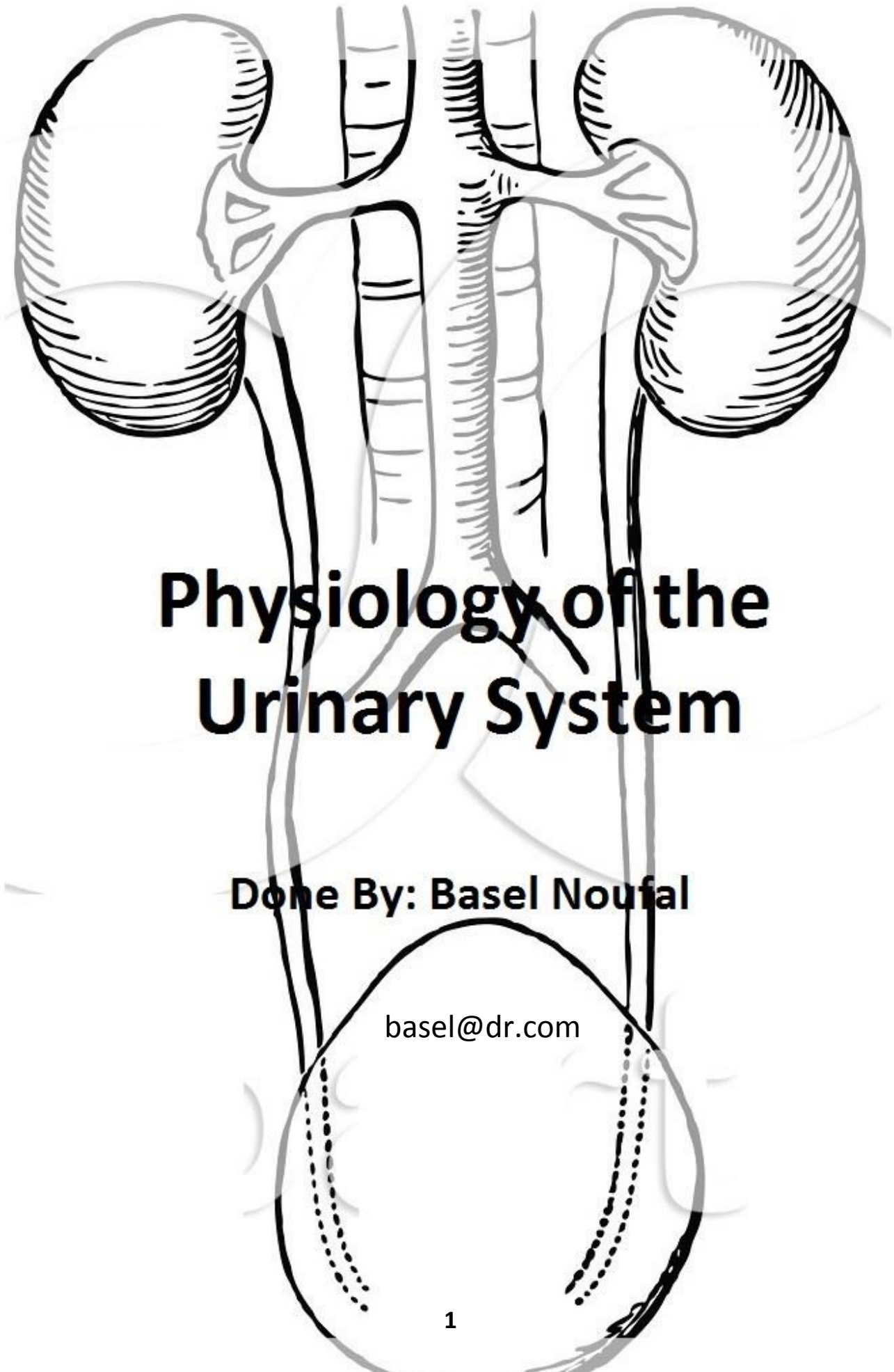

Physiology of the Urinary System

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Corrected and modified by Yanal A. Shafagoj MD. PhD

Textbook of medical physiology, by A.C. Guyton and John E, Hall•

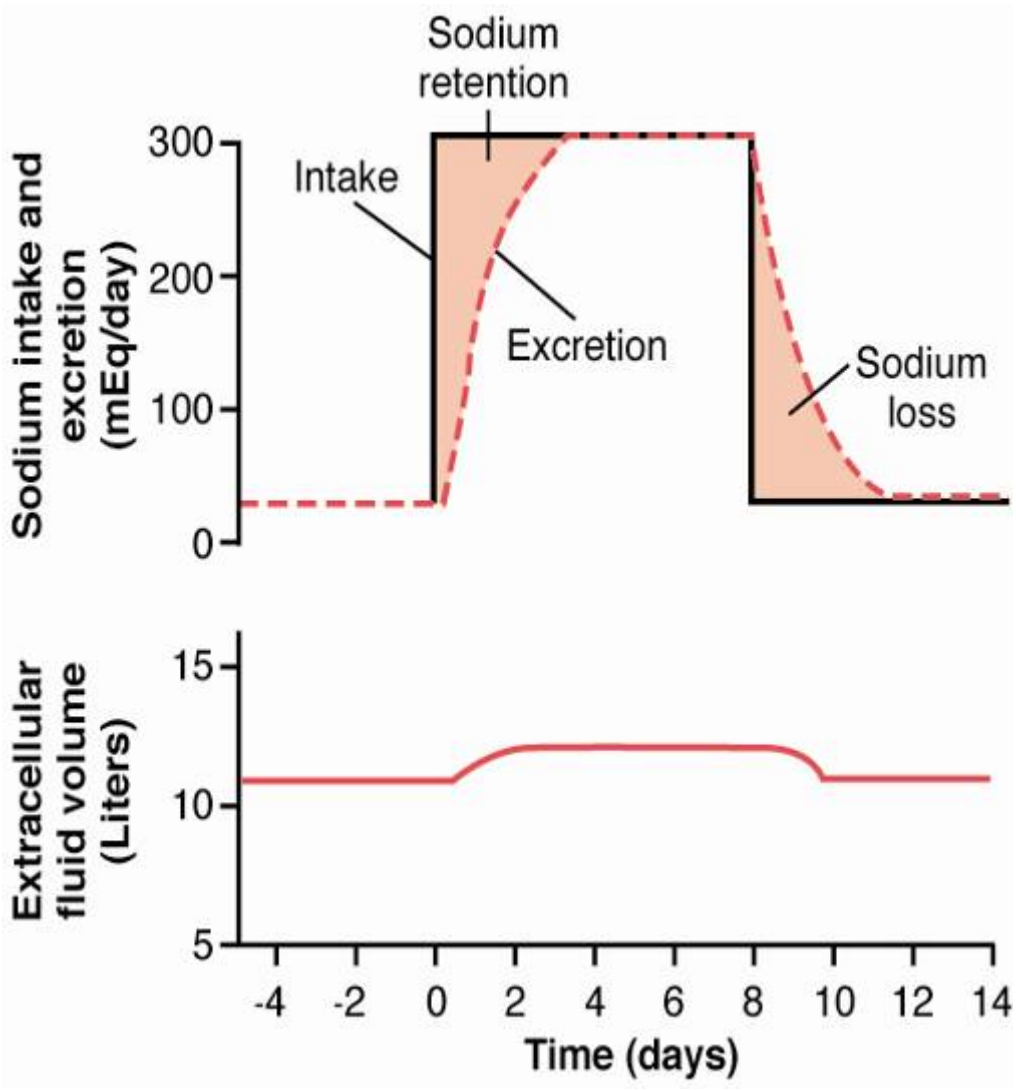
If you prefer to study from textbook, I'II send you the outline

LECTURE (1)

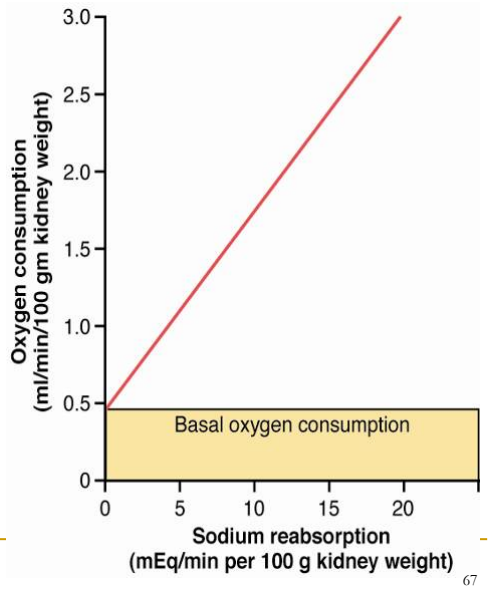
Overview of the different Functions of The Kidneys And Renal Blood Flow

Multiple Functions of the kidney:

- ✞ Remove waste products and foreign chemicals such as urea, creatinine, and uric acid, bilirubin, hydrogen etc. Those are endogenous substances. Renal failure (azotemia): means accumulation of nitrogenous wastes in blood. It means increase plasma levels of urea and nitrogen. The more the urea/creatinine levels in the plasma the more the loss of functioning nephrons. It is inversely proportional.
  - ☐ Urea (from protein metabolism): proteins→amino acids →NH_2 removed →forms ammonia, liver convert it to urea
  - ☐ Uric acid (from nucleic acid metabolism)
  - ☐ Creatinine (from muscle metabolism)
  - ☐ Bilirubin (from hemoglobin metabolism)
  - ☐ Exogenous substances such as Pesticides, Food additives, Toxins, Drugs, and Detoxifies free radicals and drugs
- ✞ Returns useful chemicals to blood such as Glucose and amino acids
- ✞ Regulates blood volume and pressure (urine making makes blood volume less and thus, blood pressure less)
- ✞ Regulates osmolarity of body fluids (dilution and concentration of urine)
- ✞ Secretes renin (renin- angiotensin-aldosterone system) and thus regulation of arterial blood pressure.
- ✞ Electrolyte balance (Na+, K+, Cl-, Ca++, P etc.) (Electrolyte homeostasis). I give an example of the Effect of increasing sodium intake 10-fold on urinary sodium excretion and extracellular fluid volume


Sodium retention
Intake
Excretion
Sodium loss
Sodium intake and excretion (mEq/day)
300
200
100
0
Extracellular fluid volume (Liters)
15
10
5
-4
-2
0
2
4
6
8
10
12
14
Time (days)

Renal oxygen consumption and sodium reabsorption



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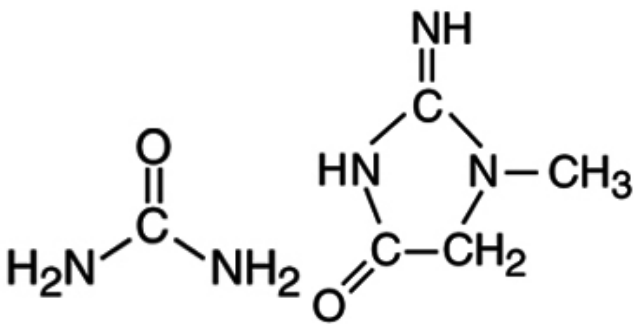
- Hormones metabolized and excreted by the kidney. Most peptide hormones (e.g. insulin, angiotensin II, etc.
- Secretes erythropoietin → (RBC production)…lack of EPO means anemia
- Convert 25-hydroxycholecalciferol into 1,25-dihydroxycholecalciferol (calcitriol), the most active form of vitamin D. Vitamin D_3 is important in calcium and phosphate metabolism
- Regulates H+ and HCO_3 and acid base balance…kidney failure leads to metabolic acidosis. Excrete acids. kidneys are the only means of excreting non-volatile acids. Regulate body fluid buffers (e.g. Bicarbonate)
- Gluconeogenesis: (conversion of non-sugar sources, particularly amino acids, into glucose at time of starvation (I don't mean Corona's time!)



Urea Creatinine

Based on physiological functions of the kidney: In end-stage renal failure kidney failure will lead to death for many reasons, for example:

- Electrolyte imbalance

* K imbalance: lead to cardiac arrhythmias

Ca imbalance: affects bone (kidney is the major organ for Ca homeostasis)

- pH disturbance: metabolic acidosis

- Kidney secret erythropoietin→ therefore, kidney failure leads to anemia
- Kidney regulates the volume of blood: kidney failure→hypertension, malignant hypertension→pulmonary edema

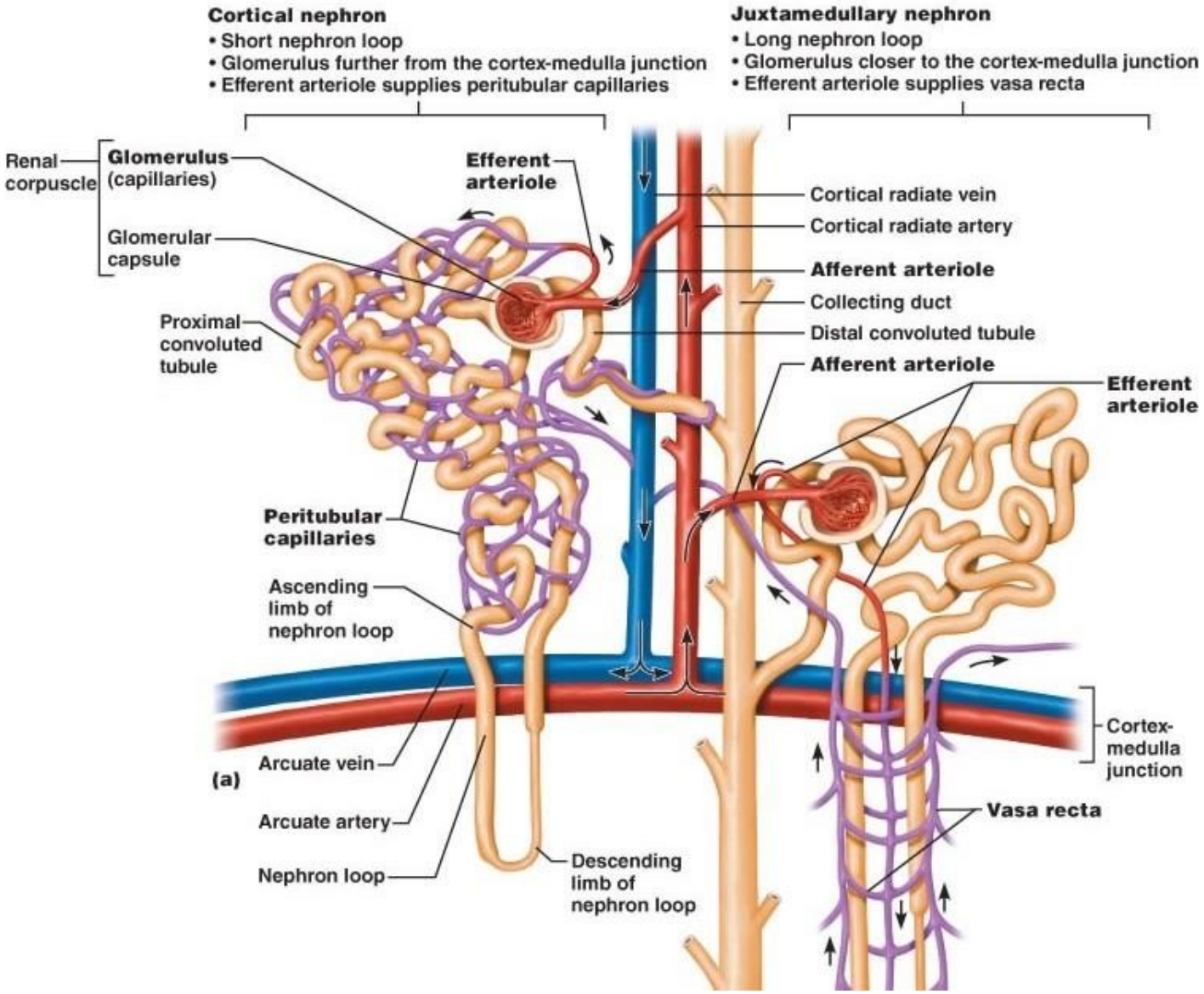
Anatomy of the Kidney…go back to your histology lectures

✞ The kidney weighs 113-170 gm.

✞ Renal artery arises as the fifth branch of the abdominal aorta. The renal artery arises from the aorta at the level of the second lumber vertebra. Because the aorta is to the left of the midline, the right renal artery is longer. The inferior vena cava lies to the right midline making the left renal vein two times longer than the right renal vein. For this reason it is better to take the donor left kidney (short artery, long vein) & place it in the right pelvis of the recipient. Multiple arteries & veins can supply the kidney.

- Cortex : contain glomeruli ----->filtration
- Medulla : contain tubules ----->secretion and reabsorption
- Cortical atrophy : glomerulonephrits
- Medullary atrophy : tubular nephritis
- Cortical nephron have short loop of Henle (85 % of the nephrons)
- Juxta-medullary nephron: Having long loop of Henle and this is important in urine concentration (15-20% of the total nephrons).
- In each kidney we have 1 million afferent arteriole & nephron.

Blood Supply of The Kidneys Structure and Function: **If you face any difference with your anatomy/histology course…consider the anatomy/histology lectures. I teach you physiology and not anatomy/histology**



✞ The renal artery (the fifth branch of the aorta) enters the kidney through its hilum and divides many times to form segmental arteries, interlobar arteries, arcuate arteries, interlobular arteries (cortical radiate arteries).

✞ Interlobular arteries divide again into many afferent arterioles.

✞ Transports arterial blood to the glomerular capillaries for filtration

✞ Each afferent arteriole enters a glomerulus and divides to form the glomerular capillaries. The site for blood filtration which operates as a nonspecific filter; in that, it will filter both useful and non-useful material. The product of the glomerulus is called filtrate or ultrafiltrate indicating lack of proteins

✞ The capillaries converge again to form efferent arterioles.

✞ Efferent arterioles leave the glomerulus and divide, once again, to form peritubular capillaries. They Transport filtered blood from the glomerulus, through the peritubular capillaries and the vasa recta, and back to the kidney venous system

✞ Peritubular capillaries rejoin to form interlobular veins, arcuate veins, interlobar veins.

✞ Interlobar veins join to form the renal vein which leaves the kidney through its hilum.

✞ Note that the glomerular capillaries form the efferent arterioles, which divide again (instead of converging) to form other capillaries (two capillary beds). This is known as the portal circulation.

✞ Vasa recta are part of the peritubular capillaries that branch off the efferent arterioles of juxtamedullary nephrons (those nephrons closest to the medulla 15% of our nephrons are of this type). They enter the medulla, and surround the loop of Henle.

✞ Each kidney contains one million nephrons; each of which is around 5-6 cm long.

✞ The cortex contains the glomeruli of the nephrons, giving the cortex a granular appearance. In contrast, the medulla, which contains most of the length of the tubules, appears striated.

✞ **Bowman's Capsule**: A sac that encloses the glomerular capillaries and transfers filtrate from the glomerulus to the Proximal Convoluted Tubule (PCT).

✞ **Proximal Convoluted Tubule (PCT)**: A thick and most active segment of the nephron that reabsorbs most of the useful substances of the filtrate: sodium (65%), water (65%), bicarbonate (90%), chloride (50%), glucose (nearly 100%!) amino acids (≈100%), etc. The primary site for secretion (elimination) of drugs, waste and hydrogen ions

✞ **Descending Limb of the Loop of Henle:** Part of the counter current multiplier, freely permeable to water and relatively impermeable to solutes (salt particles), receives filtrate from the PCT, allows water to be absorbed and sends "salty" filtrate on the next segment. "Saves water and passes the salt"

✞ **Ascending Limb of the Loop of Henle**: Part of the counter current multiplier, impermeable to water and actively transports (reabsorbs) salt (NaCl) to the interstitial fluid of the pyramids in the medulla. "Saves salt and passes the water." the passing filtrate becomes dilute and the interstitium becomes hyperosmotic.

✞ **Distal Convoluted Tubule (DCT)**: Receives dilute fluid from the ascending limb of the Loop of Henle. Variably active portion of the nephron. When aldosterone hormone is present, sodium is reabsorbed and potassium is secreted. Water and chloride follow the sodium.

✞ **Collecting Duct**: Receives fluid from the DCT. Variably active portion of the Nephron. When antidiuretic hormone (ADH) is present, this duct becomes porous to water. Water from the collecting duct fluid then moves by osmosis into the "salty" (hyperosmotic) interstitium of the medulla. Therefore, it is the most important segment in the nephrone when water homeostasis is concerned. It is the last segment to save water for the b

✞ **Peritubular Capillaries.** Transport reabsorbed materials from the PCT and DCT into kidney veins and eventually back into the general circulation. Help complete the conservation process (reabsorption) that takes place in the kidney.

✞ What has been mentioned previously is from the anatomy/histology point of view. From the physiology point of view we can divide the nephron in two major parts only:

✞ **Functional Anatomy of the Kidney**

✞ Structure & function of the kidney are closely matched. The kidney is a combination of: We like to divide the nephrons into only two parts:

✞ 1. Ultrafiltation device (the glomerular apparatus).

✞ 2. Epithelium (the rest of the nephron "the tubules"), which can modify this ultrafiltarte by two additional processes:

- Addition (secretion) or

- Removal (reabsorption) or both.

✞ Glomerular Filtration in the kidney is affected by Starling forces (Hydrostatic & Osmotic pressure…4 forces…from your CVS). In the kidney they are only three forces.

✞ Bowman's capsular space stands for the interstitium.

✞ We will come back again to Starling forces across glomerular membrane when we discuss with regulation of GFR later.

✞ Make sure to differentiate between: Filtration, secretion, reabsorption, and finally excretion

✞ **Excretion = Filtration - Reabsorption + Secretion**

✞ Filtration : somewhat variable, not selective (except forproteins), averages 20% of renal plasma flow

✞ Reabsorption : highly variable and selective most electrolytes (e.g. Na^+, K^+, Cl^-) and nutritional substances (e.g. glucose) are almost completely reabsorbed; most waste products (e.g. urea) poorly reabsorbed

✞ Secretion : highly variable; important for rapidly excreting some waste products (e.g. $H^+$and K^+), foreign substances (including drugs), and toxins

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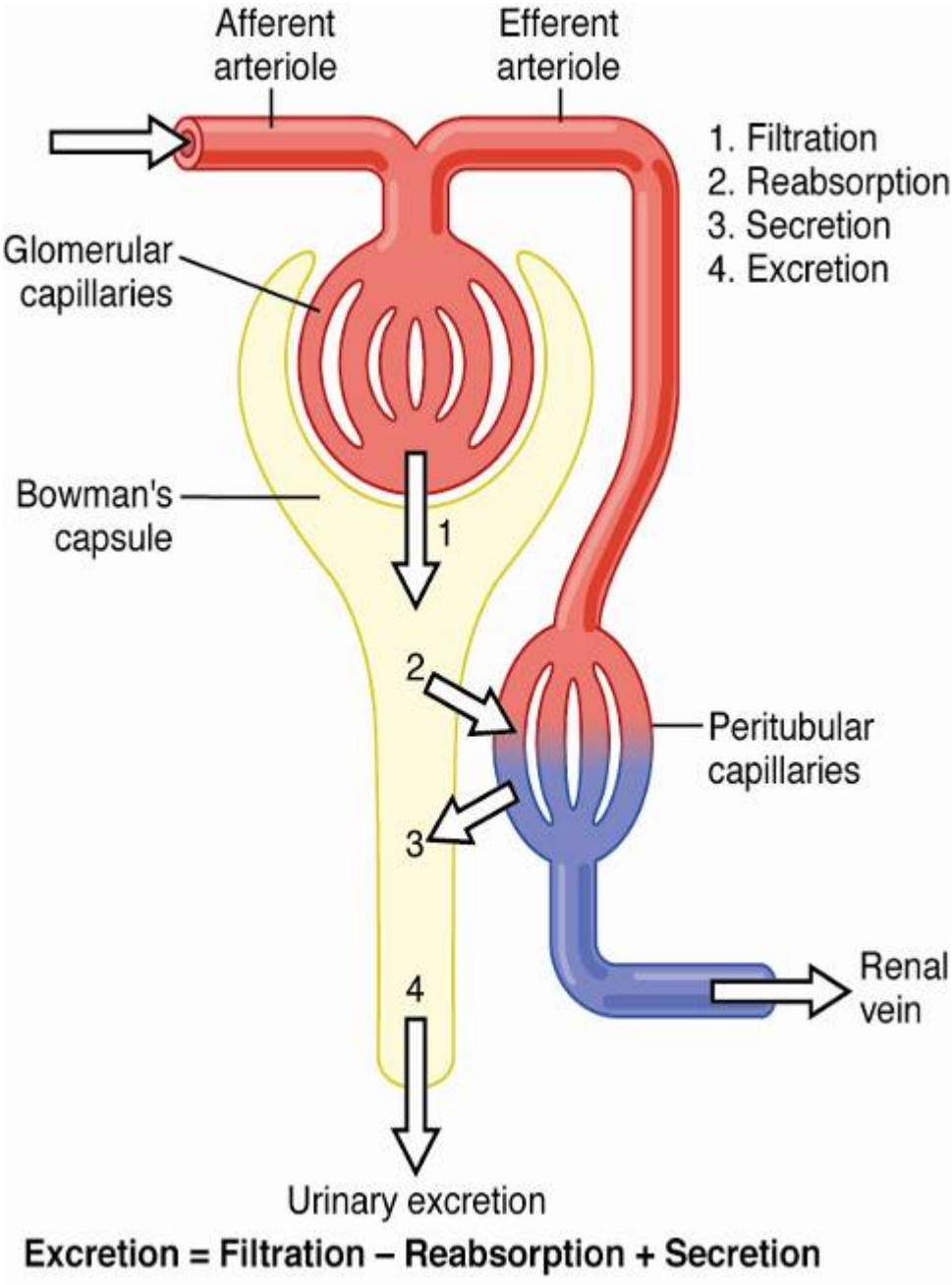
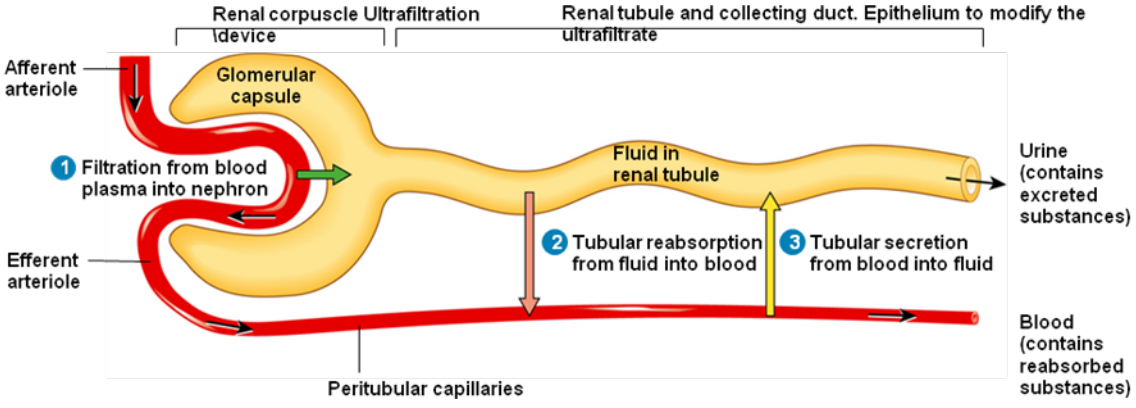


✞ **Excretion = Filtration – Reabsorption + Secretion**



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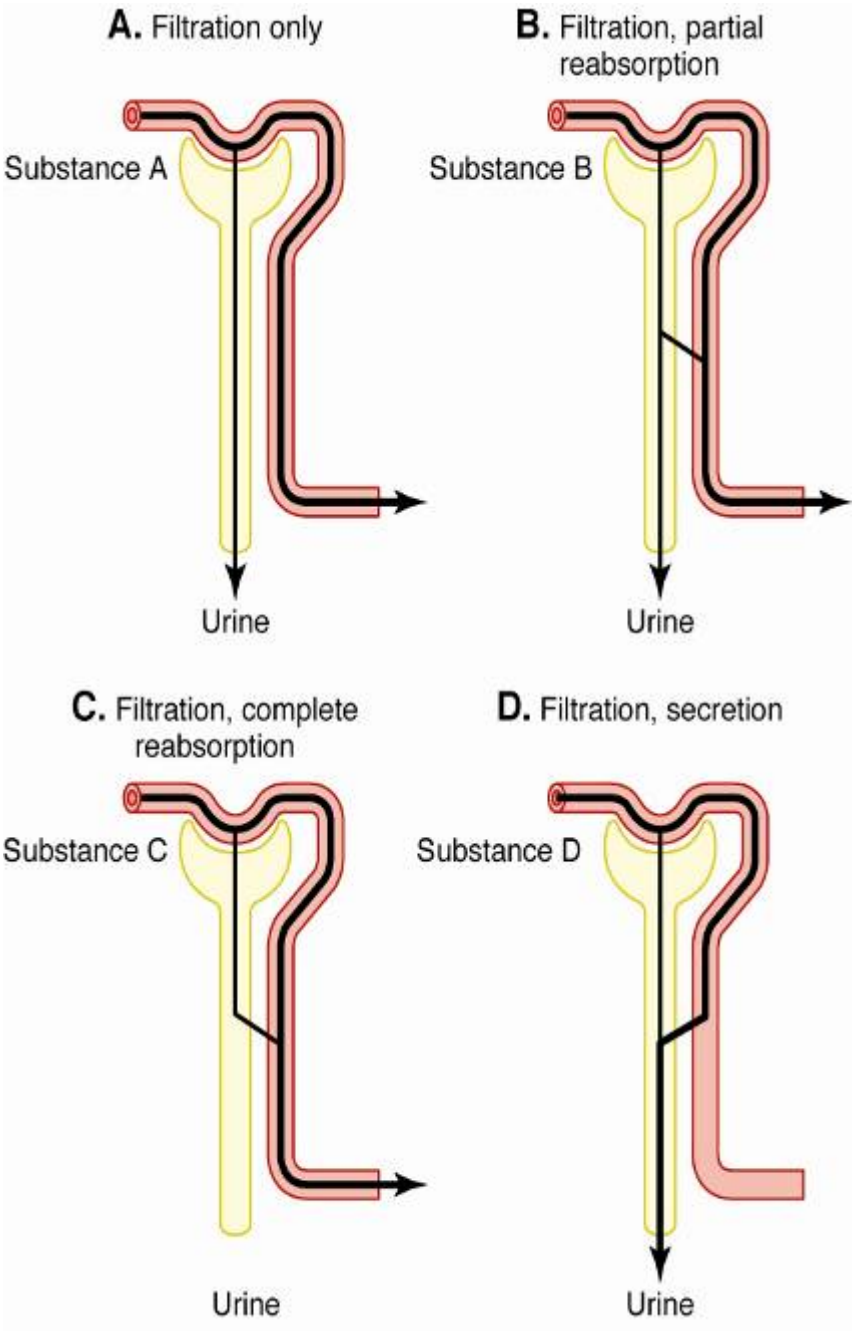
A. Filtration only
Substance A
Urine
B. Filtration, partial reabsorption
Substance B
Urine
C. Filtration, complete reabsorption
Substance C
Urine
D. Filtration, secretion
Substance D
Urine

✞ .

Renal Handling of Water and Solutes

	Filtration	Reabsorption	Excretion
Water (liters/day)	180	178.5	1.5
Sodium (mmol/day)	25,560	25,410	150
Glucose (gm/day)	180	180	0
Creatinine (gm/day)	1.8	0	1.8

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✞

- **Measuring Renal Blood Flow (RBF)**

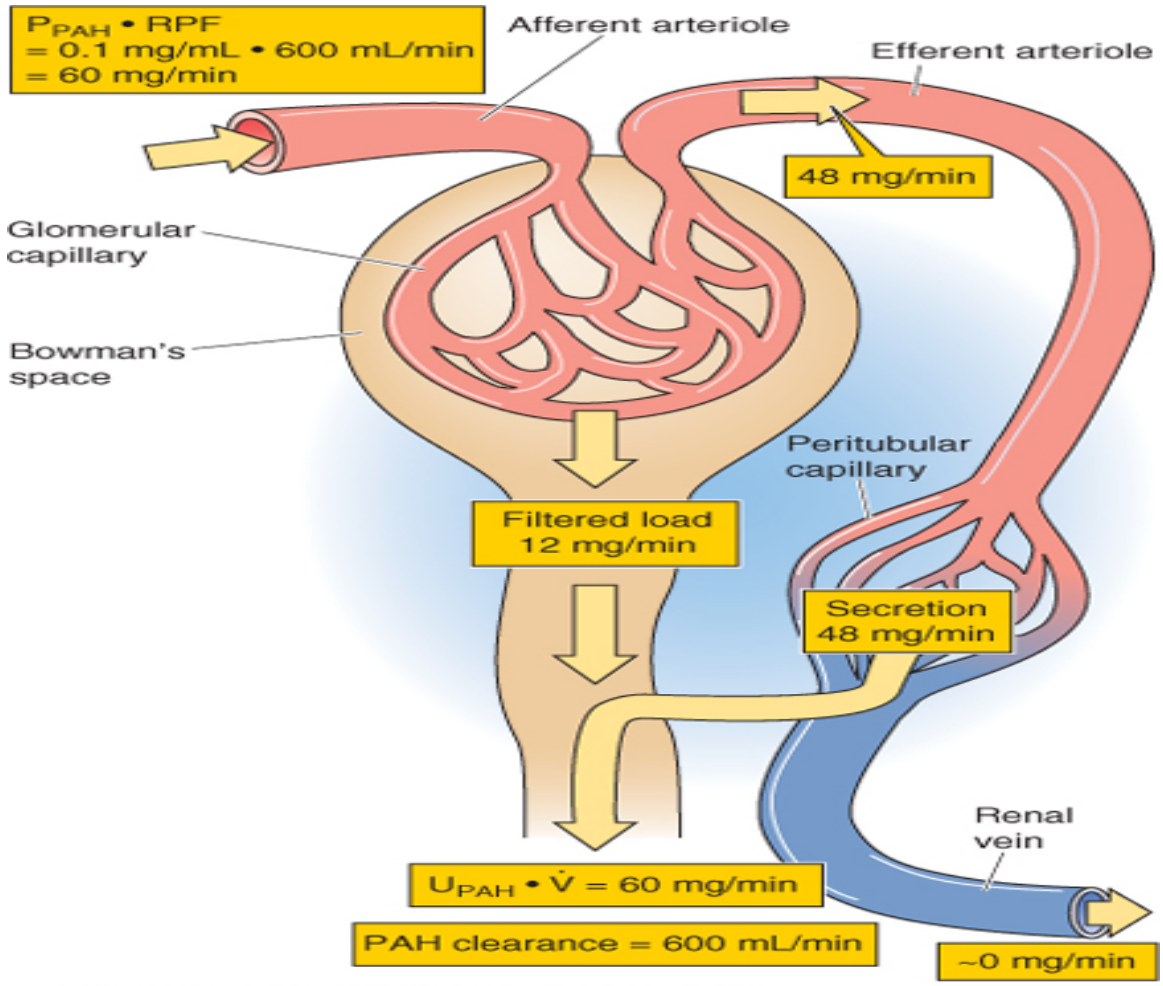
$$Cx = \left[\frac{U_x}{P_x}\right] * V \qquad RPF = \left[\frac{U_{PAH}}{P_{PAH}}\right] * V \qquad RBF = \left[\frac{RPF}{1 - Hct}\right]$$

If you understand the above 3 equations, you are in a good shape.

✞ RBF is defined as the volume of blood entering both kidneys per unit time. Can be expressed as the volume of blood which supplies each gram of the renal tissue per unit time.

✞ Through the above equation, the amount of the substance that enters the kidney has to be excreted in the urine, so we need a substance that is **totally excreted** by filtration and secretion without any reabsorption to the vein and these criteria are found in PAH. Its Renal vein concentration = 0

✞ هل فعلاً هذا الكلام ينطبق على هذه المادة أو على أي مادة أخرى في الكون؟



- The source of PAH in the urine:
  1. filtration 20% (12 mg/min)
  2. secretion 80% (48 mg/min)
  3. without any reabsorption
- RBF Averages **1.25 L/min** (1200-1250 ml/min) or **4.2 ml/g.min**. That is, **25%** of cardiac output.
- It is high compared to other organs (**0.03** and **0.5** ml/mg.min for skeletal muscles and brain, respectively…see the table below). Remember from your respiratory course, the carotid bodies receive the highest blood flow in our body: **20 ml/g.min**
- This high flow rate is consistent with the function of the kidneys, since it is a reconditioner organ (reconditioning the blood; meaning: change its composition). That is, the composition of the blood is significantly modified as it passes through the kidneys. The

blood doesn't go to the kidney simply to nourish it, but because the blood expect the kidney to change its cimposition.

- However, unlike other tissues, O_2 and nutrients concentrations do not decrease significantly as the blood leaves the kidneys. This is indicated by the arterio-venous a-vO_2 difference, which is relatively low (**1.4 ml/dl**) compared to **6** and **6.2** ml/dl for the skeletal muscles and the brain, respectively. Nevertheless, kidneys consume twice O2/per gm tissue as brain. In the heart (coronary circulation) the difference is 11 ml/dl (not much O2 reserve is left in the cardiac arteries…therefore, the heart is easily prone to ischemia).

- This O2 consumption in the kidney is directly related to Na^+ reabsorption. If GFR is high → Na^+ reabsorption is high→O2 consumption is high. When GFR is severely depressed (Acute kidney injury) → decrease need for O2

-

•Measuring Renal Blood Flow (RBF) and Renal Plasma Flow (RPF)

RPF: how much plasma enter both kidneys per minute

RBF is measured indirectly by using this equation: **RBF = RPF / (1-HCT).**

- If the RBF is 1200 ml/min and HCT is 0.45, then RPF ≈ 660 ml/min. Between 600-650 ml/min is normal. Any number you use is fine

- As mentioned earlier, we are gona use a substance X that is completely removed (cleaned) from the blood once it reaches the kidneys: i.e. Renal vein concentration of X = 0. i.e;. Actually there is no such substance. Simply because only 90% of RPF reach glomeruli (Effective RPF). 10 % of renal blood goes to nourish the kidney i.e. don't participate in the renal function…not filtered or secreted. Therefore,

- True RPF = effective RPF ÷ 0.9 . The extraction ratio of PAH =90%. (only 90% is excreted)

- $$Extraction E_{PAH} = \left[\frac{A_{PAH} - V_{PAH}}{A_{PAH}} \right] * 100\%$$

- So 585 ml/min (90%) is the effective RPF and 650 ml/min (100%) is called true or total tRPF

- The substance used commonly is the PAH (para-aminohippuric acid)

- If RPF=650 ml/min

- 125 is filtered (GFR).

- How much is the filtration fraction? Can you calculate the filtration fraction?
- FF= GFR / Renal plasma flow=20% filtered and 80% secreted.
- .
- 525 ml leaves through efferent arteriole and go to peritubular capillaries.
- 1 ml/min is the urine output. One ml out of 125 ml is excreted s urine (0.8%)

- Maintaining the RPF within its normal range is very important; even a decrease in the RPF for a short time causes the ions to accumulate in the narrow loops of Henle forming crystals and thus occluding the tubule→ total loss of kidney function. What you should remember is: in case of shock (bleeding) we care the most about the kidney. If RBF decreases →→acute kidney injury.
- Practically, the **RPF** is measured first. Then, the **RBF** can be mathematically obtained, as discussed earlier.

Remember:

- The a-vO_2, or the arterio-venous oxygen difference, is the difference in oxygen concentration between arterial and venous blood. It is used as an indication of how much oxygen is extracted from the blood capillaries.
- 55% of the blood is plasma (92% water and 8% solutes and suspended particles) while 45% is formed of suspended cells (mainly RBCs). This 45% is termed hematocrit (HCT) or packed cell volume (PCV).

Tissue	Blood flow (ml/g/min)	A-V difference (Vol %)	Flow ml/min	O_2 ml/
Heart	0.8	11	250	27
Brain	0.5	6.2 (25-30% Extraction)	750-900	
Skeletal Muscle	0.03	6	1200	70

Liver	0.6	3.4 Reconditioner organ		
SKIN	0.1			
Kidney	4.2	1.4	1250	18
Carotid bodies	20	0.5	0.6	

Don't worry…it is not expected from you to recall these numbers…relax•

Renal Clearance (if you understand the concept of clearance, you master 50% of the renal physiology)

- Defined as the volume of plasma completely cleared of a substance per unit time.
- Refers to the volume of plasma necessary to supply the amount of a substance excreted in urine per unit time.
- C_x: Is volume of plasma/min provides X for excretion/min.
- Unit of clearance: Volume/time
- Excretion rate is the amount of a substance excreted in urine per unit time. It is calculated by multiplying urine flow rate by urine concentration of the substance (U_s x V).
- Urine flow rate (urine output) is the volume of urine excreted per unit time.
- To understand the concept of clearance, assume that 60 grams of a substance were dissolved in a glass containing 1 liter of water, and after a minute, half of the substance (30 grams) were removed from the solution. This is equivalent to having two glasses of water; one contains 60 grams dissolved in 0.5 liter of water, and the second contains 0.5 liter of water without any of the substance. This means that the clearance of the substance is 0.5 L/min (i.e., 0.5 liter can be isolated after a minute keeping the amount of the substance in the other 0.5 liter the same).

Another example:

- **If we have 650 ml plasma with specific amount of X, after leaving the kidney all of the plasma was cleaned from X. 100% of the 650 ml/min. Then C_x= 650 ml/min**
- **We have 650 ml plasma with specific amount of Z, after leaving the kidney we find half of the amount of Z in the renal vein. Clearance will be 50% of the 650 C_Z= 325 ml/min**

"Use the Law of Conservation of Mass":

- **Amount excreted in the urine/min = Amount provided for excretion (by artery)/min**
- Amount Excreted of X (mg/min) = Urine output (V) * Ux = Amount provided for excretion (mg/min) = RPF * Px P=plasma
- *Conditions must be met before using "x" as RPF marker: "X" does not accumulate, made, or catabolized by the kidney*
-

Renal clearance can be stated mathematically as follows:

$$C_s \times P_s = V \times U_s$$ where:

C_s: clearance rate of the substance. P_s: Plasma concentration of the substance.
V: urine flow rate (urine output). U_s: Urine concentration of the substance.

- If the plasma concentration of a substance is 1 mg/ml, and 1 ml of urine were collected within a minute. The concentration of the substance in the urine was 70 mg/ml. Then C_s = 1 ml/min x 70 mg /ml / 1 mg/ml = 70 ml/min.

•RPF Measurement

Amount excreted = amount filtered + amount secreted – amount reabsorbed . A special substance (paraaminohippuric acid or **PAH**) is almost completely excreted. Therefore, since all the blood entering the kidneys will be cleared of PAH, the clearance of PAH is the RPF. Thus, using the clearance equation, and substituting RPF for C_s:

$$RPF \times P_s = V \times U_s$$

- PAH is only **90%** excreted and not 100%. This, in fact, is the maximum percentage achievable because **10%** of blood entering the kidneys does not participate in urine formation. Rather, it supplies the renal tissue with the necessary oxygen and nutrients.

Thus, 90% of blood entering the kidneys (true renal plasma flow) is the **effective renal plasma flow**.

- PAH clearance was measured to be 585 ml/min, which is the effective renal plasma flow. Thus, the RPF = 585/0.9, or around 650 ml/min.

- ✞ Filtration is a passive process (i.e., no transporters are needed to move substances (including water) across capillaries membranes.
- ✞ What determines the amount filtrated is the permeability of the membrane for the substance, its concentration gradient across the membrane and the time the substance remains in the glomerular capillaries. *This implies that as the concentration gradient increases, filtration rate increases linearly and unlimitedly*.
- ✞ Secretion, on the other hand, is an active process (i.e., transporter-dependent). Therefore, increasing the concentration gradient increases secretion rate *only to a limit.* Above the limit, further increase in concentration gradient does not increase secretion rate *because all the transporters have been occupied (i.e., saturated).* The transport rate at which secretion (or reabsorption, as explained later) rate reaches is maximum is designated T_{max} (transport maximum).

- The T_{max} of PAH transporters is **80 mg/min**. Therefore, to measure the RPF accurately, PAH reaching the peritubular tubules per minute must be used in small concentration (much less than 80 mg/min). Otherwise, less than 90% would be excreted, and thus the RPF would be underestimated.

- In fact, even an amount just less than 80 mg (e.g., 75 mg) would result in inaccurate RPF estimation because although not all the transporters would be occupied, *the probability for each PAH molecules to bind to a transporter would be exceedingly low*, and those PAH molecules which escape and do not bind to their transporter would be returned to the venous blood rather than excreted leading to underestimation of RPF.

- Therefore, with very low plasma concentration, most of the PAH in the urine (80%) is secreted actively by the transporters in the tubules. Only 20% is filtered and not reabsorbed. However, with much higher plasma concentrations only 80 mg/ml is excreted in the urine by secretion, and the rest is the filtered PAH. In this case, PAH clearance would approach the GFR rather than RPF.

- The difference between predicted excretion rate for PAH (assuming all PAH molecules bind to their transporter) and actual excretion rate is called splay. It is high at high PAH concentrations (i.e., just less than T_{max}) and approaches zero at lower concentrations.
- **Note:**the last two points will be further explained when glucose reabsorption is discussed.

✞ **Example:** If the plasma concentration of a substance is **2500 mg/ml** and **60%**of the substance passing through the kidneys is filtered and **10%** secreted while **20%** reabsorbed. Assuming infinitive T_{max} for the substance transporters, calculate the clearance and the RPF (per minute) given that during the next 24 hours, **720 ml** of urine were collected, and the substance concentration in urine was **100 mg/ml**.

- V = 720 ml/day = 0.5 ml/min Us = 100 mg/ml Pc = 2500 mg/ml
- Cs = (V x U) / Ps = 0.5 x 100 / 2500 = 0.02 ml/min
- Excreted = 60 + 10 -20 = 50%
- Since T_{max} is much higher than the concentration of the substance reaching peritubular capillaries, the splay phenomenon does not affect the accuracy of the calculated RPF. Thus, RPF = 0.02 / 0.50 = 0.04 ml/min. (half of the RPF was cleared)

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Lecture (2 and 3)

Glomerular Filtration Rate

Is the first step in urine formation.

By the way: Filtered load of a substance "x" : is how much of "x" is being filtered/minute.

Large amounts of plasma diffusing passively into Bowman's capsule.

✞ What is the difference between filtration and diffusion?

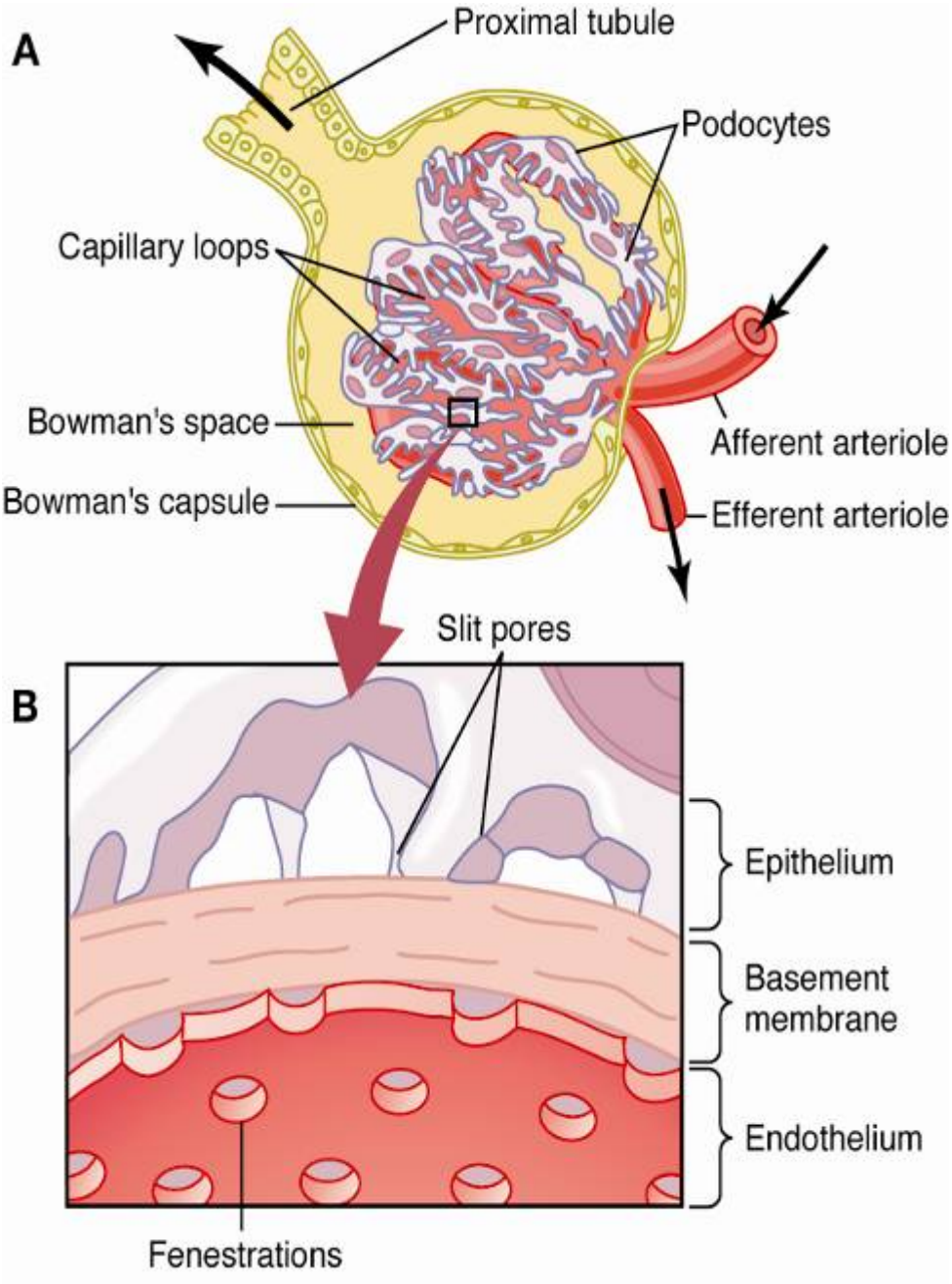
✞ Filtration is a bulk flow of fluids with the dissolved solutes. It is driven by the pressure gradient across the membrane.

✞ Diffusion is the movement of molecule by molecule. They cross the membrane based on concentration gradient (glucose) or down their electrochemical gradient (electrolytes). The composition of the filtrate is essentially similar to that of the plasma. However,

glomerular capillaries, like most other capillaries are not permeable to proteins. Also, calcium and fatty acids are not freely filtered since they are partially bound to plasma proteins. Ultrfiltrate is plasma minus proteins

- How do we know that for sure?
- By using the micropuncture technique (taking a sample from Bowman's capsule in vivo and analyze it. Due to the current circumstances, I'm not going to touch topics related to micropuncture technique.

  Note: Most systemic capillaries have an arterial end where plasma is filtered and a venous end where most filtered plasma is reabsorbed. Plasma in glomerular capillaries *is only filtered and not reabsorbed*. Another exception is gastrointestinal capillaries which function only to reabsorb nutrients.



•Glomerular Filtration Rate (GFR)

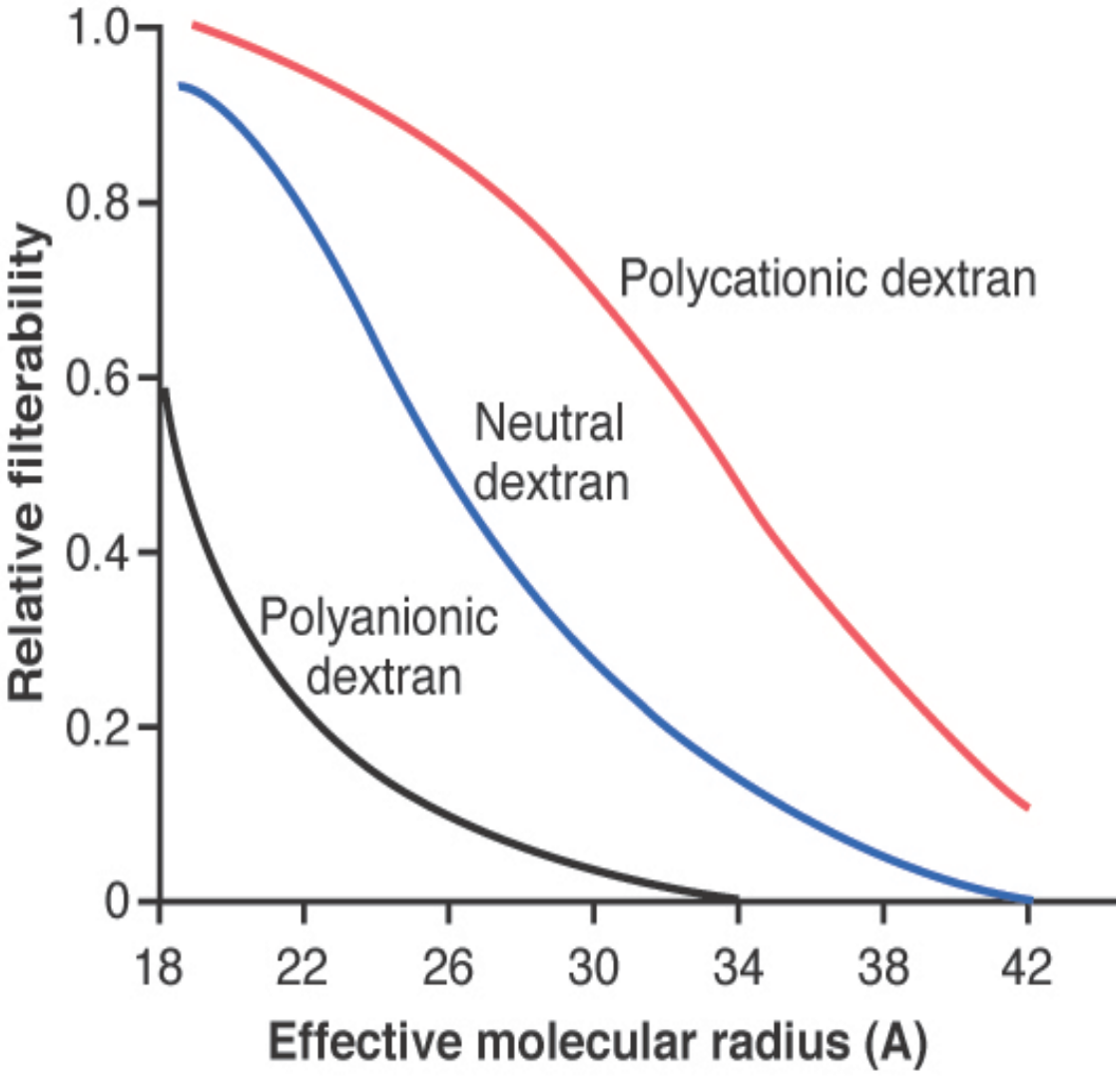
The volume of plasma filtered from the glomerular capillaries to Bowman's capsules per unit time (125 ml/min or 180 lit/day).

- You may notice that Plasma volume (3 lit) is filtered 60 times per day
  - Determined by the balance between starling forces and the capillary filtration coefficient **(K_f)**, which and is the product of the permeability of the capillary for the substance and the surface area/thickness of the filtration barrier provided for filtration.

- The permeability of the capillary for a substance, in turn, is determined by the molecular weight and the charge of the substance.

Substance	Molecular Weight	Filterability
Water	18	1.0
Sodium	23	1.0
Glucose	180	1.0
Inulin	5,500	1.0
Myoglobin	17,000	0.75
Albumin	69,000	0.005

- Cations are more readily filtered than anions because the endothelium and the basement membrane are negatively charged and thus, repel anions. Cations with a molecular weight less than 70,000 kDa are readily filtered. In contrast, anions need to be much smaller in order to pass through the capillaries. Albumin, for example, despite its relatively low molecular weight (70,000 kDa), does not cross due to its highly negative net charge. However, Cl^-, yet negatively charged, readily crosses due to its very small size.
- In nephrotic syndrome, loss of negative charge causes albumin loss and edema.
- (Remember the four cause of hypoalbuminemia: malnutrition, malabsorption, malproduction, and increased loss from the kidney).
-



- Water is filtered freely across glomerular capillaries and thus, the filterability of water is said to be 1. The filterability of other substances ranges from 0 to 1 and is determined relative to that of water. It is estimated according to its Bowman's space concentration/its plasma concentration

- The RPF averages 625ml/min; the glomerular filtration rate is 125 ml/min. Dividing these numbers yields 0.2, which is the filtration fraction.

•Starling Forces

1. **P_{GC}**: the blood hydrostatic pressure in the glomerular

85	60	59	18
Affarent arteriole	Glomerular capillary	Efferent arteriole	

capillaries which is generated by the pumping force of the heart. It averages 60 mm Hg in the glomerular capillaries. # 18 is the pressure at the beginning of the peritubular capillaries.

Table 26-3. Approximate Pressure and Vascular Resistances in the Circulation of Normal Kidney

Afferent + efferent contribute to about 70% of the intrarenal vascular resistance (mainly efferent).

	Pressure mmHg		% Total Vascular R
	Beginning	End	
Renal Artery	100	100	0
Interlobar, arcuate and interlolbular arteries	100	85	15
Afferent	85	60	25
Glomerular capillaries	60	59	1 only 1mmHg which means little resistance
Efferent	59	18	43 resistance mainly resides her
Peritubular Capillaries	18	8	10
Interlobar, arcuate and interlolbular veins	8	4	4
Renal vein	4	≈4	0

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Note that P_{GC} decreases markedly as blood passes through the arterioles (afferent and efferent), indicating high blood flow resistance in these vessels.

- P_{GC} is the determinant of GFR and is subject to physiological control
- Factors that influence P_{GC}

  - arterial pressure (effect is buffered by autoregulation of GFR)
  - afferent arteriolar resistance
  - efferent arteriolar resistance

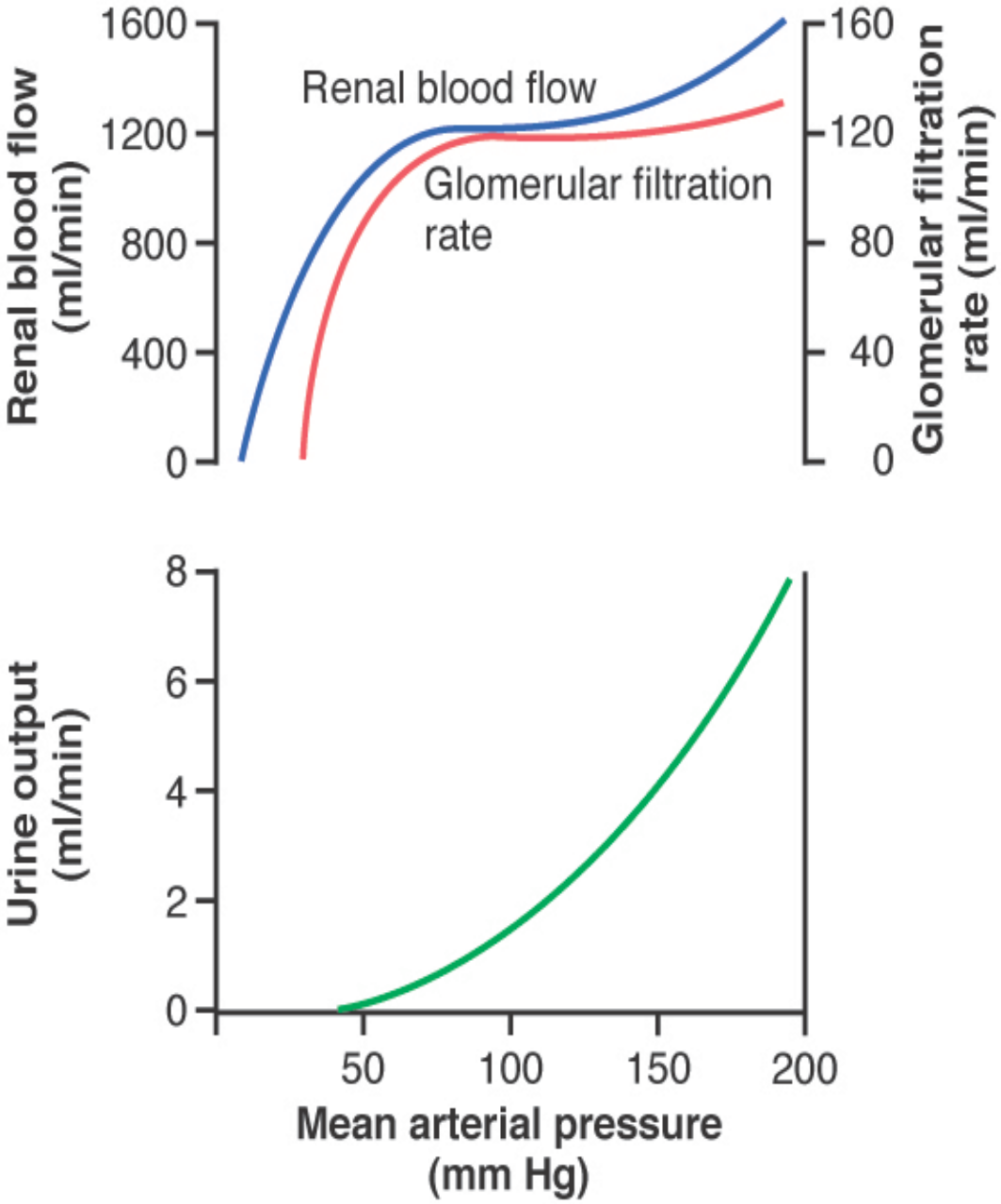
<u>Autoregulation of GFR is to be discussed with the regulation of P_{GC}</u>

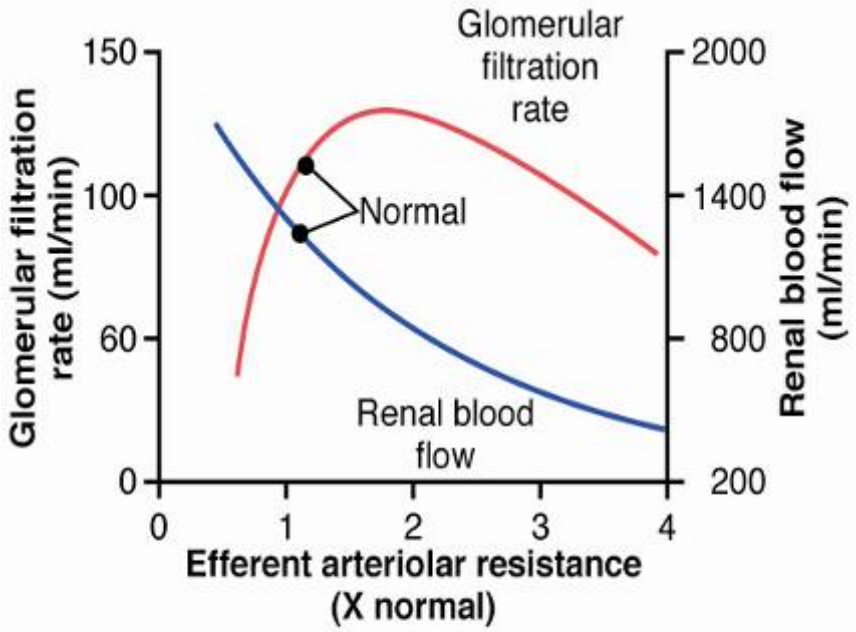
Simply: Autoregulation of GFR means the kidney (auto) can separate its GFR from the systemic ABP

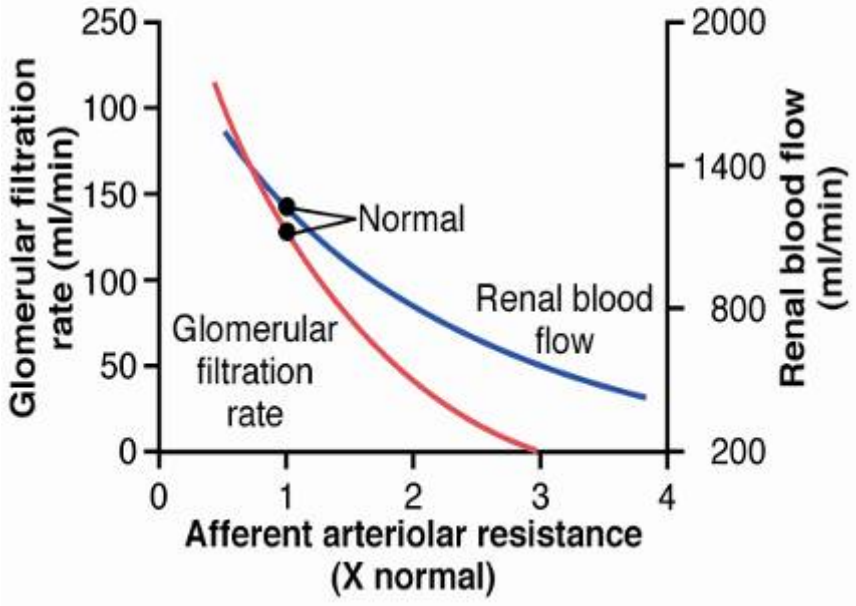
GFR fluctuates slightly in relation to changes in arterial blood pressure but this translates in a large increase in urine output… why is that?

GFR = 125ml/min and UOP is only = 1ml/min = 1.5L/day which means 124ml/min is reabsorbed (99.4% of the filtered water is reabsorbed and only 0.8% is excreted) so a little change in GFR changed the urine output a lot.

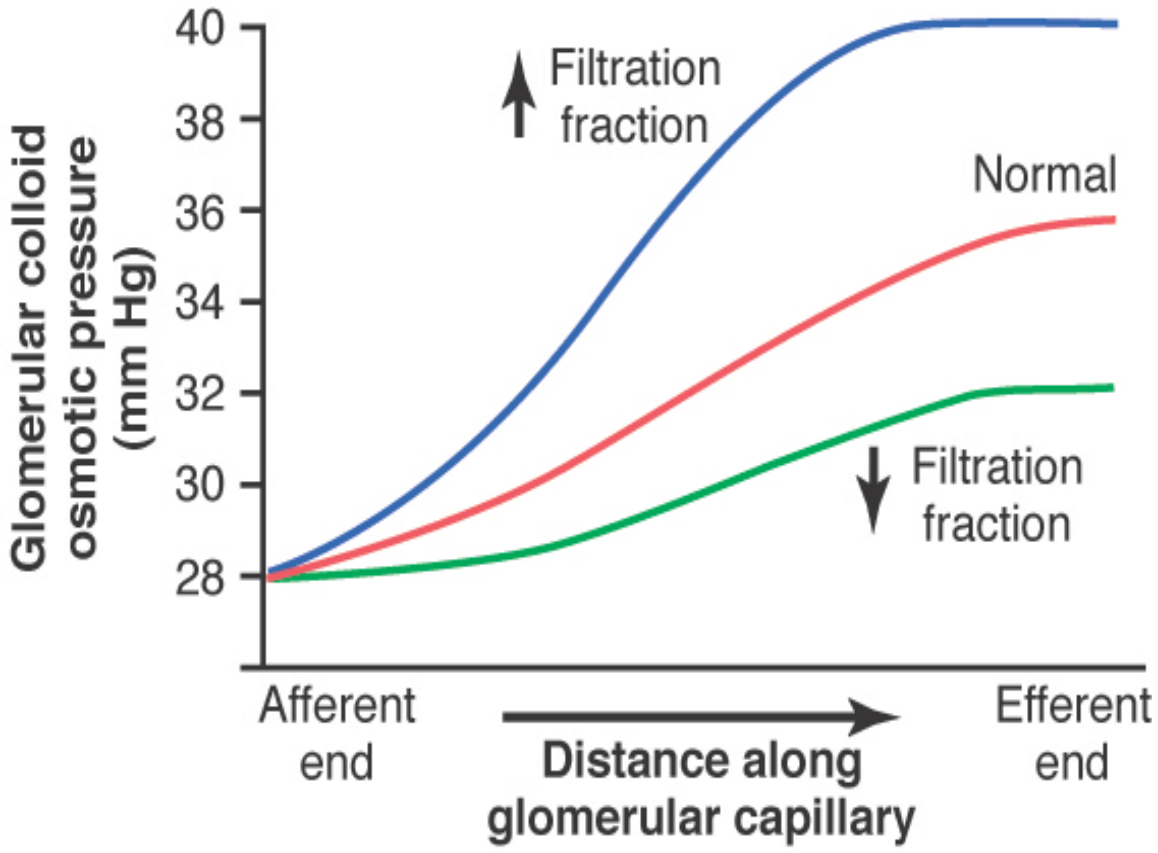
Therefore, GFR must be regulated and this is achieved mainly by the renal vascular system (glomerular capillary hydrostatic pressure) and this is controlled by afferent and efferent arterioles by the following mechanism:







2. π_c: the colloid osmotic pressure generated by the impermeable proteins in the plasma. Since 20% of plasma passing through the capillary is filtered, impermeable proteins concentration increases as they pass along the length of the capillaries from 28 mmHg to 36 mm Hg. Thus, the average π_c is approximately 32 mm Hg.

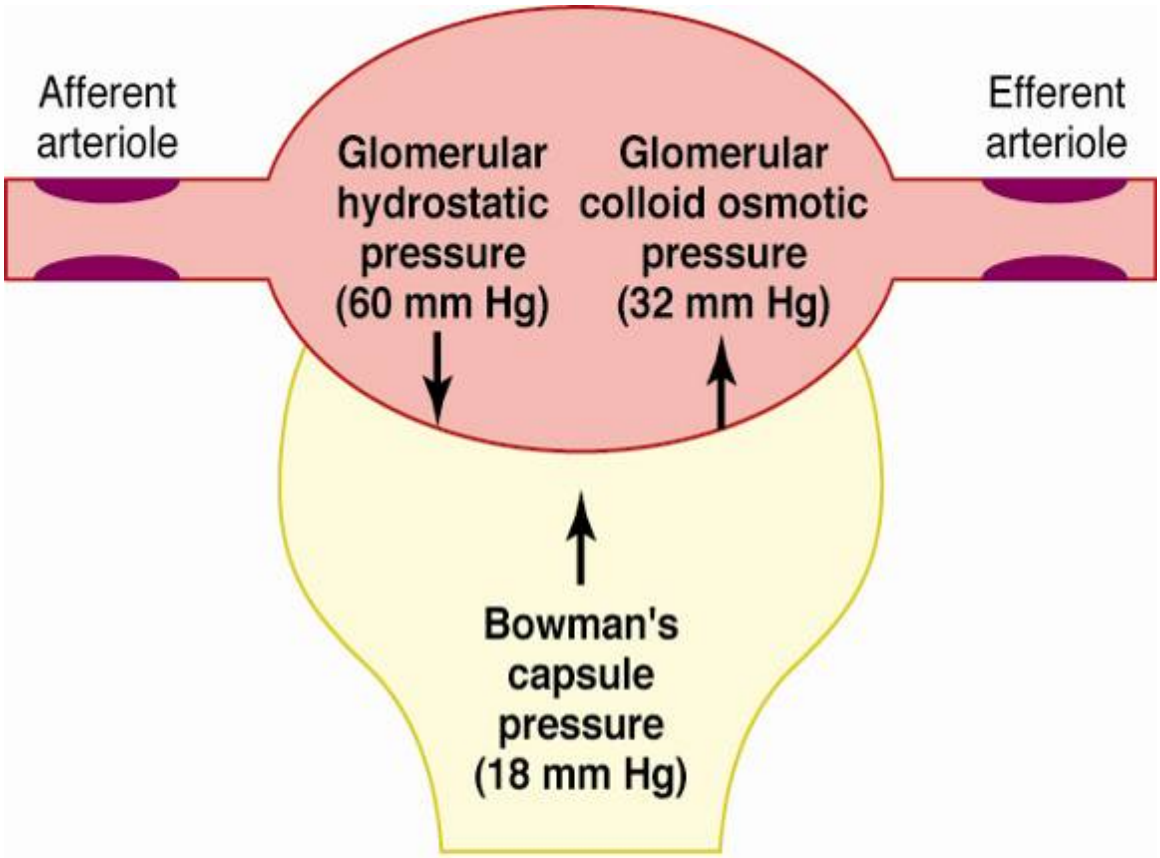


3. **P_i:** the hydrostatic pressure generated by the interstitial fluid. It is the pressure in the Bowmans space. It averages 18 mm Hg. Normally changes as a function of GFR, not a physiological regulator of GFR

4. **π_i:** the colloid osmotic pressure of the interstitial fluid. Since filtered plasma is free of proteins, it equals zero.

✦**Note**: in other organs, π_i plays an important role in determining filtration rate. This depends on the permeability of the capillaries to proteins. In the liver interstitium, for instance, π_i is very high due to the very high permeability of the liver capillaries to plasma proteins.

- P_c favors filtration while P_i and π_c favor reabsorption. Therefore, net filtration pressure equals **60 – 18 – 32, or 10 mm Hg**.



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)

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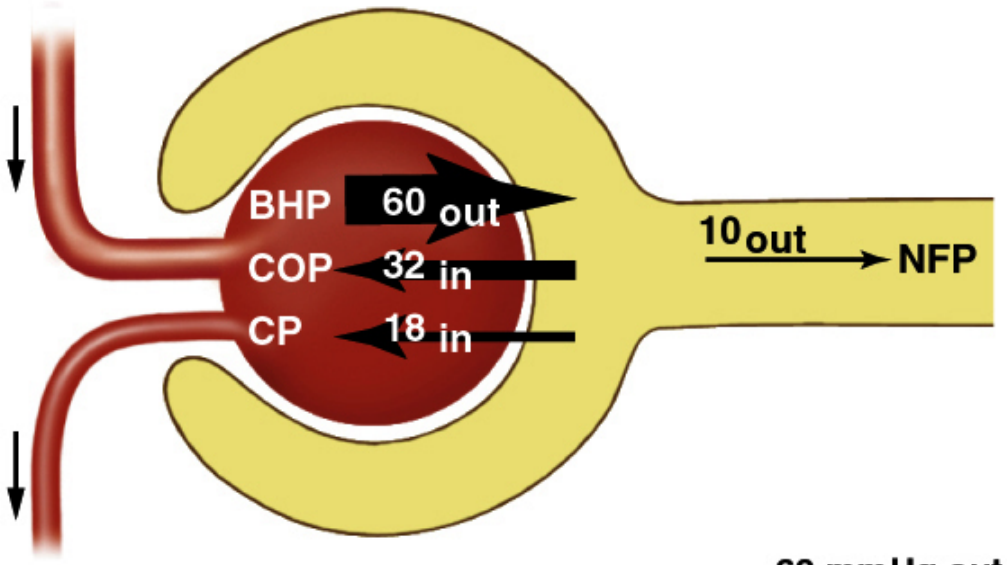
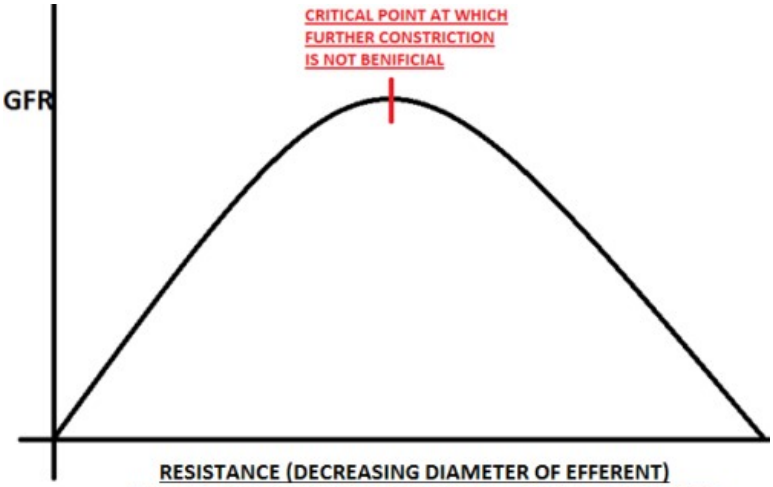
- 

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

- Any obstruction to urine flow (e.g., in prostate hypertrophy and stone formation) increases the hydrostatic pressure inside the Bowman's capsule, decreasing the GFR.
- **Note:** From the glomerular capillaries, 180 L/day are filtered. In contrast, only 20 L/day are filtered throughout the rest of the body. This is attributable to the relatively low P_c in other body capillaries, plus high **(K_f)** in the kidney.
- **Always remember Ohm's law:** Flow is directly proportional to driving force and inversely proportional to R. We replace R by **(K_f)**: GFR=P_f***(K_f) so more filtration is either due to increase in filtration pressure or (K_f)or both.**
- K_f = 12.5 ml/min per mmHg, or 4.2 ml/min per mmHg/ 100gm (400 x greater than in many other tissues)
- K_f = hydraulic conductivity * surface area. (Cannot b measured directly but indirectly, exactly like resistance, do you remember from the respiratory physiology when I told you that resistance and permeability are both vague concepts and cannot be measured directly in our body)
- Disease that can reduce K_f and GFR: hronic hypertension, obesity / diabetes mellitus increases the thickness of the basement membrane, glomerulonephritis

- Normal GFR must be maintained. Increased GFR as a result of an increase in P_c or an increase in the permeability of the capillaries, for example, results in generalized edema; decreased GFR causes waste products to accumulate in the plasma.



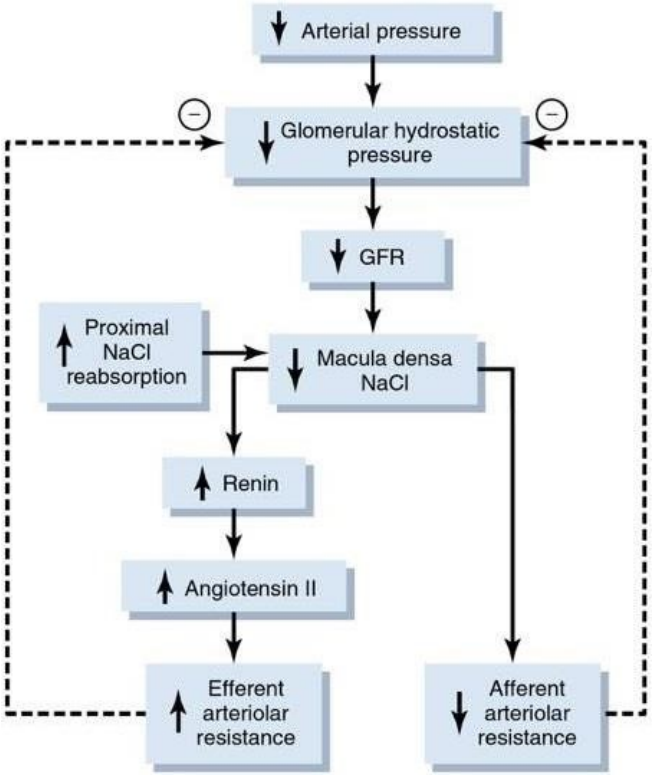
INCREASING RESISTANCE OF EFFERENT AND ITS EFFECT ON GFR

- P_c can be physiologically increased or decreased markedly by changing efferent and afferent arterioles diameters. Constricting the afferent arteriole causes decreased blood reaching the capillaries, hence decreased P_c and filtration rate. Also, constricting the efferent arterioles causes blood to accumulate in the capillaries. This results, at the beginning, in increase in P_c and filtration rate. However, after a while, fluid leaving the capillaries will leave behind very concentrated proteins (i.e., high π_c**)** which would oppose further filtration.

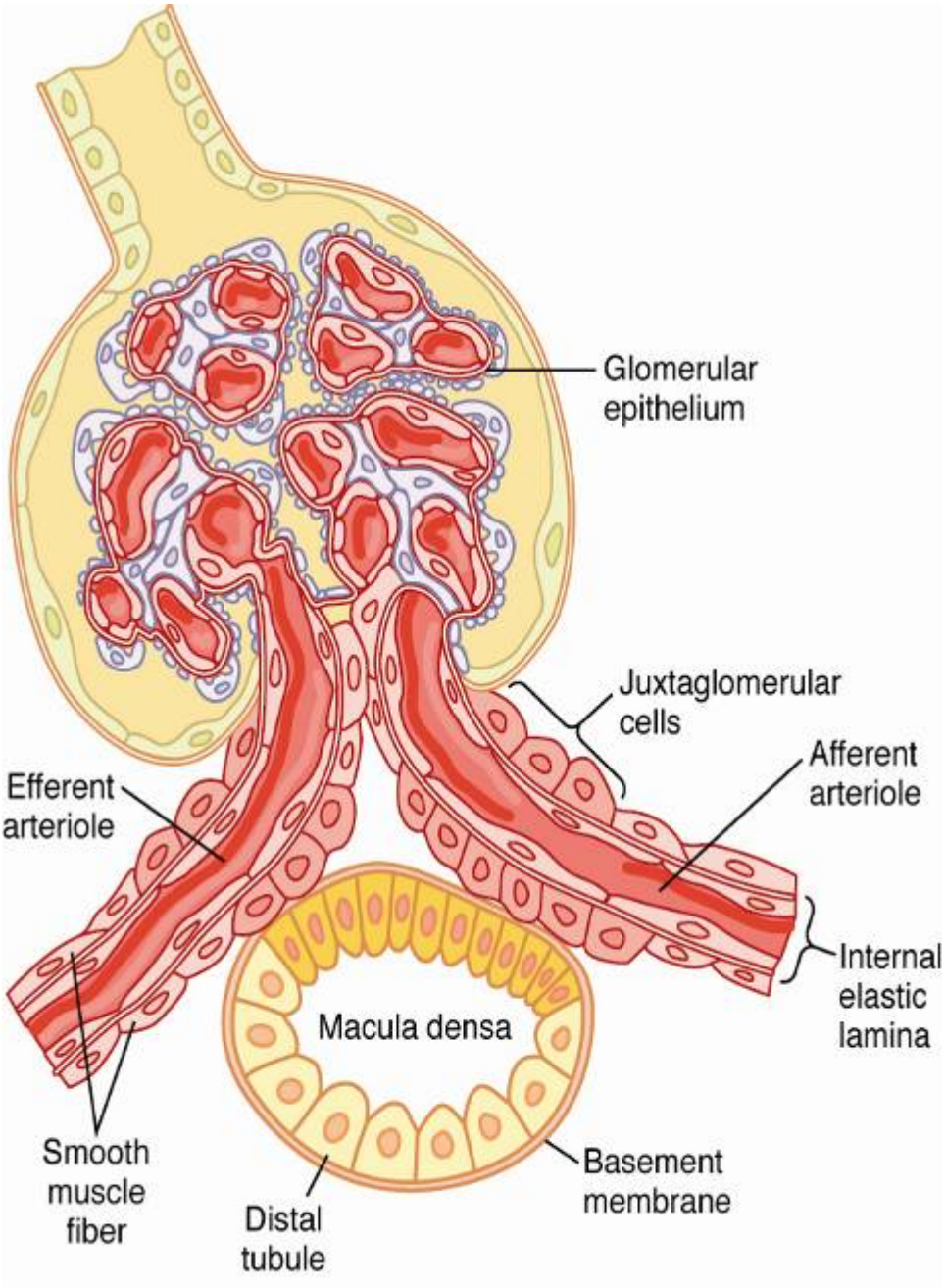
  Thus, any drug that, directly or indirectly, constricts the afferent arterioles can decrease the GFR. NSAIDs for example inhibit the formation of prostaglandins, which normally dilate the afferent arterioles. Therefore, kidney functions must be monitored regularly whith NSAIDs administration, especially for chronic diseases; Even a slight incrase in creatinine level after the administration of such drugs may require stopping the drug, especially in old-aged patients, whose GFR is already declining.

- The GFR is not affected by a small increase or decrease in mean arterial pressure (MAP). Otherwise, even an MAP of 90 mm Hg, which is not far from normal value (93 mmHg), would decrease P_c to 50 mmHg. This would, in turn, stop filtration.

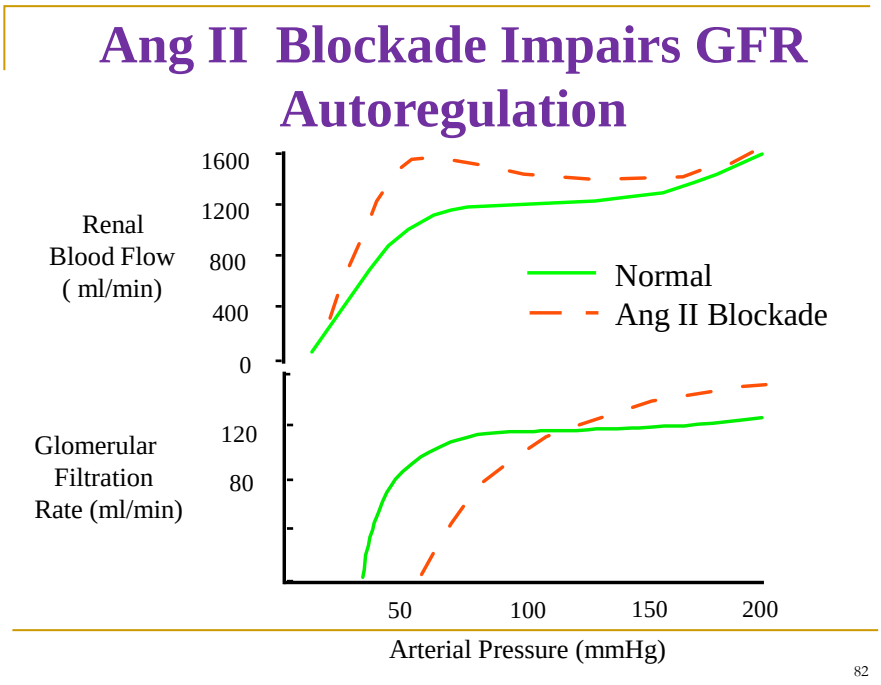
- How does the body maintain constant GFR despite the huge daily fluctuations in MAP? There are two physiological mechanisms that function to ***autoregulate* GFR** and RPF. To answer the question, the juxtaglomerular complex must be discussed first.

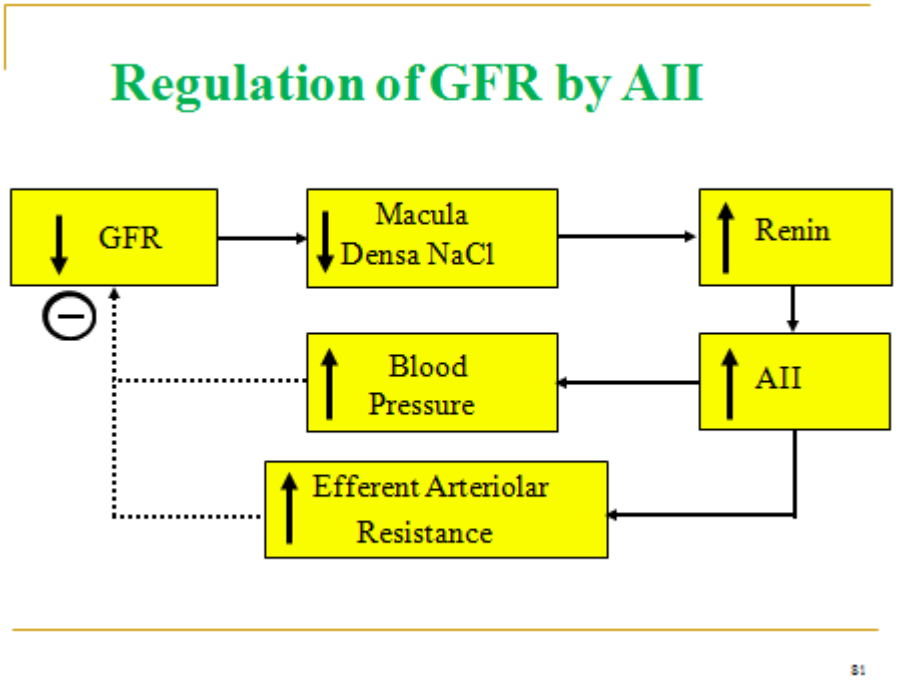


- This complex consists of 2 types of cells:
  - Macula densa which is a group of specialized epithelial cells located in the initial portion of the distal tubule.
  - Juxtaglomerular cells which are located in the walls of the efferent and afferent arterioles. They are the major storage sites for the enzyme, renin.


Glomerular epithelium
Juxtaglomerular cells
Afferent arteriole
Efferent arteriole
Internal elastic lamina
Macula densa
Smooth muscle fiber
Basement membrane
Distal tubule

✦





- Decreased GFR slows the flow rate in the loop of Henle causing increased reabsorption of Na^+ and Cl^- in the ascending loop of Henle, thereby decreasing their concentrations at the macula densa cells. This initiates a signal from the macula densa, which:
  - ✦ Decreases resistance to blood flow in the afferent arterioles raising P_c and helping returning GFR toward normal.
  - ✦ Increases renin release from the juxtaglomerular cells.

- Renin enzymatically cleaves angiotensinogen forming angiotensin I, which is further cleaved by a converting enzyme in the lungs to form angiotensin II.

- Angiotensin II helps to correct the GFR by
  - ✦ Potently constricting the arterioles of the body increasing MAP.
  - ✦ Constricting the efferent arterioles increasing P_c in the glomerular capillaries and helping returning GFR toward normal.
  - ✦ Directly increasing the reabsorption of Na^+ from the nephron, especially the proximal tubules.
  - ✦ Increasing aldosterone secretion from the adrenal glands. This increases Na+ and water reabsorption, as discussed later.

- Constricting the efferent arterioles is not only important to increase P_c in the capillaries but also to decrease P_c ahead of the efferent arterioles (i.e., peritubular capillaries). This causes the hydrostatic pressure in these vessels to decrease allowing the opposing forces to increase reabsorption, thereby conserving body fluids, at the same time get rid of waste products (urea/Cr)

- With these mechanisms, the GFR changes only a few percentage points, even with large fluctuations in MAP between the two limits (75 and 160 mm Hg).

- **Remember**: Since only 0.5% of fluids passing through most other systemic capillaries are filtered, π_c does not change significantly throughout the capillaries (i.e., remains 28 mm Hg) **Remember**: albumin, *and not globulins*, is the main protein which determines $\boldsymbol{\pi_c}$ although plasma concentration of albumin is only slightly higher than that of globulins. The reason for this is that the molecular weight of albumin is much less than that of globulins, 70,000 and 200.000, respectively. This means that 1mg/ml of albumin would contain more molecules than similar concentration of globulins. Since *osmolality is determined by the number of particles*, albumin exerts more oncotic pressure than globulins at same concentrations.

Importance of Autoregulation

Arterial Pressure	GFR	Reabsorption	Urine Volume
1- Poor Autoregulation + no change in tubular reabsorption			
100	125	124	1.0
120	150	124	26.0 = 37.4 L/day!
2- Good Autoregulation + no change in tubular reabsorption			
120	130	124	6.0
3 Good Autoregulation+adaptive increase in tubular reabsorption			
120	130	128.8	1.2

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Control of GFR and renal blood flow

1. Sympathetic Nervous System /catecholamines

$\uparrow\uparrow R_A + \uparrow R_E \longrightarrow \downarrow GFR + \downarrow\downarrow RBF$

e.g. severe hemorrhage.

Under normal conditions Sympathetic tone have little influence on RBF.

Sympathetic system may not influence RBF under normal circumstances, but in severe sympathetic stimulation it may decrease RBF significantly

2. Angiotensin II

$\uparrow R_E \longrightarrow \longleftrightarrow GFR + \downarrow RBF$

(prevents a decrease in GFR)

e.g. low sodium diet, volume depletion

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3. Prostaglandins

$\downarrow\downarrow R_A + \downarrow R_E \longrightarrow \uparrow GFR + \uparrow\uparrow RBF$

Blockade of prostaglandin synthesis → ↓ GFR

This is usually important only when there are other disturbances that are already tending to lower GFR. If Aspirin is administered which suppresses PGs then a severe decrease in GFR might occur.

e.g. nonsteroidal antiinflammatory drugs NDAID in a volume depleted patient, or a patient with heart failure, cirrhosis, etc

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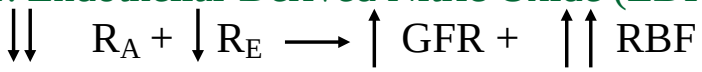
Control of GFR and renal blood flow

4. Endothelial-Derived Nitric Oxide (EDRF)



- Protects against excessive vasoconstriction
- Patients with endothelial dysfunction (e.g. atherosclerosis) may have greater risk for excessive decrease in GFR in response to stimuli such as volume depletion

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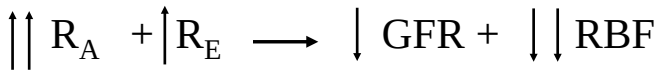
Control of GFR and renal blood flow

5. Endothelin



- Hepatorenal syndrome – decreased renal function in cirrhosis or liver disease?
- Acute renal failure (e.g. contrast media nephropathy)?
- Hypertensive patients with chronic renal failure?

Endothelin antagonists may be useful in these conditions

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Other Factors That Influence GFR

- Fever, pyrogens: increase GFR
- Glucorticoids: increase GFR
- Aging: decreases GFR 10% / decade after 40 yrs
- Hyperglycemia: increases GFR (diabetes mellitus)
- Dietary protein: high protein increases GFR
  low protein decreases GFR

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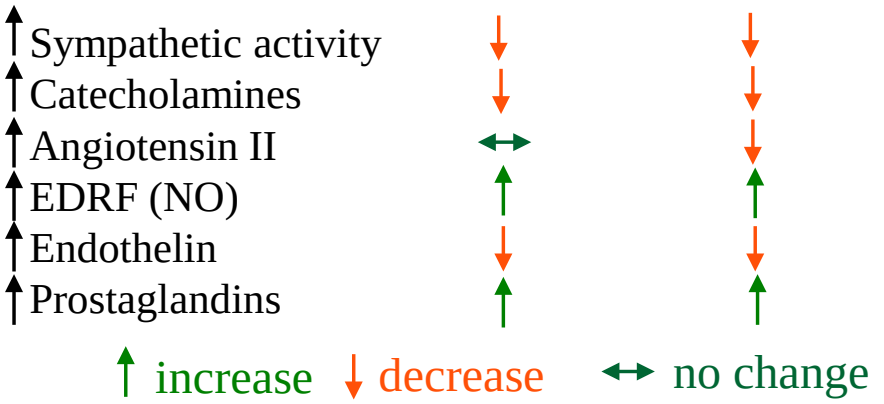
Summary of neurohumoral control of GFR and renal blood flow



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Other Factors That Influence GFR

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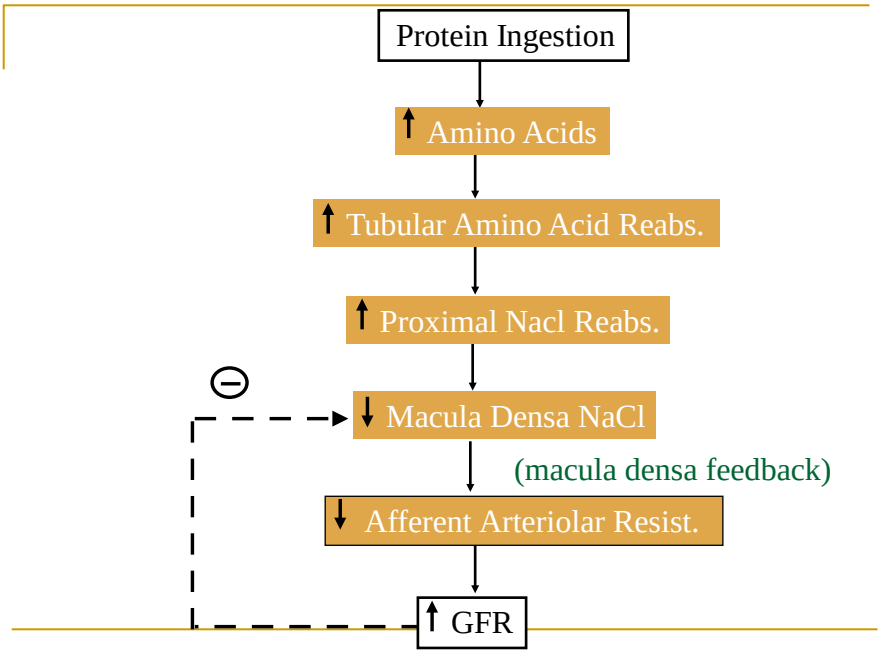

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••Measuring GFR (Both tGFR and eGFR)

Filtered Load

0 If a substance is freely filtered in the kidneys (i.e., its filterability is 1), then the filtration rate of that substance is referred to as the filtered load and is calculated as follow:

Filtered load (amount per unit time (mg/min)) = **GFR x plasma concentration**

To measure GFR, you use glomerular marker (Freely filtered, *neither absorbed nor secreted*).

Do we have such a substance? Actually we do. But we really don't use, since it is an exogenous substance and maintaining its plasma level constant is headache and actually not practical. Anyway this substance is "inulin"

- Inulin is a starch-like polymer of fructose (MW 5000) that is freely filtered (i.e., its filterability is 1). What special about this substance, making it suitable for measuring GFR, is that it is *neither absorbed nor secreted.* In other words, *Inulin that is filtered is that excreted*. Thus, the clearance of inulin is, in fact, the GFR. It doesn't under-or-over-estimate GFR. Mathematically:

- C_{inulin}=**GFR x P_s = V x U_s.**

- Regardless of its plasma concentration, C_{in} remains constant

- Let us practice calculating plasma clearance using the clearance equation. Assume that the urine production rate (V) is 2 ml/min. Let's start with the substance inulin (not insulin!). If after equilibrium (takes several hour) of inulin, your urine has 30 mg/ml and your plasma has 0.5 mg/ml of this substance, what is the inulin clearance rate? If you got 120ml/min, you are correct. If you did not get 120ml/min, look at the following calculation and recheck your work

  - 120 ml/min = 2 ml/min x 30 mg/ml/ 0.5 mg/ml

  - Test your ability to conduct further calculations by calculating the clearance rate for the following substances:

  - Substance Urine concentration Plasma concentration

  - **Urea** 7.0 mg/ml 0.2 mg/ml

  - **Glucose** 0.0 mg/ml 1.0 mg/ml

  - **Penicillin** 298 mg/ml 0.7 mg/ml

  - Remember that the urine production rate (2ml/min) will be the same for all of the above calculations. The clearance rate for each of the above substances will be: **Urea** = 70 ml/min; **Glucose** = 0 ml/min; **Penicillin** = 851 ml/min!!!too much. Were you able to get the right answers? If not, go back and restudy the clearance process.

- Inulin, like PAH, is an exogenous substance. This makes it only suitable to measure GFR for researchpurposes, and not routine clinical, purposes.

Creatinine: comes from creas in Latin means flesh اللحم

Another substance that is endogenous (it is advantage to have endogenous leased at constants rate and does not fluctuate significantly by food intake, physical activity, fasting, . Because It is endogenous source, …we don't need to infuse it to the person. It is frequently used in clinical practice o measure the GFR. Unlike urea, it is not affected by food intake, or dehydration, GIT bleeding etc.Cr concentration does not fluctuate from day to day in plasma

- Small molecule (MW is 114), so it is freely filtered. To convert mg/dl of creatinine to µmol/l, multiply by 88.4. Can you do it to urea (MW 60 concentration 15mg/dl???)

  Freely filtered, not reabsorbed but SLIGHTLY SECRETED (we will deal with this small secretion later on).

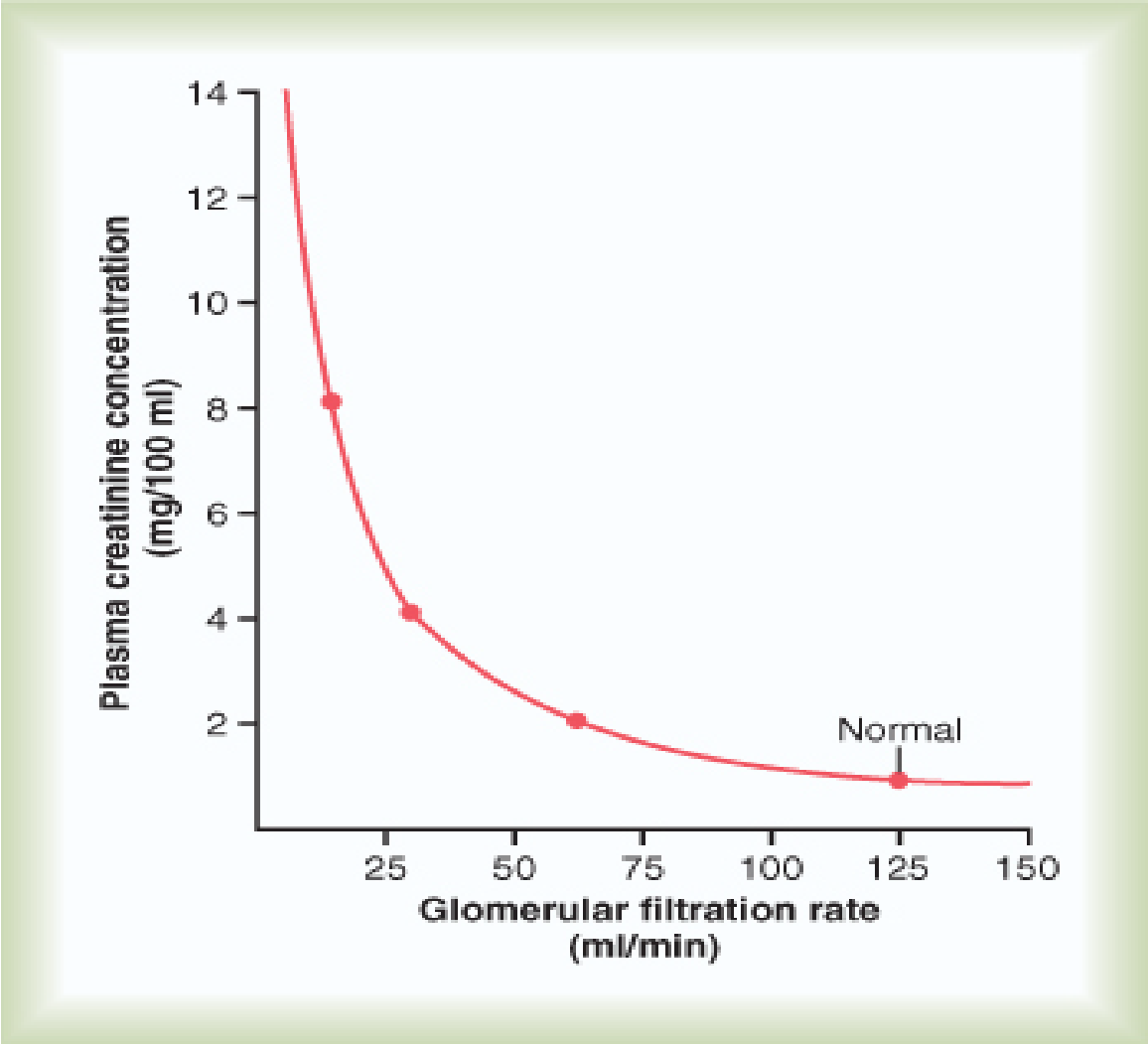
  Plasma creatinine by itself (without creatinine clearance) is a good indicator of renal function because it does not relate to food intake or level of exercise

- Creatinine in the urine comes from: 90% filtered and 10% through secretion. This has the potential to overestimates GFR by 10%. But in actuality it does not…why? In fact, it does overestimate GFR in end-stage renal failure…again WHY? Look for the answer in both cases

- Creatinine is freely filtered but around 10% of the excreted comes from secretion (overestimation of GFR at this point..wait). This overestimate the GFR. However, in plasma, 10% of creatinine is bound to proteins, and thus not filtered. This underestimates GFR. Since GFR will be 10% overestimated and 10% underestimated, measured GFR is almost the actual GFR. (they cancel each others)

- **Creatinine**
  As mentioned before, the typical reference ranges are: Men 0.7 to 1.2 mg/dL (60-110 µmol/l), for women: 0.5 to 1.0 mg/dL (about 45-90 µmol/l) . While a baseline serum creatinine of 2.0 mg/dL (150 µmol/l) may indicate normal kidney function in a male body builder (too much muscle), a serum creatinine of 0.7 mg/dL (60 µmol/l) can indicate significant renal disease in a frail old woman.

In the United States, creatinine is typically reported in mg/dL, while in Canada and Europe µmol/litre may be used. 1 mg/dL of creatinine is 88.4 µmol/l.

- **Note:** when measuring plasma creatinine concentration, you should ask the lab which one is measured (is it the free cr or the total cr?)
- Plasma concentration of creatinine is 1 mg/dl (there is wide range0.7-1.2 mg/dl). Therefore, filtered load of creatinine can be calculated by multiplying 1 mg/dl by GFR which is 125 ml/min. This yields 1.25 mg/min or 1.8 g/day. From this you can understand that we excrete 1.8 g of cr/d.
- 

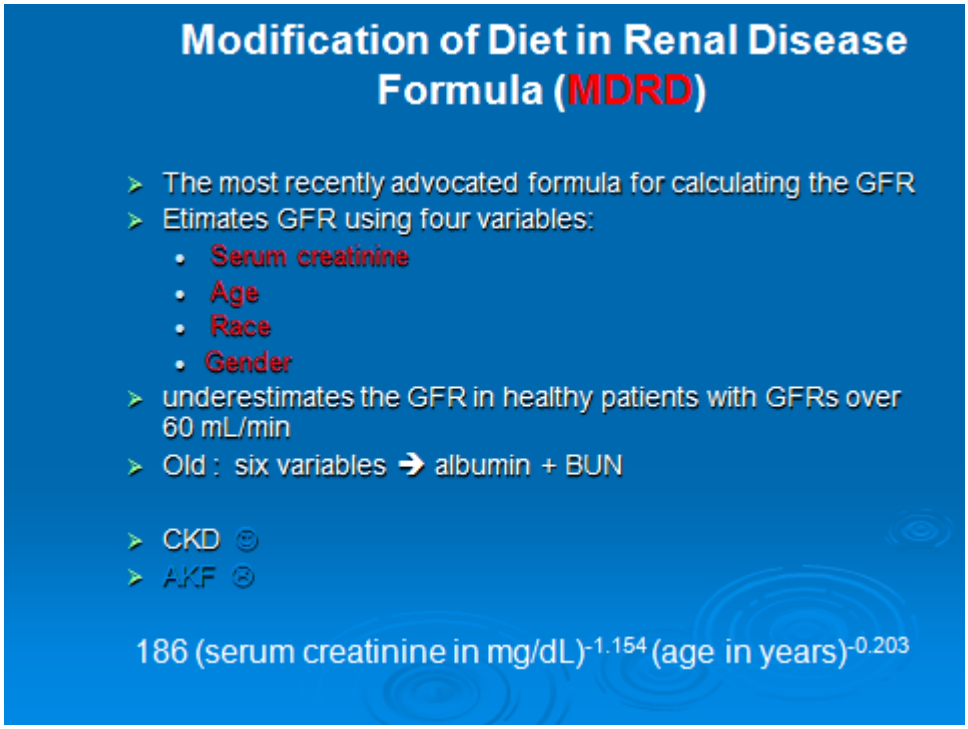
- Creatinine excretion (and formation) rate is also 1.8 g/day. It is not much affected by muscular activity and a range between 1.5 and 2 g/day is considered normal. Females and children have less muscle mass and thus less creatinine levels in plasma and urine.

- Note that the plasma creatinine concentration reflects the GFR. If, for instance, measured to be 3 mg/dl, then one can tell that this 3-fold increase is a result of a decrease in GFR to 1/3: two thirds of nephrons are gone.
- Using the equation of clearance, the clearance of creatinine or **GFR = (U_{cr} x V) / P_{cr}.**
- Plasma and urine concentrations of creatinine are easily measured. In contrast, urine volume over the day is not always compatible due to the patients' incompliance, especially elderly and children. Therefore, two equations are used to estimate GFR (ml/min/1.73m^2) without the need to collect urine. The first is used to estimate GFR for adults and the second for children:

- **GFR = (140 – age) x ideal body weight x 1 (for males) or 0.85 (for females) / (72 x P_{cr}).**
- **GFR = K x height (cm) / P_{cr}, where K depends on muscle mass which varies with child age.**

- **$C_{creatinine}$**
- Cockcroft and Gault formula (in Adults)
- eC_{cr} Estimated creatinine clearance =
- (140–age in yr) x weight (kg) x 0.85 (if female)] divided by serum creatinine concentration (mg/dl)X 72.
-
- **According to Schwartz Formula in Children** (الارقام والمعادلة للإستئناس وليس للحفظ)
- GFR (mL/min/1.73 m^2) = k * Height (cm) / Serum Creatinine (mg/dl)
- k = 0.33 in premature Infants
- k = 0.45 in Term infants to 1 year old
- k = 0.55 in Children to 13 years
- k = 0.65 in Adolescent male
- $$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$
- Cockcroft and Gault published an equation to predict creatinine clearance based on age, weight, height and plasma creatinine, together with correction factors. Although helpful, it has many inherent limitations, having been derived mostly from hospitalized men (with only nine females in the cohort), all of whom had CKD. The requirement for weight and height to be provided also restricted its ability to be reported by the laboratory. Despite these shortcomings, it has achieved a considerable prominence, more through cumulated experience than a solid evidence base
- ANY Equation which does not incorporate lean body mass will mislead us.

- **Formulas Used To Estimate GFR (You don't have to memorize** any of them). Ask Google to make the calculation for you. But it is good to understand the origin of these equations.
- Modification of Diet in Renal Disease (MDRD) formula
- Cockcroft-Gault formula
- CKD-EPI formula
- Chronic Kidney Disease Epidemiology Collaboration
- Mayo Quadratic formula
- Schwartz formula



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- The advantage of this equation over Cockcroft and Gault's was the lack of requirement for either body weight or height to be supplied and it became the preferred equation. The MDRD study equation was subsequently validated in patients with diabetic kidney disease, renal transplant recipients, and African-Americans with non-diabetic kidney disease. Given that the MDRD equation was originally derived from a group of CKD patients, its utility for healthy individuals remains unclear, and strictly it has not been validated in children under 18 years of age, in pregnant women, in patients above 70 years of age, and in ethnic groups other than African-American. More importantly, given the rise in the epidemic proportions of global obesity, the MDRD equation has not yet been validated at extremes of body weight, further limiting its usefulness in targeting individuals at higher risks of developing CKD

- Serum creatinine can be affected by age, gender, ethnicity, dietary protein intake, and lean mass and may remain within the reference range despite marked renal impairment in patients with low muscle mass. Consequently, the sensitivity of serum creatinine for the early detection of kidney disease is poor and not a good predictor when analyzing the elderly
- Conversely, theoretically, serum creatinine may be falsely increased in individuals with higher muscle mass and normal tGFR.
- **Cystatin C**, a low molecular weight basic protein (13 kD) that is freely filtered. is an endogenous filtration marker that is being considered as a potential

replacement for serum creatinine. Unlike serum creatinine, the serum concentration of cystatin remains constant up to 50 yr of age. It is commonly accepted that cystatin is produced at a constant rate in virtually all nucleated cells and that it is unaltered by inflammatory conditions. The advantages of using cystatin C as a filtration marker are less influence by age, gender, weight, and muscle mass than serum creatinine. An overall meta-analysis based on 46 studies performed on adults and children demonstrated, by means of receiver operating characteristic analysis, that cystatin C is superior to serum creatinine as a marker of kidney function.

- Blood urea varies with daily protein intake, G.I bleeding, exercise, hypercatabolic states (fever, thyrotoxicosis, trauma etc) and dehydration.
- The ratio of urea to creatinine can be used to determine the etiology of acute renal failure. Normally, the ratio is 10 to 1. The ratio usually exceeds 20 in prerenal failure due to decreased renal perfusion, such as occurs with hypertension, hemorrhage, or dehydration. Postrenal diseases, such as urinary tract obstruction, also increase the ratio between 10 and 20. In intrinsic renal disease because urea and creatinine rise proportionately. The clinical usefulness of this ratio is limited by nonrenal factors that increase urea such as; GI bleeding, parenteral nutrition, and glucocorticoid therapy. GI bleeding increases urea more than creatinine because of increased amino acid absorption from digested blood and hypovolemia.

BUN:Cr

BUN:Cr	Urea:Cr	Location	Mechanism
>20:1	>100:1	Prerenal (before the kidney)	BUN reabsorption is increased. BUN is disproportionately elevated relative to creatinine in serum. Dehydration is suspected.
10-20:1	40-100:1	Normal or Postrenal (after the kidney)	Normal range. Can also be postrenal disease. BUN reabsorption is within normal limits.
<10:1	<40:1	Intrarenal (within kidney)	Renal damage causes reduced reabsorption of BUN, therefore lowering the BUN:Cr ratio.

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- Note that the accuracy of GFR measurement using these equations is around 95%. However, in end-stage renal failure, these equations cannot be used since, in this case, GFR approaches zero and thus, excreted amount is the secreted, not filtered; thus, creatinine clearance overestimates GFR.

- the bottom line is that equations for estimation of GFR are available and accurate. Pcr and anthropometric measures are utilized without the need for 24 hour urine collection.
- Gradual loss of renal function with age is a normal process (1% each year), as in the case of the female patient in the previous example. Although her GFR is markedly reduced, it is probable that she has normal renal function. Even if she has hypertension, it is most likely due to age-related vascular degenerative processes.
- Notice that estimations of GFR are unacceptable in cases of end-stage renal disease.

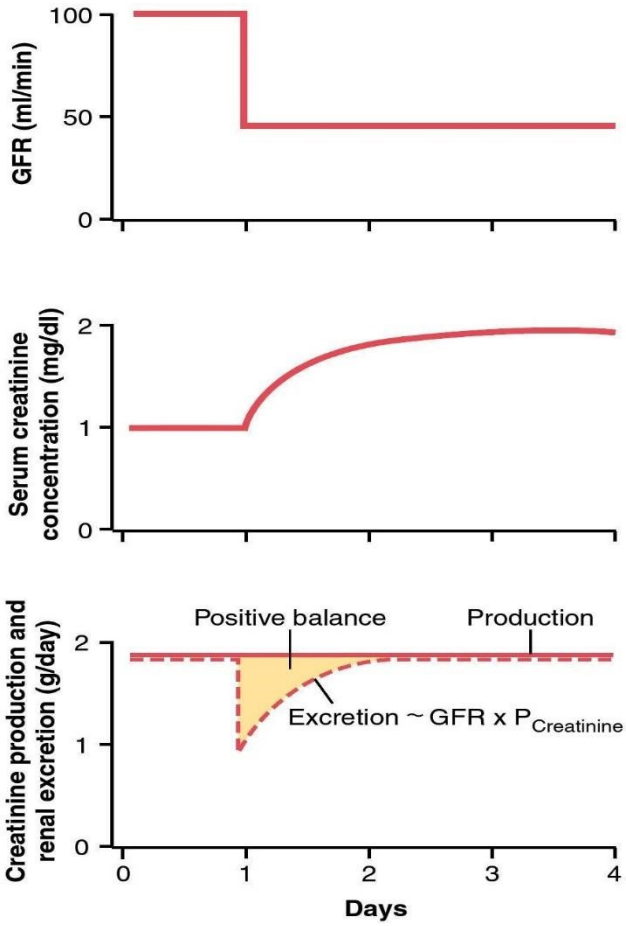
- Renal diseases are classified according to the percentage of GFR to normal:
  - **50-99%:** decreased renal preserve. Usually asymptomatic with normal urea and creatinine levels.
  - **20-49%:** renal insufficiency. Urea and creatinine levels are elevated, and usually, accompanied with anemia and hypertension. However, the patient survives with low salt and protein diet.

    5-19%: renal failure. External intervention is needed.

- **<5%:** end-stage renal failure. The patient must undergo hemodialysis and kidney transplant. oAlso, the severity of the renal diseases can be determined by the following classification:
- **60-89%:** mild; **30-59%:**moderate; **15-29%:** severe; **<15%:** end stage renal failure.

- If GFR suddenly decreases by 50%, the kidneys will transiently filter and excrete only half as much creatinine, causing accumulation of creatinine in the body fluids and raising plasma concentration twice normal.

- Plasma concentration of creatinine will continue to rise until the filtered load of creatinine (P_{Cr} × GFR) and creatinine excretion (U_{Cr} × V) return to normal and a balance between creatinine production and creatinine excretion is re-established but at the expense of elevated plasma creatinine concentration.



Age	GFR/1.73 m^2	
	Males	Females
20-29	94-140	72-110
30-39	79-137	71-121
40-49	76-120	50-102
50-59	67-109	50-102
60-69	54-98	45-75
70-79	49-79	37-61
80-89	30-60	27-55
90-99	26-44	26-42

- **Staging for Acute Kidney Injury (AKI)** GFR IS USED as a tool
- مرة أخرى ليست الارقام للحفظ ولكن لا مانع من النظر اليها لعلك ترجع لها في سنواتك السريرية)
- The *RIFLE criteria*, proposed by the acute dialysis quality initiative (ADQI) group, aid in the staging of patients with AKI

Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) classification

- Risk: GFR decrease >25%, serum creatinine increased 1.5 times or urine production of < 0.5 ml/kg/h for 6 hours
- Injury: GFR decrease > 50%, doubling of creatinine or urine production < 0.5 ml/kg/h for 12 hours
- Failure: GFR decrease > 75%, tripling of creatinine (> 4 mg/dl) OR urine output below 0.3 ml/kg/h for 24 hours or anuria for 12 hours.
- Loss: persistent AKI or complete loss of kidney function for more than 4 weeks
- End stage renal disease: need for renal replacement therapy (RRT) for more than 3 months