Toxic Response of The Kidney

General Toxicology

4th Stage / 2nd Semester

Lecturer

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Objectives of this lecture are to:

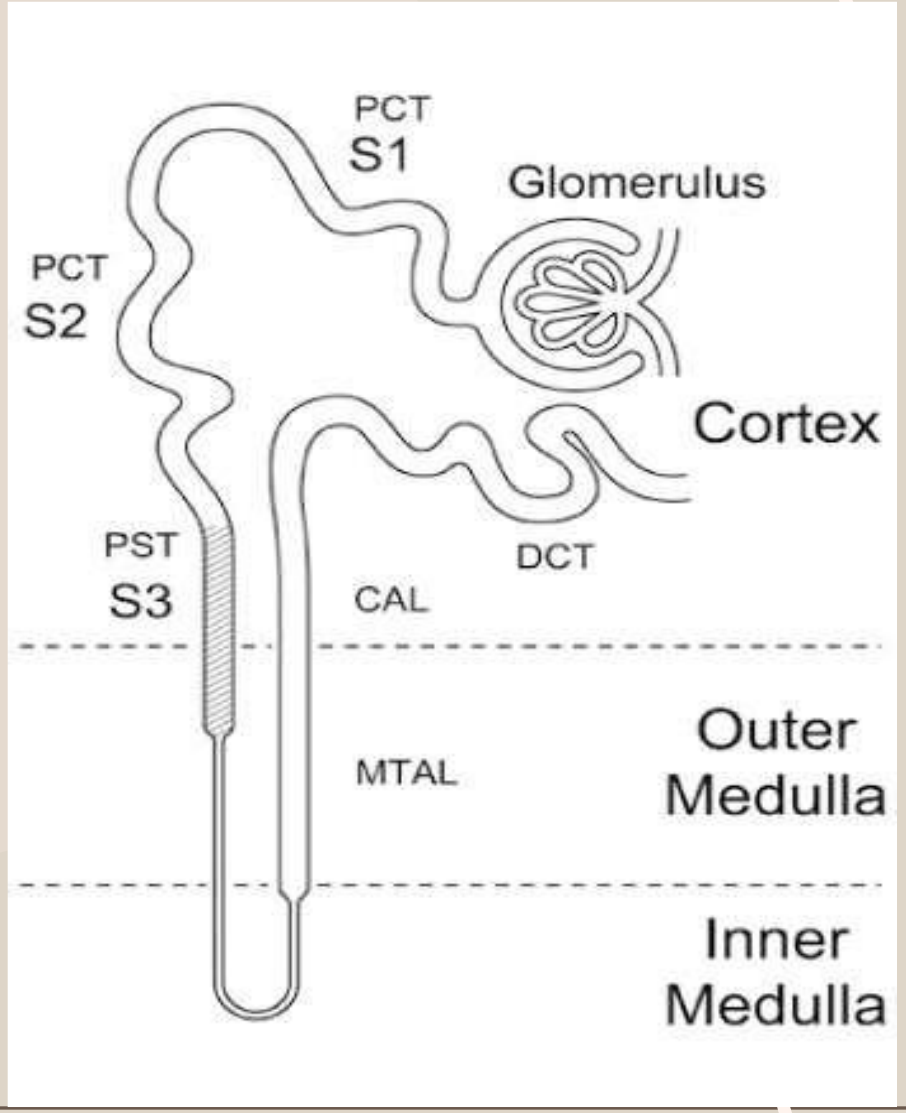
- ✓Determine kidney functions &its functional anatomy.
- ✓Explain the pathophysiologic responses of the kidney.
- ✓Determine the reasons for the susceptibility of the kidney to toxicity.
- ✓Discuss the site-selective renal injury.
- ✓Determine the mechanism of toxicity and the nephrotoxic effects of: heavy metals, halogenated hydrocarbons, and some therapeutic agents.

Functional Anatomy of the Kidney:

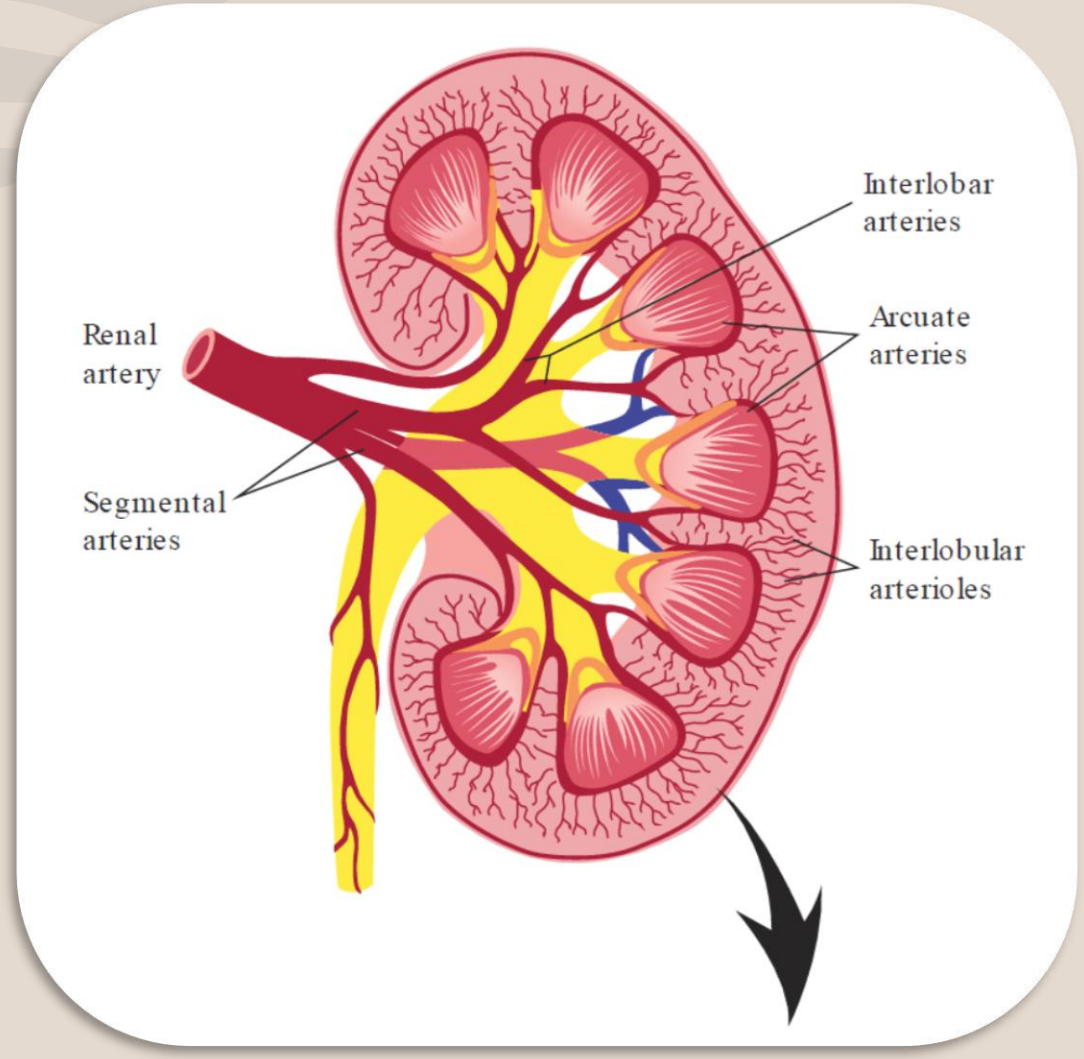
- Gross examination of a side section of the kidney reveals three anatomic areas:
  - The cortex >> constitutes the major portion of the kidney and receives a higher percentage (90%) of blood flow.
  - Medulla >> receives (6% - 10%) of blood flow
  - Papilla >> receives about (1 – 2%) of blood flow

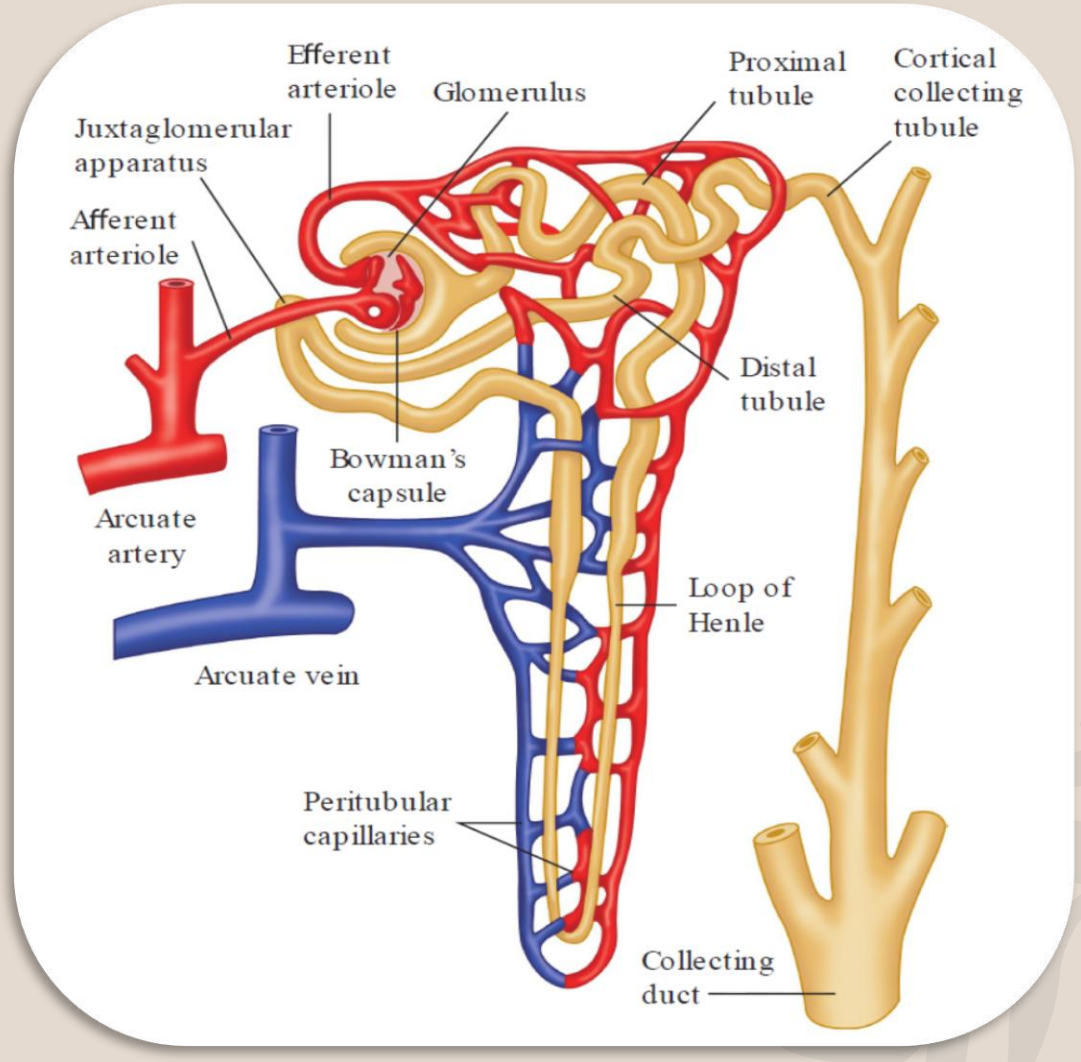
Functional Anatomy of the Kidney:

- The functional unit of the kidney is the nephron, and can be considered in three portions:
  - The vascular element
  - The glomerulus
  - The tubular element



Anatomical structure of the kidney





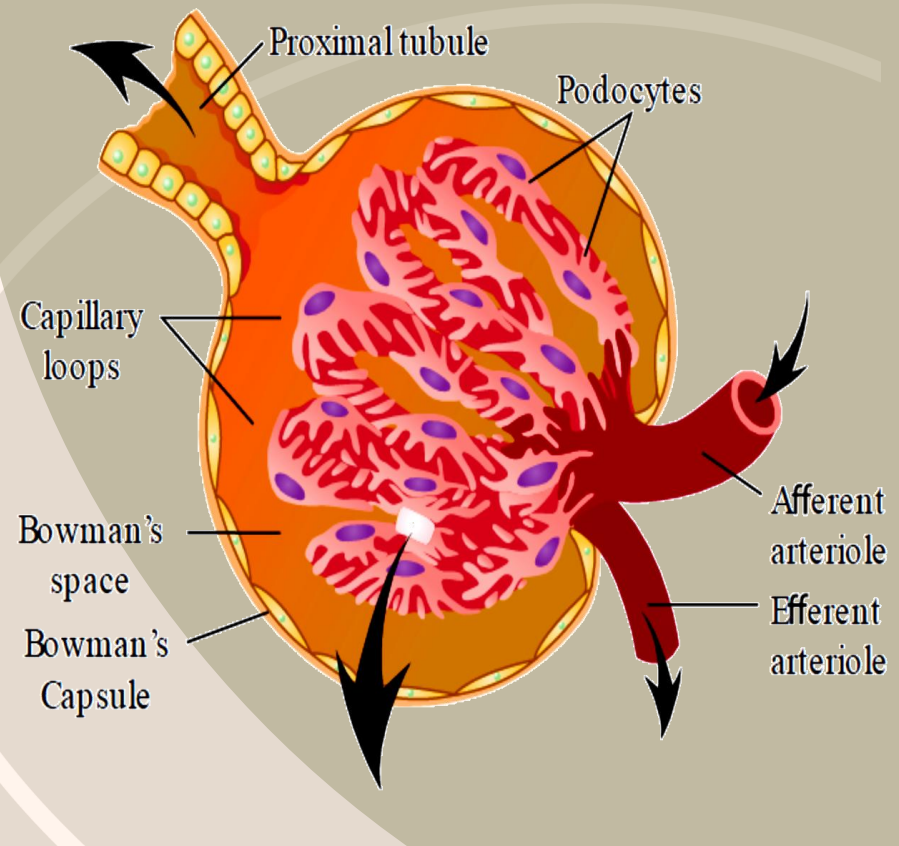
Homeostatic function of the kidney:

1. the kidney plays a principal role in the excretion of metabolic wastes
2. regulation of extracellular fluid volume, electrolyte composition, and acid-base balance.
3. the kidney synthesizes and releases hormones, such as renin and erythropoietin
4. metabolizes vitamin D3 to the active 1,25- dihydroxy vitamin D3 form.

Renal Vasculature & Glomerulus

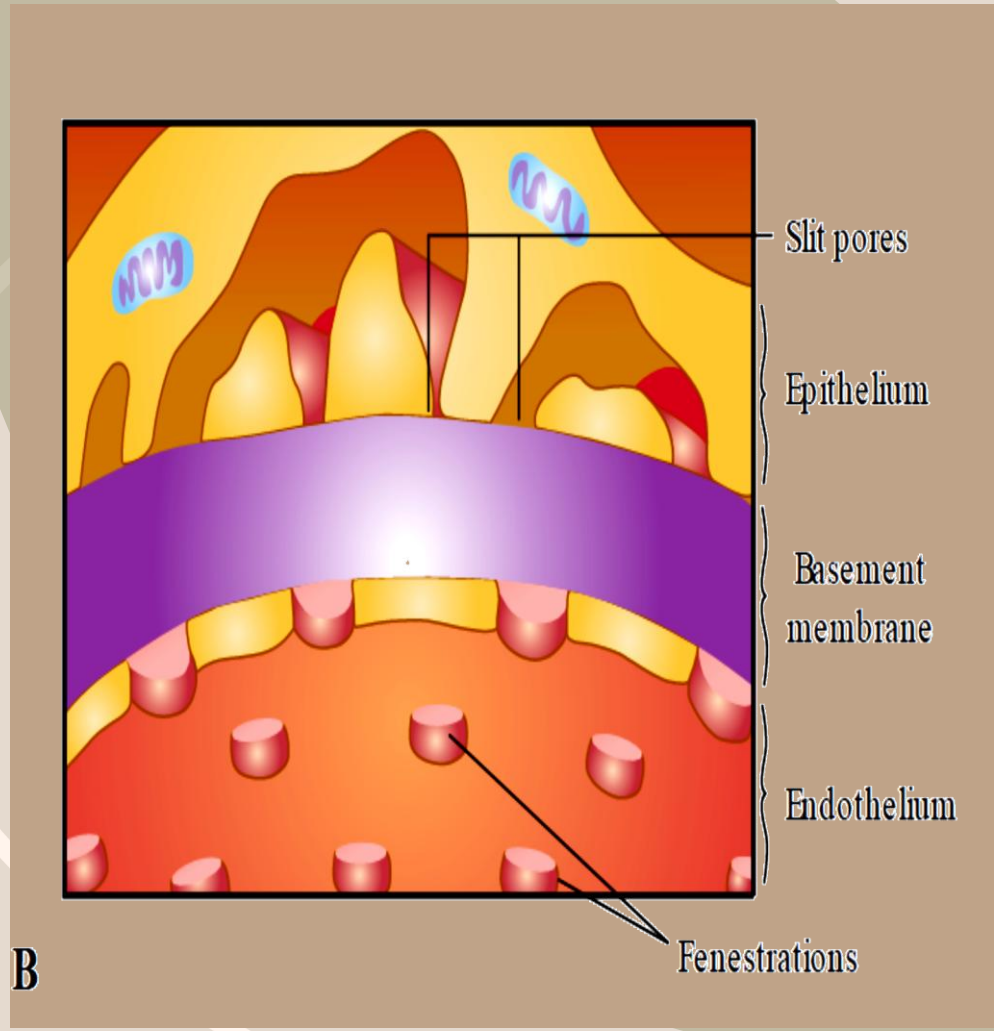
- The renal artery gives rise to the:
  - Afferent arterioles >> supply blood to the kidney
  - Efferent arterioles >> blood leaves the kidney

  These arterioles are innervated by the sympathetic nervous system & respond to
- nerve stimulation, angiotensin II, anti-diuretic hormone (ADH).



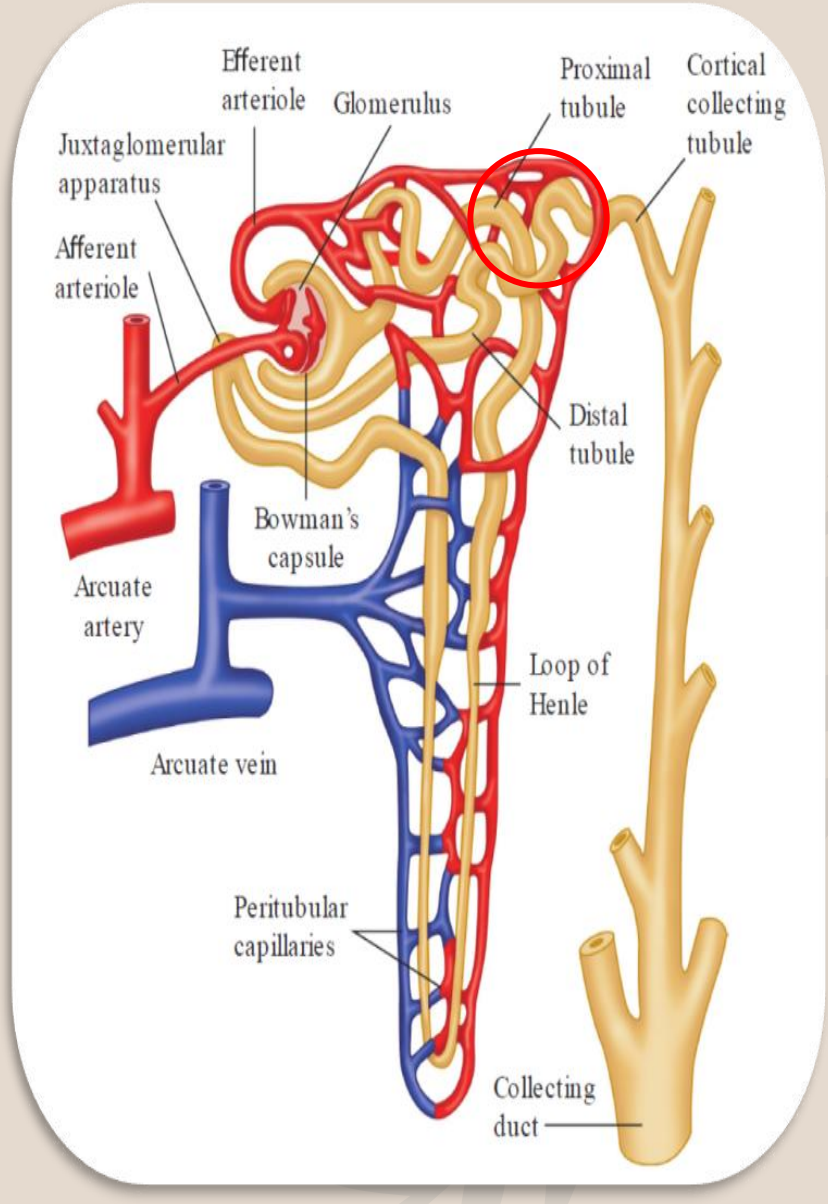
Renal Vasculature & Glomerulus

- The glomerulus is a complex, specialized capillary bed composed primarily of endothelial cells
- The glomerular capillary wall provides a
- significant barrier to the trans glomerular passage of macromolecules Thus:
  - Small molecules (inulin) (MW ~5 500), >> occurs freely
  - Large molecules (albumin) (MW 56 000–70 000), >> restricted



Proximal Tubule:

- The proximal tubule is the most important segment of the nephron, as it reabsorbs approximately 60% to 80% of solute and water filtered at the glomerulus
- The proximal tubule contains numerous transport systems capable of driving concentrative transport of many metabolic substrates, including amino acids, glucose, and citric acid cycle intermediates.
- An important excretory function of the proximal tubule is the secretion of weak organic anions and cations by specialized transporters
- Toxicant-induced injury to the proximal tubule will have major consequences on water and solute balance.

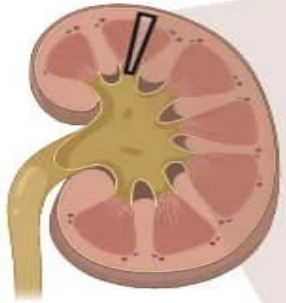


Loop of Henle, Distal tubule, Collecting Duct:

- The thin descending and the thick ascending limb of the loop of Henle are critical to the processes involved in urinary concentration.

- Approximately 25% of the filtered Na+ and K+ and 20% of the filtered water are reabsorbed by the segments of the loop of Henle.
- The macula densa comprises specialized cells located between the end of the thick ascending limb and the early distal tubule, near the afferent arteriole
- the action of antidiuretic hormone (ADH, vasopressin) enhances water permeability of the medullary collecting duct.
- Chemicals that interfere with ADH synthesis, secretion, or action therefore may impair concentrating ability.

Kidney Reabsorption and Secretion



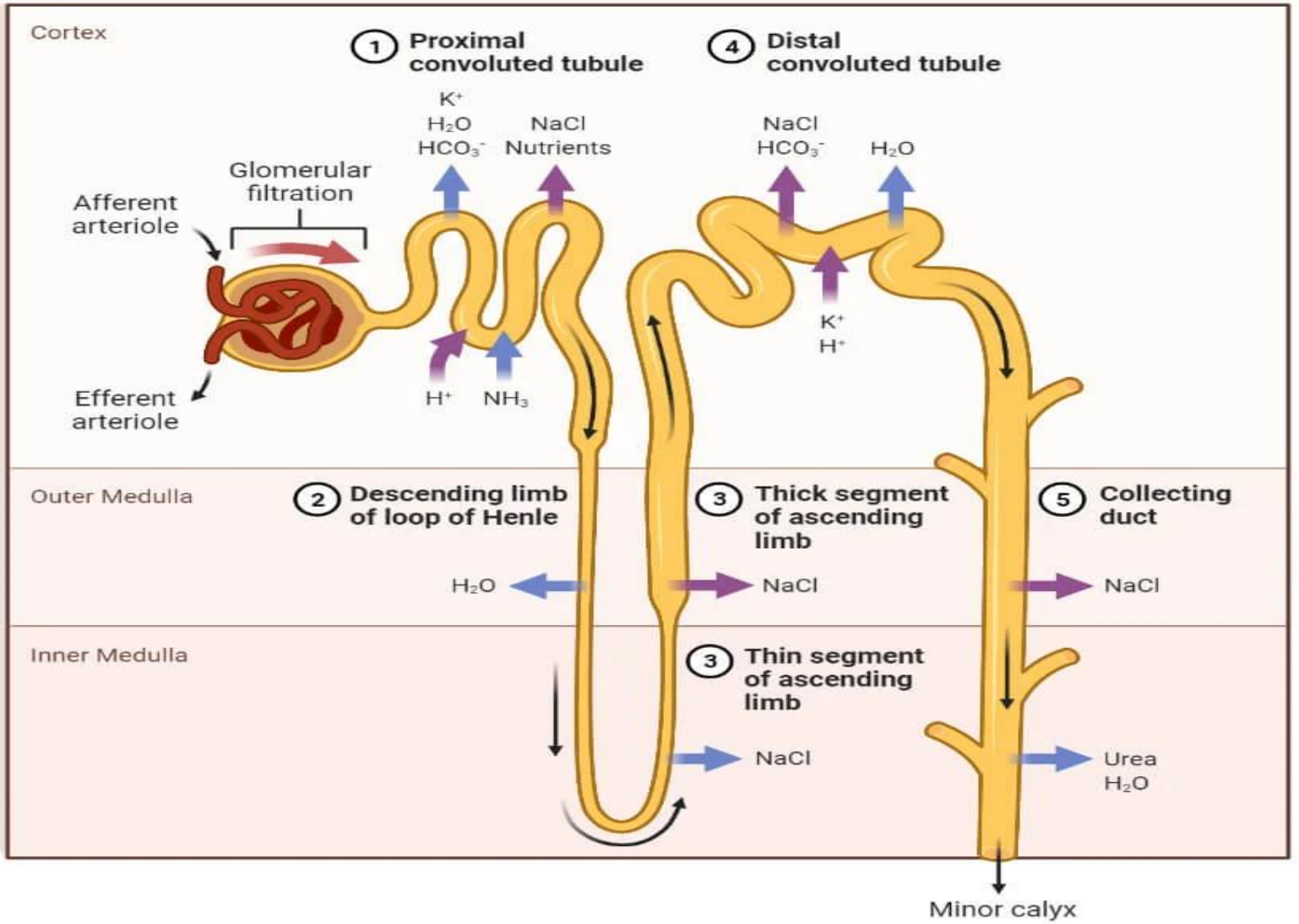
Filtration

- H_2O
- Salts (NaCl, etc.)
- HCO_3^-
- H^+
- Urea
- Glucose
- Amino acids
- Some drugs

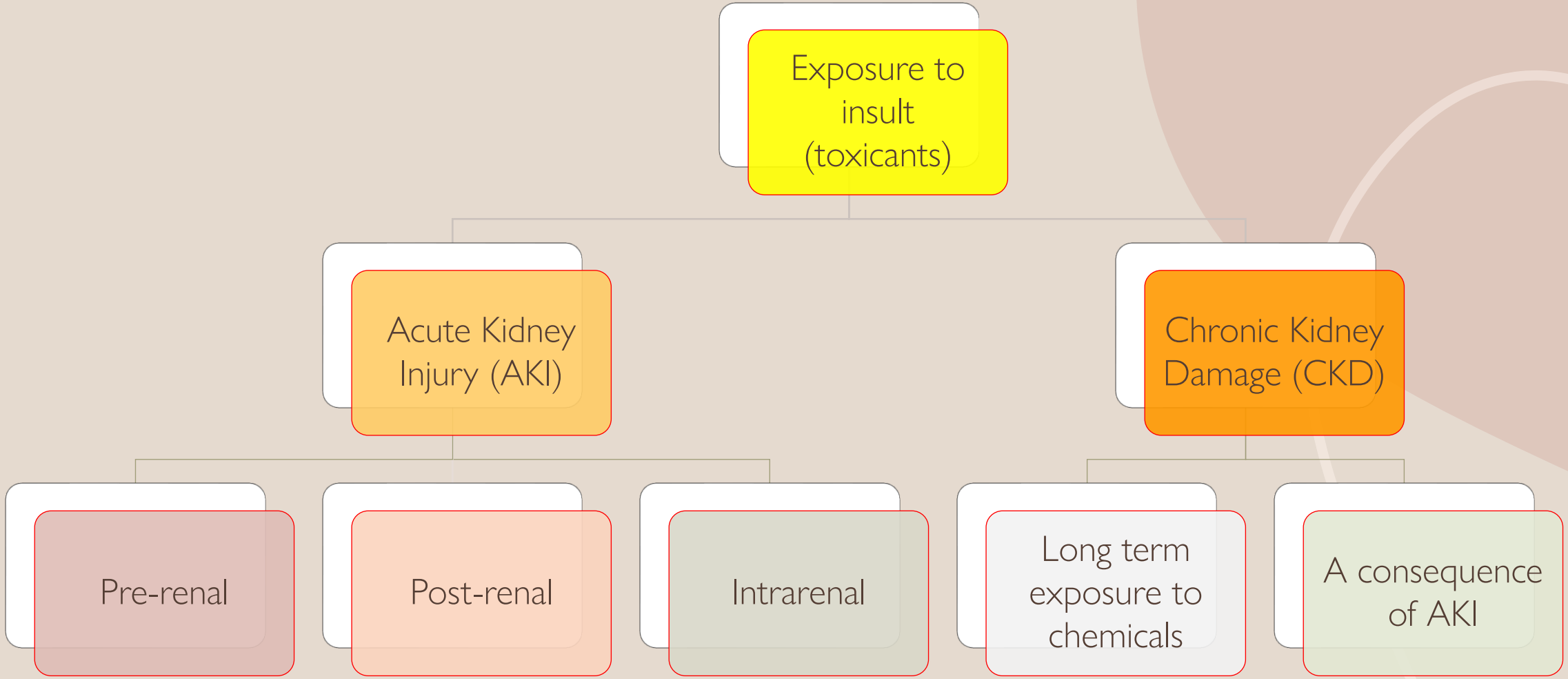
Reabsorption and secretion

Active transport

Passive transport



Toxic Responses of the Kidney:



Toxic responses of the Kidney:

1. Acute Kidney Injury (AKI):
   - One of the most common manifestations of nephrotoxic damage is acute renal failure or acute kidney injury (AKI).
   - is defined as a complex disorder that comprises multiple causative factors and occurs with varied clinical manifestations ranging from a minimal elevation in serum creatinine to anuric renal failure.
   - AKI is characterized by an abrupt decline in glomerular filtration rate with resulting azotemia, a build-up of nitrogenous wastes in the blood.

Acute Kidney Injury (AKI)

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

✓Prerenal factors (renal vasoconstriction, intravascular volume depletion, and insufficient cardiac output).

✓Postrenal factors (ureteral or bladder obstruction).

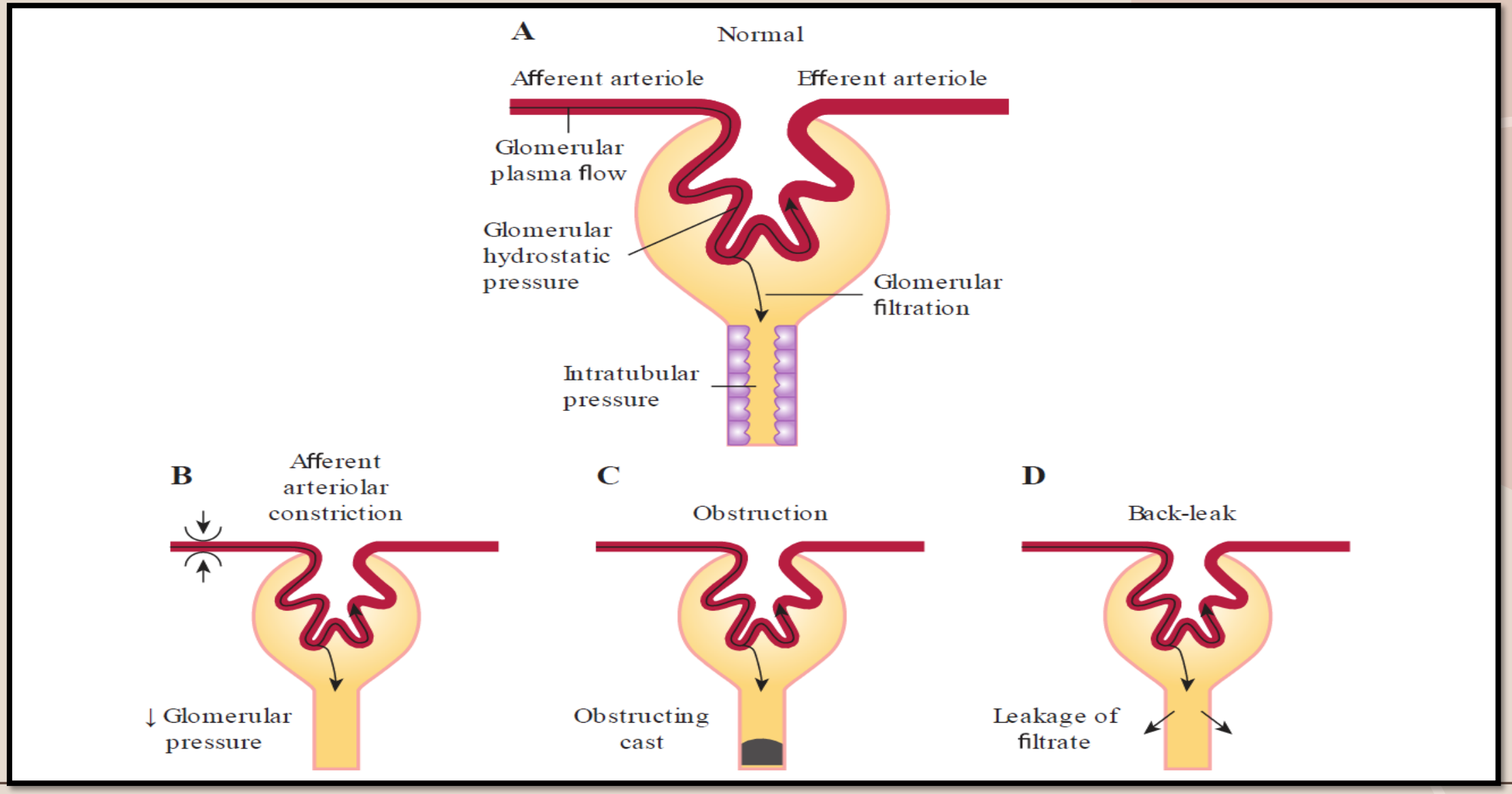
✓Intrarenal factors (glomerulonephritis, tubular cell injury, death, and interstitial nephritis).

✓The pre- and post-renal factors can lead to decreased GFR.

✓It is thought that more than 90% of AKI mediated by intrarenal factors is the result of ischemia/ reperfusion injury or nephrotoxicity.

- **Mechanisms of reduced GFR:**
  - Afferent arteriolar constriction decreases GFR by reducing blood flow, resulting in diminished capillary pressure.
  - 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.

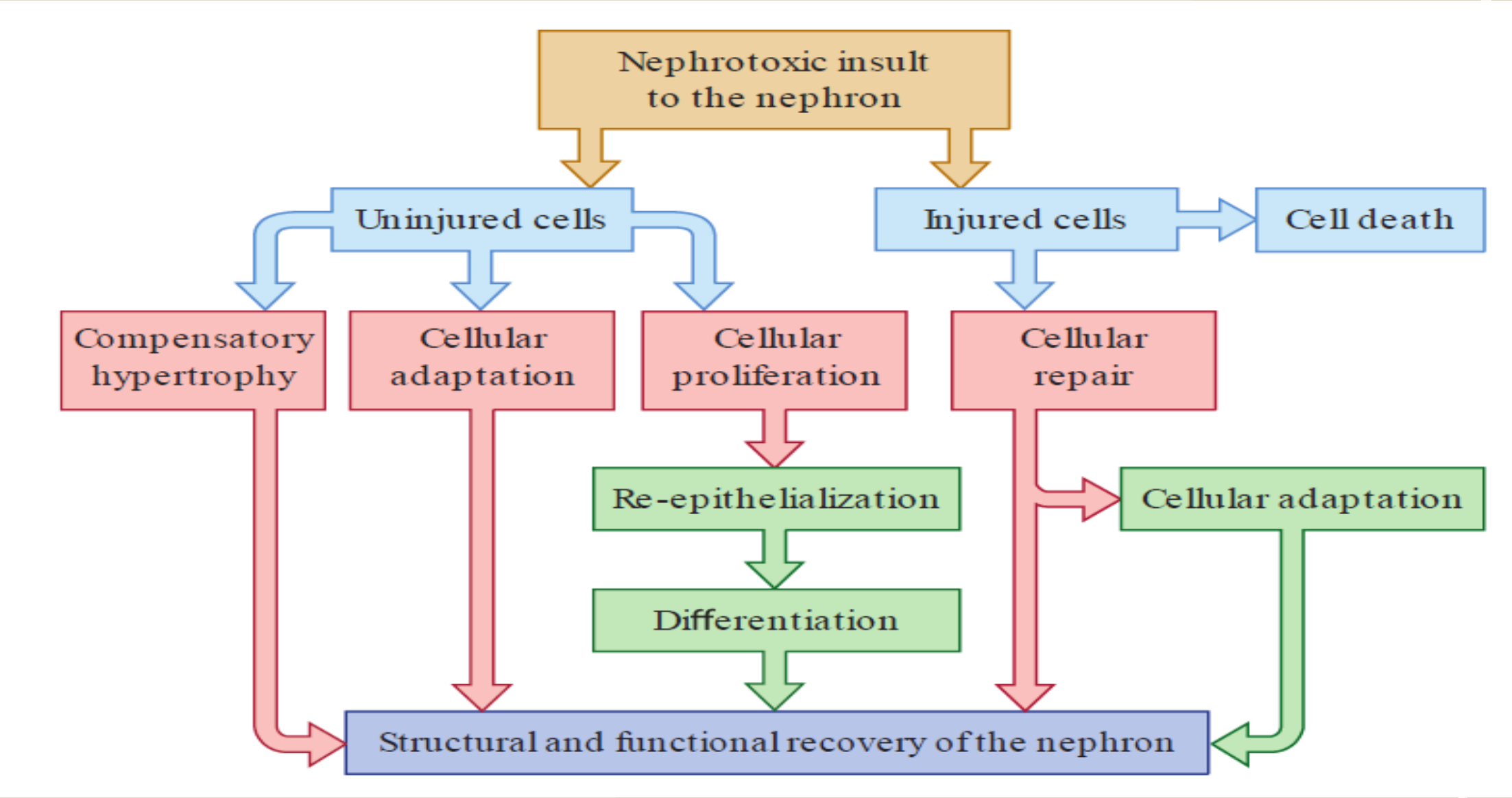
Mechanism of reduced GFR:



Adaptation Following Toxic Insult:

- The kidney has a remarkable ability to compensate for a loss in renal functional mass.
- After a population of cells is exposed to a nephron-toxicant:
- A fraction of the cells will be severely injured and will undergo cell death by apoptosis or necrosis.
- Cells that are nonlethally injured cells may undergo cell repair and/or adaptation, contributing to the recovery of the nephron.
- Cells that are uninjured and may undergo compensatory hypertrophy, adaptation, and proliferation.

Adaptation Following Toxic Insult



Toxic Responses of the Kidney:

2. Chronic Kidney Damage (CKD):

- Progressive 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, has been suggested to be a consequence of the glomerular hemodynamic response to renal injury.

- Pathogenesis of Chronic Kidney Damage

  - Following nephron loss, remnant viable nephrons increase glomerular pressures & flow, which leads to increased GFR to maintain whole-kidney GFR.
  - With time, these alterations are maladaptive, & focal glomerulosclerosis eventually develops which may lead to tubular atrophy & interstitial fibrosis.

Reasons for the Susceptibility of the Kidney to Toxicity

1. Unique physiologic and anatomic features of this organ.
2. They receive about 20–25% of the cardiac output.
3. The processes involved in forming concentrated urine also serve to concentrate potential toxicants in the tubular fluid.
4. A nontoxic concentration of a chemical in the plasma may reach toxic concentrations in the kidney.
5. Renal transport, accumulation, and metabolism of xenobiotics contribute significantly to the susceptibility of the kidney to toxic injury.

Reasons for the Susceptibility of the Kidney to Toxicity

6. The incidence and/or severity of chemically induced nephrotoxicity may be related to the sensitivity of the kidney to circulating vasoactive substances. (angiotensin II or ADH), whose actions are normally counterbalanced by the actions of increased vasodilatory prostaglandins, When prostaglandin synthesis is suppressed by NSAIDs, renal blood flow (RBF) declines markedly and AKI occurs due to the unopposed actions of vasoconstrictors.

Site Selective Injury
The glomerulus

- The glomerulus is the initial site of chemical exposure within the nephron.
- Chemicals alter glomerular permeability to proteins by altering the size- and charge-selective functions leading to proteinuria.
- (Cyclosporine, amphotericin B, and gentamicin) are chemicals that impair glomerular ultrafiltration and decrease GFR without significant loss of structural integrity.

Site Selective Injury proximal tubule

- the primary target of toxicant-induced renal injury including antibiotics, antineoplastics, halogenated hydrocarbons, mycotoxins, and heavy metals.
- It has a leaky epithelium, favoring the flux of compounds into proximal tubular cells.
- Tubular transport of organic anions and cations, low-molecular-weight proteins and peptides, GSH conjugates, and heavy metals is localized primarily to the proximal tubule.
- cytochrome P450 and cysteine conjugate β-lyase activity also are contributing factors to the enhanced susceptibility of the proximal tubule.
- nephrotoxicity requiring P450 and β-lyase-mediated bioactivation will most certainly be localized in the proximal tubule.

Site Selective Injury
The loop of Henle/collecting ducts

- Chemically induced injury to the more distal tubular structures, is an infrequent occurrence.
- Functional abnormalities 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.
- Each of these drugs induces ADH-resistant polyuria, suggesting that the concentrating defect occurs at the level of the medullary thick ascending limb and/or the collecting duct.

Site Selective Injury
The medulla/papilla

- The renal papilla is susceptible to the chronic injurious effects of abusive consumption of analgesics.
- High papillary concentrations of potential toxicants inhibition of vasodilatory prostaglandins compromise RBF to the renal medulla/papilla resulting in tissue ischemia.
- The initial target of abusive consumption of analgesics is the medullary interstitial cells, followed by degenerative changes in the medullary capillaries, loops of Henle, and collecting ducts.

Specific nephron-toxicants:

- Heavy metals:• Mercury• Cadmium
- Halogenated hydrocarbons:• Chloroform• Tetrafluoroethylene
- Therapeutic agents:

• Analgesics, e.g. Acetaminophen, & NSAIDs
• Antibiotics, e.g., Aminoglycosides
• Antifungal, Amphotericin B
• Immunosuppressant, Cyclosporine
• Antineoplastic agents, Cisplatin

Heavy Metals

- Many metals, including cadmium, chromium, lead, mercury, and platinum are nephrotoxic.

A. Mercury (Hg+2):

- Mercury is found as (elemental, organic compounds, inorganic mercurous, and mercuric salts) and exposure can happen to any of these from the environment
- salts of inorganic mercury produce a greater degree of renal injury than organic mercury compounds.
- The kidneys are the primary target organs for the accumulation of Hg2+, and the S3 segment of the proximal tubule is the initial site of toxicity.

Mercury (Hg+2)

- Mechanism of renal injury
  - their ability to bind to sulfhydryl groups of critical proteins (albumin, , glutathione, and cysteine)
  - Changes in mitochondrial morphology and function
  - Increased oxidative stress
- Mercury-induced renal injury can by managed by the administration of chelating agents (DMPS & DMSA)

Heavy Metals

B. Cadmium (Cd+2):

- Exposure to cadmium happens by contaminated food or inhaling fumes or dust containing cadmium (major route).

- Cadmium has a half-life of greater than 10 years in humans and thus accumulates in the body over time. Approximately 50 of the body burden of cadmium can be found in the kidney.

Cadmium (Cd+2)

- Cadmium produces proximal tubule dysfunction (S1 and S2 segments) and injury characterized by increases in urinary excretion of glucose, amino acids, calcium, and cellular enzymes.
- Metallothionein binds to cadmium thereby rendering it biologically inactive. This assumes that the unbound or " free concentration of cadmium is the toxic species. Once the renal metallothionein pool is saturated, free Cd 2 initiates injury.

Halogenated Hydrocarbons

- Halogenated hydrocarbons are a diverse class of compounds and are used extensively as chemical intermediates, solvents, and pesticides.
- Numerous toxic effects have been associated with acute and chronic exposure to halogenated hydrocarbons, including nephrotoxicity.

Chloroform:

- The primary cellular target is the proximal tubule, with no primary damage to the glomerulus or the distal tubule.
- Proteinuria, glucosuria, and increased BUN levels are all characteristic of chloroform-induced nephrotoxicity.
- The nephrotoxicity produced by chloroform is linked to its metabolism by renal cytochrome P450 and the formation of a phosgene.
- phosgene can react with sulfhydryl groups on protein, leading to covalent binding and injuriously reacting with cellular macromolecules.

Tetrafluoroethylene:

- Tetrafluoroethylene is conjugated with glutathione in the liver.

The GSH conjugate is secreted into the bile & small intestine where it is degraded to the cysteine S-conjugate, reabsorbed & transported to the kidney.

Although several metabolites are formed, the cysteine S-conjugate is the penultimate nephron-toxicant

Tetrafluoroethylene

- Following transport into the proximal tubule, the cysteine S- conjugate is a substrate for the cytosolic & mitochondrial forms of the enzyme cysteine conjugate β-lyase.

- The products of the reaction are ammonia, pyruvate, and active reactive thiol that is capable of binding covalently to cellular macromolecules causing cellular damage.
- The nephrotoxicity is characterized by proximal tubular necrosis, affecting the S3 segment,& functionally by an increase in urinary glucose, protein, & BUN.

Therapeutic Agents:

A. NSAIDs:

- such as aspirin, naproxen, indomethacin, and cyclooxygenase-2 inhibitors.
- Three different types of nephrotoxicity have been associated with NSAIDs administration.
  - High dose >> AKI within hours, is usually reversible upon withdrawal of the drug and is characterized by decreased RBF, GFR, and oliguria.
  - Chronic consumption of combination of NSAIDs/APAP >> more than 3 years results in an often irreversible form of nephrotoxicity known as analgesic nephropathy. The mechanism may result from chronic medullary/papillary ischemia secondary to renal vasoconstriction.

NSAIDs

- Exposure to NSAIDs for approximately 5 months >> The type of nephrotoxicity associated with NSAIDs is interstitial nephritis which is characterized by a diffuse interstitial edema with mild-to-moderate infiltration of inflammatory cells. If NSAIDs are
- discontinued, renal function improves in 1 to 3 months.

Aminoglycosides:

- such as gentamicin and amikacin, are powerful drugs for treating serious gram-negative infections.
- The therapeutic utility of aminoglycosides is limited by nephrotoxicity, ototoxicity, and neuromuscular junction blockade.
- Aminoglycoside nephrotoxicity is characterized by proximal tubular necrosis, proteinuria, and a profound decline in glomerular filtration rate.
- Renal dysfunction by aminoglycosides is characterized by a non-oliguric renal failure with reduced GFR and increased serum creatinine and BUN.

Acetaminophen:

- Large doses of acetaminophen [acetyl-para-aminophenol (APAP)] are commonly associated with hepatoxicity. However, large doses of APAP can also cause nephrotoxicity in humans & animals.
- APAP nephrotoxicity is characterized by:
- proximal tubular necrosis with increases in BUN & plasma creatinine;
- decreases in glomerular filtration rate(GFR)& clearance of para-amino hippurate(PAH); decrease RPF.
- increases in the fractional excretion of water, sodium, and potassium.
- increases in urinary glucose, protein, & brush-border enzymes.

Amphotericin B

- a polyene antifungal agent used in the treatment of systemic mycoses caused by opportunistic fungi, that has been associated with distal tubular injury
- Clinical utility of amphotericin B is limited by its nephrotoxicity, characterized functionally by polyuria resistant to antidiuretic hormone administration, hypokalemia, and mild renal tubular acidosis.
- functional integrity of the glomerulus and of the proximal and distal portions of the nephron is impaired, leading to decreases in RBF and GFR.

Cyclosporine

- Acute renal dysfunction is characterized by dose-related decreases in RBF and GFR, increases in BUN, and serum creatinine.
- The decrease in RBF and GFR is related to marked vasoconstriction induced by cyclosporine.
- Acute vasculopathy or thrombotic microangiopathy following cyclosporine treatment affects arterioles glomerular capillaries, without an inflammatory component.

Cyclosporine

- chronic nephropathy with interstitial fibrosis, and tubular atrophy.
- Histologic changes are profound they are characterized by arteriolopathy and segmental glomerular sclerosis.
- These lesions may not be reversible if cyclosporine therapy is discontinued and may result in end-stage renal disease.

Cisplatin

Cisplatin nephrotoxicity includes acute and chronic renal failure, renal magnesium wasting, and polyuria.

Early effects of cisplatin are decreases in RBF, and polyuria that are concurrent with increased electrolyte excretion.

Patients treated with cisplatin regimens permanently lose 10% to 30% of their renal function.

The nephrotoxicity of cisplatin can be grouped as:

1) tubular toxicity.
2) vascular damage.
3) glomerular injury.
4) interstitial injury.

TABLE 14–1 Mechanisms of chemically induced acute kidney injury.

Prerenal	Vasoconstriction	Crystalluria	Tubular Toxicity	Endothelial Injury	Glomerulopathy	Interstitial Nephritis
Diuretics Angiotensin receptor antagonists Angiotensin converting enzyme inhibitors Antihypertensive agents	Nonsteroidal anti-inflammatory drugs Radiocontrast agents Cyclosporine Tacrolimus Amphotericin B	Sulfonamides Methotrexate Acyclovir Triamterene Ethylene glycol Protease inhibitors	Aminoglycosides Cisplatin Vancomycin Pentamidine Radiocontrast agents Heavy metals Haloalkane- and Haloalkene-cysteine conjugates	Cyclosporine Mitomycin C Tacrolimus Cocaine Conjugated estrogens Quinine	Gold Penicillamine Nonsteroidal anti-inflammatory drugs	Antibiotics Nonsteroidal anti-inflammatory drugs Diuretics

Thank You