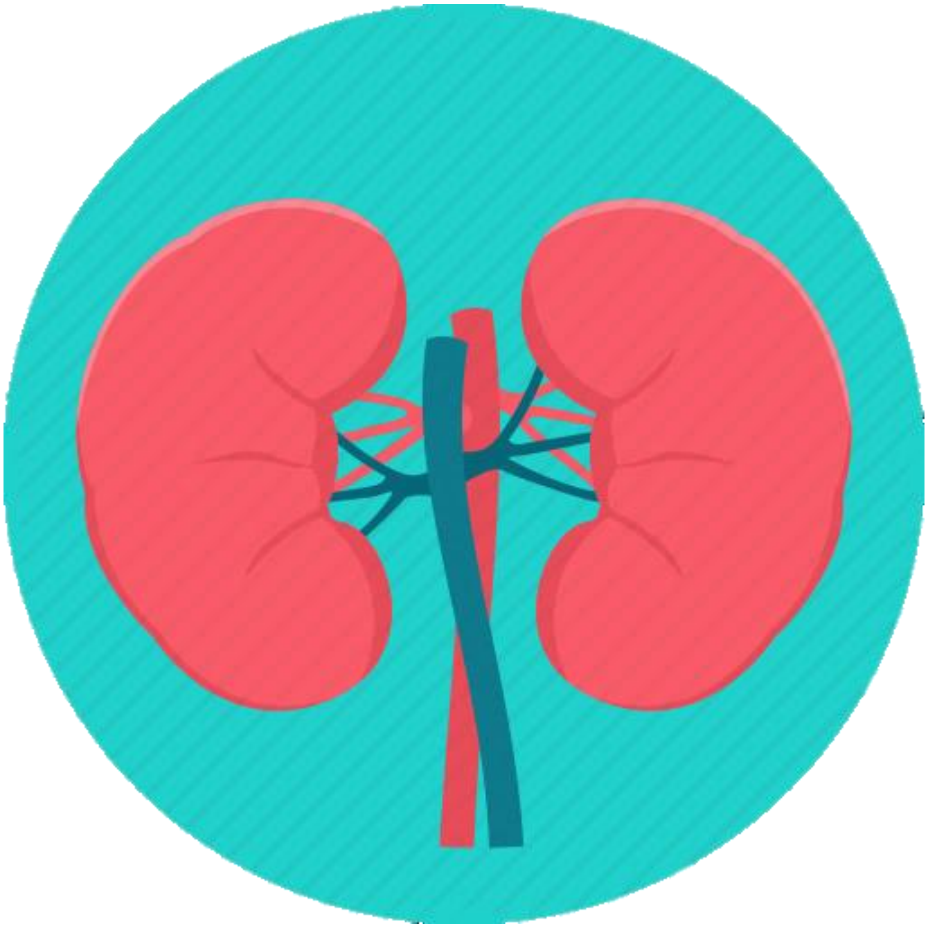
Lecture (1-3)

Renal Function & GFR



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Physiology

MED438

Functions of the kidneys:

Excretion

1. Excretion of nitrogenous wastes (urea, uric acid and creatinine) & other toxins
2. Excretion of bioactive substances such as drugs

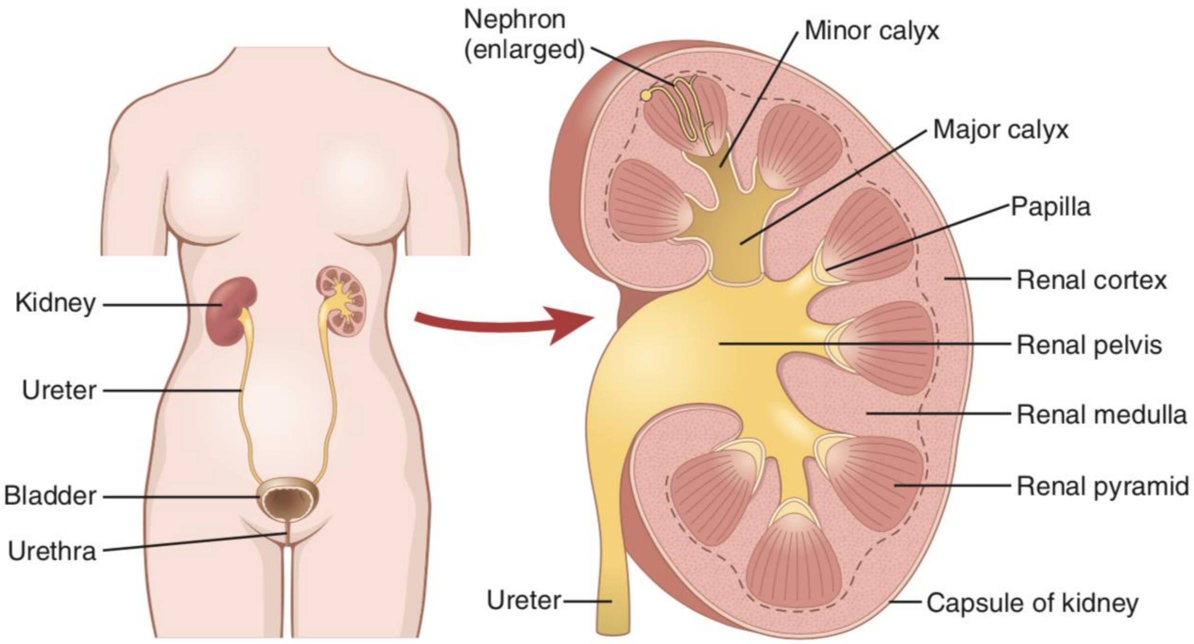
Regulation

1. Regulation of Blood pressure through ***renin***
2. Regulation of Acid Base balance
3. Regulation of water and electrolytes balance

Production

1. Production of ***erythropoietin*** to synthesize RBCs
2. Production of glucose (gluconeogenesis)
3. Production of Vitamin D (1,25-dihydrocholecalciferol)

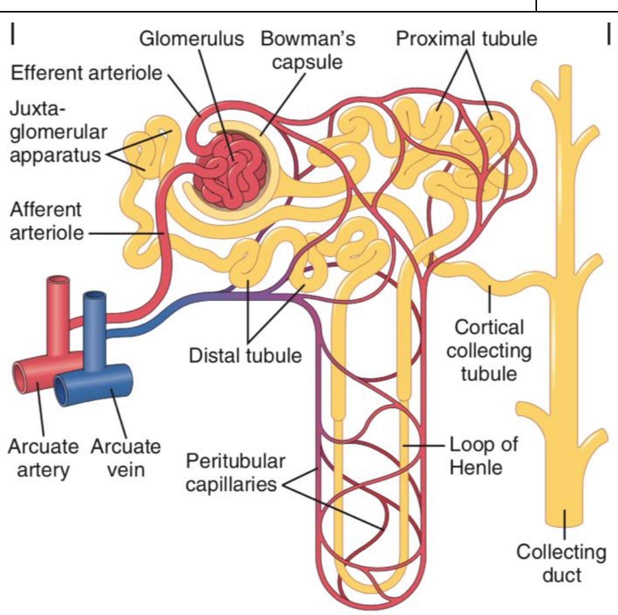
Anatomy of the kidneys

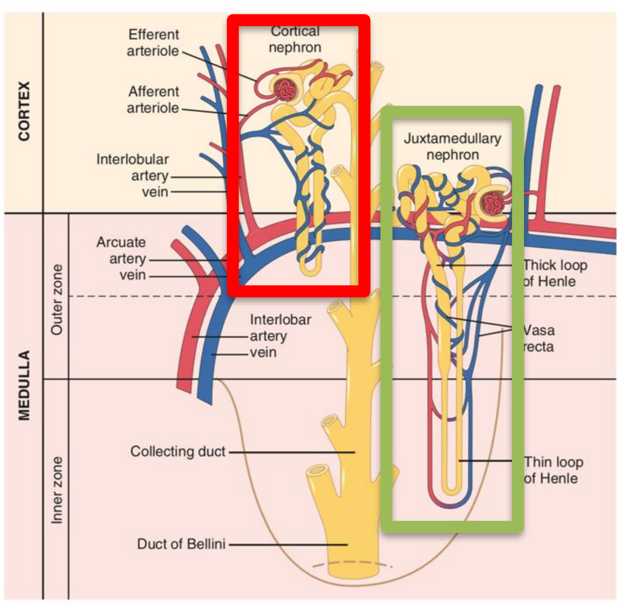


The Nephron

- Nephrons are the structural and functional units that form urine.
- There are two types of nephrons:
  1. **Cortical** (85%): located in the **upper** cortex
  2. **Juxtamedullary** (15%): located in the cortex-medullary region (receives 1-2% of RBF)
     - Loop of Henle deeply invade the medulla
     - Responsible in producing concentrated urine
- A nephron is composed of:

Renal Corpuscle	Renal Tubule
1. Glomerulus - Capillary tuft - Fenestrated endothelium **2. Glomerular (Bowman's) capsule** - Surrounds the glomerulus - Parietal: structural layer - Visceral:(epithelium) podocytes with filtration slits	**1. Proximal convoluted tubules (PCT)** - Has microvilli and mitochondria - Reabsorb water + solutes **2. Loop of Henle** - Descending: mostly thin layer - Ascending: thin then thick layer **3. Distal convoluted tubule (DCT)** - NO microvilli - Function in secretion more than reabsorption **4. Collecting tubules**** - Intercalated cells: maintain acid-base balance - Principal cells: maintain water balance ** aren't considered part of the nephron



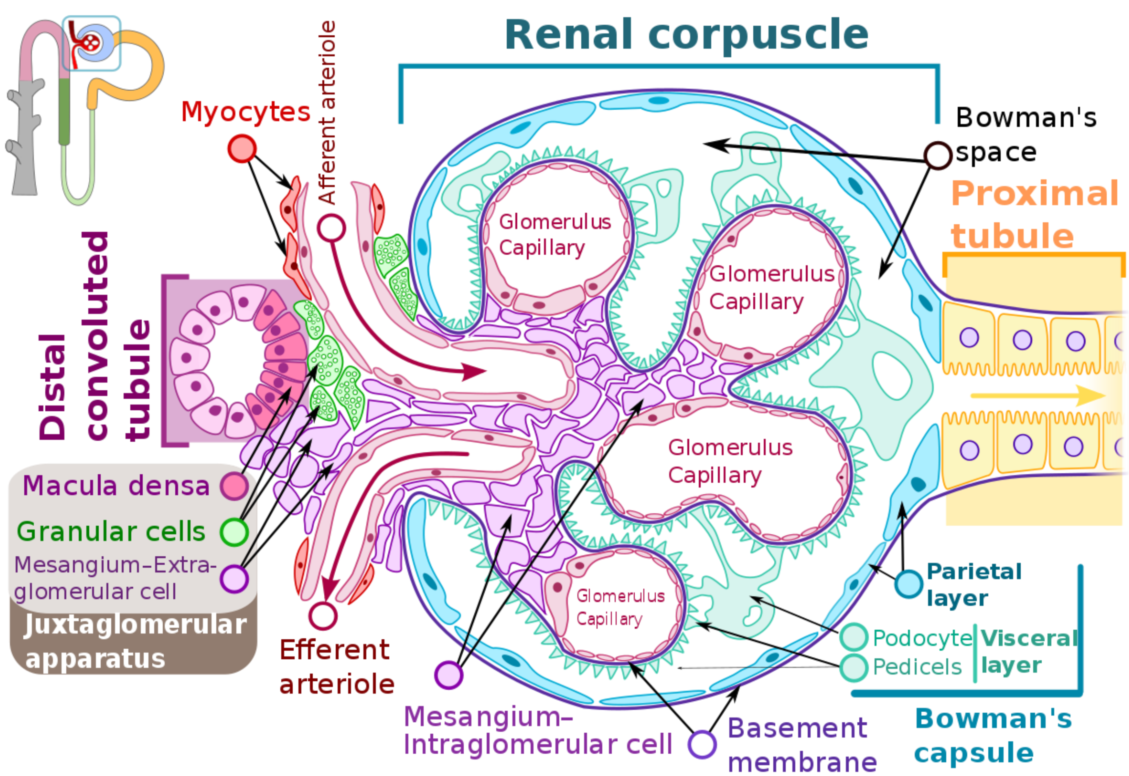


Juxtaglomerular Apparatus

- The area where the distal tubule lies against the afferent arteriole.
- The JGA consist of three types of cells:

Juxtaglomerular Apparatus
- JG cells
- Macula Densa
- Mesangial cells

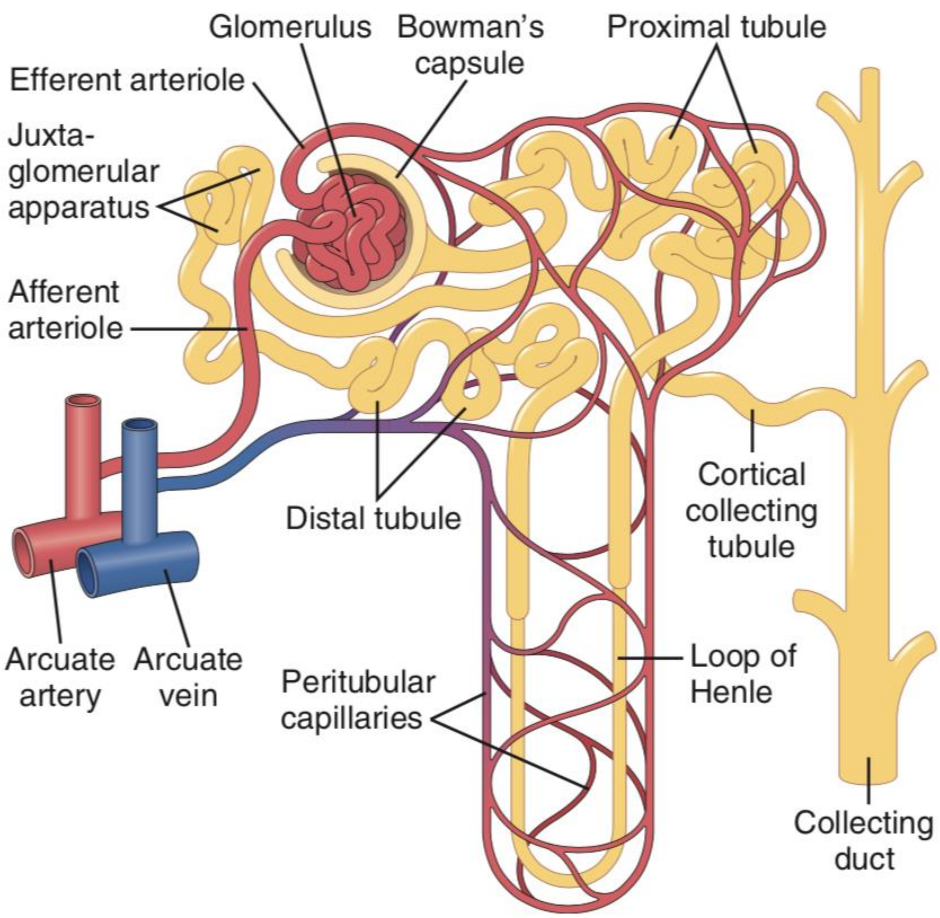
Cell	Characteristics	Function
Juxtaglomerular cells (JG)	• Enlarged smooth muscles	• Mechanoreceptors • Secrete renin
Macula Densa Adjacent to JG cells	• Tall distal tubule cells	• Chemoreceptors • Stimulate JG cells to secrete renin
Extraglomerular Mesangial cells	• Phagocytic cells • Irregular shaped cells	• adjust filtration pores (by contracting) • Regulate blood flow



Renal Blood Vessels & Blood Flow

- Renal blood flow = 20% of cardiac output
- Blood flow to each kidney (high blood flow rate) = 1200 ml/min.
- We divide the renal blood vessels into:

1. **Capillary beds:**
   - ➔ Glomerulus: produce filtrate that enters renal tubules (highest pressure = 60mmHg)
   - ➔ Peritubular: capillary network surrounding the tubules
   - ➔ Vasa recta: peritubular capillaries branching from efferent arterioles of the juxtamedullary nephron
2. **High resistance arterioles** (major site of renal resistance):
   - ➔ Afferent: deliver blood to the glomeruli (larger in diameter)
     - Protects glomerulus from systemic fluctuations (sudden changes)
   - ➔ Efferent: deliver blood to peritubular capillaries (remember E = exit)
     - Reinforce glomerulus pressure
     - Reduce hydrostatic pressure in peritubular capillaries

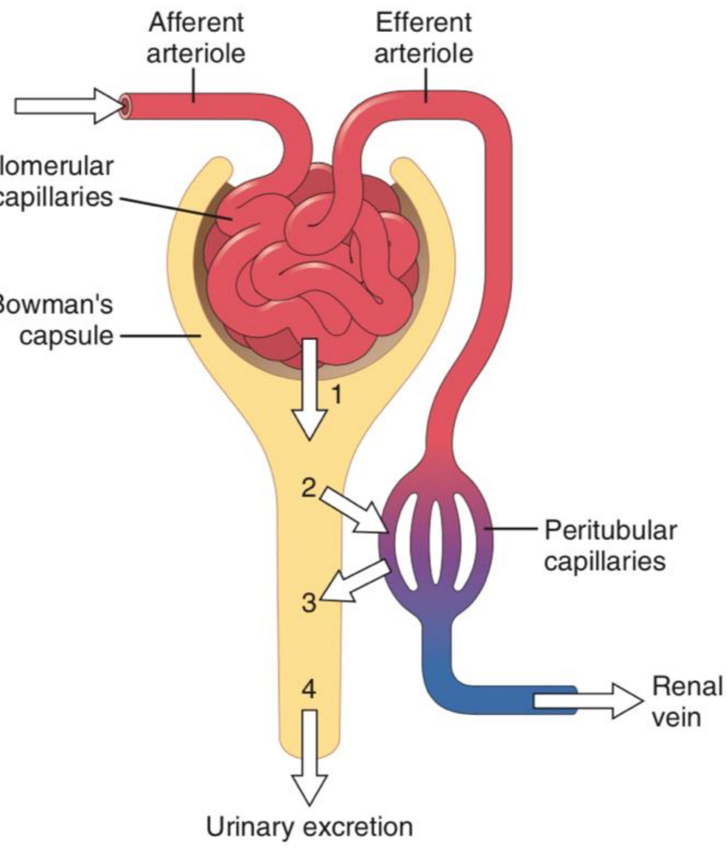


Urine Formation

- The primary function of the kidney is to remove unneeded wastes from the blood to be excreted as urine.
- The basic renal process:

Urinary excretion = Filtration – reabsorption + secretion

1. Glomerular Filtration
2. Tubular reabsorption
3. Tubular secretion
4. **Excretion**

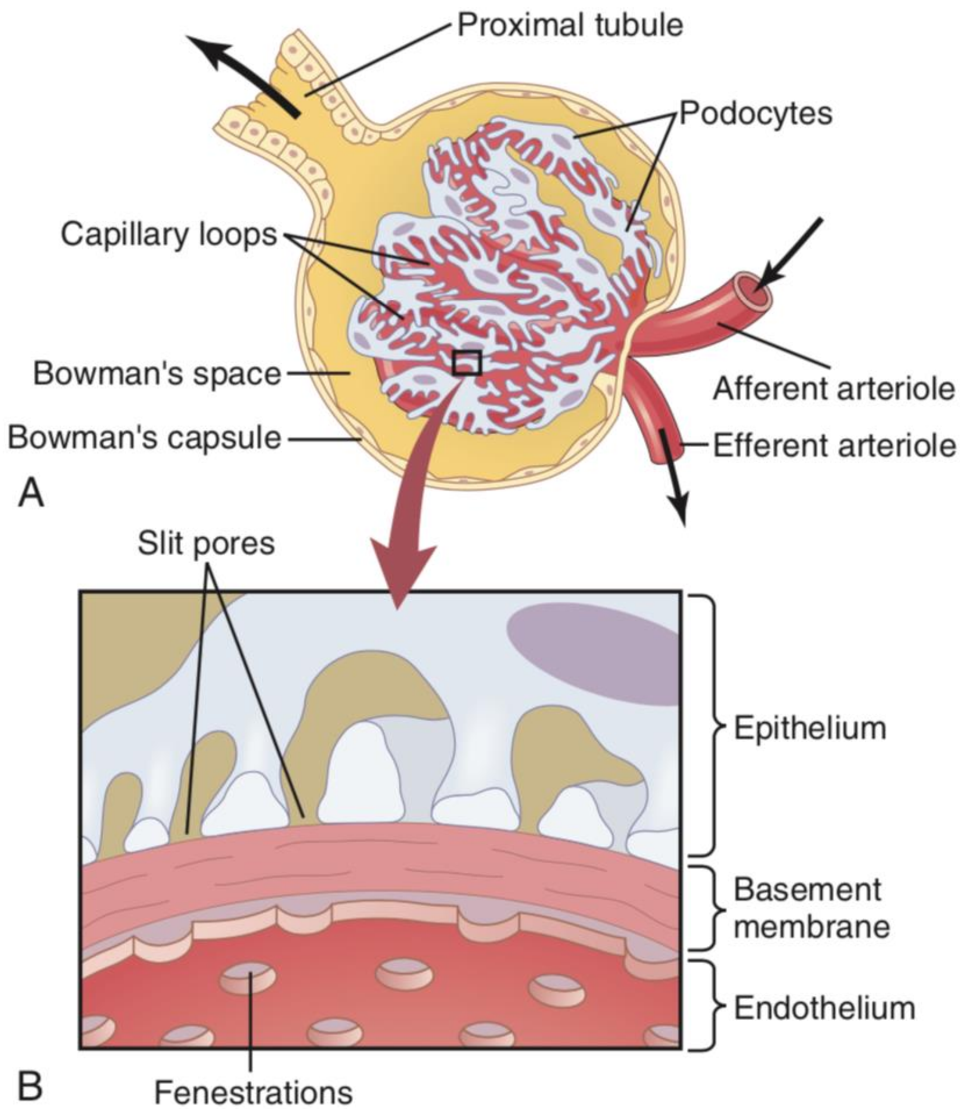


Definitions:

- **Glomerular Filtration:** filtration from the capillaries to the renal tubule
- **Tubular reabsorption:** transfer of substances from the tubules back into the blood that is in the peri-tubular capillaries
- **Tubular secretion:** selective transfer of substances from the peri-tubular capillaries back into the tubules again
- **Urine excretion:** the elimination of the substances from the body

Filtration Membrane:

- Blood in the glomerulus is separated from Bowman's capsule by a filtration barrier (glomerular membrane) that consists of three layers:
    1) Fenestrated capillary endothelium
    2) Basement membrane: fused basal laminae
    3) Podocytes: epithelial lining of Bowman's capsule with slits (pores)
- Glomerular filtration is **HIGHLY** permeable to water and small solutes
- Glomerular filtration **CAN'T** filter large proteins (>8 nm/ >70K D) due to their size and the repulsion between the **protein's** negativity such as albumin and the layers' negatively charged **glycoproteins** (type IV collagen and proteoglycans).
- **In other words, the filtrate is similar in plasma composition – proteins**



Glomerular Filtration Rate (GFR)

- GFR is the sum of all filtration rates of functioning nephrons at the glomerulus from the plasma (**~20% of renal plasma flow**)
- It ranges from 90-140 ml/min (avg. 125) depending on age, sex & body size
- It's a good index of kidney function (**GFR < 90 is an indicator of kidney disease**)
- GFR is governed by:
  1. Total surface area
  2. Filtration membrane permeability

  } **Kf:** capillary filtration coefficient
  3. **Net filtration pressure (NFP):** pressures exerted by starling forces

$$\mathbf{GFR = NFP \times Kf}$$

- **IF GFR is too HIGH** → substances can't get reabsorbed and are excreted
  - Causing dehydration and electrolytes depletion
- **IF GFR is too LOW** → everything gets reabsorbed **(more dangerous)**
  - Causing *Azotemia* or high nitrogen-containing substances in blood
- We can calculate the NFP by adding the starling forces, and as we remember the starling forces are the **hydrostatic pressure** and **oncotic pressure**
- The capsular oncotic pressure is **ZERO** since there are no proteins in the filtrate

Symbols

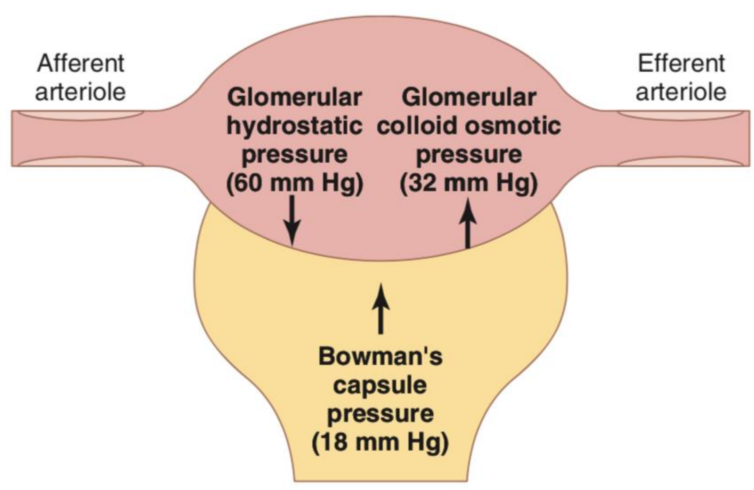
Glomerular HP (P_g/HP_g)

Capsular HP (P_c/HP_c)

Net HP = $P_g - P_c$ = 42 mmHg

Capsular OP (OP_c/π_c)

Glomerular OP (OP_g/π_g)



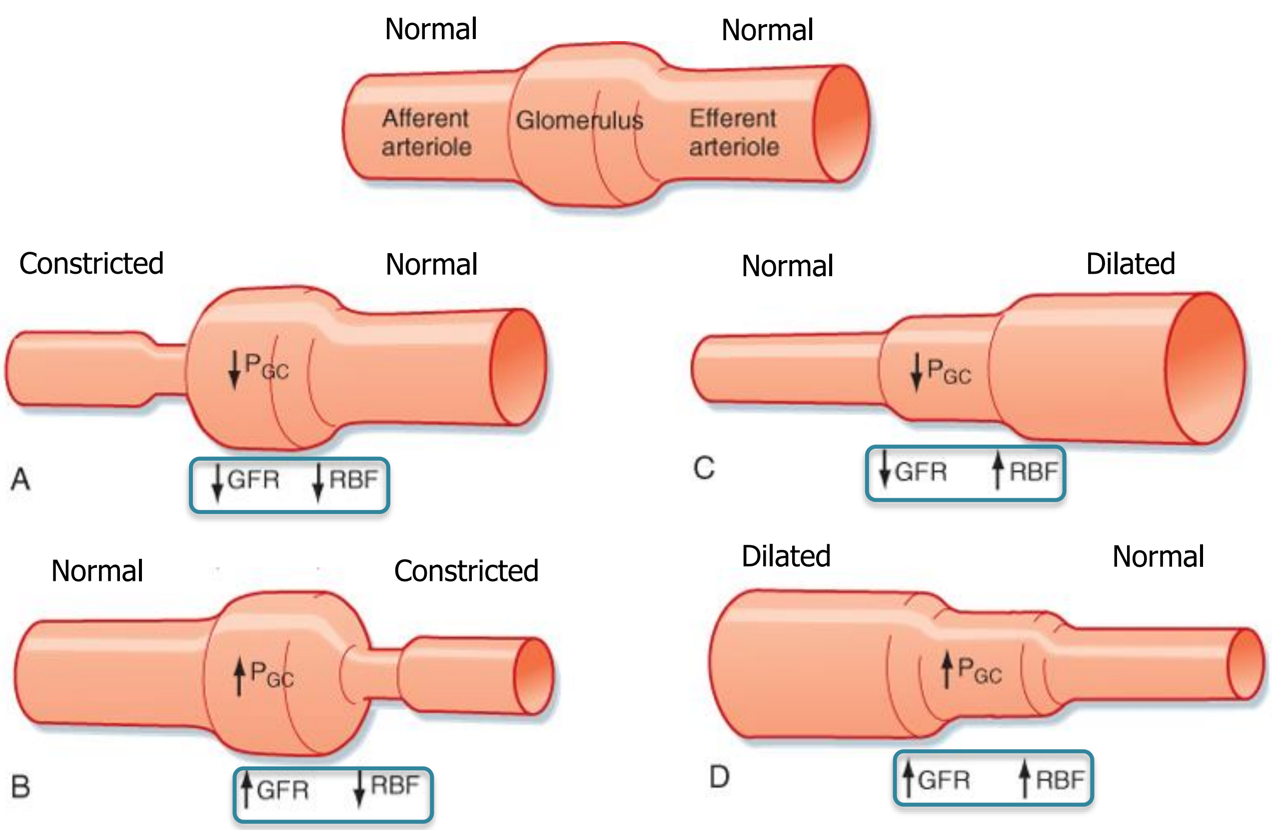
Net filtration pressure (10 mm Hg) = Glomerular hydrostatic pressure (60 mm Hg) − Bowman's capsule pressure (18 mm Hg) − Glomerular oncotic pressure (32 mm Hg)

Regulation of GFR and RBF:

- As we said GFR is very important to be regulated otherwise it may cause dehydration or azotemia
- GFR is controlled by adjusting blood pressure through intrinsic and extrinsic factors:

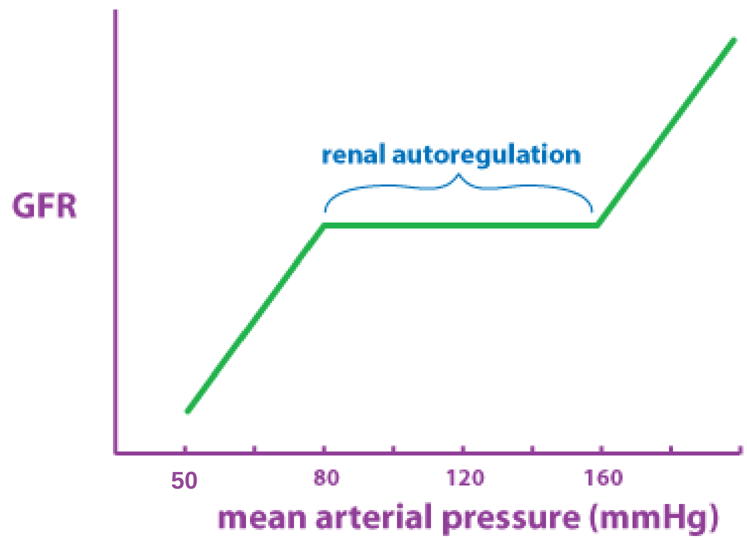
Intrinsic	Extrinsic
Autoregulation - Tubuloglomerular feedback - Myogenic mechanism	Sympathetic control
	Humoral and pharmacological factors
Hormonal control (renin-angiotensin system)	Physiological stress
	Posture

- These factors adjust GFR by constricting or dilating afferent/efferent arterioles to increase or decrease GFR by changing the **hydrostatic pressure**



Intrinsic: Autoregulation:

- In general, an increase in arterial BP will increase GFR however the body maintains constant GFR over a range of an ABP of 75-160 mmHg by **autoregulation** (it is an intrinsic property).
- Autoregulation is an intrinsic property that is independent of nerves or hormones.
- When BP <75 mmHg
  → Filtration is decreased
- When BP = 50 mmHg
  → Filtration is ceased
- The kidney achieves autoregulation by using TWO mechanisms:
  (1)Tubuloglomerular feedback
  (2)Myogenic mechanism



Autoregulation: Myogenic system

- Myogenic mechanism is the intrinsic capability of renal blood vessels to constrict or dilate the vascular smooth muscles through calcium channels.

  → When BP is high, renal blood vessels constrict to prevent an increase in GFR by decreasing renal flow

  → When BP is low, renal blood vessels dilate to prevent a drop in GFR by reducing arterial resistance and increasing blood flow.

Autoregulation: Tubuloglomerular Feedback

- In the JGA, the macula densa were sensory cells that can sense changes in ions and stimulate JG cells to increase/decrease renin production.

⇓ GFR

Example: ⇓ ABP of high protein diet

- ⇓ in NaCl delivery to DCT
- The macula densa is alerted
- GFR is restored by:

  3) Vasodilation of Afferent A
  4) Release of **renin**

- **GFR is back to normal**

⇑ GFR

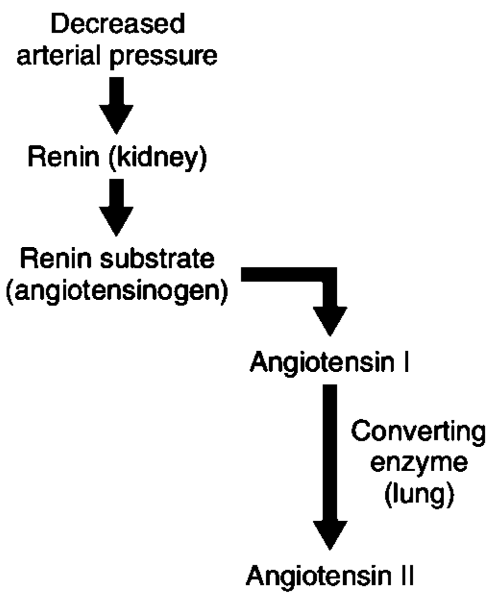
Example: ⇑ ABP

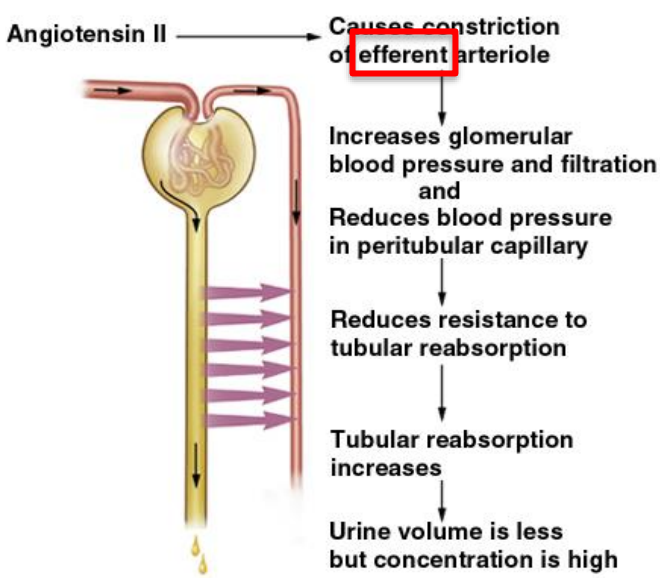
- ⇑ in NaCl delivery to DCT
- The macula densa is alerted
- GFR is restored by:

  1) Vasoconstriction of Afferent A
  2) Release of **adenosine**

- **GFR is back to normal**

Intrinsic: Hormonal Control





Angiotensin II

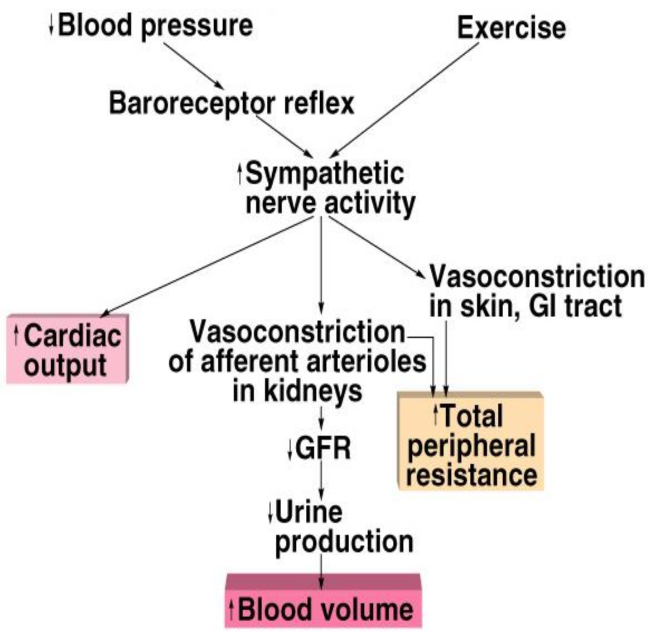
⇓ **RBF**

⇑ **GFR**

Extrinsic: Sympathetic regulation:

- When the sympathetic system is at rest
  → Renal blood vessels are maximally dilated
  → Autoregulation mechanisms prevail (overcome)
- When the sympathetic system is in action
  → Norepinephrine and epinephrine are released
  → fight or flight mode or cardiogenic shock
  → **Afferent** arterioles constrict
  → filtration is inhibited
  → Renin-angiotensin mechanism is stimulated.

Note: there's no parasympathetic effect on the kidney



Other Extrinsic Factors:

Factor	Effect	Examples
Humoral	Afferent constriction ⇓ GFR, ⇓ RBF	Epinephrine and Endothelin
	Afferent dilation ⇑ GFR, ⇑RBF	Prostaglandin D,E,I and Nitric Oxide
	Efferent constriction ⇑ GFR, ⇓ RBF	Angiotensin II

Renal (Plasma) Clearance:

- Renal clearance: is the clearance value of a substance by the kidney per min.
- It is calculated by:

$$Clearance = C_x = \frac{U_x \times V}{P_x}$$

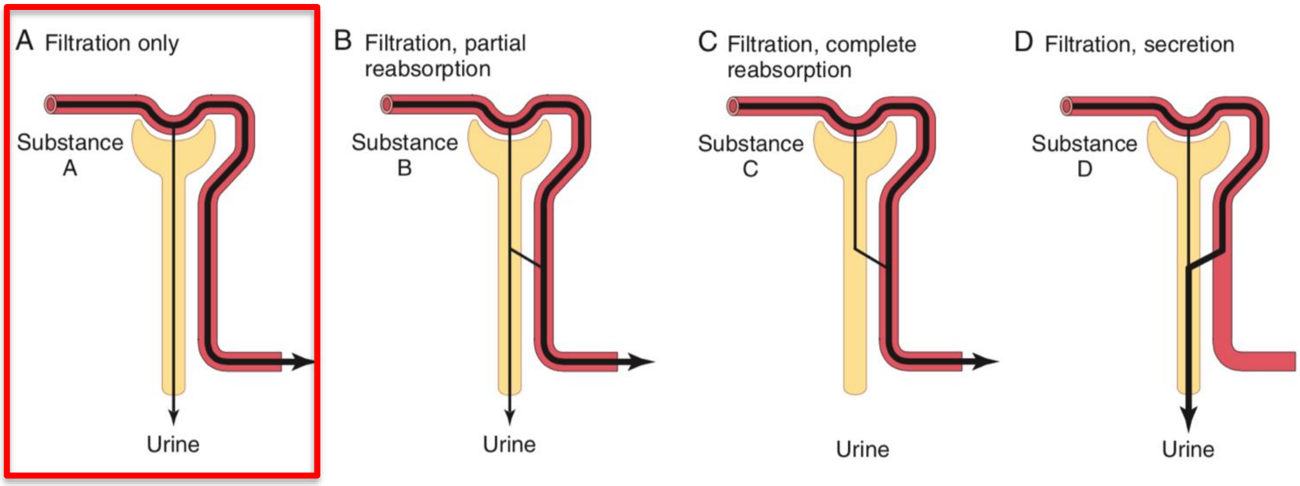
- $C_x \times P_x = amount\ filtered$
- $U_x \times V = amount\ excrteted$

- **C_x:** clearance of substance x
- **U_x:** urine concentration of substance x
- **V:** urine flow rate (ml/min)
- **P_x:** plasma concentration of substance x

- Plasma clearance tests can be used for (advantages):
  1. Measurement of GFR
  2. Measurement of RBF
  3. Renal handling of different substances

- **To calculate GFR,** we need to use an exogenous substance that meets the following criteria:
  1. Remains in plasma (doesn't enter RBCs)
  2. Doesn't affect renal function and isn't toxic
  3. Freely filtered (not metabolized, reabsorbed, nor secreted by the kidney **Fig. A**)
  4. Easily measured in plasma & urine
- If the substance used followed these criteria, its clearance value = GFR

Amount filtered = Amount excreted



Substances used to measure GFR

- If a substance follows the previous criteria, then:

$$\text{GFR} = \frac{[\text{sub}]_{\text{urine}} \times \text{Urine flow rate}}{[\text{sub}]_{\text{plasma}}}$$

- We mainly use the following 2 substances:

1) Inulin: polymer of fructose **(very precise)**

- Easily filtered
- Can't be absorbed nor secreted by the nephron
- Non-endogenous substance

<u>Assume</u>: **[inulin]** $_{\text{plasma}}$= 0,5 mg/ml; **[inulin]** $_{\text{urine}}$=30 mg/ml; **urine flow =** 2ml/min

<u>Find the GFR</u>?

$$\text{GFR} = \frac{30 \times 2}{0.5} = 120\text{ml/ min or } 172 \text{ L/day}$$

→ to convert from ml/min to L/day we multiply by 1.44

2) Creatinine: endogenous substance released by skeletal muscles

- Small quantity is secreted in the proximal tubules (less accurate)
- Method used usually detects other substances other than creatinine
- These two errors cancel out making creatinine reasonable to measure it
- Better used in **humans ONLY**

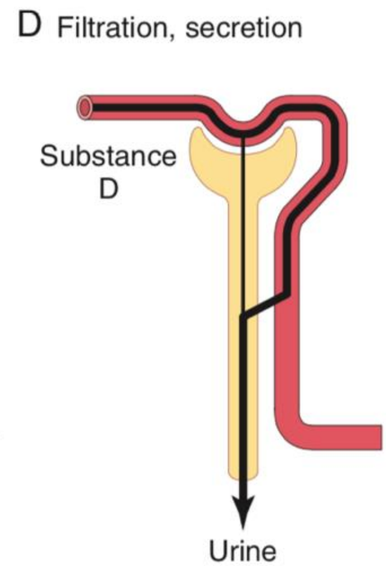
<u>Assume</u>:

[creatinine] $_{\text{plasma}}$= 1 mg/dl ; **[creatinine]** $_{\text{urine}}$=70 mg/dl; **urine flow =** 2ml/min

<u>Find the GFR</u>?

$$\text{GFR} = \frac{70 \times 2}{1} = 140 \text{ ml/min}$$

Substance used to measure RPF & RBF:



- Main substance used to measure RBF is PAHA
- They are easily filtered, secreted, yet NOT reabsorbed
- **Since they are both filtrated and secreted at the same time, they are completely removed by a single renal circulation. Therefore, its clearance rate is equal to the RPF.**
- We can calculate RPF using the clearance of PAHA
- The clearance we find is the plasma flow, and the blood is composed of plasma and hematocrit

$$C_{PAHA} = RPF = \frac{U \times V}{P}$$

$$RPF = RBF \times (1 - Hct\%)$$

$$\mathbf{RBF} = \frac{RPF}{(1 - Hct\%)}$$

Renal handling of substances

- By comparing the clearance measurement of a substance to that of inulin, we can determine whether the substance was secreted or reabsorbed.

$C_{substance} > C_{inulin}$ = substance is secreted

(C x P) + secreted (T) = U x V

(C x P): Amount filtered; U x V: Amount excreted

$C_{substance} < C_{inulin}$ = substance is absorbed

C x P = (U x V) + reabsorbed (T)

C x P: Amount filtered; (U x V): Amount excreted

Explanation:

T represents an added substance, if UV was higher than CP this means that substance T was removed from the plasma (secreted), and if CP was higher, this means that the substance was returned back to the plasma (absorbed).

Note: If the clearance of both the substance and Inulin are equal, that means it was filtered only.

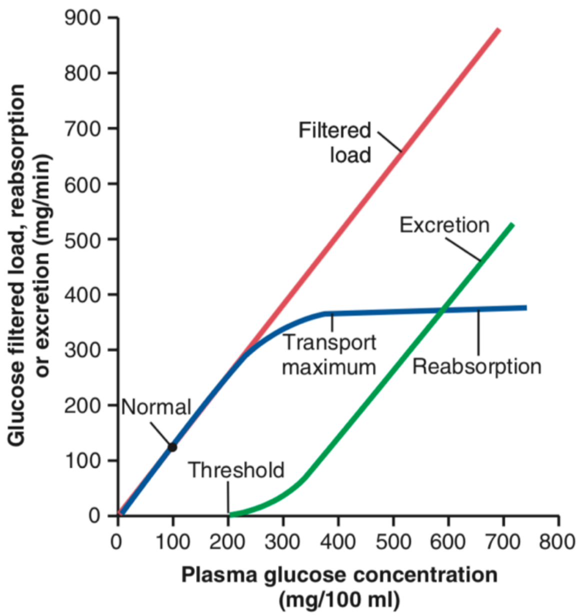
Renal Threshold:

- Renal threshold is the concentration of a substance dissolved in blood where the kidney begins to remove it into the urine (can't be reabsorbed anymore)
- After this level, filtration > reabsorption = substance gets excreted.

High threshold	Medium threshold	Low threshold	No threshold Only filtrated
• Glucose • Amino acids	• Potassium • Urea	• Phosphate • Uric acid	• Creatinine • Inulin

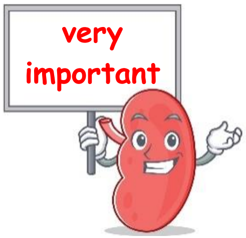
Tubular Transport Maximum:

- Tubular transport maximum (T_m): is the maximal amount of a substance (in mg) which can be transported **(reabsorbed)** by tubules per min.
- In other words, it's the rate of reabsorption at the threshold point.
- Substances with high T_m, such as: glucose & amino acids, are barely excreted by urine.



- The threshold of glucose is 180 mg/dl, at which glucose is maximally transported (T_m).
- For example, if glucose concentration in plasma was 275 mg/dl, ONLY 180 mg/dl will be reabsorbed, and the rest 95 mg/dl will be excreted.
- **Note**: kidneys don't regulate glucose level, insulin does

Quiz



1) **A hypertensive patient was admitted to the hospital complaining of a severe headache. His mean ABP was 150 mmHg. The doctor suspected kidney damage. He ordered a renal clearance test. Using the following parameters, calculate the patient's GFR**

[substance] $_{urine}$=50 mg/dl; **[substance]** $_{plasma}$=0.5mg/dl **urine flow =** 250 ml in 4 hrs

$$Urine\ Flow\ rate = \frac{250\ (ml)}{240\ (\min)} = 1.04\ ml/min$$

$$GFR = \frac{50\ \times 1.04}{0.5} = 104\ ml/min = normal$$

2) **Given the following parameters for a freely filterable substance, find whether the substance is absorbed or secreted and its value:**

GFR= 120 ml/min; **[X]** $_{plasma}$**=** 3 mg/ml; **[X]** $_{urine}$**=** 10 mg/ml; **urine flow =** 2ml/min

$$amount\ filtered\ (\ )\ amount\ excreted$$

$$GFR\ \times P\ (\ )\ U \times V$$

$$120 \times 3\ (\ ) 10 \times 2$$

$$360 > 20$$

$$substance\ is\ reabsorbed$$

3) **A patient was infused with P.A.H.A. to measure renal blood flow. She has urine flow rate of 1 ml/min, a plasma concentration of 1 mg/ml and a urine concentration of 600 mg/ml and a hematocrit level of 45%. What is his RBF?**

$$Clearance\ for\ PAHA = RPF = \frac{600 \times 1}{1} = 600 ml/min$$

$$RBF = \frac{600}{(1 - 0.45)} = 1091\ ml/min$$

Thank You

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