Toxicology

Toxic Responses of the kidney

Lec. 4

4th stage

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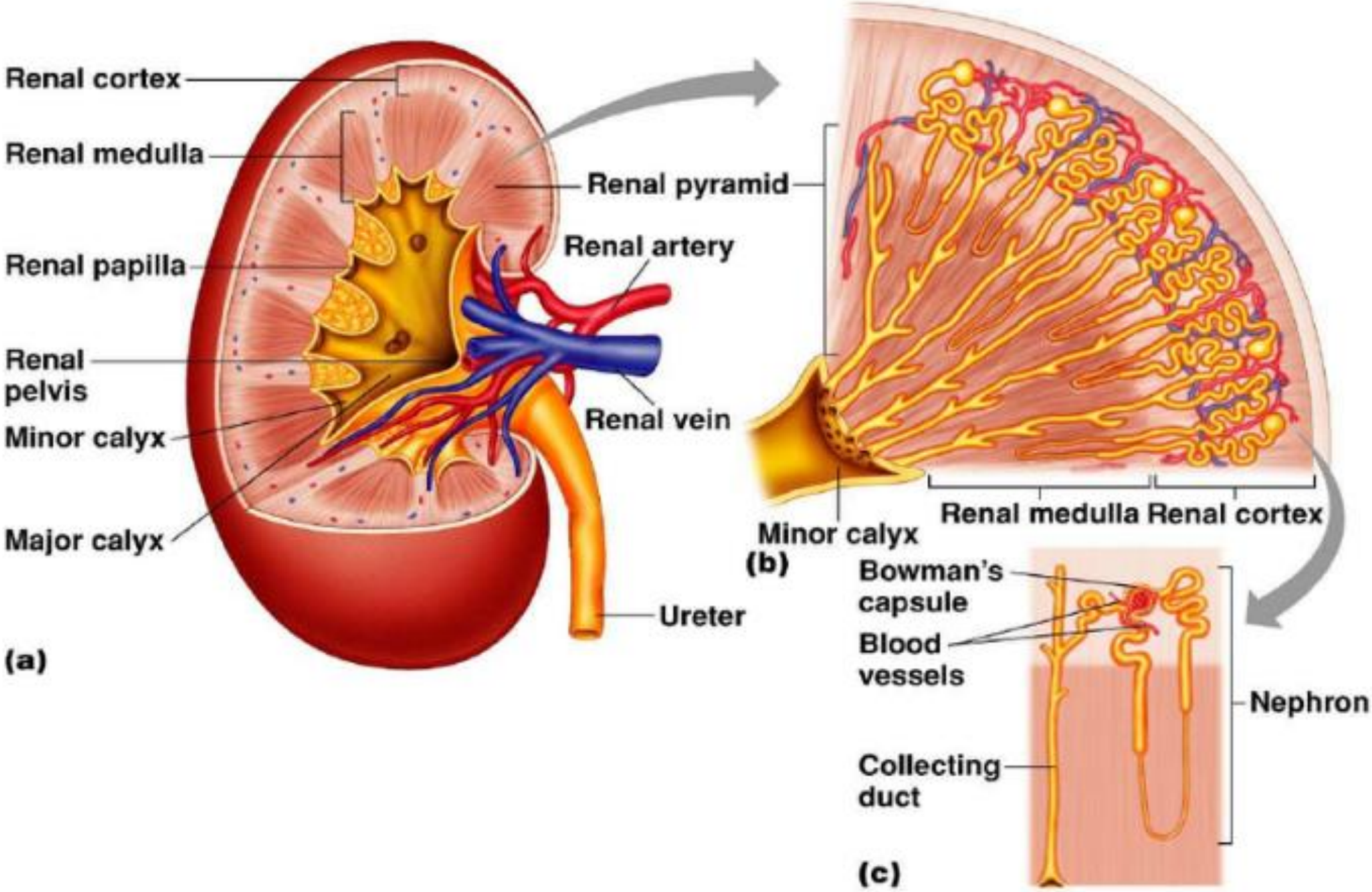
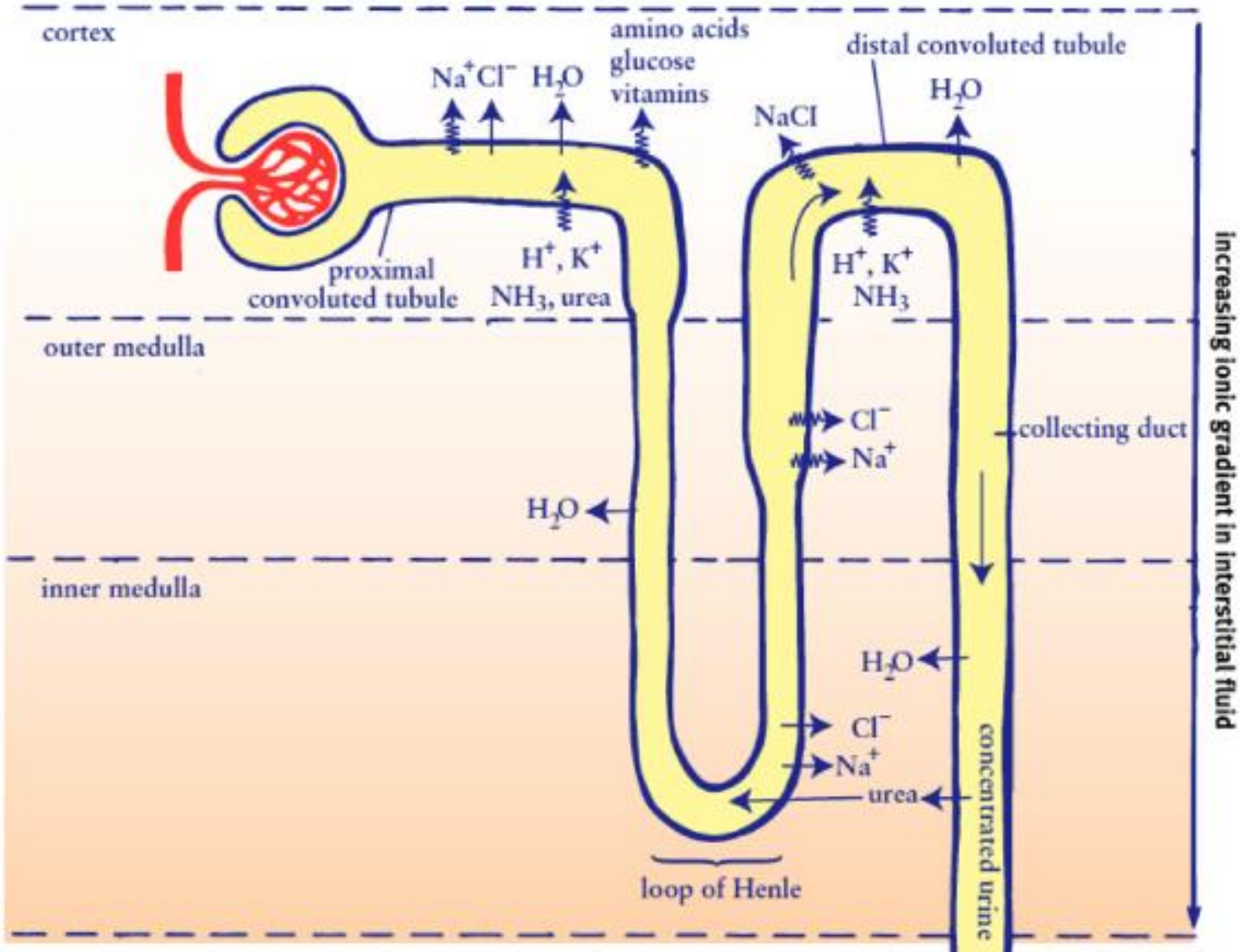
- **Nephrotoxicity** can be a potentially **serious complication** of drug therapy **or** chemical exposure.
- **Although** in most instances the **mechanisms** mediating nephrotoxicity are **unclear.**
- **Susceptibility** of the kidney to toxic injury **appears** to be *related*, *at least in part*, to the **complexities** of **renal anatomy** and **physiology**.

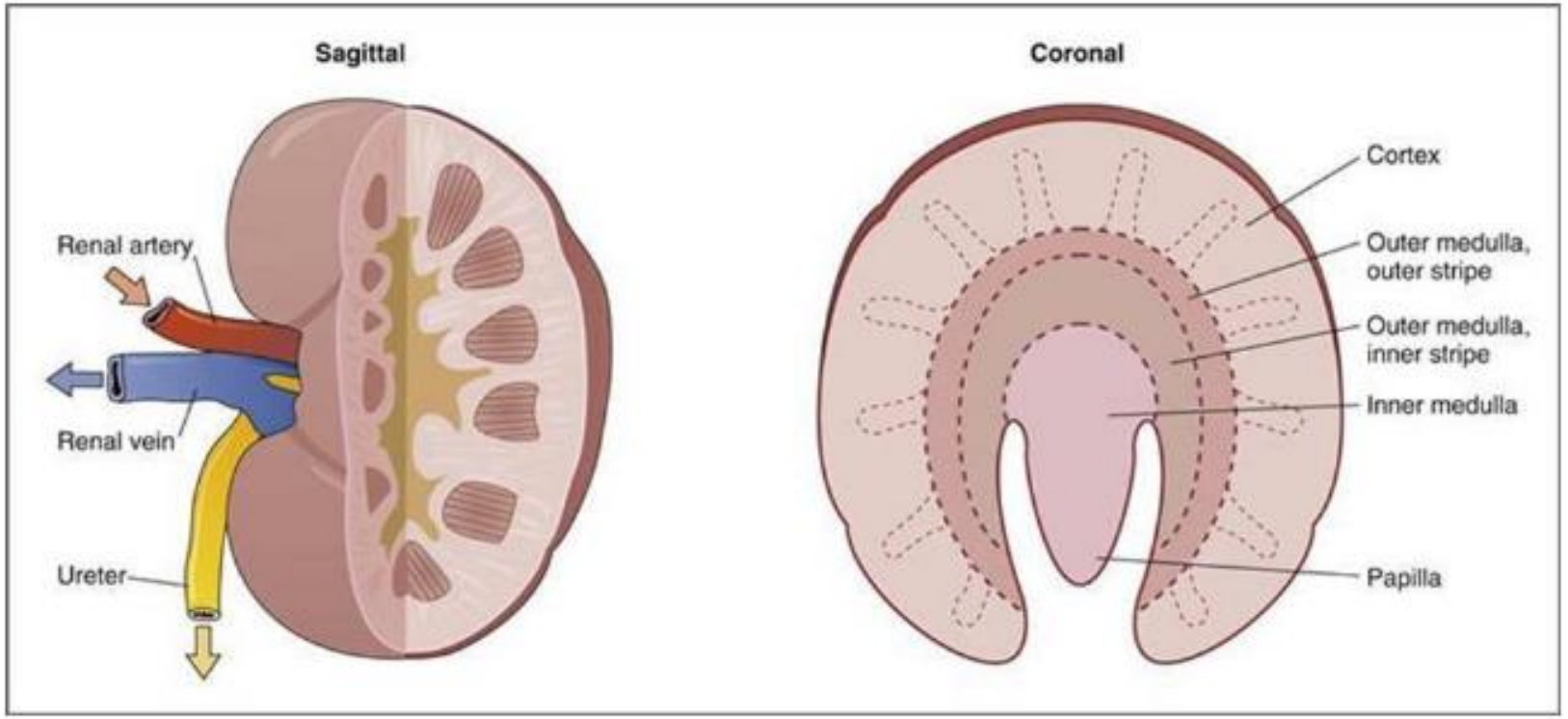

Renal cortex
Renal medulla
Renal papilla
Renal pelvis
Minor calyx
Major calyx
Renal pyramid
Renal artery
Renal vein
Ureter
(a)
Minor calyx
Renal medulla
Renal cortex
(b)
Bowman's capsule
Blood vessels
Collecting duct
Nephron
(c)


cortex
amino acids
glucose
vitamins
distal convoluted tubule
Na^+Cl^- H_2O
NaCl
H_2O
proximal
convoluted tubule
H^+, K^+
NH_3, urea
H^+, K^+
NH_3
outer medulla
Cl^-
Na^+
collecting duct
H_2O
inner medulla
H_2O
Cl^-
Na^+
urea
concentrated urine
loop of Henle
increasing ionic gradient in interstitial fluid

Structural Organization of the Kidney

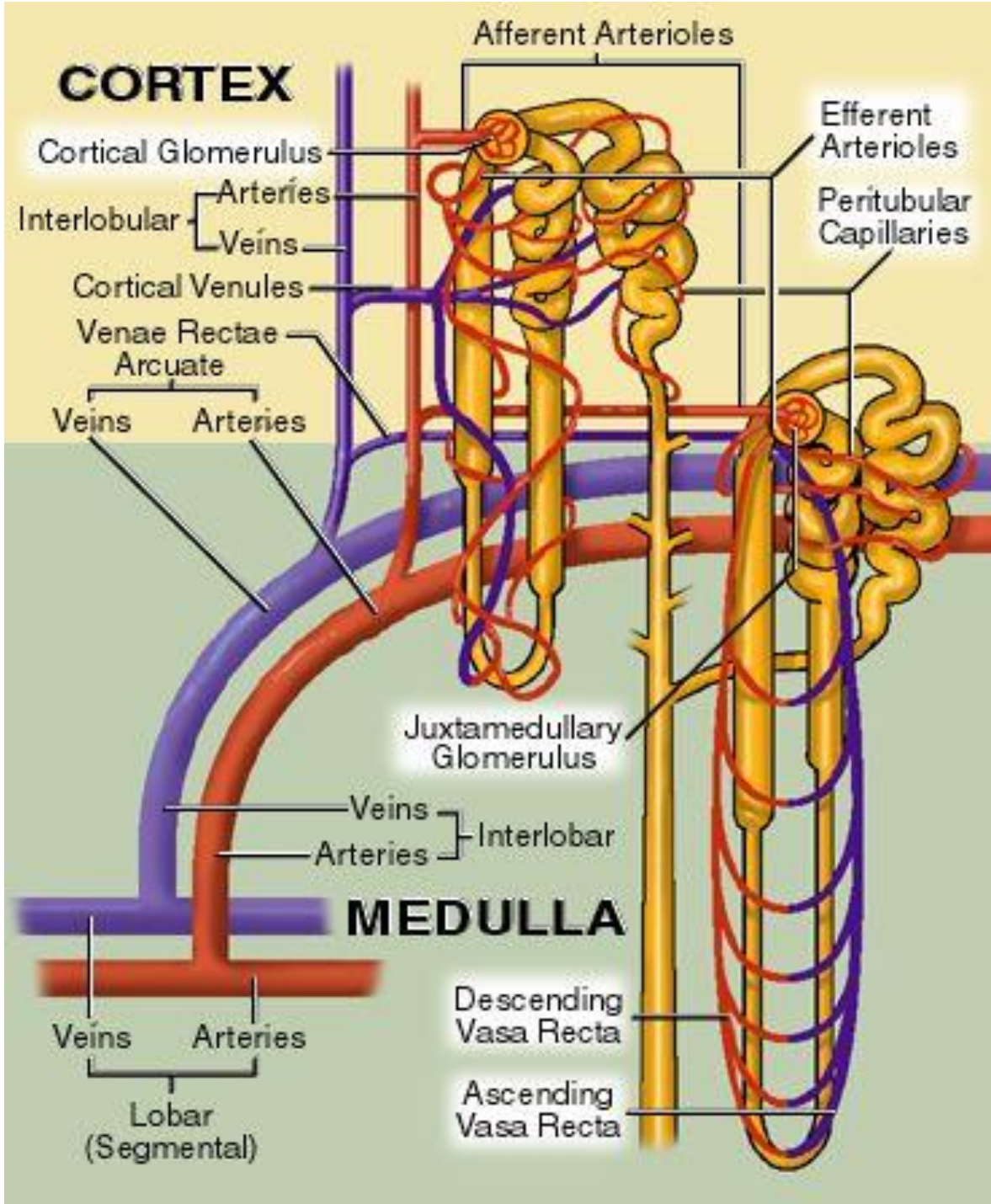
❖**Three major anatomical areas of the kidney are apparent:**

- cortex,
- medulla,
- and papilla.

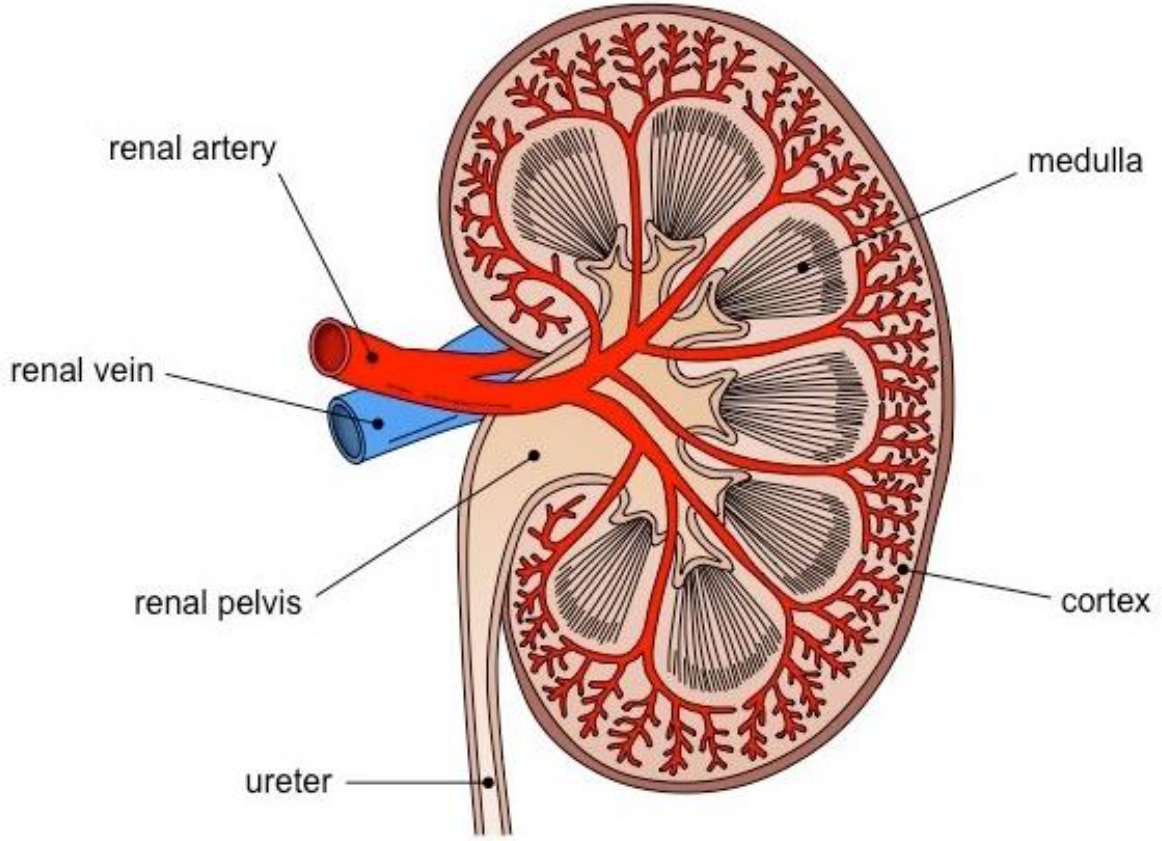


1- cortex

- The cortex is the **outermost portion** of the kidney.
- And **contains** *proximal* and distal tubules, glomeruli, and peritubular capillaries.
- **Cortical blood flow** is **high** relative to cortical volume and oxygen consumption.
- the **cortex receives** about 90% of total renal blood flow.



A blood - borne toxicant will be delivered preferentially to the **renal cortex** and therefore have a greater potential to influence cortical, *rather than medullary or papillary*, functions.



2- The renal medulla

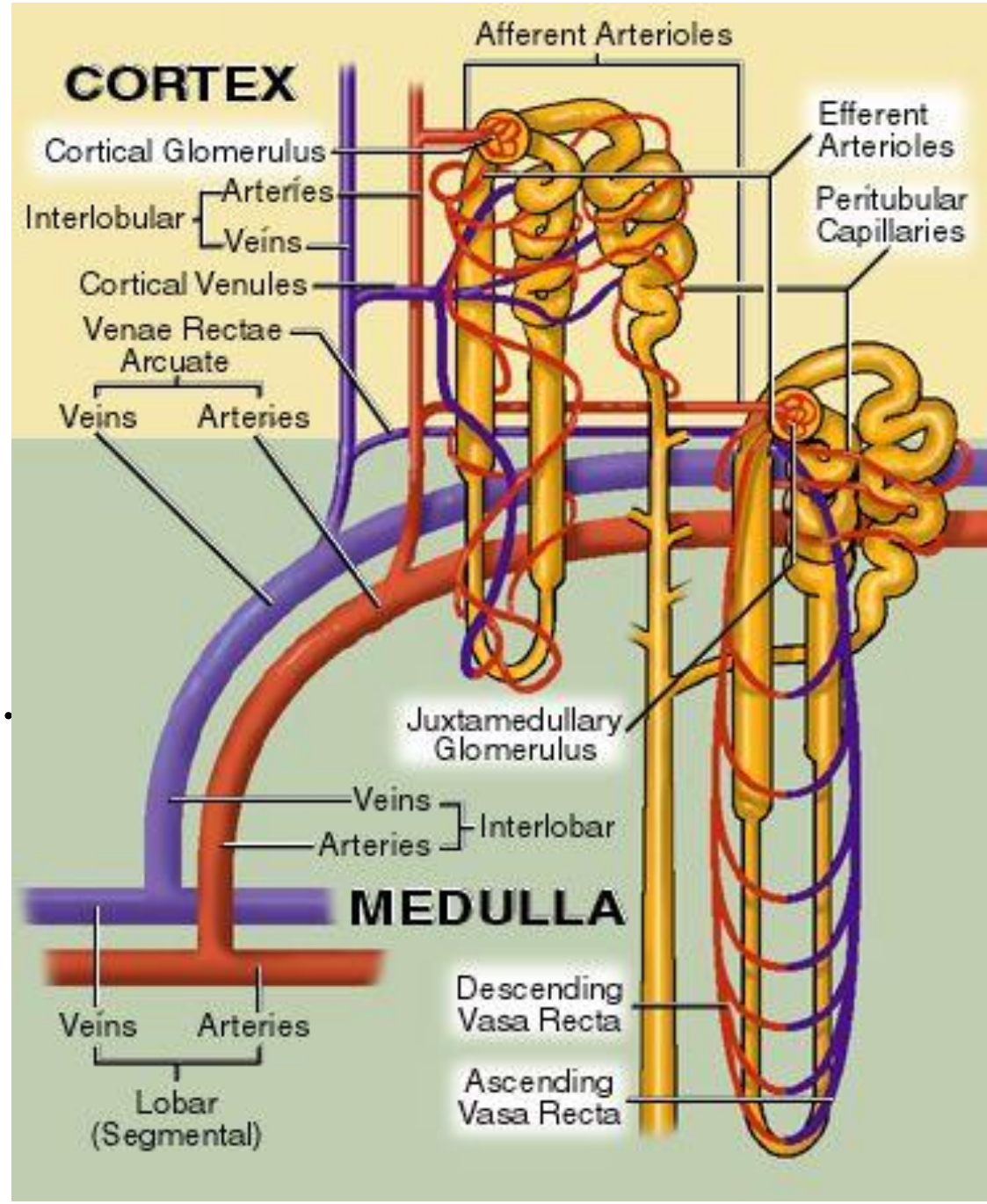
❖It is the **middle portion** of the kidney.

❖**Consists of:-**

- *loops of Henle*, vasa recta, **and** collecting ducts.

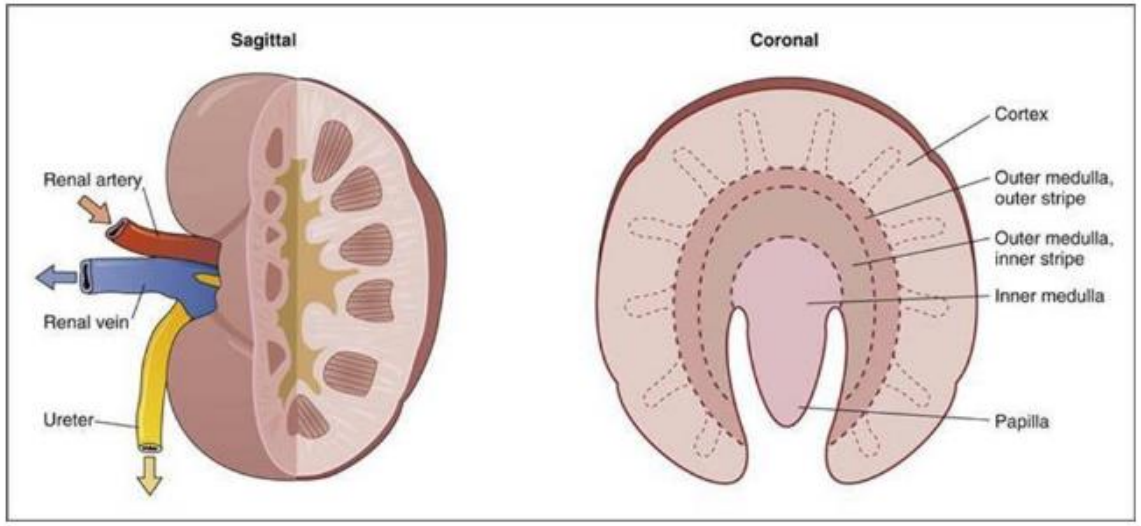
❖Medullary blood flow (about 6% of total renal blood flow)

❖is considerably **lower** than cortical flow.



- However, by virtue of its **countercurrent** arrangement between tubular and vascular components, the **medulla** may be exposed to **high concentrations of toxicants** within tubular and interstitial structures.

3- The papilla



- The smallest anatomical portion of the kidney.
- Papillary tissue consists primarily of **terminal portions** of the collecting duct system and the vasa recta.
- Papillary blood flow is low relative to *cortex* and *medulla*; less than **1%** of total renal blood flow reaches the papilla.

- **However**, **tubular fluid** is **maximally concentrated**, and the **volume of luminal fluid** is **maximally reduced** **within** the **papilla**.
- **Potential toxicants** *trapped in tubular lumens* may **attain extremely high concentrations** **within** the **papilla** during the **process of urinary concentration.**

➢ **High intraluminal concentrations of** potential toxicants may result in diffusion of these chemicals into **papillary tubular epithelial** and/or **interstitial cells**, leading to **cellular injury**.

Specific functions of the kidneys

1. **Regulation** of **extracellular fluid volume**
2. **Regulation** of **inorganic electrolyte** concentration in the extracellular fluid
3. **Regulation** of the **osmolarity** of the extracellular fluid
4. **Removal** of **metabolic waste** products
5. **Excretion** of **foreign** compounds
6. **Maintenance** of **acid-base balance**
7. **Hormone** and **enzyme** **production**

1- Regulation of extracellular fluid volume

❖It is more specifically **regulate** **plasma volume.**

❖It is important in the **long-term regulation** of **blood pressure**.

- **An increase** in plasma volume leads to an **increase** in **blood pressure.**
- **A decrease** in plasma volume leads to a **decrease** in **blood pressure**.

➢Plasma volume is regulated primarily by ***altering*** **the excretion** of **sodium** in the **urine.**

2- Regulation of inorganic electrolyte concentration in the extracellular fluid

Inorganic electrolytes regulated by the kidneys include

chloride, potassium, calcium, magnesium, sulfate, and

phosphate.

3- Regulation of the osmolarity of the extracellular fluid

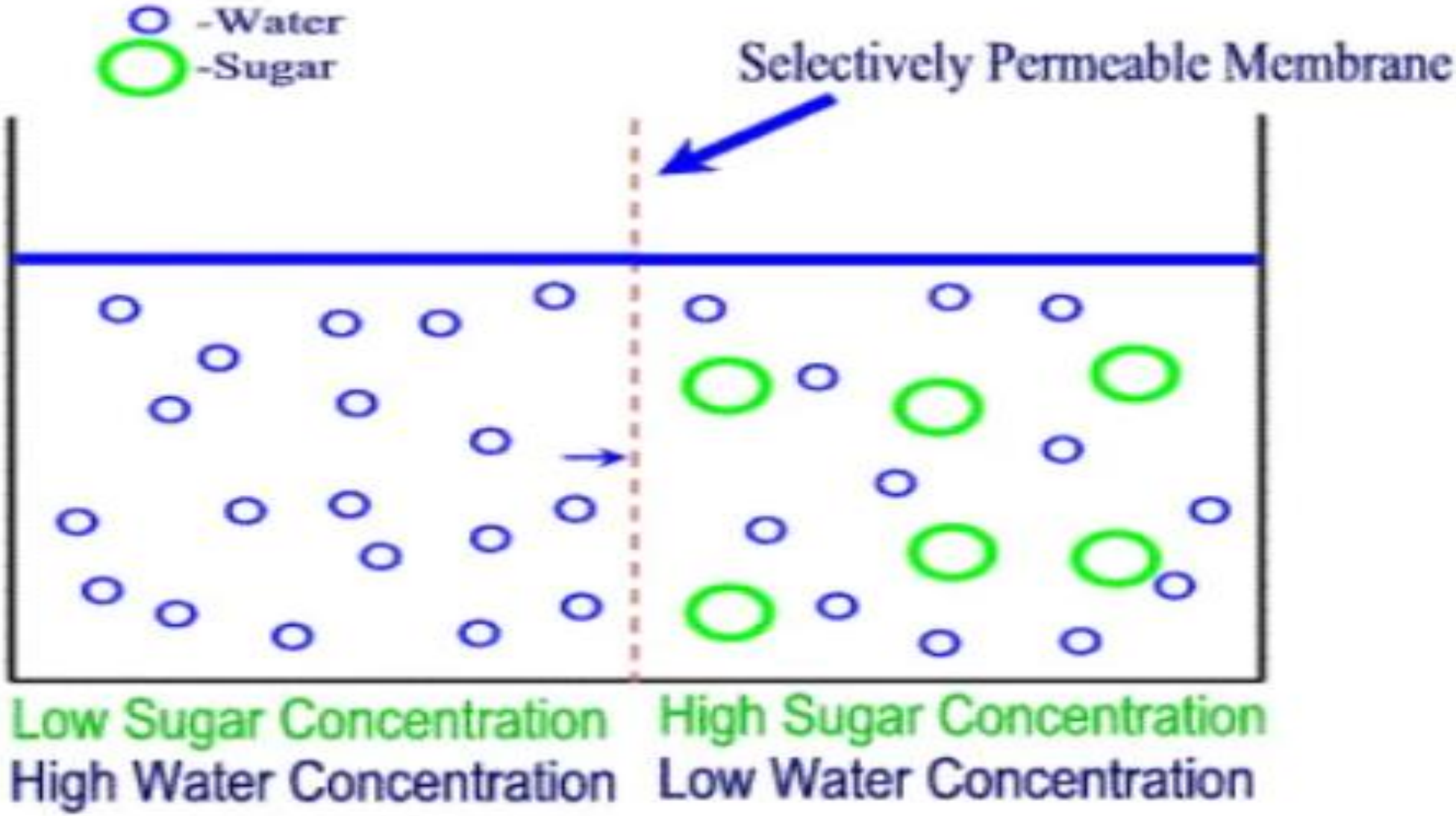
❖This regulation is specifically to **plasma osmolarity**.

❖Diffusion of water down its concentration called **osmosis**.

➢The maintenance of plasma osmolarity close to **290 mOsm** ***prevents*** any **unwanted** movement of fluid **in** or **out** of the **body's cells**.

- An **increase** in **plasma osmolarity** causes cellular dehydration.
- A **decrease** in **plasma osmolarity** causes cellular swelling and possibly lysis.

Osmosis


-Water
-Sugar
Selectively Permeable Membrane
Low Sugar Concentration
High Water Concentration
High Sugar Concentration
Low Water Concentration

4- Removal of metabolic waste products

- **The major excretory organs in the body**, the **kidneys** are **responsible for the** ***removal of many metabolic waste products.***
- **These include:**

➢ ***urea*** and ***uric acid***, which are *nitrogenous waste* products of *amino acid* and *nucleic acid* metabolism, **respectively**

➢ ***creatinine***, a breakdown product of *muscle metabolism*; and

➢ ***urobilinogen***, a metabolite of *hemoglobin* that gives urine its **yellow color**.

5- Excretion of foreign compounds

❖*Foreign compounds* excreted by the kidneys include:

- ***Drugs*** (e.g., penicillin, nonsteroidal anti-inflammatory drugs)
- ***food additives*** (e.g., saccharin, benzoate)
- ***Pesticides***

➢Other ***exogenous*** nonnutritive materials that have entered the body.

If allowed to accumulate, these substances become quite **toxic.**

6- Maintenance of acid-base balance

- **Along with the respiratory system, the renal system *maintains acid-base balance* by:**
- Altering the **excretion of hydrogen ions** and **bicarbonate ions** in the urine.

❖**When the extracellular fluid becomes acidic and pH decreases, then the kidneys act:**

1. **excrete H+ ions**
2. **conserve HCO3 – ions.**

❖**When the extracellular fluid becomes alkaline and pH increases, then the kidneys act:**

1. conserve H+ ions
2. excrete HCO3 – ions.

- **Normally**, the **pH** of the arterial blood is **7.4.**

7- Hormone and enzyme production

- Although the **kidneys** are not ***considered endocrine glands***, they are involved in ***hormone*** *and* ***enzyme production.***

➢**Erythropoietin hormone**

➢Renin

➢***25-OH Vit.D-1 alpha-hydroxylase***

Erythropoietin hormone

- The kidneys secrete ***erythropoietin,*** which stimulates the production of **red blood** cells by ***hematopoietic stem*** *cells* in the **bone marrow,.**
- One important **stimulus** for **erythropoietin** secretion by the kidneys is ***hypoxia***.
- In people with severe **kidney disease** or who have had their kidneys removed and have been placed on hemodialysis, **severe anemia develops** as a result of **decreased erythropoietin production**.

Renin

- The kidneys also contribute to **short-term arterial pressure regulation** by secreting hormones and vasoactive factors or substances (e.g., ***renin***) that lead to the **formation** of *vasoactive products* (e.g., **angiotensin II**).

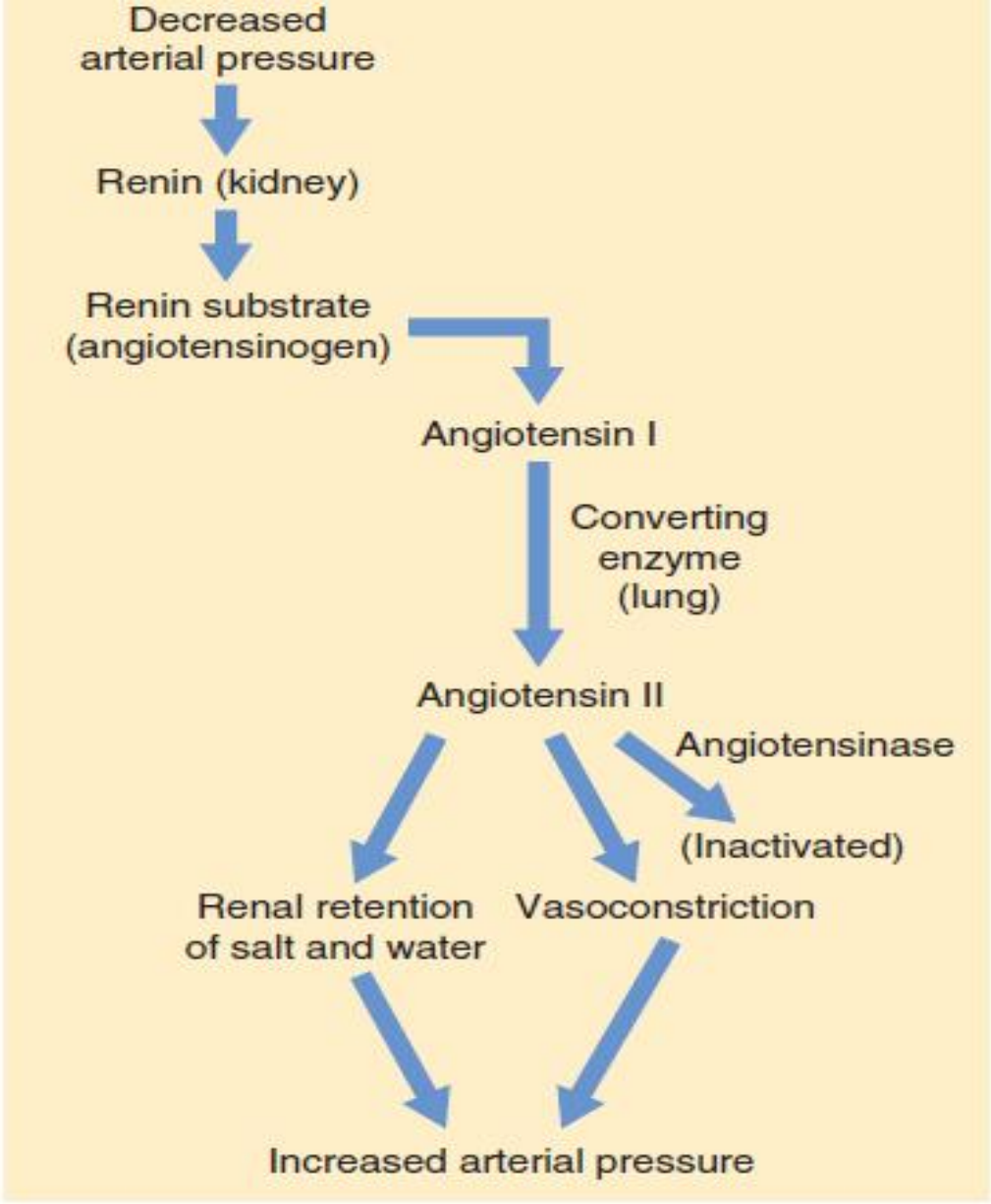


Figure 19-10. The renin-angiotensin vasoconstrictor mechanism f
arterial pressure control.

25-OH Vit.D-1 alpha-hydroxylase

- The **kidneys** produce the active form of **vitamin D, 1,25-dihydroxyvitamin D^3** *(calcitriol),* by **hydroxylating** this vitamin at the "number 1" position.

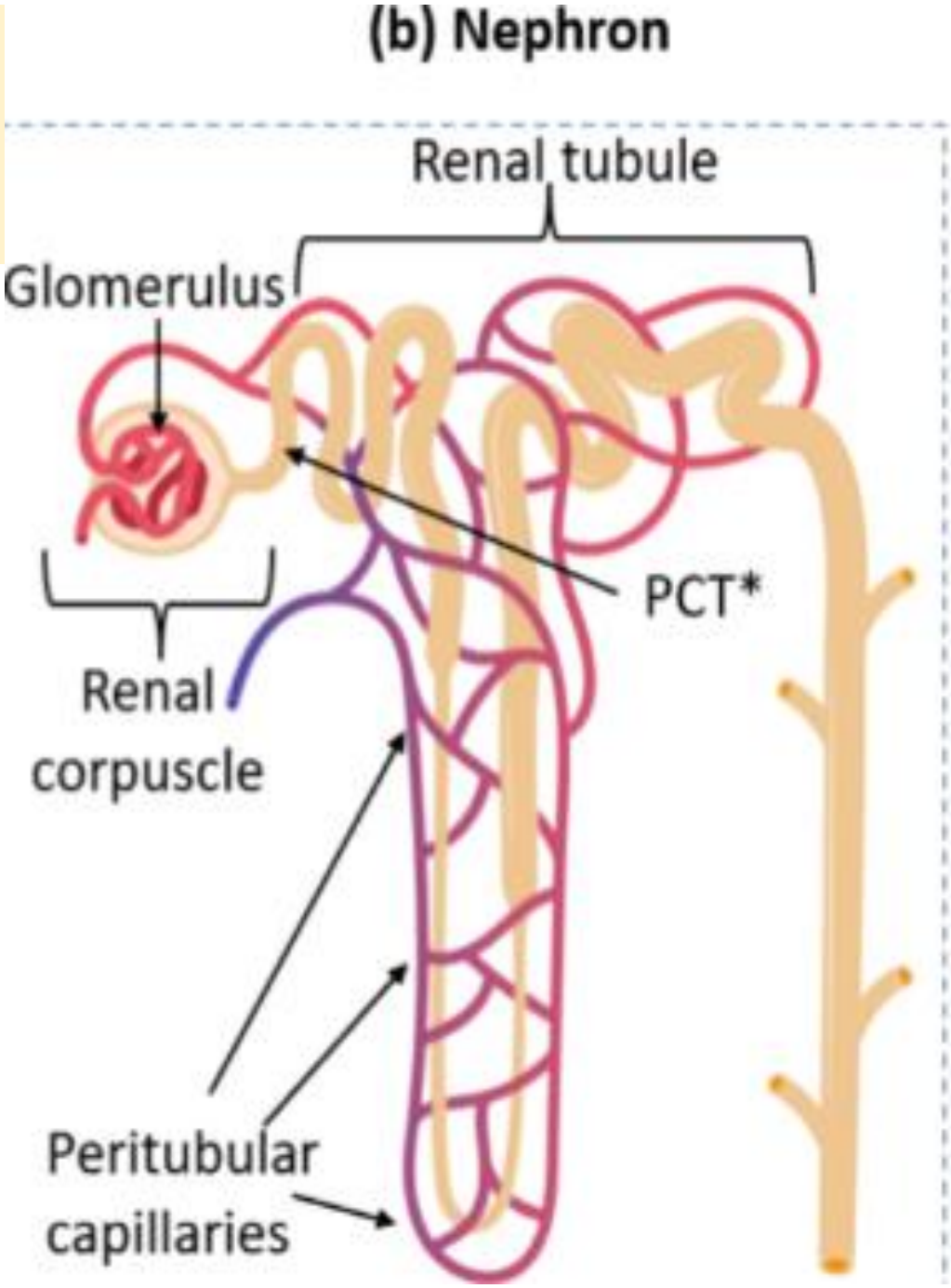
- **Calcitriol** is essential for normal **calcium deposition** in **bone** and **calcium reabsorption** by the **gastrointestinal tract**.

Functional anatomy of the kidneys

- **The functional unit of the kidney is the *nephron***
- **There are well over 1 million nephrons in each kidney.**
- ***The nephron has two components:***

1. Vascular component

2. Tubular component



1- Vascular component

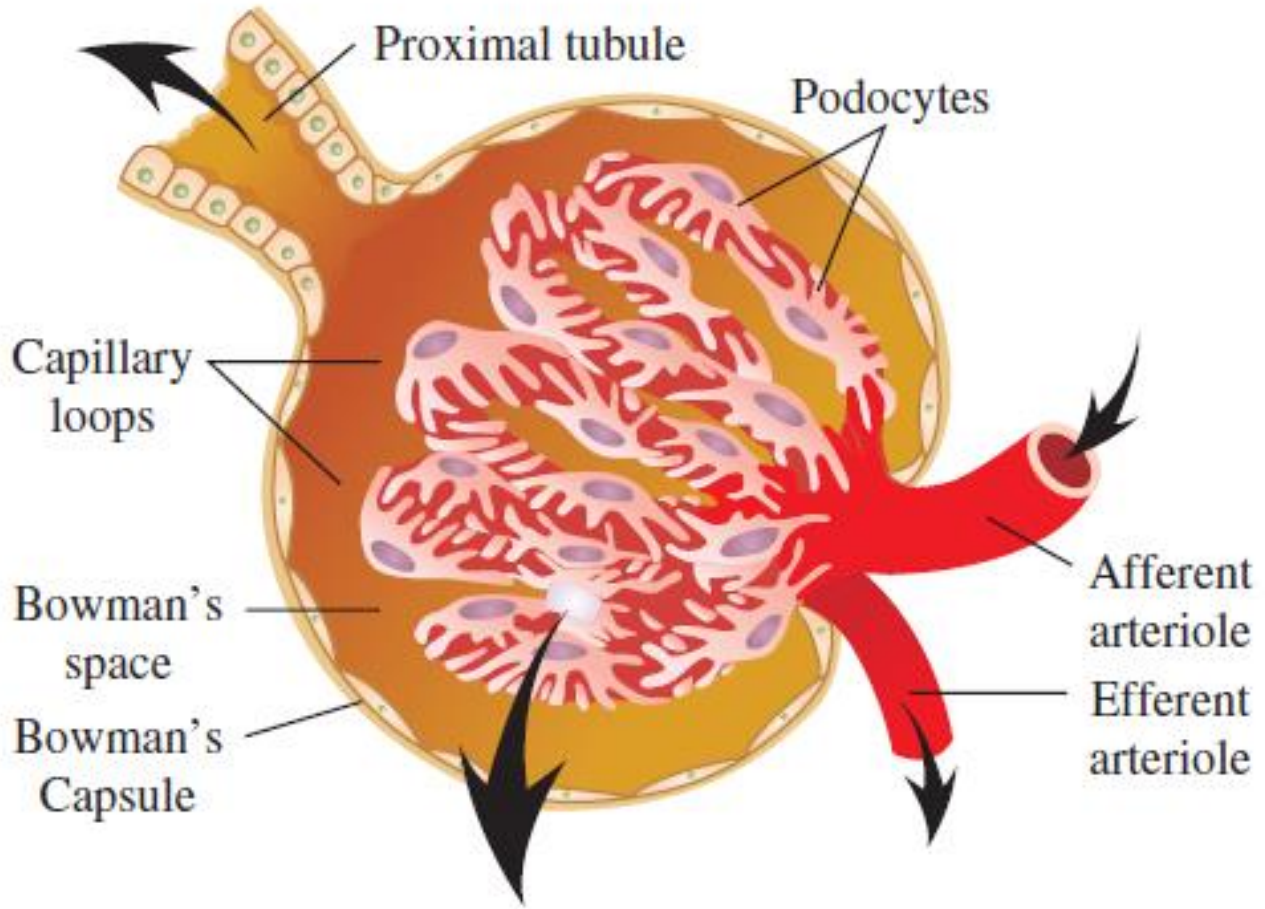
- **Filtration of the plasma** **takes place** at the ***glomerulus*** located in the cortical region of the kidney.
- **Water** and **solutes** **exit** the *vascular compartment* **through** these capillaries to be processed by the **tubular component** of the nephron.
- Blood is delivered to the glomerulus by the *afferent arterioles*. The glomerular capillaries then join to form a second arteriole referred to as the *efferent arteriole*.

- **All cellular elements of the blood** (red blood cells, white blood cells and platelets) **as well as** the unfiltered plasma continue through this vessel.
- The efferent arterioles then **lead to** a second set of capillaries **called** the ***peritubular capillaries*.**
- These capillaries provide **nourishment** to the **renal tissue** and **return** the substances reabsorbed from the tubule to the vascular compartment.
- **Peritubular capillaries** are closely associated with all portions of the renal tubules and wrap around them.
- **These capillaries** then join to form venules and progressively larger veins that remove the blood from the kidneys.

NOTE:-

the filtration is depended on :

- 1- Size (molecular weight)
- 2- Charge
- 3- Pressure



So that:-

- **Toxicants** that *neutralize* or *reduce the number of fixed anionic charges* on glomerular structural elements, therefore, **will impair** the **charge**- and/ or **size-selective properties** of the glomerulus, **resulting** in urinary excretion of polyanionic and/or high-molecular-weight proteins.

2- Tubular component

- Approximately **180 L** of filtrate is processed by the kidneys **each day**.
- about **99%** of this filtrate must be **reabsorbed** from the **renal tubule** back into the **vascular compartment**.
- Upon leaving the glomerular capillaries, the filtrate enters the tubule that consist of:

1. *Bowman's capsule*
2. *Proximal tubule*
3. *Loop of Henle* → Descending limb and Ascending limb.
4. *distal tubule*
5. *collecting duct*

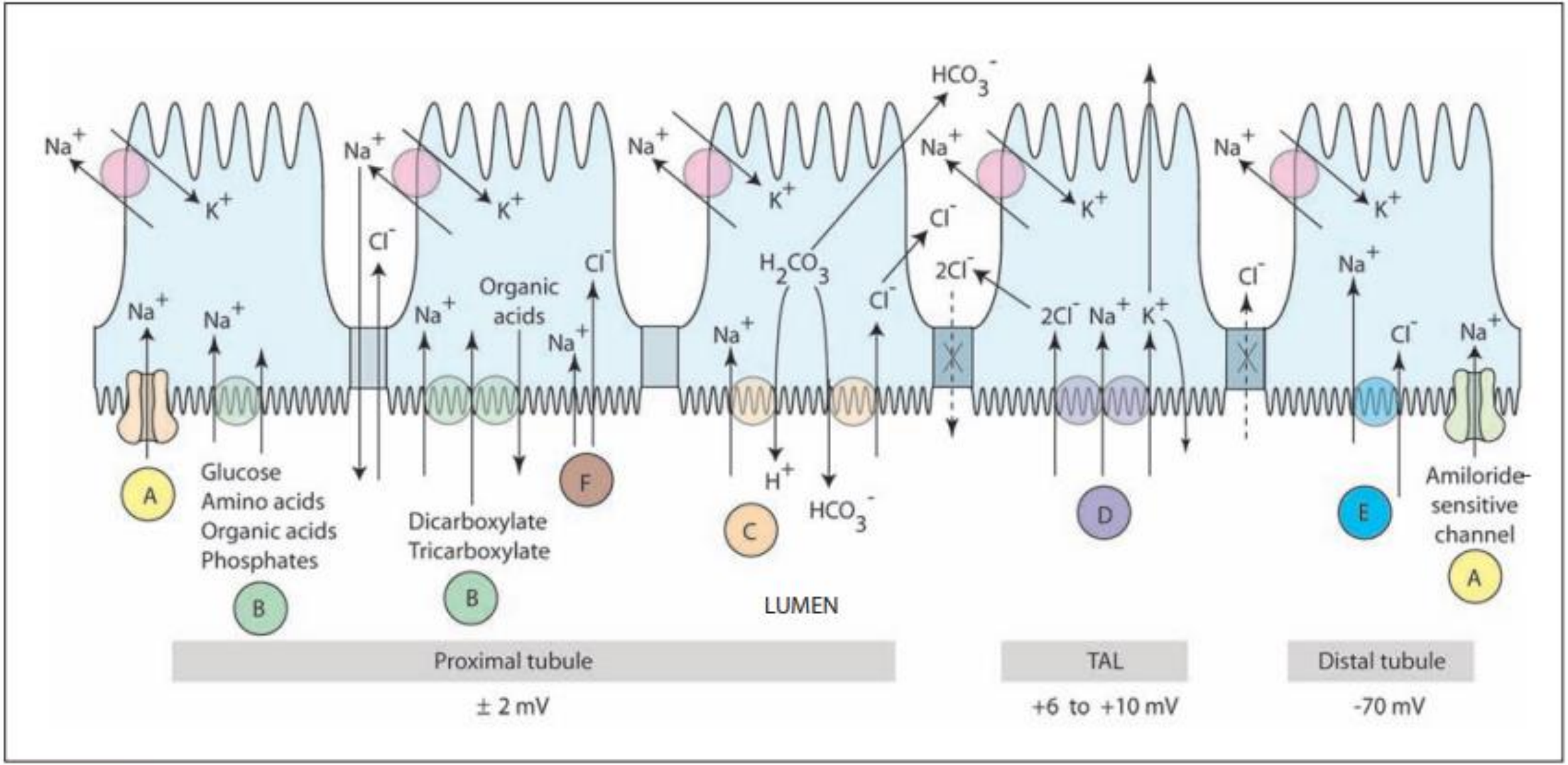


Fig. 55.2 Different mechanisms of tubular reabsorption of sodium ions. **(A)** Unitransport of Na^+; **(B)** Na^+ cotransport with non-Cl^-, non-H^+ substrates; **(C)** Na^+–H^+ exchange, usually with a parallel Cl^-–HCO_3^- uniport; **(D)** Na^+/K^+–$2Cl^-$ cotransport, **(E)** Na^+–Cl^- cotransport; and **(F)** chloride-driven Na^+ transport. TAL, thick ascending limb of the loop of Henle.

Filtration, Reabsorption, and Excretion Rates of Different Substances by the Kidneys*

	FILTERED (MEQ/24 H)	REABSORBED (MEQ/24 H)	EXCRETED (MEQ/24 H)	REABSORBED (%)
Glucose (g/day)	180	180	0	100
Bicarbonate (mEq/day)	4320	4318	2	>99.9
Sodium (mEq/day)	25,560	25,410	150	99.4
Chloride (mEq/day)	19,440	19,260	180	99.1
Water (L/day)	169	167.5	1.5	99.1
Urea (g/day)	48	24	24	50
Creatinine (g/day)	1.8	0	1.8	0

**Glomerular filtration rate: 125 mL/min = 180 L/24 h.*

Diagnosed

❖**Kidney toxicity** is usually diagnosed by **changes in excretory function**, **such as**:

I. **increases** in *urinary glucose*, *amino acid*, or *protein* excretion,

II. **Changes** in *urine volume*, *osmolarity*, or *pH*.

III. **Changes** in blood *urea nitrogen* (BUN) or *serum creatinine* concentrations **are also** *indicators of altered renal function*.

IV. **Recently**, *several biomarkers* have been approved by the Food and Drug Administration **(FDA)** as reliable indicators of **kidney toxicity**.

❖**A biomarker** is a *biochemical feature* that can be *used to diagnose* a **disease or monitor the effects of treatment**.

❖The **biomarkers approved** by the **FDA** are *all **proteins** that appear in the **urine** when **kidney damage has occurred** and include proteins* **such as:-**

I. **kidney injury molecule - 1 (KIM - 1),**

II. **β 2 - microglobulin,**

III. and **albumin.**

- **NOTE:-**

- ***Excretion** of **higher** molecular weight proteins in the urine such as albumin is suggestive of injury to the glomerulus, **while** the **presence** of **low** molecular weight proteins, such as β 2 - microglobulin is more suggestive of proximal tubule injury.*

FACTORS CONTRIBUTING TO NEPHROTOXICITY

❖**Several factors contribute to the unique susceptibility of the kidney to toxicants:-**

I. High renal blood flow

II. Concentration of chemicals in intraluminal fluid

III. Reabsorption and/or secretion of chemicals through tubular cells

IV. Biotransformation of protoxicants to reactive intermediates

High renal blood flow

➢renal blood flow is high relative to organ weight.

- *For an organ constituting less than **1% of body weight**, the kidneys **receive about 25%** of the resting cardiac output.*

➢Thus, the kidneys will **receive higher concentrations** of toxicants (per gram of tissue) **than poorly perfused tissue** such as *skeletal muscle*, *skin*, and *fat*.

❖NOTE:

- Renal blood flow is unequally distributed.
- **with cortex receiving** a **disproportionately high flow** **compared to** *medulla* and *papilla*.
- *Therefore, **a blood - borne toxicant** will be **delivered preferentially** to the renal cortex and thereby have a greater potential to influence cortical, **rather than** medullary or papillary, functions.*

Concentration of chemicals in intraluminal fluid

- The **processes involved** in forming concentrated urine also will **serve to** concentrate potential toxicants present in the glomerular filtrate.
- Reabsorptive processes along the nephron may raise the intraluminal concentration of a toxicant from 10 mM to 50 mM by the end of the **proximal** tubule, 66 mM at the hairpin turn of the **loop of Henle**, 200 mM at the end of the **distal tubule**, and as high as 2000 mM in the **collecting duct**.

- **Progressive concentration** of **toxicants** may *result in intraluminal precipitation of poorly soluble compounds, causing* ***acute renal failure*** *secondary to obstruction.*

- The **potentially tremendous concentration gradient** for passive diffusion between **lumen** and **cell** may drive even a relatively **nondiffusible toxicant into tubular cells.**

Reabsorption and/or secretion of chemicals through tubular cells

- **Active transport processes** within the proximal tubule may further raise the intracellular concentration of an **actively transported toxicant.**
- During **active secretion and/or reabsorption**, **substrates** generally **accumulate** in **proximal tubular cells** in **much higher concentrations than** present in **either** luminal fluid or peritubular blood.

Biotransformation of protoxicants to reactive intermediates

- certain **segments of the nephron** have a **capacity** for **metabolic bioactivation**.
- **For example**, the **proximal** and **distal tubules** contain isozymes of the cytochrome P450 monooxygenase system that may mediate **intrarenal bioactivation of several protoxicants.**

❖**Additionally**, **prostaglandin synthase activity** in **medullary** and **papillary interstitial cells** may be involved in **co - oxidation of protoxicants**, resulting in **selective papillary injury**.