GUS PHYSIOLOGY:

L.1:

● The kidneys produce and secrete: calcitriol, renin, kinins, erythropoietin.

● synthesize glucose during prolonged fasting (gluconeogenesis)

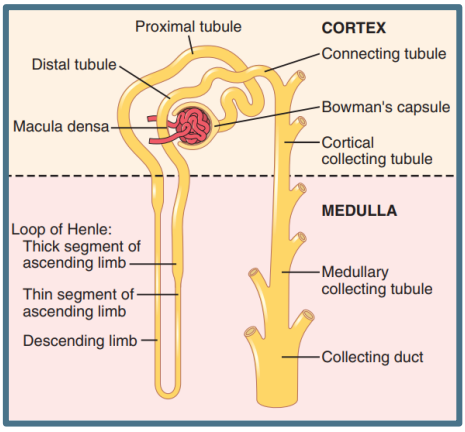
● **blood supply:** The renal artery →interlobar arteries →arcuate arteries→ interlobular arteries→ afferent arterioles→ glomerular capillaries→ efferent arteriole→ the peritubular capillaries (in cortical nephrons) / vasa recta (in juxtamedullary nephrons)

● The urine that has been formed in **nephron**→ papillary duct→ renal papilla→ minor and major calyces→ renal pelvis→ ureters→ urinary bladder.

• Each nephron is made up of:

❑Renal Corpuscle: Bowman's Capsule -Glomerulus

❑Renal Tubules: -Proximal Convoluted Tubule (PCT) -Loop of Henle (LH) -Distal Convoluted Tubule (DCT) -Collecting Duct (CD)



L.2:

Bowman's Capsule

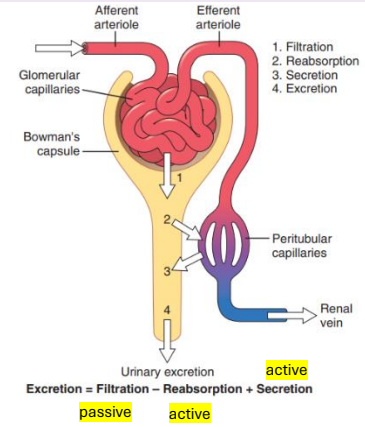
inner "visceral layer"

- podocytes

outer "parietal layer"

- s. squamous epithelial

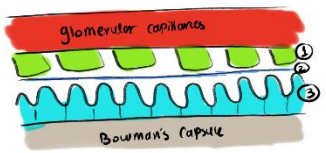
Space between layers holds filtered



Juxtaglomerular Apparatus: Arterioles contain juxtaglomerular cells near the distal convoluted tubule and **macula densa**.

Mesangial Cells: between capillaries and arterioles.

Filtration Membrane:



1. **Endothelial cells** with fenestrations facilitate filtration but prevent RBC passage.
2. **Basal lamina** with negatively charged fibers repels negatively charged proteins like albumin.
3. **Podocytes with slit-like spaces** selectively allow substances to pass through.

-The more positive charges and the smaller size, the higher filterability.

● **Renal Handling of Different Substances:**

★ filtration only→ creatinine.

★Filtered and completely reabsorbed→ glucose, AA

★filtration and partial reabsorption→ sodium and water.

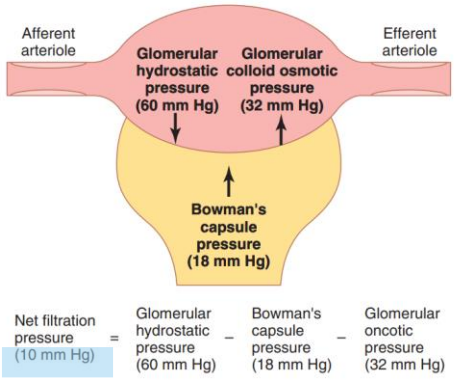
★ filtration and secretion→ toxins, often exogenous.

● **Edema:** damage the glomerular capillaries→ ↑ their permeability to large proteins→ ↑ Bowman's capsule colloid pressure→ ↑filtered fluid and ↓ reabsorption→ proteins are lost in the urine→ deficiency in blood colloid pressure→ ↑ interstitial fluids→ edema

✿FILTRATION:

● **(FF →16-20% of blood plasma / GFR →125 ml/min)** →PF being 625 ml/min→ required blood flow of 1140 ml/min to maintain a GFR of 125 ml/min, which constitutes 22.8% of the total blood volume.

Net filtration pressure:



✓ Filtration fraction (FF) (GFR / Renal Plasma Flow)

✓ GFR= K_f ✕ Net filtration pressure

✓ K_f = hydraulic conductivity x surface area

l.3:

Homeostasis of body fluids requires constant GFR by kidneys.

↑ GFR → ↓ reabsorbed

↓ GFR → ↑ reabsorbed

•**not a physiological Regulator:**

1. ↑ Kf → ↑ GFR
2. ↑Bowman's Capsule hydrostatic Pressure (PB) → ↓ GFR
3. Glomerular Capillary Oncotic Pressure (π_G)

↑FF→ ↑π_G

Filtration fraction (FF) (GFR / Renal Plasma Flow)

- ↑ GFR →↑ oncotic pressure by ↑ filtration fraction.
- ↑ renal plasma flow→ ↓ filtration fraction→↓ oncotic pressure and ↑ GFR.
- ↑ renal plasma flow initially without changing GFR→ ↑GFR due to the ↓ oncotic pressure.

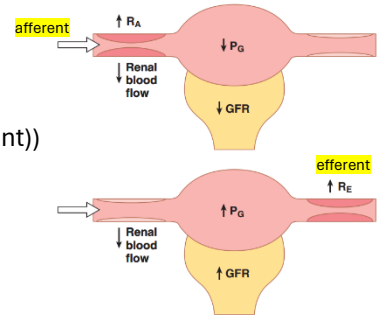
•**physiological regulator:**

Glomerular Hydrostatic Pressure (P_G):

1)arterial pressure (buffer/autoregulation (60-200 constant))

2)afferent arteriolar resistance

3)efferent arteriolar resistance



↑ resistance in efferent arteriole >**3X**→ ↓renal blood flow→ ↑FF→ ↑oncotic pressure→ ↑glomerular hydrostatic pressure→ **↓GFR.**

★ No GFR → no Na+ reabsorption →BUT oxygen consumption won't be zero, instead it will be 0.5 (Basal Oxygen Consumption)

L.4:

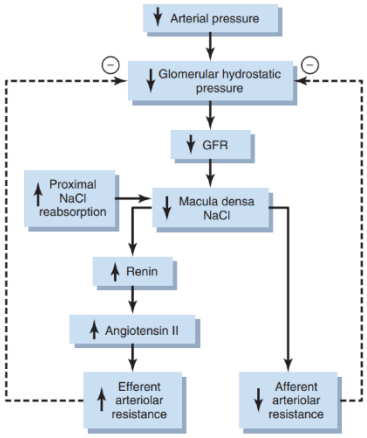
•Control of GFR and RBF:

• NEUROHUMORAL:

Hormone or Autacoid	RBF	GFR	The explanation
↑**Sympathetic activity**	↓	↓	severe sympathetic→ severe **vasoconstriction** in the Afferent arteriole more than the efferent
↑**Endothelin**	↓	↓	mainly **constricts** afferent arterioles
↑**Catecholamines**	↓	↓	
↑**Angiotensin II**	↓	⇔	production of angiotensin 2→**constricts** the **efferent** arteriole
↑**EDRF (NO)**	↑	↑	**vasodilation** in the afferent arteriole mainly
↑**Prostaglandins**	↑	↑	**vasodilation** in the afferent arteriole mainly - patients with reduced GFR (prostaglandins are necessary) → Avoid NSAID

• LOCAL (INTRINSIC):

1- tubuloglomerular feedback mechanism:



Renin secretion is regulated by: Perfusion Pressure/ Sympathetic Nerve Activity/ NaCl delivery to macula densa.

- macula densa senses ↓ **NaCl** levels signal ↓ GFR→ ↑ **NO synthesis** for vasodilation of the afferent arteriole or by **renin release**→ ↑ systemic and G hydrostatic pressure → ↑ GFR

!!And in case of **↑NaCl** levels →**inhibition of (NO)+renin release**

ლ Autoregulation→ normal renal function despite changes in arterial pressure.

2- Myogenic mechanism (faster): ↑ pressure stretches arteriole walls→ triggering rapid constriction esp. **afferent** (↑calcium influx) → ↑resistance→ ↓GFR & ↓BF

3- Ang II: ↓GFR → macula densa signals for renin release→ leading to Ang II formation→ ↑blood pressure through vasoconstriction, esp. efferent arterioles→ maintaining GFR

ლ Ang II blockade impairs GFR autoregulation but doesn't affect renal blood flow.

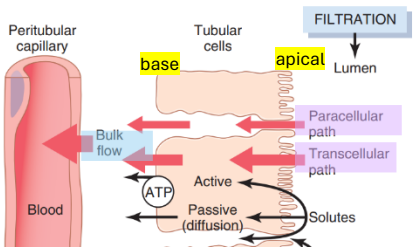
•OTHER FACTORS:

- Hyperglycemia glucocorticoids, fever, and high protein ↑ GFR/aging and low protein ↓ it.

↑blood levels of glucose or AA →↑ filtered loads →Their absorption with sodium prompts more sodium reabsorption→ ↓ sodium delivery to the macula densa triggers ↑in GFR via NO release.

L.5:

✿REABSORPTION:



•2 ways: (transcellular route) / (paracellular route)

❍ **Proximal Tubule Reabsorption:** Simple cuboidal epithelial & brush borders.

1. Sodium reabsorption: (active) 67% - gradient-time dependent.

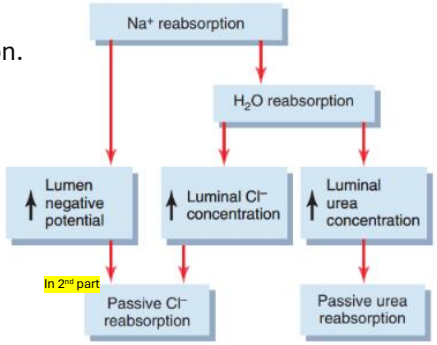
Na+/K+ ATPase pumps sodium out (Basolateral) → **↓ intracellular sodium concentration.** → Na+ diffuse into the cell through the brush border (Apical)

★ Sodium reabsorption crucial for organic acids, water, Cl-, and other anions.

2. H2O Reabsorption: Na+ reabsorption ↓tubular fluid osmolarity→ H_2O reabsorption.

- by **Aquaporin channels (transcellular)** and **paracellular paths**

3. Solvent Drag: H_2O carries along ions



4. Secondary Active Transport: Glucose and amino acid reabsorption → Down Na+ gradient, and against glucose gradient

- Transport Maximum: beyond which excess glucose is excreted in urine.

-Threshold: Some nephrons are saturated→ glucose excretion despite not reaching transport maximum

Filtered load of a substance= (substance concentration in plasma X normal GFR).

❍ **The Loop of Henle:** Simple Squamous (thin), Cuboidal (Thick).

1. Thin Descending Limb: Reabsorbs 15% of water. (hypotonic)

2. Thin Ascending Limb: Passive reabsorption of Na+, K+, Cl-.

Impermeable to water. (hypertonic)

3. Thick Ascending Limb: (isotonic)/ Diluting segment / Impermeable to water.

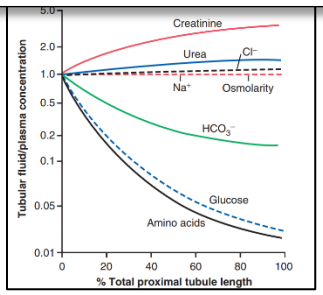
- Reabsorbs 25% of Na+ **(Na+/K+ ATPase)** /ions. (**Voltage Drag)**

- Na+/K+ ATPase **(basolateral)** |Na+/Cl-/K+ channels **(the apical surface)**

- Secretion of H+ by secondary active transport.

Furosemide: blocks Na+/Cl-/K+ reabsorption→ ions are then excreted in urine.

- Changes in Concentration in Proximal Tubule



> 1: lower reabsorption compared to water.

< 1: higher reabsorption compared to water.

= 1: relatively similar reabsorption to water.

L.6+8:

❍ **Early Distal Tubule:** simple cuboidal. / Macula densa

like the thick ascending loop, reabsorbing Na+ and other solutes, but impermeable to water, contributing to urine dilution.

❍ **Last part of Distal Tubule and Collecting Duct:** Simple cuboidal

- Includes principal and intercalated cells.

★ Principal cells:	★ Intercalated Cells:
Aldosterone: ↑activity of **ENaC** (reabsorbs Na+ and secretes K+) and **Na+/K+ ATPase**	Two types: **Type A:** for **acidosis**→ secreting H+ and reabsorbing bicarbonate (luminal H+ ATPase) **Type B:** for **alkalosis**→ secreting bicarbonate. (H+ ATPase on the opposite membrane)

- ***Thiazides:*** in early distal tubule cause diuresis.

- ***Amiloride:*** blocking ENaC, acts as a potassium-sparing diuretic→ ↓BP

- ***Aldosterone antagonists:*** inhibit ENaC and Na+/K+ATPase

✓Water permeability depends on **ADH**→ stimulates aquaporin insertion →increasing BP.

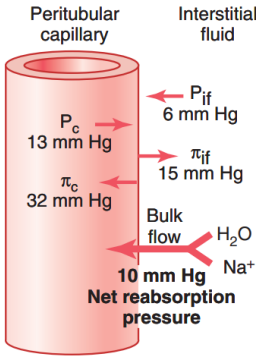
- **Cortical collecting tubules** → impermeable to urea,

- **medullary** ones are more permeable (increase interstitial osmotic pressure.)

★ Concentrations of solutes in different parts of the tubule depend on the relative reabsorption of solutes compared to water.

• Regulation of Tubular Reabsorption:

1. **Glomerulotubular Balance:** ↑Tubular Load →↑ reabsorption →minimizing changes in urine volume.
2. **Peritubular Physical Forces:**
   Hemodynamic forces.
   Net reabsorption pressure = πc + Pif - Pc - πif = 10 mmHg.
   Bulk flow (10 mmHg) →fluid from interstitial to capillary.



Reabs = Net Reabs Pressure (NRP) x Kf

= (10 mmHg) x (12.4 ml/min/mmHg) = 124

Determinants of Renal Reabsorption:

↑ Pc → ↓Reabsorption:	↑ πc → ↑Reabsorption	↑ Kf → ↑Reabsorption
• ↓ R_A → ↑ Pc • ↓ R_E → ↑ Pc • ↑ A. pressure → ↑ Pc	• ↑ π_A → ↑ πc • ↑ FF → ↑ πc	

3. **Hormones:**

Hormone	Site of Action	Effects
Aldosterone	late distal, cortical and medullary collecting tubules principal cells / intercalated cells	↑ Na+ reabsorption, ↑ K+ secretion, ↑ H+ secretion
Angiotensin II	proximal, loop, distal, collecting tubules	↑ Na+ reabsorption/ Constricts efferent arterioles
ADH	distal and collecting tubules	↑ H2O reabsorption Important controller of extracellular fluid osmolarity
ANP	distal and collecting tubules	↓ Na+ reabsorption ↑ GFR minimize blood volume expansion
Parathyroid hormone		↓ PO4 – reabsorption, ↑ Ca++ reabsorption

Angiotensin II blockade→ ↓blood pressure

Clinical Perspective:

Excess Aldosterone: (Primary aldosteronism Conn's syndrome): alkalosis

Aldosterone Deficiency: (Addison's disease).

Control of Aldosterone Secretion:

Increase: Angiotensin II. / hyperkalemia / ACTH (permissive role).

Decrease: (ANF). / High Na+ concentration (osmolality).

4. **Sympathetic Nervous System:** sympathetic nervous system is activated→ ↑sodium reabsorption+ renin release.
   severe activation of the SNS→ ↓ sodium and water excretion→ ↓ (GFR).
5. **Arterial Pressure: Pressure natriuresis:** Increased Arterial Pressure Decreases Na+ Reabsorption.
6. **Osmotic factors:**

diabetes mellitus: unreabsorbed glucose in tubules causes diuresis and water loss

osmotic diuretics (mannitol): This highly filtrated & poorly reabsorbed substance stays in the tubular fluid.

Calculation:

Reabsorption = Filtration - Excretion

Filtration = GFR × Plasma concentration

Excretion = Urine flow rate × Urine concentration

- Positive result indicates net reabsorption/ Negative result indicates net secretion.

L.7:

clearance:

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

clearance (C_s)	plasma concentration (Ps)
urine concentration (U_s)	and urine flow rate (V)

• Use of Clearance to Measure GFR: (**inulin**,125I-iothalamate (iodinated), creatinine)

freely filtered and is not reabsorbed or secreted → rate of excretion ($U_s \times V$) is equal to the filtration rate (GFR × Ps).

Thus, $GFR \times P_s = U_s \times V \rightarrow GFR = \frac{U_s \times V}{P_s} = C_s$

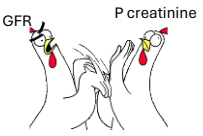
• Use of Clearance to Estimate Renal Plasma Flow: (PAH (Paraminohippuric acid))

completely cleared (filtered and secreted with no reabsorption) from the plasma, then its clearance rate would equal **renal plasma flow**.

$ERPF \times P_{pah} = U_{PAH} \times V$

$ERPF = \frac{U_{PAH} \times V}{P_{PAH}}$

$RPF = \frac{ERPF}{E_{PAH}}$ → $E_{PAH} = \frac{A_{PAH} - V_{PAH}}{A_{PAH}}$



ERPF, not RPF→ must be corrected.

Reducing GFR by 50% → serum creatinine will start increasing and then plateau → Renal excretion will decrease but then increase back to normal →excretion rate of substances will <u>not be affected by the reduction of GFR</u>

Excretion = GFR X P creatinine

L.9:

ADH: ↑ extracellular osmolarity (NaCl) → ADH release → ↑ H2O reabsorption and stimulates thirst.

- drinking 1 liter of water → urine osmolarity significantly drops → ↑ Urine flow rate → Urinary solute excretion is unaffected **(ADH's selective regulation of water secretion without altering solute excretion)**

• Formation of a dilute urine: • Continue electrolyte reabsorption **/**• Decrease water reabsorption

❀ **Mechanism:** **Proximal Tubule** (Solutes and water are reabsorbed equally) → **Descending Loop of Henle** (Water is reabsorbed → ↑ concentration of tubular fluid) →**Ascending Loop of Henle** (ions are reabsorbed, /water is impermeable → dilution of the tubular fluid) → **Distal and Collecting Tubules** (absence of ADH → more dilute urine) → excretion of a large volume of dilute urine.

Urine specific gravity: solute weight in urine(solute number & size.)

rising by .001 for every 35 to 40 mosmol/kg increase in osmolality.

Large molecules in urine can alter this relationship.

Obligatory Urine Volume: determines the minimal volume of urine in which the excreted solute can be excreted

solute must be excreted each day / max. urine osmolarity.

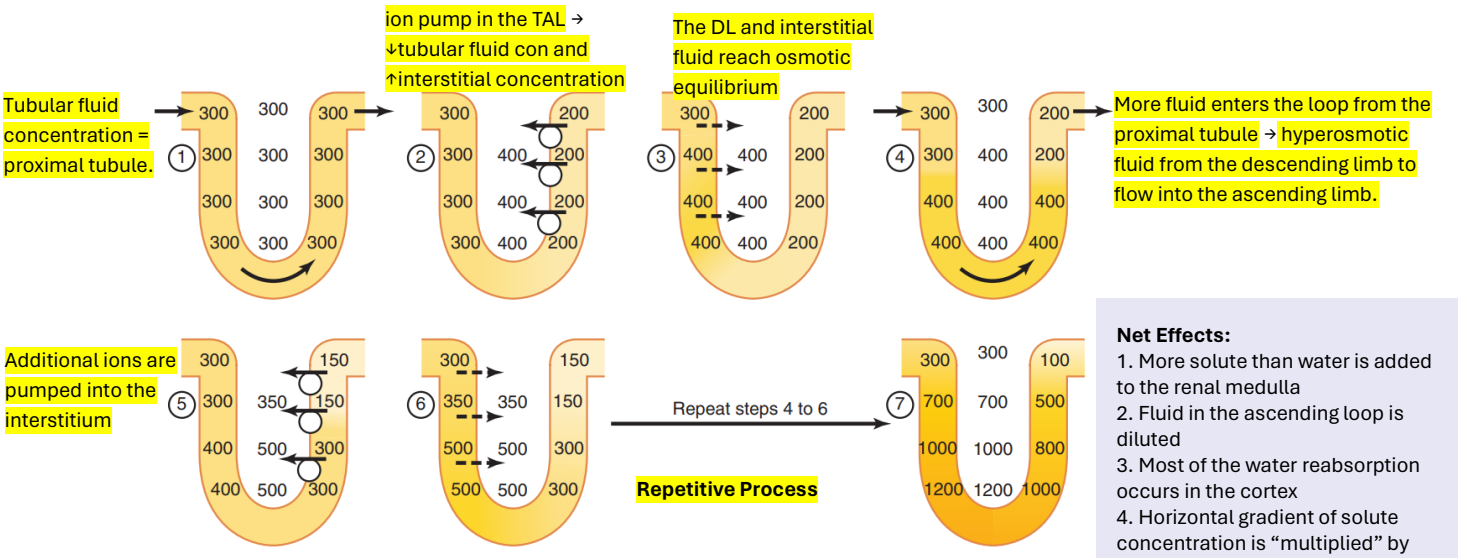
• Formation of a Concentrated Urine:

• Continue electrolyte reabsorption/ • Increase water reabsorption

❀ **Mechanism:** **ADH Effects on Reabsorption (**With ADH, both water and sodium chloride are reabsorbed in the **late distal and cortical collecting tubules,** concentrating the tubular fluid) → Higher renal blood flow in the cortex → water reabsorption, extending to the medullary collecting tubules→ The kidney reaches its maximal urine concentration

- The buildup of solute in the renal medulla is driven by: active ion transport in the loop of Henle and collecting ducts, passive urea diffusion, and limited water diffusion.

○ Countercurrent multiplier system in the loop of Henle:

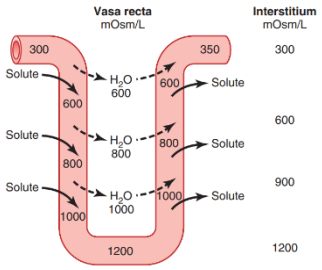


Net Effects:
1. More solute than water is added to the renal medulla
2. Fluid in the ascending loop is diluted
3. Most of the water reabsorption occurs in the cortex
4. Horizontal gradient of solute concentration is "multiplied" by countercurrent flow of fluid.

- Mechanism of Urea Reabsorption: Urea is **passively** reabsorbed in proximal tubule (but secreted by **UTA-2** in TDL) → (presence of ADH) →↑ concentrating urea→ **The inner medullary collecting tubule** is highly permeable to urea, which diffuses into the medullary interstitium **(transporters (UTA-1) and (UTA-3))**

- Recirculation of Urea: A portion of urea is recirculated from the collecting duct to the loop of Henle, contributing to the hyperosmotic renal medulla. This recirculation mechanism helps concentrate urea before excretion, crucial when water is scarce.

○ The Vasa Recta Preserve Hyperosmolarity of Renal Medulla:



Descending into the medulla, blood becomes more concentrated due to solute entry from the interstitium and water loss→ As blood ascends towards the cortex, it becomes less concentrated.

Free-Water Clearance: $C_{H_2O} = V - C_{osm} = V - \frac{(U_{osm} \times \dot{V})}{P_{osm}}$

If: $U_{osm} < P_{osm}$, C_{H2O} = +

If: $U_{osm} > P_{osm}$, C_{H2O} = -

- ✓ **Failure to Produce ADH**: Central Diabetes Insipidus
- ✓ **Inability of Kidneys to Respond to ADH:** Nephrogenic Diabetes Insipidus**:** Large dilute urine volumes produced, requiring increased fluid intake to prevent dehydration.
- ✓ **Inappropriate ADH syndrome (excess ADH)**: decreased plasma osmolarity, hyponatremia

Nephron Loss in Chronic Renal Failure: Isosthenuria With (inability to concentrate or dilute the urine)

- plasma ADH levels do not change appreciably until blood volume is reduced by about 10 percent

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