

**MINISTRY OF HEALTH SERVICE OF UKRAINE**  
**ZAPORIZHZHYA STATE MEDICAL UNIVERSITY**  
Department of Normal Physiology

**The Physiology of the Kidney and Body Fluids**  
EDUCATIONAL MANUAL

for practical lessons on physiology for students on II course of  
international faculties (specialty “General medicine”)

**Zaporizhzhia - 2016**

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**Reviewers:**

*Abramov A.V.*

*Kamyshny A.M.*

**AUTHORS:**

Sukhomlinova I.Ye.,

Tichonovskaya M.A.,

Kirsanova E.V

Yeryomina A.K.

**Sukhomlinova I.Ye.**

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Methodical instructions recommended for the students of “General Medicine” specialty who study Physiology. This educational manual contains theoretic materials, the approximate lists of questions to check quality of study. Instructions allows students to acquaint with main definitions of the course “Normal Physiology” and gives a wide list of literature sources for better understanding Normal Physiology during students independent work.

**Сухо́млінова І.Є.**

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## **INTRODUCTION**

Students' independent practical work is an important part of the syllabus in the course of Normal Physiology. It helps students to study this fundamental subject.

Systematic independent work enables to reach the final goal in the students' education. It is also important while preparing the students for their future clinical work with patients.

These theoretic materials, questions and tests will help students to get ready for the examination.

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## **1. BODY FLUID COMPARTMENTS**

### **A. TOTAL BODY WATER (TBW)**

50-70% of body weight, i.e., about 40 liters.

### **B. EXTRACELLULAR WATER (ECW)**

#### **1. General characteristics**

20% of body weight.

#### **2. Interstitial fluid (ISF)**

a. 16% of body weight, i.e., about 11 liters.

b. It has the same osmolarity as intracellular water, i.e., 290 mOsm/kg water.

c. This compartment includes lymph (3% of body weight).

d. ISF - ECW - Plasma volume

#### **3. Plasma**

a. 4.3% of body weight (3 liters)

b. RBC volume - 35% of body weight

c. Plasma has a higher osmolarity than intracellular or extracellular fluid, due to the presence of plasma proteins.

d. Most ions are in identical composition.

#### **4. Transcellular water**

a. Fluids isolated from the remainder of extracellular water by epithelial layers.

b. Includes cerebrospinal fluid, aqueous humor, gastrointestinal secretions, and urine.

c. These fluids are of varying composition, determined by epithelial pumps.

### **C. INTRACELLULAR WATER (ICW)**

1. 30-40% of body weight, comprising the largest body compartment, averaging 25 liters, with an osmolarity of 290 mOsm per kilogram water.

#### **2. Composition**

a. High  $K^+$ , protein, and organic phosphates

b. Low NaCl.

### **D. WATER AND SOLUTE DISTRIBUTION BETWEEN ICW AND ECW**

1. Water distribution is determined by the content of osmotically active substances, especially ions, since water diffuses freely along its concentration gradient.
2. Since total body water is relatively constant, changes in extracellular water are associated with compensatory changes in intracellular water.

## 2. FUNCTIONAL ANATOMY OF THE KIDNEY

1. **Cross structure** of the kidney (Fig. 1.1): cortex, medulla (inner and outer zones of outer medulla and papilla or inner medulla), pyramids, renal calyces and pelvis, ureter. Cross size and weight (300-400 g) of kidneys (about 0.5% of body weight ) in humans.

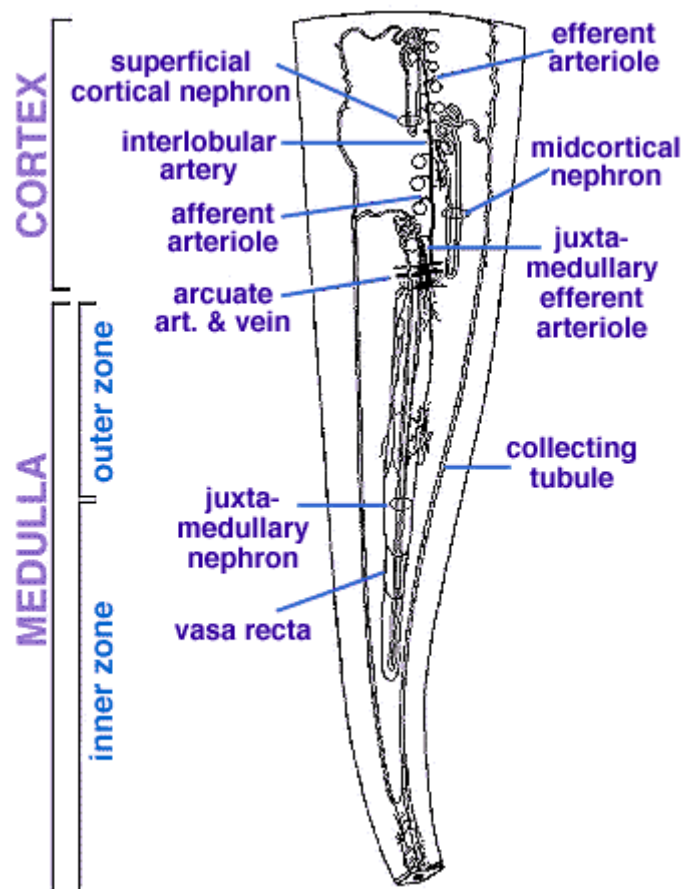
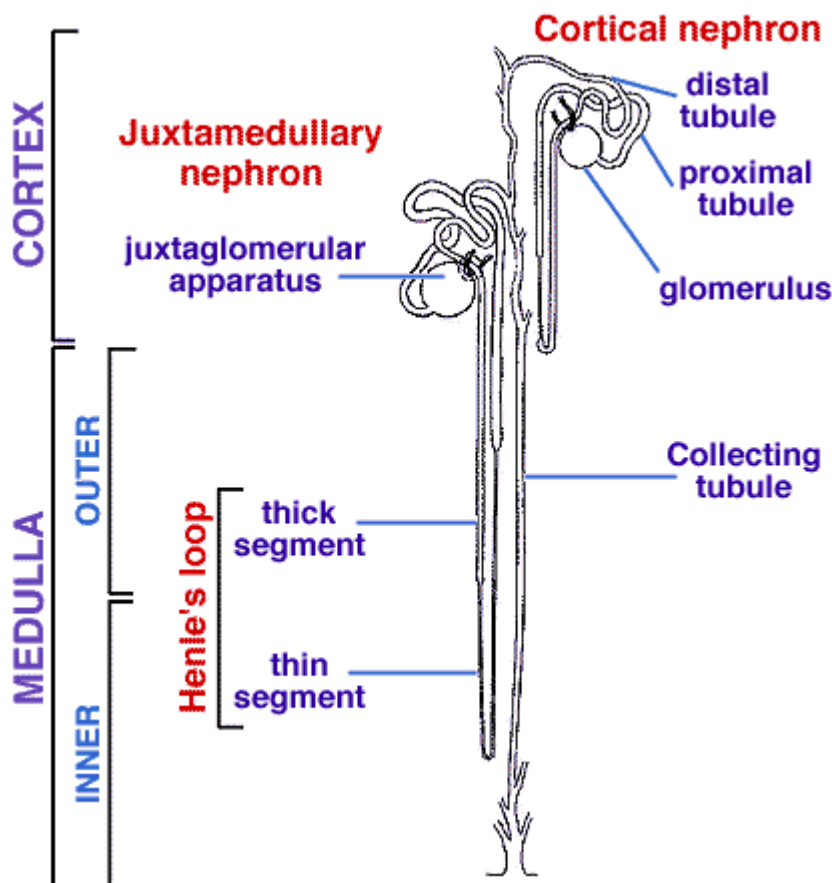


Fig1.1. Cross-section of the renal architecture

2. The **nephron** is the basic unit of renal structure and function: it has a Malpighian corpuscle, with a vascular glomerulus within a matrix formed by

mesangial cells and an epithelial Bowman's capsule. The capsule joins a series of tubules starting with the proximal tubule and followed by the loop of Henle, the distal tubule, and ending in the collecting ducts. The proximal tubule has convoluted early and intermediate segments S1 and S2 in the renal cortex and a straight segment S3 which enters the outer medulla. The loop of Henle has medullary thin descending and thin ascending limbs and a thick ascending limb with outer medullary and cortical segments. The cortical distal diluting segments includes the early distal tubule, that makes contact with the afferent arteriole at the macula densa cells forming the juxtaglomerular apparatus. This is followed by the cortical distal convolutions and the connecting segment. The collecting duct has cortical, outer medullary and inner medullary segments.



1. Fig1.2. Major sections of the nephrons and their position within the cortex and medulla
2. There are about 1 million nephrons per kidney ( $\pm 250,000$ ). There are **three types of nephrons**: (1) Superficial nephrons (30% in humans) with

glomerulus in outer cortex and loop of Henle that bends in the outer medulla. (2) Midcortical nephrons with glomerulus in the mid cortex and short loops that bend in the outer medulla (10%). Other mid cortical nephrons have loops of intermediate length that bend at various points in the inner medulla (50%). (3) Juxtamedullary nephrons have glomeruli in the inner cortex next the medulla and long loops that reach the tip of the papilla (10%). The proportion and length of the long loops of Henle increase in proportion to the urine concentrating capacity of the animal.

3. **Cells** of S1 at the PCT and at the TAL have high rates of solute transport, abundant mitochondria, extensive microvilli on the luminal plasma membrane and infoldings of the basolateral membrane. These cells are rich in basolateral Na-K ATPase. In the S2 segments of the PCT there is prominent basolateral infoldings but less microvilli and mitochondria than in S1, consistent with participation of S2 in secretory transport. In S3 there is abundant microvilli but basolateral infoldings and mitochondria are less prominent than in S1. The thin limbs of Henle have flattened cells with no mitochondria and little ATPase activity. In the collecting ducts there are 3 different cells: principal cells with abundant water channels (aquaporins) and Na-K ATPase, alpha and beta intercalated, mitochondria-rich cells with abundant proton-ATPases.

4. The initial step is the **formation of a plasma ultrafiltrate** (plasma without cells or proteins) at Bowman's space through the action of hydrostatic pressure in the glomerular capillaries. The ultrafiltrate flows along the tubules and is modified by reabsorption (retrieval) of important solutes (sodium salts, glucose, amino acids) and most water from the lumen of the tubules back into the peritubular capillary blood. The luminal fluid is also modified by secretion (addition) of solutes from the peritubular capillaries (or from the tubule cells) into the lumen. The proximal tubules reabsorb back into the peritubular capillaries about 2/3 of the Na and water and most of the bicarbonate, glucose and amino acids filtered and the little albumin that may have filtered at the glomeruli. The



medullary loop of Henle reabsorbs salts with little water making the medullary interstitium rich in solutes (hyperosmolar) and delivers a solute poor, dilute fluid to the distal tubules. Thus the loop of Henle initiates the processes of urine concentration or dilution. The distal tubules (cortical diluting segments) continue to dilute the luminal fluid through hormone stimulated transport of NaCl (aldosterone) and of Ca salts (parathormone). In the connecting segment water reabsorption becomes prominent only when antidiuretic hormone is abundant. The collecting ducts make the final fine adjustments in composition of the urine through antidiuretic hormone stimulated water and urea reabsorption, and aldosterone stimulated Na, K and H transport.

5. About 1.5 L/day of urine containing about 600 mOsm of solutes (mostly NaCl, KCl and urea) are excreted. These solutes may be excreted in as little as 0.5 L/day or in as much as 12 L/day depending on water availability. The amount of solute excreted depends on diet (more when high protein-K rich diets that generate much urea, or highly salted foods, are eaten).

6. The kidneys **regulate volume** (water content and cell volume, sodium content and ECF volume) and **composition** (concentrations of K, phosphate, bicarbonate, pH) of the body fluids. Through **renal plasma clearance** ( $C=UV/P$ ) the kidneys clean the body fluids of non-volatile end products such as urea, uric acid, and creatinine. Clearance of secreted and filtered solutes can approach renal plasma flow. Other solutes such as proteins, amino acids and glucose are **conserved** by the normal kidney and have zero clearance. The kidney produces hormones (**erythropoietin**, **renin-angiotensin** and **calcitriol**). It has also metabolic functions, participating in **degradation of peptides** such as some hormones, in fasting **gluconeogenesis** and in **transformations of amino acids** (glutamine to  $NH_4$ , synthesis of arginine and glycine).

### 3. RENAL HEMODYNAMICS

#### 1. Anatomy (Fig 2.1):

Interlobar, arcuate, interlobular arteries

Afferent and efferent arterioles

Glomerular capillaries, mesangial cells and matrix

Renal veins

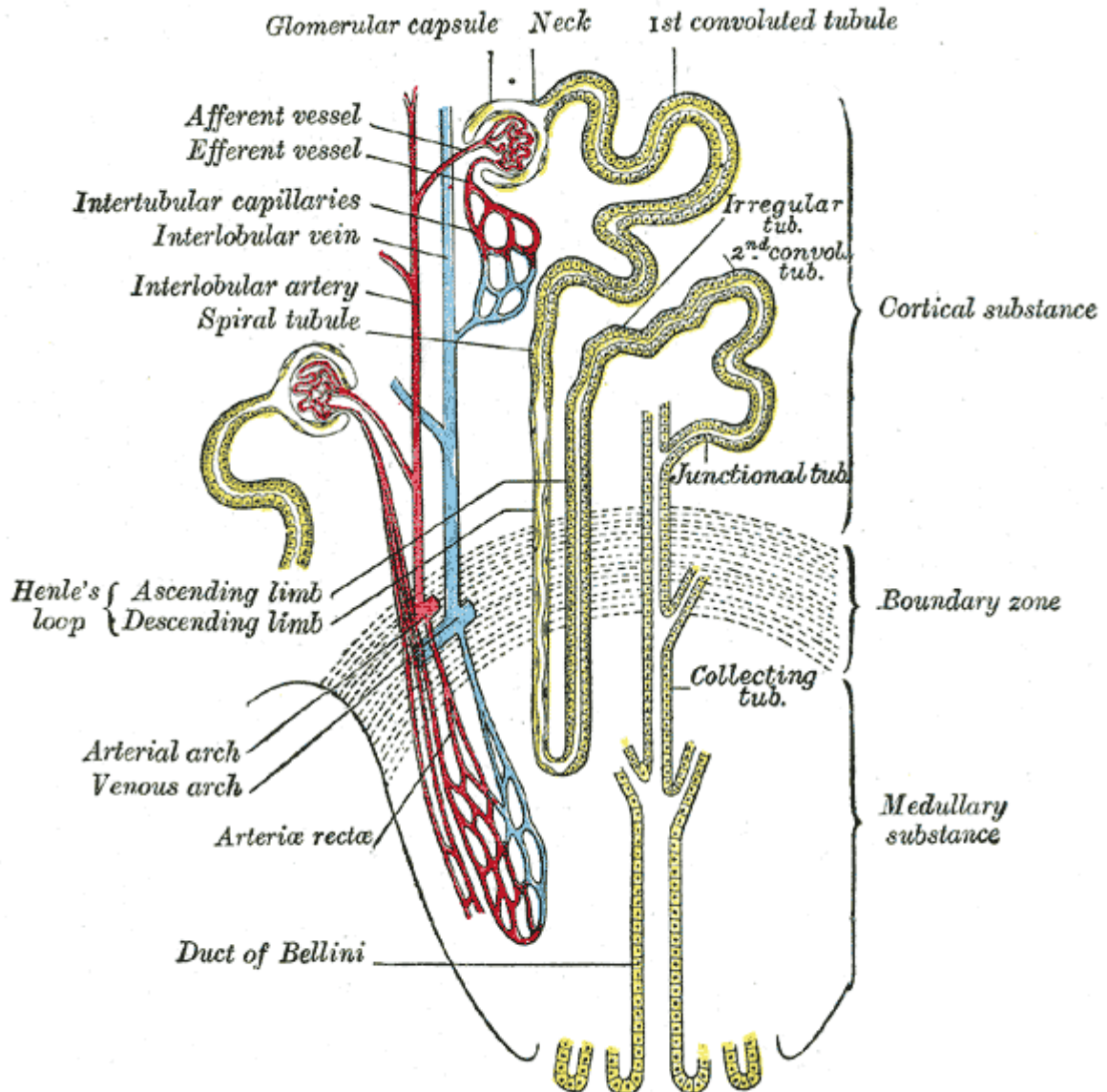


Fig 2.1. Renal hemodynamics

## 2. Pressures and Resistances:

Site of major pressure drop ( $\Delta P$ ) is in the afferent arterioles: from 100 to 45 mm Hg

In the efferent arterioles,  $\Delta P$  is from 45 in glomerular capillaries to 20 mm Hg at peritubular capillaries.

Because of the resistance of the intrarenal veins, pressure drops from 20 in peritubular capillaries to 5 mm Hg in the renal vein.

The total  $\Delta P$  is from 100 in aorta (slightly less in interlobular arteries) to 5 mm Hg in renal vein.

Note that the glomerular capillaries and the peritubular capillaries have low resistance (because there are so many of them in parallel) and therefore have low pressure drop.

### 3. **Magnitude of Renal Blood Flow:**

There is a large renal blood flow (RBF) at rest, equivalent to 1/5 of CO (1 L/min) to an organ that weighs less than 1% of body weight. Per unit mass, RBF at rest is higher than that to heart muscle or brain.

### 4. **Measurement of Renal Blood Flow:**

Clearances of p-aminohippurate  $C_p = V(U_p)/(P_p)$ , of Hippuran, or of Diodrast are about 80-90% of RPF and approximate the renal plasma flow (RPF). These clearances are called effective renal plasma flow and are less than the true RPF because (1) plasma flow through renal connective and adipose tissue is not included and (2) incomplete extraction of solutes from rapidly flowing blood in peritubular capillaries precludes total secretion of all the PAH present in the blood perfusing the tubules.

To measure RPF accurately, the concentration of PAH in the renal venous plasma (RVp) must also be known:  $RPF = V (U_p - RV_p)/(P_p - RV_p)$ . This requires catheterization of the renal vein, a feasible but not a common procedure. Note that RBF can be calculated from RPF by the equation  $RBF = RPF/(1 - \text{hematocrit})$ .

### 5. **Roles served by Renal Blood Flow:**

Sustain filtration and excretion of end products such as urea, creatinine etc.

Achieve rapid changes in body fluids volumes and composition through changes in renal excretion of water and solutes.

Serve a hemodynamic reserve function (1 L/min) in case of extreme emergency (shock). That is, the RBF can be reduced to very low levels to help sustain the blood flow in other organs (brain, heart, etc.). However, if kidney blood flow remains low for too long, renal damage will result.

Deliver sufficient oxygen and nutrients to the kidneys; usually plentiful.

## 6. Regulation of RBF:

**Autoregulation** (intrinsic) occurs at MAP between 70 and 210 mmHg when pressure changes but blood flow (and filtration rate) are nearly constant.

Autoregulation is by myogenic and tubulo-glomerular feedback (TGF) mechanisms. It occurs at the afferent arterioles

Myogenic autoregulation depends on stretch activated ion channels in vascular smooth muscle that, when stretched, allow Ca ions to enter and induce contraction.

TGF occurs between macula densa (MD) cells and cells of the afferent arteriole (juxtaglomerular apparatus). When fluid delivery and NaCl transport at MD increase (as with increased GFR or decreased PT reabsorption), there are increases in cell Na and Ca and release of arachidonic acid metabolites and adenosine that act on vascular smooth muscle cells of the afferent arteriole, causing contraction and reduced blood flow. The opposite happens when delivery and transport at the MD are decreased.

**Renin-angiotensin system** (Fig. 2.2). Renin is produced at granular cells of afferent arterioles. It is released in response to decreases in renal perfusion pressure (decreased stretch reduce cell calcium which promotes renin release), by sympathetic stimulation through renal nerves and by reduced flow and transport at MD cells (which reduce cell calcium, decrease arachidonic acid release and in turn reduce cell Ca in afferent arterioles).

Renin is a protease that reacts with angiotensinogen (renin substrate) to produce Angiotensin I (10 amino acids) which is converted to Angiotensin II (8 amino acids) by the endothelial angiotensin converting enzyme (ACE).

Angiotensin II is a potent vasoconstrictor, preferentially of the efferent arteriole, reducing RBF but maintaining or increasing filtration. It also acts on the adrenal cortex inducing release of aldosterone (a hormone that stimulates sodium reabsorption), and in the proximal tubule stimulating Na-HCO<sub>3</sub> reabsorption. At higher plasma levels AII contracts mesangial cells (which decreases filtration) and causes generalized vasoconstriction including the afferent as well as the efferent arteriole, which helps maintain central arterial blood pressure at the sacrifice of RBF and filtration.

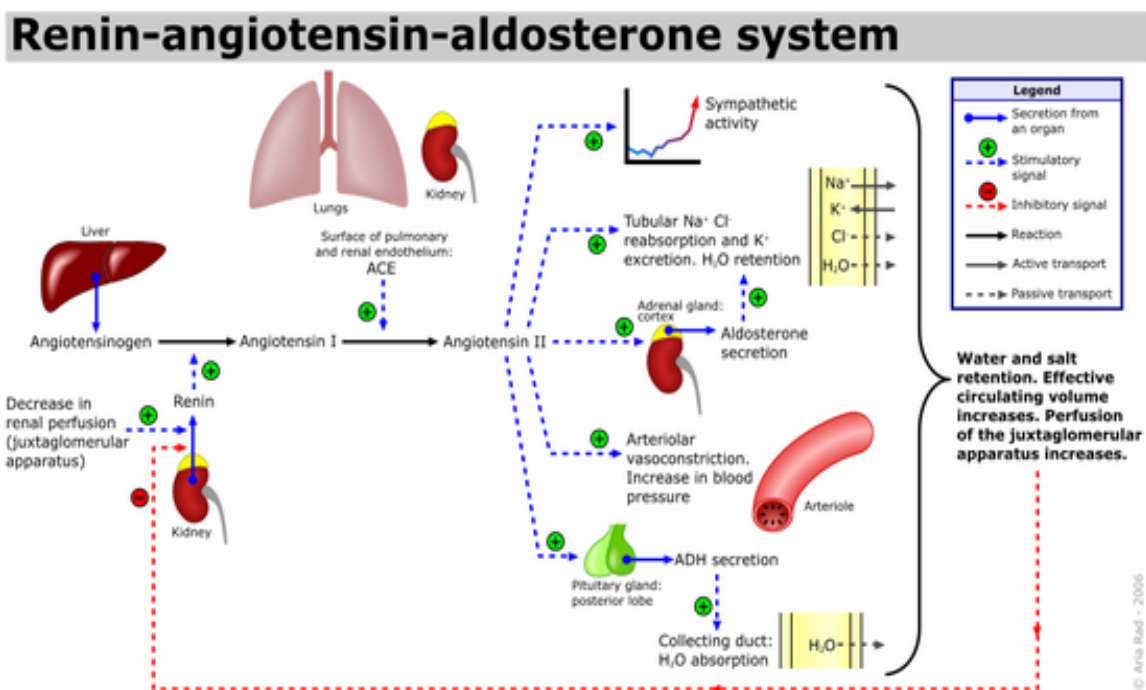


Fig. 2.2. Renin-angiotensin system

### 7. Other vasoactive agents in the kidney:

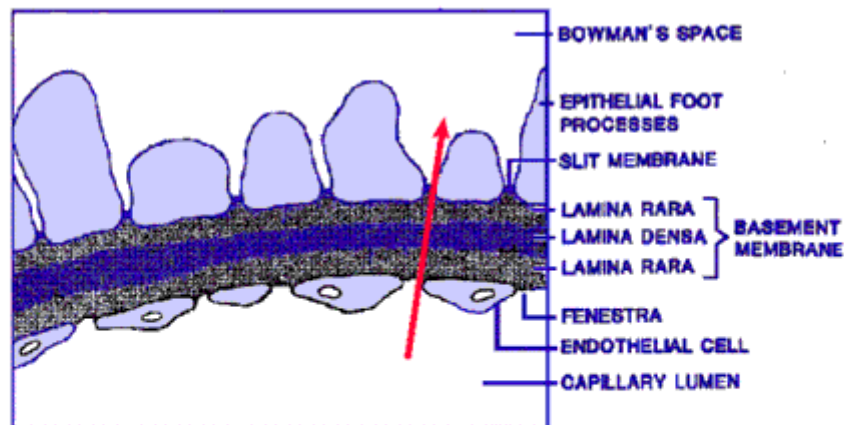
Vasoconstrictors such as endothelin and AVP reduce RBF. AVP reduces the medullary blood flow in particular and by acting on mesangial cells may also reduce filtration.

Vasodilators such as prostaglandins, nitric oxide and natriuretic peptides counteract and limit the effect of vasoconstrictors. Their absence or blockade may lead to hypertension, profound renal vasoconstriction and reduced filtration.

#### 4. GLOMERULAR FILTRATION

1. **Anatomy:** Filtration barrier (Fig. 3.1) is formed by fenestrated (375Å pore radius) vascular endothelium, glomerular basement membrane (GBM), and visceral epithelial podocytes separated by slits with diaphragms.

### FILTRATION PATHWAY



- ♦ The filtration pathway, from the capillary lumen into Bowman's space, passes through the fenestra between the endothelial cells, across the trilaminar basement membrane and across the slit membrane that connects the epithelial foot processes.
- ♦ The filtrate contains all the substances that exist in plasma at the same concentration as in plasma except for plasma proteins and substances bound to the proteins. These are filtered at smaller concentrations.

Fig. 3.1. Filtration barrier

2. progressively restrict passage of large ( $> 18\text{\AA}$  radius) and almost completely sieve out neutral molecules larger than  $40\text{\AA}$  or smaller negatively charged molecules (albumin). In disease, proteinuria may be due to loss of negative charge selectivity or to increasing numbers of large size pores.

3. **Filtrate composition:** Small MW neutral solutes ( $<6\text{ Kd}$ ) have concentrations in the filtrate equal to those in plasma (freely filtered). Larger size, particularly negatively charged solutes are sieved partially or completely. Hb, with  $68\text{ kD}$  appears in urine when there is intravascular hemolysis but negatively charged albumin also with  $68\text{ kD}$  is absent. Donnan equilibrium affects distribution

of freely filtered ions across GBM (slightly more diffusible anions and slightly less diffusible cations in filtrate than in plasma), but this effect is not large, so glomerular fluid can be described as an **ultrafiltrate of plasma**. Red cell casts appear in urine in glomerular inflammatory diseases.

4. **Glomerular Filtration Rate (GFR)** (Fig. 3.2) is the amount of filtrate formed per unit time. Normal value: 110 ml/min, 160 L/day, 20% of RPF. Each nephron filters about 55 nl/min.

Determinants of rate:  $GFR = K_f (\text{ultrafiltration coefficient}) \times P_u (\text{net ultrafiltration pressure})$ .

**Chemistry:** GBM formed by collagen, laminin, other extracellular matrix proteins such as negatively charged heparan sulfate proteoglycans. GBM provides support and has a sieving function.

**Sieving function:** GBM allows free passage of neutral molecules up to 6Kd MW (18 Å radius). Negatively charged pores  $P_u$  is 10 mm Hg at afferent arteriole end and 2-0 mmHg at efferent arteriole end of glomerular capillaries (gc).  $P_u = P(\text{hydrostatic})_{gc} - P(\text{osmotic})_{gc} - P(\text{hydrostatic})_{bs}$ . When  $P_u = 0$  by the time the capillary blood reaches the efferent arteriole, there is filtration equilibrium and GFR becomes proportional to RPF (constant filtration fraction).

$P(\text{hydrostatic})_{gc} = 45-60$  mm Hg all along the capillary (higher than in other capillaries in the body), is under both autoregulation (intrinsic) and extrinsic control, decreases with increasing afferent arteriole resistance (induced by AVP or AII, opposed by PG or ANP) and increases with efferent arteriole resistance (AII).  $P(\text{osmotic})_{gc} = 20$  at start and increases to 30 mm Hg at end of gc as filtration occurs and plasma proteins become concentrated. It opposes filtration, increases in dehydration, and decreases with plasma protein concentration in starvation, liver and kidney diseases.

# FILTRATION PRESSURES

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The major force causing filtration is the hydrostatic pressure in the glomerular capillary bed,  $P_{gc}$ .

$$P_{gc} \approx 60 \text{ mm Hg}$$

It is opposed by a smaller hydrostatic pressure within the tubule,  $P_t$ .

$$P_t \approx 20 \text{ mm Hg}$$

$\Delta P$  is the hydrostatic pressure gradient across the capillary wall:

$$\Delta P = P_{gc} - P_t \approx 60 - 20 \approx 40 \text{ mm Hg}$$

Filtration is also opposed by the colloid osmotic pressure of the blood,  $\pi_b$ .

$$\pi_b = 30 \text{ mm Hg (mean)}$$

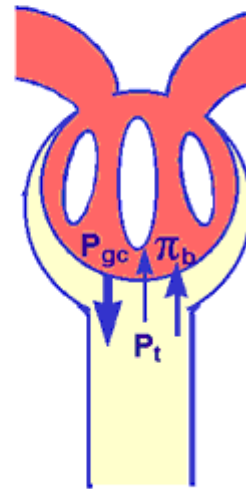


Fig. 3.2. Glomerular Filtration Rate

$K_f$  is 50x greater than in other capillaries.  $K_f$  depends on surface area for filtration (SA) and on  $L_p$ , the fluid conductivity per unit area (how easily the fluid goes through). Contraction of mesangial cells (AVP, AII) reduce SA; prostaglandins relax mesangial cells and increase SA. Excess mesangial cell proliferation (induced by PDGF and EGF) after inflammation and excess matrix production (induced by TGF) during scarring reduce SA

$L_p$  has not been measured. It is thought not to be limiting for filtration.

**GFR Measurement:** Needed as index of functioning kidney mass, to evaluate progression of renal disease and to adjust dose of drugs excreted by filtration.

**Principle:** If a solute is freely filtered (same concentration in glomerular filtrate as in plasma), is neither reabsorbed nor secreted and is not metabolized by the kidneys, then, in the steady state, the amount filtered equals the amount excreted,  $VU = GFR \times P$ , so  $VU/P = C = GFR$ . Inulin has these properties and has been used to measure GFR, but these must be injected as they do not occur naturally in the body.



Creatinine (Cr) is produced in the body from muscle phosphocreatine and its properties approach those of inulin. However, at normal GFR, 10% of excreted creatinine is secreted. Because of measurement limitations, measured Pcr is 10% higher than true Pcr, so these two errors cancel each other and  $C_{cr} = C_{inulin}$  in normal subjects. In theory, if GFR decreases Pcr must increase so  $GFR \times P_{cr}$  (and  $V_{Ucr}$ ) remain constant when a steady state is achieved. But when GFR is reduced to 1/20, Pcr does not increase 20 times but only 10 times because of Cr secretion. So changes in Pcr are an index but not an exact measure of GFR and of its changes.

## MEASUREMENT OF FILTRATION RATE

Amount entering = Amount leaving

$$GFR \times P_{in} = U_{in} \times V \quad \text{Eq. 3}$$

$$GFR = U_{in}V / P_{in} \quad \text{Eq. 4}$$

Units are ml/min

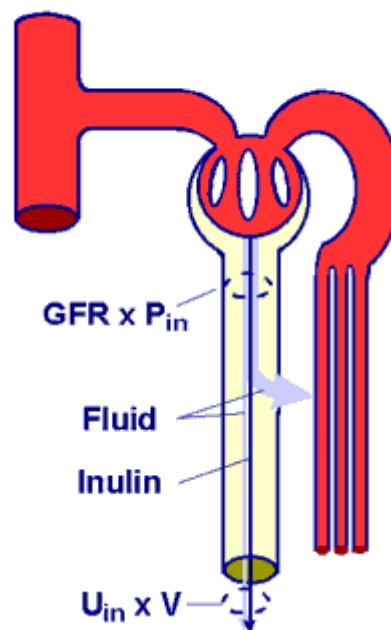


Fig. 3.3. Measurement GFR

BUN also varies inversely with GFR (uremia, azotemia). However BUN can also increase due to increased urea reabsorption (as in dehydration and volume depletion resulting in a high BUN/Pcr, typical of prerenal azotemia) or because of excess protein in the diet. In patients starved or with liver disease BUN may remain low or normal in spite of reduced GFR.

## 5. TUBULAR TRANSPORT.

**1. Basic Relations.** For a freely filtered solute, **Filtered Load** = Glomerular Filtration Rate x Plasma Concentration, or

$$\mathbf{FL = GFR \times P}$$

Note: If the solute is bound to proteins or restricted in filtration, then  $FL = WFL \times F$  (Water Filtration Rate x Concentration of solute in the filtrate water).

**Tubular Transport.** Tubular transport rate (**T**) of a solute = Difference between Filtered Load and Excretion Rate (urine concentration times urine formation rate,  $U \times V$ ), or

$$\mathbf{T = FL - UV}$$

If the filtered load is greater than the excretion rate ( $FL > UV$  or  $UV/FL < 1$ ), then the solute is **reabsorbed** along the tubule. If excretion is greater than the filtered load ( $UV > FL$  or  $UV/FL > 1$ ), then the substance is **secreted** by the tubule. Note that we can calculate only the net reabsorption or secretion, which may be the result of a combination of secretion and reabsorption in different segments of the nephron.

**Relation to Clearance (C).** If the clearance of a solute is greater than the clearance of inulin (=GFR), then the substance must be secreted. If the clearance of a solute is less than the clearance of inulin, the substance must be reabsorbed.

**Fractional Excretion.** The fraction of the FL that is excreted is called the fractional excretion, and can be calculated from  $C(\text{solute})/C(\text{inulin})$  or  $(U/P)_{\text{solute}} / (U/P)_{\text{inulin}}$ .

**2. Reabsorption.** Reabsorption may take place by transport through the tubule cells (**transcellular**) or through the space between the tubule cells (**paracellular**). Paracellular transport is by passive diffusion or by solvent drag. Transcellular transport may be mediated, passive, or a combination of the two. Transcellular transport involves luminal and basolateral steps. **Luminal steps** may be by diffusion (through channels or through the membrane lipids), or mediated by cotransport (Na with glucose, amino acids or carboxylic acids), by exchange (H with Na), or by primary ATP driven pumps (H, K).

**Basolateral transport** steps may be by primary active ATP driven pumps (Na- K, Ca, H), by facilitated carriers (glucose, amino acids other organic solutes), by coupled co-transporters (for HCO<sub>3</sub> and Na, or for K and Cl), by exchangers (Na for Ca, HCO<sub>3</sub> for Cl), or by passive diffusion through channels or through the membrane lipids.

Mediated reabsorption processes have a limiting maximal rate, i.e. they are saturable and show a **tubular transport maximum (T<sub>m</sub> or V<sub>max</sub>)**. They also exhibit a **threshold**, i.e. a plasma level after which the solute involved starts to appear in the urine. Some solutes, such as glucose, have a high threshold; they only appear in the urine at plasma levels much higher than normal. Other solutes, such as phosphate, have low threshold, i.e. they appear in urine at plasma levels only slightly above normal. Only the plasma levels of those solute with low threshold are regulated by the kidney. High capacity (V<sub>max</sub>), low affinity, transporters are usually located proximally. Low capacity, high affinity transporters are usually located more distally. This enhances the efficiency of reabsorption.

**Splay.** Because some nephrons have a lower reabsorptive capacity than average, some substances begin to appear in urine before T<sub>m</sub> is reached. This distribution of nephron reabsorptive capacity is called Splay.

**3. Secretion.** Coupled anion/cation transporters mediate the transfer of certain organic solutes from renal interstitial fluid into the tubule cells. These solutes are actively accumulated in the cells, from which they exit into the tubule lumen along concentration or electrical gradients. Many drugs are secreted in this way by the tubule cells. Some substances (NH<sub>4</sub>, glucuronide and glycine conjugates) are produced by metabolism inside the tubule cells and then enter the tubule fluid; these are also said to be secreted.

At low plasma concentrations, many secreted solutes (for example, p-aminohippurate or PAH) are extracted almost completely from the plasma as it goes through the kidneys. Secretory transport systems also exhibit saturability (T<sub>m</sub>). Only when the plasma level is well below that required to reach T<sub>m</sub> can such solutes be extracted efficiently from the blood perfusing the kidneys and their

clearance approach the RPF. Since even at low concentrations, only about 90% of substances such as PAH are excreted in one pass through the renal circulation, their clearance is termed the effective RPF.

## 6. PROXIMAL TUBULE FUNCTION

### 1. Magnitude of Proximal Tubule Reabsorption

Since  $P_{Na} = 145 \text{ mEq/L}$  and  $GFR = 180 \text{ L/day}$ , then  $26100 \text{ mEq Na/day}$  (equivalent to Na in 1.566 kilogram salt) are filtered. Only  $300 \text{ mEq Na/day}$  are excreted in the urine. Thus, about 99% is reabsorbed by the kidneys.

Most of the Na reabsorption takes place in the proximal tubule. The  $(TF/P)_{inulin} = 3$  by the end of the proximal convoluted tubules(PCT). This indicates that only 1/3 of the filtered water remains by the end of the PCT and two thirds have been reabsorbed. The Na concentration in fluid sampled at the end of the PCT equals that in plasma,  $(TF/P)_{Na} = 1$ . So, 2/3 of the filtered Na must also have been reabsorbed along the PCT.

The osmolarity of the fluid along the PCT remains nearly equal to that in plasma

## Na TRANSPORT IN THE PROXIMAL TUBULE

### THE PRIMARY ENGINE:

- ♦ Na-K-ATPase in the basolateral membrane.
- ♦ Coupled with K channels, it:
  1. Maintains a low [Na] in the cell.
  2. Maintains a high [K] in the cell.
  3. Maintains a negative membrane potential.
- ♦ These gradients drive other secondary active transport mechanisms.

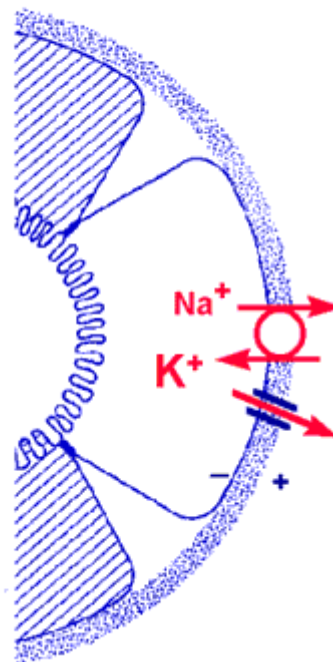


Fig. 4.1. Transport mechanisms for Na

$(TF/P)_{osm}=1$ . So 2/3 of all filtered solutes are reabsorbed along with 2/3 of the filtered water along the PCT. This is called **isoosmotic reabsorption**.

## TRANSPORT MECHANISMS FOR GLUCOSE REABSORPTION

- ♦ A Na-glucose cotransporter, located in the brush border, transports one glucose and 2 Na<sup>+</sup> ions per cycle from the filtrate into proximal tubular cells.
- ♦ This is a secondary active transport mechanism which utilizes the chemical and electrical gradients for Na<sup>+</sup> established by the Na-K-ATPase mechanism.
- ♦ Glucose is transported from the cell into the interstitial fluid by an independent mechanism.

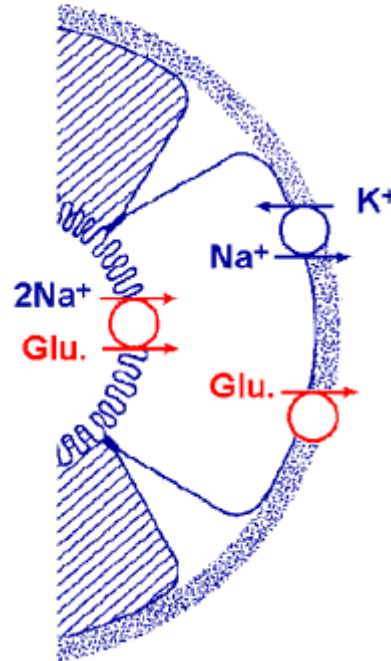


Fig. 4.2. Transport mechanisms for glucose

### 1. Transport in the S1 Proximal Tubule Segment

**Mechanisms:** Luminal Na entry (Fig. 4.1.) into S1 PCT cells via Na/H exchange (25% of the amount reabsorbed), and via cotransport with glucose (5%) and amino acids (2%) and carboxylic acids (1%), for a total of 33% of S1 Na reabsorption. The rest of the Na (66%) is reabsorbed passively by solvent drag through the paracellular pathway. Of the Na that enters the S1 PCT cells, about 3/4 is transported from the PCT cells into the interstitial space by the Na-K ATPase at the basolateral side and the rest is extruded via basolateral 3HCO<sub>3</sub>-Na cotransport.

S1 is poorly permeable to Cl and urea, which rise in concentration along S1, compensating in part for the decrease in concentrations of HCO<sub>3</sub>, glucose (Fig. 4.2.) Transport mechanisms for Na

, amino and carboxylic acids, phosphate and sulfate.

**Water reabsorption** along S1 is due to a small (4 mOsm/L) **osmotic gradient** (lumen hypo-osmotic) due to preferential reabsorption of  $\text{NaHCO}_3$ , Na with glucose, amino and carboxylic acids and an extremely **high permeability** to water, due to abundance of aquaporin water channels in PCT cell membranes.

When delivery of poorly reabsorbed solutes to the PCT increases (such as glucose in diabetes mellitus,  $\text{HCO}_3^-$  when carbonic anhydrase is inhibited, or excess filtered saline), osmotic water reabsorption and paracellular passive Na reabsorption by solvent drag decrease and an **osmotic diuresis** may develop in which up to 66% of filtered Na and water (66 ml/min) may be excreted as slightly hyperosmotic urine.

## 2. **Transport in the S2-S3 Proximal Tubule Segments**

**Along the S2 and S3 segments**, the major transport process is the reabsorption of NaCl through parallel  $\text{Cl}^-/\text{formate}^-$  and  $\text{Na}^+/\text{H}^+$  exchanges at the luminal cell membrane.

**Water reabsorption** along S2 and S3 is driven by a small (4 mOsm/L) **effective osmotic gradient** generated by the lower osmotic effect of intraluminal  $\text{Cl}^-$  (reflection coeff. = 0.8), compared to peritubular  $\text{HCO}_3^-$ , glucose, and amino acids (reflection coeff. = 1), in spite of similar intra- and peritubular total osmolarities. The water permeability in these segments is also very high.

## 3. **Proximal Tubule Transport Regulation**

**Regulation of  $\text{Na}^+$  and water reabsorption** along the proximal tubule is by **glomerular- tubular (GT) balance**: tubular reabsorption changes in proportion to the filtered load; percent or fractional reabsorption remains constant. GT balance is due to intratubular and peritubular factors. **Intratubular factors**: At the high tubule flow rate associated with high GFR, the decrease in the luminal concentrations of  $\text{HCO}_3^-$ , glucose, and amino acids along the PCT are less marked than at normal GFR. Thus, the more distal cells in S2 and S3 are exposed to higher concentrations of these solutes when GFR is higher. High concentrations promote the reabsorption of these solutes, coupled with Na which, in turn, increases the osmotic reabsorption of water.

**Peritubular factors:** When GFR increases due to a rise in efferent resistance there is an increase in peritubular capillary oncotic pressure ( $P_{\text{onc}}$ ) and a decrease in peritubular capillary hydrostatic pressure ( $P_{\text{hydro}}$ ), both of which reduce interstitial fluid pressure and promote fluid and Na reabsorption proportionally to the increase in GFR. (Note: oncotic pressure is the osmotic pressure developed by plasma proteins.)

When mean arterial pressure (MAP), afferent resistance or oncotic pressure ( $P_{\text{onc}}$ ) change, there are **adjustments** of GT balance that lead to changes in fractional reabsorption of Na and water along the PCT. Decrease in MAP, increase of afferent arteriole resistance, or increase of peritubular capillary  $P_{\text{onc}}$  (common in dehydration and volume depletion) lead to increases in proximal **fractional** reabsorption of Na and water by reducing peritubular  $P_{\text{hydro}}$  and/or interstitial fluid pressure. The reverse occurs when MAP increases, afferent resistance decreases, or peritubular capillary  $P_{\text{onc}}$  decreases (common in overhydration or volume expansion).

**Other factors:** In addition to intratubular factors and peritubular Starling forces (physical factors), proximal tubule Na transport is also regulated by hormones, such as AII and catecholamines, which will be discussed later.

## **7. COUNTERCURRENT SYSTEM and the LOOP OF HENLE (Fig. 5.1.)**

### **1. The Loop of Henle establishes medullary hyperosmolarity**

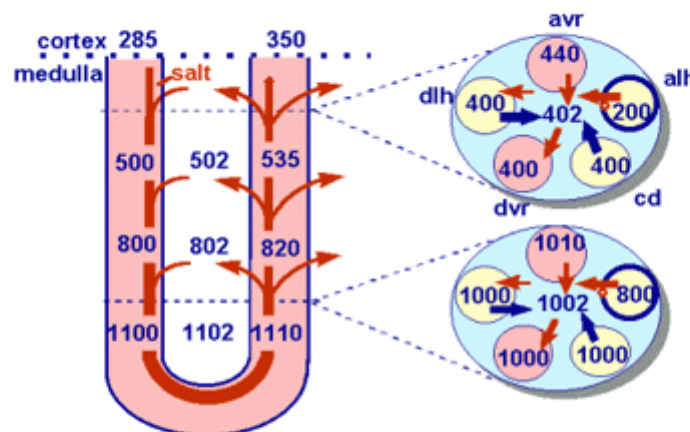
The ascending limb of the loop of Henle transports solutes (NaCl) out of the tubule lumen with little or no water, generating an hyperosmotic medullary interstitium and delivering an hyposmotic tubule fluid to the distal tubule. This is called the "single effect".

The osmolarity of the interstitium rises progressively from cortex to medulla and papilla through multiplication of the "single effect" by countercurrent flow in the branches of the loop: The single effect in fluid processed by loop segments located

near the tip of the papilla occurs in fluid already subject to the single effect when the fluid was in loop segments located closer to the cortex.

Countercurrent exchange of solutes between ascending and descending vasa recta (the renal medullary capillaries) minimizes solute washout from the medullary interstitium.

## THE COUNTERCURRENT EXCHANGER: THE VASA RECTA



- ◆ **Descending vasa recta:** Blood coming down into the medulla from the cortex comes into contact with the concentrated medullary ISF. Salt diffuses from that ISF into the blood increasing the plasma conc.
- ◆ **Ascending vasa recta:** Concentrated blood flowing up towards the cortex from the papilla loses salt to the more dilute medullary ISF.
- ◆ **Thus salt, reabsorbed from the loop of Henle, is trapped and recycled within the medulla by countercurrent flow of blood in the vasa recta.**

Fig. 5.1. Countercurrent exchange - mechanism

### 2. The countercurrent system permits forming a concentrated urine (Fig. 5.2.)

In the presence of ADH, which increases water permeability, the hyposmotic fluid that enters the distal tubule (DT) from the thick ascending limb (TAL) loses most of its water by osmotic equilibration with the surrounding cortical interstitium along the CNT and cortical collecting duct (CCD). It also continues losing NaCl through reabsorptive transport along DT, CNT and CCD, until the tubule fluid becomes isoosmotic with plasma, by the end of the CCD.



## COUNTERCURRENT CONCENTRATION OF UREA

- ♦ **Descending limb:** The tubular fluid urea concentration increases as urea diffuses in from the medullary ISF and water is reabsorbed.
- ♦ **Ascending limb:** No transport of urea or water.
- ♦ **Distal tubule, cortical and outer medullary collecting tubule:** No transport of urea, water reabsorption raises the urea concentration to a high level.
- ♦ **Inner medullary collecting tubule:** Urea is reabsorbed by facilitated diffusion into the inner medullary ISF.

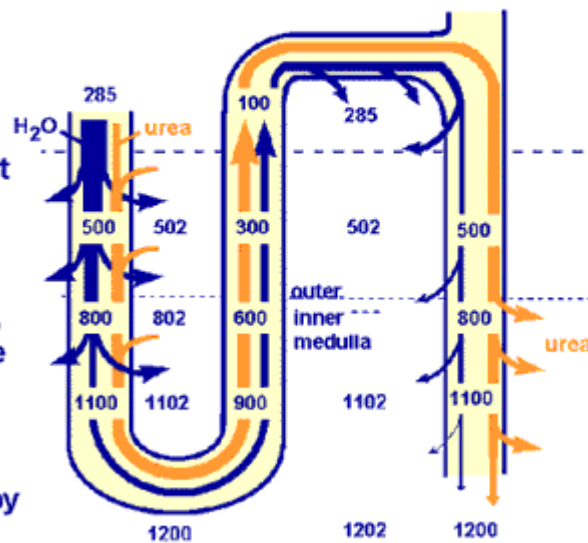


Fig. 5.2. Countercurrent concentration of urea

The relatively small amount of isoosmotic fluid that flows into the medullary collecting ducts loses progressively more and more water to the hyperosmotic medullary and papillary interstitia and is finally excreted as hyperosmotic, highly concentrated urine.

### 3. The countercurrent system permits forming a dilute urine

In the absence of ADH, the hyposmotic fluid that enters the DT from the loop of Henle, continues to be diluted by transport of NaCl via NaCl (thiazide sensitive) cotransporters into DT cells and via Na channels (amiloride sensitive) along the CD. Water reabsorption is limited so that the tubule fluid becomes more and more dilute along DT, CNT and collecting ducts (CCD, OMCD and IMCD), until it is excreted as a large volume of hyposmotic urine.

### 4. Mechanism of hyperosmotic reabsorption in the TAL

There is apical Na-K-2Cl reabsorptive cotransport with K recycling through apical K-channels, and basolateral transport of Na via the Na-K-ATPase and of Cl via Cl-channels, in the water impermeable epithelium of the TAL.

A lumen positive electrical potential difference is generated by the luminal Na-K-2Cl cotransporter operating in parallel with channels that allow K to recycle into the lumen. The lumen positive potential drives passive paracellular reabsorption of more Na<sup>+</sup> and of other cations (Mg<sup>++</sup>, Ca<sup>++</sup>)

The higher the delivery of Cl (K<sub>m</sub>=50 mM), the higher the activity of the luminal Na-K-2Cl cotransporters and the higher the rate of hyperosmotic Na reabsorption at the TAL.

### **5. Mechanism for hyperosmotic reabsorption in the TAL (thin ascending limb)**

Water abstraction along the early part of the thin descending limb (TDL) is driven by the high osmolarity (at least half due to urea) present in the medullary interstitium. In the deep nephrons, water reabsorption increases the tubule fluid osmolarity (up to 1200 mOsm/L) and the Na concentration (up to 300 mEq/L) by the bend of the loop.

Along the water impermeable TAL, Na diffuses from the tubule lumen into the medullary interstitium driven by its concentration gradient and some urea enters from the interstitium into the lumen; the osmolarity decreases as the fluid ascends along the TAL.

Operation of this passive mechanisms of Na reabsorption along the TAL is critically dependent on efficient medullary recirculation of urea from IMCD to interstitium, to TAL.

### **5. Other functions of the Loop of Henle**

Bicarbonate reabsorption through Na-H exchange  
Reabsorption of cations such as Ca<sup>2+</sup> and Mg<sup>2+</sup>

Generation of cortical to medullary gradients of gaseous NH<sub>3</sub> and O<sub>2</sub> and of medullary to cortical gradients of CO<sub>2</sub> and lactic acid

Production of Tamm-Horsfall mucoprotein (casts)

Cells survive in the hyperosmotic medullary environment through slow accumulation of osmolytes (75 mM sorbitol and 25 mM glycerophosphocholine (GPC) by synthesis, and 25 mM betaine and 10 mM inositol by Na<sup>+</sup> driven cotransport), which can be rapidly released from the cells through channels that open when the osmolarity decreases.

## **8. REGULATION OF TOTAL BODY and CELL WATER**

### **AntiDiuretic Hormone (ADH, Vasopressin) (Fig. 6.1.)**

#### **1. Sensors of changes in body water content and osmolarity**

##### **A. Role of the Hypothalamic Osmoreceptors**

Osmoreceptors are cells in hypothalamic Organus Vasculosus Lamina Terminales (OVLT). They sense increases in effective osmolarity capable of inducing decreases in cell volume (not like urea) when the osmolar concentration rises above a threshold of 280 mOsm/Kg.

Increases in effective osmolarity enhance the electrical activity of the osmoreceptor cells, which in turn increase the synthesis of antidiuretic hormone (ADH) by supraoptic and paraventricular hypothalamic neurons and release of stored ADH into the blood from the terminals of these neurosecretory cells in the posterior pituitary gland.

With a 1% (3 mOsm/Kg) increase in effective osmolarity, ADH levels increase in plasma by 2 pg/ml, reducing the urine flow to 1/3 and increasing urine concentration 3-fold, from 200 to 600 mOsm/Kg.

Inability to produce ADH in hypothalamus or release it from the posterior pituitary leads to central diabetes insipidus, a disease characterized by large urinary water loss and thirst.

##### **B. Role of the Atrial Stretch Receptors**

Left atrial stretch receptors sense changes (10%) in central blood volume and small changes in ECFV due, for example, to dietary sodium changes or to redistribution of blood between legs and central blood reservoirs (changes in position, water immersion, absence of gravity) that need not alter mean arterial pressure.

## CONTROL OF ADH SECRETION

- ◆ The **ADH** level in plasma is closely regulated by  $P_{osm}$ .
- ◆ A rise of 15 mosmole/kg  $H_2O$  from 280 to 295 takes the ADH level from the threshold level to the maximum effective concentration.
- ◆ Changes in ADH levels within this range can cause  $U_{osm}$  to vary from 50 to 1200 mosmole/kg  $H_2O$  and  $V$  from 20 to 0.8 l/day.

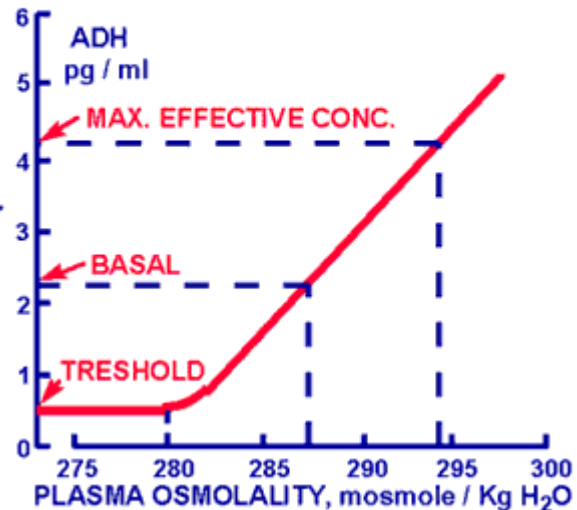


Fig. 6.1. Control of ADH

These mechano-receptors, when stretched by increased volume, send impulses via the Xth nerve to inhibit hypothalamic synthesis and posterior pituitary release of ADH, leading to an increased flow of dilute urine (water diuresis).

With continuous stretch (as in congestive heart failure) these receptors adapt and cease to inhibit synthesis and release of ADH.

Decreased stretch promotes ADH synthesis and release.

### C. Role of Systemic Arterial baroreceptors

Arterial (aortic and carotid) baroreceptors sense decreases in mean arterial pressure (MAP), reducing neural impulses via the IXth and Xth nerves to the hypothalamus, and allowing unrestrained massive release of vasopressin (ADH). This emergency response leads to water retention and general vasoconstriction that defend perfusion of the heart and brain against hypotension and /or low cardiac output.

D. Other Influences Release of ADH is increased by pain, nausea, hypoxia, smoking, and morphine. ADH release is inhibited in the cold, by opiates, alcohol, and glucocorticoids.

## 2. Metabolism of ADH

ADH is rapidly metabolized after endocytosis by liver and kidney cells. Its half life in blood is only 20 minutes.

## 3. Effects of ADH

ADH binds to V2 receptors in CD principal cells (Fig. 6.2.). These receptors, through a Gs protein, activate adenylyl cyclase, an enzyme that promotes synthesis of cyclic AMP. cAMP activates protein kinase A, an enzyme that phosphorylates several proteins, altering the cytoskeleton and allowing subapical vesicles containing aquaporin water channel proteins to fuse with the apical plasma membrane of the principal cells, increasing their permeability to water.

## MECHANISM OF ACTION OF ADH

- ♦ **ADH attaches to a V2 receptor and activates a cascade through a Gs protein, adenylyl cyclase, cAMP and protein kinase A to cause the insertion of aquaporin 2 into the apical membrane.**
- ♦ **H<sub>2</sub>O moves through aquaporin 2 in response to an osmotic gradient and thence through aquaporins 3 and 4 in the basolateral membrane**

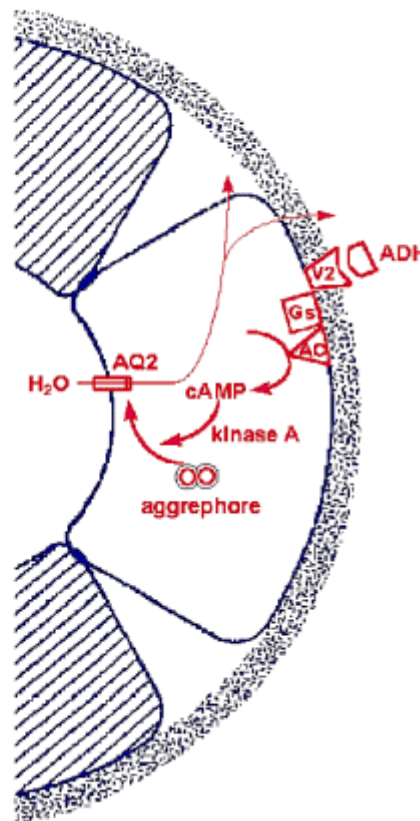


Fig. 6.2. Effects of ADH

In the absence of ADH aquaporins are retrieved from the membrane and stored in subapical vesicles (aggrephores).

Defects in V2 receptors or in ADH-dependent aquaporin (Type II) leads to lack of response to ADH and development of nephrogenic (of renal origin) diabetes insipidus.

ADH at high concentrations binds also to V1 receptors in vascular smooth muscle, mesangial cells, and platelets, which through a G protein cause activation of phospholipase C. This enzyme induces release of IP<sub>3</sub> and DAG, which in turn raise cytosolic calcium and activate protein kinase C. These activate myosin light chain kinase and produce cell contraction. As a consequence, high levels of ADH result in vasoconstriction, reductions in RPF, GFR, and renal medullary blood flow. Low levels of ADH favor increases in RPF and renal medullary washout.

The effect of ADH on urine flow is measured through changes in free water clearance.

#### **4. Free water clearance**

A dilute urine excreted in the absence of ADH can be thought of as being made up of two fluid volumes: 1) a volume which contains the urine solutes at the same concentration as in plasma and called the Osmolar clearance ( $= U_{osm} \times V / P_{osm}$ ) and 2) pure water excreted with no solutes, called positive free water clearance ( $C_{H_2O} = V - C_{osm}$ ).

A concentrated urine produced in the presence of ADH can be thought of as the difference between two volumes: 1) the volume of plasma from which the urinary solutes derive ( $C_{osm}$ ) and the (smaller) volume of urine actually excreted (V). The difference  $C_{osm} - V$  represents water free of solutes retained in the body due to the action of ADH. This is called the negative free water clearance or tubular free water reabsorption

## **9. REGULATION OF BODY Na and ECFV**

Because the major osmotically effective solutes in the ECF are Na<sup>+</sup> salts the amount of water present in the ECF compartment depends on the Na<sup>+</sup> content of the body.

### **1. Sensors of changes in ECFV.**

Atrial receptors. Small (10%) decreases in ECFV, due to corresponding changes in dietary  $\text{Na}^+$  or simply redistribution of ECFV between central (heart and lungs) and peripheral (legs) blood reservoirs, are sensed by stretch receptors at the low pressure side of the circulation, such as the atrial stretch receptors. These receptors, when less stretched send fewer neural inhibitory impulses to the central sympathetic nervous system.

Macula densa. Moderately large decreases in ECFV capable of reducing GFR or of increasing PT  $\text{Na}^+$  reabsorption will decrease the  $\text{NaCl}$  load reaching the macula densa. Decreased transport of  $\text{NaCl}$  by macula densa cells results in decreases in cytosolic  $[\text{Ca}^{2+}]_i$ , which through not well defined messengers (possibly less release of arachidonic acid metabolites or adenosine), leads to decreases in cytosolic  $[\text{Ca}^{2+}]_i$  in the granular cells of the afferent arteriole, which in turn increases renin release while decreasing the afferent arteriole vascular tone.

Renal vascular baroreceptor. Decreased stretch at the renal afferent arterioles due to large changes in ECFV resulting in low mean renal arterial pressure or increased preglomerular resistance, reduces  $\text{Ca}^{2+}$  influx into granular cells of these arterioles and promotes renin release.

Systemic arterial baroreceptors. Large decreases in ECFV, CO or systemic peripheral vascular resistance resulting in reduced MAP are sensed by the arterial (carotid and aortic) baroreceptors, which reduce the inhibitory neural afferent input to the central sympathetic centers.

## **2. Neural mediators**

Inhibitory neural afferent input to the central sympathetic centers in the hypothalamus originates in stretch receptors present on the low pressure side of the circulation such as in the left atria and reach the hypothalamus via the vagal (Xth) nerve. Inhibitory neural afferents also reach the sympathetic centers from the arterial baroreceptors through the IX and X nerves.

## ROLE OF EFFERENT SYMPATHETIC NERVE ACTIVITY

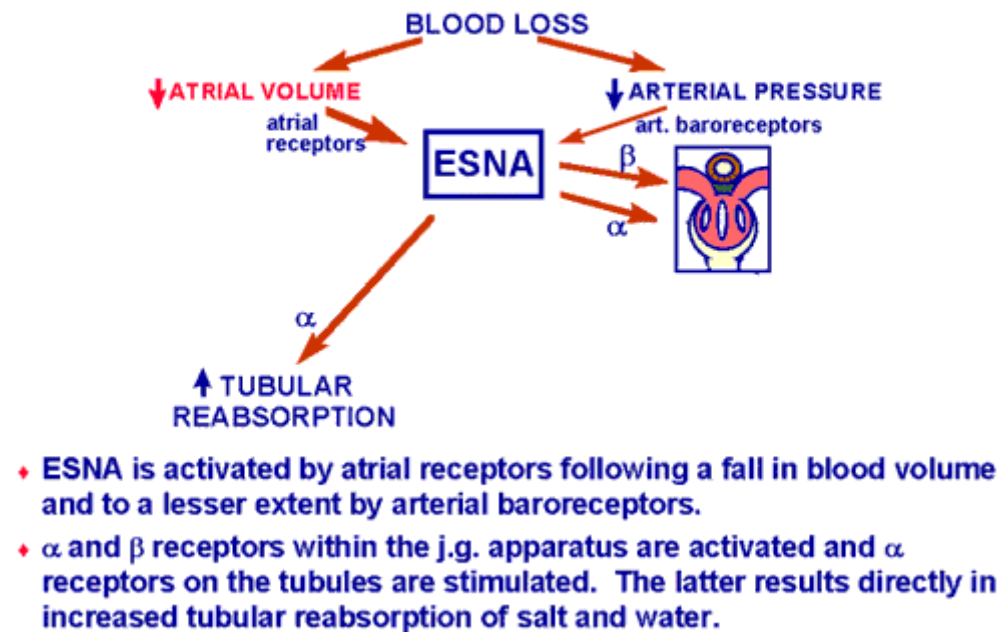


Fig. 7.1. Role of sympathetic division in regulation Na and ECFV

Sympathetic efferents reach the kidneys, specifically the granular cells of the juxtaglomerular apparatus, via the renal nerves and through  $\alpha$ -2 receptors mediate renin release in response to increases in sympathetic output.

Sympathetic efferent effects (Fig. 7.1.) are also mediated through release of catecholamines which bind to  $\alpha$ -1 receptors, leading to constriction of renal and extrarenal arterioles and mesangial cells, and stimulation of proximal tubule Na-K-ATPase.

### 3. Humoral mediators

AII (angiotensin II). Release of renin, stimulated by the sympathetics, by low MAP, or by low NaCl delivery to the macula densa, promotes conversion of plasma angiotensinogen to AI; conversion of AI to AII occurs spontaneously under the influence of ACE (angiotensin converting enzyme).

AII is an potent vasoconstrictor which reduces RPF, but because its dominant effect is on the efferent arteriole, it maintains glomerular Pc and reduces Pc at the peritubular capillaries. These effects maintain GFR, increase filtration fraction



(GFR/RPF) and peritubular capillary osmotic pressure, and increase proximal tubule reabsorption of Na and water.

In addition, AII stimulates proximal tubule Na-H exchange and Na-bicarbonate reabsorption by reducing intracellular cAMP through a Gi protein linked to the AII receptor. This effect of AII accounts for the alkalosis often seen in volume depletion. In the adrenal cortex AII is a potent stimulus for the release of aldosterone.

Aldosterone produced at the zona glomerulosa of the adrenal cortex is a potent mineralocorticoid that promotes active sodium reabsorption along DT and CD. Aldosterone is released in response to AII, high plasma K and very large decreases in plasma Na.

Aldosterone competes with cortisol for binding to its receptor in principal cells. The enzyme 11-hydroxysteroid dehydrogenase converts cortisol to non-binding cortisone, allowing aldosterone to bind to the mineralocorticoid receptor preferentially. Inhibition of this enzyme (by licorice) results in a syndrome similar to excessive production of aldosterone, due to cortisol binding.

Receptor-bound aldosterone enters the nucleus of principal cells, where it increases transcription of luminal Na channel proteins, of Na-K-ATPase and of enzymes of energy metabolism, resulting in increased luminal entry into and increased basolateral extrusion of Na from the cells. Aldosterone also accelerates K secretion by principal cells and H-secretion by  $\square$ -intercalated cells of the CD.

ANP (atrial natriuretic peptide). Increases in volume at the low pressure side of the circulation stretch the atria, which release ANP to the circulation. ANP is a potent vasodilator that increases RPF, GFR, and peritubular Pc, and thus increases filtration and reduces proximal tubule reabsorption of Na and water. In addition, ANP inhibits Na reabsorption at the CD. Peptides analogous to ANP are produced in the brain (BNP) and in the kidneys (urodilatin). An endogenous ouabain-like inhibitor of Na transport is produced in the adrenals.

#### **4. Effectors of change in renal Na excretion**

The principal cells of the CD are major targets for aldosterone stimulated distal Na reabsorption and for ANP.

Changes in osmotic pressure and hydrostatic pressure in the peritubular capillaries alter proximal Na reabsorption. These forces reduce or increase the interstitial fluid pressure and promote or inhibit fluid and Na reabsorption, respectively. Proximal Na reabsorption is stimulated by AII, which increase Na-H exchange, and by noradrenaline, that stimulates the Na-K ATPase.

Small changes in renal hemodynamics (RPF and GFR) can have large effects on renal Na excretion.

Increased MAP decreases Na reabsorption in deep but not in surface nephrons. Redistribution of filtration between nephrons affects Na excretion.

Na reabsorption in the loop of Henle is increased when medullary blood flow decreases (ADH) and diminishes when medullary blood flow washes out the osmotic gradient.

## **10. REGULATION OF BODY POTASSIUM**

$K^+$  is the major intracellular ion. Only 2% is in the ECF at a concentration of only 4 mEq/L. K is taken up by all cells via the Na-K ATPase pump. It is one of the most permeable ion across cell membranes and exits the cells mostly via K channels (and in some cells via K-H exchange or via K-Cl cotransport).

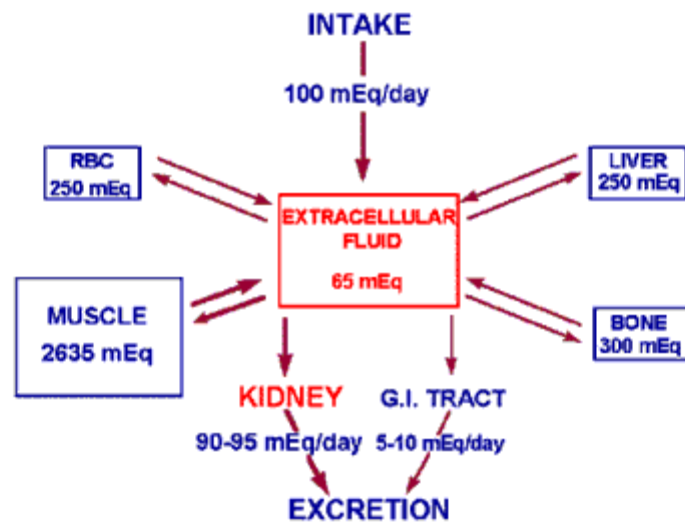
### **1. Roles of K (Fig. 8.1.)**

K is the major ion determining the resting membrane electrical potential, which in turn, limits and opposes K efflux. Thus changes in K concentrations (particularly in the ECF) have marked effects on cell excitability (heart, brain, nerve, muscle).

K is the mayor intracellular osmotically active cation and participates in cell (intracellular) volume regulation (exits with Cl when cells swell).

A constant cell K concentration is critical for enzyme activities and for cell division and growth.

## NORMAL POTASSIUM DISTRIBUTION AND BALANCE



- ♦ Over 90% of body potassium is contained within cells, principally muscle cells, and is readily exchangeable. Only 2.5% is in ECF.
- ♦ Daily intake approximately equals amount in ECF.
- ♦ The kidney excretes 90-95% of the daily intake. The rest is excreted by the GI tract.

Fig. 9.1. Roles of K

Intracellular K participates in acid base regulation through exchange for extracellular H and by influencing the rate of renal ammonium production.

Regulation of extracellular K is by tissue buffering (uptake of K excess) and by slower renal excretion.

### 2. Cellular K buffering

When K is added to the ECF, most of the added K is taken up by the cells, reducing the ECF  $K^+$  increase. Similarly, if K is lost from the ECF, some  $K^+$  leaves the cells, reducing the ECF K decline.

Buffering of ECF K through cell K uptake is impaired in the absence of aldosterone or of insulin or of catecholamines.

Cell K exit to the ECF increases when osmolarity increases (as in diabetes mellitus) and in metabolic acidosis, when it is exchanged for ECF protons ( $H^+$ ).

When cells die, they release their very high K content to the ECF.

### 3. Renal regulation of Potassium (Fig. 8.2.)

In normal function, renal K excretion balances most of the K intake (about 1.5 mEq/Kg per day). The kidneys excrete about 15 % of the filtered K load of 10 mEq/Kg per day.

Along the proximal tubule the K concentration remains nearly equal to that in plasma. Since the PCT reabsorbs about 2/3 of the filtrate water, it also reabsorbs about 2/3 (66%) of the filtered K. This reabsorption is mostly passive and is driven by the positive tubule electrical potential present along the S2 and S3 segments and by paracellular solvent drag.

Along the descending limb of the loop of Henle, K is secreted into the tubule lumen from the interstitium. Along the thick ascending limb, K is reabsorbed via Na-K-2 Cl cotransport. In the loop, there is net K reabsorption of 25% of the filtered K.

Along the distal tubule and collecting ducts, there is net secretion of K which is stimulated by aldosterone and when there is dietary K excess. Secretion decreases and becomes net reabsorption in K deficiency. Regulation of renal K excretion is in the CD and is mostly by changes in the rate of K secretion.

In the CD, K secretion is by the principal cells (via luminal K channels and basolateral Na-K ATPase) and K reabsorption is by the alpha intercalated cells via a luminal H-K ATPase.

K secretion from principal cells into the CD lumen is enhanced by luminal and cellular determinants:

Luminal determinants that stimulate K secretion are increases in tubule urine flow (which reduces the intratubular K concentration), the delivery of sodium to the CD, and the delivery of poorly reabsorbed anions (other than Cl) to the CD. Na delivery followed by its reabsorption increases K secretion by increasing the lumen negative electrical potential and by stimulating the activity of the Na-K ATPase which results in enhanced accumulation of K in the cells. The presence in the CD of poorly reabsorbed anions ( $\text{SO}_4^{2-}$ , excess of  $\text{HCO}_3^-$ , beta hydroxybutyrate, or  $\text{HPO}_4^{2-}$ ) enhances the negativity of the CD lumen, favoring K secretion.

## FACTORS AFFECTING K<sup>+</sup> SECRETION

♦ The following factors in the blood stimulate K secretion.

- **Aldosterone** stimulates Na-K ATPase and apical gNa and gK.
- **ADH** increases gK of apical membrane.
- **[K]<sub>p</sub>** increases K uptake.
- **Alkalosis** also increases K uptake.

♦ The following factors in tubular fluid also stimulate K secretion.

- **↑V** maintains favorable gradient for secretion.
- **↑Na** reduces electrical gradient across apical membrane
- **↑pH** increases apical gK.
- **↓Cl** maintains gradient for K-Cl cotransporter.

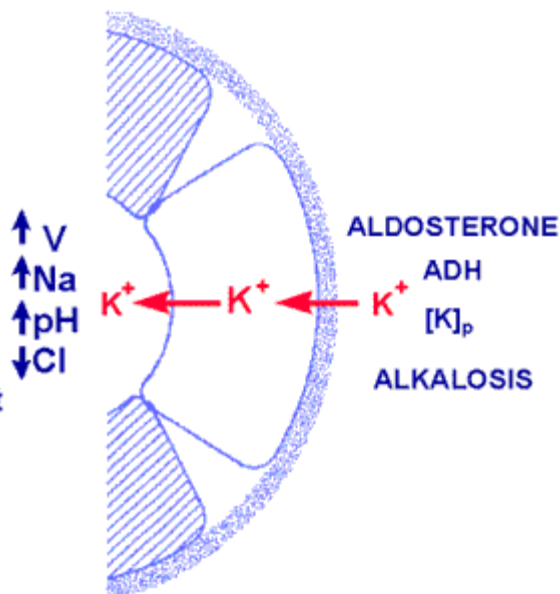


Fig. 8.2. Renal regulation of K

Cellular determinants of K secretion are the activity and abundance of K channels at the luminal cell membrane and of Na-K ATPase at the basolateral membrane. Both of these are enhanced primarily by aldosterone, and also by ADH (by decreasing urine flow, ADH reduces K secretion, but by increasing luminal permeability, ADH promotes it) and by dietary K excess. K deficiency is associated with increased activity and expression of luminal H-K ATPase in the alpha intercalated cells of the CD, which act to promote reabsorption of K from the lumen.

### 11. ACID-BASE PRINCIPLES: Blood plasma pH (Fig. 9.2.)

#### Blood plasma pH

Acids when dissolved in water yield protons (H<sup>+</sup>); bases consume or bind protons. Acidity measures the concentration of free H<sup>+</sup> in a solution. The H<sup>+</sup> concentrations in aqueous solutions are in nanoequivalents per liter (10<sup>-9</sup> Eq/L). In water there is 100 nEq/L H<sup>+</sup> (and OH<sup>-</sup>). This equals 10<sup>-7</sup> Eq/L, or, in a negative log scale, the pH

scale,  $\text{pH} = 7$ . The  $\text{pH} = \log 1/[\text{H}^+]$ . Thus pH is inversely related to  $[\text{H}^+]$ . Blood plasma has  $\text{pH}=7.4$  or  $[\text{H}^+] = 40 \text{ nEq/L}$ , which is somewhat alkaline. This pH is kept in a narrow range ( $7.40 \pm 0.02$ ) in spite of continuous ingestion and metabolic production of acids.

### **Sources of Acid**

Acid production is derived from metabolism of sulfur containing (70 mEq/day), cationic amino acids (140 mEq/day), and substances containing acid phosphates ( $\text{H}_2\text{PO}_4^-$ , 30 mEq/day). Normally, this is balanced by  $\text{H}^+$  consumption in metabolism of anionic amino acids (110 mEq/day) and other organic anions (60 mEq/day), and by urinary excretion of ammonium (40 mEq/day) and acid phosphate (30 mEq/day).

### **Buffering**

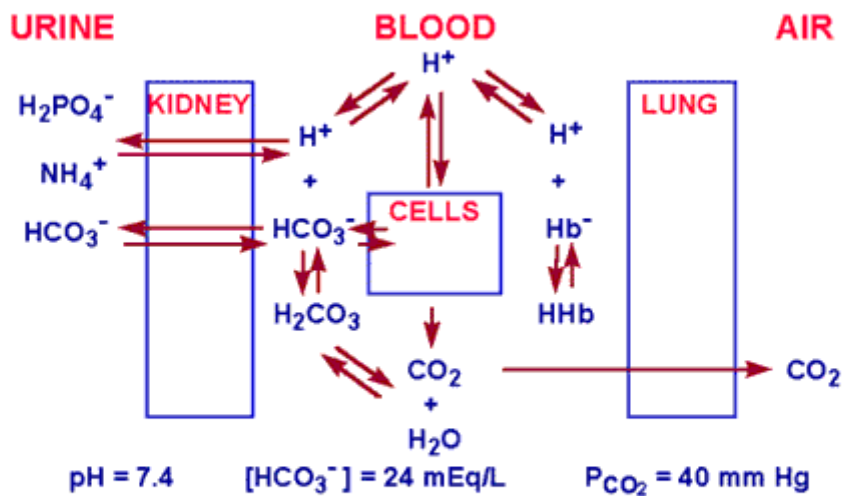
**Buffering occurs when pH changes are minimized.** It involves chemical and physiological processes.

Chemical (in the ECF) and respiratory buffering are almost immediate. ICF buffering involves transfer of  $\text{H}^+$  in or out of the ICF. Intracellular chemical buffering may be fast if it involves organic acid or slower (an intermediate step) for poorly cell permeable inorganic acids such as HCl or  $\text{H}_2\text{SO}_4$ . Long term regulation occurs through kidney urinary excretion of  $\text{H}^+$ , with resulting reabsorption and generation of base ( $\text{HCO}_3^-$ ).

**Chemical buffering** is due to conversion of a strong acid (such as HCl) into a weak acid (such as  $\text{H}_2\text{CO}_3$  or  $\text{H}_2\text{NaPO}_4$ ) through chemical reaction with a weak buffer base (such as  $\text{NaHCO}_3$  or  $\text{HNa}_2\text{PO}_4$ ). The higher the weak base concentration, the better the buffering. The weaker the resulting acid, the better the buffering.

**The weakness or strength of an acid** depends on its dissociation constant ( $K_d$ ). A weak acid when dissolved yields few protons and its  $K_d$  is small. A strong acid when dissolved dissociates completely and yields many protons; its  $K_d$  is large. The pK is the negative log of the  $K_d$ , it is inversely related to the  $K_d$ :  $\text{pK} = \log (1/K_d)$ . Weak acids have high pK. Strong acids have low pK.

## ACID-BASE BALANCE



- ♦ The blood buffers react to acid and alkali produced by cell metabolism.
- ♦ The lungs respond to changes in blood buffer equilibrium by changing the rate of acid ( $\text{CO}_2$ ) excretion into the external environment.
- ♦ The kidneys respond to changes in blood buffer equilibrium by changes in the excretion of acid and alkali into the urine.

Fig. 9.2. Acids-base balance

### Titration of a buffer

When an acid  $\text{HA}$  dissociates into  $\text{H}^+$  and buffer base ( $\text{A}^-$ ), the mass action equilibrium is :

$$[\text{H}^+] \times [\text{A}^-] = [\text{HA}] \times K_d \text{ so that } [\text{H}^+] = K_d \times ([\text{HA}]/[\text{A}^-])$$

When  $[\text{HA}] = [\text{A}^-]$ , then  $[\text{H}^+] = K_d$ .

On a log scale,  $\text{pH} = \text{pK} + \log ([\text{HA}]/[\text{A}^-])$  and when  $[\text{HA}] = [\text{A}^-]$ ,  $\log [\text{A}^-]/[\text{HA}] = \log 1 = 0$ , so  $\text{pH} = \text{pK}$ .

When the pH of a buffered solution is more alkaline (higher) than the buffer pK by 1 unit, the  $\log [\text{A}^-]/[\text{HA}] = 1$  and the ratio  $[\text{A}^-]/[\text{HA}] = 10$ . The proportion of the total buffer ( $\text{HA} + \text{A}^-$ ) in the dissociated weak base form ( $\text{A}^-$ ) will be  $10/(10+1) = 0.91$  (91%). When, by adding strong acid the solution, the pH becomes more acid than the buffer pK by one unit, the  $\log [\text{A}^-]/[\text{HA}] = -1$  and the ratio  $[\text{A}^-]/[\text{HA}] = 1/10$ . The proportion of the total buffer ( $\text{HA} + \text{A}^-$ ) in the dissociated weak base form ( $\text{A}^-$ ) will be  $1/(10+1) = 0.091$  (9.1%). So within +1 and -1 units of the buffer

pK, 91-9.1 = 82% (most) of the buffer reacts (is titrated ) with H<sup>+</sup> and is converted from A<sup>-</sup> to HA. Beyond this pK region, there is little buffering of the pH on adding acid to the buffer containing solution. Thus, buffering is only effective within the pK region of the buffer (+/- 1 pH unit).

**Isohydric principle.** When a solution (or compartment) contains more than one buffer, all buffer pairs (HA and A<sup>-</sup>) in the system are in equilibrium with the same proton concentration: Only those buffers with a pK within 1 pH unit of that in the solution participate effectively in the buffering of the solution pH.

**Buffering power or capacity** depends on the buffer concentrations and on the pK of the buffers present in that compartment.

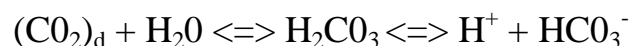
### **Body buffers**

The most abundant buffers in the body fluids are 1) bicarbonate/CO<sub>2</sub> in the ECF (400 mEq), 2) bicarbonate in the ICF and bone (another 400 mEq), 3) histidine groups of intracellular proteins (about 400 mEq), and 4) small amounts of intra and extracellular phosphates (40 mEq). These buffers (total about 1250 mEq) maintain the ECF and ICF pH within 0.3-0.4 pH units of their normal values as long as their capacity to bind protons (about 20 mEq/Kg body weight) is not exceeded.

## **12. ACID-BASE PRINCIPLES: II**

### **Bicarbonate/CO<sub>2</sub> System**

Buffering by bicarbonate/CO<sub>2</sub> comprises hydration of dissolved CO<sub>2</sub> ( [CO<sub>2</sub>]<sub>d</sub> ) and dissociation of carbonic acid:



The mass action equilibrium for the dissociation is:

$$(1) K_d = [\text{H}^+] \times [\text{HCO}_3^-] / [\text{H}_2\text{CO}_3]$$

The equilibrium of the simultaneous hydration is:

$$(2) K_h = [\text{H}_2\text{CO}_3] / ([\text{CO}_2]_d \times [\text{H}_2\text{O}])$$

From (2)  $K_h \times [\text{H}_2\text{O}] = K_1$  (constant) and  $K_1 = [\text{H}_2\text{CO}_3] / [\text{CO}_2]_d$



And (3)  $[H_2CO_3] = K_1 \times [CO_2]_d$

from Henry's Law (4)  $[CO_2]_d = \alpha \times P_{CO_2}$   $\alpha$  is the  $CO_2$  solubility coefficient.

Thus (5)  $K_d = [H^+] \times [HCO_3^-] / K_1 \times \alpha \times P_{CO_2}$

Solving for  $[H^+]$  (6)  $[H^+] = K_d K_1 \alpha P_{CO_2} / [HCO_3^-]$

Since  $K_d K_1 \alpha = 24$  (7)  $[H^+]$  (in nM) =  $24 P_{CO_2}$  (in mmHg) /  $HCO_3^-$  (in mM)  
(Henderson's equation)

Taking the negative log on both sides

(8)  $-\log [H^+] = -\log K_d K_1 + \log [HCO_3^-] / \alpha P_{CO_2}$

Calling  $-\log K_d K_1 = pK_e$  (effective pK)

(9)  $pH = pK_e + \log [HCO_3^-] / \alpha P_{CO_2}$  (Henderson-Hasselbalch equation)

where

$pK_e = 6.1$ ;  $\alpha = 0.0301$ ;  $[HCO_3^-]$  in mM;  $P_{CO_2}$  in torr (or mmHg).

### Buffering by the $HCO_3^-/CO_2$ system

In spite of its  $pK_e = 6.1$  the  $HCO_3^-/CO_2$  system functions as an effective buffer in maintaining the normal arterial blood plasma pH at 7.4 because one of its component is **volatile** and the system is **open**. Consider the following example:

The ECF contains 24 mM  $NaHCO_3$  and is equilibrated with 5.6% gaseous  $CO_2$ . At 37C and  $P_B = 760$  torr,

$P_{CO_2} = 0.056 \times (760 - 47) = 40$  torr,  $\alpha P_{CO_2} = .0301 \times 40 = 1.2$  mM and  $[HCO_3^-] / \alpha P_{CO_2} = 24 / 1.2 = 20 / 1$ ;

$\log [HCO_3^-] / \alpha P_{CO_2} = \log 20 / 1 = 1.3$ ;  $pH = 6.1 + 1.3 = 7.4$  or  $[H^+] = 24 \times 40 / 24 = 40$  nM

Buffering of strong acid in a closed system. If we had 1 L of such a bicarbonate- $CO_2$  solution in a closed container and added enough strong acid (e.g. 12 mmoles HCl) to decrease the  $[HCO_3^-]$  to about half (to 12 mM) by the reaction  $HCl + NaHCO_3 \rightleftharpoons H_2CO_3 + NaCl$ , then twelve mmoles of  $H_2CO_3$  (really of  $H_2CO_3 + CO_2(d)$ ) will be now present. Thus  $[HCO_3^-] = 12$ ;  $\alpha P_{CO_2} = 12$ ;  $P_{CO_2} = 12 / 0.03 = 400$  torr and  $[HCO_3^-] / \alpha P_{CO_2} = 1.0$ ;  $\log 1 = 0$ ;  $pH = 6.1 + 0 = 6.1$  and  $[H^+] = 24 \times 400 / 12 = 800$  nM; which represents a severe acidosis.

**Buffering of strong acid in an open system.** Suppose the container with  $\text{NaHCO}_3$  solution is open to the atmosphere and we bubble continuously 5.6%  $\text{CO}_2$  to maintain the  $P_{\text{CO}_2}$  at 40 torr. Addition of 12 mmoles of  $\text{HCl}$  will reduce  $[\text{HCO}_3^-]$  to 12 mM but the generated  $\text{H}_2\text{CO}_3$  will escape to the atmosphere by conversion to gaseous  $\text{CO}_2$  because the  $P_{\text{CO}_2}$  is maintained at 40 torr.

$$[\text{HCO}_3^-] = 12 \text{ mM}; \quad \square P_{\text{CO}_2} = 1.2 \text{ mM}; \quad [\text{HCO}_3^-] / \square P_{\text{CO}_2} = 10; \quad \log 10 = 1; \quad \text{pH} = 6.1 + 1 = 7.1; \quad [\text{H}^+] = 24 \times 40 / 12 = 80 \text{ nM}$$

**Conclusion:** The resulting pH change is much smaller in an open system than in a closed system. For a buffer pair in which the weak acid is volatile, buffering of the pH upon addition of protons to an open system is very effective. In addition for such a buffer system the effective buffering range is wider ( $>1$  pH unit above their pK) than for non volatile buffers or than for closed systems.

**Buffering of strong acid in an open and regulated system.** Alveolar ventilation ( $V_A$ ) is under neural control. Increases in  $V_A$  in response to reduced  $\text{pH}_a$  lead to increased pulmonary excretion of  $\text{CO}_2$  and lowering of the  $P_{a\text{CO}_2}$ . We can simulate this response by additional bubbling of air through the solution (simulating hyperventilation); the  $P_{\text{CO}_2}$  will be lower than normal (e.g. 20 torr), so

$$[\text{HCO}_3^-] = 12; \quad \square P_{\text{CO}_2} = 0.03 \times 20 = 0.6; \quad [\text{HCO}_3^-] / \square P_{\text{CO}_2} = 20; \quad \log 20 = 1.3; \quad \text{pH} = 6.1 + 1.3 = 7.4; \quad [\text{H}^+] = 24 \times 20 / 12 = 40 \text{ nM}$$

Thus, in an open system with perfect "physiological" control, the pH change due to addition of strong acid is completely blunted. In real life, for each 1 mM decrease in  $[\text{HCO}_3^-]$  due to acid loading, the  $P_{a\text{CO}_2}$  should fall by about 1 torr if the respiratory centers respond normally to the low  $\text{pH}_a$ . Usually the compensation is not perfect, some acidosis persists, and is limited by loss of bicarbonate in the urine due to the low  $P_{a\text{CO}_2}$  (see later).

### Base Excess and Base Deficit

**Titration of body fluids with  $\text{CO}_2$ .** When the  $P_{\text{CO}_2}$  of a pure  $\text{NaHCO}_3$  solution is elevated, the pH will decrease with little change in the  $[\text{HCO}_3^-]$ . Upon increasing the  $P_{\text{CO}_2}$ , both the  $[\text{CO}_2]_d$  and the  $[\text{H}_2\text{CO}_3]$  will increase and some of the  $\text{H}_2\text{CO}_3$  will

dissociate into  $H^+$  (responsible for the decrease in pH) and  $HC03^-$ , the increase  $[HC03^-]$ , as that in  $[H^+]$ , is in the nanomolar ( $10^{-9}M$ ) range. When the  $P_{CO_2}$  of blood is similarly raised, the decrease in pH will be smaller (since blood contains buffers) and the increase in  $[HCO_3^-]$  will be larger than observed in a pure  $NaHCO_3$  solution. This buffering of  $CO_2$  is due to the presence of non-bicarbonate buffers in blood and tissues (mostly Hb, other proteins, and phosphates). Non-bicarbonate buffers associate with  $H^+$  derived from  $H_2CO_3$ , promote formation of  $H_2CO_3$  (by hydration of  $CO_2$ ) and dissociation of  $H_2CO_3$  into  $H^+$  ions (which are buffered by these substances) and more  $HC03^-$ , which increases in concentration.

The changes in pH and  $[HCO_3^-]$  in arterial blood in vivo upon chronic exposure to changes in  $P_{aCO_2}$  (chronic hypoventilation or  $CO_2$  inhalation or chronic hyperventilation) differ from those in the acute situation. Chronic exposure to a high  $P_{aCO_2}$  results in much smaller changes in  $pH_a$  and much larger increases in plasma  $[HCO_3^-]$  than on acute exposure to the same  $P_{aCO_2}$ . This higher chronic buffering capacity for  $CO_2$  is due to the kidneys' generation of  $HC03^-$ , whose ECF concentration increases and minimizes the drop in pH due to increased  $PCO_2$ . Such "chronic" buffering of  $CO_2$  is 10 times larger than the acute buffering by non-bicarbonate buffers.

The **base excess** (BE) or **base deficit** (negative BE) is calculated from the change in  $[HCO_3^-]$  that persists in the system when the pH is brought back (by acutely changing the  $PCO_2$ ) to the standard value of 7.4. At that pH, all non-bicarbonate ECF buffers (proteins, phosphates, etc.) have the same ratio of dissociated to undissociated buffer forms as existed before addition of acid or base. The base (positive values) or acid (negative values) excess is thus reflected only by the change in Standard Bicarbonate,  $[HCO_3^-]_{st}$ , and is calculated as follows:

$$BE = \text{Change in } [HCO_3^-]_{st} = ([HCO_3^-]_x - 24) + BC \times (pH_x - 7.4)$$

$[HCO_3^-]_x$  and  $pH_x$  are the values measured in a blood sample and BC is the buffer capacity. As discussed above, the value of BC is not constant but depends on the elapsed time. In chronic acidosis the value of BC is very large (100 slykes) while

BC = 10 slykes in acute acidosis. Unfortunately the ICF is not in chemical equilibrium with the ECF and we can only give an educated guess of what is happening intracellularly. At the different stages, the product of the apparent volume of distribution of bicarbonate (40% of body weight in acute acidosis, 80% of body weight in chronic conditions) times the base deficit yield estimates of the amount (mEq) of bicarbonate to be replaced (or if in excess, to be removed). The initial target should be to bring the pH to a safe range (7.25-7.55,  $[H^+]$ , 28-56 nM), rather than to completely correct the disturbance.

### 13. RENAL REGULATION OF BICARBONATE

The kidneys regulate the  $[HCO_3^-]$  by

1) **conserving or excreting** the  $HCO_3^-$  present in the glomerular ultrafiltrate; 2) **producing new  $HCO_3^-$**  which enters the body fluids as the kidneys excrete ammonium salts and titratable acids (this sum is called **net acid**) in the urine

#### **Renal Conservation of $HCO_3^-$**

If urine pH < 6, the concentration of  $HCO_3^-$  in the urine is very low (e.g. < 0.1 mEq/L). The glomerular ultrafiltrate has 24 mM. Thus, most  $HCO_3^-$  filtered (4500 mEq/day) is reabsorbed, mostly (90%) along the proximal tubules.

#### **Proximal tubule reabsorption of bicarbonate**

**Reabsorption:**  $H^+$  secretion from cells across the **luminal** membrane is mostly in **exchange for  $Na^+$**  ions, and to a small extent, through a proton ATPase. Secreted  $H^+$  react with filtered  $HCO_3^-$  to form  $H_2CO_3$ . In the presence of carbonic anhydrase (type IV), luminal  $H_2CO_3$  rapidly dehydrates to  $CO_2 + H_2O$ . Drugs that inhibit carbonic anhydrase (e.g., acetazolamide) interfere with proximal reabsorption of  $NaHCO_3$  and induce a bicarbonate (osmotic) diuresis. **Inside the cell**, dissociation of  $H_2O$  into  $OH^-$  and  $H^+$  is promoted by **hydroxylation of  $CO_2$**  ( $OH^- + CO_2 \Rightarrow HCO_3^-$ ) to **generate bicarbonate**, catalyzed by soluble (type II) carbonic anhydrase.  $H^+$  is exchanged for  $Na^+$  ions through a high capacity isoform (NHE3) of the Na-H exchange proteins. **Bicarbonate exits** the cell through **the basolateral membrane in a 3:1 cotransport with  $Na^+$** . The net result is that  $NaHCO_3$

disappears from the lumen and appears in the blood-side of the proximal tubule cells.

**Regulation:** Proximal reabsorption  $\text{HCO}_3^-$  is stimulated by (1) **decreases in cell pH** (due to metabolic acidosis, respiratory acidosis or to decreases in cell K). Low cell pH acutely activates Na-H exchange and chronically induces expression of NHE3 and Na-3 $\text{HCO}_3$  cotransporters and (2) high levels of **Angiotensin II** stimulate Na-H exchange (e.g., contraction of the extracellular fluid).

### **$\text{HCO}_3$ reabsorption in the collecting ducts**

#### **Reabsorption**

- (1) The amount of  $\text{HCO}_3^-$  reabsorbed are much **smaller** than in the PT.
- (2) Reabsorption can be easily **saturated** by increases in  $\text{HCO}_3^-$  load (low  $V_{\max}$ ).
- (3) Can occur with **larger transepithelial pH difference** than in the proximal tubules
- (4) Most is **not mediated by luminal carbonic anhydrase**.
- (5)  **$\text{H}^+$  secretion is mostly by luminal proton (and some by proton-K+) ATPases of alpha-intercalated cells**
- (6) **Basolateral transport of  $\text{HCO}_3^-$  is via Cl- exchangers.**
- (7) Beta-intercalated cells secrete bicarbonate into the lumen and extrude  $\text{H}^+$  into the ECF.

**Regulation:  $\text{HCO}_3$  reabsorption in the CD is stimulated by the following:**

- (1) **High concentration of  $\text{H}^+$  inside** activate the  $\text{H}^+$  pumps in the cells (as in acidosis or  $\text{K}^+$  deficiency);
- (2) In respiratory or metabolic acidosis, **more proton pumps** are inserted into the luminal membranes of alpha-intercalated cells.
- (3) Low  $[\text{H}^+]$  (i.e. at more **alkaline pH**) **in the tubular fluid**.
- (4) Increase in the **negativity of the tubular lumen** (when  $\text{Na}^+$  reabsorption by principal cells is increased by **aldosterone** or when the **load of slowly reabsorbed**  $\text{PO}_4^-$ ,  $\text{SO}_4^-$  or  $\text{HCO}_3^-$  increase).
- (5) **Aldosterone** acts directly to increase  $\text{H}^+$  secreting pumps in alpha-intercalated cells.

## **Renal Production of $\text{HCO}_3^-$**

The kidneys can generate (produce) new  $\text{HCO}_3^-$  through (a) urinary excretion of ammonium ( $\text{NH}_4^+$ ) salts and (b) urinary excretion of titratable acids.

### **$\text{NH}_4^+$ excretion**

**Renal production of ammonium.** Glutamine enters proximal tubule cells from the peritubular capillary blood and from the filtrate. Within the cell, glutamine enters the mitochondria and is deamidated (by glutaminase I enzyme) and deaminated (by glutamic dehydrogenase). There result two molecules of  $\text{NH}_4^+$  and one of divalent alpha-ketoglutarate anion. This anion is oxidized to  $2 \text{HCO}_3^- + 4 \text{CO}_2 + \text{H}_2\text{O}$ .  $\text{NH}_4^+$  is secreted into the lumen through the  $\text{Na}^+\text{-H}^+$  (or  $\text{NH}_4^+$ ) exchanger. Bicarbonate exits through basolateral cotransport with  $\text{Na}^+$ . For each  $\text{NH}_4^+$  excreted, one bicarbonate enters the ECF.

**Excretion.** Ammonium produced and secreted in cortical proximal tubules is transferred to the renal medullary interstitium and from there to the collecting ducts and into the urine. The TAL reabsorbs  $\text{NH}_4^+$  via a luminal  $\text{NH}_4^+ - \text{Na}^+ 2\text{Cl}^-$  cotransporter, where it replaces some  $\text{K}^+$ .  $\text{NH}_4^+$  dissociates into  $\text{NH}_3$  (volatile) and  $\text{H}^+$ . The gaseous  $\text{NH}_3$  diffuses to the medullary interstitium and to the descending limbs where the countercurrent system generates a corticomedullary  $\text{NH}_3$  (and  $\text{NH}_4^+$ ) gradient. The  $\text{NH}_3$  diffuses from the medullary interstitium to the acid fluid in the collecting ducts where it reacts with  $\text{H}^+$  forming impermeant  $\text{NH}_4^+$  which is excreted in the urine. The more acidic the tubular fluid, the faster and larger the  $\text{NH}_3$  transfer. Urine  $\text{NH}_4^+$  (mEq/L) may be roughly estimated from the urine cation gap: urine  $[\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-]$  in mEq/L.

### **Regulation**

In **acute acidosis**, increases in renal  $\text{NH}_4^+$  excretion are due to rerouting of  $\text{NH}_3$  from renal venous blood to the urine due to a more acidic urine pH and sometimes, to increases in urine flow. In addition, an acid intracellular pH activates mitochondrial glutamine transport and metabolism (deamidation) and oxidation of the resulting alpha-ketoglutarate.

In **chronic metabolic acidosis**, there is also induction, through genomic effects on an acid  $\text{pH}_i$ , of basolateral and mitochondrial glutamine transporters, of glutaminase, and other enzymes that participate in the oxidation of glutamine. These adaptations to chronic acidosis allow large amounts of ammonium to be excreted at any urine  $\text{pH}$ , even at  $\text{pH}$  7.

### **Excretion of titratable acid**

The major buffer in urine is phosphate. At  $\text{pH}$  7.4 as in the glomerular filtrate, only 20% of the phosphate is in the di-acid phosphate form ( $\text{H}_2\text{PO}_4^-$ ) and 80% is in the monoacid form ( $\text{HPO}_4^-$ ). In the **proximal tubules**,  $\text{H}^+$  secretion progressively decreases  $\text{pH}$  (to 6.8) and titrates up to 50% of the phosphate in the lumen to the diprotonated form ( $\text{H}_2\text{PO}_4^-$ ). Luminal  $\text{Na}^+$  is reabsorbed in exchange for cell  $\text{H}^+$  and exits, together with  $\text{HCO}_3^-$  formed in the cell, across the basolateral membrane. For every proton secreted that titrates the phosphate in the lumen, there is generation of one molecule of bicarbonate that enters the circulation and helps restore the buffering capacity of the body.

$\text{H}^+$  secretion in the **collecting ducts**, through luminal proton ATPases, can acidify the urinary fluid to  $\text{pH} < 6$ . At this  $\text{pH}$  practically all phosphate has been converted to the diprotonated form. Again, one  $\text{HCO}_3^-$  is generated for each  $\text{H}^+$  secreted due to titration of the phosphate from the mono- to the di-protonated form. Diprotonated phosphates are excreted. Other buffers such as creatinine and  $\beta$ -hydroxybutyrate contribute little to TA excretion except when urine  $\text{pH}$  is  $< 5$ .

**Regulation.** The rate of urinary excretion of titratable acid depends on: a) the **urine  $\text{pH}$**  and b) the **rate of excretion of buffers** (phosphate, creatinine and  $\beta$ -hydroxybutyrate). In acidosis, titratable acid excretion is enhanced due mostly to the low urine  $\text{pH}$  and to a small increase in phosphate excretion (due to reduced reabsorption and loss of bone phosphate).  $\beta$ -hydroxybutyrate can contribute significantly (up to 30%) to the high rates (10 fold increment from 30 to 300 mmol/day) of titratable acid excretion observed in severe ketoacidosis when the urine  $\text{pH}$  reaches values as low as 4.5.

**Quantities.** The concentration of titratable acid (mEq/L) in the urine can be quantified by direct measurement or roughly estimated (with large probability of error, when urine pH < 6 and no alcohols are present in the urine) from the urinary osmolar anion gap (urine osmolarity minus the sum of urine urea (mM), glucose (mM, if present) and 2x Cl<sup>-</sup>(mEq/L) concentrations) divided by 2.

**Net acid excretion.** The sum of the NH<sub>4</sub><sup>+</sup> excretion and the titratable acids excreted (in milliequivalents) minus the bicarbonate (mEq) that might escape in the urine is called NET ACID EXCRETION and equals the milliequivalents of new bicarbonate produced (generated) by the kidneys to restore the buffer reserves of the body fluids.

## 14. ACID-BASE IMBALANCE and COMPENSATION

### Definitions

When pH<sub>a</sub> (arterial blood pH) differs from 7.4 +/- 0.02 (or the [H<sup>+</sup>] differs from 40 +/- 2 nEq/L) there occurs *acidemia* (pH<sub>a</sub> < 7.38, [H<sup>+</sup>] > 42 nEq/L) or *alkalemia* (pH<sub>a</sub> > 7.42, [H<sup>+</sup>] < 38 nEq/L).

If the pH<sub>a</sub> change is due primarily to a change in P<sub>aCO2</sub>, there is *respiratory acidosis* (P<sub>aCO2</sub> > 42 mmHg) or *respiratory alkalosis* (P<sub>aCO2</sub> < 38 mmHg).

When the pH<sub>a</sub> change is due primarily to a change in [HCO<sub>3</sub><sup>-</sup>] from its normal value of 24 mM, there is *metabolic acidosis* ([HCO<sub>3</sub><sup>-</sup>] < 22 mM) or *metabolic alkalosis* ([HCO<sub>3</sub><sup>-</sup>] > 26 mM).

**Note:** *-emia* refers to changes in blood; *acidosis* and *alkalosis* refer to pathophysiologic processes that lead to pH changes in blood

**(A) Metabolic acidosis: pH < 7.38; HCO<sub>3</sub><sup>-</sup> < 22 mM; P<sub>aCO2</sub> 1 mmHg decrease per 1 mM decrease in HCO<sub>3</sub><sup>-</sup> (acute or chronic)**

### Causes:

Metabolic acidosis is the most frequent acid-base imbalance and may be due to:

(1) **Extrarenal loss of bicarbonate**, with hyperchloremia and increased urinary excretion of NH<sub>4</sub><sup>+</sup> (evident as high urinary cation gap: [Cl<sup>-</sup>] - [Na<sup>+</sup>] - [K<sup>+</sup>] >> 0)



(2) **Urinary loss of  $\text{HCO}_3^-$**  (alkaline urine, with high bicarbonate, and little  $\text{NH}_4^+$  and thus no urine cation gap)

(3) **Accumulation of organic anions** (lactacidosis, ketoacidosis) with large plasma anion gap (due to organic anions,  $[\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] - [\text{HCO}_3^-] \gg 15$ ), abundant urinary  $\text{NH}_4^+$  but no urinary cation gap ( $\text{NH}_4^+$  is excreted with organic anions so that there is a large urinary osmolar gap:  $U_{\text{osm}} - 2([\text{Na}^+] + [\text{K}^+]) - [\text{urea}] - [\text{glucose}] \gg 0$ ). Only lactacidosis can develop in minutes (as in shock).

(4) **Decreased kidney production of  $\text{HCO}_3^-$**  (hyperchloremia, no plasma anion gap, and low urinary excretion of ammonium, (urinary cation gap = 0); severe chronic renal failure may result in metabolic acidosis with increased plasma anion gap (due to high plasma  $[\text{P}_i]$ ) and low urinary  $\text{NH}_4^+$  excretion.

### **Compensations:**

(1) **Immediate buffering** by reaction with ECF  $\text{HCO}_3^-$  represents ~40% of rapid (~2 hrs) buffering of acid.  $\text{HCl} + \text{NaHCO}_3 \Rightarrow \text{NaCl} + \text{H}_2\text{CO}_3 + \text{CO}_2 + \text{H}_2\text{O}$

(2) **Respiratory compensation.** A low  $\text{pH}_a$  stimulates  $V_A$ , so  $P_{\text{aCO}_2}$  decreases minimizing the decrease in  $\text{pH}_a$ . For each 1 mM decrease in  $[\text{HCO}_3^-]$  a 1 mmHg drop in  $P_{\text{aCO}_2}$  is expected.

Note: Because of **respiratory compensation** for metabolic acidosis,  $P_{\text{aCO}_2}$  is expected to be below its normal range or ( $P_{\text{aCO}_2} < 38 \text{ mmHg}$ ). If, because of disease, there is no respiratory compensation, then  $P_{\text{aCO}_2}$  will be normal or elevated, and the respiratory system is contributing to the acidemia (see Respiratory Acidosis below).

(3) **Tissue phase.** Entry of  $\text{H}^+$  into cells accounts for ~60% of rapid (~2 h) buffering of poorly permeable acids ( $\text{HCl}$  or  $\text{H}_2\text{SO}_4$ ). This phase is capable of buffering 100% of the acid by 24 h, and is due to the following ion exchanges and buffering of  $\text{H}^+$  by cell proteins and  $\text{HCO}_3^-$ :

(a)  $\text{Na}^+$  in the ICF for  $\text{H}^+$  from the ECF; occurs in most tissues including bone; accounts for 65% of the entry of protons into the ICF (and bone).

(b) ICF  $K^+$  for ECF  $H^+$ ; accounts for 25% of the entry of  $H^+$  into the ICF. May result in hyperkalemia (6-7 mEq/L) that affects muscle and nerve cells and induces cardiac arrhythmias.

(c) ECF  $Cl^-$  for ICF  $HCO_3^-$ ; accounts for 10% of the ICF buffering of  $H^+$ ; reduces ICF  $HCO_3^-$  and intracellular pH; occurs mostly in red cells where Hb buffers excess  $H^+$ .

(4) **Renal phase.** Generation of bicarbonate through urinary excretion of ammonium and titratable acids, restores the depleted cell  $HCO_3^-$  and buffer base reserves over 2-3 days. Manifest only in chronic stage.

**(B) Metabolic alkalosis:  $pH_a > 7.42$ ;  $[HCO_3^-] > 26$  mM;  $P_aCO_2$  0.75 mmHg increase for each 1 mM increase in  $[HCO_3^-]$  (chronic or acute)**

#### **Causes:**

(1) **Loss of gastric juice** (vomiting, suction)

(2) **Side effect of diuretics** and other forms of ECFV contraction.

(3) **Hyperaldosteronism** of volume depletion promotes renal  $H^+$  secretion, generation and retention of  $HCO_3^-$ .

(4) In hypokalemia,  **$K^+$  shifts out of cells in exchange for  $H^+$** , inducing extracellular alkalosis and intracellular acidosis.

#### **Compensations:**

(1) **Respiratory.** As  $pH_a$  increases,  $V_A$  is depressed and  $P_{aCO_2}$  increases ( **$P_{aCO_2} > 42$  mmHg**). This normalizes blood pH but is limited by ensuing hypoxia. For each 1 mM rise in  $HCO_3^-$  there is expected a 0.75 mmHg rise in  $P_{aCO_2}$ ; if this does not occur, there is a respiratory tendency to alkalosis.

(2) **Cell ionic exchanges.** Some 25% of the bicarbonate load is neutralized by  $H^+$  derived from intracellular buffers that exchange the  $H^+$  for extracellular  $Na^+$ . In addition, ~2% of extracellular  $HCO_3^-$  enters red cells in exchange for  $Cl^-$ .

(3) **Metabolic.** Increases in endogenous organic acid production neutralize ~5 % of an acute  $HCO_3^-$  load. High  $pH_a$  increases production of lactic and citric acids

which decrease  $[\text{HCO}_3^-]$ . High blood pH stimulates glycolysis and inhibits the citric acid cycle.

(4) **Renal excretion of  $\text{HCO}_3^-$**  rises when its concentration in plasma increases. Lowering of  $[\text{HCO}_3^-]_{\text{pl}}$  is limited by high renal reabsorption rate stimulated by high  $P_{\text{aCO}_2}$ , by ECF volume contraction, by hyperaldosteronism, by  $\text{K}^+$  depletion, and by hypochloremia. These tend to perpetuate the high  $[\text{HCO}_3^-]_{\text{pl}}$ . Beta-intercalated cells in CCD secrete bicarbonate, increasing its urinary excretion.

(C) **Respiratory alkalosis: pH > 7.44;  $P_{\text{aCO}_2} < 38$  mm Hg;  $[\text{HCO}_3^-]$  decreases (<24 mM) by 0.5 mM (chronic) or 0.1 mM (acute) per each 1 mmHg drop in  $P_{\text{aCO}_2}$**

**Cause: Alveolar hyperventilation** (altitude, hysteria, aspirin excess)

### **Compensations**

(1) **Cell buffers.** In the **acute** state there is a 0.1 mM decrease in  $[\text{HCO}_3^-]$  for each mmHg decrease in  $P_{\text{aCO}_2}$ . This decrease is due to enhanced dissociation of  $\text{H}^+$  from cell buffers when the  $[\text{H}^+]_i$  decreases due to the low  $P_{\text{aCO}_2}$ . Cell  $\text{H}^+$  exchange for ECF  $\text{Na}^+$  and  $\text{K}^+$  and react with the ECF  $\text{HCO}_3^-$ , reducing its concentration. Some extracellular  $\text{HCO}_3^-$  enters cells in exchange for  $\text{Cl}^-$  and is titrated by  $\text{H}^+$  dissociating from the cell buffers.

In the **chronic** state, there is a 0.5 mM decrease in  $[\text{HCO}_3^-]$  for each one mmHg decrease in  $P_{\text{aCO}_2}$ . This is due to:

(2) **Renal compensation** due to increased  $\text{HCO}_3^-$  excretion associated with the low  $P_{\text{aCO}_2}$ , which decreases  $\text{HCO}_3^-$  reabsorption. Urinary excretion of  $\text{NH}_4^+$  and titratable acid are transiently reduced, leading to accumulation of metabolic and dietary acids which help reduce ECF  $[\text{HCO}_3^-]$  ( **$[\text{HCO}_3^-] < 22$  mM**). Eventually urinary  $\text{HCO}_3^-$  excretion ceases and excretion of  $\text{NH}_4^+$  and titratable acid resumes.

(3) **Metabolic compensation** by increased production of lactic and citric acids that react with and reduce  $[\text{HCO}_3^-]_{\text{ecf}}$

(D) **Respiratory acidosis: pH < 7.38;  $P_{\text{aCO}_2} > 42$  mm Hg;  $[\text{HCO}_3^-]$  increases (>24 mM) by 0.25 mM (chronic) or 0.05 mM (acute) per each 1 mmHg rise in  $P_{\text{aCO}_2}$**

**Cause: Alveolar hypoventilation** (Fig. 12.1.)

## Compensations:

(1) **Fast cell ion exchanges.** An acute small rise in  $[\text{HCO}_3^-]_{\text{pl}}$  is due to exchange of ECF  $\text{H}^+$  for ICF (or bone)  $\text{Na}^+$  (37%) or for ICF  $\text{K}^+$  (13%) and to exchange of ECF  $\text{Cl}^-$  for ICF (red cells)  $\text{HCO}_3^-$  (30%). These rapid ionic exchanges are associated with  $\text{CO}_2$  buffering by intracellular proteins. For each 1 mmHg increment in  $P_{\text{aCO}_2}$  there is a small acute 0.06 mM increment in  $\text{HCO}_3^-$ .

## RESPIRATORY ACIDOSIS

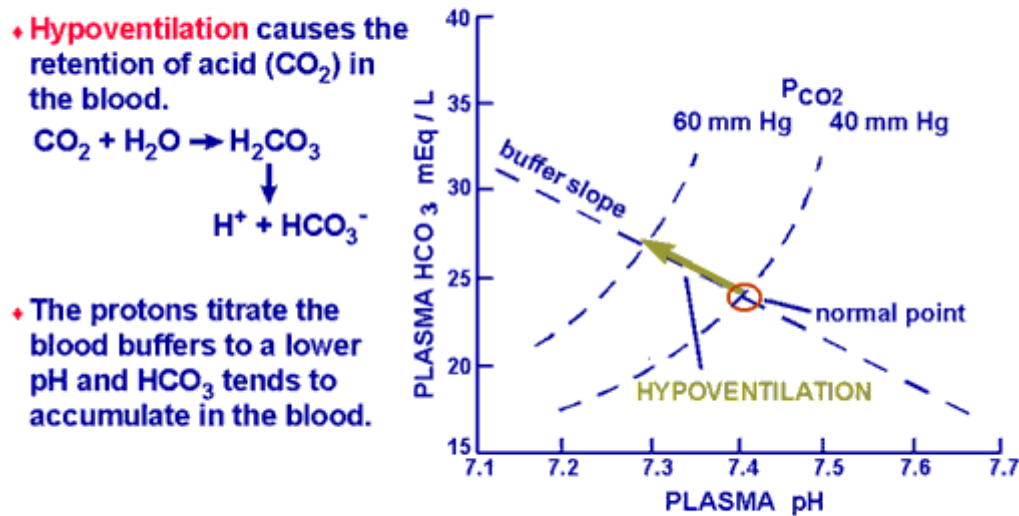


Fig. 12.1. Respiratory acidosis

(2) **Metabolic.** Reduced production of lactic acid contributes about 5% to the acute increase in  $[\text{HCO}_3^-]_{\text{pl}}$ .

(3) **Renal.** Increased  $\text{HCO}_3^-$  reabsorption stimulated by high  $P_{\text{aCO}_2}$  prevents urinary loss of bicarbonate. In the transition to the chronic stage (1-3 days), enhanced renal  $\text{NH}_4^+$ , and titratable acid excretion contribute to further increase  $[\text{HCO}_3^-]$  in ECF and ICF above normal ( $[\text{HCO}_3^-] > 26 \text{ mM}$ ), returning pH towards normal. As the pH stimulus decreases, renal  $\text{NH}_4^+$  and titratable acid excretion subside. Renal reabsorption of bicarbonate remains elevated as long as the  $P_{\text{aCO}_2}$  is high.

## 15. LABORATORY TEST

There are a number of urine tests that can be used to assess kidney function. A simple, inexpensive screening test—a routine urinalysis—is often the first test conducted if kidney problems are suspected. A small, randomly collected urine sample is examined physically for things like color, odor, appearance, and concentration (specific gravity); chemically, for substances such as protein, glucose, and pH (acidity/alkalinity); and microscopically for the presence of cellular elements (red blood cells [RBCs], white blood cells [WBCs], and epithelial cells), bacteria, crystals, and casts (structures formed by the deposit of protein, cells, and other substances in the kidney's tubules). If results indicate a possibility of disease or impaired kidney function, one or more of the following additional tests is usually performed to pinpoint the cause and the level of decline in kidney function.

*Creatinine clearance test.* This test evaluates how efficiently the kidneys clear a substance called creatinine from the blood. Creatinine, a waste product of muscle energy metabolism, is produced at a constant rate that is proportional to the individual's muscle mass. Because the body does not recycle it, all creatinine filtered by the kidneys in a given amount of time is excreted in the urine, making creatinine clearance a very specific measurement of kidney function. The test is performed on a timed urine specimen—a cumulative sample collected over a two to 24-hour period. Determination of the blood creatinine level is also required to calculate the urine clearance.

*Urea clearance test.* Urea is a waste product that is created by protein metabolism and excreted in the urine. The urea clearance test requires a blood sample to measure the amount of urea in the bloodstream and two urine specimens, collected one hour apart, to determine the amount of urea that is filtered, or cleared, by the kidneys into the urine.

*Urine osmolality test.* Urine osmolality is a measurement of the number of dissolved particles in urine. It is a more precise measurement than specific gravity for evaluating the ability of the kidneys to concentrate or dilute the urine. Kidneys that are functioning normally will excrete more water into the urine as fluid intake is increased, diluting the urine. If fluid intake is decreased, the kidneys excrete less water and the urine becomes more concentrated. The test may be done on a urine sample collected first thing in the morning, on multiple timed samples, or on a cumulative sample collected over a 24-hour period. The patient will typically be prescribed a high-protein diet for several days before the test and be asked to drink no fluids the night before the test.

*Urine protein test.* Healthy kidneys filter all proteins from the bloodstream and then reabsorb them, allowing no protein, or only slight amounts of protein, into the urine. The persistent presence of significant amounts of protein in the urine, then, is an important indicator of kidney disease. A positive screening test for protein (included in a routine **urinalysis** ) on a random urine sample is usually followed up with a test on a 24-hour urine sample that more precisely measures the quantity of protein.

There are also several blood tests that can aid in evaluating kidney function. These include:

*Blood urea nitrogen test (BUN).* Urea is a byproduct of protein metabolism. Formed in the liver, this waste product is then filtered from the blood and excreted in the urine by the kidneys. The BUN test measures the amount of nitrogen contained in the urea. High BUN levels can indicate kidney dysfunction, but because BUN is also affected by protein intake and liver function, the test is usually done together with a blood creatinine, a more specific indicator of kidney function.

*Creatinine test.* This test measures blood levels of creatinine, a by-product of muscle energy metabolism that, similar to urea, is filtered from the blood by the kidneys and excreted into the urine. Production of creatinine depends on an person's muscle mass, which usually fluctuates very little. With normal kidney function, then, the amount of creatinine in the blood remains relatively constant and normal. For this reason, and because creatinine is affected very little by liver function, an elevated blood creatinine level is a more sensitive indicator of impaired kidney function than the BUN.

*Other blood tests.* Measurement of the blood levels of other elements regulated in part by the kidneys can also be useful in evaluating kidney function. These include sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, protein, uric acid, and glucose.

### ***Results***

Normal values for many tests are determined by the patient's age and gender. Reference values can also vary by laboratory, but are generally within the following ranges:

### ***Urine tests***

*Creatinine clearance.* For a 24-hour urine collection, normal results are 90 mL/min–139 mL/min for adult males younger than 40, and 80–125 mL/min for adult females younger than 40. For people over 40, values decrease by 6.5 mL/min for each decade of life.

*Urine osmolality.* With restricted fluid intake (concentration testing), osmolality should be greater than 800 mOsm/kg of water. With increased fluid intake (dilution testing), osmolality should be less than 100 mOsm/kg in at least one of the specimens collected. A 24-hour urine osmolality should average 300–900 mOsm/kg. A random urine osmolality should average 500–800 mOsm/kg.

*Urine protein.* A 24-hour urine collection should contain no more than 150 mg of protein.

*Urine sodium.* A 24-hour urine sodium should be within 75–200 mmol/day.

### ***Blood tests***

Blood urea nitrogen (BUN) should average 8–20 mg/dL.

- Creatinine should be 0.8–1.2 mg/dL for males, and 0.6–0.9 mg/dL for females.

- Uric acid levels for males should be 3.5–7.2 mg/dL and for females 2.6–6.0 mg/dL.

Low clearance values for creatinine indicate a diminished ability of the kidneys to filter waste products from the blood and excrete them in the urine. As clearance levels decrease, blood levels of creatinine, urea, and uric acid increase. Because it can be affected by other factors, an elevated BUN, alone, is suggestive, but not diagnostic for kidney dysfunction. An abnormally elevated plasma creatinine is a more specific indicator of kidney disease than is BUN.

Low clearance values for creatinine and urea indicate a diminished ability of the kidneys to filter these waste products from the blood and to excrete them in the urine. As clearance levels decrease, blood levels of creatinine and urea nitrogen increase. Since it can be affected by other factors, an elevated BUN alone is certainly suggestive for kidney dysfunction. However, it is not diagnostic. An abnormally elevated blood creatinine, a more specific and sensitive indicator of kidney disease than the BUN, is diagnostic of impaired kidney function.

The inability of the kidneys to concentrate the urine in response to restricted fluid intake, or to dilute the urine in response to increased fluid intake during osmolality testing, may indicate decreased kidney function. Because the kidneys normally excrete almost no protein in the urine, its persistent presence, in amounts that exceed the normal 24-hour urine value, usually indicates some type of kidney disease.



## 16. CONTROL QUESTIONS:

1. Tubular reabsorption:
  - a). Selective reabsorption;
  - b). the mechanisms of reabsorption;
  - c). the mechanisms of reabsorption  $\text{Na}^+$ , glucose, amino acids, proteins, water.
2. Tubular reabsorption and secretion:
  - a). reabsorption and secretion urea;
  - b). reabsorption and secretion  $\text{K}^+$ ;
  - c). Secretion  $\text{H}^+$ ;
  - d). ammonia secretion.
3. Concentration of urine.
4. Determination the tubular reabsorption.
5. Regulation of reabsorption processes.
6. Incretory function of kidneys
7. Process of urine excretion and its regulation
8. Kidneys and hemopoiesis
9. Physiology of micturition
10. Physiologic Control of Glomerular Filtration and Renal Blood Flow.
11. Physiologic Control of tubular reabsorption.
12. Concentration of urine.
13. Determination the tubular reabsorption.
14. Regulation of reabsorption processes.
15. Incretory function of kidneys
16. Process of urine excretion and its regulation
17. Kidneys and hemopoiesis
18. Physiology of micturition

## 17. MULTIPLE CHOICE QUESTIONS (Select the single best answer)

1. Inulin can be used to measure the glomerular filtration rate because:
  - A. essentially all of the inulin delivered to the kidney is filtered
  - B. essentially all of the inulin delivered to the kidney is excreted
  - C. the amount of inulin excreted is equal to the amount of inulin filtered
  - D. the clearance of inulin is greater than the clearance of creatinine
  - E. inulin is neither filtered nor reabsorbed by the kidney
  
2. The renal "countercurrent" mechanism is dependent upon the anatomic arrangement of the:
  - A. glomerulus
  - B. loop of Henle
  - C. proximal tubule
  - D. vasa recta
  - E. B and D are correct.
  
3. Most of the water that is filtered at the renal glomeruli is:
  - A. excreted in the urine
  - B. reabsorbed by the collecting duct
  - C. secreted into the ascending vasa recta
  - D. reabsorbed by the ascending loop of Henle
  - E. reabsorbed by the proximal tube
  
4. The expected responses of the kidney to a metabolic alkalosis induced by administration of  $\text{NaHCO}_3$  would include:

- A. excretion of increased amounts of titratable acid
- B. excretion of an alkaline urine containing  $\text{HCO}_3^-$
- C. excretion of increased amounts of chloride
- D. excretion of increased amounts of ammonia
- E. B and D are correct.

5. What causes urine to flow from the kidneys to the bladder?

- A. gravity
- B. hydrostatic pressure
- C. peristalsis
- D. osmotic pressure

6. Renal secretion of a compound usually occurs from the \_\_\_\_\_ into the distal convoluted tubule.

- A. loop of Henle
- B. glomerulus
- C. vasa recta
- D. peritubular capillaries

7. The function of the countercurrent multiplier is to \_\_\_\_\_.

- A. increase the concentration of  $\text{NaCl}$
- B. decrease the concentration of  $\text{NaCl}$
- C. change the blood levels of  $\text{K}^+$
- D. conserve  $\text{K}^+$

8. The fluid in the descending limb of the loop of Henle is \_\_\_\_\_ relative to the capillaries.

- A. isotonic
- B. weakly hypotonic
- C. strongly hypotonic
- D. hypertonic

9. The countercurrent multiplier mechanism occurs at the \_\_\_\_\_.

- A. proximal convoluted tubule
- B. loop of Henle
- C. distal convoluted tubule
- D. collecting ducts

10. How much sodium is actively reabsorbed by the proximal segment of the nephron?

- A. 10%
- B. 1%
- C. 70%
- D. 99%
- E. 65%

11. Most tubular reabsorption occurs at the \_\_\_\_\_.

- A. loop of Henle
- B. distal convoluted tubule
- C. proximal convoluted tubule
- D. glomerulus

12. Which of the following is usually not found in the urine?

- A. magnesium
- B. urea
- C. uric acid
- D. glucose

13. What is the average glomerular filtration rate?

- A. 10L per day
- B. 180L per day
- C. 1,500 ml per day
- D. 1 ml per minute

14. Which of these has the highest concentration in the urine?

- A. glucose
- B. sodium
- C. uric acid
- D. phosphate

15. Which muscle metabolism waste product is eliminated by the kidneys?

- A. urea
- B. uric acid
- C. creatine
- D. creatinine

16. Which of the following are not found in the glomerular filtrate?

- A. glucose
- B. protein
- C. uric acid
- D. creatinine

17. Which process is most affected by blood pressure?

- A. tubular secretion
- B. tubular reabsorption
- C. glomerular filtration
- D. loop of Henle diffusion

18. Which blood vessels surround the loops of Henle?

- A. vasa recta
- B. peritubular capillaries
- C. interlobular arteries
- D. efferent arterioles

19. Which blood vessel conveys blood out of the nephron?

- A. efferent arteriole
- B. vasa recta
- C. peritubular capillary
- D. interlobular vein

20. Which area actually secretes renin into the blood?

- A. macula densa
- B. juxtaglomerular apparatus
- C. juxtaglomerular cells
- D. cortical nephron

21. The last part of a nephron is the \_\_\_\_\_.

- A. collecting duct
- B. renal papilla
- C. distal convoluted tubule
- D. glomerulus

22. The renal corpuscle is comprised of a glomerulus and \_\_\_\_\_.

- A. proximal convoluted tubule
- B. Bowman's capsule
- C. loop of Henle
- D. distal convoluted tubule

23. How much of the cardiac output passes through the kidneys?

- A. 10%
- B. 25%
- C. 50%
- D. 65%

24. What is the function of the renal system?

- A. maintain blood pH

- B. regulate blood pressure
- C. control blood concentration
- D. all of these

25. The kidney secretes \_\_\_\_\_ for the purpose of stimulating bone marrow activity.

- A. renin
- B. aldosterone
- C. erythropoietin
- D. somatomedin

26. What is the basic functional unit of the kidney?

- A. alveolus
- B. renal pyramid
- C. renal pelvis
- D. nephron

27. Each minor calyx receives urine from the \_\_\_\_\_.

- A. renal papillae
- B. pelvis
- C. ureter
- D. columns

28. Kidney inflammation may result in the appearance of albumin (a plasma protein) in the urine because

- A. more albumin enters the proximal tubule in the glomerular filtrate
- B. reabsorption of albumin from the proximal tubule is inhibited



- C. secretion of albumin into the distal tubule and collecting ducts is increased
- D. increased peritubular blood flow makes more albumin available for diffusion into the tubule
- E. reduced active transport of sodium ion reduces cotransport of other substances, including albumin

29. As blood passes along the glomerular capillaries from the afferent to efferent arteriole, the net filtration pressure ( $DP - Dp$ )

- A. increases
- B. decreases
- C. first decreases, reaches a minimum about half way along the capillary, then increases
- D. first increases, reaches a maximum about half way along the capillary, then decreases
- E. remains constant

30. Sodium is actively reabsorbed from the renal tubule in which of the following nephron segments?

- A. proximal tubule
- B. distal tubule
- C. thick ascending limb of the loop of Henle
- D. all of the above
- E. none of the above

31. The rate of water reabsorption from the proximal tubule is determined primarily by the

- A. rate of dissolved particle (solute) reabsorption from the proximal tubule
- B. concentration of ADH (antidiuretic hormone) in the blood

- C. osmotic pressure developed by plasma proteins in the proximal tubule
- D. active transport of water molecules by the proximal tubule cells
- E. passive filtration due to the high hydrostatic pressure in the proximal tubule

32. Urea has a higher concentration in the fluid that leaves the proximal tubule (and enters the loop of Henle) than in blood plasma because

- A. urea is synthesized by proximal tubule cells
- B. urea is secreted into the proximal tubule
- C. urea is reabsorbed from the proximal tubule but at a lesser rate than water is reabsorbed
- D. urea diffuses back into the proximal tubule because of the high urea concentration in the renal medulla
- E. urea is actively transported into Bowman's capsule from the glomerular capillaries

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33. . In the proximal tubule, penicillin is

- A. actively secreted into the tubule
- B. actively reabsorbed from the tubule
- C. passively reabsorbed from the tubule
- D. metabolized by the tubule cells
- E. neither secreted nor reabsorbed nor metabolized

34. What are the three main roles of the kidney?

- A. Regulating the water and salt content of blood, removing waste products and making a hormone that helps to control blood pressure

- B. Making a hormone that helps to control blood pressure
- C. Regulating oxygen and carbon dioxide levels in the blood, removing waste products and making a hormone that helps to control the menstrual cycle.
- D. Regulating oxygen and carbon dioxide levels in the blood
- E. Regulating water and salt content in the blood, removing diseased or damaged blood cells, and making a hormone that helps to control body temperature

35. The speed of the Glomerular filtration increased on 20% after the long starvation. What is the reason for these changes?

- A. decreasing of the oncotic pressure of plasma
- B. increasing of systemical arterial pressure
- C. increasing of penetration of kidney filter
- D. increasing filtration coefficient
- E. increasing of renal plasma flow

36. The normal kidneys are only about \_\_\_\_\_ as effective at the age of 70 as they are at the age of 40

- A. 10 percent
- B. 50 percent
- C. 25 percent
- D. 75 percent
- E. 85 percent

37. The specific gravity of the urine of the patient is low (1.002). In what parts of the nephron is the substances of the second urine concentrate?

- A. the distal convoluted tubule
- B. the glomeruls
- C. the proximal convoluted tubule
- D. ascending segment of the Henle loop
- E.  
the collecting duct

38. Creatinine is produced by the breakdown of creatine phosphate in the skeletal muscles. It is useful for determining glomerular filtration rate (GFR) because it is

- A. filtered and reabsorbed but not secreted
- B. filtered and extensively secreted but not reabsorbed
- C. filtered and reabsorbed but not secreted and filtered and extensively secreted but not reabsorbed
- D. secreted but not filtered or reabsorbed
- E. filtered and secreted to a very small extent

39. In the experiment with the isolated kidney of the rabbit the 40ml of glucose were added to the perfusion solution . The amount of urine increased because:

- A. the hydrostatic pressure of perfusion solution increases
- B. the osmotic pressure increased in the first urine
- C. the oncotic pressure decreased in the first urine
- D. the oncotic pressure increased in the first urine
- E. the osmotic pressure decreased in the first urine

40. The only place in the kidney where filtration occurs is in the

- A. renal corpuscle
- B. proximal convoluted tubule
- C. loop of Henle
- D. proximal convoluted tubule and loop of Henle
- E. distal convoluted tubule

41. The afferent arteriole of the glomerulus of the healthy person is wider than the efferent arteriole. Why does the urine formation decrease if the afferent arteriole becomes more narrow than the afferent?

- A. filtration pressure decreased
- B. the sclerosis of the kidney tissue appears
- C. filtration pressure increased
- D. the reabsorption of  $\text{Na}^+$  is violated
- E. the reabsorption of urea is violated

42. The most important solutes that contribute to the high osmolarity of the interstitial fluid in the renal medulla are

- A. potassium ions, hydrogen ions, and water
- B. sodium ions, chloride ions, and urea
- C. glucose,
- D. proteins, and calcium ions
- E. renin, aldosterone, and angiotensin

43. Renal corpuscle is:

- A. the branching of afferent arteriole

- B. the afferent arteriole, branching of capillaries and efferent arteriole
- C. the structure which has formed in the result of invagination of capillaries loops in blind end of nephron
- D. basement membrane
- E. none of these

44. Filtration fluid on through the glomerular capillaries in kidneys tubules is:

- A. tubular reabsorbtion
- B. glomerular secretion
- C. tubular secretion
- D. glomerular filtration
- E. tubular filtration

45. How does the bladder prevent stored urine from leaking out?

- A. The urethra is sealed at the bladder by a tricuspid valve that can be opened at will to allow the flow of urine
- B. There is a ring of muscle at the point where the urethra joins the bladder, and this muscle ring can be voluntarily relaxed to allow the flow of urine.
- C. The urethra is sealed at the bladder by a tricuspid valve that can be opened at will to allow the flow of urine and there is a ring of muscle at the point where the urethra joins the bladder, and this muscle ring can be voluntarily relaxed to allow the flow of urine
- D. The urethra is positioned at the top of the bladder and only allows the flow of urine when the bladder is almost full.
- E. All are correct

46. In the experiment with the isolated kidney of the rabbit the 40ml of glucose were added to the perfusion solution. The amount of urine increased because:

- A. threshold substance
- B. non- threshold substance
- C. low threshold substance
- D. substance, which may be secreted
- E. none of these

47. Which of the following chemicals is an enzyme secreted by the juxtaglomerular apparatus?

- A. Aldosterone
- B. antidiuretic hormone
- C. Aldosterone and antidiuretic hormone
- D. atrial naturetic peptide
- E. Rennin

48. What is the volume of renal blood flow?:

- A. 5-10%
- B. 15%
- C. 40-50%
- D. 20-25%
- E. 70%

49. Normally, net filtration pressure in the kidney is about

- A. 5 mm Hg
- B. 10 mm Hg
- C. 50 mm Hg, the same as in capillaries
- D. 80 mm Hg, the same as diastolic blood pressure

E. 90 mm Hg, the same as diastolic blood pressure

50. The patient suffers from the obstruction of the urether. How will the GFR change?

- A. GFR will increase
- B. GFR will decrease
- C. GFR not change none of these
- D. all of above are correct

51. Aldosterone secretion is controlled by levels of:

- A. angiotensin II
- B. plasma calcium
- C. plasma bicarbonate
- D. ADH
- E. sodium reabsorption in the distal tubule

52. Extracellular dehydration (loss of extracellular water) would be most likely to result in:

- A. increased stimulation of the osmoreceptors, and increased secretion of ADH
- B. decreased stimulation of the volume and osmoreceptors, and increased secretion of ADH
- C. decreased stimulation of the volume and osmoreceptors, and decreased secretion of ADH
- D. decreased extracellular osmolality
- E. B and D are correct.

53. The micturition reflex is centered in the \_\_\_\_\_.

- A. medulla
- B. sacral cord



- C hypothalamus
- D lumbar cord

54. Which of these is under voluntary control?

- A. urethra
- B. detrusor muscle
- C. internal sphincter
- D. external sphincter

55. What causes urine to flow from the kidneys to the bladder?

- A. gravity
- B. hydrostatic pressure
- C. peristalsis
- D. osmotic pressure

56. The compound used to assess the function of the kidney at the level of the glomerulus is \_\_\_\_\_.

- A. creatinine
- B. inulin
- C. para-aminohippuric acid
- D. creatine

57. Where does ADH have its greatest effect?

- A. loop of Henle
- B. proximal convoluted tubule
- C. distal convoluted tubule
- D. glomerulus

58. The action of aldosterone is to increase \_\_\_\_\_.

- A. sodium elimination

- B. sodium reabsorption
- C. potassium reabsorption
- D. chloride excretion

59. The targets of angiotensin II are blood vessels and \_\_\_\_\_.

- A. nerves
- B. adrenal cortex
- C. adrenal medulla
- D. kidney nephron

60. Renin acts on \_\_\_\_\_ to convert it to angiotensin I.

- A. angiotensin II
- B. angiotensinogen
- C. ACE
- D. aldosterone

61. The term "renal autoregulation" refers in part to the fact that

- A. the kidney does not require blood flow to sustain its active transport
- B. the kidney contains baroreceptors (pressure receptors) that contribute to the regulation of cardiac output
- C. renal blood flow is relatively constant over a wide range of systemic arterial pressures
- D. renal blood flow is not affected by activation of the sympathetic nerves that innervate the kidney
- E. a combination of both C and D above

62. The nerves that innervate the kidney are essential for regulating which of the following?

- A. Na-K-ATPase active transport pump rate
- B. renal autoregulation of blood flow

C. urine volume and tonicity (osmolality)

D. all of the above

E. none of the above

63. Urea has a higher concentration in the fluid that leaves the proximal tubule (and enters the loop of Henle) than in blood plasma because

A. urea is synthesized by proximal tubule cells

B. urea is secreted into the proximal tubule

C. urea is reabsorbed from the proximal tubule but at a lesser rate than water is reabsorbed

D. urea diffuses back into the proximal tubule because of the high urea concentration in the renal medulla

E. urea is actively transported into Bowman's capsule from the glomerular capillaries

64. Stimulation of the osmoreceptors in the hypothalamus would be expected to cause all of the following to increase except

A. ADH release from the pituitary

B. water reabsorption from the renal collecting duct

C. rate of urine formation

D. osmolality of urine

E. none of the above; that is, none are exceptions since all would be expected to increase

65. As fluid passes along a juxtamedullary nephron, where is its osmolality (total concentration of dissolved particles) lowest? (Note: assume a normal concentration of circulating ADH.)

A. Bowman's capsule (glomerular filtrate)

B. fluid leaving the proximal tubule and entering the loop of Henle

- C. fluid leaving the descending thin limb and entering the ascending thin limb of the loop of Henle
- D. fluid leaving the thick ascending segment of the loop of Henle and entering the distal tubule
- E. fluid leaving the collecting ducts (urine)

66. Drinking vodka (a beverage with a high ethanol content, for those of you unfamiliar with this substance) would be expected to cause excretion of a

- A. large volume of concentrated urine
- B. small volume of concentrated urine
- C. large volume of dilute urine
- D. small volume of dilute urine
- E. normal volume of urine of normal osmolality

67. In the proximal tubule, penicillin is

- A. actively secreted into the tubule
- B. actively reabsorbed from the tubule
- C. passively reabsorbed from the tubule
- D. metabolized by the tubule cells
- E. neither secreted nor reabsorbed nor metabolized
- E. normal volume of urine of normal osmolality

68. Drinking vodka (a beverage with a high ethanol content, for those of you unfamiliar with this substance) would be expected to cause excretion of a

- A. large volume of concentrated urine
- B. small volume of concentrated urine
- D. small volume of dilute urine
- E. normal volume of urine of normal osmolality

69. In a man increased diuresis, hypernatremia, hypokalemia. Hypersecretion of what hormone can be the reason of these changes?

- A. Adrenalin.
- B. Vasopressin.
- C. Cortisol.
- D. Aldosterone
- E. Parathormone.

70. The patient suffers from nephritis, he also has got anemia. What is the reason his anemia?

- A. The violation of erythropoietin production
- B. The violation of renin secretion
- C. The violation of Natriuretic hormone secretion
- D. The violation of antidiuretic hormone secretion
- E. none of right answers

71. The patient has got chronic disease of kidneys, the functions of juxtamedullar apparatus are violation. What kind of substance production do the patient's kidneys change?

- A. somatostatin
- B. endorphin
- C. Renin
- D. histamine
- E. epinephrine

72. The concentration of osmotic active substances became very high in patient's blood. Explain their influence on the volume of diuresis and what is the mechanism of influence ones?

- A. secretion antidiuretic hormone will increase, diuresis will decrease
- B. secretion antidiuretic hormone will increase, diuresis will increase

- C. secretion antidiuretic hormone and diuresis don't change
- D. secretion antidiuretic hormone doesn't change, but diuresis will decrease
- E. secretion antidiuretic hormone will increase, but diuresis doesn't change

73. The woman suffers from valvular disease of the heart. During ultrasonic examination it was determined that the right atrium became bigger than in healthy one. The patient complains on increased of diuresis. What kind of hormone has got the increase of diuresis function?

- A. aldosterone
- B. antidiuretic hormone
- C. angiotensin
- D. Natriuretic hormone
- E. none of right answers

74. The influence of aldosterone in renal tubules is expressed in:

- A. The increase of water penetration through the tubules system
- B. The increase of  $\text{Na}^+$  reabsorption and  $\text{K}^+$  secretion in renal tubules
- C. The decreasing of  $\text{Cl}^-$  reabsorption
- D. Regulation of acid-base metabolism
- E. Increasing of  $\text{Ca}^{++}$  reabsorption

75. The patient has suffered from glomerulonephritis during the last 6 years. His arterial pressure is very high. The blood's concentration of rennin is also very high. What do structures of kidney synthesize this substance?

- A. the proximal convoluted tubule
- B. the Henley's loop
- C. juxtaglomerular apparatus
- D. the collecting duct
- E. the distal convoluted tubule

76. The patient's diuresis is decrease. The concentration of the Na<sup>+</sup> ions is increase in the blood plasma, but the concentration of the K<sup>+</sup> ions is decrease. Which does hormone produce in the highest concentration? It hyper secretion is cause for this condition of the patient?

- A. aldosterone
- B. antidiuretic hormone
- C. Natriuretic hormone
- D. epinephrine
- E. parathyroid hormone

77. The patient's arterial pressure is about 220/110 mm of mercury. The diagnostics showed a pathological stenosis of the renal's Arteria. What substance is cause for hypertonia?

- A. Rennin
- B. aldosterone
- C. acetylcholine
- D. cortisone
- E. glucagons

78. Excessive amounts of glucose in the urine (greater than 1-3mg per 100mL of urine) may indicate what disorder?

- A. Diabetes insipidus
- B. Diabetes mellitus
- C. Bladder infection
- D. Urinary tract infection

79. During experiment a dog received an injection of antidiuretic hormone. After that the amount of urine decreased because:

- A. the antidiuretic hormone increase the calcium ions reabsorption

- B. the antidiuretic hormone increase the sodium ions reabsorption
- C. the antidiuretic hormone decrease the water reabsorption
- D. the antidiuretic hormone decrease the sodium ions reabsorption
- E. the antidiuretic hormone can increase the water reabsorption

80. The patient has got the chronic kidney's pathology and anemia. The specific therapy by anti anemic medicine hadn't positive effect during long time. What's cause of this patient's condition?

- A. increase of erythropoietin production
- B. decrease of erythropoietin production
- C. non production of erythropoietin
- D. non production of natriuretic hormone
- E. Increase of antidiuretic hormone

81. Antidiuretic hormone combines with ... in the tubular epithelial membrane and activates adenylyl cyclase to produce cyclic AMP. This cyclic AMP increases the permeability of the tubules for...

- A. para-aminohippuric acid, water
- B. glucose, water
- C. amino acids, water
- D. V2 receptors, water
- E. answers are incorrect

82. In a man increased diuresis, hypernatremia, hypokalemia. Hypersecretion of what hormone can be the reason of these changes?

- A. Adrenalin.
- B. Vasopressin.
- C. Kortizol.
- D. Aldosterone
- E. Parathormone.



83. The patient has got chronic disease of kidneys, the functions of juxtamedullar apparatus are violation. What kind of substance production do the patient's kidneys change?

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- C. Rennin
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- B. aldosterone
- C. acetylcholine
- D. cortisone
- E. glucagons

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- B. the antidiuretic hormone increase the sodium ions reabsorption
- C. the antidiuretic hormone decrease the water reabsorption
- D. the antidiuretic hormone decrease the sodium ions reabsorption
- E. the antidiuretic hormone can increase the water reabsorption

89. The patient has got the chronic kidney's pathology and anemia. The specific therapy by antianemic medicine hadn't positive effect during long time. What's cause of this patient's condition?

- A. increase of erythropoietin production
- B. decrease of erythropoietin production
- C. non production of erythropoietin
- D. non production of natriuretic hormone
- E. Increase of antidiuretic hormone

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- A. para-aminohippuric acid, water
- B. glucose, water
- C. amino acids, water
- D. V2 receptors, water
- E. answers are incorrect

91. The kidneys secrete the hormone erythropoietin which functions to

- A. regulate blood pressure
- B. activate vitamin D
- C. concentrate salt in the nephron
- D. control the rate of red blood cell production
- E. All are correct

92. The kidneys secrete the hormone erythropoietin which functions to

- A. regulate blood pressure
- B. activate vitamin D
- C. concentrate salt in the nephron
- D. control the rate of white blood cell production
- E. All are incorrect

93. Urea has a higher concentration in the fluid that leaves the proximal tubule (and enters the loop of Henle) than in blood plasma because

- A. urea is synthesized by proximal tubule cells
- B. urea is secreted into the proximal tubule
- C. urea is reabsorbed from the proximal tubule but at a lesser rate than water is reabsorbed
- D. urea diffuses back into the proximal tubule because of the high urea concentration in the renal medulla
- E. urea is actively transported into Bowman's capsule from the glomerular capillaries

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- A. actively secreted into the tubule
- B. actively reabsorbed from the tubule
- C. passively reabsorbed from the tubule
- D. metabolized by the tubule cells
- E. neither secreted nor reabsorbed nor metabolized

95. At which sites would the concentration of creatinine be expected to be highest?

(Note: assume the person is normally hydrated.)

- A. glomerular filtrate
- B. end of the proximal tubule
- C. end of the loop of Henle
- D. urine
- E. the concentration would be the same in all of the above, since creatinine is neither secreted or reabsorbed

96. Suppose a person loses the function of half his nephrons because of renal degenerative disease. Assuming the person survives and reaches a new steady state

and that body urea production remains normal, which of the following would be expected to decrease below normal?

- A. plasma urea concentration
- B. renal urea excretion
- C. renal urea clearance
- D. urine urea concentration
- E. all of the above

97. The following values are measured for potassium ion in a human subject.

Plasma K<sup>+</sup>                    5 meq/liter

Urine K<sup>+</sup>                    50 meq/liter

Renal creatinine clearance 80 ml/min

Urine formation rate    1.5 ml/minute

This patient's potassium clearance is closest to which of the following?

- A. 5 ml/minute
- B. 7.5 ml/minute
- C. 15 ml/minute
- D. 50 ml/minute
- E. 75 ml/minute

98. Assuming the subject in the preceding question is a normal adult, we can conclude that most likely potassium is

- A. filtered but not secreted or reabsorbed
- B. secreted but not filtered or reabsorbed
- C. reabsorbed but not secreted or filtered
- D. filtered and secreted
- E. filtered and reabsorbed

99. Stimulation of the osmoreceptors in the hypothalamus would be expected to cause all of the following to increase except

- A. ADH release from the pituitary
- B. water reabsorption from the renal collecting duct
- C. rate of urine formation
- D. osmolality of urine
- E. none of the above; that is, none are exceptions since all would be expected to increase

100. As fluid passes along a juxtamedullary nephron, where is its osmolality (total concentration of dissolved particles) lowest? (Note: assume a normal concentration of circulating ADH.)

- A. Bowman's capsule (glomerular filtrate)
- B. fluid leaving the proximal tubule and entering the loop of Henle
- C. fluid leaving the descending thin limb and entering the ascending thin limb of the loop of Henle
- D. fluid leaving the thick ascending segment of the loop of Henle and entering the distal tubule
- E. fluid leaving the collecting ducts (urine)

## 18. ANSWERS

1. C	26. D	51. A	76. A
2. E	27. A	52. A	77. A
3. E	28. A	53. B	78. B
4. B	29. B	54. D	79. D
5. C	30. D	55. C	80. B
6. D	31. A	56. B	81. D
7. A	32. C	57. C	82. D
8. D	33. A	58. B	83. C
9. B	34. A	59. B	84. D
10. E	35. A	60. B	85. C
11. C	36. B	61. C	86. A
12. D	37. E	62. E	87. A
13. C	38. E	63. E	88. D
14. B	39. B	64. C	89. B
15. D	40. A	65. D	90. D
16. B	41. A	66. C	91. D
17. C	42. B	67. A	92. E
18. B	43. B	68.	93. C
19. D	44. D	69. D	94. A
20. C	45. B	70. A	95. D
21. C	46. A	71. C	96. C
22. B	47. E	72. A	97. C
23. B	48. D	73. D	98. E
24. D	49. B	74. B	99. C
25. C	50. B	75. C	100. D

## **19. ABBREVIATIONS and SYMBOOLS**

ACE - angiotensin converting enzyme

ADH - antidiuretic hormone

AI - angiotensin I

AII - angiotensin II

ANP – atrial natriuretic peptide

AVP – arginine vasopressin

BNP – brain polipeptide

BUN – blood urea nitrogen

Cp - clearances of p-aminohippurate

CCD - cortical collecting duct

DAG - diacylglycerol

DT - distal tubule

ECFV – extracellular fluid volume

GBM - glomerular basement membrane

IMCD – inner medulla convoluted tube

IP<sub>3</sub> – inositol triphosphate

MAP – mean arterial pressure

MD - macula densa

MW – molecular weight

OMCD – outer medulla convoluted tube

OVLT - hypothalamic Organus Vasculosus Lamina Terminales

PAH - p-aminohippurate

PCT – proximal convoluted tubule

P<sub>hydro</sub> - hydrostatic pressure

PG - prostoglandin

RBF – renal blood flow

RPF - renal plasma flow

TAL - thick ascending limb

TGF - tubulo-glomerular feedback



## 20. RECOMMENDED LITERATURE

1. Alpern RJ:Renal acidification mechanisms.In Brenner BM (ed):The Kidney,6th ed.Philadelphia:WB Saunders,2000, pp 455-519.
2. Capasso G, Unwin R, Rizzo M, et al: Bicarbonate transport along the loop of Henle: molecular mechanisms and regulation. *J Nephrol* 15(Suppl 5):S88, 2002.
3. Dwyer TM,Schmidt-Nielsen B: The renal pelvis:machinery that concentrates urine in the papilla. *News Physiol Sci* 18:1, 2003.
4. Edwards A, DeLong MJ, Pallone TL: Interstitial water and solute recovery by inner medullary vasa recta. *Am J Physiol Renal Physiol* 278:F257, 2000.
5. Giebisch G, Hebert SC, Wang WH: New aspects of renal potassium transport. *Pflugers Arch* 446:289, 2003.
6. Granger JP, Alexander BT, Llinas M: Mechanisms of pressure natriuresis. *Curr Hypertens Rep* 4:15, 2002.
7. Guyton A. C. *Textbook of Medical Physiology*: Philadelphia, 2011, 1116p.
8. Hanong V.F. *Human physiology*: Lvov: BaK, 2009. – 784p.
9. K.Sembulingam. *Essentials of Medical Physiology*. Jaypee, 2013, 895p.
- 10.Knepper MA, Saidel GM, Hascall VC, Dwyer T:Concentration of solutes in the renal inner medulla: interstitial hyaluronan as a mechano-osmotic transducer. *Am J Physiol Renal Physiol* 284:F433, 2003.
- 11.Murer H, Hernando N, Forster I, Biber J: Regulation of Na/Pi transporter in the proximal tubule. *Annu Rev Physiol* 65:531, 2003.
- 12.Sujit K. Chaudhuri. *Concise Medical Physiology*.- New Central Book Agency, 2013.-752p.