*Lecture 1*

## Kidney function:

1- ***Homeostatic function***: it is the most important function of the kidney. It involves keeping the internal environment (electrolyte concentration, pH, volume) constant for proper function of enzymes and cells. It Regulates:
   - Osmolality of ECF: 300 mOsmol.
   - a. Plasma ions concentration: a. Na = 142 mEq/L
     b. K = 5 mEq/L
     c. Ca
   - ECF volume (body water = 60% of the weight: 2/3 ICF & 1/3 ECF).
   - Arterial Blood Pressure
   - Acid - Base balance pH= 7.4 (regulated by 3 systems the urinary system is one of them)

2- ***Excretion:*** getting rid of certain materials. The Kidney secretes:
   a. Metabolic end-products: E.g. urea, creatinine, uric acid & bilirubin (which are toxic and can affect the function of the body).
   b. Foreign substances: like drugs and toxins.

3- ***Biosynthesis:*** of the following:
   - Renin: regulation of water and Na through the Renin-Angiotensin System.
   - Erythropoietin: stimulates RBC formation.
   - Glucose (gluconeogenesis)
   - Angiotensingen
   - Ammonia.
   - Calciferol: (1, 25 dihydroxy , vitamin D)
   - Prostaglandins, adenosine, endthelin, nitric oxide, Bradykinin, epidermal growth factor and insulin.

→ Renal system is formed of 2 kidneys, 2 ureters, urinary bladder, urethra.
The kidneys:
   - Lie on both sides of aorta.
   - Retro peritoneal structure.
   - Fixed by fat tissue around it.

→ 1/4 of circulation go to the kidney for filtration.

## Macroscopic structure of the kidney:

- Renal capsule: surrounds the kidney
- Cortex: the dark outer layer
- Medulla: the light inner layer forms pyramids forming at their ends papillae.
- Renal Pelvis: is found in the medulla and it is formed of major and minor calyces.
- Ureter: that comes out of the pelvis.
- Bladder.

## Microscopic structure of the kidney:

- Nephron (each kidney has 1,000,000).
- Glomerulus: (blind tube invaginated to form bowman's capsule:
  - Bowman capsule.
  - Tuft of capillary.
- PCT (proximal convoluted tubule).
- Loop of Henle: only a small segment in the loop of henle is thin
  - Descending thin.
  - Ascending: - 1/3 thin, 2/3 thick.
- DCT (distal convoluted tubule).
- Collecting ducts. [5-8 nephron open in 1 CD]

## In Bowman's capsule:

An afferent arteriole enters the capsule, then break down forming tuft of capillary that unite & form the efferent arteriole going out of the capsule.

**Note:** (Arteriole → Capillary → Arteriole)

- This is called Portal Circulation.
- Only in liver & kidney.
- The aim of this circulation is filtration not Oxygen exchange.

**Juxtaglomerular apparatus** (junction of nephron & arteriole, found in DCT or thick ascending)

- Junction between thick limb & afferent of its glomerulus (DCT comes in contact with afferent arteriole).
- Area of contact contain specialized cell:
  1. Tall columnar cells in tubule (a.k.a. Macula Densa) → in DCT → Detects low Na and sends signals to granular cells to secrete renin
  2. Granular cells (a.k.a. JJ cells) → found mainly in afferent arteriole → secrete renin into blood to circulate aldosterone → increase of low BP or low Na → to increase BP

## Types of nephron:

1- Cortical nephrons (outer cortex) → makes the majority.
2- Juxtamedullary nephrons → deep glomerulus in the cortex nearer to the medulla & loop of henle goes into medulla → important in urine concentration

## Cortical Vs. Juxtamedullary nephron:

| ***Cortical nephron*** | ***Juxtamedullary*** |
|---|---|
| 80 – 85 %. | 15-20%. |
| Lie in the outer cortex. | Small glomerulus that lies deep in the cortex. |
| Short loop. | Long loop goes into medulla. |
| Peritubular capillary blood supply. | Vasa recta for blood supply, this is imp. for determining urine concentration |
| They have large glomerulus. | They have small glomerulus |

- ***vasa recta:*** long loop of blood vessel that goes deep in the medulla & supplys the long loop of henle of the Juxtamedullary nephron.

## Renal Circulation:

- Kidney has special circulation:
  Renal artery → Segmental artery → Interlobar artery (in cortex) → Arcuate Artery (in between cortex & medulla) → Interlobular artery (in medulla) → Afferent arteriole→ Glomerular capillary → Efferent arteriole → peritubular Capillary (branch of efferent arteriole) to supply the cortical nephron.
- Venous system has the same sequence & name.

## Renal blood supply:

- Cortical blood flow > Medullary flow ( the majority is to cortex).
- Cortical blood flow meant for filtration.
- Medullary blood flow is meant for regulation urine concentration

## Renal innervations:

- Sympathetic Renal plexus → vasomotor which regulates renal blood flow to the kidney
- Parasympathetic. → not proven yet if it innervates the kidney

## Principle of urine formation:

1. Filtration: glomerulus → give the filtrate.
2. Modification of filtrate as it pass along the nephron, by:
   - Absorption → occurs at the renal tubules
   - secretion → occurs at the renal tubules

- 120 ml enter the nephron but only 0.5 ml is in the urine.

## Glomerular Filtration: in Bowman's capsule

- Plasma ultra filtration: filtration of small molecules of proteins, WBC, RBC from the blood
- Composition of filtrate (same as plasma except plasma protein and blood cells):
  - Water.
  - Electrolytes (Na, K, HCO3)
  - Glucose
  - Urea
  - Creatinine
- It's an isotonic solution (300 mosmol)

## Glomerular membrane:

3 layers of filtration membrane that plasma passes through.

1. Capillary endothelial layer
2. Basement membrane layer formed of mesengial cells (which are contractile cells that control the size of filtration membrane when they contract the membrane.
3. Capsule epithelial layer podocyte (like Ameoba).

➢ The filtrate does not pass through cells, instead it passes in the gaps between adjacent cells.

## Characteristic of filtration membrane:

- Endothelial layer:
  - Fenestration to allow passage of filtrate.
  - 70 – 100 nm pores
- Basement membrane: affects filtration
  - It is negatively charged (salioprotein), therefore, positive molecules are filtered better than the –ve molecules.
  - Homogeneous coligeneous fibers with no pores.
  - Contractile mesengial cells.
  - Albumin is –vely charged so it is repelled by the basement membrane and it will not be filtered.
- Epithelial membrane:
  - The cells are Podocytes.
  - Slit pores between each two cells. (a.k.a. filtration pores/filtration slits)

➢ This filtration membrane is more permeable than any other membrane in our bodies (100 times more than muscular membrane) because of its previous characteristics

## Filtration of molecules:

Molecular size & charge regulate filtration.

- <4 nm ⟶ freely filtered whatever the charge.
- 4-8 nm ⟶ depends on the charge ⟶ negatively charge poorly filtered compared to neutral & positively charged molecules.
- >8 nm ⟶ not filtered whatever the charge.

**Note:** Albumin size is 7 but it is negative so it is not filtered.

**Nephrotic syndrome**: the negative charge of basement membrane is lost. This causes edema.

- Albumin is low in the blood and is lost in the urine because it's filtered.
- Low osmotic pressure, water will move to interstitial space and cause edema.
- Fluid from blood vessels to tissues.

*Lecture 2*

## Mechanism of urine formation:

1. glomerular filtration
2. reabsorption

## Characteristic of filtration membrane:

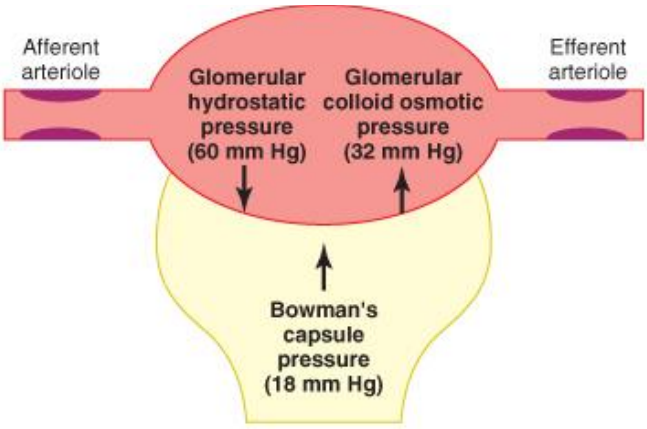
- Endothelial layer: has fenestration to allow filtration with a size of 70-100nm .
- Basement membrane: Negatively charged layer which allow filtration of (+ve) molecule.
  Contractile messengial cell.
- Epithelial membrane: in the layer of nephron
  *Podocyte:* between each 2 podocyte there are filtration slits which are of 25-60nm in size.

## Filtration pressure:

- Pressure that moves plasma out of the capillaries glomerulus into the Bowman capsule space.
- 4 different pressures that affect filtration.
- The net filtration pressure is the algebraic sum of these pressures.
- The net filtration pressure is the driving pressure of filtration.
- Some pressures are positive pushing filtration and others are negative that oppose filtration.
- Blood pressure in the capillaries comes from the heart (origin), at the level of the heart the mean arterial pressure is 100mmHg then it decreases.
  - ➢ In the kidneys the pressure is high compared to other organs because the kidney is near the abdominal aorta, and the blood doesn't travel far.

## Filtration pressure (starling force):

- Glomerular hydrostatic pressure ($P_{GC}$) ⟶ causes filtration, pushes the fluid outward = 45-60mmHg
- Glomerular osmotic pressure ($\pi_{GC}$) ⟶ causes absorption, prevents filtration, this pressure is caused by plasma protein = 32 mmHg (not constant 25 – 30 mmHg). Also called *colloid pressure.*
- Bowman hydrostatic pressure ($P_{BS}$) ⟶ cause absorption, opposes filtration, due to the presence of fluid in bowman's capsule, = 18 mmHg
- Bowman osmotic pressure ($\pi_{BS}$) = ZERO because there is no filtration of plasma protein, hence no osmotic pressure in Bowman's capsule. Also called *colloid pressure.*
  - ❖ Filtration pressure = GHP + GOP + BHP+ BOP
    +60 + (-18) + (-32) + zero = 10






## Starling force of filtration:

1. Hydrostatic pressure ($P_{Gc}$)
   - Favors filtration
   - 60 mmHg
   - Remain constant along the entire glomerular capillaries.
   - From afferent to efferent, the pressure is the same due to low resistance capillaries.
2. Hydrostatic pressure in Bowman's capsule ($P_{BS}$)
   - Opposes filtration
   - 18 mmHg
   - Due to filtered fluid in Bowman's capsule.
3. Colloid osmotic pressure in glomerular capillary ($\pi_{GC}$)
   - Opposes filtration
   - 32mmHg (it ranges 25-32)
   - Caused by plasma proteins
   - It's not constant, why? Afferent 25
     Efferent 32 → concentration of protein ↑
     Because we filtered water and not proteins so ↑ in concentration of proteins.
4. Colloid osmotic pressure in Bowman's capsule ($\pi_{BS}$): Zero (no plasma protein)

## Calculation of net filtration pressure:

Net filtration pressure = 60-18-32+0 = 10mmHg  it's the algebraic sum.

$= K_f\ (P_{GC} - P_{BS} - \pi_{GC} + \pi_{BC})$

- $K_f$ : filtration coefficient which depends on:
  1. Filtration membrane permeability
  2. Surface area
- Due to opposing pressure, the filtration pressure is 10 not 60mmHg.
- Glomerular permeability is 100 × > than skeletal capillaries permeability. Because it is more fenestrated.

## Net filtration:

- Net filtration pressure ↓ as passing along the glomerular capillaries, because the glomerular osmotic (colloid) pressure ↑
- Only plasma is filtered → hemo conc→ ↑ plasma protein conc. → ↑ oncotic pressure → ↓ net filtration pressure
- Glomerular Hydrostatic pressure from afferent to efferent is constant, but Glomerular Osmotic pressure ↑ from afferent (25) to efferent (32).
- At afferent arteriole the net filtration pressure is increasing due to decreased osmotic pressure. As plasma moves to the efferent arteriole, the net filtration pressure will decrease due to increased osmotic pressure (because we are filtering fluid but not proteins)
- Net filtration decreases at efferent side because after it leaves the glomerulus, hemo concentration, plasma protein concentration, and plasma filtered all increase, therefore, the osmotic pressure increases.
- The net filtration pressure decreases along the capillary (from afferent to efferent)

## Glomerular filtration rate (GFR)

- Amount of plasma filtered by all nephrons in both kidneys per unit time
- (125 ml/min) → it is the GFR throughout the day.
- It is being used for kidney functional test
- Variation in GFR between different species depends on number of nephrons.

## Measurement of GFR

Characteristic of substance used:  Inulin (polysaccharide) is the substance

1. Freely filtered by the kidney ( not reabsorbed or secreted → no modification)
2. Not metabolized by the kidney (because then its amount ↓ -- fake results)
3. Not toxic & stable
4. Not bounded to plasma protein (so it can be filtered)

5. Does not change renal plasma flow ( because then it gives a fake result)

**Measurement of GFR:** Test procedure: {not important}

- Intra venous loading dose of inulin followed by intra venous infusion of inulin to maintain plasma level constant (left hand)
- Urine is collected for 15 or 20 min to measure inulin concentration in urine & urine volume
- Blood sample is taken half way of urine collected to measure inulin concentration
- 3 values should be taken into consideration:
  1. inulin conc. in plasma 2. Urine 3. Urine flow rate.

**Calculation of GFR:**

- The amount of inulin excreted = $U_{in} \times U_{volume}$
- The amount of inulin filtered = $[P]_{in} \times GFR$
- As inulin is not absorbed but excreted both quantity are equal.

$$\mathbf{P_{in} \times GFR = U_{in} \times U_{volume}}$$
$$\mathbf{GFR = U_{in} \times U_{volume} / P_{in} =} \quad \textbf{ml/min}$$
**Filtration = excretion**

**Calculation of GFR &FF** (filtration fraction):

- GFR = $K_f$ × net filtration pressure
- GFR = 12.5 x 10 = 125ml/min
- $K_f$ α GFR ($\downarrow K_f$ in diabetes $\rightarrow \downarrow$ GFR) due to membrane thickness in patients with diabetes

**Filtration fraction:** The fraction of renal plasma that is filtered
= GFR/RPF (renal plasma flow)
=125/650 = 0.2 = 20% (in normal person)
→ if 10% then GFR is low, also a kidney function test.

**Factors affecting GFR:**

1. Change in $P_{GC}$
   - proportional relationship
   - $P_{GC}$ α GFR
   - Systemic blood pressure: Examples:
     a) Afferent vasoconstriction→ $\downarrow P_{GC} \rightarrow \downarrow$GFR
        *When the afferent vessels constrict, the blood flow decreases, the hydrostatic pressure ($P_{GC}$) decreases as a result the GFR decreases.*
     b) Efferent vasoconstriction→ $\uparrow P_{GC} \rightarrow \uparrow$ GFR

When the efferent vessels constrict, the blood is accumulating (not going out) in the glomerulus, as a result the hydrostatic pressure increases and the GFR increases.

2. Change in $\pi_{GC}$
   - inversely proportional relationship
   - $\pi_{GC}$ α 1/GFR → because it opposes filtration
   - ↑ $\pi_{GC}$ → ↓GFR
   - Hemoconcentration in cases of dehydration → ↑plasma protein conc.→ ↑ osmotic pressure ($\pi_{GC}$)
   - ↓ Filtration fraction → ↑ $\pi_{GC}$ → ↓GFR → ↑ hemoconcentration
3. Change in $P_{BC}$
   - inversely proportional relationship
   - $P_{BC}$ α 1/GFR
   - ↑$P_{BC}$ due to obstruction of outflow of urine → ↓ GFR
   - Urethral obstruction (stones or tumor)
   - Kidney edema ( very serious condition) → fluid accumulation in the interstitial fluid of the kidney → capsule does not allow the kidney to expand → compression of kidney → increases $P_{BC}$ → decreases GFR
4. Change of filtration coefficient
   - proportional relationship
   - Changes in glomerular capillary permeability
   - Changes in surface area
   - Filtration coefficient ($K_f$) α GFR
5. Changes in renal blood flow
   - proportional relationship

## Renal blood Flow:

- An average adult has a RBF of 1.1 L/min
- PAH is an organic acid that is filtered and secreted by the kidney, it's clearance is used for renal blood flow measurement.
- PAH is all filtered meaning that the venous blood contains none. Arterial concentration of PAH is 20g, and the venous concentration is 0g.
- In one renal circulation per minute, PAH is almost completely removed from the plasma or blood and excreted in urine.
- PAH clearance is defined as the volume of plasma cleared from PAH per minute.
- PAH = RPF/min

## Calculation of Renal Blood Flow:

- First, we calculate the RPF, then we calculate the RBF
- RBF = the amount of PAH excreted per unit time.
- More than 90% of PAH in arterial blood is removed by the kidney, 10% is remains in venous blood.
- Venous blood leaving the kidney is almost free of PAH.
- $Clearance\ of\ PAH = \frac{[U]PAH \times V/min}{[\ P\ ]PAH} = 630\ \ ml/min$
- $actual\ RPF = \frac{effective\ \ RPF\ (630)}{extraction\ \ ratio\ (0.9)} = 700\ \ ml/min$
- 700 ml/min is the plasma flow not the blood flow, so 700 is 55% of blood flow.
- $RBF = \frac{RPF\ (700)}{1-\text{hematocrit}\ \ (.55)} = 1.2\ \ L/min$

  Hematocrit = .45
- $RBF = \frac{\text{RAP} - \text{RVP}}{total\ \ renal\ \ vascular\ \ pressure}$

  RAP = renal arterial pressure
  RVP = renal venous pressure

***Note***: the kidney take 25% of cardiac output for filtration = 1.1 L/min

## Regulation of GFR & RBF:

1. **sympathetic nervous system (vasomotor):**

- In normal conditions, the nervous system has little influence
- In cases of emergency stress, there will be a ↓ in BP due to hemorrhage which ↑ the sympathetic tone → vasoconstriction of all arteries including the renal artery → ↓ RBF → vasoconstriction of afferent artery → ↓ GFR

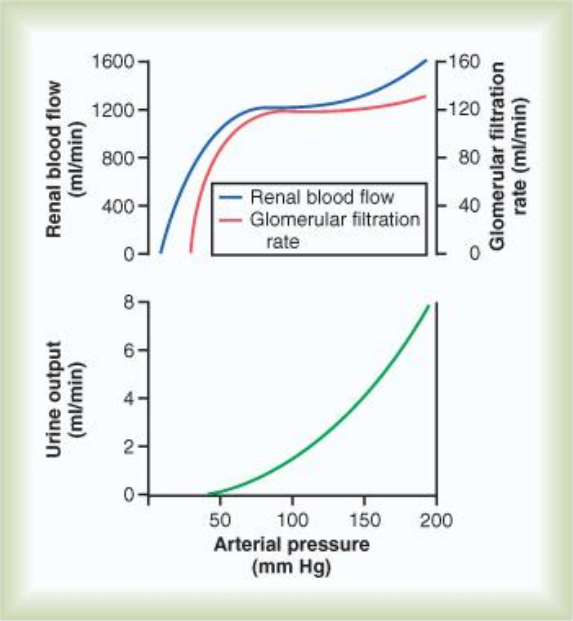
2. **Hormonal:**

- Adrenalin and noradrenalin cause vasoconstriction → ↓ GFR
- Angiotensin II → vasoconstriction of efferent artery only → ↑ GFR
- Prostaglandin, bradykinin ( which are vasodilators) they ↑ GFR

## Auto-Regulation:

- Feedback mechanism to keep RBF & GFR relatively constant, despite marked changes in ABP.
- Range of auto regulation is between 75-160 mmHg ABP (daily variation)
- Below 75 and above 160, there is no auto-regulation.
- If the ABP < 60 - 75 mmHg → ↓ GFR → kidneys shut down.
- Once the kidneys shut down, they never come back.

- If the ABP > 160 mmHg → ↑ GFR → kidney necrosis






## Tubuloglomerular feedback:

- An internal mechanism by which the kidney keeps GFR constant.
- ↓ GFR will cause slow blood flow which will ↑NaCl reabsorption → ↓ NaCl in filtrate
- macula densa senses the low Na and stimulates:
  1. ↑ rennin → ↑Angiotensin II → efferent vasoconstriction → ↑ GFR
  2. Afferent dilation → ↑ GFR

## Myogenic autoregulation:

- The ability of blood vessels to resists stretching by recoiling.
- ↑ Hydrostatic pressure → stretching vessel's wall → reflex contraction (recoil)
- Reducing the increase in BP and increase GFR

## Renin - Angiotensin aldosterone:

- Renin is released into plasma when Plasma Na is low
- Renin acts on Angiotensinogen converting is to Angiotensin I
- Angiotensin converting enzyme (ACE) converts Angiotensin I to Angiotensin II (vasoconstrictor) so it increases the BP.
- Angiotensin II act on adrenal cortex and stimulates aldostrone secretion, which acts on the kidney to increase Na reabsorption in the DCT of the nephron because of the low Na level in the blood.
- The kidney will increase the secretion of H+ and K+ so more H+ and K+ are available for exchange with Na, which will increase Na reabsorption.

## Aldosterone/Renin:

- Aldosterone release is stimulated either:
  - Directly → ↑ plasma K+ levels
  - Indirectly → ↓ Na by the renin/angiotensin system
- Renin release is stimulated by:
  - ↓ ECF Na → ↓ ECV
  - hypotension → ↑ sympathetic tone
  - ↓ in afferent pressure
- Angiotensin II is stimulated by dehydration (low ECV) this stimulates the release of aldosterone which will cause vasoconstriction.
- Role:
  - ↑ Na reabsorption in both PCT and DCT
  - Thirst sensation
  - ADH release (antidiuretic hormone) → ↑ H2O absorption to correct for the low volume (dehydration)
  - Inhibition of renin release by negative feedback mechanism

*Lecture 3*

## Clearance

### Concept of clearance:

It is the volume of plasma completely cleared of any substance by both kidneys per unite time.

*Clearance equation*:

$$C = \frac{[U]s \times V/min}{[P]s} = ml/min$$

[P]s = conc. of substance in plasma.
[U]s = conc. of substance in urine.

$$amout\ of\ S\ excreted = filterd - (reabsorbed - secreted)$$

- Renal clearance for different substances varies between 0 – 600 mL/min.
  - It is 0 mL/min when the substance is not cleared into urine.
  - 600 mL/min is the maximum in plasma
- Clearance of Inulin: 120 ml/min = GFR.
- Clearance of PAH = 630 ml/min.

### Inulin Clearance & GFR:

- The amount of inulin cleared = GFR
- As inulin is:
  1. Freely filtered.
  2. Not reabsorbed or secreted.
- Inulin clearance = GFR = 120 ml/min

### Creatinine clearance & GFR: *(simpler than inulin)*

- Creatinine is an endogenous substance used routinely to measure GFR.
- Completely filtered, but secreted in small quantity.
- Inverse relationship between GFR & plasma level of Creatinine.

$$GFR \propto \frac{1}{creatinine}$$

- Example: in normal GFR the creatinine should be 1.82 g/day
- *figure 27-19*
- If the Creatinine level is high in the blood → GFR level is low → so the kidney is not functioning well.

## Glucose & Urea clearance:

- Renal clearance of glucose = zero (does not appear in urine) ⟶ It is filtered & completely reabsorbed.
- Glucose is filtered and then completely reabsorbed, so no glucose in urine
- $[U]_s \times V_{min}$ = zero.
- Urea clearance = 40 ml/min.
- Urea filtered is partially reabsorbed.

## Inulin clearance Vs. clearance of other substance:

- Cx = Inulin clearance ⟶ substance X not absorbed or secreted ⟶ Ex. Creatinine.
- Cy < Inulin clearance ⟶ substance Y, filtered & partially absorbed ⟶ Ex. urea.
- Cz > Inulin clearance ⟶ substance Z filtered & secreted ⟶ Ex. Para amine, puric acid.
  - If substance clearance = 120 = inulin clearance ⟶ no modification (not reabsorbed or secreted)
  - If substance clearance < 120 ⟶ filtered & partially reabsorbed.
  - if substance clearance > 120 ⟶ filtered & secreted
  - if substance clearance = 0 ⟶ filtered and completely reabsorbed

## PAH clearance & renal plasma flow:

- PAH an organic acid filtered & secreted by the kidney.
- Found in the blood.
- In one renal circulation PAH is almost completely removed from the plasma & excreted in urine.
- PAH clearance = volume of plasma pass by the kidney/min.
- Can be used to measure renal blood (plasma) flow.

## Calculation of renal blood (plasma) flow:

- RPF= the amount of PAH excreted per unit time divided by the difference of its arteriovenous conc.
- more than 90% of PAH in arterial blood is removed by the kidney.
- Venous blood leaving the kidneys in almost free of PAH.

$$CPAH = \frac{[U]PAH \times Vmin}{[P]PAH} = 630\ ml/\min = effective\ renal\ plasma\ flow$$

- Actual renal plasma flow (RPF) = ERPE / extraction ratio

  RPF = 630/0.9 = 700 ml/min.
- Renal blood flow $= \frac{RPF}{1-HCT}$
- Table 27-4 (p.344)

## Regulation of renal blood flow:

- Sympathetic nervous system:
  - ↑ Sympathetic will cause vasoconstriction of afferent & efferent fibers which will cause a ↓ RBF and ↓GFR (hemorrhage) because it will take the blood to the heart and brain.
- Angiotensin II:
  - vasoconstriction of efferent.
  - During hemorrhage more rennin is secreted due to a decrease in BP.

## Types of Transport:

1. Transcellular
   - Across the renal call, has 3 mechanism of transport
     - Primary active transport
     - Secondary active transport
     - Passive transport by ion channels
2. Paracellular
   - Between the 2 cells
   - Through tight junction
   - Only one mechanism of transport → Mainly passive (bulk transport)

## PCT:

- 80 – 60% of absorption occurs in the PCT
- Has a high capacity for reabsorption
- They have the following characteristics:
  1. metabolically active epithelial cells (a lot of mitochondria)
  2. brush border (surface area)
  3. tight junction is not so tight to allow paracellular transport.
  4. contains a lot of carrier proteins
  5. special tubular epithelial cells.
- the cells of the PCT are highly permeable to water.

## Substances reabsorbed back in PCT:

1. Tubular absorption
   - Sodium (leader of reabsorption followed by the others)
   - Chloride
   - Glucose
   - Water
   - Amino acids
   - Bicarbonate
   - Phosphate
   - Urea

2. Tubular Secretion:
   - PAH
   - $H^+$
   - $K^+$

*Lecture 4*

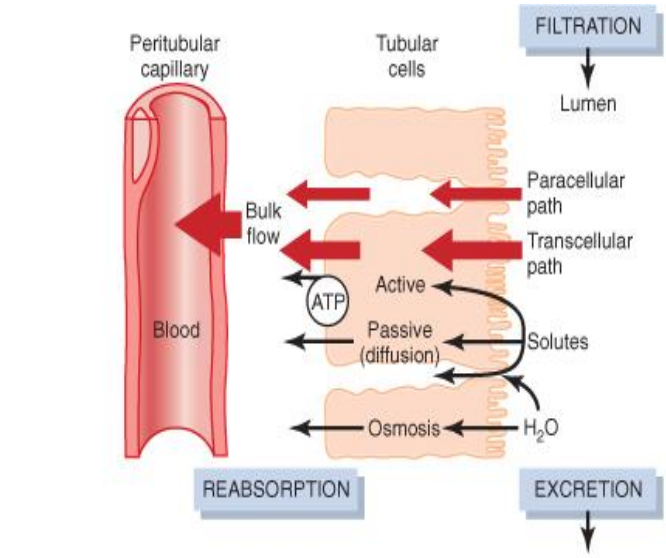
# Tubular Transport

## Tubular Function:

Modification occurs by:

1. Absorption: removing substances from lumen (filtrate) and returning it into the blood in the peritubular capillaries.
   E.g. glucose, Na, amino acids
2. Secretion: Moving substances from blood (peritubular capillary) to the lumen.
   E.g. PAH, which moves to the lumen.

## Tubular modification:






## Filtration, Reabsorption and Excretion rate:

Table 27-1. Filtration, Reabsorption, and Excretion Rates of Different Substances by the Kidneys

| | Amount Filtered | Amount Reabsorbed | Amount Excreted | % of Filtered Load Reabsorbed |
|---|---|---|---|---|
| Glucose (g/day) | 180 | 180 | 0 | 100 |
| Bicarbonate (mEq/day) | 4,320 | 4,318 | 2 | >99.9 |
| Sodium (mEq/day) | 25,560 | 25,410 | 150 | 99.4 |
| Chloride (mEq/day) | 19,440 | 19,260 | 180 | 99.1 |
| Potassium (mEq/day) | 756 | 664 | 92 | 87.8 |
| Urea (g/day) | 46.8 | 23.4 | 23.4 | 50 |
| Creatinine (g/day) | 1.8 | 0 | 1.8 | 0 |

## Calculation of tubular reabsorption or secretion from renal clearance

(Amount transported whether it is reabsorbed or secreted) :

= quantity filtered – quantity excreted in urine

Quantity filtered = Px X GFR

Quantity excreted = Ux X V

- ➢ +ve= reabsorption
- ➢ -ve=secretion
- for Inulin = zero

## Calculation of renal transport:

Tx = GFR x Px – Ux V → Quantity filtered = Px X GFR

- Calculation of Na reabsorption:
  Plasma Na conc. = 140 mEq/L
  GFR (inulin clearance) = 125 ml/min
  Urine flow rate = 1 ml/min
  Urine concentration of Na ($U_{Na}$) = 70 mEq/L
- ➢ Calculate the amount of Na transported

## Sodium Reabsorption in PCT:

- 65 – 70% of filtered sodium is reabsorbed in PCT.
- Followed by water, chloride, and glucose.
- Iso-osmotic absorption (equal quantity of solute and water – for every 60% of Na sodium absorbed, 60% of water is also being absorbed)
- Important for the absorption of glucose, amino acids, phosphate (all are Na dependant)

## Passage of Sodium absorption:

- Filtered Na travel from the lumen across the luminal membrane (brush border) into the cell, across the basolateral membrane, then into the lateral intercellular space, and finally into the peritubular capillaries.

## Mechanism of Na reabsorption

- The passage of Na across the basolateral membrane is primary active transport by Na/K ATPase. For every 3Na out, 2K in.
  - The K also leaks out.
  - Results in:
    1. low intracellular Na concentration.
    2. high peritubular osmolality
    3. high negativity inside the cell.
- Then Na enter the cell from the lumen across the luminal membrane by passive transport because of electrochemical gradient
- Electrical gradient: inside the cell = -70mV, in the lumen = -4mV
- Chemical gradient: Na concentration difference (140 mEq/L to 12 mEq/L)
- Na enters the cell through the luminal membrane from the lumen by 3 mechanisms:
  1. co-tranport with glucose and amino acids
  2. Na in exchange with Hydrogen (contra-transport)
  3. Na channel
- The passage of Na across the luminal membrane is passive transport.
- The passage of Na across the basolateral membrane is active transport.
- The passage of Na into the peritubular capillaries is by osmosis
- The overall process is secondary active transport.

## Note:

- Cotransport: 2 substances transported together in the same direction
- Contratransport: 2 substances transported together in opposite direction.

## Calculation of Na absorption:

- Plasma [Na] = 140 mEq/L
- GFR (inulin clearance) = 125 mL/min
- Urine flow rate = 1 mL/min
- Urine concentration of Na (UNa) = 70 mEq/L

→ Calculate the amount of Na transported?

= (PNa x GFR) – (UNa x V)
= (140 x 125) – (1 x 70)
= 17430

*Lecture 5*

## Chloride Reabsorption:

- Chloride reabsorption down concentration gradient (from high to low)
- Following the positively charged Na

## Water Reabsorption:

- 99% of filtered water is absorbed back, but in the PCT only 60 – 70% of it reabsorbed. The force is the osmotic gradient.
- 60 – 70% of filtered water is reabsorbed in PCT passively following Na and Cl.
  1. Extrusion of Na from the renal cell to peritubular cell. This causes osmotic force due to Na in the peritubular space.
  2. Increases osmolality of peritubular space.
  3. Drag water by osmosis to reabsorb water
- Filtrate remains iso-osmolar (because approximately equal quantity of water and solutes are absorbed).

## Uptake of NaCl and water into peritubular capillaries:

- NaCl enters the peritubular capillaries by simple diffusion
- Water follows Na due to high osmotic pressure in the capillaries.
- Osmotic (oncotic) pressure is higher due to filtration
- In peritubular capillaries, the high plasma oncotic pressure is due to fluid filtration in glomerulus but not in plasma proteins.
- The high filtration of the glomerulus the higher the reabsorption
- The higher the osmotic pressure in efferent and peritubular capillaries increases reabsorption (directly related).
- The more the GFR → the less the reabsorption

## Glomerulo-tubular balance:

- A fixed percentage of glomerulus filtrate will be reabsorbed
- The higher the filtration in the glomerulus → the higher the oncotic pressure in efferent and peritubular capillaries → the higher the reabsorption in PCT.
  - What is the osmolarity at the end of the PCT?
    →Will remain 300 because it is iso-osmic, so there is a decrease in the volume but the concentration is the same.
  - Osmolarity of the filtrate of the glomerulus equals the osmolarity of the plasma.

## Glucose reabsorption:

- In healthy adult all filtered glucose is reabsorbed & no glucose will appear in urine
- When plasma glucose $(P)_G$ is increased near 200 mg/dl , glucose begins to appear in urine – this is called the renal threshold –
- Renal threshold, is the plasma or blood level of glucose at which the glucose begins to appear in urine and it equals 200 in arterial blood and 180 in venous blood.
- As plasma glucose level is further increased, more glucose appears in the urine.
- At very high filtered glucose the reabsorption remains constant , this is called "tubular transport maximum for glucose $(Tm)_G$ .
- The maximum the kidney can reabsorb (renal tubular) equals 375 mg/min (in the female = 300 mg/min)
- At this maximum transport, all glucose carried is saturated & no more glucose can be transported.
- Glucose is carried by carrier protein; hence, this limits the absorption and transport of glucose.

## Mechanism of glucose reabsorption:

- Secondary active transport (depends on Na/K pump)
- In the Luminal membrane it is cotransported with Na
- In the Basolateral membrane by GLUT 1&2

## Glucose Titration curve:

FIGURE

- Splay : because not all nephrons reach 200 at the same time
- 375 is the limit, higher than that no matter how much plasma glucose we have, there is no increase in absorption.

## Amino Acid Reabsorption:

- Because we need amino acids, there is no tubular maximum
- All filtered Amino Acid are reabsorbed in PCT
- Across the Luminal membrane AA are co-transported with Na (passive transport)
- Across the basolateral membrane AA reabsorption is by simple diffusion

## Bicarbonate reabsorption*: (too big to be absorbed):*

- 90% of bicarbonate filtered is reabsorbed in PCT
- Filtered $HCO_3 + H_2O \rightarrow H_2CO_3$ (in the lumen)
- $H_2CO_3 \rightarrow H_2O + CO_2$ in the presence of carbonic anhydrase
- $CO_2$ diffuses into the cell + $H_2O \rightarrow H_2CO_3$ (by Carbonic anhydrase)
- $H_2CO_3 \rightarrow H^+ + HCO_3$ (by Carbonic anhydrase)
- $HCO_3$ is reabsorbed (in the blood), 24-28 mEq/dL
- $H^+$ is secreted in exchange for Na
- For each bicarbonate molecule filtered, one molecule is being formed inside the cell to be absorbed.

Lecture 6

## Phosphate reabsorption:

- Bones, teeth & skeleton (80%)
- Intracellular phosphate (20%)
- Plasma phosphate filtered is excreted in urine (1 mmol/L is freely filtered)
- Rate of absorption is under the control of PTH
- 1/3 of filtered in excreted in urine
- Reabsorbed Co-transported with Na+.
- Rate of absorption is under the control of PTH (parathyroid hormone) and vitamin D.
- Usually Na is co-transported with glucose, but phosphate competes with glucose and therefore increases phosphate reabsorption and blocks glucose reabsorption.

## Urea reabsorption:

- Plasma urea concentration 15 – 40 mg \ 100 mL.
- End product of protein metabolism is urea
- 40 – 50 % of filtered urea is reabsorbed (to the kidney not to blood):
  - passive diffusion
  - Reabsorbed in consequent of Na & $H_2O$ reabsorption.
- 50 – 60 % of urea is excreted.
- Low GFR (renal disease→ low renal blood flow) → ↑urea concentration in plasma.
- Low GFR: leads to reduction in urea filtration.
  - More urea is reabsorbed to the blood due to slow rate of filtrate

➢ The more urea in nephron the more the absorption
➢ The urea level in the blood depends on the kidney, for example:

1) no filtration, so urea remains in the blood
2) Increases reabsorption due to slow rate (low GFR), this will return the urea to the blood.

## Tubular secretion:

➢ From peritubular blood through peritubular space into renal tubular cells to tubular lumen.

*Secretion:* → passive: $NH_3$ , salicylic acid (aspirin)
→ active : tubular maximum (PAH, creatinine)
No tubular maximum ( K+, H+)

## Potassium:

- K+ is reabsorbed and secreted
- 90 % of filtered K+ is reabsorbed in the PCT.
- K+ is secreted in DCT & CD in exchange for Na+, under the control of aldosterone.
- Aldosterone is a hormone in which its secretion is indirectly stimulated by low levels of Na in the blood.

## Hydrogen:

- Excretion in exchange for Na therefore its inversely proportional to K+.
- If you have acidosis, then exchange of hydrogen and Na will occur instead of K and Na → K accumulates in the blood resulting in hyperkalemia.

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## The loop of Henle

### Descending limb: *(thin limb)*

- Permeable to water but not salt.
- No solutes absorption and 20% of filtered water is reabsorbed.
- The osmolarity of filtrate increases due to water reabsorption but not solute
- At start of descending loop osmolality is the same as plasma (≈ 280 mOsm )
- At end of descending loop osmolality = 1200 mOsm.
- The increasing osmolality is mainly due to High conc. Of NaCl & to a lesser extend to high urea concentration in filtrate.
- ***The thin loop of Henle:*** the cells of the thin segment of the descending loop of Henle are simple squamous epithelium highly permeable to water but not solutes. No mitochondria and No brush border.
- The Descending limb will concentrate the filtrate for the ascending limb so it can absorb salts properly.

### Ascending limb:

- Thick : 2\3 Thin : 1\3
- In thick limb solute is permeable but not water.
- Water is impermeable
- $Na^+$ (into the cell from the lumen), $K^+$, 2Cl reabsorbed by co-transport (luminar).
- $Na^+$ \ $K^+$ ATPase in basolateral membrane (the pump is present on both sides of limb)
- Filtrate is diluted due to solute reabsorption NOT water.
- osmolarity drops from 1200 to 200 mOsm.
- $CaHCO_3$ and Mg are also reabsorbed.

➢ From glomerulus to loop of Henle absorption:
  - 65% occurs in PCT
  - 20% occurs in loop of Henle
  - Total = 85%

➢ 25% of filtered Na, K, and Cl are reabsorbed in loop of Henle.

### The Thick ascending loop of Henle & early DCT:

- The cubodial to columnar epithelium of thick ascending loop of Henle & the early DCT are similar, they both also contain mitochondria.
- Highly permeable to solutes; particularly NaCl but not water.

## The Thick ascending loop:

- The thick ascending limb is very sensitive to diuretic drugs (Furosamide) these diuretics block the operation of the $Na^+ + k^+ + 2Cl^-$ co-transporter.
- Furosamide is a lasix drug that acts on the loop of Henle that blocks carrier protein and affects:
    1. ↓ NaCl reabsorption
    2. Isotonic fluid delivered to DCT instead of hypotonic fluid.
    3. Increased fluid excretion: Diuresis (increase in urine formation)
    4. These drugs are called " Loopa " diuretics (because they act on the loop of henle)

## Distal Tubule:

- First portion form the juxtaglomerular complex (control GFR and blood flow)
- Same reabsorption capacity as the thick segment of loop of Henle.
- Solute absorption but not $H_2O$
- Diluting segment of nephron – filtrate osmolality drops to 100 – 150 mosmol

## The late DCT and cortical collecting duct (CD):

- Cuboidal cell of the late DCT and cortical CD are of 2 distinct functional types:
    - *Principle cell* permeability to water and solutes is regulated by hormone.
    - *Intercalated cell* secretion of hydrogen ions for acid-base balancing
- 19% of filtered $H_2O$ is reabsorbed (ADH) ⟶ only 1% of filtered H2O will be secreted in urine.
- 9% of filtered Na is reabsorbed through all distal tubules, Na is reabsorbed and K is secreted.
    - The last amount of Na reabsorption is controlled by aldosterone.
- Cl is also reabsorbed.

## Cells of Medullary CD:

- Medullary CD is mainly composed of principle cells which function in water and urea reabsorption in the presence of ADH.

## Collecting Duct:

- Several nephrons open into one collecting duct.
- Collecting ducts then open into the renal pelvis.
- Water is permeable and urea is reabsorbed under the influence of ADH.
- Na is reabsorbed in exchange for K under the influence of aldosterone.

## Osmolality of filtrate along the nephron:

- Osmolality of filtrate in PCT: ***(Iso-osmolal)***
  - Similar to plasma = 290 mosm
  - Due to reabsorption of equal amounts of solutes and water.
- Osmolality of filtrate in Descending loop: ***(hyper-osmolal)***
  - Graded increase in osmolality from 300 mOsm to 1200 (maximum) at the tip of the loop.
  - Due to water reabsorption only.
- Osmolality of filtrate in ascending loop: ***(hypo-osmolal)***
  - Graded decrease in osmolality from 1200- 150 mOsm.
  - Due to solutes reabsorption only.
- osmolality of filtrate in CD:
  - Osmolality depends on ADH
  - ADH= water reabsorption = concentrate filtrate and urine = 1200 → ***hyper-osmolal***
  - No ADH = no water reabsorb = diluted filtrate and urine = 50 → ***hypo-osmolal***

## *Lecture 7*

### Urine concentration:

When water intake is normal urine:

- Flow is 1-2 ml/min (under normal conditions)
- Osmolality range is 500-700 mOsm/Kg
- It ranges according to the condition and the needs of the body:
  - Urine osmolality varies between 30-1200 mOsm.
  - Volume varies 0.5 – 20 ml/min.
- The ability of the kidney to concentrate urine (concern water) is an important function in regulating ECV & ECF osmolality by the ability to produce concentrated urine.

➢ Low osmolarity (osmolality) → diluted urine

➢ High osmolarity → concentrated urine

- Any gain or loss of water will change body extra cellular fluid osmolality.
  - ➢ Normal → 300
  - ➢ Increases → fasting and uncontrolled diabetes
  - ➢ Decreases → drinking water
- High water intake → decrease plasma osmolality → ↓ ADH → excretion of large volume of urine → ↓ plasma volume.
- Low water intake→↑plasma osmolality→ small quantity of concentrated urine, accompanied by thirst sensation

### ADH: (anti-diuretic hormone)

- Is synthesized by **supraoptic** & **paraventricular** nuclei of the hypothalamus, stored in the posterior Pituitary gland.
- It acts as an antidiuretic & vaso constrictor hormone.
- ↑plasma osmolality → osmoreceptor → trigger the release of ADH.
- ADH→↑permeability of CD to $H_2O$→↑$H_2O$ reabsorption → corrects the hyperosmolality of blood.
- ADH acts on receptors at the basolateral membrane → active cAMP→ active protein Kinase A → opening of water channel (**aquaporins**).

### Note:

- Osmoreceptors in the arteries detect the osmolality of the blood, so increased osmolality will stimulate the thirst center and ADH secretion which will conserve $H_2O$ by increasing $H_2O$ reabsorption.
- Diabetes Inspitus (false diabetes)
  - ❖ PT has no ADH
  - ❖ CD doesn't respond to ADH
  - The kidney produces large amounts of urine (polyurea).
  - Treatment: drinking water (if the patient doesn't drink a lot of water he becomes dehydrates because there is no ADH).

**Counter current multiplayer:** (loop of Henle & CD)

- Water is reabsorbed from the descending limb due to hyperosmolar medulla.
- Graded hyperosmolar medulla is formed by a mechanism called *counter current multiplayer.*
- Hyperosmolality in the medulla is due to solute (salt and urea) deposition in medullary interstitial.
- NaCl reabsorbed from the thick ascending limb of the loop.
- Urea reabsorbed from collecting duct (ADH).
- Both are deposited in the medulla to give hyperosmolality medulla.
- Water will be absorbed from the collecting duct to peritubular capillaries in the presence of ADH due to osmotic gradient between medullary interstitum & filtrate.
- Thiazaide block NaCl reabsorption on thick ascending loop→ Diuresis. (large quantities of urine are produced)
  - Salt remains in filtrate and keeps dragging water causing osmotic diuresis.
  - Due to ↓in medullary osmolality water cannot be reabsorbed from CD (No osmotic gradient).

**Counter current exchanger:**

- Occurs in Vasa recta and functions to maintain hyeperosmolar medulla which was built by counter current multiplayer
- Remove salt from one side & enters in the other side so blood keeps its osmolality constant in kidney.
- Vasa recta (specialized low blood supply for medulla) are the blood supply of medulla
  - Descending limb water pass out into hyperosmolar medulla carrying $O_2$ & nutrient NaCl will enter blood increasing its osmolality.
  - Ascending limb, water will be absorbed back to the hyperosmolar blood carrying $CO_2$ , waste product & NaCl will leave the blood deposited as it is in the medulla.
  - Therefore, blood leaves the hyperosmolar medulla undisturbed.

**Diuresis:** increased urine output for a short period

1. **water diuresis :**
   When drinking large quantities of water this will dilute ECF and decrease ADH causing no water reabsorption in CD → large volume of diluted urine (large amount of hypo-osmolar urine)
2. **Osmotic diuresis:** is the presence of osmolar active substance that drags water
   - Diabetes: filtration of excessive osmotic active substance (glucose/mannitol)
     Mannitol(salts of starches):
     - Drag water with it.
     - Large volume of hyperosmolar urine.
     - Polyurea: diabetes inspitus (no ADH).

## Bladder Innervation:

- The principal nerve supply of the bladder is by way of the *pelvic nerves,* which connect with the spinal cord through the *sacral plexus,* mainly connecting with cord segments S-2 and S-3. Coursing through the pelvic nerves are both *sensory nerve fibers* and *motor nerve fibers.* The sensory fibers detect the degree of stretch in the bladder wall. Stretch signals from the posterior urethra are especially strong and are mainly responsible for initiating the reflexes that cause bladder emptying.
  The motor nerves transmitted in the pelvic nerves are *parasympathetic fibers.* These terminate on ganglion cells located in the wall of the bladder. Short postganglionic nerves then innervate the detrusor muscle.
- *Skeletal motor fibers* transmitted through the *pudendal nerve* to the external bladder sphincter and is controlled by higher centers. These are *somatic nerve fibers* that innervate and control the voluntary skeletal muscle of the sphincter.
- The bladder receives *sympathetic* innervations from the sympathetic chain through the *hypogastric nerves,* connecting mainly with the L-2 segment of the spinal cord. The hypogastric nerve innervates the body and neck of the bladder and the internal sphincter. The efferent fibers inhibit the bladder contraction and activates the internal sphincter (inhibit micturation).These sympathetic fibers stimulate mainly the blood vessels and have little to do with bladder contraction. Some sensory nerve fibers also pass by way of the sympathetic nerves and may be important in the sensation of fullness an also pain.

## Micturition:

- Voluntary emptying of the bladder or urination
- The physiology of micturition: It is a spinal reflex facilitated or inhibited by higher centers.
- It is triggered when volume in the bladder = 400 ml.
- Distention of bladder stimulates stretch receptor in the bladder wall → reflex contraction of the bladder & relaxation of internal & external sphincters.
- This reflex is released by removing inhibitory impulses from the cerebral cortex.
- During filling phase detrusor muscle is relaxed & both sphincters are contracted.

- **Cytometrogram:** recording intravesical pressure change during filling phase.
  Figure 26-7 (p.313)
- The curve shows:
  - Initial rise in pressure with bladder filling.
  - Plateau phase slight changes in pressure within volume.
  - Sudden sharp rise in pressure (volume of more than 400) as micturition reflex is started.

## Micturition:

- Voluntary emptying of bladder or urination.
- the ureter & the urinary bladder :
  - Urine transport to bladder by ureters.
  - Regular peristaltic contraction 1-5/min.
  - Ureter enter the bladder wall obliquely (functional sphincter), this prevents urine reflux from the bladder.
- Bladder muscle (detrusor) arranged in spiral, circular, and longitudinal.
- Muscle bundle around the urethra called internal sphincter (can't be controlled)
- External sphincter is made of skeletal muscle and can be controlled

- Plot has 3 components (segments):
  I. a. initial slight rise in pressure when the 1st increment in volume is produced.
     b. a long nearly flat segment as further increments are produced (urge to void at about 150 mL)
  II. A sudden, sharp rise in pressure as the micturation reflex is triggered (sense of fullness at about 400mL).

## Abnormal Micturation:

- Interruption of afferent nerves
  Tabes dorsalis interruption of dorsal roots → reflex contraction of the bladder is lost → bladder wall is thin and distended and hypotonic → there are some contractions due to intrinsic response in the muscle → dripping of urine.
- Interruption of both afferent and efferent (pelvic tumor)
  Tumors → bladder is flaccid (bladder loses its flexibility) and distended → shrunken and hypertrophied
- Spinal cord transection
  During shock, the bladder is flaccid → over filled bladder → urine dribbles (overflow incontinence) → spinal reflex for emptying will resume with no voluntary control (the urinary bladder fills and empties on its own)