„NON SIBI, SED OMNIBUS"

MEDICAL UNIVERSITY - PLEVEN
FACULTY OF MEDICINE
Physiology

Lecture № 3

Urine formation by the kidneys. Glomerular filtration, renal blood flow and their control. Tubular reabsorption and secretion. Urine concentration and dilution. Micturition

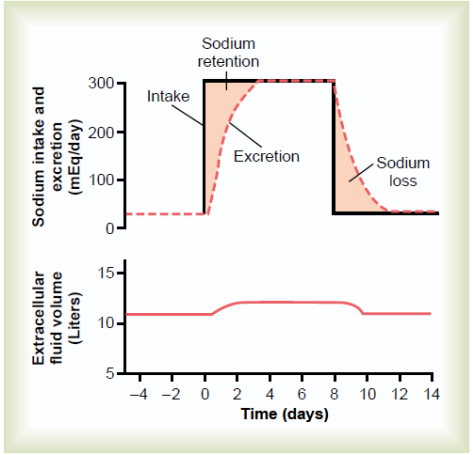
Assoc. Prof. Zdravka Radionova, MD, PhD

Objectives:

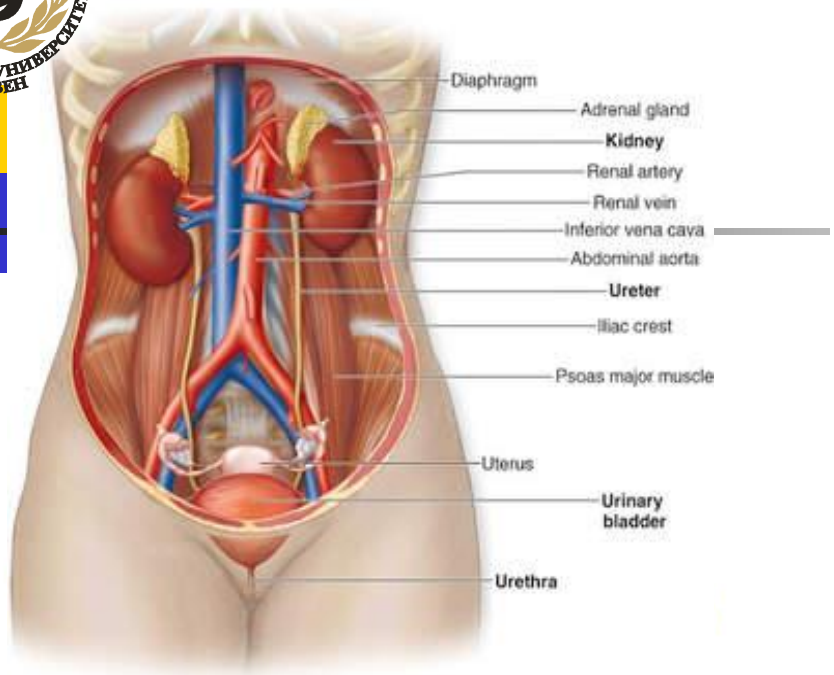
- **To understand** the:
  - physiological anatomy of the kidneys
  - structure of the nephron
  - renal blood flow ⇨ glomerular filtration
  - basic renal processes that determine the composition of the urine – R and S
  - urine concentration and dilution and their control
  - micturition reflex

❖ Functions of the kidneys

- To rid the body of waste materials (**excretion**)
- **Regulation of** (**homeostatic functions**):
  - the volume and composition of the body fluids (water and electrolytes)
  - body fluid osmolality and electrolyte concentrations
  - arterial pressure
  - acid-base balance
  - Secretion (erythropoietin, renin and calcitriol), metabolism, and excretion of hormones
  - gluconeogenesis

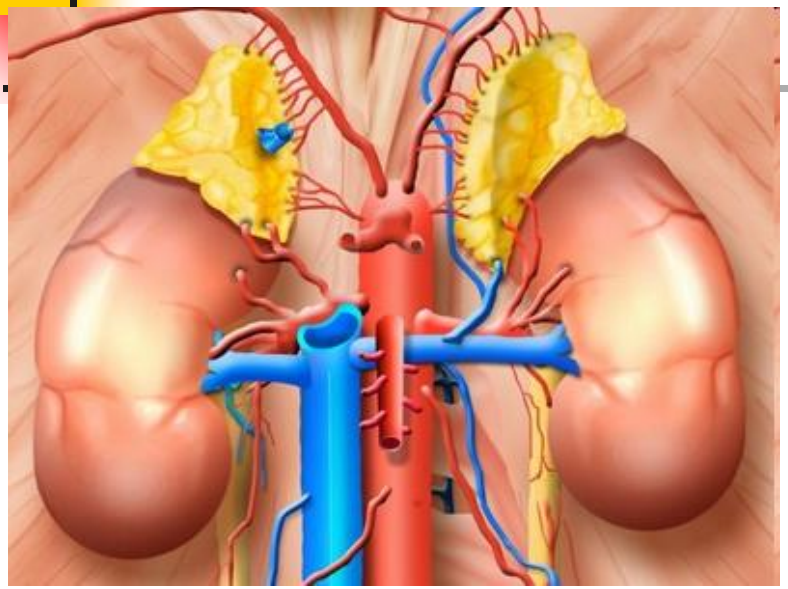


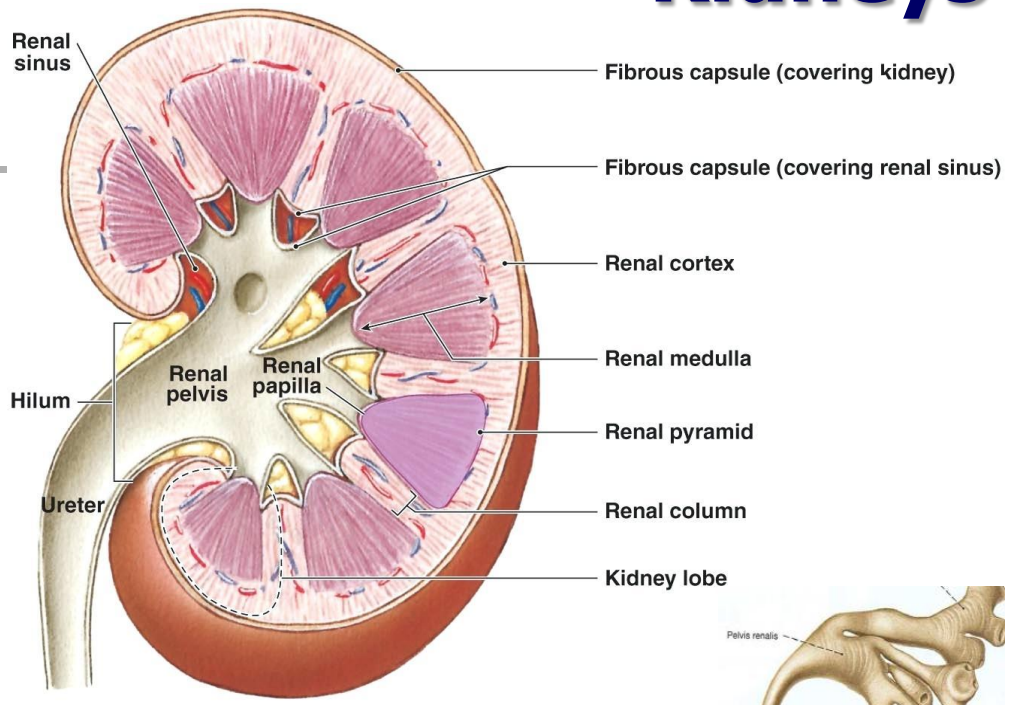
❖The Urinary System

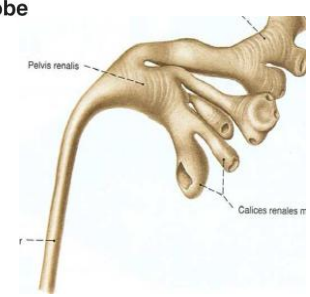


- Pair of **kidneys** on either side of the spine - bean-shaped
- Pair of **ureters** - connect kidneys to urinary bladder
- **Urinary bladder** – to collect, store, and release urine
- **Urethra** - leads from bladder outside the body

❖Physiological Anatomy of the Kidneys







Renal capsule

Renal **cortex** (5-10 mm) and renal **medulla**

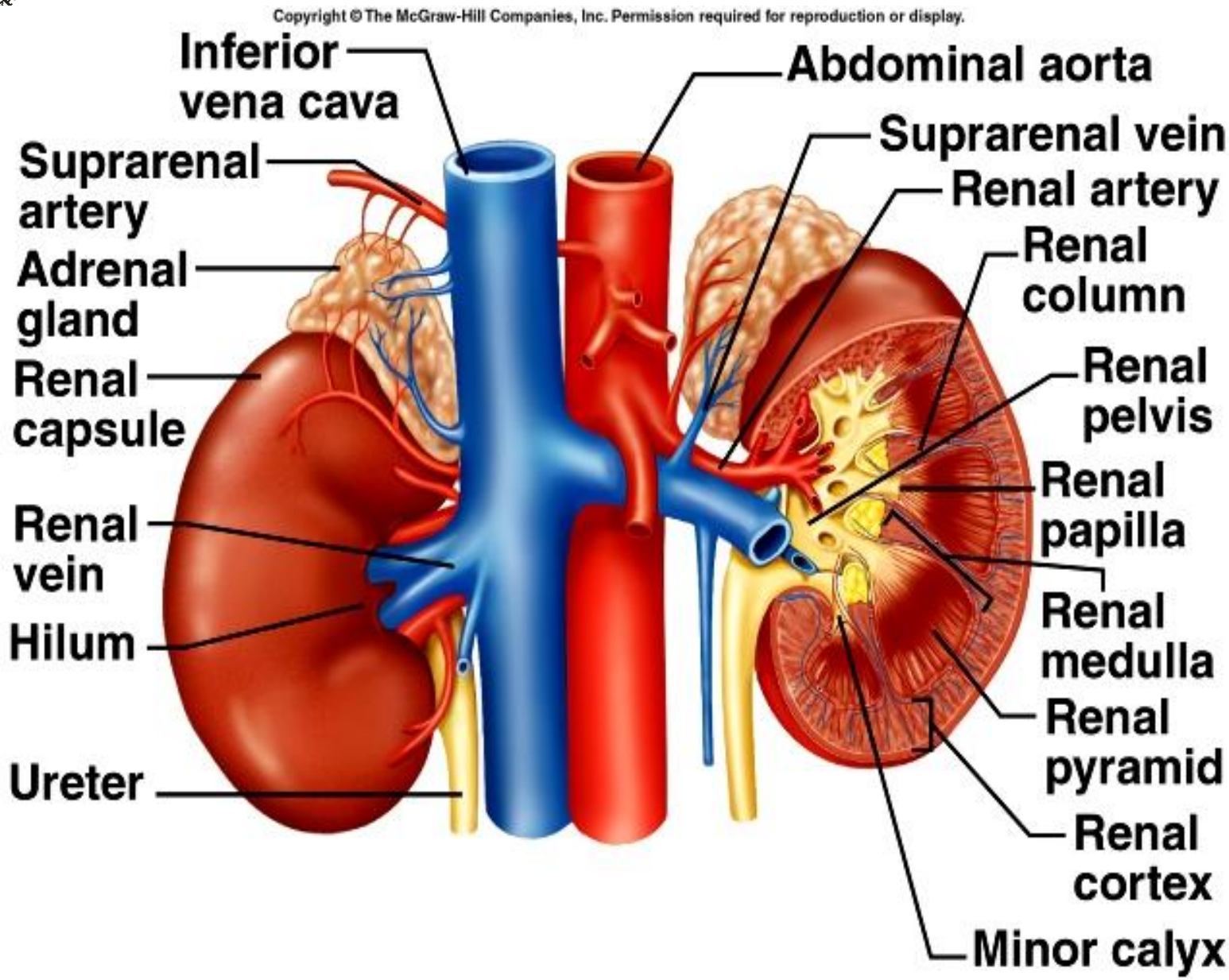
8-10 renal **pyramids** (apex - renal papilla points to the hilum)

Minor (8-9) and major (2-3) **calyces**

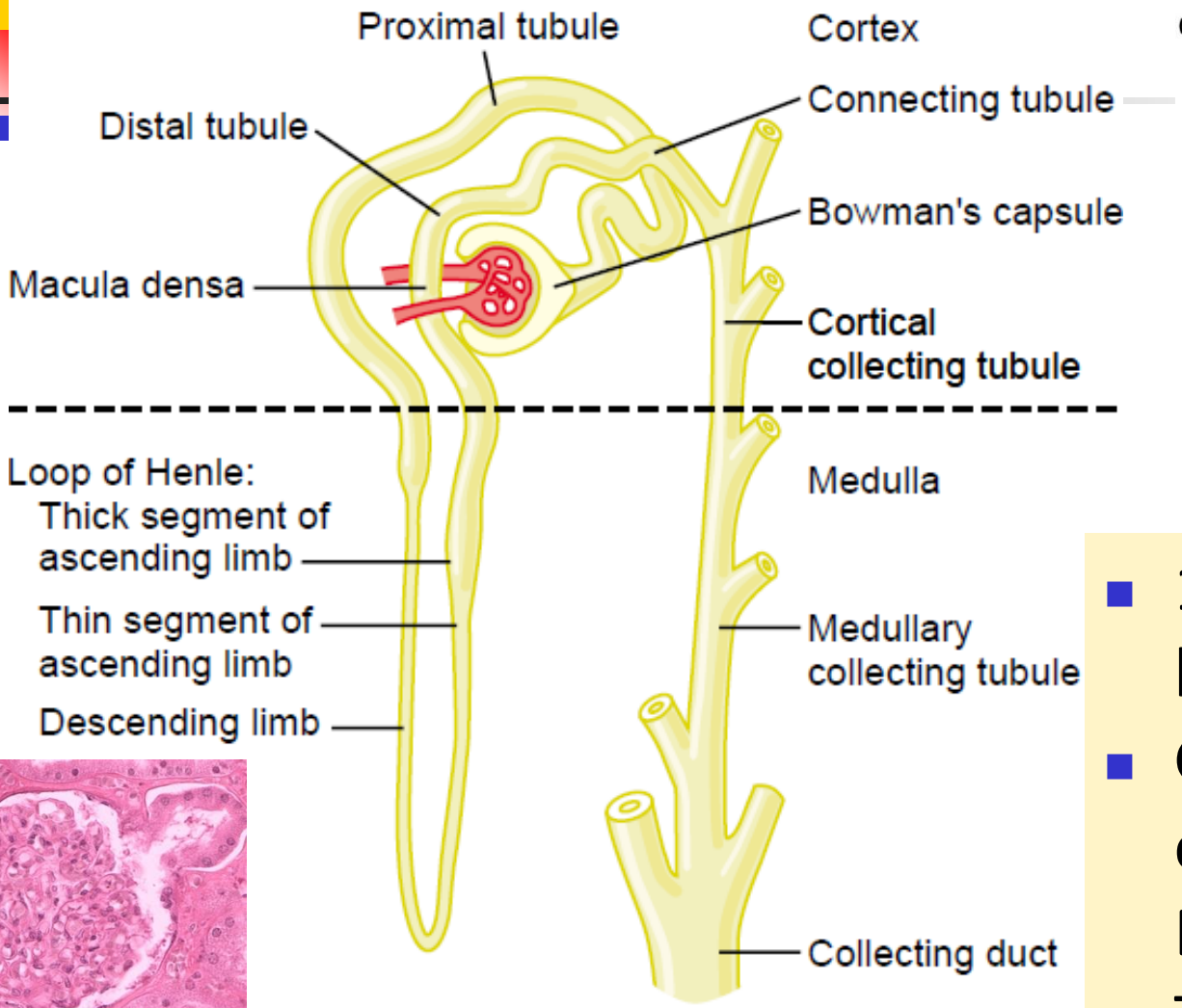
Renal **pelvis**

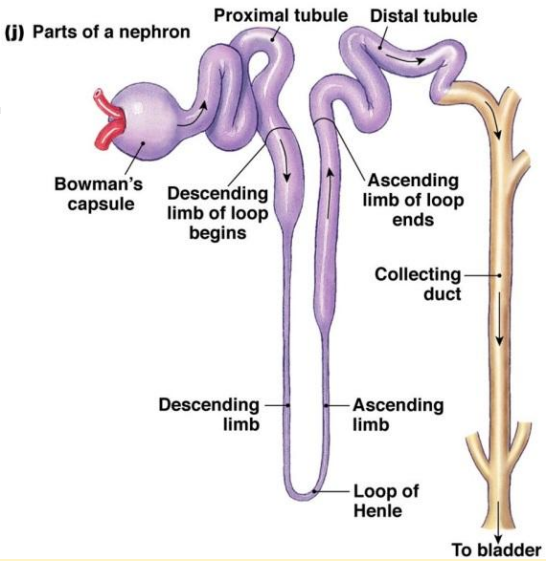
Nephron

Physiological Anatomy of the Kidneys



The Nephron - the Functional Unit of the Kidney



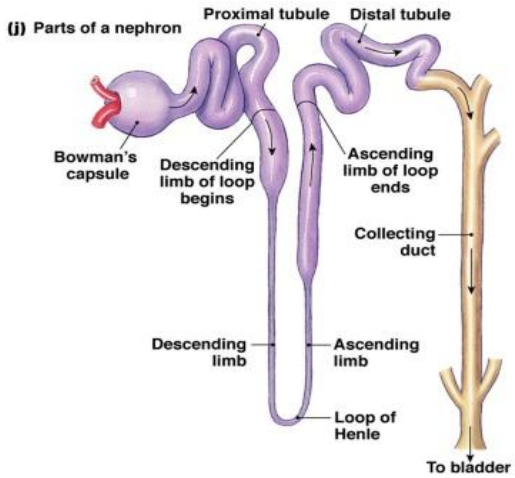


- 1 000 000 in each kidney
- Glomerulus encased in Bowman’s capsule
- Tubule

- https://www.youtube.com/watch?v=QsSdAXv5BEM

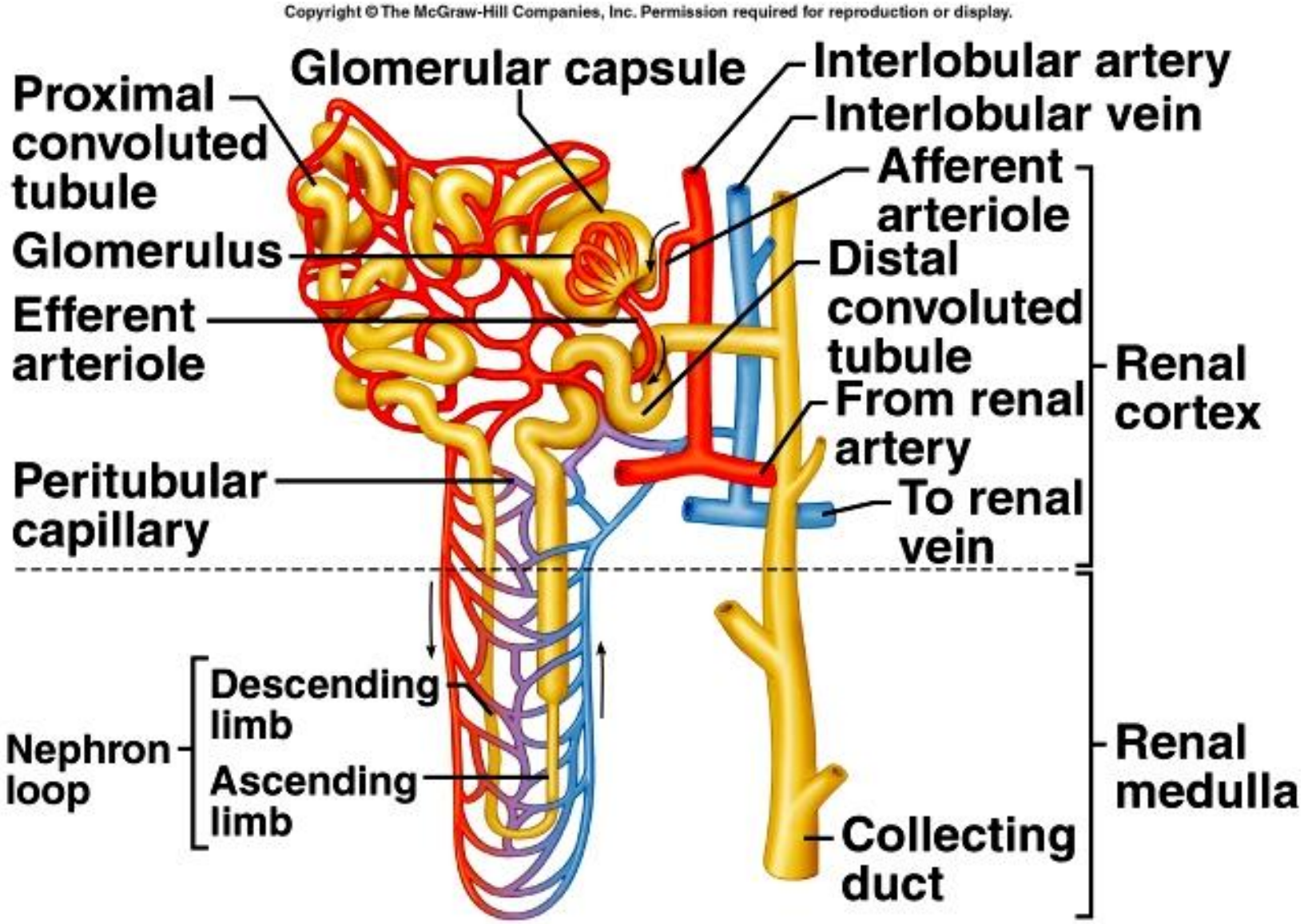
The Nephron

- **Renal corpuscle:**
  - **Glomerulus** – capillaries, filters plasma
  - Glomerular or Bowman's capsule
- **Bowman's capsule**
  - Receives filtrate
- **Proximal convoluted tubule**
  - Reabsorption of water and solutes
- **Loop of Henle** or Nephron loop
  - Regulates concentration of urine
- **Distal convoluted tubule** and **Collecting tubule, duct**
  - Reabsorption of water and electrolytes (ADH, aldosterone, ANP)
  - Tubular secretion



The kidney cannot regenerate new nephrons

The Nephron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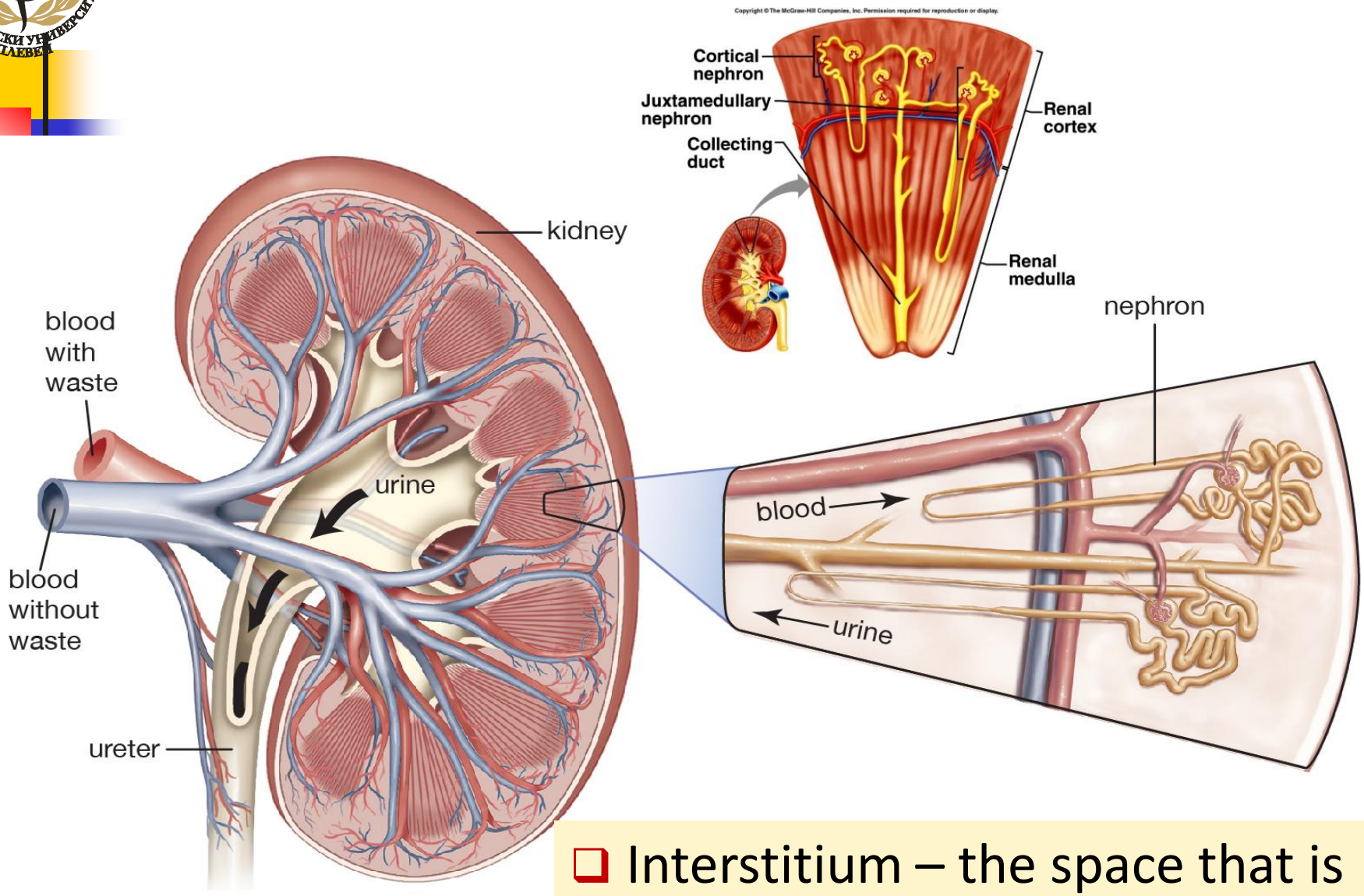
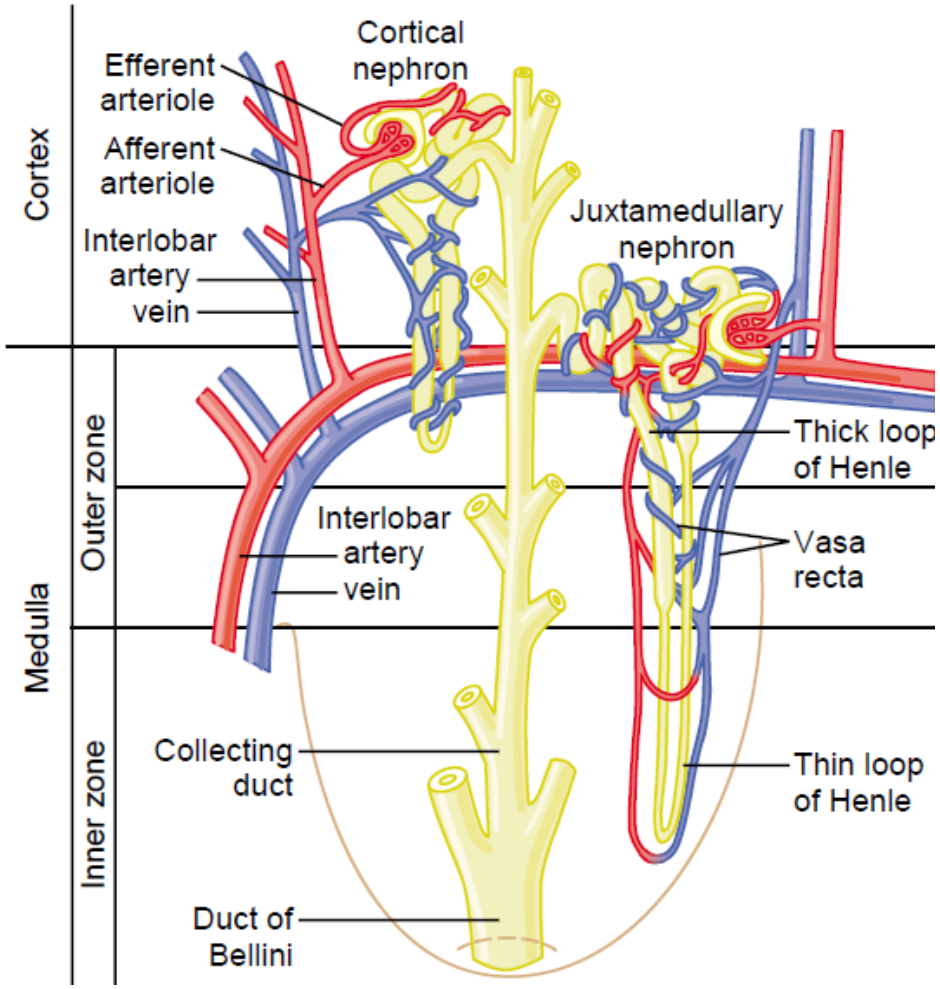
Glomerular capsule
Interlobular artery
Proximal convoluted tubule
Interlobular vein
Afferent arteriole
Glomerulus
Distal convoluted tubule
Efferent arteriole
From renal artery
Renal cortex
Peritubular capillary
To renal vein
Descending limb
Nephron loop
Ascending limb
Renal medulla
Collecting duct

General organization of the kidneys



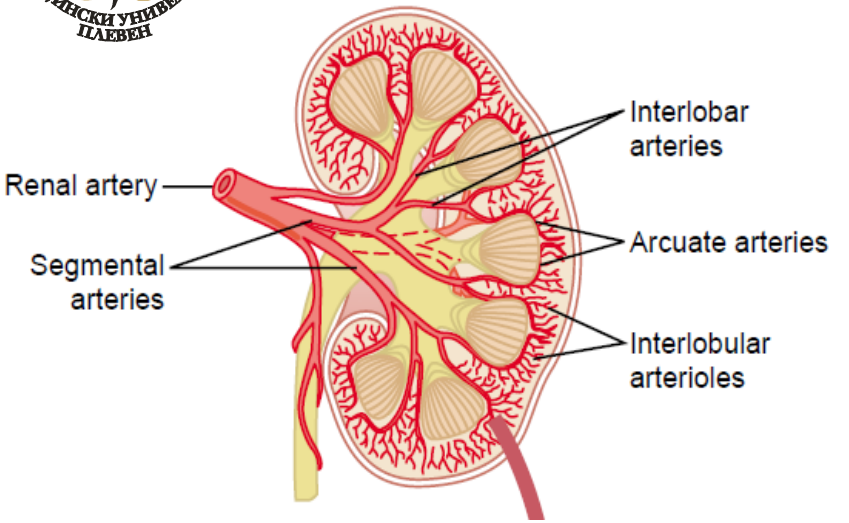
- Interstitium – the space that is not vessel or tubule

Two types of Nephrons - Cortical and Juxtamedullary: Regional Differences in Nephron Structure



- **Cortical nephrons** - 80%
  - Glomeruli in the outer cortex
  - Short loops of Henle
  - Peritubular capillaries
- **Juxtamedullary nephrons**
  - Glomeruli deep in the cortex near the medulla
  - Long loop of Henle
  - Vasa recta instead of peritubular capillaries

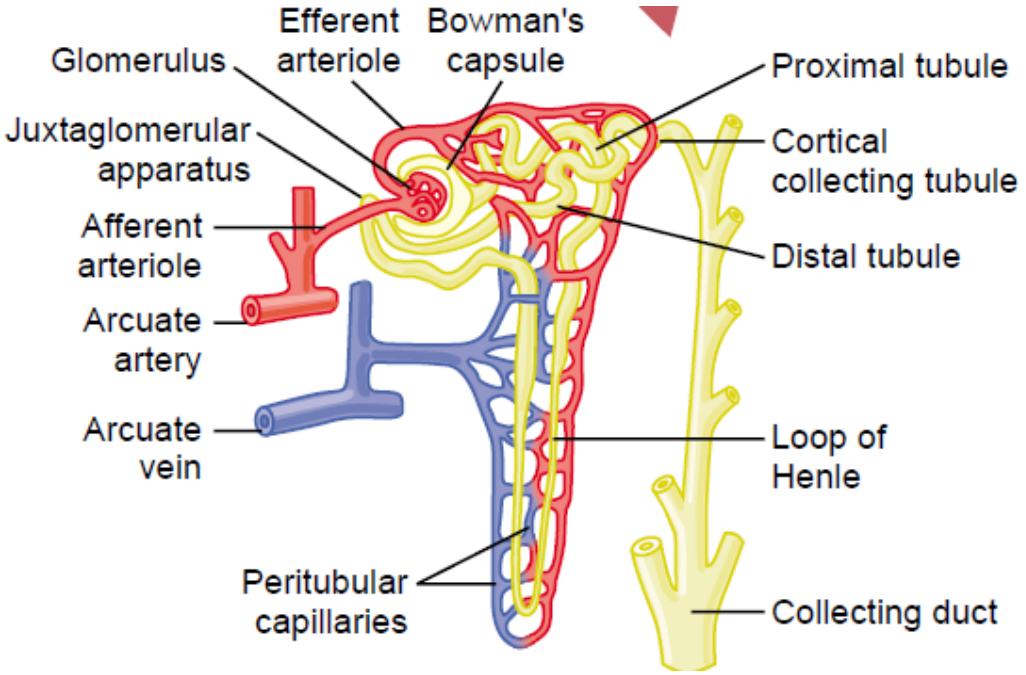
Renal Blood Supply



- 2 capillary networks
  - Glomerular – 60 mm Hg
  - Peritubular – 13 mm Hg

1300 ml/1'
Receive about 25% of cardiac output

- **Renal** artery
- **Interlobar** artery
- **Arcuate** artery
- **Interlobular** artery
- **Afferent arteriole**
- **Efferent arteriole**

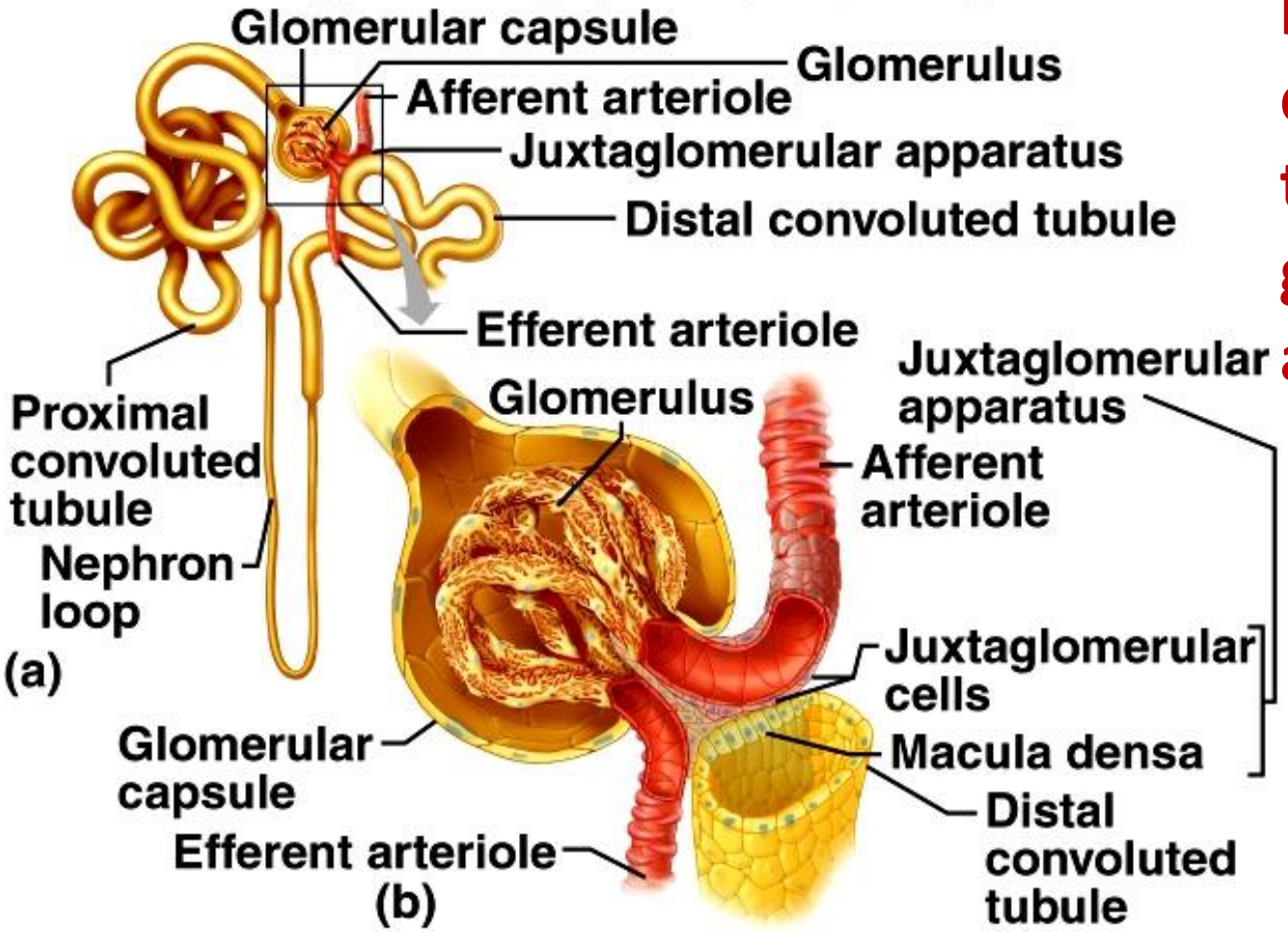


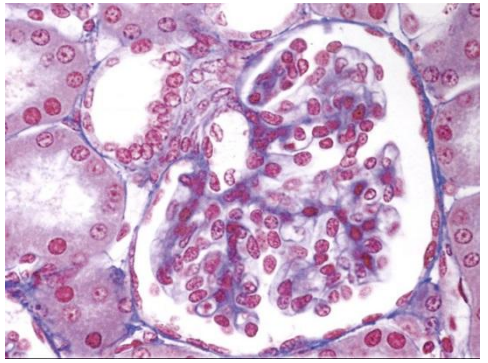
Juxtaglomerular apparatus

Vascular pole

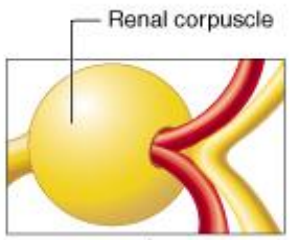
Urinary pole

- Specialized structure **formed by the distal convoluted tubule and the glomerular afferent arteriole**

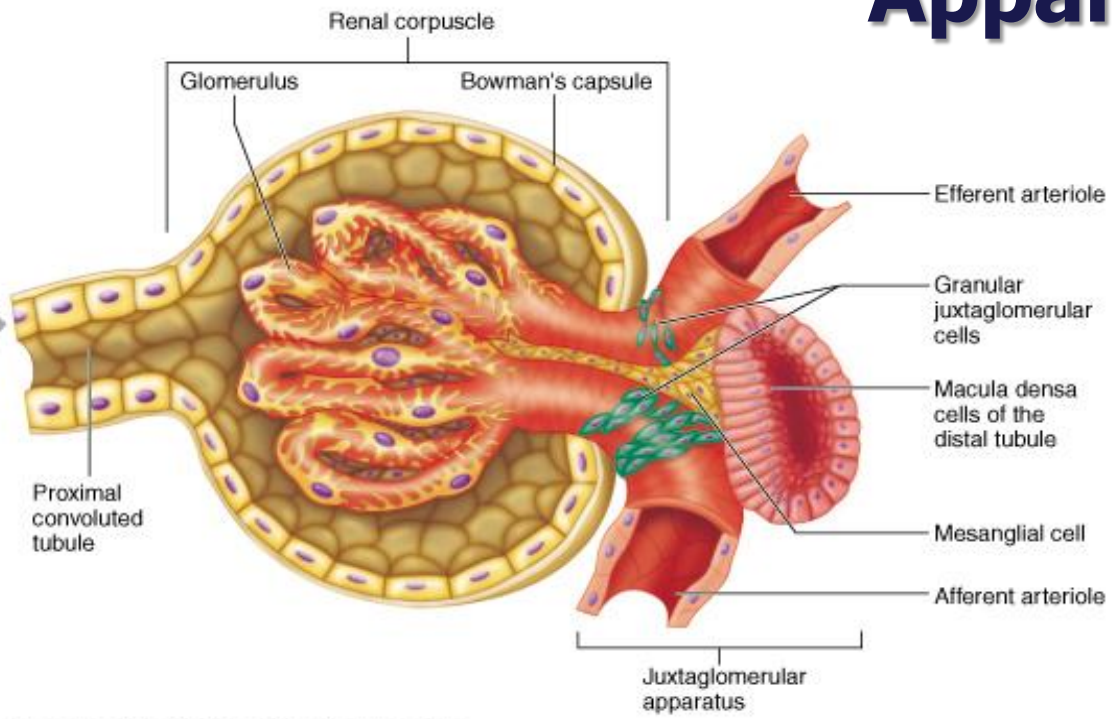




Structure of the Juxtaglomerular Apparatus



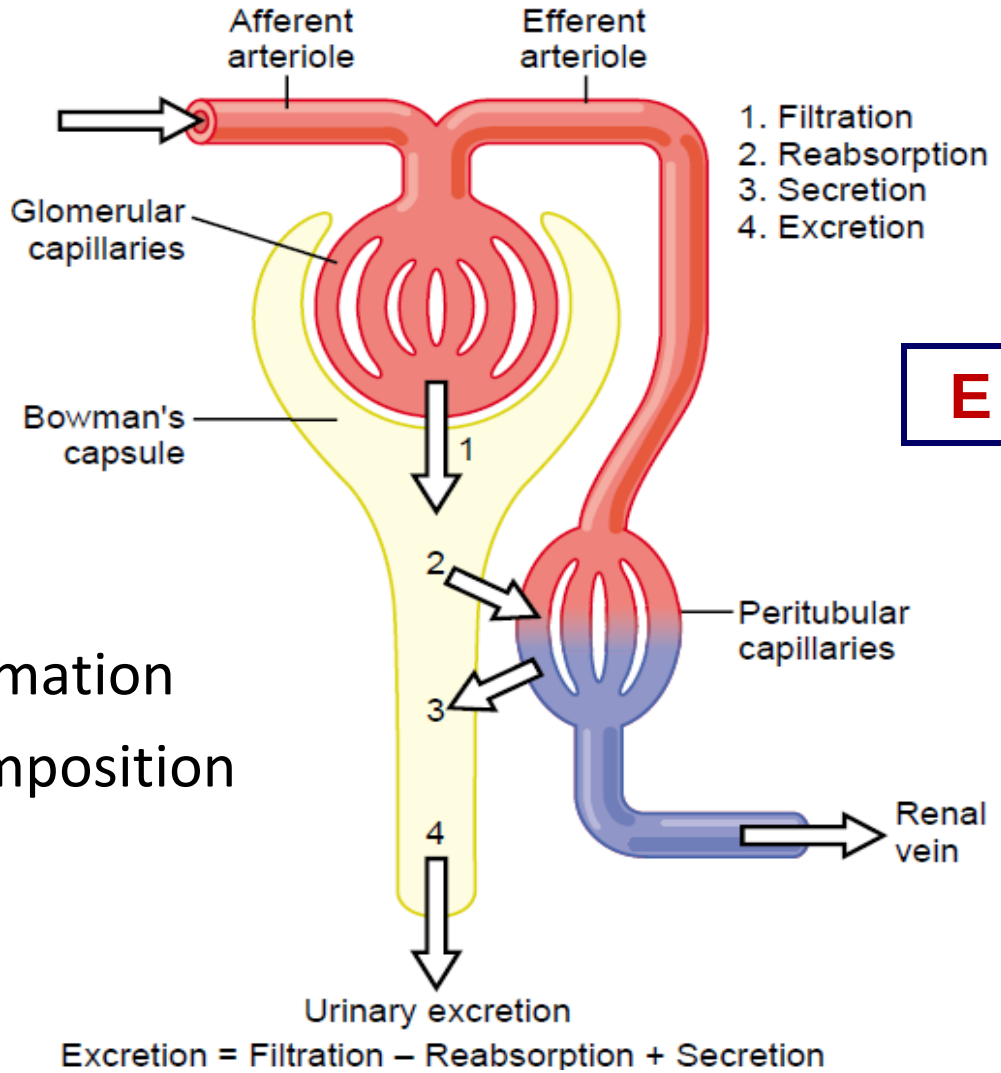
The endocrine part of the kidney near the **vascular pole** of the glomerulus



- Function: releases hormones *vitamin D and erythropoietin* and regulates blood pressure and the filtration rate of the glomerulus
- Macula densa – detects Na+ concentration in the tubular fluid
- **Renin** (enzyme) – released by Juxtaglomerular cells
- Mesangial cells – support, secrete Pg, cytokines, phagocytosis

❖Urine formation

Basic kidney processes that determine the composition of the urine

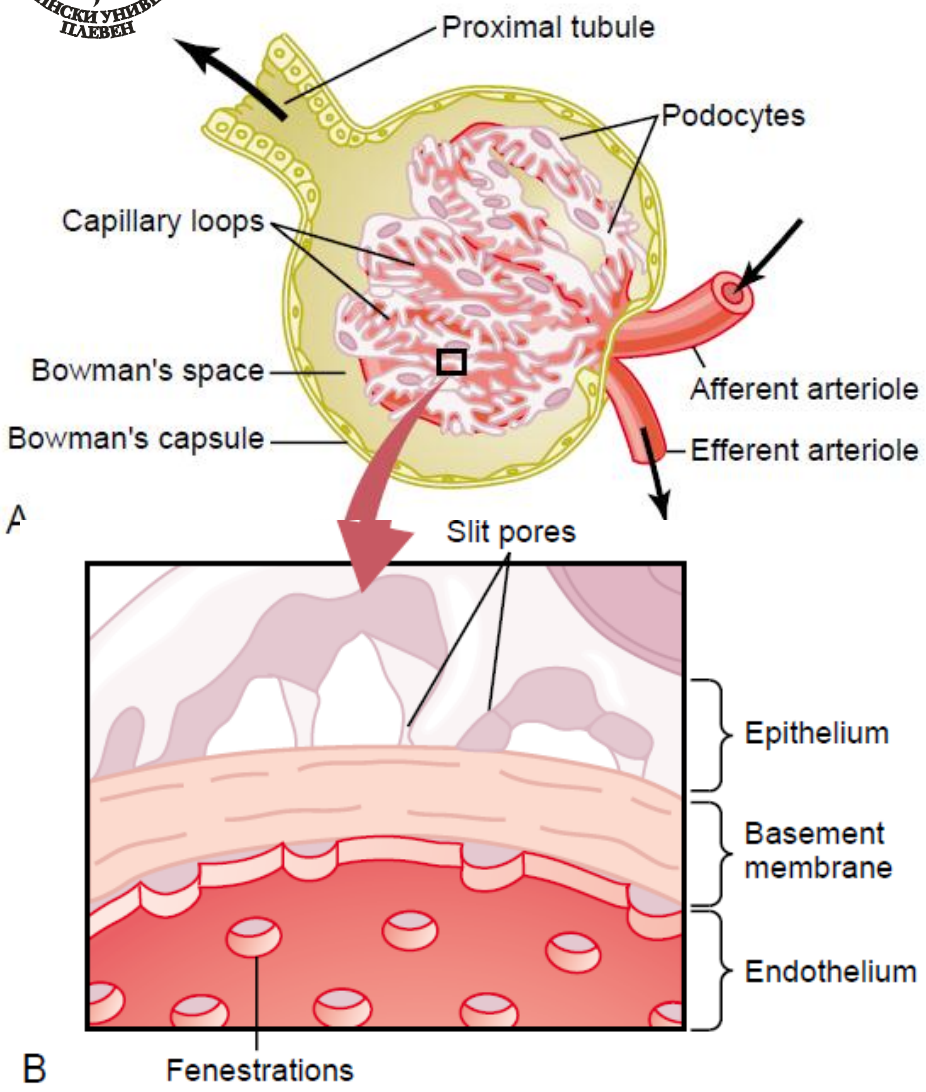


E = F - R + S

- Urine formation
- Urine composition

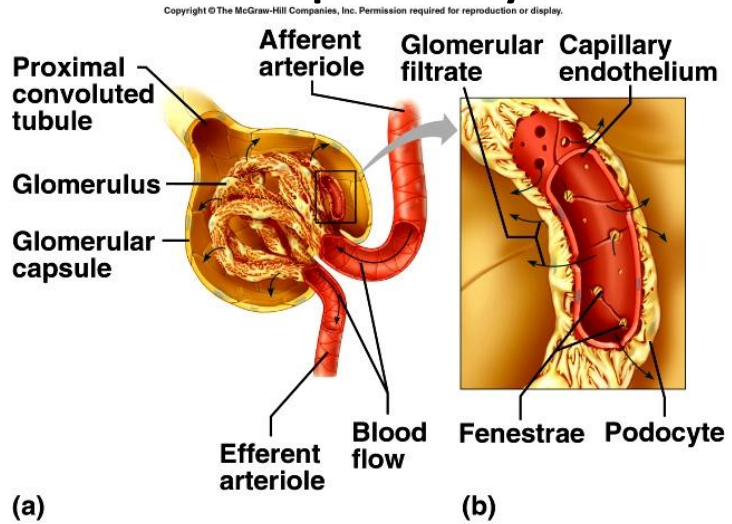
- **Renal corpuscle**

1. Glomerular Filtration



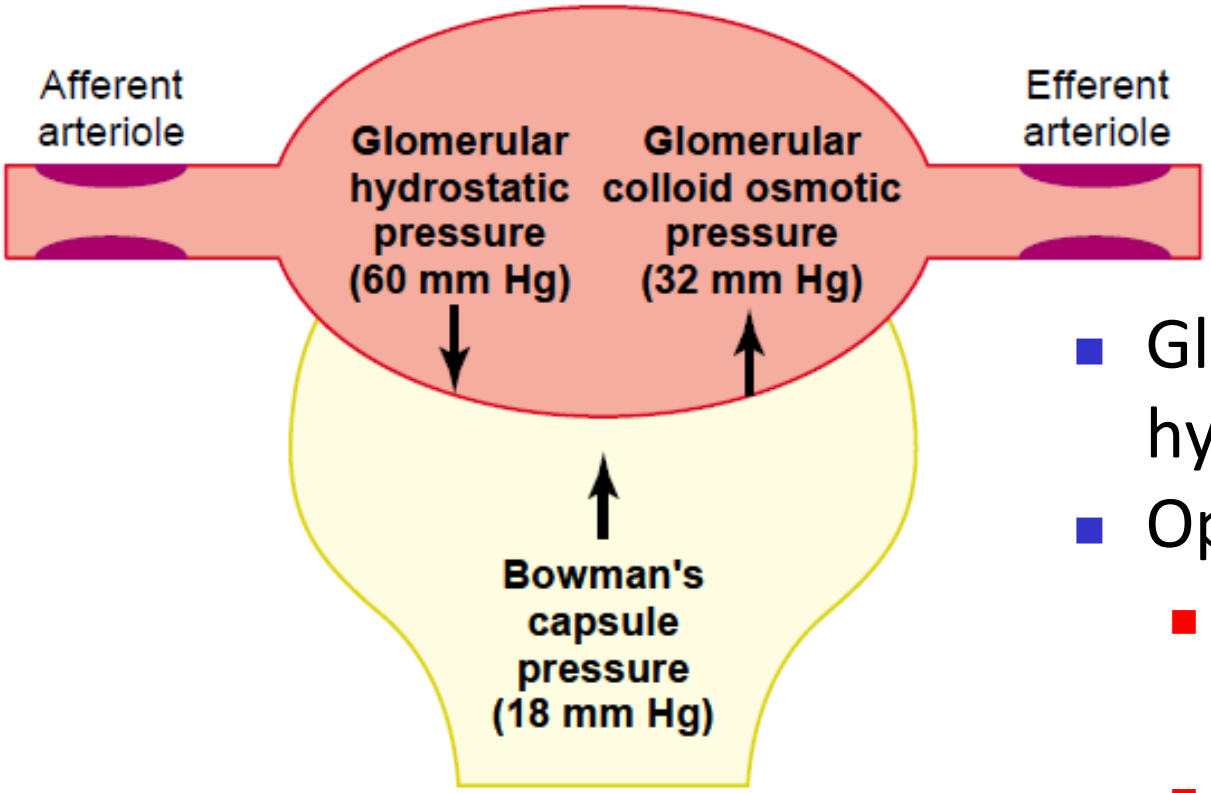
Filtration membrane - **3 layers**

- Fenestrated endothelium of capillaries
- Basement membrane of glomerulus
- Podocytes of epithelium - Slit membrane between pedicels of podocytes



- Filtration membrane

Forces causing filtration by the glomerular capillaries



- Glomerular blood hydrostatic pressure
- Opposing forces:
  - Plasma colloid osmotic pressure
  - Capsular hydrostatic pressure

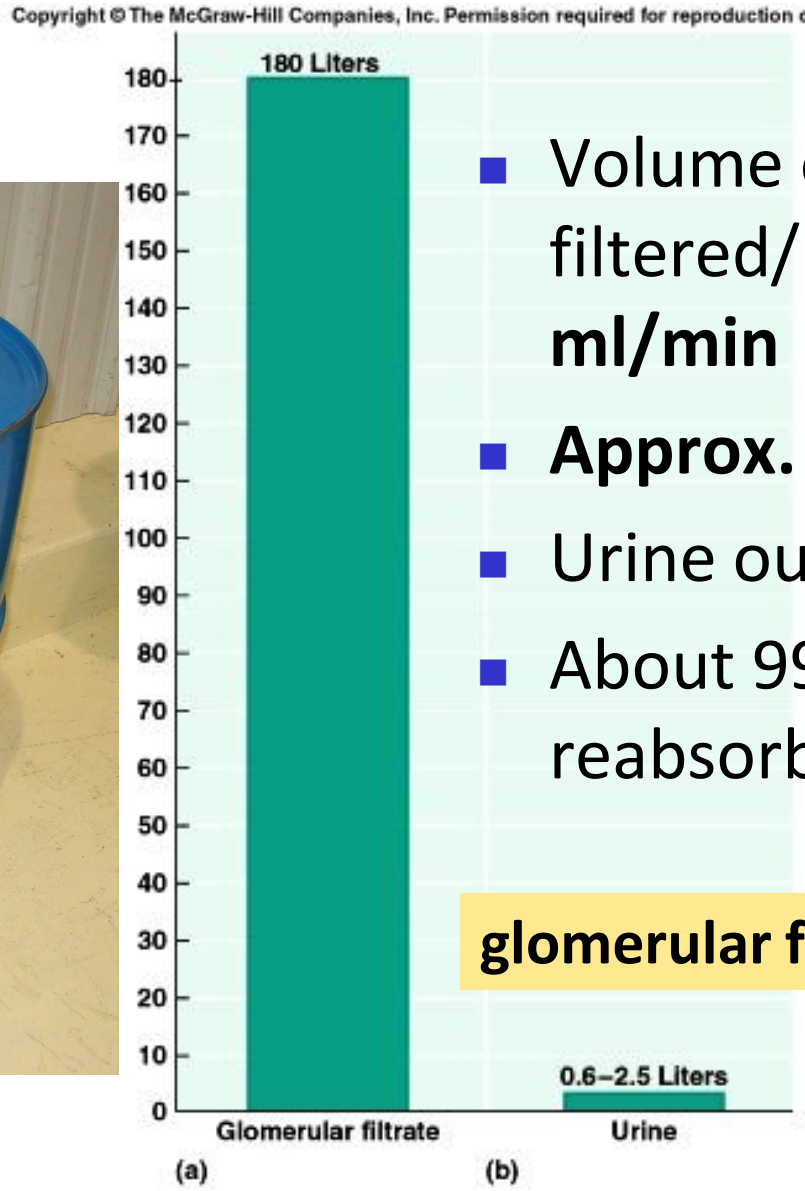
Net filtration pressure (10 mm Hg)	=	Glomerular hydrostatic pressure (60 mm Hg)	–	Bowman's capsule pressure (18 mm Hg)	–	Glomerular oncotic pressure (32 mm Hg)

Glomerular Filtration Rate

- GFR is the fluid flow rate between the glomerular capillaries and the Bowman's capsule:
- **GFR = Kf × (PG – PB – πG + πB)**
- **Kf** the *filtration constant* and is defined as the product of the hydraulic conductivity and the surface area of the glomerular capillaries
- **PG** - the hydrostatic pressure within the glomerular capillaries
- **PB** - the hydrostatic pressure within the Bowman's capsule
- **πG** - the colloid osmotic pressure within the glomerular capillaries
- **πB** - the colloid osmotic pressure within the Bowman's capsule *Considered to be zero!!!*

Glomerular Filtration Rate (GFR)

A standard 200-litre drum



- Volume of plasma filtered/unit time - **125 ml/min**
- **Approx. 180 L/24 h**
- Urine output 1-2 L/day
- About 99% of filtrate is reabsorbed

glomerular filtrate vs. urine

GFR influenced by:

- $GFR = Kf \times (PG - PB - \pi G + \pi B)$

- Blood pressure and blood flow
- Obstruction to urine outflow
- Loss of protein-free fluid
- Hormonal regulation
  - Renin – angiotensin II
  - Aldosterone
  - ADH
  - ANP

- **NA, A, endothelin, A II** – decrease the GFR
- **NO, Pg, bradykinin** – increase the GFR

Renal autoregulation

❑ The ability of the kidney to maintain relatively constant GFR despite the BP

❑ **Intrinsic mechanisms:**

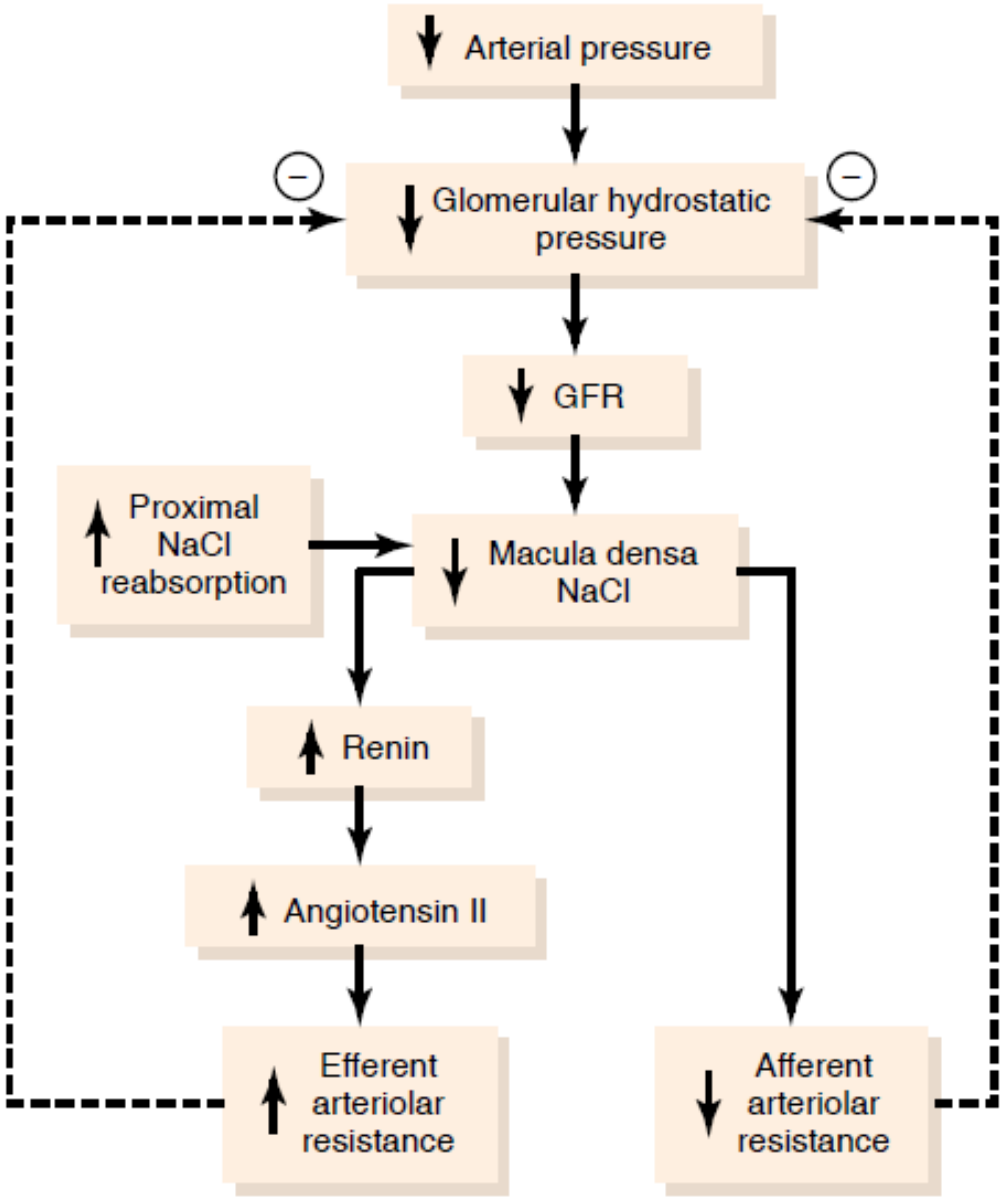
• the kidney itself (myogenic control) can adjust the **dilation or constriction of the afferent arterioles,** which counteracts changes in blood pressure – **glomerulotubular balance**. This *intrinsic* mechanism works over a large range of blood pressure (between 80 and 180 mm Hg mean arterial pressures), but can malfunction if you have kidney disease

❑ **Extrinsic mechanisms:**

• ***Neural (nervous system) control –*** *SNS constriction of the afferent arteriole*

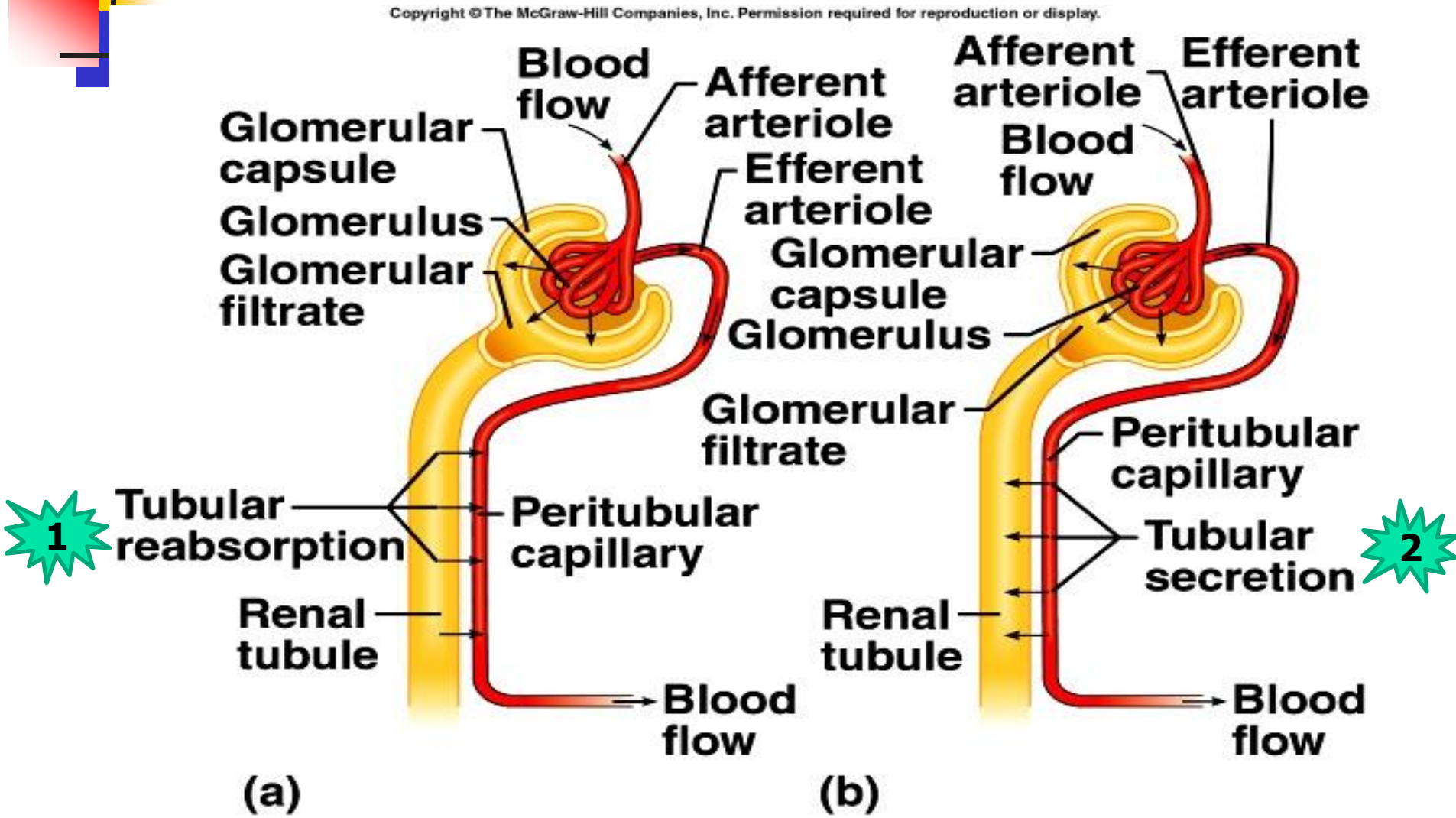
• ***Hormonal control*** - **atrial natriuretic peptide** (ANP) is a hormone that can ***increase*** the glomerular filtration rate. ANP produced in the heart and is secreted when the plasma volume increases, which increases urine production

The *extrinsic* mechanisms can override renal autoregulation and decrease the **GFR** when necessary. For example: a **large drop in BP**, which can happen if a blood loss occurs, SNS stimulates **constriction of the afferent arteriole, reducing urine production**. If further measures are needed the SNS can also activate the **renin-angiotensin-aldosterone system,** a hormone system that regulates blood pressure and fluid balance

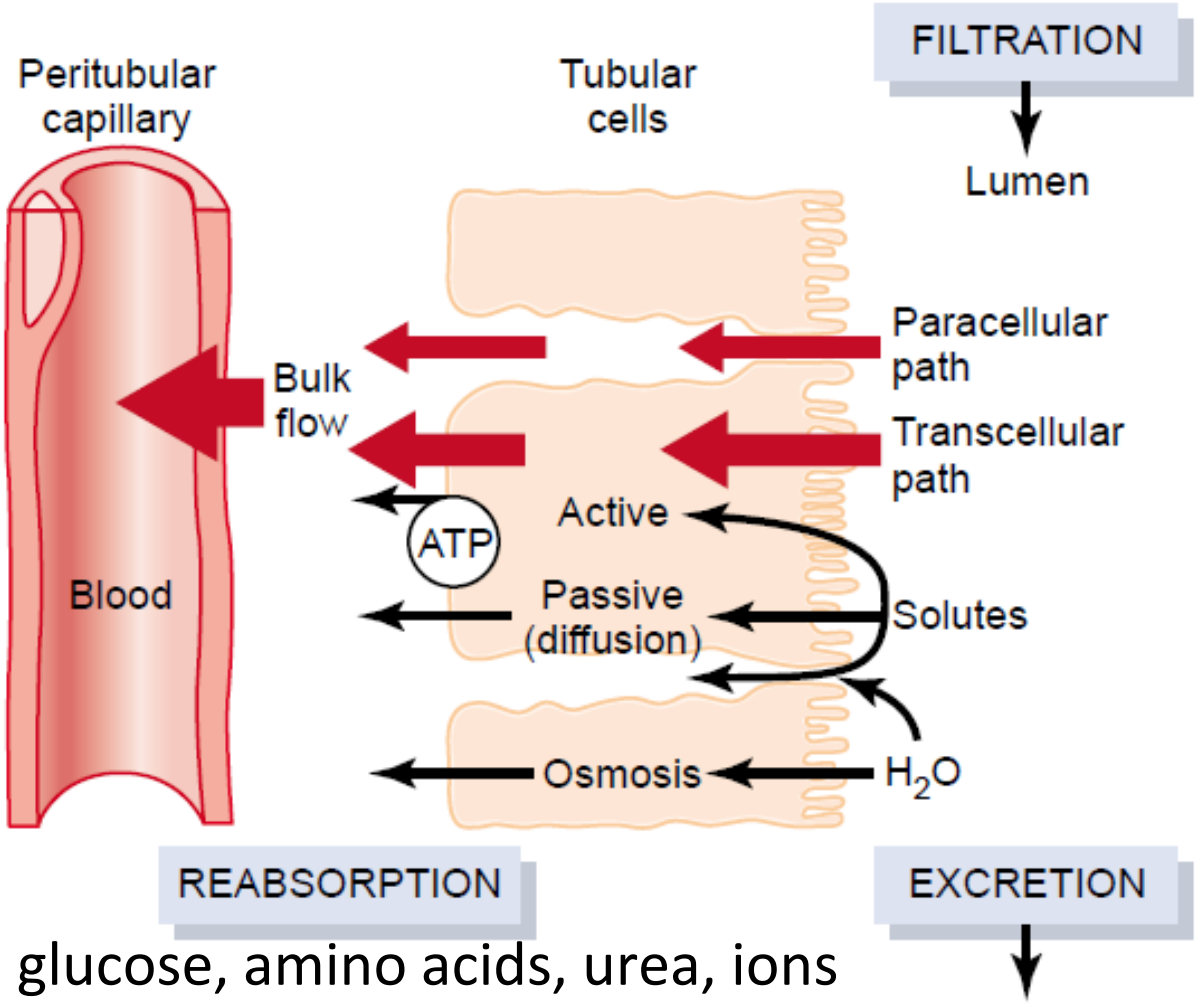


Macula densa feedback mechanism for **autoregulation** of **glomerular hydrostatic pressure** and **GFR** during decreased renal arterial pressure

2. Tubular Transport: Reabsorption and Secretion

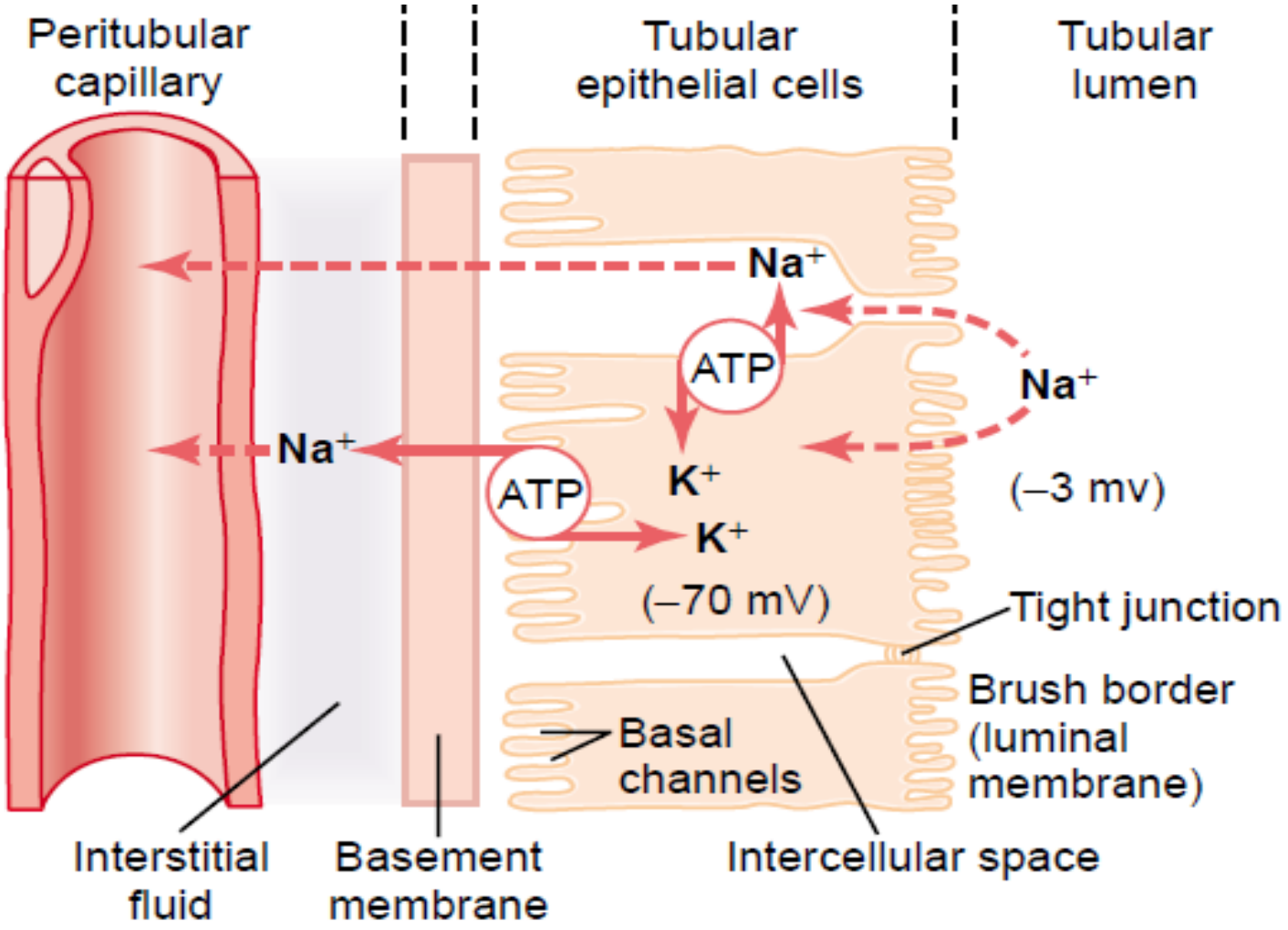


Tubular Reabsorption

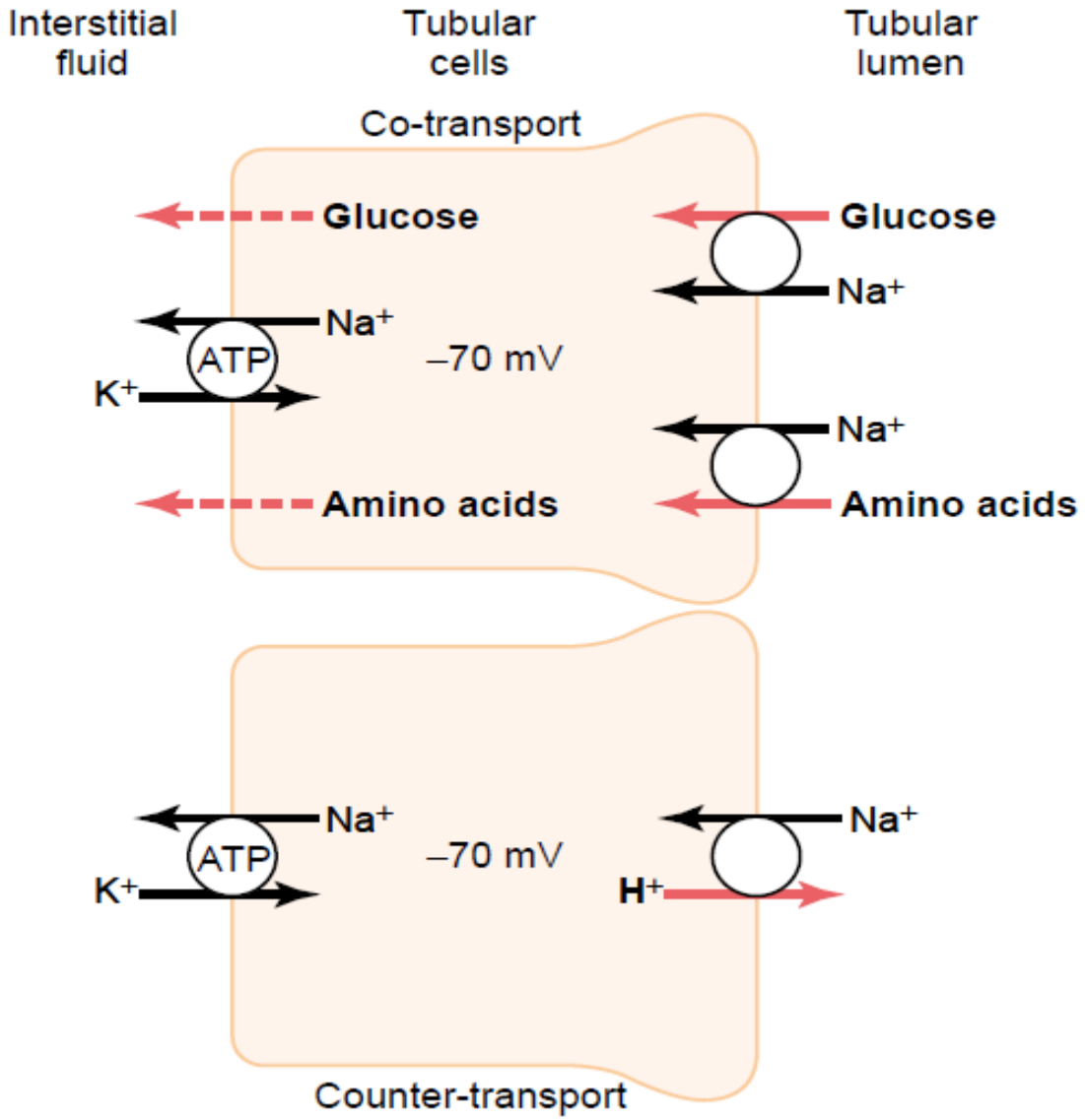


- Water, glucose, amino acids, urea, ions
- Sodium diffuses into cell; actively pumped out – drawing water with it

Sodium Transport



Secondary Active Reabsorption and Secretion into the Tubules

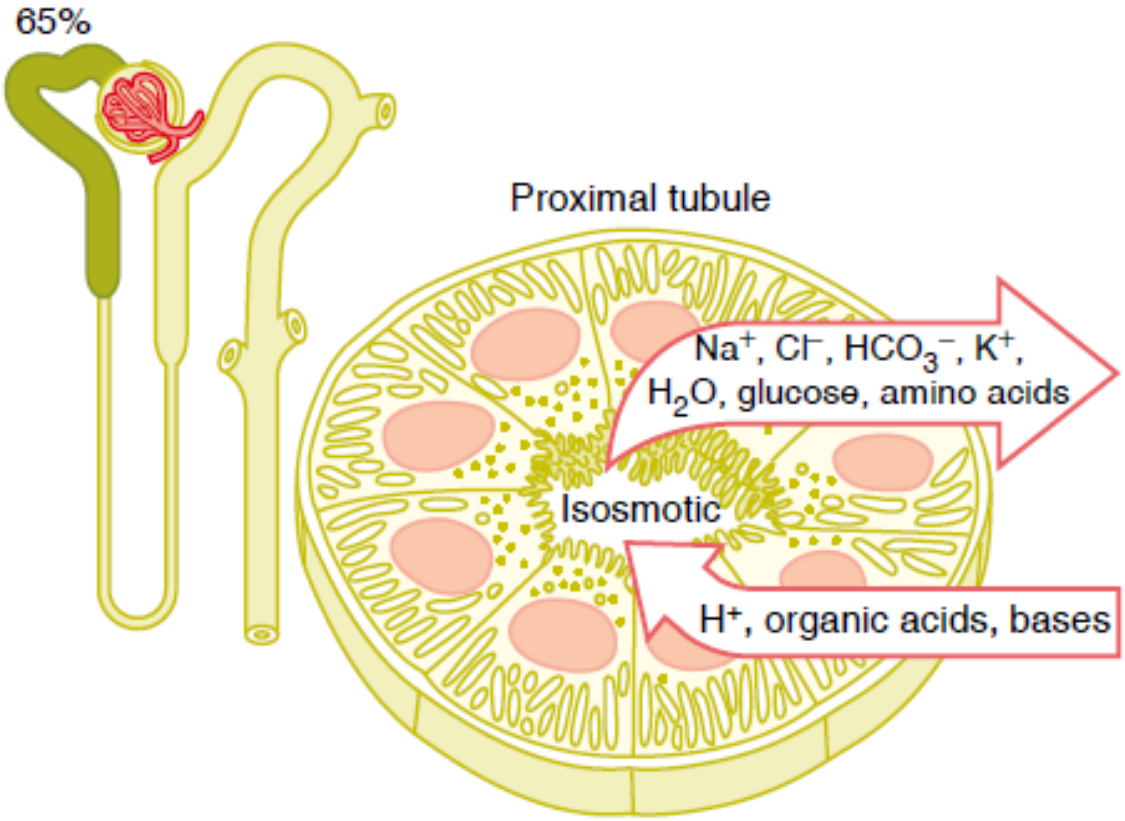


Transport Characteristics of the Proximal Tubule

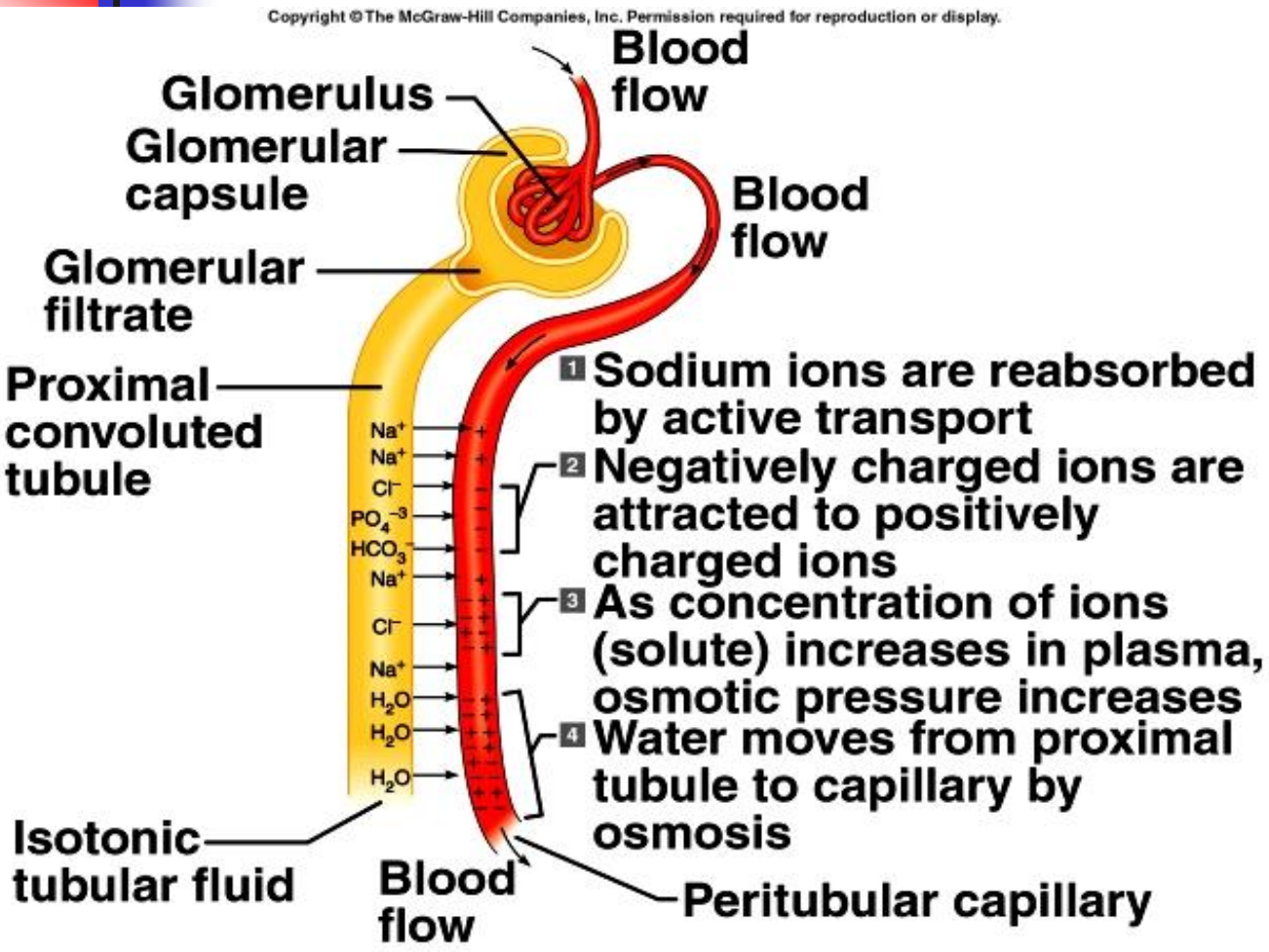
60 - 70% reabsorption

Isosmotic reabsorption

60-70% of Na+
55% of Cl-
90% of HCO3-
Glucose - 100%
Amino acids - 100 %

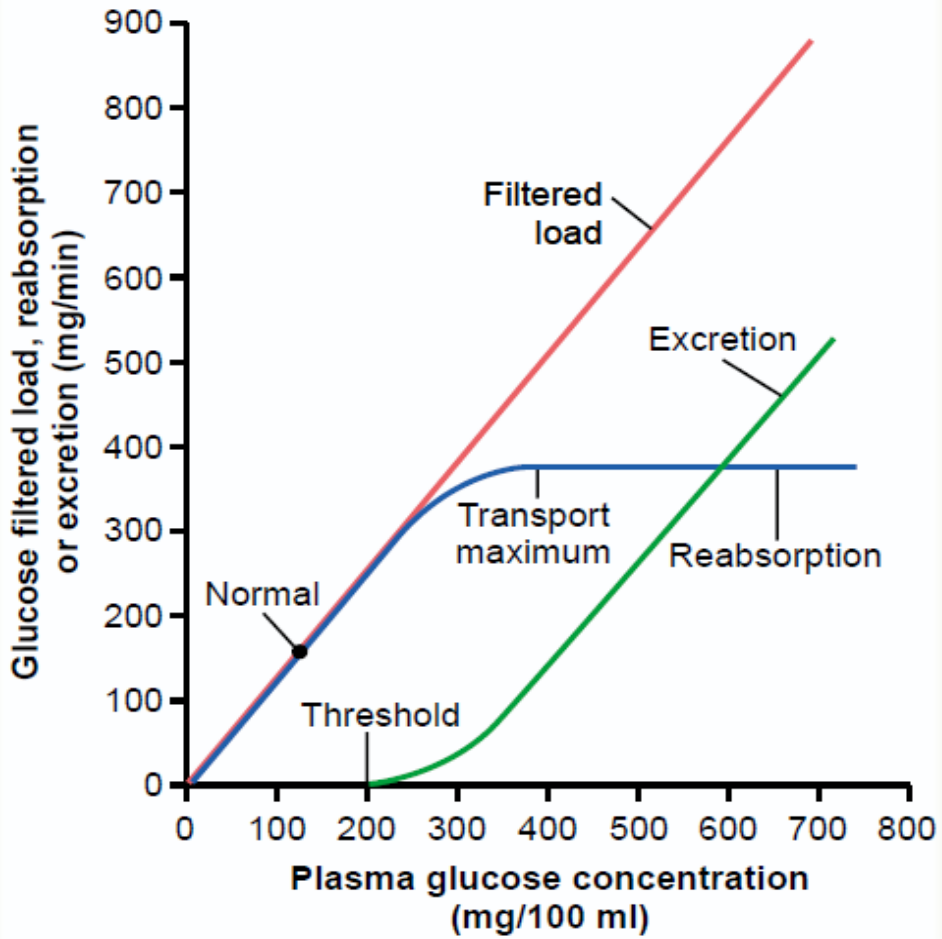


Transport Processes in the Proximal Tubule



In addition to reabsorption **(R)**, tubular secretion **(S)** – substances move from peritubular capillaries into tubules – a second chance to remove substances from blood

- **Transport maximum** – maximum amount of a substance that can be absorbed per unit time
- **Renal threshold** – plasma concentration of a substance at which it exceeds **Tm**



transport maximum **Tm**

375 mg/min

The transport maximum is the maximum rate at which glucose can be reabsorbed from the tubules

The *threshold* for glucose refers to the filtered load of glucose, at which glucose first begins to be excreted in the urine – **11 mmol/l**

Transport Characteristics of the Loop of Henle – Descending Limb

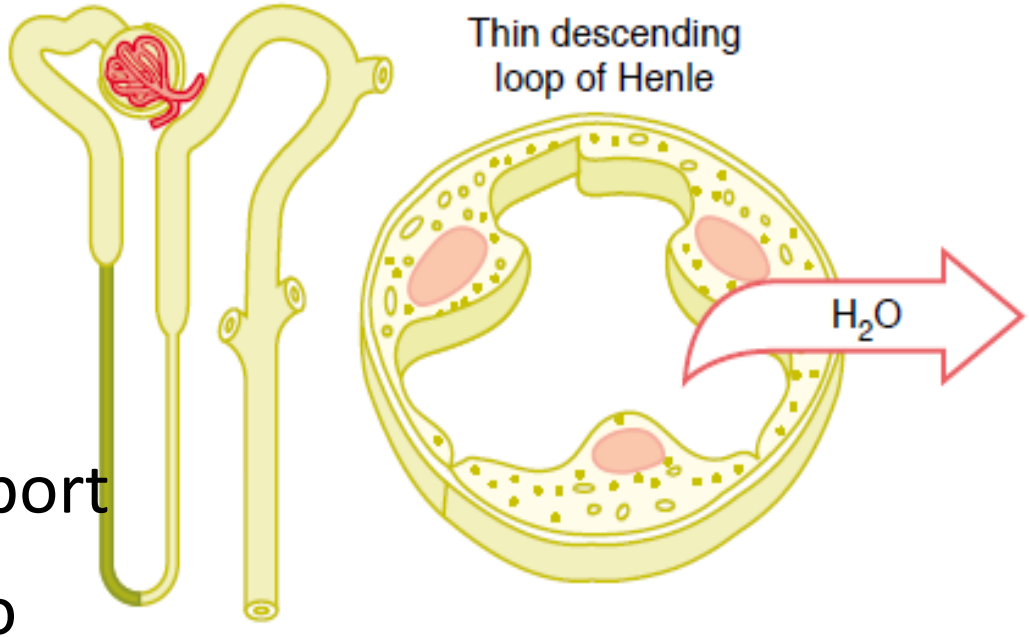
- **permeable to water**

AQP-1 water channels

- filtered water

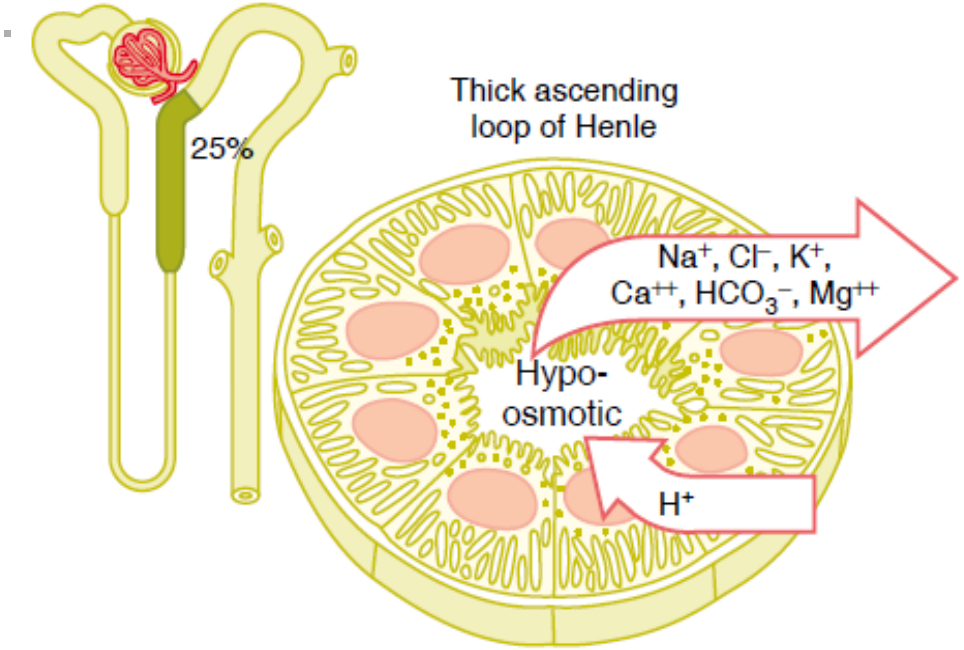
reabsorbed here

- No active sodium transport
- **minimal** permeability to sodium and urea



Transport Characteristics of the Thick Ascending Loop of Henle

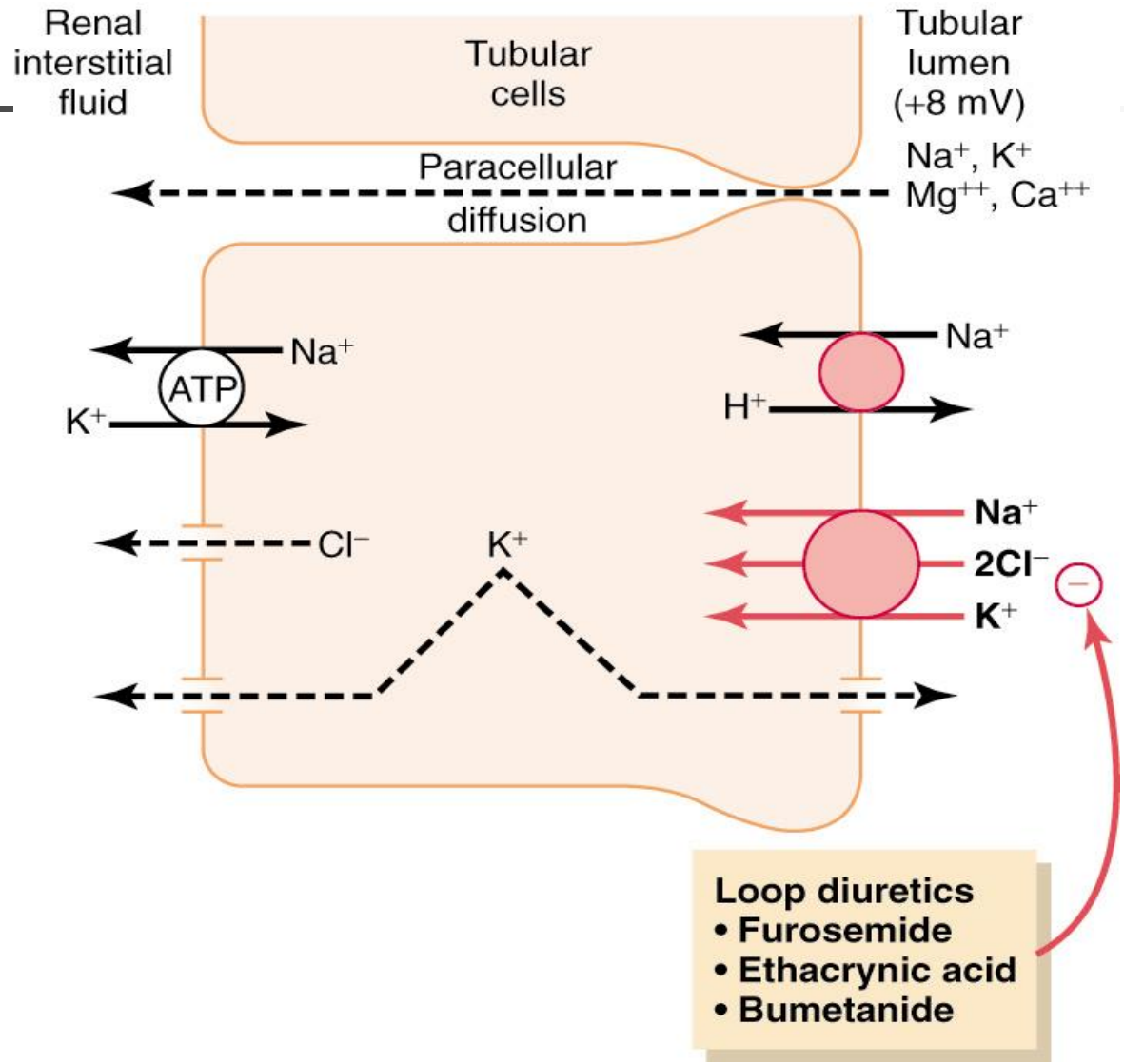
- Actively pumps sodium out of tubule to surrounding interstitial fluid ($Na^+/K+$ ATPase)
- $Na^+/2\ Cl^-/K^+$ co-transporter on luminal side
- Na+/H+ counter-transport (H+ secretion)
- Also, Ca^{+2}, HCO_3-, Mg^{+2}, K^+, and Na^+ paracellularly due to positive net charge in lumen from backflow of K+



- ❑ Impermeable to water
- ❑ 25% of sodium reabsorption
- ❑ Fluid leaving thick ascending limb is hypo-osmotic

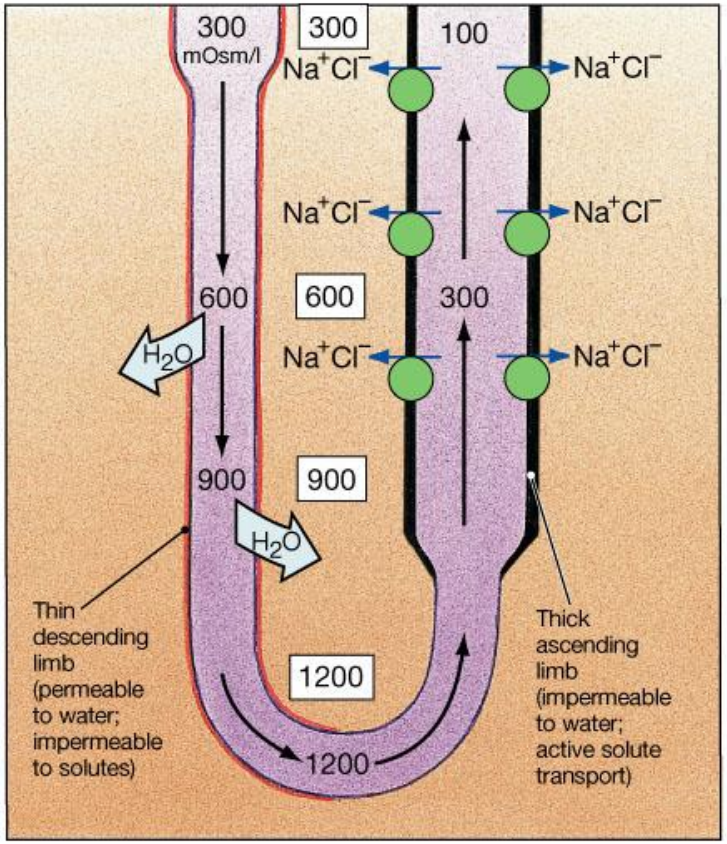
Sodium Chloride and Potassium Transport in Thick Ascending Loop of Henle

ALOH



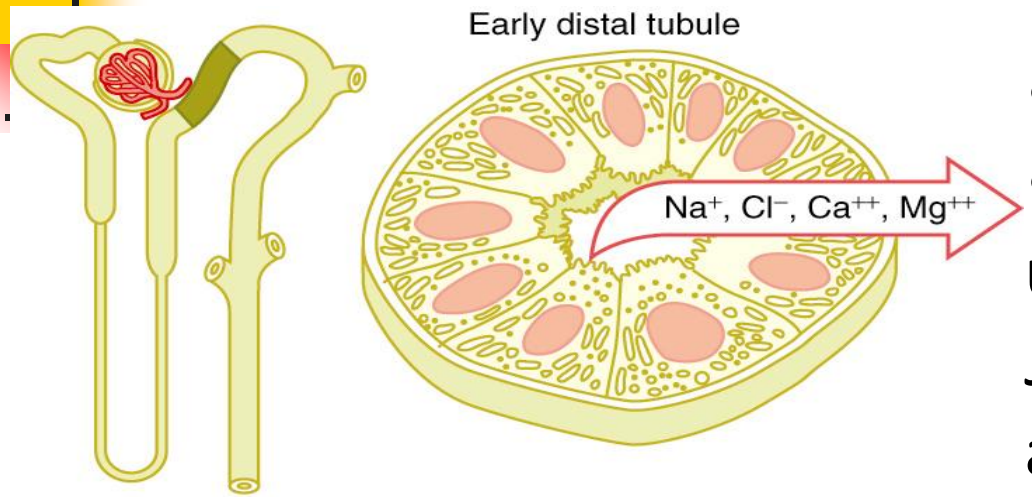
Transport Characteristics of the Thick Ascending Loop of Henle

- Cells of tubules are **NOT** permeable to water. Water can't go in or out
- Cells of tubules actively reabsorb Na+ and Cl-(out of tubule and into surrounding area). **Salt is removed but NOT water**
- Interstitial space becomes highly concentrated!
- This makes filtrate more dilute and osmolality decreases



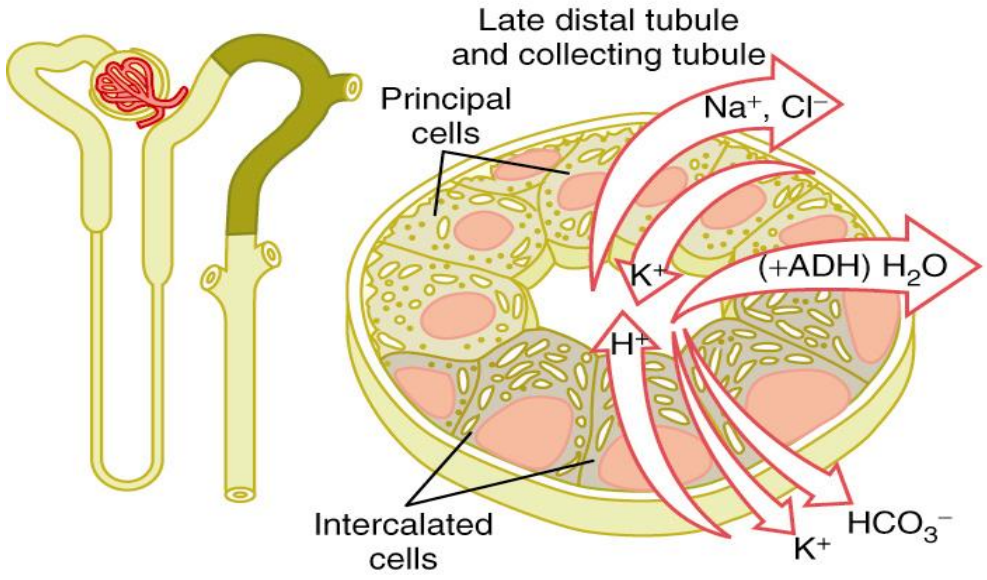
(b) Active transport of NaCl along the ascending thick limb results in the movement of water from the descending limb.

Characteristics of Early and Late Distal Tubules and Collecting Tubules



- **not** permeable to H_2O
- **not** permeable to urea

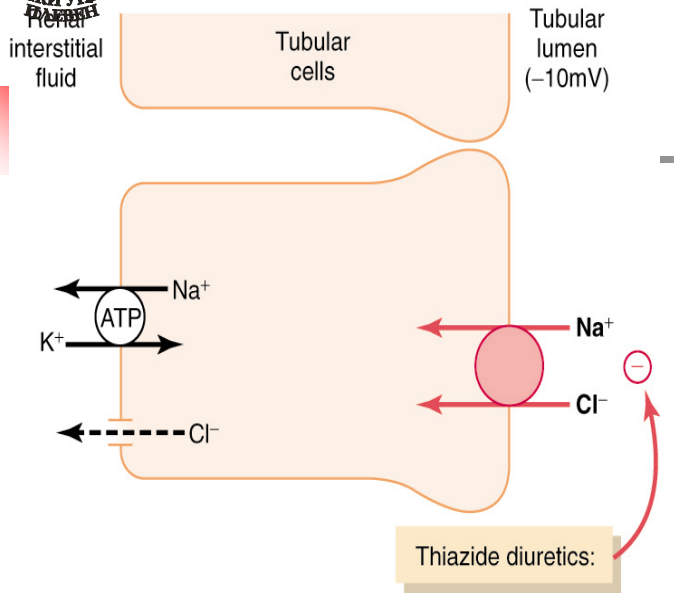
Juxtaglomerular apparatus



- **permeability to H_2O depends on hormones**
- **not** permeable to urea

Figure 27-11; Guyton and Hall

Early Distal Convoluted Tubule



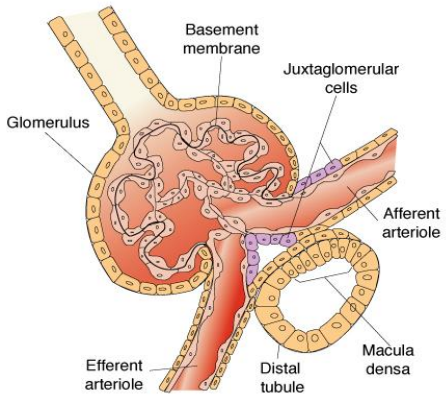
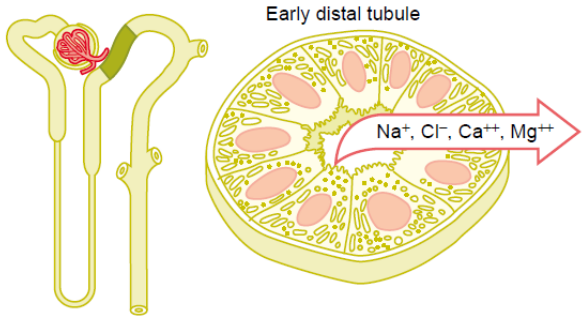


Figure 32-13 Juxtaglomerular apparatus, showing the close contact of the distal tubule with the afferent arteriole, the macula densa, and the juxtaglomerular cells.

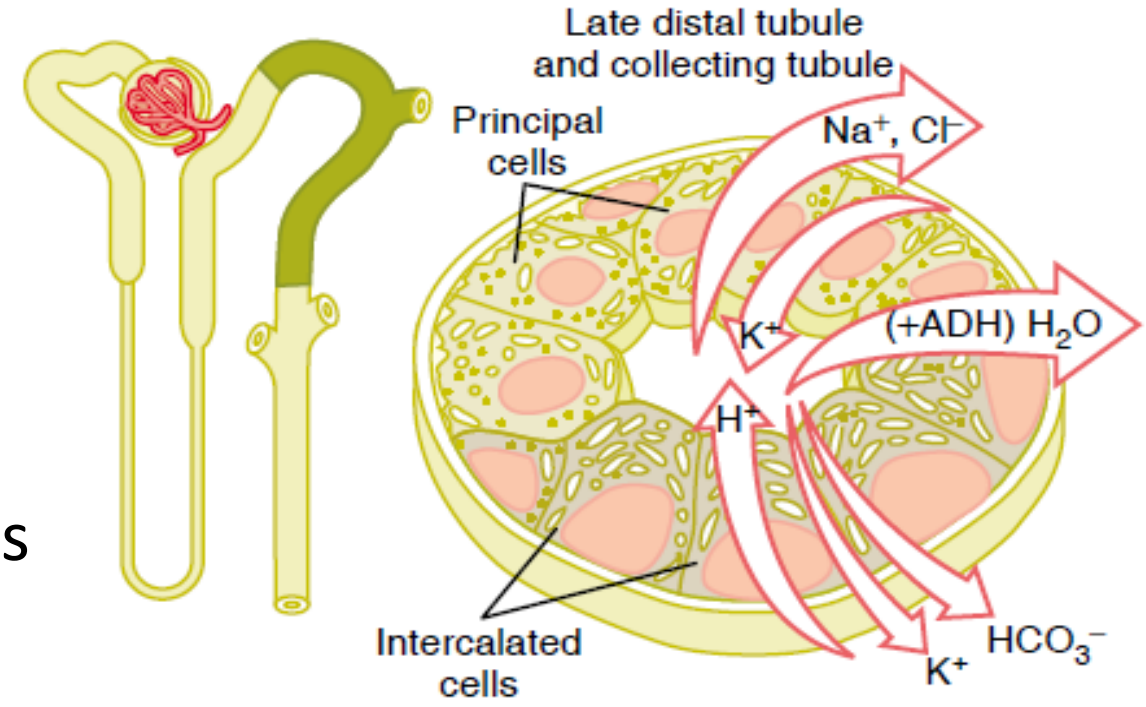
- associated with Juxtaglomerular apparatus (helps **in tubuloglomerular feedback mechanism for GFR**)
  - **Mesangial cells**: smooth muscle like properties, structural support, phagocytic activity, secrete prostaglandins
  - **Granular cells of the afferent arteriole** - make renin
  - **Macula densa** of DCT- chemoreceptors
- Not permeable to water (still diluting segment) nor urea
- Active reabsorption of Na+, Cl-, K+, Mg++
- Thiazide diuretics affect Na/Cl co-transporter

Transport Characteristics of the Distal Tubule



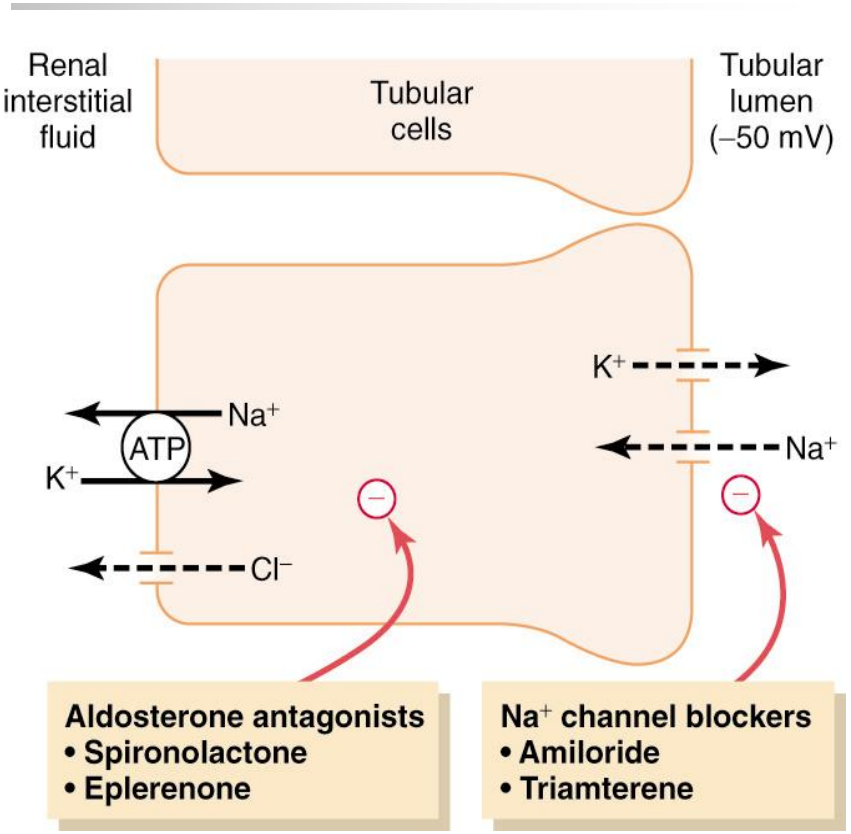
- What happens here depends on **ADH**

- **Aldosterone** affects Na+ and K+
- **ADH** – facultative water reabsorption
- **Parathyroid hormone** – increases Ca++ reabsorption

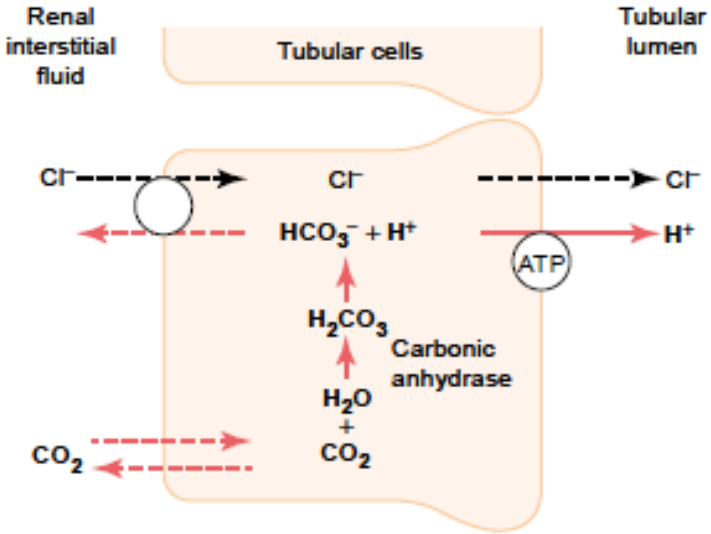


Late DCT, Collecting Tubule

- **Principal cells:**
- Reabsorb Na+ and water
- K+ secretion
- **No urea** permeability
- K+ sparing diuretics work here
  - Antagonists to aldosterone binding sites
  - Sodium channel blockers (reduces K+)
- Water reabsorption dependent on hormones



Late DCT, Collecting Tubule

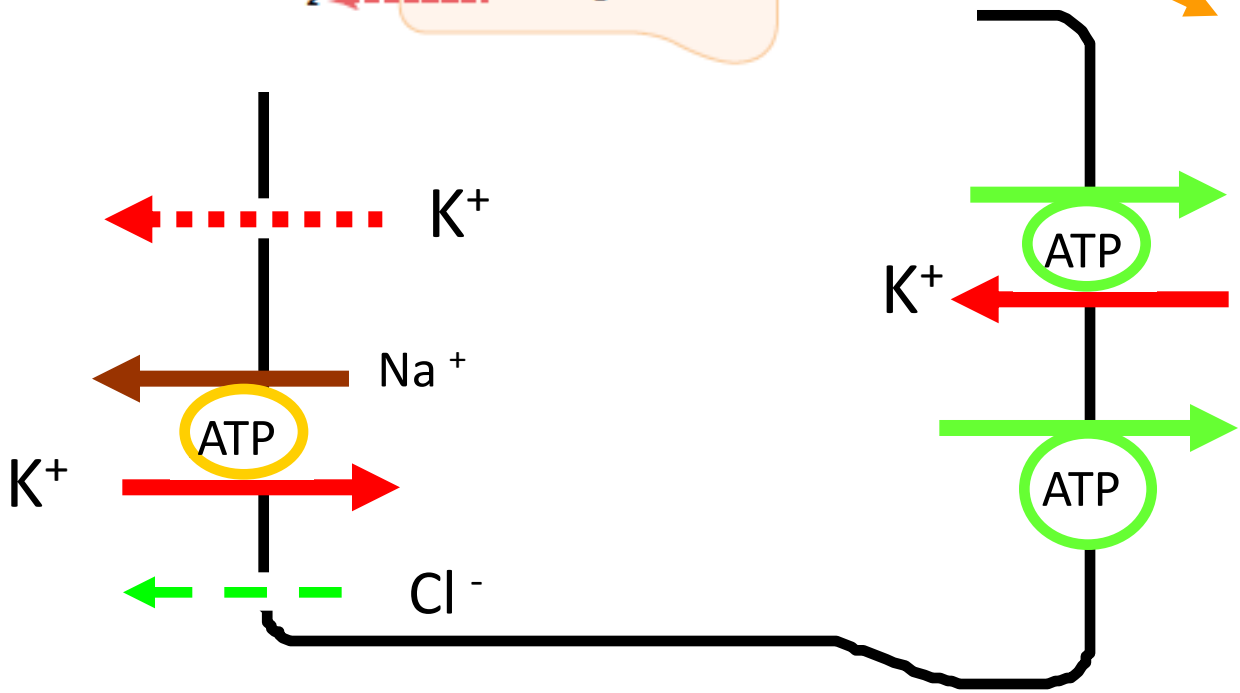


Intercalated Cells

Type A and B

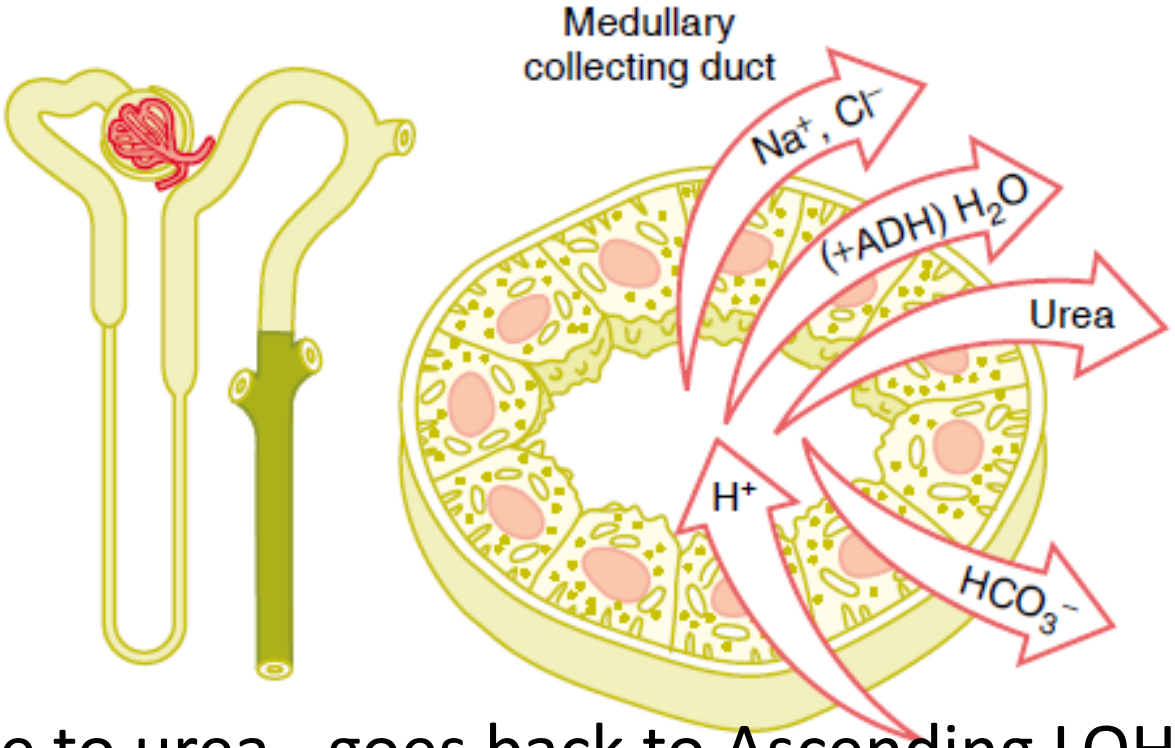
Tubular Lumen

H_2O (depends on hormones)



Reabsorb K+
Secrete H+

Transport Characteristics of the Medullary Collecting Duct



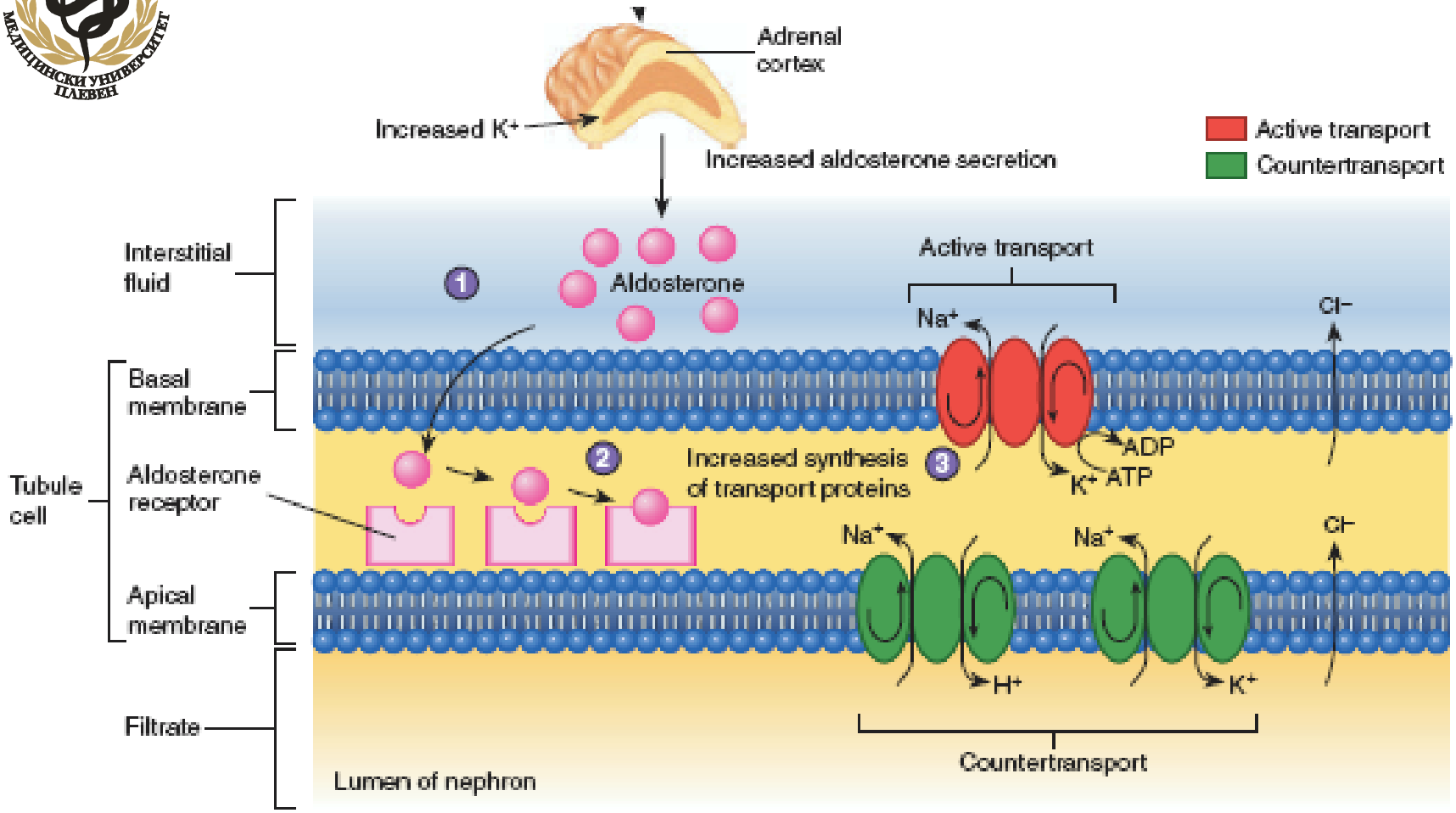
- Permeable to urea - goes back to Ascending LOH
- Can reabsorb more water (ADH dependent) important for determining final urine output
- Can secrete hydrogen ions

Hormones that Regulate Tubular Reabsorption

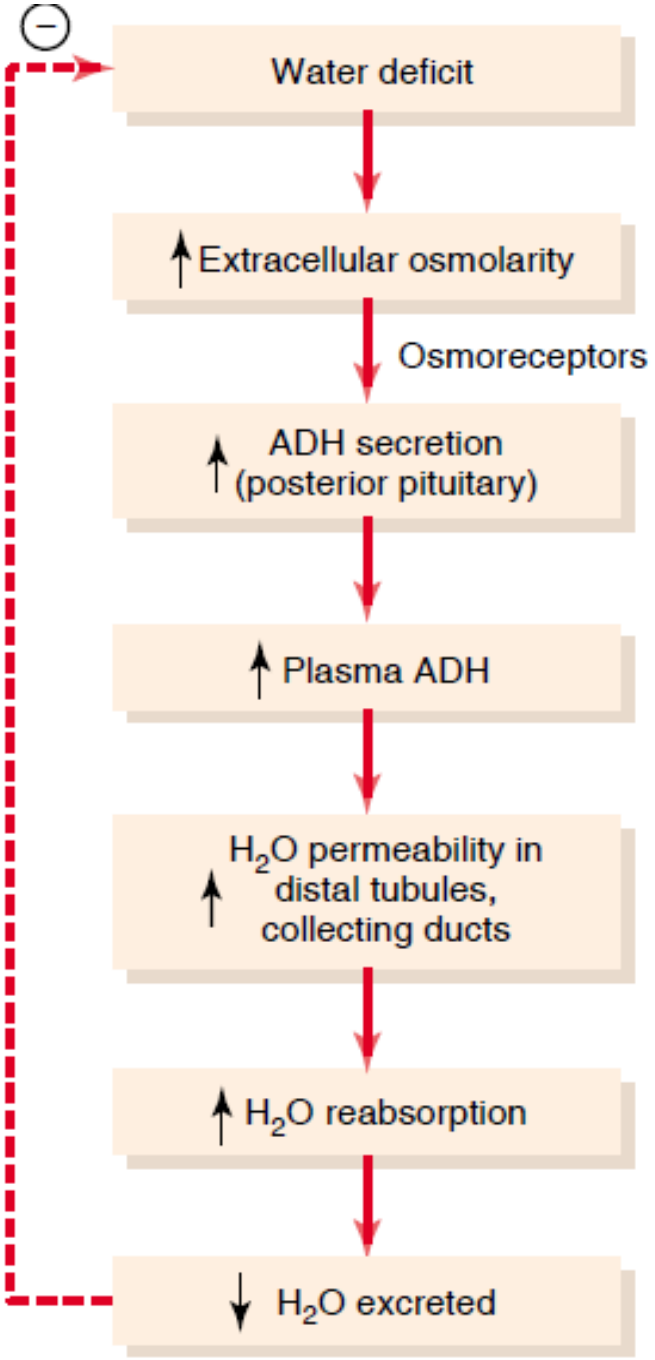
Hormones That Regulate Tubular Reabsorption

Hormone	Site of Action	Effects
Aldosterone	Collecting tubule and duct	↑ NaCl, H_2O reabsorption, ↑ K^+ secretion
Angiotensin II	Proximal tubule, thick ascending loop of Henle/distal tubule, collecting tubule	↑ NaCl, H_2O reabsorption, ↑ H^+ secretion
Antidiuretic hormone	Distal tubule/collecting tubule and duct	↑ H_2O reabsorption
Atrial natriuretic peptide	Distal tubule/collecting tubule and duct	↓ NaCl reabsorption
Parathyroid hormone	Proximal tubule, thick ascending loop of Henle/distal tubule	↓ PO_4^{---} reabsorption, ↑ Ca^{++} reabsorption

- Aldosterone



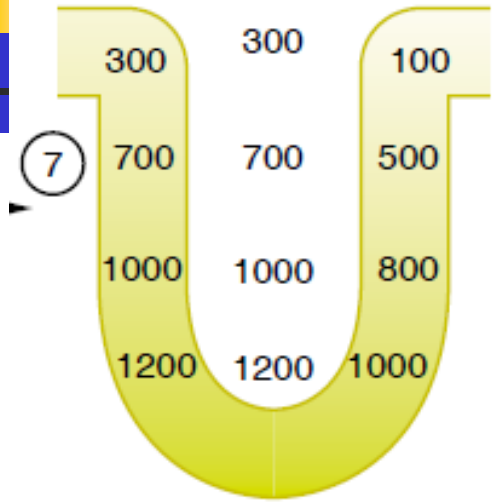
1. Aldosterone secreted from the adrenal cortex enters cells of the distal tubule.
2. Aldosterone binds to intracellular receptors and increases the synthesis of transport proteins of the apical and basal membranes.
3. Newly synthesized transport proteins increase the rate at which Na^+ are absorbed and K^+ and H^+ are secreted. Cl^- move with the Na^+ because they are attracted to the positive charge of Na^+.

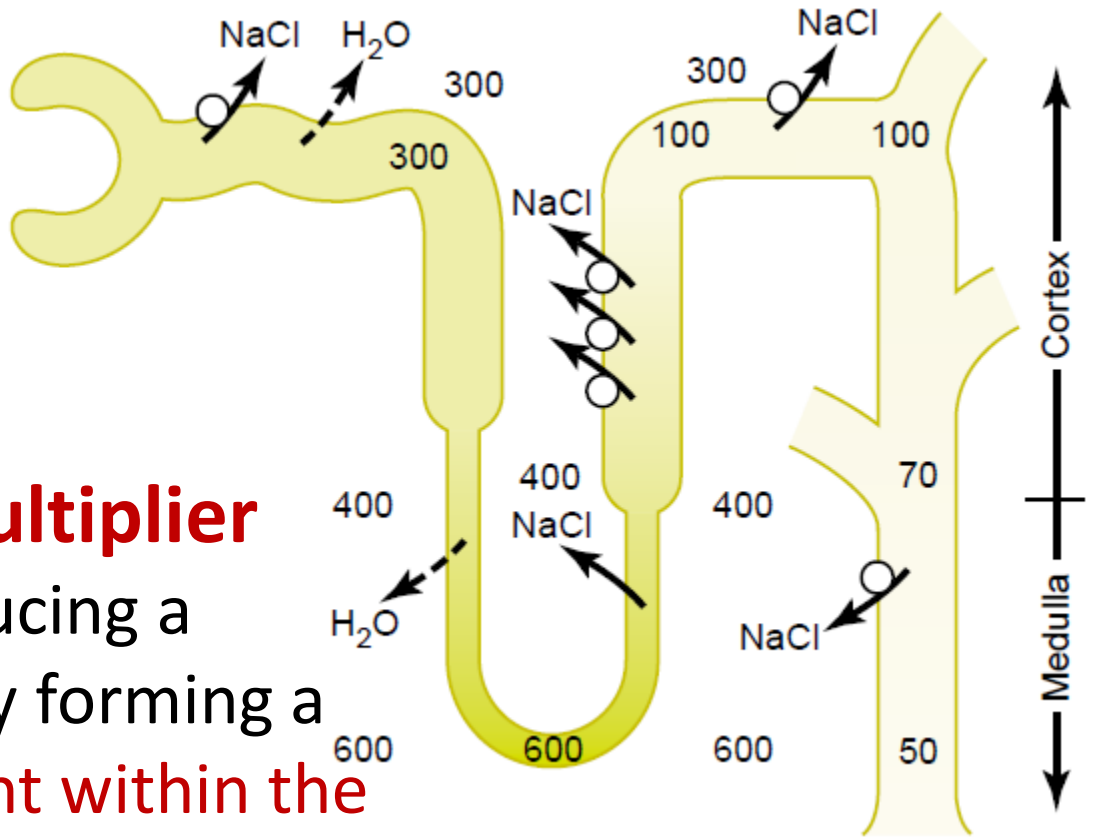


Osmoreceptor-ADH feedback mechanism for regulating ECF osmolarity in response to water deficit

- HT – SON and PVN
- Posterior pituitary
- Stimulation by :
  - Increased osmolarity
  - Decreased BP
  - Decreased blood volume
- Inability of the renal tubular segments to respond to ADH – nephrogenic diabetes insipidus
- Central diabetes insipidus – ADH lack

❖ Urine Concentration and Dilution
Formation of a Concentrated Urine





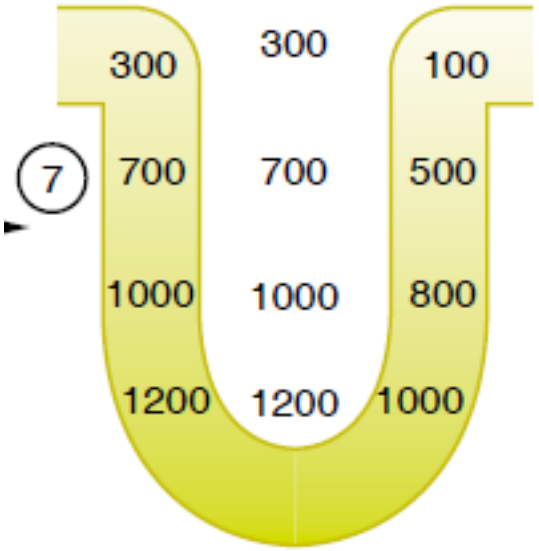
ADH - high

Countercurrent multiplier

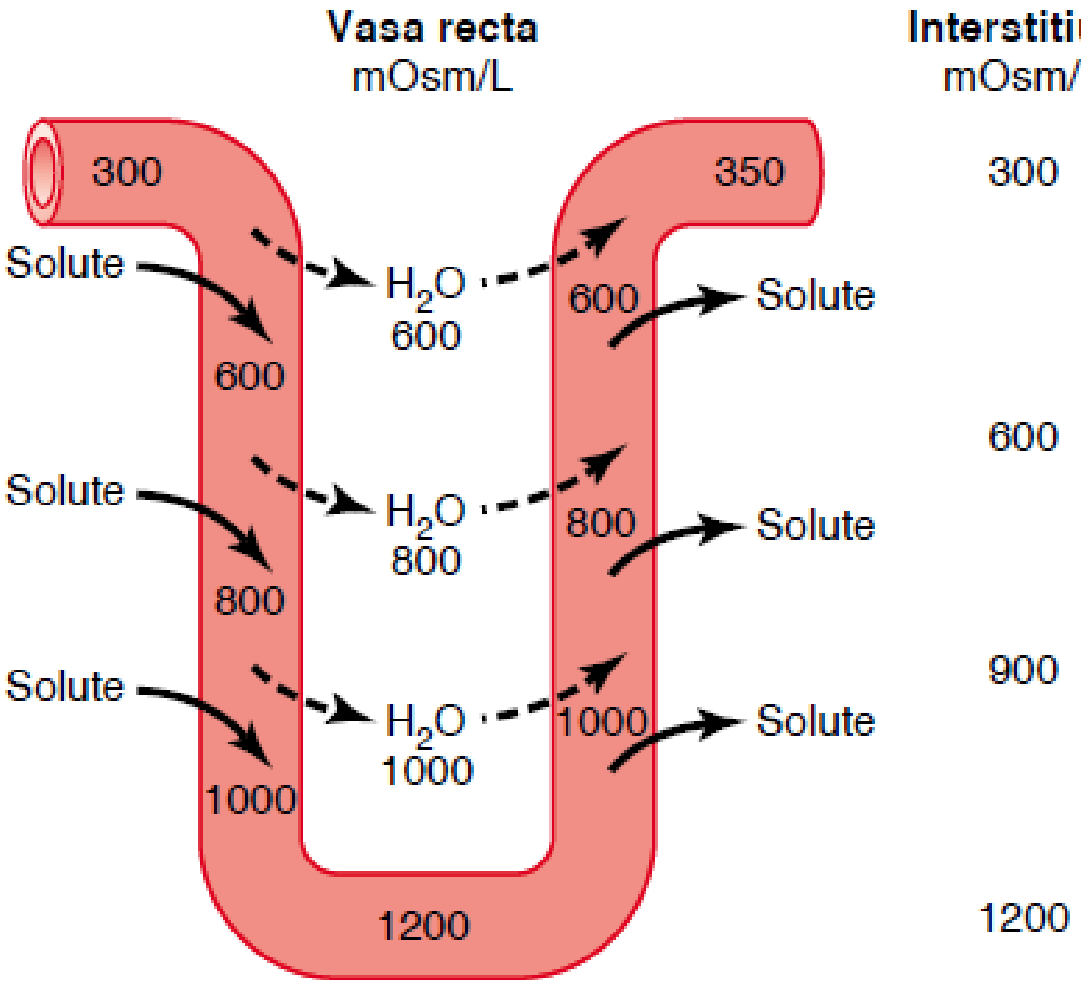
Responsible for producing a concentrated urine by forming a concentration gradient within the medulla of kidney. When ADH is present, water is reabsorbed and urine is concentrated

Purpose of the LOH - Countercurrent Multiplier

- to **create an osmotic gradient** deep in medulla of kidney to benefit the collecting duct that sits adjacent to it
- Creates “salt gradient”
- If Loop is disabled, then collecting duct adjacent to it cannot give concentrated urine
- **Concentration and volume of urine is determined by concentration gradient produced** in **Loop of Henle** **and by the presence of certain hormones**
- Urine concentration can then range from 50 mOsmol/l to 1400 mOsmol/l.

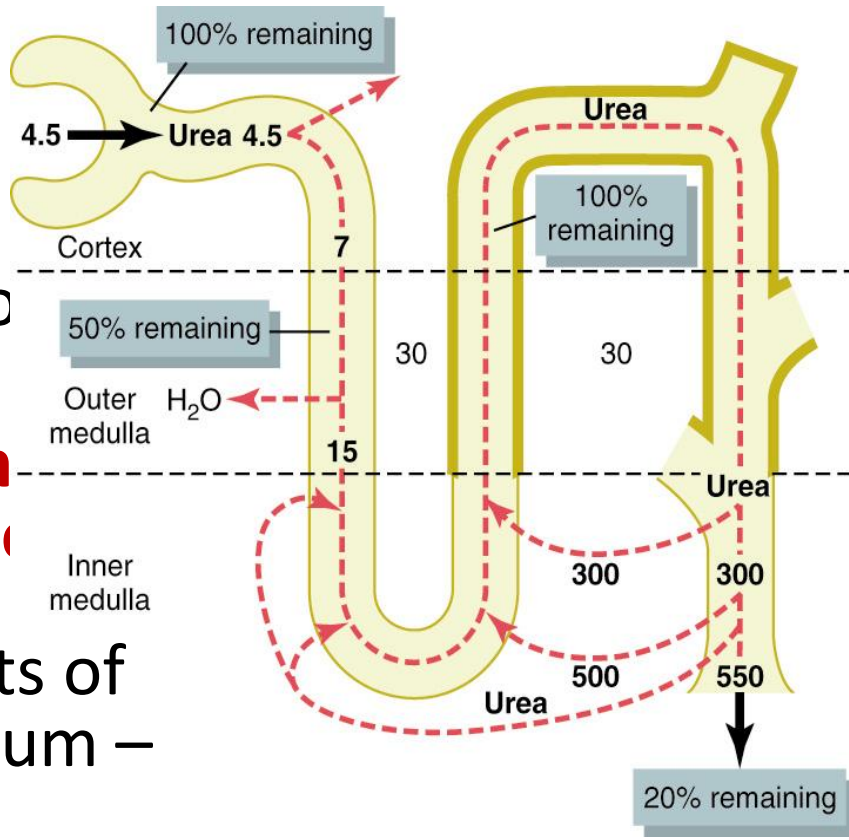


Countercurrent Exchange in the Vasa Recta



Factors That Contribute to Buildup of Solute in Renal Medulla - Countercurrent Multiplier

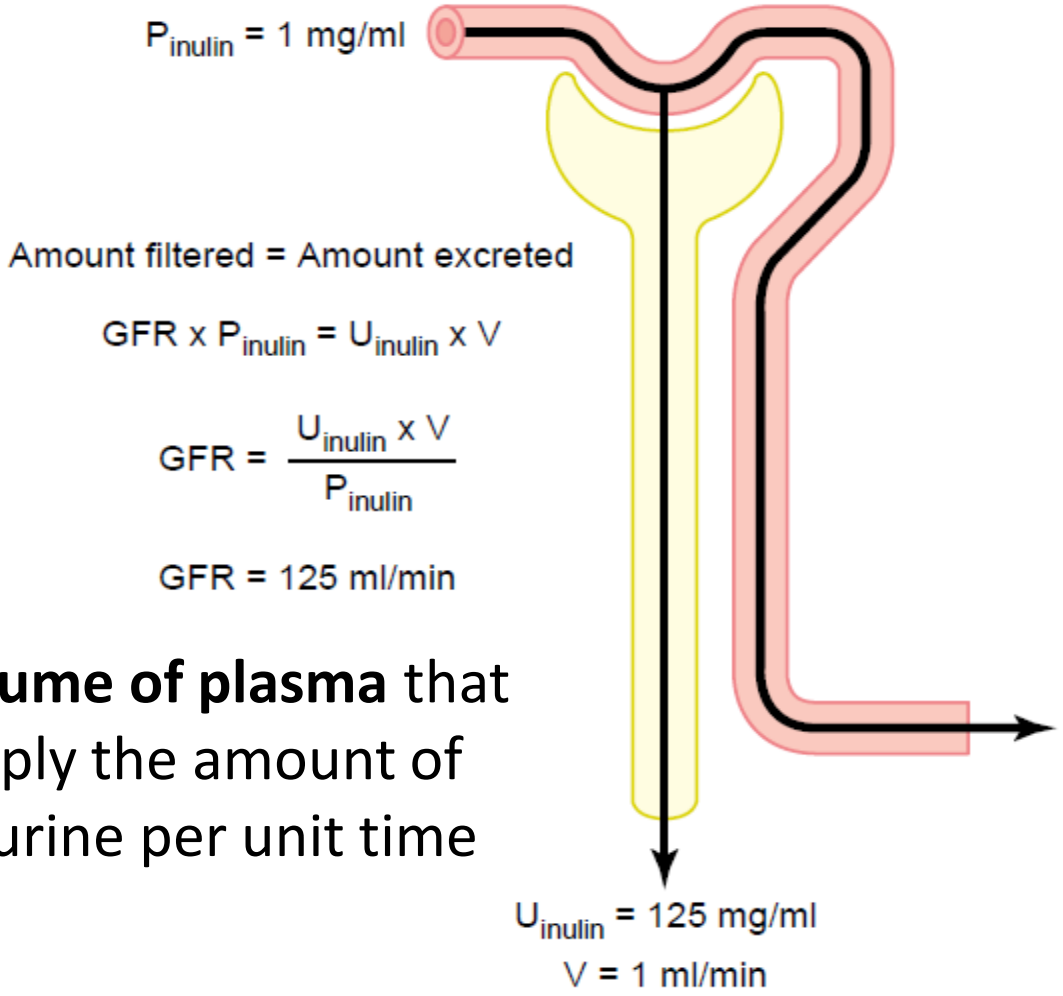
- Active transport of Na+, Cl-, K+ and other ions from thick ascending loop of Henle into medullary interstitium
- Active transport of ions from medullary collecting ducts into interstitium
- **Passive diffusion of urea from medullary collecting ducts int interstitium**
- Diffusion of only small amounts of water into medullary interstitium – most absorbed in Proximal CT
- “Sluggish blood”



❖ Use of Clearance Methods to Quantify Kidney Function

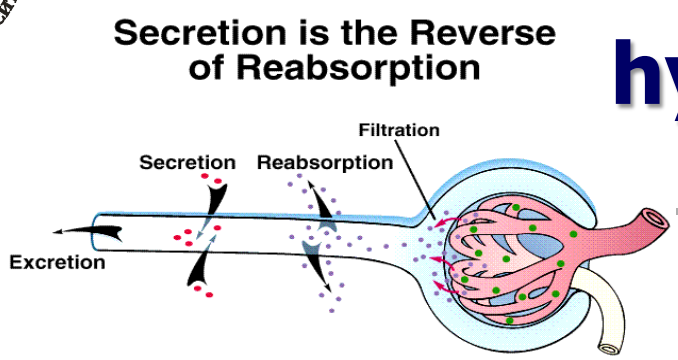
Clearance rate (Cs)

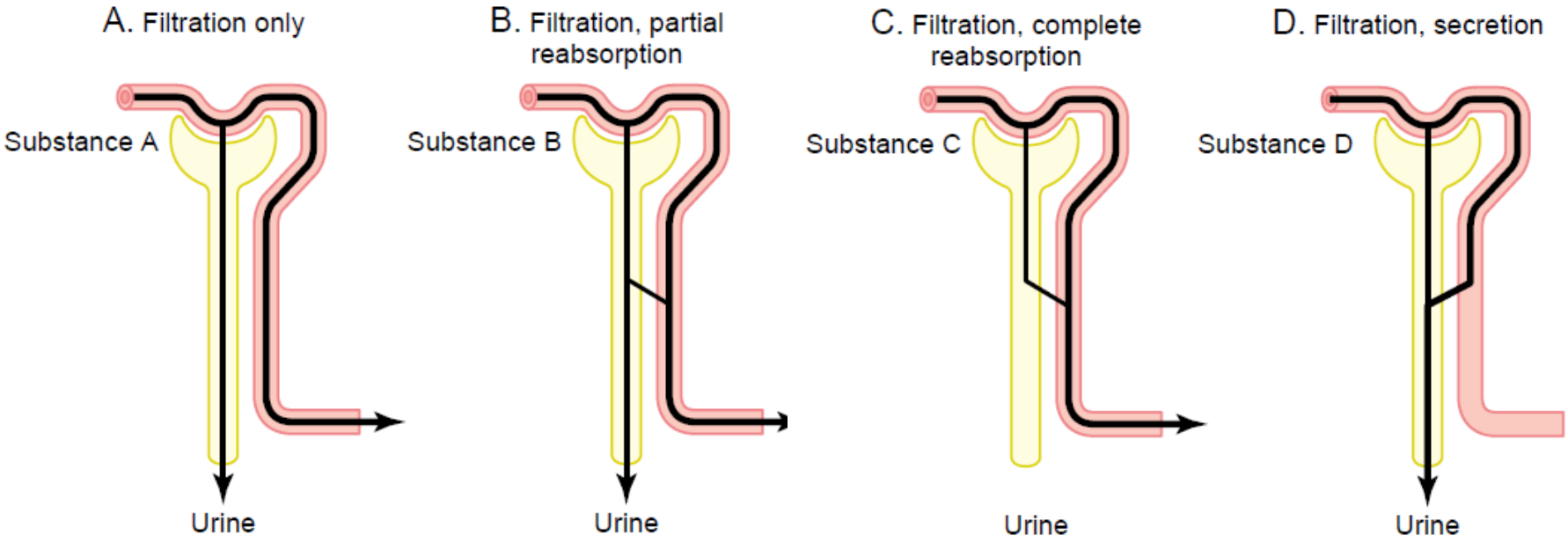
$$C_s = \frac{U_s \times V}{P_s}$$



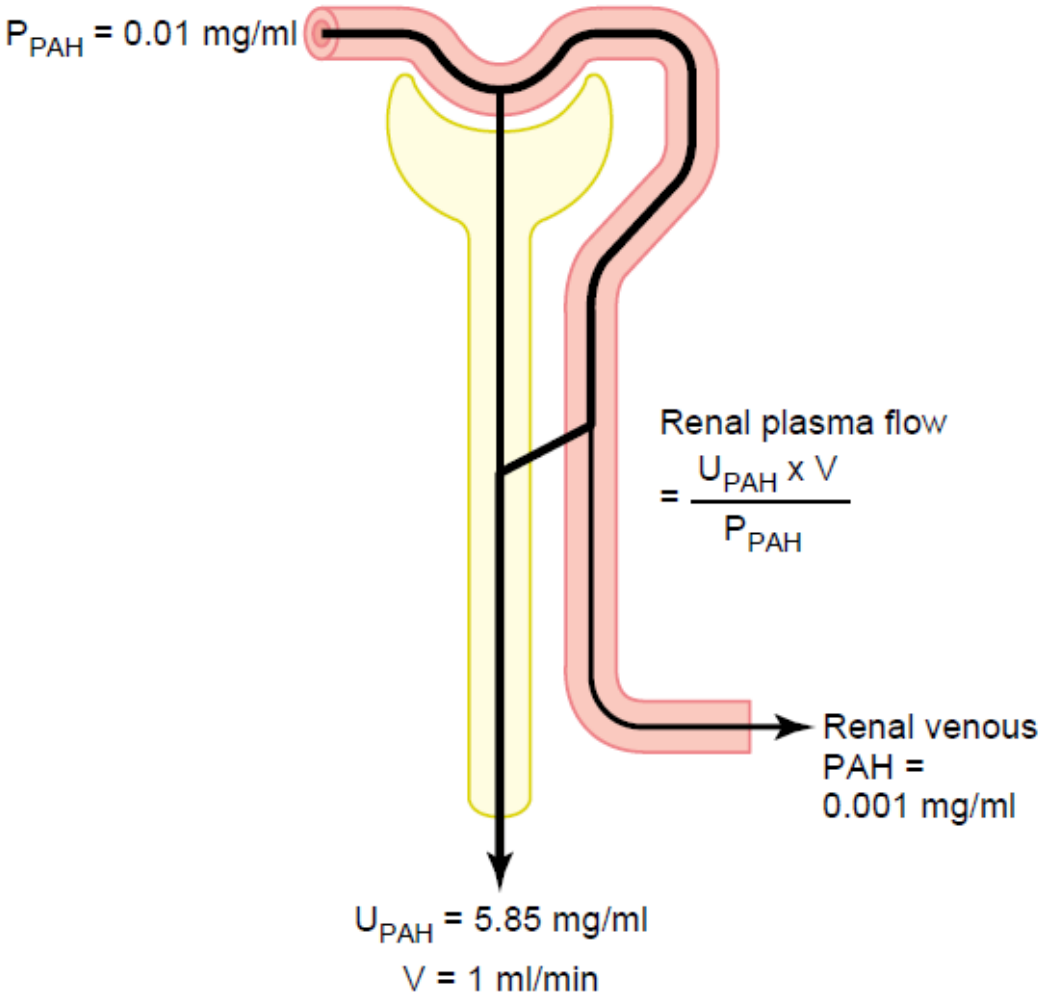
Clearance refers to the **volume of plasma** that would be necessary to supply the amount of substance excreted in the urine per unit time

Renal handling of four hypothetical substances



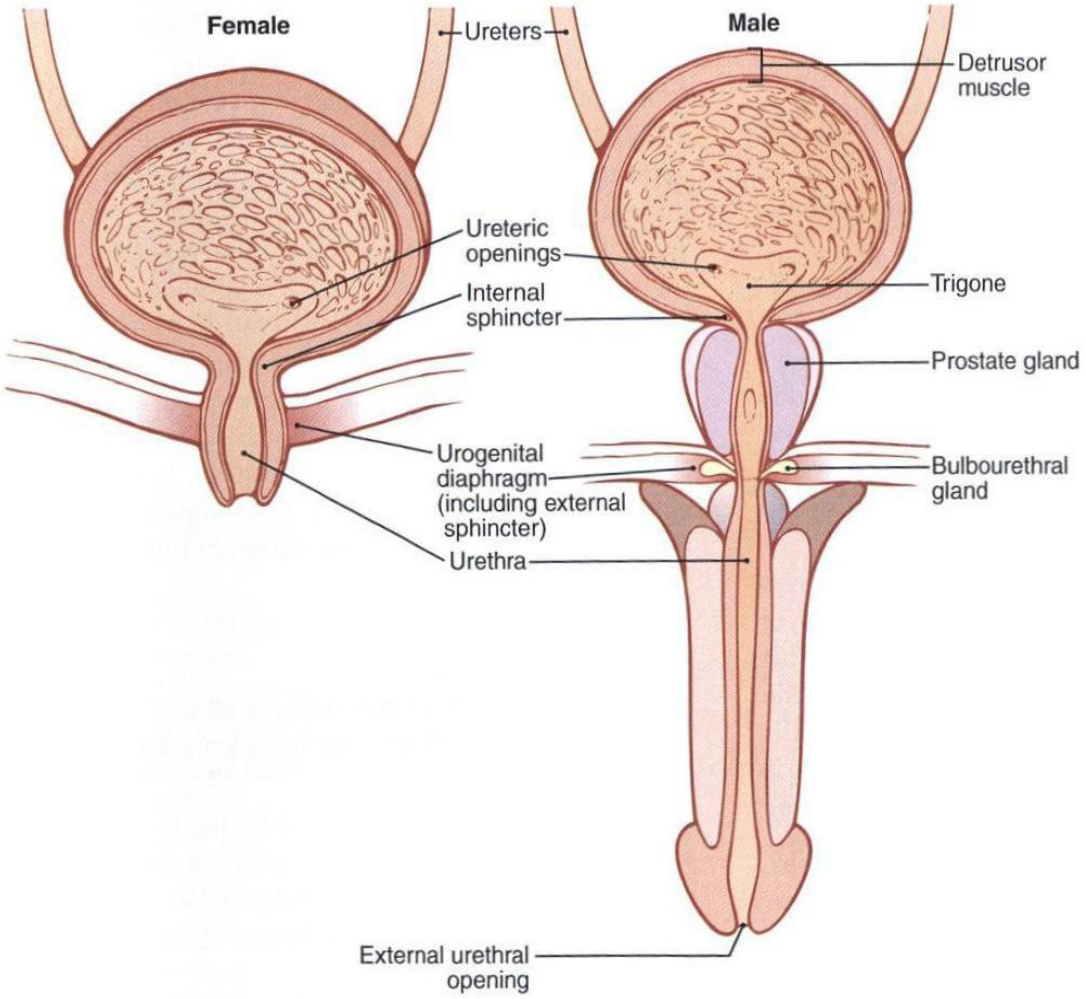


Secretory Transport Maximum



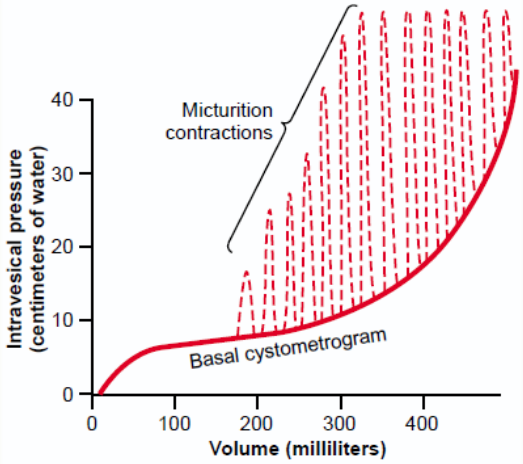
❖ Anatomy of urinary bladder and urethra in males and females

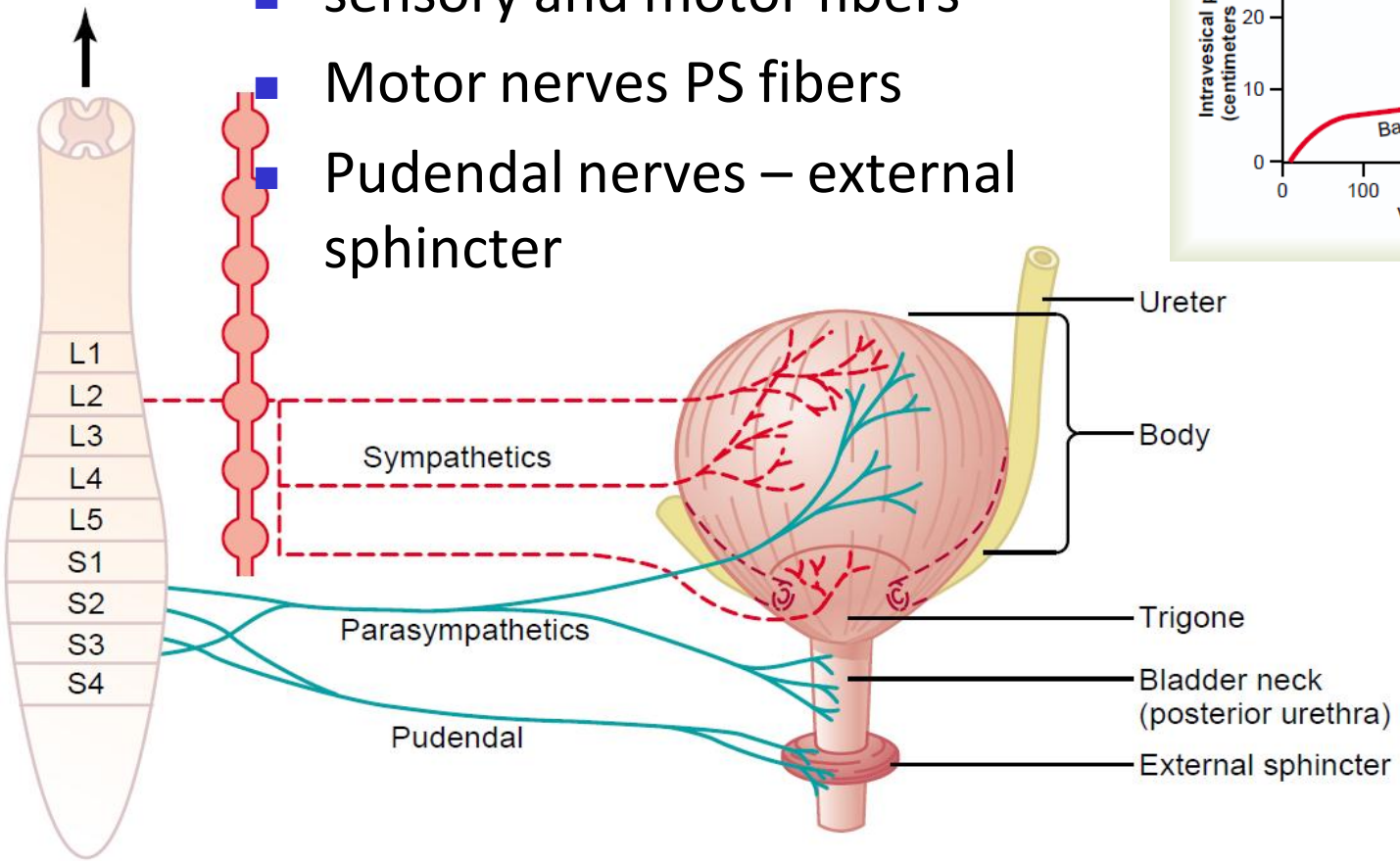
- The ureters are attached to the posterior aspect of the bladder
- Trigone
- Internal sphincter at the beginning of the neck
- External sphincter
- Length of urethra



Micturition reflex

- Pelvic nerves connect with the spinal cord (segments S2 & S3) via the sacral plexus
- sensory and motor fibers
- Motor nerves PS fibers
- Pudendal nerves – external sphincter





Urinary tract infection

- Normally, **urine is sterile** and free of foreign bacteria and viruses
- However, bacteria can enter the urinary system through the urethra causing **cystitis**, or a **urinary tract infection** (UTI)
- Symptoms of a UTI include: a burning sensation when urinating, frequent urination consisting of small amounts of urine, and the presence of blood in the urine

Bladder incontinence

- https://blausen.com/en/video/bladder-incontinence/
- **a weakness or inability to control the flow of urine from the body**
- most common in women – 10% of all women - regular incontinence, 20 % over age 75 experience daily urinary incontinence. At least 50 % have experienced incontinence at some time in their lives
- causes - **Stress incontinence** - the strength of the urethral sphincter is diminished, and it is not able to prevent urine flow when there is increased pressure from the abdomen
- *risk factors - age, damage to the urethra and childbirth*
- **Urge incontinence** occurs when the bladder muscle contracts inappropriately. Often the contractions occur regardless of the amount of urine that is in the bladder (spinal cord injury)

Urine

Volume: 0.5 – 2.5 L/24 h

- Poliuria is a condition of excessive production of urine (> 2.5 L/day)
- oliguria when < 400 mL are produced, and
- anuria one of < 100 mL per day

pH: 4.8 – 8.0

- Higher in alkalosis, lower in acidosis
- Diabetes and starvation ↓ pH
- Urinary infections ↑ pH

Specific gravity

- Normal values **1.025 -1.032**
- High specific gravity can cause precipitation of solutes and formation of kidney stones

Urine

- **Microscopic analysis**
- Casts – precipitate from cells lining the renal tubules
  - Red cells – tubule bleeding
  - White cells – tubule inflammation
  - Epithelial cells – degeneration, necrosis of tubule cells
- Red blood cells – should be few or none
  - **Hematuria** – large numbers of RBC's in urine
  - Catheterization
  - Menstruation
  - Inflamed prostate gland
  - Cystitis or bladder stones
- White blood cells
  - **Pyuria**
  - Urinary tract infection
- Crystals –
  Infection
  Inflammation
  Stones
- Bacteria

Substances not normally present in urine

- Acetone
- Bile, bilirubin
- Glucose
- Protein – albumin
  - Renal disease involving glomerulus