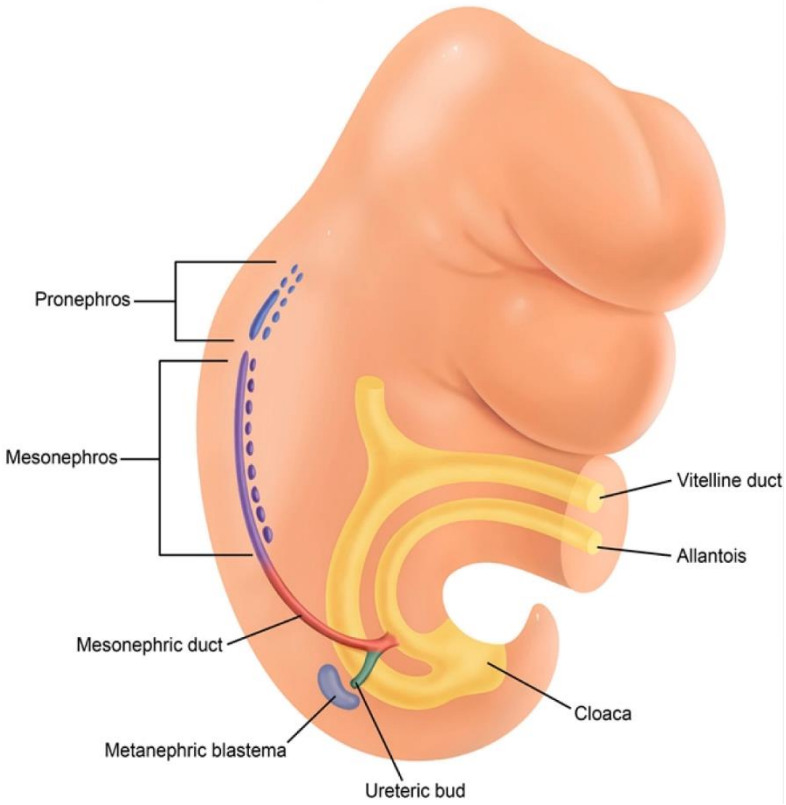
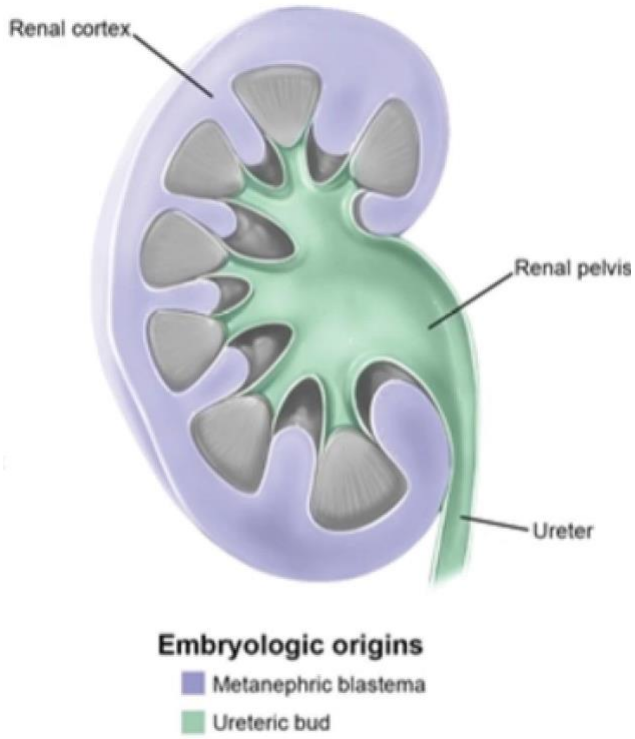
CHAPTER 1

Embryology

Embryonic kidney development





- Embryonic kidney development involves the sequential formation of 3 sets of nephric systems termed the pronephros, mesonephros, and metanephros.
- The urinary structures formed during these stages are derived from the nephrogenic cord, which develops from the urogenital ridge formed by intermediate mesoderm.
- First, the pronephros, a very primitive structure arising from the cephalic portion of the nephrogenic cord forms and later completely regresses.
- Next, the mesonephros forms from the midportion of the nephrogenic cord:

- Functions as interim kidney for 1st trimester.
- The structures of the mesonephros persist in the male as the Wolffian ducts, which ultimately form important elements of the reproductive duct system, including the ductus deferens and epididymis.
- In females, the mesonephros regresses and becomes vestigial Gartner's ducts.

- Development of the metanephros, or true kidney, begins with formation of the ureteric bud (metanephric diverticulum), which sprouts off the caudal portion of the mesonephric duct by the fifth to sixth week of gestation.

- The ureteric bud then penetrates into the sacral intermediate mesoderm to induce the formation of the metanephric mesoderm (metanephric blastema).

- The reciprocal exchange of inductive signals between the ureteric bud and metanephric blastema drives their differentiation into the structures that form the mature kidney:

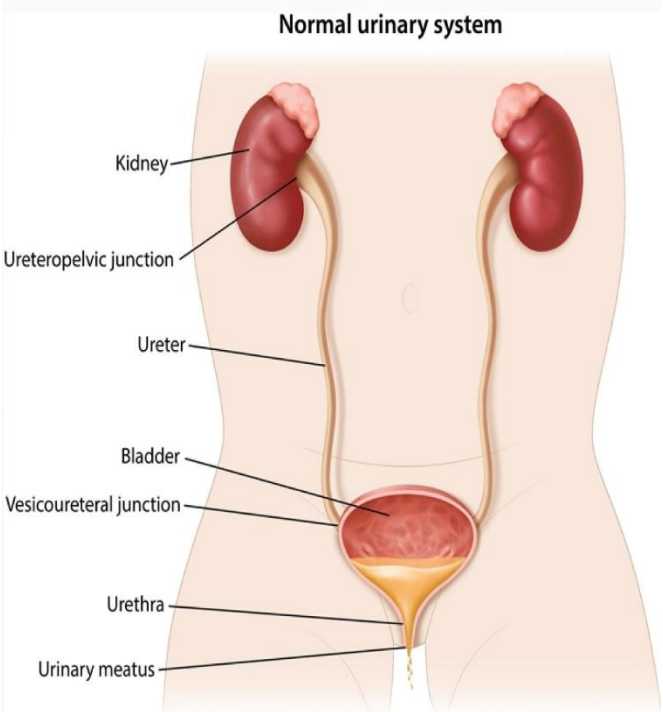
- The ureteric bud (metanephric diverticulum) → gives rise to the collecting system of the kidney, including the collecting tubules and ducts, major and minor calyces, renal pelvis, and the ureters.

- The metanephric blastema → gives rise to the glomeruli, Bowman's space, proximal tubules, the loop of Henle, and distal convoluted tubules.

- Aberrant interaction between the ureteric bud and metanephric blastema may result in several congenital malformations of the kidney (renal agenesis, multicystic dysplastic kidney).

❖ N.B:

- The ureteric bud is initially present as a solid cord, but it is fully canalized by the tenth week of gestation. Occasionally, the metanephros will begin producing urine before canalization of the ureteric bud is complete, and this leads to the development of a transient hydronephrosis.
- The ureteropelvic junction, the junction between the kidney and the ureter, is the last segment of the fetal ureter to canalize. It is also the most common site of obstruction.
- In normal fetal development, the ureters are fully canalized before the metanephros begins to produce urine (8-10th week of gestation). Inadequate recanalization of the ureteropelvic junction, the junction between the kidney and the ureter, is the most common cause of unilateral fetal hydronephrosis.



Congenital solitary functioning kidney

- Condition of being born with only one functioning kidney.
- Majority asymptomatic with compensatory hypertrophy of contralateral kidney, but anomalies in contralateral kidney are common.
- Often diagnosed prenatally via ultrasound.

Unilateral renal agenesis

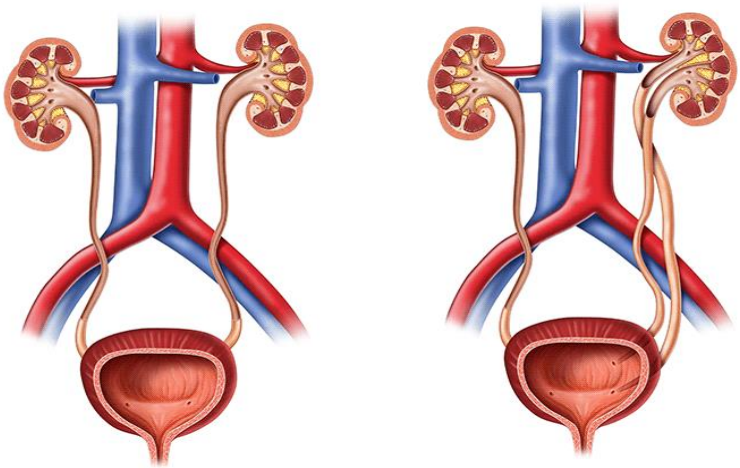
- Ureteric bud fails to develop and induce differentiation of metanephric mesenchyme → complete absence of kidney and ureter.

Multicystic dysplastic kidney

- Due to abnormal interaction between ureteric bud and metanephric mesenchyme.
- Leads to a nonfunctional kidney consisting of cysts and connective tissue.
- If unilateral (most common), generally asymptomatic with compensatory hypertrophy of contralateral kidney.

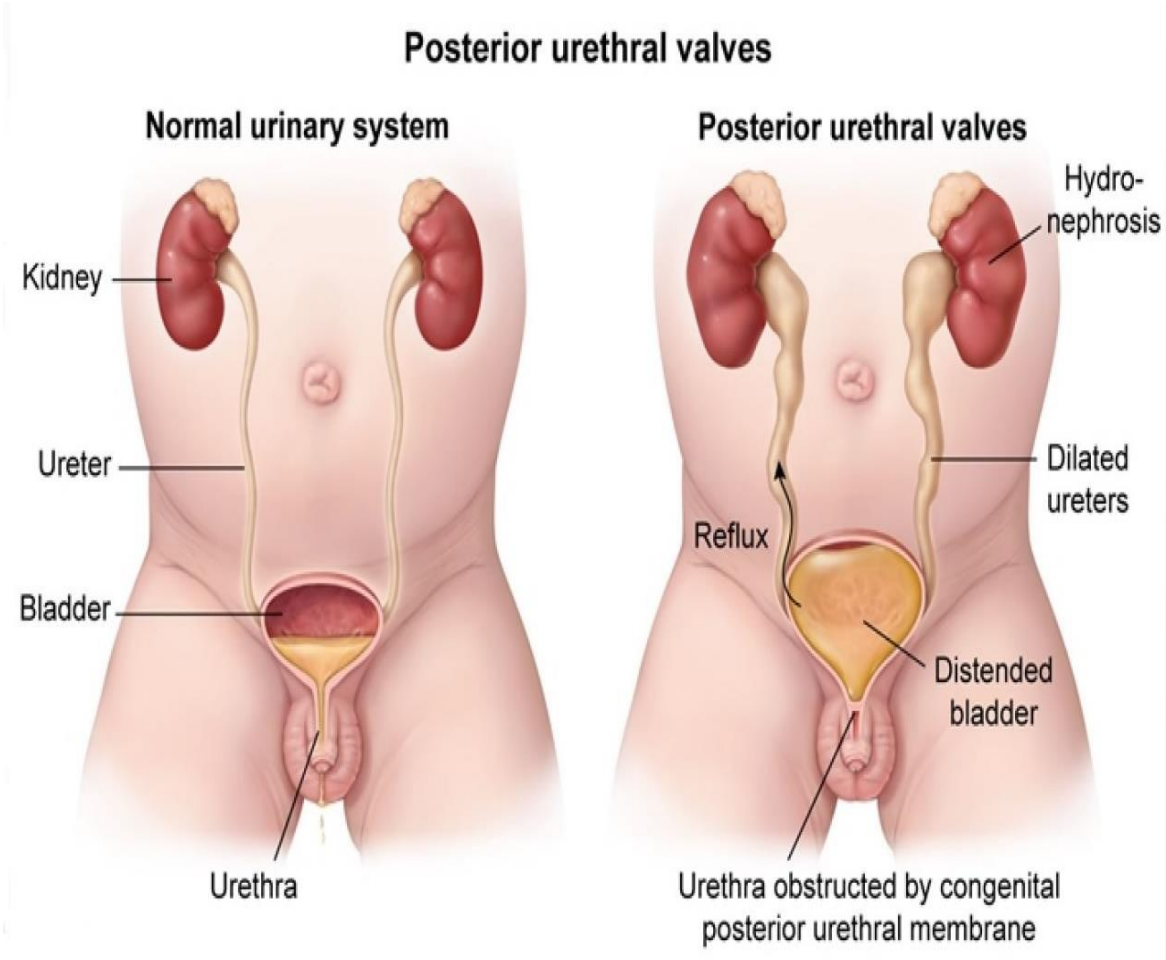
Duplex collecting system

- Bifurcation of ureteric bud before it enters metanephric blastema creates Y-shaped bifd ureter.
- Can alternatively occur when two ureteric buds reach and interact with metanephric blastema.
- Strongly associated with vesicoureteral reflux and/or ureteral obstruction, ↑ risk for UTIs.



Posterior urethral valves (PUV)

- Posterior urethral valves (PUV) are the most common cause of urinary tract obstruction in newborn boys.
- Abnormal folds in the distal prostatic urethra obstruct urinary flow, resulting in progressive dilation of the bladder, ureters, and kidneys.
- Prenatal ultrasonography findings of bladder distention, bilateral hydroureters, and bilateral hydronephrosis are highly suggestive of PUV.
- Poor urine output in utero results in oligohydramnios as fetal urine is a major source of amniotic fluid. Oligohydramnios in the second trimester is ominous and associated with high perinatal mortality because normal amniotic fluid levels are required for lung development.
- Low amniotic fluid also restricts fetal movement, leading to a cascade of physical anomalies including flat facies and limb deformities (Potter sequence).
- Other affected infants can present with poor urinary stream, straining with voiding, urosepsis, failure to thrive, and renal failure.



Amniotic fluid (AF)

- Amniotic fluid (AF) is the liquid that surrounds the fetus after the first few weeks of gestation.

- It has a number of functions that are essential for normal growth and development:

1. It helps to protect the fetus from trauma to the maternal abdomen. It cushions the umbilical cord from compression between the fetus and uterus.
2. Swallowed amniotic fluid also contributes to the development and maturation of the fetal lungs.
3. It has antibacterial properties that provide some protection from infection.

- Amniotic Fluid Production:

- In the first half of pregnancy, amniotic fluid is derived from fetal and possibly maternal compartments. Water and solutes freely traverse fetal skin and may diffuse through the amnion and chorion as well.

- By the second trimester, the fetal skin becomes keratinized, making it impermeable to further diffusion. At this time, a fetus contributes to amniotic fluid volume and composition almost exclusively through urination.

- Amniotic Fluid Elimination: The primary source of elimination is through fetal swallowing, which is then absorbed by the fetal gastrointestinal tract to the blood stream then to umbilical arteries and cross the placenta to be taken care of by the mother.

- This continuous production and elimination of amniotic fluid should maintain amniotic fluid in a steady state, but any disruption of either sides of this equation we will have abnormal volume of amniotic fluid.

- Oligohydramnios:

- Low amniotic fluid level is called oligohydramnios which occurs if the fetus is not producing urine in normal amounts or if the urinary tract is obstructed preventing amniotic fluid from getting out to the amniotic fluid.

- Causes are:

  - Renal agenesis: incompatible with life. Associated with Potter syndrome. Flat facies due to high atmospheric pressure causing compression of the fetus that is normally buffered by the amniotic fluid.
  - Bladder outlet obstruction in male infants: Posterior urethral valves (PUV).
  - Prune belly: lack of abdominal muscles, so unable to bear down and urinate.

- Polyhydramnios:

- High amniotic fluid level is called polyhydraminos which occurs when there is a problem in swallowing of amniotic fluid:
  - GIT system defect that prevents amniotic fluid from passing down to the intestine of the fetus to be absorbed to the blood stream as esophageal atresia and duodenal atresia.
  - Due to defect in swallowing mechanism as occurs in anencephaly.

- Maternal diabetes mellitus → Fetal hyperglycemia also induces osmotic diuresis and polyuria, which increases amniotic fluid volume, resulting in polyhydramnios.

Potter syndrome

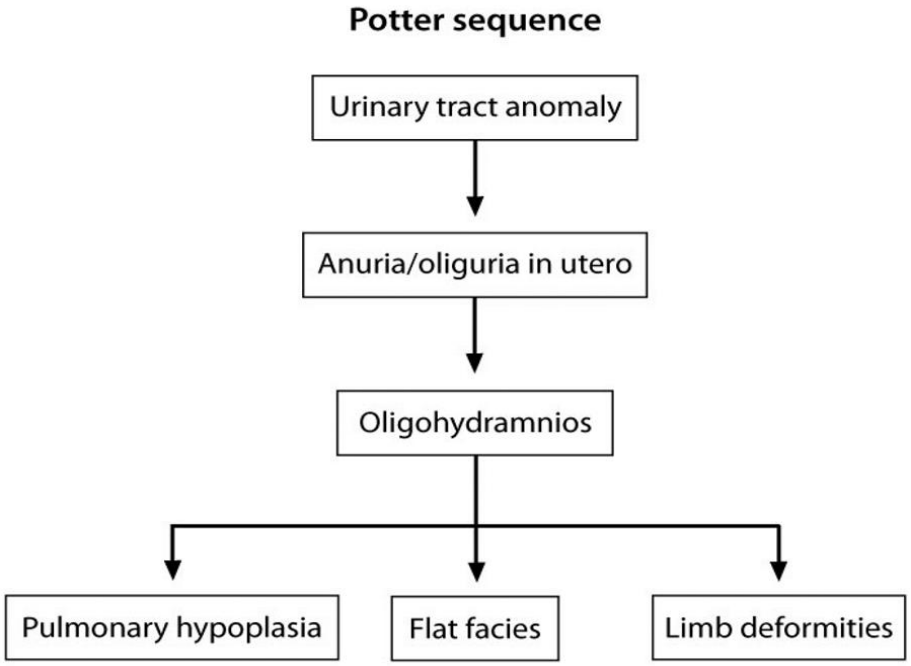
- By definition, true Potter syndrome results from bilateral renal aplasia and is a very rare condition; a similar presentation caused by other etiologies is called the Potter sequence [ARPKD, obstructive uropathy (posterior urethra valve)].

- Bilateral renal agenesis, which invariably leads to oligohydramnios or anhydramnios (decreased or absent amniotic fluid) and results in Potter syndrome.

- Oligohydramnios → compression of developing fetus → limb deformities (club feet), facial anomalies (low-set ears, retrognathia, flattened nose), compression of chest and lack of amniotic fluid aspiration into fetal lungs → pulmonary hypoplasia (cause of death).

- Respiratory failure and renal failure cause death within hours of birth in 100% of infants born with bilateral renal agenesis.

- Babies who can't "Pee" in utero develop Potter sequence.



The urachus

- During the third week of gestation, the yolk sac forms a protrusion known as the allantois that extends into the area of the urogenital sinus.

- The upper part of the urogenital sinus gives rise to the bladder during the fifth to seventh week of gestation.

- At that time the allantois, which originally connected the urogenital sinus with the yolk sac, then becomes the urachus (remnant of the allantois), a duct between the bladder and the yolk sac. This later develops into the median umbilical ligament at birth.

- Failure of urachus to obliterate (persistent of allantois remnant) before birth leads to a number of abnormalities:

1. Patent urachus:

- Connects the umbilicus and the bladder.

- Patients present with urine discharge from the umbilicus exacerbated by crying, straining, voiding and prone position.

2. Vesicourachal diverticulum:

- Failure to close the part of urachus adjacent to the bladder.

- An outpouching of the apex of the bladder which is commonly asymptomatic.

3. Urachal sinus:

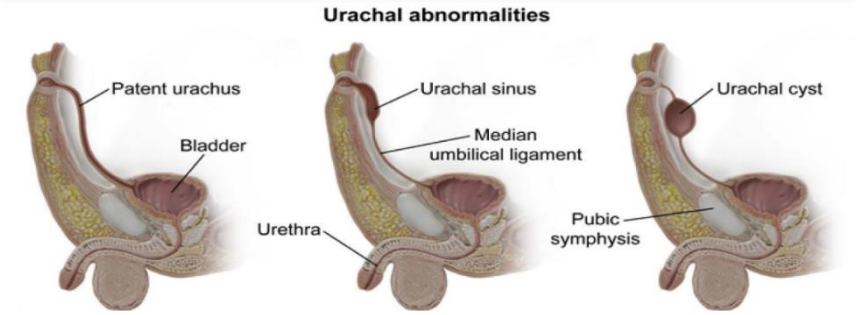
- Failure to close the distal part of urachus (adjacent to the umbilicus).

- It presents with periumbilical tenderness and purulent discharge from the umbilicus due to the persistent and recurrent infections.

4. Urachal cyst:

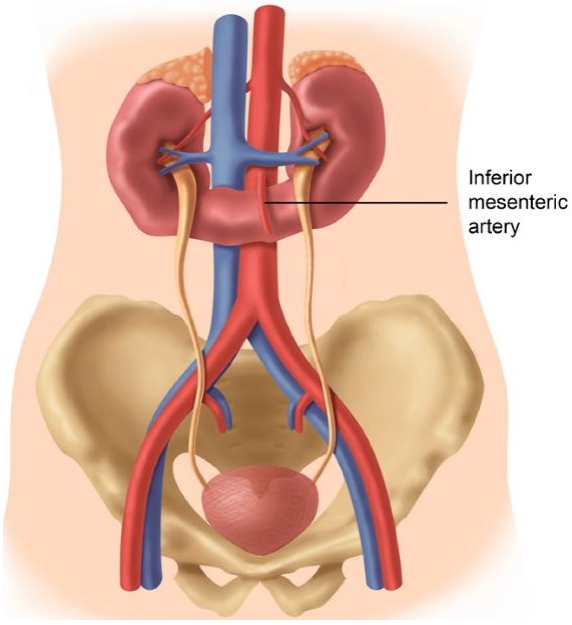
- Failure of central portion of urachus to obliterate.

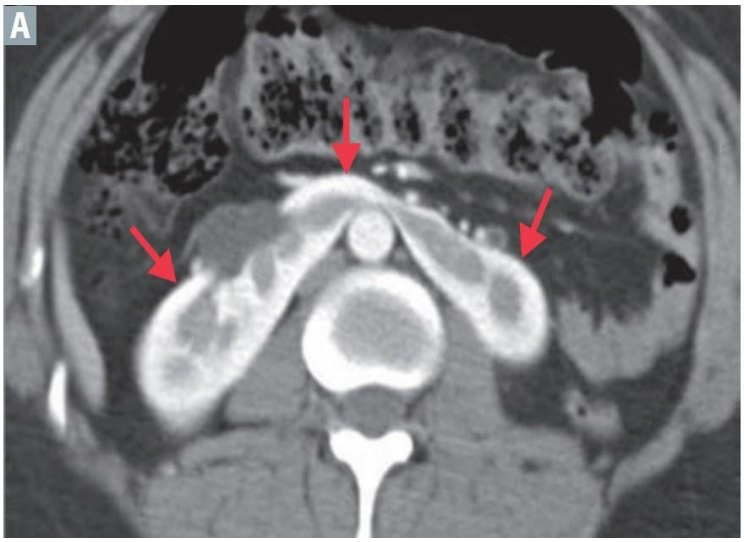
- A fluid-filled structure located between the two obliterated ends of the urachus that is most commonly asymptomatic.



Horseshoe kidney

- In horseshoe kidney, both kidneys are fused together at the poles in early embryonic life.
- The most common variant of horseshoe kidney is when the two kidneys join at their lower poles, occurring in 90% of cases. In the other 10%, fusion occurs at the upper poles.
- During embryogenesis, the fetal metanephros is initially located in the sacral region.
- In adults, the mature kidneys are located at vertebral levels T12-L3 (the kidney is slightly lower on the right compared to the left side).
- The relative ascent of the kidneys from the sacral region to their normal anatomic position results from the disproportionately rapid growth of the caudal part of the embryo.
- When fusion of the lower or upper poles of the kidney occurs, the central part of the newly formed horseshoe kidney lies across the midline anterior to the great vessels. The isthmus of horseshoe kidney usually lies anterior to the aorta and inferior vena cava and posterior to the inferior mesenteric artery.
- This centrally located isthmus becomes trapped behind the inferior mesenteric artery during the relative ascent of the kidney.
- Associated with hydronephrosis (ureteropelvic junction obstruction), renal stones, infection, ↑ risk of renal cancer.
- Higher incidence in chromosomal aneuploidy (Turner syndrome, trisomies 13, 18, 21).



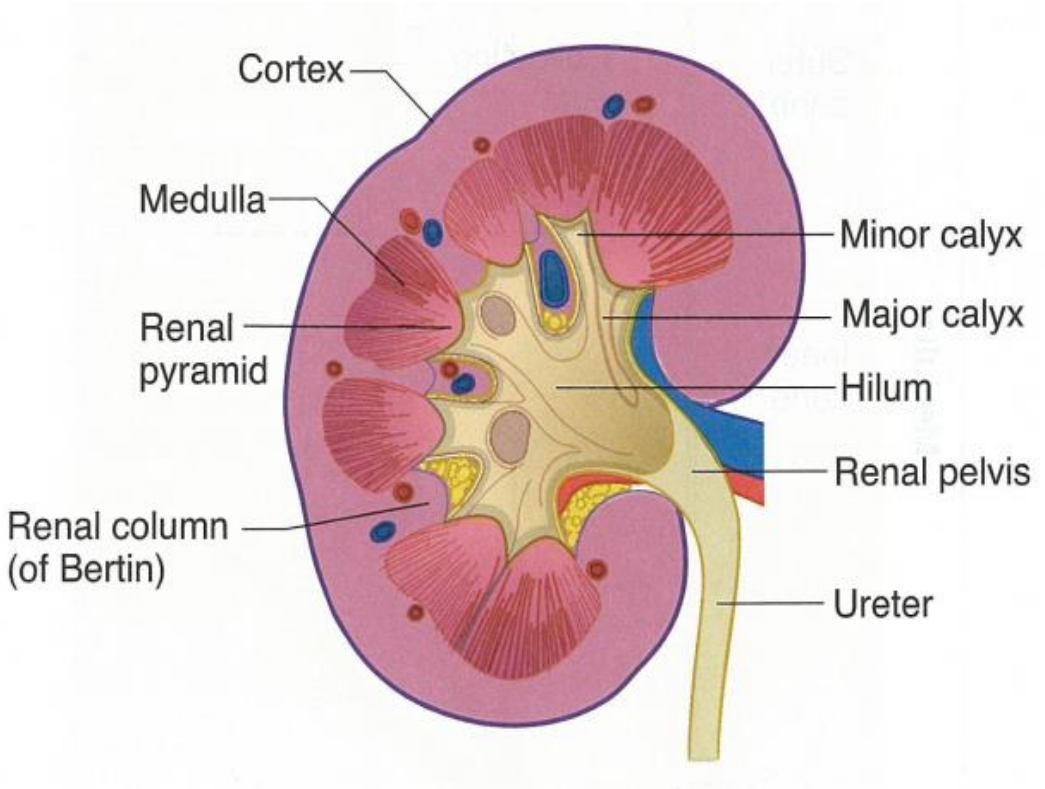


CHAPTER 2

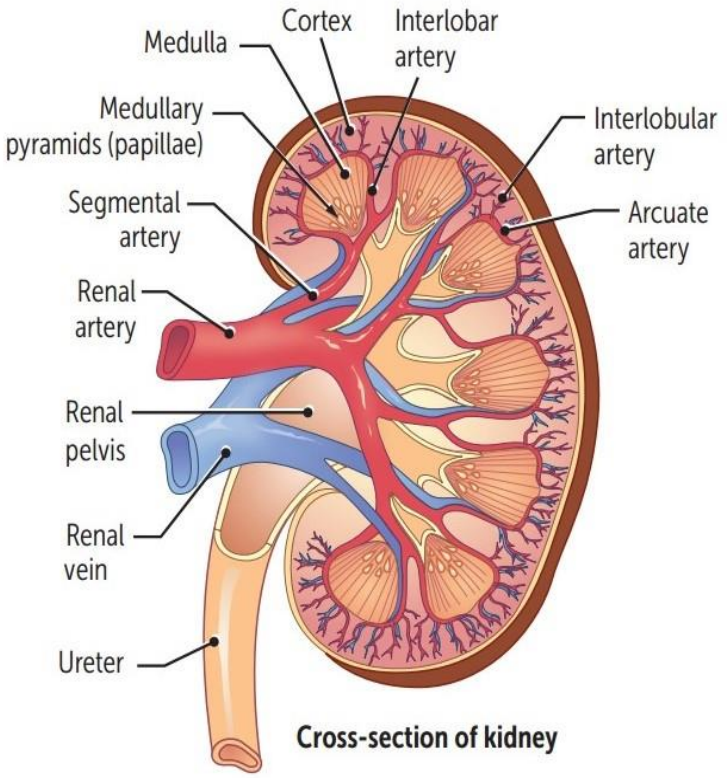
Anatomy

Physiologic anatomy of the kidney

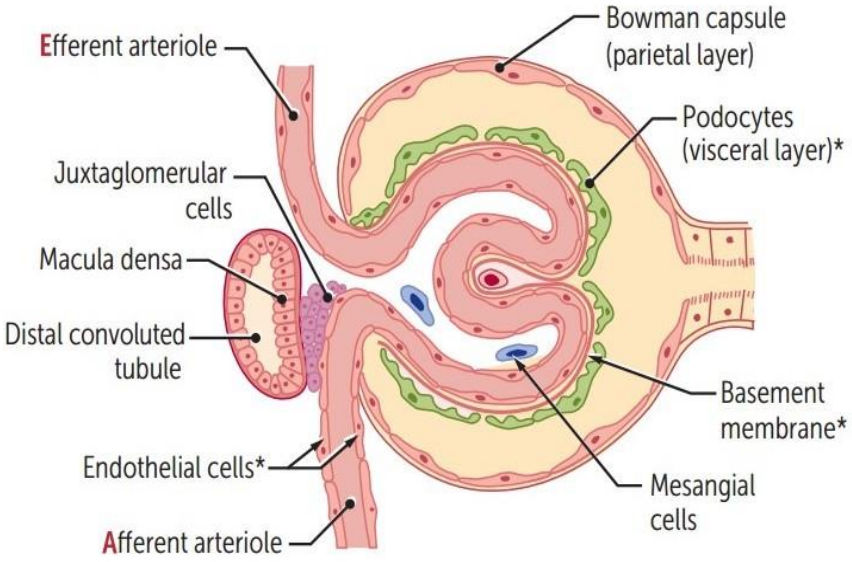
- The two kidneys lie on the posterior wall of the abdomen, outside the peritoneal cavity.
- The kidney is surrounded by thin, but tough capsule.
- The renal artery, vein, lymphatics, nerve supply and ureter enter the kidney at the hilum on its medial side.
- The renal mass is divided into 2 major regions: outer cortex and inner medulla.
- The medulla is divided into multiple renal pyramids. Each pyramid tapers to form a renal papilla.
- Each papilla projects into the pelvic space via the minor calyx.
- The minor calices converge into 2 or 3 chambers known as major calices.
- Finally, the major calices converge to form the renal pelvis.
- The calices, the renal pelvis and ureter are surrounded by smooth fibers, which force the urine from pelvis to the urinary bladder by peristaltic contractions.



Renal blood flow



Cross-section of kidney



*Components of glomerular filtration barrier.

Cross-section of glomerulus

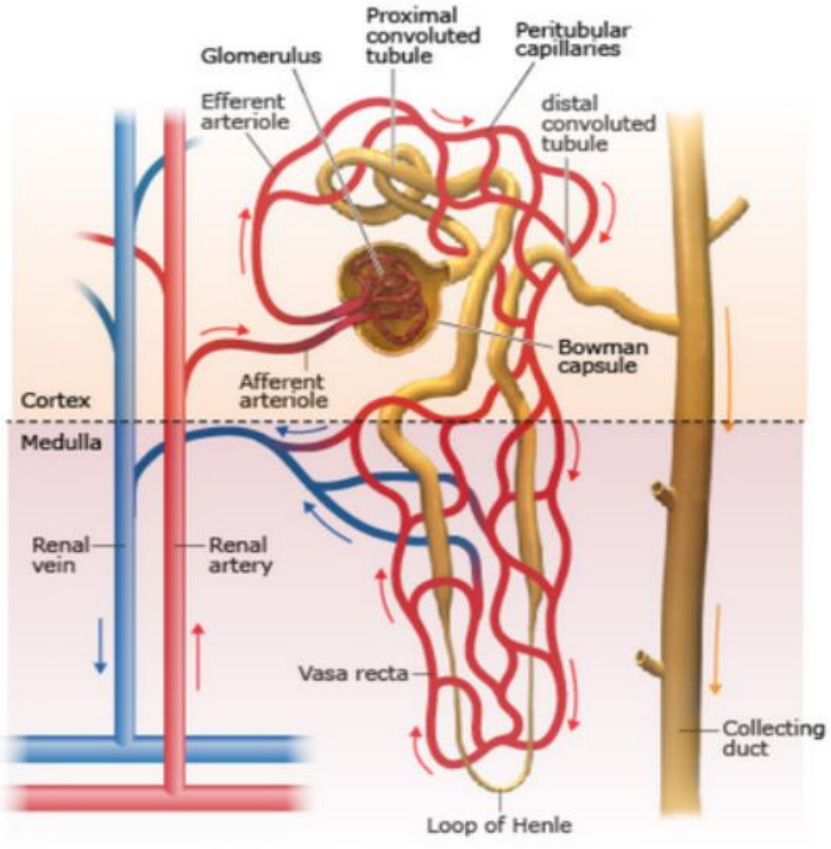
- The renal arteries are direct branches of the aorta.
- Each renal artery on entering hilum of the kidney divides to form the segmental arteries, interlobar arteries, arcuate arteries, intralobular arteries.
- The afferent arterioles arise from the interlobar arteries.
- Each afferent arteriole divides into glomerular capillaries in the glomerulus.
- The capillaries reunite to form the efferent arteriole, which in turn breaks up into the peritubular capillaries that supply the tubule.
- The capillaries draining the tubules of the cortical nephrons form a peritubular network, whereas the efferent arterioles from the juxtamedullary nephron drain not only into the peritubular network, but also into the vasa recta which lie side by side with the loops of Henle.
- The peritubular capillaries reunite to create a venous system consisting of interlobular veins → interlobar veins → renal veins.
- Left renal vein receives two additional veins: left suprarenal and left gonadal veins.
- Despite high overall renal blood flow, renal medulla receives significantly less blood flow than renal cortex → very sensitive to hypoxia → vulnerable to ischemic damage.
- Afferent = Arriving.
- Efferent = Exiting.
- Therefore, there are two capillary beds associated with each nephron:

1. The glomerular capillary bed (high pressure bed):

- It receives its blood from the afferent arteriole.
- The pressure in the glomerular capillaries is higher than in other capillary beds.
- The hydrostatic pressure in glomerular capillaries is about 60 mmHg which cause rapid filtration of fluid.

2. The peritubular capillary bed (low pressure bed):

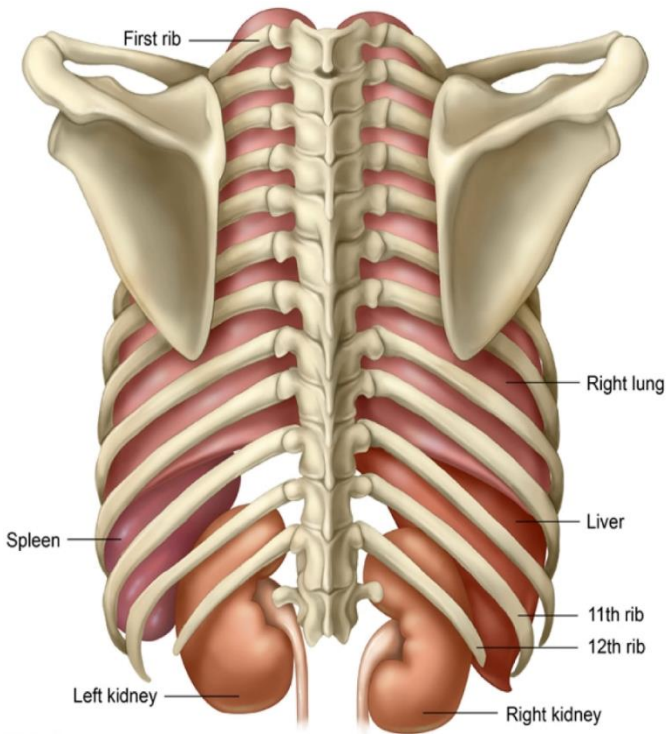
- The peritubular capillaries behave like the venous ends of other capillaries.
- The low pressure in these capillaries permits fluid reabsorption from the interstitium into the blood.

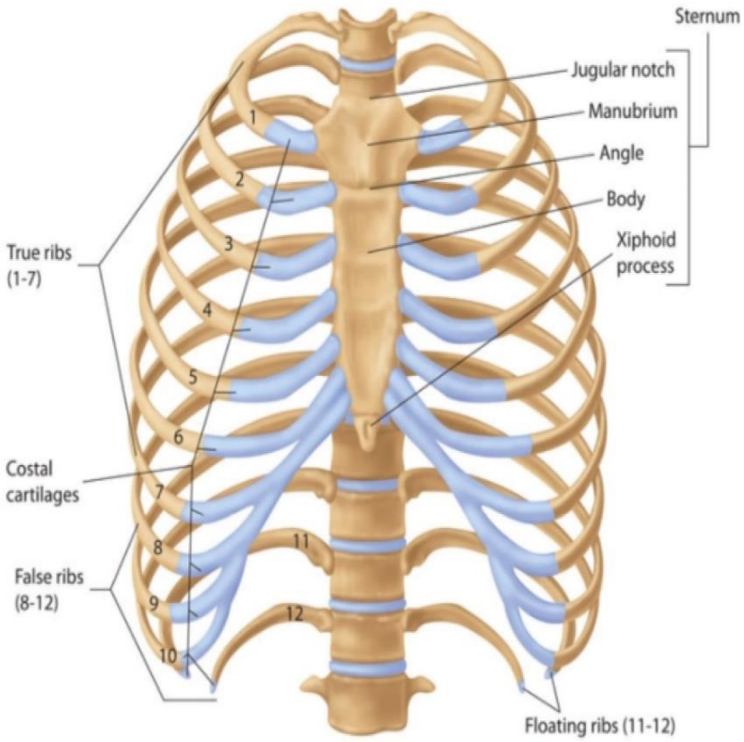


❖ N.B:

- The 12th rib overlies the parietal pleura medially and the kidney laterally.
- Recall that the 11th and 12th ribs are "floating ribs", meaning that they are not bound to the anterior rib cage by cartilage as are the more superior "false ribs".
- For this reason, the distal tip of the left 12th rib can be displaced into the retroperitoneum when fractured, lacerating the left kidney.

Posterior view of ribs & underlying organs





Nephron

- The functional unit of the kidney is the nephron.
- There are approximately 1.3 million nephrons in each human kidney.
- Each nephron is capable of forming urine (acts as functional unit).
- Each nephron is composed of:

1. Bowman's capsule:

- It starts at one end with Bowman's capsule, which is the enlarged end of the nephron.
- Bowman's capsule has been invaginated by a tuft of capillaries of the glomerulus so that it has 2 layers: the visceral layer is in direct contact with the capillary endothelium, and the parietal layer surrounds an approximately spherical urinary space.
- The parietal layer of Bowman's capsule is continuous with the walls of the proximal convoluted tubule (PCT).

2. Glomerulus:

- It is formed of a tuft of capillaries (glomerular capillaries) contained within the dilated blind end of the renal tubule (Bowman's capsule).
- The capillaries are supplied by an afferent arteriole and drained by a smaller efferent arteriole.

3. Proximal convoluted tubule:

- It lies in the cortex.
- The proximal convoluted tubule (PCT) opens at the urinary pole of Bowman's capsule.
- The PCT follows a circuitous path and ends with a straight segment that connects to the loop of Henle.

4. Loop of Henle:

- It is a U-shaped extension of the proximal convoluted tubule that dips in the renal medulla.
- The loop of Henle has a smaller diameter than the PCT and has descending and ascending limbs which go in opposite directions.

5. The distal convoluted tubule: The DCT comes back to make contact with its own glomerulus, and then connects to the collecting tubule, which receives urine from several nephrons and is open at its far end.

6. Collecting duct: The distal tubules coalesce to form collecting ducts that pass through the renal cortex and medulla to empty into the pelvis of the kidney at the apexes of the medullary pyramids.

- Types of nephrons:

- There are two types of nephrons according to the location of the glomeruli in the cortex:

1. Cortical nephrons: with their glomeruli in the outer cortex.
2. Juxtamedullary nephrons: these glomeruli lie deeper in the renal cortex, near the medulla.

- Juxta glomerular apparatus:

- The juxtaglomerular apparatus plays an important role in autoregulation of the renal blood flow and the GFR during the changes in arterial pressure and is important for regulation of arterial blood pressure through renin- angiotensin aldosterone system.

- It consists of:

1. Juxtaglomerular cells:

- These are modified smooth muscles located in the media of the afferent arterioles and to lesser extend the efferent arterioles as they enter the glomeruli.

- These cells secrete renin.

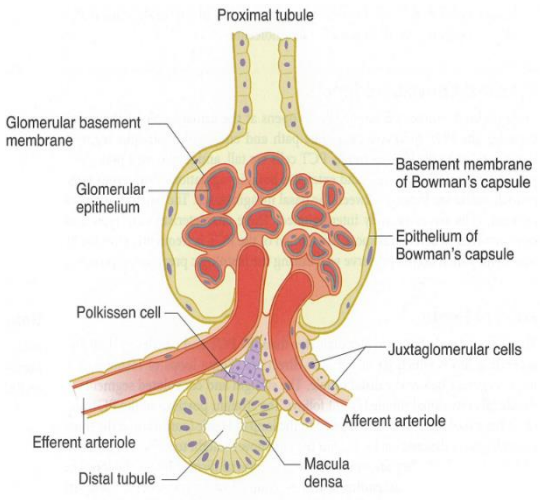
- These cells act as baroreceptors and respond to changes in perfusion pressure and are stimulated by a decreased renal perfusion or by hypovolemia, to release renin.

2. Macula densa:

- These are modified tubular cells in the initial portion of distal convoluted tubule that comes in contact with the glomerulus.

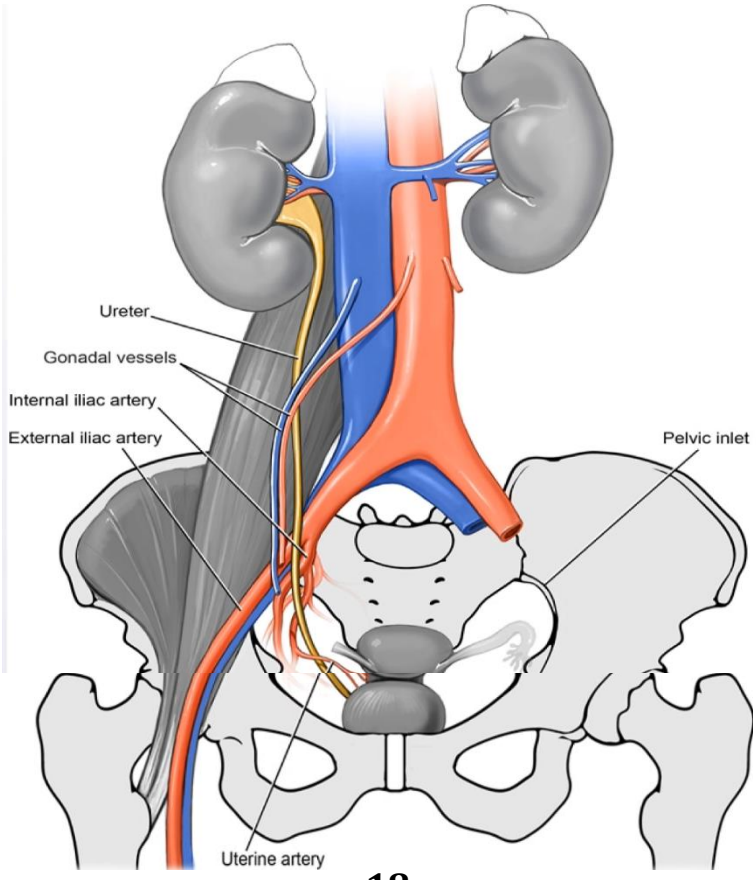
- The macula densa is in close proximity to the JG cells.

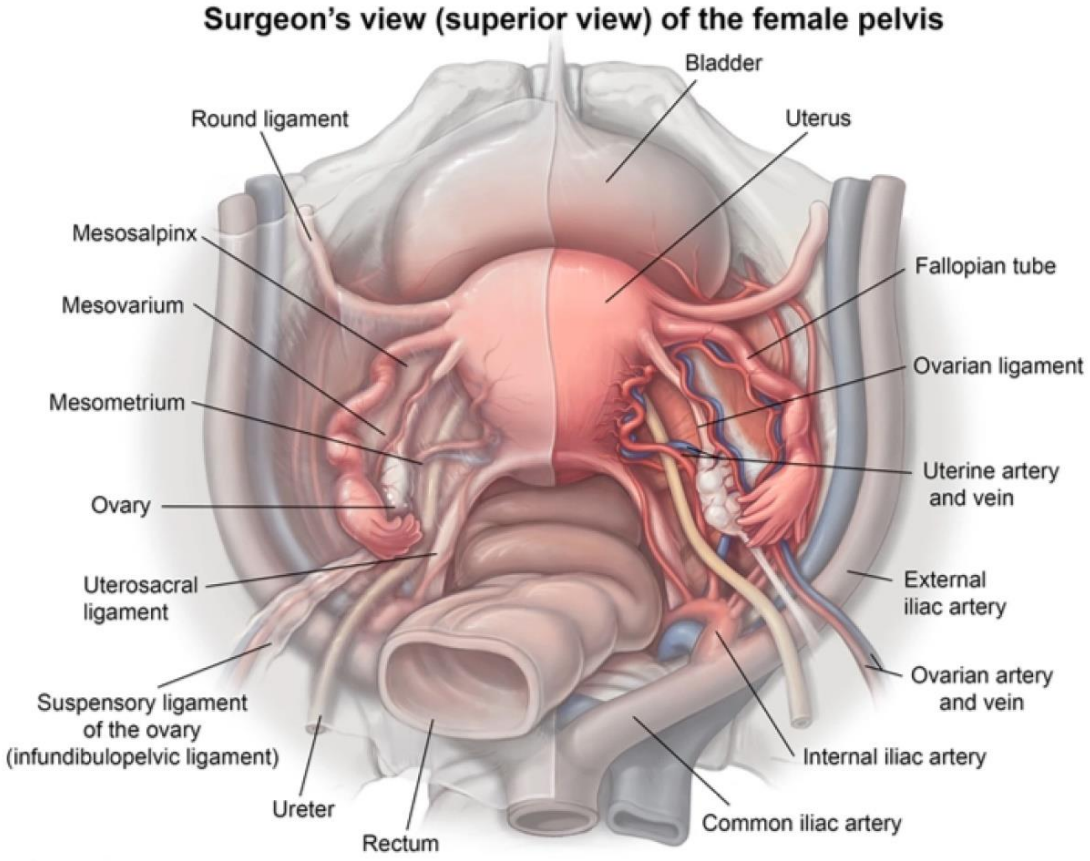
- These cells monitor the composition of the fluid in the tubular lumen at this point (function as chemoreceptors that are stimulated by a decrease of NaCl load).



Ureter

- Due to their course and close proximity to other structures, the ureters are at particular risk for injury during surgery in the pelvis.
- The ureters originate bilaterally at the renal pelvis and course interiorly toward the bladder within the retroperitoneum just anterior to the psoas muscles.
- Midway from the kidney to the pelvic inlet, the gonadal artery and vein cross over the anterior surface of the ureter.
- The ureters then gain access to the pelvis by crossing over the anterior surface of the common iliac artery near its bifurcation into the internal and external iliac arteries.
- At this point, the ureter lies medial to the gonadal vessels and anterolateral to the internal iliac artery.
- In females, the ureter then courses along the uterosacral ligament just deep to the uterine vessels ("water under the bridge") before entering the bladder.
- Water (ureters) flows over the iliacs and under the bridge (uterine artery or vas deferens).
- Gynecologic procedures involving ligation of uterine vessels traveling in cardinal ligament may damage ureter → ureteral obstruction or leak.

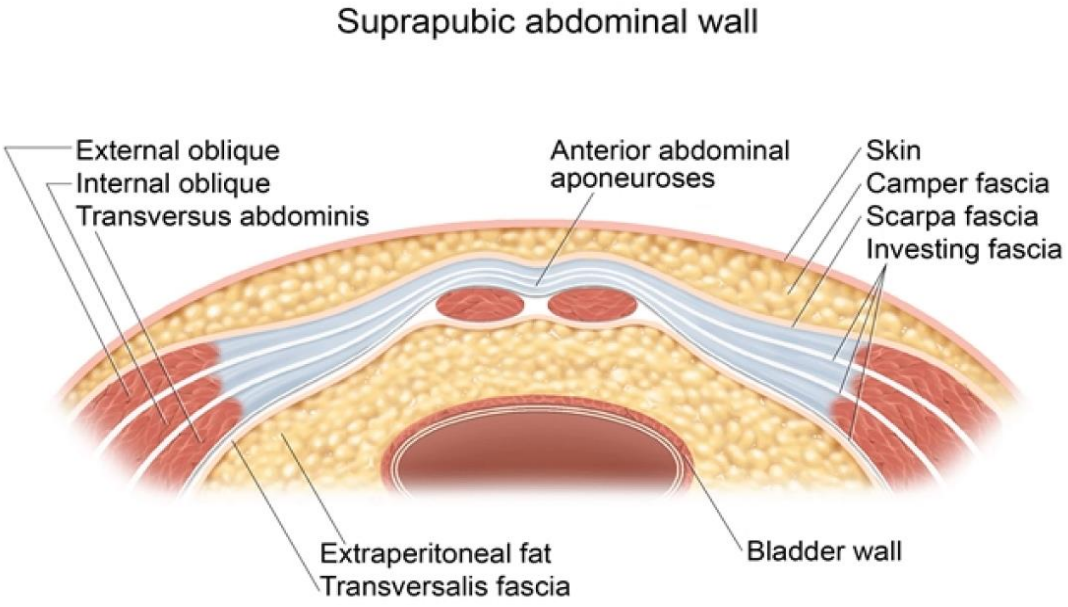




❖ N.B:

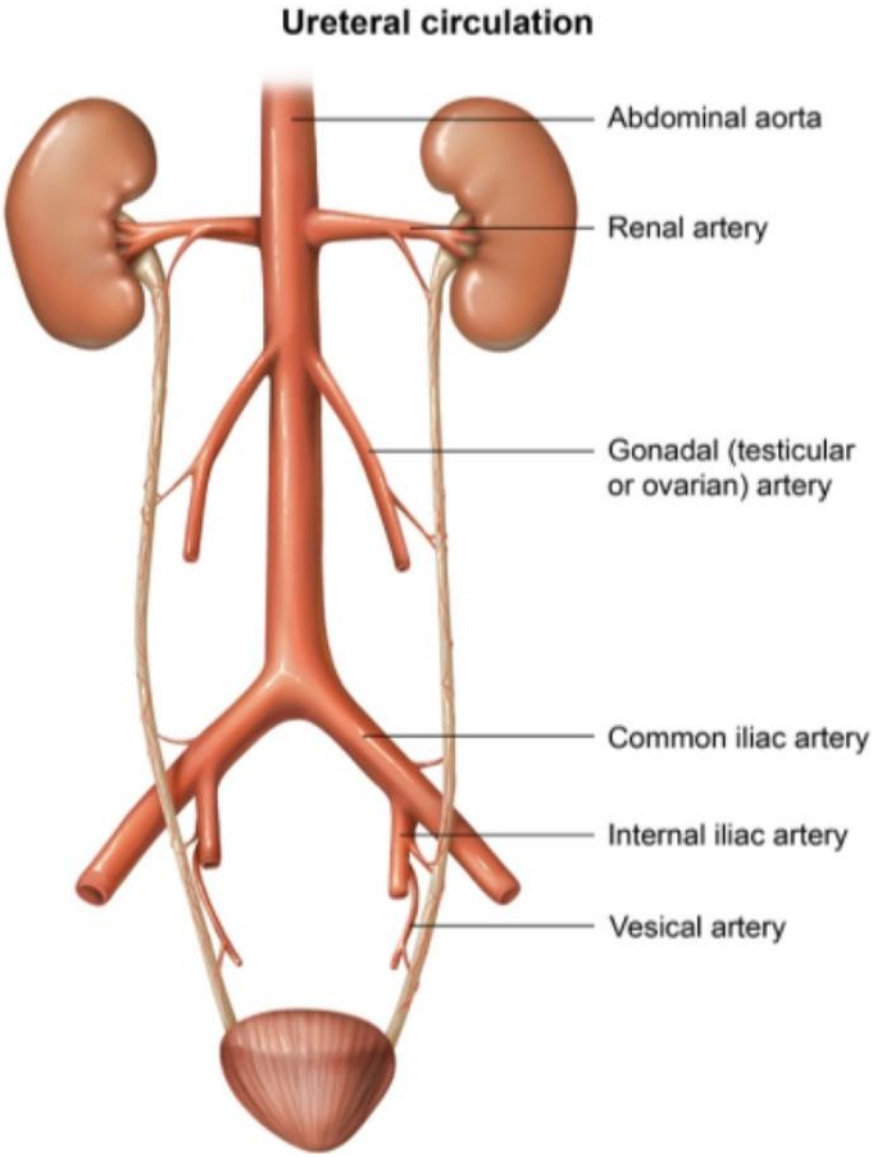
1. In a suprapubic cystostomy, the trocar and cannula pierce the aponeurosis of the abdominal wall muscles, along with the layers of the superficial fascia, transversalis fascia, and extraperitoneal fat.

- However, the peritoneum is not entered (bladder is extraperitoneal), reducing the risk of peritonitis and hemoperitoneum.



2. In a kidney transplant operation, the native kidneys are typically left in place, and the donor kidney is placed retroperitoneally in the right iliac fossa.

- Left kidney is taken during living donor transplantation because it has a longer renal vein.
- Blood supply to the donor organ is typically established by anastomosing the donor renal artery with the recipient's external iliac artery.
- Similarly, the donor renal vein is connected to the recipient's external iliac vein.
- The proximal 1/3 of the donor ureter is preserved and used to establish continuity from the collecting system of the kidney to the recipient's bladder.
- This portion of the ureter receives its blood supply from branches of the renal artery. (More distally, the ureters are supplied by branches from the aorta and iliac, gonadal and vesical arteries.)
- The proximal 1/3 of the ureter receives its blood supply from branches of the renal artery. For this reason, this portion of the donor ureter is typically viable after renal transplantation.



CHAPTER 3

Physiology

Overview of renal function

- The kidneys have several major regulatory functions, which include:

1. Regulation of water and electrolyte balance: For regulation of homeostasis, excretion of water and electrolytes must be precisely matched by intake.

2. Excretion of metabolic waste products:

- The kidneys are the primary means for eliminating waste products of metabolism.

- These products include urea, uric acid, creatinine, metabolites of various hormones and bilirubin.

3. Excretion of foreign chemicals: drugs, food additives and pesticides.

4. Endocrine function of the kidney:

A. Regulation of erythrocyte production:

- The kidneys secrete erythropoietin hormone, which stimulates the production of RBC's.
- The kidney's account for almost all the erythropoietin secreted into the circulation.
- Severe anemia develops in people with severe kidney disease as a result of decreased erythropoietin production.

B. Regulation of 1,25 dihydroxy vitamin D_3 production:

- The kidney's produce the active form of vitamin D (1, 25 dihydroxycholecalciferol) by hydroxylating this vitamin at the number 1 position.

5. Renin secretion.

6. Regulation of arterial blood pressure:

- Short term regulation: renin angiotensin aldosterone system.

- Long term regulation: through excreting variable amounts of sodium and water.

7. Regulation of acid-base balance by:

- Elimination of acids produced from the metabolism of proteins such as sulphuric acid.

- Regulation of the buffer stores in the body.

8. Gluconeogenesis:

- The kidneys synthesize glucose from amino acids during prolonged fasting and add it to the blood.

- This helps to maintain blood glucose concentration.

Fluid compartments

- 60–40–20 rule (% of body weight for average person):

- 60% total body water.
- 40% ICF, mainly composed of K, Mg, organic phosphates (ATP).
- 20% ECF, mainly composed of Na, Cl, HCO_3, albumin.

- Plasma volume can be measured by radiolabeling albumin.

- Extracellular volume can be measured by inulin or mannitol.

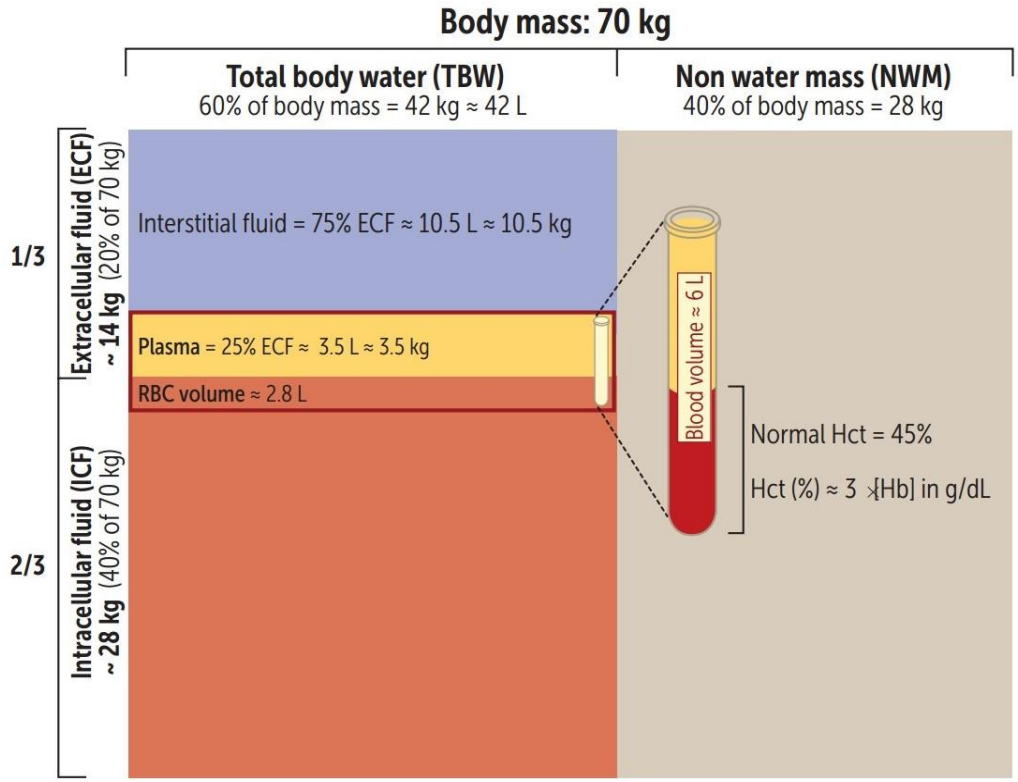
$$\text{Volume} = \frac{Amount}{Concentration}$$

- Volume = volume of distribution of the substance.
- Amount = amount of substance present.
- Concentration = concentration of substance in plasma.

- Plasma volume = TBV (total blood volume) × (1 – Hct).

$$\text{Plasma osmolarity} = (2 \times Na) + (\text{Glucose}/18) + (\text{BUN}/2.8)$$

- Serum osmolality = 285-295 mOsm/kg H_2O.



Formation of urine

- Each nephron is capable of forming urine by three processes:

1. Glomerular filtration: Filtration from the glomerular capillaries into the Bowman's capsule of a fluid that is nearly free of proteins.

2. Tubular reabsorption: It is the transfer of water and solutes from the filtrate back into the blood of peritubular capillaries.

3. Tubular secretion: It is the transfer of solutes from the peritubular capillaries into the tubular lumen.

- The term excretion refers to what finally comes out in urine.

- The rate at which different substances are excreted in urine represents the sum of three processes.

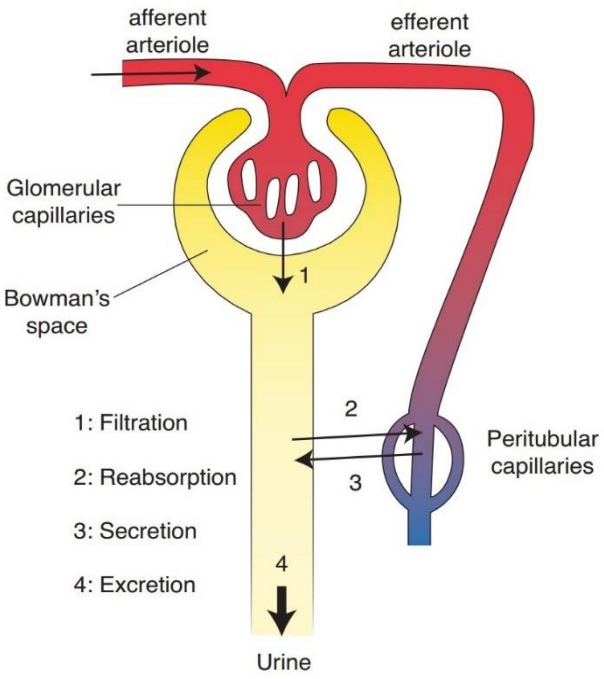
Urine excretion rate = filtration rate – reabsorption rate + secretion rate

- Reabsorption rate = filtered – excreted.

- Secretion rate = excreted – filtered.

- Excretion rate of substance x = Ux X V

- Ux: urine concentration of x; V: urine flow rate.



Excretion = (filtration – reabsorption) + secretion

Renal blood flow

- The kidney receives 20-25% of the cardiac output and under normal conditions exhibits strong autoregulation.
- Flow is regulated mainly via the resistance of the afferent arteriole.
- Two mechanisms contribute:

a. Myogenic Mechanism: Based on the intrinsic property of smooth muscle to contract when stretched.

b. Tubuloglomerular Feedback:

- The macula densa monitor the delivery of NaCl as an index of GFR (chemoreceptors).
- Decreased NaCl → dilates the afferent arteriole.
- Increased NaCl → constricts the afferent arteriole.

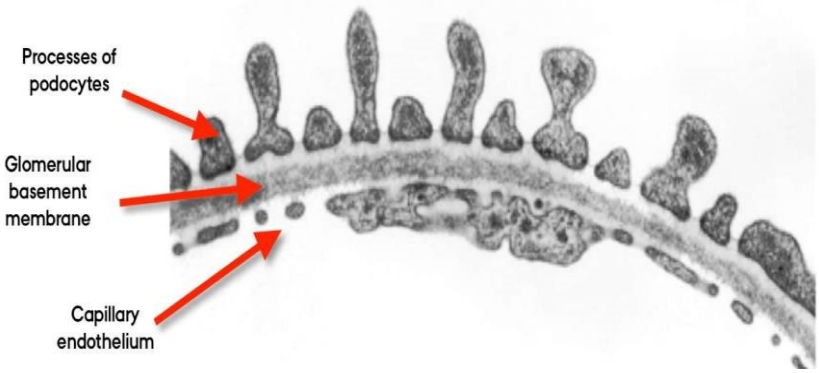
Glomerular filtration

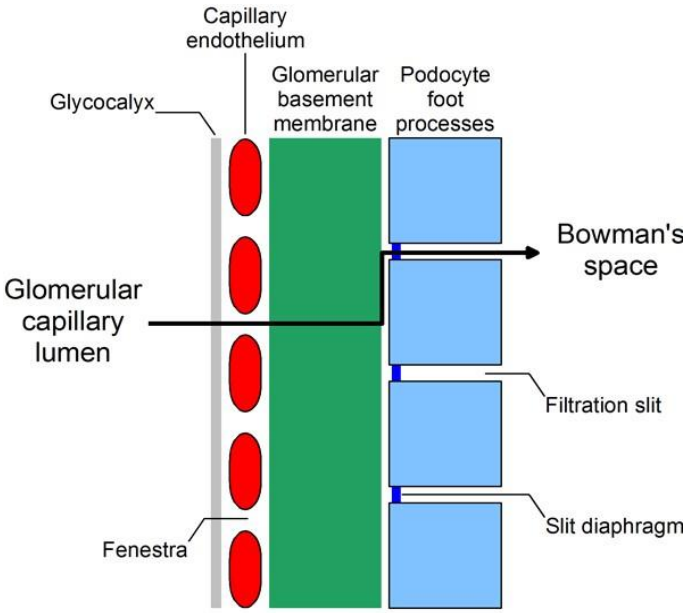
- 20% of the plasma flowing through the kidneys is filtered by the glomerular capillaries into the Bowman's capsule.
- The filtered fluid is called glomerular filtrate.
- Fluid filtered by the glomerulus is protein-free ultrafiltrate of plasma (plasma minus colloids).

Glomerular filtration barrier

- The membrane that separates the blood in the glomerular capillaries from the glomerular filtrate in Bowman's capsule.
- Responsible for filtration of plasma according to size and charge selectivity.
- It is formed of three layers:

- Fenestrated capillary endothelium.
- Basement membrane with type IV collagen chains and heparan sulfate.
- Visceral epithelial layer consisting of podocyte foot processes (FPs).





- Charge barrier:
  - All 3 layers contain ⊖ charged glycoproteins that prevent entry of ⊖ charged molecules (albumin).
  - Charge barrier is lost in nephrotic syndrome.
- Size barrier: Fenestrated capillary endothelium (prevents entry of > 100 nm molecules/blood cells); podocyte foot processes interpose with glomerular basement membrane (GBM); slit diaphragm (prevents entry of molecules > 50-60 nm).
- Materials Freely Filtered by the Kidney:
  - Electrolytes: Na, K, Cl, HCO_3, Ca.
  - Metabolites: glucose, amino acids, lactate, ketone bodies.
  - Small proteins and peptides: growth hormone, insulin, glucagon, FSH, LH, hCG.
  - Non-natural substances: mannitol, inulin, para-aminohippuric acid (PAH).
- Materials Not Freely Filtered by the Kidney:
  - Large proteins: such as albumins and globulins.
  - Lipid soluble substances bound to plasma proteins: such as T4, cortisol, progesterone, and estrogen; however, the free fraction of the lipid is filtered and appears in the urine (free cortisol).

Glomerular filtration rate

- GFR is a volume of fluid filtered into Bowman space per unit time (volume/time).
- A typical value for a healthy young individual is 120 ml/min or 180 L/day.
- If an individual donates a kidney, GFR is not reduced by 50%. The remaining kidney compensates and hypertrophies such that GFR is only reduced approximately 20-25%.
- Factors that affect GFR:

1. Hydrostatic pressure of the glomerular capillaries (P_{GC}):

- The hydrostatic pressure of the glomerular capillaries is the only force that promotes filtration.
- Under normal conditions, this is the main factor that determines GFR.

2. Oncotic pressure of the plasma (π_{GC}):

- The oncotic pressure of the plasma varies with the concentration of plasma proteins.
- Because fluid is filtered but not protein, oncotic pressure, which opposes filtration, will increase from the beginning to the end of the glomerular capillaries.
- The increased concentration of protein will be carried into the peritubular capillaries and will promote a greater net force of reabsorption.

3. Hydrostatic pressure in Bowman's space (P_{BS}):

- The hydrostatic pressure in Bowman's capsule opposes filtration.
- Normally, it is low and fairly constant and does not affect the rate of filtration.
- However, it will increase and reduce filtration whenever there is an obstruction downstream, such as a blocked ureter or urethra (postrenal failure).

4. Protein or oncotic pressure in Bowman's space (π_{BS}):

- This represents the protein or oncotic pressure in Bowman's space.
- Very little if any protein is present, and for all practical purposes this factor can be considered zero.

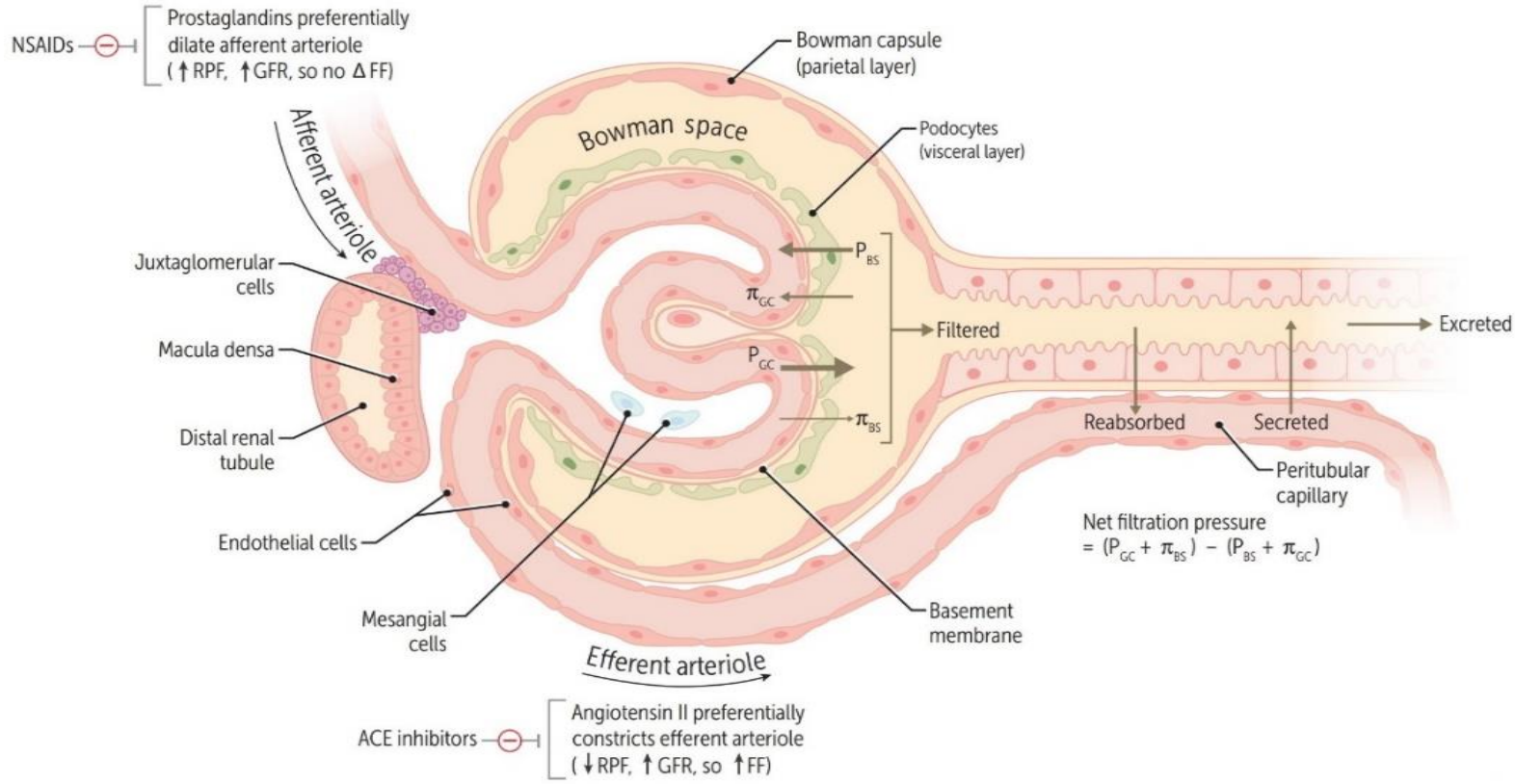
- Normal values:

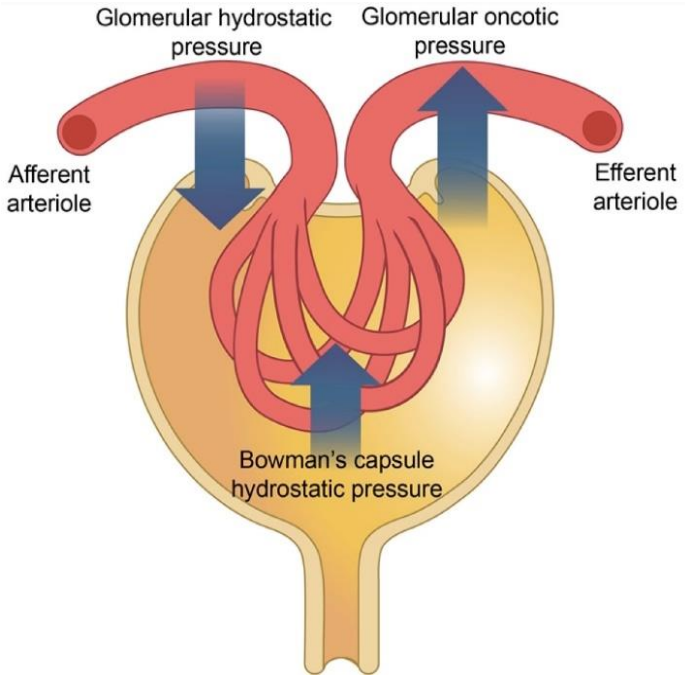
- P_{GC} = 55 mmHg.
- π_{GC}= 27 mmHg.
- P_{BS} - 18 mmHg.
- π_{BS} = 0 mmHg.

- Net filtration pressure = $(P_{GC} + \pi_{BS}) - (P_{BS} + \pi_{GC})$ = 10 mmHg

GFR = K x Net filtration pressure

- K = Filtration coefficient. This is determined mainly by capillary permeability and surface area.





Filtration Fraction (FF)

- Filtration Fraction (FF) is the fraction of the plasma entering the kidney that is filtered usually expressed as a percentage.

- It also represents the percentage filtered for any substance freely filtered.

$$FF = \frac{GFR}{RPF}$$

- GFR = 120 mL/min

- RPF (renal plasma flow) = 600 mL/min

$$= \frac{120\ mL/min}{600\ mL/min} = 0.20 \text{ or } 20\%$$

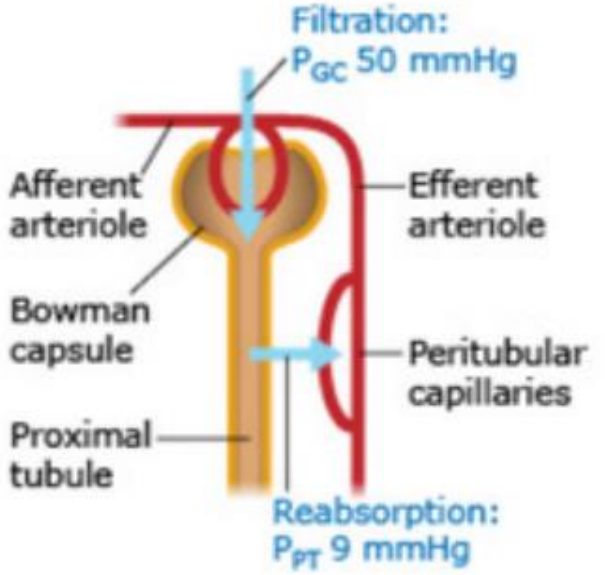
- <u>Factors Affecting FF:</u>

- In many circumstances, the main factor affecting FF is renal plasma flow.

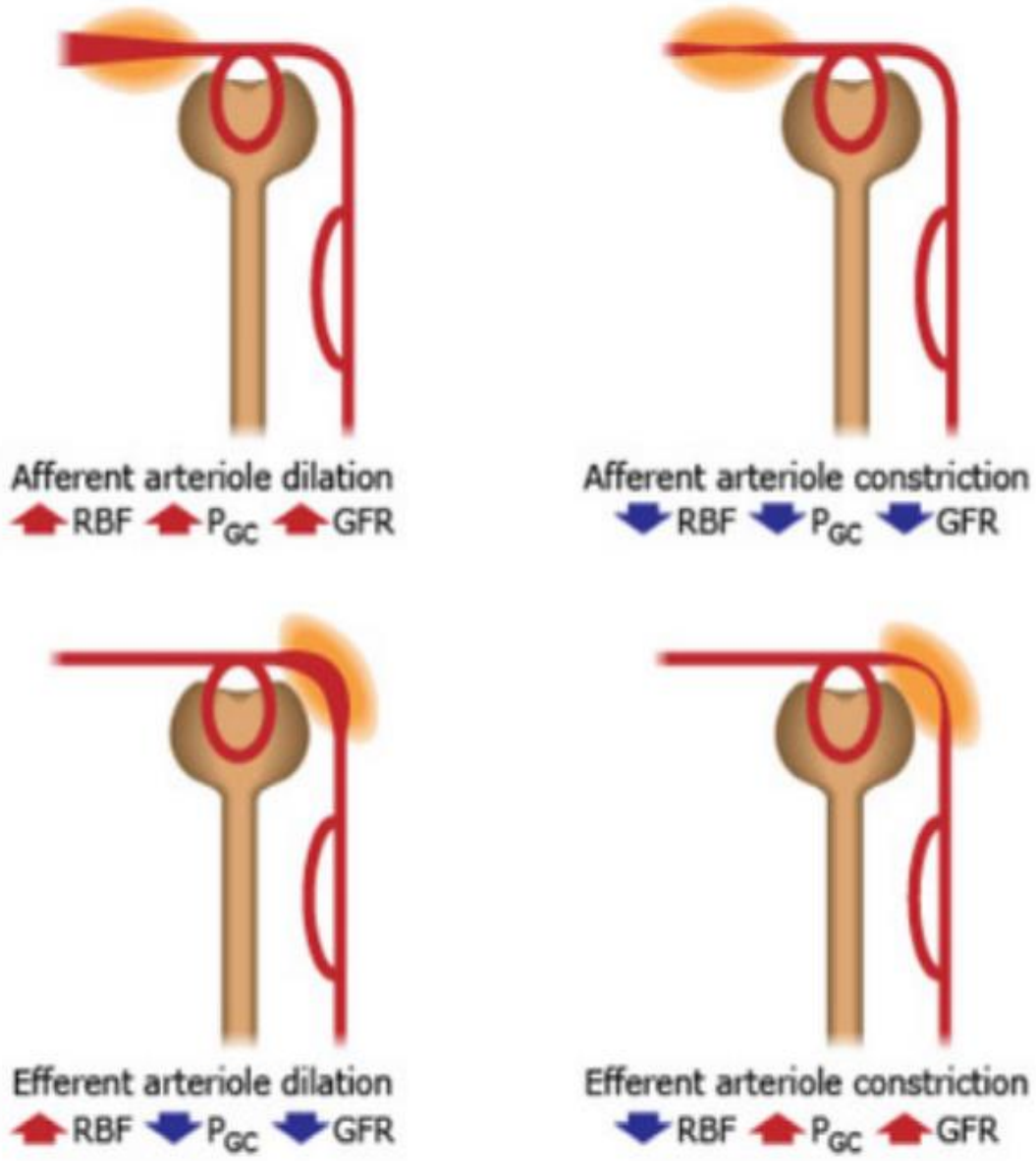
- The longer the fluid remains in the glomerular capillaries, the greater the percentage of the fluid that tends to be filtered.

- Therefore, as flow decreases, FF will always have a tendency to increase.

- Based on the preceding discussion, the following should be expected for afferent versus efferent constriction:



P_{GC} = Pressure glomerular capillaries
P_{PT} = Pressure peritubular capillaries



- Prostaglandins Dilate Afferent arteriole (PDA).
- Angiotensin II inhibitors Constrict Efferent arteriole (ACE).

Effect	GFR	RPF	FF (GFR/RPF)
Afferent arteriole constriction	↓	↓	__
Efferent arteriole constriction	↑	↓	↑
↑ plasma protein concentration	↓	__	↓
↓ plasma protein concentration	↑	__	↑
Constriction of ureter	↓	__	↓
Dehydration	↓	↓↓	↑

- Constriction of the efferent arteriole:

- Constriction of the efferent arteriole produces a significant increase in glomerular capillary hydrostatic pressure because of the reduction in glomerular blood outflow.

- This produces a corresponding increase in GFR.

- Efferent arteriolar constriction also reduces renal plasma flow (RPF).

- The increase in GFR along with the decrease in RPF leads to an increased filtration fraction (FF) because FF=GFR/RPF.

- Effects of Angiotensin II:

- Angiotensin II is a very potent vasoconstrictor and has a major role in maintaining blood pressure.

- In the kidney, it has a more pronounced constrictor action on the efferent arteriole.

- In the setting of a mild to moderate drop in blood pressure, the relative selective constriction of the efferent arteriole by angiotensin II helps maintain P_{GC} and GFR.

- Because angiotensin constricts the efferent more than the afferent arterioles, it tends to preserve glomerular capillary pressure as renal resistance increases and plasma flow decreases.

- Constriction of ureter:

- Ureteral constriction increases the hydrostatic pressure proximal to the constriction.

- This pressure increase is transmitted back to Bowman's space, decreasing the GFR.

- Ureteral constriction or obstruction acutely decreases the GFR and glomerular filtration fraction.

FF = GFR / RPF

- Effects of Sympathetic Nervous System:

- Sympathetic neurons innervate the afferent and efferent arterioles.

- Increased activity constricts, but the main effect is on the afferent. As a consequence:
  - ↓↓ RPF (constriction of the afferent and efferent which are connected in series).
  - ↓ GFR.
  - ↑ FF.
  - ↑ Forces promoting reabsorption in the peritubular capillaries because of a lower capillary hydrostatic pressure and an increase in plasma oncotic pressure (proteins are more concentrated).

- Less is filtered but a greater percentage of the filtrate is reabsorbed. Fluid and electrolytes are conserved.

- There is no parasympathetic innervation of the kidney.

Filtered Load

- GFR is the rate at which fluid is filtered (mL/min).
- Filtered load is the rate at which a substance is filtered (mg/min).

Filtered Load = GFR x Px (plasma concentration of substance x).

- This equation is only valid for a freely filtered substance.
- GFR units = volume/time (mL/min).
- Px units = amount/volume (mg/mL)

Renal clearance

- Renal clearance is a theoretical volume of plasma from which a substance is removed and excreted in the urine.

- Thus, the cleared volume depends on the amount excreted per unit time and the plasma concentration.

$$\text{Clearance of x} = \frac{Excretion\ rate\ of\ x}{Px} = \frac{Ux\ X\ V}{Px}$$

- Ux = urine concentration of x (amount/volume).
- V = urine flow (volume/time).
- Px = plasma concentration of x (amount/volume).

- Note: The urine and plasma concentration units must match in order to cancel.

- <u>Clearance as an Index of GFR and Renal Function:</u>
- GFR is considered the clinical index of renal function.

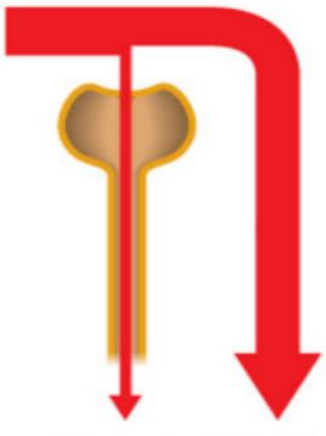
- Renal failure is a failure in GFR.

- Acute renal failure is a fairly sudden loss of GFR and, in most cases, is potentially reversible. Chronic renal failure involves a loss of functioning nephrons and, thus, is not reversible.

- <u>The clearance of a substance can be used as an index of GFR and renal function if:</u>
  - It is freely filtered.
  - Not reabsorbed, secreted, or metabolized by the kidney.

- Substances include inulin and mannitol.

- Even though the clearance of any of these substances would provide a gold standard for GFR, they are not used clinically. Instead, the plasma level of creatinine is the clinical index of GFR.



- Creatinine:

- Breakdown product of skeletal muscle.

- Constant release into the circulation in proportion to muscle mass.

- Freely filtered, not reabsorbed, slightly secreted.

- Slightly overestimates GFR because creatinine is slightly secreted by renal tubules.

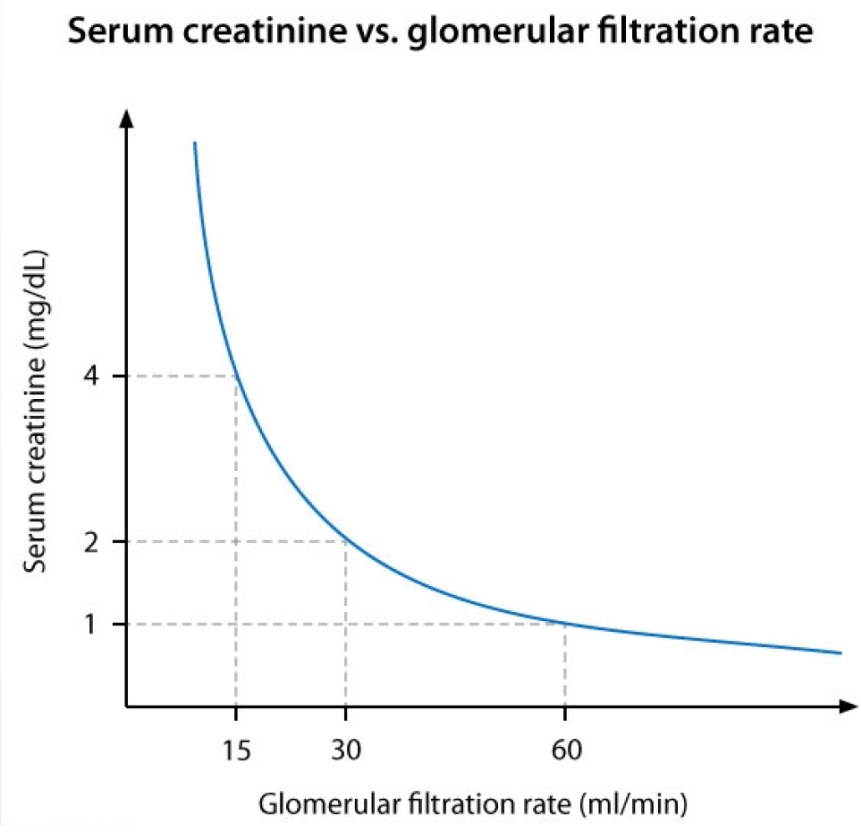
- Assuming creatinine production remains constant:
  - Creatinine production = creatinine excretion = filtered load of creatinine = Pcr x GFR.
  - Thus, if creatinine production remains constant, a decrease in GFR would be reflected by an increase in plasma creatinine concentration, and an increase in GFR would be reflected by a decrease in plasma creatinine.

- The relationship between serum creatinine and GFR is nonlinear.

- Serum creatinine levels begin to rise significantly as the GFR declines to <60 mL/min.

- Even though it is the clinical standard, the plasma level of creatinine is not a sensitive index of GFR. It will only demonstrate large changes in GFR.

- With muscle injury, plasma creatinine is elevated and not an index of GFR.



Renal transport and clearance

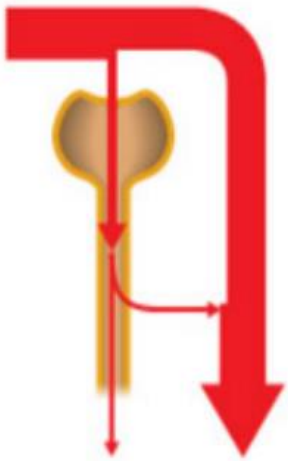
1. Substances freely filtered and completely reabsorbed:

- Clearance = 0.
- Ex: glucose, amino acids.
- Once glucose exceeds its renal threshold, it appears in the urine

Filtered Substances and Complete Reabsorption

2. Substances freely filtered and partially reabsorbed:

- If Clearance of substance x < GFR → net tubular reabsorption of X.
- Ex: sodium, potassium, urea.



Filtered Substances and Partial Reabsorption

3. Substances freely filtered and no net tubular transport (no reabsorption or secretion):

- Clearance = GFR → no net secretion or reabsorption.

- Ex: inulin and mannitol.

Filtered Substances and No Net Tubular Transport

4. Substance freely filtered and partially secreted:

- If Clearance of substance x > GFR → net tubular secretion of X.

- Ex: Creatinine.

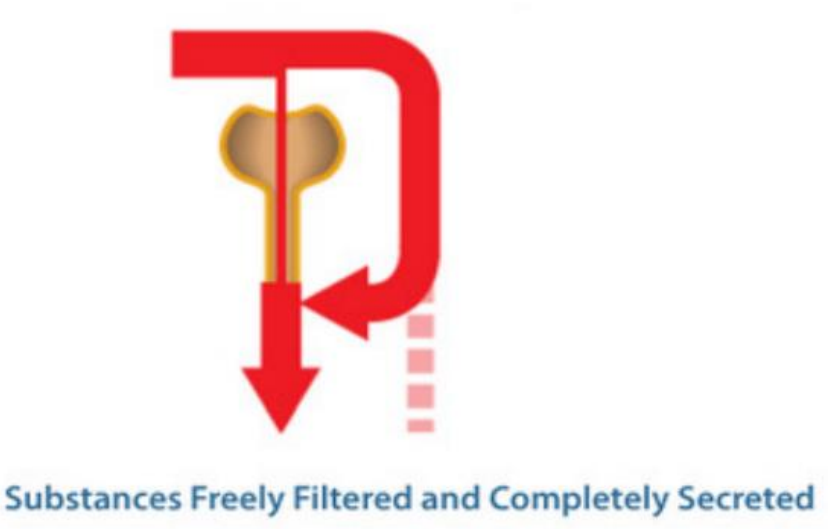
Substances Filtered and Partially Secreted

5. Substance is freely filtered and complete secreted:

- Clearance = RPF.

- Under these conditions, the substance would not be present in the renal venous blood.

- RPF is best estimated with PAH clearance (at low plasma concentrations of PAH → carriers not saturated).


Substances Freely Filtered and Completely Secreted

Reabsorption

- Reabsorption along the nephron segment can be active or passive.

- Active reabsorption involves a protein carrier and is powered by ATP. The substance is moved against its electrical-chemical gradient.

- Active reabsorption can be divided into two basic types based on the observed dynamics of the reabsorption:

1. Transport Maximum Systems:

- Systems have a transport maximum (with increased load the reabsorption rate increases until the transport carriers are saturated).

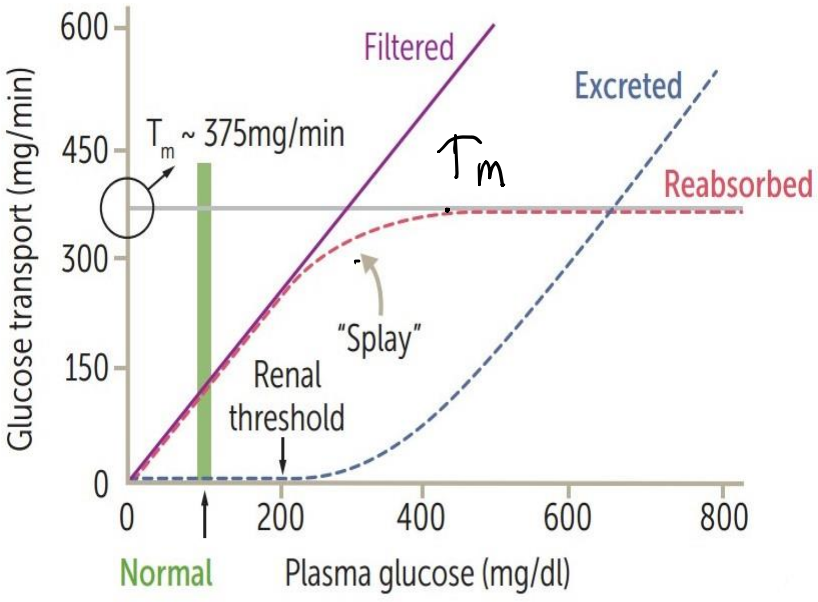
- At that point, the reabsorption rate is at a maximum (T_m).

- An example is the reabsorption of glucose in the proximal tubule.

- General Dynamics of the system:

- Exhibits saturation kinetics.
- Transporters have a high affinity for substrate.
- Back leak is minimal or absent.
- Back leak is the same as back diffusion. It is the diffusion of the substance once released into the interstitum back into the tubule lumen.
- Back leak does not occur because the tubular membrane system is impermeable to the substrate.

- Overall, the filtered load is completely reabsorbed until the carriers are saturated. Remaining substrate is excreted.



- At low filtered loads below carrier saturation, filtration rate = reabsorption rate and urine glucose is zero.
- Glucose appears in the urine when, in some nephrons, the carriers become saturated.
- The plasma level of glucose where this occurs is referred to as renal (plasma) threshold.
- The curving of the reabsorption line into the plateau (called splay) is because not all nephrons are saturated at the same filtered load due to the heterogeneity of nephrons.
- At the beginning of splay some nephrons are saturated. As splay continues more and more nephrons become saturated.
- T_m is not reached until the plateau where all nephrons are saturated.
- Threshold is the plasma level at which glucose appears in the urine (beginning of splay).
- T_m is the rate of reabsorption when all the carriers are saturated (beyond splay on the plateau).
- T_m dynamics is exhibited by all natural organic substances reabsorbed in the proximal tubule except urea.
- Glucose as an example:

- Glucose at a normal plasma level (range 60–120 mg/dL) is completely reabsorbed in proximal convoluted tubule (PCT) by Na/glucose cotransport.
- In adults, at plasma glucose of ~ 200 mg/dL, glucosuria begins (threshold). At rate of ~ 375 mg/min, all transporters are fully saturated (T_m).
- Normal pregnancy is associated with ↑ GFR. With ↑ filtration of all substances, including glucose, the glucose threshold occurs at lower plasma glucose concentrations → glucosuria at normal plasma glucose levels.
- Sodium-glucose cotransporter 2 (SGLT2) inhibitors (-gliflozin drugs) result in glucosuria at plasma concentrations < 200 mg/dL.

2. Gradient Time System:

- General Dynamics of the System:

- Carriers are always operating below capacity (never saturated).
- Affinity for the substrate is low.
- High back leak.

- Some of the sodium reabsorbed leaks back into the tubule lumen.

- This is because the proximal tubule has leaky tight junctions to sodium.

- The system is also leaky to potassium, chloride and water in a gradient-time system, the slower the flow the greater the percentage of the filtrate reabsorbed.

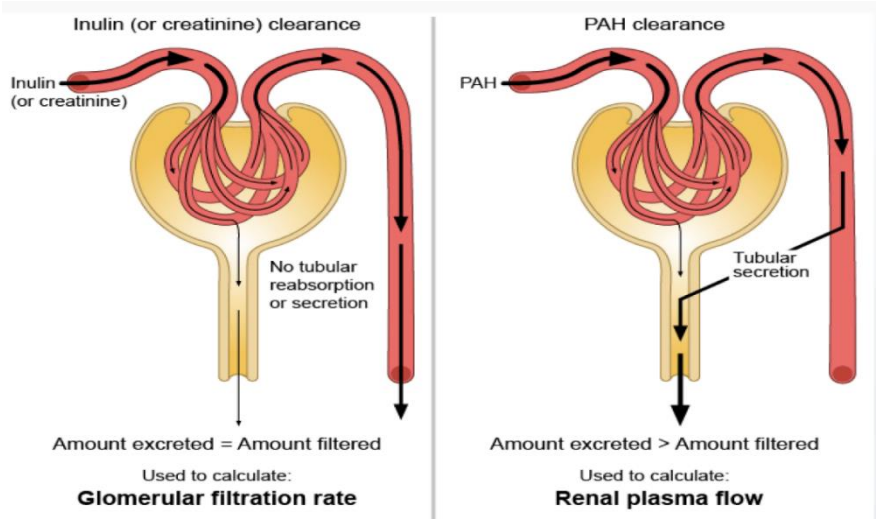
Secretion

- The proximal tubule is an important site for the secretion of organic substances.
- Many waste products (bile salts, urate) and non-natural organic substances (para-amino hippuricacid, and penicillin are rapidly cleared by active secretion into the proximal tubule).
- It is a fairly nonspecific transport system that exhibits T_m dynamics.
- <u>The following shows the dynamics for PAH:</u>

- PAH is freely filtered, actively secreted, but cannot be reabsorbed.
- The plasma flow to the peritubular capillaries is entirely cleared at low plasma concentrations of PAH (carriers not saturated).
- Because PAH is both filtered and secreted by the glomerulus and renal tubules, the calculated clearance of this acid can be used to estimate the renal plasma flow (RPF).
- At low plasma levels of PAH, clearance is renal plasma flow and no PAH appears in the renal venous blood.
- When the carriers are saturated, some of the plasma delivered to the peritubular capillaries is not cleared of PAH. Clearance is below renal plasma flow and some PAH appears in the renal venous blood.
- At very high plasma concentrations of PAH, only a small fraction of the plasma delivered to the peritubular capillaries is cleared of PAH, Clearance is now slightly above GFR.

- <u>In a nutshell:</u>

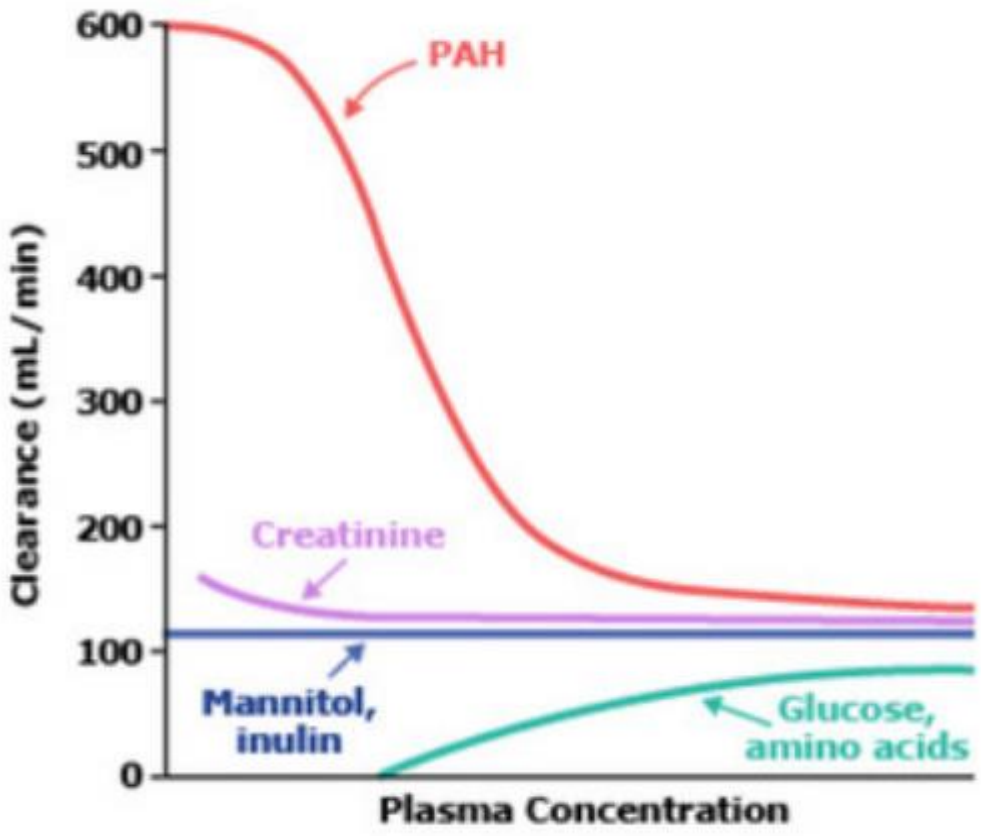
- At low plasma levels, the clearance of PAH is a good index of renal plasma flow.
- At high plasma levels, its clearance is a good index of GFR.



- Graphical Representation of the Clearance of Some Substance Types:

- Only those substances whose clearance can be easily related to their plasma level are shown.

- For example, sodium's clearance is not a function of its plasma concentration and cannot be depicted as a curve on the graph.



- Also, data presented is at a renal plasma flow of 600 mL/min and a GFR of 120 mL/min:

1. Mannitol, Inulin:

- Because its line is parallel to the X-axis, the clearance of inulin is independent of its plasma concentration.

- As the plasma levels rise, the filtered load and the excretion rise but the volume cleared remains at GFR.

- If GFR increases the curve shifts upward. If GFR decreases the curve shifts downward.

2. Glucose, Amino Acids:

- At low plasma levels, there is no glucose in the urine and clearance is zero.

- The curve begins where glucose first appears in the urine. That plasma level on the X-axis by definition is renal threshold.

- As the plasma level rises further, a smaller proportion of the filtered glucose is reabsorbed and clearance increases.

- Its clearance will approach that of inulin, but never equal inulin and GFR as long some glucose is reabsorbed.

3. PAH:

- At low plasma concentrations→ PAH is cleared from the 120 mL/min filtered and the 480 ml/min delivered to the peritubular capillaries.

- As such, the venous plasma concentration is zero.

- As the curve dips down clearance is less than renal plasma flow.

- At this point, some of the PAH in the 480 mL/min delivered to the peritubular capillaries is not secreted.

- In some nephrons, the transport carriers are saturated and PAH is present in the renal venous bloods.

- As the plasma level goes higher, a smaller proportion delivered to the peritubular capillaries is secreted.

- Clearance decreases further and approaches GFR.

- If secretion of PAH was completely Inhibited, no matter what the plasma concentration, its clearance would equal GFR.

4. Creatinine:

- Since creatinine exhibits some net secretion, its clearance is always slightly greater than GFR.

- But note that despite large variation in the plasma level its clearance remains close to GFR.

❖ N.B:

1. Glucose is normally filtered at the glomerulus and completely reabsorbed by the proximal tubule.

- Inhibition of sodium-coupled, carrier-mediated transport of glucose by the proximal tubule would cause the glucose clearance to approach the value of the GFR, which is typically estimated by calculating the clearance of inulin.

2. Inulin clearance can be used to estimate the GFR and to calculate the total filtration rate of a freely filtered substance when the plasma concentration of the substance is known.

- If the substance is subsequently reabsorbed from the nephron lumen, then the net renal excretion rate of the substance will be equal to its filtration rate minus the total tubular reabsorption rate.
- Excretion rate of substance x = total filtration rate – total tubular reabsorption
- Total filtration rate = GFR X Px (plasma concentration of substance x)

- The GFR is approximately equal to inulin clearance because inulin is neither secreted nor reabsorbed by the renal tubules.
- So, the Net Excretion Rate of Substance x = (Inulin Clearance) X (Plasma Concentration of Substance x) - (Tubular Reabsorption of Substance A).

3. The RPF is provided by the renal blood flow, which delivers both erythrocytes and plasma to the kidney.
- The hematocrit is the fraction of the blood volume occupied by erythrocytes. Thus, the fraction of the blood volume occupied by plasma is equivalent to (1 - hematocrit).
- The RBF can therefore be determined by dividing the RPF by the fraction of the blood volume occupied by plasma as follows:
- RBF = (RPF) / (1 - hematocrit)
- Renal Plasma Flow = (1 - Hematocrit) (Renal Blood Flow).

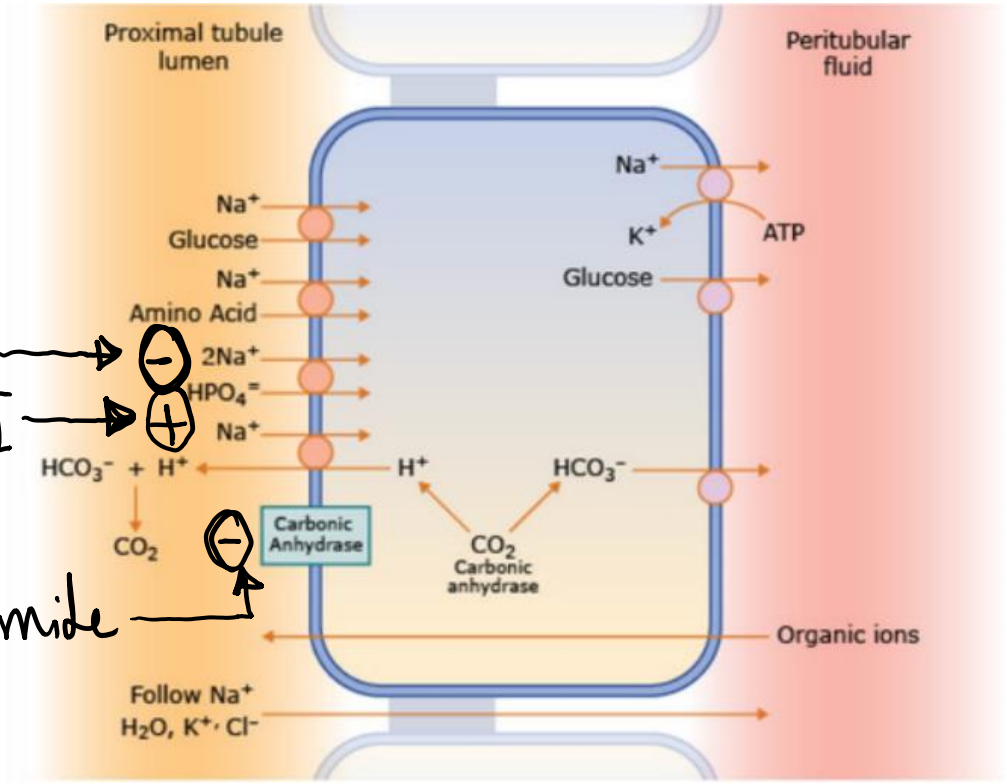
4. The filtration fraction is the fraction of the RPF that is filtered across the glomerular capillaries into Bowman's space.
- It can be calculated by dividing the GFR by the RPF.
- The GFR can be estimated with the creatinine clearance or inulin clearance, while the RPF is estimated with the PAH clearance.

5. PAH (para-aminohippurate) is filtered at the glomerulus into Bowman's space and is subsequently secreted into the nephron lumen by the proximal tubule.
- Thus, the lowest concentration of PAH in luminal fluid is in Bowman's space because in bowman's space there is no reabsorption or secretion.

Regional transport along the nephron

Proximal Tubule

- The fluid delivered to the proximal tubule from Bowman space is the isotonic GFR (120 mL/min).
- Thus, osmolarity is close to 300 mOsm and the concentration of any freely filtered substance is the same as the plasma concentration.



- All substances reabsorbed in the proximal tubule depend directly or indirectly on the Na/K-ATPase pump. Complete inhibition of the Na/K ATPase pump means nothing is reabsorbed in the proximal tubule.
- Since most of what is filtered is reabsorbed in the proximal tubule, the Na/K-ATPase pump is the most energy-demanding process of the nephron.
- In primary active transport, ATP is consumed directly by the transporting protein, (the Na/K-ATPase pump).
- Secondary active transport depends indirectly on ATP as a source of energy, as in the cotransport of Na-glucose in the proximal tubule. This process depends on ATP utilized by the Na/K-ATPase pump.

- **Electrolyte and Water Transport:**

- Two thirds of the filtered sodium are reabsorbed via active transport, primary and secondary.

- Two thirds of the filtered water and potassium follow the sodium (leaky tight junctions).

- Because equal proportions of sodium, potassium and water are reabsorbed, their concentrations do not change along the length of the proximal tubule.

- Osmolaiirity remains at 300 mOsm.

- 80 to 90% of the filtered bicarbonate is reabsorbed by an indirect mechanism.

- Because greater than two thirds of the bicarbonate are reabsorbed, less than two thirds of the chloride are reabsorbed to maintain electrical neutrality.

- Bicarbonate concentration decreases and chloride concentration increases along the length of the proximal tubule.

- **Metabolites:**

- Most metabolites are completely reabsorbed in this segment via secondary active transport. This includes glucose, ketone bodies, peptides, and amino acids.

- Concentration at the end of the proximal tubule is zero.

- Urea is partially passively reabsorbed (50% in PCT), Urea tends to follow the water, but not proportionately.

- **Secretion:**

- Active secretion of the metabolites, creatinine, urate and many non-natural substances (PAH, penicillin, etc.).

- **PTH:** Inhibits Na/PO_4 cotransport → ↑ PO_4 excretion.

- **AT II:** Stimulates Na/H exchange → ↑ Na, H_2O, and HCO_3 reabsorption (permitting contraction alkalosis).

- <u>Summary:</u>

- Approximate two thirds of the major electrolytes and water is reabsorbed as well as complete reabsorption of many metabolites. Osmolarity has not changed but the volume has been reduced from 120 ml each minute to 40 ml per minute.

- Bowman Space Fluid:

- If a substance is freely filtered → its concentration in the Bowman space is the same as in the plasma.

- The tubular fluid concentration divided by the plasma concentration is 1 (TF/P = 1.0).

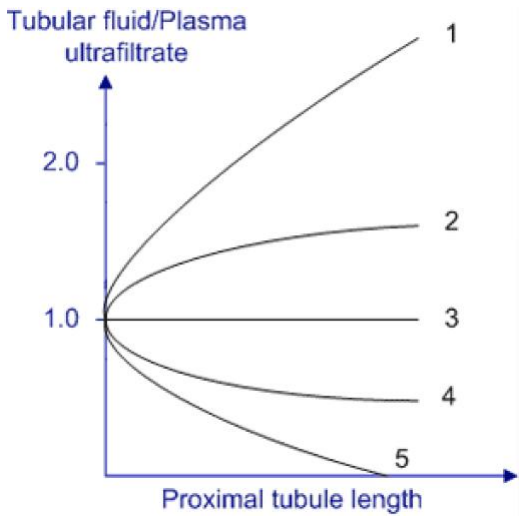
- The osmolarity of the filtrate will be the same as the ECF (300 mOsm).

- Concentrations of various compounds along the length of the proximal tubules in human kidneys:

- The tubular fluid/plasma ultrafiltrate value in the graph below is calculated by taking the tubular fluid concentration of a given substance in the proximal tubule and dividing that value by the initial concentration of that substance within Bowman's capsule.

- Thus, an upward (positive) slope indicates an increasing concentration of that substance as fluid moves toward distal parts of the tubule, which is usually the result of secretion or non-reabsorption of that substance.

- A downward slope indicates active reabsorption of that substance in the proximal tubule.



A. Line 1 on the above graph indicates a substance with a rapidly increasing concentration in the tubular fluid:

- Substances that behave in this fashion are freely filtered from the glomerular capillaries and are poorly reabsorbed from the proximal tubule.

- Because water is reabsorbed faster than these substances, their concentration in the proximal tubule increases.

- Chemicals that behave in this manner include creatinine, inulin, and paraaminohippuric acid (PAH).

B. Line 2 is indicative of the behavior of urea in the proximal tubular fluid:

- Urea is freely filtered from the glomerular capillaries and is poorly reabsorbed from the proximal tubule, but less so than PAH or inulin.

- Renal handling of urea varies throughout the different tubular systems, but it is ultimately secreted in very high concentrations, as it is a waste product of metabolism.

C. Line 3 indicates no concentration change along the proximal tubule:

- This line could represent the osmolality of the tubular fluid in this segment, as well as the sodium or potassium concentration; sodium and potassium are reabsorbed in concentrations approximately equal with water in the proximal tubule.

D. Line 4 represents the behavior of bicarbonate in the proximal tubule:

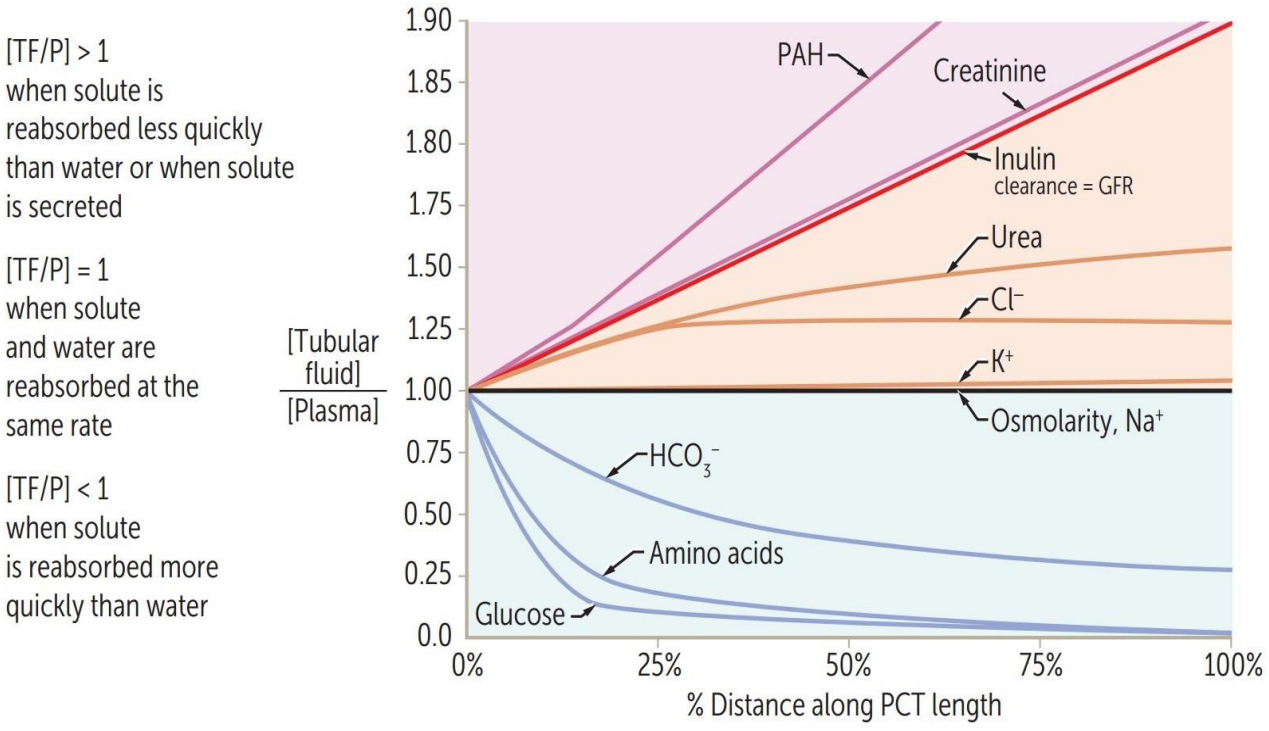
- Bicarbonate is actively reabsorbed in the proximal tubule due to the activity of carbonic anhydrase within proximal tubular cells.

- Because greater than two thirds of the bicarbonate are reabsorbed (80- 90%), the concentration of bicarbonate to decrease as fluid runs along the proximal tubule.

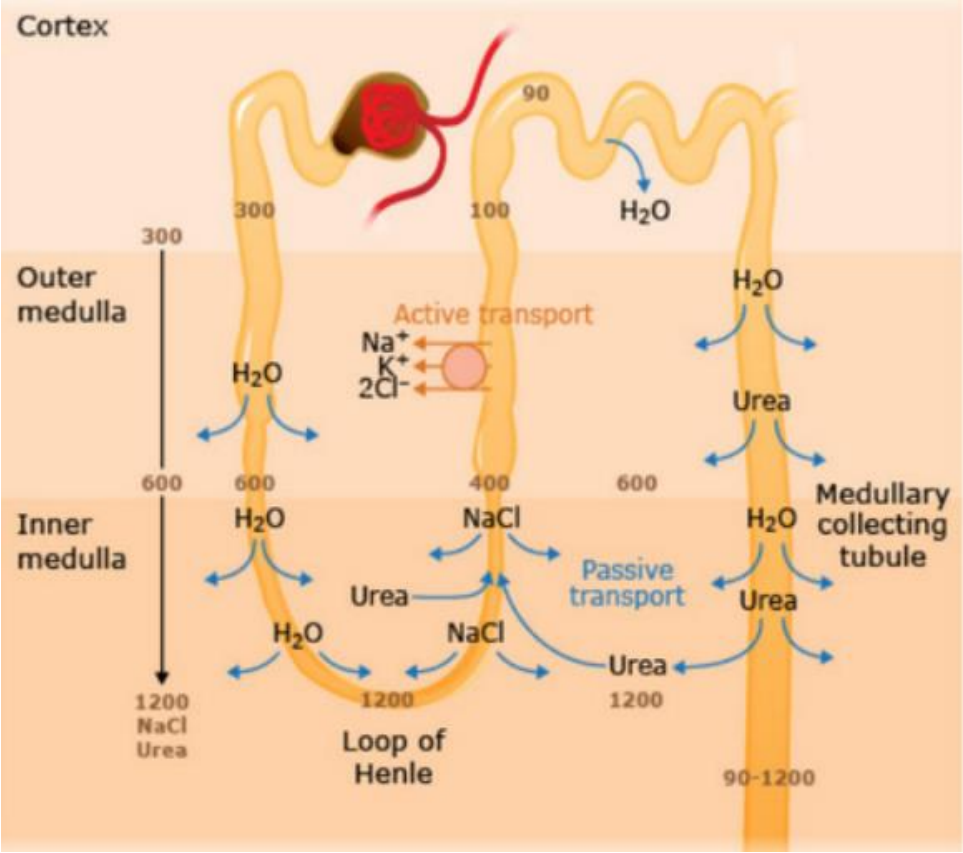
E. Line 5 indicates solutes that are avidly reabsorbed in the proximal tubule: Most notably, these include glucose and amino acids.

- So, in a nutshell:

- The concentrations of PAH, creatinine, inulin, and urea increase as fluid runs along the proximal tubule, while the concentrations of bicarbonate, glucose, and amino acids decrease.



Loop of Henle



- Receives the isotonic fluid delivered from the proximal tubule which has been reduced to one third of the original volume.

- <u>The loop of Henle has three main functions:</u>

1. It continues the reabsorption of water and electrolytes, up to about 25% of the filtered electrolytes are reabsorbed in this segment.

2. It acts as a countercurrent multiplier, which creates an osmolar gradient within the medullary interstitium:

- This gradient allows ADH acting on the collecting duct to concentrate the urine.

- In order for the countercurrent multiplier to maintain this gradient there must be a fairly low flow through the system.

- High flow reduces the interstitial gradient and ADH is unable to form a concentrated urine.

- In other words, if the proximal tubule does not do its job and the loop flow is too high as occurs in an uncontrolled diabetic a dilute urine will be formed.

3. It must reabsorb more electrolytes than water and deliver a hypotonic fluid to the distal tubule.

- In order to carry out its functions as a countercurrent multiplier, the loop of Henle must have specific functional characteristics:

A. First: A countercurrent flow (descending and ascending limb).

B. Second:

- The loop of Henle is located in the renal medulla, where the interstitium is hypertonic (higher osmolarity than that of plasma).

- The descending limb of the loop of Henle is permeable to water via medullary hypertonicity, but most of the ions are retained in the lumen → Makes urine hypertonic (Concentrating segment of the nephron).

- Equilibrium will occur with the interstitium and the osmolarity at the tip of the loop of Henle is the highest of any nephron segment.

- At the end of the collecting duct the osmolarity can equal this value but only with the maximum effect of ADH.

- In the absence of ADH, tubular fluid is most concentrated at the end of the descending limb of the loop of Henle.

C. Third:

- The thick and thin ascending limbs of the loop of Henle are impermeable to water. In the ascending limb, the osmolarity of the tubular fluid decreases due to passive reabsorption of NaCl in the thin region as well as active transport of electrolytes out of the lumen by the Na/K/2Cl cotransporter in the thick portion.

- Electrolytes are absorbed passively in the thin ascending limb, drawn out by urea which in this segment acts as an osmotic agent, and actively in the thick ascending limb.

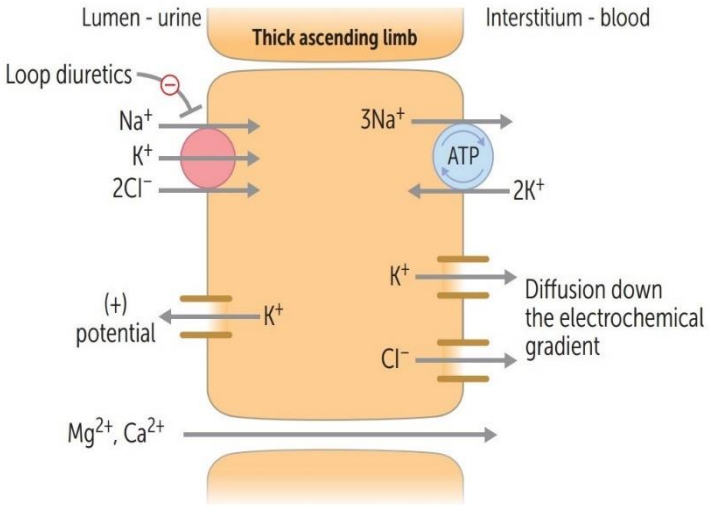
- Because osmolarity decreases in the ascending limb, it is referred to as the diluting segment of the nephron. In fact, the fluid leaving the loop is hypotonic.

- Like the proximal tubule it is powered by the Na/K-ATPase pump on the basolateral membrane of the thick ascending limb.

- On the luminal membrane the Na, K, and Cl enter via a protein mediated transport.

- This is an electro-neutral event; however, some of the potassium diffuses back down its electrochemical gradient into the tubule lumen creating the net positive luminal potential.

- The positive luminal charge facilitates the reabsorption of the divalent calcium and magnesium via a paracellular pathway.

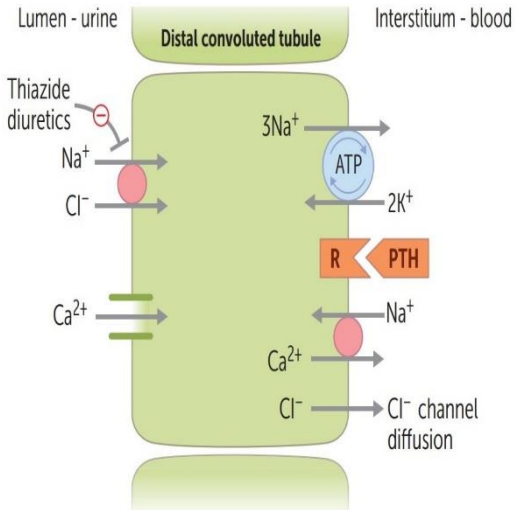


❖ N.B:

- Loop diuretics (furosemide) selectively inhibit the Na/K/2Cl cotransporter and reduce the positive luminal charge increasing the excretion of calcium and magnesium as well as the major electrolytes → Hypocalcemia.

Early Distal Tube

- The early distal tubule is similar to the ascending limb of Henle in that Na and Cl continue to be reabsorbed without water, further reducing the tubule osmolarity.
- Only about 5-10% of the filtered NaCl is reabsorbed in this segment.
- Na and Cl enter the cell via an electrically neutral cotransporter.
- Because there is no recycling of K, there is no positive luminal potential in this segment.
- Ca continues to be reabsorbed, passively across the luminal membrane but actively across the basal membrane. The process is regulated by parathyroid hormone.
- PTH → ↑Ca/Na exchange → ↑ Ca reabsorption.



❖ N.B:

- Thiazide diuretics inhibit the Nacl cotransporter mainly in the distal tubule.
- Unlike loop diuretics which inhibit Ca reabsorption, thiazides enhance Ca reabsorption.
- They are less powerful diuretics than loop diuretics, since less NaCl is reabsorbed in this segment.

Late Distal Tubule and Collecting Duct

- The late distal tubule and the collecting duct are similar.

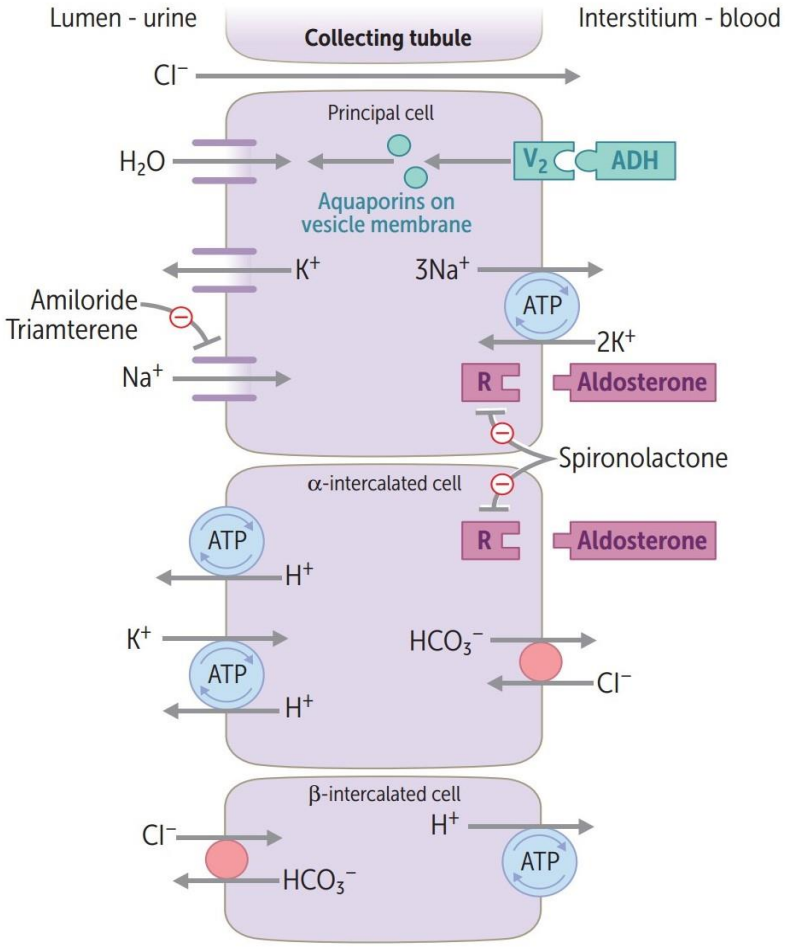
- The tubular membrane contains principal and intercalated cells.

- 3–5% Na reabsorbed.

- The water permeability of the cortical and medullary collecting ducts is regulated by vasopressin:

- If the water intake of the individual is high, vasopressin is not released and water permeability of the collecting duct system is low, producing dilute urine.

- In contrast, water deprivation stimulates vasopressin secretion, leading to marked reabsorption of water in the collecting ducts and the production of low-volume, high-osmolar urine.



A. Principal Cells:

- Principal cells reabsorb sodium and chloride with water and secrete potassium.
- Sodium diffuses across the luminal membrane through selective epithelial sodium channels (ENaC). It is then actively pumped (Na/K ATPse) across the basal membrane.
- Transport at the luminal and basal membrane is controlled by aldosterone.
- The unique aspect is that an equivalent amount of chloride does not follow the sodium.
- This creates a negative charge in the luminal fluid.
- This negative charge promotes potassium and hydrogen secretion into the luminal fluid.
- ADH: acts at V_2 receptor → insertion of aquaporin H_2O channels on apical side.

B. Intercalated Cells:

- In α-intercalated cells: lumen negativity → ↑ H ATPase activity → ↑ H secretion → ↑ HCO_3/Cl exchanger activity.
- They are represented by two different populations.
- Those that secrete hydrogen into the luminal fluid and generate brand new bicarbonate which is then secreted into the general circulation.
- Others do exactly the reverse. They secrete bicarbonate into the luminal fluid and hydrogen into the general circulation.
- When the body has a net production of fixed inorganic acids the former dominate.
- In a respiratory alkalosis, for example, the latter dominate forming an alkaline urine.

❖ N.B:

- Potassium sparing diuretics reduce potassium secretion by antagonizing the effects of aldosterone in the late distal and collecting duct.
- Spironolactone acts by a direct antagonism of the mineralocorticoid receptors.

Water deprivation

↓

Increases plasma osmolarity

↓

Stimulates osmoreceptors in anterior hypothalamus

↓

Increases secretion of ADH from posterior pituitary

↓

Increases water permeability of late distal tubule and collecting duct

↓

Increases water reabsorption

↓

Increases urine osmolarity
and
decreases urine volume

↓

Decreases plasma osmolarity toward normal

Water intake

↓

Decreases plasma osmolarity

↓

Inhibits osmoreceptors in anterior hypothalamus

↓

Decreases secretion of ADH from posterior pituitary

↓

Decreases water permeability of late distal tubule and collecting duct

↓

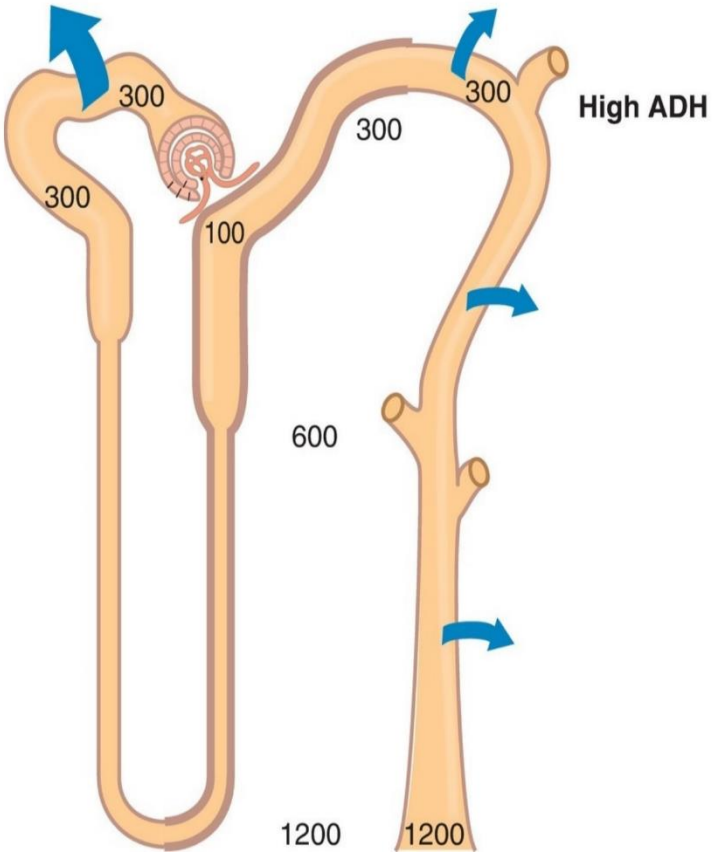
Decreases water reabsorption

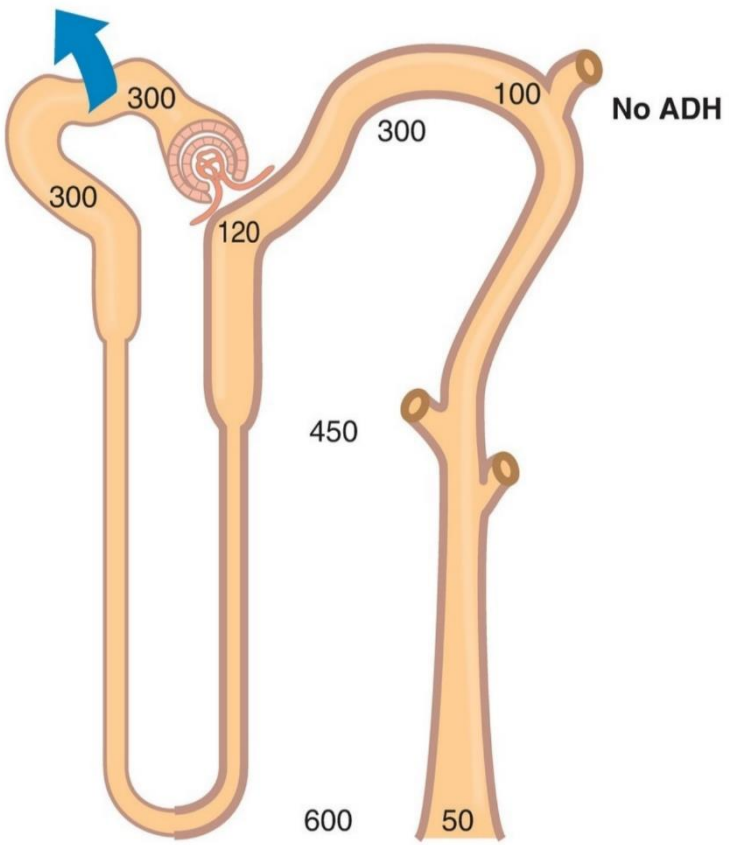
↓

Decreases urine osmolarity
and
increases urine volume

↓

Increases plasma osmolarity toward normal





Hydrogen Secretion and Acidification of the Urine

- The amount of fixed acid generated by an individual is mainly determined by diet.
- The fixed acid is neutralized by plasma bicarbonate and the generation of an equivalent amount of bicarbonate in the distal nephron prevents a metabolic acidosis.
- Hydrogen ions are actively secreted into the tubular lumen by two mechanisms. However, very few are excreted as free ions.
- Almost all are buffered mainly with phosphate or combined with ammonia.
- Hydrogen ions can be actively pumped until the luminal pH drops to 4.0-4.5. Almost all the hydrogen ions secreted are buffered.
- Two systems are involved, phosphate buffer system and ammonium.

1. Phosphate Buffer System:

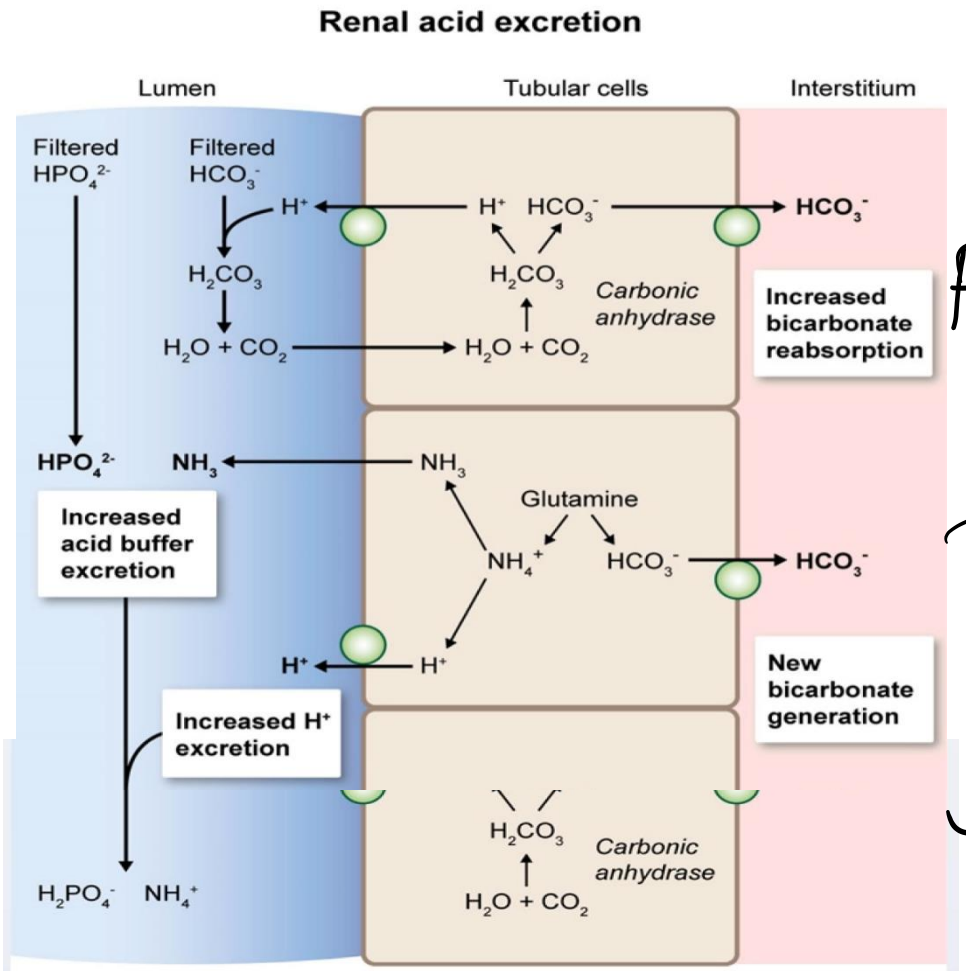
- Mono-hydrogen phosphate (HPO_4) is freely filtered and partially reabsorbed in early segments, mainly the proximal tubule.
- The phosphate delivered to the collecting duct will buffer about one third of the secreted hydrogen ions depending on the diet.
- Mono-hydrogen phosphate (HPO_4) + H → dihydrogen phosphate (H_2PO_4).

2. Ammonium:

- Ammonia is produced by cells of the proximal tubule from glutamine and delivered to the collecting duct.
- Ammonia production is based on need. In an acidosis, ammonia production increases, in an alkalosis it decreases.
- Ammonia (NH_3) combines with hydrogen ions (H) to form ammonium (NH_4).
- SO, if you have a question asking you to calculate the reabsorption rate of bicarbonate in collecting ducts, giving you the urine ammonium and phosphate?

Phosphate + ammonium = total acid lost in the urine

Total acid lost in the urine = gain of new bicarbonate

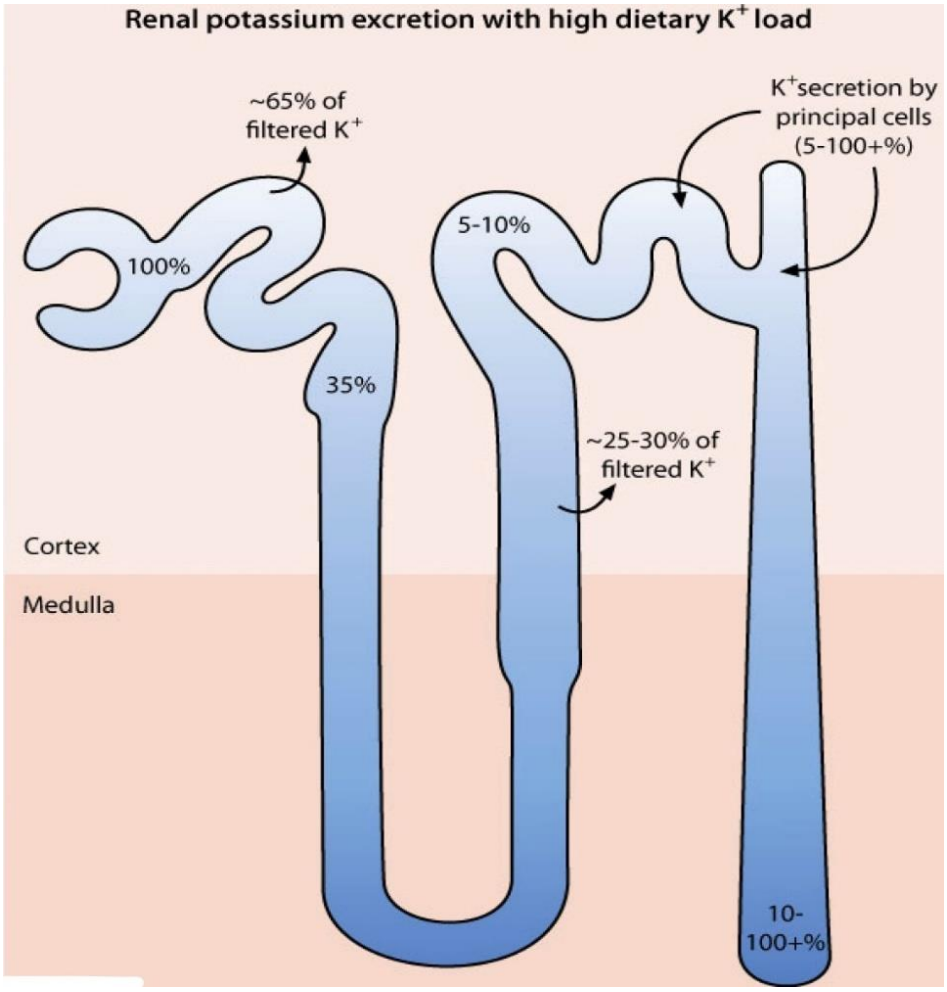


❖ N.B:

1. Because K is freely filtered across the glomerular membrane, K concentration within Bowman's space is equal to that in the glomerular capillaries and represents 100% of the filtered load.

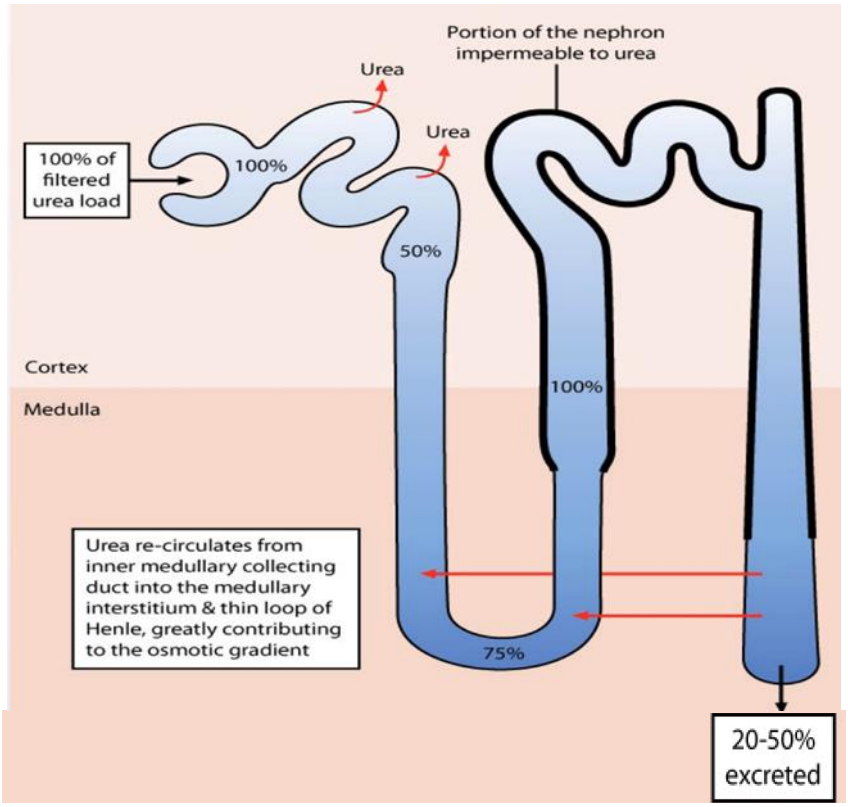
- The degree of K filtration by the kidney depends on the glomerular filtration rate, which is relatively constant in healthy individuals.
- Patients with renal failure may develop elevated plasma K due to failure to filter a sufficient quantity of plasma through the glomeruli.
- Approximately 2/3 of the filtered K load is reabsorbed in the proximal tubule.
- The thick ascending limb of the loop of Henle further resorbs about 25% of the filtered K load through the action of the Na/K/2CI cotransporter.
- These processes occur at a relatively fixed rate and do not play a significant role in the regulation of K excretion in the urine.
- Even in hyperkalemic states, patients will reabsorb the majority of filtered K in the proximal tubule and loop of Henle.
- The principal and intercalated cells of the late distal and cortical collecting tubules are the primary mediators of K regulation.
- Hypokalemia stimulates reabsorption of K via apically located H/K-ATPases on intercalated cells and can cause the amount of K in the collecting tubule to approach 1 % of the filtered load.
- Conversely, conditions of normal or increased K load stimulate principal cells to secrete K through apical K channels.

- High dietary K intake can cause the amount of K in the collecting tubules to actually exceed that of the filtered load.



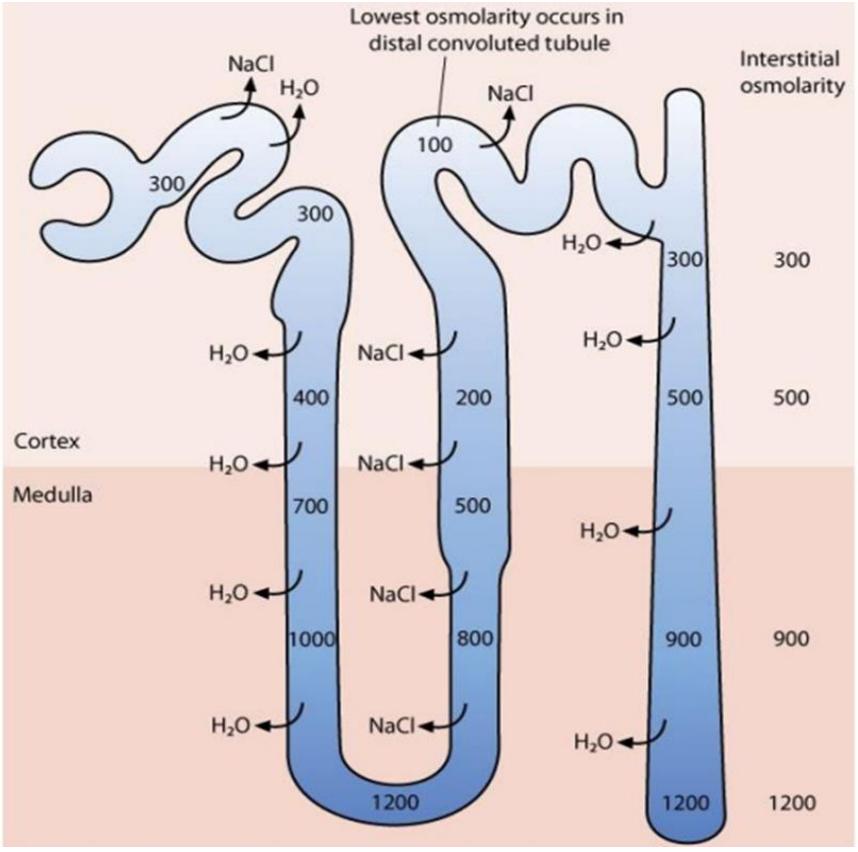
2. The medullary portion of the collecting duct is of particular importance in the production of maximally concentrated urine as the medullary interstitium is the region of highest osmolarity in the kidney.

- Although the cortical collecting duct is impermeable to urea, vasopressin activates urea transporters in the medullary collecting duct, increasing urea reabsorption and decreasing renal urea clearance.
- This passive reabsorption of urea into the medullary interstitium in the presence of ADH significantly increases the medullary osmotic gradient, allowing the production of maximally concentrated urine.
- In the setting of high serum ADH levels, a large osmotic gradient drives the absorption of free water into the hypertonic medullary interstitium.
- As water leaves the tubular fluid, urea concentration greatly increases.
- When ADH levels are high, this urea reabsorption contributes up to 50% of total osmolarity of the medulla, further increasing the water-absorbing capacity of the nephron.



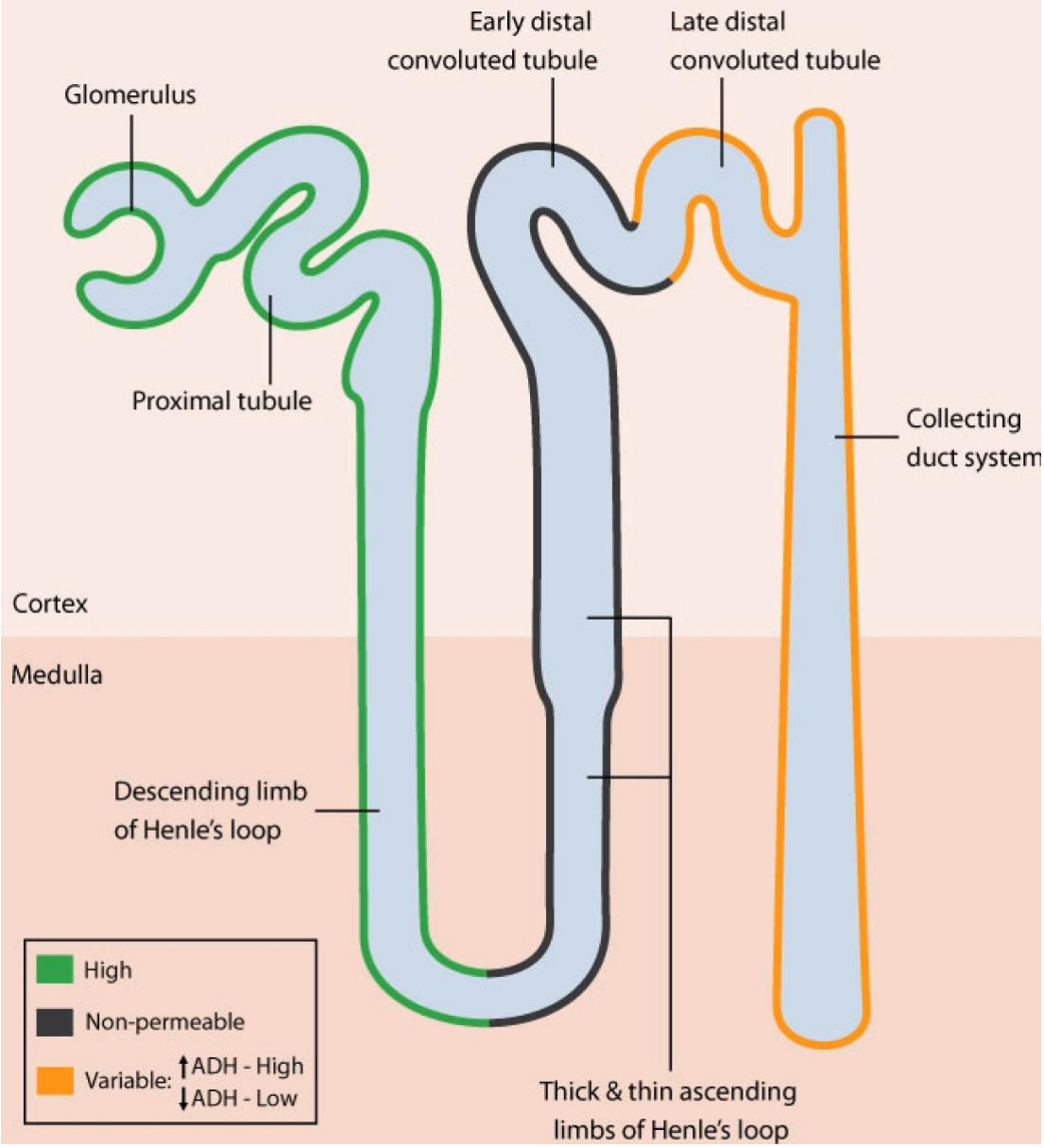
3. The osmolarity at the tip of the loop of Henle is the highest of any nephron segment.

- At the end of the collecting duct the osmolarity can equal this value but only with the maximum effect of ADH.
- Lowest osmolarity occurs in distal convoluted tubules.



4. Regardless of the patient's hydration status, the majority of water reabsorption in the nephron occurs in the proximal tubule passively with the reabsorption of solutes.

- In the presence of ADH: the collecting ducts contain the most concentrated fluid in the nephron, while the thick ascending limb of the loop of Henle and distal convoluted tubule contain the most dilute fluid.
- In the absence of ADH: the tubular fluid is most concentrated at the tip of the loop of Henle and most dilute in the collecting ducts.



Pathophysiology of Potassium Dynamics

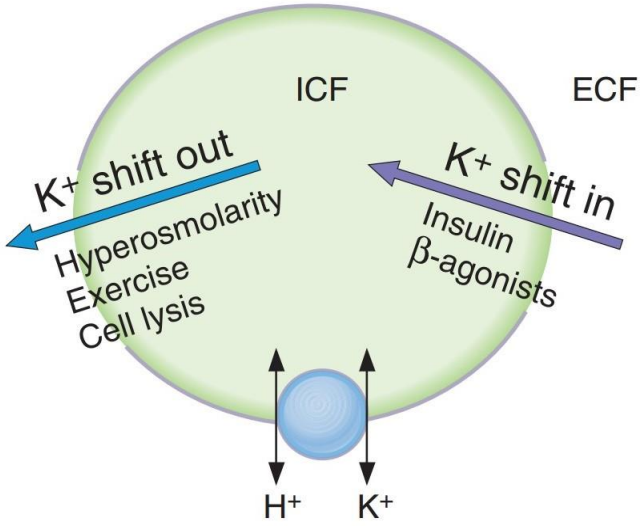
- Almost all body potassium is in the ICF (95%).

- Potassium Regulation:

- Concentration in ECF closely regulated.

- <3,5 mEq/L = hypokalemia.

- > 5 mEq/L = hyperkalemia.



- Causes of Hypokalemia:

- Diuretic use is the most common cause.

- Hyperaldosteronism: Renal function intact (Conn syndrome), renal arterial stenosis, renin secreting tumor.

- ECF → ICF; metabolic alkalosis, hypoosmolar state.

- ↑ Insulin, catecholamines and β-adrenergic agonists (↑ Na/K ATPase).

- Diuresis with ketoacidosis, renal tubular acidosis.

- Consequences of Hypokalemia:

- More negative resting membrane potential; decreased excitability in nerves and muscle.

- Skeletal muscle weakness, arrhythmias.

- EKG: heightened U waves, depressed T waves.

- Causes of Hyperkalemia:

- Hypoaldosteronism (ACE inhibitors, potassium-sparing diuretics).
- Renal failure.
- Hypoinsulinemia, ↓ catecholamine responses (B-blockers).
- Muscle trauma, tissue necrosis (burns).
- ICF → ECF; metabolic acidosis, hyperosmolar states.
- Digitalis (blocks Na/K ATPase).

- Consequences of Hyperkalemia:

- Arrhythmias most serious consequences.
- Neuromuscular weakness.
- EKG: elevated T waves.

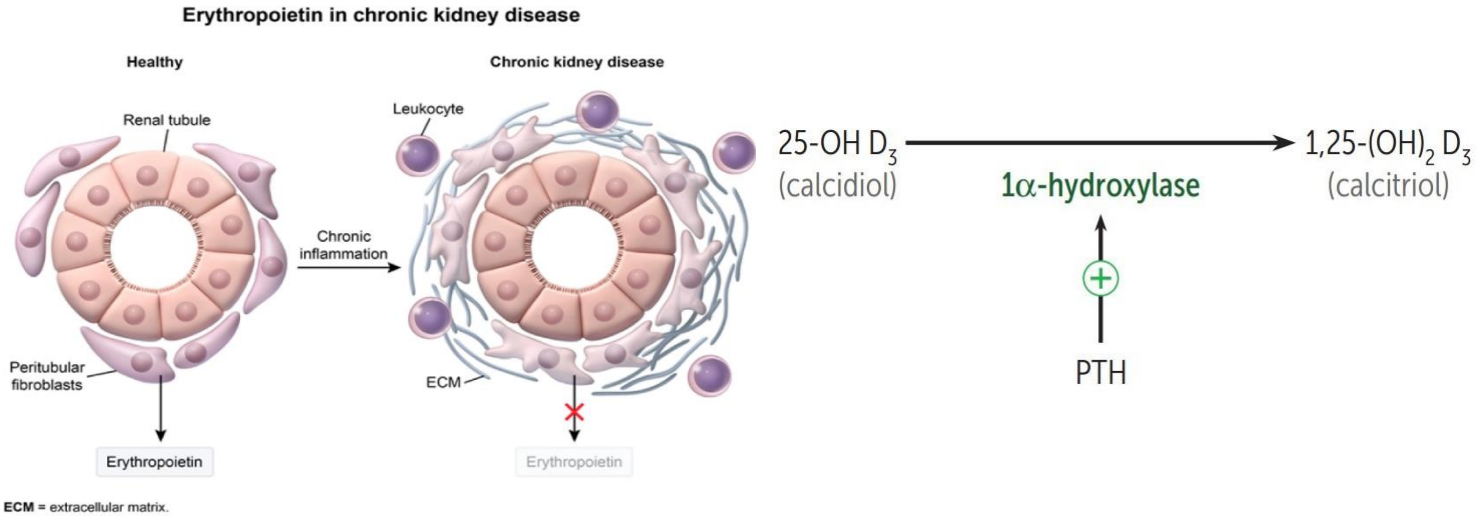
Electrolyte disturbances

Electrolyte	Low serum concentration	High serum concentration
Sodium	Nausea, malaise, stupor, coma, seizures	Irritability, stupor, coma
Potassium	U waves and flattened T waves on ECG, arrhythmias, muscle cramps, spasm, weakness	Wide QRS and peaked T waves on ECG, arrhythmias, muscle weakness
Calcium	Tetany, seizures, QT prolongation, twitching (Chvostek sign), spasm (Trousseau sign)	Stones (renal), bones (pain), groans (abdominal pain), thrones (↑ urinary frequency), psychiatric overtones (anxiety, altered mental status)
Magnesium	Tetany, torsades de pointes, hypokalemia, hypocalcemia (when [Mg] < 1.0 mEq/L)	↓ DTRs, lethargy, bradycardia, hypotension, cardiac arrest, hypocalcemia
Phosphate	Bone loss, osteomalacia (adults), rickets (children)	Renal stones, metastatic calcifications, hypocalcemia

Kidney endocrine functions

1. Erythropoietin:

- Released by interstitial cells in peritubular capillary bed in response to hypoxia.
- EPO acts on erythrocyte precursor cells in the bone marrow to stimulate red blood cell production.
- Patients with chronic kidney disease have inflammatory damage to renal EPO-producing cells and often develop normocytic anemia due to insufficient EPO.



2. 1,25-(OH)2 D_3:

- PCT cells convert 25-OH vitamin D to 1,25-(OH)2 vitamin D (active form).

3. Renin:

- Secreted by JG cells in response to ↓ renal arterial pressure and ↑ renal sympathetic discharge (β1 effect).

4. Prostaglandins:

- Paracrine secretion vasodilates the afferent arterioles to ↑ RBF.
- NSAIDs block renal-protective prostaglandin synthesis → constriction of afferent arteriole and ↓ GFR; this may result in acute renal failure.

5. Dopamine:

- Secreted by PCT cells, promotes natriuresis.
- At low doses; dilates interlobular arteries, afferent arterioles, efferent arterioles → ↑ RBF, little or no change in GFR.
- At higher doses; acts as vasoconstrictor.

Hormones acting on kidney

Atrial natriuretic peptide

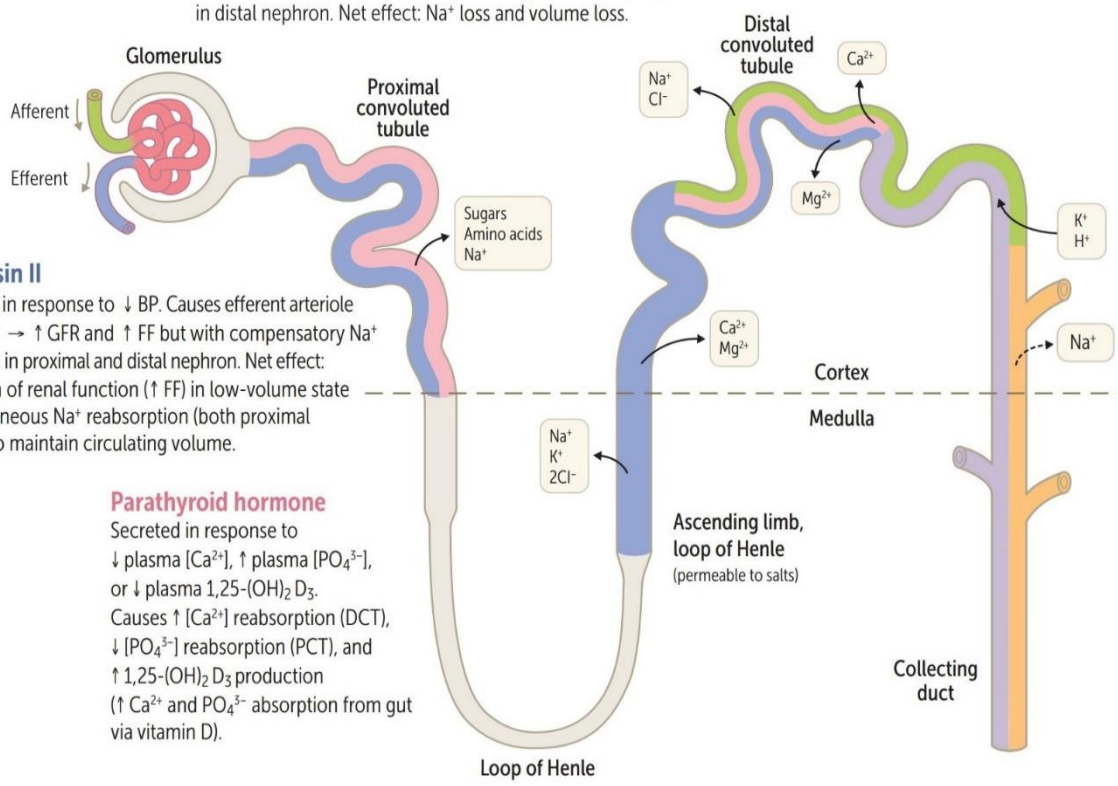
Secreted in response to ↑ atrial pressure. Causes ↑ GFR and ↑ Na^+ filtration with no compensatory Na^+ reabsorption in distal nephron. Net effect: Na^+ loss and volume loss.

Angiotensin II

Synthesized in response to ↓ BP. Causes efferent arteriole constriction → ↑ GFR and ↑ FF but with compensatory Na^+ reabsorption in proximal and distal nephron. Net effect: preservation of renal function (↑ FF) in low-volume state with simultaneous Na^+ reabsorption (both proximal and distal) to maintain circulating volume.

Parathyroid hormone

Secreted in response to ↓ plasma $[Ca^{2+}]$, ↑ plasma $[PO_4^{3-}]$, or ↓ plasma 1,25-$(OH)_2$ D_3. Causes ↑ $[Ca^{2+}]$ reabsorption (DCT), ↓ $[PO_4^{3-}]$ reabsorption (PCT), and ↑ 1,25-$(OH)_2$ D_3 production (↑ Ca^{2+} and PO_4^{3-} absorption from gut via vitamin D).



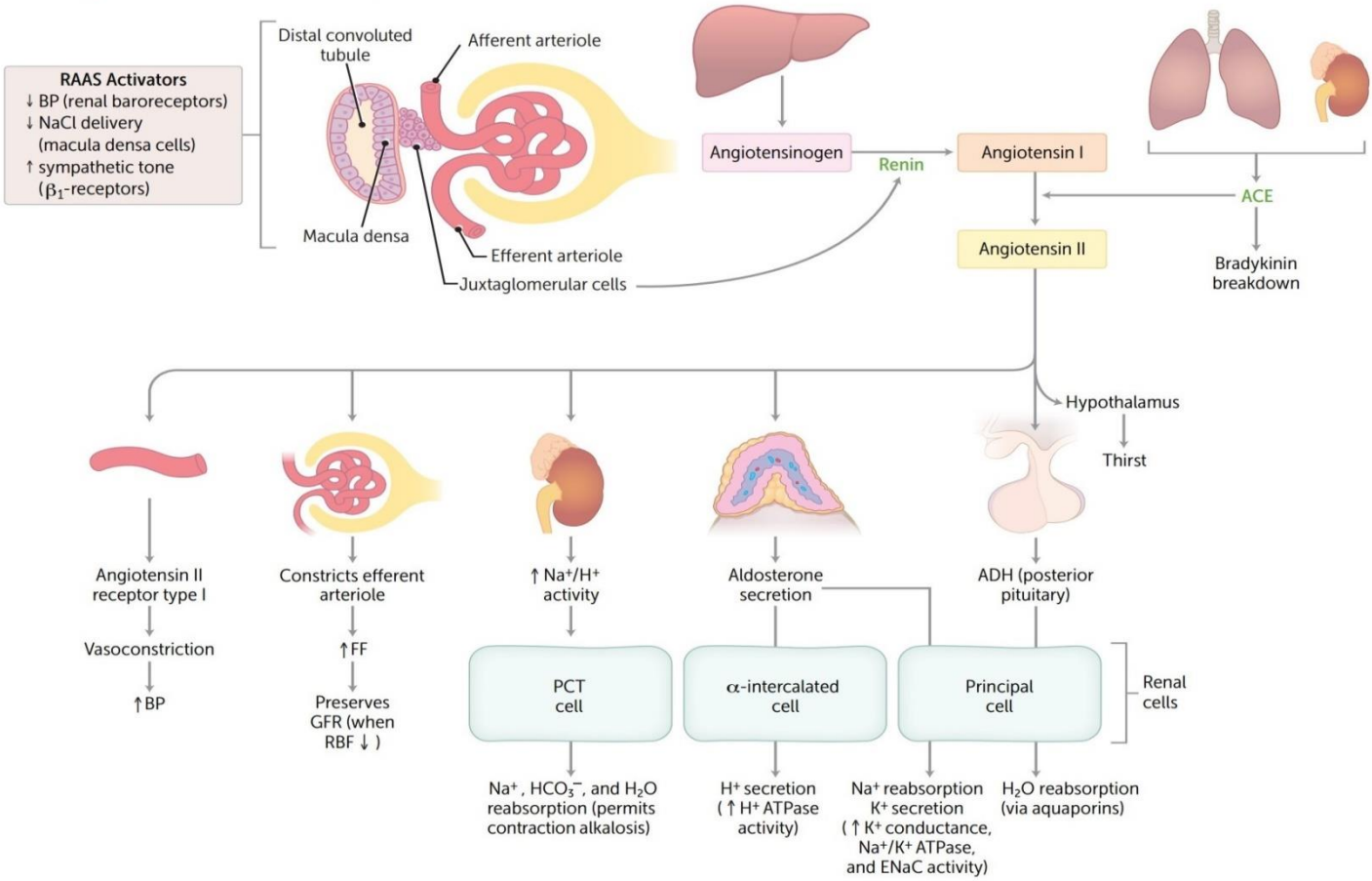
Aldosterone

Secreted in response to ↓ blood volume (via AT II) and ↑ plasma $[K^+]$; causes ↑ Na^+ reabsorption, ↑ K^+ secretion, ↑ H^+ secretion.

ADH (vasopressin)

Secreted in response to ↑ plasma osmolarity and ↓ blood volume. Binds to receptors on principal cells, causing ↑ number of aquaporins and ↑ H_2O reabsorption.
↑ reabsorption of urea in collecting ducts to maximize corticopapillary osmotic gradient.

Renin-angiotensin-aldosterone system



Acid base disturbance

- The CO_2-bicarbonate buffer system can be seen below. It is one of the major buffer systems of the blood.

$$H_2O + CO_2 \overset{CA}{\rightleftharpoons} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

- Since only three parameters are monitored clinically the above can be reduced as shown below:

$$CO_2 \longleftrightarrow H^+ + HCO_3^-$$

- Recall that the respiratory system plays the key role in regulating CO_2, while the kidneys serve as the long-term regulators of H and HCO_3. Thus, these 2 organ systems are paramount in our discussion of acid-base regulation.

Acid-base physiology

	pH	P_{CO_2}	$[HCO_3^-]$	COMPENSATORY RESPONSE
Metabolic acidosis	↓	↓	↓	Hyperventilation (immediate)
Metabolic alkalosis	↑	↑	↑	Hypoventilation (immediate)
Respiratory acidosis	↓	↑	↑	↑ renal $[HCO_3^-]$ reabsorption (delayed)
Respiratory alkalosis	↑	↓	↓	↓ renal $[HCO_3^-]$ reabsorption (delayed)

Key: ↓ ↑ = compensatory response.

Henderson-Hasselbalch equation: $pH = 6.1 + \log \frac{[HCO_3^-]}{0.03\ P_{CO_2}}$

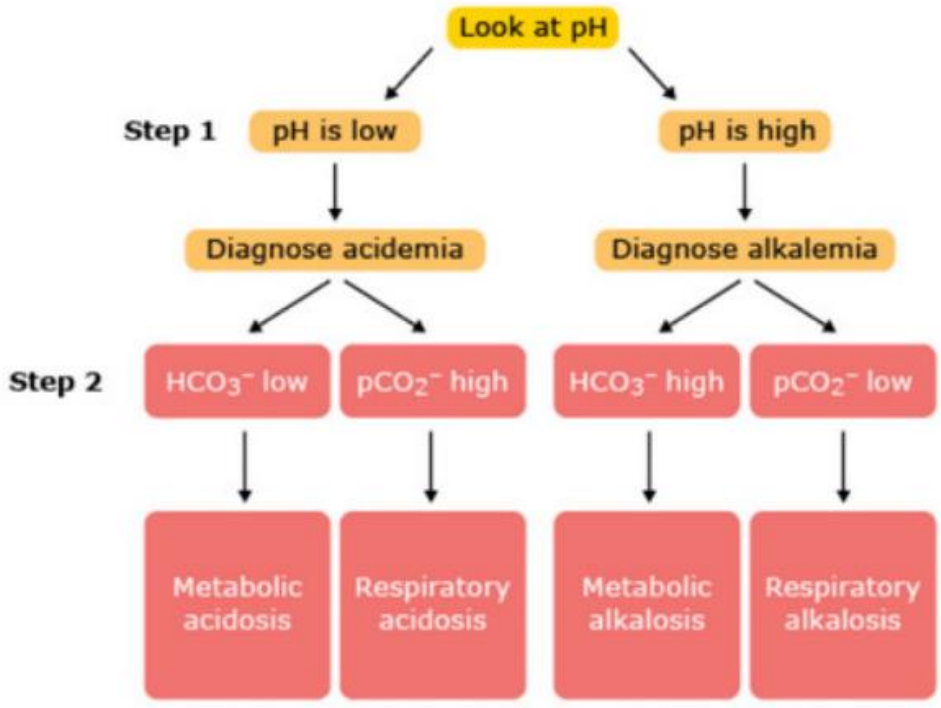
Determining a Primary Problem

- Normal systemic arterial values:

pH	= 7.400 (7.35–7.45)
PCO_2	= 40 mmHg (35–45)
HCO_3	= 24 mM (22–26)

- Determining the problem is the first stage in the analysis.
- It is a two-step approach.
- <u>Once the problem is established it is then appropriate to consider compensation:</u>

- Step 1: From the pH, is it acidemia (acidosis) or alkalemia (alkalosis)?
- Step 2: From the CO_2 and HCO_3, is it respiratory (CO_2), or metabolic (HCO_3), or both?



A. Acidosis:

- If the pH is depressed, it is an acidosis.
- If the CO_2 is elevated, there is a respiratory component to the acidosis (but it could also include a metabolic component).

- If there is an acidosis and the CO_2 is not elevated, the only possible explanation is the presence of a metabolic acidosis (bicarbonate must be reduced).

- If the CO_2 is elevated and the bicarbonate is depressed, it is a combined respiratory and metabolic acidosis.

B. Alkalosis:

- If the pH is elevated, it is an alkalosis.

- If the CO_2 is depressed, there is a respiratory component to the alkalosis (but it could also include a metabolic component).

- If there is an alkalosis and the CO_2 is not depressed, the only possible explanation is the presence of a metabolic alkalosis (bicarbonate must be elevated).

- If the CO_2 is depressed and the bicarbonate is elevated, it is a combined respiratory and metabolic alkalosis.

C. Combined disturbances:

- If the CO_2 and the HCO_3 have moved in the opposite direction from normal, it is a combined or a mixed disturbance. It is more likely to test the combined acidosis than the combined alkalosis.

- Combined respiratory and metabolic acidosis: CO_2 ↑ and HCO_3 ↓.

- Combined respiratory and metabolic alkalosis: CO_2 ↓ and HCO_3 ↑.

Plasma Anion Gap

- In the plasma, the cations balance the anions.

- However, many plasma cations and anions are not routinely measured.

- Primary measured ones: Na, Cl, HCO_3.

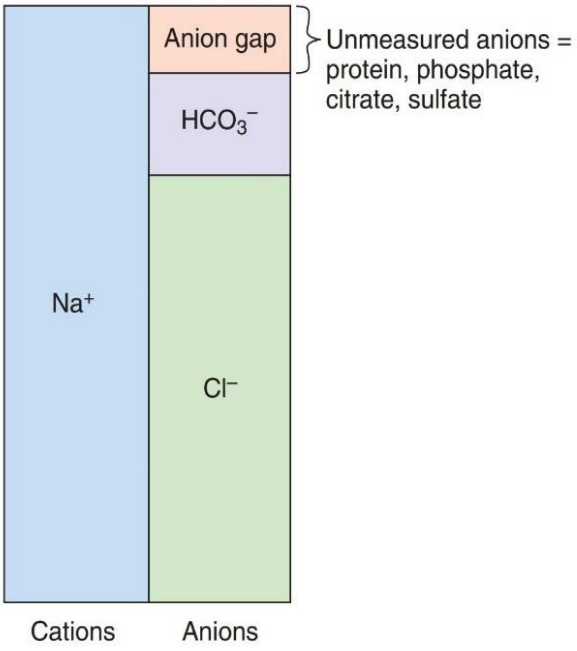
- The real balance is given by the equation:

$$\text{Anion gap} = Na - (Cl + HCO_3)$$

- Normal anion gap (8–12 mEq/L)

- An anion gap > 12 could indicate a metabolic acidosis.

- An anion gap > 20 always Indicates a metabolic acidosis.



- Normal anion gap metabolic acidosis (hyperchloremic metabolic acidosis):

- HARD-ASS:
- Hyperalimentation.
- Addison disease.
- Renal tubular acidosis.
- Diarrhea.
- Acetazolamide.
- Spironolactone.
- Saline infusion.

- High Anion gap metabolic acidosis (anions retained):

- MUDPILES:
- Methanol (formic acid).
- Uremia.
- Diabetic ketoacidosis.
- Propylene glycol.
- Iron tablets or Isoniazid.
- Lactic acidosis.
- Ethylene glycol (oxalic acid).
- Salicylates (late).

- Acute salicylate intoxication:

- Typically occurs in adults after an intentional overdose, although accidental overdose is also common due to the fact that salicylates are found in numerous over-the-counter preparations.

- Salicylate intoxication causes two different acid-base abnormalities simultaneously:

A. Respiratory alkalosis:

- The first disturbance to occur and starts soon after ingestion.

- Salicylates directly stimulate the medullary respiratory center resulting in hyperventilation, increased loss of CO_2 in the expired air, and respiratory alkalosis.

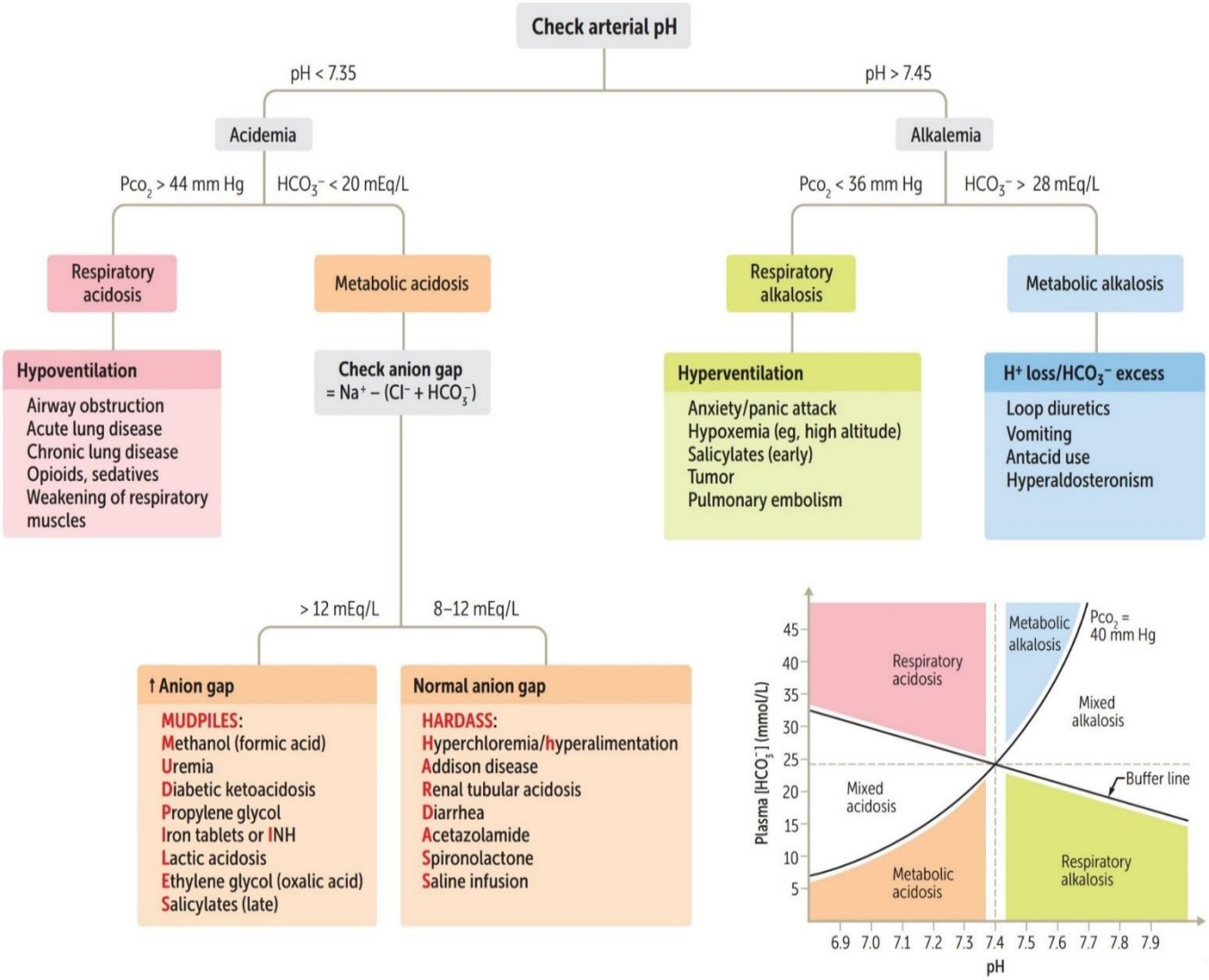
B. Anion gap metabolic acidosis:

- A few hours after ingestion, an anion gap metabolic acidosis begins to develop due to the accumulation of organic acids in the blood.

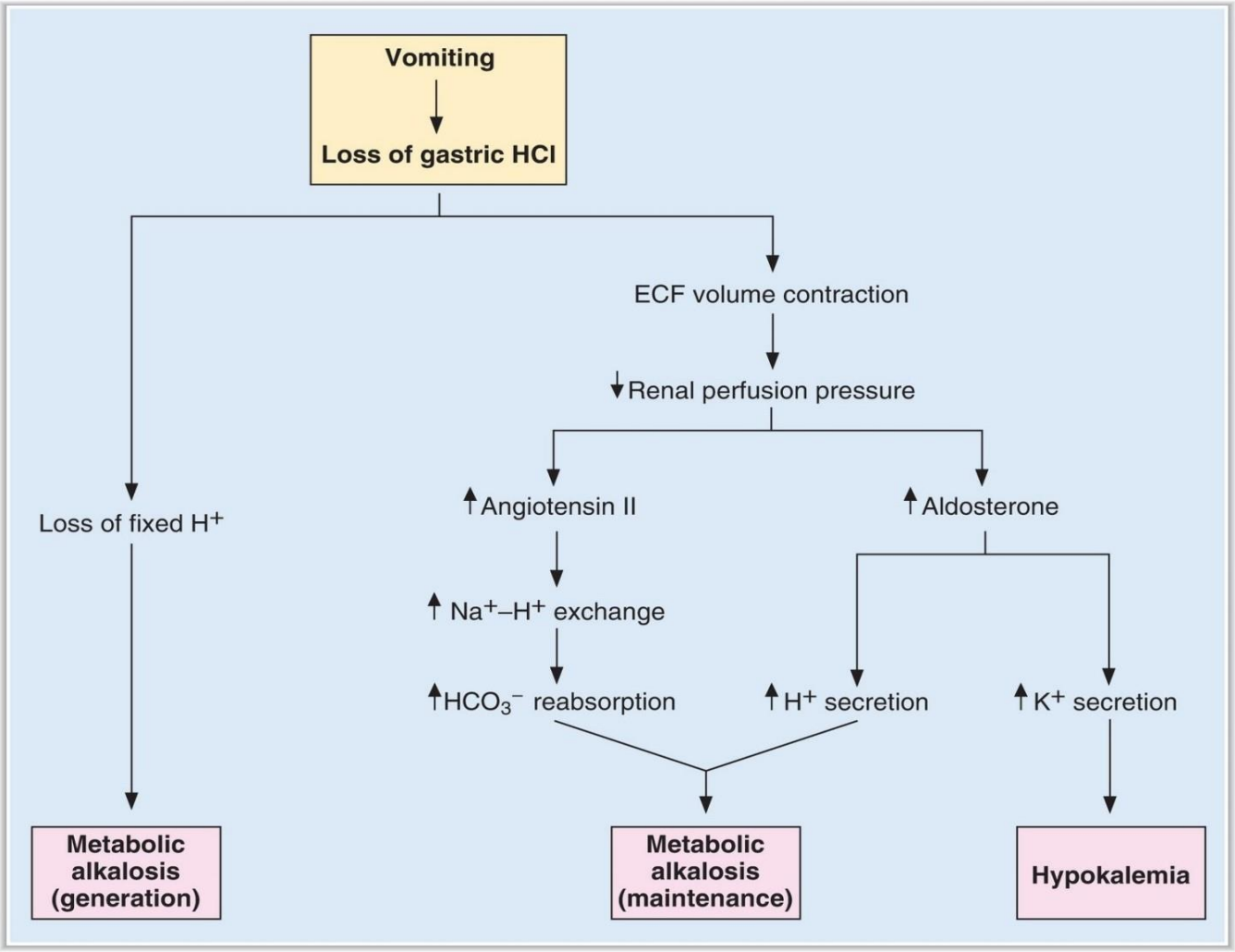
- At high concentrations, salicylates increase lipolysis, uncouple oxidative phosphorylation, and inhibit the citric acid cycle resulting in the accumulation of metabolic intermediates like ketoacids, lactate, and pyruvate.

- Since salicylate intoxication will present as a mixed disorder, pH could lie anywhere between a severe acidosis and alkalosis and may be normal or close to normal.

- Respiratory alkalosis is identifiable on an arterial blood gas analysis by a low $PaCO_2$.



Contraction alkalosis



- Loss of H from the stomach by vomiting causes increased blood [HCO_3] and metabolic alkalosis. Because Cl is lost from the stomach along with H, hypochloremia and ECF volume contraction occur.

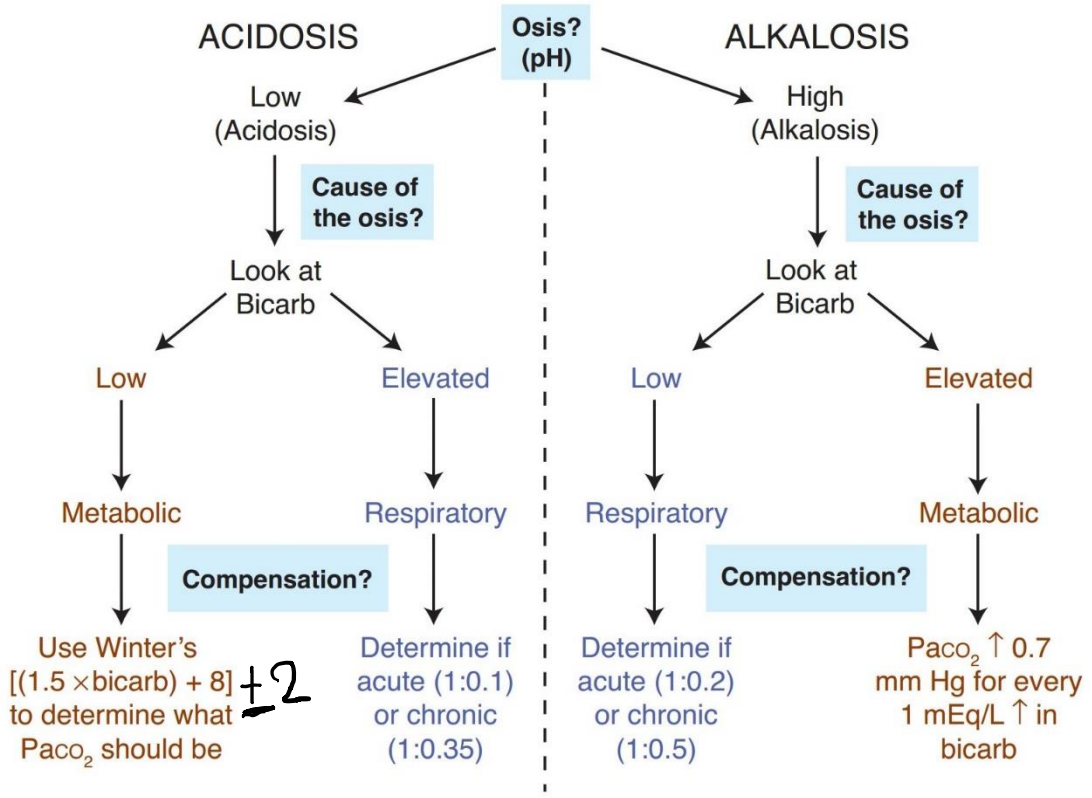
- ECF volume contraction is associated with decreased blood volume and decreased renal perfusion pressure. As a result, renin secretion is increased, production of angiotensin II is increased, and secretion of aldosterone is increased. Thus, the ECF volume contraction worsens the metabolic alkalosis because angiotensin II increases HCO_3 reabsorption in the proximal tubule (contraction alkalosis).

- The increased levels of aldosterone (secondary to ECF volume contraction) cause increased distal K secretion and hypokalemia. Increased aldosterone also causes increased distal H secretion, further worsening the metabolic alkalosis.

- Treatment consists of NaCl infusion to correct ECF volume contraction (which is maintaining the metabolic alkalosis and causing hypokalemia) and administration of K to replace K lost in the urine.

Compensatory mechanisms

- In a respiratory problem, the kidneys compensate (delayed).
- In a metabolic problem, the respiratory system compensates (immediate).
- The kidneys will also respond in a metabolic disturbance by returning HCO_3 toward normal.
- This is more correctly considered, not compensation, but an attempt to eliminate the disturbance.



Acid-base disorders	
Primary disorder	**Appropriate compensation**
Metabolic acidosis	$PaCO_2 = 1.5$ (serum HCO_3) + 8 ± 2
Metabolic alkalosis	↑ $PaCO_2$ by 0.7 mm Hg for every 1 mEq/L rise in serum HCO_3
Acute respiratory acidosis	Acute: ↑ Serum HCO_3 by 1 mEq/L for every 10 mm Hg rise in $PaCO_2$ Chronic: ↑ Serum HCO_3 by 3 mEq/L for every 10 mm Hg rise in $PaCO_2$
Acute respiratory alkalosis	Acute: ↓ Serum HCO_3 by 2 mEq/L for every 10 mm Hg decrease in $PaCO_2$ Chronic: ↓ Serum HCO_3 by 5 mEq/L for every 10 mm Hg decrease in $PaCO_2$

1. Respiratory Compensation:

- In a metabolic disturbance, there should be a partial respiratory compensation.
- The respiratory system responds quickly to a metabolic problem.
- Metabolic Acidosis: hyperventilation ↓ PCO_2.
- Metabolic Alkalosis: hypoventilation ↑ PCO_2.

❖ N.B:

- Predicted respiratory compensation for a simple metabolic acidosis can be calculated using the Winter's formula.
- If measured PCO_2 differs significantly from predicted PCO_2, then a mixed acid-base disorder is likely present:

$$PCO_2 = 1.5\ [HCO_3] + 8 \pm 2$$

- When the steady-state $PaCO_2$ persists above the range given by Winter's formula, there is superimposed respiratory acidosis and respiratory failure.
- Normal $PaCO_2$ in patient with metabolic acidosis indicates that he is unable to generate an appropriate compensatory respiratory response.
- As a result, he has a mixed acid-base disturbance consisting of metabolic and respiratory acidosis.

2. Renal Compensation:

- Unlike the respiratory system, the kidney is slow to respond to a disturbance.
- Thus, acute respiratory disturbances will be uncompensated.
- In an acidosis, the kidney increases the production of HCO_3 and the excretion of acid in the urine. Plasma bicarbonate rises.
- In an alkalosis, the kidney excretes HCO_3 (alkaline urine). Plasma bicarbonate decreases.
- Partially compensated respiratory acidosis: HCO_3 above the normal range.
- Partially compensated respiratory alkalosis: HCO_3 below the normal range.

Winter's formula
$PaCO_2 = (1.5 * HCO_3\text{-}) + 8 \pm 2$

- Used to evaluate respiratory compensation when there is metabolic acidosis
- $PaCO_2$ > predicted: concurrent respiratory acidosis
- $PaCO_2$ < predicted: concurrent respiratory alkalosis

Some ABGs showing disturbance follow below:

Example 1: pH 7.3, HCO_3^- 14 mEq/L, PCO_2 30 mm Hg, PO_2 95 mm Hg

Example 2: pH 7.6, HCO_3^- 20 mEq/L, PCO_2 20 mm Hg, PO_2 95 mm Hg

Example 3: pH 7.2, HCO_3^- 30 mEq/L, PCO_2 80 mm Hg, PO_2 70 mm Hg

Example 4: pH 7.6, HCO_3^- 44 mEq/L, PCO_2 52 mm Hg, PO_2 70 mm Hg

Example 5: HCO_3- 20 mEq/L, PCO_2 55 mm Hg

Answers

Example 1: What is the osis? pH is low, so acidosis. **Cause of the osis?** HCO_3^- is low, so metabolic acidosis. **Compensation?** Use Winter's to compute predicted PCO_2: $(14 \times 1.5) + 8 = 29$. Patient's is 30, which is within 2, thus this is a **metabolic acidosis with respiratory compensation.**

Example 2: What is the osis? pH is high, so alkalosis. **Cause of the osis?** HCO_3^- is low, so respiratory alkalosis. **Compensation?** Must determine if acute (uncompensated) or chronic (compensated). PCO_2 is 20 below normal, thus acute: $20 \times 0.2 = 4$, so HCO_3^- will be around 20 (24 – 4). If chronic, it would be $20 \times 0.5 = 10$, so HCO_3^- would be around 14 (24 – 10). The measured equals the predicted acute, thus this is an **acute respiratory alkalosis.**

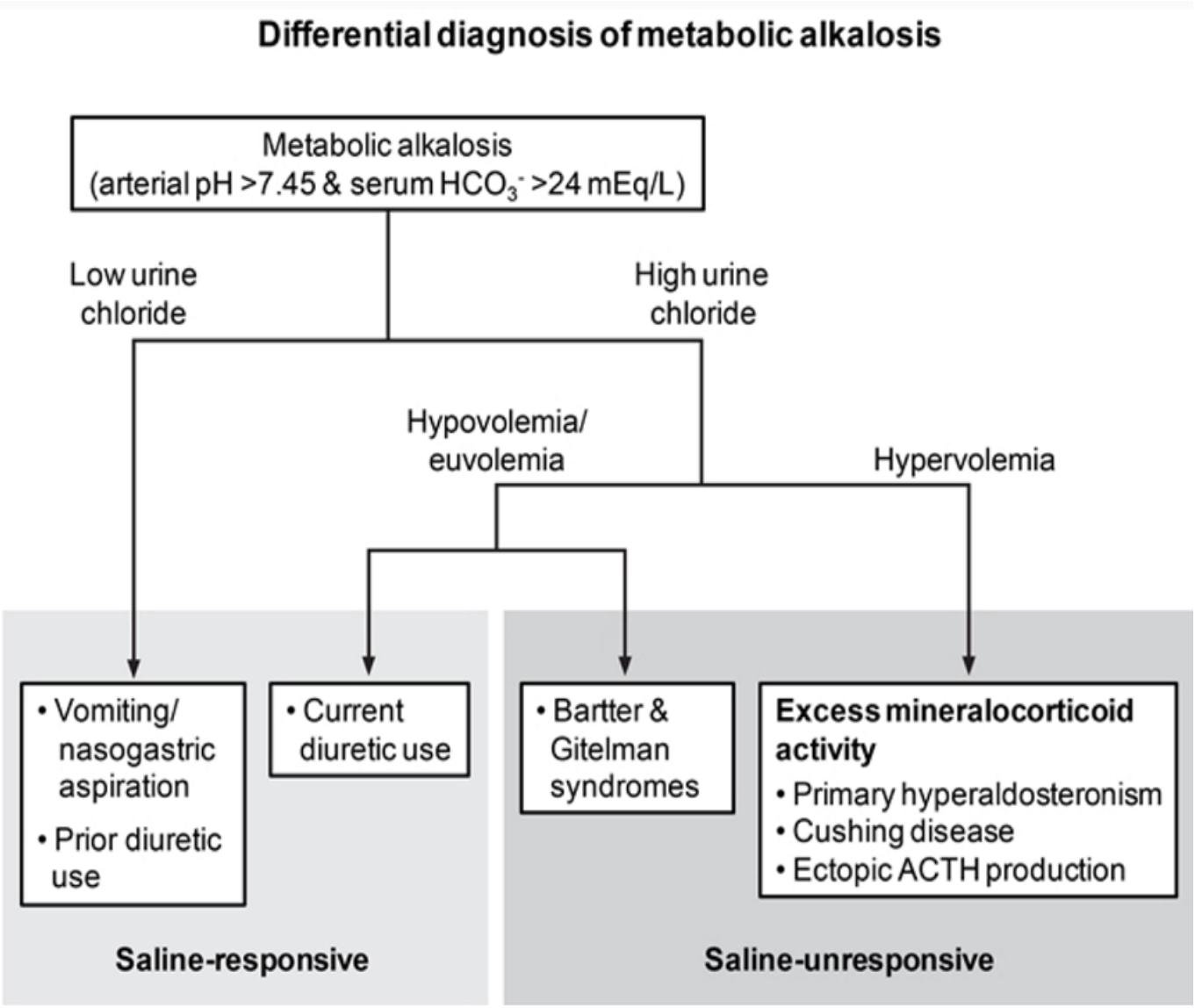
Example 3: What is the osis? pH is low, so acidosis. **Cause of the osis?** HCO_3^- is high, so respiratory acidosis. **Compensation?** Must determine if acute (uncompensated) or chronic (compensated). PCO_2 is 40 greater than normal, thus acute: $40 \times 0.1 = 4$, so HCO_3^- will be around 28 (24 + 4). If chronic, it will be $40 \times 0.35 = 14$, so HCO_3^- will be around 38 (24 + 14). The measured is much closer to the predicted acute, thus this is an **acute respiratory acidosis.**

Example 4: What is the osis? pH is high, so alkalosis. **Cause of the osis?** HCO_3^- is high, so metabolic alkalosis. **Compensation?** The respiratory compensation is to reduce ventilation, thereby increasing $PaCO_2$. Thus, we need to compute what $PaCO_2$ should be in a patient with this acid-base disorder. Calculation: HCO_3^- is 20 greater than normal of 24, $20 \times 0.7 = 14$, thus $PaCO_2$ should be 14 mm Hg greater than the normal of 40, thus $40 + 14 = 54$ (predicted $PaCO_2$). Patient's is 52, which is within 2, so this is a **metabolic alkalosis with respiratory compensation.**

Example 5: No pH is given, but we can still figure out the acid-base disorder. HCO_3^- is low, so this must be a metabolic acidosis or respiratory alkalosis (review Follow the Bicarbonate Trail). $PaCO_2$ is well above normal, ruling out a respiratory alkalosis, thus there is a **mixed metabolic and respiratory acidosis.** Note that $PaCO_2$ and HCO_3^- went in opposite directions, so we know there is a mixed disturbance. The low HCO_3^- indicates the metabolic acidosis, while the high $PaCO_2$ indicates respiratory acidosis. If this were simply a respiratory acidosis, HCO_3^- would be elevated, not reduced.

❖ N.B:

- Checking the patient's volume status and the urine chloride are important steps in the workup of metabolic alkalosis.



- The most common causes of metabolic alkalosis are:

1. Vomiting or nasogastric suctioning:

- Loss of H and Cl ions (hydrochloric acid) in gastric secretions causes a net gain of alkali in the body, leading to metabolic alkalosis.
- Loss of Cl (hypochloremia) also impairs HCO_3 excretion by the kidney, worsening the metabolic alkalosis.
- These patients present with hypotension (due to volume loss) and low urine Cl.
- The alkalosis can be corrected by volume and Cl- repletion with isotonic saline (saline-responsive).

2. Thiazide or loop diuretic use:

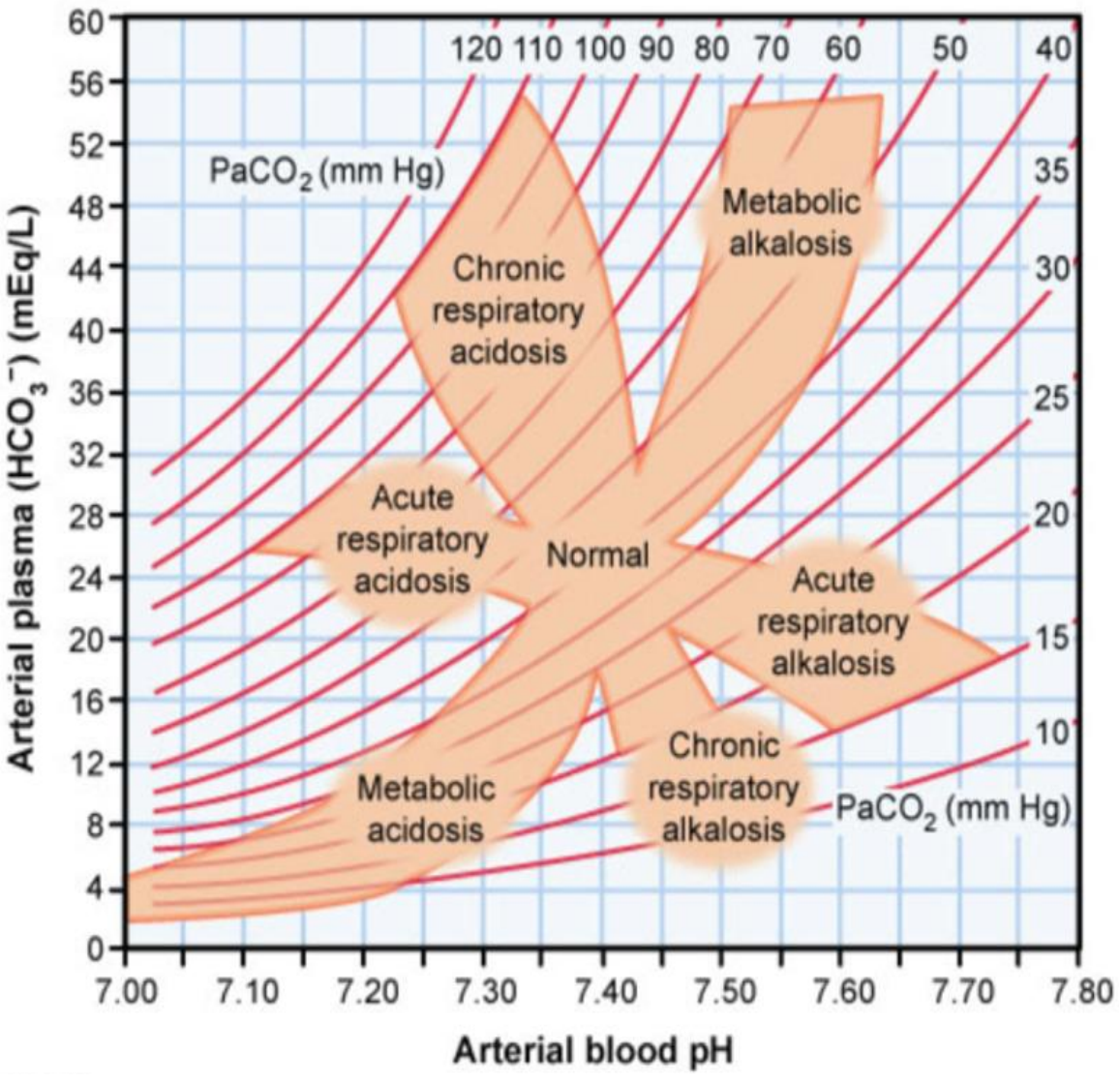
- Thiazide and loop diuretics block absorption of Na and Cl ions at the distal convoluted tubule and loop of Henle, respectively.
- As a result, distal delivery of NaCl increases while the ensuing volume depletion stimulates aldosterone secretion.
- These mechanisms increase Na reabsorption in the collecting tubule at the expense of increased K and H urinary losses, leading to metabolic alkalosis.
- Patients present with high urine Cl when diuretic use is ongoing, and low urine Cl after it is stopped.
- The alkalosis can be corrected by volume and NaCl repletion with isotonic saline (saline-responsive).

3. Mineralocorticoid excess state:

- The increased mineralocorticoid activity seen in primary hyperaldosteronism (Conn syndrome) or primary hypercortisolism (Cushing syndrome) is also associated with metabolic alkalosis.
- Persistent mineralocorticoid activity increases Na reabsorption and urinary K and H losses, leading to a relative increase in serum HCO_3.
- These patients present with hypertension and high urine Cl due to the expanded extracellular fluid volume causing pressure natriuresis.
- The alkalosis cannot be corrected with isotonic saline due to persistent mineralocorticoid activity (saline-unresponsive).

Davenport Diagram

- Horace Davenport developed a graphical display for the acid-base disorders and their compensations.
- Arterial pH is on the X-axis and HCO_3 is on the Y-axis.
- As stated earlier the Henderson-Hasselbach equation has three variables, pH, HCO_3, and PCO_2.
- If two are known, the third is fixed.
- Therefore, at a given pH and HCO_3 there can only be one value for CO_2, CO_2 isobars can be constructed and appears as curved lines on the graph.
- The CO_2 isobar of 40 must go through the normal point where pH = 7.4 and HCO_3 = 24.



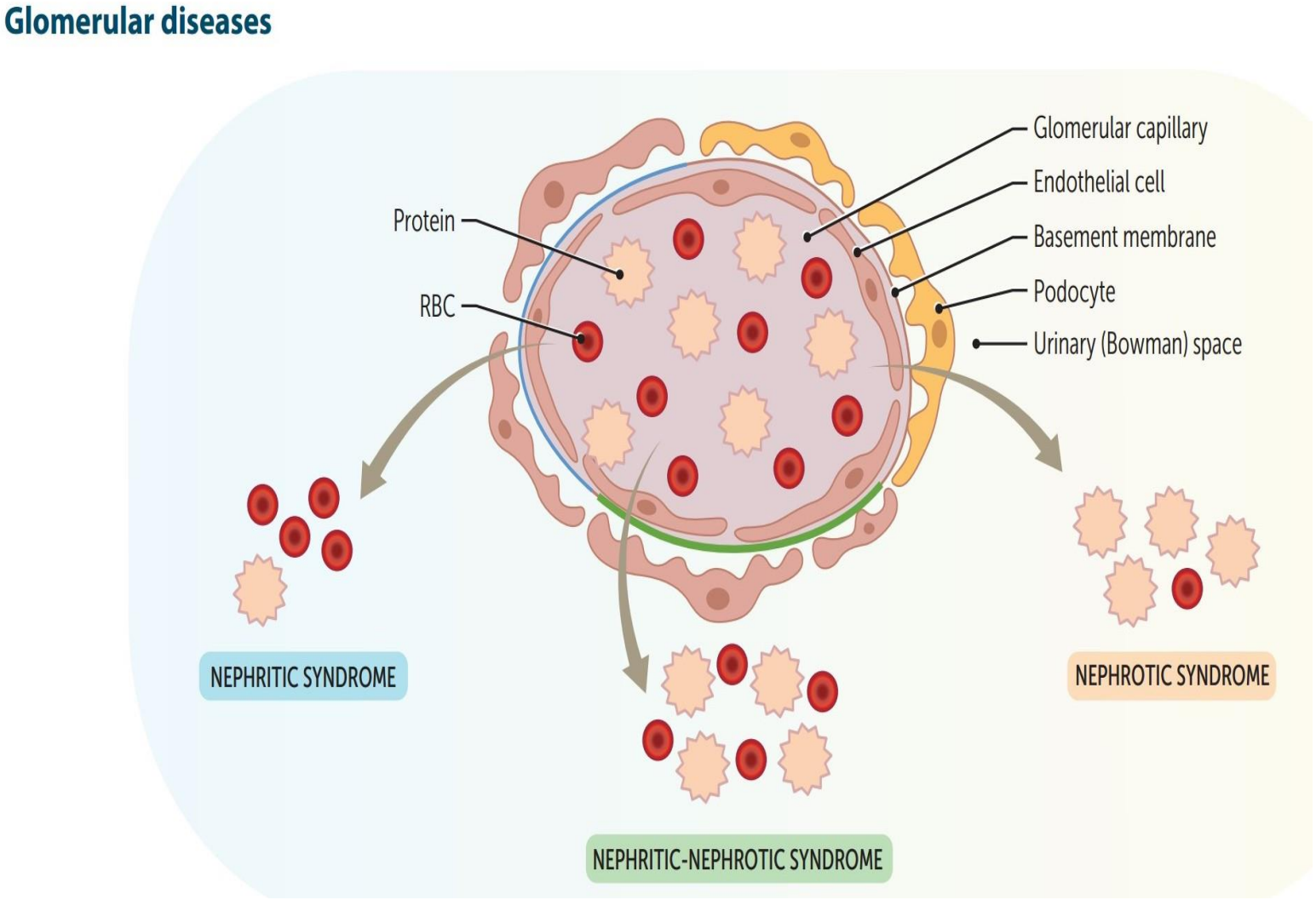
CHAPTER 4

Pathology

Glomerular diseases

❖ Nomenclature of glomerular disorders:

Type	Characteristics	Example
Focal	< 50% of glomeruli are involved	Focal segmental glomerulosclerosis
Diffuse	> 50% of glomeruli are involved	Diffuse proliferative glomerulonephritis
Proliferative	Hypercellular glomeruli	Membranoproliferative glomerulonephritis
Membranous	Thickening of glomerular basement membrane (GBM)	Membranous nephropathy
Primary glomerular Disease	A 1° disease of the kidney specifically impacting the glomeruli	Minimal change disease
Secondary glomerular Disease	A systemic disease or disease of another organ system that also impacts the glomeruli	SLE, diabetic nephropathy

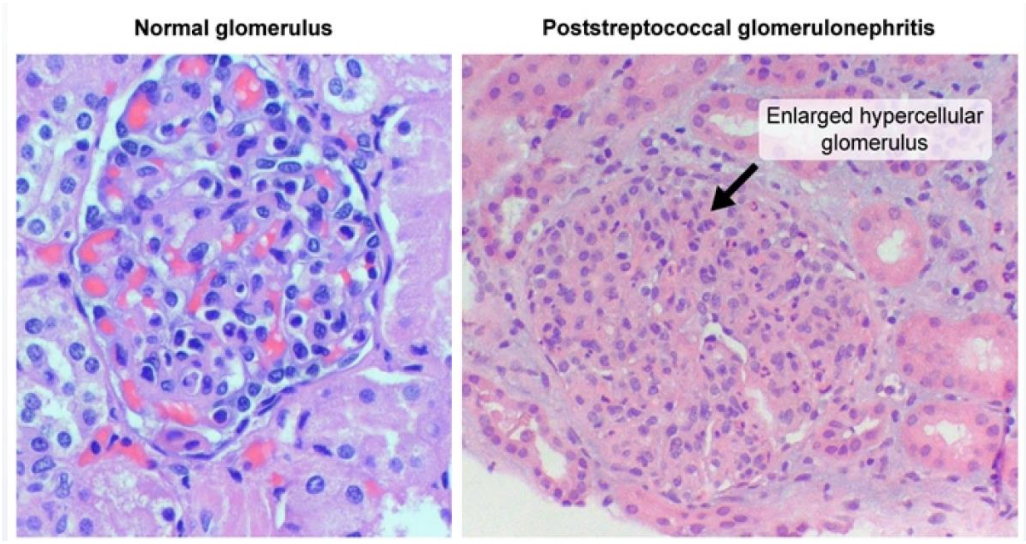


Nephritic syndrome

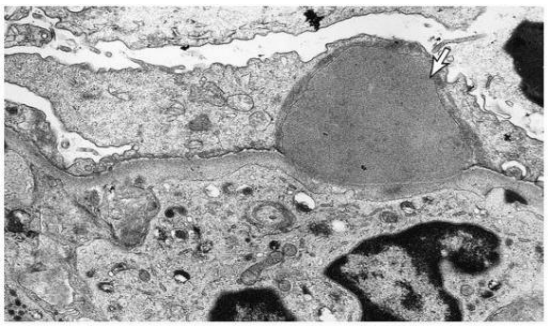
- NephrItic syndrome = Inflammatory process.
- Glomerular inflammation → GBM damage → loss of RBCs into urine → hematuria.
- Hematuria, RBC casts and dysmorphic RBCs in urine → ↓ GFR → oliguria, azotemia, ↑ renin release, salt retention with periorbital edema and hypertension.
- Proteinuria often in the subnephrotic range (< 3.5 g/day) but in severe cases may be in nephrotic range.
- Biopsy reveals hypercellular, inflamed glomeruli. Immune-complex deposition activates complement; C5a attracts neutrophils, which mediate damage.

1. Acute poststreptococcal glomerulonephritis:

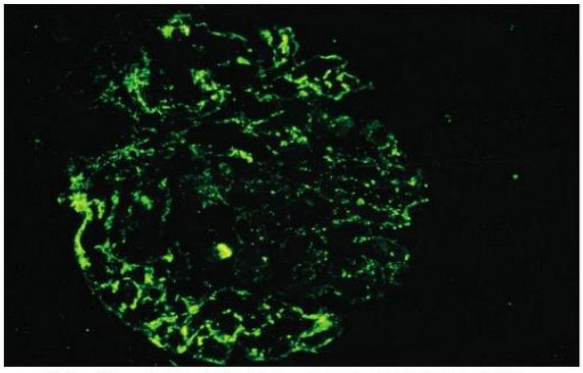
- Most frequently seen in children.
- Type III hypersensitivity reaction.
- Poststreptococcal glomerulonephritis usually manifests in 2-4 weeks after a streptococcal infection of either the pharynx ("strep throat") or skin (impetigo).
- The disease is caused by the nephritogenic strains of group A β-hemolytic streptococci (which carry the M protein virulence factor).
- It is an immune-complex mediated condition where antibodies to the streptococcal antigen form, bind streptococcal antigen circulating in the blood and subsequently fix complement in the glomeruli causing inflammation and kidney manifestations.
- This explains why there is a latent period between the actual streptococcal infection and the onset of the nephritis.
- Presents with peripheral and periorbital edema, tea or cola-colored urine, HTN.
- ⊕ strep titers/serologies (elevated antistreptococcal antibody (ASO) titers, or anti-DNase), ↓ complement levels (C3) due to consumption.
- Resolves spontaneously in most children; may progress to renal insufficiency in adults.
- LM:
  - The classic histologic picture is that of enlarged, hypercellular glomeruli.
  - The hypercellularity is diffuse (involves all lobules of all glomeruli) and is caused by leukocyte infiltration, and the proliferation of endothelial and mesangial cells.



- EM:
  - Electron microscopy shows subepithelial humps.
  - The electron-dense deposits on the epithelial side of the glomerular basement membrane (subepithelial humps) seen in patients with poststreptococcal glomerulonephritis represent immune complexes composed of IgG, IgM and C3.



- IF:
  - Immunofluorescence reveals coarse granular ("starry sky" granular appearance) deposits of IgG and C3 that have a characteristic "lumpy-bumpy" appearance.



- Treatment is supportive.

❖ N.B:

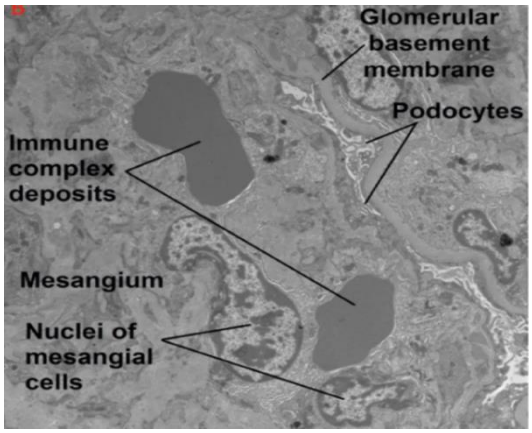
- When an older child or young adult presents with edema, hematuria and proteinuria a few weeks following a skin or pharyngeal infection, poststreptococcal glomerulonephritis (PSGN) is the most likely diagnosis.
- Age is the most important prognostic factor in patients with poststreptococcal glomerulonephritis.
- 95% of children recover completely with conservative therapy, 1-2 % develop chronic glomerulonephritis, and less than 1% progress to RPGN.
- The prognosis in adults is not as good. Only 60% of sporadic cases in adults will resolve completely; the rest will develop chronic glomerulonephritis or RPGN.

2. Diffuse proliferative glomerulonephritis (DPGN):

- Due to SLE or membranoproliferative glomerulonephritis.
- Most common cause of death in SLE.
- LM: "wire looping" of capillaries. (think "wire lupus").
- EM: subendothelial and sometimes intramembranous IgG-based ICs often with C3 deposition.
- IF: granular.
- DPGN and MPGN often present as nephrotic syndrome and nephritic syndrome concurrently.

3. IgA nephropathy (Berger disease):

- IgA immune complex deposition in mesangium of glomeruli; most common nephropathy worldwide.
- Presents during childhood.
- Presents as episodic gross or microscopic hematuria with RBCs casts, usually following mucosal infections (gastroenteritis or respiratory infection).
- IgA production is increased during infection.
- Patients usually present with painless hematuria 2-3 days following an upper respiratory tract infection.
- The hematuria typically lasts for several days and then subsides temporarily, returning every few months.
- LM: mesangial proliferation.
- IF: IgA-based IC deposits in mesangium.
- EM: mesangial IC deposition.
- The subsequent course is highly variable. Many patients maintain normal renal function for decades. In approximately 25-50% of cases, there is a slow Progression to chronic renal failure.



❖ N.B:

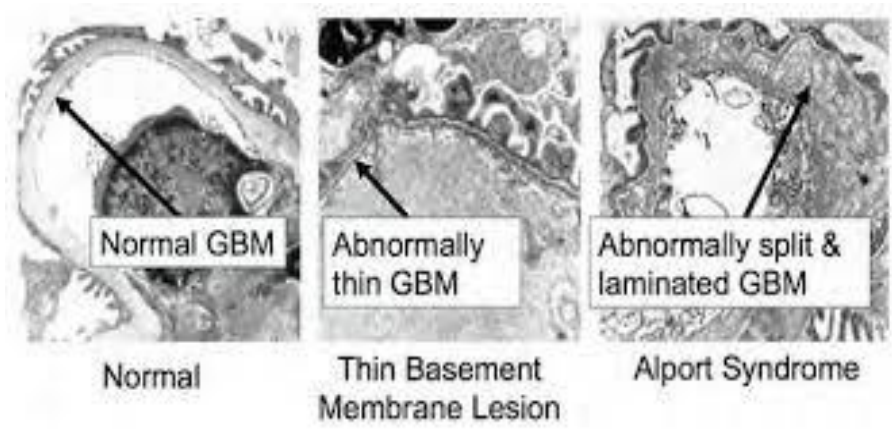
- When IgA nephropathy is accompanied by extrarenal symptoms (abdominal pain, purpuric skin lesions), the diagnosis is Henoch-Schonlein purpura.
- The following organ systems may be involved:

1. Skin: purpuric lesions on extensor surfaces of arms, legs, and buttocks.
2. Gastrointestinal syndrome: abdominal pain, vomiting, intestinal bleeding, and intussusception.
3. Renal involvement: IgA nephropathy.

- When the purpuric skin lesions are biopsied, light microscopy reveals a necrotizing vasculitis of the small dermal vessels and areas of subepidermal hemorrhage.
- Immunofluorescence microscopy shows IgA deposition in dermal capillaries.

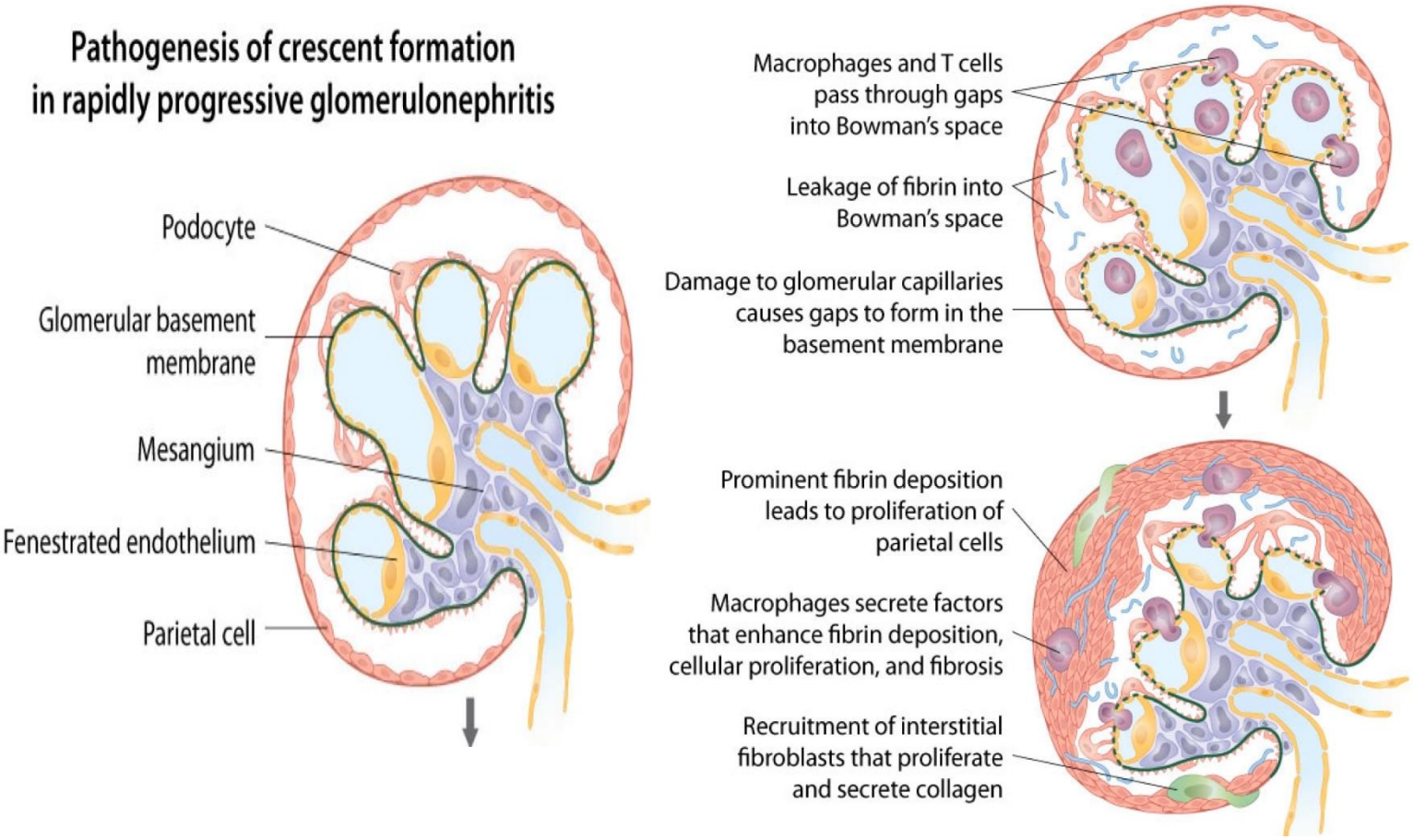
4. Alport syndrome:

- Mutation in alpha 3 chain of type IV collagen → thinning and splitting of glomerular basement membrane.
- Most commonly X-linked dominant.
- Eye problems (retinopathy, lens dislocation), glomerulonephritis, sensorineural deafness.
- "can't see, can't pee, can't hear a bee".
- EM: "basket-weave" appearance due to irregular thickening of GBM



4. Rapidly progressive (crescentic glomerulonephritis) RPGN:

- Nephritic syndrome that progresses to renal failure in weeks to months.
- Clinical picture and IF help resolve etiology.
- LM:
  - Crescent moon shape.
  - The presence of crescents in the damaged glomeruli on light microscopy is diagnostic of RPGN.
  - The crescents in RPGN consist of proliferated glomerular parietal cells, monocytes, and macrophages that have migrated into Bowman's space, as well as abundant fibrin between the cellular layers of the crescents.
  - Deposition of fibrin within Bowman's space is an essential pathologic step in crescent formation and finding of crescents on light microscopy is diagnostic of rapidly progressive glomerulonephritis (RPGN).
  - As the disease progresses, crescents become sclerotic and obliterate Bowman's space, thus impeding glomerular function.

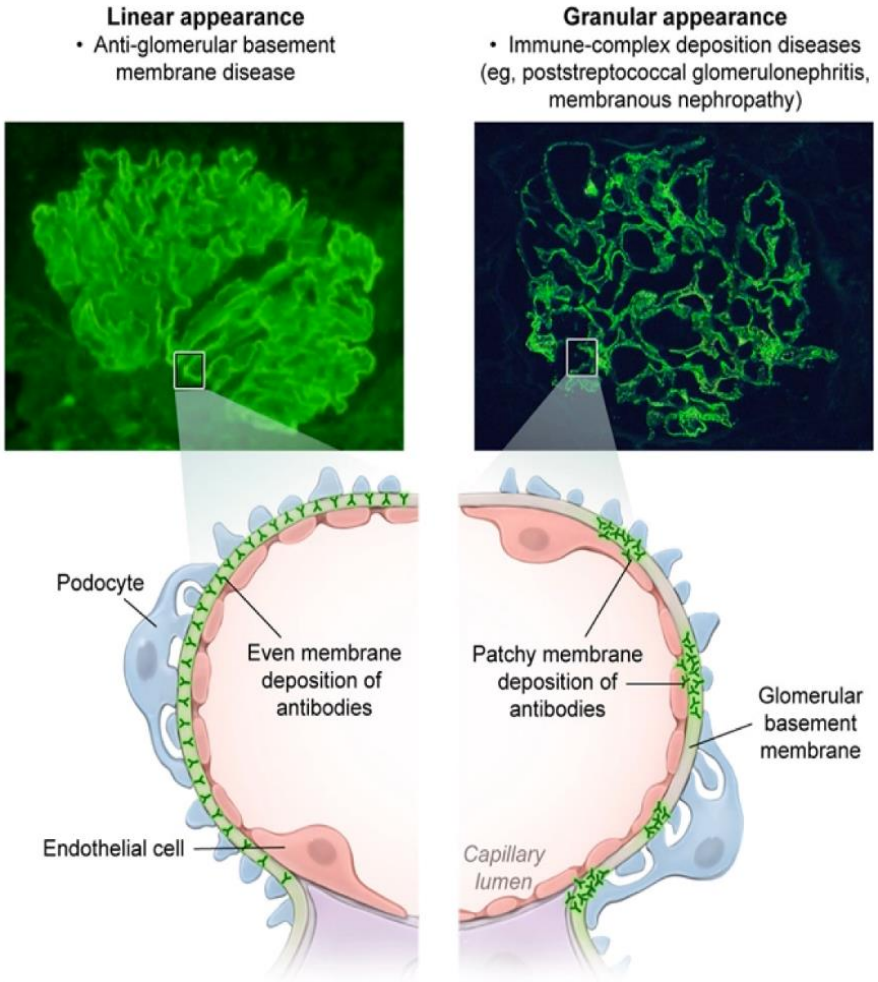


- RPGN can be caused by a number of different diseases.

- <u>RPGN is divided into 3 types based on immunologic findings:</u>

A. Type 1 RPGN (Linear IF):

- Type 1 RPGN is found in association with Goodpasture syndrome (anti-GBM disease).
- It is characterized by anti-glomerular basement membrane (anti-GBM) antibodies.
- On immunofluorescence, linear deposits of IgG and C3 along the glomerular basement membrane are characteristic.
- Anti-GBM antibodies cross-react with pulmonary alveolar basement membranes, producing pulmonary hemorrhages (hemoptysis).
- The combination of renal failure with pulmonary hemorrhage (hemoptysis) is the typical clinical presentation of anti-GBM disease.
- Treatment: plasmapheresis.



B. Type 2 RPGN (Granular IF):

- Type 2 RPGN can be a complication of poststreptococcal glomerulonephritis (most common), diffuse proliferative glomerulonephritis, SLE, IgA nephropathy, or Henoch-Schonlein purpura.

- It is immune-complex mediated.

- There is a "lumpy bumpy" granular pattern of staining on immunofluorescence microscopy.

C. Type 3 RPGN (Negative IF/Pauci-immune):

- This condition is often associated with granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis but can also be idiopathic.

- It is called "pauci immune" because there is no immunoglobulin or complement deposits on the basement membrane.

- Although crescent formation is obvious on light microscopy, there are no immunoglobulins or complement deposits found by immunofluorescent studies as in other types of RPGN, such as RPGN type 1 (anti-GBM disease or Goodpasture syndrome) and RPGN type 2 (immune complex-mediated disease).

- Most patients with type 3 RPGN have ANCA (anti-neutrophil cytoplasmic antibodies) in their serum.

- Patients with Wegener's present with renal failure, pulmonary symptoms (cough, dyspnea, hemoptysis), and upper respiratory tract symptoms (epistaxis, mucosal ulceration, chronic sinusitis).

❖ N.B:

- The presence of antibodies against neutrophil myeloperoxidase, also known as perinuclear staining antineutrophil cytoplasmic antibodies (p-ANCA), suggest microscopic polyangiitis.
- Antineutrophil Cytoplasmic antibodies are also called "ANCA":

- C-ANCA = anti-proteinase-3 antibodies.
- P-ANCA = anti-myeloperoxidase antibodies.

Wegener: C-ANCA. Microscopic polyangiitis: P-ANCA.

Pathological findings in nephritic syndromes

	Cause of glomerular injury	Characteristic biopsy features
Poststreptococcal glomerulonephritis	Antibodies against streptococcal antigens that deposit in GBM	IF - C3 granular staining along GBM EM - **Subepithelial humps**
Anti-GBM disease	Antibodies against type IV collagen in GBM	LM - Glomerular crescents IF - **Linear staining (IgG)** along GBM
Rapidly progressive glomerulonephritis	**Severe** immunologic injury (eg, anti-GBM antibodies, immune complex deposition)	LM - Glomerular **crescents** IF - Fibrin in crescents
IgA nephropathy	Deposition of IgA-containing complexes	LM - Mesangial hypercellularity IF - **IgA in mesangium**
Alport syndrome	Defective type IV collagen in GBM	EM - **Lamellated appearance of GBM**

EM = electron microscopy; **GBM** = glomerular basement membrane; **IF** = immunofluorescence; **LM** = light

Nephrotic syndrome

- Nephrotic syndrome is a condition marked by massive proteinuria (>3.5 g/day), hypoalbuminemia (<2.5 g/dL), generalized edema, hyperlipidemia, and lipiduria.

- The pathogenesis of nephrotic syndrome is detailed below:

1. The initial event is an increased permeability of the glomerular capillary wall to plasma proteins caused by structural or physicochemical changes:

- This leads to massive urine protein loss → Frothy, foamy urine.

- The protein loss is predominantly albumin, but globulins can also be lost in certain diseases.

2. Proteinuria leads to a decrease in the serum albumin concentration:

- The albumin loss is so dramatic that increased liver albumin synthesis cannot fully compensate.

- Thus, there is a drop in colloid osmotic pressure in the blood; as a result, fluid moves into the interstitial tissue, and edema occurs.

3. The fluid shift from the intravascular compartment into the interstitium results in a depletion of intravascular volume, thereby reducing renal perfusion pressure → This triggers the renin-angiotensin-aldosterone system, which leads to an increase in aldosterone synthesis (secondary hyperaldosteronism), resulting in sodium retention.

- The decreased intravascular volume also stimulates antidiuretic hormone (ADH) secretion, which increases water retention in the collecting ducts.

- The ultimate result is sodium and water retention.

- This sequence of events exacerbates the edema.

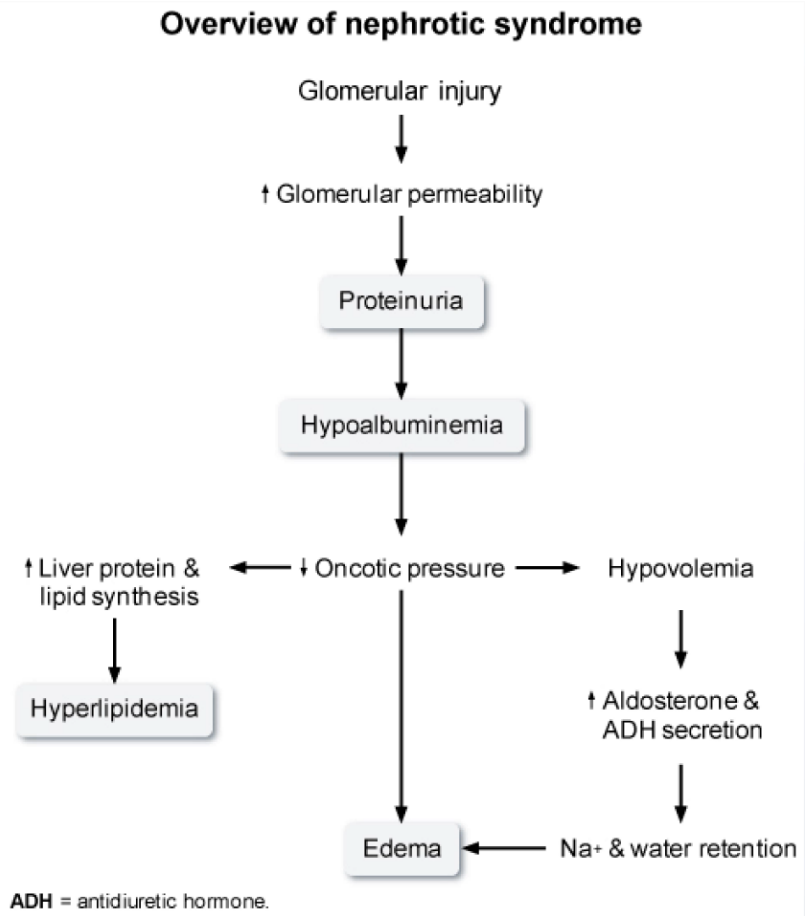
4. To compensate for the decreased plasma albumin concentration, the liver increases its synthesis of proteins, including lipoproteins.

- This increase in lipoprotein production, along with the decrease in lipid catabolism due to low plasma levels of lipoprotein lipase and abnormal transport of circulating lipid particles, contributes to the increased cholesterol, triglyceride, VLDL, LDL, lipoprotein, and apoprotein concentrations seen in nephrotic syndrome.

5. The increase in serum lipoproteins is followed by lipiduria. Hyperlipidemia and hypcrcholesterolemia → may result in fatty casts in urine

6. Associated with hypercoagulable state (thromboembolism) due to antithrombin (AT) III loss in urine and ↑ risk of infection due to loss of immunoglobulins in urine and soft tissue compromise by edema.

- Loss of anticoagulant factors, especially antithrombin III, is responsible for the thrombotic and thromboembolic complications of nephrotic syndrome. Renal vein thrombosis can be a manifestation of this hypercoagulable state.
- Patients present with sudden onset abdominal or flank pain and gross hematuria.
- When renal vein thrombosis occurs on the left side in male patients, the obstruction impedes venous flow from the left testis, and left-sided varicocele appears.



- Nephritic-nephrotic syndrome:

- Severe GBM damage → loss of RBCs into urine + impaired charge barrier → hematuria+ proteinuria.

- Nephrotic-range proteinuria (> 3.5 g/day) and concomitant features of nephrotic syndrome

- Can occur with any form of nephritic syndrome, but is most common with:
  - Diffuse proliferative glomerulonephritis.
  - Membranoproliferative glomerulonephritis.

- Although nephrotic syndrome can result from a number of different disease processes, the pathogenesis underlying its symptoms is consistent in the vast majority of patients.

1. Minimal change disease (lipoid nephrosis):

- The most common cause of nephrotic syndrome in children between 2 and 8 years old is minimal change disease (MCD), also called as lipoid nephrosis.

- MCD is caused by a primary defect in immunologic function, as suggested by its association with respiratory infections, immunizations, and atopic disorders, as well as its excellent response to steroid therapy.

- This immune dysfunction leads to overproduction of a specific cytokine (possibly IL-13) that causes direct damage to the podocytes, leading to retraction and fusion of the foot processes with reduced numbers of slit diaphragms as well as decreases anionic properties of GBM.

- This damage causes increased translocation of albumin, but not other serum proteins, through the podocyte barrier, resulting in selective albuminuria (loss of albumin, but not immunoglobulin).

- This results in a selective loss of albumin in the urine, in contrast to the nonselective proteinuria seen with other forms of nephrotic syndrome (membranous nephropathy, focal segmental glomerulosclerosis).

- Causes:
  - Often 1° (idiopathic) and may be triggered by recent infection, immunization, or with atopic disorders.
  - Rarely, may be 2° to Hodgkin lymphoma (cytokine-mediated damage).

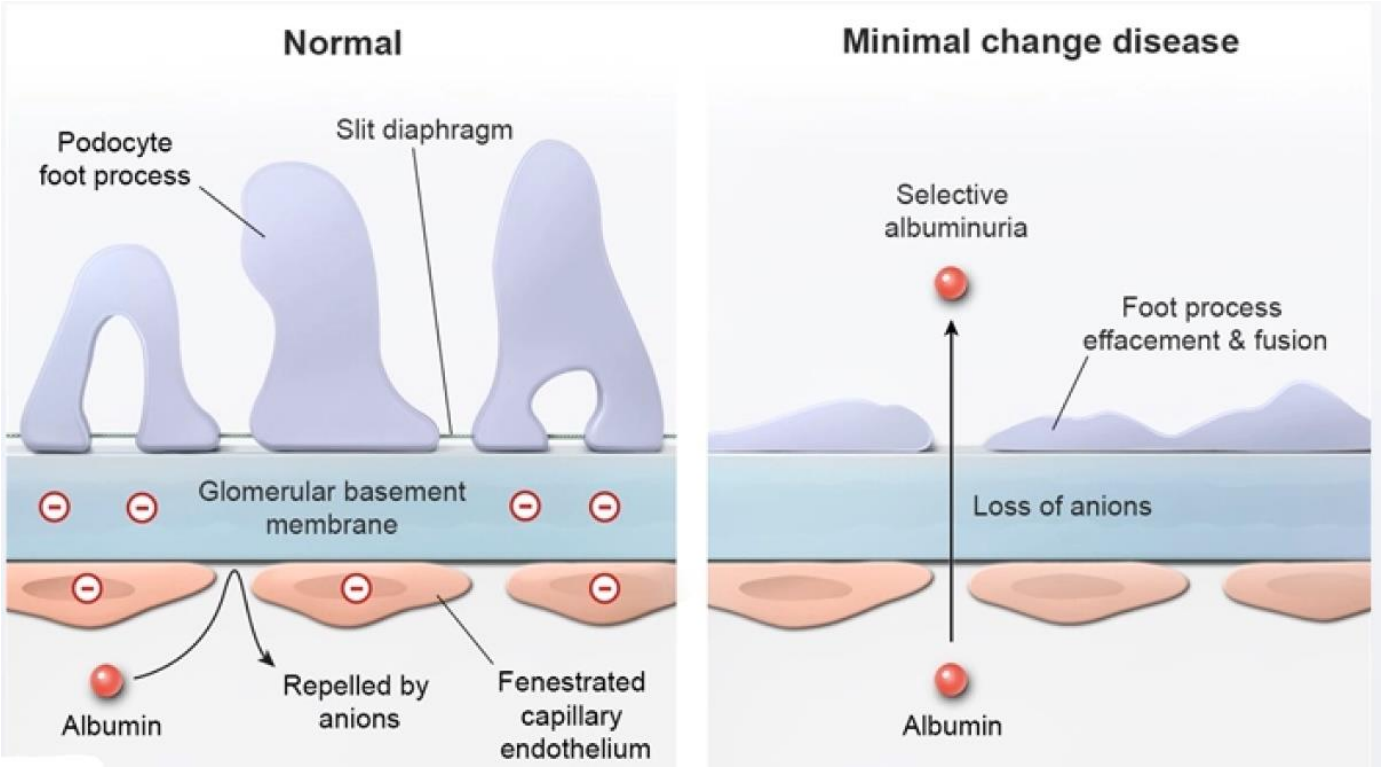
- LM: Light microscopy shows normal glomeruli.

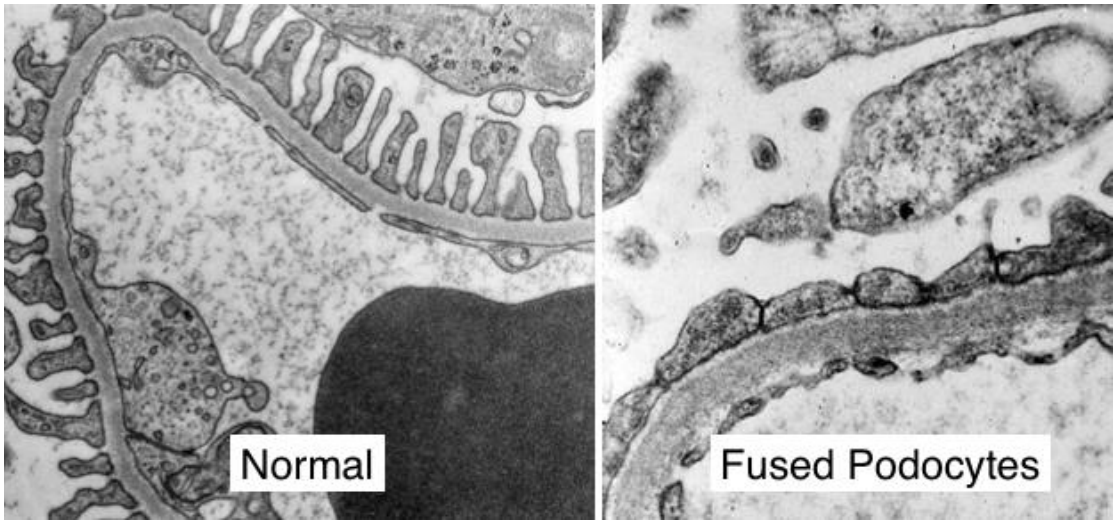
- EM: Pathognomonic finding is a diffuse effacement of the foot processes of podocytes found on electron microscopy.

- IF: immunofluorescence fails to reveal any immunoglobulin or complement deposits.

- Renal function is also normal.

- An important feature of this condition is its rapid response to corticosteroid therapy.





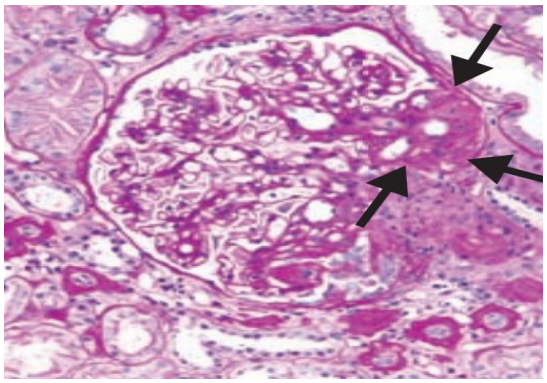
2. Focal segmental glomerulosclerosis (FSGS):

- Most common cause of nephrotic syndrome in Hispanics and African Americans.

- Focal (some glomeruli) and segmental (involving only part of the glomerulus) sclerosis on H&E stain.

- Can be 1° (idiopathic) or 2° to other conditions (HIV infection, sickle cell disease, heroin abuse, massive obesity, interferon treatment, chronic kidney disease due to congenital malformations).

- LM: segmental sclerosis and hyalinosis.



- EM: effacement of foot process similar to minimal change disease.

- IF: often ⊖ but may be ⊕ for nonspecific focal deposits of IgM, C3, C1.

- Poor response to steroids; progresses to chronic renal failure.

3. Membranous nephropathy:

- Most common cause of nephrotic syndrome in Caucasian adults.

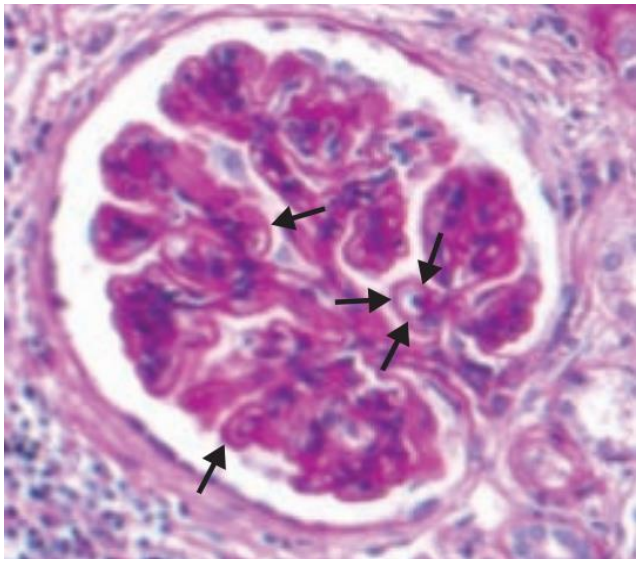
- Causes:

  - Usually idiopathic. Idiopathic membranous nephropathy is associated with circulating IgG4 antibodies to the phospholipase A2 receptor (PLA2R is a transmembrane receptor found in high concentrations in glomerular podocytes), which might play a role in the development of the disease.

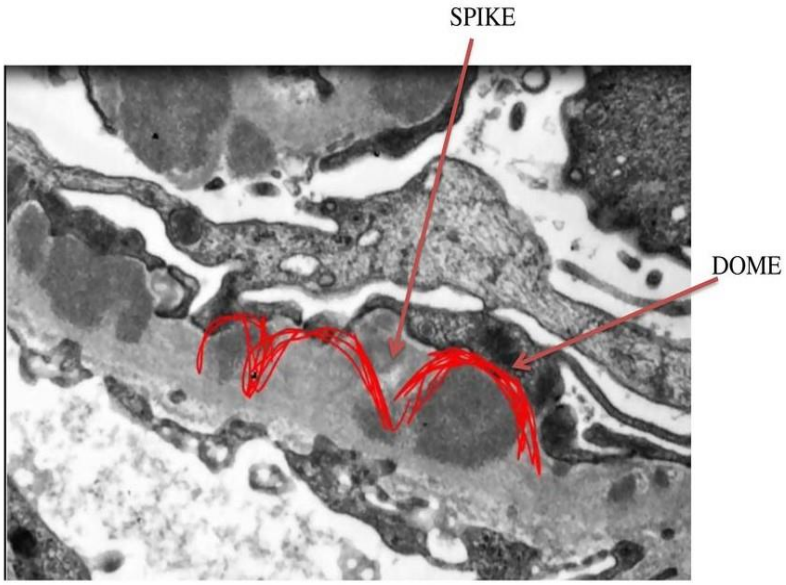
  - May be secondary to infections (hepatitis B or C), solid tumors, SLE (Nephrotic presentation of SLE), or drugs (NSAIDs and penicillamine).

- The presence of nephrotic syndrome and underlying malignancy suggest membranous glomerulopathy.

- LM: diffuse capillary and GBM thickening.



- EM: "spike and dome" appearance with subepithelial deposits.



- IF: granular as a result of immune complex deposition.

- Poor response to steroids; progresses to chronic renal failure.

4. Membranoproliferative glomerulonephritis (MPGN):

- MPGN is a form of glomerular disease that affects both the glomerular mesangium and the basement membrane.

- MPGN is a Nephritic-nephrotic syndrome: severe nephritic syndrome with profound GBM damage that damages the glomerular filtration charge barrier → nephrotic-range proteinuria (> 3.5 g/day) and concomitant features of nephrotic syndrome.

- Divided into two types based on location of deposits:

A. Type 1:

- Associated with HBV and HCV.

- Location of deposits: subendothelial IC deposits with granular IF.

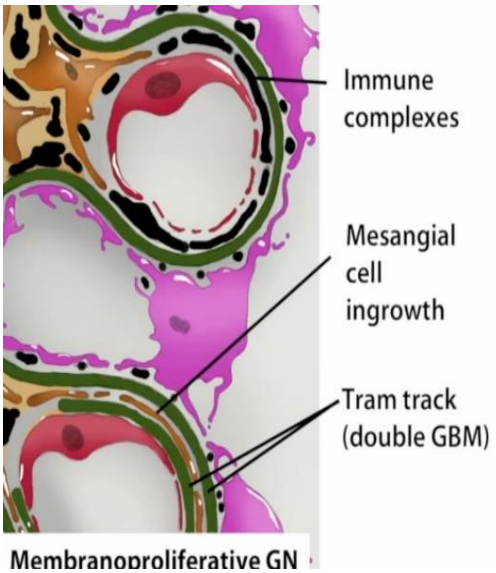
B. Type II (dense deposit disease):

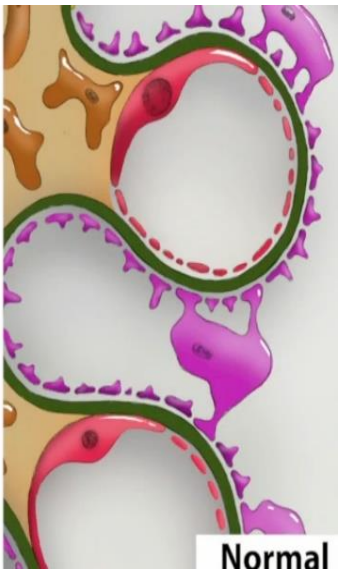
- Associated with C3 nephritic factor (autoantibody that stabilizes C3 convertase, leading to overactivation of complement, inflammation, and low levels of circulating C3)

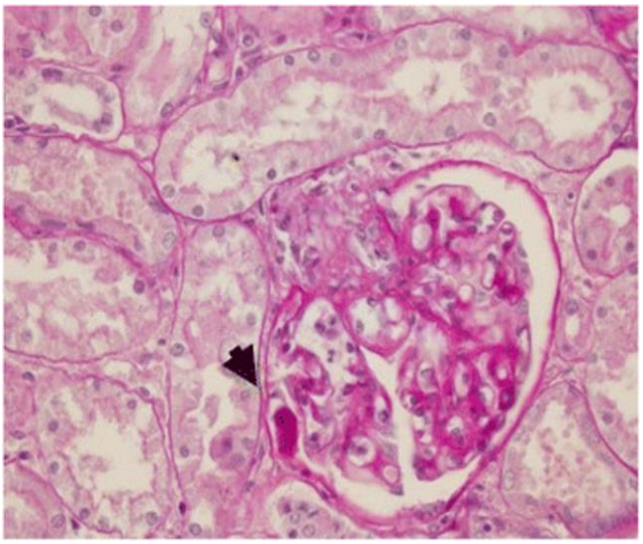
- Location of deposits: intramembranous deposits, also called dense deposit disease.

- LM: Both types → mesangial ingrowth → GBM splitting → "tram-track" on H&E and PAS E stains.

- Poor response to steroids; progresses to chronic renal failure.

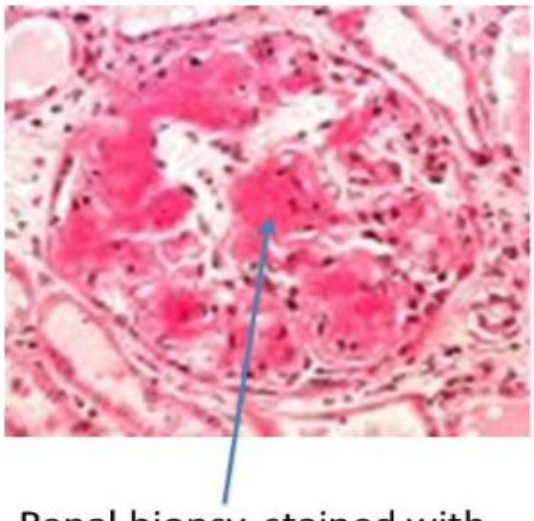




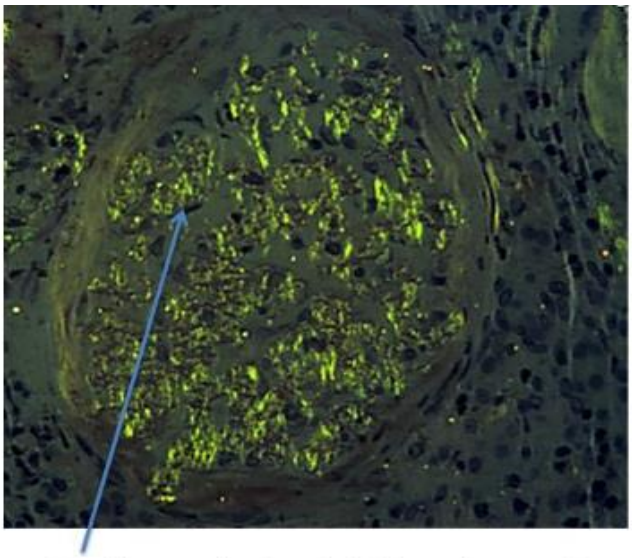


5. Amyloidosis:

- Kidney is the most commonly involved organ in systemic amyloidosis.
- Amyloid deposits in the mesangium, resulting in nephrotic syndrome.
- Characterized by apple-green birefringence under polarized light after staining with Congo red.
- LM: Congo red stain shows apple-green birefringence under polarized light.
- Associated with chronic conditions that predispose to amyloid deposition (AL amyloid, AA amyloid).



Renal biopsy, stained with Congo Red.



Under polarized light, the stain displays apple-green birefringence.

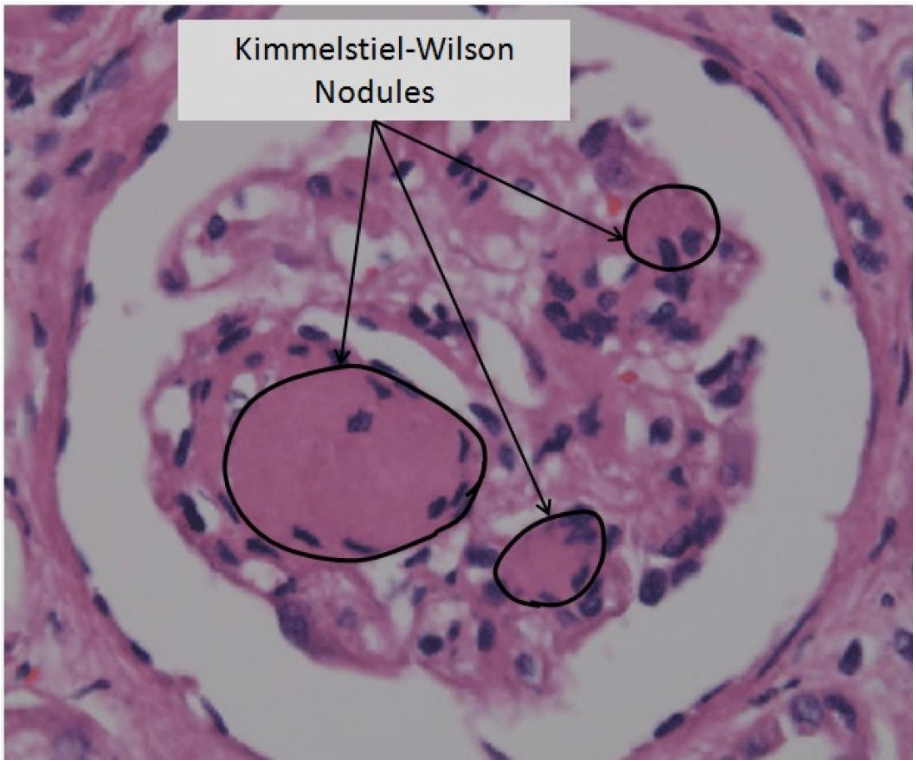
6. Diabetic glomerulonephropathy:

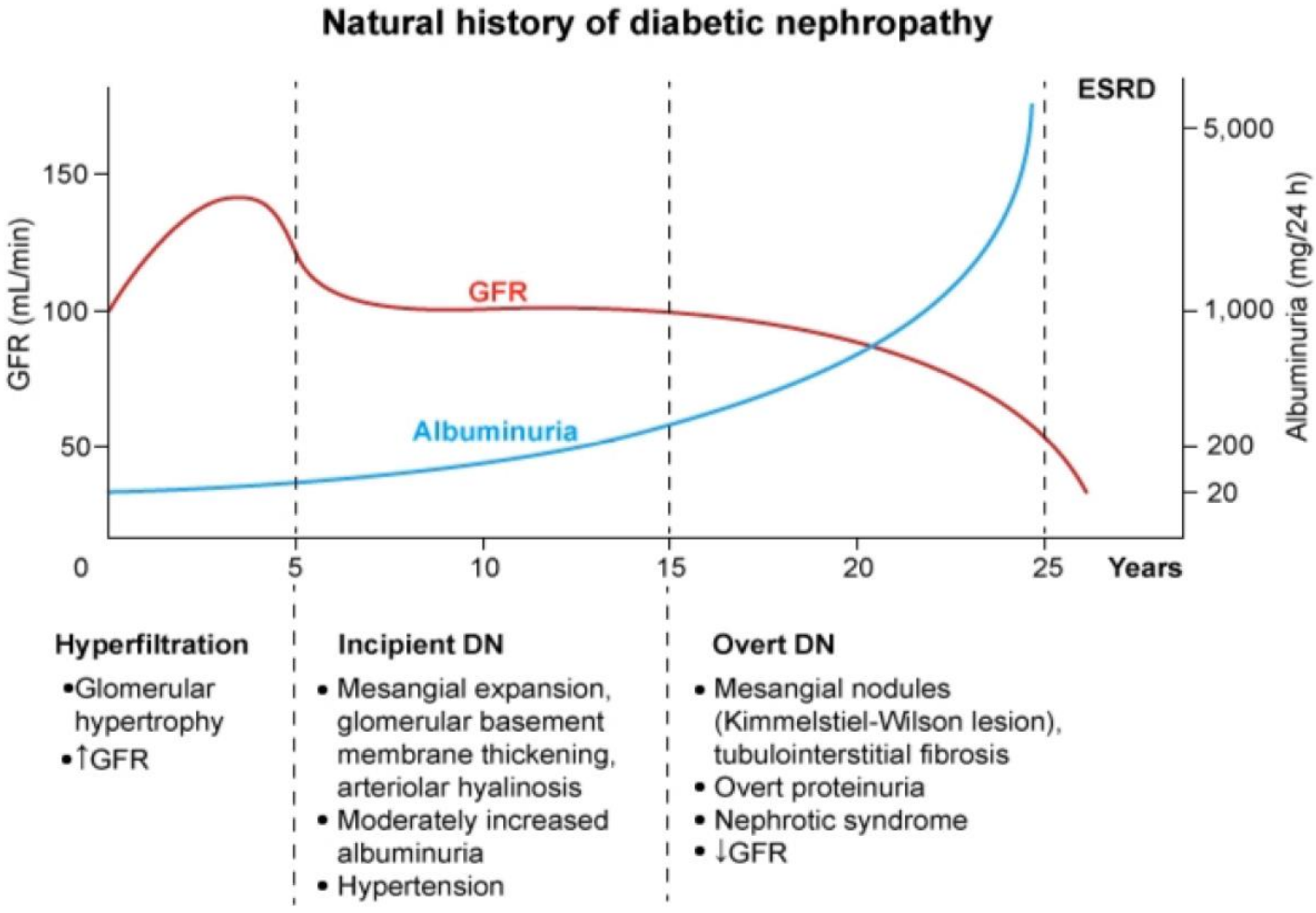
- Diabetic nephropathy is the most common cause of dialysis-requiring end stage renal disease in the United States, accountable for 30-40% of chronic renal failure.

- It occurs in both type I and type II diabetics.

- Pathogenesis:
  - A High serum glucose leads to non-enzymatic glycosylation of the vascular basement membrane resulting in hyaline arteriolosclerosis.
  - Non-enzymatic glycosylation of GBM → ↑ permeability, thickening.
  - None-nzymatic glycosylation of efferent arterioles → ↑ GFR → mesangial expansion.
  - Glomerular efferent arteriole is more affected than the afferent arteriole, leading to high glomerular filtration pressure.
  - Hyperfiltration injury → microalbuminuria.
  - Early detection of evolving diabetic nephropathy is accomplished by screening for microalbuminuria, which is defined as 30 to 300 mg/day in a 24-h collection or 30 to 300 micrograms of protein per milligram of creatinine in a spot collection.
  - Early detection of microalbuminuria allows earlier treatment.
  - Eventually progresses to nephrotic syndrome.
  - Characterized by sclerosis of the mesangium with formation of Kimmelstiel- Wilson nodules.
  - Nodular glomerulosclerosis (Kimmelstiel-Wilson disease), the morphologic sign that is pathognomonic for diabetic nephropathy.
  - K-W nodules are ovoid or spherical in shape, tend to be localized in the periphery of the glomerulus, are both laminated and eosinophilic on H&E stain and are PAS (+).
  - When the nodules enlarge, they may compress glomerular tufts and impair glomerular function.

- ACE inhibitors and ARBs slow progression of hyperfiltration-induced damage.





DN = diabetic nephropathy; **ESRD** = end-stage renal disease; **GFR** = glomerular filtration rate.

Nephrolithiasis

- Nephrolithiasis is a common disorder that usually presents clinically with unilateral flank pain, colicky pain radiating to groin, hematuria and the passage of a stone.

- Urine supersaturation is the main mechanism underlying renal stone formation.

- Thus, the concentration of stone-forming constituents, such as calcium, oxalate, and uric acid, is usually increased in patients with nephrolithiasis.

- Urine supersaturation can occur due to increased intake or increased excretion of these compounds.

- Low fluid intake also contributes to urine supersaturation, because the urinary concentrations of all stone-forming substances are increased. When supersaturation occurs, precipitation and aggregation of crystals follows.

- By increasing fluid intake, patients can help prevent the formation of all types of renal calculi, thus preventing stone formation. All patients with a history of nephrolithiasis should be advised to consume ample fluids.

1. Calcium oxalate and/ or calcium phosphate:

- The most common type of kidney stones are those composed of calcium salts, such calcium oxalate and calcium phosphate.

- Calcium stones represent 75% of all renal calculi. Calcium oxalate more common than calcium phosphate stones.

- Causes:

  - Most common cause is idiopathic hypercalciuria; hypercalcemia and its related causes must be excluded. In this condition, there is an increased concentration of calcium in urine, with normal serum calcium levels (normocalcemia, hypercalciuria).

  - Can result from ethylene glycol (antifreeze) ingestion, vitamin C abuse, hypocitraturia, malabsorption (Crohn disease).

- Precipitated with:

A. Calcium oxalate:

  - Precipitate with hypocitraturia.

  - A high urine citrate concentration has a stone-preventing effect, as citrate binds to free (ionized) calcium, preventing its precipitation and facilitating its excretion. Potassium citrate is often prescribed to prevent recurrent calcium stones in adults when dietary modifications are unsuccessful.

B. Calcium phosphate: ↑ Ph.

- Imaging: Radiopaque in x-ray and ct.

- Crystal shape: Shaped like envelope or dumbbell.

- Treatment: Hydrochlorothiazide (calcium-sparing diuretic), citrate and low Na diet.

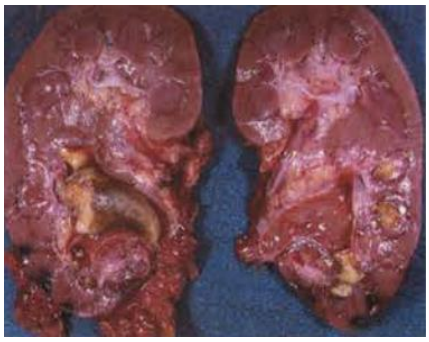
2. Ammonium, magnesium, phosphate:

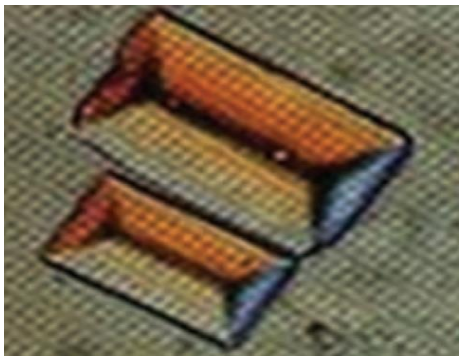
- Also known as struvite; account for 15% of stones (Second most common type).

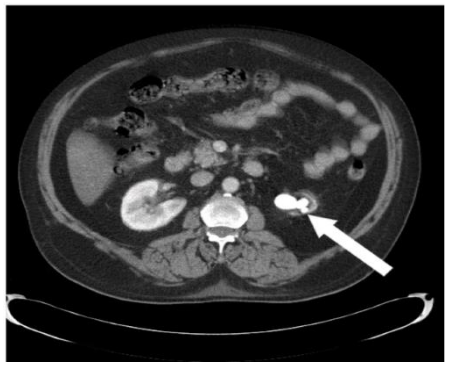
- Precipitated with:
  - ↑ urine Ph.
  - Most common cause is infection with urease-positive organisms (Proteus mirabilis, Staphylococcus, saprophyticus, Klebsiella) that hydrolyze urea to ammonia → urine alkalinization; alkaline urine leads to formation of stone.
  - Classically, results in staghorn calculi in renal calyces which act as a nidus for urinary tract infections.

- Imaging: Radiopaque in x-ray and ct.

- Crystal shape: coffin lid.







- Treatment: surgical removal of stone (due to size) and eradication of pathogen (to prevent recurrence).

3. Uric acid:

- Third most common stone (5%).

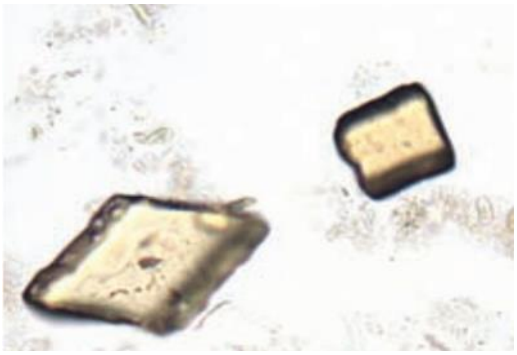
- Precipitated with: Uric acid is soluble at physiologic pH, but precipitates in an acidic Ph.

- Risk factors: increased uric acid concentration (high protein diets, gout, myeloproliferative disorders), increased urine concentration (hot arid climates, dehydration), certain inborn errors of metabolism (Lesch-Nyhan syndrome).

- Strong association with hyperuricemia (gout). Often seen in diseases with ↑ cell turnover (leukemia).

- Crystal shape: Rhomboid or rosettes.

- Imaging: radiolUcent (as opposed to other types of stones which are radiopaque) in x-ray and minimally visible on ct.



- Treatment: hydration and alkalinization of urine (potassium bicarbonate); allopurinol is also administered in patients with gout.

❖ N.B:

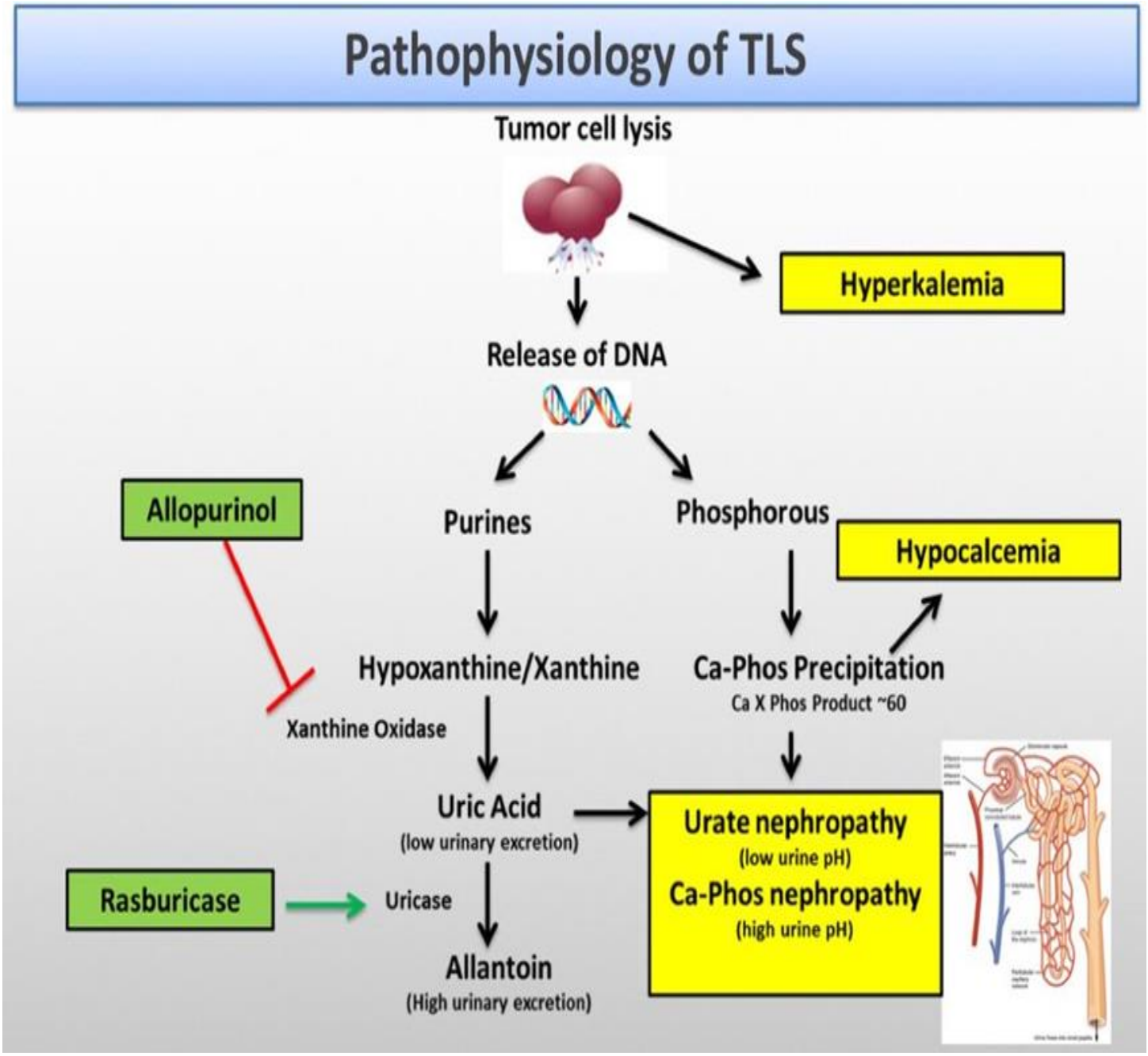
1. Patients with chronic diarrhea or those who have had a colectomy have reduced bicarbonate reabsorption from the gut → chronic metabolic acidosis.

- The kidneys compensate by increasing the excretion of hydrogen ions (H) and reabsorption of bicarbonate in the collecting ducts.
- This lowers urine pH (acidic urine), increasing the conversion of soluble urate ion into insoluble uric acid.

2. Tumor lysis syndrome is an oncologic emergency.

- It often develops during chemotherapy for high-grade lymphomas, leukemias, and other tumors that have rapid cell turnover and high sensitivity to chemotherapy.
- When a large number of tumor cells are destroyed during chemotherapy, intracellular ions, such as potassium, phosphorous, and uric acid (a metabolite of tumor nucleic acid), are released into the serum and are then filtered by the kidneys.
- Uric acid is soluble at physiologic pH, but precipitates in an acidic environment.

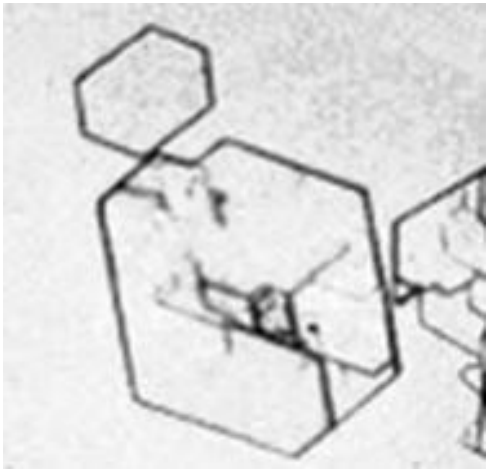
- The lowest pH along the nephron is found in the distal tubules and collecting ducts; so these are the segments of the nephron that become obstructed by uric acid crystals.
- Obstructive uropathy and acute renal failure follow.
- The risk of tumor lysis syndrome can be reduced by urine alkalinization and hydration. Additionally, allopurinol (a xanthine oxidase inhibitor) is used to reduce uric acid production during the breakdown of tumor cells.



4. Cystine:

- Hereditary (autosomal recessive) rare cause of nephrolithiasis, most commonly seen in children.

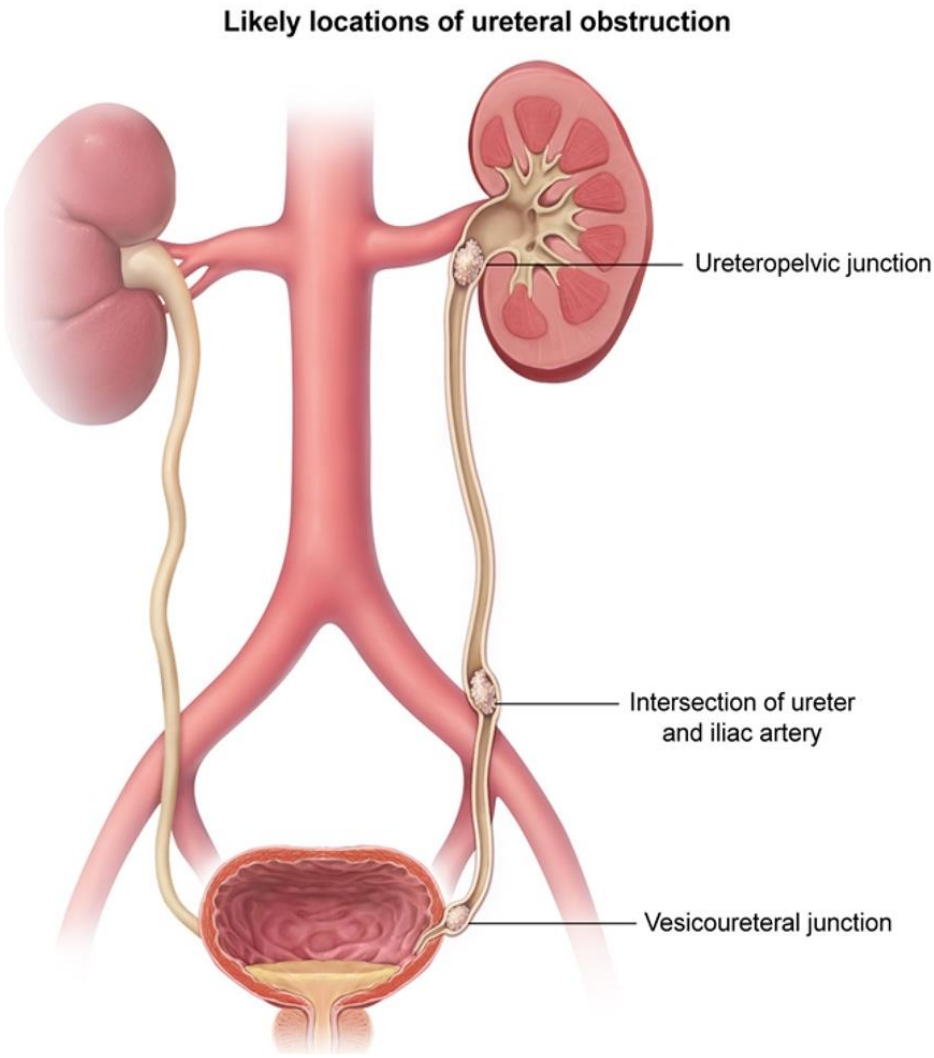
- Precipitated by:
  - Low urine pH.
  - Associated with cystinuria (a genetic defect of tubules that results in decreased reabsorption of cysteine).
  - Cystine, Ornithine, Lysine and Arginine (COLA) are dibasic amino acids that share a common transport mechanism in the kidney and intestinal lumen.
  - In the gut, these amino acids are reabsorbed via a high affinity transporter on jejunal cells.
  - In the kidneys, these substances are filtered at the glomerulus and reabsorbed by a similar transmembrane channel on proximal tubular cells.
  - Inherited defects of this transport channel lead to defects in renal and intestinal reabsorption, thus causing these amino acids to be excreted in urine and feces.
  - Ornithine, lysine, and arginine are soluble in urine; cystine, however, is relatively insoluble.
- The only clinical manifestation of this disorder is lifelong recurrent urolithiasis.
- It may form staghorn calculi in children.
- Imaging: faintly Radiopaque in x-ray and moderately radiopaque in ct.
- Crystal shape: hexagonal cystine crystals. "SIXtine" stones have SIX sides".



- Sodium cyanide nitroprusside test ⊕:
  - The detection of cystine in urine is important not only for establishing a diagnosis, but also for monitoring treatment effects and for predicting the rate of stone formation.
  - The sodium cyanide-nitroprusside test detects sulfhydryl groups, and is a rapid qualitative determinant of the presence of urine cystine.
  - The cyanide added to the urine converts cystine to cysteine.
  - The nitroprusside then binds cysteine, causing a purple discoloration in 2-10 minutes.
- Treatment of cystinuria involves hydration and alkalinization of urine.

❖ N.B:

- Recurrent nephrolithiasis in a young patient should alert you to the possibility of an inborn error of metabolism (cystinuria).
- Staghorn calculi in adults → most probably struvite stones.
- Staghorn calculi in children → most probably cystinuria.



Hydronephrosis

- Definition:

- Hydronephrosis is a dilation of the renal pelvis and calyces due to obstruction of urine flow.

- Causes:

- Nephrolithiasis, tumor (cervical cancer), anatomic abnormality, pregnancy, injury to ureter, or functional disorders (such as neurogenic bladder) are common causes.

- In older males, benign prostatic hyperplasia is the most common cause of urinary obstruction.

- Other causes include retroperitoneal fibrosis, vesicoureteral reflux.

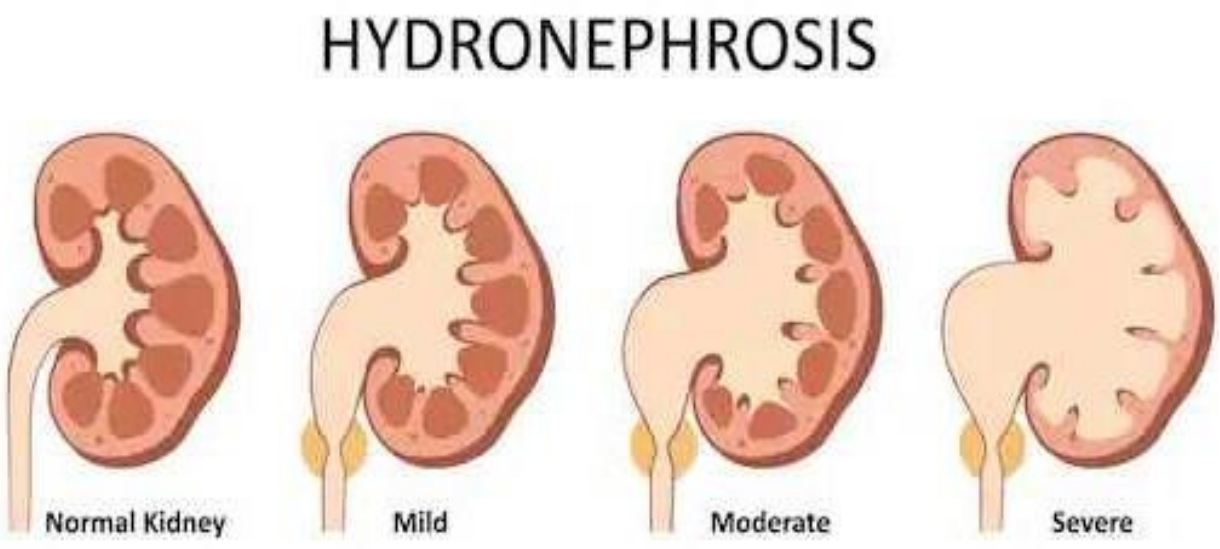
- Finding:

- The obstruction causes urinary stasis proximal to the blockage with gradually increasing urinary pressure and subsequent dilatation of ureters, urinary pelvis and calices.

- When urinary pressure reaches a critical level, it overcomes renal blood flow and disables glomerular filtration. Ischemia, nephron loss, and cortical atrophy follow.

- Serum creatinine becomes elevated only if obstruction is bilateral or if patient has only one kidney.

- Microscopic changes consist of dilation of the tubular lumen, flattening of the tubular epithelium, and interstitial fibrosis with patches of mononuclear infiltration.



Vesicoureteral reflux

- Definition:

- Vesicoureteral reflux is the most common pediatric urologic problem and is present in ~30%-45% of children with recurrent urinary tract infections (UTI).

- Normal urine should have unidirectional flow from the kidneys, ureters, bladder, and out the urethra.

- Patients with severe VUR have urinary reflux from the bladder into the kidney, and the regurgitant urine causes dilation of the ureters (hydroureter) and kidneys (hydronephrosis).

- Causes:

- The normal vesicoureteral junction does not allow retrograde flow of urine.

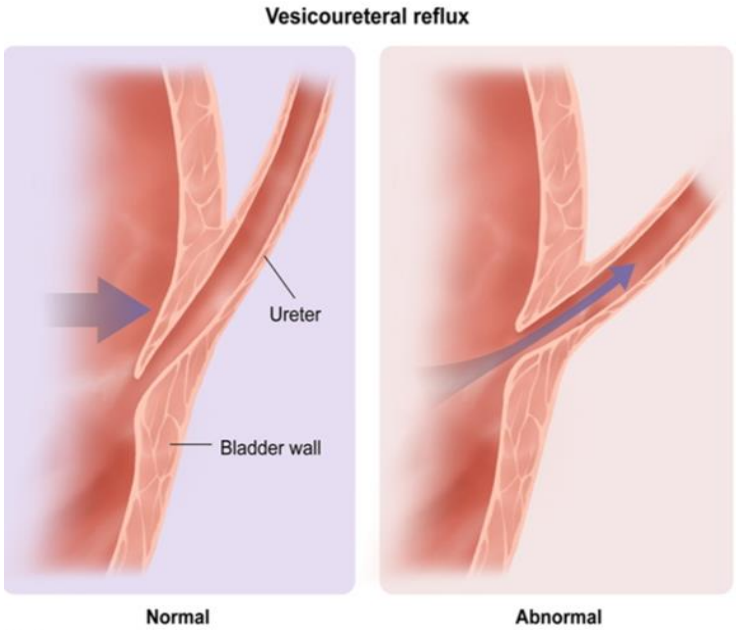
- If there is an anatomic abnormality of this area (short intramural ureter → fails to close completely during bladder contraction → VUR), or an increase in bladder pressure (posterior urethral valve), or recurrent cystitis (Frequent bladder infections may weaken the vesicoureteral junction and facilitate reflux), some urine returns to the ureter, bringing along any pathogens present in the bladder (vesicoureteral reflux).

- Finding:

- Recurrent and/or chronic pyelonephritis can lead to blunting of calices (calyceal clubbing) and focal parenchymal scarring, most commonly at the upper and lower poles of the kidney.

- Complications include parenchymal scarring, secondary hypertension, and renal insufficiency.

- Recurrent urinary tract infections (UTIs) in infants and children are a serious problem as they often involve the kidney and signify a congenital urinary tract anomaly → renal ultrasound to evaluate for anatomic abnormalities.



Urine incontinence

- **Definition:**

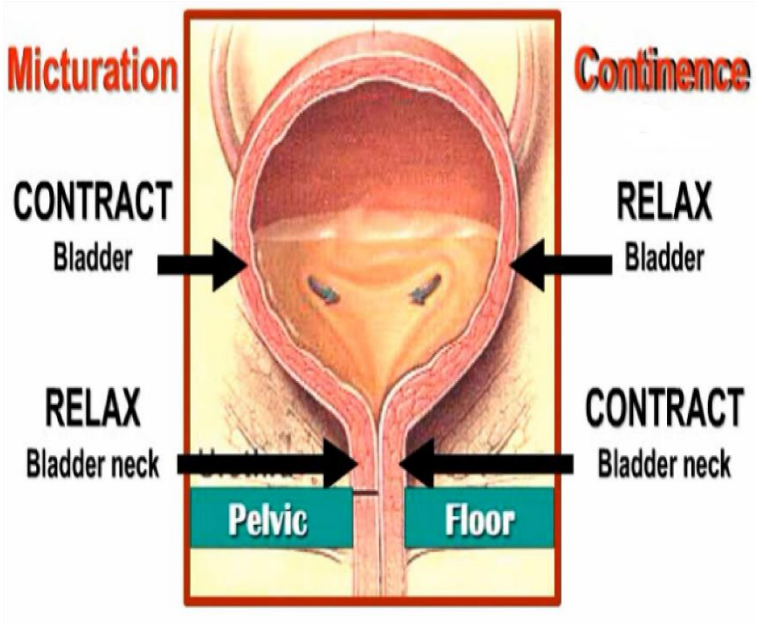
- Urinary incontinence is the inability to hold urine, producing involuntary urinary leakage.

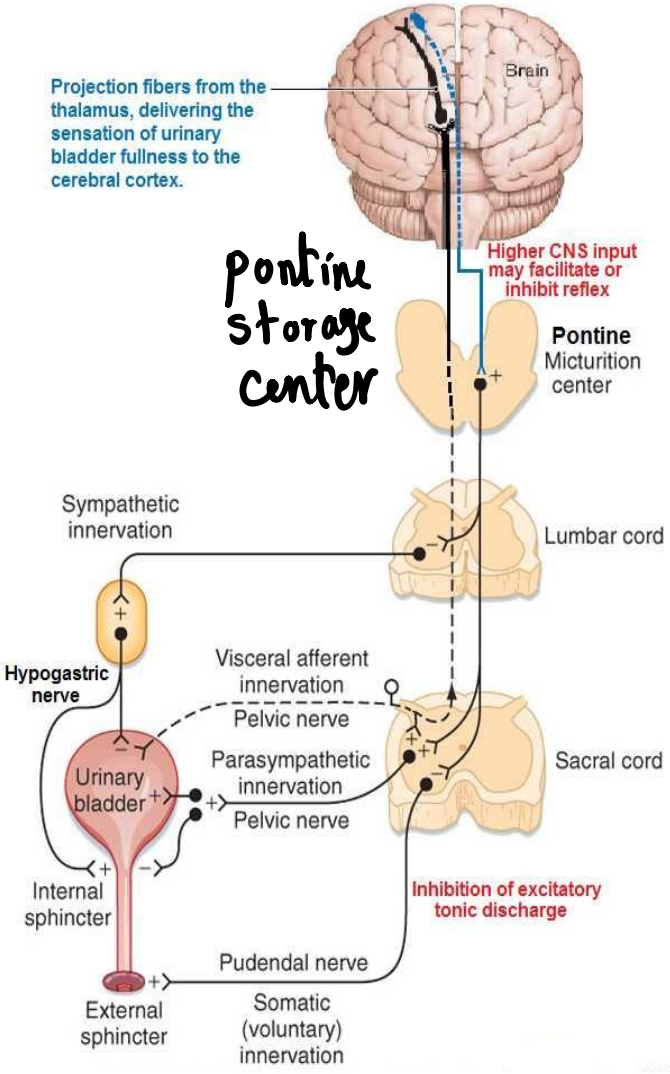
- **Physiology of Continence:**

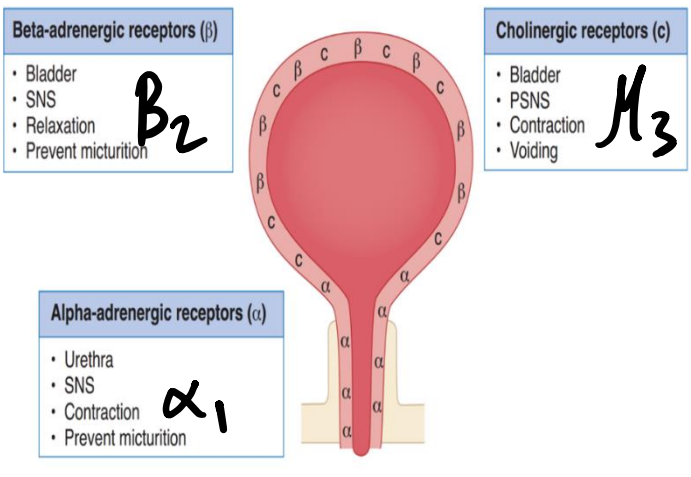
- Continence and micturition involve a balance between urethral closure and detrusor muscle activity.

- Urethral pressure normally exceeds bladder pressure, resulting in urine remaining in the bladder. The proximal urethra and bladder are normally both within the pelvis. Intraabdominal pressure increases (from coughing and sneezing) are transmitted to both urethra and bladder equally, leaving the pressure differential unchanged, resulting in continence.

- Normal voiding is the result of changes in both of these pressure factors: urethral pressure falls, and bladder pressure rises. Spontaneous bladder muscle (detrusor) contractions are normally easily suppressed voluntarily.







Stress Incontinence

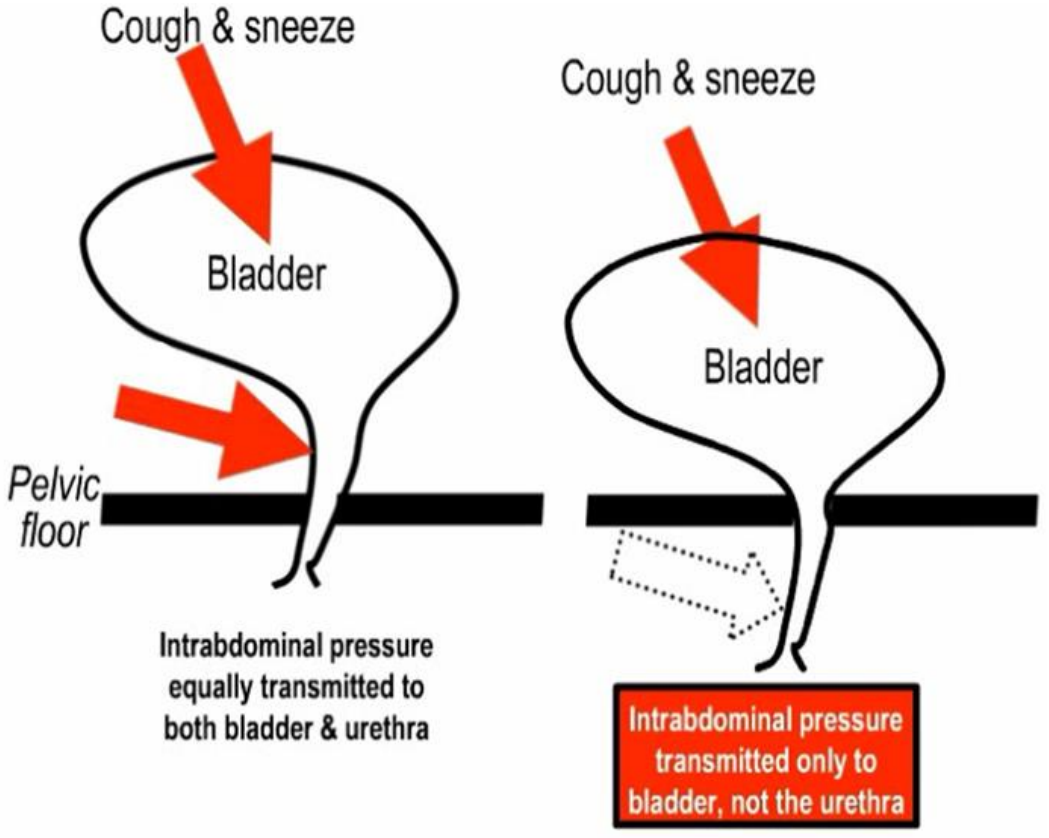
- Mechanism of incontinence:

- The pelvic floor (levator ani) muscles form a U-shaped sling around the pelvic viscera and hold the bladder and urethra in the appropriate anatomic position.

- Injury to the pelvic floor muscles can result in urethral hypermobility and urethral prolapse out of the pelvis → urethral sphincter dysfunction.

- Rises in bladder pressure because of intraabdominal pressure increases (coughing and sneezing) are not transmitted to the proximal urethra because it is no longer a pelvic structure owing to loss of support from pelvic relaxation.

- ⊕ bladder stress test (directly observed leakage from urethra upon coughing or Valsalva maneuver).



- Associations: Stress incontinence typically results from pelvic floor weakness, often in association with obesity, multiparity, pelvic and prostate surgery.

- Treatment: Pelvic floor muscle strengthening (Kegel) exercises which targets the levator ani muscle to improve support around the urethra and bladder, weight loss, pessaries.

Urge (Hypertonic) Incontinence

- Mechanism of incontinence:

- Involuntary rise in bladder pressure occur from idiopathic detrusor contractions that cannot be voluntarily suppressed.

- Detrusor overactivity → leak with urge to void immediately.

- Associations:

- UTI.

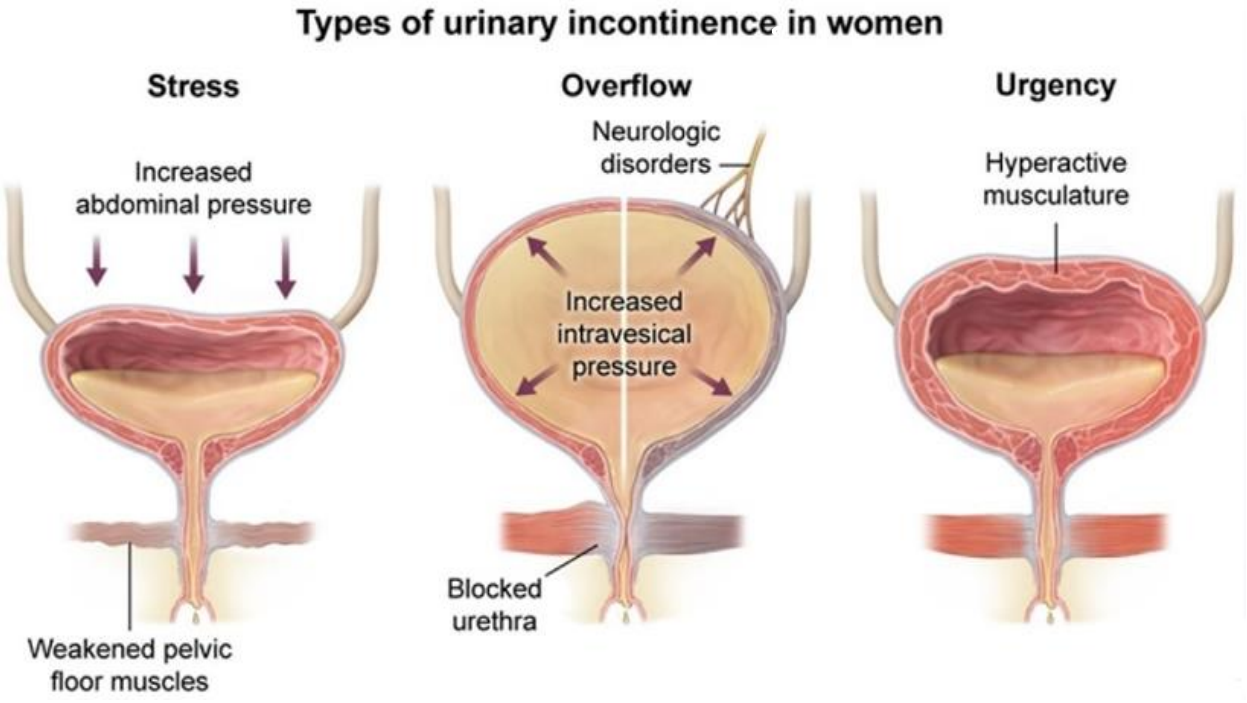
- Patients with multiple sclerosis often develop a spastic bladder a few weeks after developing an acute lesion of the spinal cord. The bladder does not distend/relax properly due to loss of descending inhibitory control from the upper motor neuron. As the disease progresses, the bladder can become atonic and dilated, leading to overflow incontinence.

- Urodynamic studies show little or no residual urine after emptying.

- Treatment:

- First-line treatments for urgency incontinence are bladder training and pelvic floor muscle exercises.

- Nonresponders can use an antimuscarinic agent (oxybutynin for overactive bladder) to decrease detrusor activity.



Overflow (Hypotonic) Incontinence

- Mechanism of incontinence:

- Rises in bladder pressure occur gradually from an overdistended, hypotonic bladder or due to outlet obstruction.

- When the bladder pressure exceeds the urethral pressure, involuntary urine loss occurs but only until the bladder pressure equals urethral pressure.

- The bladder never empties. Then the process begins all over.

- Associations:

- This may be caused by denervated bladder (diabetic neuropathy) or systemic medications (anticholinergics) or outlet obstruction (BPH).

- Diabetic autonomic neuropathy is common in type 1 diabetics. Patients initially have infrequent urination due to loss of autonomic afferent innervation and inability to sense a full bladder. Involvement of efferent fibers to the bladder subsequently causes incomplete emptying.

- Urodynamic studies show ↑ postvoid residual volume.

- Treatment: Catheterization, relieve obstruction (α-blockers for BPH).

❖ N.B:

- Mixed incontinence has features of both stress and urgency incontinence.

Urinary tract infection

- Infection of urethra, bladder, or kidney.
- Most commonly arises due to ascending infection; increased incidence in females.
- Females are more susceptible to UTIs due to having urethras that are both closer to the rectum and shorter than in males.
- Risk factors include sexual intercourse ("honeymoon cystitis"), urinary stasis, and catheters, diabetes mellitus, impaired bladder emptying.
- The bladder mucosa normally does not allow bacterial attachment; normal urine is bactericidal due to high urea content and high osmolarity; and urine flow washes the bacteria downstream.

Cystitis

- Infection of the bladder.
- Presents as dysuria, urinary frequency, urgency, and suprapubic pain; systemic signs (fever, chills) are usually absent.
- Urethritis and cystitis are both characterized by the clinical features of dysuria, frequency, urgency, pyuria, and bacteriuria, but suprapubic pressure and tenderness is more specific to cystitis.
- Etiology:
  - E coli (80%).
  - Stapliylococcus saprophytics: increased incidence in young, sexually active women (but E. coli is still more common in this population).
  - Klebsiella pneumoniae.
  - Proteus mirabilis: alkaline urine with ammonia scent.
- Laboratory findings:
  - Urinalysis: cloudy urine with> 10 WBCs/high power field (hpf).
  - Dipstick: Positive leukocyte esterase (due to pyuria) and nitrites (indicate gram ⊖ organisms, especially E coli convert nitrates to nitrites).
  - Culture: greater than 100,000 colony forming units (gold standard).
  - Sterile pyuria is the presence of pyuria (> 10 WBCs/hpf and leukocyte esterase) with a negative urine culture.

- Sterile pyuria and ⊖ urine cultures suggest urethritis by Neisseria gonorrhoeae or Chlamydia trachomatis.

▪ Treatment: antibiotics (TMP-SMX, nitrofurantoin).

Pyelonephritis

▪ Infection of the kidney.

▪ Causes:

- Usually due to ascending infection (E coli is most common); increased risk with vesicoureteral reflux.

- Hematogenous spread to kidney.

▪ Risk factors:

- Risk factors include indwelling urinary catheter, urinary tract obstruction, vesicoureteral reflux, diabetes mellitus, pregnancy.

- Vesicoureteral reflux is necessary in the pathogenesis of acute pyelonephritis; without reflux, bacteria remain localized in the bladder and do not reach the ureters or renal tissue.

1. Acute pyelonephritis:

▪ If pathogens ascend via the ureter to penetrate kidney parenchyma, systemic signs of the disease become prominent.

▪ Acute pyelonephritis manifests clinically with flank and abdominal pain, fever, shaking chills, nausea, and vomiting in addition to symptoms of cystitis

▪ Costovertebral angle tenderness is commonly found on physical examination.

▪ Urinalysis shows pyuria, WBC casts, bacteriuria, and often hematuria.

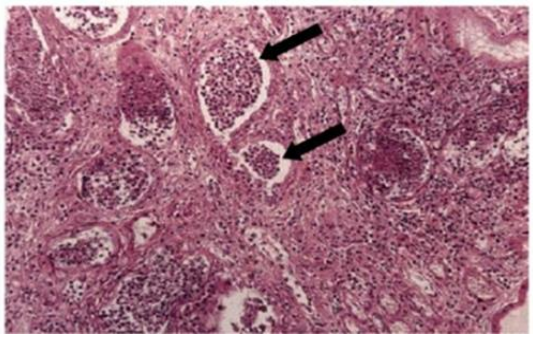
▪ Pyuria and bacteriuria are non-specific and are found in both upper and lower UTIs, but WBC casts are pathognomonic for pyelonephritis when UTI is present.

▪ WBC casts are formed in tubules and are pathognomonic for acute pyelonephritis when accompanied by systemic manifestations of febrile illness.

▪ WBC casts are also seen with acute interstitial nephritis, but clinical presentation is different.

▪ The image above shows massive infiltration of the interstitium by polymorphonuclear leukocytes (neutrophils) as well as a large number of neutrophils in the tubular lumina (arrows). This is the typical

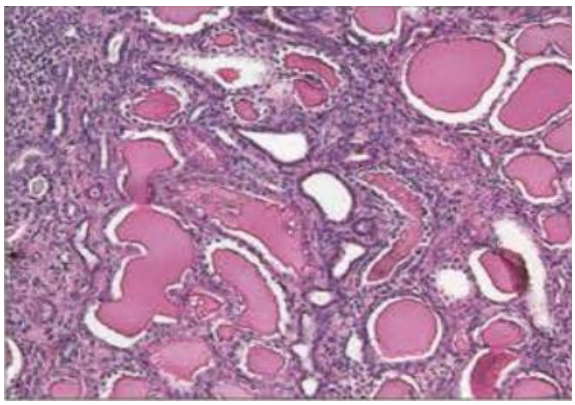
microscopic presentation of acute pyelonephritis, which can be easily distinguished from normal kidney by the diffusely increased cellularity and WBC casts.

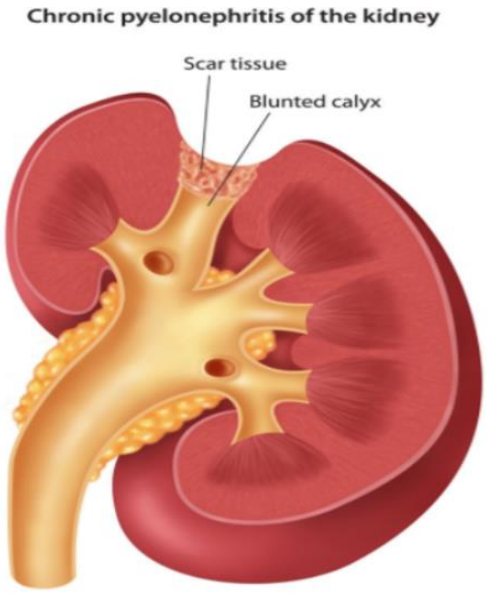


- Complications include chronic pyelonephritis, renal papillary necrosis, perinephric abscess, urosepsis.

2. Chronic pyelonephritis:

- Interstitial fibrosis and atrophy of tubules due to multiple bouts of acute pyelonephritis.
- Due to vesicoureteral reflux (children) or obstruction (BPH or cervical carcinoma).
- Leads to cortical scarring with blunted calyces: scarring at upper and lower poles is characteristic of vesicoureteral reflux.
- Atrophic tubules containing eosinophilic proteinaceous material resemble thyroid follicles (thyroidization of the kidney); waxy casts may be seen in urine.





3. Xanthogranulomatous pyelonephritis:

- It is rare; grossly orange nodules that can mimic tumor nodules; characterized by widespread kidney damage due to granulomatous tissue containing foamy macrophages.
- Associated with Proteus infection.

❖ N.B:

- Catheter-associated urinary tract infection (UTI) is a frequent complication in hospitalized patients.
- Common symptoms are fever and pyuria.
- Suprapubic, flank, and costovertebral tenderness and new-onset altered mental status (delirium) can also occur.
- The diagnosis is based on a positive urine culture and ruling out other systemic infections (pneumonia).
- Duration of catheterization is the most significant risk factor for UTI. Preventive measures include avoiding unnecessary catheterization, using sterile technique when inserting the catheter, and removing the catheter promptly when no longer needed.

Renal failure

Acute kidney injury

- Acute kidney injury (AKI), formerly called acute renal failure (ARF), which you may encounter as a synonym, is defined as abrupt decline in renal function resulting in a sudden rise in BUN and creatinine over several hours to days.

- Hallmark is azotemia (Increased nitrogenous waste products in the blood, urea and creatinine), often with oliguria (low urine output).

- AKI is classified as prerenal, postrenal, or intrarenal to determine the site of the defect.

- Develops fairly rapidly and is generally reversible:

A. Prerenal azotemia:

- Pathophysiology:
  - Due to decreased blood flow to kidneys; common cause of ARF.
  - Decreased blood flow results in → ↓ GFR, azotemia, and oliguria.
  - Reabsorption of fluid and BUN ensues (serum BUN:Cr ratio> 20); tubular function remains intact (fractional excretion of sodium, FENa < 1% and urine osmolality > 500 mOsm/kg).
  - Increased renin and Angiotensin II.

- Etiology:
  - Hypovolemia.
  - ↓ Cardiac output.
  - ↓ Effective circulating volume (HF, liver failure).

- Urine osmolarity (mOsm/kg): > 500.

- Urine Na (mEq/L): <20.

- EE_{Na}: <1%.

- Serum BUN/Cr: >20 (BUN is reabsorbed, creatinine is not).

B. Postrenal azotemia:

- Pathophysiology:
  - Due to obstruction of urinary tract downstream from the kidney (bilateral).
  - Decreased outflow results in ↓ GFR, azotemia, and oliguria.

- During early stage of obstruction, increased tubular pressure" forces" BUN into the blood (serum BUN:Cr ratio> 20); tubular function remains intact (FENa < 1% and urine osm > 500 mOsm/kg).

- With long-standing obstruction, tubular damage ensues, resulting in decreased reabsorption of BUN (serum BUN:Cr ratio < 15), decreased reabsorption of sodium (FENa > 2%), and inability to concentrate urine (urine osm < 500 mOsm/kg).

- Etiology:
  - Stones.
  - BPH.
  - Neoplasm.
  - Congenital anomalies.

- Urine osmolarity (mOsm/kg): Varies.

- Urine Na (mEq/L): Varies.

- EE_{Na}: Varies.

- Serum BUN/Cr: Varies.

C. Intrarenal:

- Pathophysiology:
  - In ATN, patchy necrosis → debris obstructing tubules and fluid backflow → ↓ GFR.

  - In ATN, epithelial/granular casts.

- Etiology:

A. Tubules and interstitium:
  - Acute tubular necrosis (ischemia, sepsis, infection, nephrotoxins).
  - Acute interstitial nephritis.

B. Glomerulus: Acute glomerulonephritis.

C. Vascular:
  - Vasculitis.
  - Malignant hypertension.
  - TTP-HUS.

- Urine osmolarity (mOsm/kg): <350.

- Urine Na (mEq/L): >40.

- EE_{Na}: >2%.

- Serum BUN/Cr: <15.

❖ N.B:

1. BUN/creatinine ratio:

- The first clue to the diagnosis of prerenal or postrenal azotemia is a BUN/creatinine ratio > 20. There is also a low urine sodium and low fractional excretion of sodium (FeNa <1%) because the kidney perceives the body as being volume-depleted (hence, there will be a vigorous sodium and water reabsorption by the kidney). This results in a very high urine osmolality as well, because the kidney attempts to retain all the water it can in the kidney, and therefore excretes very concentrated urine. Concentrated urine has high urine osmolality (>500).

- The initial clue to the diagnosis of intrinsic renal diseases is a BUN/creatinine ratio < 15; by itself this ratio simply implies the damage is intrarenal (inside the kidney itself), as opposed to abnormalities of perfusion (prerenal) or drainage (postrenal). Further clues to the diagnosis of ATN are high urine sodium (>40), high fractional excretion of sodium (>1%), and low urine osmolality (<350). This is because tubular cells are responsible for forming either concentrated or dilute urine. If the tubular cells die from ischemia, then the kidney can neither concentrate nor dilute the urine. Dead cells don't work.

2. Urine Sodium and Fractional Excretion of Sodium:

- Decreased blood pressure (or decreased intravascular volume) normally will increase aldosterone.

- Increased aldosterone increases sodium reabsorption. It is normal for urine sodium to decrease when there is decreased renal perfusion because aldosterone levels rise.

3. Urine Osmolality:

- When intravascular volume is low, normally ADH levels should rise. A healthy kidney will reabsorb more water to fill the vasculature and increase renal perfusion.

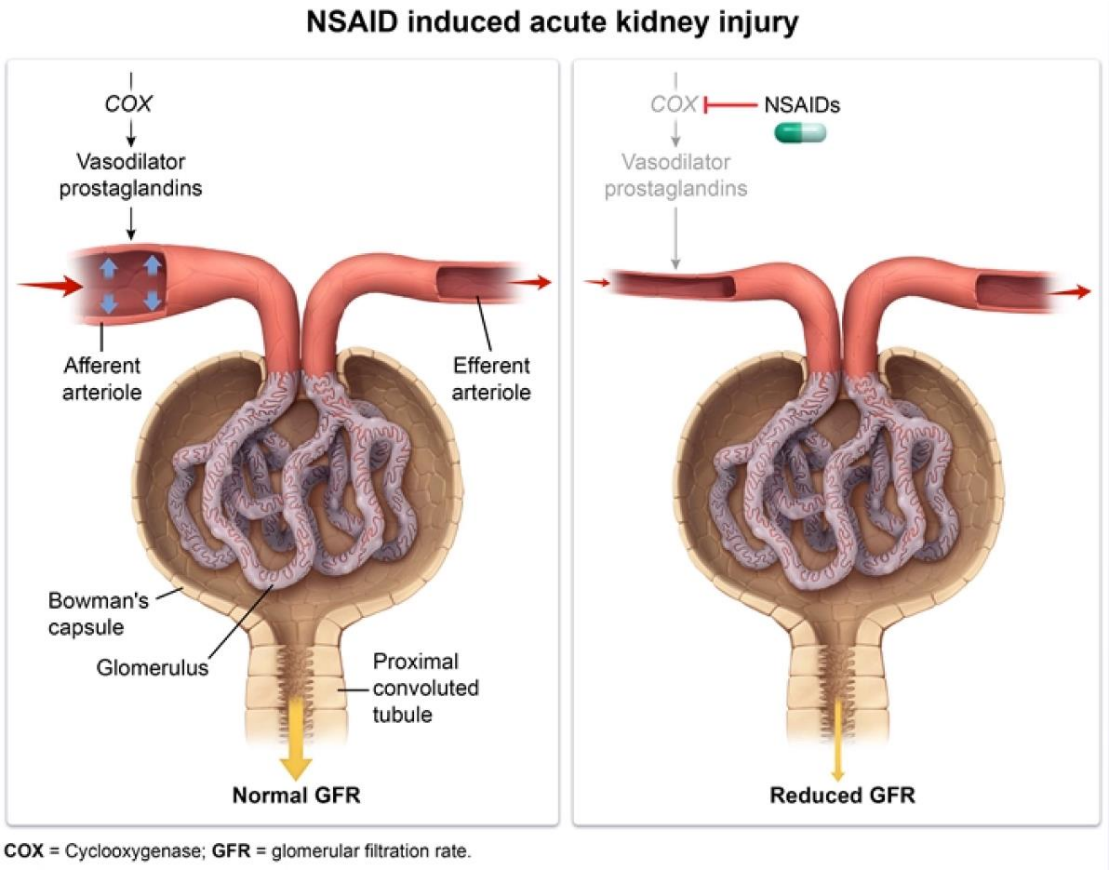
- When more water is reabsorbed from the urine, will the urine be more concentrated, or dilute? Increased water reabsorption leads to an increase in urine osmolality → more concentrated urine.

- Normal tubule cells reabsorb water. In ATN, the urine cannot be concentrated because the tubule cells are damaged.

❖ N.B:

- Patients with intravascular volume depletion (congestive heart failure, diarrhea, excessive diuresis) and chronic kidney disease depend on renal prostaglandin production to dilate the afferent glomerular arteriole and maintain the glomerular filtration rate.
- Nonsteroidal anti-inflammatory drugs inhibit prostaglandin synthesis, which can cause prerenal azotemia in at-risk patients.

- Prolonged NSAID use can cause chronic kidney disease (analgesic nephropathy) due to papillary necrosis and chronic interstitial nephritis.



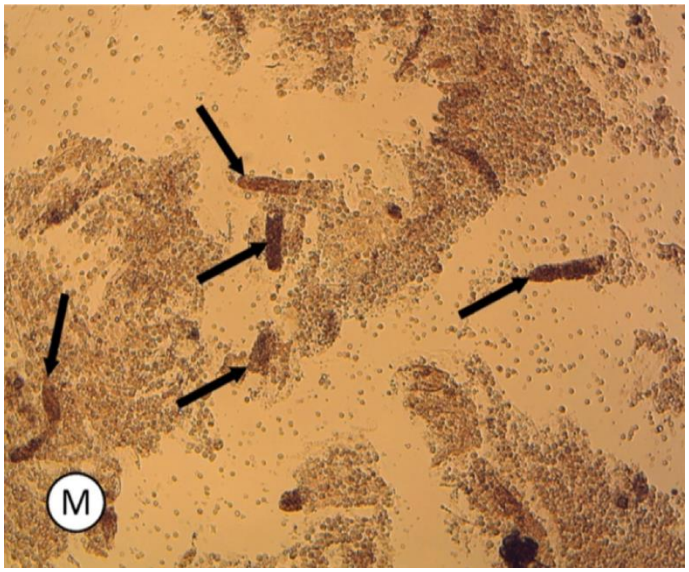
COX = Cyclooxygenase; **GFR** = glomerular filtration rate.

Acute tubular necrosis

- Injury and necrosis of tubular epithelial cells; most common cause of acute renal failure (intrarenal azotemia).

- Necrotic cells plug tubules; obstruction decreases GFR.

- Muddy brown casts, which are pathognomonic for ATN, are a variant of granular pigmented casts.



- Dysfunctional tubular epithelium results in decreased reabsorption of BUN (serum BUN/Cr ratio < 15), decreased reabsorption of sodium (FENa > 2%), and inability to concentrate urine (urine osm < 350 mOsm/kg).

- Etiology:

A. Ischemia:

- Ischemic ATN is one of the most common causes of intrinsic renal failure in hospitalized patients (cardiogenic shock, hemorrhage, acute MI, sepsis).

- Often preceded by prerenal azotemia

- Renal ischemia triggers hypoxic changes in tubular epithelial cells (especially in proximal tubules and the thick ascending limb of Henle's loop), decreasing their functional capacity.

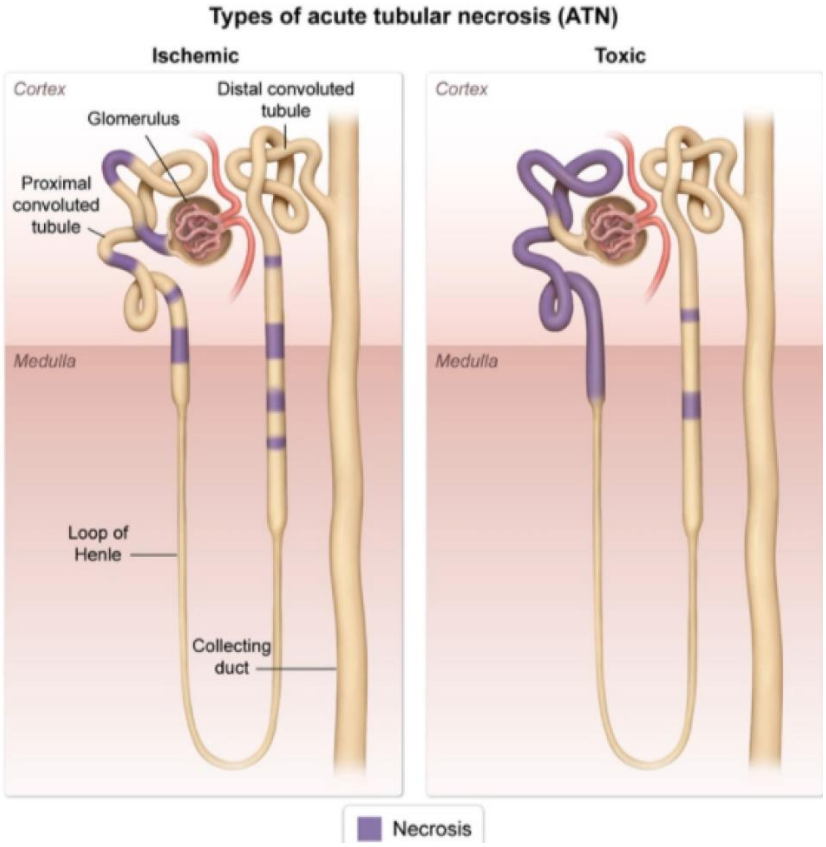
- Proximal tubules and the thick ascending limb of Henle's loop are located in the outer medulla of the kidney, an area that even under normal conditions has a low blood supply. In addition, the proximal tubules and ascending limb participate in the active (ATP-consuming) transport of ions. When oxygen delivery to the kidney is compromised, these portions of nephron will suffer first.

B. Nephrotoxic:

- Toxic agents result in necrosis of tubules.

- Proximal tubule is particularly susceptible.

- Causes include aminoglycosides (most common), heavy metals (lead), myoglobinuria (from crush injury to muscle), ethylene glycol (associated with oxalate crystals in urine), radiocontrast dye, and urate (tumor lysis syndrome).



- The clinical course of ATN may be divided into the initiation, maintenance (oliguric), and recovery phases.

1. The initiation phase:

- Corresponds to the original insult (ischemia).

- Renal tubule cell damage begins to evolve, but is not yet established, during this phase GFR starts to fall, and urine output decreases.

2. The maintenance (oliguric) phase:

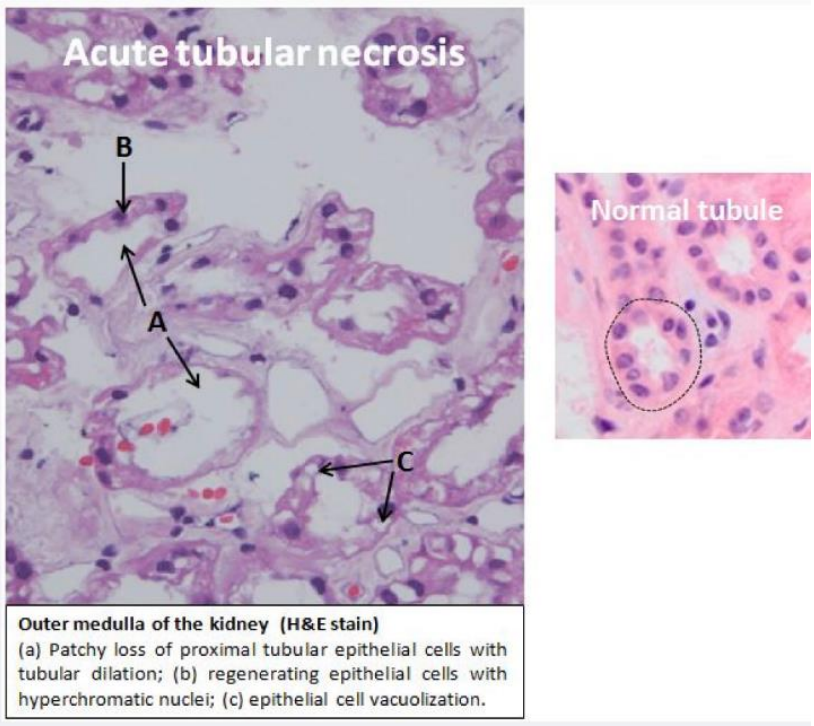
- Renal tubule injury is established, the GFR stabilizes at a level well below normal, and urine output is low/absent.

- This second phase of ATN usually lasts for 1 - 2 weeks.

- Risk of hyperkalemia, metabolic acidosis, uremia.

- Light microscopy in this stage shows granular casts in the tubular lumina.

- Flattening of tubular epithelial cells and tubular epithelial necrosis with denudation of the tubular basement membrane are also seen.



Outer medulla of the kidney (H&E stain)
(a) Patchy loss of proximal tubular epithelial cells with tubular dilation; (b) regenerating epithelial cells with hyperchromatic nuclei; (c) epithelial cell vacuolization.

3. The recovery (polyuric) phase of ATN:

- Most patients with ATN experience tubular re-epithelization and regain renal function.

- The recovery phase of acute tubular necrosis is characterized by abnormal diuresis due to increased GFR with abnormal tubular activity (because the renal tubules cannot yet function fully). So, recovery phase would have volume and electrolytes depletion (polyuria and hypokalemia).

- During the recovery phase (polyuric phase) of acute tubular necrosis, patients can become dehydrated and can develop severe hypokalemia due to high volume, hypotonic urine.

- The gradual normalization of GFR occur, leading to complete restoration of renal function in the majority of patients.

▪ Treatment:

- Reversible, but often requires supportive dialysis since electrolyte imbalances can be fatal.

- Oliguria can persist for 2-3 weeks before recovery; tubular cells (stable cells) take time to reenter the cell cycle and regenerate.

Stages of acute tubular necrosis	
Initiation stage (24-36 hours)	• Tubular injury resulting from: ◦ Ischemia (eg, hemorrhage, acute MI, sepsis, shock) ◦ Cytotoxins (eg, radiologic contrast agents, aminoglycosides, myoglobin)
Maintenance stage (1-3 weeks)	• Oliguric renal failure (↓ GFR, ↓ urine output, fluid overload) • ↑ Creatinine/BUN, ↑ potassium, metabolic acidosis
Recovery phase (months)	• Gradual increase in urine output, leading to high-volume diuresis • Continued impairment of renal tubular function, resulting in electrolyte wasting (↓↓ potassium, magnesium, phosphorus, calcium)
BUN = blood urea nitrogen; **GFR** = glomerular filtration rate; **MI** = myocardial infarction.	

❖ N.B:

1. Ethylene glycol is a widely available substance found in automobile antifreeze, engine coolants and hydraulic brake fluids.

- Ethylene glycol is rapidly absorbed from the GI tract and metabolized to:
- Oxalic acid → precipitates as calcium oxalate crystals in the renal tubules.
- Glycolic acid → toxic to renal tubules.
- Ethylene glycol ingestion leads to acute renal failure due to the precipitation of calcium oxalate crystals in renal tubules and subsequent damage to tubular epithelium.
- Typical clinical findings include anion gap metabolic acidosis, increased osmolar gap, and presence of calcium oxalate crystals in urine.

2. Rhabdomyolysis is characterized by myocyte injury with the release of intracellular muscle contents (myoglobin, electrolytes) into the circulation.

- It is common in crush injuries, prolonged muscle activity (seizure), or drug use.
- Positive blood on urine dipstick (a reaction that detects the heme pigment in both hemoglobin and myoglobin) in the absence of red blood cells on microscopic urinalysis suggests myoglobinuria.
- Renal injury in rhabdomyolysis results from myoglobin filtration and degradation within the glomeruli. Heme pigment is released, which causes acute tubular necrosis by direct cytotoxicity and renal vasoconstriction.
- Hyperkalemia, hyperphosphatemia, and hyperuricemia also occur due to myocyte lysis.

Diffuse cortical necrosis

- Acute generalized cortical infarction of both kidneys. Irreversible type of prerenal kidney injury caused by drop in blood perfusion to the renal cortex.

- Associated with obstetric catastrophes (abruptio placentae), septic shock.

- Likely due to a combination of vasospasm and DIC.

Acute interstitial nephritis

- Also called tubulointerstitial nephritis.

- Drug-induced hypersensitivity involving the interstitium and tubules; results in acute renal failure (intrarenal azotemia).

- Pathogenesis:

- As the name of the condition implies, damage primarily involves the interstitium, leaving the glomeruli intact.

- IgE-mediated hypersensitivity combined with cell-mediated reactions are thought to be involved in the pathogenesis of AIN.

- Many patients have increased levels of eosinophils and IgE in serum; also, granuloma formation may be observed.

- Interstitial edema and infiltration with mononuclear cells (lymphocytes and macrophages) are typical.

- Peripheral eosinophilia and eosinophiluria are the most important clues.

- Finding:

- Clinically, patients with AIN present with fever, maculopapular rash, and acute renal failure.

- Fever, maculopapular rash and symptoms of acute renal failure one to three weeks after beginning treatment with (B-lactam antibiotic, NSAIDs, sulfonamides, rifampin, and diuretics) are highly suggestive of acute interstitial nephritis.

- Less commonly may be 2° to other processes such as systemic infections (Mycoplasma) or autoimmune diseases (Sjögren syndrome, SLE, sarcoidosis).

- Remember these 5 P'S:
  - Pee (diuretics).
  - Pain-free (NSAIDs).
  - Penicillins and cephalosporins.
  - Proton pump inhibitors.
  - RifamPin.
  - Sulfa drugs.

- Symptoms almost always resolve completely after cessation of the offending medication.

- May progress to renal papillary necrosis.

Chronic interstitial nephritis

- Cause:

- Chronic use of NSAIDs (chronic joint pain) → analgesic nephropathy.

- Pathogenesis:

- NSAID-associated chronic renal injury is morphologically characterized by papillary necrosis and chronic interstitial nephritis:

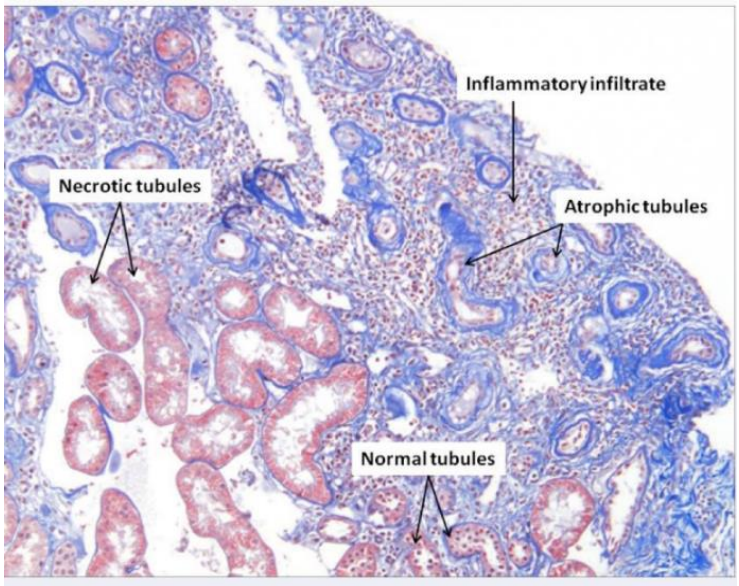
  - NSAIDs concentrate in the renal medulla, allowing higher levels in the papillae than in the renal cortex. Decreased prostaglandin synthesis promoting ischemia → papillary necrosis.

  - NSAIDs also uncouple the oxidative phosphorylation in renal mitochondria, thus causing direct cell damage. With prolonged NSAID use, the major pathophysiologic abnormality is chronic interstitial nephritis.

- Pathology:

- Patchy interstitial inflammation with subsequent fibrosis.

- Tubular atrophy, papillary necrosis and scarring.



- Finding:

- Modest elevation in serum creatinine.

- Evidence of tubular dysfunction (polyuria, nocturia).

- Mild proteinuria.

- Microscopic hematuria and sterile pyuria may also be seen on urinalysis.

Renal papillary necrosis

- Necrosis of renal papillae → Sloughing of necrotic renal papillae → gross hematuria.

- Acute, colicky flank pain is a common symptom due to acute ureteral obstruction from sloughed papillae.

- The following conditions are most strongly associated with papillary necrosis (SAAD papa with papillary necrosis):

1. Sickle cell disease or trait:

- Sickling causes obstruction of small kidney vessels and predisposes to ischemia.

- This occurs most commonly in children and young adults.

- The abrupt onset of gross hematuria in a patient with family history of sickle cell disease suggests renal papillary necrosis.

2. Analgesic nephropathy:

- Phenacetin, the most nephrotoxic analgesic drug, has been withdrawn from the U.S. market.

- Many of the other NSAIDs, however, inhibit renal blood flow by decreasing prostaglandins synthesis.

3. Acute pyelonephritis and urinary tract obstruction:

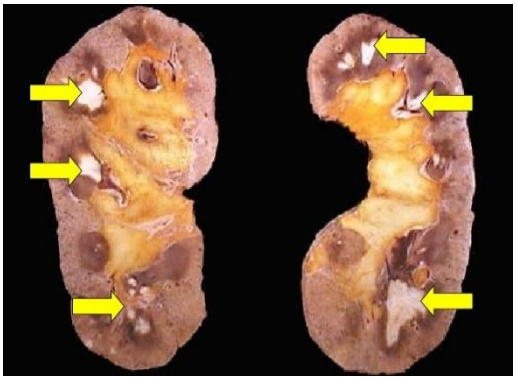
- The edematous interstitium of the pyelonephritis kidney compresses the medullary vasculature, thus predisposing the patient to ischemia.

4. Diabetes mellitus:

- Diabetic metabolic abnormalities, including non-enzymatic glycosylation, cause changes in vascular walls, leading to compromised renal vasculature.

- Macroscopic pathological findings include gray-white or yellow necrosis of the tips or distal two-thirds of renal pyramids.

- Microscopically, the tissue shows coagulative infarct necrosis, with preserved tubule outlines.



Chronic Renal Failure

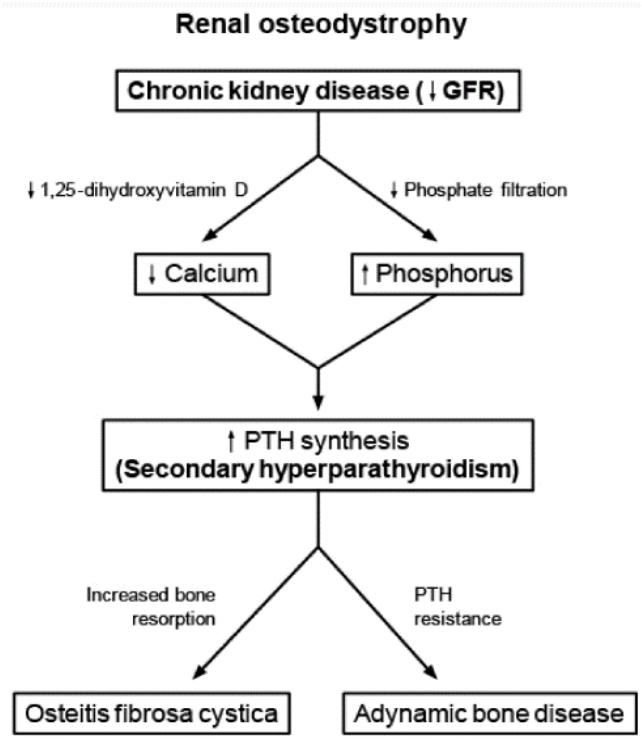
- May result from glomerular, tubular, inflammatory, or vascular insults.
- Most common causes are diabetes mellitus, hypertension, and glomerular disease.
- Main cause is diabetes; second is hypertension.
- Develops slowly and is characterized by an irreversible loss of nephrons.
- Incremental reductions in GFR define the stages of chronic kidney disease.
- Decline in renal filtration can lead to excess retained nitrogenous waste products and electrolyte disturbances.
- Consequences of renal failure (MAD HUNGER):

- Metabolic Acidosis
- Dyslipidemia (especially ↑ triglycerides) due to lipoprotein lipase inactivation in uremia.
- Hyperkalemia.
- Uremia (clinical syndrome marked by↑BUN):
  - Nausea and anorexia.
  - Pericarditis.
  - Asterixis.
  - Encephalopathy.
  - Platelet dysfunction (functional thrombocytopenia).
- Na/H_2O retention (HF, pulmonary edema, hypertension).
- Growth retardation and developmental delay.
- Erythropoietin failure (anemia).
- Renal osteodystrophy:
  - Renal osteodystrophy is a bone disease that occurs in chronic kidney diseases (subperiosteal thinning of bones).
  - The activity of renal alpha hydroxylase is decreased in chronic kidney disease, which causes the decreased formation of 1,25-dihyroxy vitamin D.

- The gastrointestinal absorption of calcium is consequently decreased; the ultimate result is a decrease in serum calcium.

- Another electrolyte change is the elevation of phosphorous because chronic renal disease impairs its excretion.

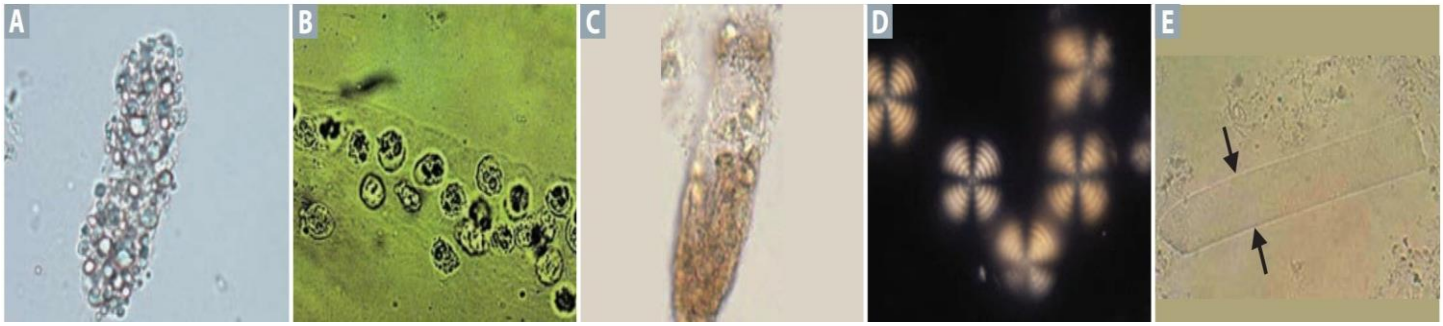
- The result of the decrease in 1,25-dihydroxy vitamin D, the decrease in serum calcium, and the increase in serum phosphorus is an increase in the secretion of parathyroid hormone, a state termed "secondary hyperparathyroidism".



❖ N.B:

- Presence of casts indicates that hematuria/pyuria is of glomerular or renal tubular origin.
- Bladder cancer, kidney stones → hematuria, no casts.
- Acute cystitis → pyuria, no casts.

RBC casts (A)	**Glomerulonephritis, malignant hypertension.**
WBC casts (B)	Tubulointerstitial inflammation, acute pyelonephritis, transplant rejection.
Granular casts (C)	Acute tubular necrosis. Can be "muddy brown" in appearance.
Fatty casts ("oval fat bodies")	Nephrotic syndrome. Associated with "Maltese cross" sign (D).
Waxy casts	End-stage renal disease/chronic renal failure.
Hyaline casts (E)	Nonspecific, can be a normal finding, often seen in concentrated urine samples.



Cardiorenal syndrome

- The pathophysiology of cardiorenal syndrome is multifactorial and includes both hemodynamic alterations related to the low output state and resultant neurohormonal changes.

- Decreased cardiac output results in renal hypoperfusion, which triggers the following adaptations:

- Renin-angiotensin-aldosterone system (RAAS) activation, leading to increased proximal tubular sodium reabsorption (direct effect of angiotensin II)

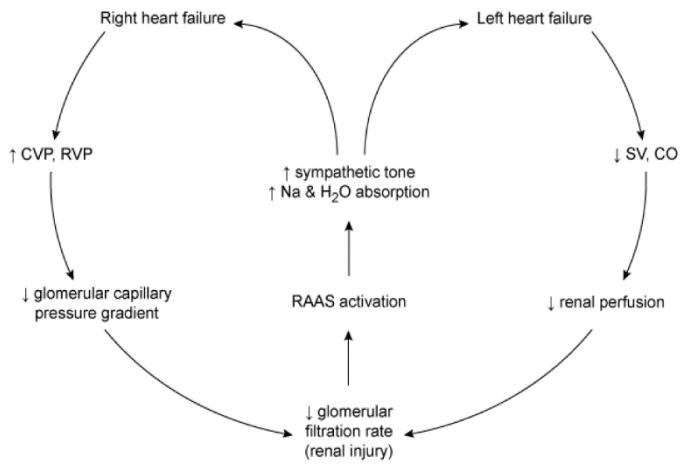
- Antidiuretic hormone release, resulting in increased free water reabsorption in the collecting ducts

- Sympathetic nervous system activation, resulting in systemic vasoconstriction

- In the short-term, these adaptions increase the effective arterial blood volume and maintain systemic perfusion, allowing for a relatively normal glomerular filtration rate. However, over time, widespread vasoconstriction increases the afterload (the resistance the heart must pump against) and ventricular overfilling leads to decreased pump efficiency, lowering cardiac output and furthering renal hypoperfusion.

- At a certain point, the decrease in cardiac output becomes overwhelming and glomerular filtration rate begins to drop.

Cardiorenal syndrome



CO = cardiac output; **CVP** = central venous pressure; **RAAS** = renin-angiotensin-aldosterone system; **RVP** = renal vein perfusion; **SV** = stoke volume.

Renal tubular defects

- Fanconi syndrome is first (PCT), the rest are in alphabetic order.

1. Fanconi Syndrome:

- Generalized dysfunction of proximal tubule cells of unclear cause.

- Likely due to a defect in cellular energy metabolism resulting in multiple transport abnormalities.

- Results in impaired reabsorption of multiple substances, including glucose, amino acids, phosphate, and bicarbonate.

- Causes:

- Idiopathic.
- Drug toxicity (fosfamide, cisplatin, tenofovir, expired tetracyclines).
- Lead poisoning.
- Multiple myeloma.
- Inherited disorders: Wilson disease, cystinosis, tyrosinemia, glycogen storage disease. The most common is cystinosis, a rare disorder of cysteine deposition in tissues.

- Clinical Manifestations:

- Urinary solutes and glucose loss lead to osmotic diuresis → polyuria, polydipsia, and dehydration.

- Multiple metabolic abnormalities due to Impaired reabsorption of phosphate and bicarbonate directly leads to:
  - Metabolic acidosis: type II renal tubular acidosis.
  - Hypophosphatemia.
- Osmotic diuresis → increased distal Na delivery, distal K and Ca loss → secondary hypokalemia and hypocalcemia.

- Major complication:

- Abnormal bone formation with resultant growth impairment and failure to thrive. The bone defects (rickets or osteomalacia) result from acidosis, hypophosphatemia, and hypocalcemia.

2. Bartter syndrome:

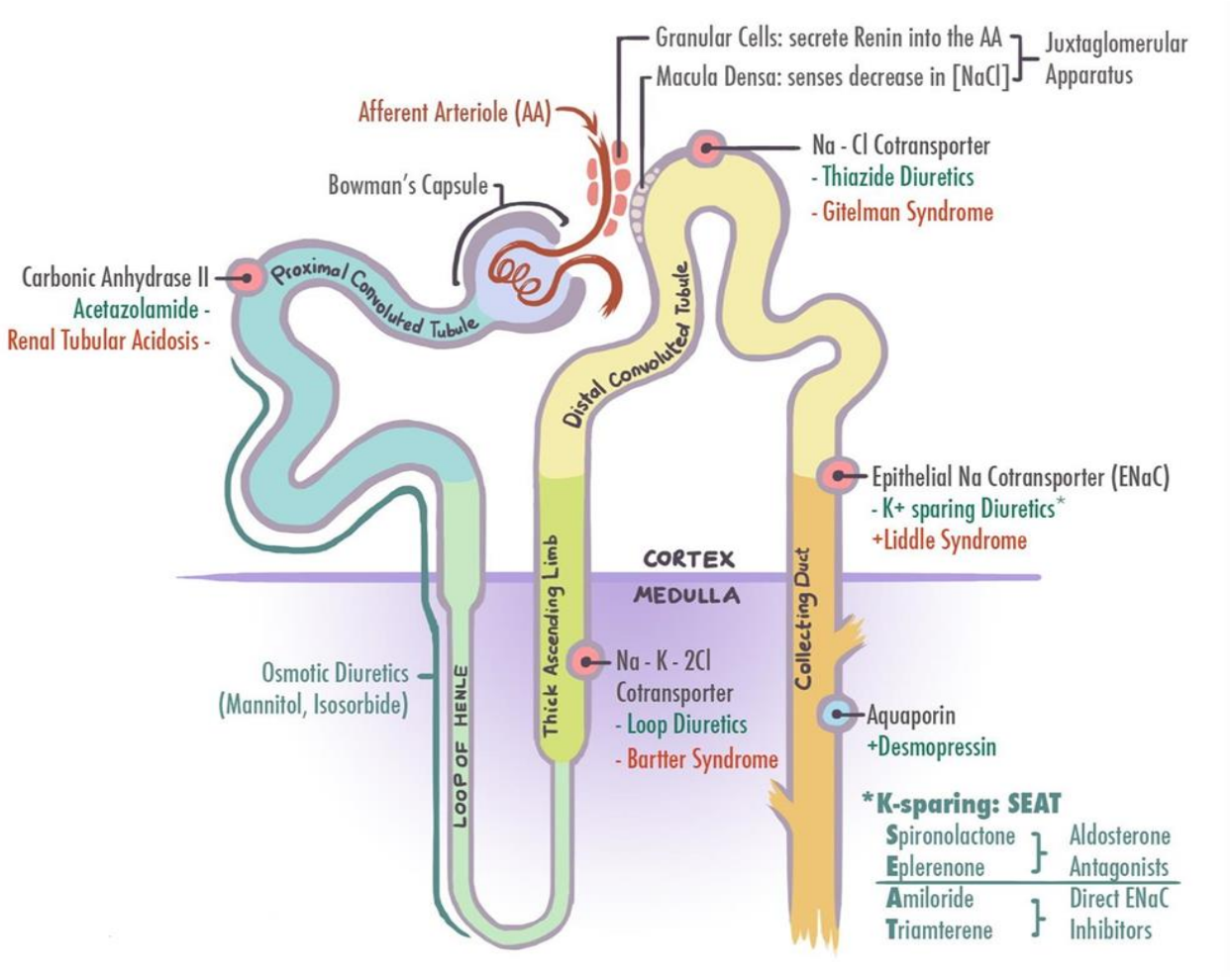
- Defect: The underlying pathology is defective sodium and chloride reabsorption in the thick ascending limb of the Henle loop (Affects Na/K/2Cl) cotransporter, resulting in hypovolemia and consequent activation of the renin-angiotensin aldosterone system (RAAS).

- Cause: Autosomal recessive.

- Effects:

- Activated RAAS causes an increase in potassium and hydrogen ion secretion, leading to hypokalemia and metabolic alkalosis with hypercalciuria.

- Presents similarly to chronic loop diuretic use.



3. Gitellman syndrome:

- Defect: Reabsorptive defect of NaCl in DCT.

- Cause: Autosomal recessive.

- Effects:

- Leads to hypokalemia, hypomagnesemia, metabolic alkalosis, hypocalciuria.

- Similar to using lifelong thiazide diuretics.

- Less severe than Bartter syndrome.

- Urine chloride level is markedly elevated in Bartter and Gitelman syndromes.

4. Liddle syndrome:

- Defect:

- Gain of function mutation → ↑ Na reabsorption in collecting tubules (↑ activity of epithelial Na channel).

- Cause: Autosomal dominant.

- Effects:

- Results in hypertension, hypokalemia, metabolic alkalosis, ↓ aldosterone.

- Presents like hyperaldosteronism, but aldosterone is nearly undetectable.

- Treatment: Amiloride (by blocking Na channels in the cortical collecting tubule).

5. Syndrome of Apparent Mineralocorticoid Excess:

- Defect:

- Autosomal recessive.

- It results from mutations in the gene which encodes the kidney isozyme of 11β-hydroxysteroid dehydrogenase (11β-HSD).

- In an unaffected individual, this isozyme inactivates circulating cortisol to the less-active metabolite cortisone (inactive on the mineralocorticoid receptors).

- Can be acquired disorder from glycyrrhetinic acid (present in licorice, which blocks activity of 11β-hydroxysteroid dehydrogenase).

- Effects:

- The inactivating mutation leads to elevated local concentrations of cortisol in the kidney.

- Cortisol at high concentrations can cross-react and activate the mineralocorticoid receptor, leading to aldosterone-like effects in the kidney.

- Excess cortisol in from enzyme deficiency → ↑ mineralocorticoid receptor activity → hypertension, hypokalemia, metabolic alkalosis.

- Low serum aldosterone levels.

- Cortisol tries to be the SAME as aldosterone.

- Treatment:

- Corticosteroids (exogenous corticosteroids ↓ endogenous cortisol production → ↓ mineralocorticoid receptor activation).

Renal tubular acidosis

- A disorder of the renal tubules that leads to acidosis and electrolyte disturbances due to impaired renal hydrogen ion excretion (type 1), impaired HCO_3 reabsorption (type 2), or abnormal aldosterone production or response (type 4).

- Produces a Normal anion gap metabolic acidosis (hyperchloremic metabolic acidosis).

- There are three main types:

1. Distal renal Tubular Acidosis (Type I):

- Defect: Defect in ability of α intercalated cells to secrete H and regenerate HCO_3 → metabolic acidosis but an inappropriately high urine pH.

- Urine pH: Urine pH > 5.5.

- Serum K: hypokalemia (The defect here is in H/K ATPase channel which normally excrete H and reabsorb K → acidosis + hypokalemia).

- Causes: Amphotericin B toxicity, Analgesic nephropathy, congenital Anomalies (obstruction) of urinary tract, Autoimmune diseases (SLE).

- Association: Associated with ↑ risk for calcium phosphate kidney stones (due to ↑ urine pH and ↑ bone turnover related to buffering).

2. Proximal renal Tubular (Acidosis Type II):

- Defect:
  - Defect in PCT HCO_3 reabsorption →↑ excretion of HCO_3 in urine and subsequent metabolic acidosis.
  - Urine is acidified by α-intercalated cells in collecting tubule, but not enough to overcome ↑ HCO_3 excretion.

- Urine pH:
  - > 5.5 when resorptive threshold for serum HCO_3 exceeded.
  - < 5.5 when HCO_3 depleted below resorptive threshold.

- Serum K: hypokalemia.

- Causes: Fanconi syndrome, multiple myeloma, and carbonic anhydrase inhibitors.

- Association: ↑ risk for hypophosphatemic rickets (in Fanconi syndrome).

3. Hyperkalemic renal tubular acidosis (type 4):

- Defect:
  - Hypoaldosteronism or aldosterone resistance → hyperkalemia and metabolic acidosis → ↓NH_3 synthesis in PCT → ↓ NH_4 excretion.

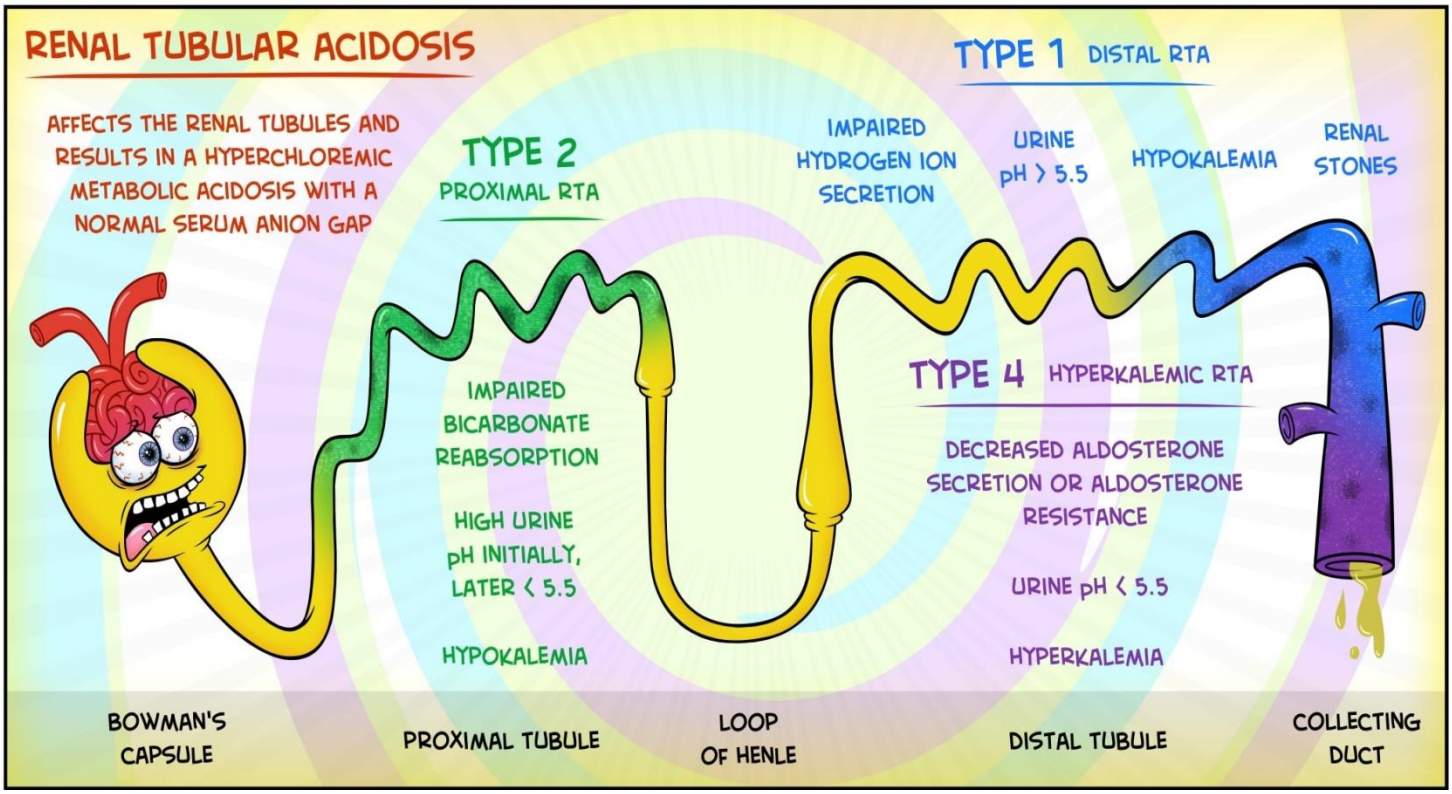
  - Some of the excess potassium enters the cells, with electroneutrality being maintained by the movement of cellular hydrogen ions into the extracellular fluid → PCT intracellular alkalosis → ↓ ammonium production in the proximal tubule.

- Urine pH: < 5.5 (↓ NH_4 excretion → ↓ buffering capacity).

- Serum K: hyperkalemia.

- Causes:
  - ↓ aldosterone production (diabetic hyporeninism, ACE inhibitors, ARBs, NSAIDs, heparin, cyclosporine, adrenal insufficiency).

  - Aldosterone resistance (K-sparing diuretics, nephropathy due to obstruction, TMP/SMX).



Renal cyst disorders

1. Autosomal dominant polycystic kidney disease:

- Genetics:

- An autosomal dominant condition that is the most common hereditary cause of renal failure in adults.

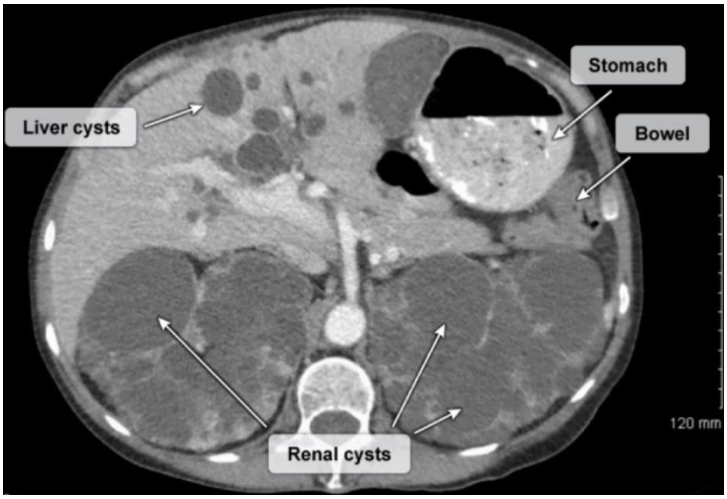
- Mutation in PKD1 (85% of cases, chromosome 16) or PKD2 (15% of cases, chromosome 4) which codes for fibrocystin (Fibrocystin is found in the epithelial cells of both the renal tubule and the bile ducts; deficiency leads to the characteristic polycystic dilation of both structures).

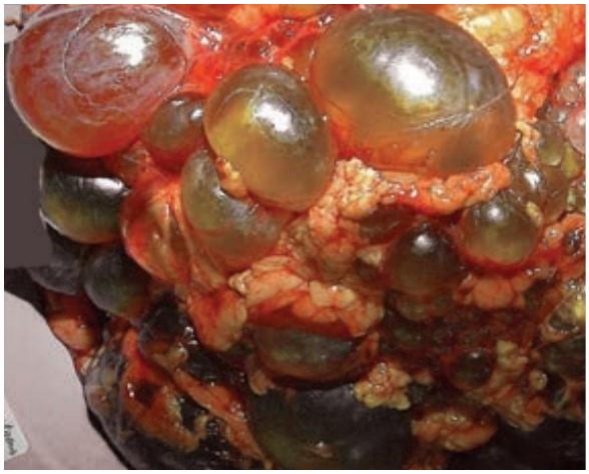
- Pathologic features:

- Patients with ADPKD are born with multiple microscopic cysts (in cortex and medulla) in both kidneys (bilateral) that progressively enlarge over the decades.

- In newborns, the kidneys are of normal size, and the cysts are too small to be detected on abdominal ultrasonography. Renal cysts can usually be seen on imaging by the 3rd to 4th decade of life. The contrast-enhanced CT scan bleow shows multiple renal cysts and hepatic cysts.

- Patients often remain asymptomatic until their 4th or 5th decade (adult onset), when enlargement of the cysts begins to impair renal function.





- Clinical features:

- As the cysts enlarge, they compress the renal parenchyma and cause symptoms.

- Renal dysfunction continues to worsen with age, and about 50% of adults progress to end-stage renal disease by age 70.

- Other renal complications include hypertension (caused by ↑ renin production), abdominal and flank pain (due to dilation of the cysts and stretching of the renal capsule), gross hematuria (cyst rupture), urinary tract infection, and kidney stones.

- Extrarenal manifestations include liver cysts, intracranial berry aneurysms that may rupture, diverticulosis and mitral valve prolapse.

- The liver cysts usually do not cause loss of liver function but may cause pain if they are large.

▪ Treatment:

- If hypertension or proteinuria develops, treat with ACE inhibitors or ARBs.

Autosomal dominant polycystic kidney disease	
Genetics	• Autosomal dominant mutation in **PKD-1** or **PKD-2** causes ↑ tubular cell proliferation & fluid secretion
Pathologic features	• **Cyst formation** occurs at any point in the nephron, with <5% of nephrons affected • Microscopic cysts present at birth **progressively enlarge** over the decades, causing atrophy & fibrosis of surrounding parenchyma

Clinical features	• Patients often asymptomatic
	• Abdominal & flank pain
	• **Hypertension**
	• **Hematuria** (cyst rupture)
	• **Progressive renal failure**
	• Extrarenal manifestations
	  • Liver cysts
	  • **Cerebral aneurysms**

Diagnosis	• Abdominal imaging shows multiple renal cysts

2. Autosomal recessive polycystic kidney disease:

▪ Cystic dilation of collecting ducts.

▪ Often presents in infancy (juvenile onset).

▪ Associated with congenital hepatic fibrosis.

▪ In its most severe phenotype, autosomal recessive polycystic kidney disease can be detected on prenatal sonogram along with oligohydramnios → Potter sequence (flattened facies, limb deformities, pulmonary hypoplasia) and is associated with high mortality.

▪ Concerns beyond neonatal period include systemic hypertension, progressive renal insufficiency, and portal hypertension from congenital hepatic fibrosis.

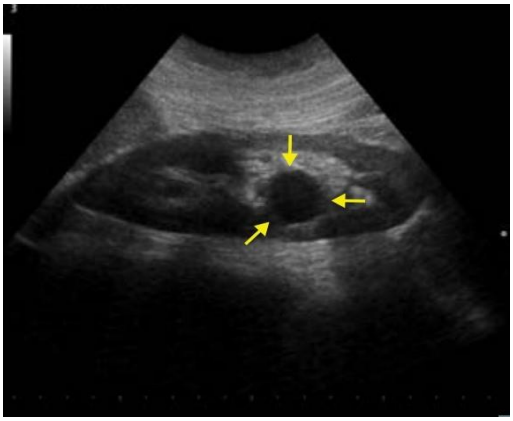
3. Autosomal dominant tubulointerstitial kidney disease:

- Also called medullary cystic kidney disease.
- Inherited (autosomal dominant) defect leading to cysts in the medullary collecting ducts.
- Causes tubulointerstitial fibrosis and progressive renal insufficiency with inability to concentrate urine.
- Parenchymal fibrosis results in shrunken kidneys and worsening renal failure.
- Medullary cysts usually not visualized; smaller kidneys on ultrasound.
- Poor prognosis.

4. Simple vs complex renal cysts:

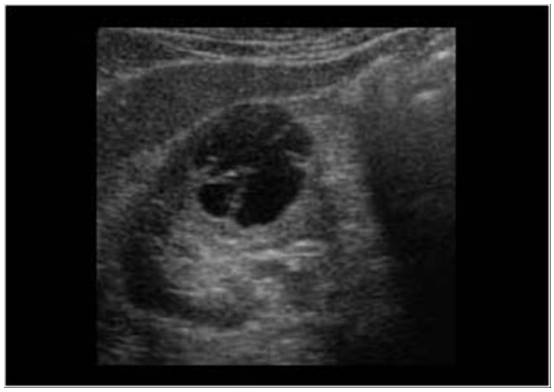
A. Simple cyst:

- Simple cysts are filled with ultrafiltrate (anechoic on ultrasound).
- Very common and account for majority of all renal masses.
- Found incidentally and typically asymptomatic.



B. Complex cysts:

- Include those that are septated, enhanced, or have solid components on imaging.
- Require follow-up or removal due to risk of renal cell carcinoma.



Atheroembolic renal disease

- Atheroembolism occurs when an atherosclerotic plaque is disrupted and cholesterol crystals and debris are showered into the circulation. This leads to partial or total occlusion of arterioles with resultant tissue or organ ischemia.

- Atheroembolism is most commonly seen as a complication of cardiac catheterization and other vascular procedures.

- Clinical manifestations can be immediate or delayed (>30 days after inciting event). Atherosclerotic plaques in the aortic arch can embolize to the brain and cause cerebral infarction. Diffuse showering of emboli into the peripheral circulation can cause intestinal ischemia, and acute kidney injury.

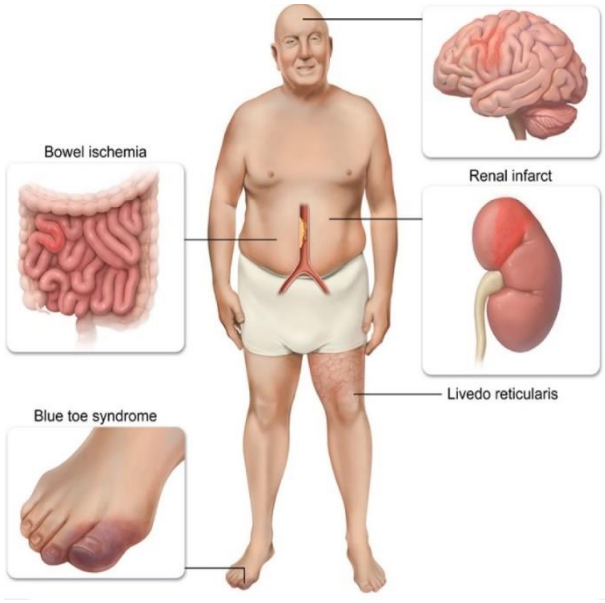
- Skin manifestations are the most common complication (34% of patients) and include "blue toe syndrome" (cyanotic toes with intact pulses), livedo reticularis (reticular, lacy skin discoloration/erythema that blanches on pressure), gangrene, and ulcers.

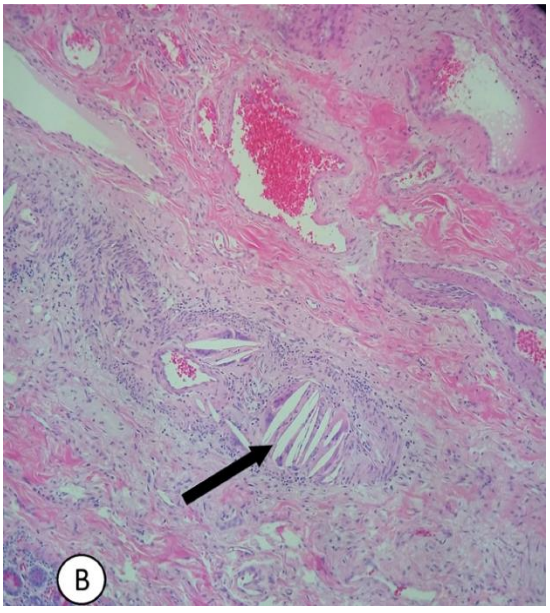
- Examination of the retina may show Hollenhorst plaques, bright, yellow, refractile plaques in the retinal artery.

- The combination of cyanotic toe discoloration and renal failure (increased creatinine level) in an elderly patient following an invasive vascular procedure (angiography, angioplasty, aortic surgery) is characteristic of atheroembolic disease of the renal arteries.

- Renal biopsy shows needle-shaped cholesterol crystals that partially or completely obstruct renal arterioles.

- Treatment is supportive and includes statin therapy for risk factor reduction and prevention of recurrent cholesterol embolism. Many never recover normal renal function.

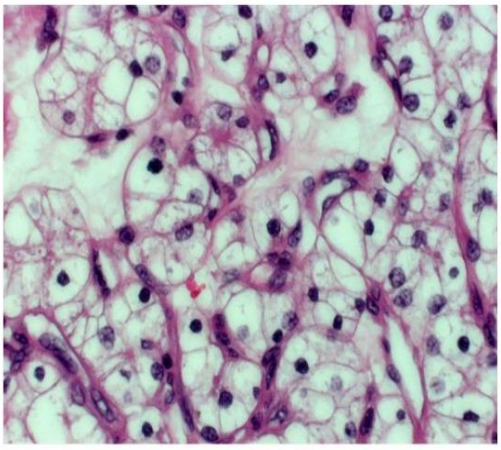
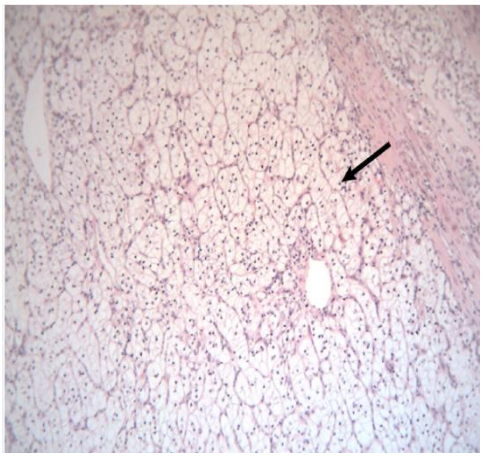
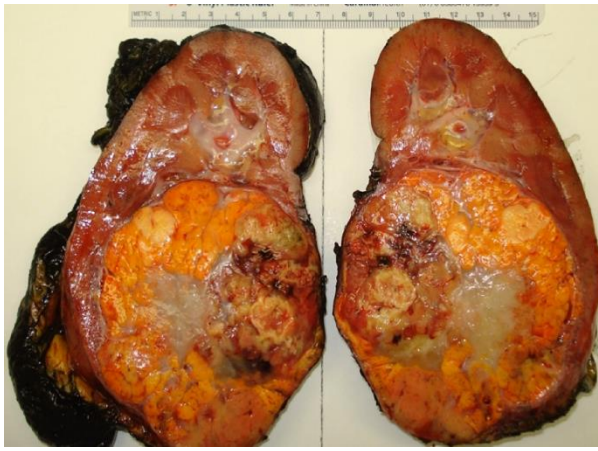




Renal neoplasia

Renal cell carcinoma

- Renal cell carcinoma (RCC) is the most common renal neoplasm, accounting for approximately 70% of all kidney tumors.
- These neoplasms originate from the epithelium of the proximal renal tubules, and typically affect patients who are 60 to 70 years old → Polygonal clear cells filled with accumulated lipids and carbohydrate.
- Often golden-yellow due to ↑ lipid content.
- Microscopically, clear cell carcinoma (the most common subtype of RCC) appears as cuboidal or polygonal cells with clear abundant cytoplasm and eccentric nuclei.
- The cytoplasm appears clear due to the high glycogen and lipid content of the tumor that dissolves during tissue preparation. For the same reason, this neoplasm is often golden-yellow on macroscopic examination.
- Risk factors include smoking and obesity.

- <u>It may be hereditary or sporadic:</u>

- Sporadic tumors classically arise in adult males (average age is 60 years) as a single tumor in the upper pole of the kidney; major risk factor for sporadic tumors is cigarette smoke.
- Hereditary tumors arise in younger adults and are often bilateral. Von Hippel-Lindau disease is an autosomal dominant disorder associated with inactivation of the VHL gene on chromosome 3 leading to increased risk for hemangioblastoma of the cerebellum and renal cell carcinoma (RCC = 3 letters = chromosome 3).

- Finding:

- Patients with renal cell carcinoma develop clinical symptoms late in the course of the disease.

- The classic triad of hematuria, flank pain, and palpable abdominal mass occurs in less than 10% of cases. Non-specific symptoms such as fever, malaise, anorexia, and weight loss are more common.

- Paraneoplastic syndromes due to the secretion of biologically active substances (EPO, renin, PTHrP, or ACTH) by the tumor cells may also occur.

- For example, erythrocytosis and polycythemia can occur due to constitutive secretion of erythropoietin → elevated hematocrit.

- Hypercalcemia due to synthesis of parathyroid hormone-related peptide is also common.

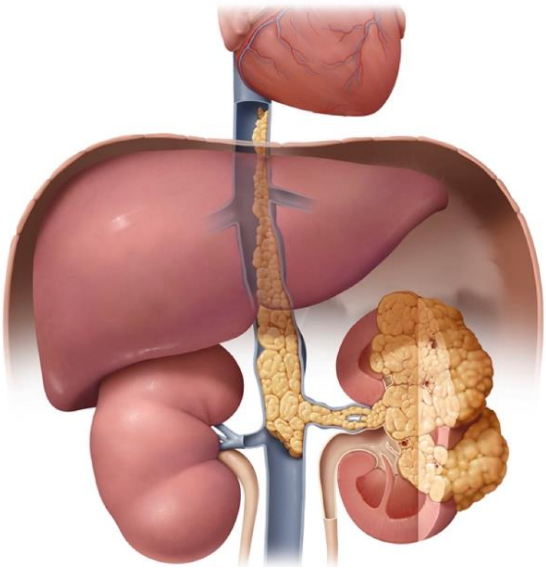
- Rarely may present with left-sided varicocele. Involvement of the left renal vein by carcinoma blocks drainage of the left spermatic vein leading to varicocele.

- Inferior vena cava obstruction can occur by intraluminal extension of the tumor. Obstruction of the inferior vena cava produces symmetric bilateral lower extremity edema, often associated with prominent development of venous collaterals in the abdominal wall.

- Renal cell carcinoma is often detected incidentally since localizing symptoms only develop in advanced disease. Therefore, it is not uncommon for metastases to be discovered earlier than the primary neoplasm.

- Renal cell carcinoma hematogenously spread → metastasis to lung and bone. The lungs are the most common site, with pulmonary metastases found in about half of all cases of disseminated disease. Bone metastases are the next most common.

Renal cell carcinoma & IVC obstruction



- Treatment:

- Surgery/ablation if localized disease.

- Immunotherapy (aldesleukin) or targeted therapy for advanced/metastatic disease.

- Resistant to chemotherapy and radiation therapy.

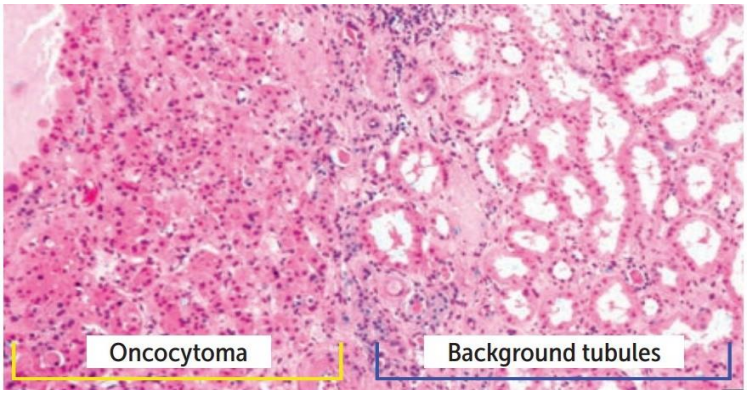
Renal oncocytoma

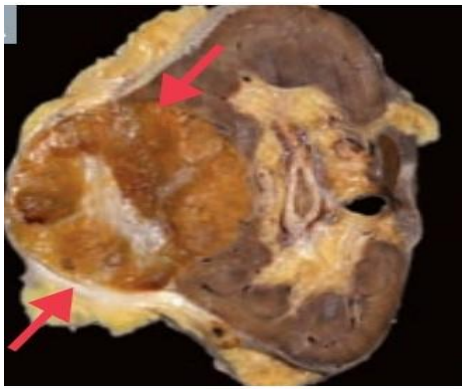
- Benign epithelial cell tumor arising from collecting ducts (arrows point to well circumscribed mass with central scar).

- Large eosinophilic cells with abundant mitochondria (oncocytes) without perinuclear clearing (vs chromophobe renal cell carcinoma).

- Presents with painless hematuria, flank pain, abdominal mass.

- Often resected to exclude malignancy (renal cell carcinoma).





Wilms tumor

- Most common renal malignancy of early childhood (ages 2-4).

- "Loss of function" mutations of tumor suppressor genes WT1 or WT2 on chromosome 11.

- Contains embryonic glomerular structures.

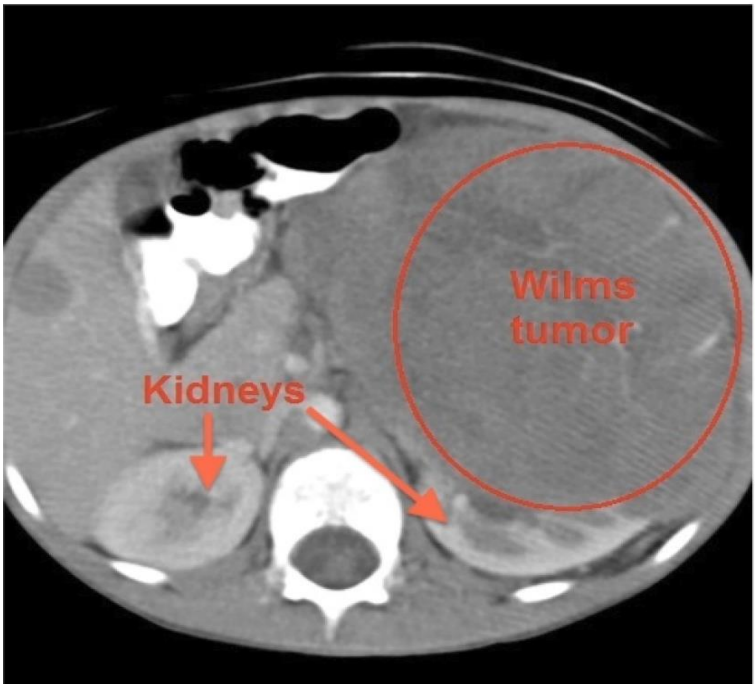
- It should be suspected in a toddler with a firm, smooth, unilateral abdominal mass that doesn't cross the midline and hematuria (vs. Neuroblastoma, which presents with firm, irregular mass that can cross the midline). The most common presentation is an asymptomatic abdominal mass that is found incidentally by a caretaker or physician. Some patients have abdominal pain, hypertension, hematuria, and fever.

- May be a part of several syndromes:

- WAGR complex: Wilms tumor, Aniridia (absence of iris), Genitourinary malformations, mental Retardation/intellectual disability (WT1 deletion)

- Denys-Drash: Wilms tumor, early-onset nephrotic syndrome, male pseudohermaphroditism (WT1 mutation).

- Beckwith-Wiedemann: Wilms tumor, macroglossia, organomegaly, hemihypertrophy (WT2 mutation).



Lower urinary tract carcinoma

- Gross painless hematuria in an older adult should be considered a sign of urothelial cancer until proven otherwise.

- Bladder carcinomas arise from the transitional epithelium lining the bladder.

- These tumors are called urothelial (or transitional cell) carcinomas.

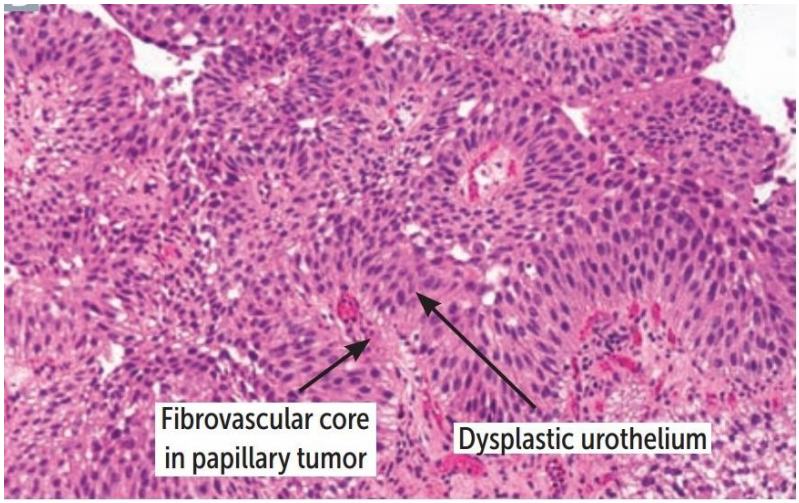
- Urothelial carcinomas compose 90% of malignant bladder neoplasms.

- Squamous cell carcinomas and adenocarcinomas of the bladder are rare.

- Tumor penetration of the bladder wall is the major determinant of prognosis.

Urothelial (Transitional) cell carcinoma

- Most common tumor of urinary tract system (can occur in renal calyces, renal pelvis, ureters, and bladder).
- It is more often seen in smokers and individuals with occupational exposure to rubber, plastics, aromatic amine-containing dyes, textiles, or leather.
- Peak incidence of this neoplasm occurs in the seventh and eight decades of life, with men affected more than women.
- Painless hematuria (no casts) suggests bladder cancer.
- Multifocal sessile or papillary tumors.
- Associated with problems in your Pee SAC: Phenacetin, Smoking, Aniline dyes, and Cyclophosphamide.



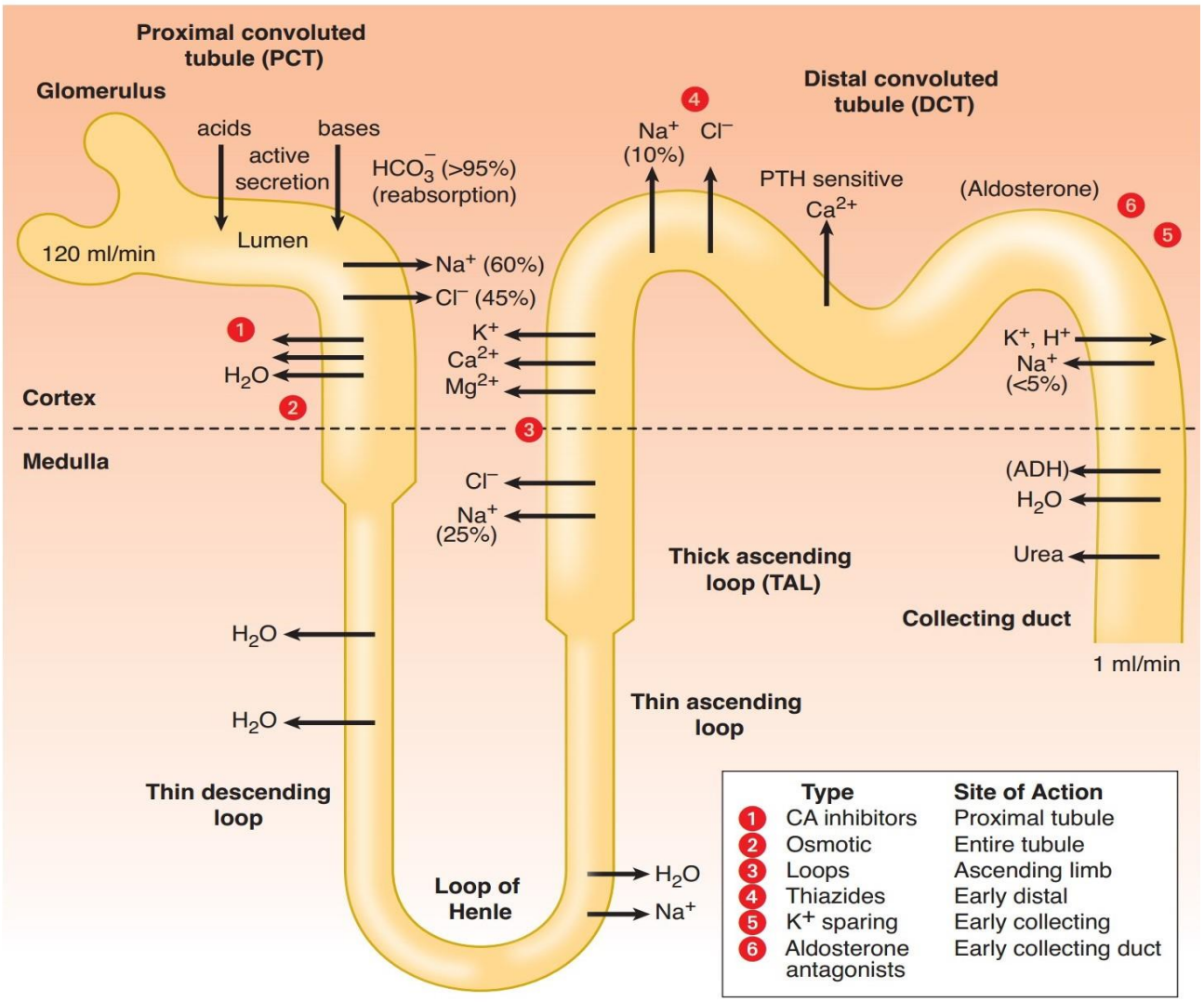
Squamous cell carcinoma of the bladder

- Chronic irritation of urinary bladder → squamous metaplasia → dysplasia and squamous cell carcinoma.
- Risk factors include Schistosoma haematobium infection (Middle East), chronic cystitis, smoking, chronic nephrolithiasis.
- Presents with painless hematuria.

CHAPTER 5

Pharmacology

Diuretics



Mannitol

- Mechanism of action:

- The proximal tubule is the main site of action of carbonic anhydrase inhibitors and mannitol.

- Mannitol is an osmotic diuretic that works by increasing plasma or tubular fluid osmolality.

- Increased plasma and fluid osmolality causes extraction of water from the interstitial space into the vascular space or tubular lumen, with subsequent diuresis.

- In the brain, water redistribution from the tissues into the plasma helps reduce edema and intracranial pressure in the setting of cerebral edema.

- Clinical use: Drug overdose, elevated intracranial/intraocular pressure.

- Adverse effects:

- Pulmonary edema, hypo- or hypernatremia, and dehydration.

- Pulmonary edema is caused by the rapid rise in volume that can also increase the overall hydrostatic pressure in the vasculature. Therefore, osmotic diuretics should be cautiously used in high-risk patients, such as those with congestive heart failure (CHF) or preexisting pulmonary edema.

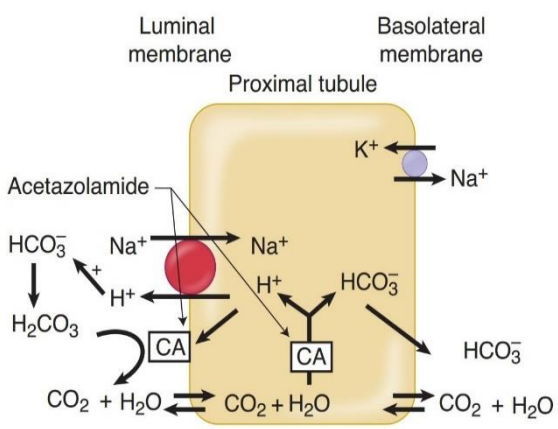
- Overaggressive treatment with osmotic diuretics can lead to excessive volume depletion and eventual hypernatremia in certain patients.

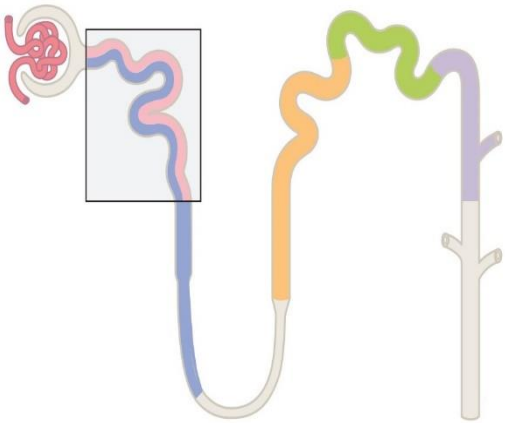
- Contraindication: anuria, HF.

Acetazolamide

- Mechanism of action:

- Carbonic anhydrase inhibition (found also in the eye and and ventricles of the brain), results in:
  - ↓ H formation inside PCT cell → ↓Na/H antiport → ↑ Na and HCO_3 in lumen → ↑ diuresis.





- Clinical use:

- Glaucoma (↓ aqueous humor production).

- Pseudotumor cerebri (↓ CSF production).

- Urinary alkalinization.

- Metabolic alkalosis.

- Altitude sickness:
  - Climbing mountains → hyperventilation →respiratory alkalosis.
  - Acetazolamide is taken as a prophylaxis because it produces acidosis which is protective.

- Adverse effects:

- Hypokalemia.
- Metabolic acidosis ("Acid"azolamide causes Acidosis).
- Proximal renal tubular acidosis.
- NH_3 toxicity.
- Paresthesias.
- Renal stones (calcium stones due to alkaline urine).
- Sulfa allergy.

Loop diuretics

- Drugs:

- Furosemide, torsemide, bumetanide.

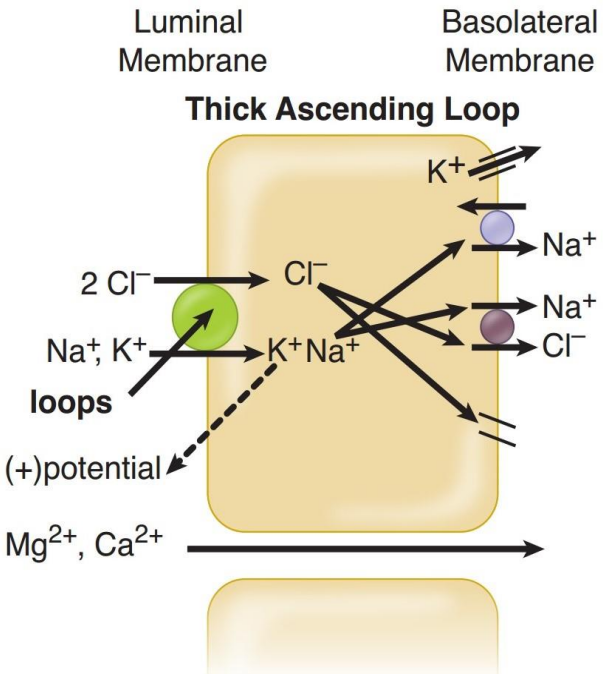
- Sulfonamide loop diuretics.

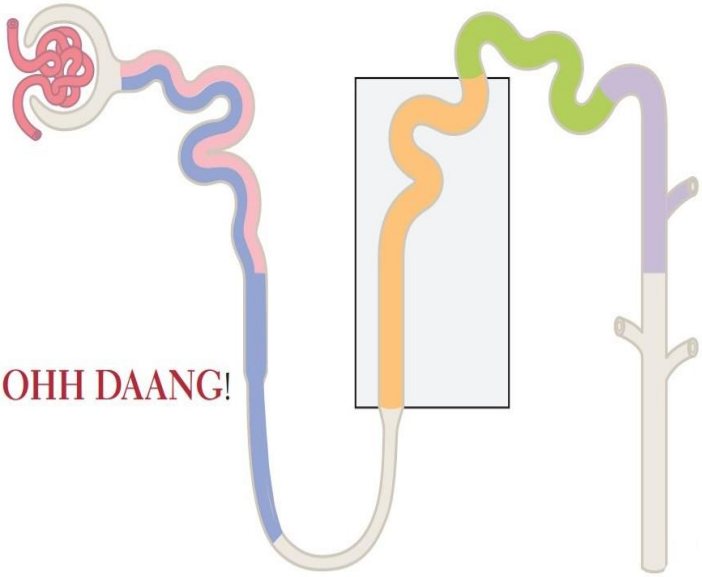
- Mechanism of action:

- Na/K/2Cl transporter inhibition in thick ascending limb of loop of Henle, results in:
  - ↓ intracellular K.
  - ↓ back diffusion of K.
  - ↓ positive potential.
  - ↓ reabsorption of Ca and Mg.
  - ↑diuresis.

- Abolish hypertonicity of medulla, preventing concentration of urine.

- Associated with ↑ PGE (vasodilatory effect on afferent arteriole); inhibited by NSAIDs.





- Clinical use:

- Edematous states (HF, cirrhosis, nephrotic syndrome, pulmonary edema), Hypertension, Hypercalcemia.

- Loop diuretics are the agent of choice in the acute setting of pulmonary edema, as they provide the maximum amount of diuresis in the shortest period of time.

- Adverse effects (OHH DAANG!):

- Ototoxicity.
- Hypokalemia, Hypomagnesaemia, Hypocalcaemia (Loops Lose Ca).
- Dehydration.
- Allergy (sulfa).
- Metabolic Alkalosis.
- Nephritis (interstitial)
- Gout (loop and thiazide diuretics are weak acids that compete with uric acid in proximal tubules for active secretion) → hyperuricemia.

❖ N.B:

1. Since the ascending limb of the loop of Henle has significant reabsorptive capacity, loop diuretics are the most potent diuretics with excellent efficacy.
   - Normally, only a small portion of filtered sodium reaches the distal tubules, so diuretics that work beyond the loop of Henle are not as efficacious.

2. Ototoxicity secondary to loop diuretics usually occurs with higher dosages, rapid intravenous administration, or when they are used in combination with other ototoxic agents (aminoglycosides, salicylates, cisplatin).
   - It typically presents as tinnitus, vertigo, hearing impairment, or deafness. Hearing impairment and deafness are usually reversible but have been reported to be permanent in some cases.
   - Of the loop diuretics, ethacrynic acid appears to have the greatest risk for ototoxicity.

Ethacrynic acid

- Mechanism of action:

- Non-sulfonamide inhibitor of cotransport system (Na/K/2Cl) of thick ascending limb of loop of Henle.

- Clinical use: Diuresis in patients allergic to sulfa drugs.

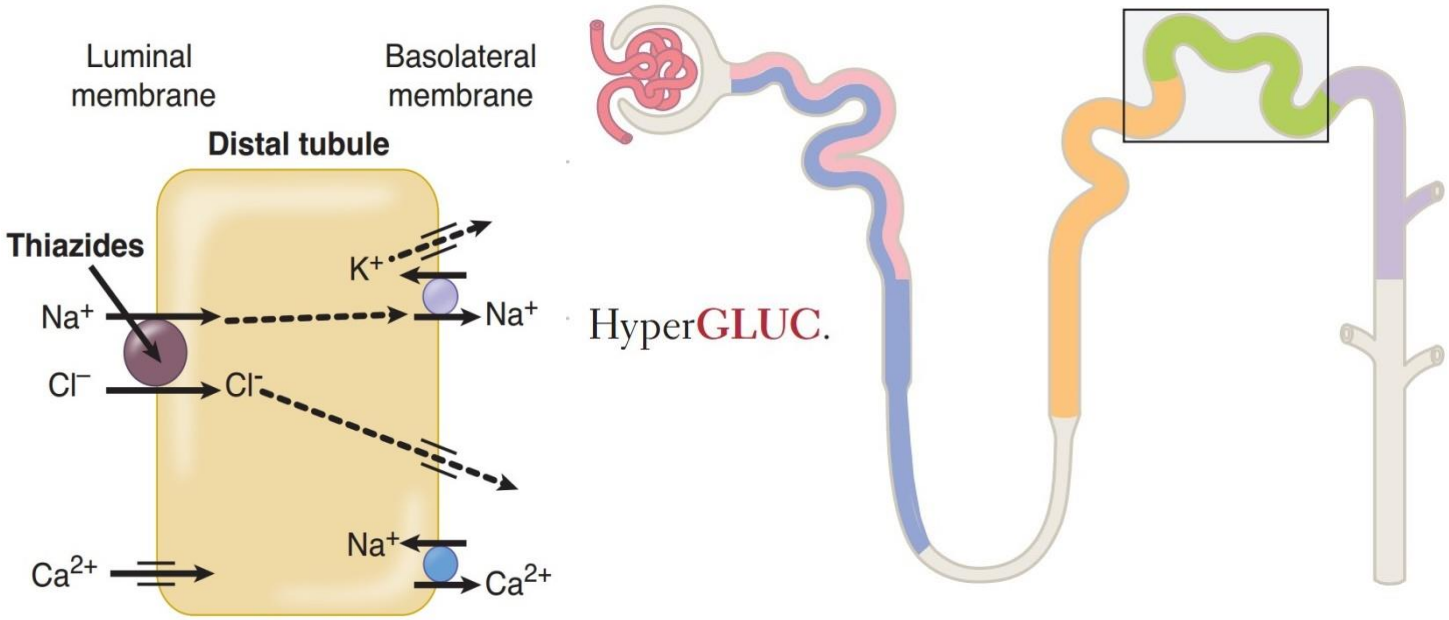
- Adverse effects: Similar to furosemide, but more ototoxic.

Thiazide diuretics

- Drugs: hydrochlorothiazide, chlorothiazide, indapamide, and metolazone.

- Mechanism of action:

- Na/Cl transporter inhibition in the distal convoluted tubules, results in:
  - ↑ luminal Na and Cl in DCT.
  - ↑ diuresis.



- Clinical use:

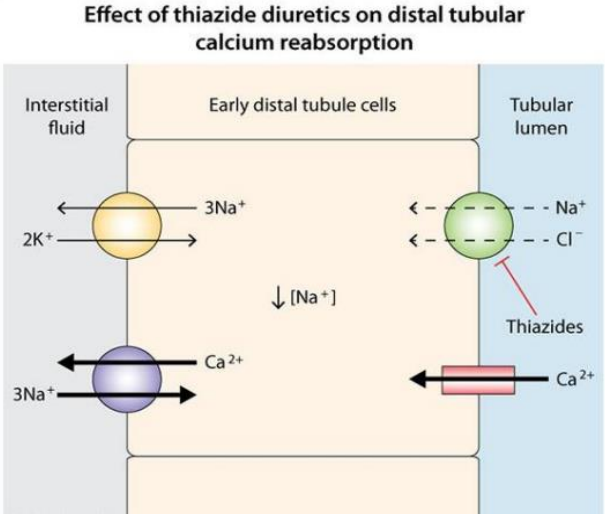
- Hypertension.
- HF.
- Idiopathic hypercalciuria and recurrent calcium kidney stones (hypocalcuria).
- Osteoporosis.
- Nephrogenic diabetes insipidus (Thiazides → loss of Na → proximal tubule compensation for sodium loss → ↑ water reabsorption).

- Adverse effects:

- Sulfa allergy.
- Hypokalemic metabolic alkalosis.
- Hyponatremia.
- HyperGLUC:
  - HyperGlycemia (hypokalemia → ↓ insulin secretion → hyperglycemia).
  - HyperLipidemia (secondary to ↓insulin secretion).
  - HyperUricemia (loop and thiazide diuretics are weak acids that compete with uric acid in proximal tubules for active secretion) → hyperuricemia.
  - HyperCalcemia.

❖ N.B:

- Hypercalciuria is a risk factor for calcium stone formation, the most common type of kidney stone.
- In patients with recurrent calcium-based nephrolithiasis, thiazide diuretics can help prevent stone formation by decreasing urine Ca excretion.
- Thiazides increase Ca reabsorption through inhibition of the Na/CL cotransporter on the apical side of distal convoluted tubule cells decreases intracellular Na concentrations.
- This activates the basolateral Na/Ca antiporter, which pumps Na into the cell in exchange for Ca.
- The resulting decrease in intracellular Ca concentration enhances luminal Ca reabsorption across the apical membrane.



Potassium-sparing diuretics

- Drugs:

- Spironolactone and Eplerenone; Amiloride, and Triamterene. Keep your SEAT.

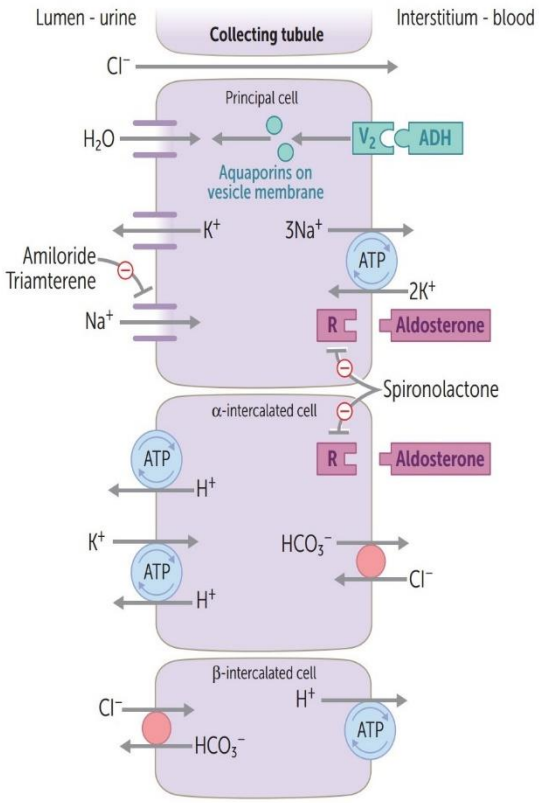
- Mechanism of action:

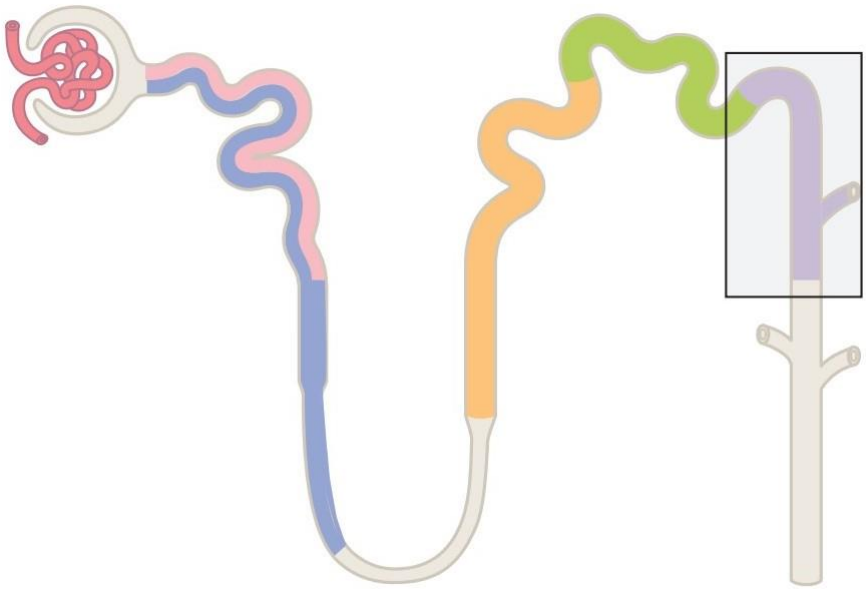
- Spironolactone and eplerenone are competitive aldosterone receptor antagonists in cortical collecting tubule with very mild diuretic effects.

- Triamterene and amiloride act at the same part of the tubule by blocking Na channels in the cortical collecting tubule.

- Clinical use:

- Hyperaldosteronism.
- K depletion (Adjunct to K wasting diuretics).
- HF.
- Hepatic ascites (spironolactone).
- Nephrogenic DI (amiloride).
- Female hirsutism (block androgen receptors).





- Adverse effects:

- Hyperkalemia and metabolic acidosis.
- Hyperkalemia can lead to arrhythmias.
- Endocrine effects with spironolactone (gynecomastia, decreased libido, and impotence).
- Eplerenone is a newer and more selective aldosterone antagonist that may produce less endocrine effects.

❖ N.B:

1. Spironolactone is an aldosterone antagonist with mild diuretic effects.

- Based on results from the RALES trial, addition of low dose spironolactone to standard therapy (ACEIs, digoxin, a diuretic), significantly reduced morbidity and mortality in class III and IV heart failure patients.
- In congestive heart failure patients, activation of the renin-angiotensin-aldosterone system leads to elevated aldosterone levels.
- Aldosterone is known to cause ventricular remodeling leading to cardiac fibrosis.
- The benefits of spironolactone in heart failure patients are more than likely secondary to inhibition of the neurohormonal effects of aldosterone, particularly on the heart leading to decreased ventricular remodeling and cardiac fibrosis.

2. Lithium therapy reduces the ability of the kidneys to concentrate urine primarily by antagonizing the action of vasopressin (antidiuretic hormone) in the collecting tubules and ducts.

- Nephrogenic diabetes insipidus caused by lithium usually resolves following discontinuation of the drug.

Electrolyte changes associated with the use of diuretics

A. Urine NaCl:

- ↑ with all diuretics (strength varies based on potency of diuretic effect).
- Serum NaCl may decrease as a result.

B. Urine K:

- ↑ especially with loop and thiazide diuretics.
- Serum K may decrease as a result.
- Diuretics that cause hypokalemia increase the risk of digoxin toxicity (because K and digoxin work on the same site).

C. Urine Ca:

- ↑ with loop diuretics: ↓ paracellular Ca reabsorption → hypocalcemia.
- ↓ with thiazides: enhanced Ca reabsorption.
- Thiazide diuretics cause hypercalcemia; loop diuretics cause hypocalcemia.

D. Blood Ph:

- ↓ (acidemia):

- Carbonic anhydrase inhibitors: ↓ HCO_3 reabsorption.
- K sparing diuretics: aldosterone blockade prevents K secretion and H secretion. Additionally, hyperkalemia leads to K entering all cells (via H/K exchanger) in exchange for H exiting cells.

- ↑(alkalemia):

- Loop diuretics and thiazides cause alkalemia through several mechanisms:

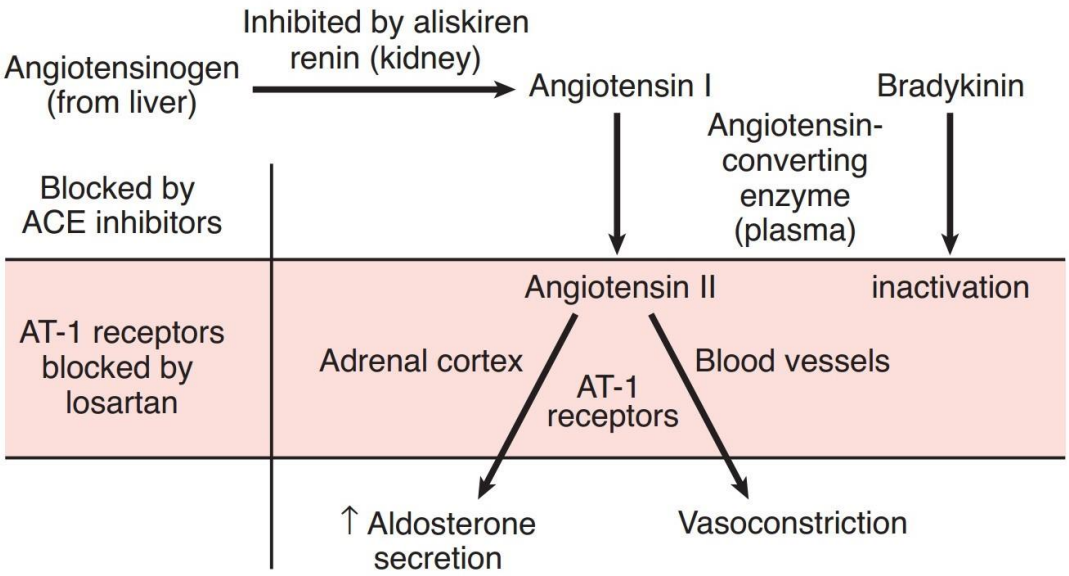
1. Volume contraction → activation of the renin-angiotensin-aldosterone system → ↑ AT II → ↑ Na/H exchange in PCT → ↑ HCO_3 reabsorption (contraction alkalosis).
2. Aldosterone acts on the collecting tubule to enhance Na reabsorption and promote K and H loss. Therefore, loop and thiazide diuretics cause hypokalemia and metabolic alkalosis secondary to volume contraction (Contraction alkalosis).
3. Other cause for metabolic alkalosis in thiazide and loop diuretics is K loss leads to K exiting all cells (via H/K exchanger) in exchange for H entering cells.

Angiotensin converting enzyme inhibitors

- Drugs: Captopril, enalapril, lisinopril, ramipril (-pril).

- Mechanism of action:

- Block formation of angiotensin II.
- Resulting in prevention of AT 1 receptor stimulation.
- ↓ aldosterone, ↓ GFR by preventing constriction of efferent arterioles.
- Levels of renin ↑ due to loss of negative feedback.
- ACEIs prevent bradykinin degradation (a potent vasodilator).



- Clinical use:

- Hypertension, HF (↓ mortality), proteinuria, diabetic nephropathy (protective).
- Prevent unfavorable heart remodeling as a result of chronic hypertension.
- In diabetic nephropathy, ↓ intraglomerular pressure, slowing GBM thickening.

- Adverse effects (CATCHH):

- Cough.
- Angioedema (due to bradykinin, contraindicated in C1 esterase inhibitor deficiency). Angioedema is a rare, but life-threatening, side-effect.
- Teratogen (fetal renal malformations).

- ↑ Creatinine (↓GFR), Hyperkalemia, and Hypotension.

- Used with caution in bilateral renal artery stenosis, because ACE inhibitors will further ↓ GFR → acute renal failure.

Angiotensin II receptor blockers

- Drugs: Losartan, candesartan, valsartan (-sartan)

- Mechanism of action:
- Selectively block binding of angiotensin II to AT1 receptor.

- Effects similar to ACE inhibitors, but ARBs do not increase bradykinin.

- Clinical use:
- Hypertension, HF, proteinuria, or diabetic nephropathy with intolerance to ACE inhibitors (cough, angioedema).

- Adverse effects:
- Hyperkalemia, ↓ GFR, hypotension; teratogen.

Aliskiren

- Mechanism of action:
- Direct renin inhibitor, blocks conversion of angiotensinogen to angiotensin I.

- Same results as ACEIs on BP mechanisms, but Aliskiren does not interfere with bradykinin degradation.

- Clinical use: Hypertension.

- Adverse effects:
- Hyperkalemia, ↓ GFR, hypotension.

- Relatively contraindicated in patients already taking ACE inhibitors or ARBs