Renal (Kidney) Physiology

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Jul, 2021

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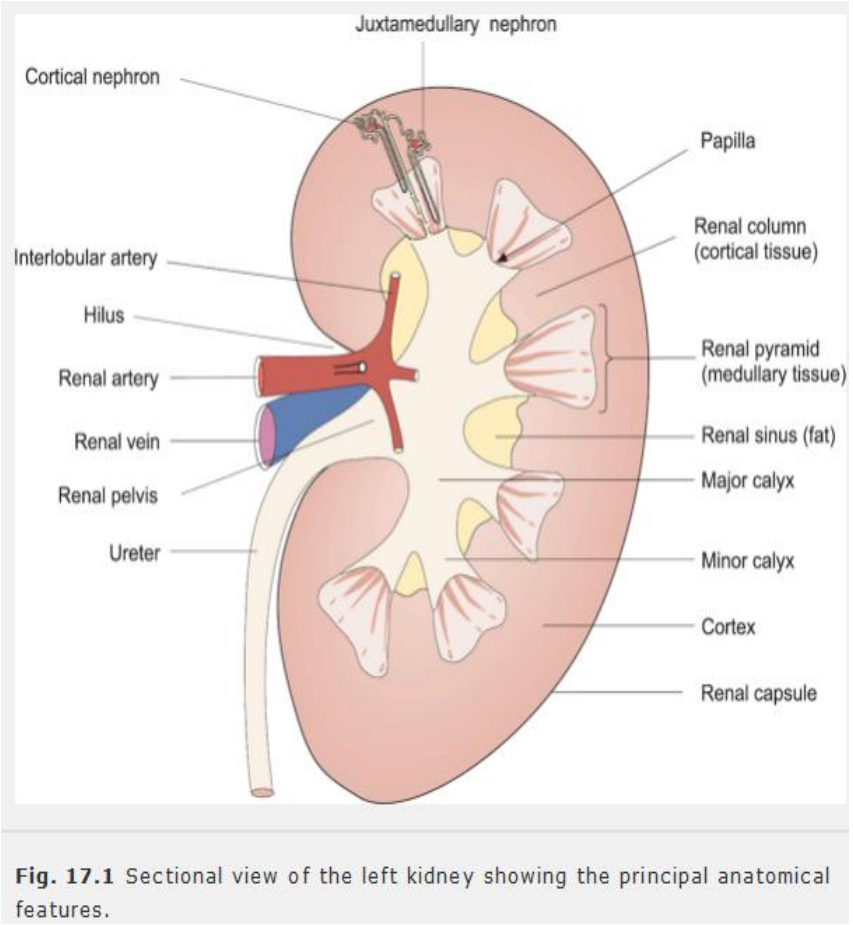


Fig. 17.1 Sectional view of the left kidney showing the principal anatomical features.

Cont… course outline (general)

1. Functional structure of the kidney
   - Gross structure
   - Renal blood supply
   - Renal nerve supply
2. The Nephron
   - Types
   - Functional structure of the Nephron
   - The Justaglomerular apparatus
3. The 3-processes of Urine formation
   1. Glomerular filtration
   2. Renal reabsorption
   3. Renal secretion

(Cont) Contents

a. Glomerular filtration

- **Structure of the glomerulus**
- **Glomerular filtration rate (GFR)**
  - **a. Factors that influence GFR (filtration forces)**
  - **b. Mechanisms of auto-regulation in regulating GFR & RBF**

b. Reabsorption processes

a. Reabsorption at different parts of the tubule through different transport mechanisms like: passive diffusion, Facilitated diffusion, active transport, secondary co-transport, solvent drug, transcellular and paracellular transport

(e.g., H_20, Na^+, K^+, PO_4= , HCO_3, etc)

b. Concept of transport maximum (Tm)

e.g glucose transport

c. Reabsorption of substances from interstitium to peritubular capillary

Contents

c. Secretion

- Secretion of substances at different parts of the tubules

4. **Control of urine volume by concentration & dilution processes**

- Counter current multiplier and exchanger systems

- The effect of ADH in concentration and dilution of urine

(Cont)… contents

5. Mechanisms involved in the regulation of ECF (H_2O, salt, acid-base & electrolyte) balance

6. Effect of diuretic agents at different parts of the Nephron
7. Micturition reflex
8. Concept of clearance
9. The role of kidney in acid base balance
10. Regulation of electrolyte balance by the kidney

Kidney (renal) Physiology, Introduction

"The **composition** of the internal environment is determined ***not*** *by what the* ***mouth ingests,*** *but by what the* ***kidney retains"***

General functions of the Kidney

A. Kidney is involved in the regulation of:

- **H_20 and electrolyte balance**
- **Acid-base (pH) balance**
- **ABP (arterial blood pressure)**
- **Blood volume etc.**

B. Excretion

- **Excretion of metabolic wastes in urine**

(e.g., creatinine, urea, uric acid, drugs, hormones etc.)

C. Hormone & metabolic function

- Hormones: **Renin, erythropoietin, Vit. D_3**
- **Metabolic: glucose production by gluconeogenesis**

Functional structures of the kidney

A. Shape: Bean shaped

Wt: both weigh ~ 300g

Blood supply: ~ 20% CO

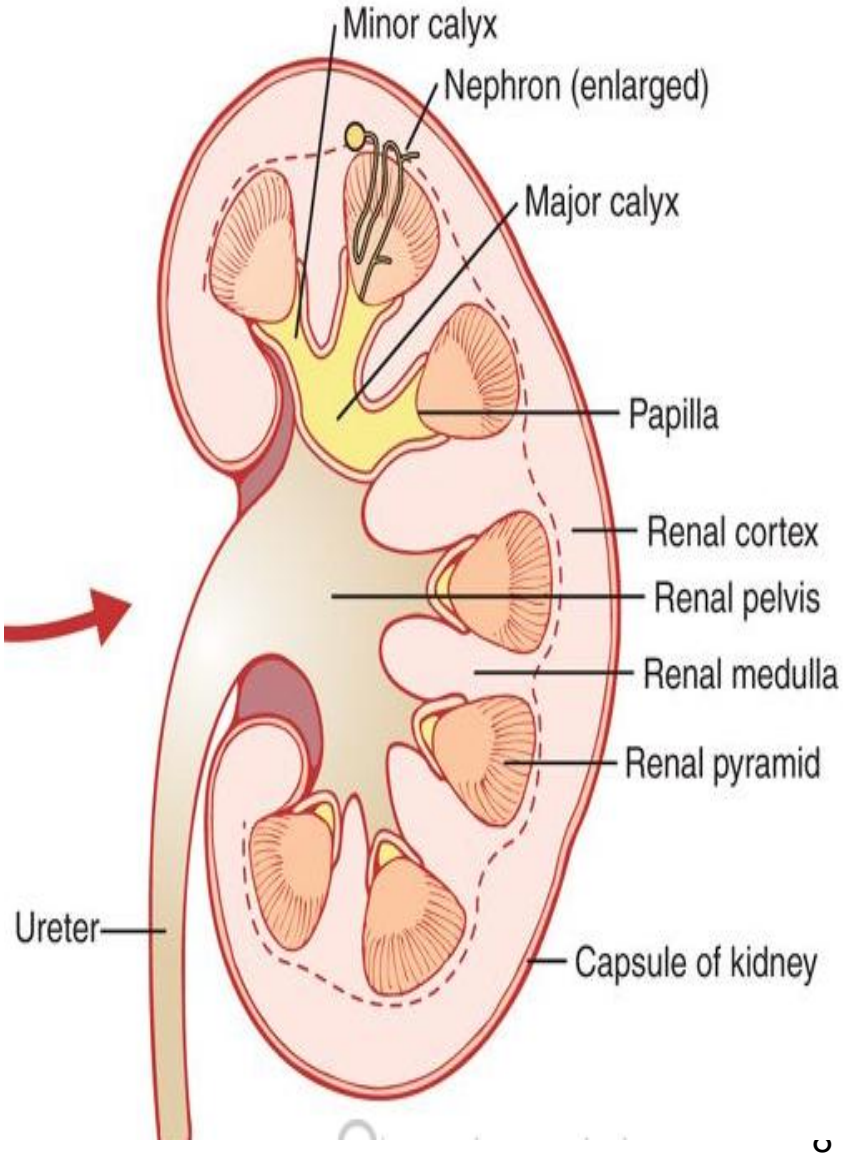
B. Transverse portions

- Cortex: light outer region
  Medulla: dark inner region

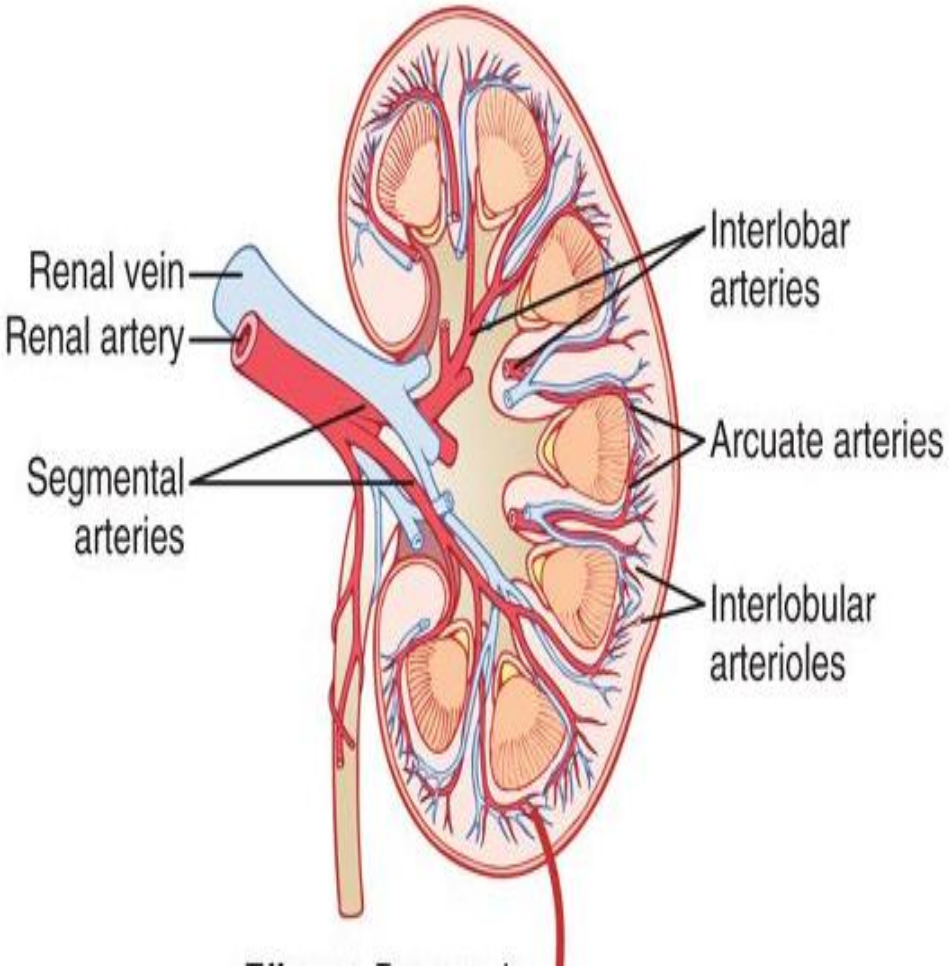
C. Deeper structures

Nerves, blood vessels + lymphatic's enter through Helium and reach to renal medulla, renal pyramids, renal papilla, renal cortex ..

Finally urine formed accumulates at the pelvis and passes to the **ureter**



Circulatory path in the kidney



- Renal artery >
- Segmental artery >
- Interlobar arteries >
- Interlobular arteries >
- Arcuate arteries >
- Afferent arteriole >
- Glomerular capillaries
- Efferent arteriole >
- Peritubular capillaries
- Then follows the vein side of the circulation, until it reaches Renal vein

Nephrons and aging

Nephrons are the structural and functional unit of the kidney.

Nephrons account to about **2 mill** in both kidneys and each nephron can produce a urine. Their numbers **decrease** in **old** ages **(>40 years)**

Though their Numbers keep on decreasing after age **40**, the remaining Nephrons can take **increased load** and function properly. So, no **significant** functional change may be observed

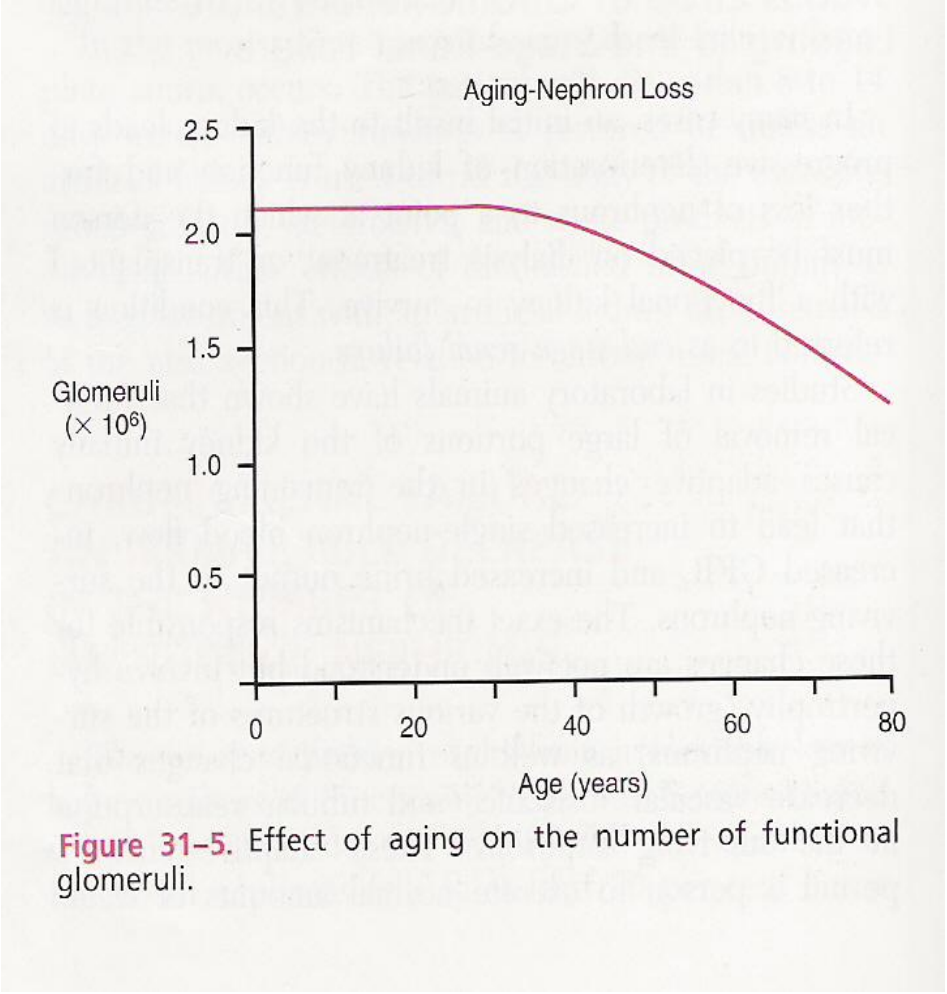
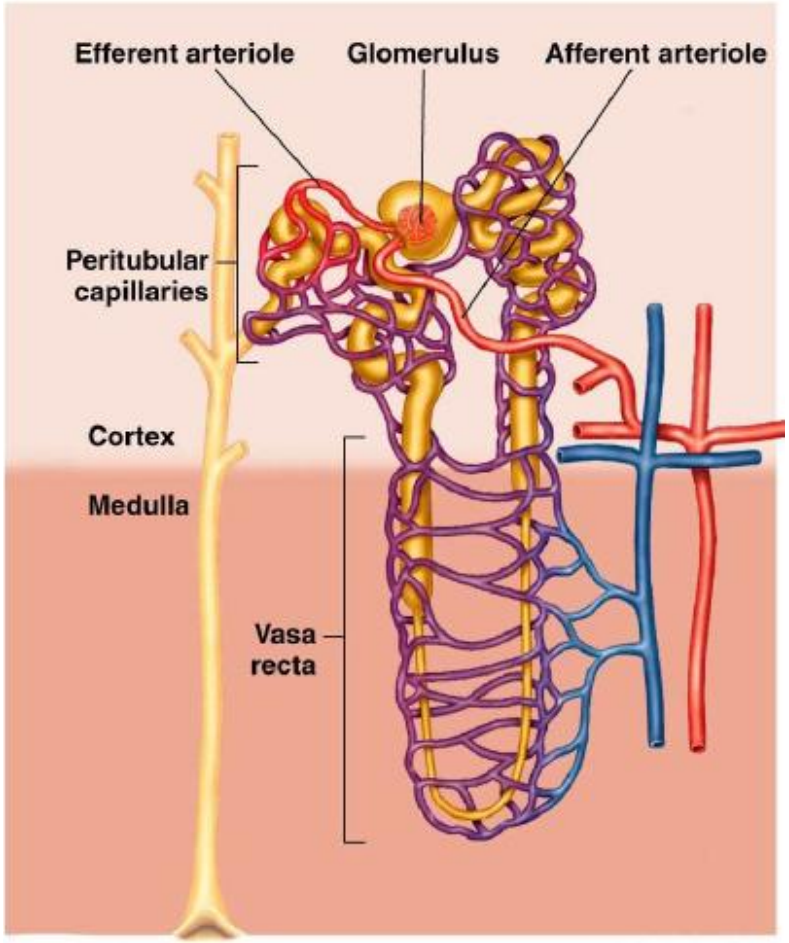
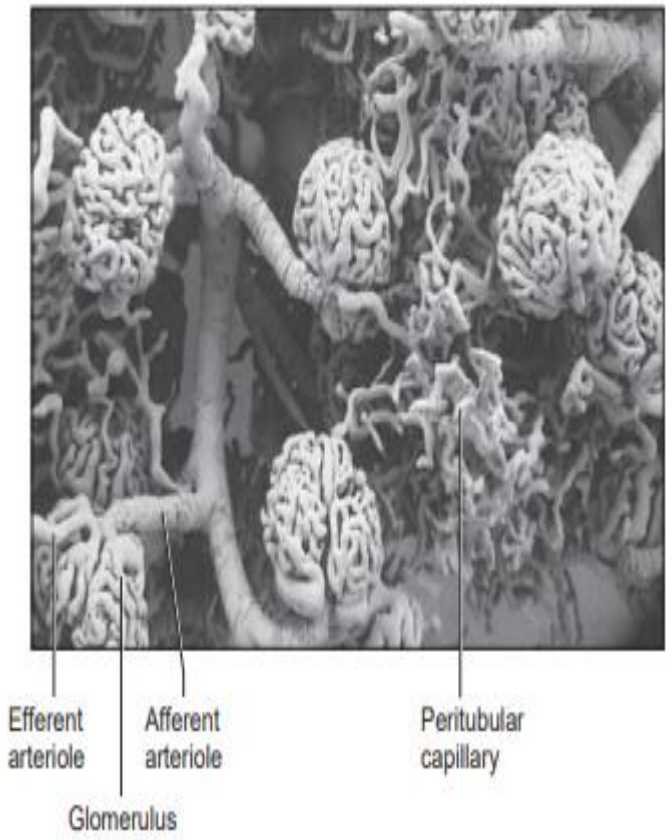


Figure 31–5. Effect of aging on the number of functional glomeruli.

Nephron and peritubular capillaries (PC): PC surround the nephron figure vs scanned electron micrograph





Different parts of the Nephron

a. Glomerulus: is a capillary tuft and is a place of filtration

b. Proximal convoluted tubule: place of major absorption

c. Loop of Henle:

a. Descending thin segment
-hyperosmolar

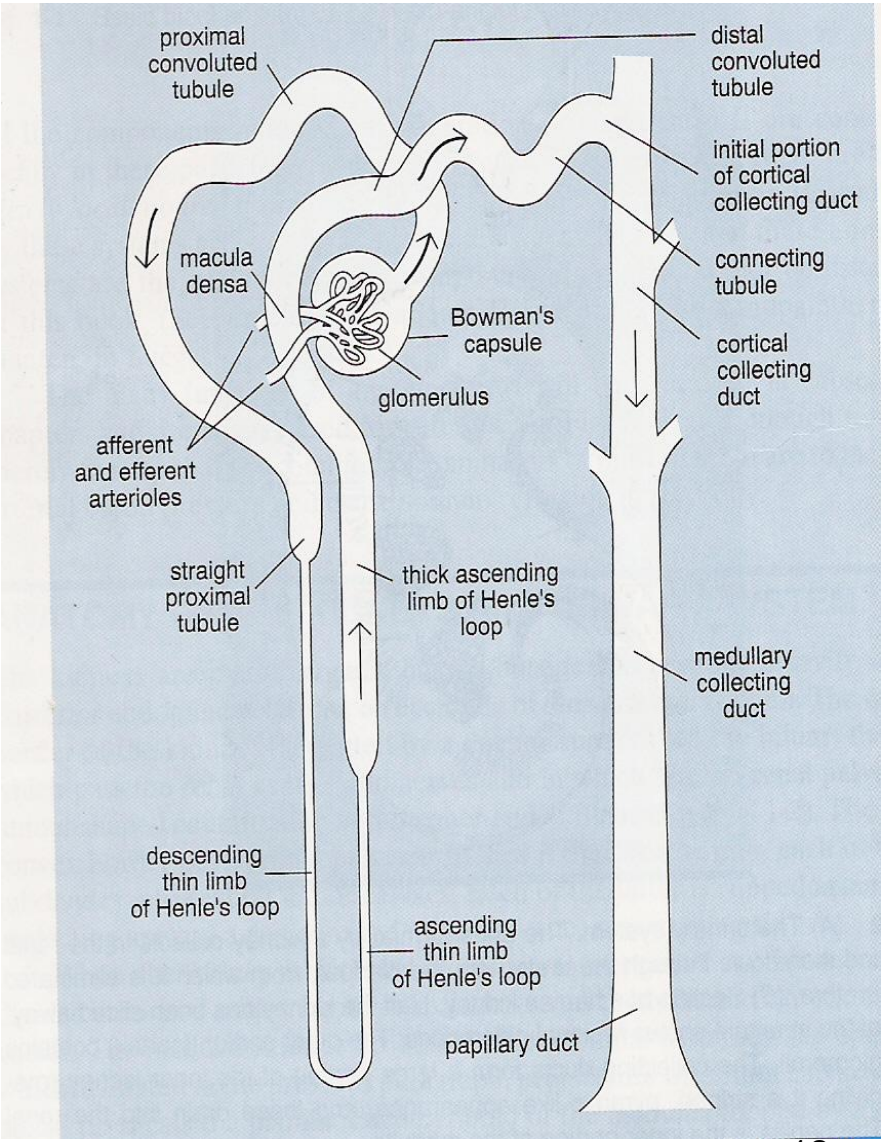
b. Ascending thick segment
- hyposmolar

d. Distal convoluted tubule :

a. diluting segment

e. Collecting tubule & collecting duct

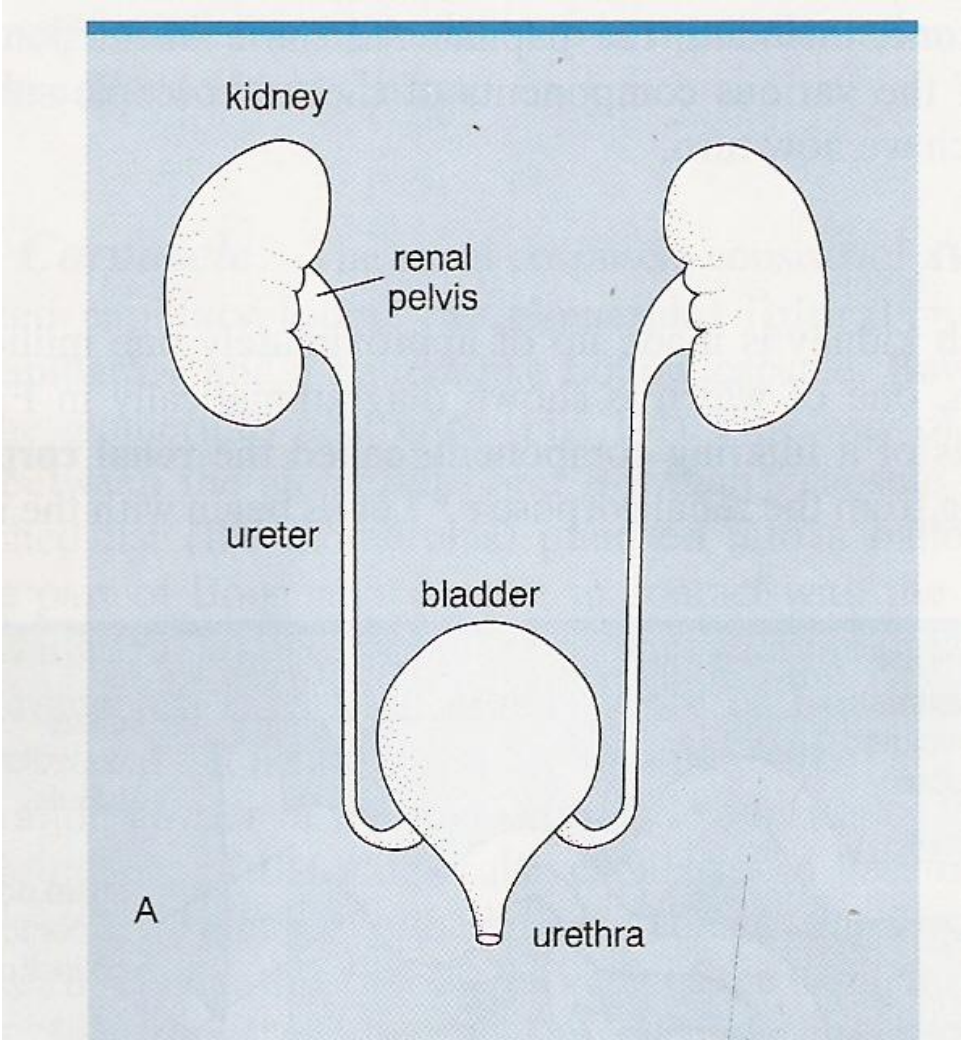
- site of ADH activity for concentration and dilution of urine



Kidney, the urinary tract

The urinary tract

Urine formed by the nephrons collect in renal pelvis and flows down to ureter > then to bladder > regulated by internal and external sphincter > urethra > and finally, expelled to outside



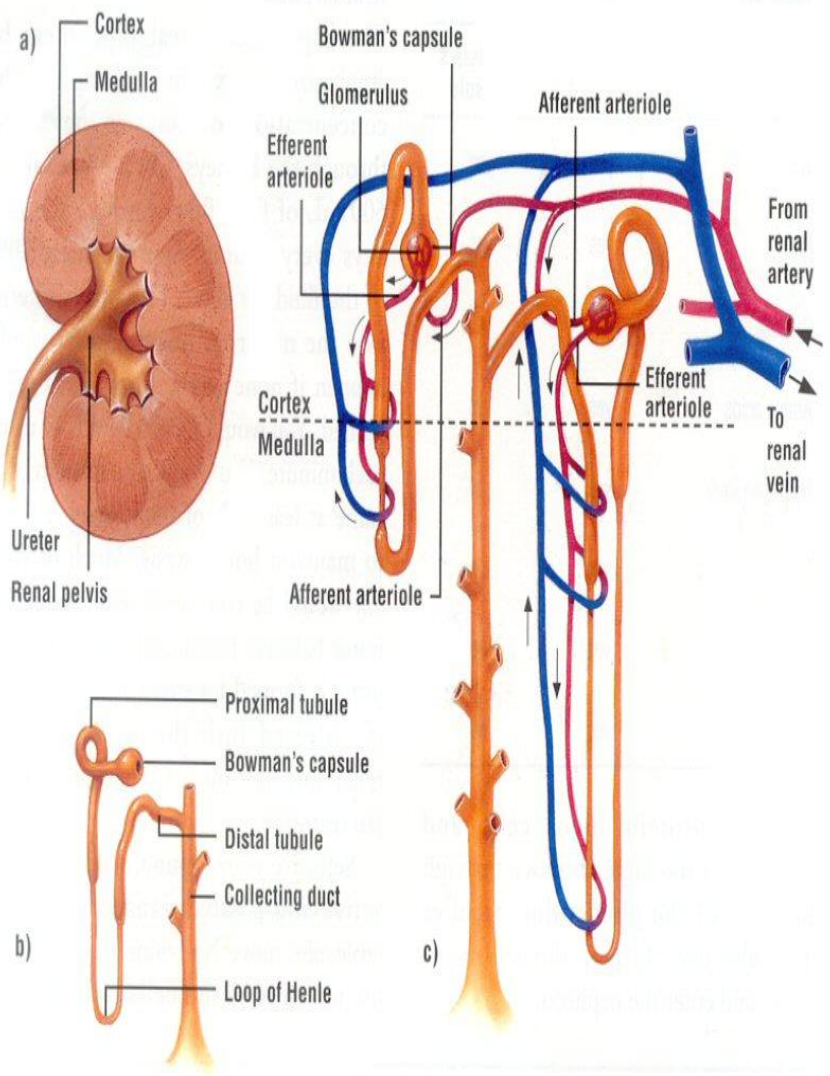
2-types, Cortical & juxtamedullary nephrons

A. Cortical Nephrons

- Located in the cortex part
- Have short Henley's loop
- make up 85% of the nephrons, mainly in humans
- descend as far as the outer
- layer of the medulla

B. Juxta Medullary Neph

- Located deep into the central medulla
- Involved in the conc. of urine (desert rodents can concentrate their urine more than 20 times the normal output).



Structure of the glome

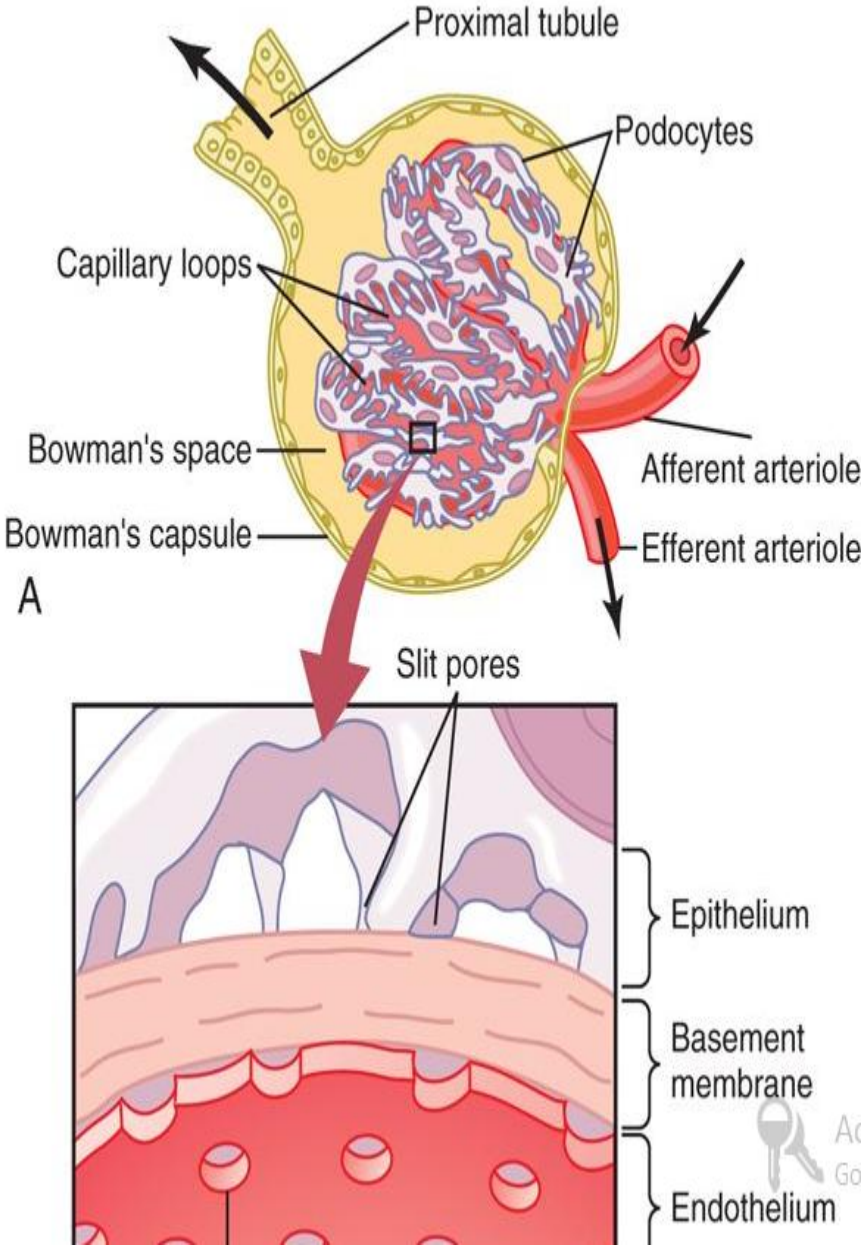
3-layers of the filtrate

a. **Capillary Endothelial layer with fenestrae (pores). Are single layers and more permeable to water and solutes than other capillaries**

b. **Basement membrane**: is a gelatinous glycoprotein layer that can repel **protein like albumin**.

c. **The Bowman's Epithelial layer with podocytes.**

Podocytes are finger-like processes that are negatively charged and repel proteins. It has slits for filtration



Justaglomerular apparatus and its function

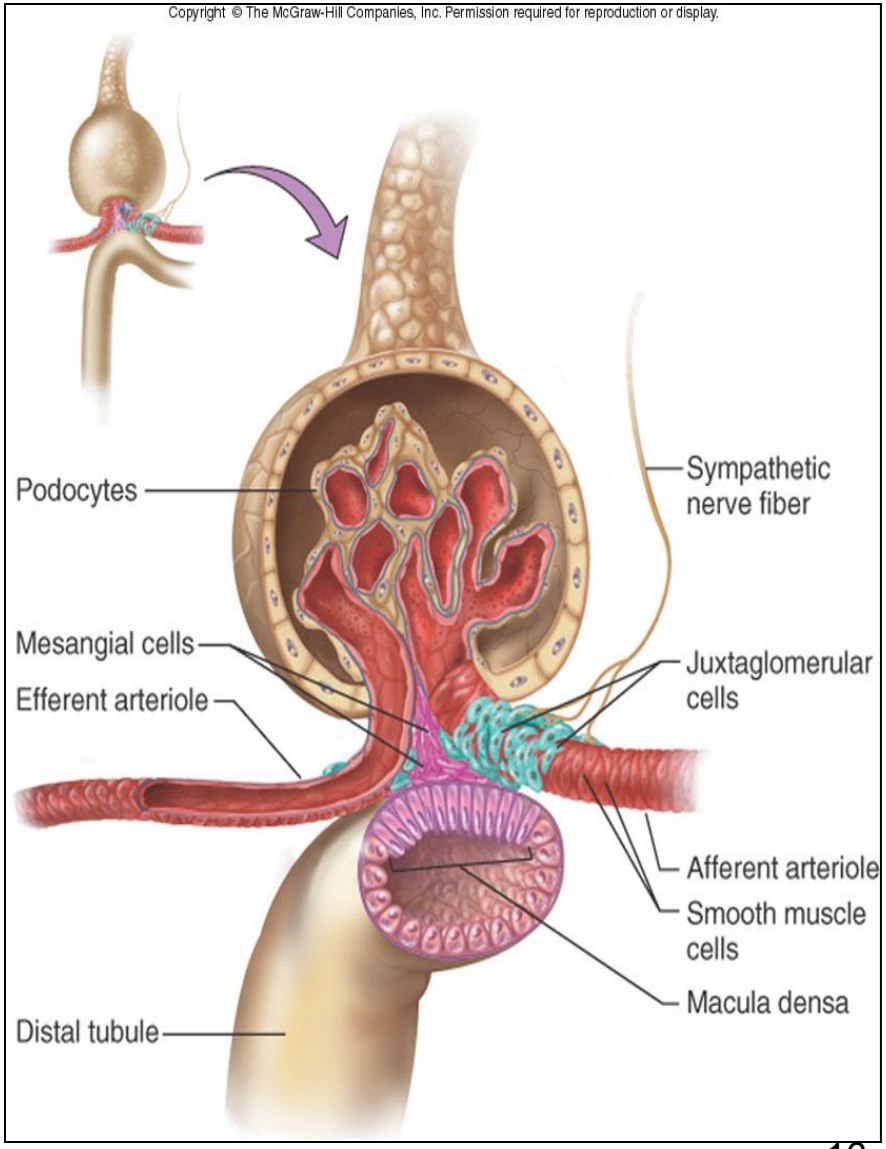
JG-apparatus consist of Macula densa cells and juxtaglomerular cells.

Macula densa (MD) are cells located at distal tubule and attach to afferent and efferent arterioles. MD cells detect the level of NaCl+ in the filtrate.

E.g.,

-When ABP drops, NaCl delivery also drops and this effect causes the afferent arteriole to dilate and increase blood flow and GFR also increases.

The opposite i.e., more NaCl in the filtrate constricts afferent arteriole and as the result decrease blood flow and GFR



Juxtaglomerular apparatus

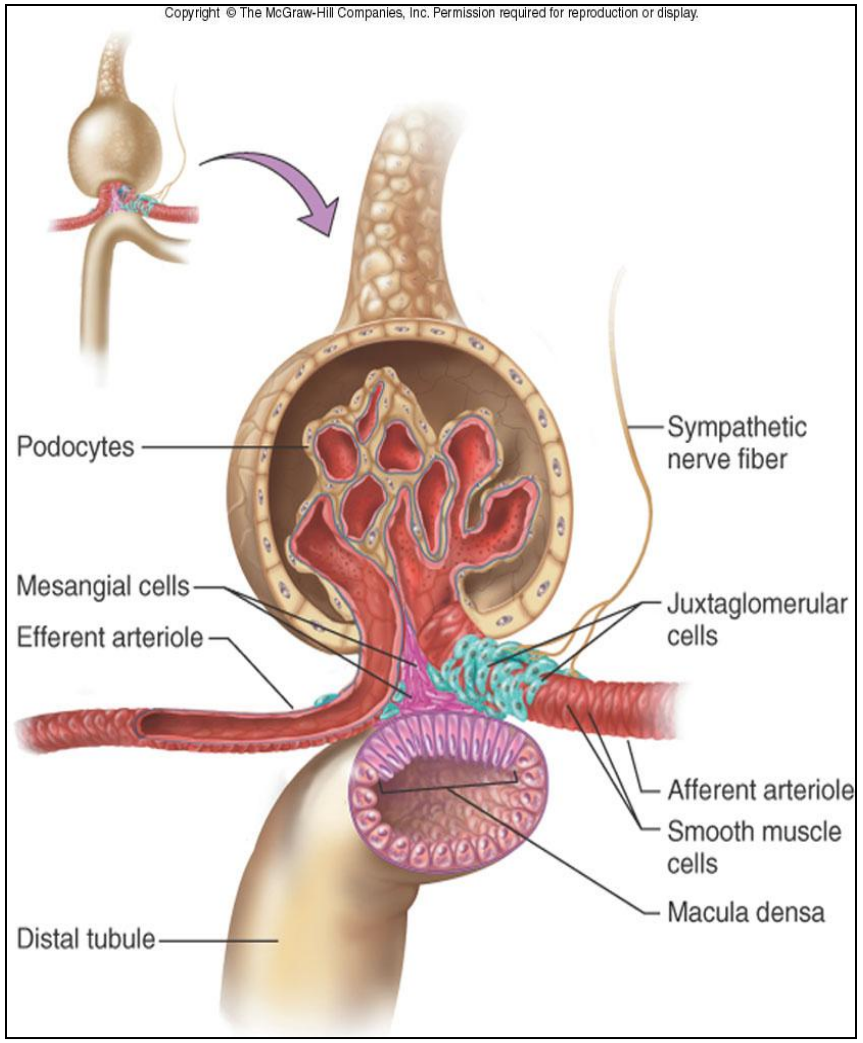
In summary,

JGA is very important because it helps regulate:

a. **RBF**

b. **GFR and**

c. **ABP (arterial blood pressure**



Pressure difference and blood flow in the kidney

Pressure differences in the kidney allows easy filtration of substances from the blood.

-Two kidneys receive show double capillary beds.

1. glomerular capillary

2. Peritubular capillary

- Importance of having 2-capillary beds that are connected in series is to promote better:

a. Filtration &

b. reabsorption processes to take place

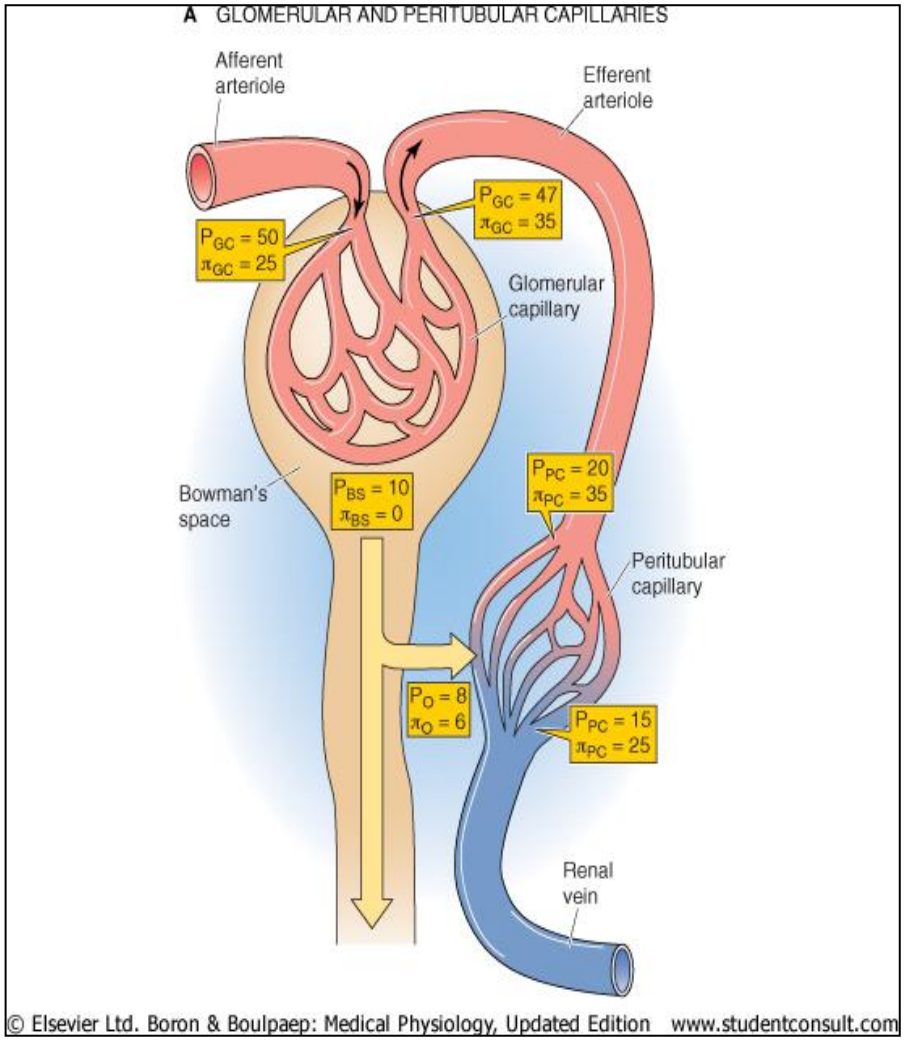
a. **During filtration: Glomerular capillaries** show **high pressure (60 mm Hg)** which is important to filter substances to the tubules (**narrow efferent** arteriole causes increased resistance to blood flow, thereby increasing pressure).

b. **During reabsorption: Peritubular capillaries** show **low pressure**s (13 mm Hg) and this low pressure gradient helps to promotes efficient reabsorption **of substances from the interestitium. The** low pressure allows rapid fluid absorption to the blood.

Peritubular Reabsorption

Peritubular capillaries provide nutrients for tubules by reabsorbing solutes from the interstitium.

<u>Oncotic (protein) pressure</u> is greater than hydrostatic pressure inside peritubular capillaries and this makes reabsorption to be easier.



Urine formation: 3-basic mechanisms of urine formation include:

1. **Glomerular filtration**

   125 ml/min=180L/day

   The entire plasma is filtered 60 times / day

   $$\frac{\text{180,000 ml filtrate}}{\text{3000 ml plasma}} = \text{60X}$$

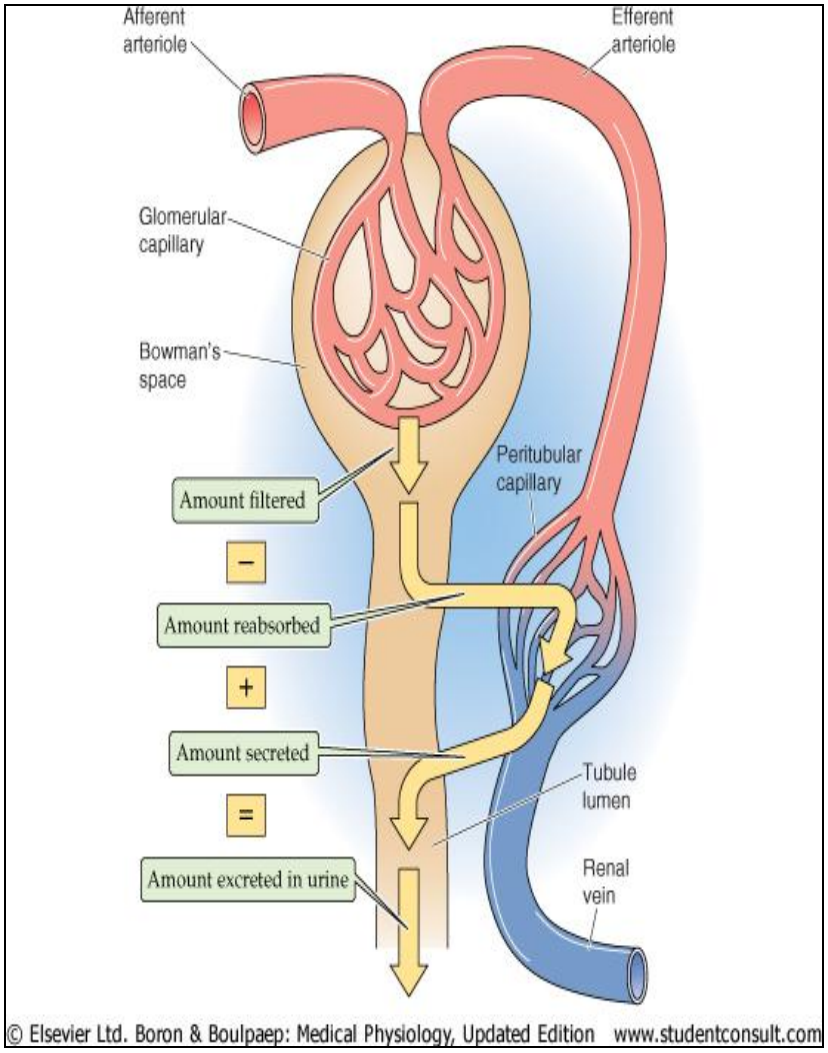
2. **Tubular Reabsorption**

   -178.5 L/day (99%)

   - 1.5 L/day lost (<1%)

3. **Tubular secretion**

   (e.g. H+ , K+ etc)



Filtration & Reabsorption forces that produce the filtrate in Bowman's capsule (Starlings forces)

a. Glomerular capillary or hydrostatic pressure, 60 mm Hg (pushing force)
b. Plasma oncotic (protein) Pressure (32 mm Hg) (a force opposing filtration (pulling force)
c. Bowman's capsule hydrostatic pressure (18 mm Hg), (pulling force)
d. Bowman's capsule Oncotic pressure (no protein in Bowman's capsule, so produces no force, "0" mm Hg)

The formula for net filtration pressure (NFP) is:

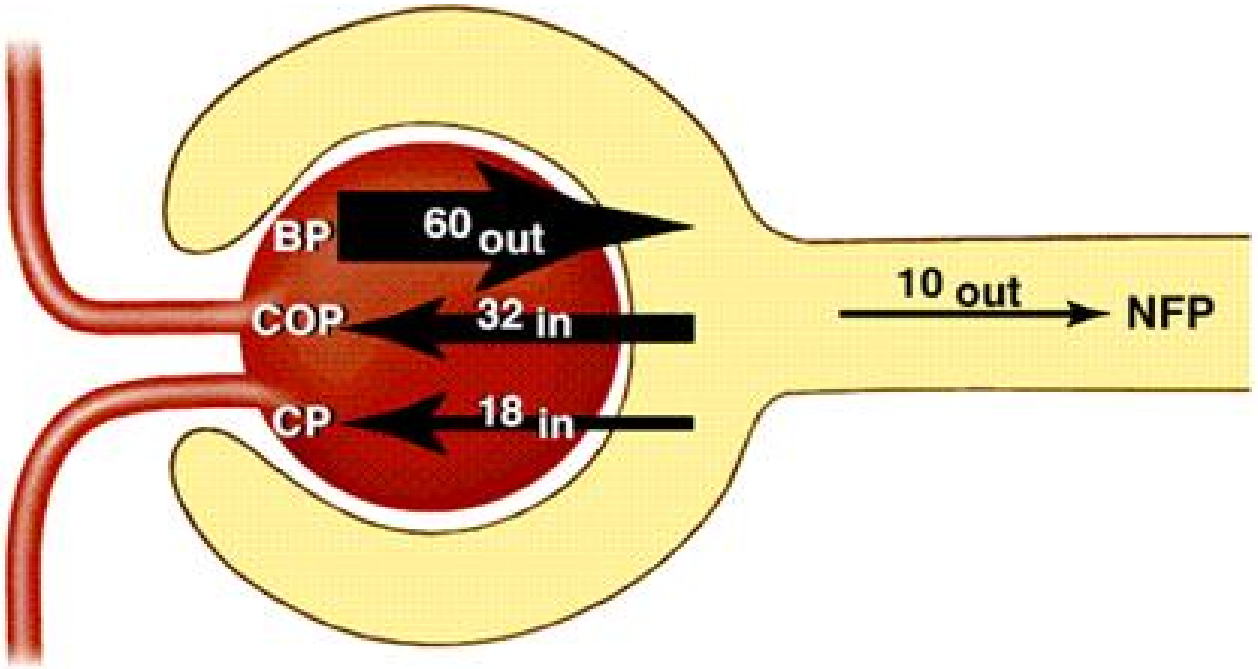
NFP = (pushing) - (Pulling)

NFP = 60 – (32 + 18)

= 10 mm Hg

This 10 mm Hg causes filtration to occur. The filtrate joins bowman's capsule and then to proximal tubule.

Starlings forces in figure



Capillary blood pressure (BP)	60 mmHg out
Colloid osmotic pressure (COP)	– 32 mmHg in
Capsular pressure (CP)	– 18 mmHg in
Net filtration pressure (NFP)	10 mmHg out

Other filtration and reabsorption forces

- Also the following factors regulate **the Net-filtration** rate ***in glomerular capillaries as well as Peritubular capillaries***.
- Net-filtration pressure is the product of K_f (filtration coefficient) and starlings forces.

NFP = K_f x Starlings forces

- **K_f (filtration coefficient) is dependent on 2-factors:**
  - **a. Surface area of the glomerular capillaries**
  - **b. Opening of capillaries**

So, diseases that affect the surface area and pores to open the capillaries can affect filtrations of substances.

Regulation of GFR

GFR is maintained by 2-major factors despite changes in arterial blood pressure (ABP):

1. **Intrinsic mechanism: divided into**
    a. Myogenic (stress relaxation)
    b. Tubulo-glomerular negative feed-back
    c. Mesangial cells

2. **Extrinsic mechanism: divided into**
    a. Nervous (mainly sympathetic)
    b. Hormonal (RAS)

Factors that determine or maintain GFR generally include intrinsic and extrinsic mechanisms

a. <u>Myogenic regulation (stress relaxation)</u>

When MAP increases, the pressure in the afferent arteriole rises and **stretches** the smooth muscle of the afferent arteriole, finally causing increased GFR. Ca2+ ion influx causes smooth muscles to contract.

- The increase in GFR causes **reflex contraction** of the **afferent arterioles causing a decrease in ABP.**
- **The decrease in ABP causes the opposite effect (i.e., a a fall in GFR).**

A fall in MAP causes a decrease in GFR, but later relaxation of the afferent arteriole results in increased blood flow that increases the GFR

2. Tubuloglomerular Feedback

Changes in GFR cause a change in **tubular fluid flow**. This change in the flow is detected by the specialized cells of the **macula densa that senses the Na+ level in the filtrate fluid.**

Case 1. How is GFR regulated by negative feed back mechanism when increase in GFR is caused by high ABP?

Increase in ABP raises GFR. This increased GFR causes increased Na+ level in the filtrate.

The macula densa cells detect the increased Na+ level and by paracrine connection cause the afferent arteriole to constrict. The vasoconstriction results in decrease of ABP and blood flow that in turn decrease the GFR.

The paracrine substance released and cause the constriction is **adenosine**.

2. Tubulo-glomerular feed-back continued

Case 2: ***How is GFR regulated by negative feed back mechanism when the decrease in GFR is caused by low ABP and low renal blood flow?***

A decrease in ABP decreases GFR. This decrease in GFR causes decreased Na+ level in the filtrate. The macula densa cells detect the decrease in Na+ level and by paracrine connection cause the afferent arteriole to dialate (relax).

The vasodilatation results in increased blood flow and ABP that in turn increase the GFR. The paracrine substances released to cause relaxation of afferent arteriole include: nitrous oxide (NO, Renin, prostaglandin E2 etc).

Here it is important to notice that Renin causes Ang II secretion that constricts predominantly the efferent arteriole and raises the GFR. However continuous constriction of Ang II on efferent arteriole does not have an effect of increasing GFR.

Intrinsic control of GFR cont…

3. Mesangial Cells

The mesangial cells are **modified smooth muscle cells** that surround the glomerular capillaries.

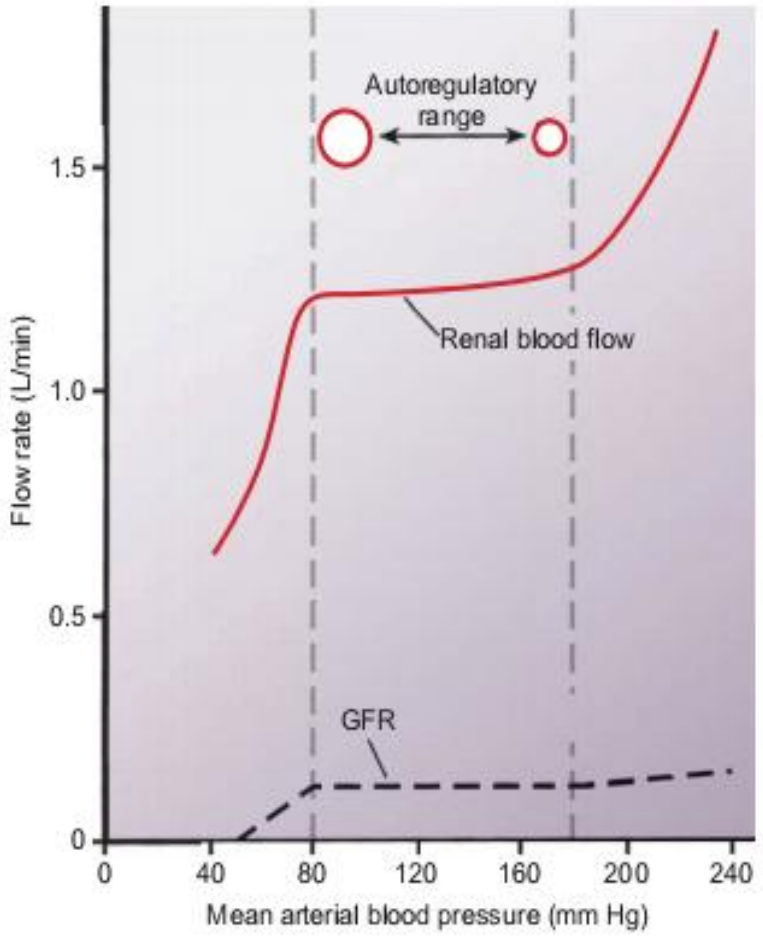
When blood pressure **increases** this causes the mesangial cells to **stretch**

In in response to stretch, the mesangial cells **contract** and **decrease the surface area** of the **capillaries** available for filtration.

Importance of intrinsic (local) mechanisms of the kidney in autoregulation (AR) of GFR & RBF

- AR is an intrinsic (local) mechanism of the kidney by which GFR and RBF remain constant in conditions of wide changes in ABP (arterial blood pressure).

- Between ~80 - 200 mm Hg, GFR and RBF remain more or less constant. So, controlling a constant GFR maintains constant *H_2O and solute level* in the body



Extrinsic Control of Glomerular Filtration

- Extrinsic control involve **nervous and hormonal** regulation

A. Nervous (SNS):

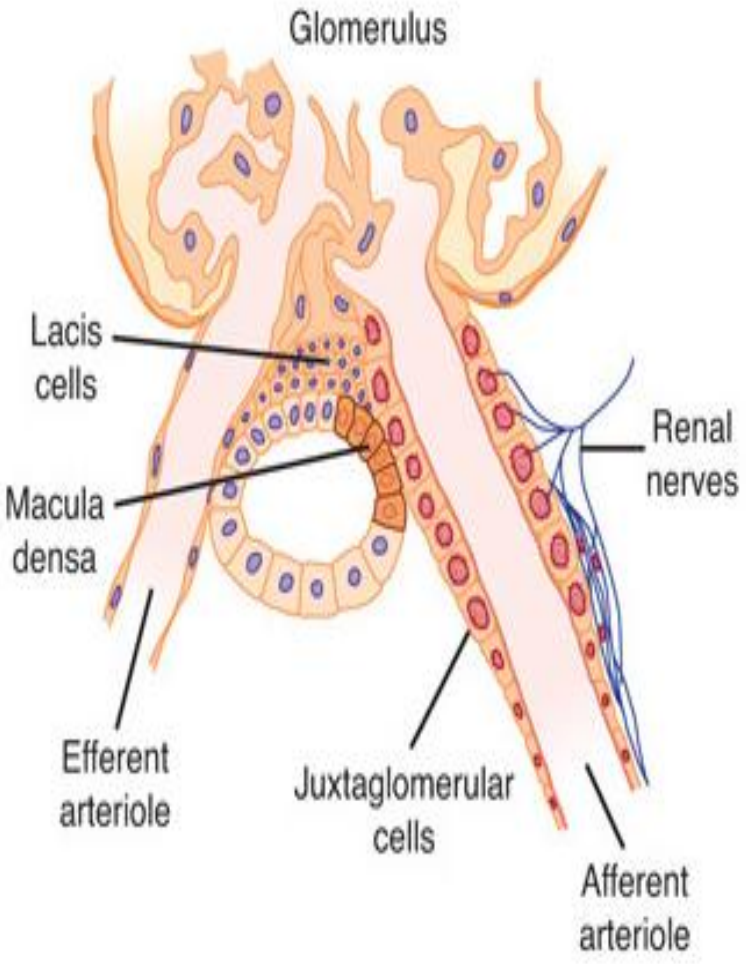
Any stress causes an increase in ABP that normally increases the GFR.

The increased stress increases the **sympathetic activity** which later causes the **afferent** and **efferent arterioles** to **contract and decrease** blood flow and thereby **GFR.** The blood is diverted to other active organs.

(cont…)Sympathetic effect on GFR

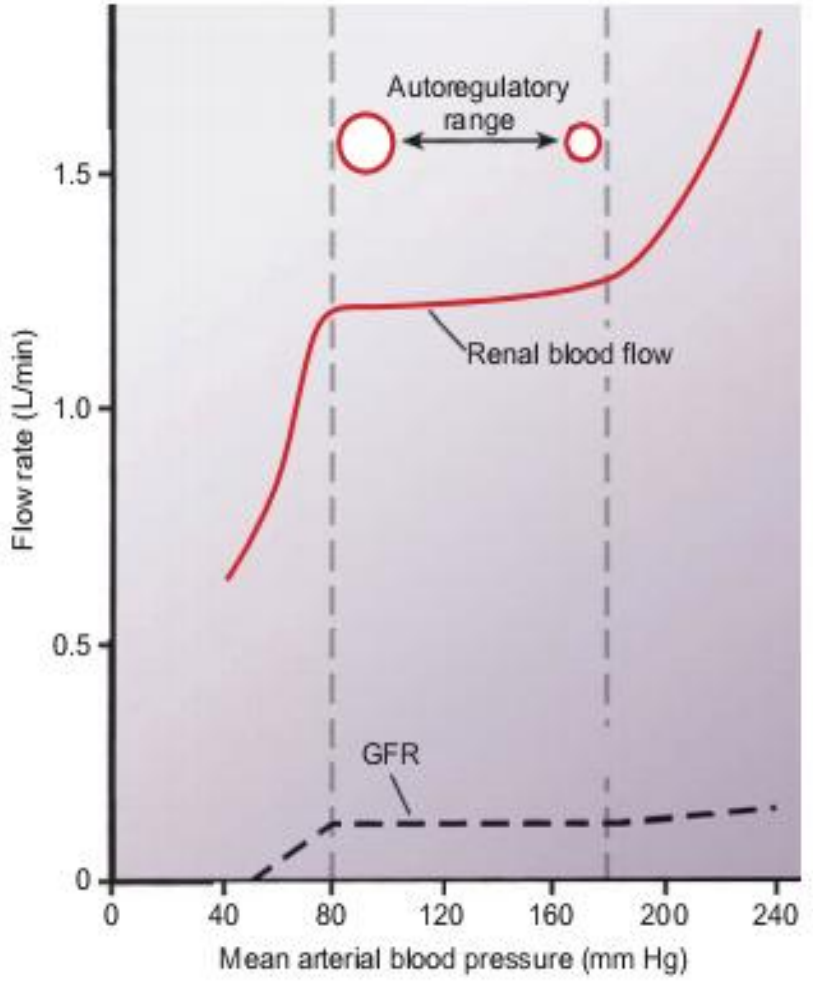
Increased Sympathetic stimulation = decreases GFR and it is mediated by *adrenergic receptors.*

Renal blood flow is decreased during exercise and heavy stress.



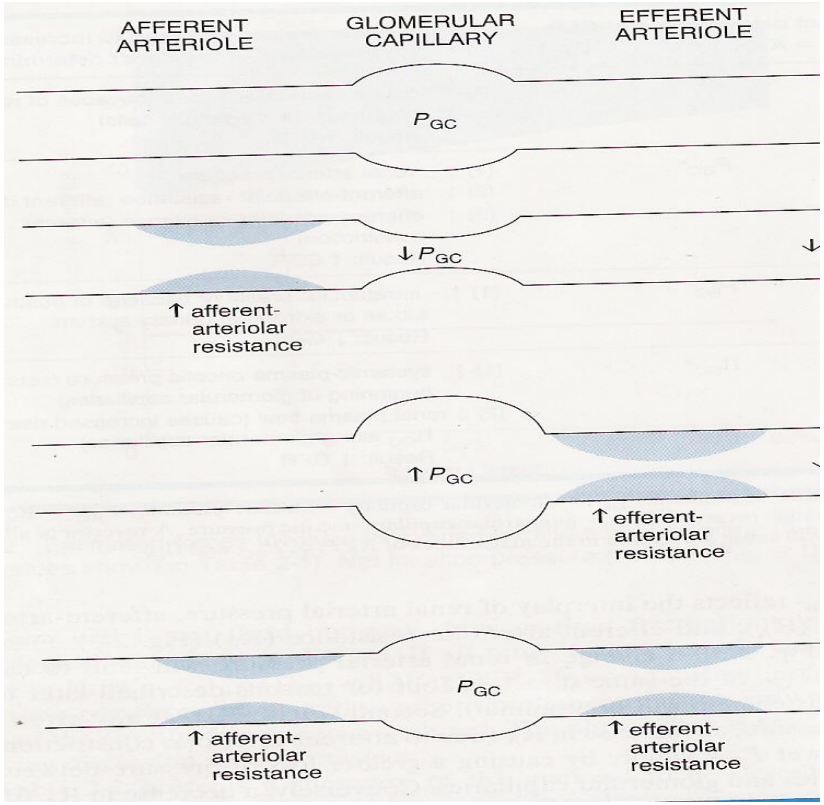
Comparison of Intrinsic & extrinsic effect in controlling GFR

- The intrinsic control of GFR works only over a limited range of MAP (i.e. between 80-200 mm Hg)
- Outside this range, intrinsic control is not important to maintain a constant GFR.
- For this reason, it is said that the nervous (i.e., SNS) effect **overrides** the effect of the intrinsic control of the GFR.



Diameter of the renal arterioles also regulate GFR

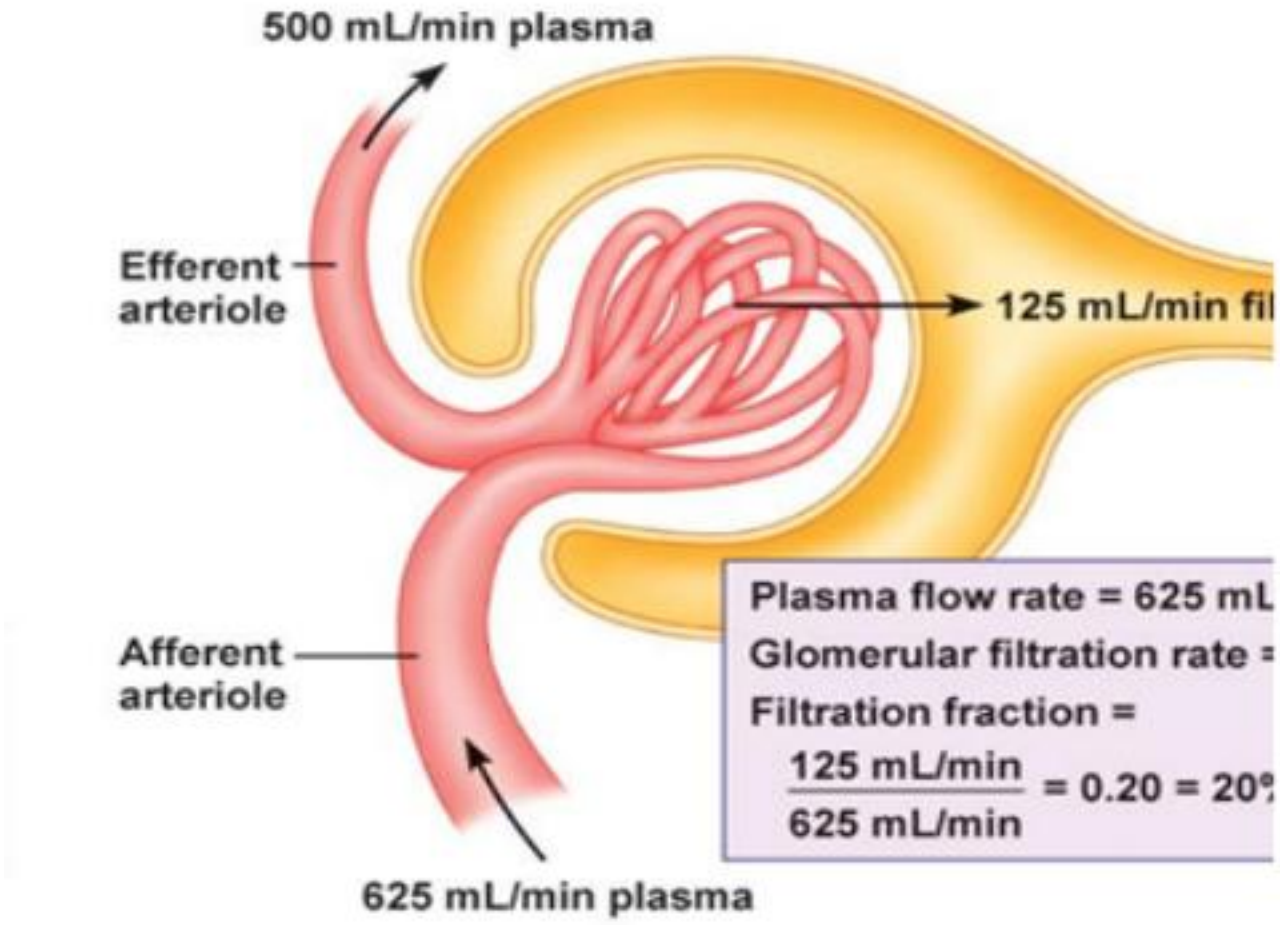
1. **Afferent** arteriolar **constriction** : **Decreases GFR** because constriction increases arteriolar resistance that causes decreased blood flow to the Glomerulus and this in turn decreases glomerular pressure that results in **decreased GFR**



2. **Efferent** arteriolar **constriction**: **increase GFR**

Constriction of the effecrent arterioles increase resistance to blood flow and this effect results in **increased GFR**

Filtration fraction in the kidney



(b) Glomerular filtration rate and filtration fraction

Filtration fraction in the kidney

Filtration Fraction (FF): is a fraction of renal plasma flow which becomes Glomerular filtrate. It is also an important way to know the normal function of the kidney. FF can be affected by many factors (e.g. catecholamines increase FF by selectively constricting efferent arterioles and raise FF)

$$\mathbf{FF = \frac{GFR}{RPF} \times 100}$$

$$\mathbf{= \frac{125}{650} \times 100}$$

= **19 % - 20%** of the renal plasma flow accounts to the **GFR**

Filtered load (tubular load)

The quantity of a particular solute that is filtered per unit time is called **filtered load (tubular load).**

The filtered load (FL) = GFR X plasma concentration of any substance.

For example, for glucose, whose normal average concentration is **100 mg/100 ml = 1 mg/ml**, the filtered load under normal conditions would be:

GFR (125 ml/min) x 1 mg/ml = 125 mg/min

Hormonal effects of GFR regulation

- Involved hormones are:
  a. RAS (renin-Angiotensin-Aldosterone)
  b. Catecholamines

RAS system in the regulation of GFR

A decrease in

1. **ABP (arterial blood pressure)**
2. **blood volume**,
3. **ECF- volume** and
4. **osmolality**

- Cause release of Renin from juxtaglomerular apparatus
- Renin then produces Angiotensin II which in turn causes **constriction of efferent arterioles** to cause an increase in GFR (look the next slide)
- This has the effect of increasing arterial blood pressure

High protein diet (amino acids) and high CHO-diet (glucose) increases GFR

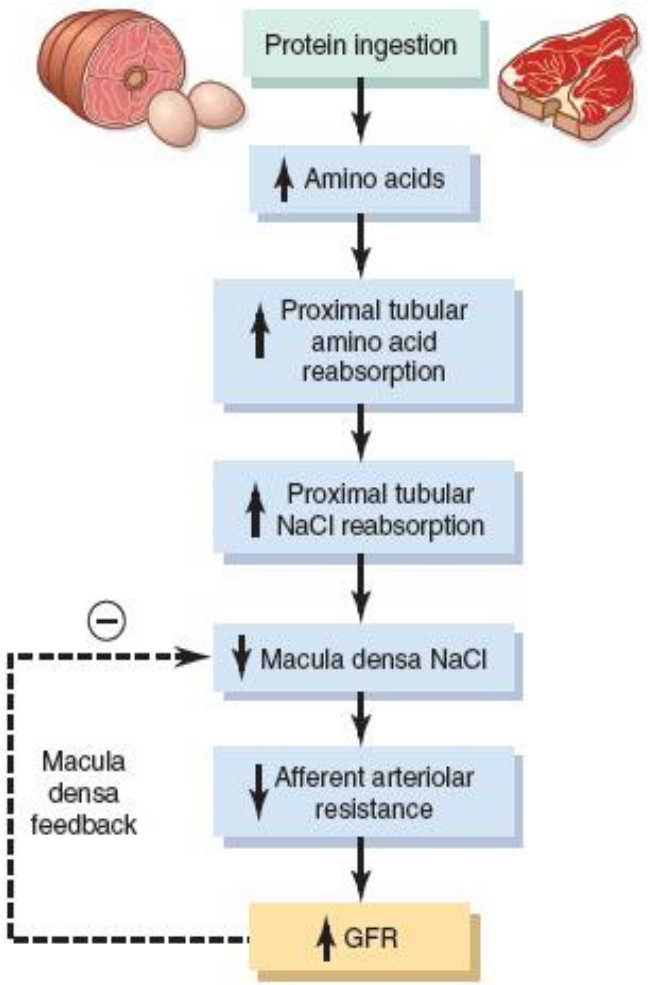


Figure 27-12. Possible role of macula densa feedback in mediating increased glomerular filtration rate *(GFR)* after a high-protein meal.

- **A high-protein meal increases amino acids into the blood, which are reabsorbed in the proximal tubule.**
- **Na+ reabsorption also increases due to 2nd-active transport.**
- **Macula densa Na+ delivery decreases.**
- **Paracrine connection to afferent arteriole relaxes and vasodilate causing increased renal blood flow to the glomerulus**
- **The end result is increased GFR**

ANP on ECF-Volume regulation

- **Atrial natriuretic peptide (ANP) for volume regulation.**
- It is **released upon stretch of the atria**—for example, following **volume expansion.**
- This hormone has several actions that **increase Na *excretion***.
- ANP acts on **the kidneys to increase RBF & GFR** and ***inhibits Na reabsorption*** by the inner medullary collecting ducts.
- **It also causes Vasodilation** used to decreases ABP

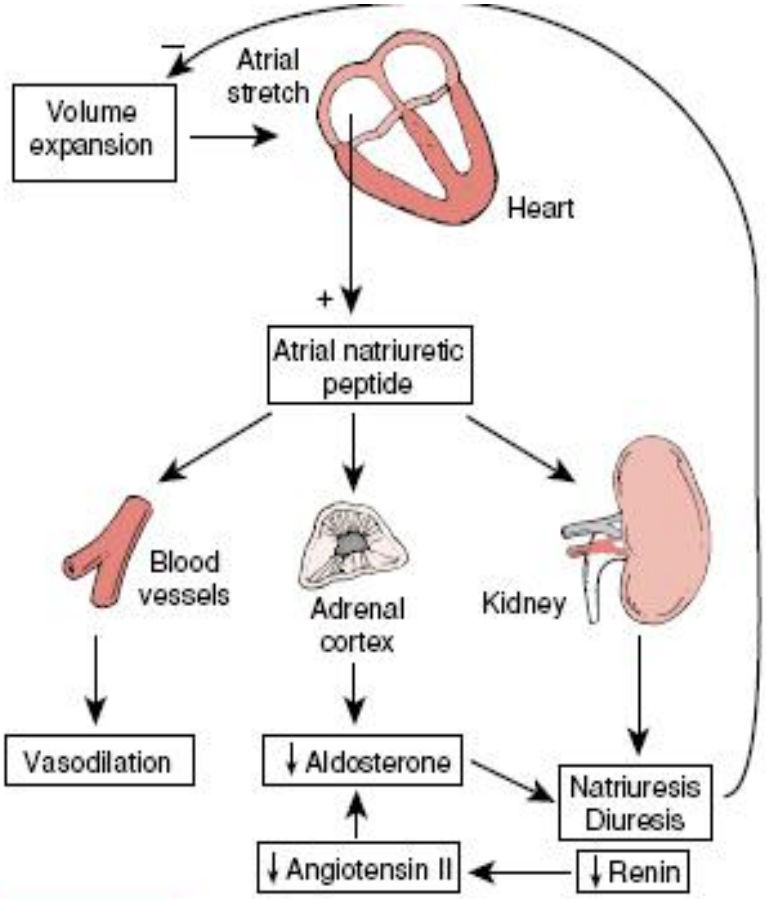


FIGURE 24.10 Atrial natriuretic peptide and its actions. ANP release from the cardiac atria is stimulated by blood volume expansion, which stretches the atria. ANP produces effects that bring blood volume back toward normal, such as increased Na^+ excretion.

Different transport systems along the tubules

All transport mechanisms are involved in the kidney. These are:

a. Diffusion
b. Facilitated diffusion
c. Primary active transport
e. Secondary active transport
f. Endocytosis &
g. Exocytosis

Transport in the kidney tubules

1. **<u>Transcellular route</u>**:

Substances passing ***<u>through</u>*** luminal epithelial cells or through basolateral membrane (**mostly active** transport)

- Na+ then follows H_2O

2. **<u>Para-cellular route</u>:**

Solutes passing *between* **tight junctions or lateral spaces (mostly diffusion)**

<u>Symport</u> (co-transport)

-Na with Glucose & aa

<u>Antiport</u> (opposite or counter transport): Na+ & K+ or H+ ions moving in opposite direction

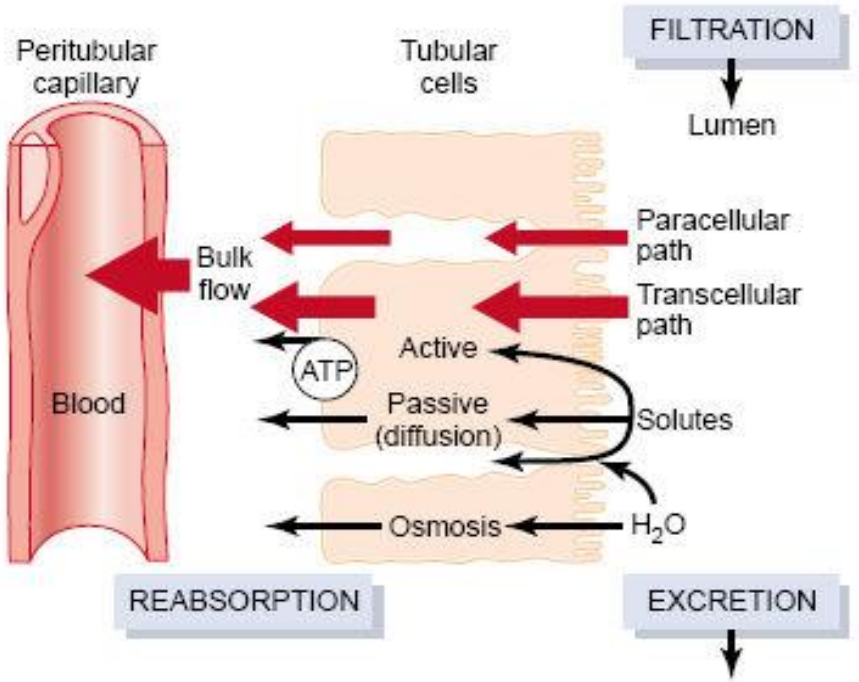


Figure 27–1

Reabsorption of filtered water and solutes from the tubular lumen across the tubular epithelial cells, through the renal interstitium, and back into the blood. Solutes are transported through the cells (transcellular route) by passive diffusion or active transport, or between the cells (paracellular route) by diffusion. Water is transported through the cells and between the tubular cells by osmosis. Transport of water and solutes from the interstitial fluid into the peritubular capillaries occurs by ultrafiltration (bulk flow).

Paracellular transport, mostly starlings forces and bulk flow

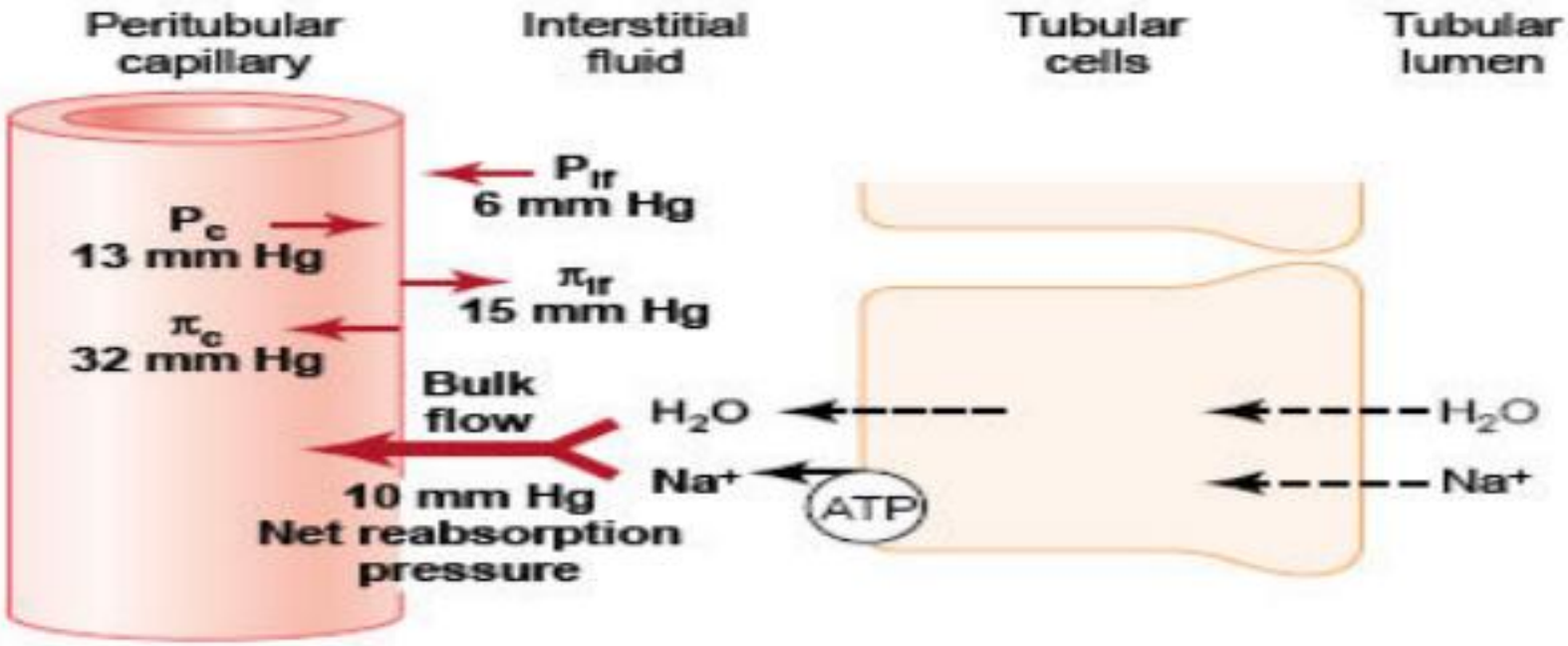


Figure 27–15

Summary of the hydrostatic and colloid osmotic forces that determine fluid reabsorption by the peritubular capillaries. The numerical values shown are estimates of the normal values for humans. The net reabsorptive pressure is normally about 10 mm Hg, causing fluid and solutes to be reabsorbed into the peritubular capillaries as they are transported across the renal tubular cells. ATP, adenosine triphosphate; P_c, peritubular capillary hydrostatic pressure; P_{if}, interstitial fluid hydrostatic pressure; π_c, peritubular capillary colloid osmotic pressure; π_{if}, interstitial fluid colloid osmotic pressure.

Secondary co transport (active)

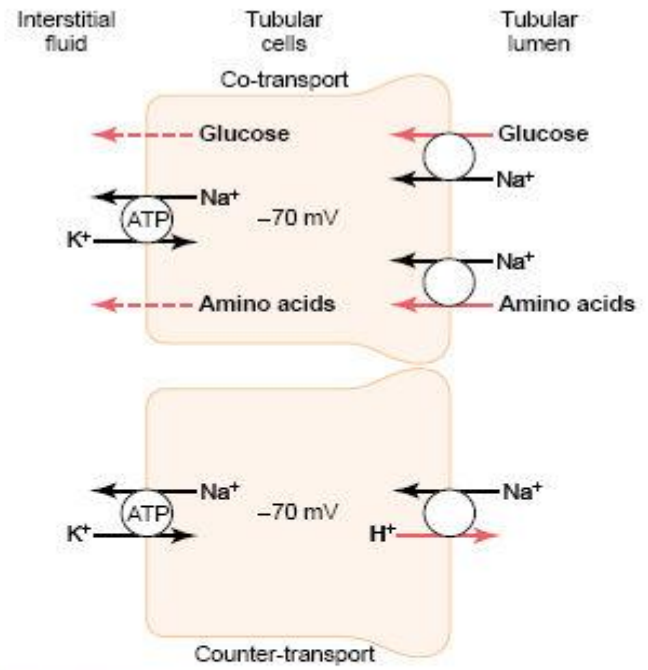


Figure 27–3

Mechanisms of secondary active transport. The upper cell shows the *co-transport* of glucose and amino acids along with sodium ions through the apical side of the tubular epithelial cells, followed by facilitated diffusion through the basolateral membranes. The lower cell shows the *counter-transport* of hydrogen ions from the interior of the cell across the apical membrane and into the tubular lumen; movement of sodium ions into the cell, down an electrochemical gradient established by the sodium-potassium pump on the basolateral membrane, provides the energy for transport of the hydrogen ions from inside the cell into the tubular lumen.

2ndary active transport

- Glucose and amino acids are transported at the luminal side together with Na+ ion.
- Na+ ion goes down its conc. Gradient
- Glucose & aa goes against their conc. Gradients. ATP is utilized at basolateral side.
- SGLT

Facilitated diffusion: (GLUT)

Glucose and AA are

transported from epithelial cell to interstitium by facilitated diffusion at basolateral side.

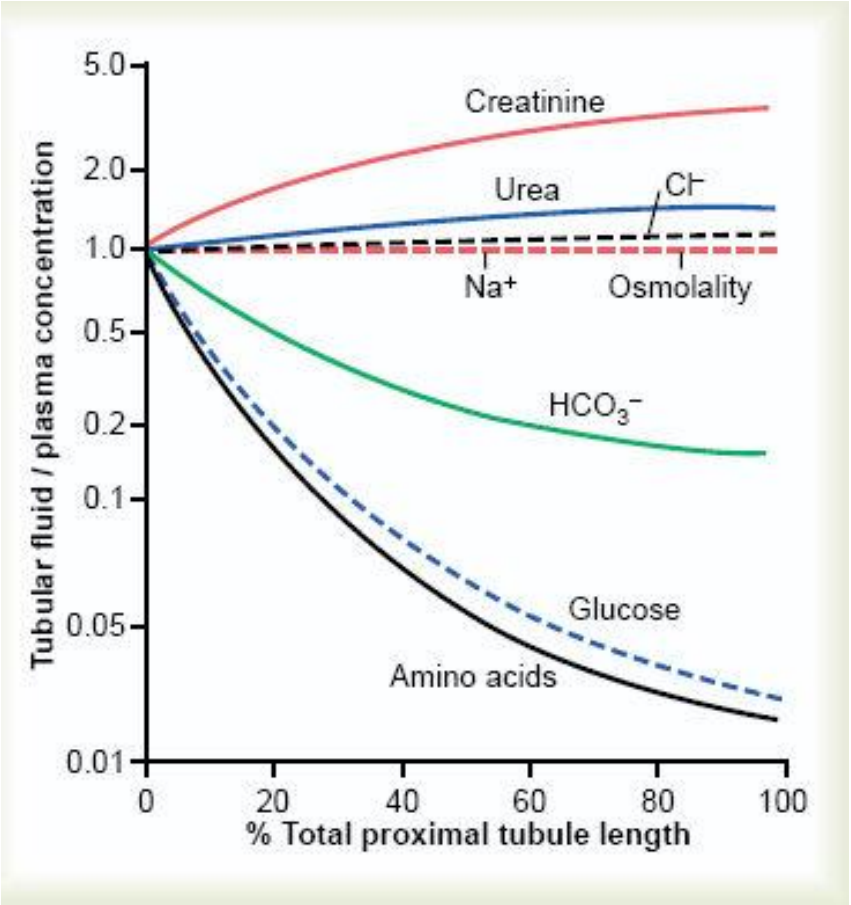
Reabsorption in proximal tubule

In the proximal tubule about 65% of the filtrate is reabsorbed. These includes: electrolytes like Na+, K+, Cl-, etc;

Moreover, organic substances like, glucose, aa, etc. are 100% reabsorbed

However, H+ and NH3+, uric acid are secreted into the tubule

Tonicity = isosmotic (~300mOsm/L).



Reabsorption in the Loop of Henley (LoH)

20 % of the filtrate joins the LoH

a. Descending limb of LoH

H_2O escapes to the interstitium from the lumen and creates

hyper-osmolar environment inside the lumen (~ 1200 mOsm/l)

b. Ascending limb of LoH

Is impermeable to H_2O but permeable to solutes.

NaCl transport to the interstitium causes a hypo-osmolar environment inside the tubules (~100 mOsm/l).

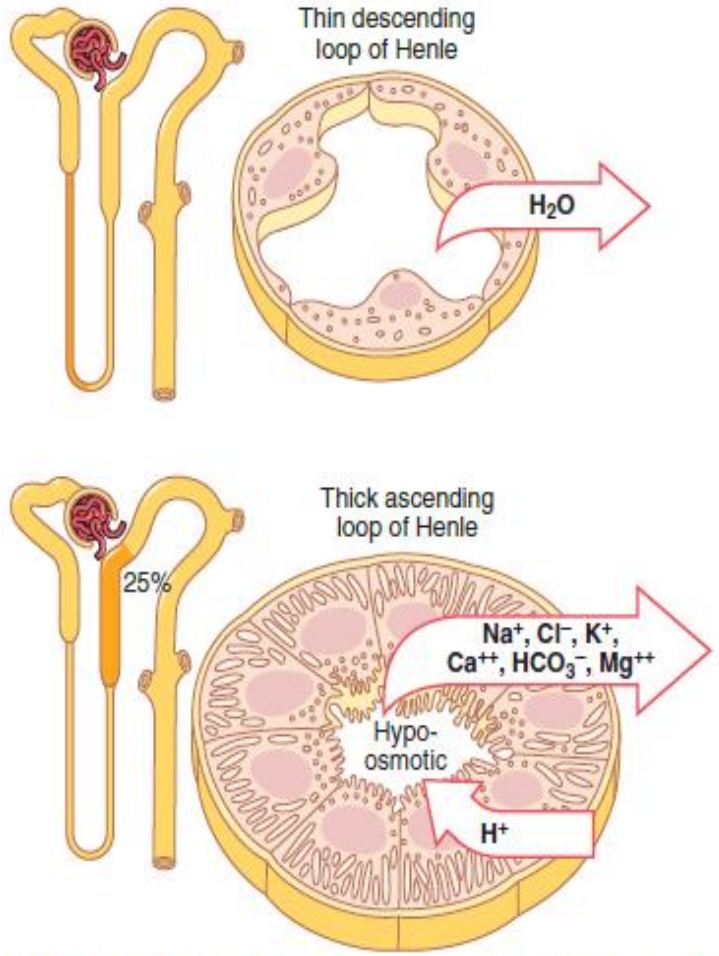


Figure 28-8. Cellular ultrastructure and transport characteristics of the thin descending loop of Henle (*top*) and the thick ascending segment of the loop of Henle (*bottom*). The descending part of the

Reabsorption of the filtrate in distal tubule and collecting duct

- In the distal tubule some 19% of the dilute filtrate arrives.
- Some 18 to 19% of the filtrate is reabsorbed in the distal and collecting duct
- Only 1 to 2 liters of the filtrate (1%) is excreted as urine, where ADH plays a big role in concentration and dilution of urine

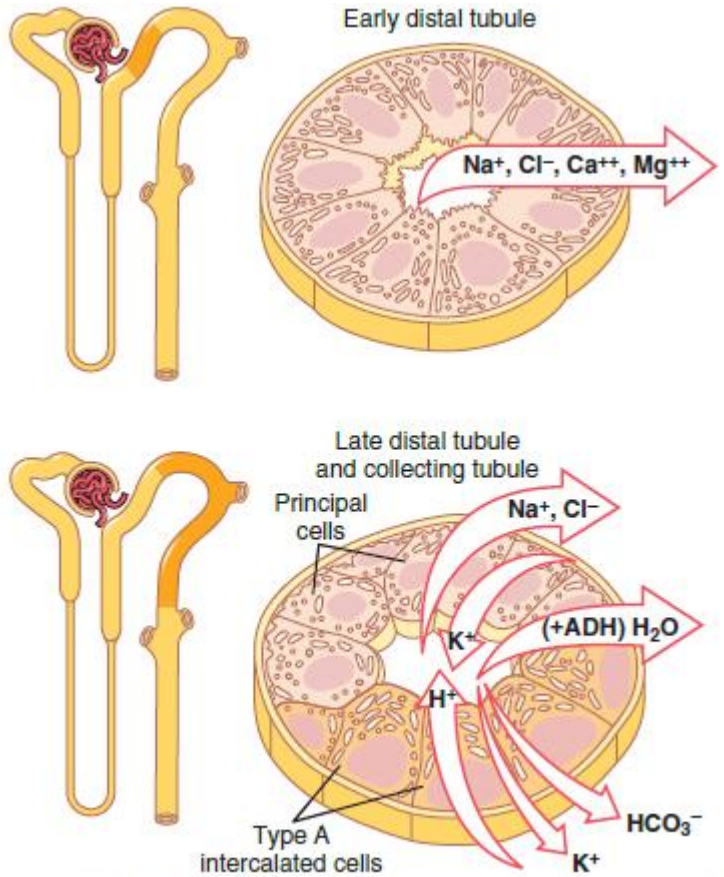
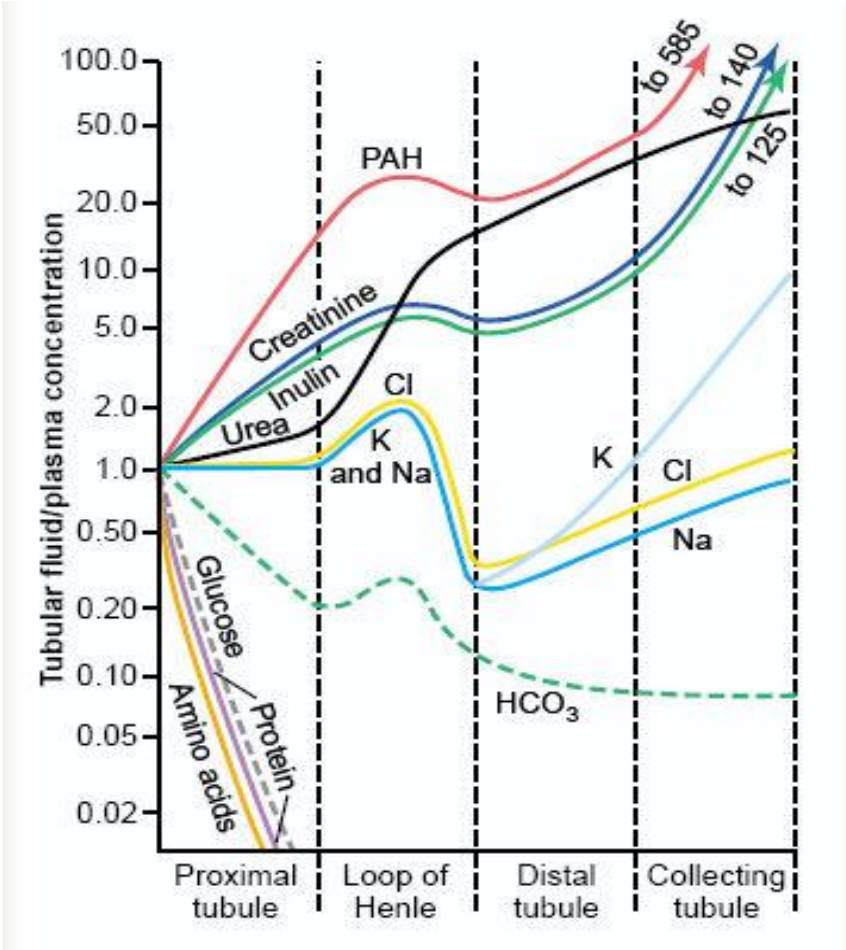


Figure 28-11. Cellular ultrastructure and transport characteristics of the early distal tubule and the late distal tubule and collecting tubule.

Summary of reabsorption and secretion in the tubules

Reabsorption: Almost 65% of the filtrate is reabsorbed in the proximal tubule. The rest are reabsorbed along the tubule

Secretion: K+, H+, Creatinine, urea and other wastes are finally excreted with urine



Nervous and Hormonal control of tubular reabsorption

Hormonal

1. **Aldosterone**: increases Na + reabsorption and increases K+ secretion

2. **Angiotensin II**. Increases Na + and H_2O reabsorption at the distal tubule

3. **ADH**: Increases H_2O reabsorption at distal & collecting duct

Nervous

SNS stimulation increases **Renin** release that in turn enhances **Angiotensin II** formation (effect s above)

Tubular transport maximum (T_M)

- **Tm is the maximum rate (mg/min) at which substances are completely reabsorbed or secreted in the kidney tubules. Tm depends on the saturation level of "Carrier proteins:**

E.g., Glucose:

Tm for glucose = 375 mg/min. When tubular load is less than 375 mg/min, then all of the glucose will be reabsorbed from the tubules.

If the plasma glucose level increases and causes the tubular load to be > 375 mg/min; the extra glucose is excreted with the urine, b/s all carriers for glucose are saturated (e.g., Diabetic patients).

Cont… Renal transport maximum (T_M)

- **The plasma glucose level of a healthy person almost never becomes high enough to cause glucose excretion in the urine even after eating meal. However. in un-controlled diabetes mellitus, plasma glucose may rise to high levels causing the Tm to exceed resulting in urinary glucose excretion.**
- **When the blood glucose level increases above about > 180 mg/dL, the proximal tubule becomes saturated (carriers occupied) and glucose will be excreted in the urine.**

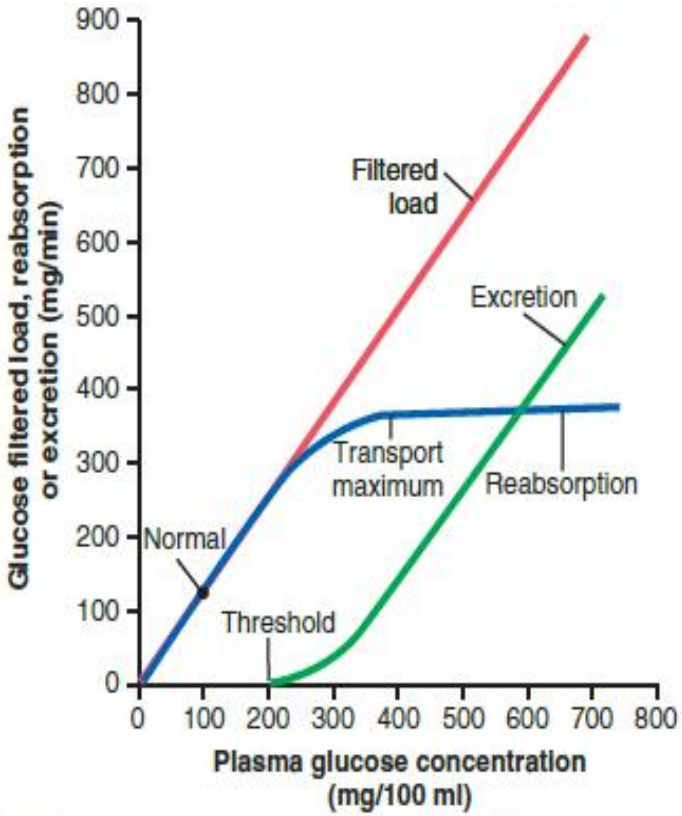


Figure 28-4. Relations among the filtered load of glucose, the rate of glucose reabsorption by the renal tubules, and the rate of glucose excretion in the urine. The *transport maximum* is the maximum rate at which glucose can be reabsorbed from the tubules. The *threshold* for glucose refers to the filtered load of glucose at which glucose first begins to be excreted in the urine.

Cont… Tm, meaning of Splay

- Splay appears to occur because kidney nephron **do not have the same tubular maximum.**

- **Some nephrons excrete the solute (glucose) before other nephrons reach their transport maximum.**

- **Most of the solutes like; amino acids,**
- **$PO4^{2-}$,**
- **Sulfate,**
- **Urates,**
- **lactate, etc. have their own specific transport maximums.**

Tubular secretion, toxic or unwanted metabolic by-products are secreted

- Transports from the **Peritubular capillaries** and **interstitial fluid** into the tubular lumen.

- **Creatinine, NH_3, urea**, **uric acid & some drugs** are excreted
- **K^+, H^+** are secreted actively mainly from the **distal tubule**

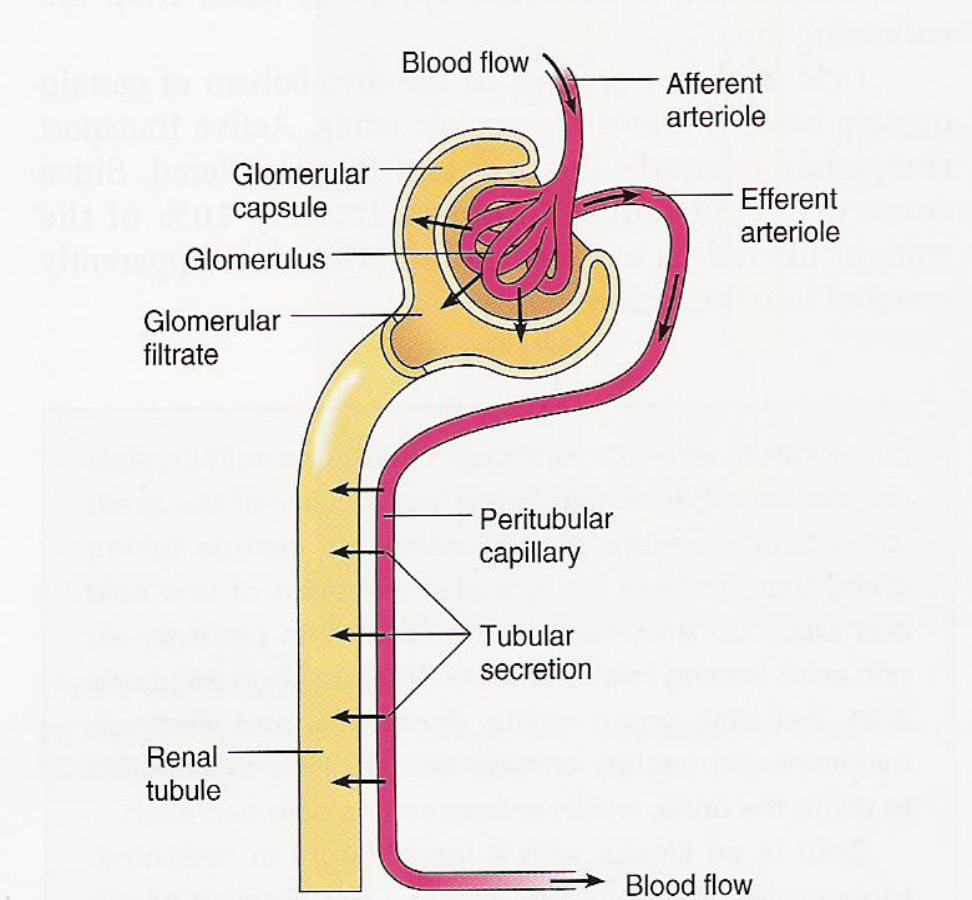


FIGURE 20.25
Secretory mechanisms move substances from the plasma of the peritubular capillary into the fluid of the renal tubule.

Concentration and dilution of urine

A. Why is it necessary to excrete a concentrated urine?

- ***To save water and thus control ECF-volume during dehydration***

B. Why necessary to excrete a dilute urine?

-To remove excess H_2O (fluid overload) from the body during hyperhydration.

- **Generally, concentration and dilution of urine is important to regulate the water and solute (osmolality) level of the ECF-volume.**

Causes of dehydration and over-hydration that induce concentrated or dilute urine

Some causes of dehydration include:

- Increased sweating,
- Thirst
- Physical exertion
- Vomiting
- Diarrhea, etc.

- **Some cuses of fluid overload (hyperhydration) include:**
- Diseases like Diabetes insipidus
- Edema (different types)
- hypotonic fluid intake by mouth (e.g., athletes take excess H_2O after marathon run)

Mechanisms of concentration & dilution of Urine

3-important mechanisms are involved in concentration and dilution of urine:

1. **Counter current multiplier** and **counter current exchanger** systems that produce **Hyperosmolar medullary interestitium**

2. **The presence and absence of ADH, mainly at the collecting duct**

3. **The reabsorption of urea from collecting duct that has an effect of increasing the Osmolarity of the medullary interstitium.**

Counter current multiplier and counter current exchanger systems

- **Counter current multiplier (occurs at the Loop of Henley (LoH)**
- Solute concentration keeps on increasing in the tubules and forms **hyperosmolar** concentration at the tip of the LoH and interstitium.
- At the tip of the LoH, the solute conc. reaches **~1200** mOsm/l compared with 300 mOsm/L at the proximal tubule

- **Counter current exchanger (**occurs at **vasa recta).**
- **It 's importance is that it** prevents **washout or removal** of solutes (salts) from medullary interstitium, thereby maintaining the **hyperosmolar** environment intact in medullary interstitium. Blood flow is sluggish.
- It also nourishes the tubules with O2 and nutrients

The **hyperosmolar** environment is important **to reabsorb H_2O** from collecting duct by osmosis

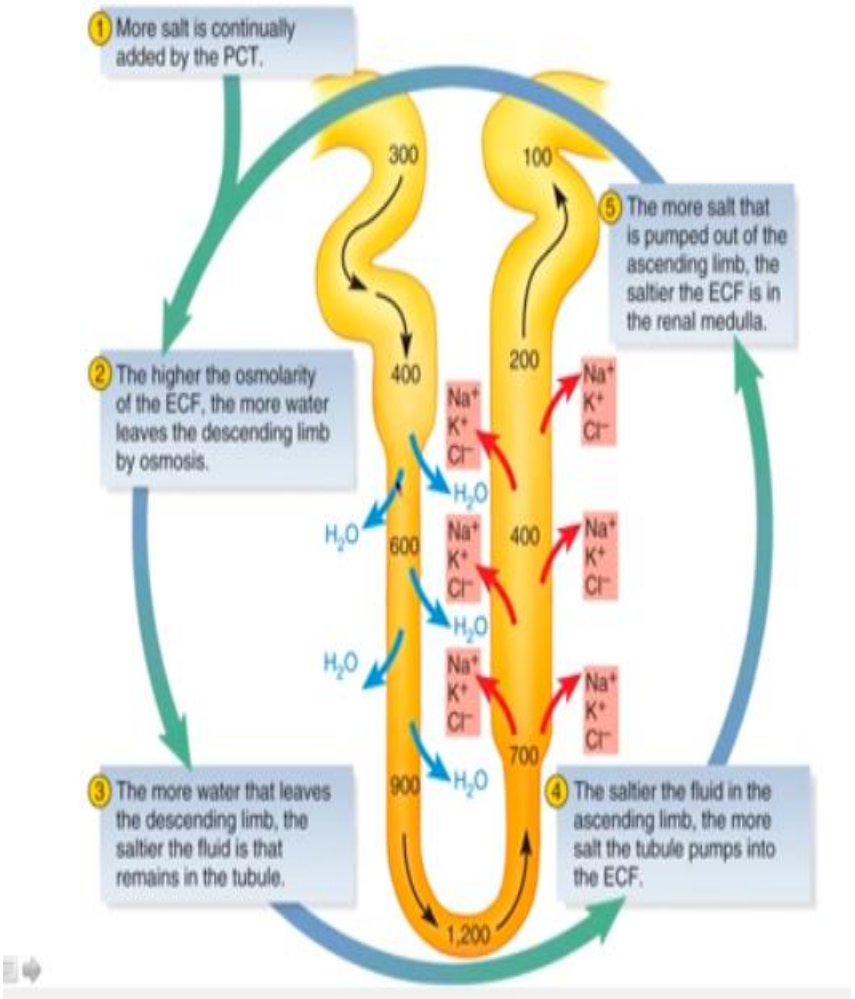
Counter current multiplier system, causes hyper-osmolarity by pumping solutes like: Na+, K+, Cl- , Mg2+, into the medulla interstitium from the thick portion of the LoH

Counter current multiplier

A. The **descending** tubule is **permeable to water**

B. The **ascending** (thick tubule) is **only permeable** to solutes like (Na, Cl, K+ etc), but **not to water**

Result: The net result of the counter current multiplier system is to produce **hyper-osmotic interstitial fluid** in the medulla.



Urea increases hyper-osmolarity in the medullary interstitium

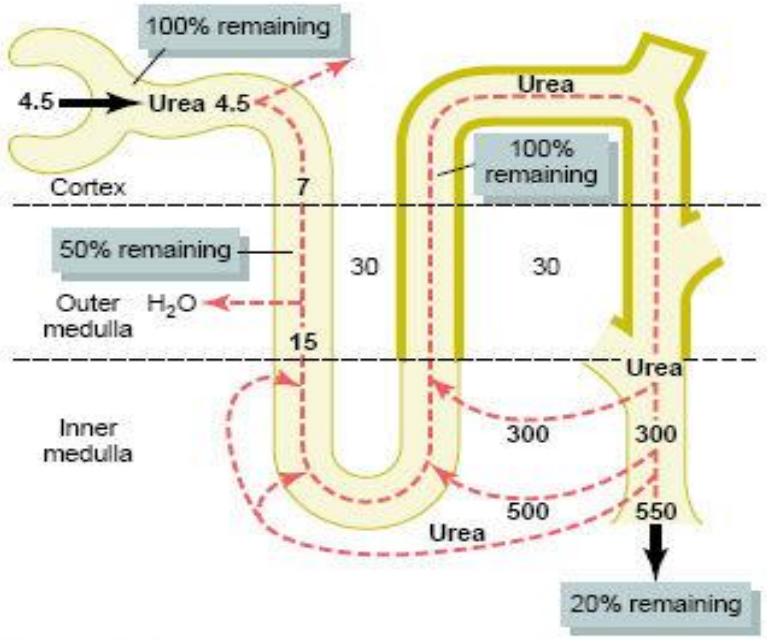


Figure 28–5

Recirculation of urea absorbed from the medullary collecting duct into the interstitial fluid. This urea diffuses into the thin loop of Henle, and then passes through the distal tubules, and finally passes back into the collecting duct. The recirculation of urea helps to trap urea in the renal medulla and contributes to the hyperosmolarity of the renal medulla. The heavy dark lines, from the thick ascending loop of Henle to the medullary collecting ducts, indicate that these segments are not very permeable to urea. (Numerical values are in milliosmoles per liter of urea during antidiuresis, when large amounts of antidiuretic hormone are present. Percentages of the filtered load of urea that remain in the tubules are indicated in the boxes.)

The hyperosmolarity of the medullary Interestitium **is not** only due to **Na, Cl , K+ or Mg2+ efflux to the medullary interstitium,** but also **due to urea. In fact urea accounts to 50% of the osmolar concentration.**

Urea is transported **by facilitated diffusion** from the **collecting duct** and accumulates in the medulla to cause the **hyperosmolar** environment.

A **high-protein diet** increases the ability of the kidneys to **concentrate** urine by producing urea as by product.

Compare concentrated & dilute urine, High ADH = Conc. Urine & Low ADH = dilute urine

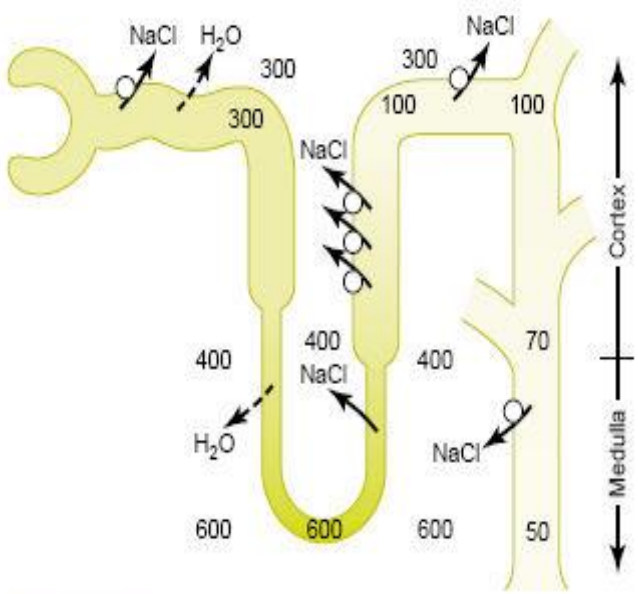


Figure 28–2

Formation of a dilute urine when antidiuretic hormone (ADH) levels are very low. Note that in the ascending loop of Henle, the tubular fluid becomes very dilute. In the distal tubules and collecting tubules, the tubular fluid is further diluted by the reabsorption of sodium chloride and the failure to reabsorb water when ADH levels are very low. The failure to reabsorb water and continued reabsorption of solutes lead to a large volume of dilute urine. (Numerical values are in milliosmoles per liter.)

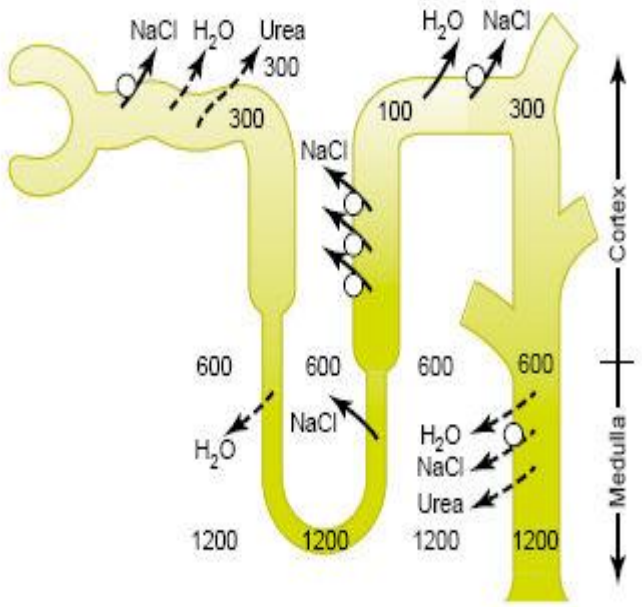


Figure 28–4

Formation of a concentrated urine when antidiuretic hormone (ADH) levels are high. Note that the fluid leaving the loop of Henle is dilute but becomes concentrated as water is absorbed from the distal tubules and collecting tubules. With high ADH levels, the osmolarity of the urine is about the same as the osmolarity of the renal medullary interstitial fluid in the papilla, which is about 1200 mOsm/L. (Numerical values are in milliosmoles per liter.)

ADH transport to collecting

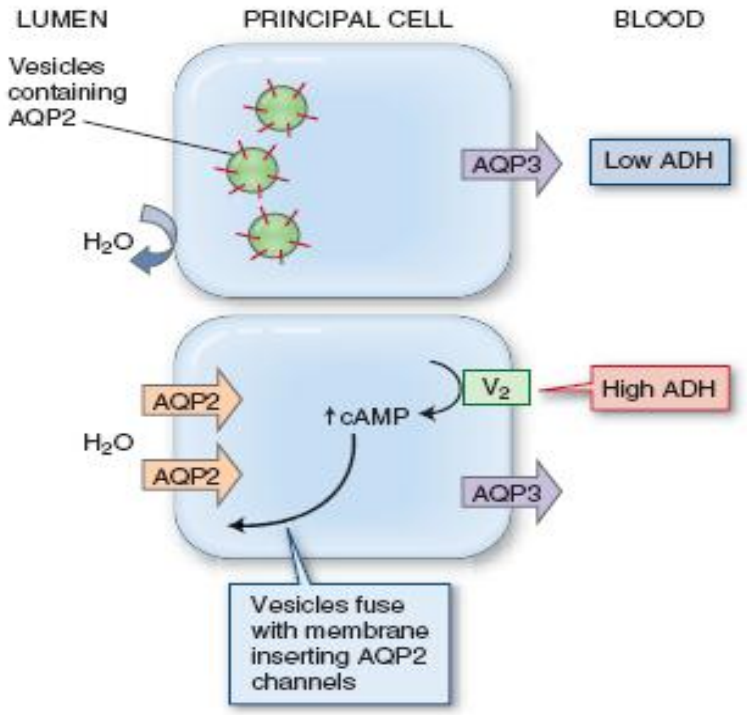


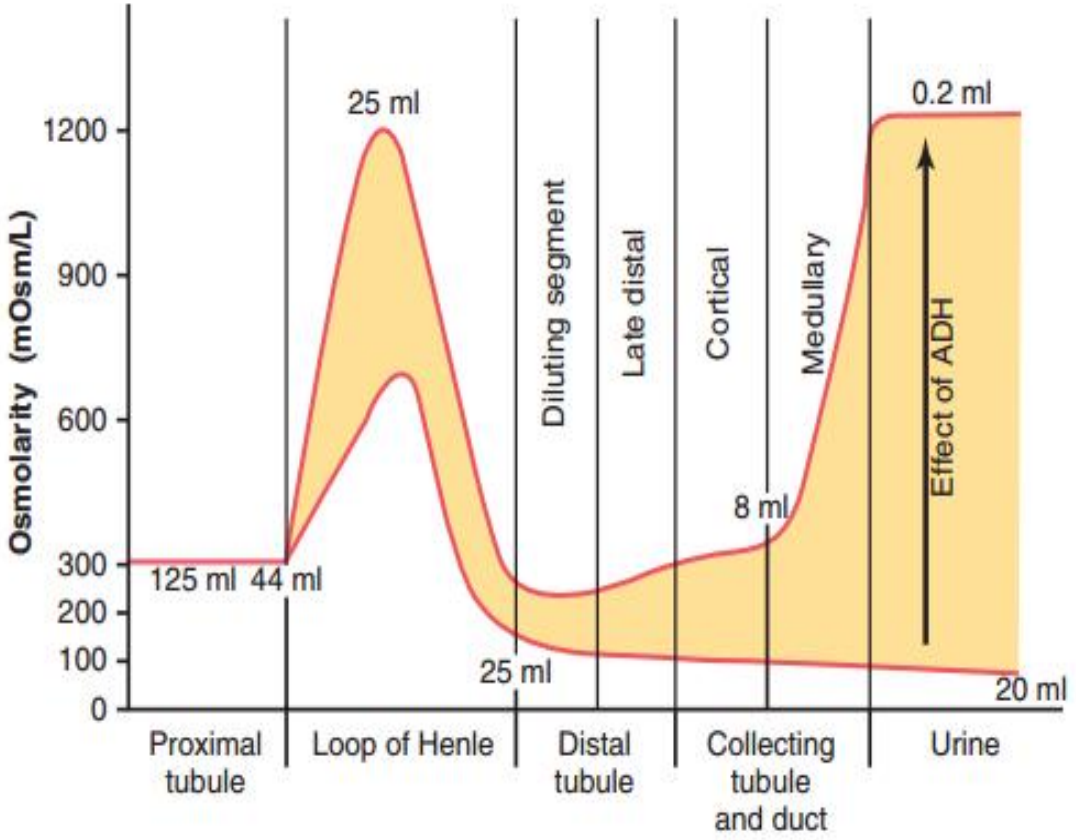
Figure 6-27: Aquaporin 2 (AQP 2) water channel expression in the collecting duct. In the absence of antidiuretic hormone (ADH), the water permeability in the collecting duct is low because water channels are not present in the apical membranes. AQP3 channels are expressed continually in the basolateral membrane. Binding of ADH to the V_2 receptors on the basolateral membrane of the principal cells causes insertion of vesicles containing AQP2 water channels into the apical cell membrane, completing the pathway for water flux.

- **Because ADH is a hormone that moves with the blood, it's receptors called V2-receptors are found on the basolateral side of the epithelial cells of the collecting duct.**

- **Stimulation with ADH causes activation of cAMP that in turn causes *aquaporins (*water channels) to move to luminal side and allow water to be reabsorbed to the interstitium (ECF)**

Relation of osmolality to ADH production

- Changes in the level of fluid osmolality at different levels of the Nephrons in **the presence and absence of ADH**



Substances that increase or decrease secretion of ADH

Table 28–2

Regulation of ADH Secretion

Increase ADH	Decrease ADH
↑ Plasma osmolarity	↓ Plasma osmolarity
↓ Blood volume	↑ Blood volume
↓ Blood pressure	↑ Blood pressure
Nausea	
Hypoxia	
Drugs:	Drugs:
Morphine	Alcohol
Nicotine	Clonidine (antihypertensive drug)
Cyclophosphamide	Haloperidol (dopamine blocker)

Disorders of urinary concentrating ability

- **Facultative**:
  H_2O is reabsorbed with the **presence of ADH (in collecting duct).**

- **Obligatory**:
  H_2O reabsorption takes place **without the presence of ADH (proximal tubule)**

2-types of diseases occurring due to low ADH

a. **Central (brain):**

Diabetes insipidus: low ADH secretion from the hypothalamic brain (injury, congenital etc.).

a. **Nephrogenic (kidney):**

D. insipidus: when the distal and collecting duct receptors do not respond to ADH.

In both cases dehydration occurs

Counter current exchange in the vasa recta

The vasa recta is a region where the peritubular capillary extends down to the medulla and surrounds the loop of Henley by forming a U-turn.

NaCl and urea diffuse out of the **ascending limb** and **enter into** the **descending** limb, while

Water diffuses out of the descending limb and **enter into the ascending** limb (vise-versa). This effect, therefore, ***maintains the Salt level or hyperosmolarity*** in the medullary interstitium

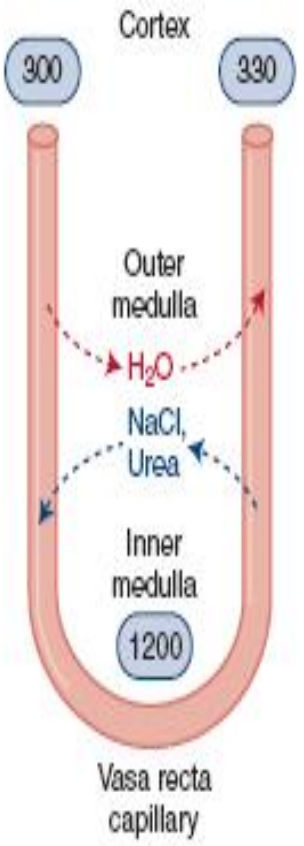
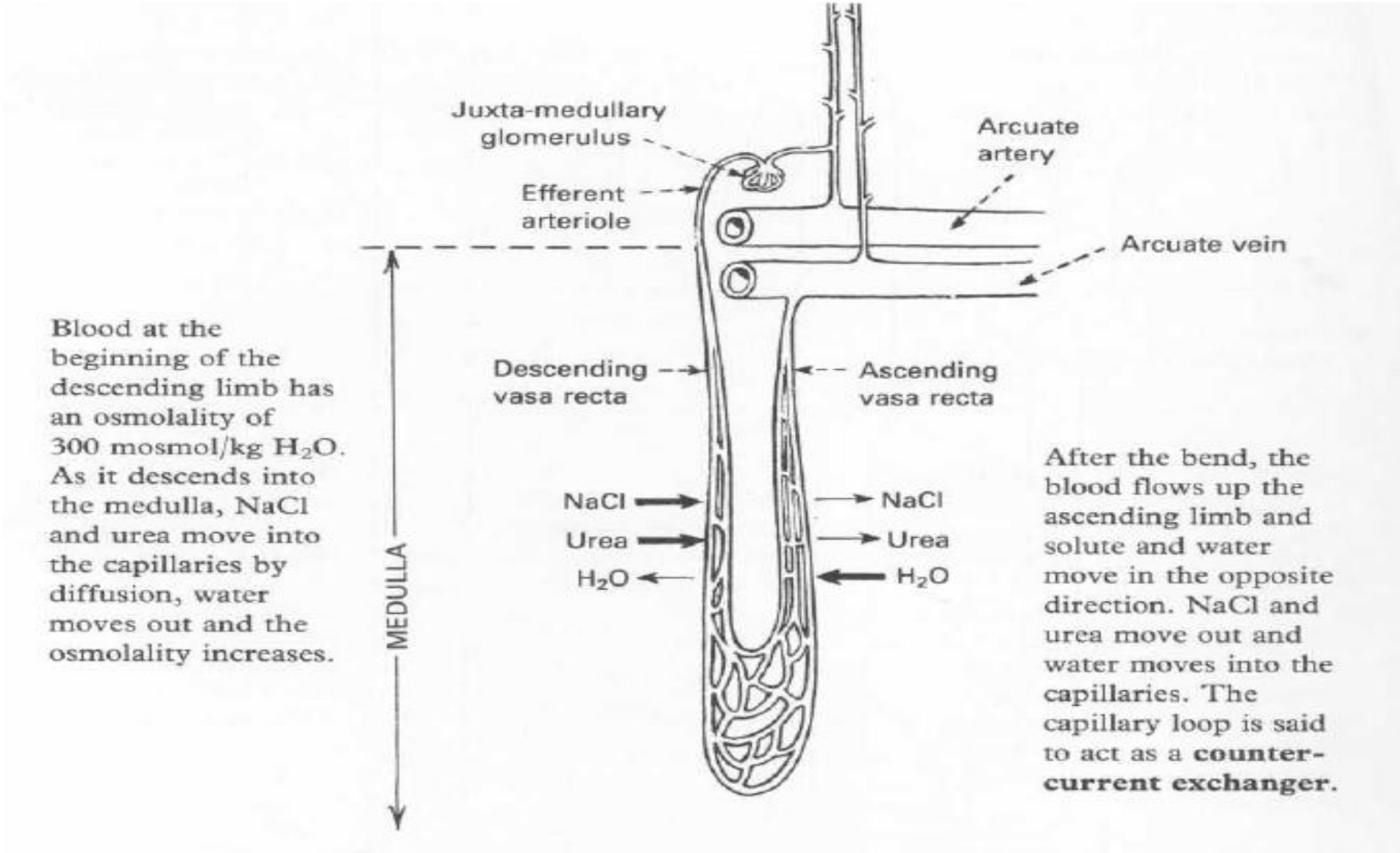
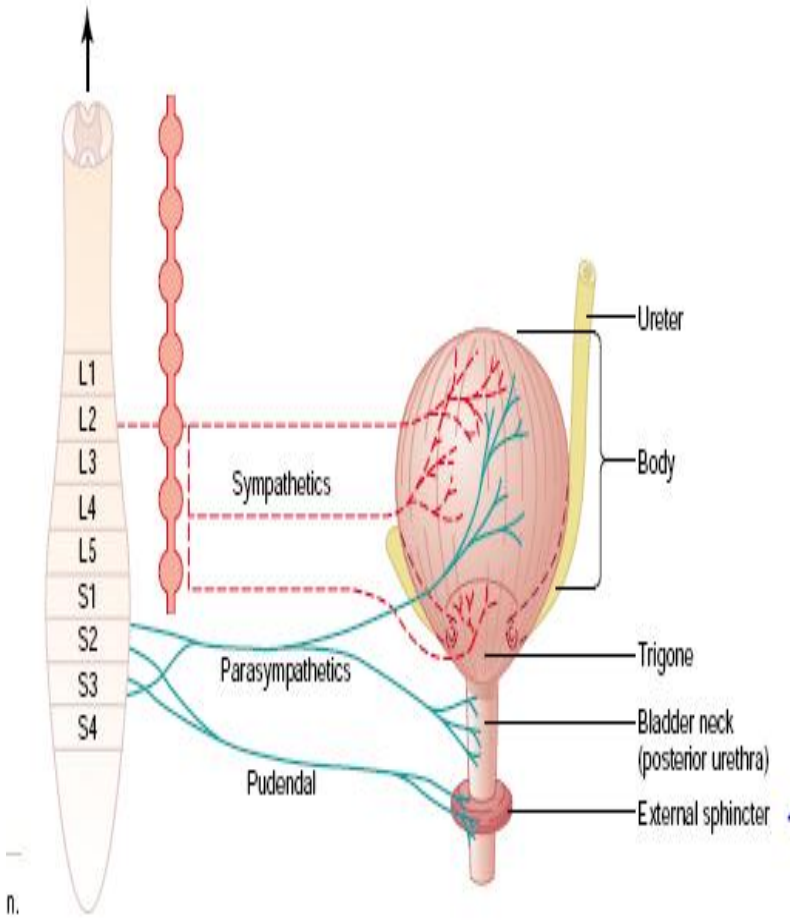


Figure 6-26: Countercurrent exchange. Numbers indicate typical osmolarity (mOsm/L) during maximal antidiuresis. Passive cycling of solutes from the ascending to the descending limbs of the vasa recta capillaries traps solutes in the medullary interstitium.

Function of the vasa recta



Micturition reflex Urinary bladder and its innervation



-It is mainly **Spinal reflex,** but can also be regulated by higher centers.

1. Autonomic fibers

-PNS (pelvic nerves) innervates the bladder and causes contraction (Ach is the neurotransmitter)

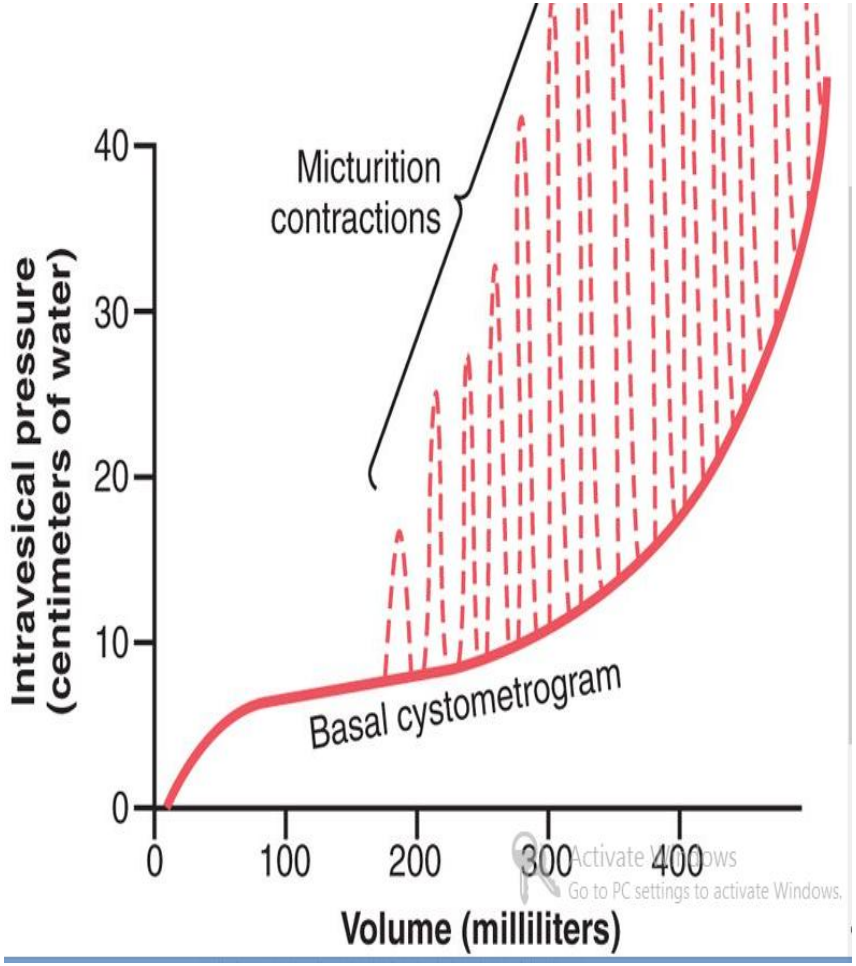
- SNS also innervates the bladder and **internal sphincter** causing it to contract. Important **at rest**

-Stretch receptors are stimulated when the bladder is filled **(~500 ml)**

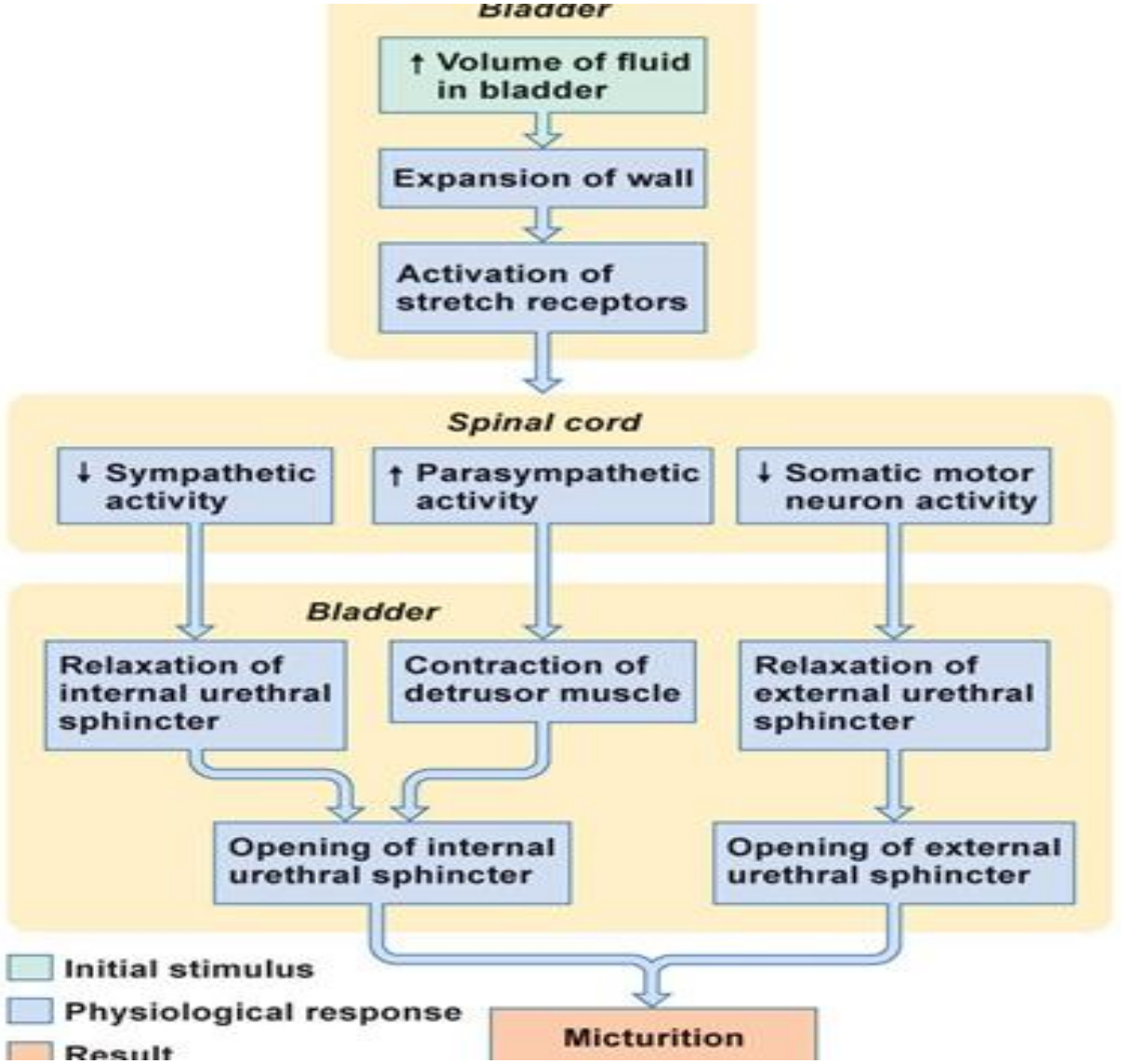
2. - Somatic fibers innervate the **external sphincter** (motor skeletal muscle which is voluntary in action)

cytometry measures pressure inside the bladder and its fullness

- As the bladder continues to fill, Micturition reflexes become more frequent and cause greater contractions of the **detrusor** muscles of the bladder.
- When one **Micturition contractions** start, it is **self-regenerative and** receptors are activated to a greater degree to cause strong degree of contraction. **After about 500 ml, urination becomes involuntary**



Micturation reflex



Concept of clearance

- **Clearance: is defined as the rate at which the kidneys remove, (i.e., "clear"), a substance away from the plasma.**
- **Clearance has a very important implication clinically, b/s it indicates the efficiency of the kidneys to clear the plasma of a given substance.**

- **By using clearance method, one can calculate:**
- **GFR (glomerular filtration rate)**
- **It can also be used to know how different substances are reabsorbed or secreted**

Formula to calculate clearance

The general formula to calculate clearance (Cx) is:

$$= Cx\ (ml/min) = \frac{Ux\ (mg/ml) \times Vx\ (ml/min)}{Px\ (mg/ml)}$$

Ux= The concentration of a substance (X) in urine (mg/ml)

Px = The concentration of the substance (X) in plasma (mg/ml)

Vx = Urine volume/min (ml/min)

A substance should be filtered freely, but should not be reabsorbed or secreted to be equal to GFR. Good examples are inulin and Creatinine.

- **To understand the clearance concept, consider first substances such as *inulin or Creatinine* that are neither reabsorbed nor secreted by the nephron.**
- **Their clearance is almost equal to GFR (125 ml/min)**

Creatinine (Cr) and Glucose clearance

- **Creatinine (Cr) clearance:**

It is a product of muscle metabolism which can be used instead of **inulin.**

- GFR= $\frac{\text{UCr mg/ml x V (ml/min)}}{\text{PCr mg/ml}}$

Though values calculated for Cr clearance are similar, they however, **over-estimate GFR** by **about 10%.**

- This is b/s, there is **some secretion** into the proximal tubule.

- Glucose Clearance

- Glucose like inulin is freely filtered, but all the glucose filtered is reabsorbed.

Therefore,

- No plasma ends up losing glucose.
- **Thus, the clearance of glucose is zero (0).**

Plasma creatinine and GFR

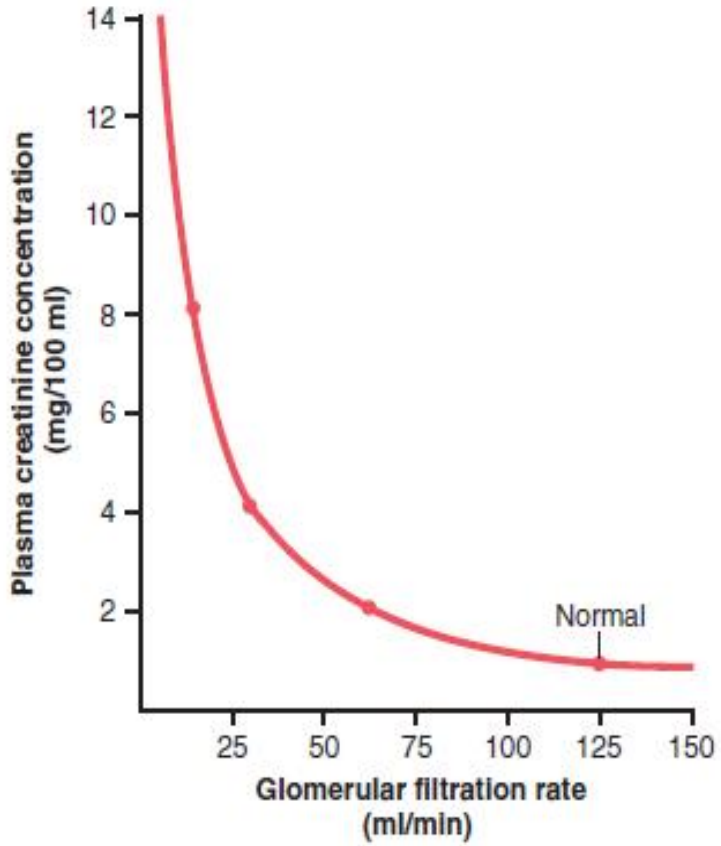


Figure 28-22. Approximate relationship between glomerular filtration rate (GFR) and plasma creatinine concentration under steady-state conditions. Decreasing GFR by 50 percent will increase plasma creatinine to twice normal if creatinine production by the body remains constant.

- An approximation of *changes in GFR, can be* obtained by simply measuring plasma Cr (creatinine) concentration.
- This is b/s plasma Creatinine (PCr), is **inversely** proportional to GFR:

Diuretics

- **Definition: Are substances that increase urine output.**

- **Diuretic substances inhibit solute reabsorption (electrolytes) and by so doing prevent the intake of water to the ECF.**

- **Generally, diuretics help in reduction of ECF volume and indirectly suppress edema formation or prevent increase in ABP. Types:**

a. *Osmotic diuretics*

b. Loop diuretics

c. Diuretics that inhibit ADH at collecting duct

etc.

Diuretics

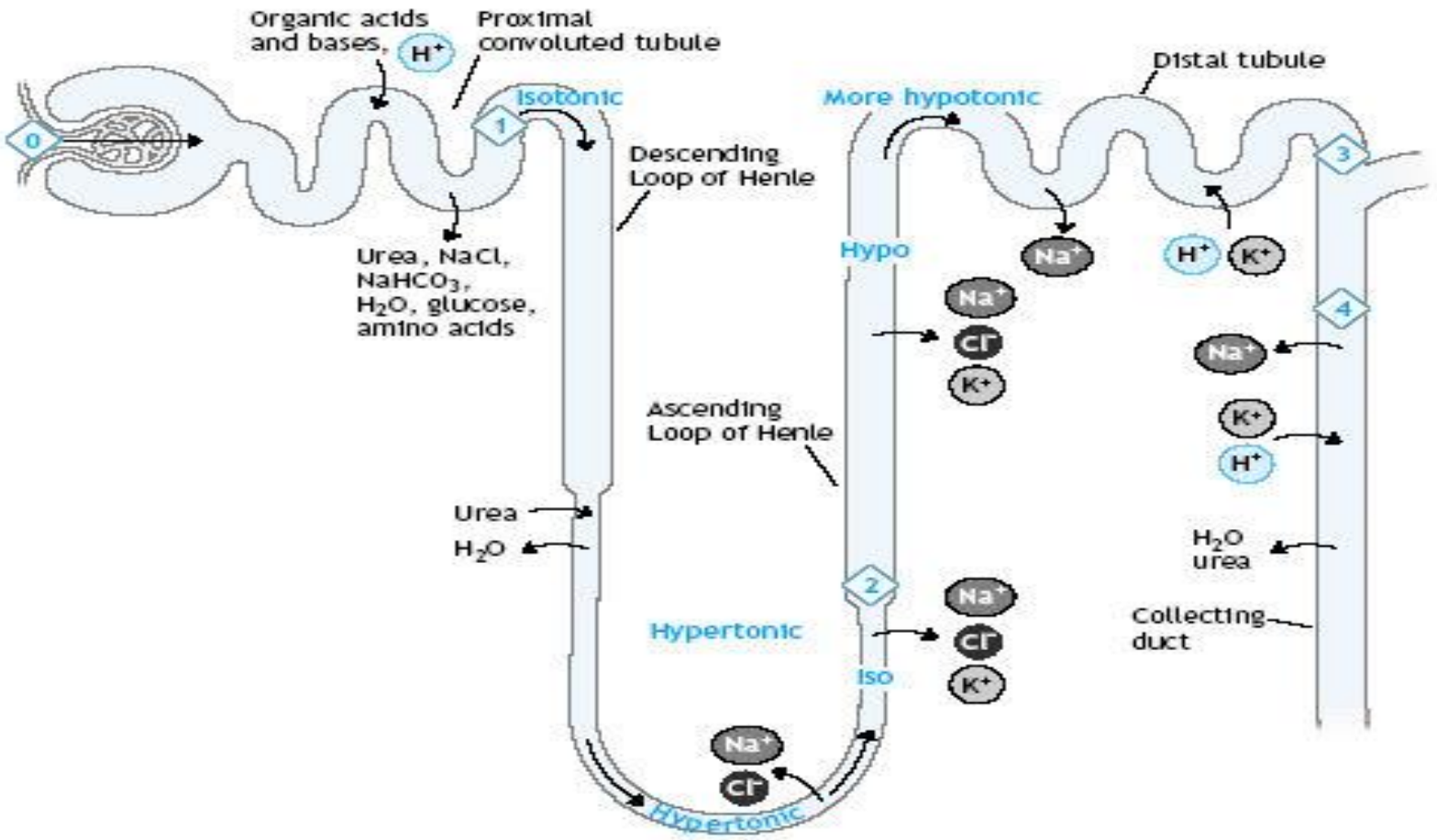


Figure 4–16. Osmotic diuretics (eg, mannitol) work in all parts of the nephron (*0*). Carbonic anhydrase inhibitors (eg, acetazolamide) block the acid secretion system in the proximal tubule (*1*). Loop diuretics (eg, furosemide) act on the thick ascending loop of Henle, which is impermeable to both water and urea (*2*). Thiazide diuretics (eg, hydrochlorothiazide) act on the distal convoluted tubule (*3*). Antagonists to aldosterone (eg, amiloride) and V_2 vasopressin receptor antagonists (eg, lithium) act on the collecting ducts (*4*).

Sites of Diuretics and their clinical uses

TABLE 6-3. Sites of Diuretic Action and Clinical Uses

Class	Agents	Mechanism of Action	Examples of Use
Loop diuretics	Furosemide Bumetanide Torsemide	Inhibition of $Na^+/K^+/2Cl^-$ cotransport in the thick ascending limb	• Pulmonary edema • Hypertension • Heart failure
Thiazides	Hydrochlorothiazide	Inhibition of Na/Cl cotransport in the distal tubule	• Hypertension • Heart failure (supplement to loop diuretics)
K^+-sparing	Spironolactone Amiloride Triamterene	Aldosterone receptor antagonist Na^+ channel inhibition in the cortical collecting duct	• Hypertension due to hyperaldosteronism • Supplement to loop or thiazide diuretics to reduce K^+ wasting
Carbonic anhydrase inhibitors	Acetazolamide	Kidney: in the proximal tubule & other organs expressing carbonic anhydrase	• Rarely used to treat heart failure • Loss of HCO_3^- in urine useful in acute mountain sickness and in metabolic alkalosis • Glaucoma (eye) • Epilepsy (central nervous system)

Acid-base balance (introduction)

- Acids release H+ in solution; bases accept H+.
- The [H+] in extracellular fluid is 0.00004 mmol/L

- A logarithmic pH scale is used to express these very small H+ values:
- $pH = 1/[H^+]$

$pH = -\log_{10}[H^+]$

Volatile vs fixed acids

Volatile: e.g. CO_2

Daily metabolism produces about 15,000 mmol of CO_2 (volatile acid).

Fixed: diet

Metabolism produces an additional 70 mmol of fixed acids (also called metabolic or nonvolatile acid), including phosphoric and sulfuric acids

pH < 6.8 and pH > 8 = death can occur

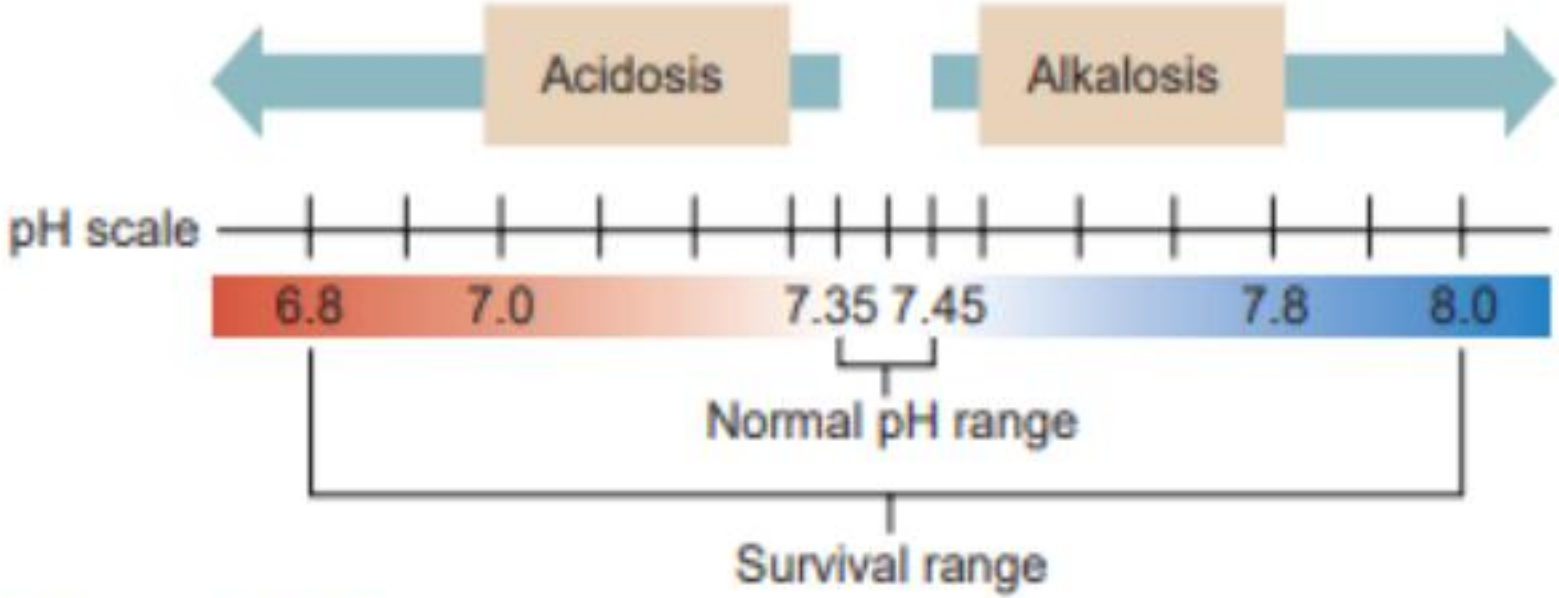


Figure 18.9

If the pH of arterial blood drops to 6.8 or rises to 8.0 for more than a few hours, the person usually cannot survive.

Acid-base balance

Henderson-Hasselbalach equation is important and please revise.

$$PH = 6.1 + \log_{10} \frac{HCO3^-}{PCO2}$$

- **The ratio b/n bicarbonate and PCO2 drive the pH level in the blood (20:1).**
- **Increase in HCO3 raises pH (alkalosis), but increase in PCO3 decreases blood pH (acidosis).**

$$CO_2 + H_2O = H_2CO_3 = H^+ + HCO_3^-$$

The ratio of HCO_3 to PCO_2 is: 20:1

$$\frac{HCO_3}{CO_2} = \frac{20}{1}$$

The bicarbonate (HCO3) buffer of the ECF is the most important buffer system.

3-ways of acid-base imbalances

The body regulates acid base imbalances by 3-methods:

A. Chemical buffers

B. The lung (CO2)

C. Kidney (HCO3)

Chemical buffers regulate the pH within seconds and is the 1st line of defense

- **A. Chemical buffers**

4-types of chemical buffers exist. Some in intracellular fluid (ICF) & others in the ECF.

1. **Bicarbonate buffer (ECF)**
2. **Protein buffers (ICF)**
3. **Hemoglobin (ICF)**
4. **Phosphate (ICF)**

Respiratory acidosis, causes & compensations

Cause of respiratory acidosis

hypoventilation

- The **lung fails** to expire CO2 produced by metabolism.

So, a lot of CO_2 accumulates in the body making the pH <7.4

a. Respiratory depression (e.g., drugs, sedatives cause hypoventilation)

b. Pulmonary diseases that cause hypoventilation

Emphysema, asthma etc.

Compensation

By the kidney:

- The kidney **increases the reabsorption of HCO_3**
- HCO_3 neutralizes & increases the pH back to normal.
- Note: increased H+ can not stimulate rate of breathing, b/s the lung is the initial cause of the problem

Some of the factors that lead to respiratory acidosis due to accumulation of CO_2 gas

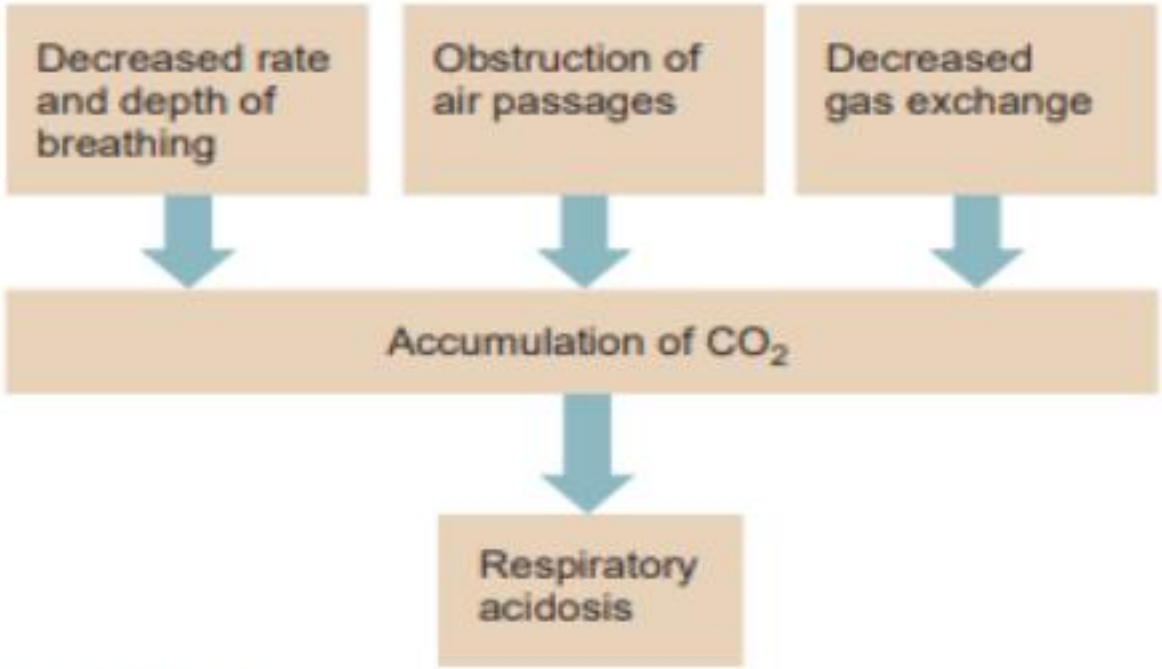


Figure 18.11
Some of the factors that lead to respiratory acidosis.

Respiratory alkalosis, causes & compensation

Respiratory alkalosis

Causes:

Hyper-ventilation

Removal of CO_2 occurs due to excess breathing.

This causes a drop in PCO_2 in the body

e.g., High altitude hypoxia, or anxiety plus madness etc. cause loss of CO_2 to the atmosphere

Compensation

Kidney loses a lot of HCO_3 through the urine, until the pH reaches to normal level. In other words, alkalinity decreases due to loss of HCO_3

Metabolic acidosis causes and compensation

- **Cause: diet! and derangements of metabolism**

Accumulation of acids in the body e.g. lactic acid, keto acids, HCl, phosphoric and sulfuric acid)

- Starvation: keto-acidosis mostly fats burn instead of CHO

- Hypoxia: decreased O2, thus glycolysis dominates and lactic acid is generated

Severe diaharia: large amounts of HCO_3 is lost, acid production (HCl) dominates

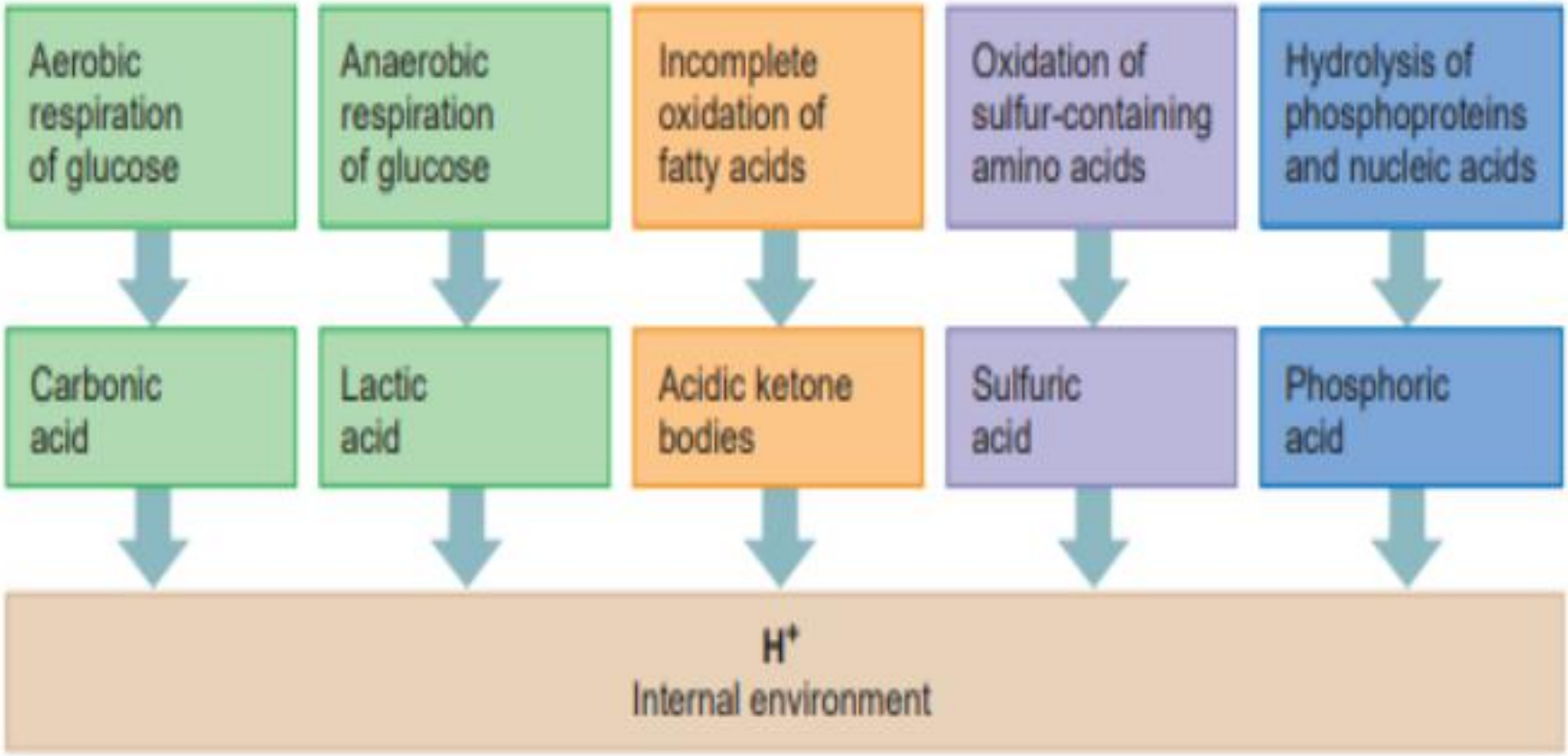
Compensation:

By the lung (respiratory means) .

a. **Hyper-ventilation** causes **washout of CO2** and decreases H+ indirectly from body fluids

$H + HCO_3 = H_2CO_3 = \mathbf{CO_2} + H_2O$

How acids or excess H+ ion is produced by metabolism (Metabolic acidosis)



Some of the factors that lead to metabolic acidosis

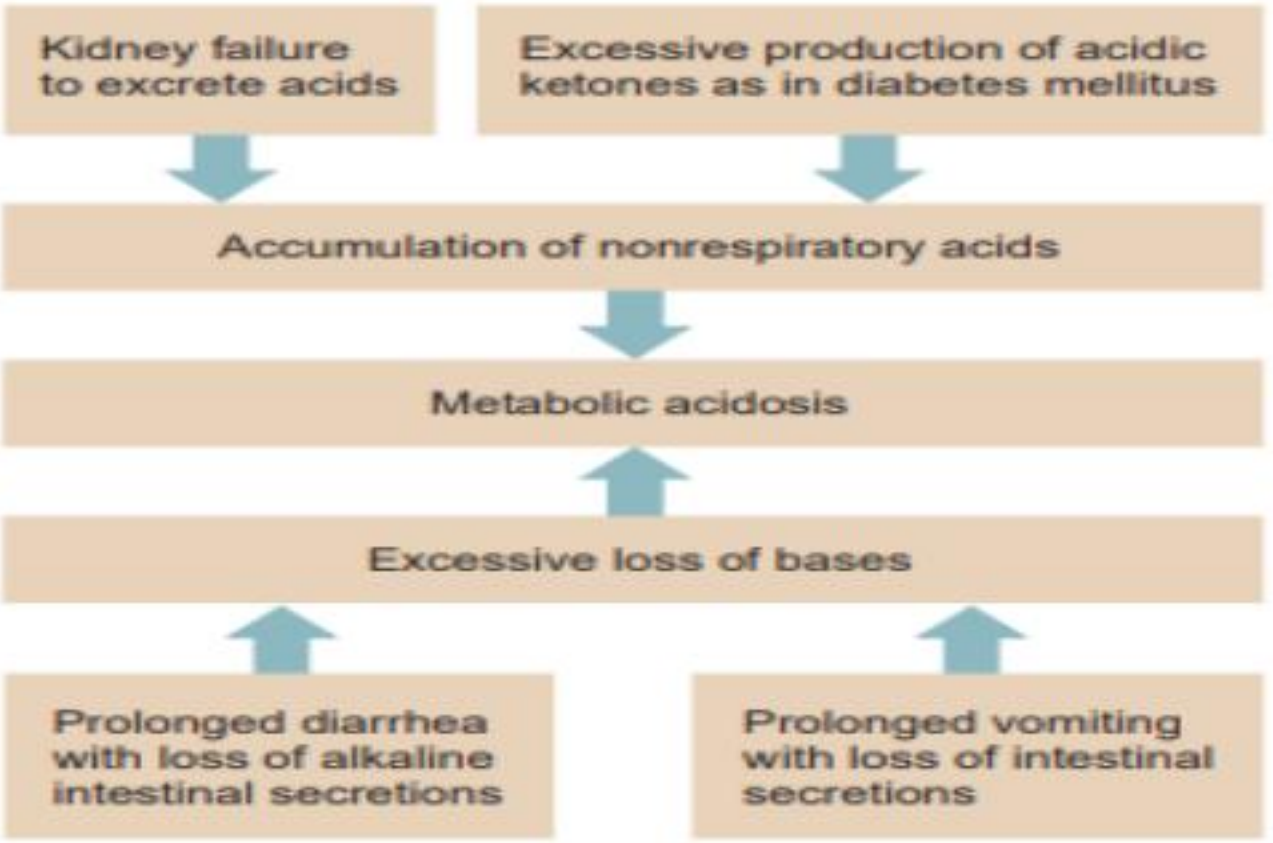


Figure 18.12
Some of the factors that lead to metabolic acidosis.

Metabolic Alkalosis, causes and compensation

Metabolic alkalosis:

Cause: an increase in

HCO_3 production in the body

a. **Prolonged vomiting**: HCl acid from the stomach is lost and this effect elevates blood HCO3 level.

b. **Hyper-aldosteronism**: causes increase HCO3 reabsorption

Compensation of metabolic alkalosis:

The respiratory system inhibits respiration (causes lower breathing rate)

Hypo-ventilation causes retention of CO2 and causes the pH to come to normal

Factors that lead to metabolic alkalosis

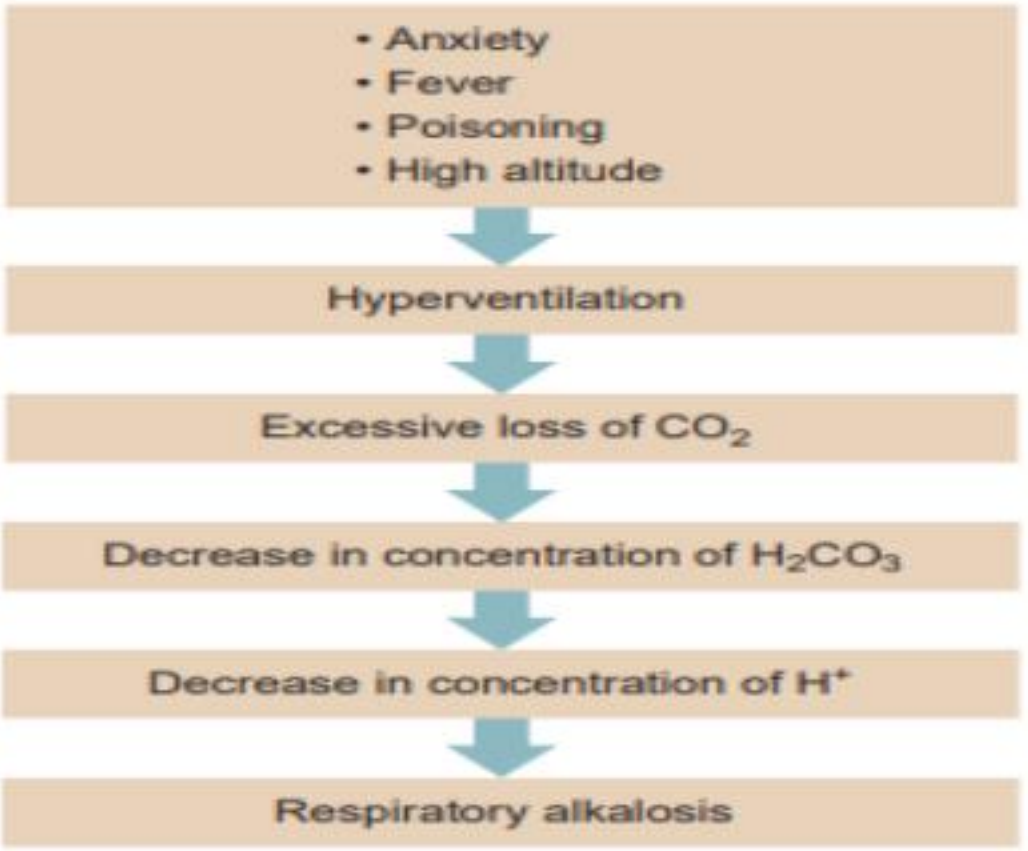


Figure 18.13
Some of the factors that lead to respiratory alkalosis.

Summary for Arterial blood gas (ABG) interpretation

Remember the following **normal ranges** for:

- **PCO_2** that implies **respiratory**
- **HCO_3-** that implies **metabolic**

1. pH = acidosis < 7.35--N---- 7.45 >alkalosis

2. $PaCO_3$ = alkalosis < 35 ---N-----45 > acidosis

3. HCO_3 = acidosis < 22---N-----26> alkalosis

Exercise on Acid-base imbalances

- A person with lung disease (e.g.COPD) has the following blood gas results. Interpret his Acid-base complications
- Study the normal ranges, then say whether it is acidosis or alkalosis (refer slide 88).
- pH = 7.26
- PCO2 = 59
- HCO3 = 42

	Acidosis	**normal**	**alkalosis**
pH 7.26	-		-
PCO2 59	-		
HCO3 42			

- A. Respiratory alkalosis
- **B. Respiratory acidosis**
- C. Metabolic alkalosis
- D. Metabolic acidosis
- NB: 3 in a row (acid, ph, PCO_3)= respiratory acidosis

Exercise, on acid-base balance

- pH = 7.35---- 7.45
- Pa CO2 = 35 ----45
- HCO3 = 22 ---- 26
- Question: assume a patient with the following ABG. Find his complication? (Rome: Three in a row concept)
- **pH = 7.50** **pH 7.33**
- **PCO3= 50** **CO2= 54**
- **HCO3 = 42** **HCO3= 30** **find?**

Acidosis	Normal	alkalosis
-	-	**- pH = 5.50**
- CO2=50	**-**	**-**
-	-	**- HCO3= 42**

- **Answer = Metabolic alkalosis, partially compensated**

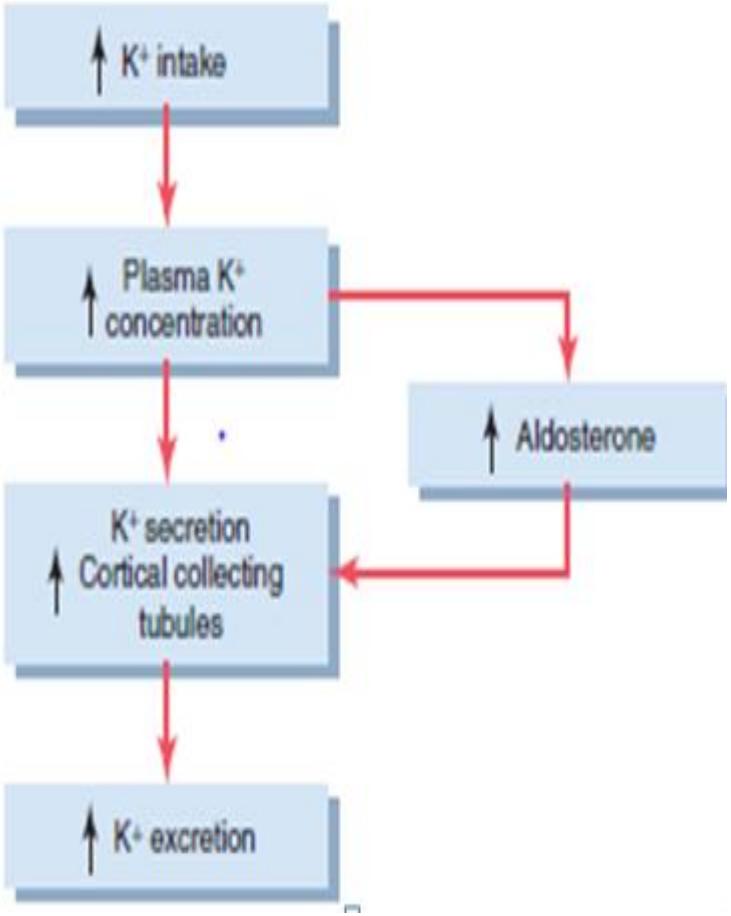
Self-study on acid-base balance & their compensations

Please check the “intermate ” on: “acid-base balance/ “TIC-TAC-TOA method of studying acid-base imbalances & compensations. (easy, exams on pH will follow the same style of assessing ABG-procedure).

Know concept of:

- **un-compensated**
- **Fully- compensated**
- **Partially compensated acid-base balance**

Electrolyte regulation by the kidney: K+



- Remember K+ is an important electrolyte in resting membrane potential generation and in heart function. So, it should be tightly regulated. Look the figure and its interaction with aldosterone.

- Increase in K+ ion in ECF causes increased release secretion of Aldsteron that in turn increases K+ excretion through the urine

Ca2+ regulation by the kidney

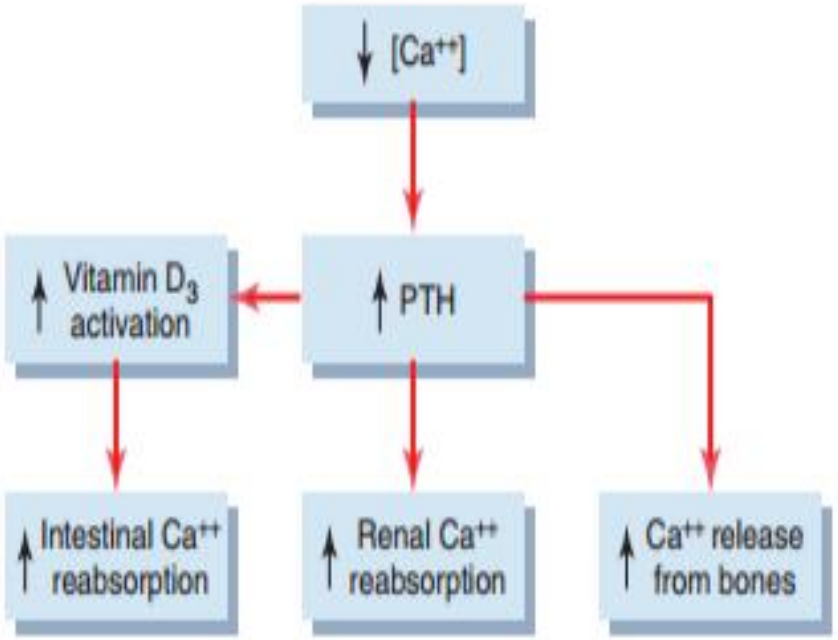
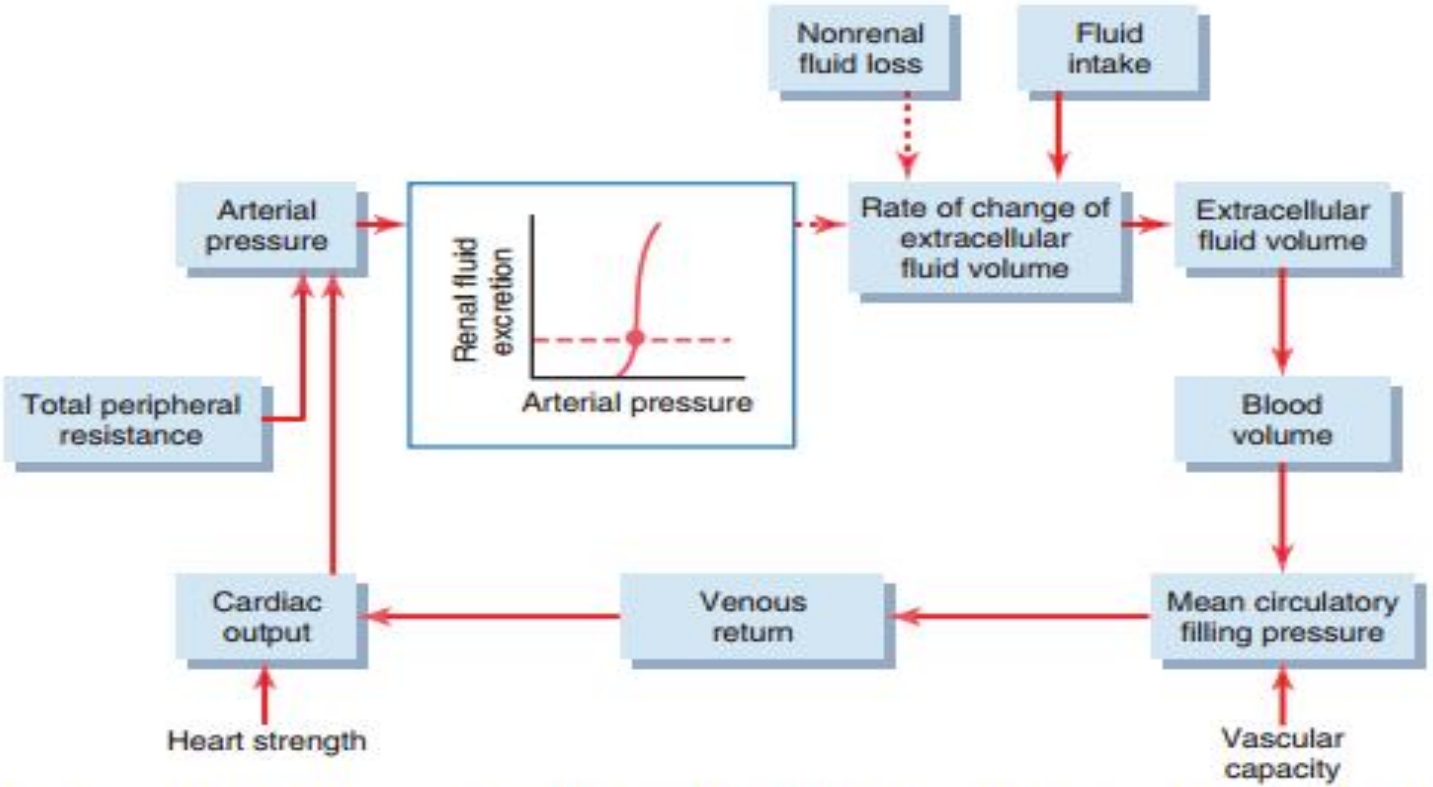


Figure 30-11. Compensatory responses to decreased plasma ionized calcium concentration mediated by parathyroid hormone *(PTH)* and vitamin D.

- The kidney synthesizes Vit D3 to reabsorb Ca2+ from the intestine. This way, it regulates ca2+ level in the plasma

Basic renal-body fluid feedback mechanism for blood volume, ECF-volume and ABP.



he basic renal–body fluid feedback mechanism for control of blood volume, extracellular fluid volume, and arterial

- Thanks