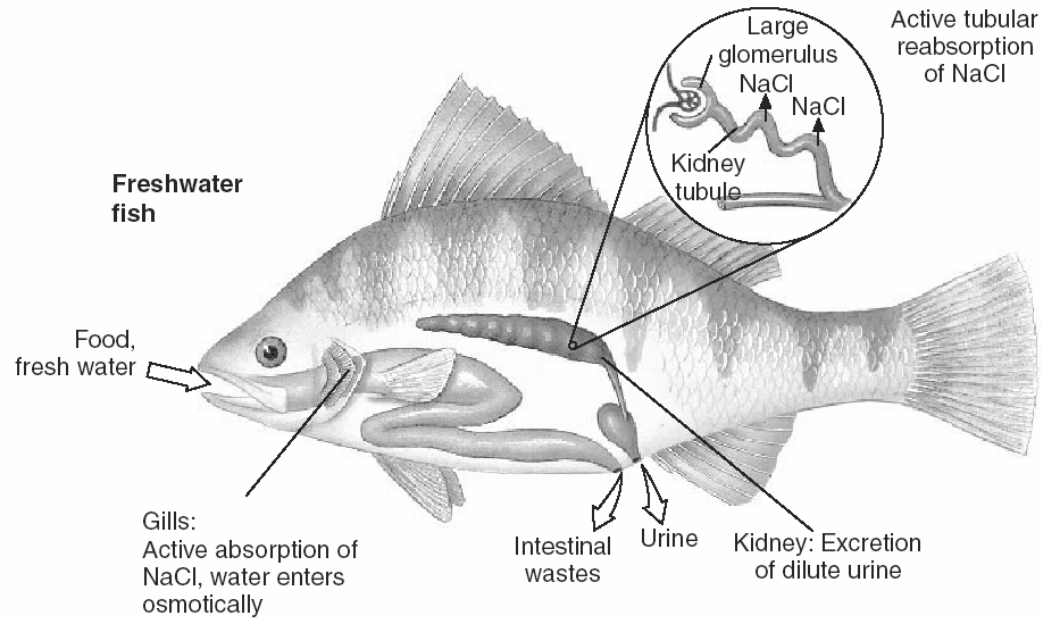
Glomerulus

Tubule

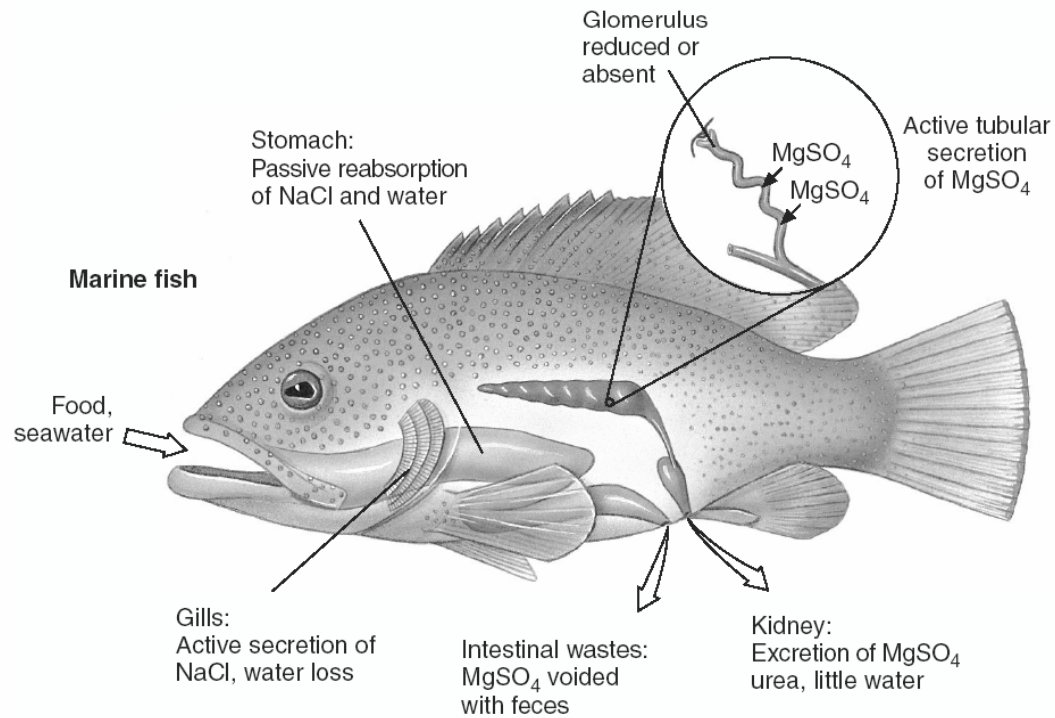


**Tubule+Interstitium = Tubulointerstitium**

Circulatory system



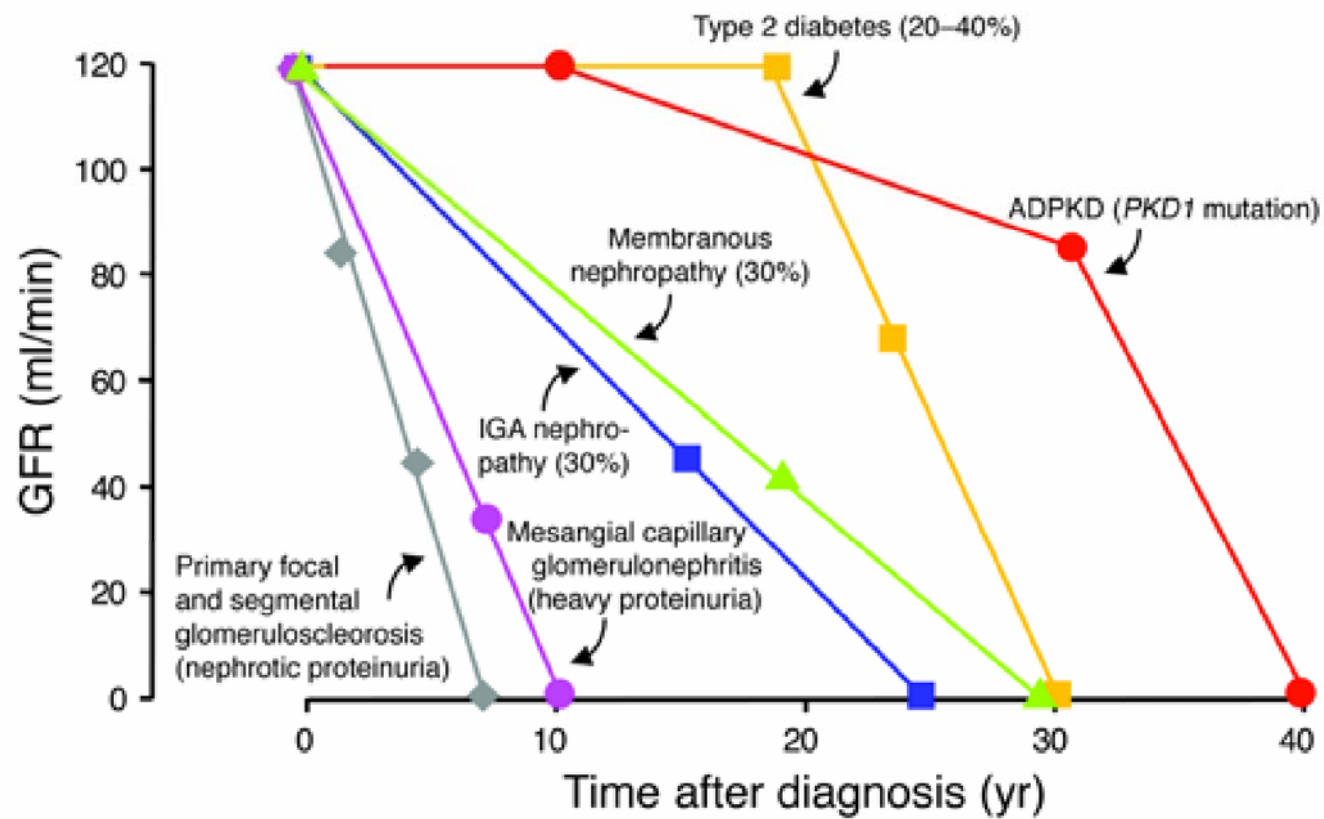
Ancient excretory system

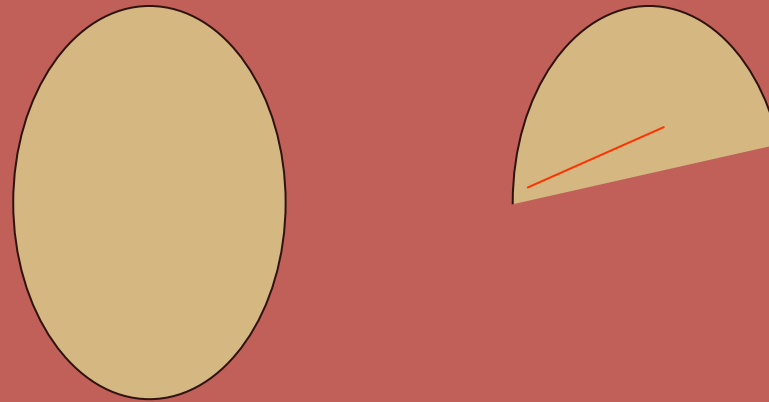
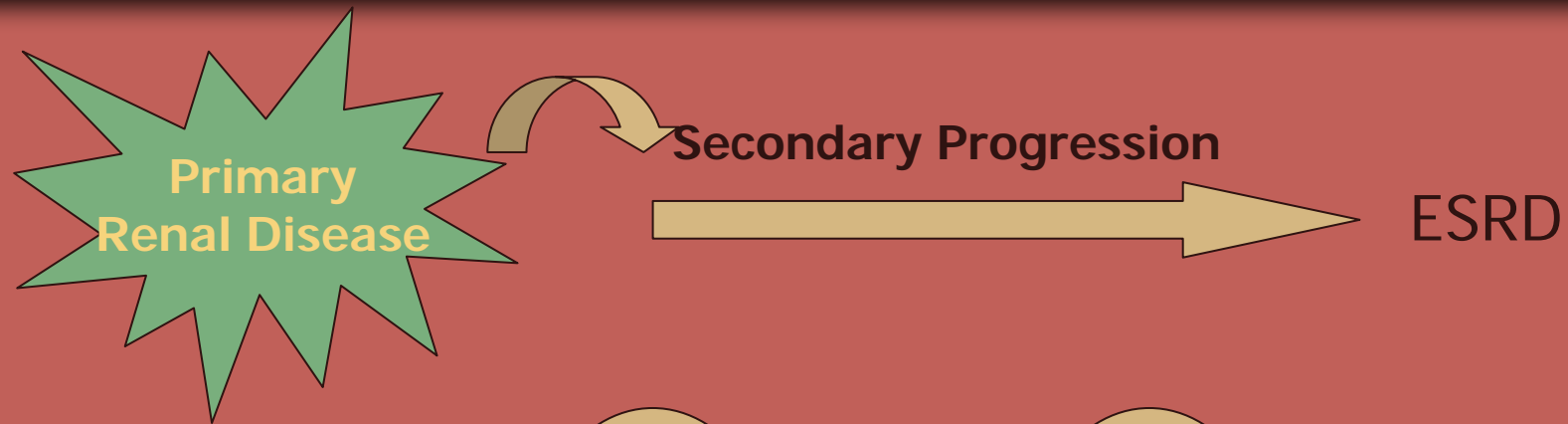


**Primary  
Renal Disease**

**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)

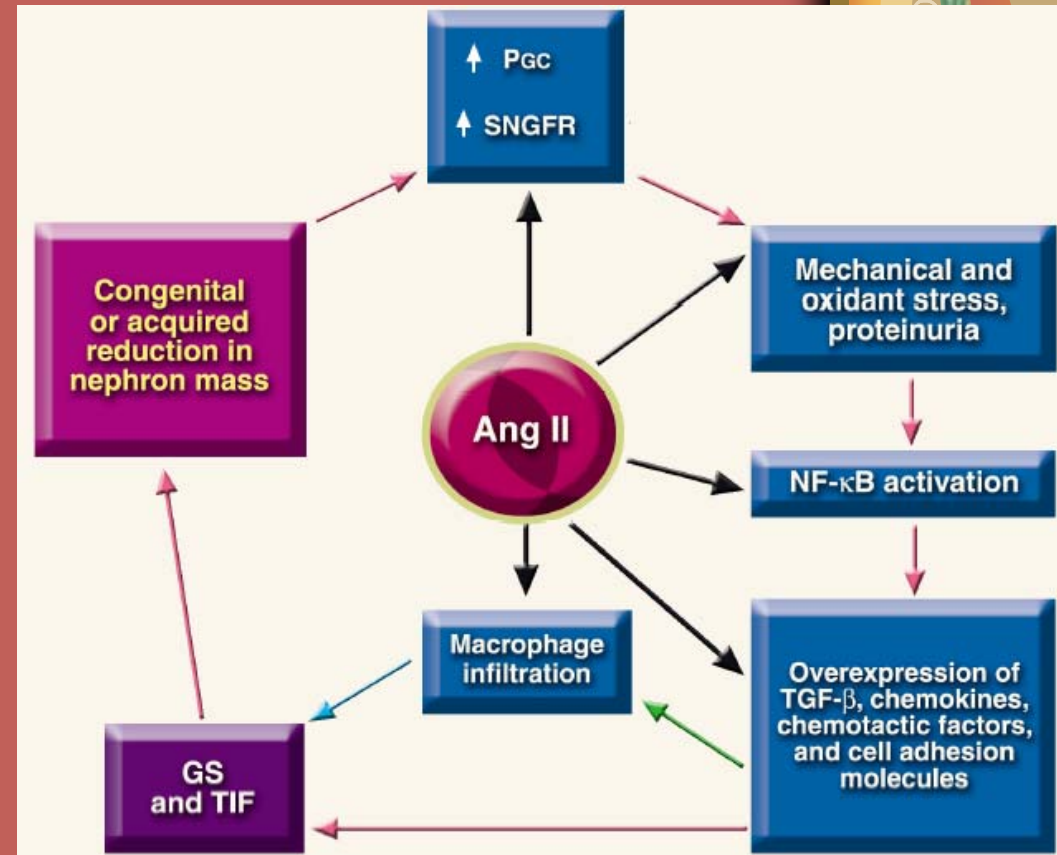
All textbooks

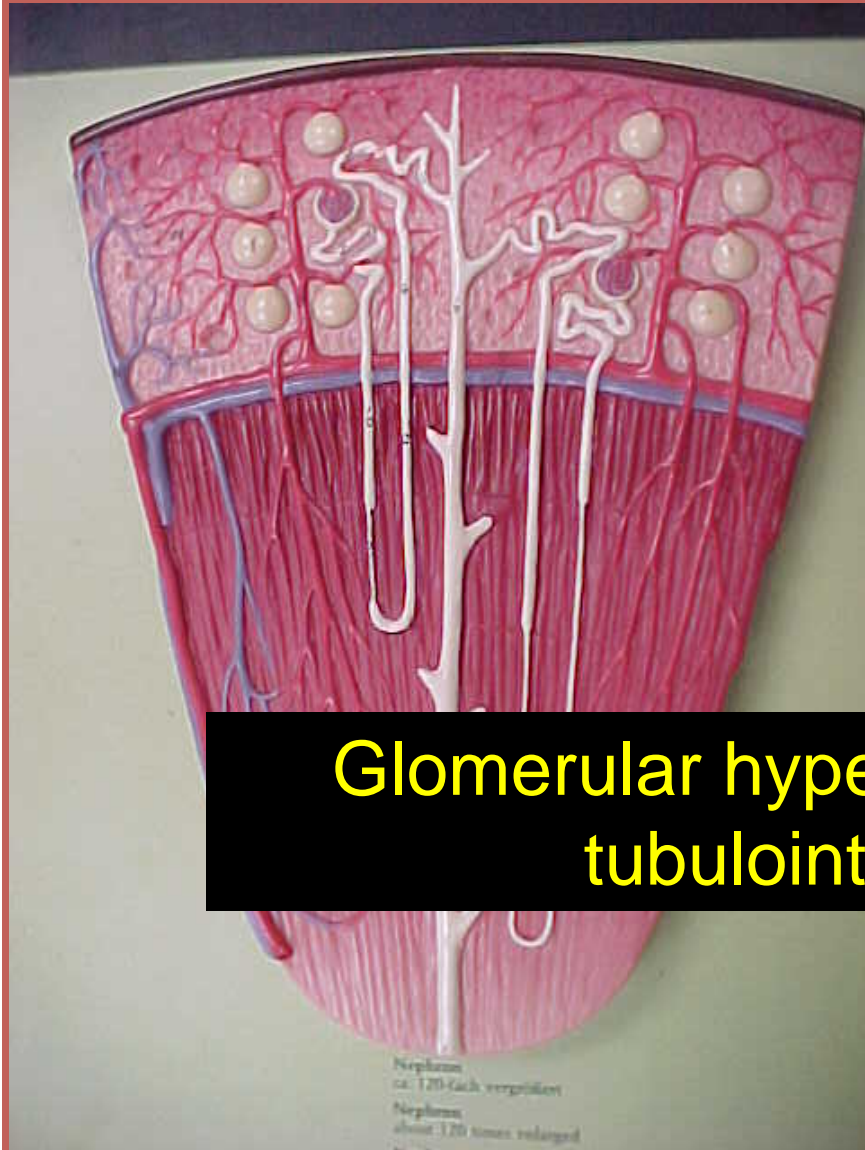


# Glomerular hyperfiltration +hypertension

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

RAS plays Central Role



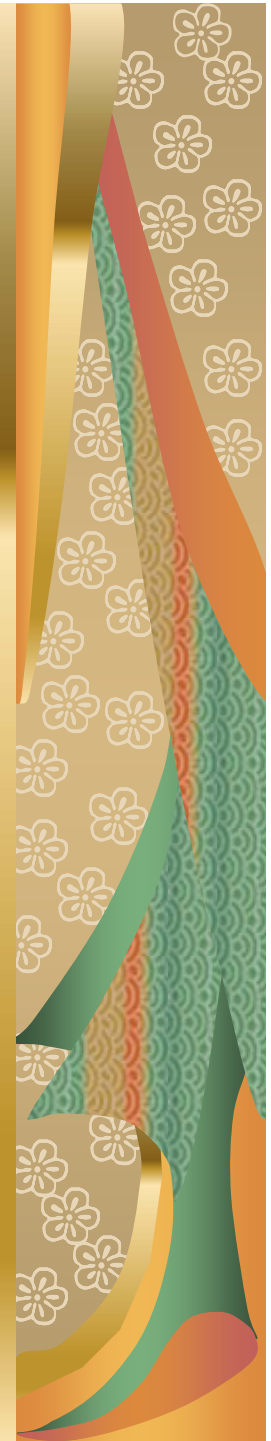


Early 90s many groups

Tubulointerstitium damage  
(inflammation, fibrosis)  
relate to progression

NOT glomerular damage

Glomerular hyperfiltration damage  
tubulointerstitium ?





# Tubulointerstitium

Injuries



Inflammation



Minimal fibrosis

Injuries ??



Uncontrolled Inflammation ?



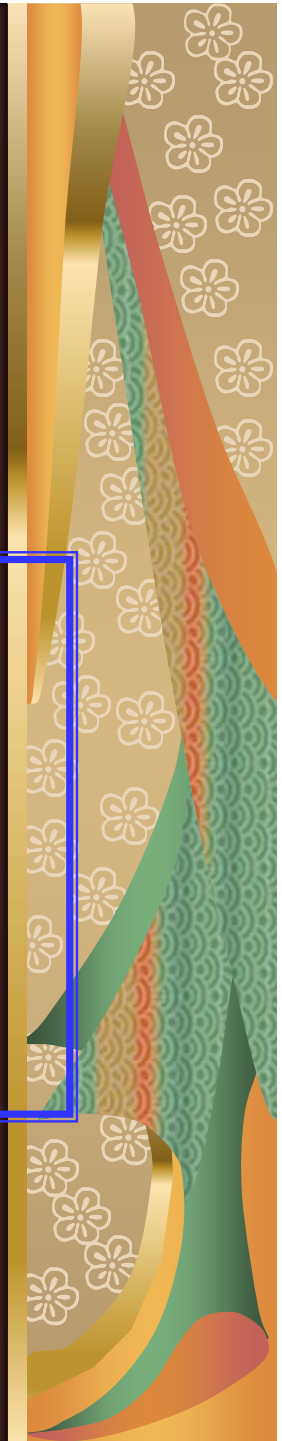
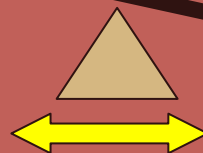
Extensive fibrosis

Healing

Severity ?

Unhealed scar

Chronicity ?



# Key insults ?

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



Review Article

*Mechanisms of Disease*

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

**PATHOPHYSIOLOGY OF PROGRESSIVE NEPHROPATHIES**

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

**I**N 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.<sup>1</sup> 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.<sup>2,3</sup> Afferent arteriolar tone decreases more than efferent arteriolar tone, and therefore, the hydraulic pressure in glomerular capillaries rises<sup>4</sup> 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.<sup>5</sup> 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<sup>6,7</sup> or diabetes mellitus<sup>8,9</sup> 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

epithelial cells, ultimately resulting in a nephritogenic effect.<sup>12</sup> A vicious cycle of changes in renal hemodynamics and loss of nephrons lead first to hyperfiltration and then to the loss of more nephrons.

We will review recent data on the pathophysiology of glomerular hyperfiltration, its role in the progression of chronic renal disease, and the mechanisms by which it leads to interstitial damage. We will also review experimental data linking the renoprotective effects of ACE inhibitors to their ability to reduce glomerular hyperfiltration, and the degree of proteinuria as a marker of the progression of chronic renal disease by abnormal loss of protein in the urine of proteinuric nephropathy.

**ACTIVATION OF THE RENIN-ANGIOTENSIN SYSTEM AND INFLAMMATION BY FILTRATE**

**Evidence from Animal Models**

That increased glomerular filtration of protein accelerates the natural slow, progressive loss of nephrons that occurs in all chronic renal diseases was initially suggested by studies in animals. In a series of experiments, biopsy specimens from rats with nephrosis<sup>13</sup> or age-related proteinuria<sup>14</sup> showed accumulation of filtered protein in the interstitium, causing injury to proximal tubular cells, causing tubular atrophy and interstitial fibrosis, followed by glomerular sclerosis. In subsequent studies, in rats with glomerular proteinuria, intravenous injections of albumin, glomerular proteinuria was consistently followed by interstitial lesions and scarring events and nature of the renal injury were identical to those in rats with proteinuric nephropathy, suggesting that the way of injury.

Filtered proteins are reabsorbed by proximal tubular cells, leading to

1998 Remuzzi G

Glomerular hyperfiltration

Proteinuria

Interstitial damage

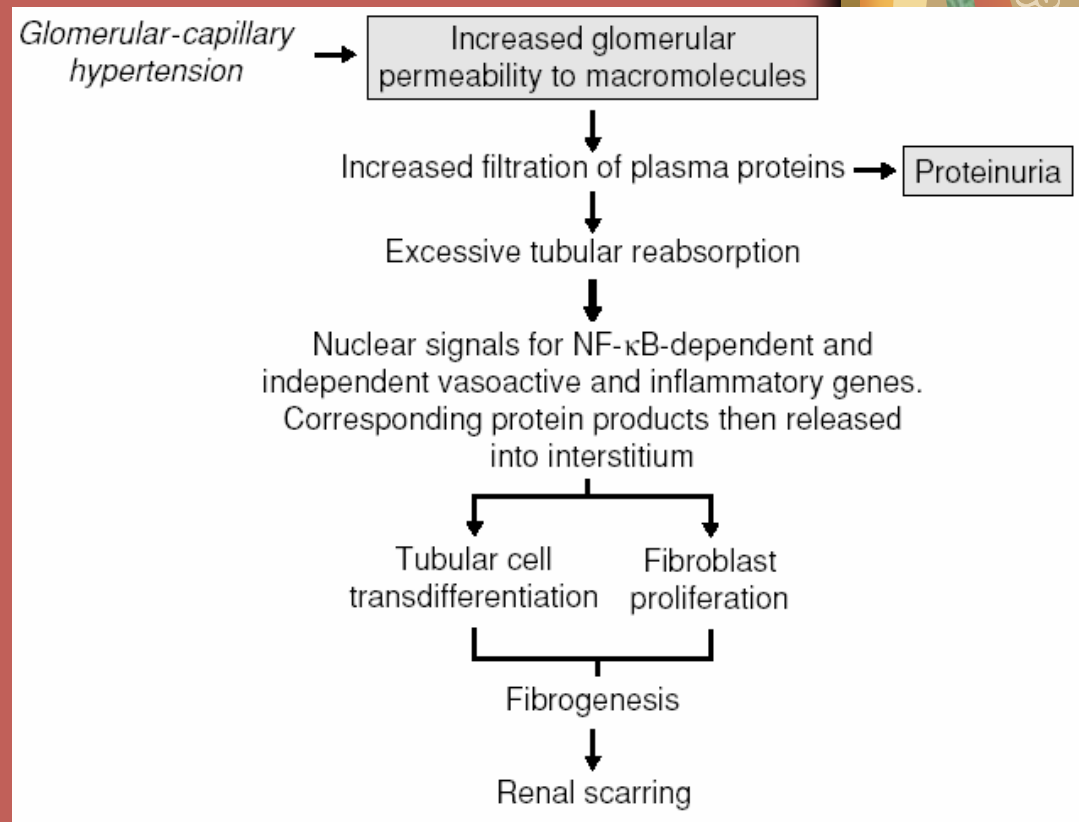
Why should hemodynamic changes — specifically, glomerular hypertension — lead to progressive renal injury? One possible explanation is that the high glomerular capillary pressure enlarges the radius of the pores in the glomerular membrane by a mechanism that is mediated at least in part by angiotensin II.<sup>10,11</sup> 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

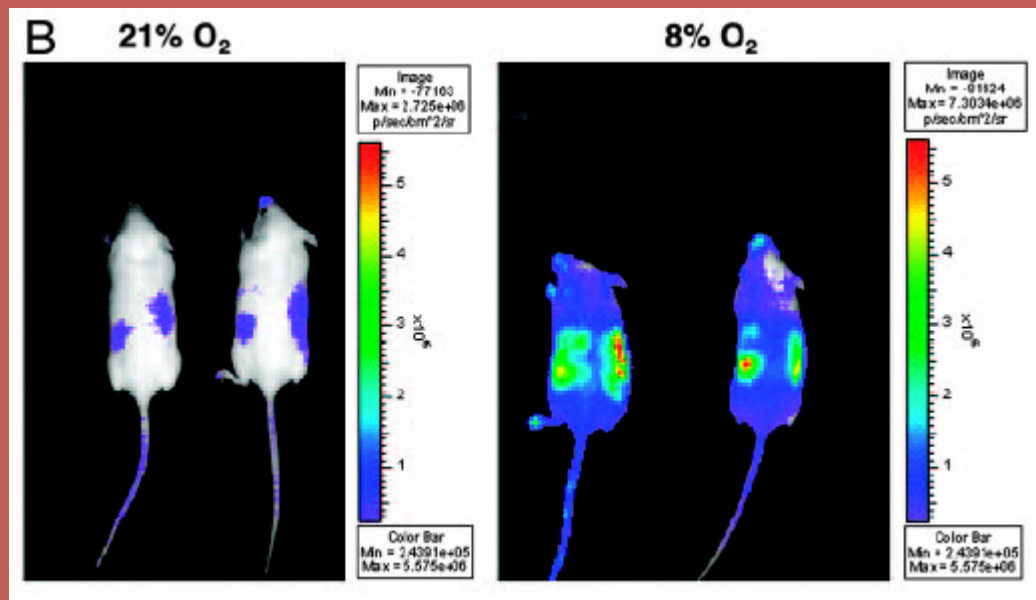
■ Many endocytosis machineries at tubular cell

■ Proteinuria, albuminuria, transferin, Fatty acid bounded albumin.





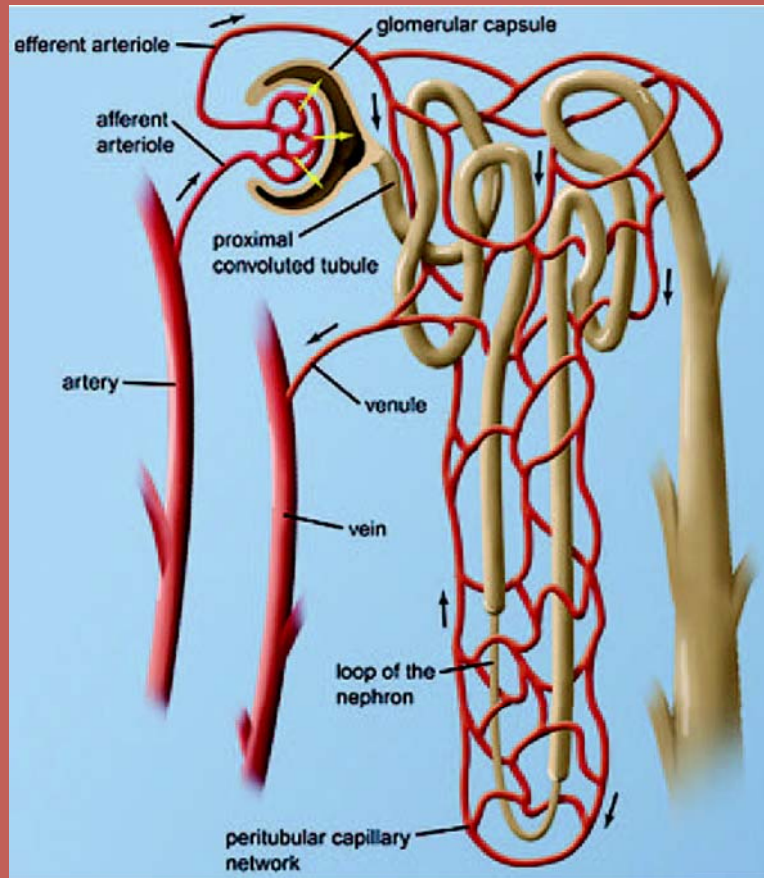
# Dana-Faber hypoxia reporting mice



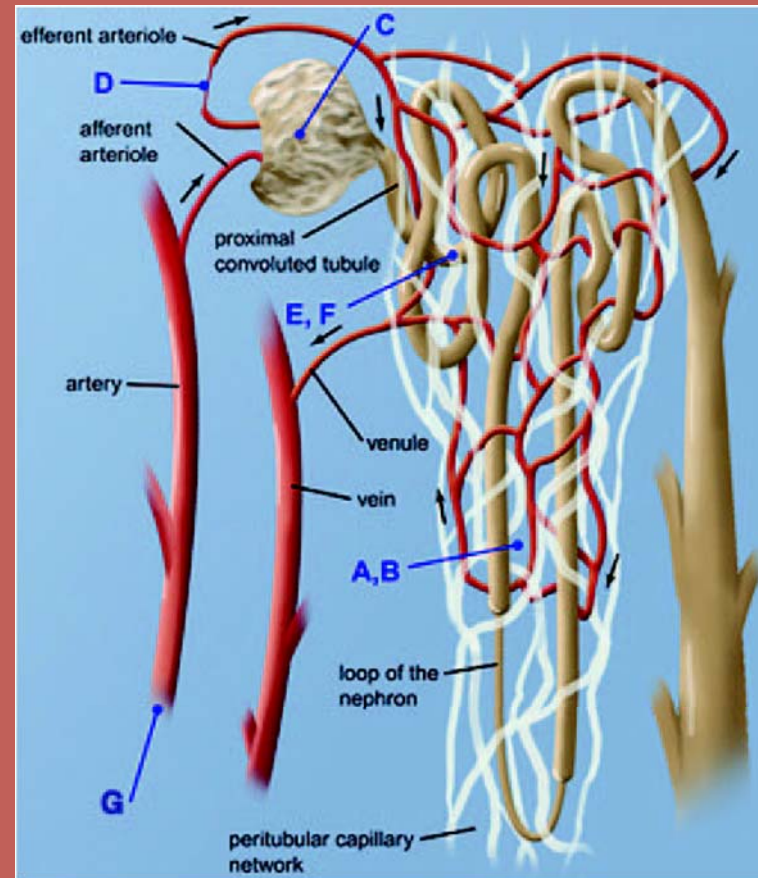
Safran M, PNAS 103, Jan 2006

# Peritubular Capillary derangement

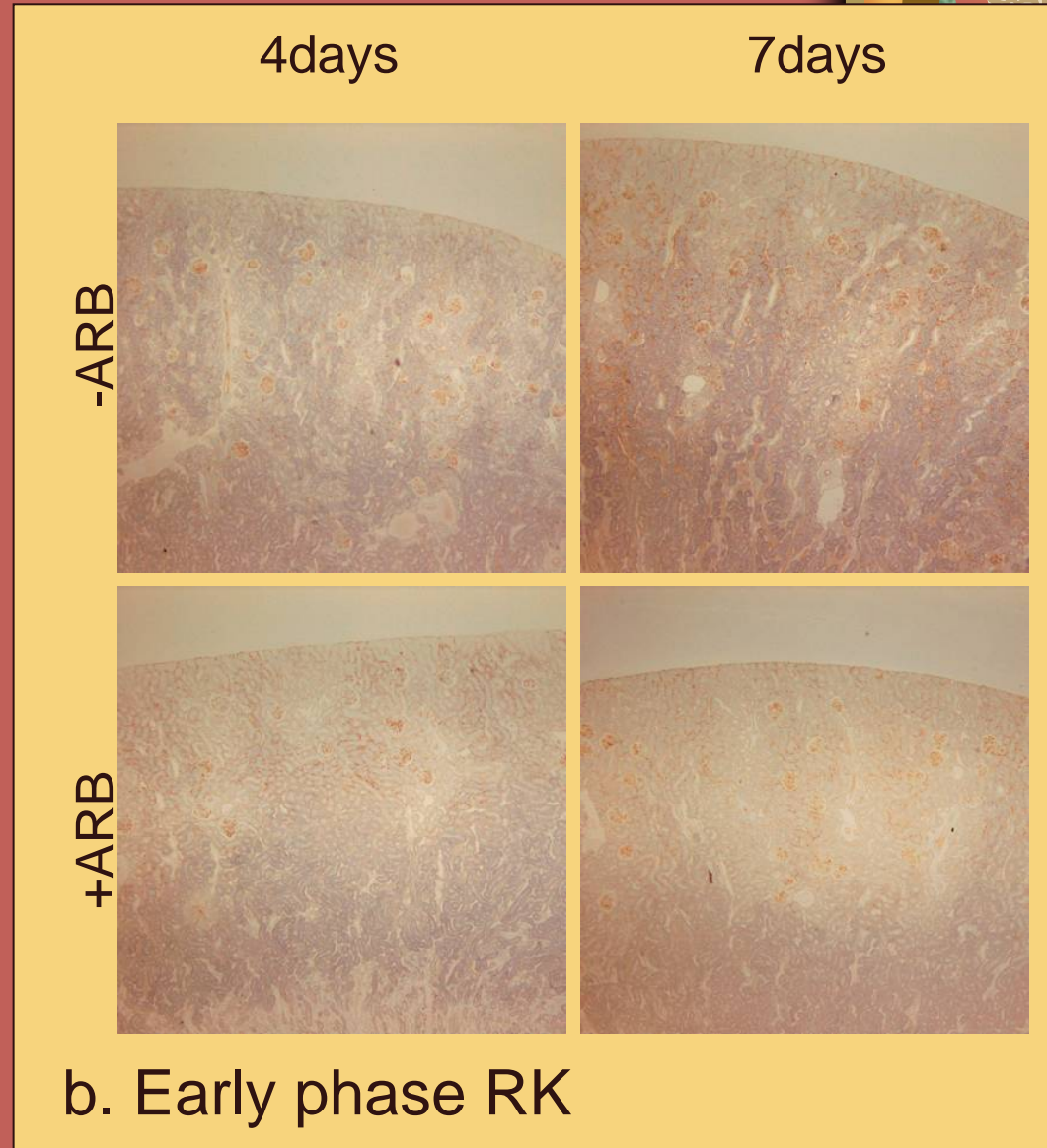
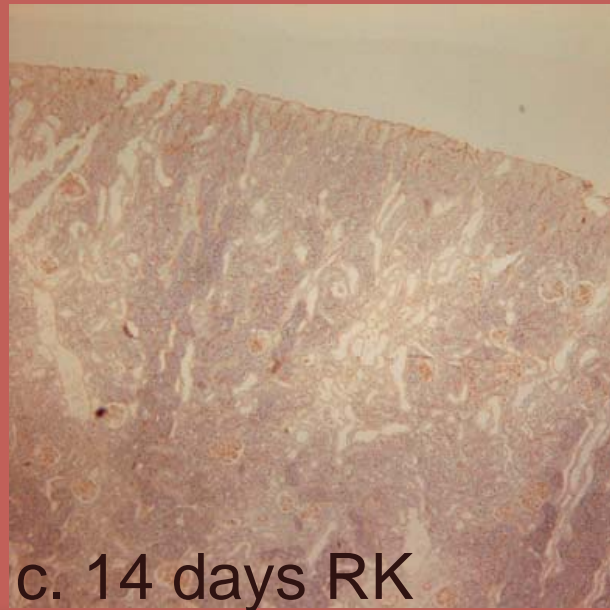
Normal



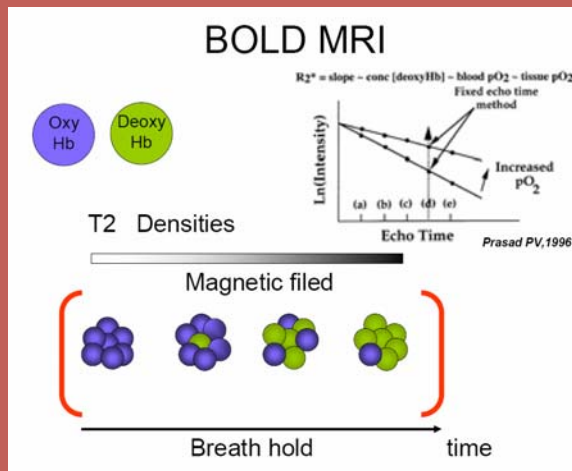
Chronic renal failure



## Tubulointerstitial hypoxia occurred at the early onset







Normal  
subject  
(pt No.2)

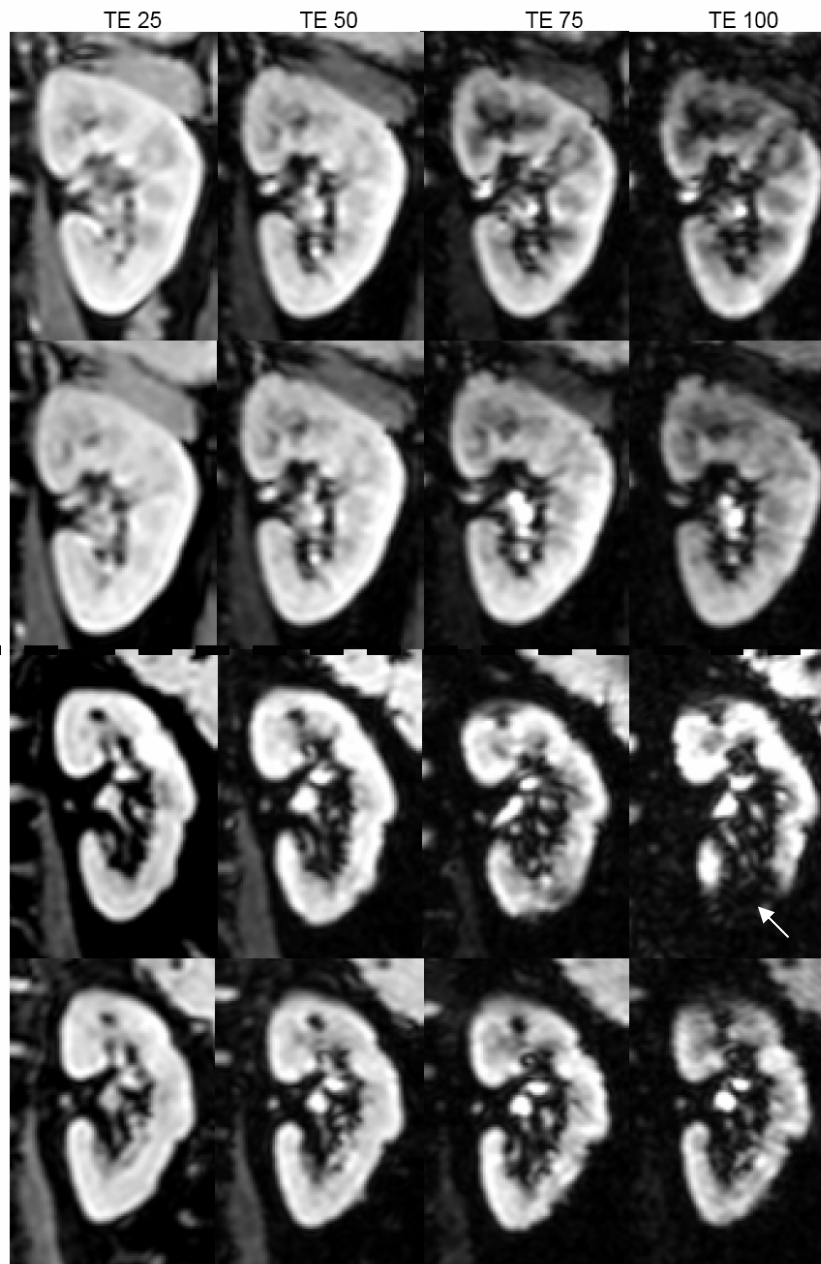
Pre  
ARB

Post  
ARB

CKD  
(pt No.5)

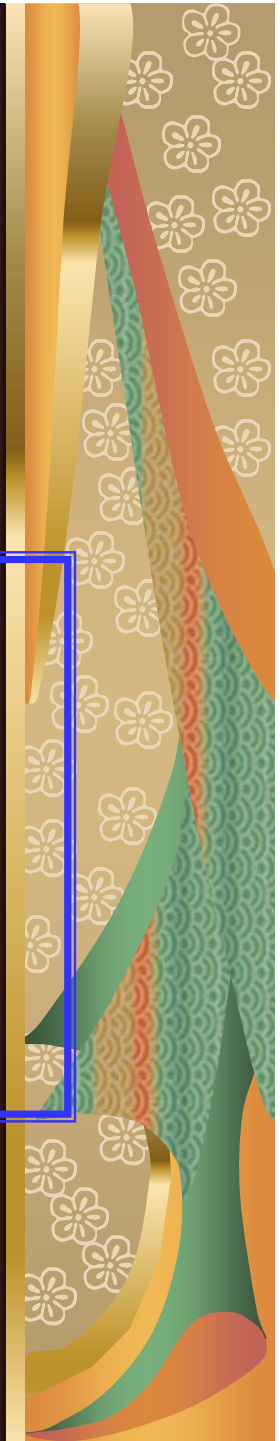
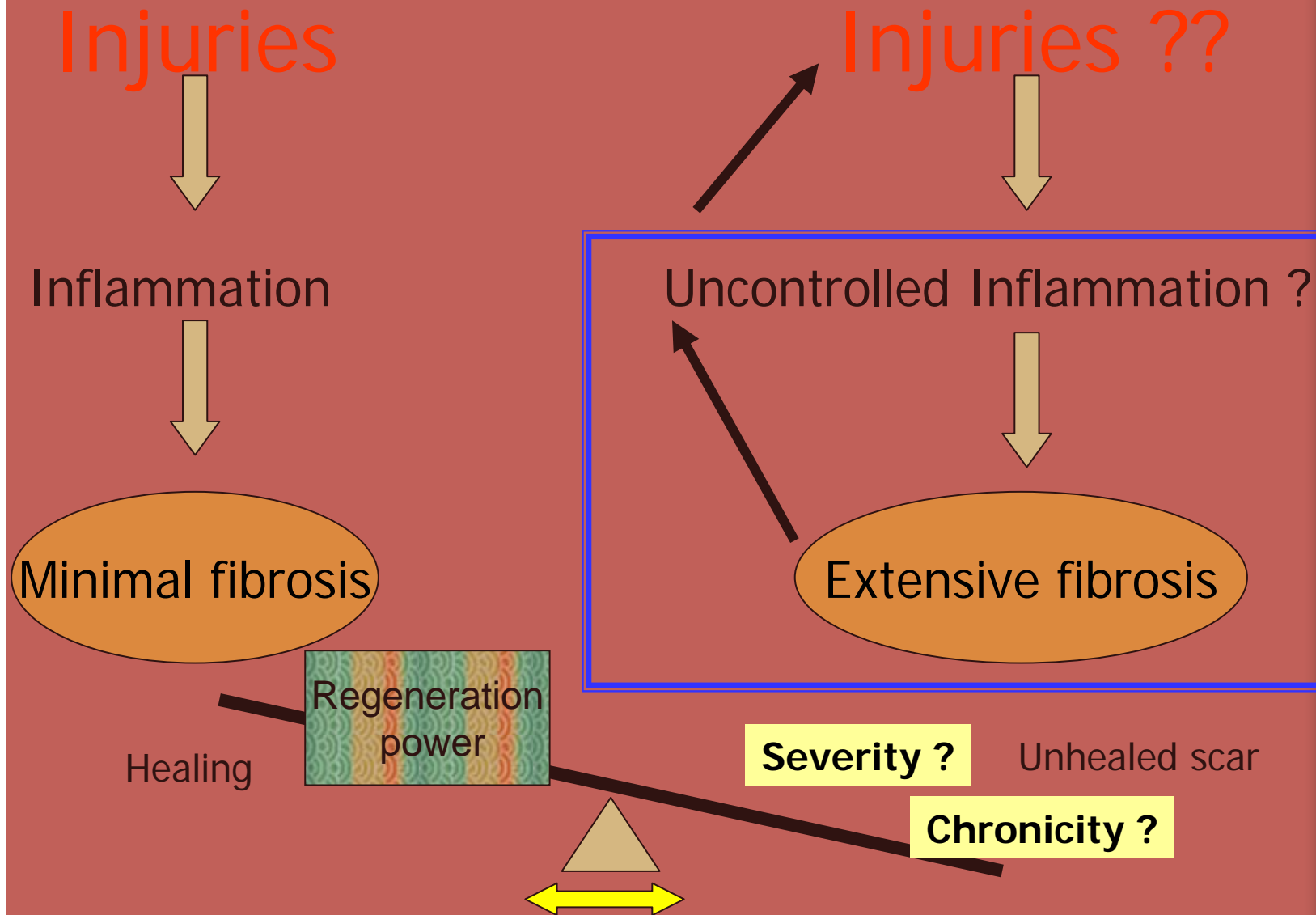
Pre  
ARB

Post  
ARB

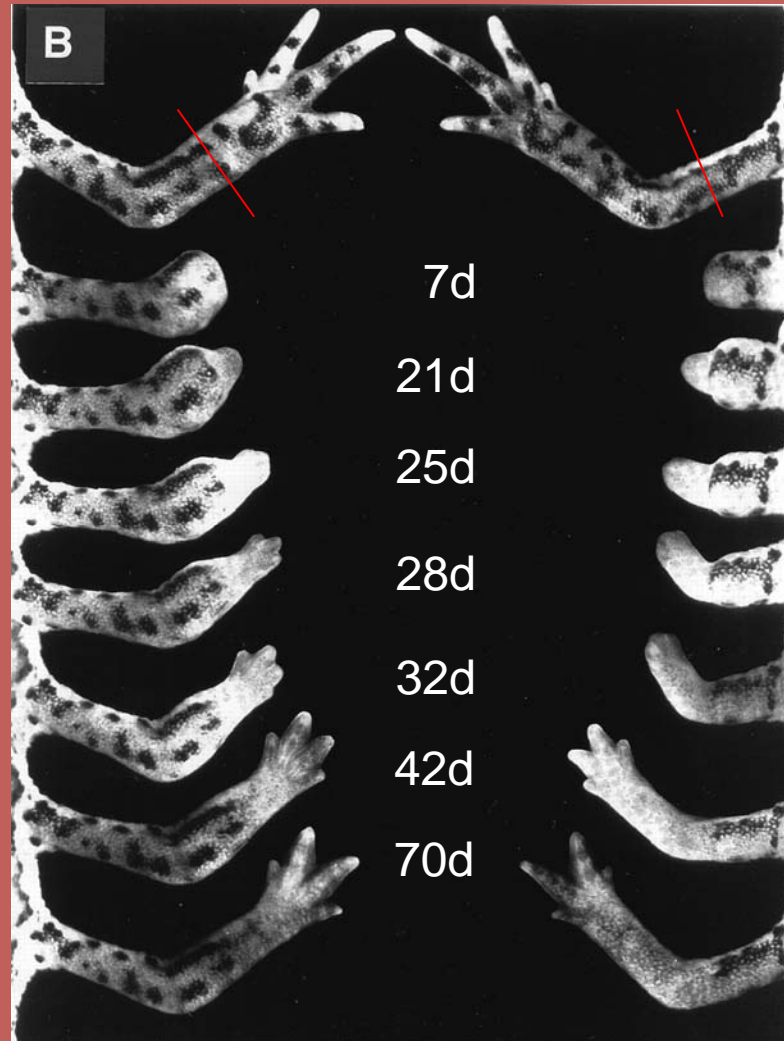
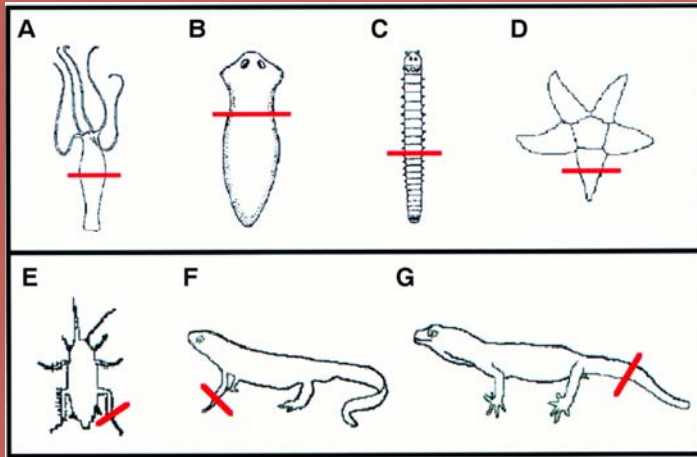




# Tubulointerstitium



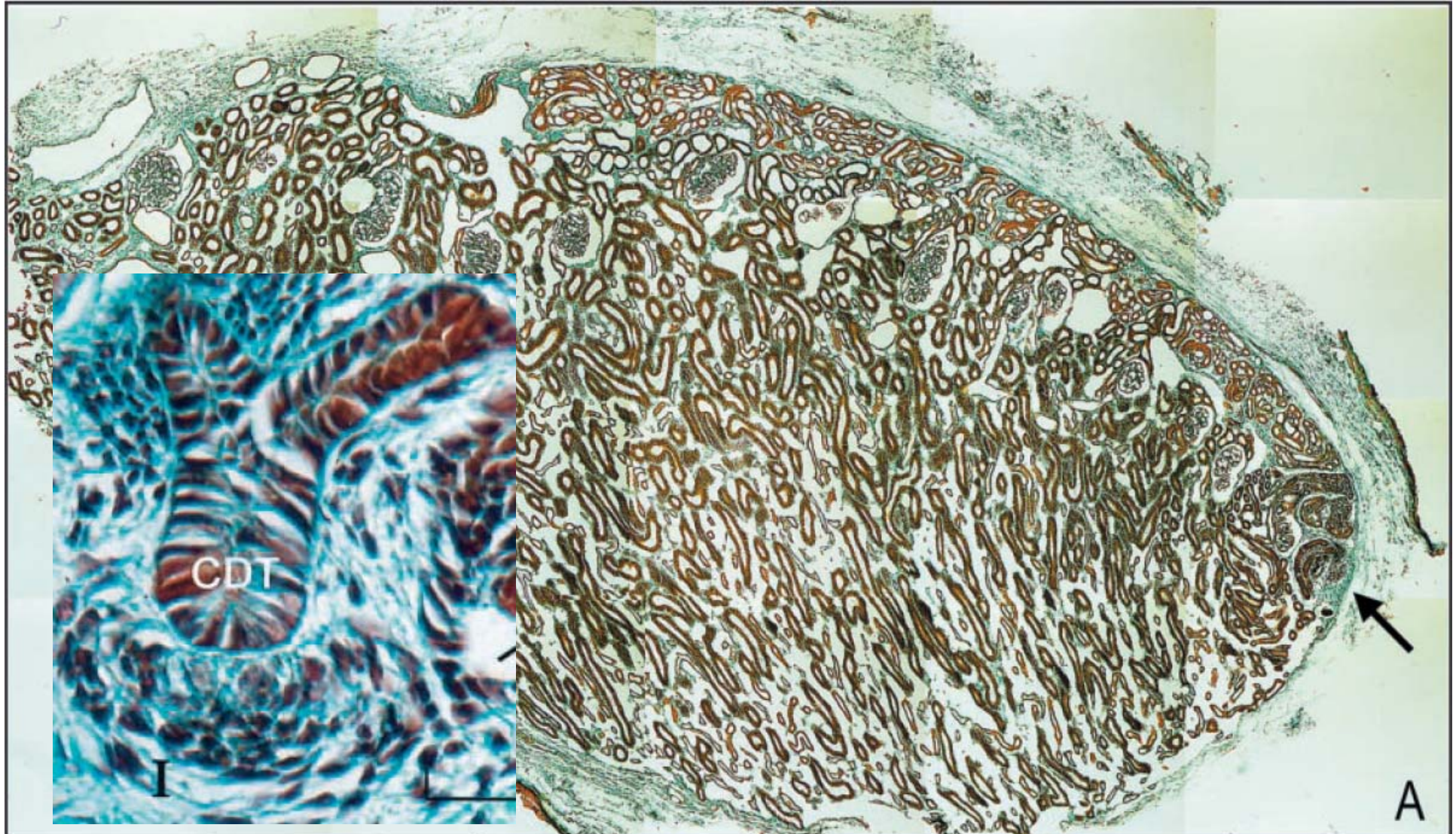
# Superpower of Healing





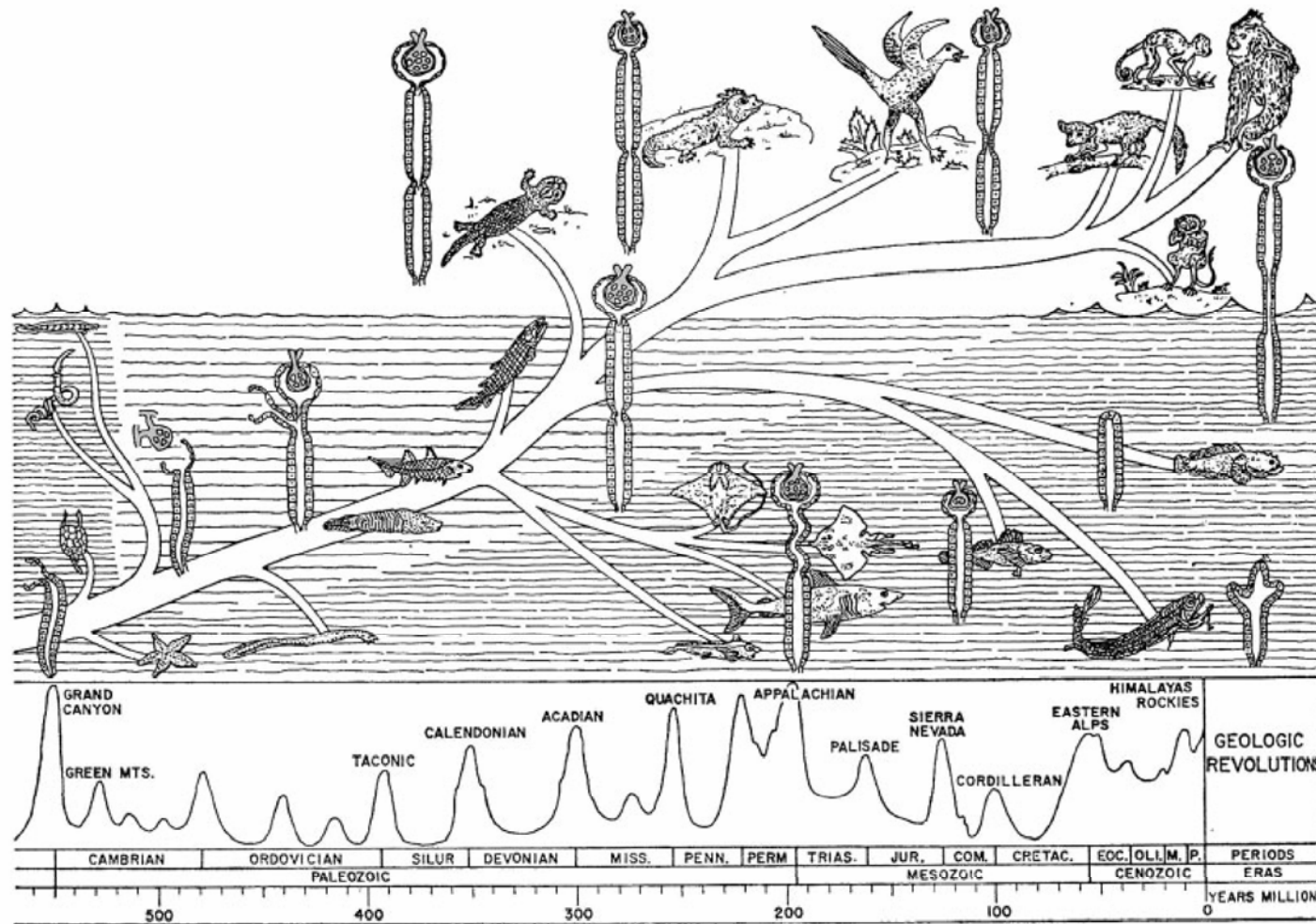


Skate fish



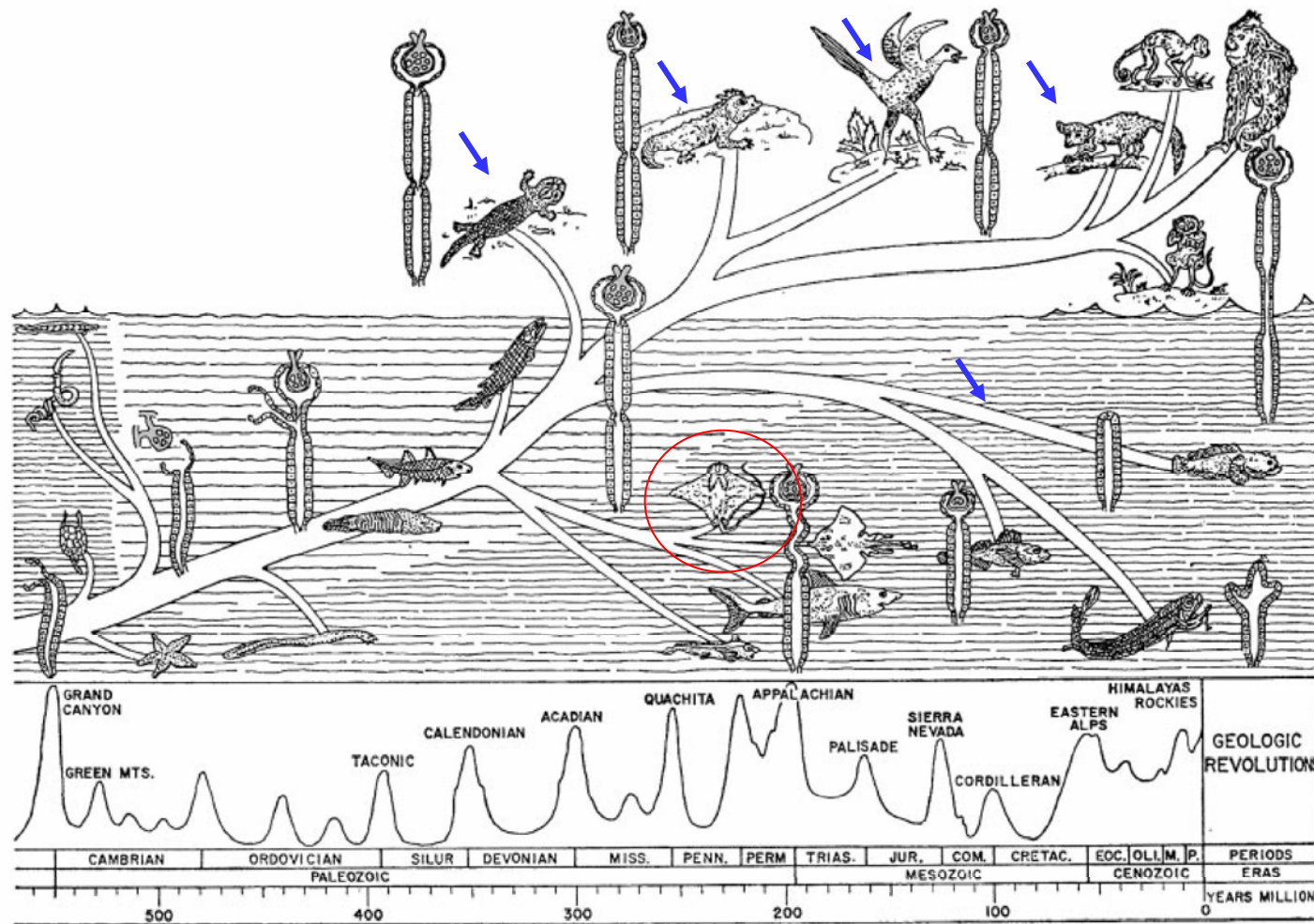


# The Evolution of Kidney





# The Evolution of Kidney



# Tubulointerstitium

Injuries



Inflammation



Minimal fibrosis

Injuries

proteinuria  
hypoxia



Uncontrolled Inflammation ?



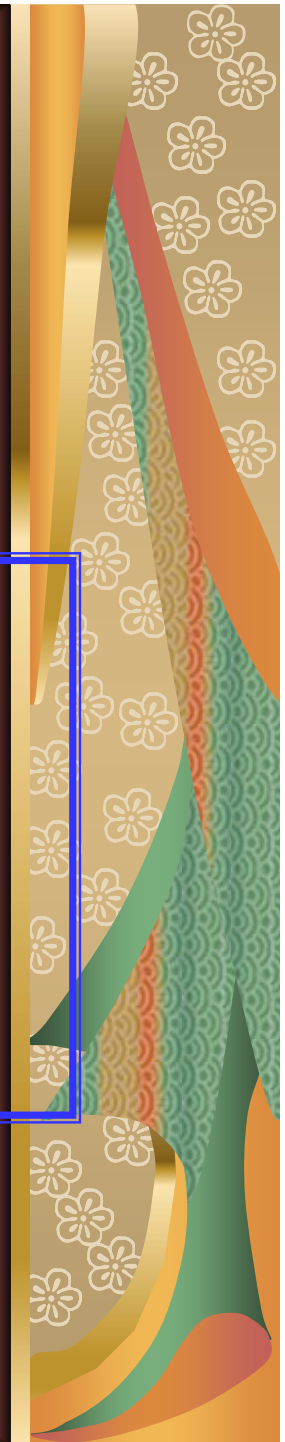
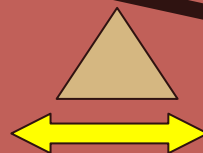
Extensive fibrosis

Healing

Severity ?

Unhealed scar

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# The Evolution of Kidney

