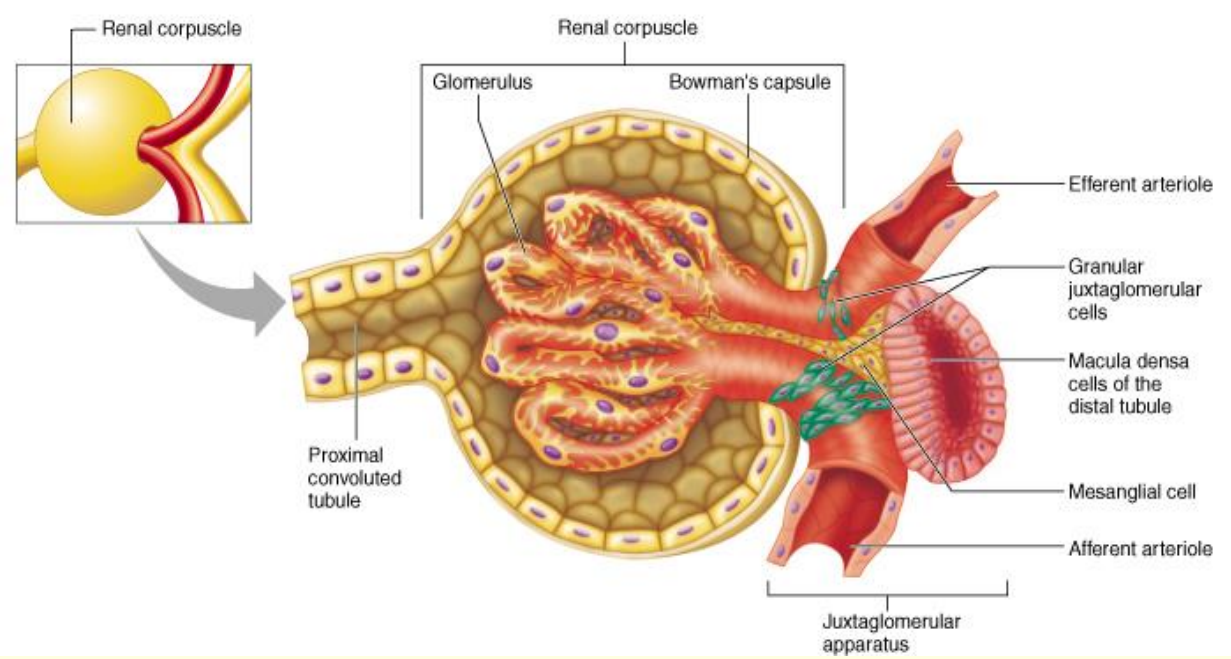
GLOMERULAR FILTATION RATE, REGULATION OF GFR AND RENAL CLEARANCE



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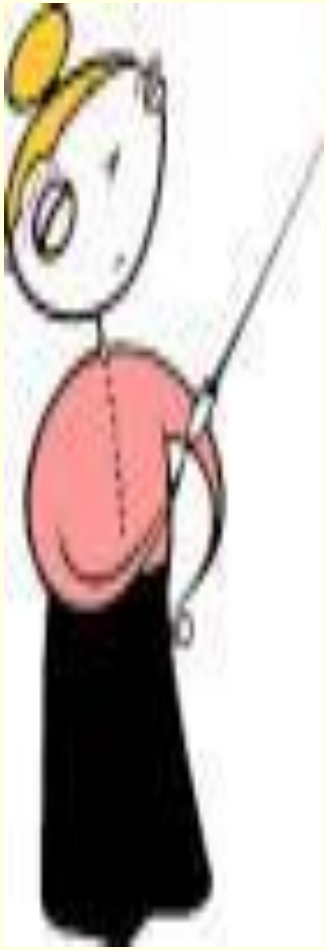
LECTURE OUTLINES



- Juxta glomerular apparatus [JGA]
- Glomerular Membrane
- Glomerular Filtration
- Glomerular Filtration Rare [GFR]
- Normal GFR
- Regulation of Glomerular Filtration Rare [GFR]
- Renal Clearance

GLOMERULAR MEMBRANE

The glomerular capillary membrane is similar to that of other capillaries. It has three major layers:

[i] Endothelial layer of the glomerular membrane has a fenestrae.

[ii] The basement membrane.

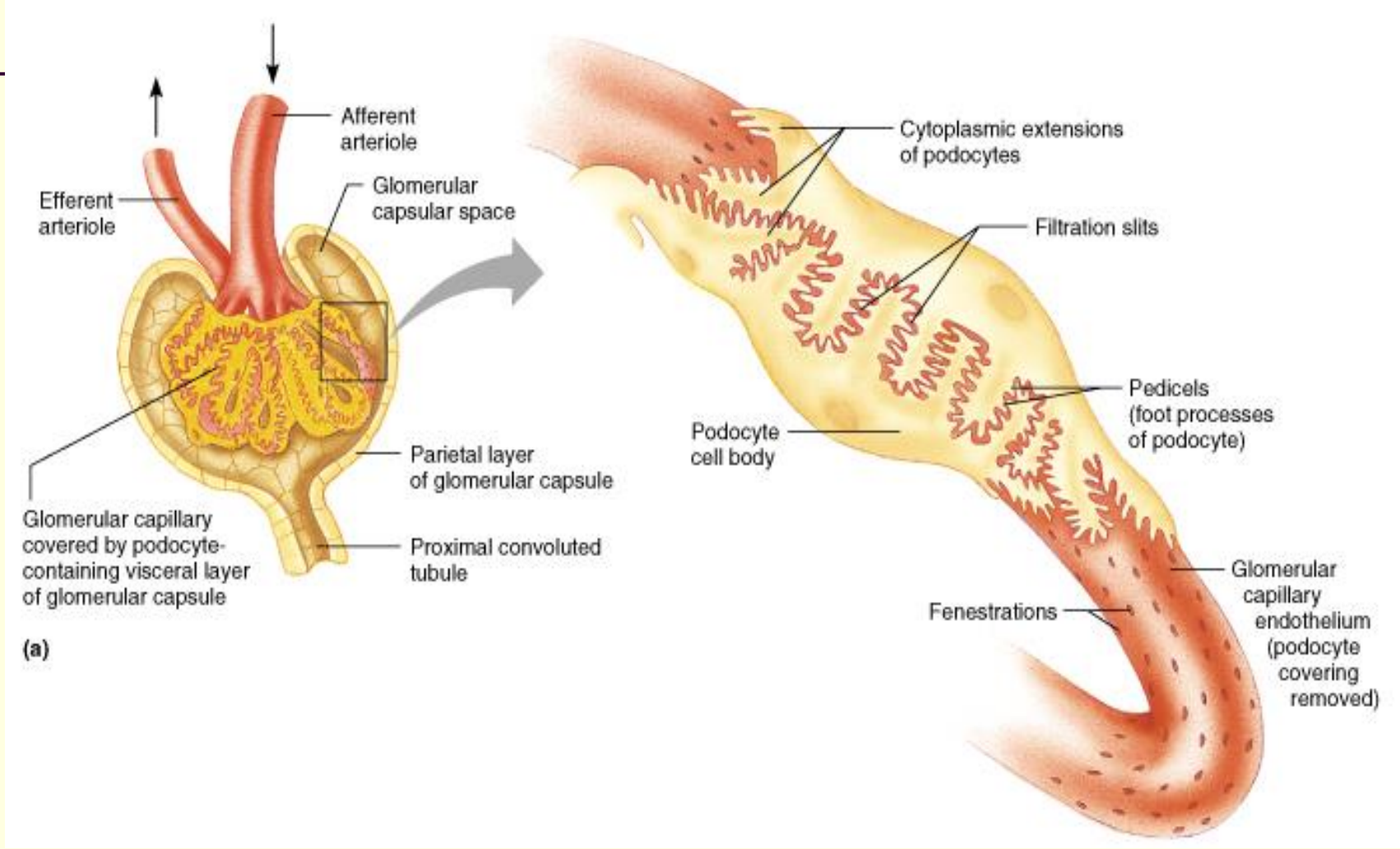
[iii] A layer of epithelial cells [podocytes] on the outer surfaces of the glomerular capillaries which have pores.

GLOMERULAR MEMBRANE

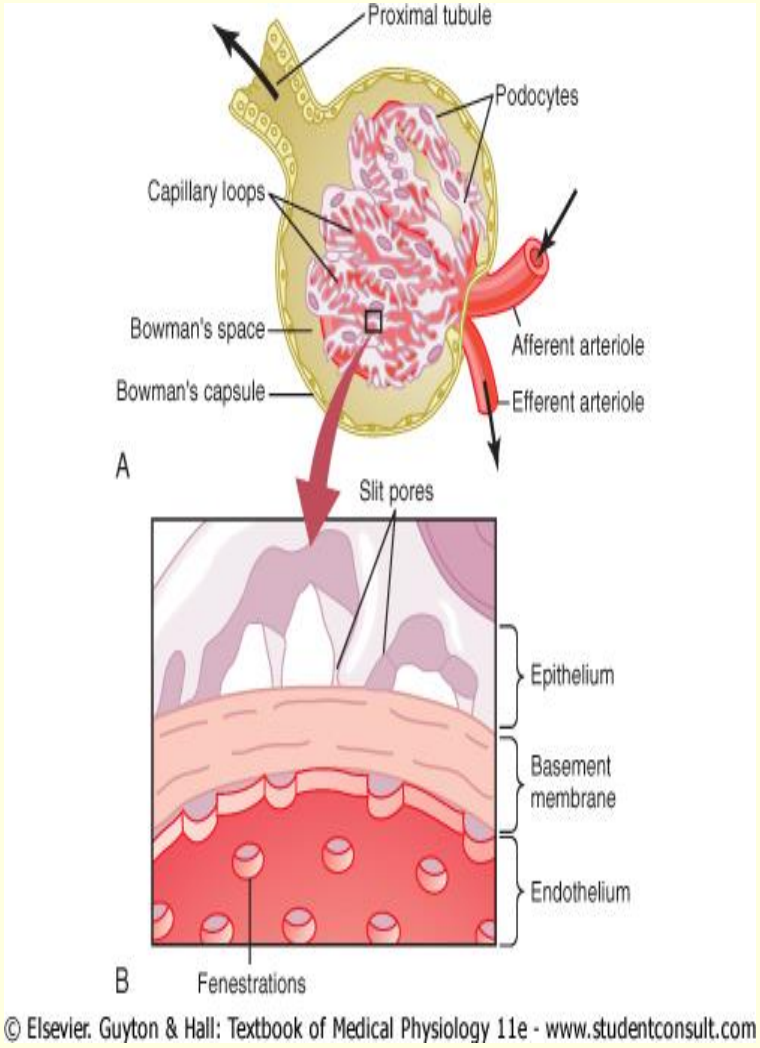
Fenestrae: Capillary endothelial cells lining the glomerulus are perforated by thousands of small holes called fenestrae.

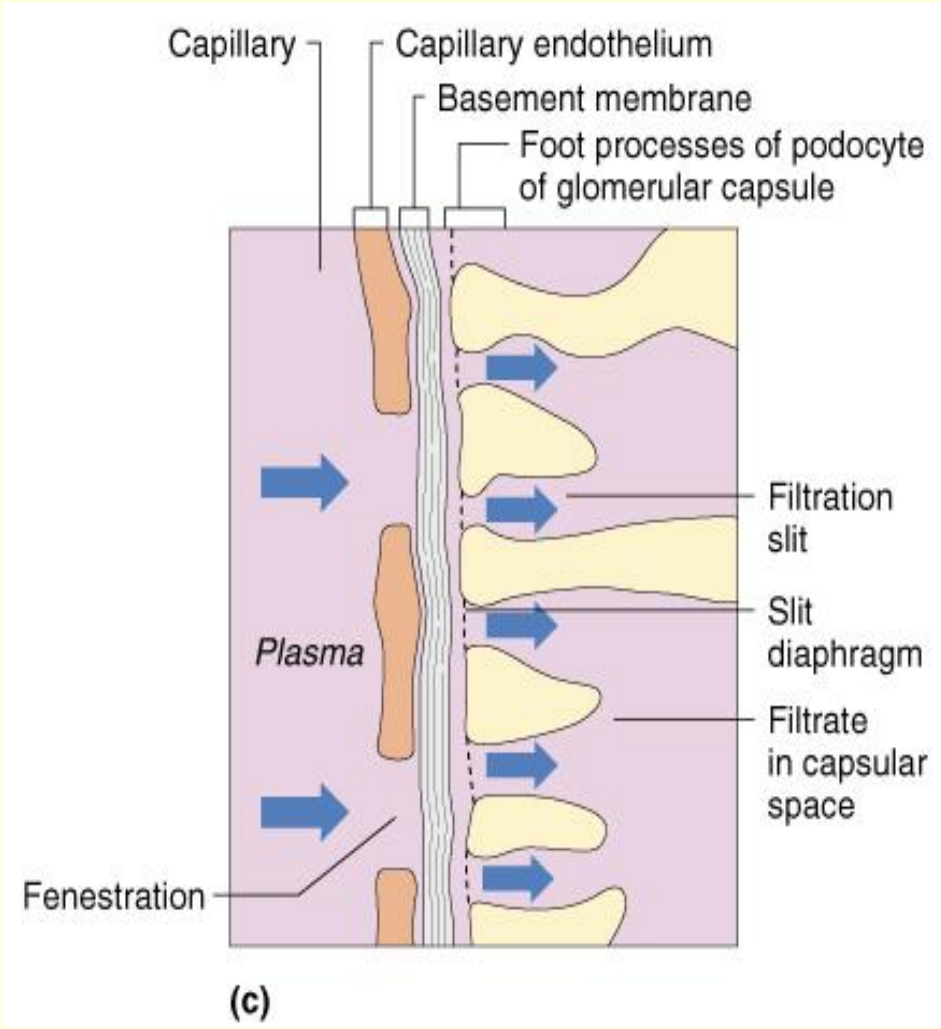
Slit pores: Epithelial layer is not a continuous layer but instead consists mainly of fingerlike projections that cover the basement membrane, these fingers form slits which are called slit pores.

GLOMERULAR MEMBRANE



GLOMERULAR MEMBRANE





GLOMERULAR MEMBRANE

- **Glomerular permeability:** The glomerular filtrate passes through three different layers i.e. endothelial layer, basement membrane, and epithelial layer
- Each of these layers is several hundred times as porous as the usual capillary membrane.
- Despite this tremendous permeability of the glomerular membrane, it has an extremely high degree of selectivity for the sizes of molecules that it allows to pass.

GLOMERULAR MEMBRANE

Does proteins pass through glomerular membrane

Glomerular membrane is completely impermeable to all plasma proteins.

Causes of impermeability [Pores size]: Pores of the glomerular membrane are large enough to allow neutral molecules with diameter up to 8 nanometers to pass through. Even though the molecular diameter of the plasma protein (albumin) molecule is only about 6 nanometers, it still not pass through the membrane.

GLOMERULAR MEMBRANE

DOES PROTEINS PASS THROUGH GLOMERULAR MEMBRANE

Negative charge:

The basement membrane of the glomerular pores are lined with a complex of proteoglycans that have very strong -ve electrical charges. Similarly the plasma proteins have -ve charges.

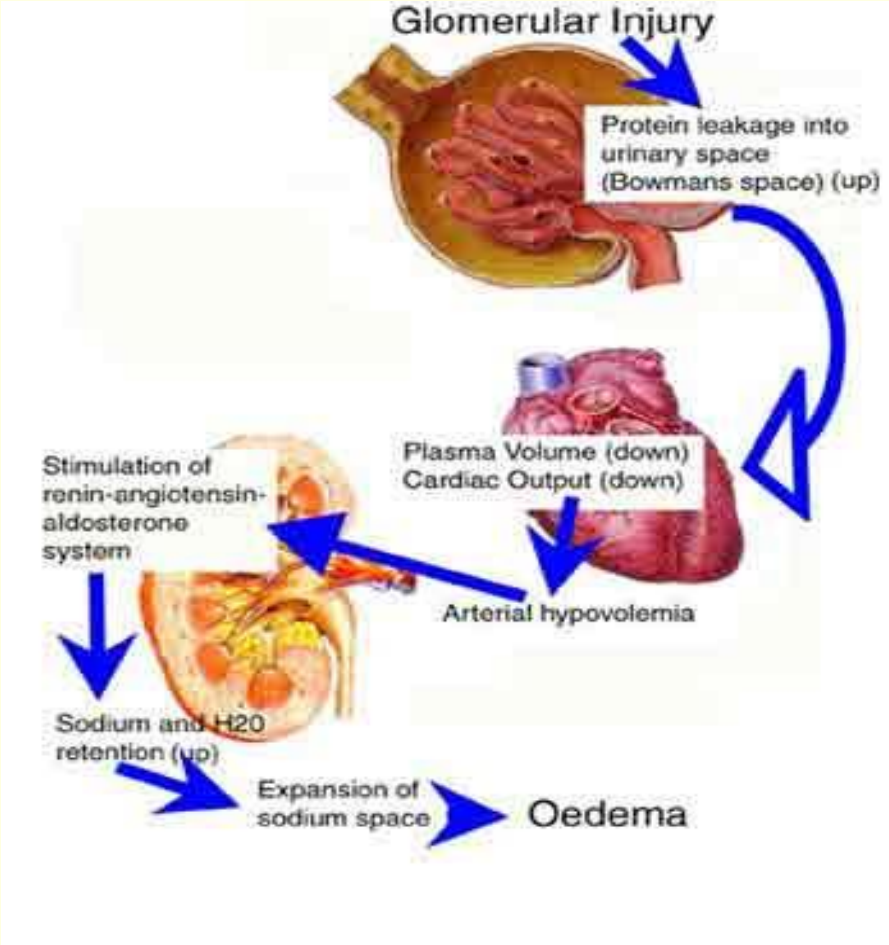
Therefore electrostatic repulsion of the molecules by the pore walls keeps virtually all protein molecules > 69,000 molecular weight from passing through.

GLOMERULAR PERMEABILITY

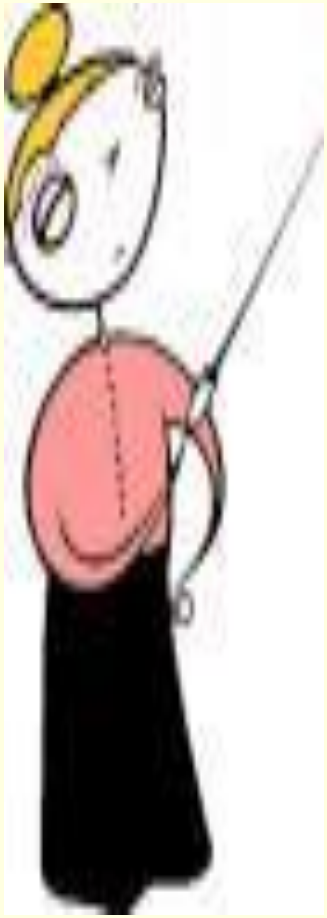
- The permeability of the glomerular capillaries is about 50 times that of the capillaries in skeletal muscle.
- Neutral substances with effective molecular diameters of less than 4 nm are freely filtered. Filtration of neutral substances with diameters of more than 8 nm approaches zero.
- Sialoproteins in glomerular capillary wall are negatively charged. The negative charges repel negatively charged substances in blood

GLOMERULAR PERMEABILITY
Proteins Leakage

- The presence of significant amounts of albumin in the urine is called **albuminuria.**
- In nephritis, the negative charges in the glomerular wall are dissipated, and albuminuria can occur for this reason without an increase in the size of the "pores" in the membrane.



GLOMEULAR FILTRATION RATE



GLOMEULAR FILTRATION RATE (GFR)

GLOMERULAR FILTRATION RATE
GFR

Definition: This is the fluid that filters through the glomerulus into the Bowman's capsule per minute.

GLOMEULAR CAPSULE

- **Glomerulus:** Each nephron contains clumps of capillaries. These capillaries are highly porous and allow large amounts of solute-rich, virtually protein-free fluid filtrate to pass from the blood into the glomerular capsule

- **Glomerular capsule/ Bowman's capsule:** A cup-shaped structure (a blind pouch) that encloses the glomerulus. First part of the nephron that moves fluid out of the body.

GLOMERULAR FILTATION

Glomerular Filtration

The First Step in Urine Formation: Urine formation begins with filtration of large amounts of fluid through the glomerular capillaries into Bowman's capsule.

Composition: The glomerular capillaries are relatively impermeable to proteins, so that the filtered fluid [called the glomerular filtrate] is essentially protein-free and devoid of cellular elements, including red blood cells.

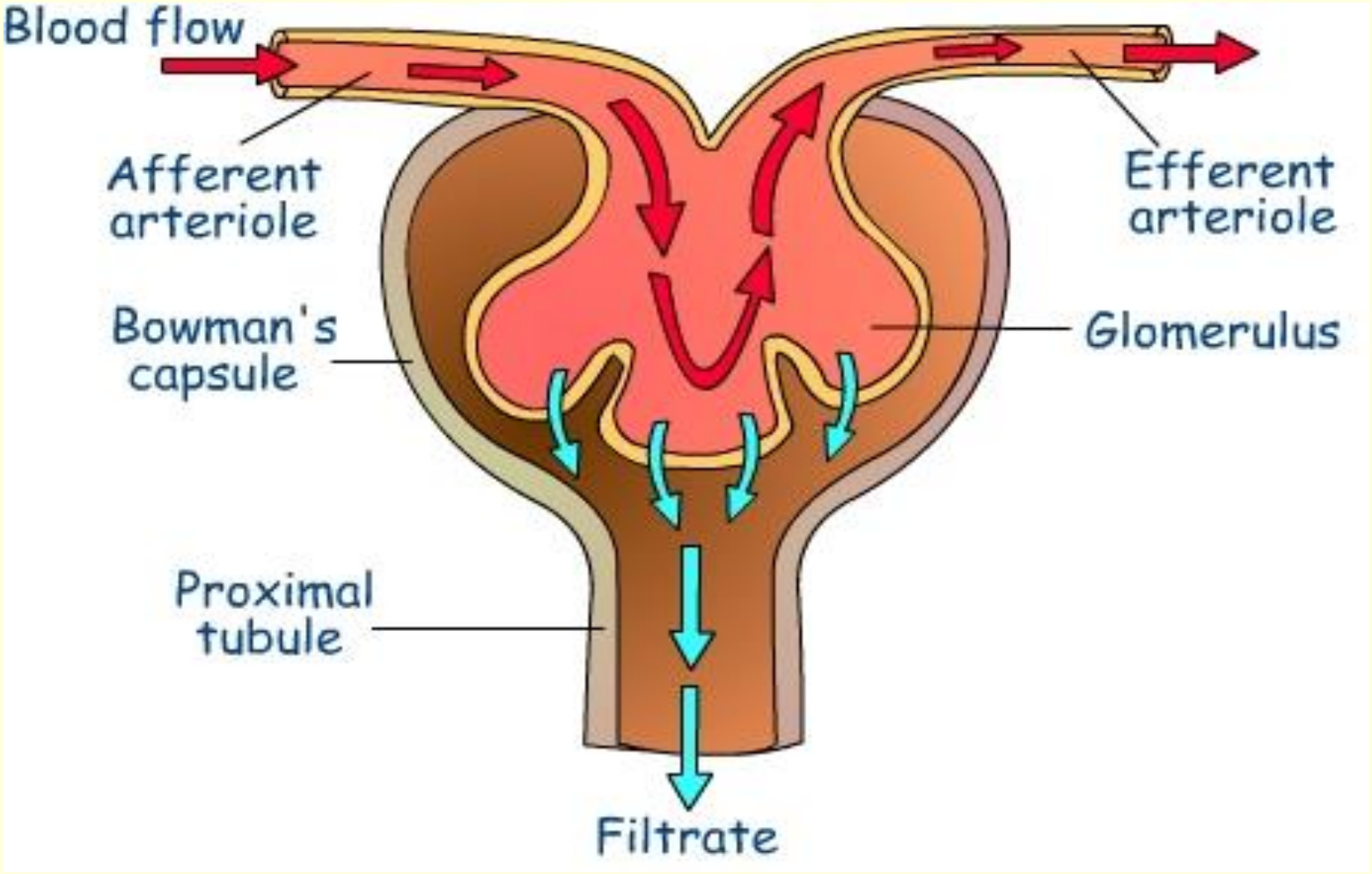
GLOMEULAR CAPSULE

Afferent arterioles: Has a larger diameter than the efferent arteriole

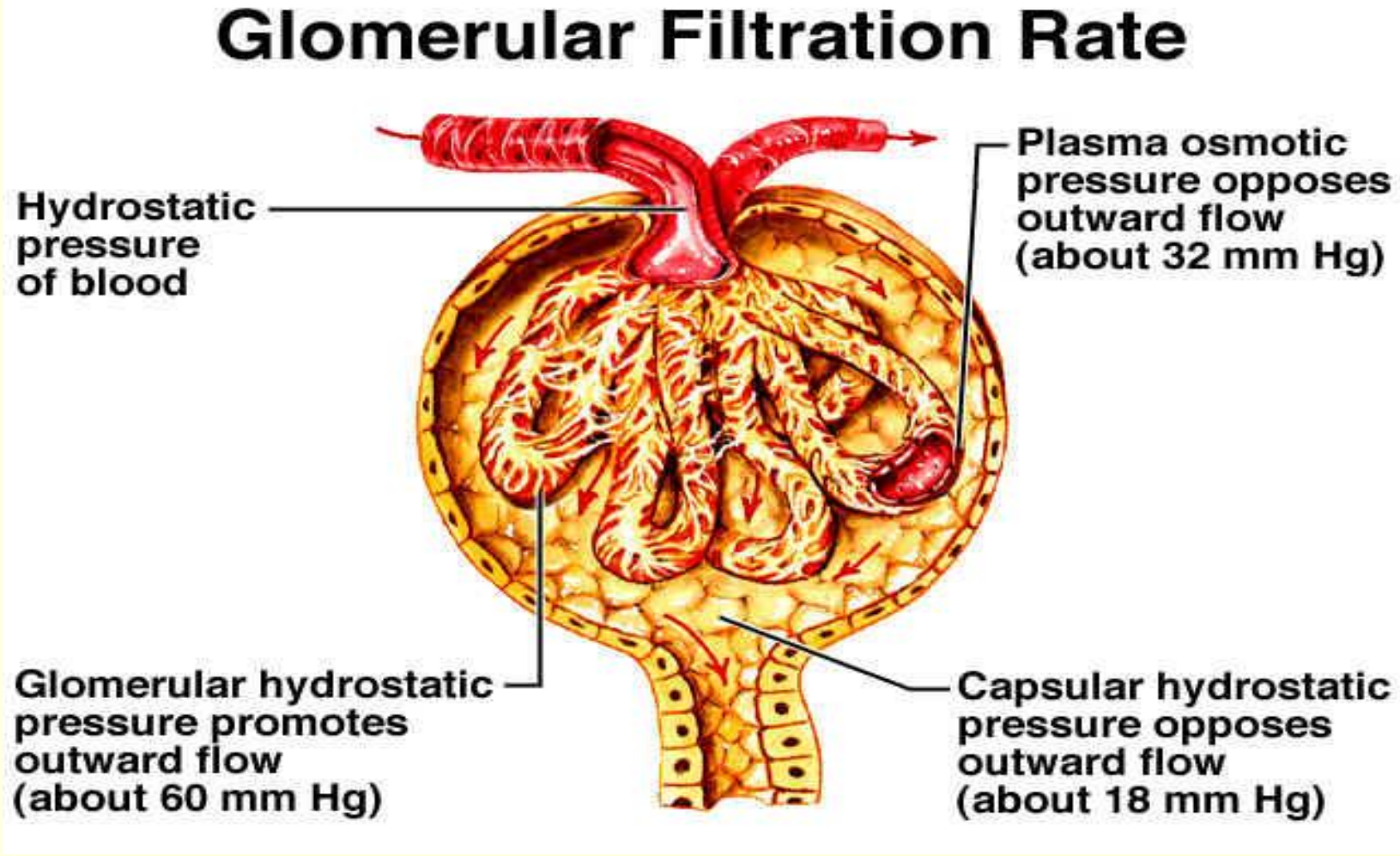
- This is one of the reasons that blood pressure is high in the glomerulus. The elevated blood pressure is needed to force fluid out of the bloodstream and into the nephron.

Efferent arterioles: Carry the newly filtered blood away from the glomerulus. Narrower diameter than the afferent vessels keeps glomerular pressure high.

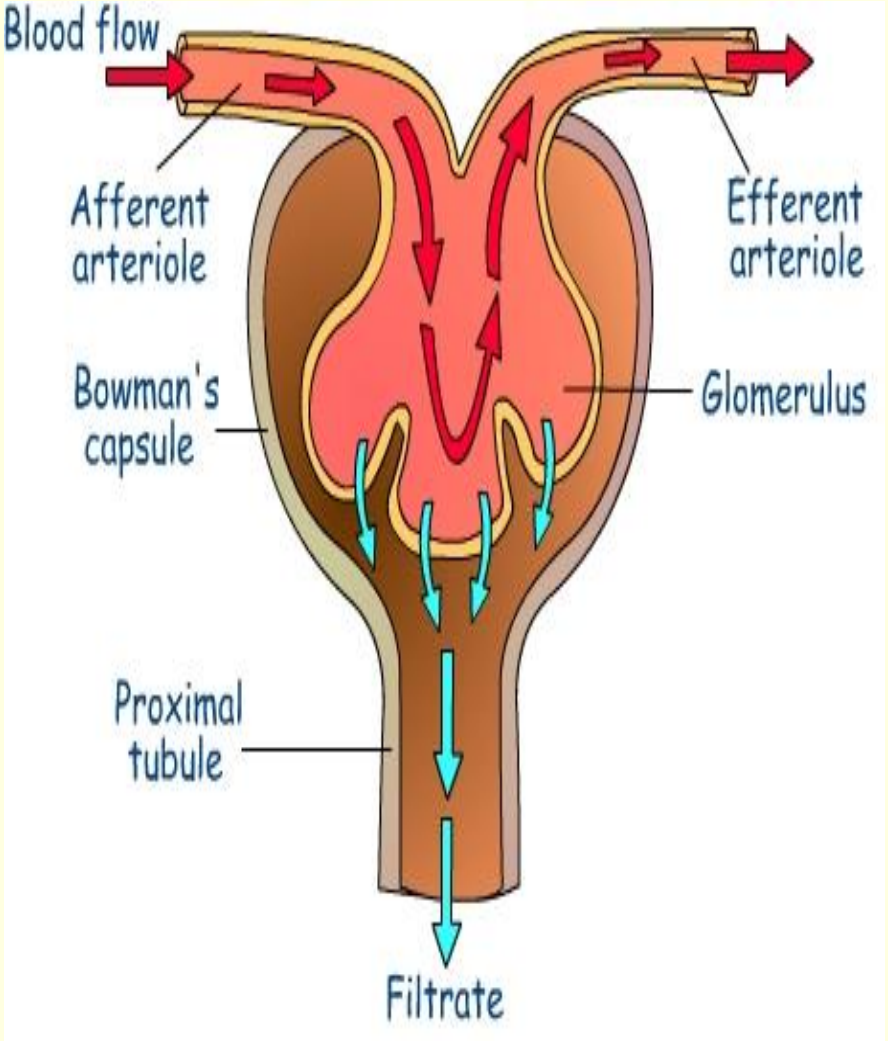
GLOMERULAR FILTRATION



GLOMERULAR FILTATION RATE



GLOMERULAR FILTRATION RATE
GFR



This is the first step in urine formation

The glomerular capillaries are relatively impermeable to proteins, so that glomerular filtrate is essentially protein-free and devoid of cellular elements, including red blood cells.

GLOMERULAR FILTATION RATE
GFR

- **Normal GFR:** The GFR in an average-sized normal man is approximately 125 mL/min. OR 180 L/d
- Its magnitude correlates fairly well with body surface area
- In females 10% lower than those in men even after correction for surface area.
- The normal urine volume is about 1 L/d. Thus, 99% or more of the filtrate is normally reabsorbed.
- GFR= Filtration pressure x Filtration co-efficient.

FILTRATION FRACTION (FF)

Filtration fraction (FF) This is the fraction of the renal plasma flow that becomes glomerular filtrate. It is about 20%.

In a normal healthy subject the percentage of the renal plasma flow that pass into the glomerular capsule is about 20%

- The ratio of the **Glomerular filtration rate** **to the renal plasma flow** (RPF).
- The **filtration fraction,** is normally 0.16–0.20.
- The GFR varies less than the RPF. When there is a fall in systemic BP, the GFR falls less than the RPF because of efferent arteriolar constriction, and consequently the filtration fraction rises.

FILTRATION FRACTION (FF)

The **filtration fraction,** is normally equal to 0.16–0.20

Renal Blood flow= 1200 ml

It is about 20 % of the cardiac out put

Plasma volume = 55 % ,

Plasma flow is equal to 660 ml

FF= GFR/ RPF

FF= 125/660=0.18

FILTRATION FRACTION (FF)

The fraction of RPF (Filtration fraction) that gets filtered is:

$$\text{Filtration fraction (FF)} = \frac{\text{GFR}}{\text{RPF}} = \frac{125}{625} = 0.2$$

Meaning that 20% of plasma passing through the glomerulus gets filtered.

PRESSURES ACTING ON GLOMERULAR FILTATION

- The pressure responsible for filtrate formation
- NFP= Glomerular hydrostatic pressure (HP_g) minus the oncotic pressure of glomerular blood (OP_g) combined with the capsular hydrostatic pressure (HP_c)
- $NFP = HP_g – (OP_g + HP_c)$

PRESSURES ACTING ON GLOMERULAR FILTATION

- Filtration Pressure is the force that drives the fluid and its dissolved substances through the glomerular filter

Net Filtration pressure NFP: [Net Hydrostatic Pressure NHP] is the difference between three pressures:

1. Glomerular (blood) hydrostatic pressure [GHP or GBHP]=60
2. Bowman's Capsular Hydrostatic Pressure [CHP]=18
3. (Blood) Colloid Osmotic Pressure [BCOP]=32

The relationship can be expressed by: NPF=GBHP–(CHP+BCOP)

PRESSURES ACTING ON GLOMERULAR FILTATION

1. Glomerular (blood) hydrostatic pressure [GHP or GBHP]

=60 mmHg

2. Bowman's Capsular Hydrostatic Pressure [CHP]

=18mmHg

3. (Blood) Colloid Osmotic Pressure [BCOP] =32 mmHg

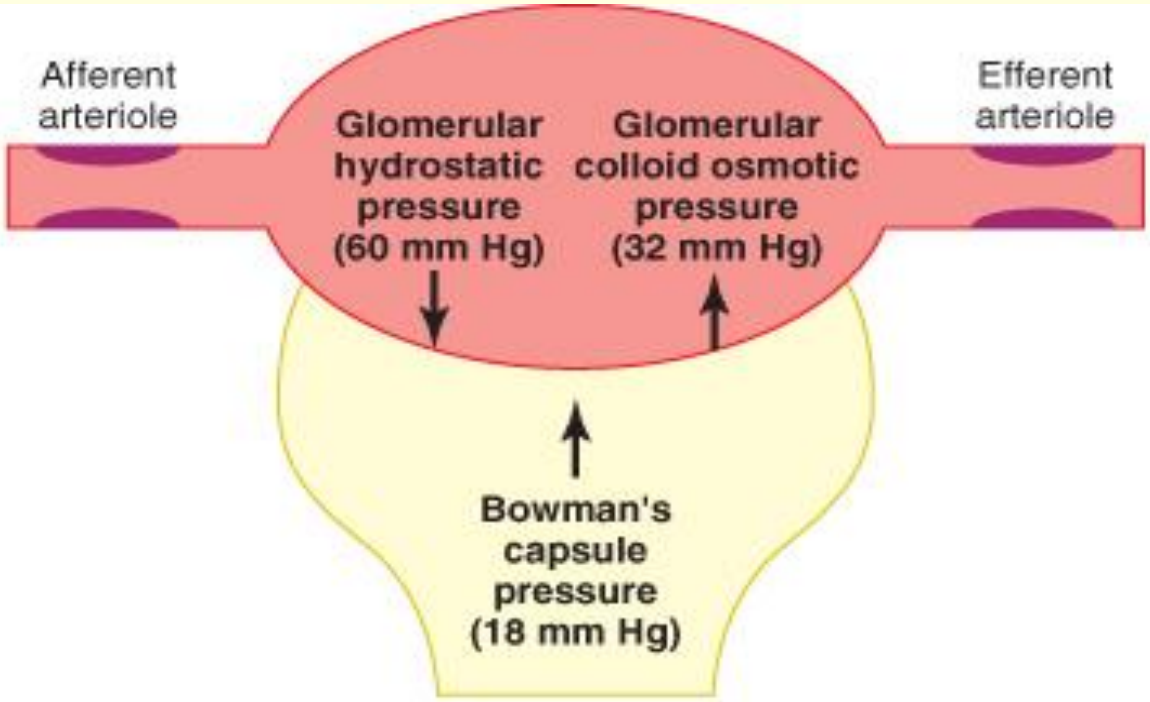
The relationship can be expressed by:

NPF= GBHP– [CHP + BCOP]

60- [18 + 32 =50]

NPF 60-50=10 mmHg

NET GLOMERULAR FILTRATION 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)

REGULATION OF GLOMERULAR FILTRATION

- The factors governing filtration across the glomerular capillaries are the same as those governing filtration across all other capillaries [Dynamics of Blood]

Example:

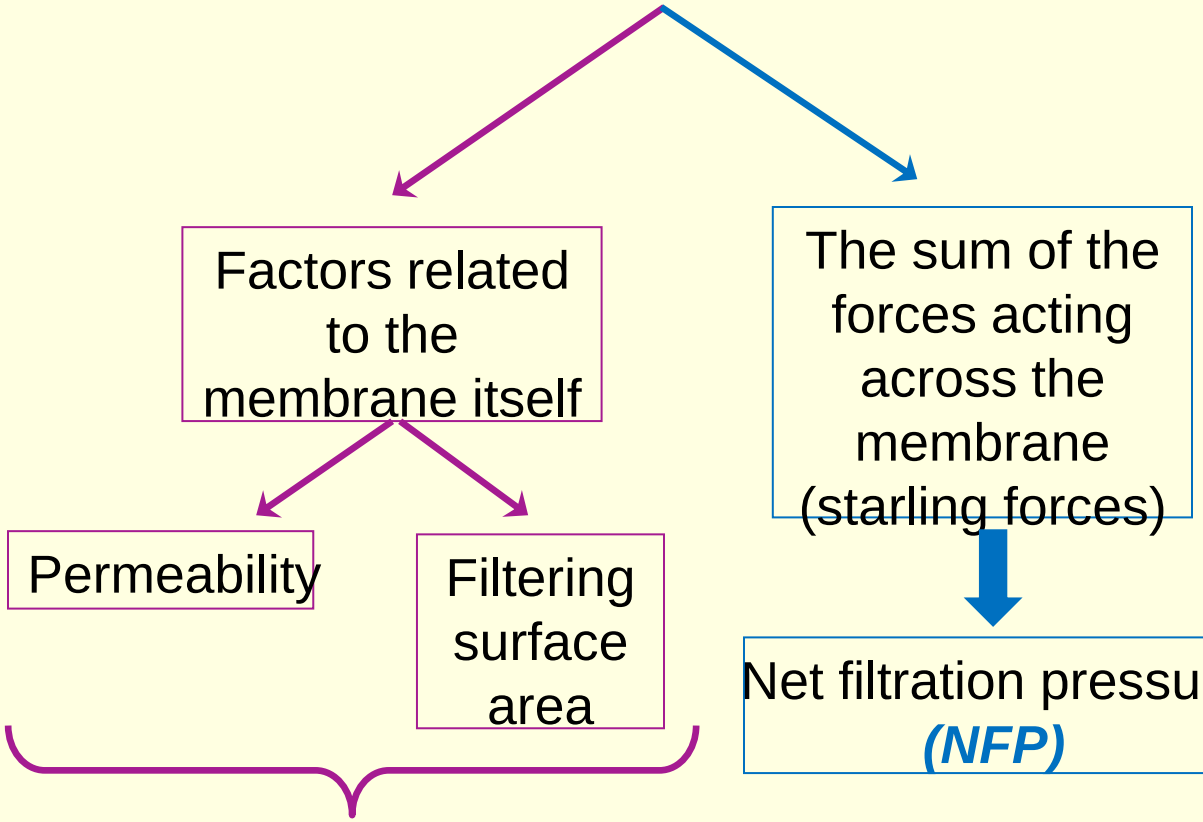
- Size of the capillary bed
- The permeability of the capillaries
- The hydrostatic and osmotic pressure gradients across the capillary wall.

REGULATION OF GLOMERULAR FILTRATION

- $K_{f:}$ The glomerular ultrafiltration coefficient, is the product of the glomerular capillary wall (ie, permeability)
- $P_{GC:}$ Osmotic pressure of the plasma in the glomerular capillaries
- P_T : Hydrostatic pressure in the tubule
- $_{GC}$: Osmotic pressure of plasma in the glomerular capillaries,
- $_T$ the osmotic pressure of the filtrate in the tubule.

Glomerular Filtration Rate (GFR)

Factors controls (determines) the GFR?



GFR = 125 ml/min
OR 180 L/day

Capillary filtration coefficient (Kf)

GFR = Kf X NFP

FACTORS AFFECTING GLOMERULAR FILTRATION RATE

Increasing Factors

1. Increased renal blood flow
2. Increased glomerular pressure
3. Increased blood pressure
4. Efferent arteriolar constriction

Decreasing Factors

1. Increased plasma colloid osmotic pressure
2. Increased Bowman's capsule pressure
3. Afferent arteriolar constriction
4. Sympathetic stimulation, causing afferent arteriolar constriction.

REGULATION OF GLOMERULAR FILTRATION [SYMPATHETIC NERVOUS SYSTEM]

Regulation	Major Stimulus	Mechanism	Effect on GFR
Sympathetic Nerves (Autonomic)	Acute fall in systematic blood pressure. Release of norepinephrine	Constriction of afferent arterioles	Decrease GFR and filtrate volume to maintain blood volume

REGULATION OF GLOMERULAR FILTRATION [NEURAL REGILATION]

Regulation	Major Stimulus	Mechanism	Effect on GFR
Tubuloglomerular feedback	Rapid increase in Na+ and Cl- In lumen at the macula densa due to increased BP	Decreased release of Nitric Oxide by JGA causing AA constriction	Decrease GFR and filtrate volume

REGULATION OF GLOMERULAR FILTRATION [HORMONAL]

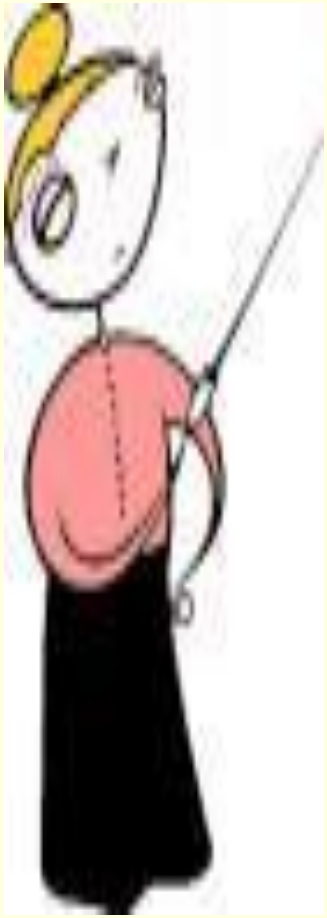
Regulation	Major Stimulus	Mechanism	Effect on GFR
Angiotensin II	Decreased blood volume or decreased blood pressure	Constriction of both afferent and efferent arterioles	Decreases GFR
Atrial natriuretic peptide	Stretching of the arterial walls due to increased blood volume	Relaxation of the mesangial cells increasing filtration surface	Increases GFR

FACTORS AFFECTING GLOMERULAR FILTRATION RATE

Hormone or Autacoid	Effect on GFR
Norepinephrine	= Decrease GFR
Epinephrine	= Decrease GFR
Endothelin	= Decrease GFR
Angiotensin II	Decrease GFR
Endothelial-derived nitric oxide	= Increased GFR
Prostaglandins	= Increased GFR

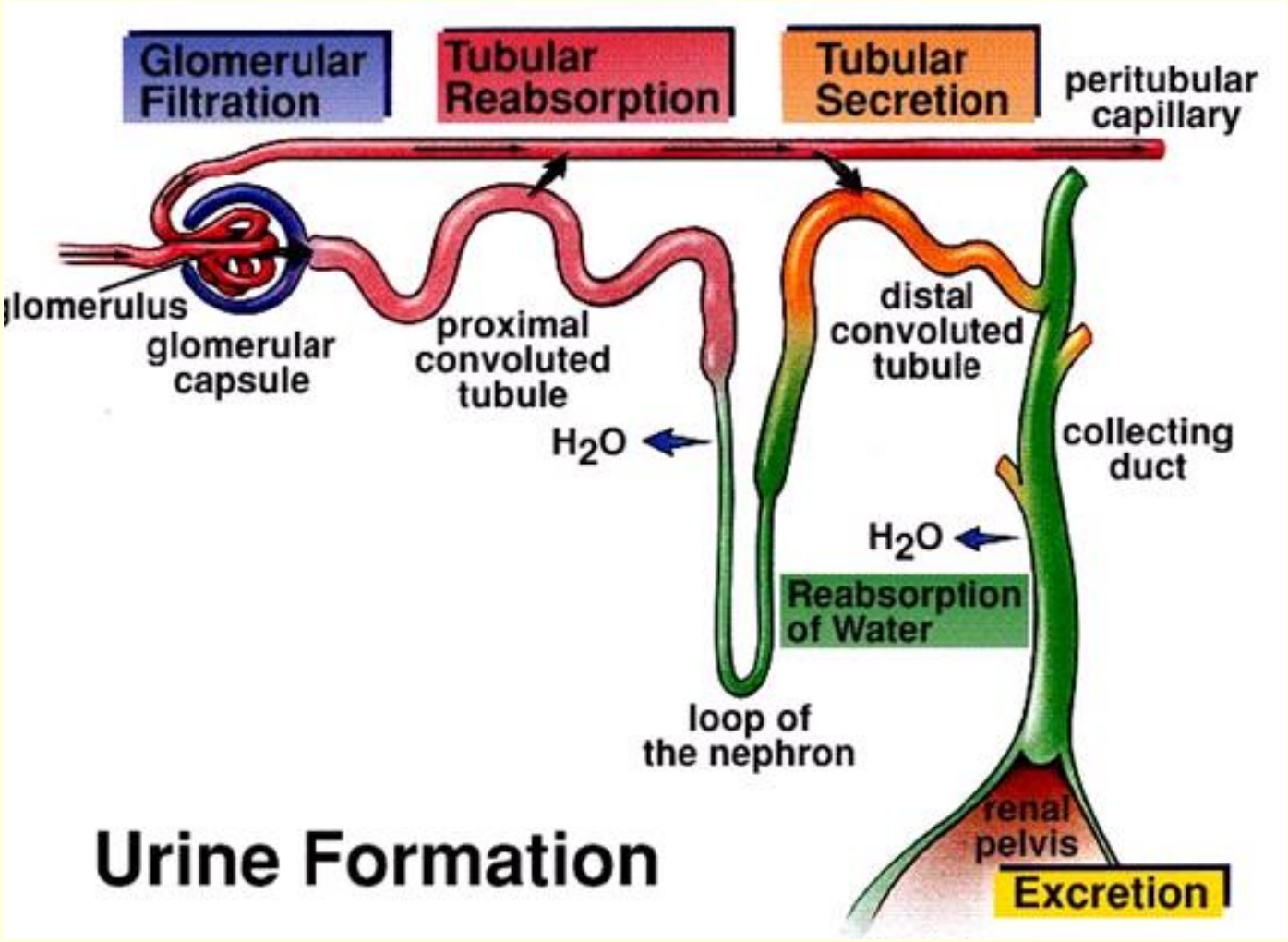
MEASURING GLOMERULAR FILTATION RATE

- The **glomerular filtration rate (GFR)** can be measured in animals and humans by measuring the excretion and plasma level of a substance that is freely filtered through the glomeruli and neither secreted nor reabsorbed by the tubules.
- The amount of such a substance in the urine per unit of time must have been provided by filtering exactly the number of ml of plasma that contained this amount.



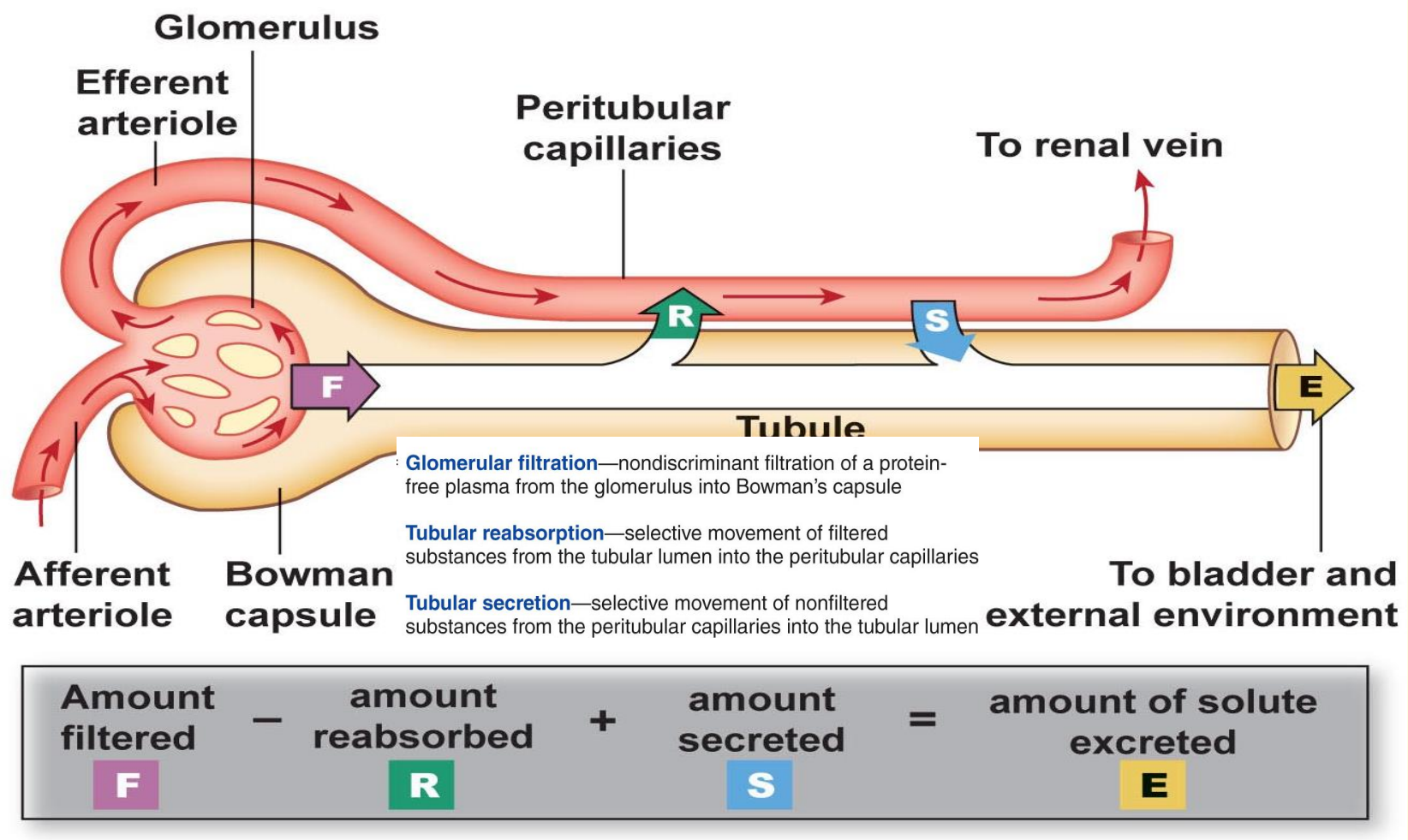
RENAL CLEARANCE

THE NEPHRON
FILTRATION, REABSORPTION, SECRETION & EXCRETION



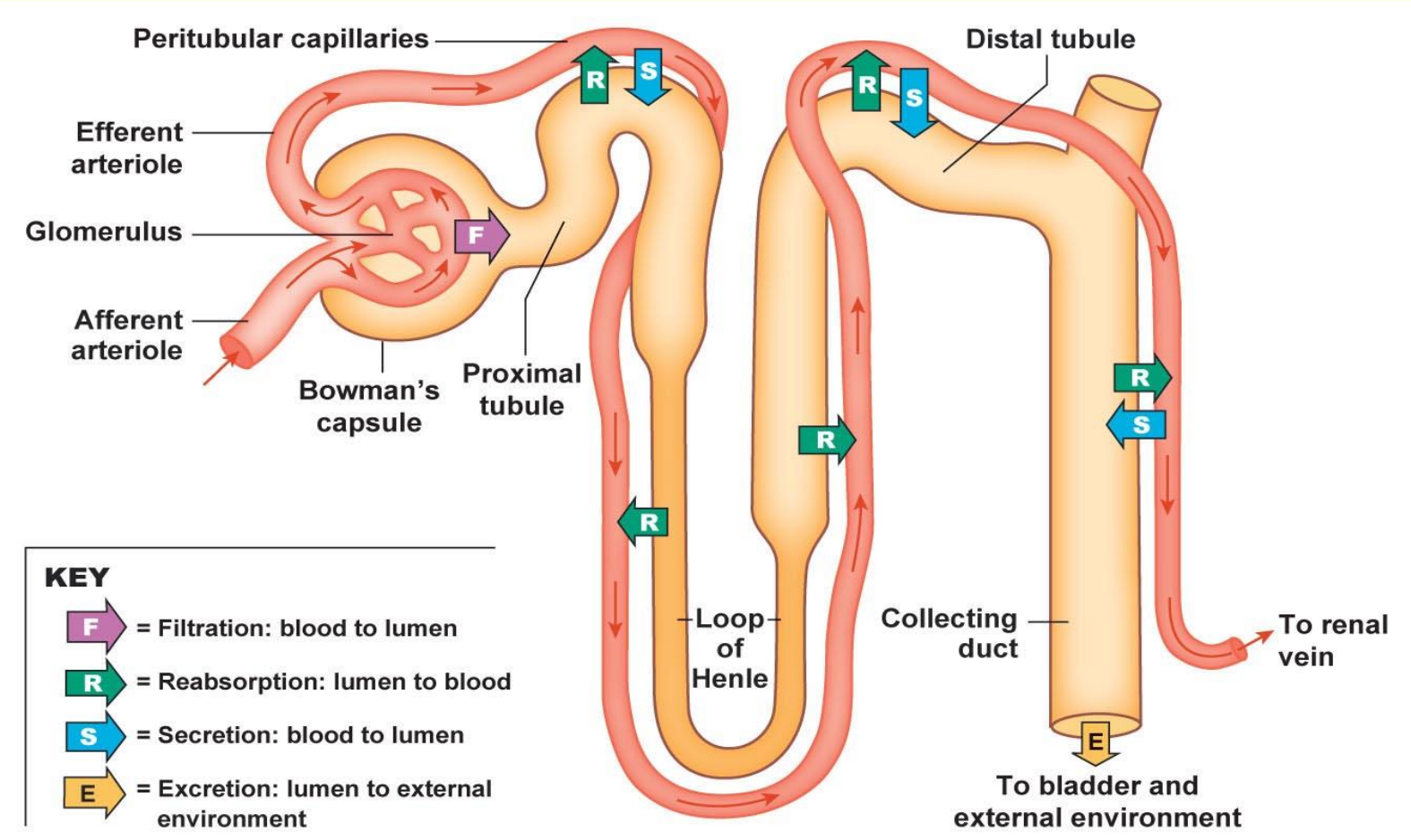
THE NEPHRON SIMPLIFIED FUNCTIONS

- Glomerular Filtration: From Gl to BC
- Tubular Reabsorption: From Tubule to PC
- Tubular Secretion: From PC into tubules
- Excretion: From tubules to bladder



Excretion = Filtration – Reabsorption + Secretion

THE NEPHRON
FILTRATION, REABSORPTION, SECRETION & EXCRETION



Renal Clearance

Renal clearance

The renal clearance of a substance is an expression of the degree to which the substance is removed from the blood plasma and excreted into the urine

e. g. Substance x

Rate of excretion of x = $U_x.V$

Need to relate the amount excreted to the plasma concentration (= P_x)

$$\text{Clearance of x } (C_x) = \frac{U_x.V}{P_x}$$

Renal Clearance

- Substance must be freely filtered and neither reabsorbed nor secreted in the tubules
- Substance suitable for measuring the GFR should be nontoxic and not metabolized by the body.
- Inulin, a polymer of fructose with a molecular weight of 5200 that meets the criteria in humans and most animals and is extensively used to measure GFR.

Renal Clearance

What is the importance of renal clearance?

To quantify several aspects of renal functions:

- rate of glomerular filtration
- Rate of bl flow
- Assess severity of renal damage
- Tubular reabsorption.
- Tubular secretion of different substances.

Renal Clearance

Criteria of a substance used for GFR measurement:

a)freely filtered

b)not secreted by the tubular cells,

c)not reabsorbed by the tubular cells.

d)should not be toxic

e)should not be metabolized

f)easily measurable.

Renal Clearance

Clearance tests

Types of Clearance tests	
Endogenous	**Exogenous**
Creatinine	Inulin
Urea	Para-amino hippuric acid (PAHA)
Uric acid	Diodrast (di-iodo pyridone acetic acid)

- Calculation: $\frac{U \times V}{P}$

Where:

U = concentration of substance in urine (mg/dl)

V = volume of urine excreted per minute (ml/min)

P = concentration of substance in plasma/serum (mg/dl)

Renal Clearance

If the plasma inulin concentration = 25mg/dl

Urine inulin concentration =400mg/dl

Urine flow = 3ml/min

$$C_{IN} = \frac{U_{IN}\dot{V}}{P_{IN}} =$$

400 / 25 = 16*3=48

GFR: 48 ml/min

Renal Clearance

$$C_{In} = \frac{U_{In} \times V}{P_{In}} \text{ ml/minute}$$

where, C_{In} = inulin clearance in ml/minute

U_{In} = inulin concentration in mg per 1.0 ml of urine

V = volume of urine in ml/minute

P_{In} = inulin concentration in mg per 1.0 ml of plasma

The normal inulin clearance value is 125 ml per minute.

Renal Clearance

$$U_{IN} = 35\ mg/mL$$

$$\dot{V} = 0.9\ mL/min$$

$$P_{IN} = 0.25\ mg/mL$$

$$C_{IN} = \frac{U_{IN}\dot{V}}{P_{IN}} = \frac{35 \times 0.9}{0.25}$$

$$C_{IN} = 126\ mL/min$$

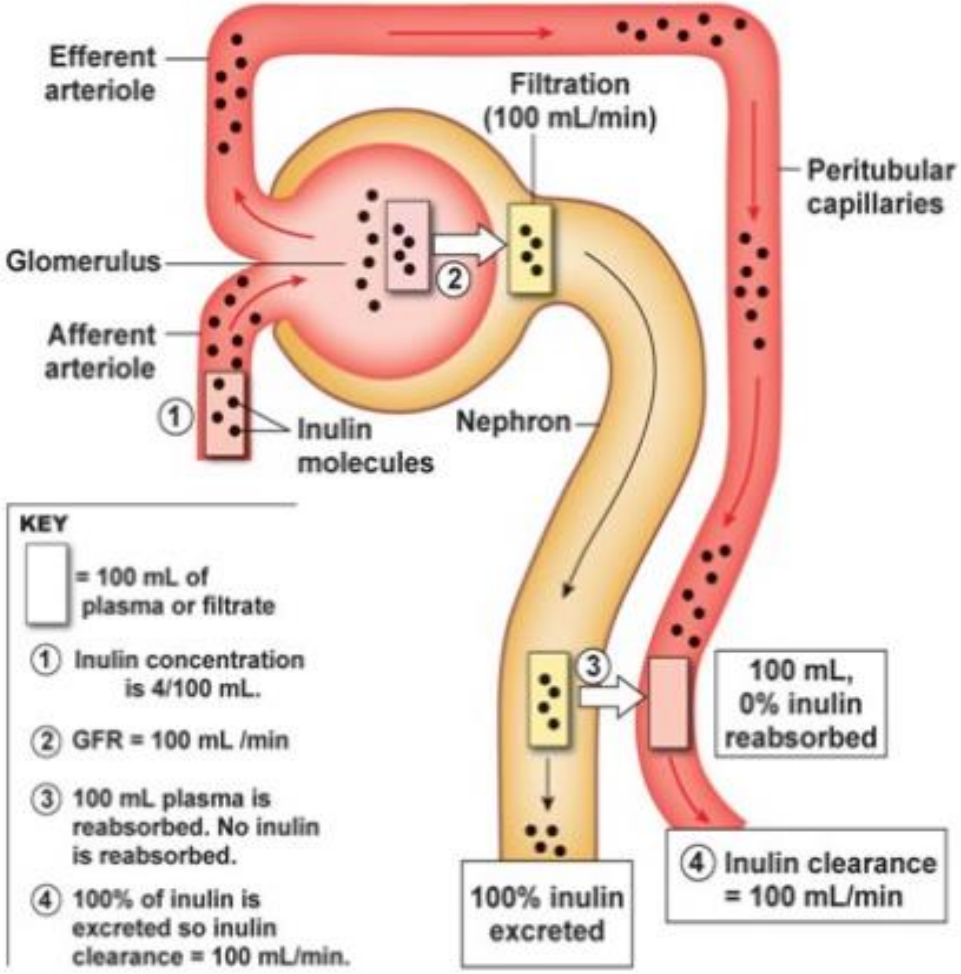
Renal Clearance

Nephron Excretion & Clearance

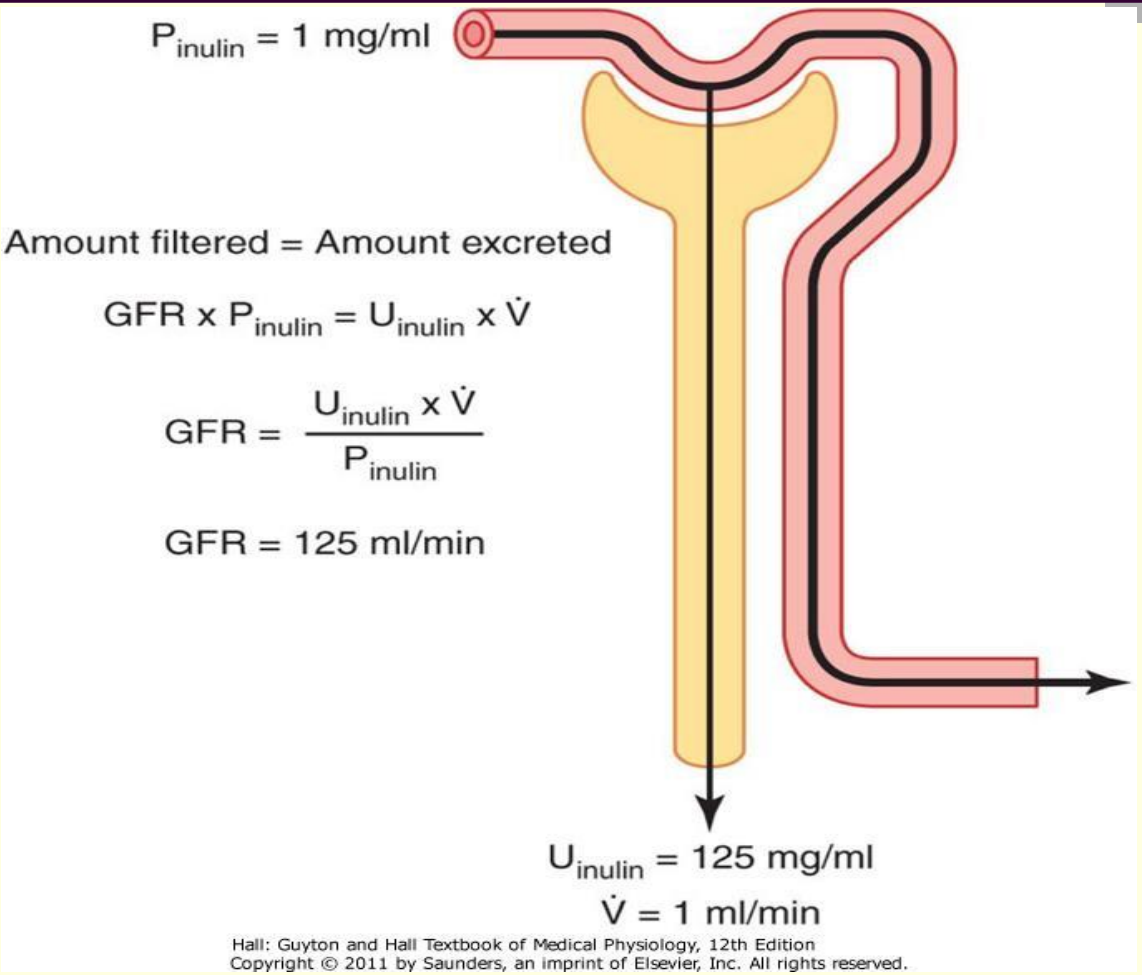
Inulin

A plant product that is filtered but not reabsorbed or secreted

Used to determine clearance rate and therefore nephron function



Renal Clearance



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