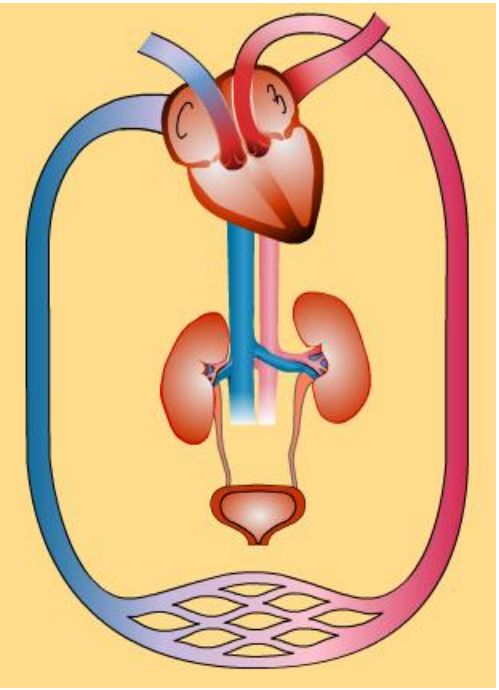

# Diuretics

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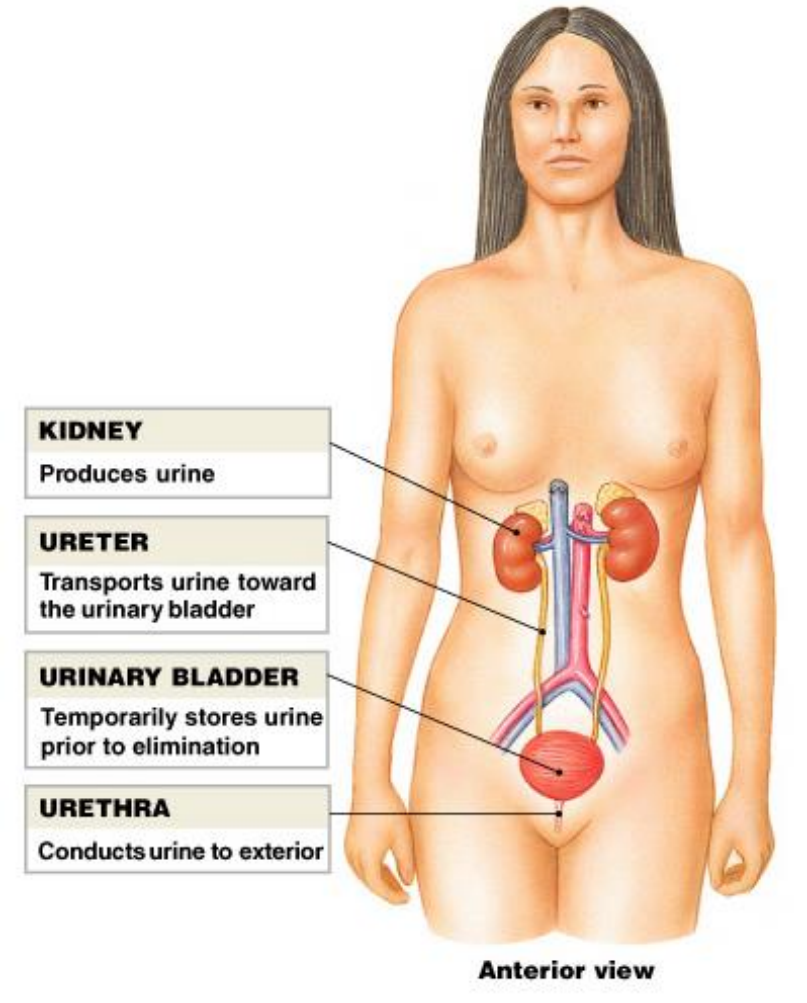
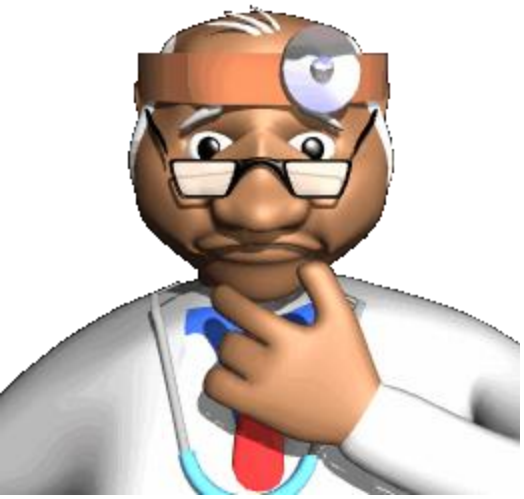
# 3 Functions of the Urinary System



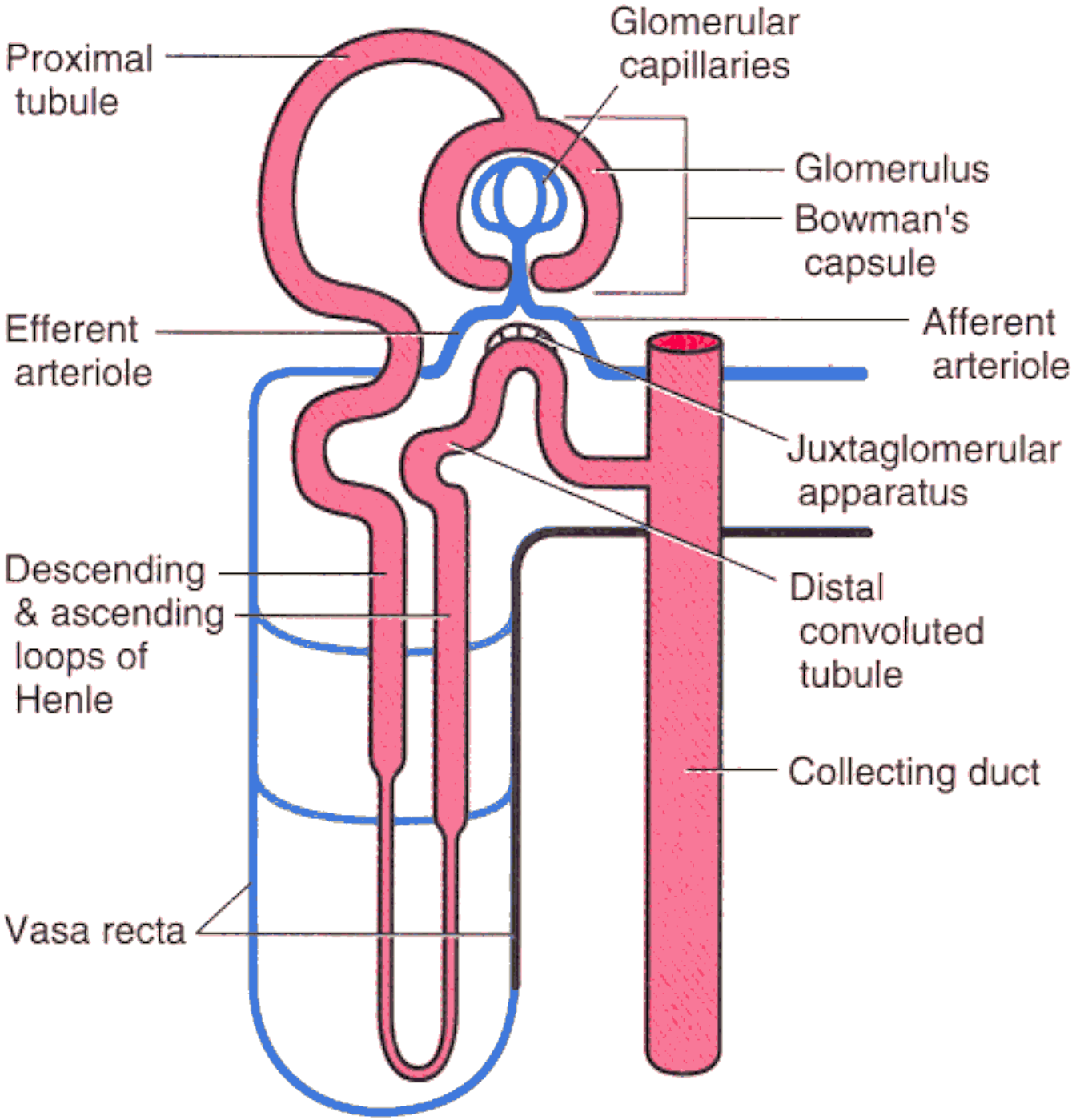

1. **Excretion:**
   - removal of organic wastes from body fluids
2. **Elimination:**
   - discharge of waste products
3. **Homeostatic regulation:**
   - of blood plasma volume and solute concentration

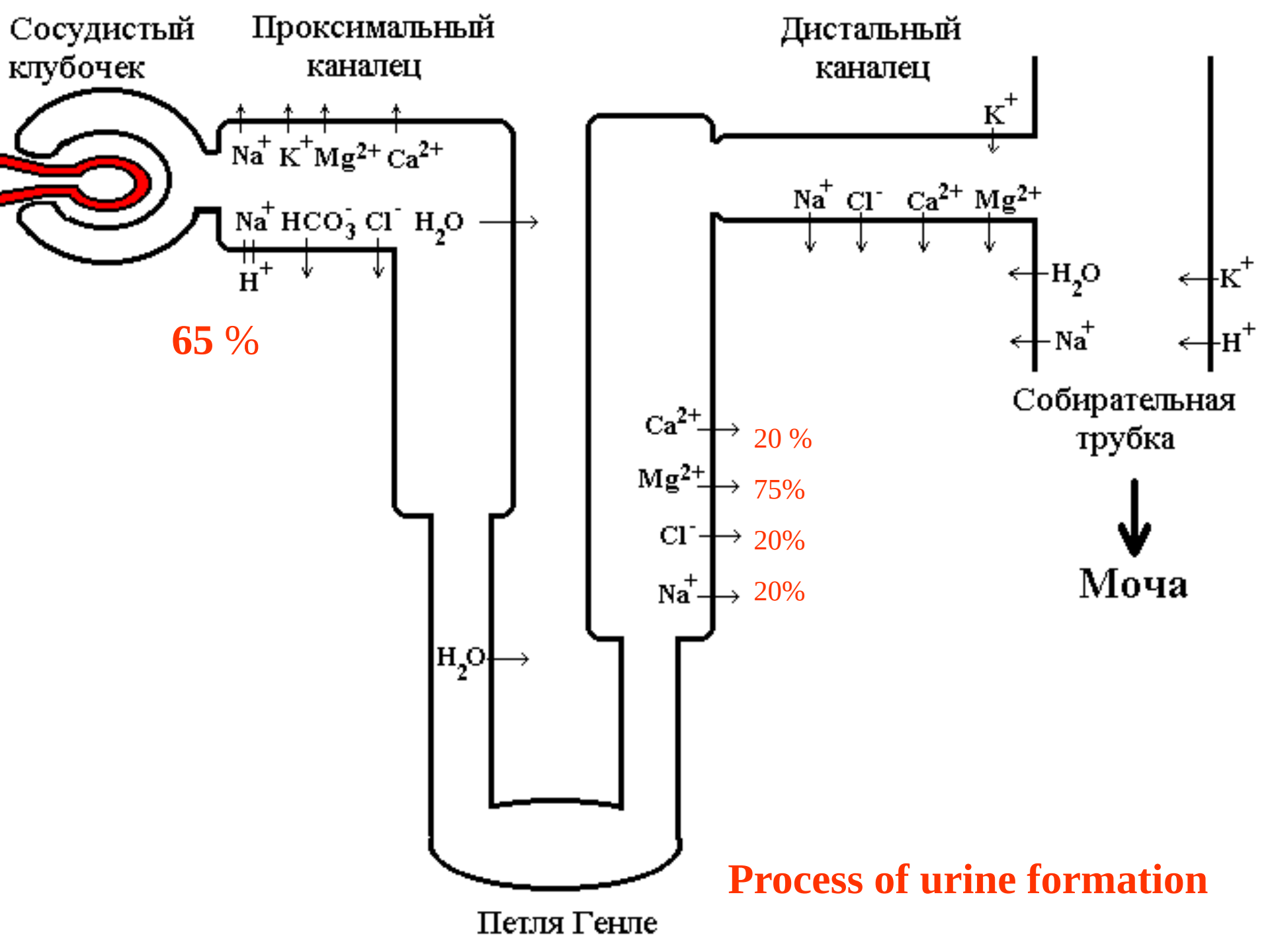


# Diuretics: Definitions

- Diuretic: substance that promotes the excretion of urine
- Natriuretic:  substance that promotes the renal excretion of sodium

# Nephron Structure




Сосудистый клубочек
Проксимальный каналец
Дистальный каналец
$Na^+$ $K^+$ $Mg^{2+}$ $Ca^{2+}$
$Na^+$ $HCO_3^-$ $Cl^-$ $H_2O$
$H^+$
65 %
$K^+$
$Na^+$ $Cl^-$ $Ca^{2+}$ $Mg^{2+}$
$H_2O$
$Na^+$
$K^+$
$H^+$
Собирательная трубка
$Ca^{2+}$ → 20 %
$Mg^{2+}$ → 75%
$Cl^-$ → 20%
$Na^+$ → 20%
$H_2O$
Моча
Петля Генле
Process of urine formation

# Classification of DIURETICS

## A. according to the place of action:

### Acting in Glomerulus

- glycosides
- methylxantines
- vasodilators

### Acting in proximal convoluted tubule (PCT)

- **carboanhydrase inhibitors:** acetazolamide (diacarb), sultiam

### Acting thick ascending limb of the loop of Henle (TAL)

- furosemide, torasemide, ethacrynic acid, bumetanide

In distal convoluted tubule(DCT) (initial portion)

- *thiazide diuretics*
- Hydrochlorthyazide, cyclopentazide, polythiazide
- *Thiazide like diuretics*
- Chlorthalidone, clopamide, indapamide

In Terminal portion of the cortical collecting tubule and collecting tubule:

- ***antagonists of aldosterone:***
- **competitive aldosterone antagonists:** spironolactone
- **noncompetitive:** amiloride, triamterene.

In All nephron:

- Osmotic diuretics: mannitole and urea

# B. According to the duration of action

- **A. Rapid and shot action**:
- from several minutes until 1 h; duration – 2-8 h:
- Osmotic diuretics: mannitol, urea,
- Loop diuretics: Furosemide , Ethacrynic acid, Bumetanide, Torasemide
- **B. Medium action**:
- from 1-3 h; duration – 8-24 h:
- thiazide diuretics: hydrochlorthyazide
- thiazide like diuretics: clopamide, indapamid,
- noncompetitive aldosterone antagoniats: amiloride, triamterene.
- Carbonic Anhydrase Inhibitors: acetazolamide

- **C. Lent and long action**:
- from 2-4 h til 2-5 days; duration – 2-7 days
- Thiazide diuretics: polythiazide;
- Thiazide like diuretics- chlortalidon,;
- Competitive aldosterone antagonists: spironolactone

# C. According to the potency

- **A. *Very potent diuretics (high efficacy)—10-35% glomerular filtrate appears in the urine*:**
- Osmotic diuretics:
- Loop diuretics
- **B. *Moderately potent diuretics—5-10% glomerular filtrate appears in the urine. Moderate/intermediate efficacy.*):**
- Thiazide diuretics: Chlorthiazide, Polythiazide, Hydrochlorthiazide, Cyclothiazide, Methiclothiazide
- Thiazide like diuretics- chlortalidon, clopamide,
- Carbonic Anhydrase Inhibitors: acetazolamide
- **C. *Weak diuretics (low efficacy)—only 5% of the glomerular filtrate appears in the urine.***
- K+ sparing diuretics: triamterene, amiloride, spironolactone
- digitales, Xanthine derivatives, vasodilatores etc.

- **D. According to the mechanism of action**
- **inhibits epithelial proteins (receptors, channels):**
- 1. Loop diuretics—(high ceiling diuretics) (**see drugs in previous classification**)
- 2. Thiazide diuretics:
- Chlorthiazide Polythiazid Hydrochlorthiazide Cyclothiazide
- 3. Thiazide like diuretics- chlortalidon, clopamide,
- 4. noncompetitive aldosterone antagoniats: amiloride, triamterene.

**promote osmotic diuresis:**

- osmotic diuretics: mannitol, ureea

**enzymes inhibitors:**

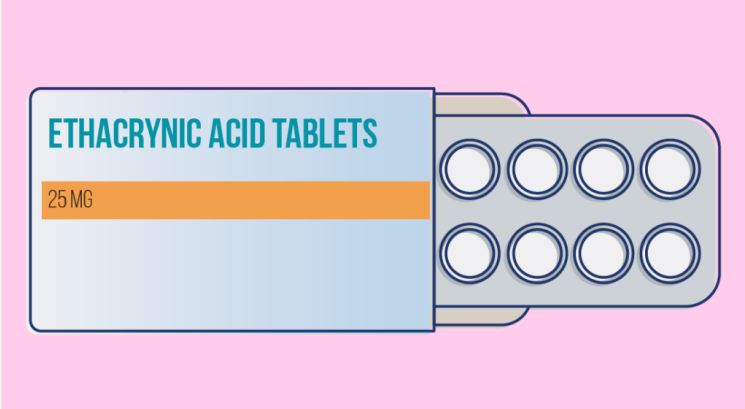
- Carbonic Anhydrase Inhibitors: acetazolamide

**hormones antagonists:**

- Competitive aldosterone antagonists: spironolactone
- increase glomerular filtration rate: glycosides, methylxantines, vasodiltors

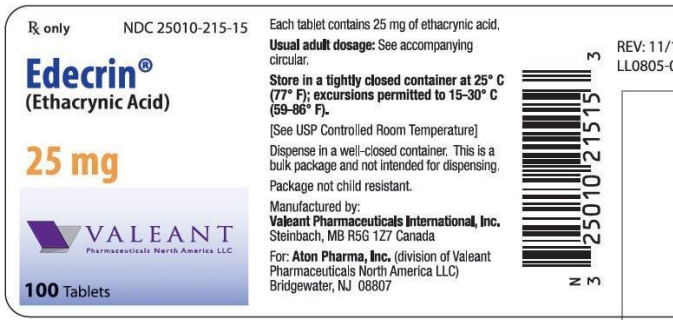
# LOOP DIURETICS-

## “ceiling diuretics”





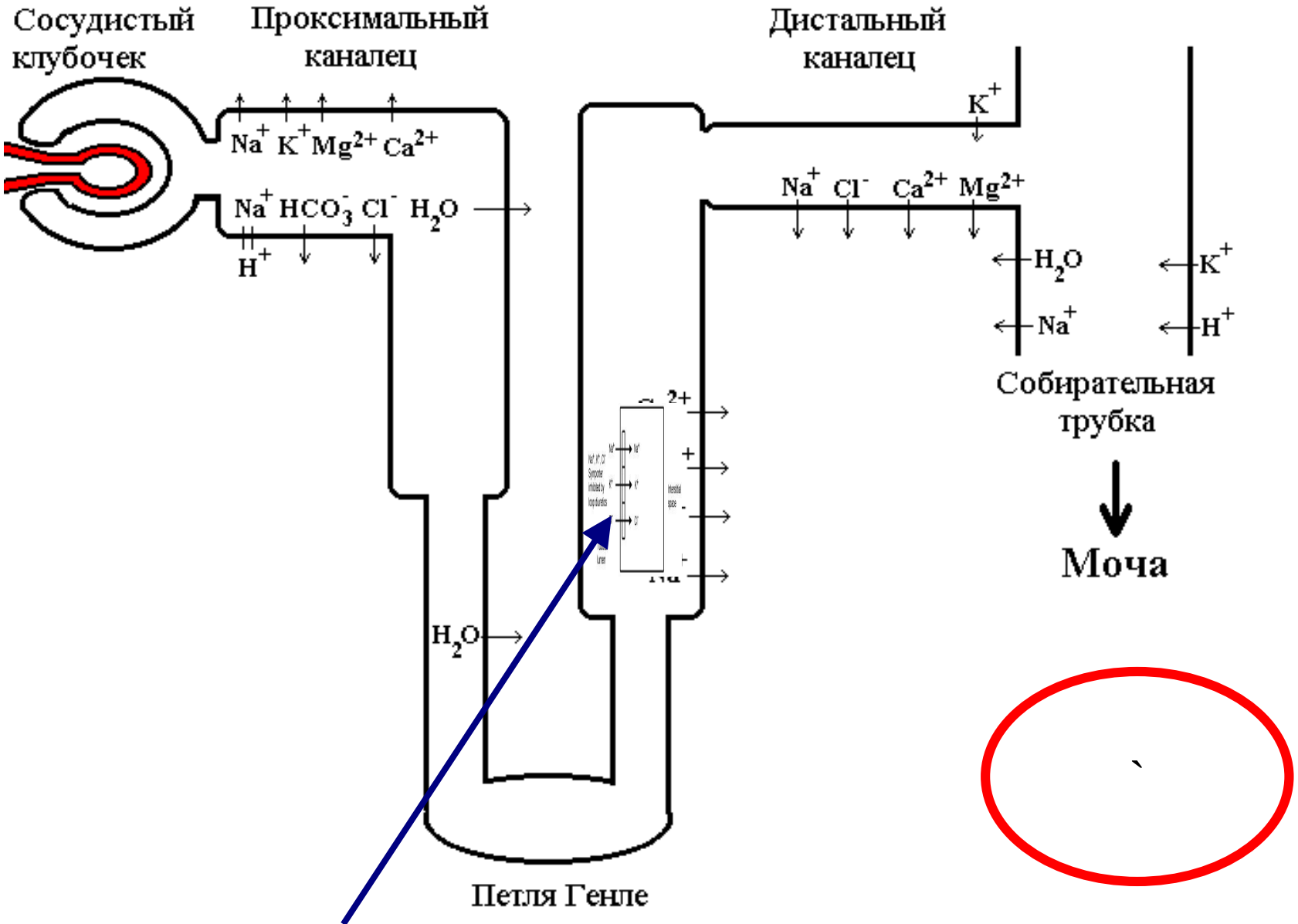




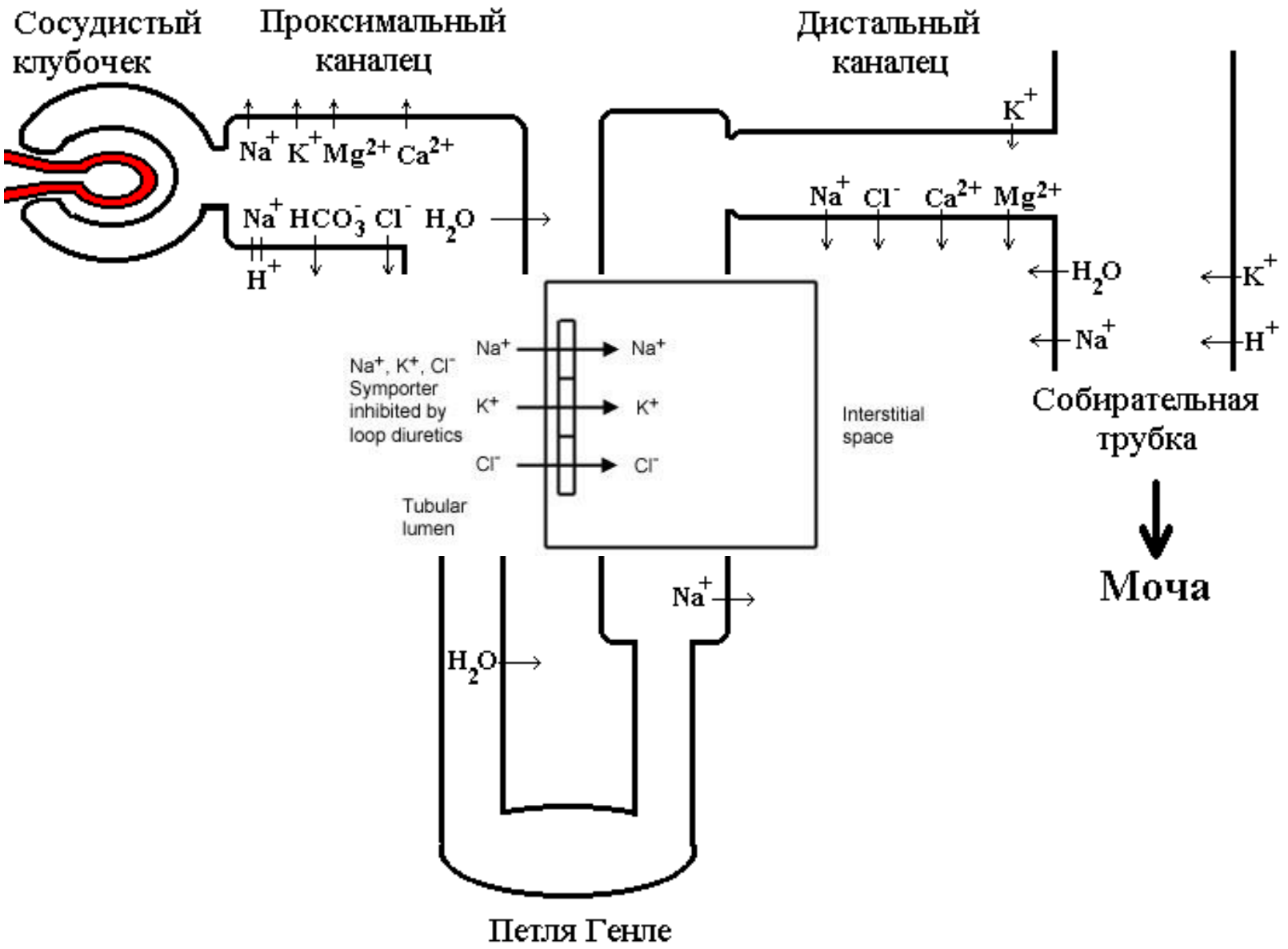
# Mechanism of action

- ***Na+-K+-2Cl- simporter*** **causes concomitant reabsorption of Na+, K+ and 2Cl;**
- **inhibits the 1 Na+/2 Cl- /1 K+cotransported reabsorption of the thick ascending limb of the loop of Henle;**
- ***Loop diuretics*** **bind with the site for Cl- of Na+-K+-2Cl- simporter and thus block the working of the simporter.**
- **As a result there is loss of Na+ as well as K+ and Cl- via urine.**
- **- may increase urinary output to 45 liters/day (25% of glomerular filtrate)**

# Place of action of loop diuretics



# Place of action of loop diuretics



# Efects

- high intensity effect;
- inhibit glycolysis, adenylate cyclase, phosphodiesterase and prostaglandin dehydrogenase:
- Causes losses of Na (primary), K, Cl, Mg, Ca:
- Urine acidification - stimulates distal secretion of H+;
- Increases renal blood flow and redistribution of blood from the medulla to the cortical;
- lowering of blood pressure.

# PHARMACOKINETICS

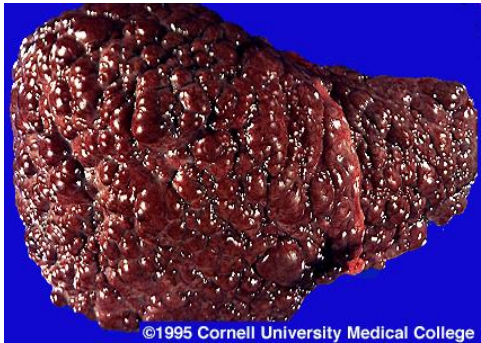
- Fast absorption, medium bioavailability
- Plasma protein binding - 99%
- Distribution in extracellular fluid
- Rapid elimination
  - Renal - by glomerular filtration and tubular secretion, unchanged
  - By faeces – 25%
- $T_{1/2}$ = 92 minutes

# Loop diuretics - Indications

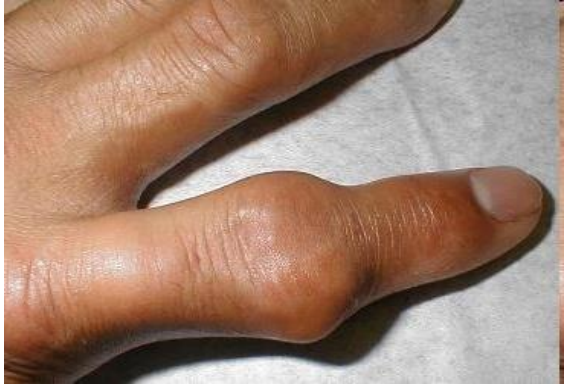
- All types of edema - CI, RI, cirrhosis
- Of choice - in serious thiazide-resistant edema
- May be associated with thiazide - increase efficiency
- They are also effective in low GF situations
- Hypertention - monotherapy, in combination with other hypotensives
- acute renal insuficiency with oliguria - removes oliguria, does not influence RI evolution
- pulmonary edema - iv
- Cerebral edema
- Acute drug intoxication - Bromine, iodine, flora intoxication
- Forced diuresis

# Loop diuretics – Contraindications

- hypovolemia with dehydration
- decompensated cirrhosis
- digital poisoning
- prudence - severe IC, DZ, gout, urinary obstruction, trim I pregnancy
- lactation (ethylic acid)
- children up to 2 years old;
- hypersensitivity to the preparation.
- hypokalaemia, marked hyponatremia
- Necessary - electrolyte control, urea, serum creatinine



- *Side effects*
- - hypotension (hypovolemia)
- - hypokalemia
- - metabolic alkalosis (due to hypokalemia)
- - hypomagnesemia (increased tubular flow rate)
- - hypocalcemia
- - azotemia (competition between urea and loop diuretics at the organic acid transporter)
- Ototoxicity
- Rarely - pancreatitis, interstitial nephritis, rash, leukopenia, thrombocytopenia,
- Metabolic effects-hyperuricemia, hyperglycemia, increase triglyceride and cholesterol levels, increase LDL cholesterol and decrease HDL cholesterol.



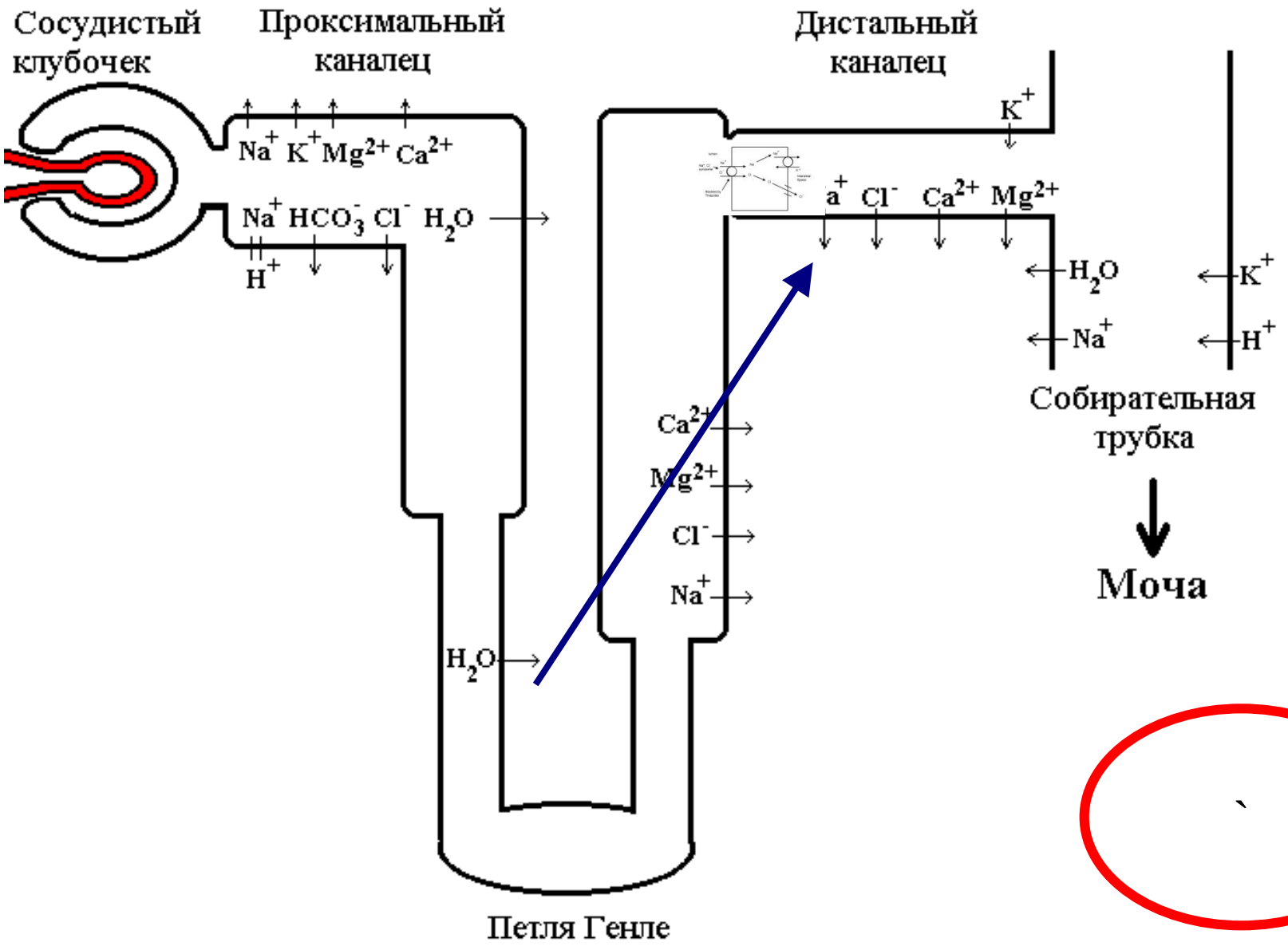
# FUROSEMIDE

- *General information*
- - administered orally or IV
- - extensively bound to plasma proteins
- - eliminated by the organic acid transporter of the proximal tubule of the kidneys
- *Medical uses*
- - treatment of severe hypertension
- - treatment of systemic edema
- - treatment of pulmonary edema
- - treatment of ascites (due to liver cirrhosis)
- - treatment of acute- and chronic renal failure (increased water excretion)
- - treatment of hypercalcemia (inhibition of calcium reabsorption)

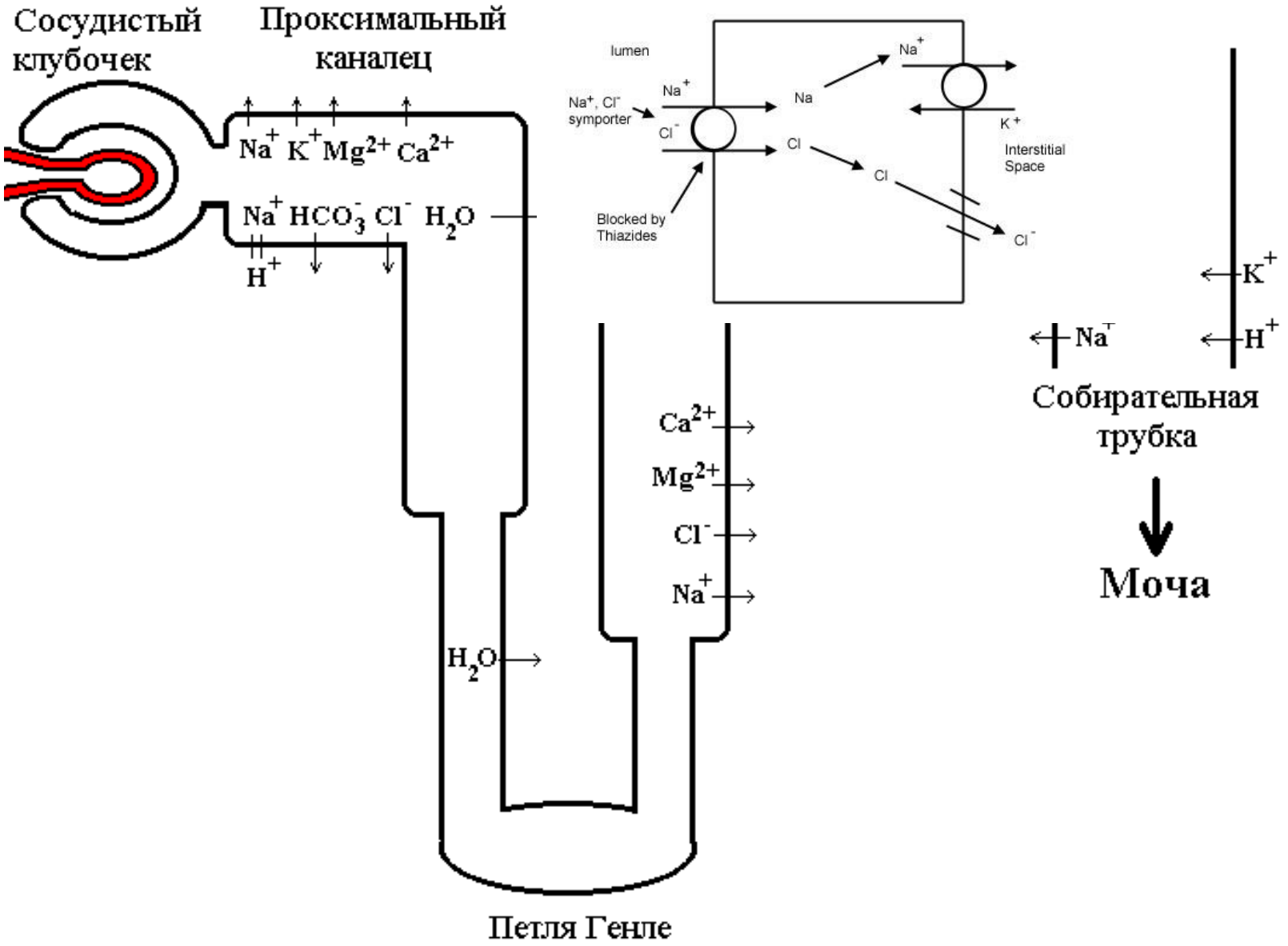
# THIAZIDE DIURETICS

- may increase urinary output to 10 liters/day (5% of glomerular filtrate)
- **Mechanism of action:** inhibit the sodium/chloride cotransported reabsorption of the distal tubule

# Site of action of thiazides



# Site of action of thiazides



# Effects - Thiazide diuretics

- They have moderate effect;
- - The latency of the effect is long: 1 - 2 h.
- - Duration of effect is long: 12 - 24 h.
- The eliminated urine is iso or hyperosmolar, is rich in Na +, K +, and poor in Ca ++.
- - pH: at low doses is acid; at high doses is alkaline, because high doses also inhibit carbohydrazide
- - Decreased renal plasma flow - are not effective and may worsen renal failure.
- Due to long latency, they can not be used in hypertensive emergencies or APE.

# Indications - thiazides and like thiazides

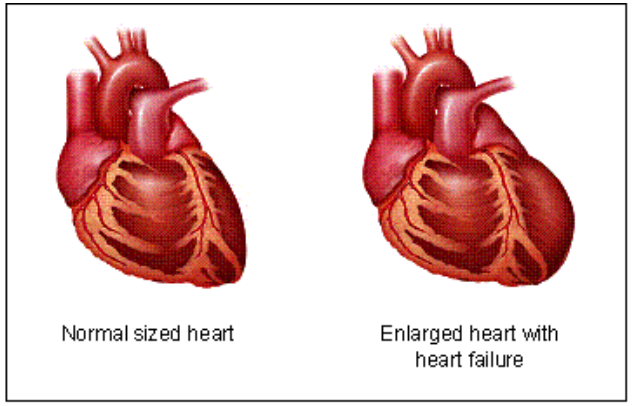
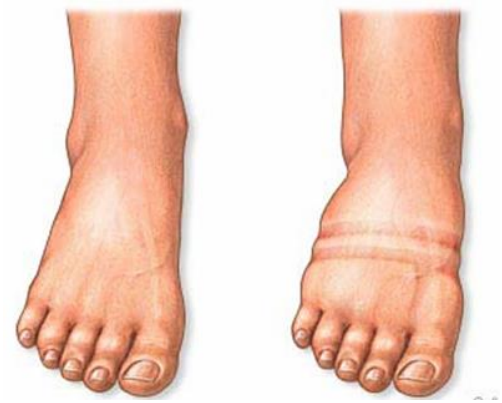
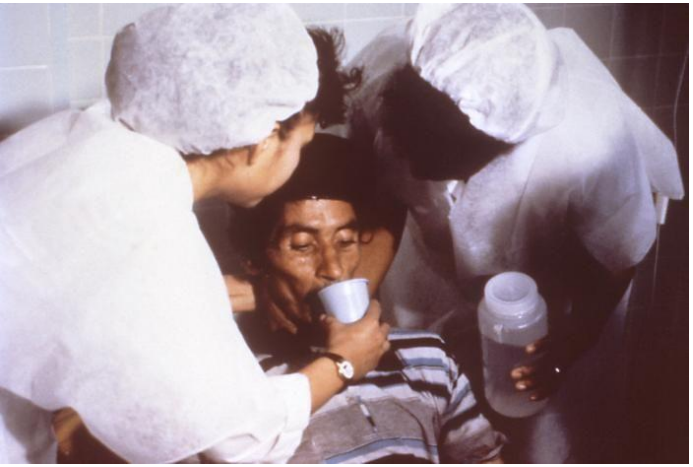
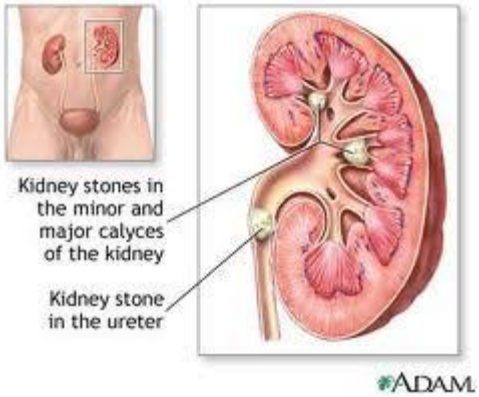
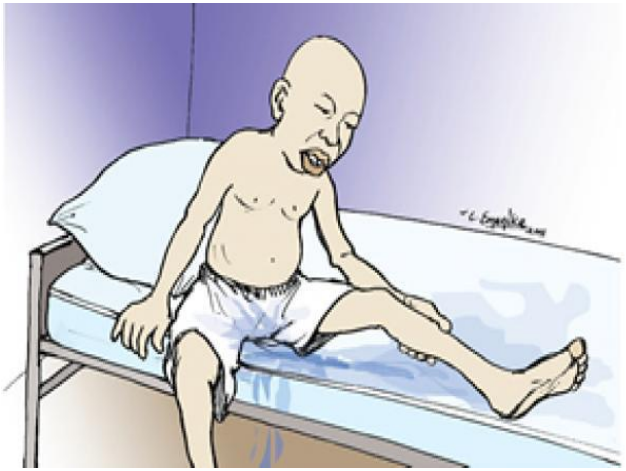



Figure 1: Normal vs. Enlarged Heart

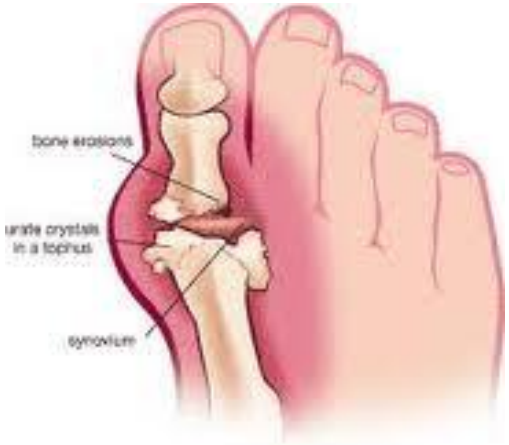


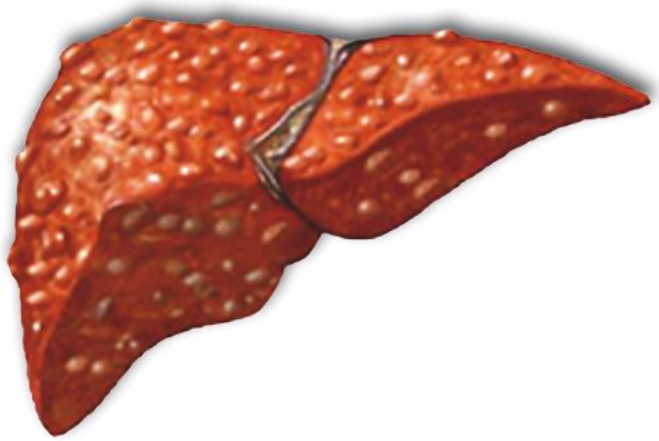


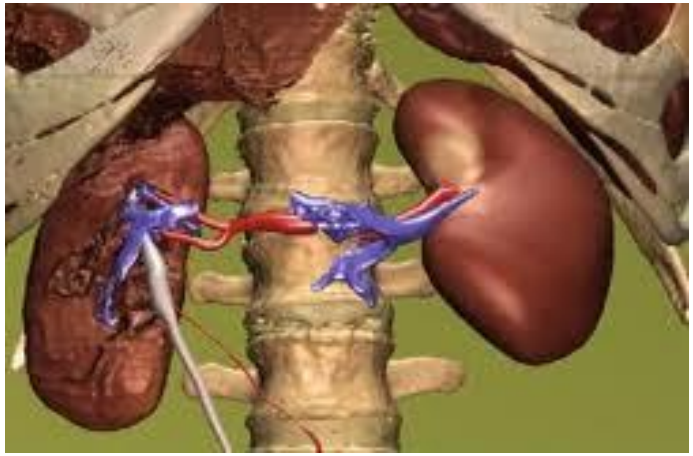


# Contraindications: thiazides and like

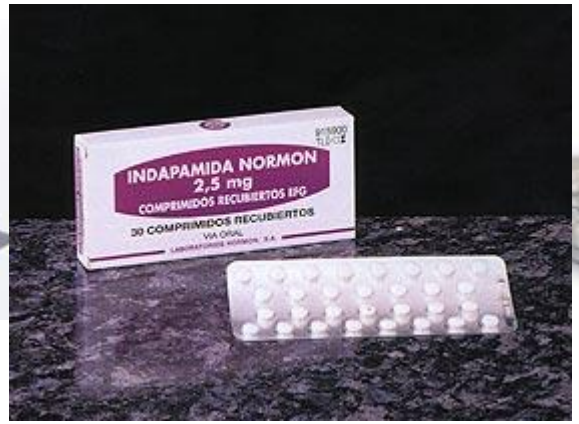





## *Side effects*

- - hypotension (vasodilation)
- - hyperglycemia (inhibition of insulin secretion)
- - hypokalemia (increased tubular flow rate)
- - metabolic alkalosis (due to hypokalemia)
- - azotemia (competition between urea and thiazide diuretics at the organic acid transporter)
- - hyperlipoproteinemia
- - male impotence
- **Increase** plasma levels of **LDL cholesterol, and triglycerides.**

- **LIKE THIAZIDES: Indapamide, Xipamid etc;**
- **Indapamide has a long lasting effect: 24-48 hours,**
- **the vasodilator effect is more intense.**
- **It is used in HTA.**



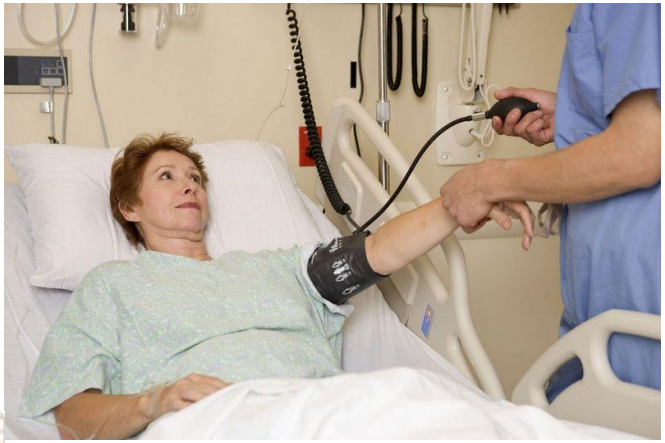

# Thiazides and like

## Pharmacokinetics

- indicate the morning of the empty stomach;
- absorb well, bioavailability of 60-80%;
- is coupled with 40-65% protein;
- Vd great;
- do not obey metabolism;
- is excreted unchanged;;
- T0.5 about 5-10 hours for hydrochlorothiazide, cyclomethiazide, but higher for other drugs.

# Thiazides and like








# HYDROCHLORTHIAZIDE

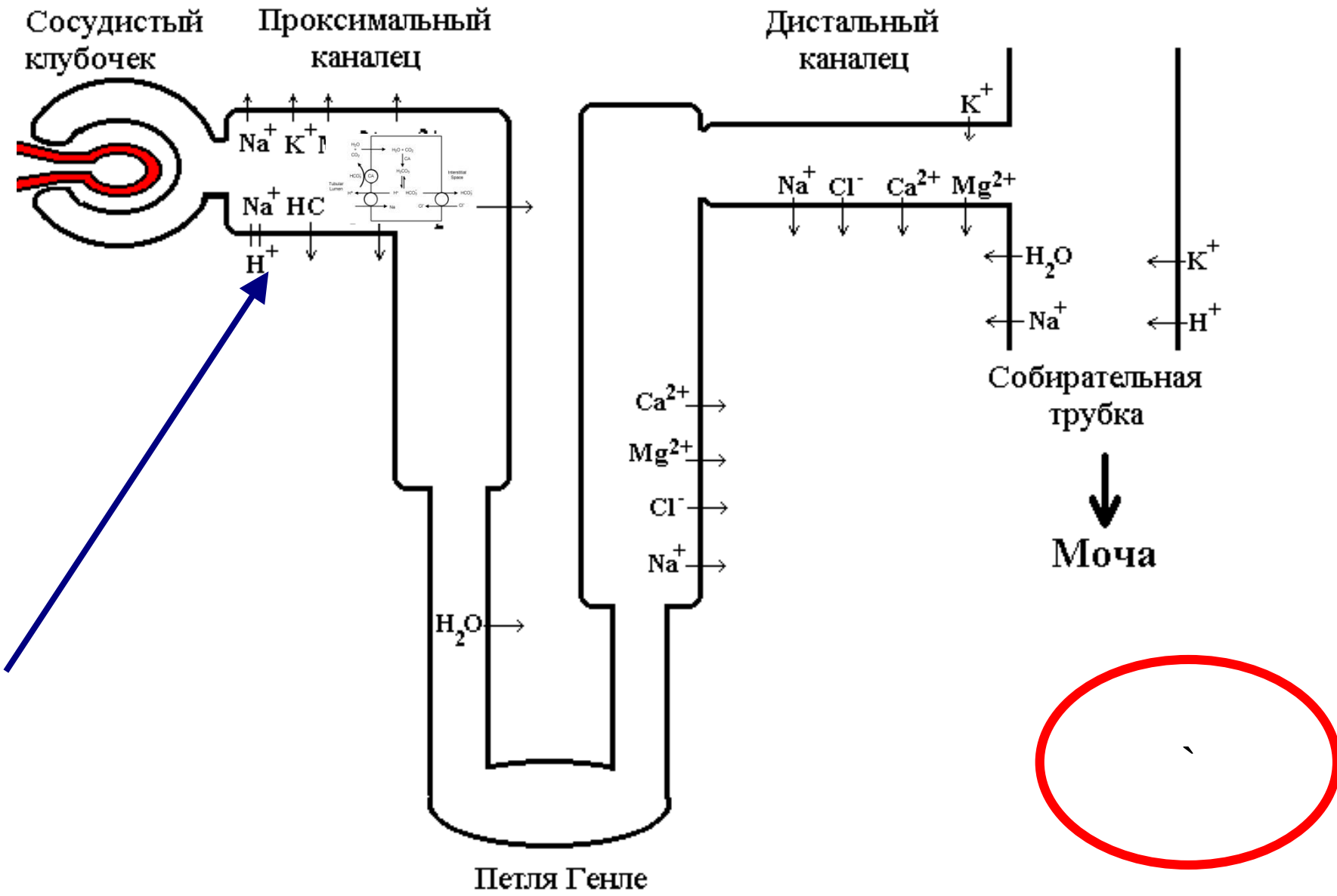
- *General information*
- - administered orally
- - eliminated by the organic acid transporter of the proximal tubule of the kidneys
- *Medical uses*
- - treatment of hypertension (due to decreased water reabsorption and vasodilation)
- - treatment of chronic resistant edema (together with loop diuretics)
- - prophylaxis of urolithiasis (increased tubular flow rate and no inhibition of Ca reabsorption)
- - treatment of diabetes insipidus (paradoxal decrease in urinary output)

# (CARBONIC ANHYDRASE) INHIBITORS

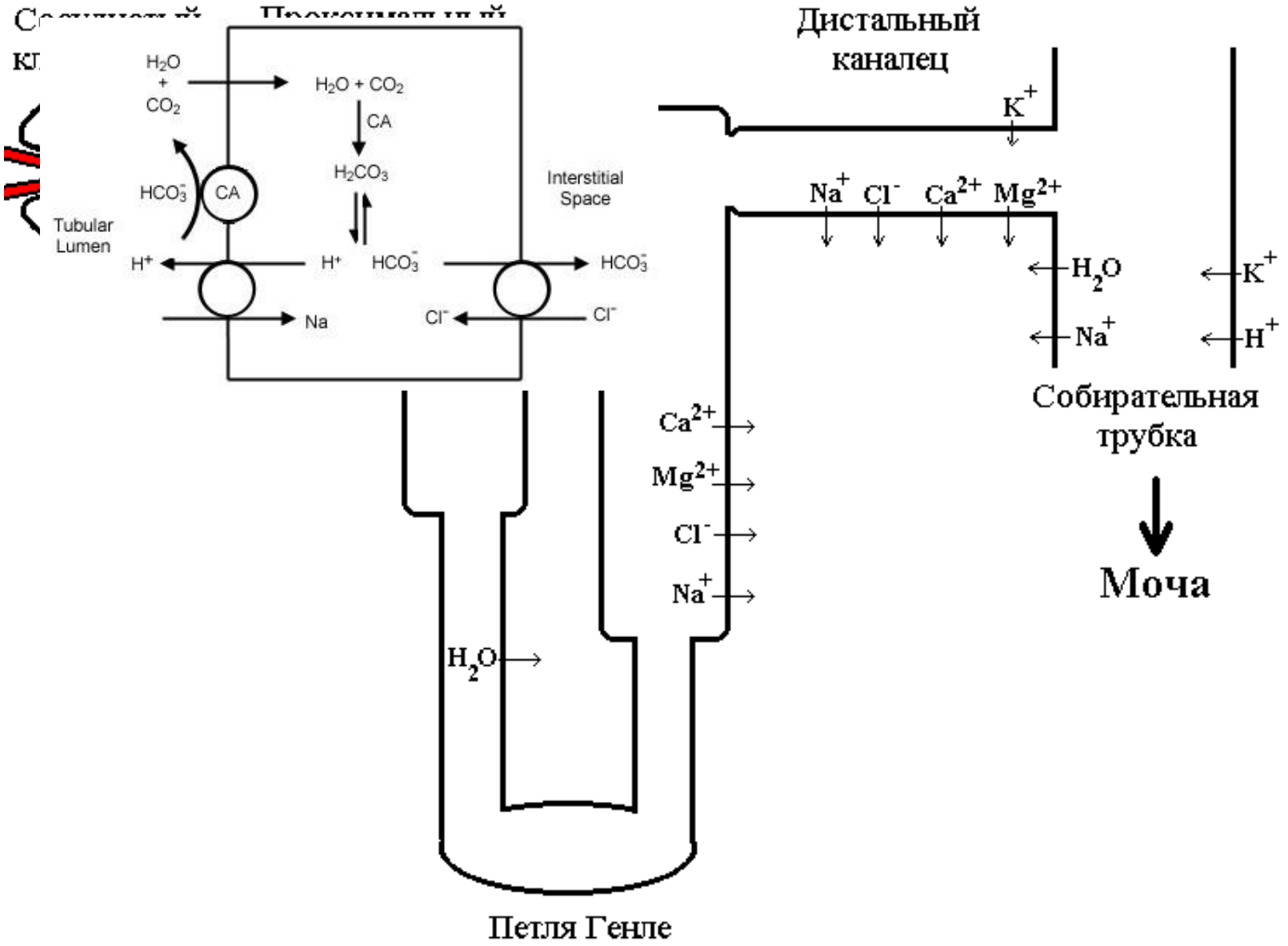
- - may increase urinary output to 10 liters/day (5% of glomerlular filtrate)
- *Mechanism of action:* carbonic anhydrase is the main enzyme responsible for metabolic pH buffering
- ***Drugs*** inhibit intracellular carbonic anhydrase in the tubular epithelium of the distal tubule
- - this leads to decreased intracellular hydrogen ion concentration and following disruption of the hydrogen ion/sodium antiporter

- **CA↓**
- **$HCO_3^- + H^+ \xrightarrow{CA} H_2CO_3 \xrightarrow{} H_2O + CO_2$**

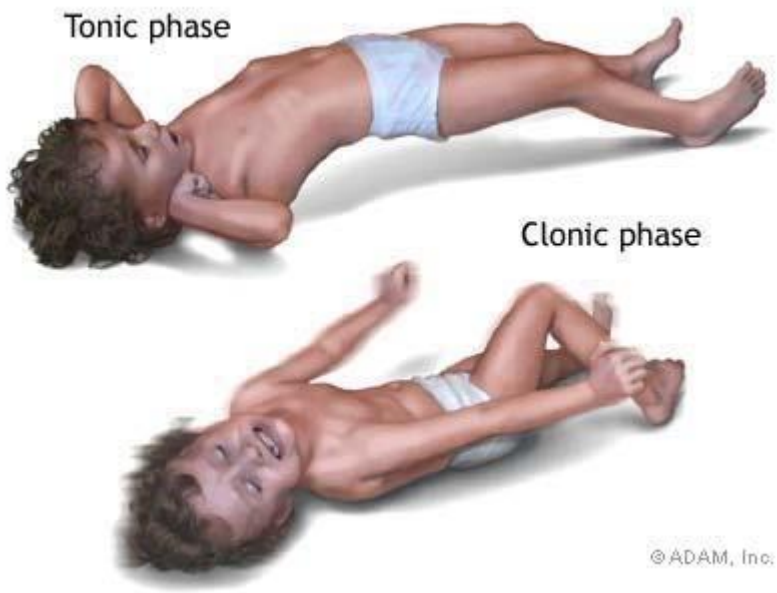
# The place of action of carbohydrazide inhibitors



# The place of action of carbohydrazide inhibitors



# Carboanhydrase inhibitors indications




# Carboanhydrase inhibitors

## Contraindications

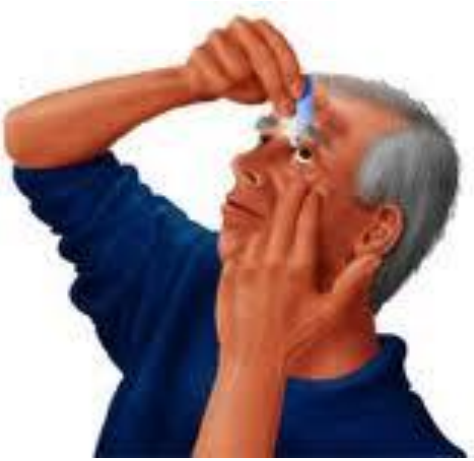
- hypersensitivity
- severe hepatic failure, cirrhosis of the liver;
- renal failure;
- adrenal insufficiency;
- precautions for patients with diabetes, acidosis, pregnancy

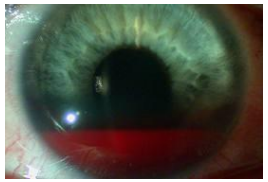
# Carboanhydrase inhibitors

## Adverse reactions

- metabolic acidosis;
- urine alcalosis
- phosphaturia and hypercalciuria with the formation of kidney stones;
- hypokalaemia, hyponatraemia;
- drowsiness and paresthesia at high doses;
- alergic reactions.
- Because they are similar to the sulfamide structure, they can cause red marrow suppression!

# Carboanhydrase inhibitors






# ACETAZOLAMIDE

- *General information*
- - not used as a diuretic
- *Medical uses*
- - treatment of glaucoma (carbonic anhydrase is also involved in production of the aquous humor of the eye)
- - treatment of epilepsy
- *Side effects*
- - hypokalemia (increased tubular flow rate)
- - metabolic acidosis (decreased hydrogen secretion and increased loss of bicarbonate due to no hydrogen ion in the tubular fluid to react with to form carbondioxide and water)

# POTASSIUM-SPARING DIURETICS (ALDOSTERONE RECEPTOR ANTAGOISTS)

- - may increase urinary output to 5 liters/day (3% of glomerular filtrate)
- - potassium-sparing diuretics antagonize the effect of aldosterone in the late distal tubule

# SPIRONOLACTONE

- *General information*
- - direct antagonist of aldosterone at the intracellular aldosterone receptors in the late distal tubule, thus inhibiting expression of aldosterone-dependent sodium reabsorption, and potassium and hydrogen ion secretion
- - administered orally
- *Medical uses*
- - coadministered with non-potassium sparing diuretics to preserve potassium
- - treatment of hyperaldosteronism (“conn’s syndrome”)
- *Side effects*
- - hyperkalemia (decreased potassium secretion)
- - metabolic acidosis
- - testicular atrophy, - impotence, - gynecomastia
- - amenorrhea

# Competitive antagonists of aldosterone

**Efects.**

- weak or very weak effect
- duration of effect: very long 3-5 days
- eleminate urine is rich in Na + and poor in K +.
- the effect is even more intense as the amount of aldosterone is greater => it does not work at all in the absence of aldosterone

# Competitive antagonists of aldosterone

## Indications

- hyperaldosteronism :
- a) primary - Conn's disease
- b) secondary: nephrotic syndrome, cirrhosis
- hypertension;
- edema in newborns and children in the first few months of life.
- refractory edema, in combination with furosemide;
- hypokalaemia, prophylaxis and treatment;
- situations requiring increased potassium in the body (familial paralysis, serious myasthenia, ectopic arrhythmias with hypokalaemia, ileus with hypokalaemia).

# Competitive antagonists of aldosterone

## Contraindications

- hypercalcaemia, hyponatraemia;
- acute renal insufficiency;
- severe liver failure;
- pregnancy (1st trimester), lactation;
- with caution in: chronic renal failure, diabetes mellitus, acidosis in children, association with potassium preparations, conversion enzyme inhibitors.

# Competitive antagonists of aldosterone

## Adverse reactions

- hyperkalaemia, hyponatraemia;
- metabolic acidosis;
- dyspeptic disorders
- gynecomastia, impotence in men;
- hirsutism in women;
- somnolence, headache, rash

# Competitive antagonists of aldosterone

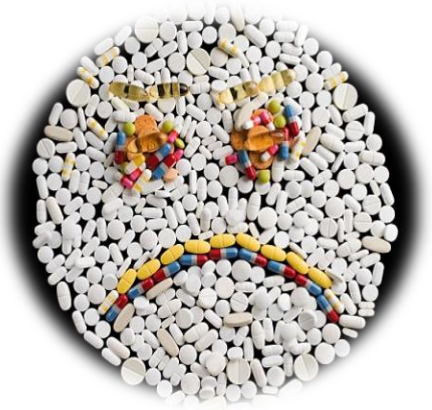
## Pharmacokinetics

- is indicated after the meal;
- absorption is 90% and bioavailability is 30-70%;
- 90% protein binding;
- It is metabolized in the liver in several active metabolites (canreon - 70% of activity);
- Eliminate 50% by urine and 50% by bile;
- T 0.5 - 10-35 hours

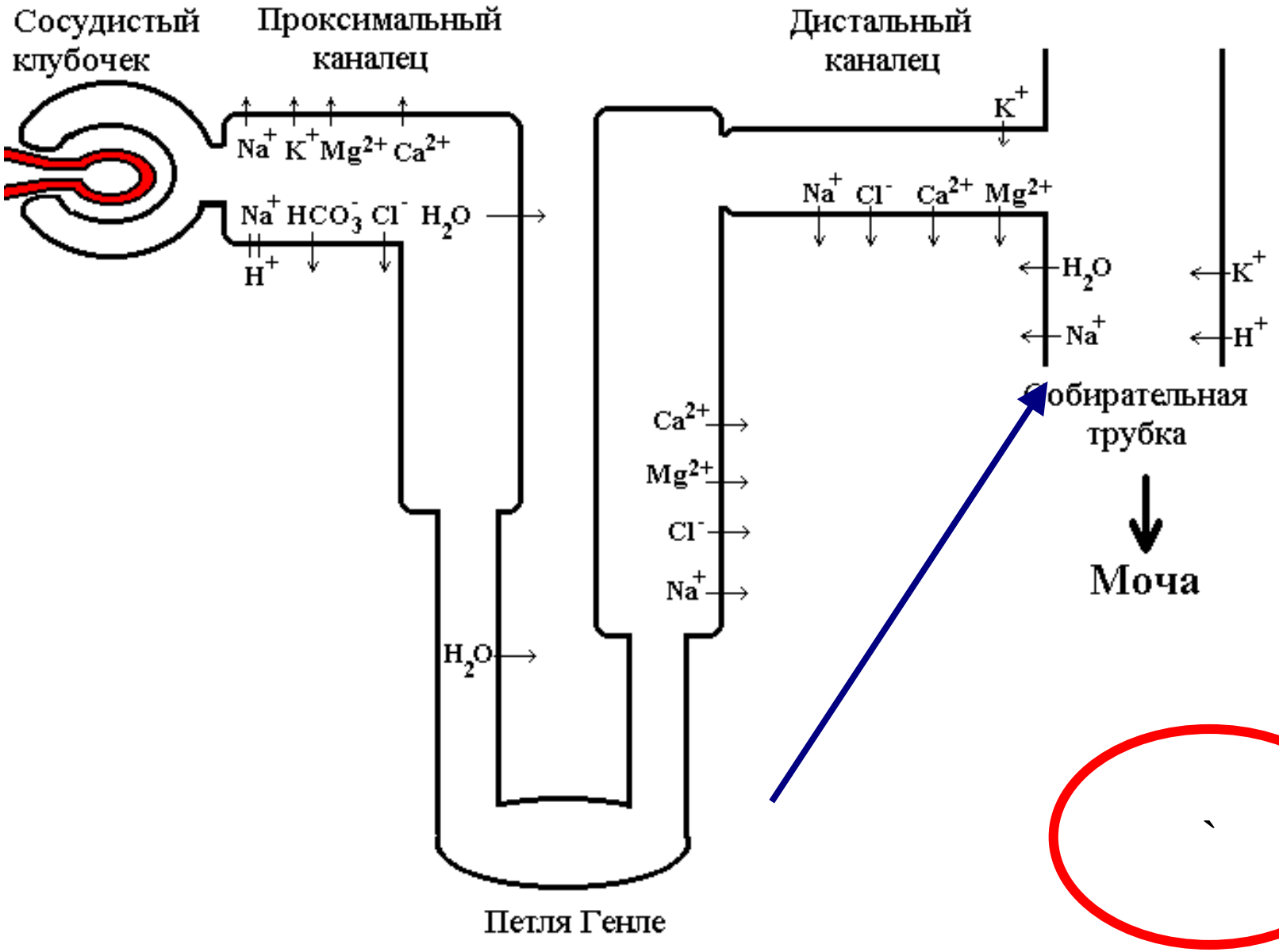
# Non-competing antagonists of aldosterone

## Mechanism of action

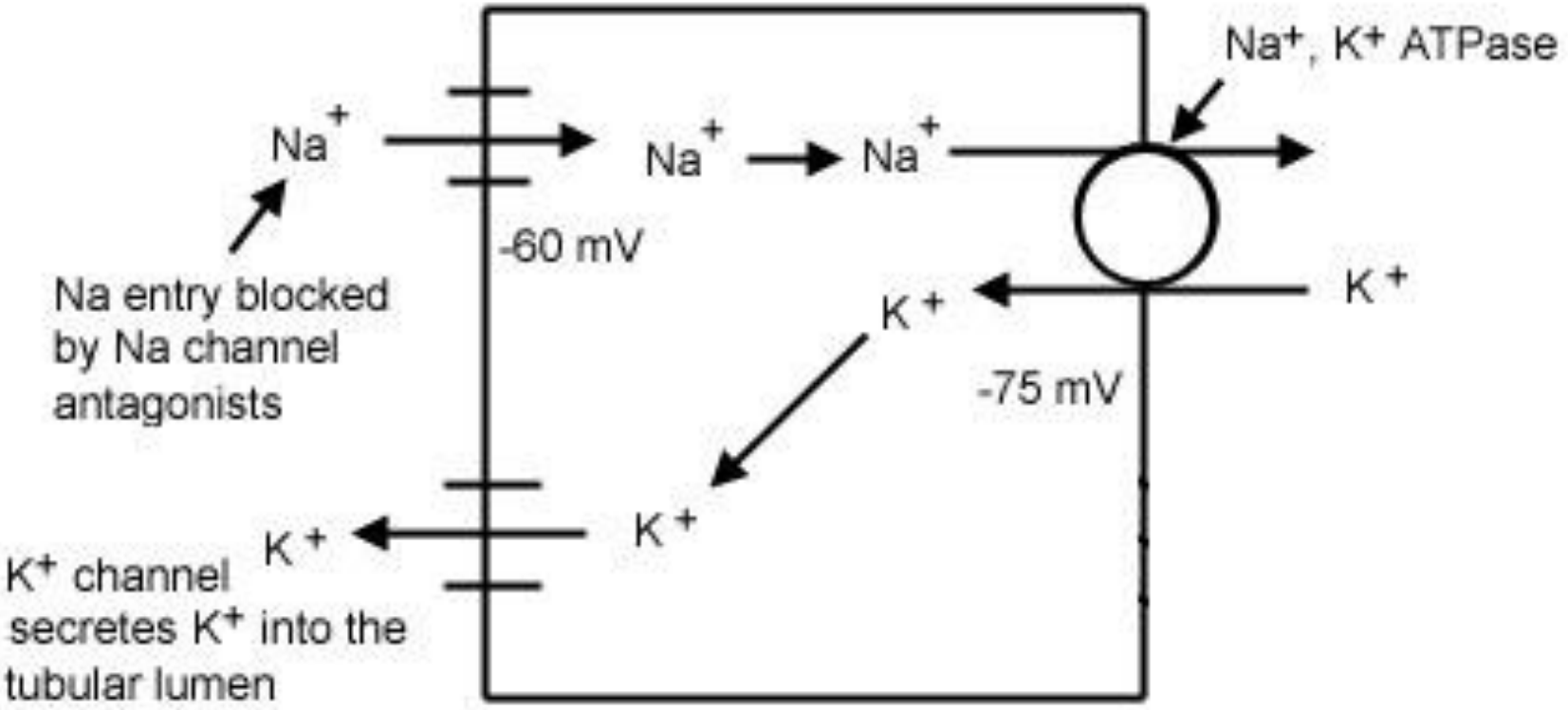
- triamterene and amiloride inhibit renal epithelial channels for Na;
- by influencing the Na-transporting proteins, and reducing K-secretion is secondary.



# Place of action - Non-competing antagonists of aldosterone



# Non-competing antagonists of aldosterone



# Non-competing antagonists of aldosterone

## Indications

- chronic cardiovascular disease (arterial hypertension, etc.)
- chronic heart failure;
- in combination with diuretics that cause hypokalaemia.

# Non-competing antagonists of aldosterone

## Contraindications

- Diseases and all conditions accompanied by hyperkalaemia, hypercalcemia, hyponatraemia;
- acute renal insufficiency;
- severe liver failure;
- pregnancy (1st trimester), lactation;

**Caution in:**

- chronic renal failure, diabetes mellitus, acidosis in children, association with potassium preparations, conversion enzyme inhibitors

# Non-competing antagonists of aldosterone

## Adverse reactions

- The most important adverse reaction - hyperkaliemia,
- hyponatremia;
- metabolic acidosis;
- dyspeptic disorders
- traimteren: muscle pain, megaloblastic anemia, hyperglycemia, hyperazotaemia;
- amiloride: paraesthesia, collapse, muscle pain, hyperglycaemia

# Non-competing antagonists of aldosterone

## pharmacokinetics

- is indicated after the meal;
- absorption -50-70% for triamterene and 90% for amiloride;
- 80% protein coupling;
- triamterene is predominantly metabolised;
- triamterene is eliminated by bile, and amiloride via urine, predominantly unchanged;
- T 0.5 represents triamterene - 1.5-2.5 hours, amiloride - 24 hours

# TRIAMTERENE

*General information*

- - indirect antagonist of aldosterone by blocking the aldosterone-dependent sodium reabsorption and potassium secretion
- - administered orally

*Medical uses*

- - coadministered with non-potassium sparing diuretics to preserve potassium

*Side effects*

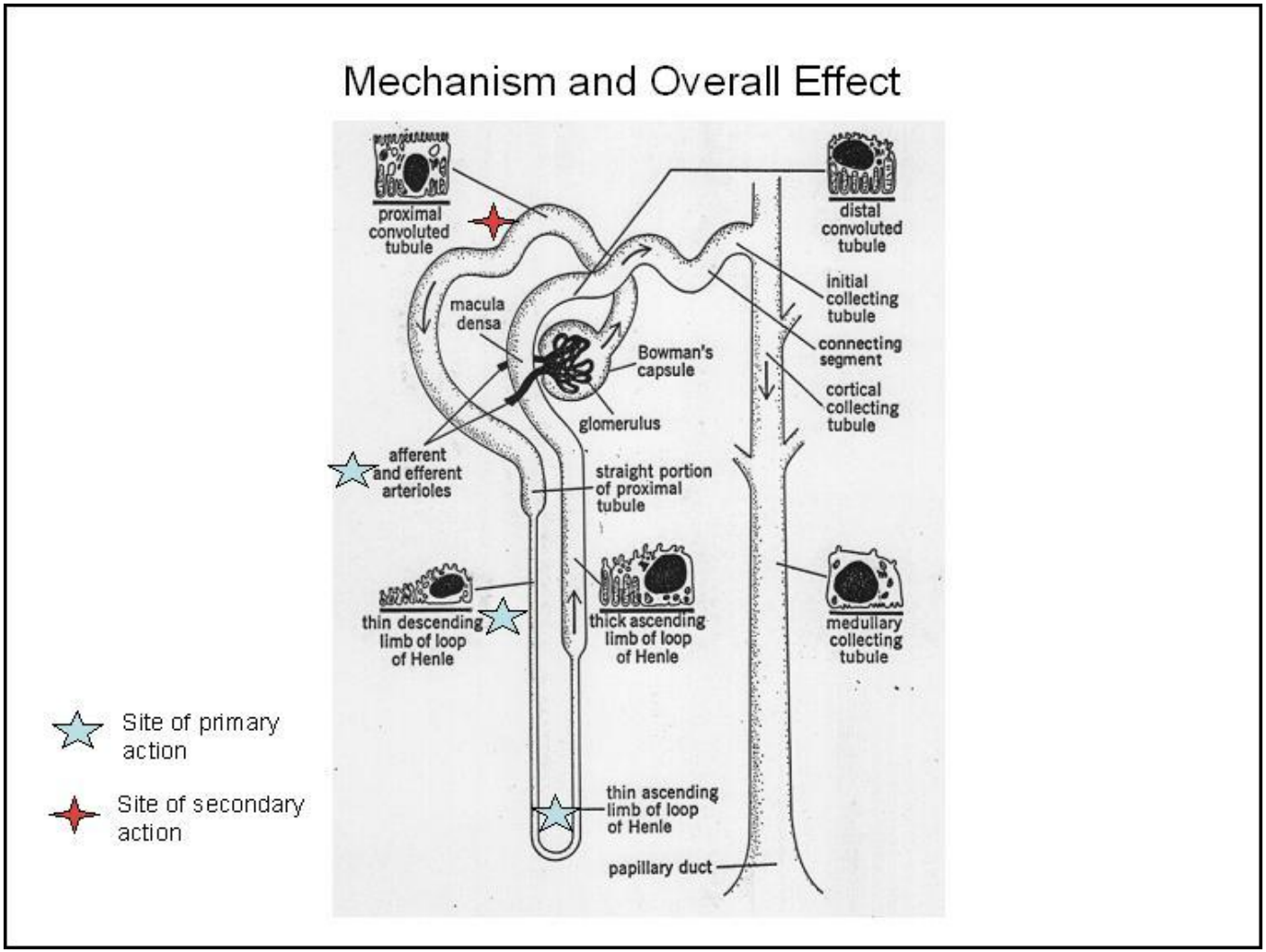
- - hyperkalemia
- - metabolic acidosis (due to hyperkalemia)
- AMILORIDE - same as triamterene

# Osmotic diuretics

# Osmotic diuretics

- are hyperosmolar substances,
- pharmacologically inert,
- with a high rate of glomerular filtration
- which does not re-absorb tubularly.

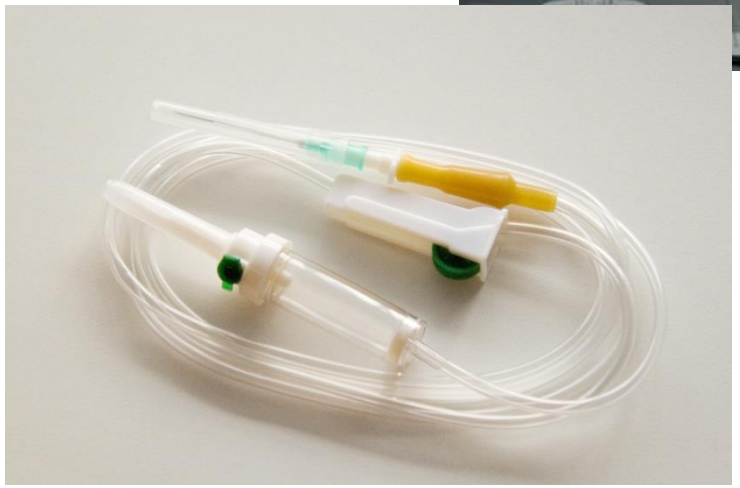
# Mechanism of action



# OSMOTIC DIURETICS

- osmotic diuretics do not increase urinary output by the way of inhibition of sodium reabsorption
- - however, osmotic diuretics also act by increasing the tubular oncotic pressure
- - the osmotic diuretics are chemical compounds that are unable to leave the intravascular fluid space except at the large fenestrations of the glomerular capillaries (freely filtered), and are unable to be reabsorbed by the tubular epithelium
- - this results in an increased intravascular- and tubular oncotic pressure

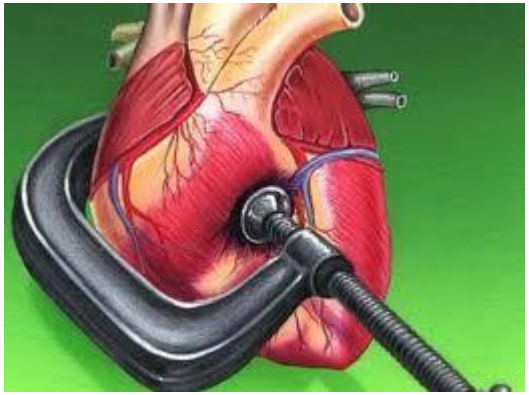
# Osmotic diuretics - MANITOL

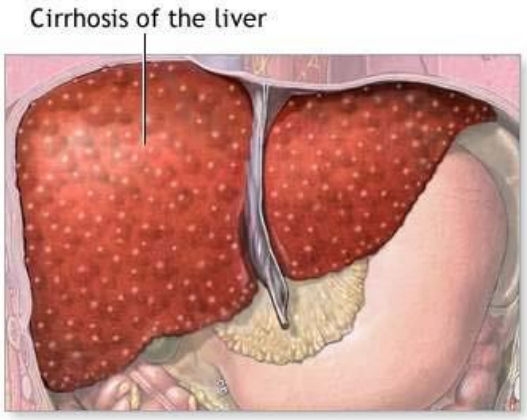


# Osmotic diuretics - MANITOL

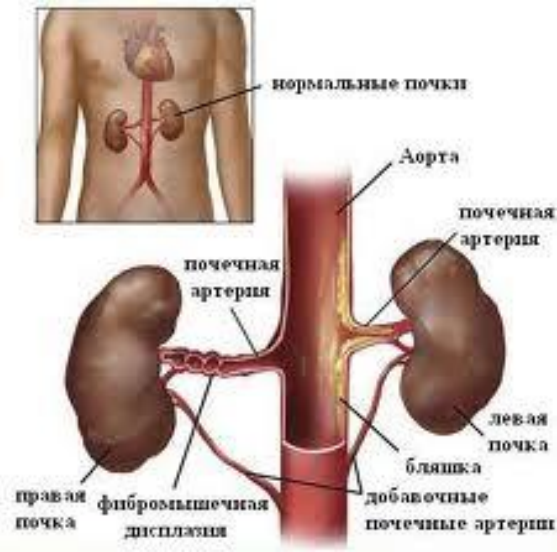
- **Indications**
  - **Prevention of anuria - post surgical interventions, shock, burns**
  - **Early phases of IRA - prevent the development of kidney ischemia**
  - **Acute drug intoxications - nephrotoxic, barbiturates,**
  - **!!! Mobilizes water from tissues**
  - **Cerebral edema**
  - **Acute congestive glaucoma crisis**

# Osmotic Diuretics - Contraindications

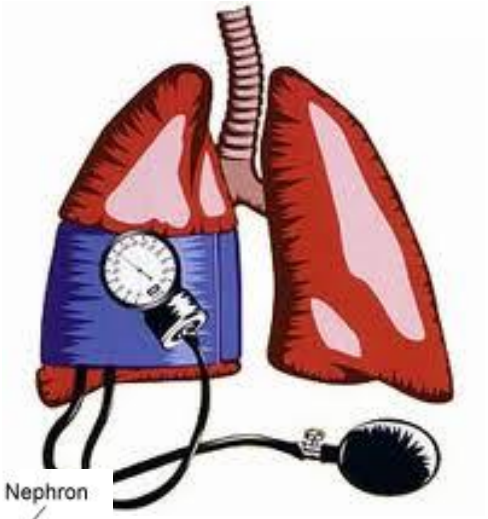



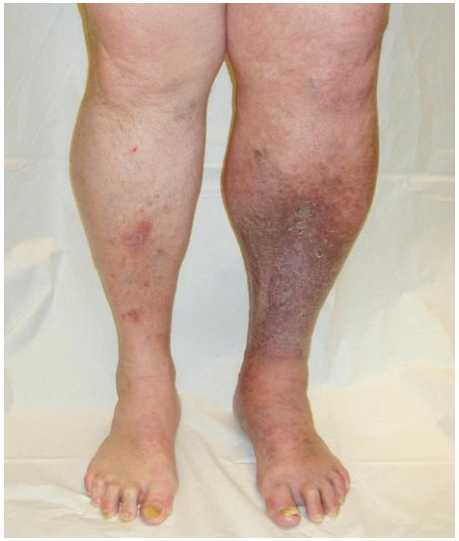


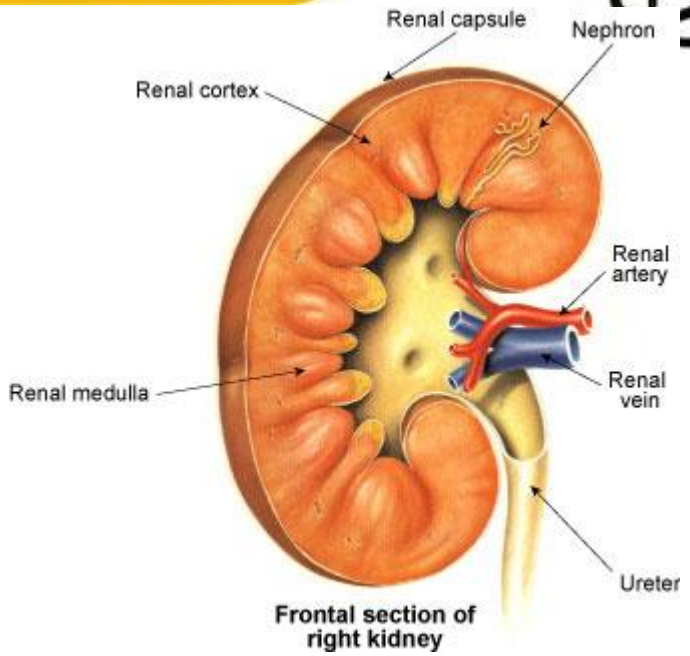


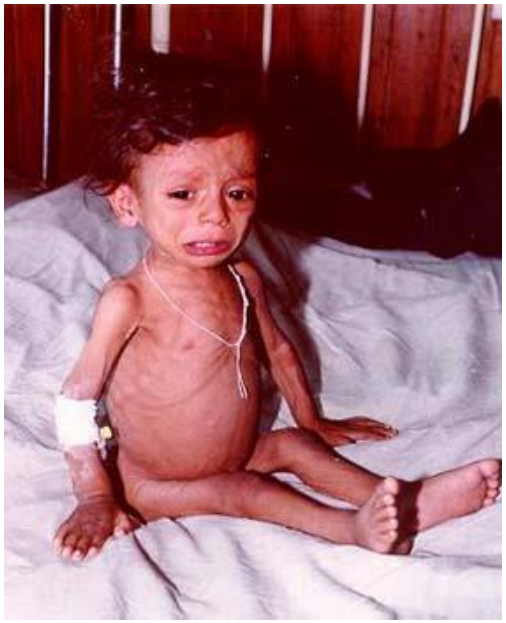



# Osmotic diuretics Adverse reactions







# Toxicity and Adverse Effects

- Osmotic diuretics increase the excretion of all electrolytes.
- The increase in extracellular fluid volume could exacerbate congestive heart failure or pulmonary congestion

# Osmotic diuretics

**pharmacokinetics**

- is indicated intravenously by infusion, does not leave the vascular bed;
- do not absorb at internal administration;
- is predominantly distributed in the vascular bed;
- not metabolized;
- are subjected to glomerular filtration,
- not tubular reabsorption;
- is removed for 30-60 min.

# Osmotic diuretics




# Vă mulţumesc pentru atenţie!