الفسلجة
مرحلة ثانية

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Urinary system
Lec. 1

The Role of the Kidneys in the Body Includes:

- Regulation of the volume and composition of the ECF, by maintaining a balance between intake and output of water and electrolytes in the body.
- Excretion and elimination of waste products of metabolism, such as the excretion of urea, creatinine and uric acids; as well as the excretion of various toxins such as drugs and food additives.
- The kidneys act as endocrine glands producing hormones, such as “erythropoietin hormone” and renin.
- Playing a dominant role in the long-term and short-term regulation of arterial blood pressure.
- Kidneys along with the respiratory system contribute to acid-base regulation.
- Finally, kidneys synthesize glucose from aminoacids and other precursors.

The Process of Urine Formation:

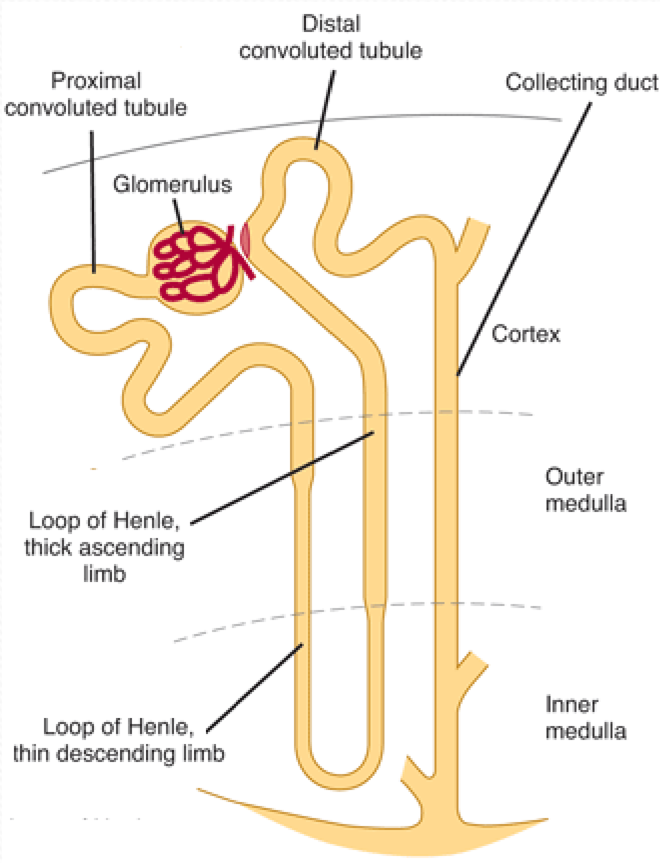
- Urine formation begins with the **filtration of plasma through the GC** into the Bowman's space.

- As the filtered fluid flows through the remaining portions of the tubule, its composition is altered as a result of two main processes:

- **Tubular reabsorption**.

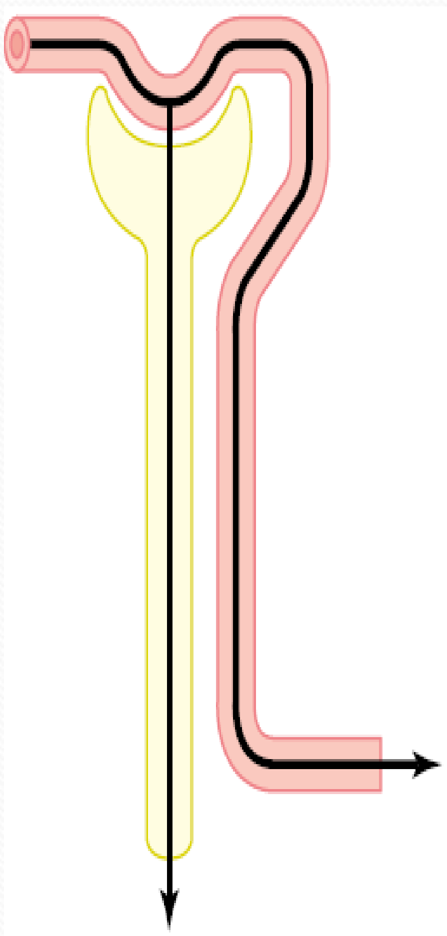
- **Tubular secretion**.

and both processes will produce the final product, *urine*.



Concept of Clearance:

- The renal clearance of a substance is the volume of plasma that is completely cleared or cleaned of that substance by the kidney per unit of time.
- (usually expressed as mL/ minute).
- somewhat **abstract** (**theoretical**), **because no single volume of plasma that is completely cleared of a substance**.
- However, renal clearance provides a useful way of quantifying renal excretory functions.
- It can be used to quantify the rate at which blood flows through the kidneys, as well as to measure the basic kidney functions such as GFR.



Concept of Clearance:

- Renal clearance of a substance (S) is calculated by dividing the urinary excretion rate of (S) ($U_S \times V^\bullet$) by its plasma concentration (P_S), as expressed below:

$$C_S = \frac{U_S \times V^\bullet}{P_S}$$

- Where: U_S = urine concentration of S.

  $V^\bullet$ = urine flow rate/ minute = (0.9 mL/ minute).

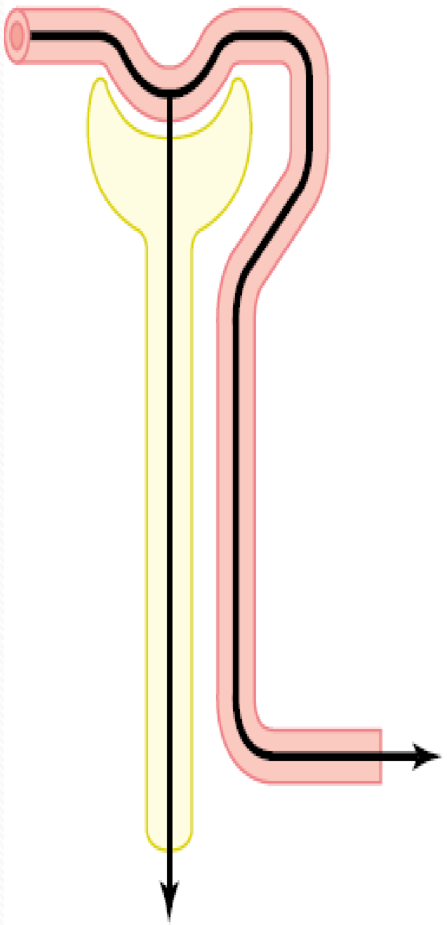
  P_S = plasma concentration of S.

- Clearance of any substance depends on the behavior of the tubular cell towards that substance:

- If a substance like inulin, which is freely filtered at the glomerulus level and is neither reabsorbed nor secreted by the renal tubule, then its clearance equals to GFR.

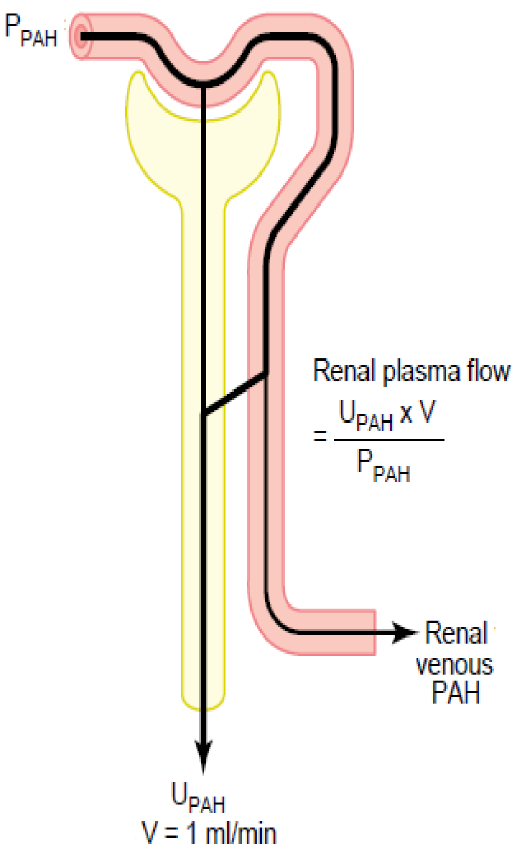
- On the other hand, if a substance is reabsorbed by the renal tubule, its clearance is lower than the GFR.

- Finally, if a substance that is in addition to filtration is secreted by the renal tubule, then its clearance is higher than the GFR.



Estimation of Renal Plasma Flow (RPF):

- ***Theoretically***, if a substance **is *completely* cleared** from the plasma, i.e. **its extraction ratio is 100%**,
- Then, its clearance rate equals the **total renal plasma flow** (**RPF**).
- Such a substance should have the following criteria:
    - **should be freely filtered,**
    - **should be not metabolized by the kidney,**
    - **should be not stored or produced by the kidneys,**
    - **should be completely secreted by the renal tubules.**
- Para-aminohippuric acid (PAH) is about 90% cleared or extracted from plasma in a single circulation through the kidneys.
- *the volume of plasma that is completely cleared of PAH per unit of time; must equal, nearly, the total plasma volume that passes through both kidneys per unit of time (RPF).*
- The value that is obtained should be referred to as **effective renal plasma flow (ERPF)** to indicate that the level in renal venous plasma was not measured: i.e., (arterial concentration minus renal venous concentration divided by arterial concentration) is high.



Estimation of Renal Plasma Flow (RPF):

$$ERPF = C_{PAH} = \frac{U_{PAH} \times \dot{V}}{P_{PAH}}$$

Where: U_{PAH} = 14 mg/ mL.

$\dot{V}$ = urine flow rate.

P_{PAH} = 0.02 mg/ mL.

ERPF = 630 mL/ minute.

- To calculate the actual RPF, we divide (ERPF/ extraction ratio) of the PAH; as follows:

$$\textit{Actual RPF} = \frac{ERPF}{\text{Extraction ratio}_{PAH}} = \frac{630}{0.90} = 700 \text{ mL/ minute.}$$

- From the RPF, the total renal blood flow (RBF) can be calculated by dividing the RPF by (1 – hematocrit), as follows:
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$$RBF = \frac{RPF}{1 - 0.45} = \frac{700}{0.55} = 1273 \text{ mL/ minute.}$$

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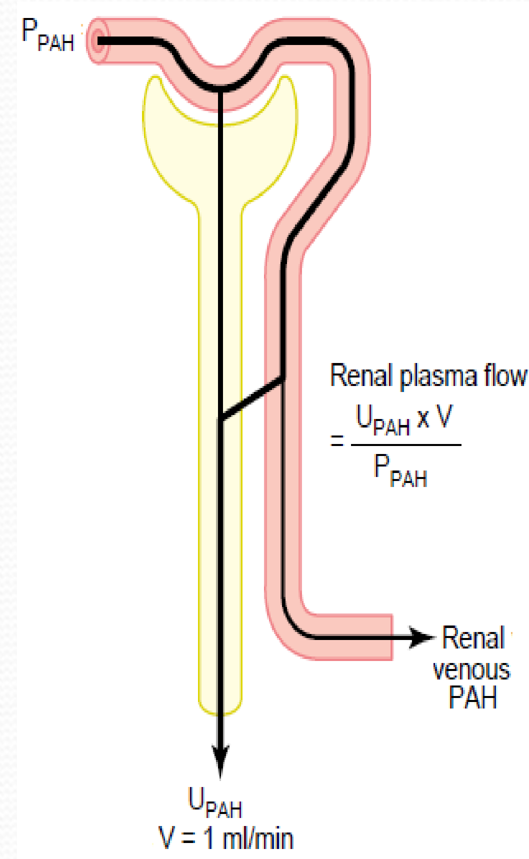


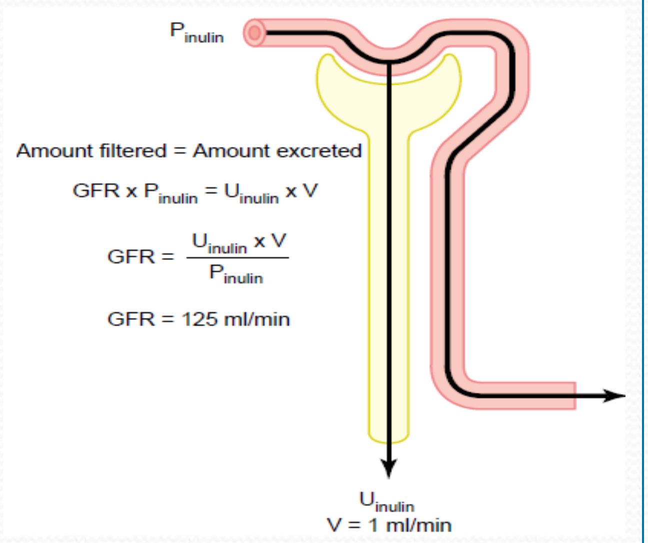
Glomerular Filtration Rate (GFR):

- **GFR can be defined as the volume of plasma that is filtered by the GC in both kidneys per unit of time.**
- The substance used for the measurement of GFR should be:
  - **freely filtered,**
  - **neither reabsorbed nor secreted by the renal tubules,**
  - **Moreover, it should be non-toxic,**
  - **not metabolized by the body.**
- The substance that has such criteria is inulin, a polymer of fructose.
- Inulin is not produced in the body and must be given by intravenous infusion to produce a constant plasma level. Therefore, GFR can be calculated as the clearance of inulin as follows:

$$GFR \times P_{inulin} = U_{inulin} \times \dot{V}$$

$$GFR = \frac{U_{inulin} \times \dot{V}}{P_{inulin}} = C_{inulin}$$

Where: U_{inulin} = inulin concentration in urine = 35 mg/ mL.
$\dot{V}$ = **urine flow rate = 0.9 mL/ minute**.
P_{inulin} = plasma concentration of inulin = 0.25 mg/ mL.



- **GFR = 125 mL/ minute**

Glomerular Filtration Rate (GFR):

N.B. The clearance of creatinine (the byproduct of muscle metabolism) can also be used to assess GFR,

- because its measurement does not require IV infusion into the patient, it is more widely used clinically.
- However, **creatinine clearance is not a perfect marker**, because a small amount of it is secreted by the tubules, so that the amount excreted slightly exceeds the amount filtered.
- Nevertheless, there is normally an overestimation of the plasma creatinine; hence, both errors tend to cancel each other.
- From above, the GFR in an average-sized normal man approximately = **125 mL/minute**, which equals to (**180 L/day**), whereas the normal urine volume is about (**1 L/ day**).
- **Thus, 99% or more of the filtrate is normally reabsorbed.**

- **Filtration Fraction:** It represents the ratio of the GFR to the renal plasma flow (RPF) which is normally around (**0.20** or **20%**)

Glomerular Filtration Rate (GFR):

Factors Affecting the GFR:

1. The Glomerular capillary membrane:

- The high permeability is due to the special structure of the glomerular membrane, These are the capillary endothelium and the specialized epithelium of the capsule made up of podocytes overlying the GC:

a. The presence of fenestrae in the endothelium of the GC with pores that are "70 – 90 nm" in diameter are responsible for the high filtration rate across the glomerular capillary membrane.

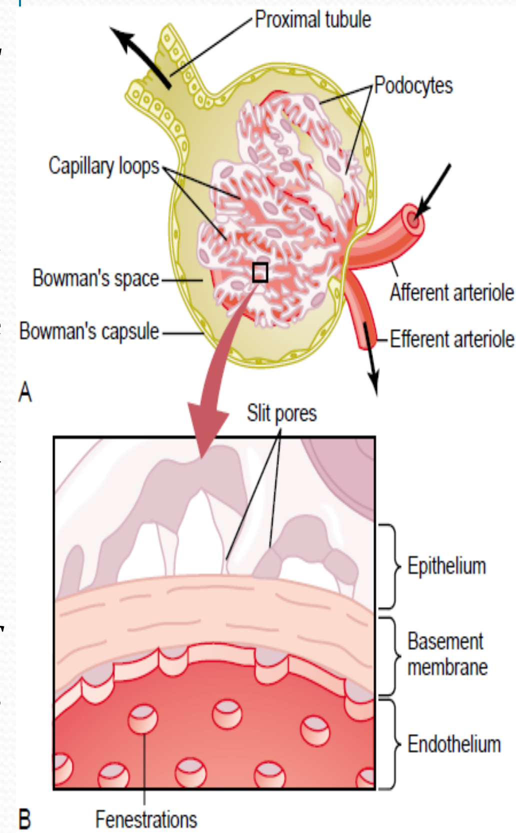
b. In addition, the podocytes is not a continuous layer with numerous pseudopodia (foot-like processes) that interdegitate to form the filtration slits along the capillary wall.

- Those two layers are separated by a "basal lamina" consisting of a meshwork of glycoproteins that has strong negative electrical charges, giving the membrane its high selectivity.

- Functionally, the glomerular membrane permits the free passage of neutral substances up to (4 nm) in diameter and almost totally excludes those with diameters greater than (8 nm). Between these values, filtration is inversely proportional to diameter and charge.

2. The Net Filtration Pressure.

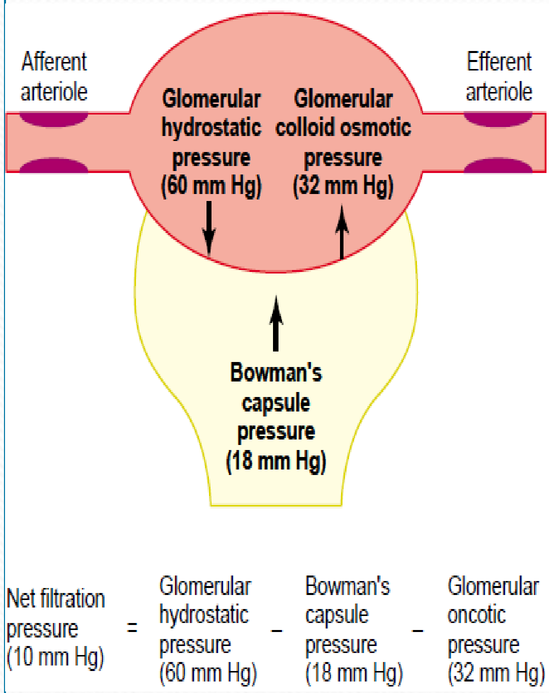
3. Size of the capillary bed (Effective filtration surface area).



Determinants of the GFR:

2. G F R = Kf × Net filtration pressure

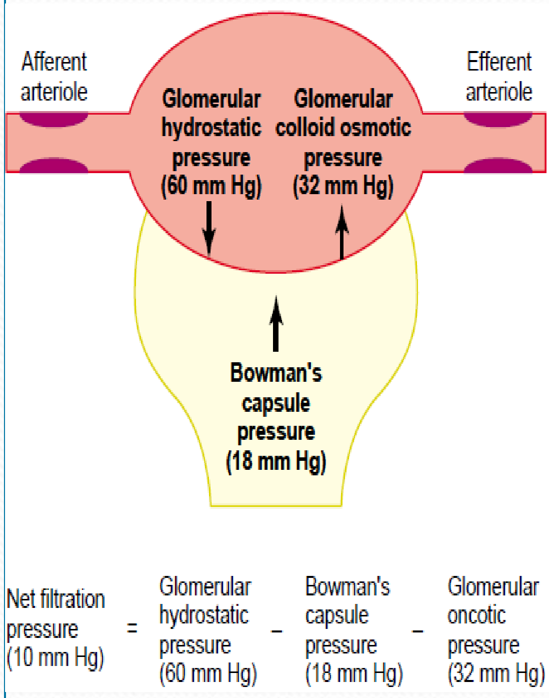
- Kf is a measure of the product of the hydraulic conductivity and surface area of the glomerular capillaries.
- hydraulic conductivity describes the ease with which a fluid (usually water) can move through pore spaces or fractures.
- Estimated experimentally, Kf = GFR/Net filtration pressure and is calculated to be about 12.5 ml/min/mm Hg of filteration pressure.
- This high Kf for the glomerular capillaries, about 400 times as high as other capillary systems of the body contributes tremendously to the rapid rate of fluid filtration.
- changes in Kf , probably do not provide a primary mechanism for the normal day-to-day regulation of GFR.
- Some diseases, however, lower Kf by reducing the number of functional glomerular capillaries (reducing surface area for filtration); or by increasing the thickness of the glomerular capillary membrane (reducing its hydraulic conductivity).
- e.g., chronic, uncontrolled hypertension and diabetes mellitus.



Determinants of the GFR:

The Net Filtration Pressure:

- The net filtration pressure represents the sum of the hydrostatic and colloid osmotic forces that either favor or oppose filtration :
  - i. hydrostatic pressure inside glomerular capillaries, (P_G), which promotes filtration;
  - ii. hydrostatic pressure in Bowman's capsule (P_B), which opposes filtration;
  - iii. colloid osmotic pressure of the glomerular capillary plasma proteins (π_G), which opposes filtration;
  - iv. colloid osmotic pressure of the proteins in Bowman's capsule (π_B), which promotes filtration (normally = 0).
- So, $GFR = K_f \times (P_G - P_B - \pi_G)$
- changes in Bowman's capsule pressure normally do not serve as a primary means for regulating GFR.
- Precipitation of "stones" that lodge in the urinary tract, raises Bowman's capsule pressure and reduces GFR and eventually can damage or even destroy the kidney.



Determinants of the GFR:

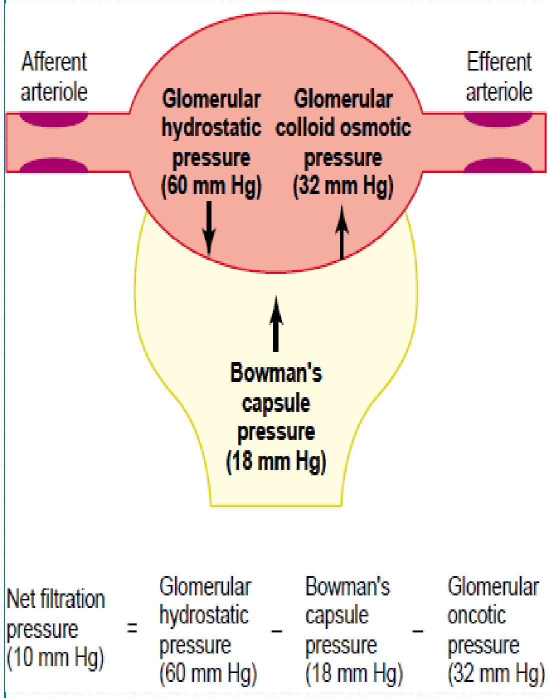
The Net Filtration Pressure:

- Factors that influence the glomerular capillary (π_G) are:

    (1) the arterial plasma colloid osmotic pressure ,

    (2) the fraction of plasma filtered by the GC (filtration fraction).

- Increasing the arterial plasma colloid osmotic pressure raises the (πG), which in turn decreases GFR.
- Increasing the filtration fraction also concentrates the plasma proteins and raises (πG).
- Filtration fraction can be increased either by raising GFR or by reducing renal plasma flow (FF = GFR/renal plasma flow).
- Changes in glomerular hydrostatic pressure serve as the primary means for physiologic regulation of GFR. Increases in (PG) raise GFR, and vice versa.
- Glomerular hydrostatic pressure is determined by three variables, under physiologic control: (1) arterial pressure, (2) afferent arteriolar resistance, and (3) efferent arteriolar resistance.
- Increased arterial pressure tends to raise glomerular (PG) and, therefore, to increase GFR. However, this effect is buffered by autoregulatory mechanisms.)
- Increased resistance of afferent arterioles reduces glomerular hydrostatic pressure and decreases GFR.
- Constriction of the efferent arterioles increases the resistance to outflow from the GC. This raises the glomerular (PG) , as long as it does not reduce renal blood flow too much, GFR increases slightly.
- Thus, efferent arteriolar constriction has a biphasic effect on GFR. At moderate levels of constriction, there is a slight increase in GFR, but with severe constriction (more than about a threefold increase in efferent arteriolar resistance, there is a decrease in GFR.



Physiologic Control of GFR & Renal Blood Flow

1. The Sympathetic NS Activation:

- Essentially all the blood vessels of the kidneys, including the afferent and the efferent arterioles, are richly innervated by sympathetic nerve fibers.
- Strong sympathetic activation can constrict the renal arterioles and decrease renal blood flow and GFR, while, moderate or mild stimulation has little influence.
- The renal sympathetic nerves are most important in reducing GFR during severe, acute disturbances lasting for a few (minutes- hours), e.g., brain ischemia, or severe hemorrhage.

2. Hormonal and Autacoid Control of GFR and Renal Circulation:

Hormones and Autacoids That Influence Glomerular Filtration Rate (GFR)

Hormone or Autacoid	Effect on GFR
Norepinephrine	↓
Epinephrine	↓
Endothelin	↓
Angiotensin II	↔ (prevents ↓)
Endothelial-derived nitric oxide	↑
Prostaglandins	↑

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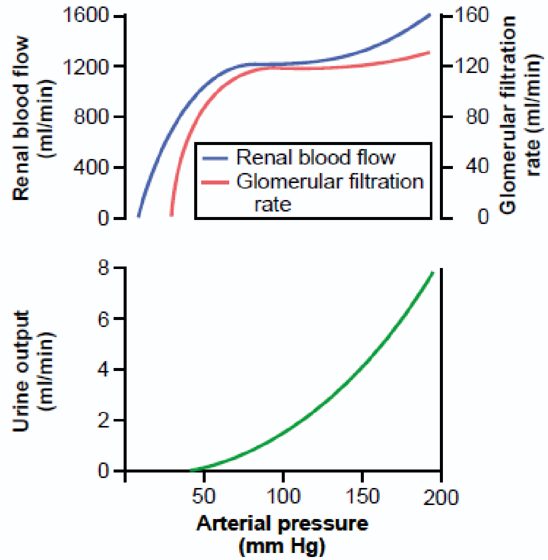
Physiologic Control of GFR & Renal Blood Flow

3. The Autoregulation of GFR and Renal Blood Flow:

- Feedback mechanisms intrinsic to the kidneys normally keep the RBF and GFR relatively constant, despite marked changes in arterial blood pressure; even in kidneys that have been removed from the body.
- This relative constancy of GFR and renal blood flow is referred to as *autoregulation*.
- A decrease in arterial pressure to as low as 75 mm Hg or an increase to as high as 160 mm Hg changes GFR only a few percentage points.



i. Role of Tubuloglomerular Feedback Mechanism:

- This feedback mechanism helps to ensure a relatively constant delivery of NaCl to the distal tubule and helps prevent spurious fluctuations in renal excretion.
- This mechanism has two components that act together : (1)an afferent arteriolar feedback and (2)an efferent arteriolar feedback.
- These feedback mechanisms depend on special anatomical arrangements of the *juxtaglomerular complex (apparatus)*.
- Decreased macula densa NaCl delivery causes a signal that lead to dilation of afferent arterioles and increased renin release:

a. it decreases resistance to blood flow in the afferent arterioles, which raises P_G and helps return GFR toward normal.

b. it increases renin release from the juxtaglomerular cells, which finally lead to angiotensin II formation that constricts the efferent arterioles, increases P_G and returning GFR toward normal.