DIURETICS

DR. SHABANA ALI

DIURETICS

Drugs which increase the excretion of sodium and water from the body by an action on the kidney

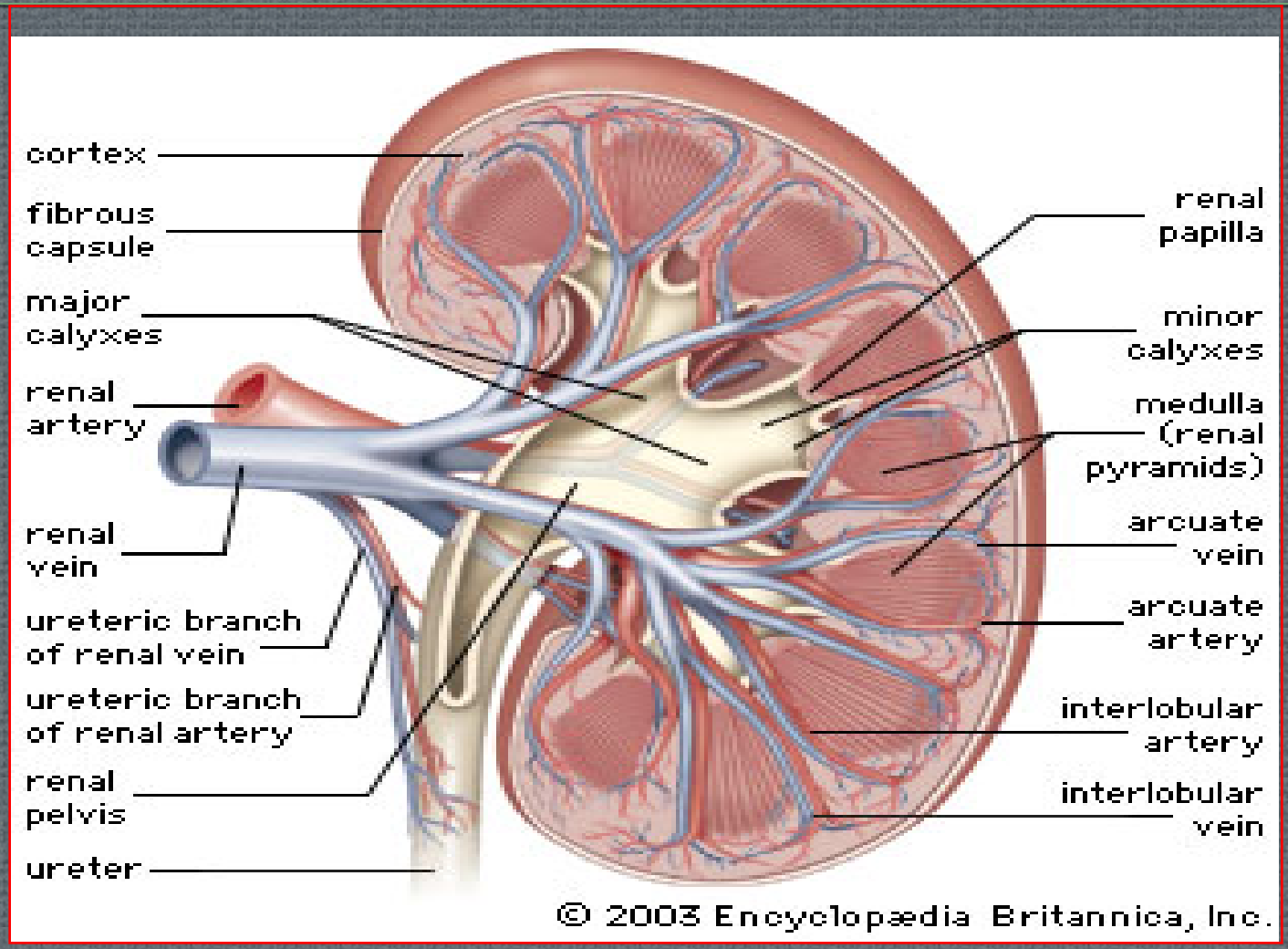
Natriuretics

- Cause increase in renal Na excretion + increase water excretion; usually called diuretics

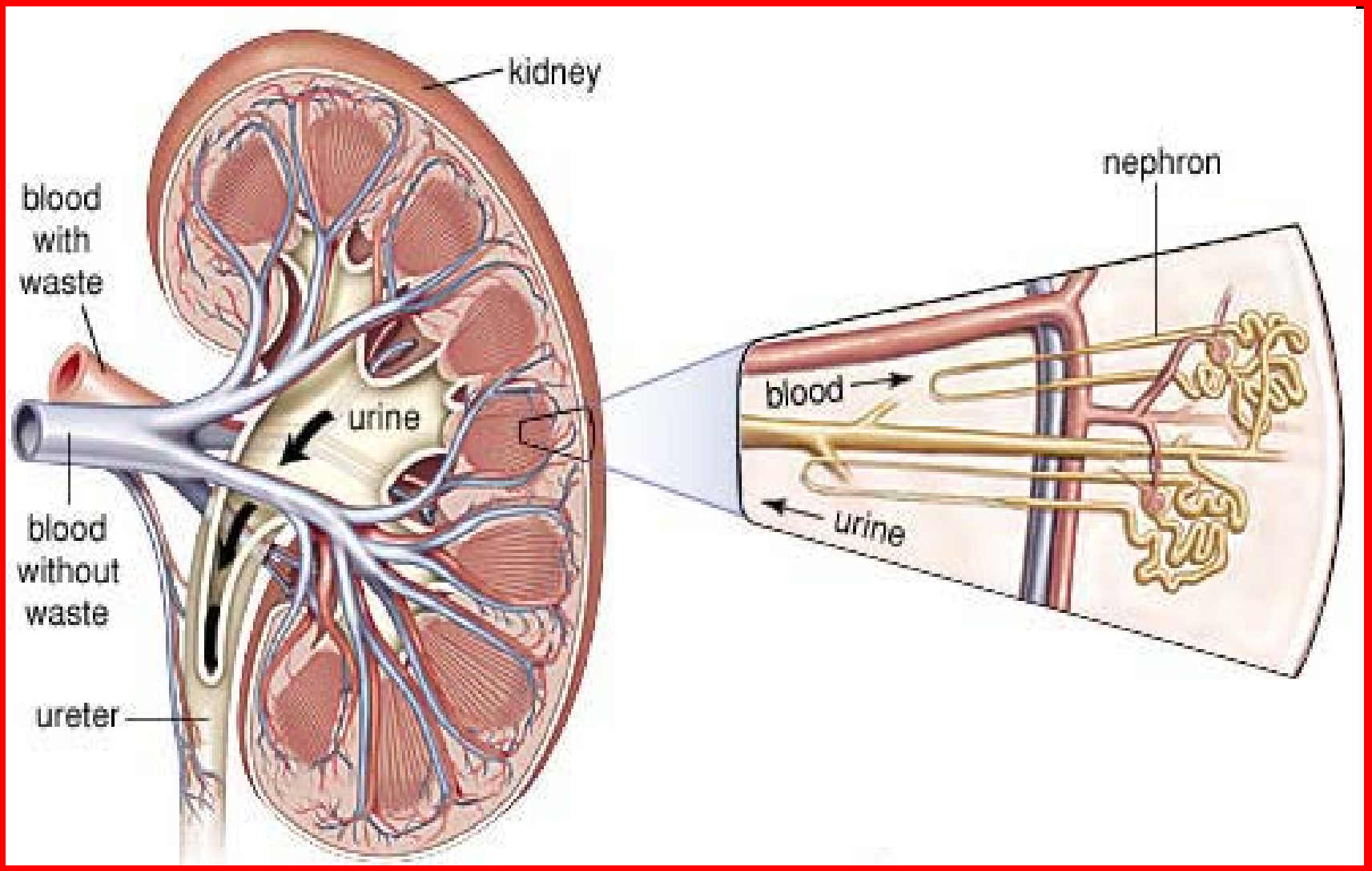
Functions of Kidney

- Excretion of waste products (urea, uric acid & creatinine)
- Regulation of salt & electrolytes; volume of ECF; acid base balance
- About 99% filtered H_2O, much of filtered salt+ some sub. reabsorbed into blood & some sub. Secreted (urine=1.5 L/24 h)

Renal Anatomy



Renal Anatomy

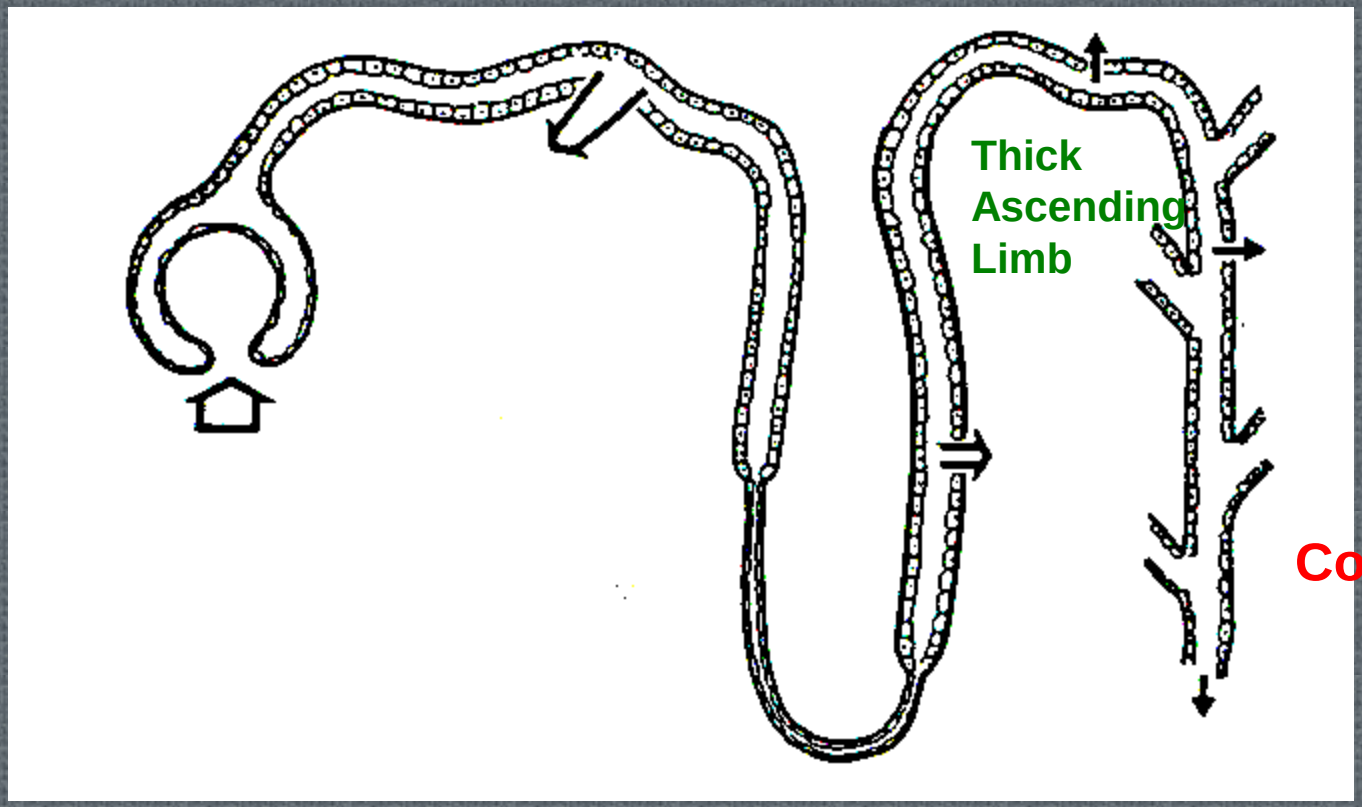


STRUCTURE OF NEPHRON

Proximal tubule

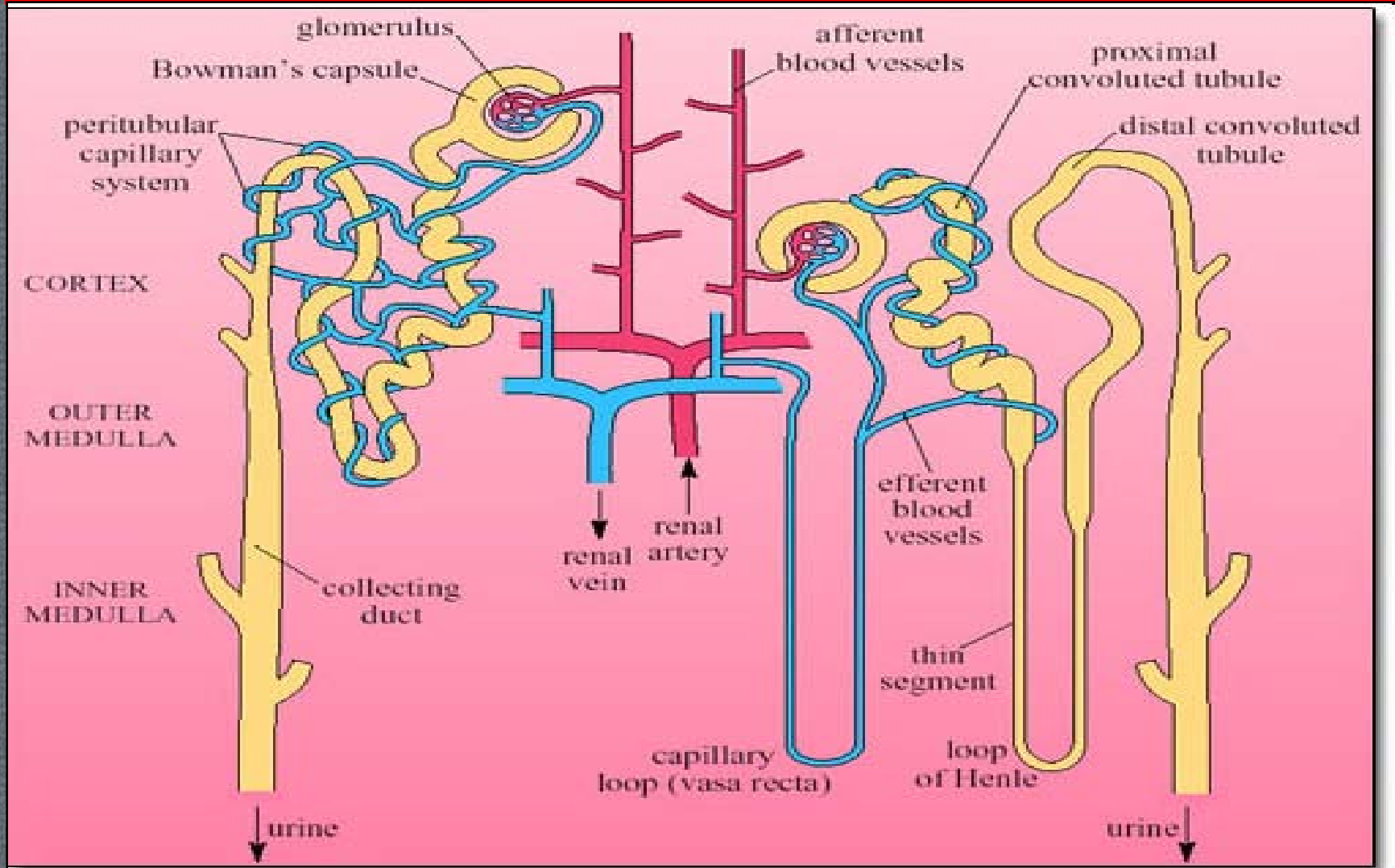
Loop of Henle

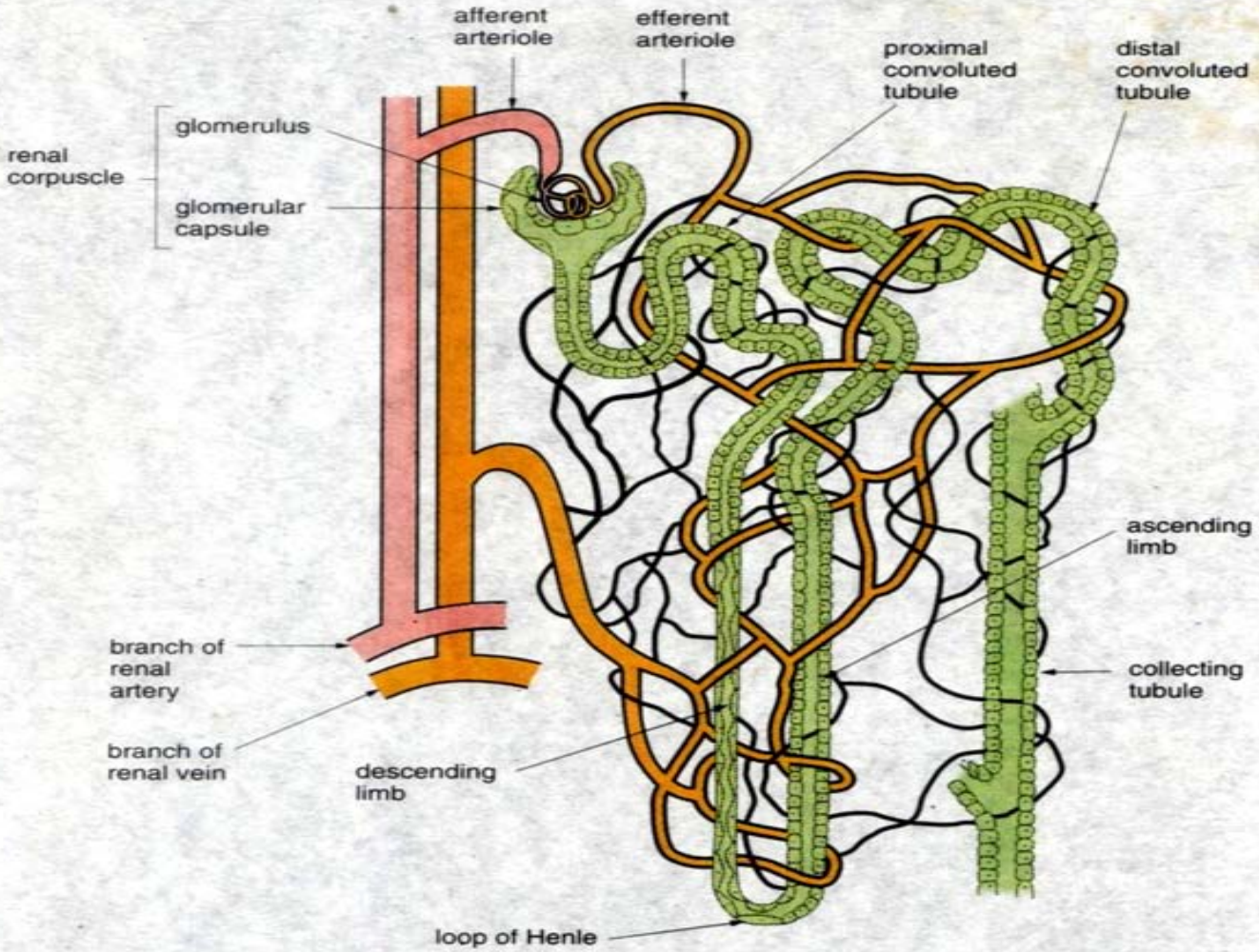
Distal tubule



Collecting duct

BLOOD SUPPLY TO NEPHRON





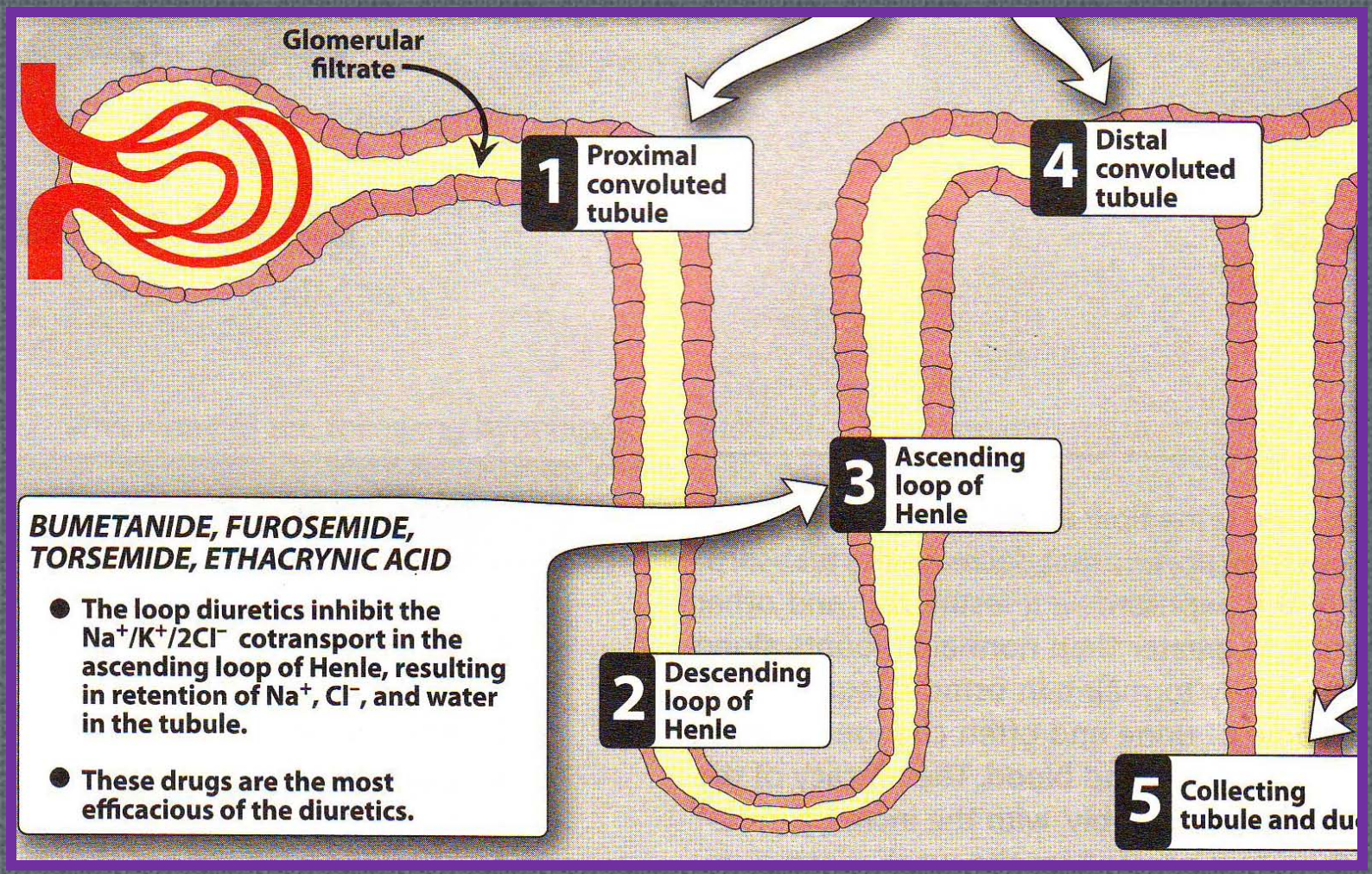
Kidney nephron and blood vessels

TUBULAR FUNCTION

- Apex (luminal surface) of each tubular cell is surrounded by tight junction
- Movement of ions + water across epithelium occur through:

i) Through cells (transcellular pathway)
ii) B/w cells through tight junctions (paracellular pathway)

Major locations of ions & water exchange in the nephron



CLASSIFICATION OF DIURETICS

1) Carbonic anhydrase Inhibitors
2) Loop Diuretics
3) Thiazide Diuretics
4) Potassium Sparing Diuretics
5) Agents altering water excretion
   - *a) Osmotic diuretics*
   - *b) Antidiuretic hormone (ADH) agonists*
   - *c) Antidiuretic hormone (ADH) antagonists*

1) Carbonic Anhydrase Inhibitors (CAI)

- Carbonic anhydrsase enzyme (luminal memb. of convoluted tubule)= catalyze dehydration of H_2CO_3
- CAI= block $NaHCO_3$ reabsorption & cause diuresis

- ***Acetazolamide*** = prototype

Pharmacokinetics of CAI

- Well absorbed after oral intake
- Diuresis of HCO_3=apparent within 30 min; maximal at 2 h & persists for 12h
- Excretion of drug by secretion in PT S2 segment
- Reduced dose in renal insufficiency

Pharmacodynamics

a) Effect of CAI on Kidney

- Inhibition of **Carbonic anhydrase** activity
- Decrease HCO_3 reabsorption in

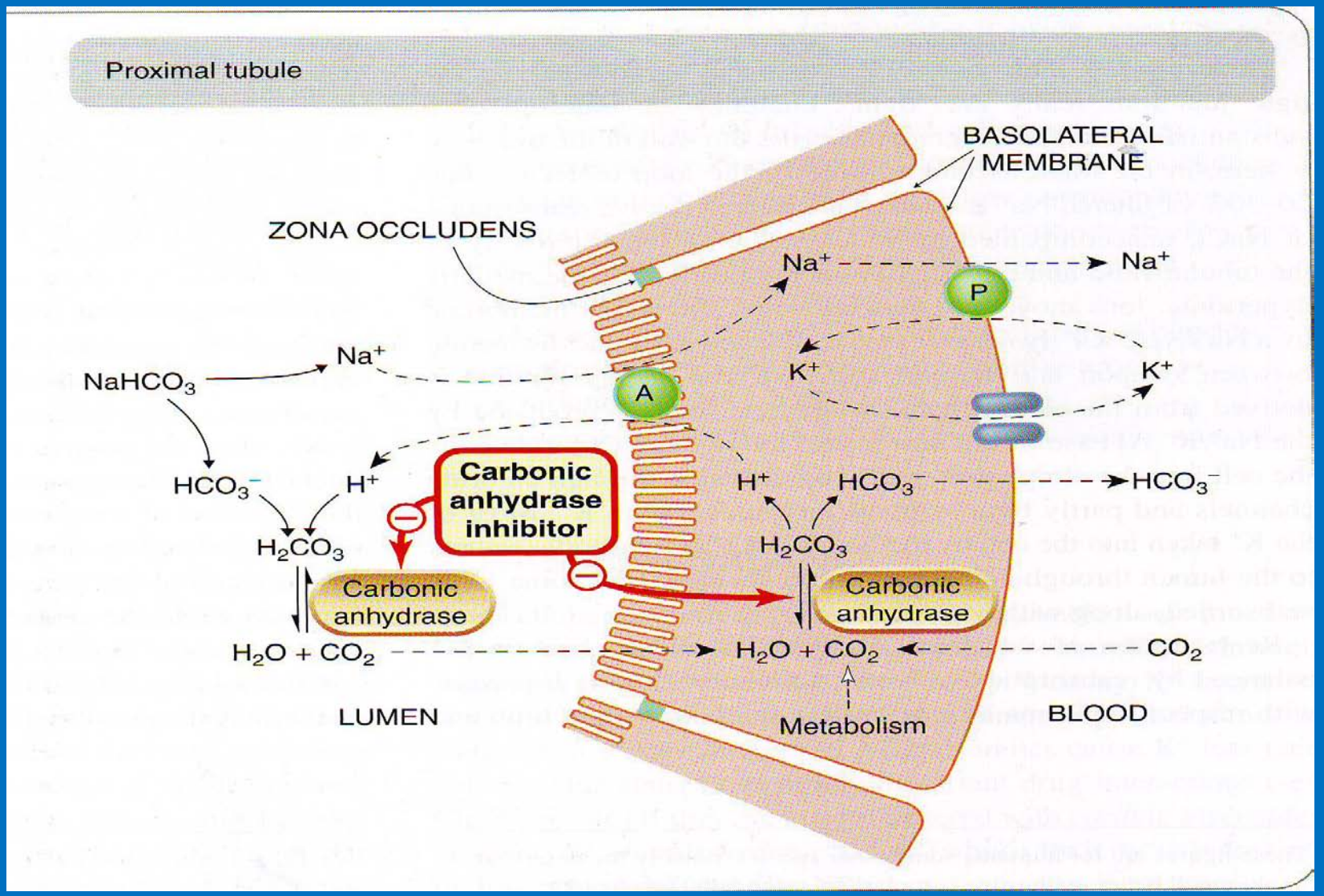
⇩

- ***Proximal convoluted Tubule***
  - With safe dose= 85% blockade of HCO3 reabsorption occurs; d/c ability to exchange Na+ for H+=mild diuresis

The Proximal Convoluted Tubule Functions

- Epithelium of PCT= leaky (tight junctions r not so tight) & permeable to ions & H_2O
- 60-70% Na+ reabsorption occurs (by Na/H exchanger) in PCT accompanied by passive absorption of H_2O
- HCO_3 reabsorption by PCT is initiated by action of Na^+/H^+ exchanger & depends on carbonic anhydrase enzyme

Transport of ions and site of action of CAI in proximal tubule



b) Effect of CAI on other organs

Eye

- Ciliary body secrets HCO3 from blood into aqueous humour; inhibited by CAI

CSF

- Formation of CSF by choroid plexus involves HCO_3 secretion inhibited by CAI

Clinical Indications of CAI

A) Glaucoma

Reduction of aqueous humor formation by CAI ⇒ ⇩ intraocular pressure

E.g., *Dorzolamide, brizolamide*

B) Urinary Alkalinization

CAI= ↑ renal excretion of cystine, uric acid & other weak acids by raising urinary pH

Prolonged therapy with **Acetazolamide** requires HCO_3 administration

C) Metabolic Alkalosis

- Acetazolamide produces small diuresis for correction of volume overload in severe heart failure + when alkalosis due to excessive use of diuretics in HF
- Also rapidly correct metabolic alkalosis due to respiratory acidosis

D) Acute Mountain Sickness

- Mountain travelers=weakness, dizziness, insomnia, headache & nausea; pulmonary or cerebral edema (serious)

- ***Acetazolamide*** = d/c CSF formation & d/c pH of CSF & brain; ↑ ventilation

E) Other uses of CAI

- As adjuvant in treatment of epilepsy
- In hypokalemic periodic paralysis
- To ↑ urinary phosphate excretion during sever hyperphosphatemia

Toxicity of CAI

A. Hyperchloremic Metabolic Acidosis

Chronic reduction of body HCO_3 stores by CAI= acidosis ⇒ limits diuretic efficacy of these drugs

B. Renal Stones

CAI= make urine pH alkaline=renal stone formation from salts ↑ (Ca salts r insoluble at alkaline pH)

C.Renal Potassium

- K^+ wasting can occur b/c Na^+ presented to collecting tubule is partially reabsorbed; increasing lumen-negative electrical potential

D. Other Toxicities

Drowsiness, parasthesias, accumulation of CAI in renal failure patients lead to nervous system toxicity, hypersensitivity reaction (fever, rashes, bone marrow suppression & interstitial nephritis)

Contraindications

- CAI induced alkalinization of urine = d/c urinary excretion of NH+ and contribute to development of hyperammonia & hepatic encephalopathy in cirrhosis patients

Loop Diuretics

- Selectively inhibit NaCl reabsorption in thick ascending limb of loop of Henle
- Most efficacious agents b/c
  - Their effect is not limited by development of acidosis
  - NaCl absorptive capacity of loop of Henle is large
- E.g., *Furosemide & Ethacrynic acid (prototype), bumetamide & torsemide*

Loop of Henle

- Descending + Ascending portion (thick & thin segments)
- Up to 30 % of filtered Na^+ is reabsorbed

Descending Loop of Henle

- Descending thin limb (DTL)= highly permeable to water but impermeable to NaCl & urea
- Water reabsorption occurs---3 fold ↑ in salt conc.
- Osmotic diuretics exert part of their action in this region

Ascending loop of Henle

- Ascending thin limb (ATL) & Thick ascending limb (TAL) = permeable to NaCl & urea but impermeable to water
- Active reabsorption of $Na^+/K^+/2Cl^-$ = by cotransporter

Cont.

- Mg^{+} & Ca^{2+} enter interstitial fluid via paracellular pathway
- Reabsorption (25-30%) of NaCl occur
- Loop diuretics effect here (most effecious)

Loop Diuretics-Pharmacodynamics

Mechanism of Action

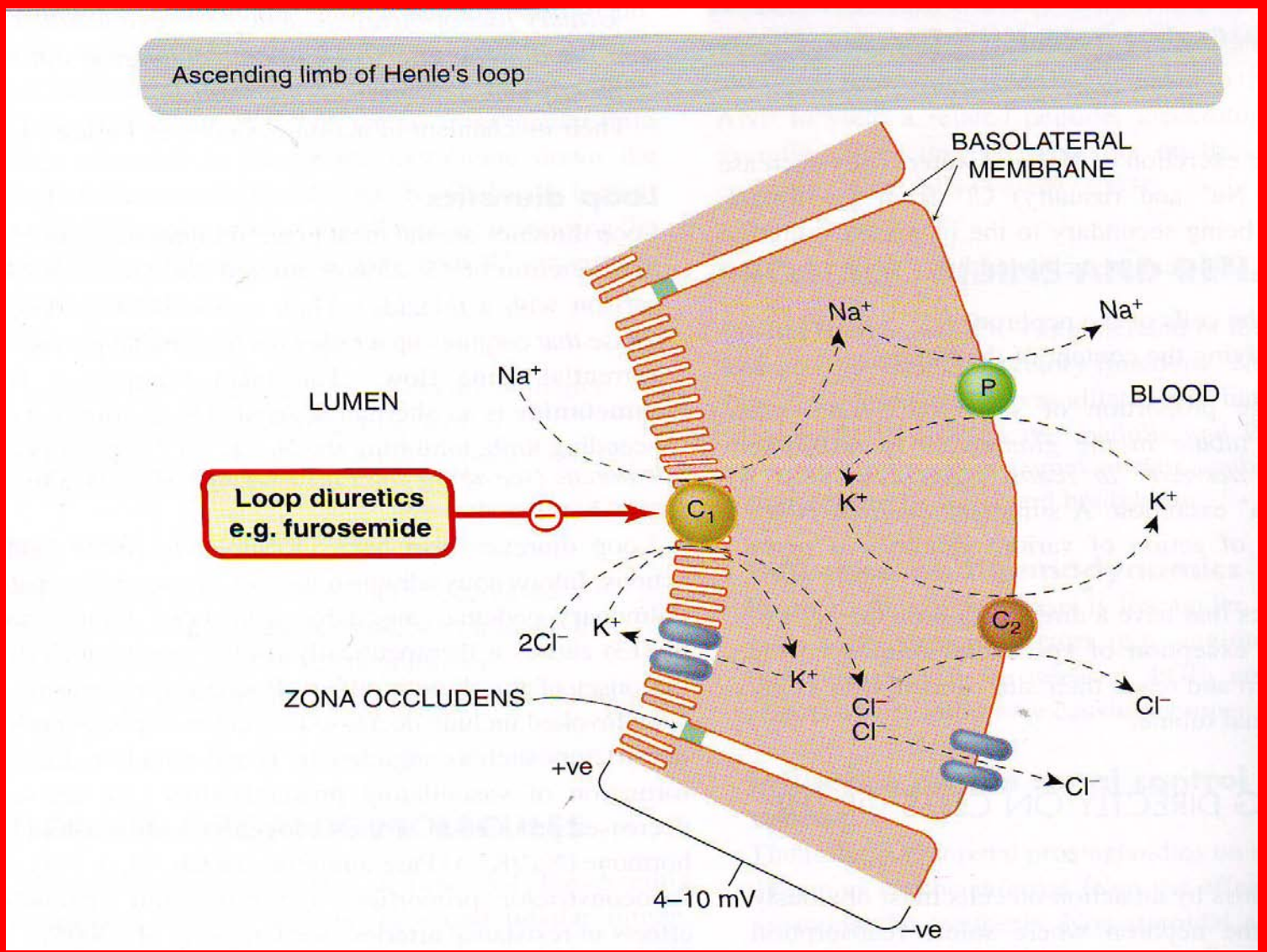
i) Inhibition of $Na^+/K^+/2Cl^-$ transporter in TAL

Contribution of this transporter=K accumulation within cell ⇨ back diffusion of K into the tubular lumen ⇨ lumen +ve electrical potential ⇨ reabsorption of cations (Mg^+ & Ca^{2+})

- Prolonged use can cause hypomagnesemia

Cont.

TRANSPORT OF IONS & ACTION OF LOOP DIURETICS IN ASCENDING LOOP OF HENLE



ii) Loop diuretics induce **synthesis of renal PG** which take part in renal actions of these diuretics

iii) Furosemide ↑ **renal blood flow** (by vasodilation)

iv) Both furosemide & ethacrynic acid also **reduce pulmonary congestion** & left ventricular filling pressure in heart failure

Pharmacokinetics of Loop Diuretics

- Rapidly absorbed (rapid onset of action)
- Absorption of oral torsemide is more rapid (1 h) than that of furosemide (2-3 h) & is nearly as complete as with i.v. administration
- Eliminated by kidney by GF & tubular secretion
- Cont.

- Duration of effect for furosemide= 2-3 h
- ‘’ ‘’ ‘’ ‘’’’’’’’’’’’’’’’’’’’’’’’torsemide= 4-6 h

- Secretion of loop diuretics is reduced if NSAID or probencid are given along with them (due to competition b/w diuretics & NSAID in PT)

Clinical Uses of Loop Diuretics

A. Most important Uses

- Acute pulmonary edema, other edematous conditions & acute hypercalcemia

B. Other Indications

i) Hyperkalemia

Drugs ↑ urinary excretion of K in mild hyperkalemia

Cont.

ii) Acute Renal failure

Loop agents ↑ rate of urine flow & enhance K excretion

iii) Anion overdose

Loop diuretics = useful in treating toxic ingestion of Bromide, Fluoride & Iodide (reabsorbed in TAL)

Toxicity of Loop diuretics

A) Hypokalemic Metabolic alkalosis

By inhibiting salt reabsorption in TAL, loop diuretics ↑ delivery to collecting duct⇒↑secretion of K & H by duct causing hypokalemia metabolic alkalosis

B) Ototoxicity

Dose related hearing loss ---reversible

Especially in patients with d/c renal functions or receiving other ototoxic agents (aminoglycoside antibiotics)

Cont.

C) Hyperuricemia

Hyperuricemia can precipitate attack of gout; caused by hypovolemia associated enhancement of uric acid reabsorption in PT

D) Hypomagnesia

Mg^+ depletion is more common in patients with dietary Mg^+ depletion

E) Allergic & Other Reaction

All loop diuretics (except ethacrynic acid) are sulfonamides

Sulfonamides= Skin rashes, eosinophilia, interstial nephritis (less often)

Ethacrynic acid= allergic reaction much less common

Cont.

Other adverse reactions

- Dehydration, hyponatremia (less common as compared to that with thiazides

Contraindications

Furosemide, bumetamide & torsemide = allergic cross reactivity in patients sensitive to other sulphonamides

Overuse of diuretic = dangerous for hepatic cirrhosis, renal failure or heart failure

Thiazide Diuretics

- They inhibit NaCl transport predominantly in distal convoluted tubule (DCT)
- Some members retain carbonic anhydrase inhibitory activity

- Prototype= **Chlorothiazide** & its derivative **Hydrochlorothiazide**

Phramcokinetics of Thiazides

- All thiazides can be given orally but there are differences in their metabolism
- **Chlorothiazide** (parent) = not very lipid soluble; must be given in large doses & is the only thiazide available for parenteral administration
- Cont.

- **Chlorothalidone**= slowly absorbed ; longer duration of action
- **Indapamide**= excreted primarily by biliary system

- **All of thiazides are secreted by organic acid secretary system in PT & compete with secretion of uric acid by that system**
- **Thiazide use= d/c uric acid secretion & ↑serum uric acid level**

Distal Convoluted Tubule

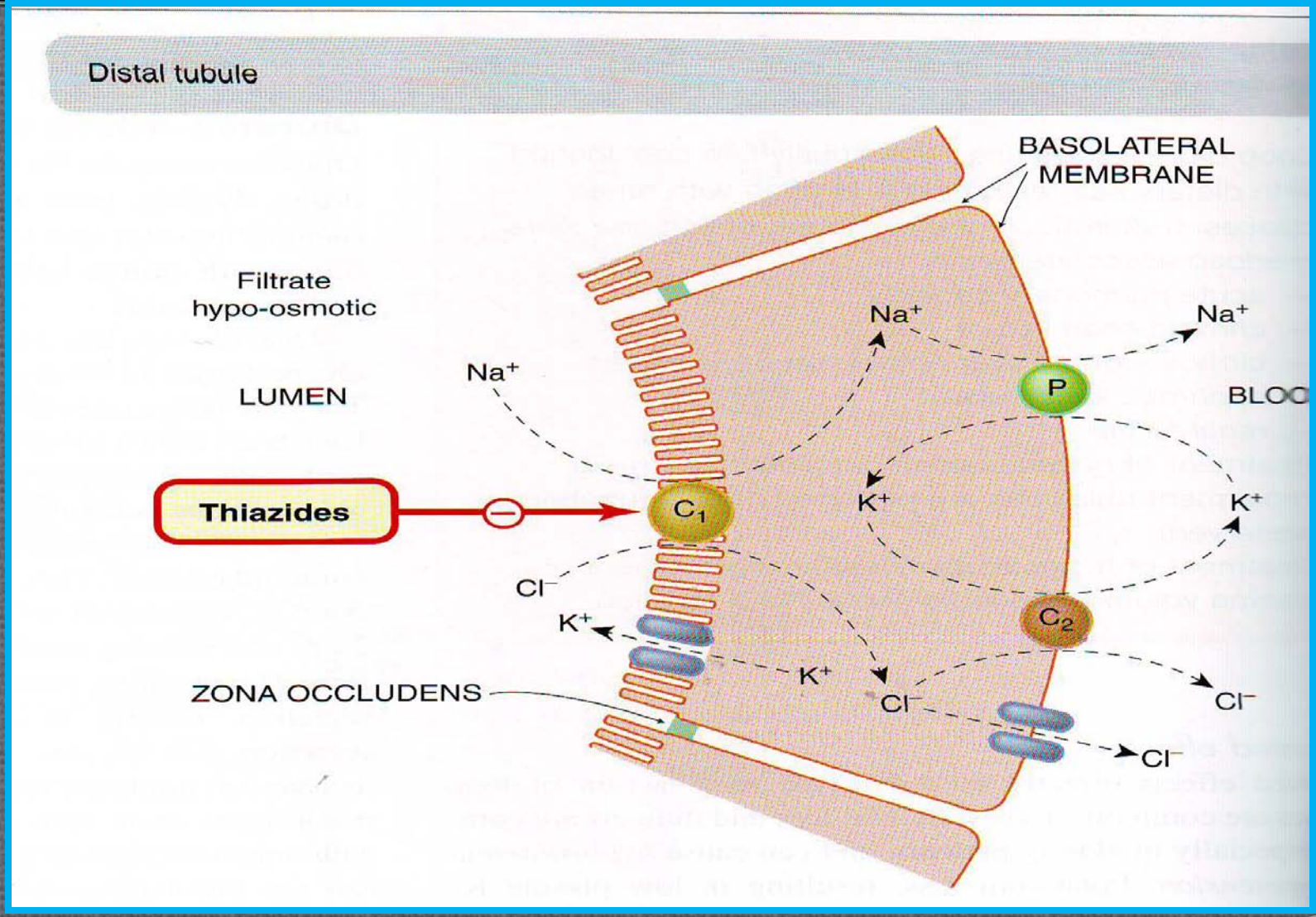
- Cells of DCT = impermeable to water
- ~ 10% filtered NaCl = reabsorbed via Na^+/Cl^- transporter (sensitive to thiazide)
- Ca^{2+} reabsorption = by channel & by Na^+/Ca^{2+} exchanger into interstitial fluid
- Ca^{2+} excretion by parathyroid hormone

Pharmacodynamics of Thiazides

- Thiazides inhibit NaCl reabsorption from luminal side in **DCT** by blocking Na^+/Cl^-transporter
- They have less effect on in PT
- Thiazides usually ↑ Ca^{2+} reabsorption by exerting their effect on both proximal (volume depletion) & distal convoluted tubules (↑Na/Ca exchanger)
- Cont.

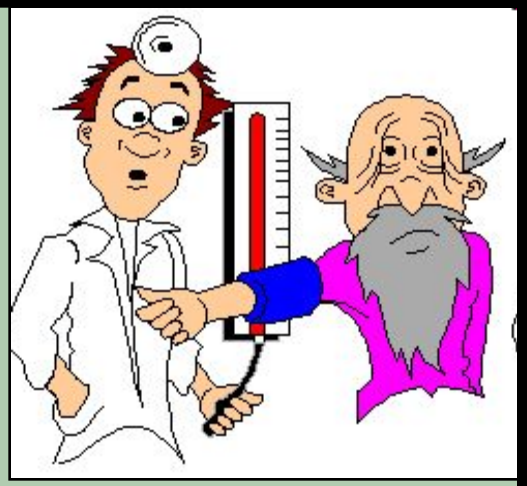
- The action of thiazides in part depends on renal prostaglandin production & actions can be blocked by NSAIDs
- Useful for treatment of kidney stones (Ca2+ oxalate) caused by hypercalciuria

Transport of ions & action of thiazides in distal convoluted tubule



Clinical uses of Thiazide Diuretics

- **Hypertension**
- **Heart failure**
- **Nephrogenic diabetes inspidus**
- **Nephrolithiasis (kidney stones) due to idiopathic hyprcalciuria**



Toxicity of Thiazides

A) Hypokalemia

B/c thiazide ↑ Na in filtrate arriving at distal tubule, more K^+ is also exchanged for Na^+, resulting continual loss of K^+ from body

B) Hyperurecemia

Thiazides ↑ serum uric acid by d/cing amount of acid excreted by organic acid secretary system leading to accumulation of uric acid in joints (gout)

C) Impaired CHO tolerance

Diabetics who take thiazides for HTN may develop hyperglycemia due to impaired release of insulin

D) Hyperlipidemia

- Thiazides cause 5-15% ↑ in total serum cholesterol & LDL (may return to baseline)

E) Hyponatremia

Due to combination of hypovolemia-induced elevation of ADH, reduction in diluting capacity of kidney & increased thirst

F) Allergic Reactions

- Thiazides are sulfonamides
- Photosensitivity or generalized dermatitis occurs rarely
- Serious allergic reactions are extremely rare; including hemolytic anemia, thrombocytopenia & acute necrotizing pancreatitis

G) Other Toxicites

- Weakness, fatigability, paresthesias & impotence (due to volume depletion)

Contraindications

Excessive use is dangerous in= Hepatic cirrhosis, borderline renal failure or heart failure

Potassium Sparing Diuretics

- Prevent K+ secretion by antagonizing the effects of aldosterone at late distal & cortical collecting tubules

Inhibition of Aldosterone

i) Direct pharmacological antagonism of mineralocorticoid receptors (**spironolactone, eplerenone)**

Cont.

ii) by inhibition of Na influx through ion channels in luminal membrane (**amiloride & triamterene)**

PK & Chemistry

Spironolactone= synthetic steroid acts as competitive antagonist to aldosterone

Slow onset of action (several days for full therapeutic effect)

cont.

Eplerenone

Spironolactone analog with greater selectivity for aldosterone receptor

Amiloride & Triamterene

Direct inhibitors of Na influx in CCT

Triamterene

Extensively metabolized,; shorter half life; excreted by urine

Collecting Tubule & Collecting Duct

- Tight junction are impermeable to water & ions
- Movement of ions & water is under control of hormones

Aldosterone = ↑ Na+ reabsorption & promotes K+ excretion

ADH = ↑ reabsorption of water in collecting duct (concentrated urine)

Pharmacodynamics of K sparing diuretics

- They reduce Na+ absroption (K+ secretion) in collecting tubules & ducts by antagonizing aldosterone receptor

Spironolactone & eplerenone

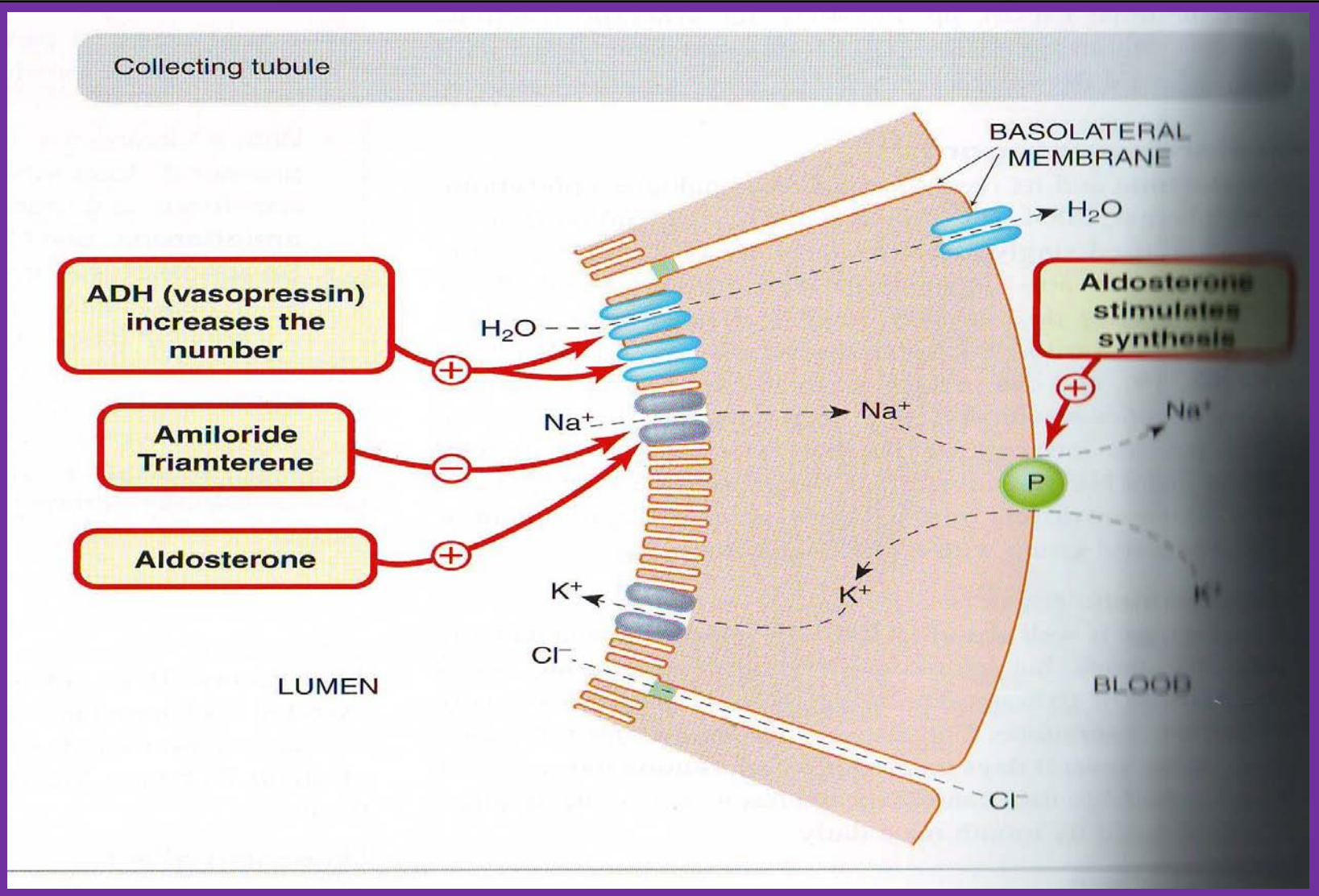
- Bind to aldosterone receptor + reduce formation of metabolite of aldosterone

Cont.

Amiloride & Triamterene

- Interfere with Na entry through epithelial Na ion channel in CT; K secretion does not occur
- Actions of K sparing inhibited by NSAIDs b/c actions of aldosterone antagonist depends on renal PG production

Transport of ions and action of K+ sparing diuretics in collecting tubule



Clinical Indications

- Useful in states of mineralocorticoid excess or hyperaldosteronism

Hyperaldosteronism

- Primary (Conn's syndrome, ectopic adrenocorticotropic hormone production)
- Secondary (heart failure, hepatic cirrhosis, nephrotic syndrome)

Toxicity

A) Hyperkalemia

Mild, moderate or life threatening hyperkalemia (with renal insufficiency), when K sparing agent is used alone

K-sparing + thiazide = hypokalemia (by thiazide) & metabolic alkalosis d/c

B) Hyperchloremic Metabolic acidosis

- By inhibiting H+ secretion in parallel with K+ secretion , these agents cause acidosis

C) Gynecomestia

- Synthetic steroids cause endocrine abnormalities by acting on other steroid receptors
- Spironolcatone cause gynecomestia, impotence

D) Acute renal failure

- Combination of triamterene +indomethacin cause acute renal failure

E) Kidney stones

Triamterene is slightly soluble & precipitate in urine ----kidney stone

Contraindications

- K-sparing agent + agent that block renin angiotensin system (β-blockers or ACEI) = ↑chances of hyperkalemia
- Doses of **triamterene** & **spironolactone** carefully adjusted in liver disease (b/c of ↓ metabolism)
- **Ketoconazole** & **itraconazole** (inhibitors of CYP3A4)↑ blood levels of eplerenone

Agents that alter water excretion

- **Osmotic Diuretics**
- **Antidiuretic Hormone (ADH) agonists**
- **Antidiuretic Hormone (ADH) Antagonists**

1- Osmotic Diuretics

- PT & distal limb of Loop of Henle=freely permeable to water
- Osmotically active agent filtered but not reabsorbed causes water to be retained in these segments & promotes water diuresis
- These agents ↓ intracranial pressure & promote removal of renal toxins

Mannitol= Prototype

Pharmacokinetics

- Poorly absorbed
- Must be given parenterally
- If given orally, mannitol causes osmotic diarrhea
- Mannitol is not metabolized; excreted by GF within 30-60 min without any important reabsorption or secretion

Pharmacodynamics

- Effect on PT & descending limb of loop of Henle

Mannitol= prevents normal absorption of water as result of urine volume ↑⇒↑ urine flow rate⇒ ↓contact time b/w fluid & tubular epithelium ; ↓ Na & H_2O reabsorption

Resulting natriuresis is of lesser magnitude than water diuresis, leading to excessive water loss & hypernatremia

Clinical Uses

A) To increase urine volume

Osmotic diuretics ↑ water excretion in preference to Na excretion ; useful in Na retention

B) Reduction of intracranial & intraocular pressure

Intracranial pressure = ↓ in neurological conditions

Intraocular pressure =↓ before ophthalmologic procedures

Toxicity

A) Extracellular volume expansion

Mannitol

Rapidly distributed in extracellular compartment=extract water from cells—leads to expansion of extracellular volume prior diuresis & hyponatremia---complicate heart failure, produce pulmonary edema

- Headache, nausea, vomiting

B) Dehydration, Hyperkalemia & Hypernatremia

- Excessive use of mannitol without adequate water replacement can lead to severe dehydration, free water loss & hypernatremia, hyperkalemia

2- Antidiuretic Hormone (ADH) agonists

- **Vasopressin** & **desmopressin** =used in treatment of central diabetes inspidus
- Produce renal action by acting on V2 & V1a receptors

3- Antidiuretic Hormone (ADH) Antagonists

- ***Conivaptan, lithium & demeclocycline***

Pk

All are orally active

Pd

Conivaptan---antagonsit at V1a & V2 receptors

Uses

Congestive heart failure syndrome of inappropriate ADH (SIADH)

Clinical Pharmacology of Diuretic agents

A) Edematous states

B) Non edematous states

A) Edematous states

Reabsorption of NACl ↑⇒retention of water ⇒ ↑ blood volume & expansion of extravascular fluid compartment=edema of tissues

Cont.

i) Heart Failure

Heart failure= CO↓⇒ hypovolemia to kidney ⇒ renal retention of salt & water ⇒↑blood volume ⇒↑blood flow returned to heart⇒ diseased heart can not increase its out put⇒↑vascular volume ⇒ edema

Treatment

Loop diuretics (usually)

Thiazides + loop diuretics (severe edema)

Cont.

MOA of Diuretics in Heart failure

a) ⇓ salt + water retention ⇒ ⇓ blood volume, ICF + ⇓ preload + ⇓ ventricular filling pressure

b) ⇓ venous press. ⇒ ⇓edema & its symptoms + ⇓ cardiac size (improve pump function)

ii) Kidney disease

- Many glomeruls diseases associated with diabetes mellitus or systemic lupus erythematosus exhibit renal retention of salt & water $\Rightarrow$ edema or HTN develops
- Diuretics are effective for these patients
- In diabetic nephropathy with hyperkalemia=

Cont.

- thiazide or loop diuretics ↑ K excretion by increasing delivery of salt to K-secreting collecting tubule
- **Loop diuretics** are best choice to treat edema in kidney disease
- Acetazolamide=avoided (acidosis)
- K-sparing diuretics=hyperkalemia
- Thiazides= ineffective when GF rate falls <30ml/min

iii) Hepatic Cirrhosis

- Liver disease is associated with edema, ascites along with ↑ portal hydrostatic pressures & ↓ plasma oncotic pressure

- Ascites & edema severe=diuretic useful
- Cirrhotic patients =resistant to loop diuretics (d/c secretion of drug into tubular fluid)
- Cont.

- Spironolactone & eplerenone = effective for cirrhotic edema
- Combination of loop diuretics + aldosterone antagonist useful in some patients

Non edematous state

1) Hypertension

- Thiazide diuretics= diuretic actions + mild vasodilating actions

2) Nephrolithiasis

About 2/3rd kidney stone patients=Ca Phosphate or Ca oxalate

Cont.

- These patients have defect in Ca2+ reabsorption in PT ⇒ hypercalciurea
- Thiazide diuretics=↑ Ca reabsorption in DCT and ↓ urinary Ca conc.

3) Hypercalcemia

Medical emergency

Loop diuretics= ↓ Ca reabsorption=effective in Ca diuresis

4) Diabetes Insipidus

- **Diabetes insipidus**= due to deficient production of ADH (neurogenic or central DI) or kidney problem (nephrogenic DI)

- Supplementary **ADH** or its analog is effective
- **Thiazide** diuretics= reduce polyuria & polydipsia in both types of diabetes inspidus

Cont.

- (through plasma volume reduction, +fall in GF, ↑proximal reabsorption of NaCl & H2O & ↓ delivery of fluid to downstream diluting segments