

**UNIVERSITY OF JORDAN**  
**DEPT. OF PHYSIOLOGY & BIOCHEMISTRY**  
**RENAL PHYSIOLOGY**

**For Third-Year Medical Students** Spring 2017/2018 Course Outline

Textbook of medical physiology, by A.C. Guyton and John E. Hall,  
Thirteenth edition, 2016. (Numbers in parenthesis and small font are for the 12<sup>th</sup> edition)

**The (10) lectures will cover the following topics:**

1. Functional anatomy of the kidney. Role of the renal system in homeostasis (the functions of the kidney)...*one lecture.*
2. Glomerular filtration...*two lectures.*
3. Tubular reabsorption and secretion...*two lectures.*
4. Concentration and dilution of urine...*one lectures.*
5. Role of kidneys in Acid-base balance...*two lectures.*
6. Pathophysiology and dialysis...*one lecture.*

**INTRODUCTION TO RENAL PHYSIOLOGY**  
**(Lecture 1)**

**Lecture Outline:**

- I. General physiological concepts and overview of the kidney.
- II. Functional Anatomy of the Kidney.
  - A. Gross Anatomy.
  - B. Internal anatomy.
  - C. Innervation of the Kidney.
  - D. Blood supply
- III. The nephron
  - A. Types
  - B. Ultrastructure
  - C. The Juxtaglomerular Apparatus.
- IV. Renal Plasma Flow (RPF) and Renal Blood Flow (RBF) estimation.

**OBJECTIVES:** After attending this lecture, and completing the required reading, students should be able to:

1. Know the amount and distribution of water in body compartments. 305-9 (285-289)
2. Define: osmole, mole, equivalent, osmolarity, osmolality. These are very important terms and should be considered seriously. 53-54 and 310-12 (51-52 and 289-293)
4. list the primary function of the renal system. 323-324 (303-4)
5. Identify the external & internal gross anatomical features of the kidneys. 324-6 (305-6).
6. Draw and describe all parts of a nephron from the glomerular (Bowman's) capsule to the collecting tubule. Show the following : (+++ your histology course).  
glomerular (Bowman) capsule, proximal tubule (early convoluted & late straight), loop of Henle (thin descending, thin and thick ascending distal tubule (early straight & late convoluted), & collecting duct

(cortical, outer medullary, & inner medullary). Collectively, the kidney is a combination of:

- A. Ultrafiltration device (the glomerular apparatus)
  - B. Epithelium which modifies the ultrafiltrate (tubules)
7. List the structural differences between cortical & juxtamedullary nephrons. 326 (306).
  8. Compare the structural differences among nephron segments using the following criteria : # of mitochondria, brush border, intercellular & basal channels & tight junctions. 353-8 (329-334) + (Histology lects.
  9. Describe the structure of the glomerular filtration barrier (endothelial-capsular membrane). How is this membrane adapted for filtration? (Understand how the characteristics of glomerular filtration barrier are incorporated in value of  $K_f$ ) (335-6) 312-3+ lecture 3.
  10. Describe the structure & importance of the juxtaglomerular apparatus (JGA). Fig. 27-10 (26-18)
  11. How are nephrons supplied with blood? Follow the blood flow through the kidney beginning in the renal artery & ending in the renal vein. Special attention to: afferent arteriole, efferent arteriole, glomerular capillaries, peritubular capillaries & vasa recta. 340-342 (316-319)
  12. Have an idea about the nerve supply to the kidneys.
  13. Define RPF and RBF.
  14. Describe the method used to estimate RPF & RBF (effective and true RPF). know why PAH is used for this purpose and why  $C_{PAH}$  underestimate RPF by 10%. 340-3

Notes:

The major processes involved in formation of the urine require that the kidneys receive a rich blood supply in order to proceed normally. The ultrafiltrate produced at the glomerulus comes from this blood supply. In humans, the normal renal plasma flow (for both kidneys combined) is about 650 ml/min. If we assume that the hematocrit is about 46%, then the total renal blood flow (again for both kidneys combined) is about 1200 ml/min or about one forth the resting cardiac output.

## **ASSESSMENT OF RENAL FUNCTION**

# GLOMERULAR FILTRATION

## (Lecture 2)

### Lecture Outline:

- I. Glomerular filtration Rate (GFR).
  - Tubular load.
  - Measurements.
  - Dynamics.
  - Control
- II. Regulation of Renal Blood Flow.

**OBJECTIVES:** After attending this lecture and completing the required reading, students should be able to:

1. Understand the three major processes involved in the formation of the urine:
  - Formation of an ultrafiltrate of the plasma at the renal glomerulus.
  - Reabsorption of filtered water and other substances by the renal tubules.
  - Secretion of substances into the initial filtrate by the renal tubules.
2. Define the process of ultrafiltration at the renal glomerulus. Define filtration coefficient (K<sub>f</sub>), filtration fraction, extraction ratio & tubular load. Chapter 26-27 (310-314, 341-3)
3. List the major differences which make the permeability of the glomerular capillary more than the systemic capillary “as above”
4. Describe the dynamics of GFR (Starling forces), compare them with those of systemic capillary. Set up an equation to indicate how effective filtration pressure (P<sub>eff</sub>) is calculated. Chapter 27 (314-316)

### Balance of Forces (Starling pressures) Involved in Glomerular Ultrafiltration

	Rat	Dog
Mean Arterial Pressure (mmHg)	110	100
Glomerular Capillary Hydrostatic Pressure (mmHg)	45	60
Bowman's Space Hydrostatic Pressure (mmHg)	10	18
Capillary Colloid Osmotic Pressure (mmHg)	28	32

5. Which forces (Starling pressures) are regulated physiologically and which are not?
6. GFR is a product of filtration coefficient (K<sub>f</sub>) and filtration pressure. Analyze (K<sub>f</sub>) in more details. “K<sub>f</sub>= constant of proportionality called the filtration coefficient. It is a function of the area (A) of the capillary available for filtration and the permeability per unit area.
7. Define ultrafiltrate and determine its composition. What methods scientists used to study the composition of ultrafiltrate. 335-336 (312-3)
8. Why albumin is restricted from filtration (size, charge, and shape

- limits of particles filtered). Fig 27-3 (Fig. 26-12 pp313) Table 27-1 (Table 26-1)
9. Describe the method used to measure GFR (Inulin or creatinine clearance).365-6 and table 28-4 (340-2): Still more in coming lectures.
  10. List the glomerular marker criteria.
  11. Why at different plasma inulin concentration, the calculated GFR is constant. (lecture).
  12. Why is it needed to uncouple renal function from systemic arterial BP (autoregulation of GER). Too low or too high GFR is not desirable, WHY?
  13. know the mechanism of autoregulation of GFR (tubuloglomerular feedback). Understand and describe the relationship of plasma flow along the glomerular capillaries to the rate at which glomerular ultrafiltrate is formed. 342-4 Table 27-3 Fig.27-9(319-321 (Table 26-3 pp 317) Fig 26-17 pp 319)
  14. Draw a curve showing the relationship between systemic arterial blood pressure, RBF, GFR, and urine output.

**Note:**

GFR “in men  $125 \pm 15$  ml/min/1.73 m<sup>2</sup> (surface area) and in women is  $110 \pm 15$  ml/min/1.73 m<sup>2</sup> (10-15% less)

**Autoregulation:**

Under normal circumstances, the renal blood flow remains remarkably constant despite changes in systemic mean arterial pressure (and thus the mean arterial pressure delivered to the kidneys in the renal arteries). This independence of blood flow from mean arterial pressure is termed autoregulation because the control resides within the organ itself.

**TUBULAR FUNCTION I  
GENERAL CONCEPTS  
(Lecture 3) Chapter 28**

## Lecture Outline:

- I. The micropuncture technique.
- II. Different forms of transport.
- III. Clearance : definition, usages & interpretations.

**OBJECTIVES:** After attending this lecture and completing the required reading, students should be able to:

1. Describe the micropuncture technique: usage & limitations (lecture).
2. Give a general account of how micropuncture technique can aid our understanding in tubular reabsorption and secretion.(lecture).
3. know the general principles of transepithelial solute & water transport. (323-328) + previous physiology lectures.
  - Passive transport: Movement of a substance down its electrochemical gradient. This may or may not involve a carrier.
  - Active transport: primary & secondary active (cotransport countertransport).
  - Tubular maximum ( $T_m$ ): This represents a maximum rate of transport that the tubules cannot exceed.Gradient limitation: This represents a limitation of transport by the concentration gradient against which it can occur.
4. Distinguish transport steps in the reabsorptive process at luminal and peritubular membranes, with glucose and amino acids as examples.
5. **Understand the concept of clearance in renal physiology.**  
Clearance of X ( $C_x$ ): (minimum amount of plasma per unit time which provides the amount of X excreted in the urine in the same unit of time) ... pay attention to the unit... Why clearance is important concept in renal physiology? Link this concept to net reabsorption or secretion for substance X.
6. Use the appropriate equations to estimate  $C_{\text{inulin}}$ . Comprehend relationship of inulin clearance to glomerular filtration rate.
7.  $T_m$  for PAH is 80 mg/min. Draw a curve having a plasma concentration of PAH in the X-axis, and make the Y-axis as PAH (filtered, secreted, excreted, and clearance). This is the PAH titration curve. Show the  $T_m$  & splay.
8. In contrast with inulin; at different plasma [PAH], the estimated RPF is not the same. How do we determine the critical plasma [PAH].
9. Why  $C_{\text{PAH}}$  &  $C_{\text{creatinine}}$  are important.
10. Why at high plasma concentrations, both  $C_{\text{PAH}}$  and  $C_{\text{Glucose}}$  converge to  $C_{\text{Inulin}}$ .
11. Interpret the followings.  
 $C_x = \text{zero}$        $C_x = C_{\text{Inulin}}$        $C_x > C_{\text{Inulin}}$        $C_x < C_{\text{Inulin}}$
12. Using micropuncture technique, interpret the followings:

$$\begin{aligned} (TF/P)_x &= 1 & (TF/P)_x &> 1. & (TF/P)_x &< 1. \\ (TF/P)_x / (TF/P)_{\text{Inulin}} &= 1. & (TF/P)_x / (TF/P)_{\text{Inulin}} &> 1. \\ (TF/P)_x / (TF/P)_{\text{Inulin}} &< 1. \end{aligned}$$

14. Calculate the rate of net renal tubular reabsorption or secretion.

( $\pm T_x$ ) Net reabsorption or secretion = amount filtered - amount excreted

-This can be determined for the whole kidney by subtracting the rate at which the substance is excreted from the rate at which it is filtered, as shown in the equation below:

$$\pm T_x \text{ (mg/min)} = (\text{GFR (ml/min)} * P_x \text{ (mg/ml)}) - (U_x \text{ (mg/ml)} * V \text{ (ml/min)}).$$

Therefore, interpret the following for a freely filtered substance:

-  $T_x = \text{zero}$  -  $T_x > \text{zero}$  (+ve value) -  $T_x < \text{zero}$  (-ve value).

15. If you understand the above, you can speculate the concentration of X at different points across the nephron. Figs. 28-7 & 28-15 (Figs. 27-7 & 27-14)

Note:

Calculation of GFR:

$$\text{GFR} = \frac{[U_{in} * V]}{[P_{in}]}$$

*The term "clearance" has been applied to the value computed by this equation. The reason for this term is that the value represents the quantity of blood plasma from which the substance in question (in this case, inulin) has been completely removed (cleared) during its passage through the kidney*

### **Creatinine clearance:**

Creatinine is an endogenous substance that is formed from creatine in muscles and normally is maintained at a constant level in the plasma for any given individual. The clearance of creatinine is used clinically as a measure of GFR (and we will use it for this purpose in the laboratory exercise on human renal function). However, although creatinine is freely filtered, it is also secreted to a small extent by the organic cation transport system in the renal tubules. Therefore, the clearance of endogenous creatinine always exceeds the simultaneous clearance of inulin by a small amount and gives a measure of GFR that is greater than the true GFR. However, this difference is small and the convenience of using endogenous creatinine, which does not have to be infused, more than makes up for this small error.

**GFR decreases 1%/yr after the age of 40**

**$C_{cr}$  decreases 8 ml/min/1.73 m<sup>2</sup>/decade after the age of 30**

### **Estimation:**

**GFR = [(140-age in yr) X (weight in kg)]/(72 X serum creatinine in mg/dl).**

Values for women are 85% of the predicted.

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

## TUBULAR FUNCTION II

### REABSORPTION AND SECRETION

#### (Lecture 4) Chapter 28

#### **Lecture Outline:**

- I. Absorptive capabilities of different tubule segments.
- II. Filtration plus tubular reabsorption of amino acids and glucose.

### III. Transport maximum (T<sub>m</sub>) and Glucose Titration curve

**OBJECTIVES:** After attending this lecture and completing the required reading, students should be able to:

1. Define tubular reabsorption. Why is it important? (323-4)
2. What chemical substances are normally reabsorbed by the kidney?  
Table 28-1 (Table 27-1)
3. Describe how glucose & amino acids are transported. Where does this process occur? (Fig.2803) (Fig. 27-3)
  - Glucose reabsorption involves two steps:
    - 1- transport into the cells against an electrochemical gradient at the luminal membrane by sodium-coupled secondary active transport; and
    - 2- transport from the cells into the peritubular fluid (and thence into the blood) down an electrochemical gradient via carrier-mediated diffusion.
4. What is tubular transport maximum (T<sub>m</sub>)? 331
5. Draw a diagram illustrating glucose titration curve (GTC). Indicate renal threshold & T<sub>m</sub> for glucose. Fig028-4 (Fig. 27-4).
  - Glucose has a maximum rate of reabsorption (T<sub>m</sub>). In humans, this is about 375 mg/min which is reached at a plasma concentration of about 3 mg/ml (300 mg/dl).
6. Distinguish between renal glycosuria and that due to D.M.
7. Understand why the kidney is not a major regulator for blood glucose, but it does regulate blood phosphate levels. Draw phosphate titration curve.
8. Draw a nephron & show approximately [TF/P] of : inulin, glucose, & amino acids at 5 different sites across the nephron. Fig 28-15 (Fig.27-14)
9. Define tubular secretion. Why is it physiologically important?
10. What chemical substances are normally secreted by the kidney?
11. Probencid decreases penicillin clearance across the kidney. Is this clinically important.

**Note:**

#### **Comparison Of Glucose Clearance With Inulin Clearance**

Clearance of glucose can be compared with clearance of inulin. At low plasma concentrations of glucose, all filtered glucose is reabsorbed, no glucose appears in the urine, and there is no clearance of glucose (no plasma is cleared of glucose by renal excretion). Once the Threshold is exceeded, glucose starts appearing in the urine and a glucose clearance can be measured. From this



point on, as the plasma glucose concentration is increased, glucose clearance increases. However, at very high plasma concentrations, the glucose clearance begins to level off and approaches the inulin clearance asymptotically. This occurs because the plasma clearance of glucose comes to be more and more the result of the glucose filtered. The amount of glucose reabsorbed remains constant and has a smaller and smaller effect on the degree to which plasma is cleared of glucose. **Remember:**

Glucose clearance represents the quantity of plasma from which glucose is completely removed (cleared) during its passage through the kidney.

- Transport of Glucose as example of tubular reabsorption:

- Two **sodium-glucose cotransporters have been identified, cloned, and sequenced from the luminal membrane of proximal tubules.**

These are termed SGLT1 (very high affinity for glucose but only a small capacity) and SGLT2 (modest affinity for glucose but a large capacity). SGLT stands for sodium glucose luminal transporter.

- Carrier-mediated passive transport of glucose from the cells into the peritubular fluid involves transporters belonging to a family of passive glucose transporters found in many cells. This is the GLUT family (for Glucose Transporters).

- Amino acids, inorganic phosphate, lactate, citrate (and other Krebs cycle intermediates) are reabsorbed by similar processes in proximal tubules.

## Proteinuria:

Less than 150 mg/day are excreted.

Screening test for proteinuria

DIPSTICK GRADE	Protein concentration mg/dl
0	0-5
Traces	5-20
+1	30
+2	100
+3	300
+4	1000

## TUBULAR FUNCTION III REABSORPTION AND SECRETION (Lecture 5+6)

Lecture Outline:

- I. Filtration plus tubular reabsorption of  $\text{Na}^+$ .
- II. Gradient and time dependency of Na transport.
- III. Rate of NaCl transport & its effect in ECF volume.

#### IV. Tubular secretion of $K^+$ & $H^+$

**OBJECTIVES:** After attending this lecture and completing the required reading, students should be able to:

1. Understand  $Na^+$  compartmentalization & why it is directly related to ECF volume contraction & expansion.
2. Identify the excretory routes for  $Na^+$  (Sodium balance).
3. Explain why  $Na^+$  reabsorption is of a special physiological interest. link it with ECF volume, pH,  $K^+$  transport .. etc. How  $K^+$  &  $H^+$  are related to sodium reabsorption?
4. Calculate the filtered load for  $Na^+$ , the rate of loss in the urine, and finally the rate of reabsorption.
5. Compare the functional differences among nephron segments using the following criteria: permeability to urea, NaCl, & water.  
329-334
  - Recall the steps in the movement of  $Na^+$ ,  $Cl^-$ ,  $K^+$ ,  $H^+$ , and water across the luminal and peritubular membranes of the proximal tubule. Understand why  $Na^+$  transport at proximal tubule is gradient-time dependent (no  $T_m$ ).
  - Recall the steps in the movement of  $Na^+$ ,  $Cl^-$ ,  $K^+$ ,  $H^+$ , and water across the luminal and peritubular membranes of distal nephron segments.
6. Draw a diagram illustrating the reabsorption of Na relative to that of water at different nephron segments.
7. What are the three factors which regulate  $Na^+$  transport in the nephron (GFR, Aldosterone, and ANF). Write the mechanism of action of aldosterone on  $Na^+$  reabsorption.
8. How chloride reabsorption is related to sodium reabsorption?
9. Understand how Aldosterone, thirst center, ADH, & salt appetite are involved in the regulation of ECF volume.
10. Understand the compartmentalization of  $K^+$  at our body.
11. Define : hyperkalemia & hypokalemia. Why do we care about  $[K^+]$ ? refer back to your CVS lectures.
12. Recall the processes involved in regulation of  $K^+$  excretion, including:
  - a. Tubule sites of regulation
  - b. Regulation processes at basolateral and luminal membranes
  - c. Effects of dietary intake of potassium
  - d. Effects of alkalosis and acidosis
  - e. Effects of diuretics
  - f. Effects of aldosterone
  - g. Effects of dietary intake of sodium

13. How the kidney handle the  $K^+$  (filtered, reabsorbed, secreted, clearance) and the role of the *principal* cells.

**Note:**

**Renal Regulation of  $K^+$  Balance:**

Because the dietary intake of  $K^+$  is so variable and is not regulated physiologically, overall  $K^+$  balance is regulated by regulation of renal  $K^+$  excretion.  $K^+$  is freely filtered at the glomerulus and about 65% of the filtered load is reabsorbed in the proximal tubule so that about 35% remains at the end of the proximal tubule. Approximately 25% more of the filtered load is reabsorbed in the thick ascending limb of Henle's Loop so that about 10% remains at the beginning of the early distal tubule. This degree of reabsorption in the proximal tubule and thick ascending limb (total of 90%) occurs in the normal kidney regardless of the body's need to excrete or conserve  $K^+$ . Therefore, regulation of the amount of  $K^+$  excreted occurs in the late distal tubule and collecting ducts. Reabsorption can occur in the intercalated cells, but at normal dietary intake most of the regulation involves various degrees of secretion by the principal cells.

**Regulation of  $K^+$  Excretion**

Amount of  $K^+$  excreted in the urine depends primarily on amount of  $K^+$  secreted into the tubule lumen by the principal cells of the late distal tubule and cortical and early outer medullary collecting ducts.

**Factors controlling this  $K^+$  secretion are:**

1. Transport of  $K^+$  into **principal cells** at basolateral membrane via  $Na^+/K^+$  ATPase which determines the  $K^+$  content of the cells and the major driving force for  $K^+$  secretion into the lumen. This transport into the cells is controlled in turn by:
  - a.) Dietary intake of  $K^+$ .
  - b.) Mineralocorticoids (aldosterone).
  - c.)  $H^+$  balance.
  - d.) Dietary intake of  $Na^+$ .
2. Changes in volume flow rate along the lumen of late distal tubules and cortical and early outer medullary collecting ducts. Volume flow can be influenced by:
  - a.) Dietary intake of  $Na^+$ .
  - b.) Major diuretics.
  - c.)  $H^+$  balance.

3. Magnitude of electrical potential across the luminal and basolateral membranes of principal cells.
4. Changes in permeability of luminal membrane of principal cells to  $K^+$  (aldosterone and  $H^+$  balance).

With extreme need to conserve  $K^+$  (low dietary  $K^+$  intake or extreme  $K^+$  loss by non-renal routes or with extremely low dietary  $Na^+$  intake or extreme  $Na^+$  loss), secretion of  $K^+$  by principal cells not only ceases, but  $K^+$  reabsorption by alpha-intercalated cells (primarily in inner medullary collecting ducts) is enhanced.

## **$Ca^{++}$ homeostasis**

Ninety-nine percent of calcium is found in the skeleton, which serves as a vast reservoir or bank from which calcium can be drawn for homeostatic needs. Responsibility for the control of ionized serum calcium in mammalian species depends on the interaction among 3 calciotropic hormones (PTH, calcitonin, and vitamin D) and 3 target organs (kidney, bone, and intestine). Hypercalcemia is a common and potentially life-threatening condition. To understand the clinical sequelae of disorders of calcium homeostasis, it is important to review the role of calcium in biologic systems.

Eukaryotic cells maintain a steep transmembrane gradient for calcium, with the extracellular calcium concentration [ $Ca^{++}$ ] of 1 to 1.3 mmol/L, (which is 10,000 times greater than the free, resting intracellular calcium concentration of 100 nmol/L). Several properties of the cell are responsible for this gradient. The plasma membrane is relatively impermeable to calcium, an order of magnitude less than to potassium, sodium, and chloride. Membrane pumps counteract the small passive leak of calcium into the cell down the electrochemical gradient. In addition, 95% of intracellular calcium is bound to macromolecules (such as proteins and nucleic acids) and is contained in intracellular organelles (such as the nucleus, endoplasmic reticulum, and mitochondria).

In the process of assuring a balance between calcium intake and output, the kidney filters approximately 10,000 mg of calcium per day, reabsorbs 98%, and excretes 2% of the filtered load. A variety of factors influence renal calcium handling.

Total urinary calcium excretion increases with increased dietary calcium. Calcium excretion is facilitated by increased sodium chloride intake because of the inhibition of proximal tubular calcium reabsorption as a result of volume expansion. This relationship is exploited clinically in the use of sodium chloride loading in the treatment of severe hypercalcemia. Calcium excretion is also increased by the administration of loop diuretics such as furosemide. PTH blocks sodium-dependent phosphate cotransport in the proximal and distal tubules, which results in an increase in phosphate excretion. PTH decreases

calcium reabsorption in the proximal tubule but stimulates calcium absorption in the distal tubule, with the overall effect being net calcium absorption. In proximal tubular cells, PTH activates the 25(OH)D 3 1- $\alpha$ -hydroxylase, which catalyzes the synthesis of the most active metabolite of vitamin D, 1,25(OH)<sub>2</sub>D<sub>3</sub>. Increased levels of 1,25(OH)<sub>2</sub>D<sub>3</sub> directly stimulate the intestinal absorption of calcium and phosphate and the mobilization of calcium and phosphate from bone by both genomic and nongenomic mechanisms. In a negative feedback loop, 1,25(OH)<sub>2</sub>D<sub>3</sub> acts through the vitamin D receptor (VDR) to inhibit PTH gene transcription, PTH hormone secretion, and parathyroid cell proliferation. Conversely, reduced levels of 1,25(OH)<sub>2</sub>D<sub>3</sub> are present in patients with uremia and are associated with parathyroid hyperplasia.

## **CONCENTRATION AND DILUTION OF URINE** **(Lecture 7) Chapter (29)**

### **Lecture Outline:**

- I. Dilution of urine
- II. Concentration of urine.
  - The Countercurrent Mechanism.
    - Countercurrent Multiplier & Exchanger.
    - Hyperosmolarity of the Medullary Interstitial Fluid.
- III. ADH & aldosterone, osmoreceptors, volume receptors & thirst receptors.

**Objectives:** After attending this lecture and completing the required

reading, students should be able to:

1. List “Again as in lecture (1 Body fluids)” the several compartments & describe how they are separated. (285-293)
2. Understand volumes and osmolalities of extracellular and intracellular fluid in abnormal states.
3. Understand what is meant by fluid balance? How are fluid balance & electrolyte balance related?
4. Describe the avenues of fluid intake & fluid output. Indicate volume in each case Table 25-1, Fig. 25-1.
5. Understand why we need to drink water ? how you relate this to the so called “**minimum obligatory urine output**” ? (345)
6. Interpret:  
obligatory urine output is increased when a) our body undergoes hypercatabolism such as fever, trauma, hyperthyroidism, and exercise, b) increase food intake, or c) impaired maximum concentrating ability of the kidneys. (346-7)
7. Give a general idea regarding the importance of making diluted or concentrated urine.
  - making concentrated urine means conservation of body water
  - making diluted urine mean eliminating excess water from the body.
  - By doing this, the kidney can regulate plasma osmolarity and  $\text{Na}^+$  concentration by altering the rate of excretion of  $\text{H}_2\text{O}$  independently of  $\text{Na}^+$  excretion mainly through ADH.
8. Why it was easy for scientist to understand the ability of kidney to make diluted urine, however, a concentrated urine was a puzzle for them.
9. Some species fail to produce concentrated urine. WHY?( 311-2)
10. List the two major conditions needed before the kidney can produce a concentrated urine. (346-8)
11. Give general overview of the countercurrent mechanism.  
(countercurrent multiplier & exchanger) 348-354
12. Draw a nephron & indicate the tonicity of the fluids at the following points : Bowman's capsule, late proximal, the medullary collecting duct & finally in the urine. Fig 29-5 (Fig. 28-5).
13. Know the origin of the hyperosmolarity of medullary interstitium.  
Know the contribution of  $\text{NaCl}$  & urea in this hyperosmolar media?
14. Understand and describe the renal handling of urea.
15. Understand and describe the significance of urea in the renal concentrating process.
16. Understand and describe the relationship of excretion and, thus, clearance of urea to hydration.
17. Why the medullary interstitium is hyperosmolar while the cortical

is not.

18. Drinking sea water is life threatening; WHY?
19. Distinguish obligatory from facultative water reabsorption.
20. Discuss the role of ADH, thirst, and aldosterone in regulating ECF volume. (355-60).
21. The control of ADH release:
  1. increased osmolarity
  2. decreased blood pressure, and
  3. decreased blood volume.
22. Use Specific Gravity (S.G) to test the ability of the kidney to make concentrated urine:
23. Understand and apply methods for determining the effectiveness of the renal concentrating and diluting mechanisms (primarily osmolar and free-water clearances).
24. Understand the disorders of urinary concentrating ability:
  - 1. Inappropriate secretion of ADH. Either too much or too little. Central & nephrogenic diabetes insipidus.
  - 2. Impairment of counter current mechanism. (Using diuretics and their mechanism of action). (402-4).

**Note:**

**Understanding the concentrating and diluting process in the mammalian kidney requires understanding three processes that function in concert:**

1. The function of the loops of Henle as countercurrent multipliers to establish an osmotic gradient that increases from the cortex to the tip of the papilla.
2. The function of the vasa recta as countercurrent exchangers to help maintain this gradient.
3. The function of antidiuretic hormone to alter the permeability of the late distal tubule (connecting tubule) and cortical and medullary collecting ducts to water.

In chronic renal disease, the kidney first loses its ability to concentrate urine. Later on the ability to dilute urine is lost as well, so the S.G becomes fixed at 1.010 (S.G of plasma). The ability to dilute urine is lost when 80% of the nephrons mass have been destroyed.

**S.G versus osmolality:**

One mole of any solution contains the same number of particles (Avogadro's number:  $6.02 \times 10^{23}$ ). The freezing point of any solution with a concentration of one Mole/kg water is  $-1.86^\circ\text{C}$ . This solution is called osmolal solution. The change in temperature is called *molal freezing point constant* ( $K_f$ ) this is equal one Osmole. To calculate the osmolality of a solution you use an osmometer. It calculate the freezing point of the solution and compare it to  $K_f$ . For instant the freezing point for plasma equals  $-0.53^\circ\text{C}$ . Therefore the osmolality of plasma equals  $-0.53/-1.86 \times 1000 = 285 \text{ mOsm}$ .

**S.G** depends on the mass of the particles present in a given weight of urine (mass/mass) and is a traditional measure of urine concentration (very simple test).

- 1.003    diluted urine (compared to plasma)
- 1.010    isotonic urine (the same as plasma).
- 1.040    concentrated urine (compared to plasma)

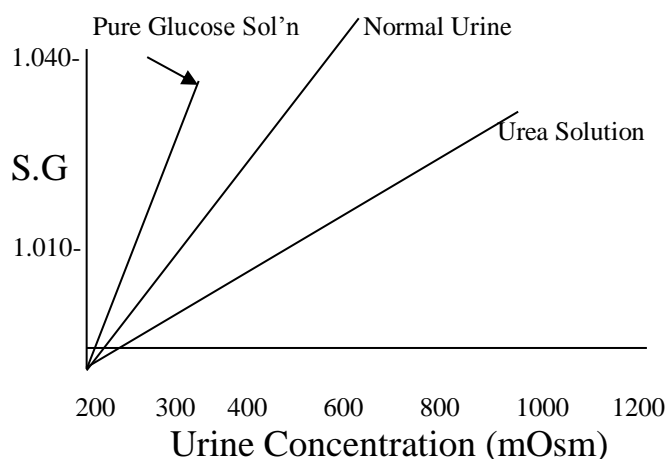
Osmolality depends on the number of particles (number/mass) and is a much better index of true renal concentrating ability.

Hyperosmolar urine reflects good renal concentrating ability. However, high S.G. urine may occur in a kidney with depressed concentrating ability (especially when large molecules are present in the urine such as glucose, albumin, contrast media, casts, blood, pus cells). But if all these are absent, we can predict osmolality from S.G (e.g. 1.006) as follows:

Take the last 2 digits (for example: 06) and multiply by 40

$$06 \times 40 = 240 \text{ mOsm/L}$$

Normal urine osmolality is  $\approx 600 \text{ mOsm/lit}$  (Fig. 28-1).





**ACID BASE BALANCE I**  
**(Lecture 8)**  
**Chapter 31 (Chapter 30)**

**Lecture outline:**

- I. Acid-base balance.
  - Acidosis.
  - Alkalosis
- II. Defense Against Changes in hydrogen ion concentration  $[H^+]$  .
  - Acid-base buffers.
  - Lungs
  - Kidneys.

**Objectives:** After attending this lecture and completing the required reading, students should be able to:

1. Define the following: acid (strong & weak), base (strong & weak),

acidosis & alkalosis.

2. Understand what is meant by acid-base balance.  
(H<sup>+</sup> intake + H<sup>+</sup> production = H<sup>+</sup> removal from the body = H<sup>+</sup> balance)

3. Why keeping [H<sup>+</sup>] in ECF under control is so crucial? Recall the pH range of the blood compatible with human life.
4. The H<sup>+</sup> concentration: Determine the hydrogen ion concentration of the blood when given the pH of the blood and determine the pH of the blood when given the hydrogen ion concentration.

- [H<sup>+</sup>] in ECF ≈ 40 nM/L ( ranges from 4 times less to 4 times more than normal... 10-160 nM/L). Na<sup>+</sup> or K<sup>+</sup> can vary to only small percentages.
- Compare the [H<sup>+</sup>] with that of [Na<sup>+</sup>].

5. Understand and be able to use the Henderson-Hasselbalch equation especially as applied to the bicarbonate-carbonic acid buffer system

$$pH = 6.1 + \log \left[ \frac{Salt}{Acid} \right]$$
$$pH = pK + \log \left[ \frac{HCO_3^-}{0.03 * PCO_2} \right]$$

6. What is the normal pH of: arterial, venous, intracellular, proximal tubule, collecting duct, & freshly voided urine?  
pH of arterial blood below 6.8 or above 8.0 is not compatible with life except for few hours.

7. What is meant by acidosis and alkalosis:

- low pH → high [H<sup>+</sup>] = acidosis.
- high pH → low [H<sup>+</sup>] = alkalosis.

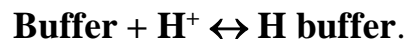
8. Define volatile acid and non-volatile acid and give appropriate examples. Why we are more concerned with the production of 1 mM/kg of H<sup>+</sup> in form of fixed (non-volatile) acids. Because the lungs cannot eliminate these acids, they are called *fixed acids*. In the same time we don't pay attention to 10 M of H<sup>+</sup> produced per day in form of CO<sub>2</sub>.
9. Define the first line of defense in maintaining blood pH within its normal range. Compare the different avenues our body uses to restore our ECF pH back to normal, (body buffers, respiration, & kidney), taking in consideration their speed of reaction & capacity.

10. Buffers:

- definition, function, types, strength, capacity, importance etc.,
- Define a buffer and describe the characteristics that make a buffer effective at a given pH.
- Describe how carbonic acid (volatile acid) produced by metabolism is buffered.

**HINTS:**

- Buffer is a combination of weak acid with its salt.



- if  $\text{H}^+$  is added...reaction moves to the right, if  $\text{H}^+$  is reduced, reaction moves to left.
- buffers don't eliminate  $\text{H}^+$  or add it to body but keep it tied up. until balance can be reestablished. It act with a fraction of a second and is a first line of defense.
- All chemicals can buffer about 1000 mM  $\text{H}^+$  before there is any serious fall in pH.

11. Recall the principal buffers of the body ( $\text{HCO}_3^-$ - $\text{H}_2\text{CO}_3$ ;  $\text{HPO}_4^-$ - $\text{H}_2\text{PO}_4^-$ , proteins).

12. What determine the buffering power and capacity of any system.

- The buffering power is a product of 3 variables: total concentration, relative concentration (pK relative to pH of the surrounding) and

renewal

tendency.

- The importance of pK being close to normal pH (refer back to buffer titration curve (Fig. 30-1). The buffer system is still reasonably effective for 1.0 pH unit on either directions. For  $\text{HCO}_3^-$ - $\text{H}_2\text{CO}_3$  system:  $6.1 \pm 1$  (5.1 - 7.1). WHY?

13. Explain how the above three buffer system help to maintain the pH of body fluids. Give an example in each case.

14. Explain why the bicarbonate-carbonic acid system is such an effective buffer system in the body.

15. The  $\text{HPO}_4^-$ - $\text{H}_2\text{PO}_4^-$  buffer system is specially important in tubular & intracellular fluids. What is the excretion rate of phosphate (mM/day).

16. The protein buffer system (their capacity, location, and importance).

17. Blood buffering capacity is due to: 55%  $\text{HCO}_3^-$ , 35% Hb, 5%  $\text{HPO}_4^-$

18. Understand the Isohydric Principle : All Buffers in a Common

Solutions are in equilibrium with the same ( $H^+$ )

$$H^+ = K_1 * \left[ \frac{HA_1}{A_1} \right] = K_2 * \left[ \frac{HA_2}{A_2} \right] \text{ etc}$$

19. Respiratory Regulations of acid-base Balance: Describe how respiration is related to the maintenance of pH. (Fig. 30-2,3). onset, capacity, etc...
20. A decrease in pH  $\rightarrow$  more pronounced effect in  $\uparrow$  alveolar ventilation when compared with the  $\downarrow$  ventilation due to high pH  $\rightarrow$ . WHY? (alkalosis is prevented from acting because of low  $P_{aO_2}$ ).
21. Respiratory compensation can return pH back to normal up to 50-75% normal. WHY it is not 100%? The response occurs within 3-12 min.

**Note:**

The pH range of the systemic plasma compatible with life is 6.8 to 8.0. Because the pH scale is logarithmic, the  $[H^+]$  is 158 nEq/L at pH 6.8 and 10 nEq/L at pH 8.0. Thus, the body is capable of sustaining a greater increase in  $[H^+]$  (from 40 to 158 nEq/L) than decrease in  $[H^+]$  (from 40 to 10 nEq/L). In other words, the body is capable of tolerating a greater change in the acid direction than in the alkaline direction. Still, at the lowest pH compatible with life (6.8), the free  $H^+$  concentration (158 nEq/L) is extremely small compared to the concentration of the other ions of the extracellular fluid (e.g., for  $Na^+$  the concentration is 145,000,000 nEq/L).

**Henderson-Hasselbalch Equation:**

$$pH = pK' + \log \left[ \frac{\text{Salt}}{\text{Acid}} \right]$$

$$pH = pK + \log \left[ \frac{HCO_3^-}{0.03 * PCO_2} \right]$$

From examining the equation, several aspects concerning buffers and their evaluation become apparent.

1. The deviation in pH upon the addition of an acid or base depends on the change in the ratio of the concentration of the salt of the acid (proton acceptor) to the concentration of the acid (proton donor) in the last term of the equation.
2. The nearer this ratio is to 1.0 initially, the smaller the change in pH

- that will be induced by a given addition of acid or base.
3. Since the  $\log_{10}$  of 1.0 is 0, a buffer system is most efficient at a pH that is identical to its  $pK'$ . In other words, to maintain a pH of 7.4, the most effective chemical buffering system would be one whose  $pK'$  was 7.4 because at a pH of 7.4 the ratio of the components (salt of the acid to the acid) would be 1.0.
  4. At any specific ratio of the two components of the buffer system, there will be less change in ratio upon addition of a given quantity of acid or base if the of the components of the buffer system are high rather than low.

**ACID BASE BALANCE II**  
**Renal Control of Acid-Base Balance**  
**(Lecture 9)**  
**Chapter 31 (30)**

Lecture outline:

- I. The Role of The Kidney in Acid-base balance.
- II. The Urinary Buffers.

Objectives : After attending the lecture, the student should be able to perform the following tasks:

1. Explain the role of the kidneys in maintaining normal pH. How renal system respond to any change in pH in general.
2. What are the three major goals of the kidney in **Acid-Base Balance**.
  - A.** secretion of  $H^+$ . How it is secreted?. Why the kidney cannot excrete the 80 mM of fixed acids in the urine as a free  $H^+$ .  
Therefore, how  $H^+$  is eliminated from the kidney?
  - B.** reabsorption of almost all filtered  $HCO_3^-$ . How it is reabsorbed?

Kidneys must not lose  $\text{HCO}_3^-$  in the urine, a task which is more important than secreting the nonvolatile acids. WHY?  
 C. making new  $\text{HCO}_3^-$  ( $\text{HCO}_3^-$  gain). How is it made?

3 . Complete the following table for the  $\text{HCO}_3^-$  (mEq/day)

<u>Filtered</u>	<u>Reabsorbed</u>	<u>Gained</u>	<u>Excreted</u>
-----------------	-------------------	---------------	-----------------

4. Secretion of  $\text{H}^+$  & Reabsorption of  $\text{HCO}_3^-$  in the Renal Tubules

- which parts of the nephron are involved...
- quantity or % in each part.
- forms of transport and lowest possible pH in each part

5. Interpret :

- Bicarbonate is continuously attacked by the fixed acids.
- Reabsorption of the filtered  $\text{HCO}_3^-$  is linked to  $\text{H}^+$  secretion (net secretion of  $\text{H} = \text{zero}$ ).
- The pH of the proximal tubule is usually less acidic than the pH of the distal tubule, even though most of the  $\text{H}^+$  is secreted in the proximal.
- The majority of the  $\text{H}^+$  secretion is in countertransport with  $\text{Na}^+$  in the proximal tubule. This is never against a very high concentration gradient (only  $\sim 4$  times), but it is tremendous in amount (95%). The rest (5%) is actively secreted against a 900 fold concentration gradient (in distal tubule).

6. The urinary  $\text{HPO}_4^{=}$  buffer system and the generation of new  $\text{HCO}_3^-$ .

- 30-40 mEq/day of  $\text{H}_2\text{PO}_4^-$  can be excreted/day

- Define and understand the concept of titratable acidity.

The # of mEq of NaOH needs to be added to the urine to bring its pH back to 7.4. It indicates how much  $\text{H}^+$  is secreted in form of phosphate, citrate, urate...etc. This does not include the  $\text{H}^+$  secreted as  $\text{NH}_4^+$  because its pK is 9.2.

7. Understand how the renal tubular secretion of hydrogen ions and their subsequent excretion as titratable acid leads to the generation of new bicarbonate in the body.

8.  $\text{NH}_3$ - $\text{NH}_4^+$  system and the generation of new  $\text{HCO}_3^-$

- $\text{NH}_3$  ammonia :  $\text{NH}_4^+$  ammonium ion: (don't confuse ammonium  $\text{NH}_4^+$  and ammonia  $\text{NH}_3$ ,. ammonium is an ion; ammonia is not).
- $\text{NH}_4^+$  excretion is usually 30-40 mM/day.
- $\text{NH}_4^+$  as a buffer system is more important than  $\text{HPO}_4^{=}$ . WHY?
- Mechanism of secretion.

- Max. capacity of the kidney to secrete  $\text{NH}_4^+ = 500 \text{ mM/day}$ .
- In acidosis net  $\text{H}^+$  excretion  $\uparrow\uparrow\uparrow$  mainly at the expense of  $\text{NH}_4^+$ .
- in alkalosis excretion of  $\text{NH}_4^+$  drops to zero. There is -ve acid secretion because of excretion of  $\text{HCO}_3^-$ .

## 9. Quantitative Renal Acid-Base Excretion:

$\text{HCO}_3^-$  added to blood/day =  $\text{NH}_4\text{Cl}$  excretion + titratable acids -  $\text{HCO}_3^-$  Net  $\text{H}^+$  excretion =  $\text{NH}_4^+$  + titratable acids -  $\text{HCO}_3^-$ .

## Acid-Base Imbalance III

### (Lecture 10)

### Chapter 31 (30)

#### Lecture Outline :

- I. Acidosis Vs Alkalosis
- II. Metabolic Vs Respiratory.
- III. Compensation.

**Objectives:** After attending the lecture, the student should be able to perform the following tasks:

1. Define acid-base imbalances & their effects on the body.
2. Imagine that our buffers can take care of 1000 mM of  $\text{H}^+$  per day and kidney can handle up to 500 mM (total = 1,500 mM of  $\text{H}^+$ )... meaning... a normal person should never develop acidosis or alkalosis no matter what he eats or does.
3. Acidosis and Alkalosis
  - Associated with other abnormalities.
  - predominant tendency to acidosis.
3. What is meant by metabolic & respiratory disturbances in pH.
  - metabolic disorder  $\rightarrow$  affect  $\text{HCO}_3^-$
  - respiratory disorder  $\rightarrow$  affect  $\text{PCO}_2$ .
4. **Respiratory Acidosis** : usually results from pathological condition.
  - interference with gas exchange: pneumonia, lack of lung tissue

- depression of respiratory center (trauma, drugs, tumor).
  - interference with mechanical ventilation: phrenic paralysis, diaphragmatic fatigue.
5. **Metabolic acidosis** : non-respiratory acidosis is better term, but metabolic acidosis is most commonly used.
- ↓ normal  $H^+$  excretion : Renal failure.
  - ↑  $H^+$  production: fasting, starvation, D.M, infection, burn ...etc.
  - ↑ Loss of base: diarrhea, diuretics, vomiting.
  - ingestion: aspirin,  $NH_4Cl$ .
6. **Respiratory Alkalosis**: rarely pathological.
- voluntary and involuntary hyperventilation.
  - hysteria.
  - encephalitis (rare).
  - high altitude.
7. **Metabolic Alkalosis**: (not common).
1. ↓ base loss: ↑ aldosterone.
  2. loss of acid: vomiting, diuretics.
  3. ↑ base uptake.
8. **Compensation**: Briefly: How are acidosis & alkalosis compensated & related ?
- Since renal compensation is not noticed before 24 hr. any respiratory imbalance is classified to:
- acute: renal compensation has not occurred &  $HCO_3^-$  is  $\approx$  normal.
  - chronic: renal compensation has occurred &  $HCO_3^-$  is shifted.
9. To be able to distinguish between respiratory & metabolic acidosis & alkalosis, study the following table and complete it when it is appropriate:

	pH	$P_aCO_2$	$HCO_3^-$	Ventilation	Causes
M. Acidosis	↓	↓	↓		
M. Alkalosis	↑	↑	↑		
R. Acidosis	↓	↑	↑		
R. alkalosis	↑	↓	↓		

Note: both  $HCO_3^-$  &  $PCO_2$  are shifted in the same direction.

10. Simple Vs mixed acid-base imbalance:

- mixed (complex) disorder (either term can be used).

\* **M. Acidosis**      for every ↓ 1 mEq  $HCO_3^- \rightarrow 1.2$  mm Hg  $PCO_2$  ↓ too.

\*\***M. Alkalosis**      for every 1 mEq ↑ in  $HCO_3^- \rightarrow 0.7$  mmHg ↑ in  $PCO_2$

\*\*\***R. Acidosis**



Acute: for every 10 mmHg  $\uparrow$  in  $\text{PCO}_2 \rightarrow 1 \text{ mEq } \uparrow$  in  $\text{HCO}_3^-$   
 Chronic for every 10 mmHg  $\uparrow$  in  $\text{PCO}_2 \rightarrow 3.5 \text{ mEq } \uparrow$  in  $\text{HCO}_3^-$

\*\*\*\***R. Alkalosis**

Acute for every 10 mmHg  $\downarrow$   $\text{PCO}_2 \rightarrow 2 \text{ mEq } \downarrow$   $\text{HCO}_3^-$   
 Chronic for every 10 mmHg  $\downarrow$   $\text{PCO}_2 \rightarrow 5 \text{ mEq } \downarrow$   $\text{HCO}_3^-$

- \* if  $\text{PCO}_2 \downarrow$  more than expected  $\rightarrow$  superimposed R. alkalosis too.
- \* if  $\text{PCO}_2 \downarrow$  less than expected  $\rightarrow$  superimposed R. acidosis too.
- \*\* if  $\text{PCO}_2 \uparrow$  more than expected  $\rightarrow$  superimposed R. acidosis too.
- \*\* if  $\text{PCO}_2 \uparrow$  less than expected  $\rightarrow$  superimposed R. alkalosis too.
- \*\*\* if  $\text{HCO}_3^- \uparrow$  more than expected  $\rightarrow$  superimposed M. alkalosis too.
- \*\*\* if  $\text{HCO}_3^- \uparrow$  less than expected  $\rightarrow$  superimposed M. acidosis too.
- \*\*\*\* if  $\text{HCO}_3^- \downarrow$  more than expected  $\rightarrow$  superimposed M. acidosis too.
- \*\*\*\* if  $\text{HCO}_3^- \downarrow$  less than expected  $\rightarrow$  superimposed M. alkalosis too.

**GOOD LUCK**

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 PHYSIOLOGY**