Renal system

PHYSIOLOGY

Very important

Extra information

References :

- GUYTON AND HALL 12th edition
- LINDA 5th edition

* Guyton corners, anything that is colored with grey is EXTRA explanation

Renal functions & glomerular filtration

Objectives :

- Enumerate general functions of the kidney
- Identify and describe that the nephron is the structural and function Unit of the kidney
- Explain glomerular filtration membrane & filtration forces
- Describe mechanism of filtration & composition of the glomerular filtrate
- Calculate the net filtration pressure using parameters of Starling forces

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What are the function of the kidney ?

- The kidneys serve many important homeostatic functions, including the following :
  - Regulation of water and electrolyte balances (K , Na , Cl , …)
  - Regulation of body fluid osmolality and electrolyte concentrations.
  - Excretion of metabolic waste products and foreign chemicals (**UREA** ' from the metabolism of amino acids ' . **CREATININE** from muscle creatine ' , **URIC ACID** ' from nucleic acids ')
  - Regulation of arterial blood pressure (RAS , excretion of excess salt and water)
  - Regulation of acid-base balance. (along with lung).
  - Detoxification and excretion of drug.
  - Synthesizing function :
    - Active form of vit. D (D3) = 1,25 dihydroxycholicalciferol.
    - Erythropoietin production.
    - Renin formation
    - Gluconeogenesis (synthesis of glucose from amino acid during prolonged fasting)

- Creatinine is the more specific than urea in diagnosing renal diseases. **Why**? Because unlike creatinine, urea is affected by the diet (E.g. urea is increased when protein consumption is increased).
- Secretion is excretion **within** the body, excretion is excreting a substance out of the body.
- People with renal failure have deficiency in vitamin D, leading to osteoporosis.
- Juxtamedullary cells secrete renin.

EXTRA

Chapter 26 – page 304

- **Guyton corner :'** remember from CVS block '

- Regulation of arterial blood pressure : the kidneys play a dominant role in long-term regulation of arterial pressure by excreting variable amounts of sodium and water. The kidneys also contribute to short-term arterial pressure regulation by secreting hormones and vasoactive factors or substances (e.g., renin) that lead to the formation of vasoactive products (e.g., angiotensin II).

- **Guyton corner : '** remember from Foundation block '

- **Regulation of Erythrocyte Production :**

The kidneys secrete erythropoietin, which stimulates the production of blood cells by hematopoietic stem cells in the bone marrow. One important stimulus for erythropoietin secretion by the kidneys is hypoxia. The kidneys normally account for almost all the erythropoietin secreted into the circulation. In people with severe kidney disease or who have had their kidneys removed and have been placed on hemodialysis, severe anemia develops as a result of decreased erythropoietin production.

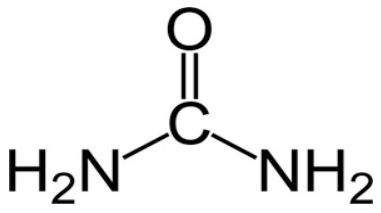
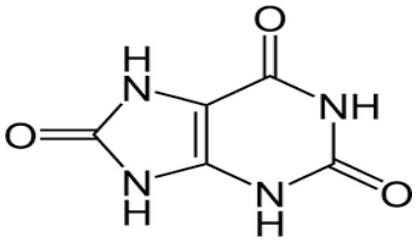
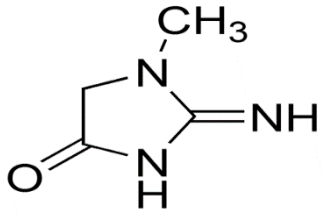
- **Guyton corner : '** remember from MSK block '

- **Glucose synthesis :**

The kidneys' capacity to add glucose to the blood during prolonged periods of fasting **rivals** that of the liver.

Nitrogenous wastes

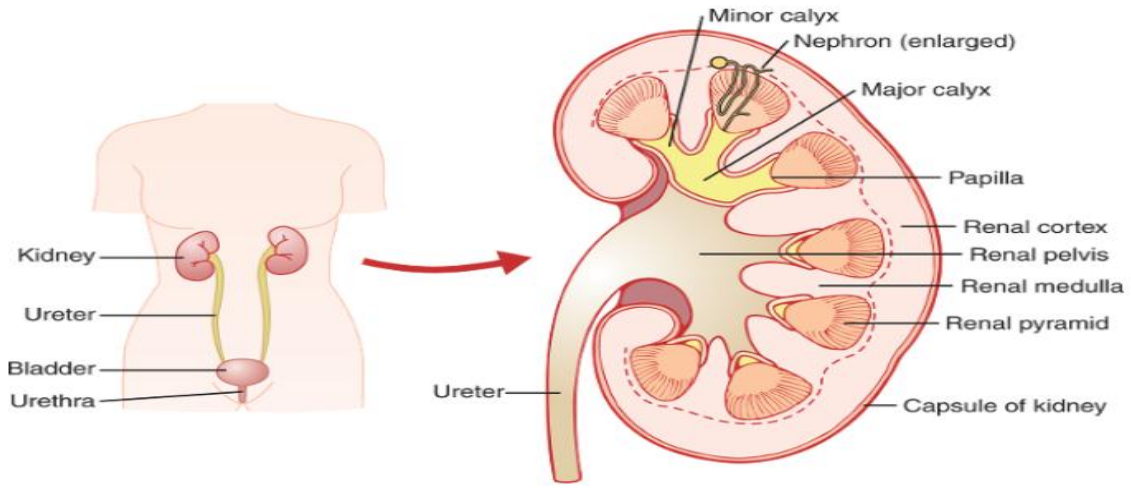
- **UREA** : Proteins → amino acid → NH2 removed → forms ammonia , **liver** converts to urea.

Nitrogenous wastes		
Urea	**Uric acid**	**Creatinine**
		

Physiology and anatomy of kidneys

*For better understanding, you should study **anatomy of kidney** before these few slides.*

- Each kidney of the adult human weight about 150 gram and is about the size of clenched fist.



- **Guyton corner :** (page 304)

- General Organization of the Kidneys and Urinary Tract

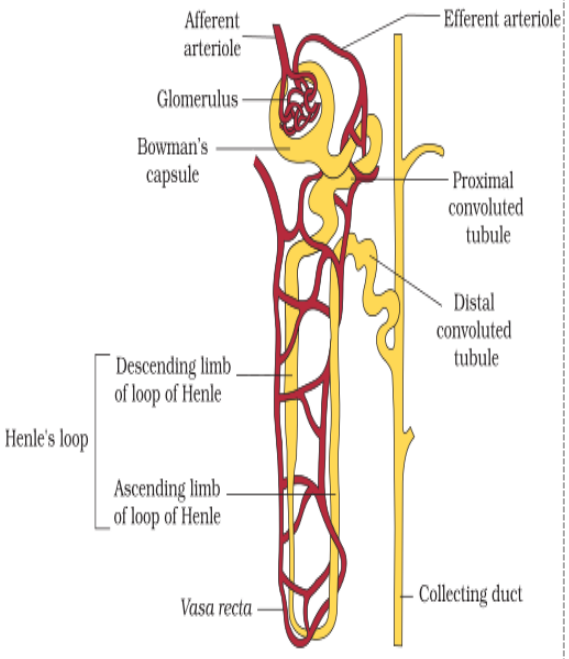
The medial side of each kidney contains an indented region called the hilum through which pass the renal artery and vein, lymphatics, nerve supply, and ureter, which carries the final urine from the kidney to the bladder, where it is stored until emptied. The kidney is surrounded by a tough, fibrous capsule that protects its delicate inner structures.

The functional unit of the kidney

- **Nephron** : is the functional and structural unit of the kidney.
- Each kidney in the human body contains about 800,000 to 1,000,000 *"one million"* nephrons , **each** capable of **urine formation**.

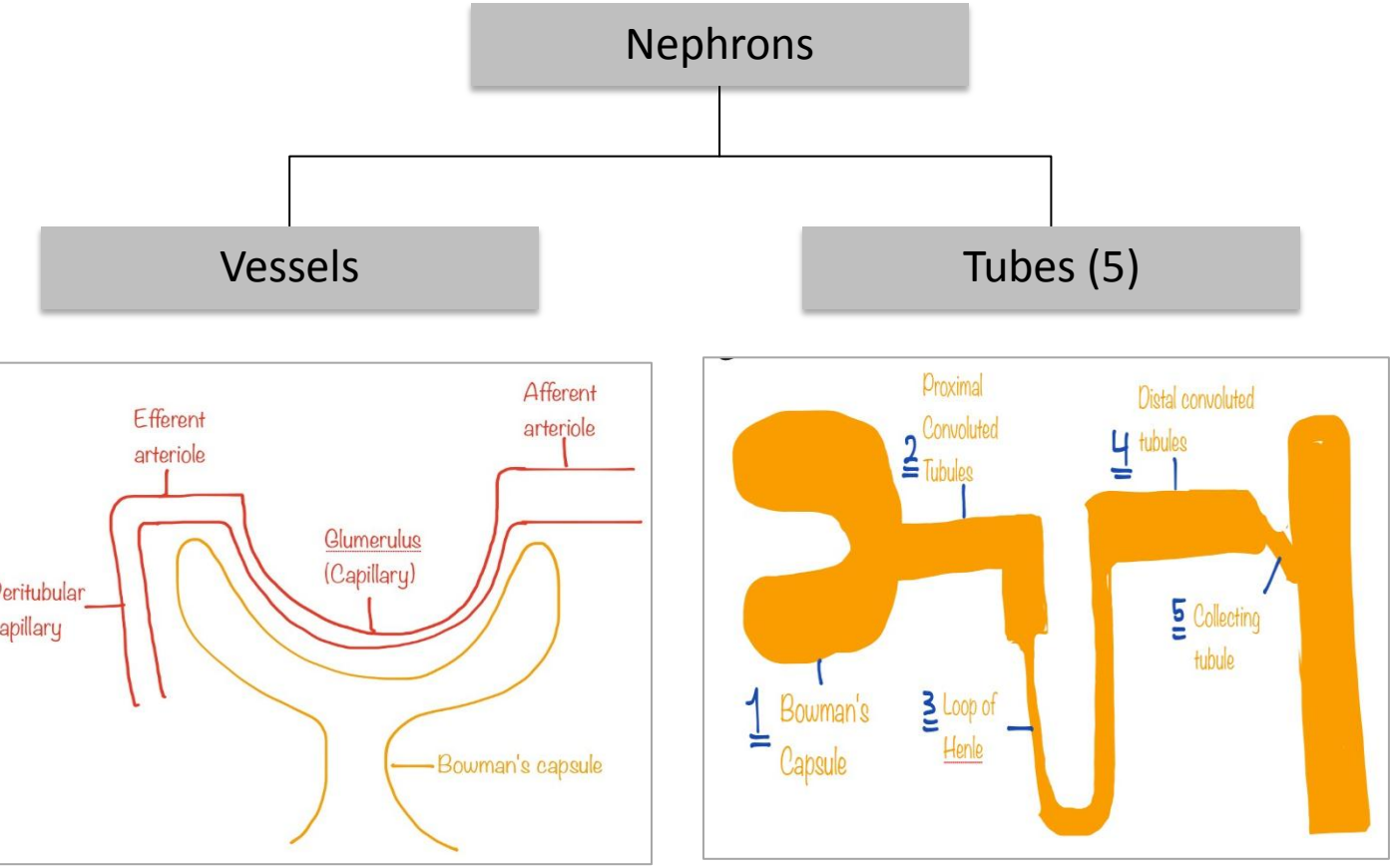
- **Guyton corner :** (page 305)
- **The Nephron Is the Functional Unit of the Kidney:**

The kidney cannot regenerate new nephrons. Therefore, with renal injury, disease, or normal aging, there is a gradual decrease in nephron number. After age 40, the number of functioning nephrons usually decreases about 10 percent every 10 years; thus, at age 80, many people have 40 percent fewer functioning nephrons than they did at age 40. This loss is not life threatening because adaptive changes in the remaining nephrons allow them to excrete the proper amounts of water, electrolytes, and waste products.



Extra

- Note that the pressures along the afferent arteriole, glumerulus and efferent arteriole are high. **Why**? To increase filtration.
- Note that the afferent arteriole is larger than the efferent arteriole.



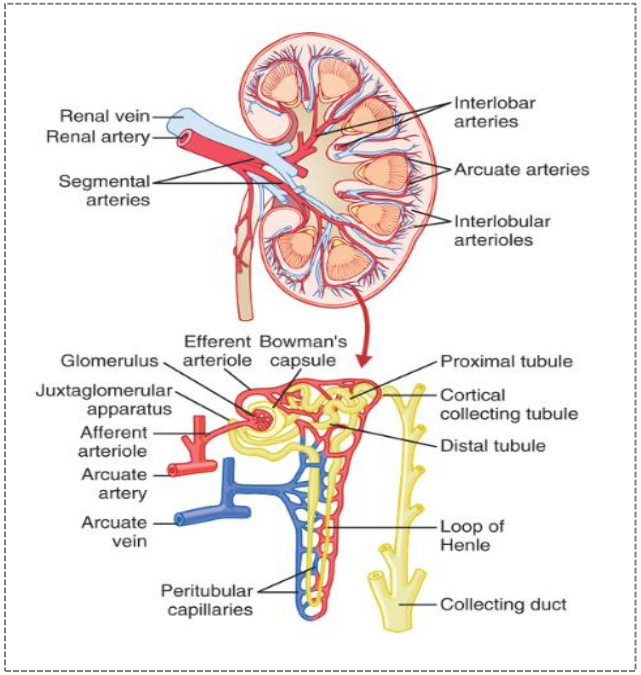
These figures are similar to those drawn by Dr.manan in the lecture. Thanks deema :)

Structure of nephron

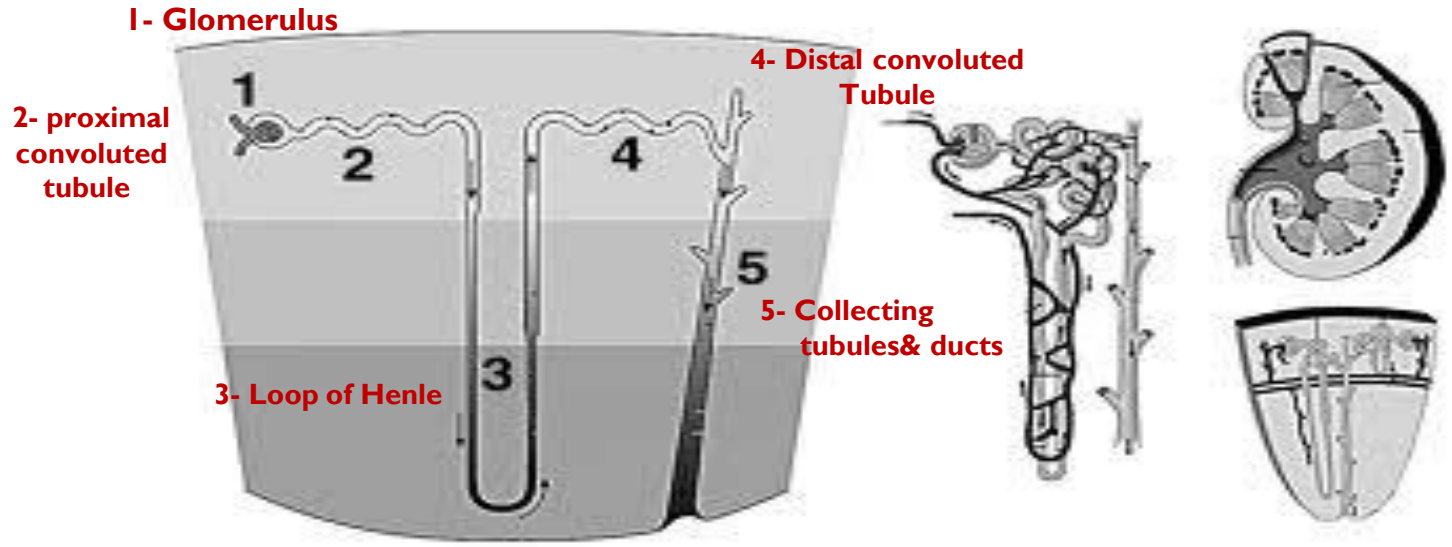
- **The Glomerulus**: capillary tuft in which large amount of fluid is filtered from blood.
- **Bowman's capsule**: around the Glomerulus and receives the filtrate.
- **Tubules**: in which filtered fluid eventually is converted into urine.
- Glomerular filtrate collects in capsular space , flow into renal tubule.

- **Guyton corner : (page 305)**
  - **The Nephron Is the Functional Unit of the Kidney:**

Each nephron contains (1) a tuft of glomerular capillaries called the glomerulus, through which large amounts of fluid are filtered from the blood, and (2) a long tubule in which the filtered fluid is converted into urine on its way to the pelvis of the kidney.



Structure of a Nephron

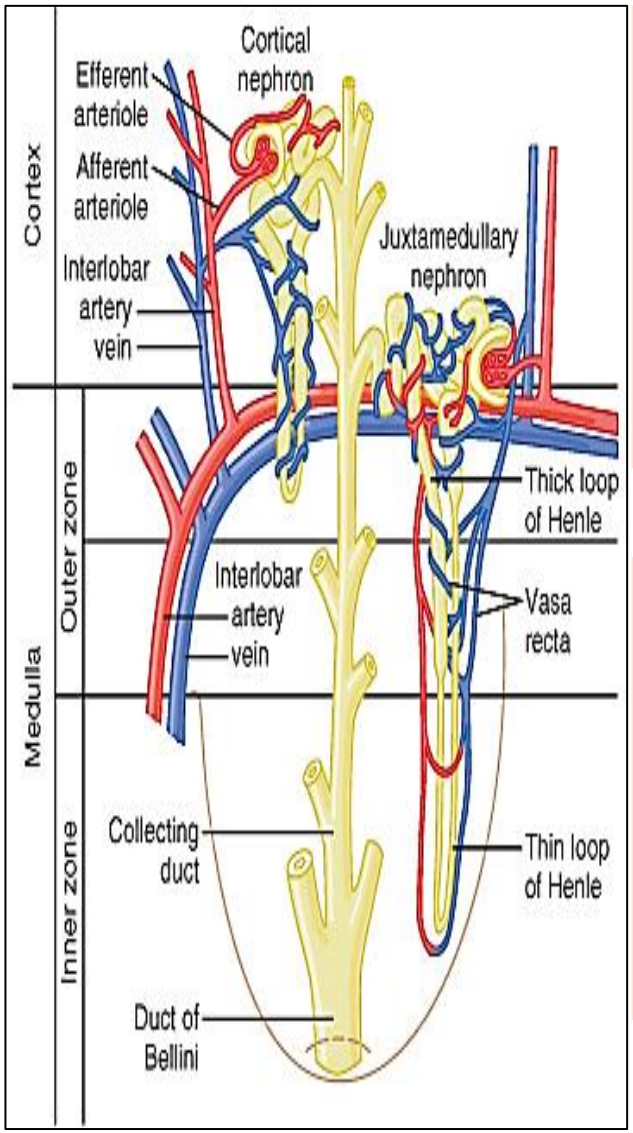


- **The renal tubule is divided into different sections with different structural and functional characteristics:**

  - Proximal tubules (in the cortex).
  - Loop of Henle.
  - Distal tubule (in the renal cortex).
  - Connecting tubule, cortical collecting, and the cortical collecting ducts, which run downward in the medulla and become: Medullary collecting ducts.

Structure of a Nephron, Cont..

Types of nephrons	
Cortical nephrons: (85%)	**Juxtamedullary nephrons: (15%)**
-Their glomeruli in the outer portion of cortex and have short loops of Henle -Peritubular capillaries	-Have long loops extended into the medulla -Vasa recta -Maintain salt gradient, helps conserve water



Originates in outer 2/3 of cortex.

Originates in inner 1/3 of cortex.

- **1-2 %** Blood Flows Through Juxtamedullary Nephrons

- Juxtamedullary arterioles have Vasa Recta instead of peritubular capillaries.
- Juxtamedullary nephrons are counter current in structure, allowing more water reabsorption.
- You'd expect camels to have abundant Juxtamedullary arterioles (For more water reabsorption).

Structure of a Nephron, Cont..

- **Guyton corner :**

Each nephron has some differences from the others, depending on how deep the nephron lies within the kidney mass. Those nephrons that have glomeruli located in the outer cortex are called cortical nephrons; they have short loops of Henle that penetrate only a short distance into the medulla About 20 to 30 percent of the nephrons have glomeruli that lie deep in the renal cortex near the medulla and are called *juxtamedullary nephrons.* These nephrons have long loops of Henle that dip deeply into the medulla, in some cases all the way to the tips of the renal papillae.

The vascular structures supplying the juxtamedullary nephrons also differ from those supplying the cortical nephrons. For the cortical nephrons, the entire tubular system is surrounded by an extensive network of peritubular capillaries. For the juxtamedullary nephrons, long efferent arterioles extend from the glomeruli down into the outer medulla and then divide into specialized peritubular capillaries called vasa recta that extend downward into the medulla, lying side by side with the loops of Henle. Like the loops of Henle, the vasa recta return toward the cortex and empty into the cortical veins. This specialized network of capillaries in the medulla plays an essential role in the formation of a concentrated urine

- **Linda corner:**

Bowman's space is continuous with the first portion of the nephron. Blood is ultra filtered across the glomerular capillaries into Bowman's space, which is the first step in urine formation. The remainder of the nephron is a tubular structure lined with epithelial cells, which serve the functions of reabsorption and secretion. The nephron or renal tubule comprises the following segments (beginning with Bowman's space): the proximal convoluted tubule, the proximal straight tubule, the loop of Henle (which contains a thin descending limb, a thin ascending limb, and a thick ascending limb), the distal convoluted tubule, and the collecting ducts. Each segment of the nephron is functionally distinct, and the epithelial cells lining each segment have a different ultrastructure. For example, the cells of the proximal convoluted tubule are unique in having an extensive development of microvilli, called a brush border, on their luminal side. The brush border provides a large surface area for the major reabsorptive function of the proximal convoluted tubule. There are two types of nephrons, superficial cortical nephrons and juxtamedullary nephrons, which are distinguished by the location of their glomeruli. The superficial cortical nephrons have their glomeruli in the outer cortex. These nephrons have relatively short loops of Henle, which descend only into the outer medulla. The juxtamedullary nephrons have their glomeruli near the corticomedullary border. The glomeruli of the juxtamedullary nephrons are larger than those of the superficial cortical nephrons and, accordingly, have higher glomerular filtration rates. The juxtamedullary nephrons are characterized by long loops of Henle that descend deep into the inner medulla and papilla and are essential for the concentration of urine.

Renal Blood Vessels

- **DELIVERS BLOOD INTO THE GLOMERULI**

AFFERENT ARTERIOLE

GLOMERULI

- **CAPILLARY NETWORK THAT PRODUCES FILTRATE THAT ENTERS THE URINARY TUBULES.**

- **DELIVERS BLOOD FROM GLOMERULI TO PERITUBULAR CAPILLARIES.**

EFFERENT ARTERIOLE

PERITUBULAR CAPILLARIES

- **VASA RECTA**

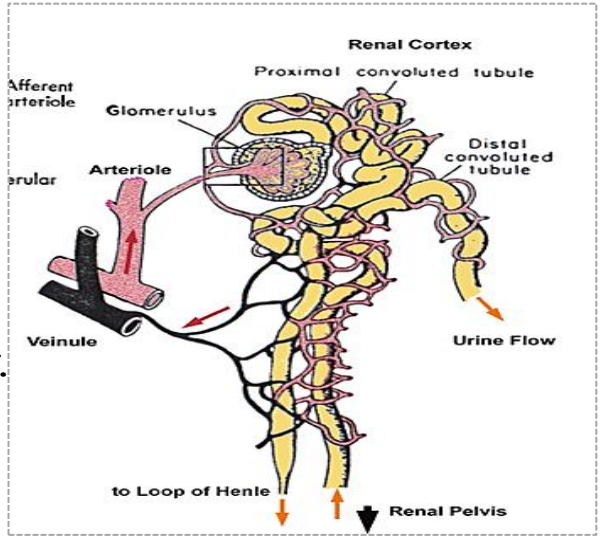
- Although blood circulation in the kidneys passes through two capillary beds (Glomeruli and peritubular capillaries), it is not considered a portal circulation. **Why**? Because glomeruli contain arterial capillaries only (There's no venous blood).
- In the blood supply of the kidney, the straight arterioles of kidney (or vasa recta renis) are a series of straight capillaries in the medulla (Latin: vasa, "vessels"; recta, "straight").

- **Linda corner:**

Blood enters each kidney via a renal artery, which branches into interlobar arteries, arcuate arteries, and then cortical radial arteries. The smallest arteries sub- divide into the first set of arterioles, the afferent arterioles. The afferent arterioles deliver blood to the first capillary network, the glomerular capillaries, across which ultrafiltration occurs. Blood leaves the glomerular capillaries via a second set of arterioles, the efferent arterioles, which deliver blood to a second capillary network, the peritubular capillaries. The peritubular capillaries surround the nephrons. Solutes and water are reabsorbed into the peritubular capillaries, and a few solutes are secreted from the peritubular capillaries. Blood from the peritubular capillaries flows into small veins and then into the renal vein. The blood supply of superficial cortical nephrons differs from that of juxtamedullary nephrons. In the superficial nephrons, peritubular capillaries branch off the efferent arterioles and deliver nutrients to the epithelial cells. These capillaries also serve as the blood supply for reabsorption and secretion. In the juxtamedullary nephrons, the peritubular capillaries have a specialization called the vasa recta, which are long, hairpin-shaped blood vessels that follow the same course as the loop of Henle. The vasa recta serve as osmotic exchangers for the production of concentrated urine.

Renal blood flow

- Renal blood flow to the kidney represents 20% of cardiac output.
- The blood flows to each kidney through a renal artery.
- Features of renal circulation:
  - High blood flow rate (**1200** ml/min). "Range: 1018-1200"
  - Presence of two capillary beds: ***glomerular*** *and* ***peritubular***.
  - Efferent and afferent arterioles are major sites of renal resistance.



- **Guyton corner :**

-In an average 70-kilogram man, the combined blood flow percent of the cardiac output. Considering that the two kidneys constitute only about 0.4 percent of the total body weight, one can readily see that they receive an extremely high blood flow compared with other organs. As with other tissues, blood flow supplies the kidneys with nutrients and removes waste products. However, the high flow to the kidneys greatly exceeds this need.
-the kidneys normally consume oxygen at twice the rate of the brain but have almost seven times the blood flow of the brain. Thus, the oxygen delivered to the kidneys far exceeds their metabolic needs, and the arterial-venous extraction of oxygen is relatively low compared with that of most other tissues.
-Most of the renal vascular resistance resides in three major segments: interlobular arteries, afferent arterioles, controlled by the sympathetic nervous system, various hormones, and local internal renal control mechanisms. An increase in the resistance of any of the vascular segments of the kidneys tends to reduce the renal blood flow, whereas a decrease in vascular resistance increases renal blood flow if renal artery and renal vein pressures remain constant.
-The outer part of the kidney, the renal cortex, receives most of the kidney's blood flow. Blood flow in the renal medulla accounts for only 1 to 2 percent of the total renal blood flow. Flow to the renal medulla is supplied by a specialized portion of the peritubular capillary system called the *vasa recta.*

- **Linda corner:**

As with blood flow in any organ, RBF (Q) is directly proportional to the **pressure gradient** (ΔP) between the renal artery and the renal vein, and it is inversely proportional to the **resistance** (R) of the renal vasculature. (Recall that Q = ΔP/R. Recall, also, that resistance is provided mainly by the arterioles.) The kidneys are unusual, however, in that there are *two sets of arterioles,* the afferent and the efferent. The major mechanism for changing blood flow is by changing arteriolar resistance. In the kidney, this can be accomplished by changing afferent arteriolar resistance and/ or efferent arteriolar resistance.

Urine formation

- The primary function of the kidney is to 'clear' unneeded substances from the blood to be excreted in urine.

- **Steps of urine formation (basic renal processes):**

  1- Glomerular filtration:

  Filtration of fluid from glomerular capillaries <u>into</u> the renal tubules.

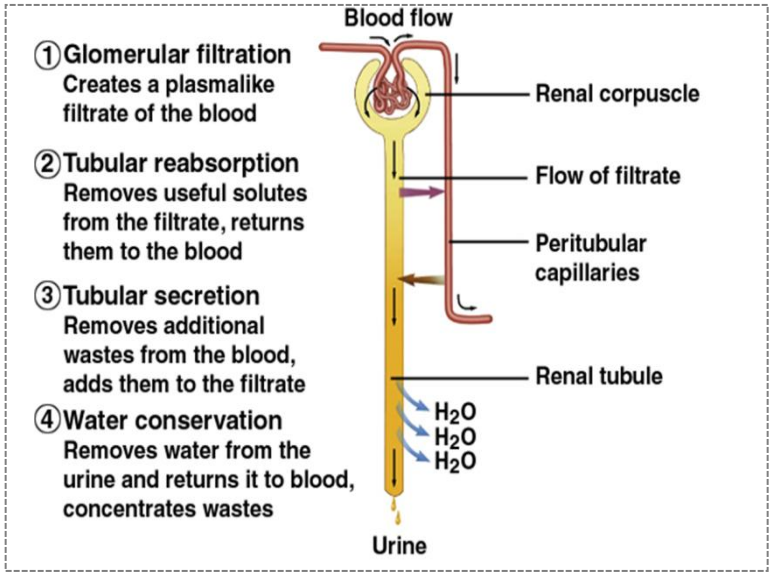
  2- Tubular reabsorption

  3- Tubular secretion.

  4- Excretion.

Urinary excretion rate = Filtration rate - reabsorption + secretion

- More filtration, more urine production.
- More reabsorption, less urine production.
- Note that only plasma (excluding plasma proteins) is filtered into the capsule.
- Plasma proteins are not filtered. Why?
  1. Because they're negatively charged, they repel the negative basement membrane of the glumerular barrier.
  2. Because they're large in size.
- Filtrate = Plasma – Plasma proteins

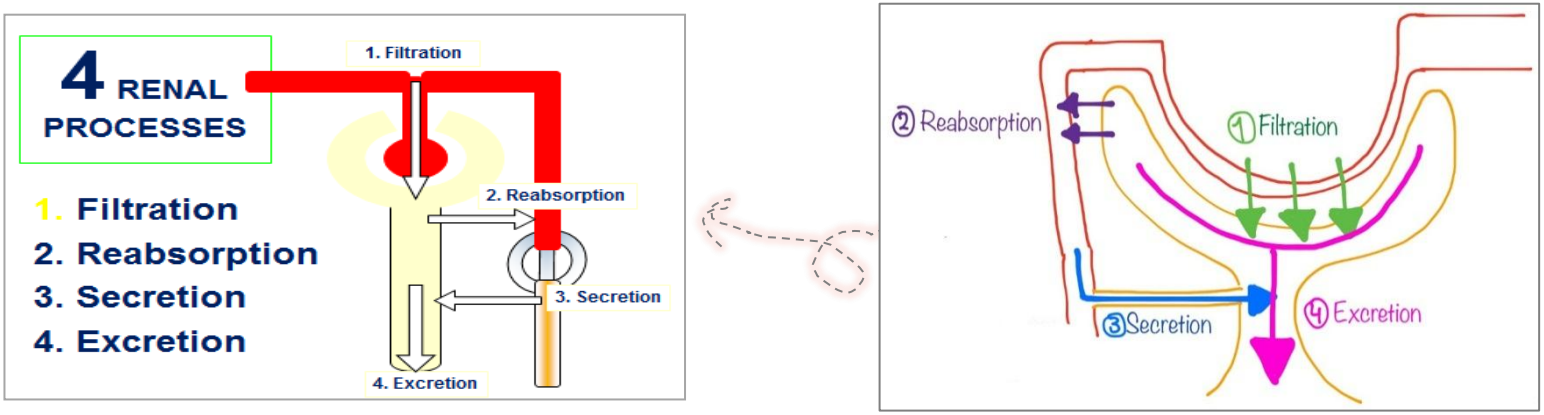


Extra

- **Guyton corner :**

The rates at which different substances are excreted in the urine represent the sum of three renal processes, (1) glomerular filtration, (2) reabsorption of substances from the renal tubules into the blood, and (3) secretion of substances from the blood into the renal tubules. Expressed mathematically , Urinary Excretion Rate = Filtration Rate – Reabsorption Rate + Secretion Rate Urine formation begins when a large amount of fluid that is virtually free of protein is filtered from the glomerular capillaries into Bowman's capsule. Most substances in the plasma, except for proteins, are freely filtered, so their concentration in the glomerular filtrate in Bowman's capsule is almost the same as in the plasma. As filtered fluid leaves Bowman's capsule and passes through the tubules, it is modified by reabsorption of water and specific solutes back into the blood or by secretion of other substances from the peritubular capillaries into the tubules .

In general, tubular reabsorption is quantitatively more important than tubular secretion in the formation of urine, but secretion plays an important role in determining the amounts of potassium and hydrogen ions and a few other substances that are excreted in the urine. Most substances that must be cleared from the blood, especially the end products of metabolism such as urea, creatinine, uric acid, and urates, are poorly reabsorbed and are therefore excreted in large amounts in the urine. Certain foreign substances and drugs are also poorly reabsorbed but, in addition, are secreted from the blood into the tubules, so their excretion rates are high. Conversely, electrolytes, such as sodium ions, chloride ions, and bicarbonate ions, are highly reabsorbed, so only small amounts appear in the urine. Certain nutritional substances, such as amino acids and glucose, are completely reabsorbed from the tubules and do not appear in the urine even though large amounts are filtered by the glomerular capillaries.



This figure is similar to that drawn by Dr.manan in the lecture. Thanks deema :)

Glomerular filtration rate (GFR)

- The **FIRST** step in urine formation is glomerular filtration.
  - It is the filtration of fluid from the glomerular capillaries into the renal tubules.
  - It contains all substances present in plasma except proteins.
  - GFR is normally 125 ml/min = 20% renal plasma flow.

In order to answer the following questions, please continue reading the lecture….

-What is glomerular membrane?

-What controls passage of molecules through this membrane?

-What are the forces responsible for passage of fluid (filtrate) through this membrane?

Extra

- Glumerular membrane is made up of:
  - Endothelial cells
  - Basement membrane
  - Podocytes (visceral layer of the capsule)
- Passage of molecules through the membrane depends on:
  1. Molecular weight
  2. Electrical charge

- Gluemerular filtration rate depends on:

1. Net Filtration pressure: (Which depends on)

A. Hydrostatic pressure of the capillary:

- Arterial blood pressure
- Afferent
  - Vasoconstriction (sympathetic stimulation) ➛ Reduced hydrostatic capillary pressure ➛ Less GFR
  - Vasodilation (parasympathetic stimulation) ➛ More hydrostatic capillary pressure ➛ More GFR
- Efferent
  - Vasoconstriction (Angiotensin II or **strong** sympthetic stimulation) ➛ More hydrostatic capillary pressure ➛ More GFR
  - Vasodilation ➛ Less hydrostatic pressure ➛ Less GFR
  - Severe vasoconstriction ➛ More hydrostatic capillary pressure and **even more** oncotic capillary pressure ➛ Less GFR

B. Oncotic pressure of the capillary:

C. Hydrostatic pressure of the capsule (affected by obstruction):

- Tumors (e.g. prostatic cancer)
- Prostatic hyperplasia/hypertrophy

2 . Capillary filtration coefficient: (Which depends on)

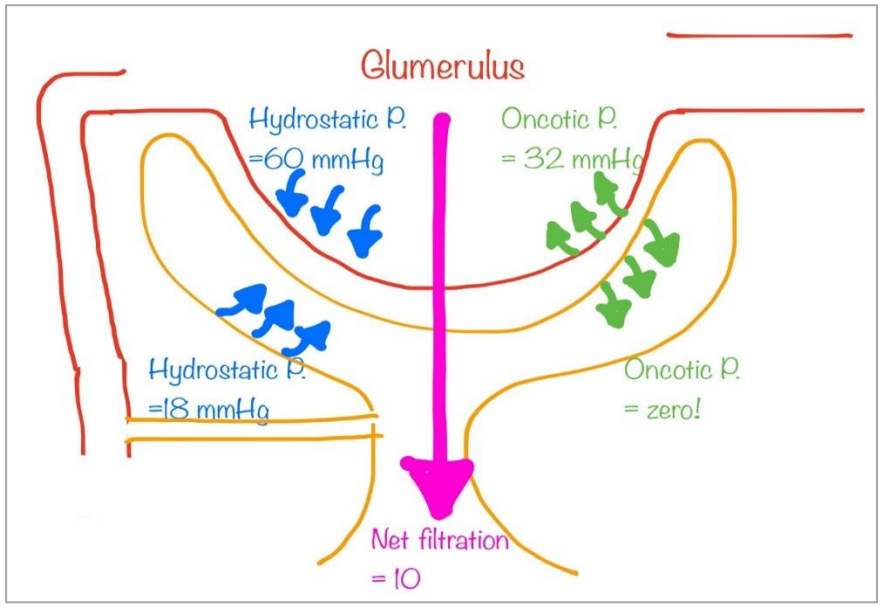
A. Filtration barrier permeability

B. Surface area of the filtration barrier

Extra

- Note that, as the afferent arteriole constricts in response to sympathetic stimulation, prostaglandins are released to cause vasodilation to prevent further damage and renal failure. This explains why NSAIDs should not be given at this point.

- Why is the oncotic pressure of the capsule zero? Because usually, plasma proteins do not cross the filtration barrier.
- Early in diabetes, GFR is high. It drops later due to membrane thickening.
- Diabetes and hypertension thicken the membrane, reducing permeability and filtration coefficient.



This figure is similar to that drawn by Dr.manan in the lecture. Thanks deema :)

Glomerular membrane

- Blood in the glomerulus is separated from the fluid in the Bowman's space by a filtration barrier (glomerular membrane) consisting of three layers:

1- Single layer of capillary **endothelium**.

2- Single epithelial lining of Bowman's capsule **(Podocytes)**

During filtration the fluid moves between their foot processes (pseudopodia).

3- **Basement membrane** between endothelium and epithelium.

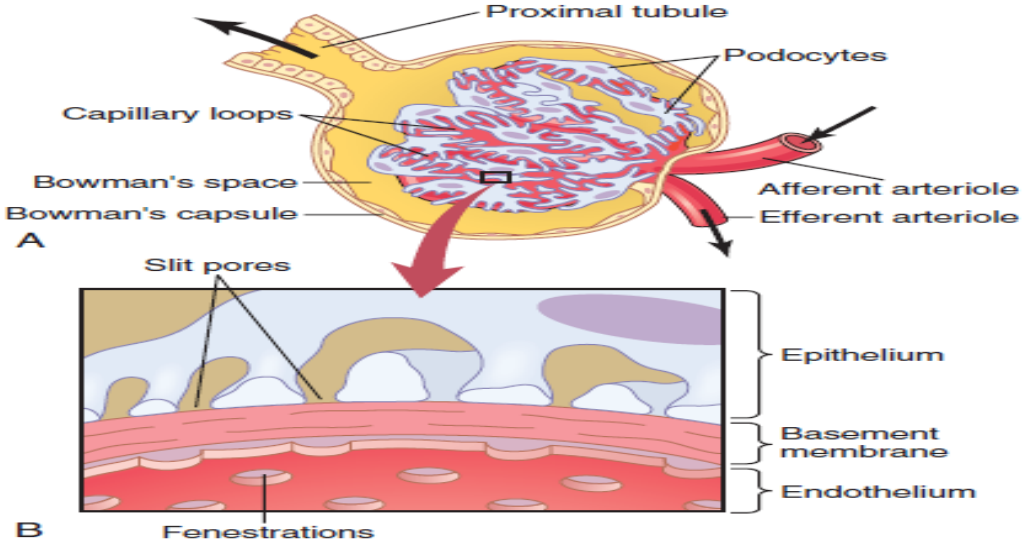
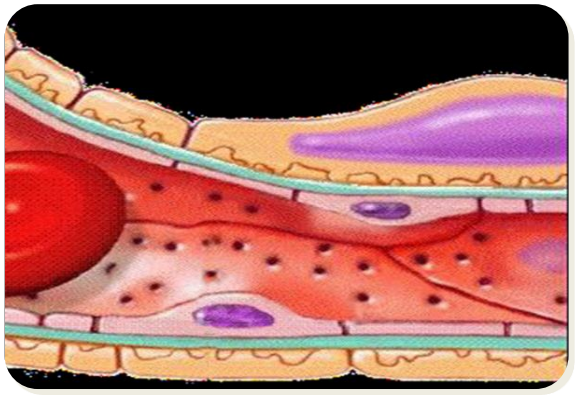
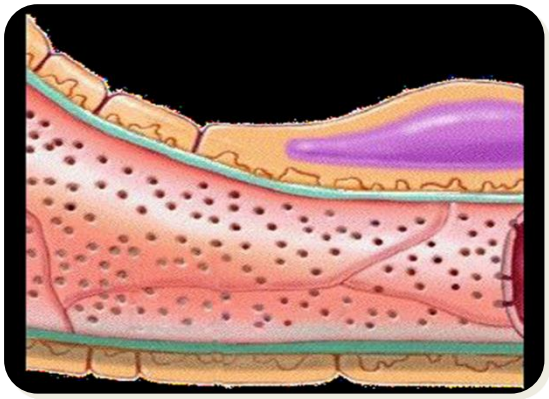


Figure 27-2. A, Basic ultrastructure of the glomerular capillaries. **B,** Cross section of the glomerular capillary membrane and its major components: capillary endothelium, basement membrane, and epithelium (podocytes).

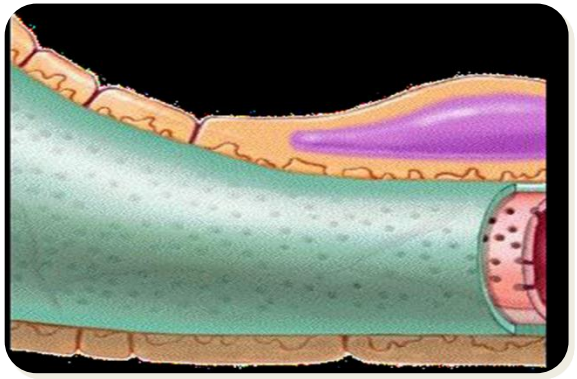
Glomerular membrane



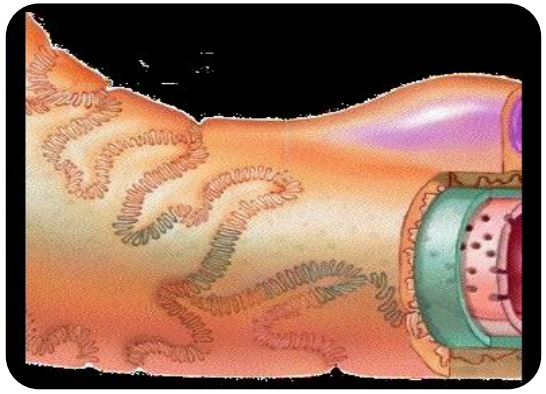
Capillary endothelium
Here we see a glomerular capillary in longitudinal section



Capillary endothelium



Basement membrane



Podocytes
(cell body with nucleus) ,
Filtration slits

EXTRA

- **Guyton corner :**

The glomerular capillary membrane is similar to that of other capillaries, except that it has three (instead of the usual two) major layers: (1) the *endothelium* of the capillary, (2) a *basement membrane,* and (3) a layer of *epithelialcells (podocytes)* surrounding the outer surface of the capillary basement membrane Together, these layers make up the filtration barrier, which, despite the three layers, filters several hundred times as much water and solutes as the usual capillary membrane. Even with this high rate of filtration, the glomerular capillary membrane normally prevents filtration of plasma proteins.

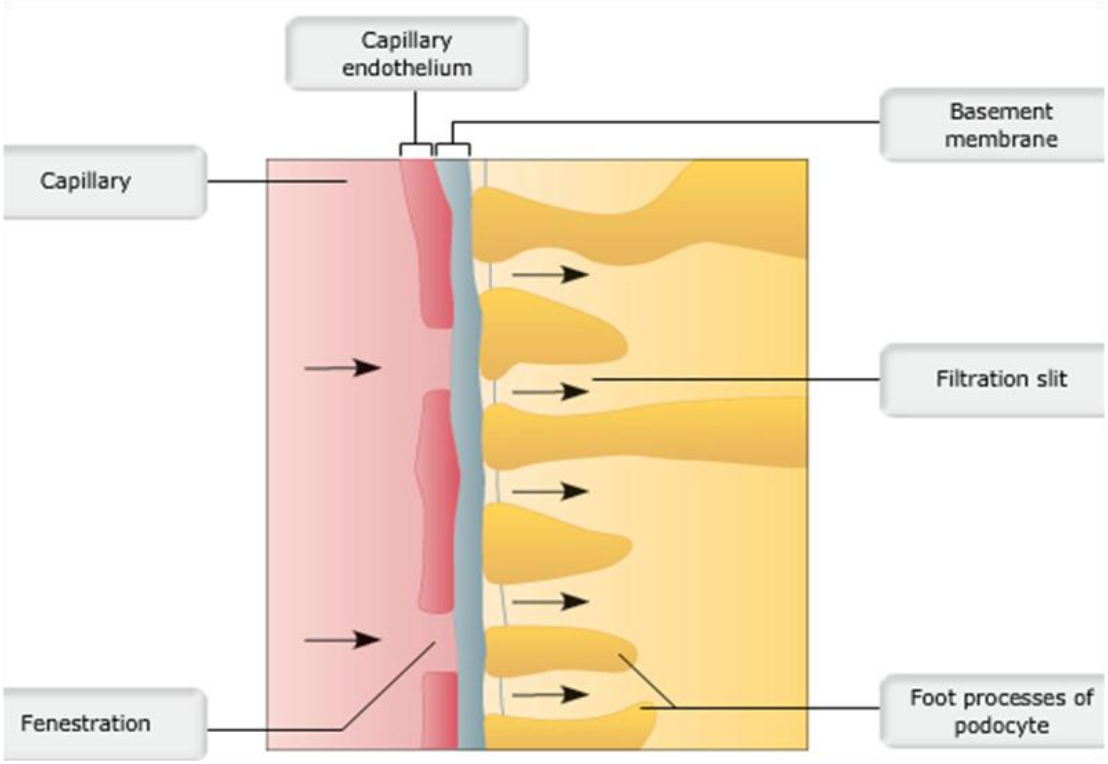
The high filtration rate across the glomerular capillary membrane is due partly to its special characteristics. The capillary *endothelium* is perforated by thousands of small holes called *fenestrae,* similar to the fenestrated capillaries found in the liver. Although the fenestrations are relatively large, endothelial cells are richly endowed
with fixed negative charges that hinder the passage of plasma proteins.

Surrounding the endothelium is the *basement membrane,* which consists of a meshwork of collagen and proteoglycan fibrillae that have large spaces through which large amounts of water and small solutes can filter. The basement membrane effectively prevents filtration of plasma proteins, in part because of strong negative electrical charges associated with the proteoglycans.

The final part of the glomerular membrane is a layer of epithelial cells that line the outer surface of the glomerulus. These cells are not continuous but have long footlike processes (podocytes) that encircle the outer surface of the capillaries The foot processes are separated by gaps called *slit pores* through which the glomerular filtrate moves. The epithelial cells, which also have negative charges, provide additional restriction to filtration of plasma proteins. Thus, all layers of the glomerular capillary wall provide a barrier to filtration of plasma proteins.

FILTRATION MEMBRANE

- Endothelium
- Endothelium of Glomerular Capillaries
- Basement Membrane
- Podocyte



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(1) the endothelium of the capillary,
(2) a basement membrane, and (3) a layer of epithelial cells (podocytes) surrounding the outer surface of the capillary basement membrane.
Together, these layers make up the filtration barrier, which, despite the three layers, filters several hundred times as much water and solutes as the usual capillary membrane. Even with this high rate of filtration, the glomerular capillary membrane normally prevents filtration of plasma proteins. The high filtration rate across the glomerular capillary membrane is due partly to its special characteristics. The capillary *endothelium* is perforated by thousands of small holes called *fenestrae,* similar to the fenestrated capillaries found in the liver, although smaller than the fenestrae of the liver. Although the fenestrations are relatively large, endothelial cell proteins are richly endowed with fixed negative charges that hinder the passage of plasma proteins.
Surrounding the endothelium is the *basement membrane,* which consists of a meshwork of collagen and proteoglycan fibrillae that have large spaces through which large amounts of water and small solutes can filter. The basement membrane effectively prevents filtration of plasma proteins, in part because of strong negative electrical charges associated with the proteoglycans. The final part of the glomerular membrane is a layer of epithelial cells that line the outer surface of the glomerulus. These cells are not continuous but have long footlike processes (podocytes) that encircle the outer surface of the capillaries .The foot processes are separated by gaps called *slit pores* through which the glomerular filtrate moves. The epithelial cells, which also have negative charges, provide additional restriction to filtration of plasma proteins. Thus, all layers of the glomerular capillary wall provide a barrier to filtration of plasma proteins.

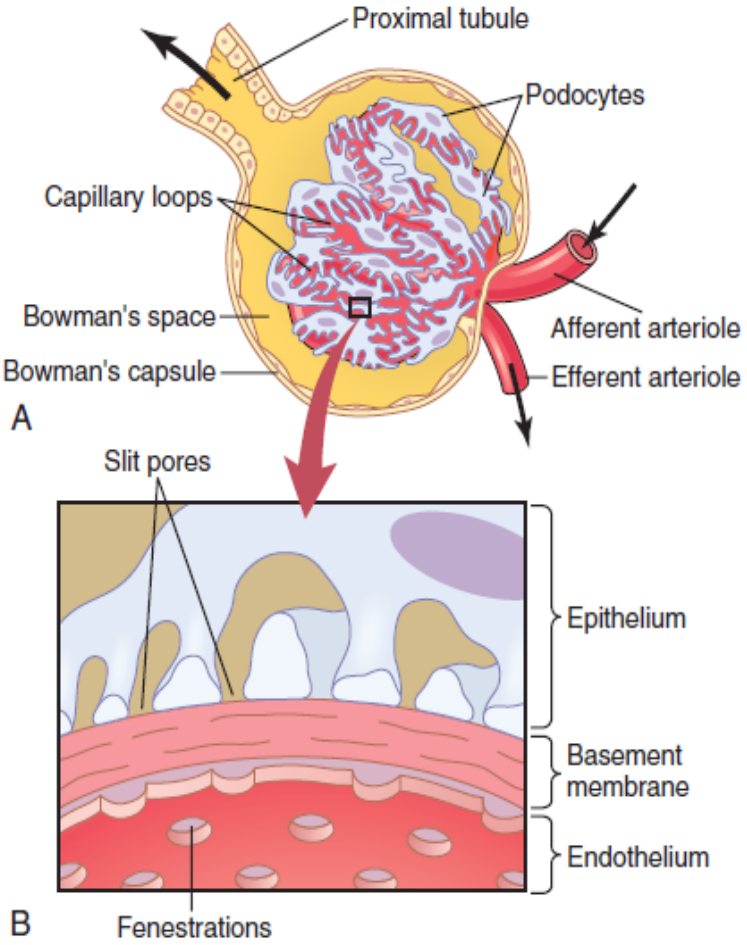


Figure 27-2. A, Basic ultrastructure of the glomerular capillaries. **B,** Cross section of the glomerular capillary membrane and its major components: capillary endothelium, basement membrane, and epithelium (podocytes).

Extra

- **Linda corner: Layers of the Glomerular Capillary**

ENDOTHELIUM

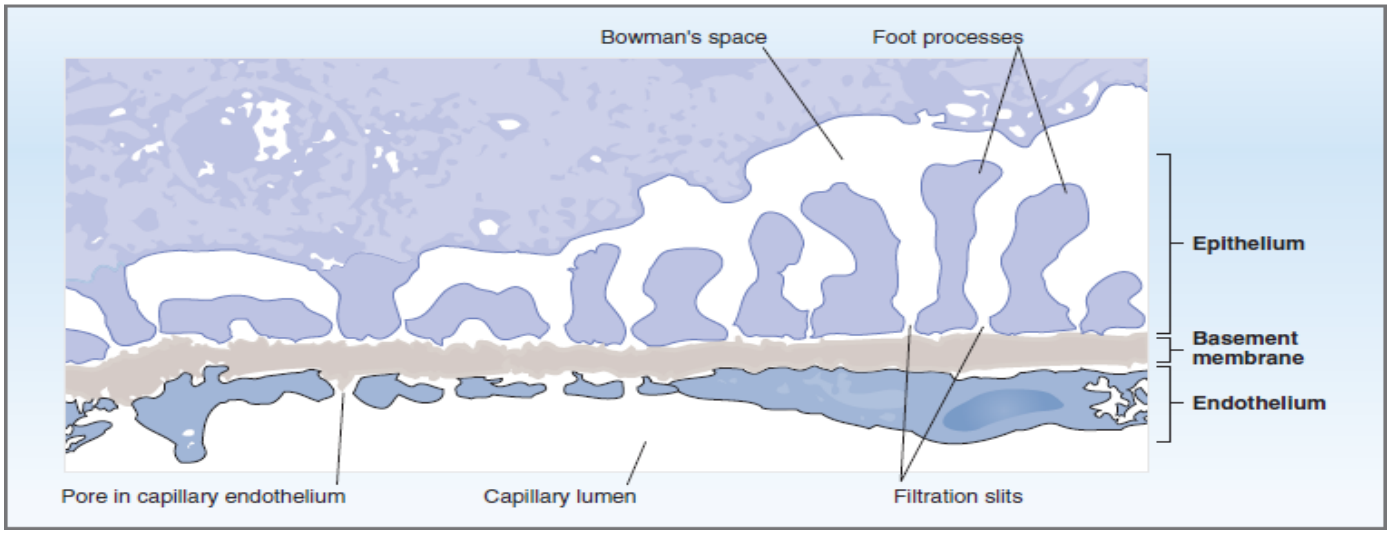
The endothelial cell layer has pores 70 to 100 nanometers (nm) in diameter. Because these pores are relatively large, fluid, dissolved solutes, and plasma proteins all are filtered across this layer of the glomerular capillary barrier. On the other hand, the pores are not so large that blood cells can be filtered.

BASEMENT MEMBRANE

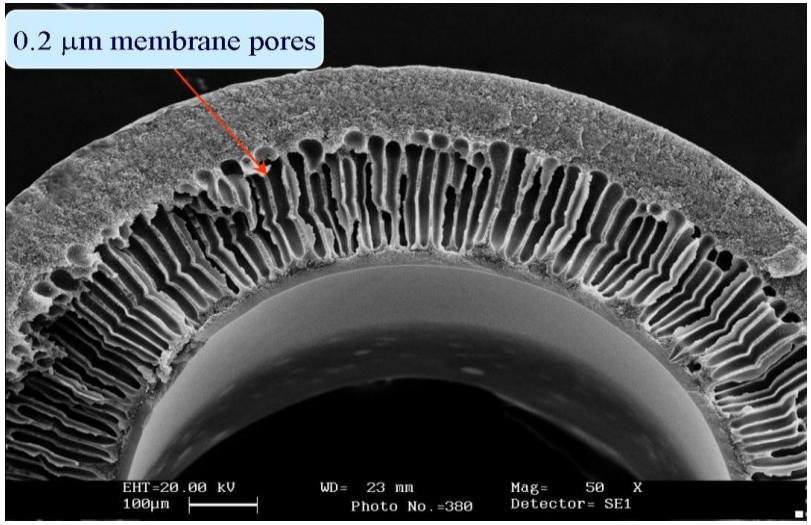
The basement membrane has three layers. The **lamina rara interna** is fused to the endothelium; the **lamina densa** is located in the middle of the basement membrane; and the **lamina rara externa** is fused to the epithelial cell layer. The multilayered basement membrane does not permit filtration of plasma proteins and, therefore, constitutes the most significant barrier of the glomerular capillary.

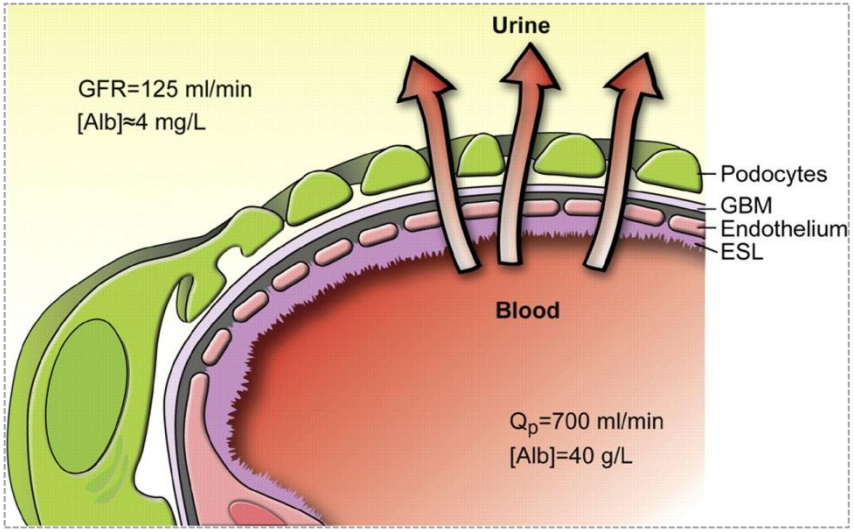
EPITHELIUM

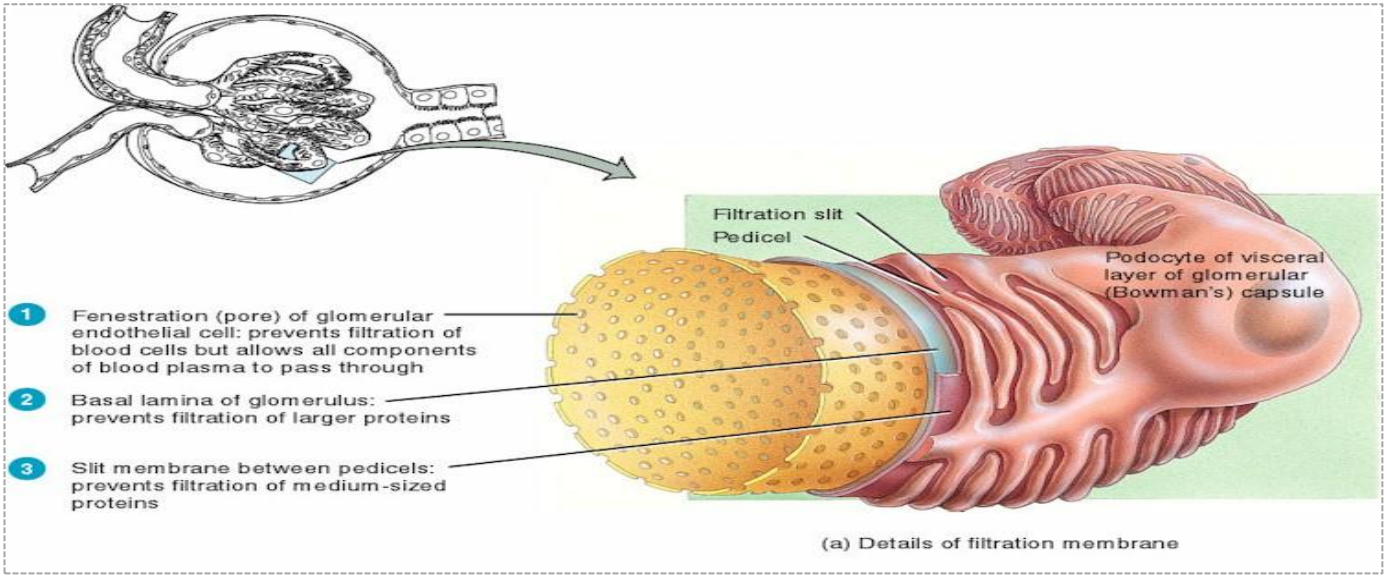
The epithelial cell layer consists of specialized cells called **podocytes,** which are attached to the basement membrane by **foot processes.** Between the foot processes are **filtration slits,** 25 to 60 nm in diameter, which are bridged by thin diaphragms. Because of the relatively small size of the filtration slits, the epithelial layer (in addition to the basement membrane)



Extra

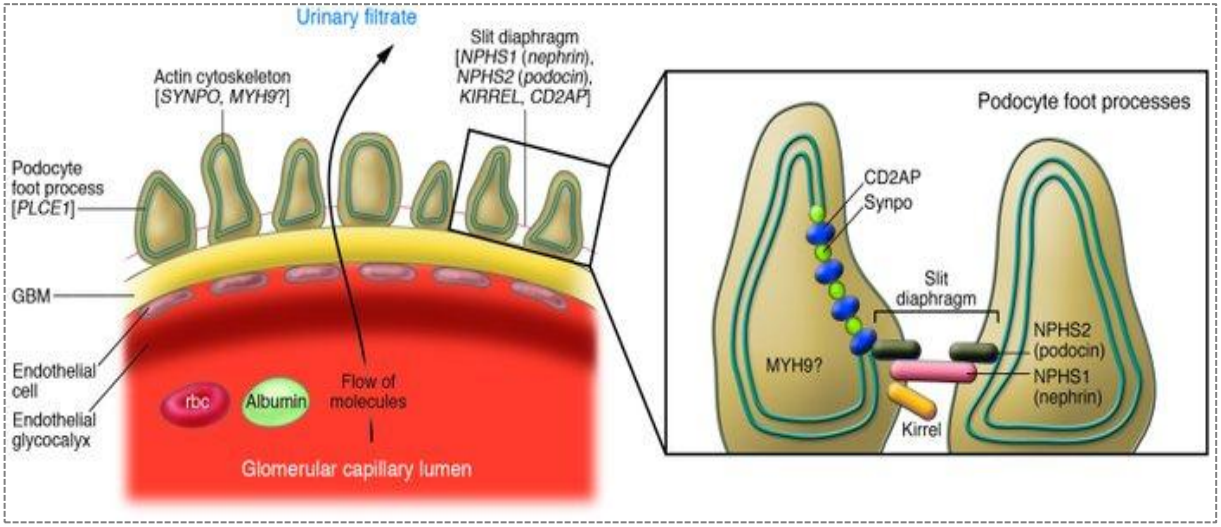

0.2 μm membrane pores
EHT=20.00 kV
100μm
WD= 23 mm
Photo No.=380
Mag= 50 X
Detector= SE1


Urine
GFR=125 ml/min
[Alb]≈4 mg/L
Podocytes
GBM
Endothelium
ESL
Blood
Q_p=700 ml/min
[Alb]=40 g/L


Filtration slit
Pedicel
Podocyte of visceral layer of glomerular (Bowman's) capsule
1 Fenestration (pore) of glomerular endothelial cell: prevents filtration of blood cells but allows all components of blood plasma to pass through
2 Basal lamina of glomerulus: prevents filtration of larger proteins
3 Slit membrane between pedicels: prevents filtration of medium-sized proteins
(a) Details of filtration membrane

Characteristics of glomerular membrane

- Allow passage of molecules up to 70,000 D
- **Albumin** does not normally pass as they are repelled by the negative charge of the glycoproteins material of basement membrane.
- **Blood cells** do not normally pass through the membrane.



- Albumin is exactly the size of the fenestrae (i.e. it's size allows it to be filtered) but it is negatively charged and thus repelled by the negative basement membrane.
- Certain renal diseases neutralize the negative charge of the basement membrane and eventually causing albuminuria.

Glomerular filtration rate (GFR)

The rate of production of filtrate from plasma (ml/min) = 20% of renal plasma flow
99% of filtrate **reabsorbed** and 1 to 2 L urine excreted

How does 180 L/day of our 5L blood is filtered? Because 99% of the filtrate is reabsorbed. Excreting only ~1-2 L in the urine.

GFR = K_f x Net Filtration Pressure

Kf = 12.5
The glomerular capillary filtration coefficient
It depends on permeability and surface area of filtration barrier

NFP = 10 mmHg
the net filtration pressure across the glomerular capillaries

GFR = 12.5 X 10 = 125 **ml/min** = 180 **L/day**

- **Linda corner:**

K_f, filtration coefficient, is the water permeability or hydraulic conductance of the glomerular capillary wall. The two factors that contribute to K_f are the water permeability per unit of surface area and the total surface area. K_f for glomerular capillaries is more than 100-fold that for systemic capillaries (e.g., skeletal muscle capillaries) because of the combination of a higher total surface area and a higher intrinsic water permeability of the barrier. The consequence of this extremely high K_f is that much more fluid is filtered from glomerular capillaries than from other capillaries (i.e., GFR is 180 L/day)

Forces controlling GFR :Starling's forces

- The net filtration pressure (NFP) is the **sum** of :

Hydrostatic pressure inside glomerular capillaries (PG) = **60** mmHg
Promotes filtration

Hydrostatic pressure in Bowman's capsule (PB) = **18** mmHg
Opposes filtration

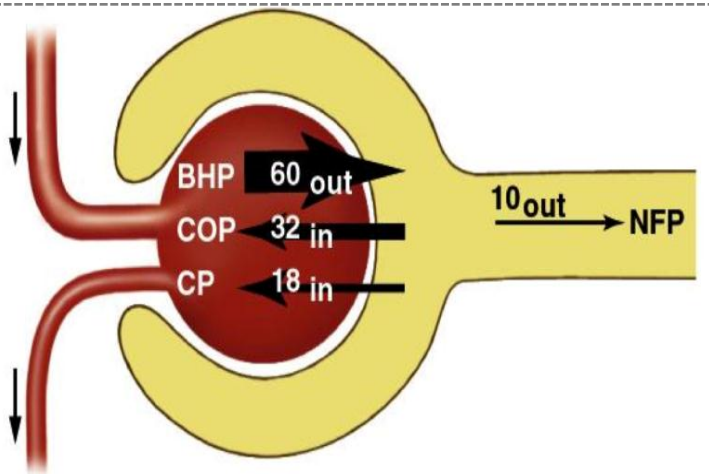
Colloid osmotic pressure of glomerular plasma proteins (Πg) = **32** mmHg
Opposes filtration

Colloid Osmotic Pressure of Bowman's proteins (Πb) = **0** mmHg
Promotes filtration

As we knew that filtration membrane doesn't allow proteins to pass therefore **bowman's space has NO proteins** which means oncotic pressure = 0 mmHg

So, NFP = 60 – 32 – 18 = +10 mmHg

Control of GFR



Blood hydrostatic pressure (BHP)	60 mmHg out
Colloid osmotic pressure (COP)	–32 mmHg in
Capsular pressure (CP)	–18 mmHg in
Net filtration pressure (NFP)	10 mmHg ou

$$GFR = K_f[(P_{GC} - P_{BS}) - \pi_{GC}]$$

where

GFR = Glomerular filtration rate (mL/min)

K_f = Hydraulic conductance (mL/min • mm Hg)

or

Filtration coefficient (mL/min • mm Hg)

P_{GC} = Hydrostatic pressure in glomerular capillary (mm Hg)

P_{BS} = Hydrostatic pressure in Bowman's space (mm Hg)

π_{GC} = Oncotic pressure in glomerular capillary (mm Hg)

GFR = Kf x [(Pg – Pb) – (πg – πb)]

GFR = Kf x [(60 – 18) – (32 – 0)]

- **Guyton corner :**

[Forces favouring filtration] :

1) Glomerular hydrostatic pressure= 60 mmHg. **2)** Bowman's capsule colloid osmotic pressure = zero mmHg

[Forces opposing filtration] :

1) Bowman's capsule hydrostatic pressure = 18 mmHg. **2)** Glomerular colloid osmotic pressure = 32 mmHg

- NFP = 60-18-32 = +10 mmHg

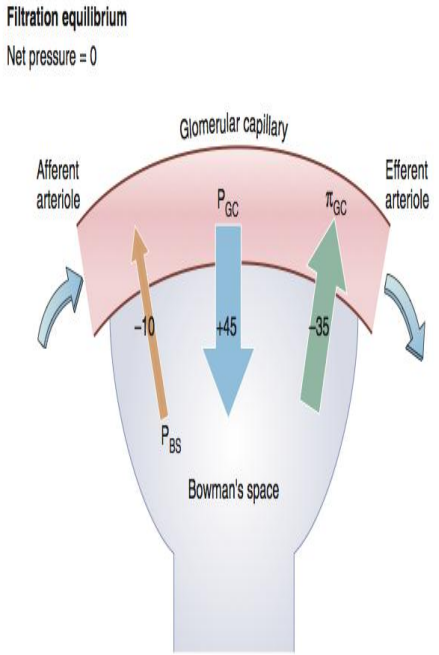
Extra

- **Linda corner:**

♦ **πGC**, **oncotic pressure in glomerular capillaries,** is another force opposing filtration. πGC is determined by the protein concentration of glomerular capillary blood. πGC *does not remain constant* along the capillary length; rather, it progressively increases as fluid is filtered out of the capillary. πGC eventually increases to the point where net ultrafiltration pressure becomes zero and glomerular filtration stops (called filtration equilibrium).

Figure 6-10*B* shows the three Starling pressures at the **end of the glomerular capillary.** At this point, the blood has been extensively filtered and is about to leave the glomerular capillary to enter the efferent arteriole. The sum of the three Starling pressures now is zero. Because net ultrafiltration is zero, no filtration can occur, a point called **filtration equilibrium.**

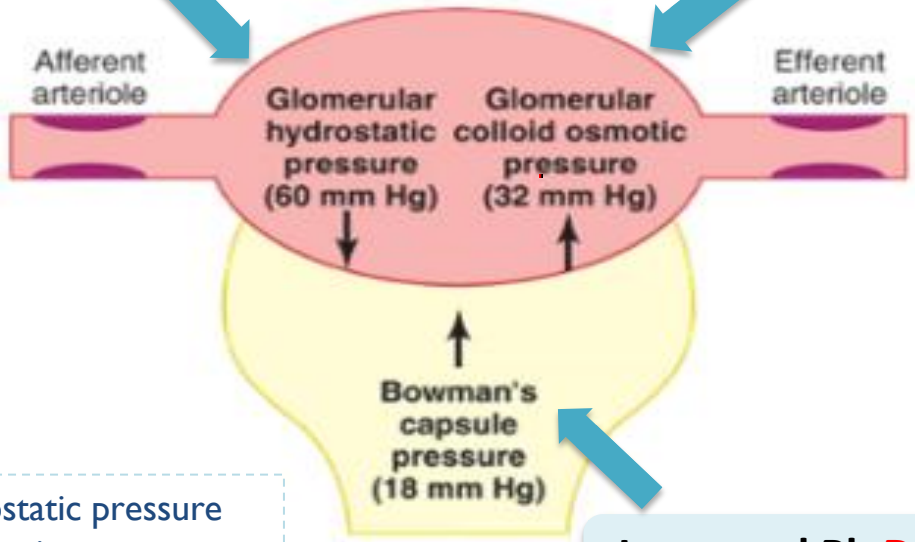
Conveniently, filtration equilibrium normally occurs at the end of the glomerular capillary. An important question to ask is *What causes filtration equilibrium to occur?* Stated differently, *Which Starling pressure has changed to make the net ultrafiltration pressure zero?* To answer this question, compare the Starling pressures at the beginning of the glomerular capillary with those at the end of the capillary. The only pressure that changes is πGC, the oncotic pressure of glomerular capillary blood. As fluid is filtered out of the glomerular capillary, protein is left behind and the protein concentration and πGC increase. By the end of the glomerular capillary, πGC has increased to the point where the net ultrafiltration pressure becomes zero. (A related point is that this blood leaving the glomerular capillaries will become peritubular capillary blood. The peritubular capillary blood will, therefore, have a high oncotic pressure [πc], which becomes a driving force for reabsorption in the proximal tubule of the nephron.) There is no decrease in PGC along the length of the glomerular capillaries, as occurs in systemic capillaries. The difference for glomerular capillaries is the presence of a second set of arterioles, the efferent arterioles. Constriction of efferent arterioles prevents the decline in PGC that would otherwise occur as fluid is filtered out along the length of the glomerular capillaries.



How changes in forces determining GFR affect GFR ?

Increased Pg Increases GFR.
This pressure is affected by:
- ABP.(arterial blood pressure)
- Afferent & Efferent arteriolar resistance

Increased π g Decreases GFR



Pg = Glomerular hydrostatic pressure
Pb = Bowman's hydrostatic pressure
π g = Colloid osmotic pressure of glomerular plasma proteins

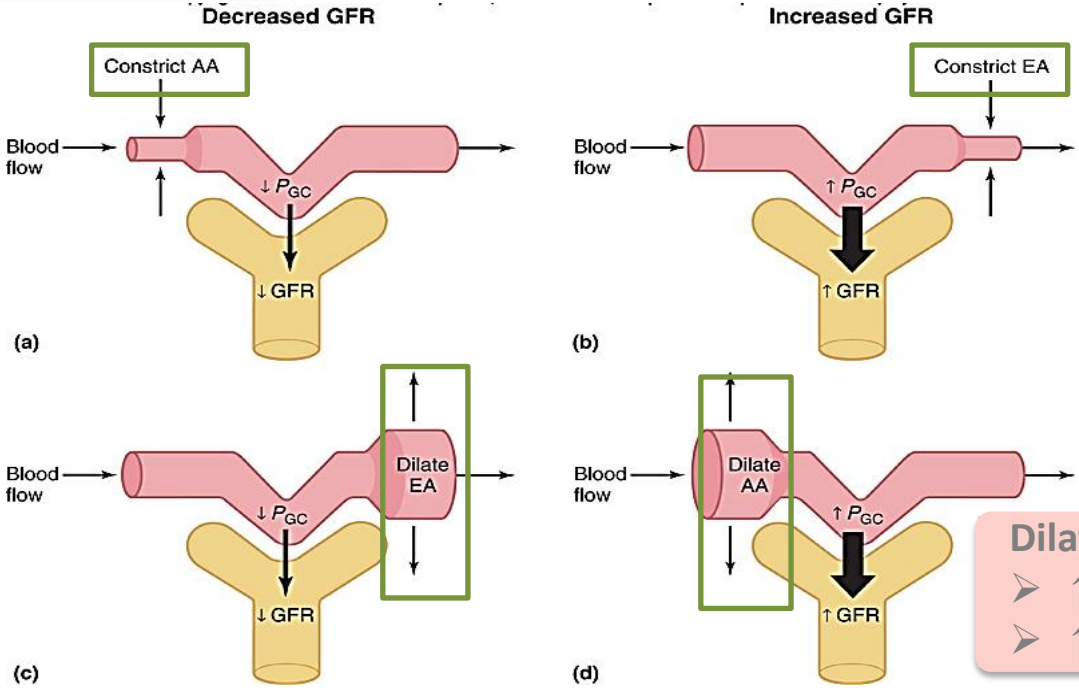
Increased Pb Decreases GFR
In urinary obstruction
e.g. stones or tumors.

Afferent & Efferent Arteriolar Resistance Affect

- As vasodilation and vasoconstriction of the afferent and efferent arterioles alter the blood flow through the glomerular capillaries, there are corresponding alterations in the glomerular filtration rate **(GFR).**

Constriction of Afferent
E.g.: Sympathetic
- ↓PGC
- ↓GFR

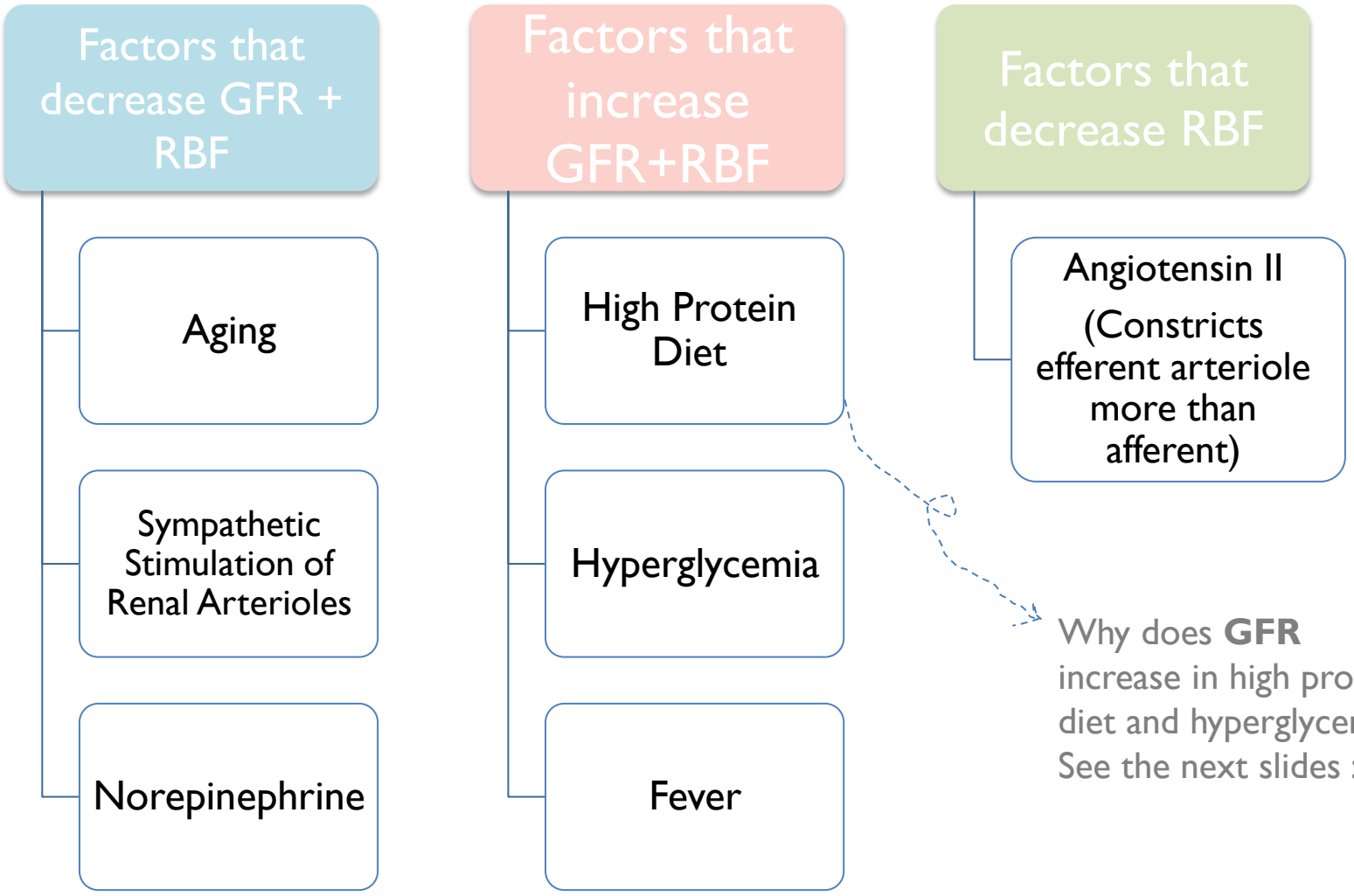
Constriction of Efferent
E.g.: Angiotensin II
- ↑PGC
- ↑GFR



Dilation of Efferent
- ↓PGC
- ↓GFR

Dilation of Afferent
- ↑PGC
- ↑GFR

Factors Affecting Renal Blood Flow and GFR



EXTRA

This slide has questions that the doctor gave us as homework, have a look at them.

- Q1 : Read more about **Renin**; where is it synthesized ?

- **Guyton corner :**

The Renin-Angiotensin System : Its Role in Arterial Pressure Control

Aside from the capability of the kidneys to control arterial pressure through changes in extracellular fluid volume, the kidneys also have another powerful mechanism for controlling pressure. It is the renin-angiotensin system.

Renin is a protein enzyme released by the kidneys when the arterial pressure falls too low. In turn, it raises the arterial pressure in several ways, thus helping to correct the initial fall in pressure.

Renin is synthesized and stored in an inactive form called *prorenin* in the *juxtaglomerular cells* (JG cells) of the kidneys. The JG cells are modified smooth muscle cells located *in the walls of the afferent arterioles immediately proximal to the glomeruli*. When the arterial pressure falls, intrinsic reactions in the kidneys themselves cause many of the prorenin molecules in the JG cells to split and release renin. Most of the renin enters the renal blood and then passes out of the kidneys to circulate throughout the entire body. However, small amounts of the renin do remain in the local fluids of the kidney and initiate several intrarenal functions. *Page 220*

- Q2 :Why does **GFR** increase in high protein diet and hyperglycemia ?

Please check the answer in the next slide !

EXTRA

- **Guyton corner :** *Page 321*

Other Factors That Increase Renal Blood Flow and GFR: High Protein Intake and Increased Blood Glucose

Although renal blood flow and GFR are relatively stable under most conditions, there are circumstances in which these variables change significantly. For example, a high protein intake is known to increase both renal blood flow and GFR. With a chronic high-protein diet, such as one that contains large amounts of meat, the increases in GFR and renal blood flow are due partly to growth of the kidneys. However, GFR and renal blood flow increase 20 to 30 percent within 1 or 2 hours after a person eats a high-protein meal.

One likely explanation for the increased GFR is the following: A high-protein meal increases the release of amino acids into the blood, which are reabsorbed in the proximal tubule. Because amino acids and sodium are reabsorbed together by the proximal tubules, increased amino acid reabsorption also stimulates sodium reabsorption in the proximal tubules. This decreases sodium delivery to the macula densa which elicits a tubuloglomerular feedback–mediated decrease in resistance of the afferent arterioles, as discussed earlier. The decreased afferent arteriolar resistance then raises renal blood flow and GFR. This increased GFR allows sodium excretion to be maintained at a nearly normal level while increasing the excretion of the waste products of protein metabolism, such as urea.

A similar mechanism may also explain the marked increases in renal blood flow and GFR that occur with large increases in blood glucose levels in uncontrolled diabetes mellitus. Because glucose, like some of the amino acids, is also reabsorbed along with sodium in the proximal tubule, increased glucose delivery to the tubules causes them to reabsorb excess sodium along with glucose. This, in turn, decreases delivery of sodium chloride to the macula densa, activating a tubuloglomerular feedback-mediated dilation of the afferent arterioles and subsequent increases in renal blood flow and GFR.

These examples demonstrate that renal blood flow and GFR per se are not the primary variables controlled by the tubuloglomerular feedback mechanism. The main purpose of this feedback is to ensure a constant delivery of sodium chloride to the distal tubule, where final processing of the urine takes place. Thus, disturbances that tend to increase reabsorption of sodium chloride at tubular sites before the macula densa tend to elicit increased renal blood flow and GFR, which helps return distal sodium chloride delivery toward normal so that normal rates of sodium and water excretion can be maintained .

An opposite sequence of events occurs when proximal tubular reabsorption is reduced. For example, when the proximal tubules are damaged (which can occur as a result of poisoning by heavy metals, such as mercury, or large doses of drugs, such as tetracyclines), their ability to reabsorb sodium chloride is decreased. As a consequence, large amounts of sodium chloride are delivered to the distal tubule and, without appropriate compensations, would quickly cause excessive volume depletion. One of the important compensatory responses appears to be a tubuloglomerular feedback–mediated renal vasoconstriction that occurs in response to the increased sodium chloride delivery to the macula densa in these circumstances. These examples again demonstrate the importance of this feedback mechanism in ensuring that the distal tubule receives the proper rate of delivery of sodium chloride, other tubular fluid solutes, and tubular fluid volume so that appropriate amounts of these substances are excreted in the urine.

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- Hissah almuzini
- Johara Almalki
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- Lojain alsiwat
- Munerah AlOmari
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- Malak alshareef
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- Nojood alhaidri
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- Noura alTawil
- Norah Alakeel
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- Saad Almutairy