Al Mustaqbal University College
Department of Pharmacy
4th stage
Toxicology

Lect. 4

Toxic Responses of The Kidney part1

Qassim A Zigam

Background

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 extracellular fluid volume, electrolyte composition, and acid-base balance.
3. Synthesizes and releases hormones such as renin and erythropoietin
4. Metabolizes vitamin D3 to the active 1,25-dihydroxy vitamin D3 form.

Background

- A toxic insult to the kidney therefore could disrupt any or all of these functions and could have profound effects on total body metabolism.
- Fortunately, the kidneys are equipped with a variety of detoxification mechanisms and have considerable functional reserve and regenerative capacities.

Background

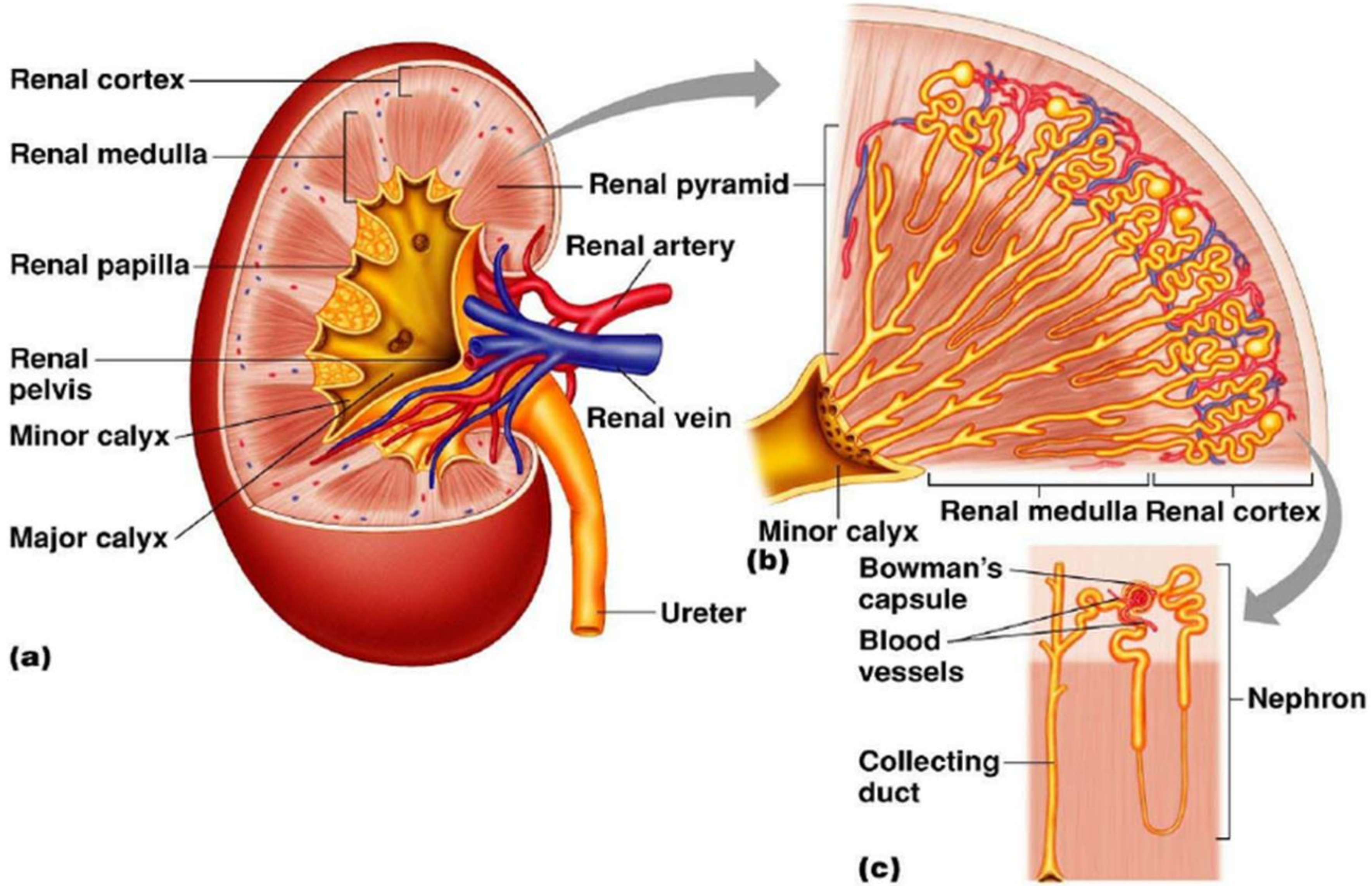
- Nonetheless, the nature and severity of the toxic insult may be such that these detoxification and compensatory mechanisms are overwhelmed, and kidney injury ensues.
- The outcome of renal failure can be profound; permanent renal damage may result, requiring chronic dialysis treatment or kidney transplantation.

FUNCTIONAL ANATOMY

- Gross examination of a sagittal section of the kidney reveals three clearly demarcated anatomic areas: the cortex, medulla, and papilla
- The cortex constitutes the major portion of the kidney and receives a higher percentage (90%) of blood flow compared to the medulla (about 6% to 10%) or papilla (1% to 2%).

FUNCTIONAL ANATOMY

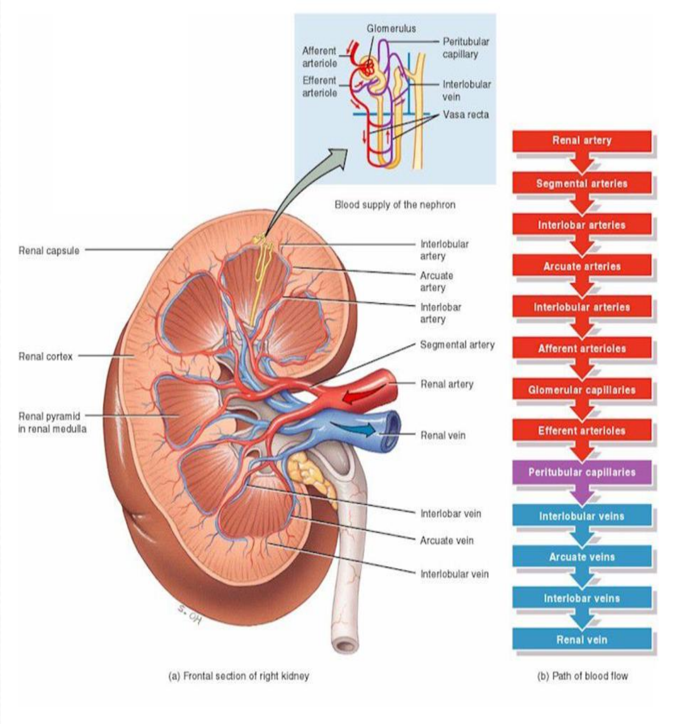
- Thus, when a blood-borne toxicant is delivered to the kidney, a high percentage of the material will be delivered to the cortex and will have a greater opportunity to influence cortical rather than medullary or papillary functions.
- However, medullary and papillary tissues are exposed to higher luminal 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.


Renal cortex
Renal medulla
Renal papilla
Renal pelvis
Minor calyx
Major calyx
Renal pyramid
Renal artery
Renal vein
Ureter
(a)
Minor calyx
Renal medulla
Renal cortex
(b)
Bowman's capsule
Blood vessels
Collecting duct
Nephron
(c)

FUNCTIONAL ANATOMY

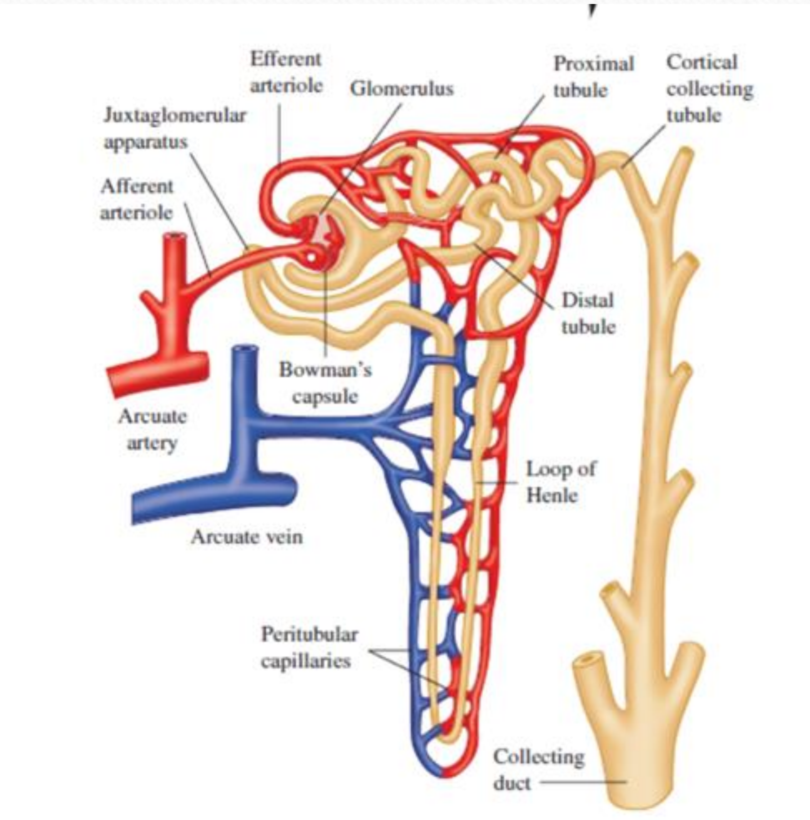
- The ***functional unit of the kidney, the nephron***, may be considered in three portions:

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



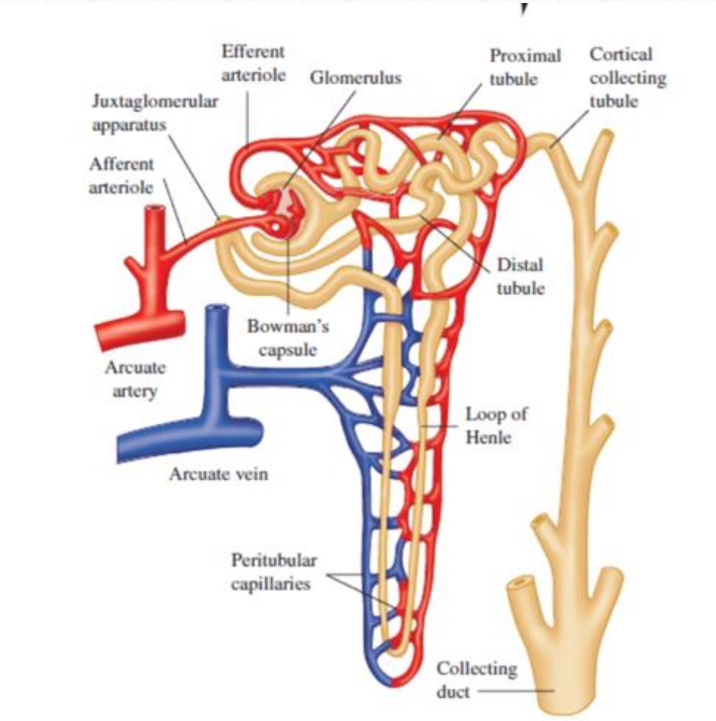
Renal Vasculature

- The renal artery branches successively into interlobar, arcuate, and interlobular arteries.
- The last of these give rise to the afferent arterioles, which supply the glomerulus blood then leaves the glomerular capillaries via the efferent arteriole.



Renal Vasculature

- Both the afferent and efferent arterioles, arranged in a series before and after the glomerular capillary tuft respectively,
- They are ideally situated to control glomerular capillary pressure and glomerular plasma flow rate.

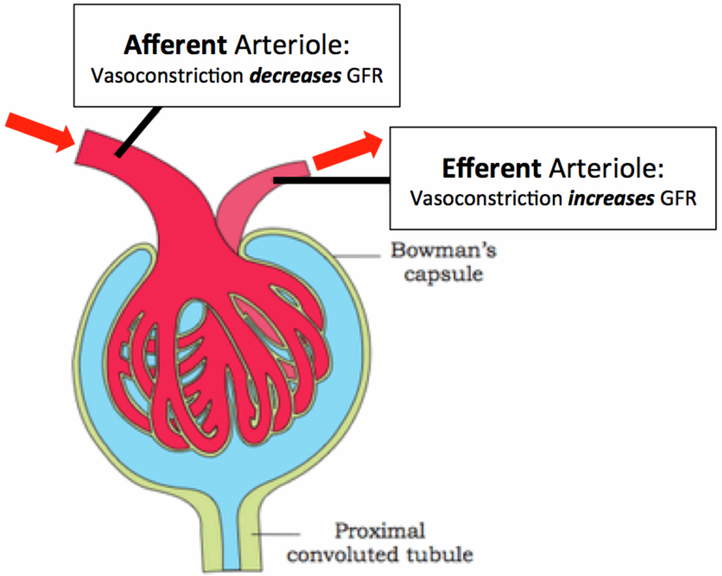


Renal Vasculature

- Indeed, these arterioles are innervated by the sympathetic nervous system and contract in response to:

✓ Nerve stimulation, Angiotensin II, Vasopressin, Endothelin, Adenosine, Norepinephrine.

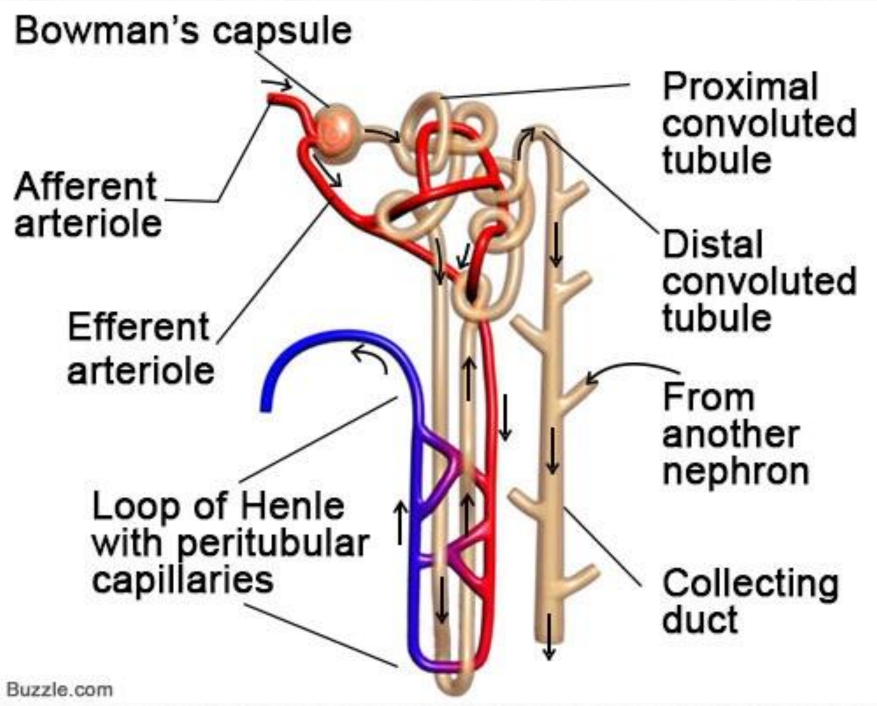
- Decreasing glomerular filtration rate and renal blood blow.



Microvascular modulation of glomerular filtration rate (GFR)

Renal Vasculature

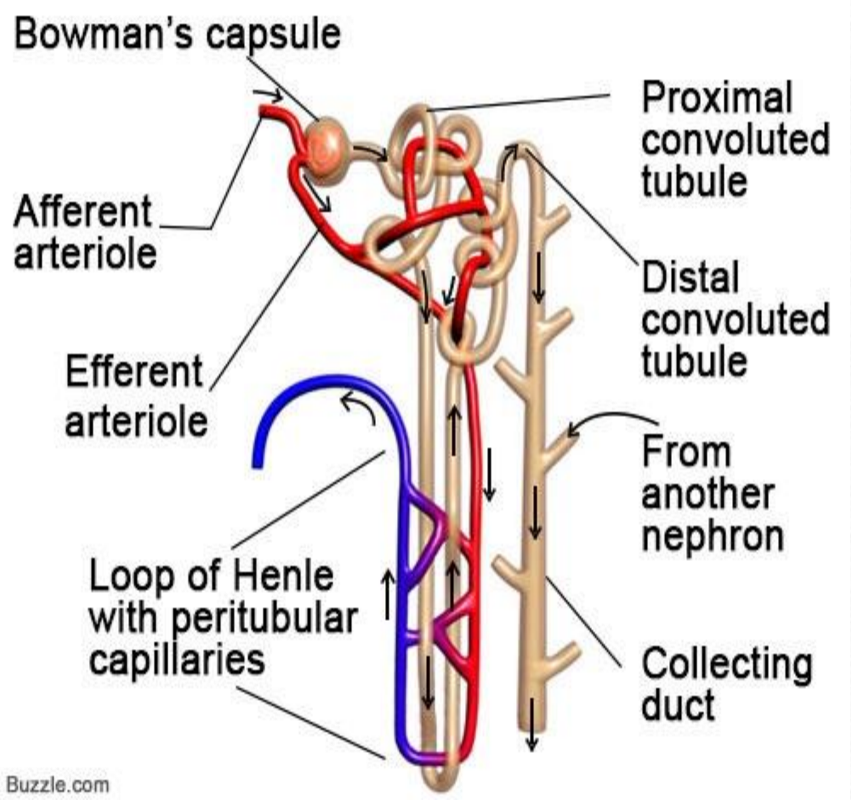
- The efferent arterioles draining the cortical glomeruli branch into a peritubular capillary network, whereas those draining the juxtamedullary glomeruli form a capillary loop, the vasa recta, supplying the medullary structures.



Renal Vasculature

- These postglomerular capillary loops provide:

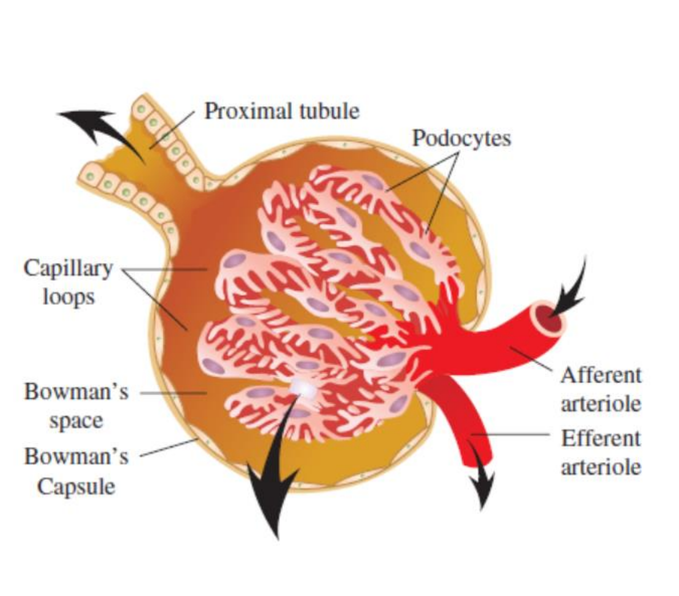
1. An efficient arrangement for delivery of nutrients to the postglomerular tubular structures
2. Delivery of wastes to the tubule for excretion
3. Return of reabsorbed electrolytes, nutrients, and water to the systemic circulation



Glomerulus

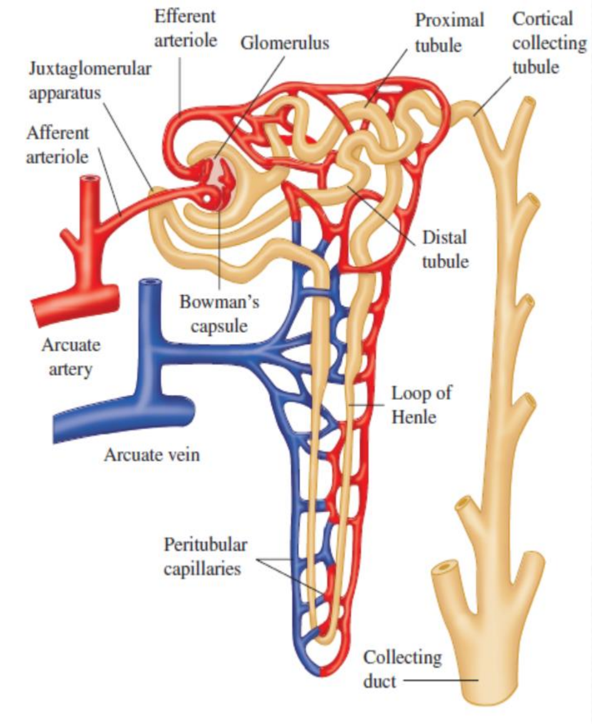
- The glomerulus is a complex, specialized capillary bed composed primarily of

1. Endothelial cells that are characterized by an attenuated and fenestrated cytoplasm,
2. Visceral epithelial cells characterized by a cell body (podocyte) from which many trabeculae and pedicles (foot processes) extend,
3. Glomerular basement membrane (GBM), which is a trilamellar structure sandwiched between the endothelial and epithelial cells



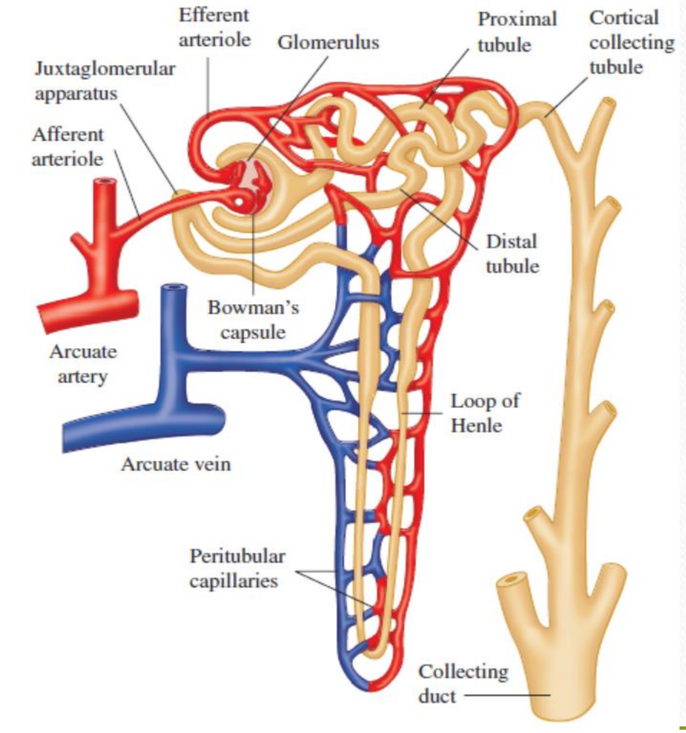
Proximal Tubule

- The proximal tubule consists of three discrete segments: the S1 (pars convoluta), S2 (transition between pars convoluta and pars recta), and S3 (the pars recta) segments.
- The proximal tubule is the workhorse of the nephron, as it reabsorbs approximately 60% to 80% of solute and water filtered at the glomerulus.
- Toxicant-induced injury to the proximal tubule, therefore, will have major consequences for water and solute balance.



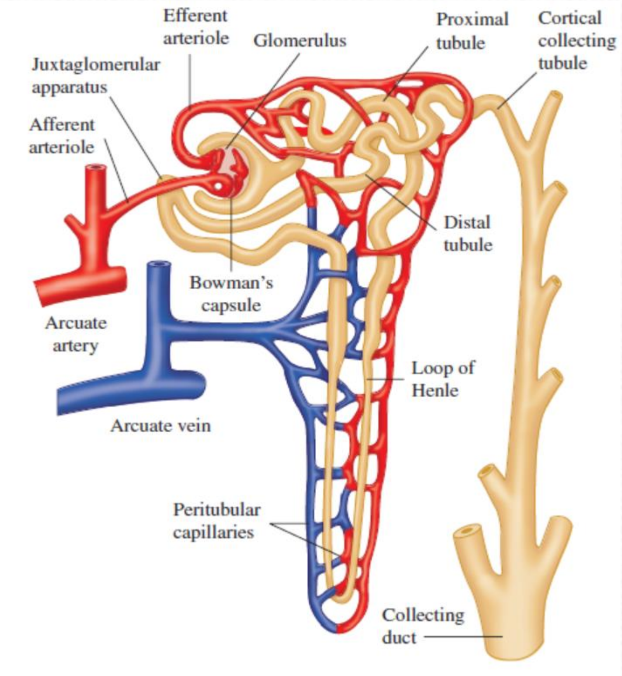
Loop of Henle

- The thin descending and ascending limbs 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.



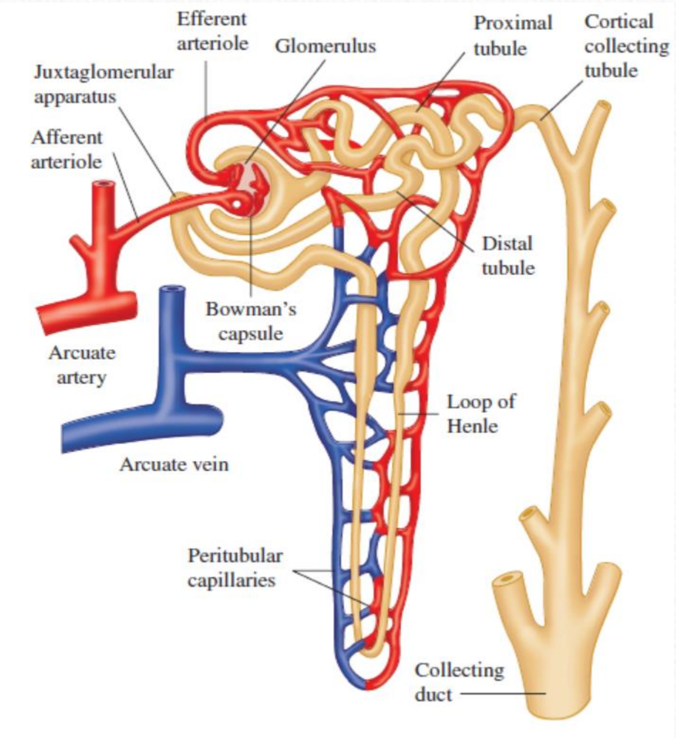
Loop of Henle

- The thin ascending limb is relatively impermeable to water and urea, and Na^+ and Cl^- are reabsorbed by passive diffusion.
- The thick ascending limb is impermeable to water, and active transport of Na^+ and Cl^- is mediated by the Na^+/K^+-2Cl^- cotransport mechanism, with the energy provided by the Na^+, K^+-ATPase.



Distal Tubule and Collecting Duct

- The late distal tubule, cortical collecting tubule, and medullary collecting duct perform the final regulation and fine-tuning of urinary volume and composition.
- The remaining Na+ is reabsorbed in conjunction with K+ and H+ secretion in the late distal tubule and cortical collecting tubule.



PATHOPHYSIOLOGIC RESPONSES OF THE KIDNEY

- Acute Kidney Injury
- Chronic Kidney Disease

Acute Kidney Injury

- It is ne 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

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 loss resulting in back leak; renal vasculature damage; interstitial nephritis)

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 back leak of glomerular filtrate and a decrease in GFR.

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 GFR.
- If a chemical causes intrarenal inflammation, then tubular and vascular damage may follow with decreases in GFR.

Acute Kidney Injury

It has been estimated that

- prerenal factors are responsible for AKI in 55% to 60% of patients,
- intrarenal factors are responsible for AKI in 35% to 40% of patients,
- postrenal factors are responsible for AKI in less than 5% of patients

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, may be 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.

TANK YOU FOR YOUR ATTENTION