**-Requirements for diluted urine** : there should be no ADH or very little ADH , no interstitial hyperosmolarity, and we can use diuretics .These are the cases where urine can be diluted .

**-in case of concentrated urine** there should be ADH, without ADH there is no concentration even if there is hyper-osmolarity of medullary interstitium because ADH opens the water channels .Hyper-osmolarity from the medulla and urea ‘’ it is responsible for 50% of concentration’’ are both required for this concentration ,last but not least the presence of an active vasa recta because it reserves this concentrated urine .

\*In order to determine whether the urine is concentrated or diluted you have to measure what is called **free water clearance** ( water without any solutes) we calculate it by subtracting osmolar clearance from volume , if the free water clearance is **positive** it means that the urine is **diluted** , if it was **negative** that means that the urine is **concentrated** in other words if the urinary osmolarity/plasma osmolarity is less than 1 the clearance will be positive if it is more than 1 the clearance will be negative.

**\*Disorders of Urine Concentrating Ability** : if there is no ADH there’s no ability to concentrate urine. the reasons of ADH deficiency may be : 1.diabetes insipidus "relative or absolute deficiency of ADH" , 2.the absence or the abnormalities in the receptors " for the action of the hormone you should have the hormone and the receptor in the case that they are not active this is called nephrogenic diabetes insipidus " so it is a failure to respond to ADH because of the receptors is impaired for Nacl reabsorption , 3.drugs induced renal damage ,4. Malnutrition “decreased urea concentration " remember that urea is responsible for 50% of the urine concentration” ,5.kidney disease: pyelonephritis, hydronephrosis , chronic renal failure.

Ability to concentrate urine "the graph ": normally the maximal urine concentration is 1200 mOsm/L **(if the kidney is normal )**, but if the number of nephrons becomes less the concentrating ability will become less . The abnormality in concentrating urine is an indication of renal disease so the diluted will become minimum 50 and then it goes to 300 which is the maximum.

Total renal excretion ( the table ) " the doctor said that the numbers are not very important he just read the slides "

Control of extracellular osmolarity :

the mechanism of secretion of ADH; it is secreted in response to a change in the osmolarity "hyperomolarity and hypernatremia " so ADH stimulates thirst with the help of another hormone which is angiotensin 2.

Osmoreceptorantidiuretic hormone (ADH) feedback mechanism :

There is water deficit ,ADH increases the osmolarity of the extracellular fluid and that activates the osmoreceptors in the hypothalamus , ADH secretion becomes high in the posterior pituitary , as well as plasma ADH becomes high as a result water reabsorption so it will increase water excretion so this will make a negative feedback on water deficit.

Hypothalamus is the source of ADH , it is secreted in hypothalamus receptors then released to posterior pituitary , acts on the distal tubules and collecting ducts of the kidney.

**The stimuli for ADH secretion** : 1. increase osmolarity , 2.decreased blood volume " cardiopulmonary reflexes " [RECALL: in regulation of blood pressure when there is a decrease in the blood volume ,there is regulation of the receptors in right atrium to the receptors in hypothalamus so it will release ADH which in turn will reabsorb water so it will increase the extracellular fluid volume and that will increase the blood pressure] , 3.other stimuli, the most important one is nicotine : people who smoke do not have much urination because when there is an increase in the sympathetic stimulation the ability to urinate will be more because GFR will decrease so reabsorption will decrease.

Slide 31 : if the plasma osmolarity increases ADH increase and the curve is curvy linear not linear .

Factors that decreases the ADH secretion are the opposite of those who stimulate it .Other factors: clonidine (antihypertensive drugs) ,haloperidol (antipsychotic, Tourette’s) and alcohol. (slide 32)

\*Stimuli for thirst and factors that decrease thirst are the same as slides 33 and 34 .

Slide 35 : for the normal curve whatever the sodium intake there is regulation for sodium in the plasma to be almost constant due to the compensation of loss of water or conservation of water , ADH causes reabsorption and if it is blocked then this will change sodium concentration so there will be a high variation in sodium concentration and the curve will change .

-if the intake of sodium is high it's concentration will be high and vice versa and this means that the regulation for sodium concentration in plasma is blocked , but in the normal situation whatever is the intake of sodium the concentration will be constant, so the relation will be linear and this is **the normal negative feedback** which decreases the variation (in the case of the block, there’s no negative feedback and the variation increases ) . an example of the negative feedback receptors is the baroreceptors that regulate blood pressure ;if they are absent the blood pressure will be too high then too low " according to the change in gravity ".

if we block aldosterone’s receptors there will be no change in sodium concentration if ADH is present since ADH is the one that controls water ,so aldosterone will go parallel it will decrease sodium concentration but not too much " there is less variation" . any decrease in aldosterone will decrease sodium concentration and vice versa but it will be parallel to the curve . angiotensin 2 has a direct effect on sodium concentration but not like aldosterone , aldosterone is more important in regulating sodium chloride.

**A beginning of a new lecture ‘’ regulation of acid- base balance (PH)’’:**

We talked in the previous lectures about renal and urinary systems that the main function of them is the regulation of acid- base balance by buffers.

\***acid- base balance regulation occurs By two major systems : respiratory system and renal system** .respiratory through release of CO2 and O2 conservation , normal PH is between 7.35 to 7.45 decrease in the PH is called acidosis and increase in PH is called alkalosis , in the case of acidosis the decrease of PH means the increase of hydrogen ions because PH=log 1/{H+} or –log {H+} , the opposite is for alkalosis .

There are two types of acidosis and alkalosis : first type is due to the abnormality in renal system that is called **metabolic** acidosis or metabolic acido-alkalosis so the **cause of metabolic is usually the kidney** , the second type is **respiratory** and **the cause is the lung**.

-for example if someone has a respiratory failure he is not taking a good respiration ,this means that he is collecting more CO2 in his blood , CO2 will bind to water and in the presence of carbonic anhydrase this will form carbonic acid . carbonic acid in the presence of carbonic anhydrase 2 dissociates to hydrogen and bicarbonate and this will increase hydrogen concentration . As a conclusion **respiratory** failure (too much CO2) causes acidosis . now in case of acidosis in the metabolic , the kidney will make effect by bicarbs excretion and reabsorption , if we have less bicarbonate in our body there will be acidosis but in this case metabolic acidosis .

-in order to differentiate between metabolic and respiratory ,we look to CO2 and bicarbs , if the CO2 is high it will be respiratory , if the bicarbonate is low it will be metabolic and vice versa applied to alkalosis.

- If we are talking about respiratory alkalosis it means CO2 is low " hyper ventilation" .this might occur in psychotic people ,which in turn stimulates the nerves in the neuromuscular junction ,resulting in spasm . This might become dangerous by driving the person to bite his own tongue and then swallow it . The treatment for this case is by making the person breathe through a paper bag to get back CO2 and PH changes eventually .

- in order to prevent acidosis and alkalosis from development we have to regulate hydrogen concentration in our extracellular fluid to stay almost normal . normally our body from metabolism and the food we eat that is rich with phosphorous and phosphate makes phosphoric acid and also here is sulfate that makes sulfuric acid ,these acid have to be excreted .they are called **"non-volatile acids** " so each day we are consuming 80 mmol of non-volatile acids .

[volatile acids : CO2 is one of them and they can be regulated by respiration .]

Slide 2 : hydrogen is precisely regulated at PH range (7.2-7.45) below **7.2 is acidosis and above 7.45 is alkalosis** .

1. Body fluids chemical buffers (rapid but temporary) : proteins are important intracellular buffers ( more intracellular than extracellular) and the best example is hemoglobin in RBC's
2. Lungs (rapid, eliminates CO2) : when hydrogen increases this will increase ventilation and in turn increases CO2 loss . this what we might face in the case of diabetes mellitus in this case there will be acidosis because of the retention of ketone bodies ( if there is no insulin ,carbohydrates will be converted to ketone bodies that are acids and those people will have hyperventilation then it will stop and begin again and continue in a cycle ).
3. Kidneys (slow, powerful); eliminates non-volatile acids:

There is something in the regulation that is called **the gain**

**(how much is being corrected/ how much is still in error)** . if the gain is high the system will be more powerful as a regulator and controller system , so the gain in the kidney is very high but unfortunately it's very slow , in contrast, the gain in the respiratory is low but rapid .

- an example in the control of blood pressure there are two systems;the first is the short term system which is the baroreceptor which regulates the blood pressure in ml seconds but their gain is low and it means that it doesn’t correct the blood pressure 100% there will still be some error .

\*the kidney eliminates the non-volatile acids through the secretion of hydrogen , reabsorption of bicarbonate and the most important one is the generation of new bicarbonate. since food generates extra acids , the body needs to compensate for this by generating new bicarbonate for the neutralization . and **the source for this generation is CO2** . buffers that generate new bicarbonate are ammonia and phosphate ,these buffers are responsible of the generation of new bicarbonate while other buffers reabsorb bicarbonate.

Slide 3 : buffer system of the body :

1.Bicarbonate : most important extracellular buffer because it's very rapid

2.Phosphate 3.Ammonia

4.Protein : is an important intracellular buffer

(60-70% of buffering is in the cells)

Slide 4 : importance of buffer system :

Normal hydrogen concentration (the number is not very important ), Amount of non-volatile acids produced is around 60-80 mmol/day from food and those 80 mmol must be excreted. then we will divide it by 42( which is the percentage of extracellular fluid in our body if the body weight is 70 then 70\*60=42 )

So the result will be 47,500 times > normal H+ concentration so it is much less than the normal PH so it must be excreted .

Slide 5 :same as the slide

Slide 6 : the curve

From the curve we can notice that in the middle there is a significant change in the PH but at the sides of the curve any little change won’t affect the PH that much .as a conclusion anything around the pKa will result in a greater change, if Pka is more closer to PH the effectiveness of the buffering system is more .

Slide 7 : in the bicarbonate buffer the Pka is 6.1 which is not very close to normal extracellular PH (7.4) but it is okay because **it's very rapid and also it’s regulated by two systems : lungs and the kidney.**

Slide 8 : if the concentration of hydrogen is more this will increase the alveolar ventilation and decreases Pco2 which makes a negative feedback on PH , the respiratory centers don't respond to Pco2 but for [H+] because CO2 binds with water and dissociates to give hydrogen therefore hydrogen stimulates the respiratory centers .

The doctor talked about some points from doctor yanal’s lectures about central and peripheral chemoreceptors ; the central chemoreceptors they adapt after a while and the peripheral chemoreceptors will remain the effective ones , in case of chronic respiratory disease because of chronic change of PH the central chemoreceptors adapt so they are no more going to respond to hydrogen concentration or PH but the peripheral are sensitive to any change in PO2 because of that we must be very careful with chronic respiratory disease patients not to give them 100% oxygen or he will die because the oxygen will inhibit the chemoreceptors resulting in no more peripheral chemoreceptors that his survival depends on .

Feedback Gain = 1.0 to 3.0 is not that much high but it is high in the renal although they are slow. for example if blood pressure is 100 then it increased to 120 the baroreceptors will modify it to 105 ,the correction is 15 and the error is 5 so the gain is 3 which is very low but body fluid renal system it will increase the blood pressure to 100.001 the correction is almost 20 and the error is almost zero so the gain is 20/0 which equals infinity so the gain is infinite (very high).

Slide 9 : Kidneys eliminate non-volatile acids (H2SO4, H3PO4) (~ 80 mmol/day) then filtration will occur to bicarbonate and what is filtered is reabsorbed and around 1 mmol will be excreted . the new 80 mmol of H+ will be titrated by generating new bicarbonate 80 mmol by the use of ammonia and phosphate buffers.

Kidneys conserve HCO3- and excrete acidic or basic urine depending on body needs.

Slide 10 : bicarbonate in the proximal tubule will not remain like sodium instead it decreases because there are more reabsorption for bicarbonate but not like glucose and amino acids 100% and what is left is 1 mEq/day . **the reabsorption is more in the proximal tubule not because of the carbonate but because the secretion of hydrogen**.

Slide 12 : in proximal tubules ; bicarbonate that is filtered is reabsorbed , hydrogen is secreted in exchange with sodium , hydrogen will bind to bicarbonate which in turn will be converted to carbonic acid and then it will dissociate by the help of carbonic anhydrase to HCO3- and water , CO2 is a gas and it's lipid soluble, it will get out of the cell and bind to water forming carbonic acid and then it will dissociate to bicarbonate and hydrogen , bicarbonate will be reabsorbed .

-the buffer is bicarbonate and the Pka is 6.8 and the tubular PH; the lowest is 6.8 not more and not less because tight junctions are not tight in the proximal tubule instead they are loose , whereas in the distal tubule they are tight so the distal can maintain higher gradient for PH ( it might reach 4.5) and it’s the least PH that can be maintained so there is no urine with PH less than 4.5 , in the distal tubule there is a hydrogen pump and the buffer is carbonate buffer so the highest PH is 6.7 due to looseness of tight junctions in the proximal tubule and the minimal is 4.5 due to strength of tight junctions in distal tubules.

 