**Al-Mustaqbal University College**
**Department of Pharmacy**
**General Toxicology**
**4th stage**
**Lecture: 6**

# Toxic Response on Kidney

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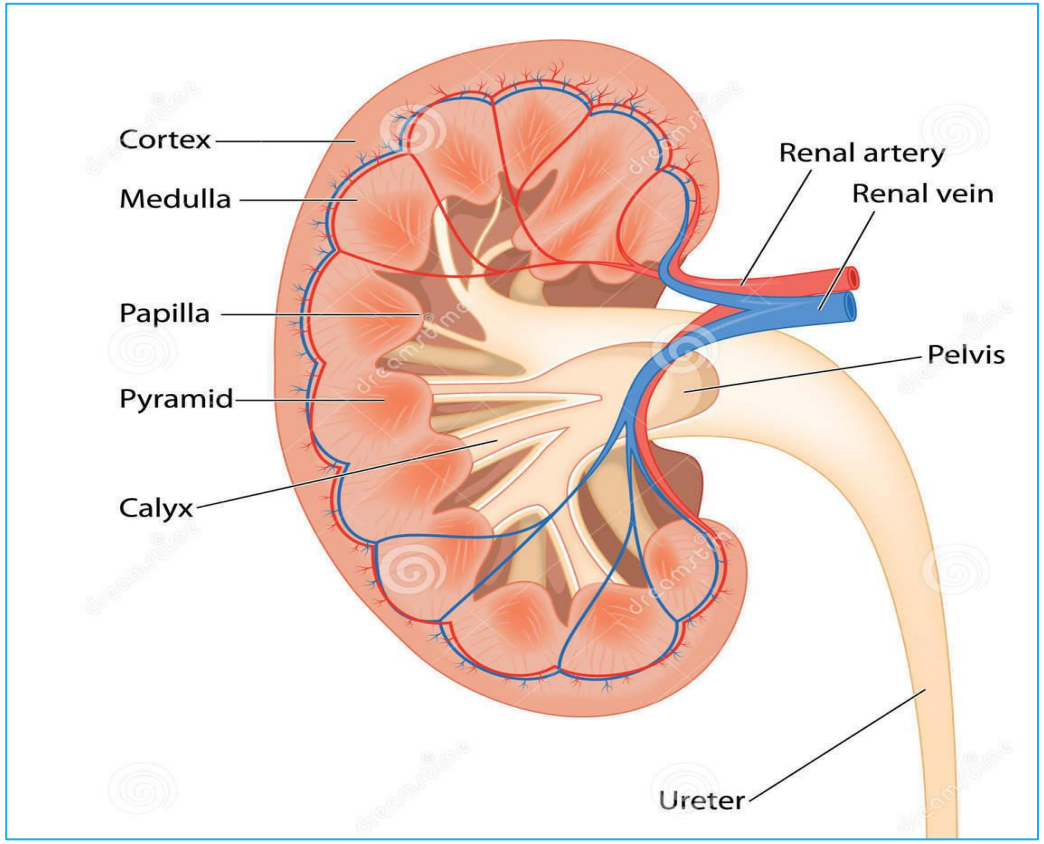
# Functional Anatomy

✓**Gross examination of a sagittal section of the kidney reveals three clearly demarcated anatomic areas:**

1. **Cortex**
2. **Medulla**
3. **Papilla**

✓**The cortex constitutes the major portion of the kidney and receives a disproportionately higher percentage (90%) of blood flow compared to the medulla (about 6% to 10%) or papilla (1% to 2%).**

# Functional Anatomy




*Schematic of the human kidney*

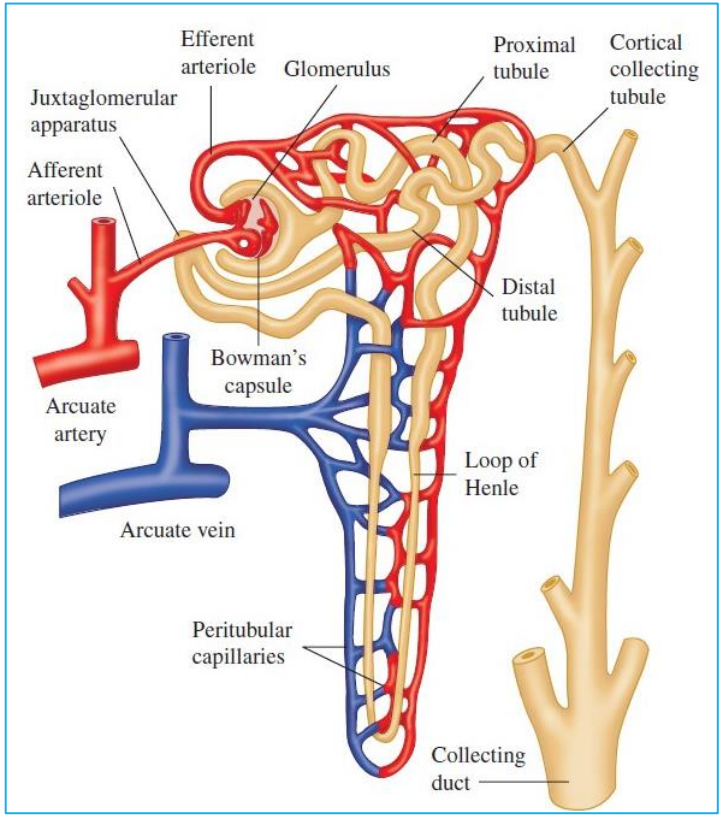
# Functional Anatomy

- ✓Thus, when a **blood-borne toxicant** is delivered to the kidney, a **high percentage** of the material will be delivered to the **cortex** and will have a greater **opportunity** to influence **cortical** rather than **medullary or papillary** functions.
- ✓However, **medullary** and **papillary** tissues are exposed to **higher luminal** concentrations of **toxicants** for **prolonged** periods of time, a consequence of the more concentrated tubular fluid and the more sluggish flow of blood and filtrate in these regions.

# Functional Anatomy

✓**The functional unit of the kidney, the nephron, may be considered in three portions:**

1. **The vascular element**
2. **The glomerulus**
3. **The tubular element**



# Functional Anatomy

✓**The functional integrity of the mammalian kidney is vital to total body homeostasis because the kidney plays a principal role in:**

1. **The excretion of metabolic wastes**
2. **The regulation of EC fluid volume, electrolyte composition, and acid-base balance.**
3. **Synthesis and releases hormones such as renin and erythropoietin**
4. **Metabolism of vitamin D3 to the active 1,25-dihydroxy vitamin D3 form.**

✓**A toxic insult to the kidney therefore could disrupt any or all of these functions.**

# Acute Kidney Injury

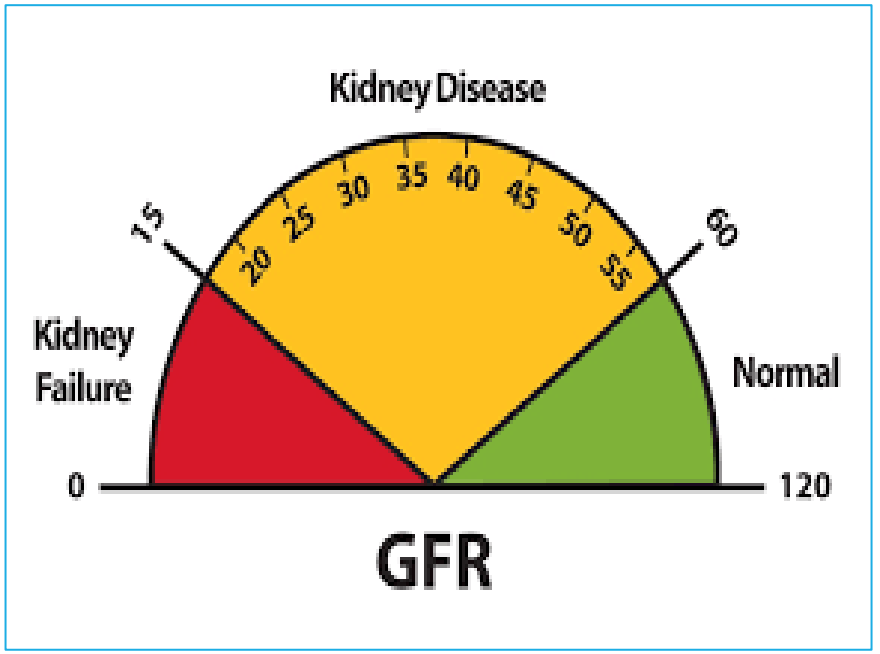
- ✓**AKI is one of the most common manifestations of nephrotoxic damage.**
- ✓**AKI is a group of syndromes that comprises multiple causative factors with varied clinical manifestations ranging from a minimal elevation in serum creatinine to anuric renal failure.**
- ✓**AKI classification is based on the extent of serum creatinine increases or changes in urine output.**

# Acute Kidney Injury

✓**GFR** is equal to the **total filtration rates** of the functioning **nephrons** in the kidney.

✓GFR is considered the optimal way to measure **kidney function** and it depends on four factors:

1. Adequate blood flow to the glomerulus
2. Adequate glomerular capillary pressure
3. Glomerular permeability
4. Low intratubular pressure.




GFR in ml/min/1.73m²

# Acute Kidney Injury

✓Any decline in GFR is complex and may result from:

## 1. Prerenal factors:

✓For example, renal VC, IV volume depletion, and insufficient CO.\

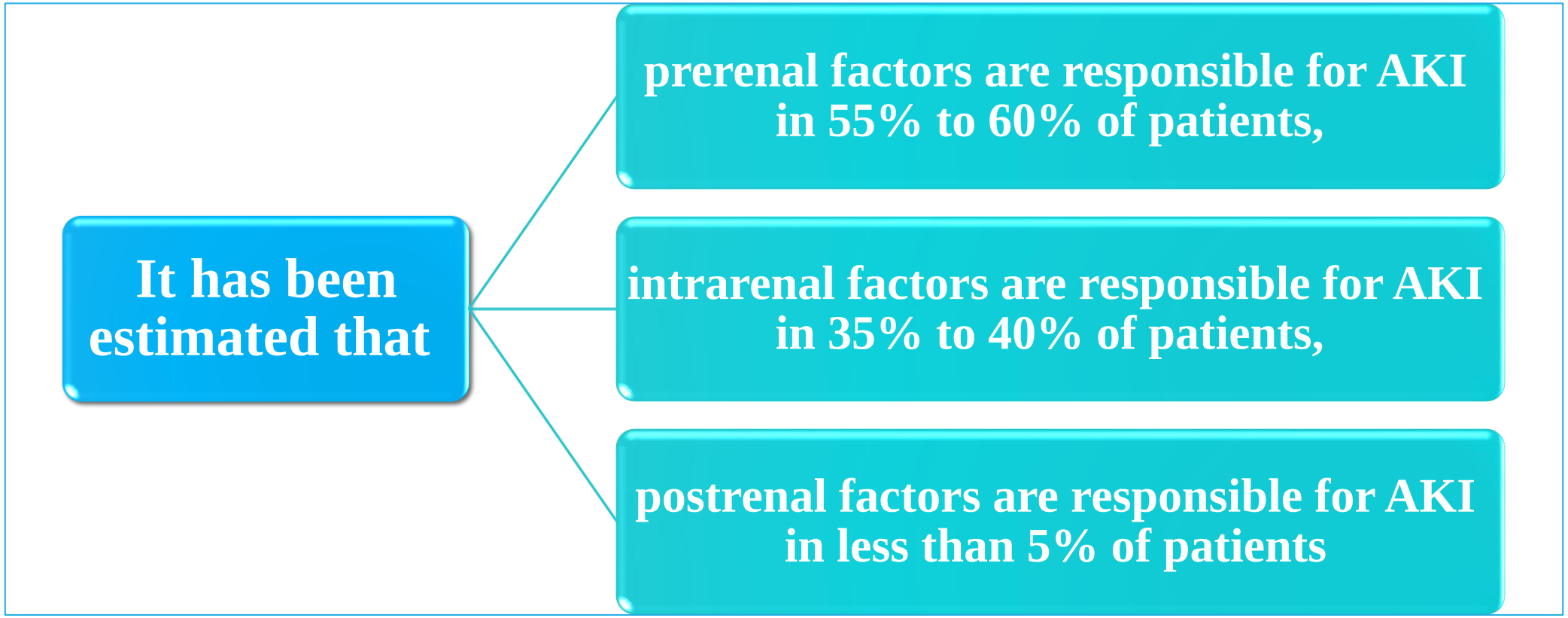
## 2. Postrenal factors:

✓Like ureteral or bladder obstruction.

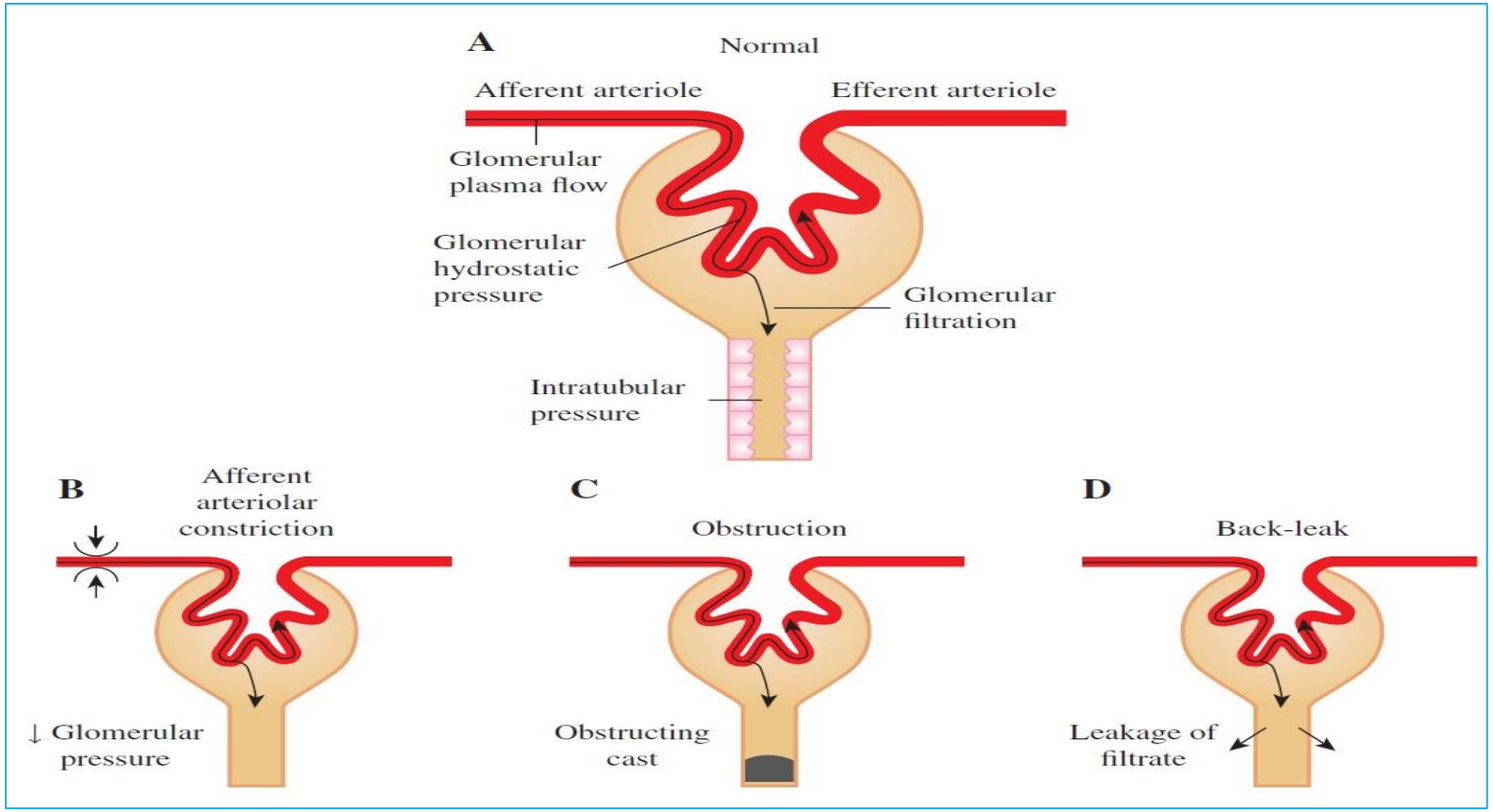
## 3. Intrarenal factors:

✓Like glomerulonephritis, tubular cell injury, death, and loss; renal vasculature damage; and interstitial nephritis.

# Acute Kidney Injury



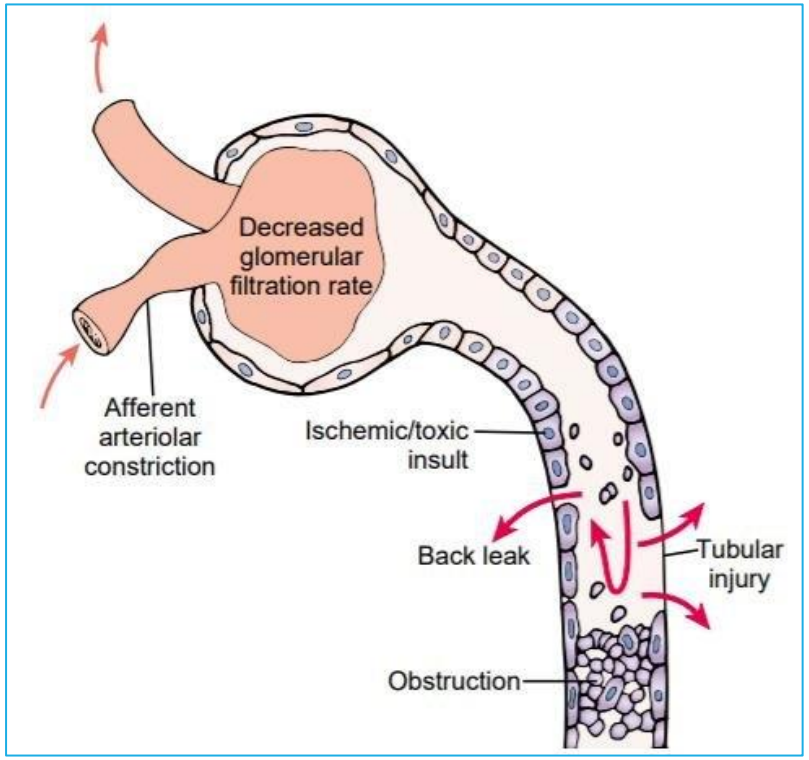
# Acute Kidney Injury




**Mechanisms of reduction of the GFR.**

# Acute Kidney Injury

- ✓If a chemical causes tubular damage directly, then tubular casts can cause tubular obstruction, increased tubular pressure, and decreased GFR.
- ✓The tubular damage may result in epithelial cell death/loss, leading to a back leak of glomerular filtrate and a decrease in GFR.




Casts obstruction & back leak of glomerular filtrate

# Acute Kidney Injury

- ✓**If a chemical causes intrarenal vascular damage with hemodynamic alterations that lead to vasoconstriction.**
- ✓**The resulting medullary hypoxia may cause tubular damage and/or decreases in perfusion pressure, glomerular hydrostatic pressure, and finally GFR.**
- ✓**If a chemical causes intrarenal inflammation, then tubular and vascular damage may follow with decreases in GFR.**

# Adaptation Following Toxic Insult

- ✓**Fortunately, the kidney has a remarkable ability to compensate for a loss of renal functional mass.**
- ✓**Renal studies have revealed that following unilateral nephrectomy, the GFR of the remnant kidney increases by approximately 40% to 60%.**
- ✓**This effect is associated with early compensatory increases in glomerular plasma flow rate and glomerular hydraulic pressure.**

# Adaptation Mechanisms

1. **The cells that are nonlethally injured may undergo cell repair and/or adaptation and contribute to the recovery of the nephron.**

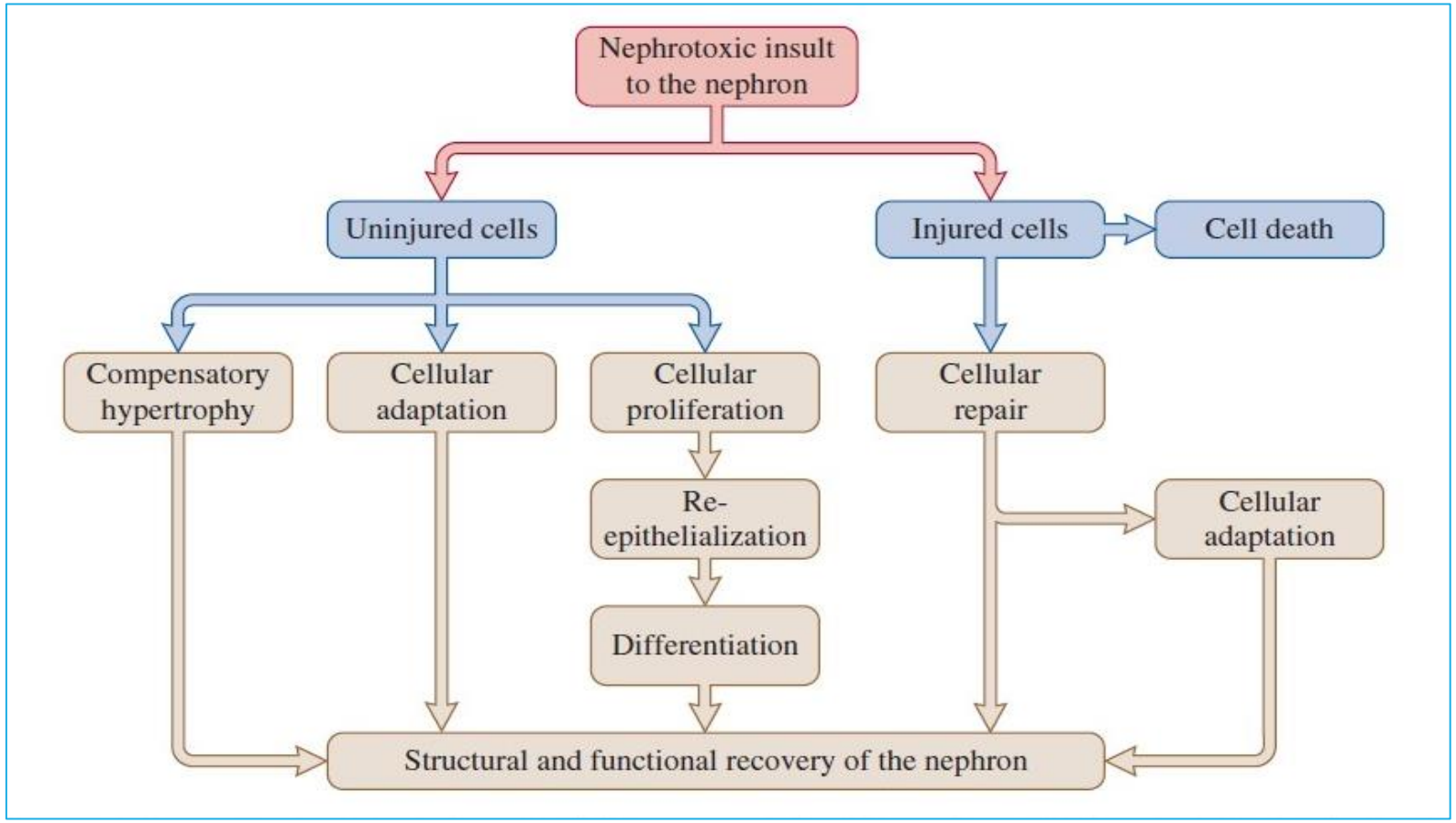
2. **In addition, there is a population of cells that are uninjured may undergo compensatory hypertrophy, adaptation, and proliferation.**

# Adaptation Mechanisms

3. **Surviving tubular epithelial cells replace dead and detached cells through dedifferentiation, proliferation, migration, and redifferentiation.**

4. **Growth factors such as EGF & HB-EGF delivered to tubular epithelial cells may help in the proliferative response of the nephron.**

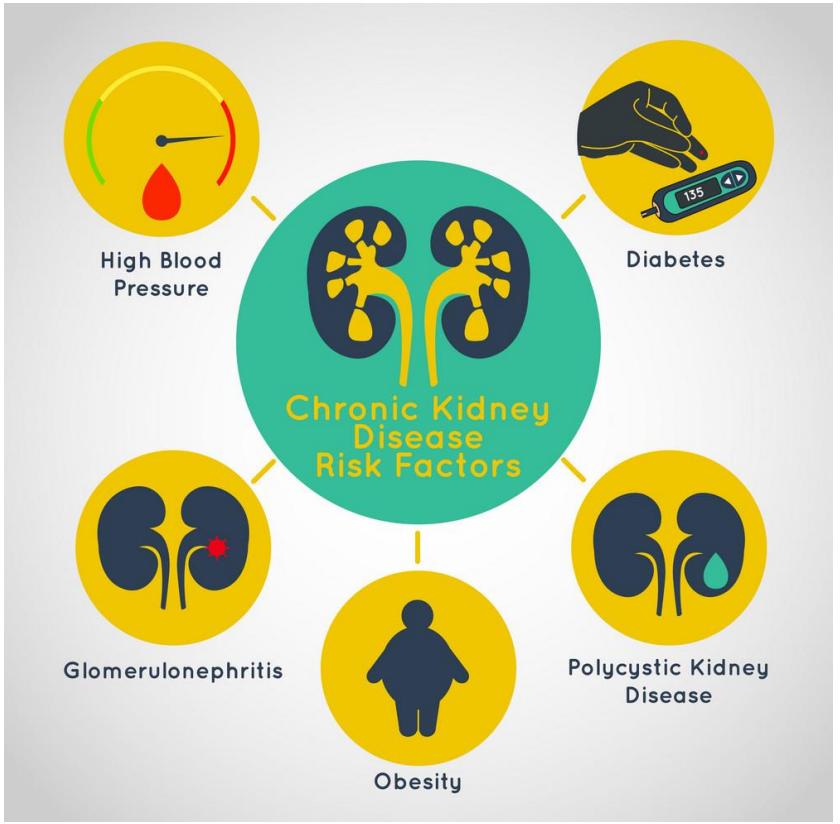
# Adaptation Mechanisms




**The response of the nephron to a nephrotoxic insult**

# Chronic Kidney Disease

- ✓ It is generally thought that progression to chronic kidney disease (CKD) and end-stage renal failure is not simply a function of a primary renal insult.
- ✓ It is related to secondary pathophysiologic processes triggered by the initial injury.



# Chronic Kidney Disease

- ✓**Deterioration** of renal function may occur with **long-term exposure** to a variety of **chemicals** (e.g., analgesics, lithium, and cyclosporine).
- ✓The **progression** of chronic renal disease, for example, maybe a **consequence** of the glomerular hemodynamic response to renal injury.

# Chronic Kidney Disease

- ✓**Following nephron loss, there are adaptive increases in glomerular pressures and flows that increase the single-nephron GFR of remnant viable nephrons.**
- ✓**Although these compensatory mechanisms serve to maintain whole-kidney GFR, evidence has accumulated to suggest that, with time, these alterations are maladaptive and faster the progression of renal failure.**

# Incidence and Severity of Toxic Nephropathy

- ✓ **A wide variety of drugs, environmental chemicals, and metals can cause nephrotoxicity.**
- ✓ **Nephrotoxicity is a recognized clinical liability of certain classes of drugs, in particular, antibiotics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs), radiocontrast media, and anticancer agents.**

# Incidence and Severity of Toxic Nephropathy

- ✓**Approximately 70% of the patients presenting with drug-induced AKI were non oliguric.**
- ✓**The pathologic findings revealed acute tubular necrosis in 60%, approximately 50% recovered completely.**
- ✓**The consequences of AKI can be profound, as permanent renal damage may result and dialysis or renal transplantation may be required.**

# Incidence and Severity of Toxic Nephropathy

- ✓**CKD leading to end-stage renal failure has been associated with long-term abuse of analgesics.**
- ✓**The incidence of analgesic nephropathy has been reported to be as high as 20% to 25%.**
- ✓**Other chemicals, such as lithium, cyclosporine, NSAIDs, lead, and cadmium may produce chronic tubulointerstitial nephropathy with progressive loss of renal function.**

# Susceptibility of the Kidney to Toxicity

- ✓The **susceptibility** of the kidney to the **toxic effects** of chemicals can be **attributed** to its **unique physiologic and anatomic features**.
- ✓As kidneys **constitute** only **0.5%** of total body mass, they **receive** about **20% to 25%** of the resting **CO**.
- ✓Consequently, **any** drug or chemical in the systemic circulation will be **delivered** to these organs in **relatively high amounts**.

# Susceptibility of the Kidney to Toxicity

- ✓The processes involved in forming **concentrated urine** also serve to **concentrate** potential toxicants in the tubular fluid.
- ✓As water and electrolytes are **reabsorbed** from the glomerular filtrate, chemicals in the tubular fluid may be **concentrated**, thereby driving **passive diffusion** of toxicants into tubular cells.
- ✓Therefore, a **nontoxic** concentration of a chemical in the **plasma** may reach **toxic** concentrations in **the kidney**.

# Susceptibility of the Kidney to Toxicity

- ✓ **Also, renal transport, accumulation, and metabolism of xenobiotics contribute significantly to the susceptibility of the kidney to toxic injury.**
- ✓ **In addition to intrarenal factors, the incidence and/or severity of chemically induced nephrotoxicity may be related to the sensitivity of the kidney to circulating vasoactive substances.**

# Site-Selective Injury

- ✓Many **nephrotoxicants** have their primary effects **on discrete segments** or **regions** of the nephron.
- ✓For example, the **proximal tubule** is the primary target for most nephrotoxic **antibiotics, antineoplastics, halogenated hydrocarbons, mycotoxins, and heavy metals,**
- ✓Whereas the **glomerulus** is the primary site for **immune complexes**, the **loop of Henle/collecting ducts** **for fluoride ions**, and the **medulla/papilla** for **chronically consumed analgesic mixtures**.

# Site-Selective Injury

✓**The reasons underlying this site-selective injury are complex but can be attributed in part to site-specific differences in:**

1. **Blood flow**
2. **Transport, and accumulation of chemicals,**
3. **Physicochemical properties of the epithelium**
4. **Reactivity of cellular/molecular targets**
5. **Balance of bioactivation/detoxification reactions**
6. **Cellular energetics**
7. **Regenerative/repair mechanisms**

# Glomerular Injury

- ✓The glomerulus is the initial site of chemical exposure within the nephron, and a number of nephrotoxicants produce structural injury to this segment.
- ✓In certain instances, chemicals alter glomerular permeability to proteins by altering the size- and charge-selective functions.
- ✓Both puromycin aminonucleoside and doxorubicin target glomerular epithelial cells, resulting in changes in size and charge selectivity and proteinuria.

# Glomerular Injury

- ✓ **Cyclosporine, amphotericin B, and gentamicin are examples of chemicals that impair glomerular ultrafiltration without significant loss of structural integrity and decrease GFR.**
- ✓ **Amphotericin B decreases GFR by causing renal vasoconstriction and decreasing the glomerular capillary ultrafiltration coefficient (Kf), an effect probably mediated through the endothelial cells.**

# Glomerular Injury

- ✓**Because of its polycationic nature, the aminoglycoside gentamicin interacts with the anionic sites on the endothelial cells, decreasing Kf, and GFR.**
- ✓**Meanwhile, cyclosporine not only causes renal vasoconstriction and vascular damage but also is injurious to the glomerular endothelial cell.**

# Proximal Tubular Injury

- ✓**The proximal tubule is the most common site of toxicant-induced renal injury.**
- ✓**The reasons for this relate in part to the selective accumulation of xenobiotics into this segment of the nephron.**
- ✓**More importantly, tubular transport of organic anions and cations, low-molecular-weight proteins and peptides, GSH conjugates, and heavy metals is localized primarily if not exclusively to the proximal tubule.**

# Proximal Tubular Injury

✓**Proximal tubular cells appear to be more susceptible to ischemic injury than distal tubular cells.**

✓**Therefore, the proximal tubule will likely be the primary site of toxicity for chemicals that interfere with RBF, cellular energetics, and/or mitochondrial function.**

# Distal Tubular Structures Injury

- ✓**Chemically induced injury to the more distal tubular structures, compared to the proximal tubule, is an infrequent occurrence.**
- ✓**Functional abnormalities at these sites manifest primarily as impaired concentrating ability and/or acidification defects.**
- ✓**Drugs that have been associated with acute injury to the more distal tubular structures include amphotericin B, cisplatin, and methoxyflurane.**

# Distal Tubular Structures Injury

- ✓**Each of these drugs induces an ADH-resistant polyuria, suggesting that the concentrating defect occurs at the level of the medullary thick ascending limb and/or the collecting duct.**
- ✓**However, the mechanisms mediating these drug-induced concentrating defects appear to be different.**

# Distal Tubular Structures Injury

- ✓**Amphotericin B** is highly lipophilic and interacts with lipid sterols such as cholesterol, resulting in the formation of **transmembrane channels or pores** and disrupting membrane permeability.
- ✓Thus, **amphotericin** effectively **transforms** the tight distal tubular epithelium into one that is leaky to water and ions and impairs reabsorption at these sites.

# Distal Tubular Structures Injury

✓**The mechanisms mediating cisplatin-induced polyuria occur in two phases:**

1. **The first phase is responsive to vasopressin and inhibitors of prostaglandin synthesis.**
2. **The second phase is not responsive to vasopressin or prostaglandin synthesis inhibitors but is associated with decreased papillary solute content.**

# Distal Tubular Structures Injury

- ✓**Methoxyflurane** nephrotoxicity is associated with the **inhibitory** effects of the metabolite **fluoride** on solute and water reabsorption.
- ✓**Fluoride inhibits** sodium chloride reabsorption in the thick ascending limb and **inhibits ADH-mediated reabsorption** of water, possibly due to disruption in adenylate cyclase.

# Papillary Injury

- ✓**The renal papilla is susceptible to the chronic injurious effects of abusive consumption of analgesics.**
- ✓**The initial target is the medullary interstitial cells, followed by degenerative changes in the medullary capillaries, loops of Henle, and collecting ducts.**

# Papillary Injury

- ✓ **The intrarenal gradient for prostaglandin H synthase activity has been implicated as a contributing factor for induced-papillary injury.**
- ✓ **This activity is highest in the medulla and least in the cortex, and the prostaglandin hydroperoxidase component metabolizes phenacetin to reactive intermediates capable of covalent binding to cellular macromolecules.**

# Papillary Injury

✓**Other factors may contribute to this site-selective injury, including:**

1. **High papillary concentrations of potential toxicants**
2. **Inhibition of vasodilatory prostaglandins**

✓**These two factors compromise RBF to the renal medulla/papilla, resulting in tissue ischemia.**

# THANK YOU
# FOR YOUR ATTENTION