### SYLLABUS

**Physiology (PHYL 5013) – Spring Semester 2014**

**Renal and Acid-Base Physiology**

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**Office Hours (3.029V):**

Drop by anytime or by appointment. I prefer questions in person and not via email. We can work through questions and solve problems more quickly, comprehensively and with greater clarity face-to-face.

**Preparing for the class:**

Come prepared to learn. This means becoming familiar with the topic of discussion before class to include doing the reading and taking other necessary steps to have a good grasp of the material. Class time is about asking questions and getting clarification. It should not be the first time you considered the material. If you come prepared to learn, you will get more from the lectures.

**Reading:**

Please do some reading before class. You can use this study guide in addition to the 12th edition of *Vander’s Human Physiology* by Widmaier, Raff & Strang for which this study guide was prepared. The information should be mutually supportive and consistent. I provide this study guide as an additional resource to this book.
LEARNING OBJECTIVES

Lecture 1 – March 27, 2014
Introduction and Anatomy
Objectives: Understand the general functions of the kidney, and identify the structure/function hierarchy of the kidney at the tissue and cellular levels.
General Comments: After studying this material you should be able to:
1) List the 6 functions of the kidney
2) Define the basic functional unit of the kidney (renal nephron) and its parts
   a) explain glomerular function
   b) explain tubular function
3) Distinguish between the 3 types of renal nephron with respect to locale and function
4) Know the endocrine products secreted by the kidney
5) Recognize the relationship between tubular segments and the glomerulus, and to each other

Lecture 2 – March 27, 2014
Filtration and Renal Blood Flow
Objectives: Understand the process and outcome of renal filtration and the forces and sites that control renal filtration and renal blood flow. Understand how these relate to control of blood pressure.
General Comments: After studying this material you should:
1) Understand the ultrastructure of the renal glomerulus
2) Recognize the Starling forces driving filtration and renal hemodynamics
3) Know and understand the components of the filtration barrier (sieve)
4) Understand the mechanisms and sites controlling filtration
5) Have a simple understanding of how hormones, disease and drugs may affect the renal glomerulus and thus, renal hemodynamics, filtration and blood pressure

Lecture 3 – March 28, 2014
Tubule Function
Objectives: Understand the function of each tubule segment.
General Comments: After studying this material you should:
1) Understand the basic processes of epithelial transport
2) Know the specific mechanisms (proteins) underlying transport for each tubule segment
3) Understand how transport in specific tubule segments is regulated
4) Understand the significance to the whole organism of specific tubule transport
5) Begin to understand where and why diuretics work
6) Understand glomerulotubular balance and the forces regulating it
7) Recognize the effects of specific hormones on tubular transport

Lecture 4 – March 31, 2014
Renal Indices (assessment of renal function)
Objectives: Understand renal indices and be able to perform simple calculations to quantify renal function.
General Comments: After studying this material you should:
1) Understand what clearance means and be able to calculate clearance, particularly Cx, C_in, C_cr, and C_{PAH}
2) Understand the significance of P_{cr} values
3) Understand and calculate filtered load, excretion rate, filtration fraction and fractional reabsorption and excretion, as well as transport maximums
4) Determine whether a substance is filtered or undergoes net secretion or reabsorption using renal indices.

Lecture 5 – April 3, 2014
NaCl and water balance
Objectives: Understand how control of tubular transport and GFR function together to establish NaCl and water balance.
General Comments: After studying this material you should:
1) Understand the counter-current multiplier
2) Understand the tubule segments important for concentrating and diluting urine
3) Know the hormones and mechanisms that regulate Na and water reabsorption
4) Understand how plasma osmolality is controlled
5) Understand and calculate free water clearance and osmolar clearance
Lecture 6 – April 4, 2014

Blood Pressure Control

Objectives: Understand how we maintain blood volume and pressure.

General Comments: After studying this material you should:
1) Understand total body water and fluid compartments and how they are controlled
2) Understand the concept of effective circulating volume and how NaCl excretion modifies it
3) Recognize the hormones and their sites of action involved in regulating effective circulating volume
4) Understand how the glomerulus and tubule function to regulate ECV
5) Understand the systemic role of the kidney in protecting ECV
6) Understand disease states the impinge upon ECV and electrolyte status

Lecture 7 – April 7, 2014

Regulation of K⁺, Mg++, Ca++, PO₄²⁻, and Micturition

Objectives: Understand how the kidney handles K⁺, Mg++, Ca++, and P, and the process of micturition.

General Comments: After studying this material you should:
1) Understand where K is reabsorbed and secreted
2) Know the mechanism of action of hormones controlling K
3) Understand the role of PTH and calcitriol
4) Understand where and how Ca and P are reabsorbed
5) Understand where and how Mg is reabsorbed
6) Understand the process of micturition and regulation of this response
   a. recognize the control elements regulating bladder filling and emptying
   b. understand the mechanisms controlling filling and emptying
   c. understand reciprocal regulation of the bladder by sympathetic and parasympathetic innervation
   d. recognize the different types of muscles controlling bladder filling and emptying
   e. understand the micturition reflex
   f. understand voluntary and involuntary control of bladder emptying

Lecture 8 – April 7, 2014

Regulation of H⁺ and HCO₃⁻

Objectives: Understand how the kidney handles H⁺ and HCO₃⁻.

General Comments: After studying this material you should:
1) Understand the importance of the kidney and lungs in acid-base balance
2) Recognize where acid comes form
3) Understand how we buffer acid/base systemically
4) Understand where and how H and bicarb are secreted and reabsorbed in the kidney (i.e. proximal and distal acidification)
5) Know the cellular proteins involved in this transport
6) Recognize the role of glutamine and titratable acids in H and bicarb reabsorption
7) Understand the contribution of the ammonia/ammonium buffering system and ammonium recycling to urinary acidification

Lecture 9 – April 10, 2014

Acid-base challenges

Objectives: Understand acid-base regulation in humans.

General Comments: After studying this material you should:
1) Understand the kidney’s role in acid-base balance
2) Understand the lung’s role in acid-base balance
3) Know what acidosis and alkalosis mean
4) Understand simple acid base disorders
5) Recognize mixed acid-base disorders and understand dysfunction associated with them
6) Understand renal and lung compensation mechanism
8) Recognize the importance of anion gap
9) Understand how electrolyte and acid-base disorders are relate
STUDY GUIDE
Physiology (PHYL 5013) – Spring 2014

Renal and Acid-Base Physiology

James D. Stockand, Ph.D.
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Reading Schedule:
This study guide is designed to be used with the 12th ed. of Vander’s Human Physiology authored by E.P. Widmaier, H. Raff and K.T. Strang. You may find that I cover material in a bit different order, but what I say and what the book says are the same. I just use bad English to say it.

General Introduction:
The kidney is one of the best-understood organs in the human body. This is particularly true when considering its role/function on the organism, organ system, and organ and tissue levels. Most contemporary research of the kidney is at the cellular and molecular levels and focuses on understanding physiology and the basis of dysfunction associated with numerous human diseases. This makes discussion of Renal Physiology very broad in scope and intense. Students often find this breadth of coverage difficult to organize and retain. To help with this, lectures over the next two weeks are divided into two general themes. First, we discuss the two functional units of the active component of the kidney, the renal nephron (there are about 1 million of these per kidney). The two functional units are the renal corpuscle (referred to in our course simply as the glomerulus) and the renal tubule, which for our discussion includes the collecting duct system. This discussion will primarily be at a cellular and/or tissue level. We then integrate this information and develop the function of the kidney in the context of the entire organism. So, we work backwards from the cell/protein toward organ function in the context of the entire animal.

As indicated above, much is known about the kidney and there are a number of complementary ways to present this information. Thus, I will often present the same information from different perspectives. I do this with the hope that it provides a more complete understanding of the kidney. Most of what we know about the kidney has arisen from study of diseases and the use of certain drugs (i.e. diuretics). Often throughout lecture, I will refer to these. Don’t lose focus of the major points for this digression to discussion of disease and drugs should reinforce earlier points about physiology. I do not expect you to memorize these diseases and drugs. I will allude to them only as examples. If you do see them on a test, the test question will include description of the pathophysiology underlying the disease or the effector of the drug. While I will not specifically test you on the names of the drugs, you will be responsible for knowing how inhibition of their target affects physiology. For instance, acetazolamide is a diuretic that targets carbonic anhydrase in the proximal tubule to increase excretion of Na leading to an associated increase in urine volume. I will not ask you what does acetazolamide target or what happens when you administer acetazolamide; however, I will ask what happens when the carbonic anhydrase in the proximal tubule is inhibited with respect to Na excretion and urine volume. Concentrate on the physiology!

As future dentists you may find it key to focus on the kidney’s role in regulating serum calcium and phosphate levels for this is important to teeth and bone, and the kidney’s role in clearing drugs and regulating acid-base balance. The latter also influences serum Ca++ / phosphate levels, and renal clearance is important to how the body rids itself of common drugs that you may one day be prescribing/using in the clinic.

I am here to help you learn. My goal is that after this section you will have good understanding and retention of the basic facts relevant to the kidney and be able to use these facts to solve problems. Developing such diagnostic/problem solving skills ultimately will make you better dentists. Good luck, and remember I am only one of many resources, including the lecture notes, book, tutors, classmates and other faculty. Use all your resources as needed. If you have any questions please do not hesitate to approach me. I am very flexible in setting up appointments and often can answer questions right away.
Objectives: Understand the general functions of the kidney, and identify the structure/function hierarchy of the kidney at the tissue and cellular levels.

General Comments: After studying this material you should be able to:

1) List the 6 functions of the kidney
2) Define the basic functional unit of the kidney (renal nephron) and its parts
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3) Distinguish between the 3 types of renal nephron with respect to locale and function
4) Know the endocrine products secreted by the kidney
5) Recognize the relationship between tubular segments and the glomerulus, and to each other

Overview:

Functions of the kidney –
1) Regulate body fluid volume and composition
2) Blood pressure regulation
3) Rid the body of waste products and foreign substances
4) Regulate acid-base balance
5) Endocrine function – renin, calcitriol (vitamin D), erythropoietin
6) Gluconeogenesis

Functional anatomy of the kidney –
1) Gross structure of the kidney: cortex, medulla and pelvis.

2) The nephron is the basic unit of structure and function: it contains a corpuscle with a vascular glomerulus surrounded by a matrix formed by glomerular mesangial cells and the epithelial cells of Bowman’s capsule (the beginning of the renal tubule). Bowman’s capsule joins a series of hollow tubules (one epithelial cell thick) starting with the proximal tubule, followed by the loop of Henle and distal tubule, which coalesce into the collecting duct system and release into the renal pelvis. The epithelial lining of the tubule separates the internal environment of our bodies from the external environment (inside the tubule).

The renal corpuscle is fed by the vascular afferent arteriole and drained by the vascular efferent arteriole with plasma moving between the arterioles through a glomerular capillary a single endothelial cell thick. The efferent arteriole leads into a 2nd set of capillaries termed peritubular capillaries (for superficial and midcortical nephrons; see below) and vasa recta (for juxtamedullary nephrons; see below). Only the peritubular capillaries (and vasa recta) nourish the kidney, the glomerular capillaries are a unique set of capillaries used exclusively to filter plasma (see below). Peritubular capillaries, which parallel the tubules, serve as the reservoir (capacitor) for transport into (secretion) and from (reabsorption) the tubular lumen (see below). Since peritubular capillaries are in the cortex and only a few vasa recta perfuse the medulla, the medulla receives less oxygenated blood making this area prone to hypoxia.

The proximal tubule (PT) for our discussion is divided into early and late segments. The PT is found in the cortex and dives into the outer medulla.

The Loop of Henle found in the medulla has a descending thin limb, a hairpin turn, an ascending thin limb and a thick ascending limb (TAL) with the TAL being in the outer medulla and cortex.

The distal tubule (DT), which is in the cortex, contains several distinct segments. For this class, we will consider these segments as one homogenous group, but realize that it is not this simple. The macula densa is found at the junction of the TAL and DT. The macula densa abuts the glomerulus and contacts the afferent arteriole. Together the macula densa, afferent arteriole and corpuscle granular cells/extraglomerular mesangial cells form the juxtaglomerular apparatus (JGA).

Several distal tubules from numerous nephrons coalesce into the collecting duct (CD) system with these ducts initiating in the cortex (cortical CD) and diving down into the medulla (medullary CD). Ultimately, collecting ducts spill urine into the renal pelvis.

3) Each human kidney contains – 1 million nephrons (+/- 0.25 million). There are 3 types of nephrons: a. superficial nephrons (30%) with glomeruli in the outer cortex and loops of Henle that barely enter the outer medulla; b. midcortical nephrons (60%) with glomeruli in the mid cortex with short loops that enter the medulla only a short way (1/6) and others with intermediate length loops that dive into the inner medulla (5/6); c. juxtamedullary nephrons (10%) with glomeruli near the cortical-medullary border and long loops that reach the tip of the medulla. The lengths of the loop of Henle and the
distance they dip into the medulla increase in proportion to their ability to concentrate urine. Thus, superficial and midcortical nephrons are involved primarily in the excretory function of the kidney with regards to waste, whereas, the juxtamedullary nephrons are more central to fine-tunning plasma electrolyte and water concentrations, and systemic acid/base balance.

4) General themes: the renal nephron is a hollow tubule only 1 epithelial cell thick. Each epithelial cell is polarized having a luminal (also called apical) plasma membrane (faces the urine) and a basolateral (also called serosal) plasma membrane (faces the blood). All renal epithelial cells contain the \( \text{Na}^+/\text{K}^+-\text{ATPase} \) on the basolateral membrane, which provides the energy for solute and thus, ultimately water transport. Renal epithelial cells perform a barrier function separating the urine from the interstitial fluid. This barrier function is dependent on the lipid composition of the apical membrane and tight junctions connecting epithelial cells. Some segments present a better barrier (are tighter). Thus, vectorial solute and water movement (transport function of epithelial cells) is an emergent property dependent on the barrier function and the different proteins in the apical and serosal membranes, ultimately driven by the energy of the Na/K-ATPase. Solute and water can move between (paracellular) cells in a leaky epithelium and across the plasma membranes of a tight epithelium (transcellular) with the proper transport proteins.

Movement out of the tubule into the interstitial fluid is termed reabsorption; movement into the tubule from the interstitial fluid is termed secretion. Molecules moved out of the renal nephron into the renal pelvis/ureter are ultimately excreted. Movement of plasma across the glomerular capillary into the tubule (at Bowman’s capsule) is termed filtration.

5) The initial step in formation of urine is formation of plasma ultrafiltrate (plasma lacking cells and protein, but in osmotic equilibrium with blood) in Bowman’s space through the actions of hydrostatic and oncotic (pressure developed by plasma proteins) pressure in the glomerular capillaries and Bowman's space. This process is termed ultrafiltration. Filtration pressures are controlled by dynamic vascular elements in the renal afferent and efferent arterioles, as well as the smooth muscle like mesangial cells. As ultrafiltrate flows down the nephron, it is modified by reabsorption, secretion and in some instances metabolism. Solutes and water are reabsorbed and secreted across the tubular epithelium into and out of the peritubular capillaries and/or vasa recta. That filtered and not reabsorbed is excreted. Similarly, that secreted and not reabsorbed is excreted.

Bulk reabsorption happens in the PT with about 2/3 of the total volume and solutes, and all of the glucose and filtered amino acids/proteins reabsorbed here. Transport in the proximal tubule, as well as the loop, is constitutive. Hormones influence transport in the distal tubule and collecting duct segments. The prior segments function to return useful substances that were filtered to the body while keeping filtered waste in the urine. These latter segments fine-tune solute and water concentrations in the final urine and thus, blood.

PT – Bulk reabsorption. Leaky epithelium leading to isosmotic reabsorption. Reabsorption not regulated with the exception of the actions of PTH on phosphate handling.

Loop of Henle - Develops the hyperosmotic medulla needed for concentrating and diluting urine. The thin descending limb is permeable to water (concentrates urine) but has no solute transport function. The TAL is extremely tight and actively reabsorbs NaCl but NOT water (dilutes urine). Solute reabsorption at the TAL creates the osmotic driving force for water reabsorption out of the thin descending limb and the CD. Transport in the loop is not regulated by hormones but rather is constitutive. At the end of the loop, urine has an osmolality below plasma. The loop is targeted by loop diuretics like furosemide, which are the most powerful diuretics available. Moreover, several human diseases associated with renal salt wasting are caused by protein dysfunction in the loop. That filtered and not reabsorbed is excreted. Similarly, that secreted and not reabsorbed is excreted.

DT – Hormones begin to regulate transport here. This is a tight epithelium with electroneutral NaCl reabsorption. Ca\(^{++}\) is also reabsorbed here. This portion of the nephron further dilutes urine. Targeted by diuretics that preserve plasma calcium levels.

CD – Transport here regulated by hormones allowing this segment to fine-tune electrolyte and water concentrations in the urine and thus, plasma. (Again, this makes understanding of the physiology of this nephron segment extremely important to a practicing clinician.) The CD is a tight epithelium with an adjustable water permeability (dependent on the hormone ADH).

Blood has an osmolality of about 285 mOsm/Kg (for this course, I often use the round number of 300 mOsm/kg). The kidney, which weighs about 0.5% of total body weight, receives about 1/5 of the cardiac output (1 L/min, removing the volume due to RBC = 750 ml/min) filtering at a rate of 125 ml/min. So, the filtration fraction (amount of plasma received that is filtered into the tubule as ultrafiltrate) is about 0.17. From this ultrafiltrate (125 ml/min x 60 min/hr x 24 hr/day = 180
L/day), about 1.5 L/day of urine containing mostly NaCl, urea and other waste at 600 mOsm is excreted. Volume and osmolality are controlled by hormone action on the distal tubule and collecting duct system in response to systemic cues.

7) The kidneys regulate **body fluid volume and composition** by controlling solute and water movement. Solute movement is controlled often by directly acting upon the solutes, on the other hand, water movement follows via osmosis that of osmolytes. In some portions of the kidney (i.e. collecting duct), water moves through proteins (still following osmolytes) and thus, can be regulated. The kidney **removes foreign substances** like drugs, and harmful, non-volatile waste from the body (urea, uric acid, and creatinine) by clearing these substances from the plasma (i.e. filtering them but not reabsorbing them). The kidney controls **blood pressure** by directly influencing blood volume and vascular resistance, as well as secreting a hormone (renin) from the JGA that ultimately influences vascular resistance and volume. The kidney in fact has an **endocrine function** secreting several hormones, including renin, calcitriol (activated vitamin D; the kidney doesn’t actually secreted VD3 but rather activates it through hydroxylation to produce 1,25-(OH)2VD3 ), and erythropoietin. The kidney also has a metabolic function, such as degrading some hormones/proteins and producing glucose via **gluconeogenesis** during times of fasting, and transforming amino acids (i.e. glutamine to NH₄). The kidney also plays an essential role in proper **acid-base balance**.
Objectives: Understand the process and outcome of renal filtration and the forces and sites that control renal filtration and renal blood flow. Understand how these relate to control of blood pressure.

General Comments: After studying this material you should:
1) Understand the ultrastructure of the renal glomerulus
2) Recognize the Starling forces driving filtration and renal hemodynamics
3) Know and understand the components of the filtration barrier (sieve)
4) Understand the mechanisms and sites controlling filtration
5) Have a simple understanding of how hormones, disease and drugs may affect the renal glomerulus and thus, renal hemodynamics, filtration and blood pressure

Overview:
Ultrafiltration –
1) Anatomy – The filtration barrier (sieve) is formed by a) fenestrated glomerular capillary endothelial cells (holes ~37 nm radius), b) basal lamina (also termed glomerular basement membrane, GBM) secreted and maintained by glomerular mesangial cells (repels by negative charge) and c) slit pores (~ 2-3 nm radius) covered by slit diaphragms between the foot structure of podocytes (visceral epithelial cells of Bowman’s capsule; parietal is the outer epithelial layer).

GBM formed by collagen, laminin, and heparin sulfate proteoglycans has a negative charge. The GMB provides support to the structure and a sieving function that repels most plasma proteins that also carry a negative charge. The slit pores further sieve on size and the fenestrated endothelial impede filtration of blood cells.

2) Sieving function – The filtration barrier impedes filtration of blood cells and blood proteins, but allows filtration of plasma with its fluid and electrolytes. Filtration is isoosmotic driven by Starling forces! The size limitation for filtration begins with proteins having a radius of ~ 2 nm if they are neutral and < 2 nm if they carry a negative charge: a protein with a radius of 6 nm, independent of charge, cannot cross the filtration sieve.

3) Diseases of the sieve – There are human diseases that result in loss of either the charge (GBM; i.e. Goodpasture’s disease) or size barrier (slit diaphragms/podocyte, i.e. minimal change nephropathy) or both. These are sometimes easily diagnosed by comparing the relative excretion (reflecting filtration) of a smallish (~ 2-3 nm i.e. transferrin, T) negative protein and a larger (~ 5.5 nm, i.e. immunoglobulin G, IgG) neutral protein. The IgG/T ratio in urine usually equals 0.1. If the ratio increases it means there is a relative loss of the size barrier, whereas, if it decreases it means a relative loss of the charge barrier. Proteinuria is a (pathological) state where plasma protein is found in the urine and can result from a loss of either size or charge barrier or both. Proteinuria usually indicates disease of the glomerulus.

4) Ultrafiltrate contains small neutral molecules in osmotic equilibrium with plasma (~285 mOsm). This means that it contains most of the plasma electrolytes, and small solutes such as glucose and amino acids, but contains little plasma protein and no blood cells.

Renal hemodynamics -
5) Pressure and resistances: The afferent arteriole provides the single greatest resistance to blood flow in the kidney and thus, has the greatest drop in blood pressure from 100 to 45 mmHg. Pressure drop across the efferent arteriole, which is in series with the afferent arteriole, though, is also high from 45 to 20 mmHg. (The total resistance of glomerular capillaries in parallel is less than the individual components and therefore, there is little pressure change resulting from the glomerular capillaries.) Recall that \[ Q = \frac{\Delta P}{R} \], where \( Q \) is blood flow, \( \Delta P \) is pressure difference and \( R \) is vascular resistance approximated by \( 1/r^4 \) where \( r \) is arteriole radius: \[ Q_{\text{kid}} = \frac{(P_{\text{renal artery}} - P_{\text{renal vein}})}{R_{\text{kid}}} \]. This \( Q_{\text{kid}} \) is also termed renal blood flow (RBF). Thus, the afferent and efferent arterioles present a significant resistance to RBF with \( R_{\text{kid}} \alpha R_a + R_e \). The kidneys receive 1/5 of cardiac output (CO) meaning that the kidneys provide a substantial portion of the resistance that the blood pumped from the heart encounters. Since \( MAP = CO \times TPR \), where \( MAP \) is mean arterial pressure and \( TPR \) is total peripheral resistance, \( R_{\text{kid}} \) is a major factor in setting \( MAP \). Thus, \( MAP \) is proportional to \( R_a + R_e \) and RBF is proportional to \( 1 / R_a + R_e \).

Since the kidneys receive 1/5 of CO and only weigh about 0.5% of total body weight, they are one of the mostly highly perfused organs and at rest have higher blood flow than the heart, brain or muscles.

6) Function of RBF - a. drives glomerular filtration, b. peritubular capillary and vasa recta blood flow (exchange with tubular fluid and kidney cell nutrition) and c. serves as a hemodynamic fluid reservoir to counter drops in MAP.

7) Regulation of RBF: effector elements, afferent (\( R_a \)) and efferent (\( R_e \)) arterioles.
Intrinsic autoregulation mechanisms that attempt to maintain RBF (and GFR, see below) during normal variations in MAP (occurs when MAP is 90-180 mmHg). This is a protective function intrinsic to the kidney which allows us to maintain RBF and ultimately GFR pretty much constant throughout many different daily activities.

- a) Myogenic response – the vascular smooth muscle cells surrounding the afferent arteriole are elastic and oppose stretching with the opposite force of contraction. Simply put, the afferent arteriole does not have as much of an increase in radius as one would expect in response to a given distending force (MAP). Increased transmural pressure at Ra leads to less of an increase in RBF than expected.

- b) Tubuloglomerular feedback (TGF) – Recall that the MD, afferent arteriole and extraglomerular mesangial/granular cells form the JGA. As an increase in urine flow is sensed at the MD it sends a signal to contract the afferent arteriole increasing Rs. Similarly as urine flow at the MD decreases, Rs decreases. RBF and urine flow at the macula densa are inversely related.

Extrinsic regulation always overpowers intrinsic regulation and is mediated by hormones and neuronal signals arising from outside the kidney. Allows RBF and GFR to change as needed in response to systemic cues.

- a) sympathetically innervation of the afferent arteriole – afferent smooth muscle contain alpha adrenergic receptors that mediate constriction to increase Rs. This is a protective function that enables RBF to be decreased as a result of increases in RKid, which lead in turn to increases in TPR to protect MAP, as well as shunting blood to more important organs during times of need (i.e. hemorrhaging) resulting in expansion of volume in the arterial circulation.

- b) hormones – i) vasoconstrictors – vasopressin (AVP, also called antidiuretic hormone or ADH) and angiotensin II (AngII) increase both Rs and Ra to decrease RBF (having little effect on GFR; see below), but at the same time raise MAP.

Renin-angiotensin-aldosterone system (RAAS): Recall that renin secretion from the JGA is the limiting step in AngII levels with the plasma protein angiotensinogen (produced by the liver) being converted by the enzyme/hormone renin (from granular cells of the JGA) to AngI and AngI converted to AngII by angiotensin converting enzyme (ACE, found mainly in the endothelial cells of pulmonary capillaries). Renin release form the JGA is dependent on renal sympathetic nerve activity, JGA stretch and urine flow to the MD. Increased sympathetic activity increases renin release, and increases and decreases in renal pressure at JGA and urine flow to MD decrease and increase, respectively, renin release. Thus, renal blood pressure and urine flow are inversely related to renin release, but sympathetic activity is positively related to renin release.

- ii) vasodilators – atrial natriuretic factor (ANF, released from the heart in response to increases in blood volume sensed as stretching of the heart) decreases Rs (having more of an effect here compared to Rs) to increase RBF (and decrease MAP).

8) Glomerular filtration rate (GFR, ~ 110 to 125 ml/min, 180 L/day, 20% RBF) – is the rate of filtration at both kidneys. It is equal to the sum of all single nephron glomerular filtration rates (SNGFR, ~ 60 nl/min).

There is a lot of unused capacity in snGFR. Thus, GFR is maintained relatively normal even with a loss of 1/2-2/3 of total renal mass.

Starling forces governing ultrafiltration

9) Dynamics of ultrafiltration – filtration pressures include glomerular capillary and Bowman’s space hydrostatic and oncotic pressures. Filtration rate is also dependent on the glomerular capillary surface area (A) controlled by glomerular mesangial cells. GFR is much greater than filtration at systemic capillaries due to the large area available for filtration and high hydraulic conductivity (permeability; Lh) making the Kf (ultrafiltration coefficient) of glomerular capillaries about 100-fold that of systemic capillaries. Note, hydrostatic pressure in the glomerulus is also about double that in systemic capillaries.

Determinants of GFR = Kf x PUF, where Kf is filtration coefficient (equal to LhA) and PUF is filtration pressure. PUF = 17 mmHg at the afferent arteriole end and 8 mmHg at the efferent arteriole end of the glomerular capillary.

PUF = (PGC – PBS) – (πGC – πBS), where P is respective hydrostatic pressures and π respective oncotic pressures.

Example at afferent end PUF = (60 mmHg – 15 mmHg) – (28 mmHg – 0 mmHg) = 17 mmHg

Example at efferent end PUF = (58 mmHg – 15 mmHg) – (35 mmHg – 0 mmHg) = 8 mmHg

Note: Since plasma protein is not filtered leaving little protein in Bowman’s space, the oncotic pressure of BS is 0. Oncotic pressure increases as a function of the length of the glomerular capillary. This is due to fluid movement out of the plasma by filtering into Bowman's space, which concentrates plasma protein. Note that there is only a small drop in glomerular capillary hydrostatic pressure as a function of length. This is so because glomerular capillaries are not resistance vessels.

GFR = Kf x [(PGC – PBS) – (πGC)]

Ultrafiltration pressure is set, in part, by PGC, which is regulated by the Rs/Ra ratio. Thus, GFR α Rs/Ra.

10) Regulation of GFR: effectors are afferent and efferent arterioles and glomerular mesangial cells.
a. changes in $P_{GC}$
   1) $R_a$ is inversely related to $P_{GC}$ and GFR.
   2) $R_e$ is positively related to $P_{GC}$ and GFR.
   3) its actually the ratio of $R_e/R_a$ that is important
      i) AngII by increasing both changes the ratio very little
      ii) ANP by preferentially decreasing $R_a$ increases the ratio
   4) $P_{GC}$ is also (positively) influenced by renal arterial pressure, which is a reflection of MAP
      i) increased by AngII, AVP
      ii) decreased by ANP and NO

Summary, ANP greatly increases GFR by increasing $R_e/R_a$. AngII has little effect on GFR for it does not change the $R_e/R_a$ ratio. AngII, however, decreases RBF (and increases MAP) by increasing the sum of $R_e + R_a$ whereas, ANP increases RBF (and decreases MAP) by decreasing the sum of these two resistances in series. Thus, the two vascular arterioles surrounding the glomerular capillary enable differential regulation of MAP, RBF and GFR to a certain degree. This allows us to change blood pressure without drastically affecting kidney function.
Lecture 3 – March 28, 2014

Tubule function

Objectives: Understand the function of each tubule segment.

General Comments: After studying this material you should:
1) Understand the basic processes of epithelial transport
2) Know the specific mechanisms (proteins) underlying transport for each tubule segment
3) Understand how transport in specific tubule segments is regulated
4) Understand the significance to the whole organism of specific tubule transport
5) Begin to understand where and why diuretics work
6) Understand glomerulotubular balance and the forces regulating it
7) Recognize the effects of specific hormones on tubular transport

Overview:
1) general – Re-familiarize yourselves with epithelial transport (i.e. - passive versus active transport, simple versus carrier mediated, primary and secondary active, coupled transport including co- and anti-port) and the forces driving each type of transport. Realize that carrier mediated transport (that is transport involving a protein other than an ion channel) can saturate. Re-familiarize with routes of transport (i.e. paracellular and transcellular) and the types of forces driving each (i.e. paracellular is always passive and transcellular can be either passive or active). Re-familiarize yourself with the emergent properties of an epithelium that allow transport (i.e. barrier properties and formation of polarized membranes). Understand the differences between electroneutral and electrogenic transport. Realize that transport proteins, epithelial polarity and tight junctions make transport selectivity as well as directional.

All vectorial renal solute and water transport is dependent on the gradient (energy) provided by the basolateral Na/K-ATPase.

Water movement through either the cell (using aquaporin type water channels) or between cells is always passive (osmosis).

The activity and selectivity of proteins in the plasma membrane of tubule epithelial cells provides specificity that enables reabsorption of essential electrolytes and nutrients and volume (in the form of water) while leaving waste in the urine.

2) proximal tubule – isosmotic reabsorption, and secretion of organic cations and anions. All filtered protein and small polypeptide chains reabsorbed here across the cell via endo/exocytosis. Two-thirds of the filtered load of is reabsorbed here.

Early PT:
Luminal events – Na/H exchange, and Na/X (X = glucose, amino acids, lactate, P, but NOT chloride) cotransporters.

Basolateral events – Most Na moved by the Na/K-ATPase. The remaining moved by the 3Na+-HCO3- cotransporter. Bicarb is also exchanged for Cl via the basolateral HCO3-/Cl exchanger. Reabsorbed glucose and amino acids exit via facilitated diffusion or 2nd active transport.

Paracellular – Water follows the movement of Na plus its associated anion or neutral solute (i.e. glucose). If there is a high concentration of non-reabsorbable solute in the filtered load (i.e. mannitol) or if the transport maximum is reached for a reabsorbed solute (i.e. glucose in diabetes), water cannot be properly reabsorbed in the PT, which leads to diuresis. This is why people with diabetes mellitus have elevated urine volumes.

Carbonic anhydrase (CA) plays an important role in Na-HCO3 reabsorption in the early part of the PT. This enzyme (in the cytosol) metabolizes carbon dioxide and water into carbonic acid (H2CO3), which quickly dissociates into H+ and HCO3-. The hydrogen ion is exchanged for Na at the luminal membrane and the bicarbonate anion crosses the basolateral membrane. The exchanged hydrogen ion then finds a filtered bicarbonate anion in the lumen transiently forming carbonic acid, which CA located on the extracellular face of the apical membrane then metabolizes into CO2 and water with the (small, non-polar)
CO₂ entering the cell to be metabolized by intracellular CA. Because of this function, CA is a target for diuretics, such as acetazolamide. Blocking CA activity impedes Na-HCO₃ reabsorption at the PT leaving it and its associated water in the urine.

**Summary – NaHCO₃ and NaX reabsorption.** Bulk isoosmotic reabsorption, reabsorption of all filtered glucose, amino acids, and bicarbonate and most other solutes, except chloride. Since Cl⁻ is not reabsorbed and Na⁺ is reabsorbed with some neutral molecules, the lumen of the early portion of the PT is negative. As Na and other solutes are reabsorbed with water isoosmotically in the early PT, Cl⁻, as well as non-reabsorbable solutes, such as inulin and creatinine, become concentrated (relative to plasma levels) in the urine here.

**Late PT**

**Luminal events** – Na/H exchanger, and Cl/formate exchanger with formic acid recycling.

**Basolateral events** – Na/K-ATPase.

**Paracellular** – Again, there is much paracellular movement of water from osmosis. Also Cl⁻ moves through the paracellular pathway due to concentration of Cl⁻ in the early PT. This builds a lumen positive charge. Positive cations are reabsorbed passively paracellularly due to the lumen positive potential.

**Summary – Parallel operation of Na/H and Cl/formate exchange with formic acid recycling at the apical membrane allows net NaCl and water reabsorption. Build up of the lumen positive charge drives passive reabsorption of cations, such as Na⁺, K⁺ and Ca²⁺.**

Note that in the PT, reabsorption of all solutes and ions are ultimately coupled to Na reabsorption. Thus, anything that affects Na handling will affect these as well.

**Organic anion and cation secretion in the late PT** – Many organic cations and anions are end-products of metabolism; however, most drugs, including penicillin, also fall into this category. PT cells have semi-specific luminal organic anion/Cl antiporters and organic cation/H exchangers. On the basolateral membrane there is a facilitative transporter for organic cations (driven against its gradient by the cell negative potential) and an organic anion-di/tricarboxylate exchanger, which runs in parallel with the Na-di/tricarboxylate cotransporter. Here the di or tri-carboxylate recycles across the basolateral membrane. The most prevalent di/tri-carboxylate is alpha ketoglutarate. (PAH, urate and penicillin are secreted by the same organic anion transporter.)

**Glomerulotubular balance (G-T balance)** - Simply put means that tubular reabsorption changes in proportion to filtered load, which is set by GFR, to maintain a constant fractional reabsorption. G-T balance is due to both intratubular and peritubular factors. Elevated GFR increases the filtered load of Na and thus, there is more Na-coupled reabsorption in the PT. Water follows. When GFR increases, peritubular capillary oncotic pressure is increased. This promotes fluid and Na reabsorption at the PT proportionately to increases in GFR.

**Regulation of PT transport** - For the most part, transport at the PT is constitutive and not regulated. Transport is primarily driven by filtered load, which reflects GFR, with G-T balance coupling reabsorption with filtration rate. The exception to this rule is that parathyroid hormone (PTH) targets the PT to affect Pi transport by affecting the Na/Pi symporter (NaPi) one of the many types of Na/X transporters discussed above in 2.

3) Loop of Henle – the only part of the loop that has active solute transport is the TAL. However, the thin descending limb has passive water reabsorption. Note, the TAL has very little water, urea and ammonia permeability. Thus, we have hypoosmotic reabsorption (concentration) in the descending limb and hyperosmotic reabsorption (diluting) in the ascending limb.

The osmolytes pumped out of the TAL create the osmotic force drawing water reabsorption at the descending limb.

**Luminal events at the TAL** – These cells contain an apical tri-transporter that allows Na/K/Cl to enter the cell. K is recycled at the luminal membrane through K channels. Luminal K recycling builds a lumen positive potential that drives Mg²⁺ (as well as some Na⁺, Ca²⁺, and K⁺) reabsorption through luminal TRP channels.
The tri-transporter is blocked by loop diuretics such as furosemide (Lasix). These are the most powerful diuretics.

**Basolateral events at the TAL** – Na exits across the Na/K-ATPase and Cl exits through a Cl channel.

**Summary** – NaCl and Mg are reabsorbed in the TAL with reabsorption dependent on K recycling at the apical membrane. The tri-transporter is the most effective diuretic target, because transport in the TAL ties into the concentrating/diluting mechanism (ie. It is central to establishing an axial corticomedullary osmotic gradient.)

**Regulation** – reabsorption in the TAL and thus, in the descending limb are constitutive and not normally considered to be regulated directly; however, they are influenced by delivery of solute and urine flow.

4) Distal tubule – hyperosmotic NaCl reabsorption with low water permeability.

**Luminal events** – NaCl enters the cell on the thiazide-sensitive NaCl cotransporter (NCC). Ca ++ enters the cell via an apical Ca channel.

**Basolateral events** – Na exits the cell on the Na/K-ATPase and Cl via a basolateral ion channel. Ca ++ exits the cell via the Na/Ca exchanger.

**Regulation** – The DT is also targeted by PTH to affect Ca reabsorption.

5) Collecting duct – regulated NaCl and water (urea follows water) reabsorption. This segment is the only segment to have an adjustable water permeability dependent on the hormone antidiuretic hormone (ADH; also called vasopressin). This segment also contains three types of cells: Principal cells and alpha and beta intercalated cells. The prior cells reabsorb NaCl and water and secrete K; and the latter secrete H (alpha cells, also reabsorb K) and bicarb (beta cells). Principal cells prevail in the cortical collecting duct with intercalated cells increasing in number in the medullary collecting duct.

**Events at the luminal membrane of principal cells** – Na enters via the amiloride-sensitive epithelial Na channel (ENaC). This ion channel is the end-target of the steroid hormone aldosterone, which is produced in the adrenal cortex in response to AngII (which increases when blood pressure is low) and K. Aldosterone stimulates ENaC activity to facilitate Na reabsorption. Water enters principal cells via aquaporin type 2 channels, which are activated by ADH, which is secreted from the posterior pituitary gland in response to an increase in plasma osmolarity. Normally the water permeability of the CD is low; however, with ADH it is extremely high. Interestingly, urea permeability positively correlates with that of water in this segment and thus, ADH also increases urea permeability (likely also through AQP2 channels).

**Events at the basolateral membrane of principal cells** – Na exits on the Na/K-ATPase and water via a constitutively active/present water channel.

Amiloride and competitive inhibitors of aldosterone (spironolactone/aldactone) are termed K sparing diuretics. These block Na reabsorption by directly and indirectly affecting ENaC. Since K secretion is directly coupled to Na reabsorption, they also prevent K secretion (and ultimately decrease K excretion). These weak diuretics are often used in conjunction with more powerful loop diuretics to counter the K wasting associated with loop diuretic usage.

**Intercalated cells – alpha** – contains a luminal H-ATPase and H/K-ATPase, which functions as a ATP dependent H-K exchanger. Together these proteins allow the secretion of a large amount of acid against its concentration gradient. Of course this acid comes from CA action inside the cell with bicarb existing across the basolateral membrane. Here, H and K move in the opposite directions. This, in part, explains why massive acid secretion, such as during acidosis, can increase plasma K levels. So, acidosis is often associated with hyperkalemia and alkalosis with hypokalemia (more about this later).

**Beta** – These cells contain an apical Cl/HCO3 antiporter and allow for bicarb secretion. Again bicarb comes from cytosolic CA actions with acid exiting across the basolateral membrane.

Acid and bicarb secretion from intercalated cells is not directly regulated by hormones but rather controlled by mass action reflecting plasma pH.
Lecture 4 – March 31, 2014
Renal indices (assessment of renal function)

Objectives: Understand renal indices and be able to perform simple calculations to quantify renal function.

General Comments: After studying this material you should:
1) Understand what clearance means and be able to calculate clearance, particularly \( C_{in} \), \( C_{in} \), \( C_{er} \), and \( C_{PAH} \)
2) Understand the significance of \( P_c \) values
3) Understand and calculate filtered load, excretion rate, filtration fraction and fractional reabsorption and excretion, as well as transport maximums
4) Determine whether a substance is filtered or undergoes net secretion or reabsorption using renal indices.

Formulas:

**glomerular function**

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

**tubular function**

\[
\text{Fex} = \left[ \frac{(U_{x}V)(P_{x} \times \text{GFR})}{(U_{x}P_{x})} \right] \times 100\%
\]

**nephron function**

\[
\text{C}_x = \frac{U_{x}V}{P_{x}}
\]

Overview:

1) The kidney can affect a substance in plasma by filtration, secretion and reabsorption. *Simply put, what enters the kidney through the renal artery must come out in the urine or venous blood.*

Measurements of renal function provide important information about functioning kidney mass, progression of renal (as well as other) disease, and allow physicians to adjust drug doses appropriately.

2) The amount of a substance, which is freely filtered, that enters the renal tubule (**filtered load**) over a given time is simply plasma concentration of that substance \( (P_x) \) multiplied by the glomerular filtration rate \( \text{GFR} \). Units are in mass per time. \( \text{GFR} \) in \( \text{ml/min} \) \( x \) \( P_x \) in \( \text{mg/ml} = \text{FL}_x \) in \( \text{mg/min} \). \( \text{FL}_x \) in \( \text{mg/min} \)

3) The amount of a substance excreted per time is equal to the filtered load minus the amount transported into/out of the tubule (we *always talk about net transport with secretion being positive and reabsorption being negative*) over the given time period. Another way of calculating **excretion rate** \( (U_xV) \) is simply measuring the urinary concentration of the substance \( (U_x) \) in volume of urine produced over a certain time \( (V) \). Units are in \( \text{mg/ml} \) \( x \) \( \text{ml/min} = \text{mg/min} \).

4) The plasma volume that is cleared completely by the kidney of a substance over a unit time can be calculated by determining **clearance** \( (C_x) \), which is the amount excreted in urine per unit time \( (U_xV) \) divided by the plasma concentration of that substance \( (P_x) \). This is a rate and has units of \( \text{ml/min} \). **Clearance of a substance is the idealized volume of plasma completely rid of the substance by the kidney per unit time. Clearance speaks about blood not the substance cleared. You have to think of it as the kidney doing its job to rid blood of waste. Clearance of substance X is how well the kidney rids the blood of substance X.**

5) Inulin is a polysaccharide that is freely filtered, but not secreted, reabsorbed or metabolized. Thus, calculating its clearance \( (C_{in}) \) yields glomerular filtration rate. It is not always practical to use inulin in the clinic (it must be infused at a steady rate via an IV for an extended time). Thus, **creatinine clearance** \( (C_{cr}) \) is more often used to calculate GFR. For our purposes, creatinine can be considered to be freely filtered and not transported, where \( C_{cr} = \text{GFR} \). (Since a small amount of creatinine is secreted into the tubule, it overestimates GFR by about 10%, but the clinical laboratory method used to evaluate plasma creatinine levels overestimates it by 10%.) Thus, these two errors cancel. Creatinine clearance is used clinically because it is a naturally occurring substance in humans (made by metabolism of creatine-monophosphate in skeletal muscle) released at a constant rate. Realize that \( C_{cr} \) is only an index of renal function and does not always exactly match GFR. This is particularly true when GFR approaches 0 and creatinine secretion begins to set UV or when creatinine secretion becomes saturated.

Looking at the values of \( P_c \) over time can yield important information about loss of GFR resulting from kidney disease.

6) PAH is an organic anion that is freely filtered and secreted. Thus, all PAH that enters the kidney via the renal artery over a given time ends up excreted in the urine. Quantifying its clearance then will yield renal plasma flow (how much plasma is delivered to the kidney per unit time). Since PAH is actively secreted by the PT, raising plasma concentration too high can saturate the secretion mechanism of this anion into the urine and thus, give a misleading value for RPF.
The amount of plasma brought to the glomerulus that is filtered is filtration fraction (FF). It is calculated by dividing GFR by RPF, and can give you some indication about glomerular function. Thus, Ccr/Crhl is useful.

Tubular function -
7) To determine transport rate and find if it is saturated use: T_x = U_xV - (GFR x P_x). This formula considers both the excretion rate (UV) and filtered load (GFR x P) with their difference being the transport rate (a positive value means net secretion and a negative value means net reabsorption). Once the transport becomes saturated, excretion rate will parallel filtered load with T_x no longer changing. Just remember: Ex = FL + T_x.

8) Glucose is freely filtered and completely reabsorbed in the PT. Thus, its clearance is normally 0 (C_glu = (0 x 1.5 L/day) / (1 mg/ml)). If plasma glucose gets too high, as in diabetes mellitus, the filtered load (i.e. 10 mg/ml x 125 ml/min = 1,250 mg/min) can exceed the ability of the PT to reabsorb this substance (T_m = 375 mg/min). You will then find glucose in the urine, and can use the following formula to calculate its transport maximum: T_glu = U_gluV - (GFR x P_glu). Normally U_gluV is zero for glucose; because T_glu exceeds the filtered load of glucose (GFR x P_glu). As you exceed the transport maximum (T_m) for glucose, the excretion rate of glucose begins to be linearly related to the filtered load of glucose.

9) Another way of understanding transport maximums is to consider that clearance for a solute entirely reabsorbed is 0 until its filtered load (reflecting its plasma levels) exceeds the transport maximum. Similarly clearance of a substance that is secreted remains constant over increasing plasma concentrations until its transport maximum is reached where it then decreases, because the kidney simply cannot secret it fast enough. Clearance of a substance only filtered is constant.

10) Since inulin and creatinine clearance are good indicators of GFR with their excretion rate equal to their filtered load, comparing the clearance of substance X (which is freely filtered) to Cin or Cx can determine if X goes through net secretion or reabsorption in the tubule. If C_x/C_in = 1, it suggests that X is only filtered; if C_x/C_in < 1, it suggests that X is net reabsorbed; if C_x/C_in > 1, it suggests that X is net secreted.

*What does comparing C_x/C_in of a substance not secreted or reabsorbed tell you? (A: How much is bound and cannot be filtered). If X is bound to plasma protein, C_x can be lower than C_in even though X is not reabsorbed.

11) Another way to assess tubular handling of a substance is to look at fraction excretion (Fex) and reabsorption (Fr). Fractional excretion tells you how much of the filtered load is excreted, and fractional reabsorption, how much of the filtered load is reabsorbed. These are easily performed in the clinic, and are independent of time. We just need one sample (instead of multiple samples over time) measuring plasma and urine concentrations of creatinine and substance X. Fex = [(U_xP_c) / (U_cP_x)] x 100%; Fr = 100% - Fex. You can also just use C_x/C_cr in your calculation of fractional excretion since V in the denominator of each fraction is the same and cancels.

Example – A patients with Liddle’s syndrome, which is a monogenic form of Mendelian hypertension, has inappropriate Na reabsorption at the CD. Fex of Na usually increases quickly after a normal person is put on a high Na diet. In this patient with Liddle’s syndrome it does not. Interestingly, a lot of essential hypertension is Na-sensitive suggesting that F_ex of Na is also inappropriately regulated in these cases.

12) Questions to think about. If the clearance of substance X is greater than GFR, does X go through net reabsorption or secretion? If a diuretic is used to decrease fractional Na reabsorption, does the clearance of Na increase or decrease? Does X undergo net secretion when U_xV/FL_x < 1? Theoretically, what does it mean if glucose clearance exceeds inulin’s?
Objectives: Understand how control of tubular transport and GFR function together to establish NaCl and water balance.

General Comments: After studying this material you should:
1) Understand the counter-current multiplier
2) Understand the tubule segments important for concentrating and diluting urine
3) Know the hormones and mechanisms that regulate Na and water reabsorption
4) Understand how plasma osmolality is controlled
5) Understand and calculate free water clearance and osmolar clearance

Overview:
1) NaCl and water are constitutively reabsorbed in the PT and loop of Henle. Plasma NaCl and water is fine-tuned by hormone action on the collecting duct, which in conjunction with the loop of Henle allows urine to be concentrated and diluted.

2) Countercurrent multiplier – The Loop of Henle establishes medullary hyperosmolarity: The TAL reabsorbs NaCl but not water. This single effect of hyperosmotic reabsorption at the TAL delivers hypoosmotic urine to the collecting duct, and generates a hyperosmotic medullary interstitium. Note, we have just separated movement of salt and water! We will again at the collecting duct to tap into the hyperosmotic medulla.

Medullary interstitial osmolarity increases progressively from the cortex to the medulla. This is due to multiplication of the single effect by countercurrent flow in the descending and ascending limbs of the Loop of Henle. Each single effect happens to urine already processed by a previous single effect. Recall that the descending limb is freely permeable to water. Thus, as urine enters the Loop from the PT it becomes concentrated as water is progressively reabsorbed out of the descending thin limb. At the hairpin turn, urea and Na equilibrate and thus, urine osmolites are about half urea and half NaCl. As the fluid moves up to the TAL, NaCl, but not urea or water is reabsorbed. This dilutes the urine and produces the driving force for water to be reabsorbed at the descending thin limb and collecting duct. As the dilute urine, containing mostly urea, enters the collecting duct, more Na is reabsorbed. Then, ADH by acting upon water channels enables water to be reabsorbed. Water flows down its concentration gradient, out of the urine into the interstitial fluid. This further concentrates urea and non-reabsorbable waste. Urea then diffuses passively down its concentration gradient into the interstitium and recycles into urine at the hairpin turn of the Loop of Henle. Thus, the hyperosmotic medullary interstitium is dependent on the countercurrent multiplier system of the Loop, as well as urea recycling and ADH allowing water (and urea) reabsorption out of the collecting duct.

To produce concentrated urine, we must have ADH, which increases both water and urea permeability at the collecting duct. With ADH the medullary interstitial fluid osmolarity can reach 1200-1400 mOsm. When ADH is not present, medullary interstitial fluid osmolarity is only about 300-600 mOsm. This is so, because we don’t have urea recycling.

To secrete a dilute urine, we simply don’t tap into the medullary osmolarity gradient, because ADH isn’t around.
Without ADH around, we can still control how much Na we reabsorb with aldosterone. Thus, water and Na reabsorption can be fine tuned independently by the actions of ADH and aldosterone. What would the medullary osmolarity be in the presence of loop diuretics?

The total amount of solute excreted is not directly affected by ADH. ADH just sets the volume this solute is excreted in and thus, affects the osmolarity of the urine (and plasma). The total amount of solute excreted is set by filtered load and hormones, such as aldosterone, that influence electrolyte transport.

Note that the countercurrent system permits formation of concentrated as well as dilute urine. Diuretics block both actions allowing excretion of a large volume of urine that has the osmolarity of plasma. Basically, diuretics impede the kidneys ability to process urine and thus, what comes out of the kidney is equal to what enters it at the glomerulus via filtration - i.e. plasma. This is why diuretics work to decrease edema and blood pressure!

3) Looking at osmolar clearance ($C_{\text{osm}}$) and clearance of free water ($C_{\text{H}_2\text{O}}$) tells us about renal water and osmolyte handling. Recall that a solution has both a solute and water concentration; though, it is difficult to measure water concentration. We can calculate $C_{\text{osm}}$ from measuring plasma and urine osmolality and then use these values to back calculate $C_{\text{H}_2\text{O}}$ from urine volume per time ($V = C_{\text{osm}} + C_{\text{H}_2\text{O}}$). Osmolar clearance ($C_{\text{osm}}$) refers to the virtual volume of plasma cleared of all osmolytes. We represent this volume as the urine volume containing all the urine osmolytes in osmotic equilibrium with blood. Free water clearance ($C_{\text{H}_2\text{O}}$) then is the virtual volume of plasma missing its osmolytes added to (or taken away from) this to equal actual urine volume. The free water volume contains no osmolytes and can be positive or negative depending whether the kidney is reabsorbing water without the osmolytes (i.e. Na) or reabsorbing Na without the water. If this number is negative, it means that the total urine osmolarity is greater than plasma (concentrated urine) and water is being preferentially retained over osmolytes.

A quick way of calculating $P_{\text{osm}} = 2.1 \times P_{\text{Na}}$.

4) ADH acts upon $C_{\text{H}_2\text{O}}$ and thus, affects V. ADH decreases $C_{\text{H}_2\text{O}}$.

Questions to think about: What is $C_{\text{H}_2\text{O}}$ in the presence of loop diuretics? What is $C_{\text{H}_2\text{O}}$ in somebody with advanced diabetes mellitus compared to somebody with diabetes insipidus. How does V compare in these two types of diabetes? What is $C_{\text{H}_2\text{O}}$ in a person treated with mannitol. Which type of diuretic would you give a person with polydipsia (psychosis associated with uncontrolled consumption of large volumes of water), a loop diuretic or a V2 antagonist? Is ADH doing its job in a person with normal blood pressure, hypernatremia (increased plasma Na) and a $C_{\text{H}_2\text{O}} > 0$?

Example: Joe produces 1 L/day of urine that has an osmolarity of 600 mOsm. John excretes 6 L/day of urine having an osmolarity of 100 mOsm. Let’s look at their osmolar clearance (considering plasma to be about 300 mOsm):

Joe: $V = 1$ L/day, $C_{\text{osm}} = 2$ L/day (from UV/P; 600 mOsm x 1L / 300 mOsm), thus, $C_{\text{H}_2\text{O}}$ must be -1 L/day

John: $V = 6$ L/day, $C_{\text{osm}} = 2$ L/day (from UV/P; 100 mOsm x 6L / 300 mOsm), thus $C_{\text{H}_2\text{O}}$ must be 4 L/day

Joe is retaining free water and John is excreting free water but both are ridding the body of the same amount of waste (600 mOsm/day). They are just doing it in different volumes of urine.
5) Counter current flow and exchange between the descending and ascending limbs of the vasa recta minimize solute washout from the medulla.

6) Regulation of body fluid volume/composition. 
Osmolarity is under the domain of ADH acting upon collecting duct principal cells. Osmosensors are in the hypothalamus. These sense effective plasma osmolality capable of increasing and decreasing cell volume. These cells only sense effective osmolytes, such as NaCl and not urea, which is freely diffusible and has little effect on cell volume. (So, these cells actually sense tonicity and not osmolarity.) Increased osmolality/tonicity (cell shrinkage) increases firing of osmosensors, which synapse on ADH secreting cells (in the paraventricular nucleus, PVN and supraoptic neuron, SON) in the posterior pituitary to increase release of ADH. ADH targets principal cells of the collecting duct via V2 causing insertion of AQ2 type water channels into the luminal membrane resulting in an increase in apical water permeability. Water then flows via osmosis from the urine into the medullary interstitium, where it is ultimately reabsorbed into the circulation to decreases osmolality, which then acts in a negative feedback manner, by allowing osmosensor cells to return to a normal volume, to decreases ADH release. **Note that ADH does not control plasma volume, but rather plasma osmolarity.** Release of ADH is also modified by extrarenal pressure sensors located in the aortic arch (responding to MAP) and left atrium and pulmonary vessels (responding to vascular volume). Activation by these receptors signal to the posterior pituitary via the sympathetic nervous system to increase the amount of ADH released per unit change in osmolality and affect the set point of ADH release (low pressure decreases it from 280 mOsm/kg and higher pressures increases it). Thus, the primary control of ADH release is osmolarity with modification by MAP and vascular volume. This allows us in emergencies to conserve water and thus, MAP even in the face of decreasing plasma osmolarity.

Our thirsting is also directly coupled to ADH, plasma osmolality, blood volume and MAP, with increased ADH and decreases in volume and MAP causing us to thirst. AngII has a similar action to ADH to evoke thirst by affecting the thirsting center in the hypothalamus.

*Plasma volume* is under the control of the renin-angiotensin-aldosterone system (RAAS), which is discussed later.

**You do not need to memorize the following diuretics or diseases, but do have to know what happens when their target protein is inhibited.**

7) Diuretics disrupt our ability to concentrate urine. They most often do this by blocking Na reabsorption and thus, obligate water to be excreted with this osmolyte. Similarly, freely filtered but non-reabsorbable molecules, such as mannitol, can also obligate water to be excreted. Finally, diuretics can disrupt the ability of water to follow solute reabsorption.

**Types of diuretics:**
- a) osmotic – they obligate water to be excreted with a freely filtered, unreabsorbable molecule. Example – mannitol.
- b) classic - 1) carbonic anhydrase inhibitors – affect the PT and disrupt Na reabsorption. Example – acetazolamide and mercurial diuretics.
  2) tritransporter inhibitors – affect the TAL and disrupt Na reabsorption. Completely break down the counter current multiplier system. Example – furosemide. What would the \(U_{\text{osm}}\) be with their use? Often called loop diuretics. These are the most powerful.
  3) inhibitors of NCC – affect the DT and disrupt Na reabsorption. Example - thiazide
  4) K sparing diuretics – affect the collecting duct to disrupt Na reabsorption and K secretion. They target ENaC (amiloride and triamterene) or aldosterone signaling to ENaC (aldactone).
- c) free water diuretics – Uncouple the ability of water to follow solute reabsorption in the collecting duct. Block the actions of ADH or inhibit the water channel. Example - V2 antagonists. What would the medullary osmolarity be during use of these diuretics?

8) Disease directly affecting water reabsorption.
- a) diabetes insipidus – cause excretion of a large volume of dilute urine.
  1) Nephrogenic DI – A defect intrinsic to the kidney resulting in end-organ resistance to ADH. ADH is high but cant get AQ2 to the apical membrane or AQ2 once there is not functional. This is very rare. What would the medullary osmolarity be? What would the plasma concentration of ADH be?  
  2) Central DI – A defect in secretion of functional ADH. This is much more common.
- b) SIADH (syndrome of inappropriate ADH secretion) – Usually an ectopic tumor in the lungs that releases functional ADH. (Recall that lung tissue and pituitary cells are close to each other early in development.) A similar disease would result from hypersecretion of ADH from the pituitary. What would the plasma Na concentration be? What about urine osmolarity?
Blood pressure control

Objectives: Understand how we maintain blood volume and pressure.

General Comments: After studying this material you should:
1) Understand total body water and fluid compartments and how they are controlled
2) Understand the concept of effective circulating volume and how NaCl excretion modifies it
3) Recognize the hormones and their sites of action involved in regulating effective circulating volume
4) Understand how the glomerulus and tubule function to regulate ECV
5) Understand the systemic role of the kidney in protecting ECV
6) Understand disease states the impinge upon ECV and electrolyte status

Overview:
1) One misconception about renal function and human physiology is that ADH action on water reabsorption sets plasma volume. This is not so. It sets plasma osmolality. Plasma volume is set by renal handling of Na. This is best understood by considering total body water and fluid compartments.

2) Total body water (TBW, ~ 42 L or ~0.6 x body weight) is all the water in the body combined. Total body water can be divided into two major fluid compartments: that in cells (intracellular) and that outside of cells (extracellular). Intracellular fluid (ICF) is about 2/3 of TBW or 28 L. Extracellular fluid is 1/3 of TBW or 14 L. Extracellular fluid can be further subdivided into plasma (1/4 or 3.5 L) and interstitial fluid (ISF, 3/4 or 10.5L).

3) The major cation and anions in ECF are Na⁺ and Cl⁻ and HCO₃⁻. ISF and plasma have similar compositions, except that plasma contains more protein; however, we will consider their ionic compositions to be the same. The major cation and anions in ICF are K⁺ and Pi (PO₄³⁻), organic anions (OA⁻) and protein (Pr⁻). Though they differ in ionic composition, the ICF and ECF are in osmotic equilibrium! So, water moves back and forth freely. Depending on which compartment has the greatest amount of osmolytes. Thus, controlling [Na] controls the forces drawing water into the ECF and thus, controls ECF volume.

4) Water exchanges freely between compartments; however, osmolytes do not. Free water movement allows all of our body fluid compartments to be, except during rapid responses to changes in osmolality, in osmotic equilibrium. The force driving water movement is osmosis. Remember, to direct water movement across a barrier, such as a plasma membrane, solutes must be non-permeable (effective osmolytes). NaCl, mannitol, and plasma proteins are effective osmolytes. Urea is not and glucose to a lesser degree. The effectiveness of an osmolyte can sometimes depend on the activity of proteins. For instance, Na is effective because the Na/K-ATPase effectively extrudes it from the cell as quickly as it enters. Glucose is not effective most of the time, because insulin via the glucose transporter insures that it enters/exits the cell down its concentration gradient freely.

5) For circulatory function, such as oxygen and nutrient delivery, plasma volume, which sets mean arterial pressure, is most important. For maintaining the proper cell volume and osmolarity, interstitial fluid is most important. But realize effecting one fluid compartment will ultimately affect the others.

6) Case scenarios to understand why Na controls volume and ADH (or water addition/subtraction) controls osmolality:

A. Addition of water to the ECF: This water initially expands the ECF; however, it decreases its tonicity. This causes water to enter from the ECF to the ICF. Since water will move until a new osmotic equilibrium is reached, the ECF will expand by 1/3 of the added volume and the ICF by 2/3 of the added volume. Plasma and ISF will expand by 1/12 and 1/4 of the added volume. Thus, most of the added water enters the ICF compartment with both compartments having a decrease in osmolality.

B. Addition of isotonic (0.9%) saline to the ECF: This will expand the ECF whilst maintaining osmotic equilibrium and thus, ICF will stay the same and ECF will increase by exactly the amount added. This will result in plasma and ISF increasing by 1/4 and 3/4 of the additional volume, respectively.

7) Since Na and its anions are the most abundant osmolytes in the ECF, alterations in Na balance initially disturb ECF osmolality, but water quickly leaves the ICF or ADH is released to increase water reabsorption at the kidney to correct for changes in plasma osmolality. Either way, the ECF volume increases while the ICF decreases or stays the same. Thus, conservation of Na by the kidneys initially increase ECF osmolality, as well as drawing water from the ICF to reach a new equilibrium where both the ICF and ECF osmolalities have increased. An increases in osmolality causes ADH to be released until enough free water is reabsorbed or ingested to set osmolality back to ~ 280 mOsm/kg with water distributing evenly between ICF and ECF. Thus, the little water initially lost from the ICF due to Na entering the ECF is replaced (or actually...
never leaves). Thus, the consequences of increased Na reabsorption are primarily to expand the ECF with ADH maintaining osmolality. Therefore, the ECF but not the ICF increases proportionately to the amount of Na reabsorbed at the kidneys.

8) Normal Na ingestion is about 8 g or 140 mEq per day. Thus, the kidney excretes 140 mEq of Na a day; however, it has the capacity to excrete or retain much more (from 10 – 1000 mEq/day). This discretionary Na handling is controlled by hormones; specifically, by the RAAS pathway. A defect in our ability to handle Na will lead to inappropriate changes in blood volume and thus, pressure.

9) The kidneys response to changes in Na balance are not instantaneous and can take from hours to days. If Na intake exceeds excretion we are in **positive Na balance**, when Na intake is less than excretion rate, we are in **negative Na balance**. During states of positive Na balance (hypernatremia), blood pressure is increased, and conversely, in states of negative Na balance (hyponatremia) blood pressure is decreased. Remember that we have other means for acutely regulating blood pressure, such as affecting CO and TPR. These can compensate for transient changes in Na balance; however, they cannot compensate for chronic changes in Na balance.

10) **Effective circulating volume (ECV)** is the ECF that effectively perfuses tissue. It is a component of the plasma fluid volume. It reflects the blood volume in the arterial circulation is dependent on MAP for delivery.

ECV is directly proportional to ECF. Thus, it can be influenced by Na reabsorption in the kidneys.

11) Sensors that control ECV actually sense pressure or volume and are often referred to as baroreceptors. They are the extrarenal and intrarenal baroreceptors, as well as the pressure sensor in the JGA and sensor of urine flow at the MD.
   a) volume/pressure – located in atria and pulmonary vessels, sense volume or fullness due to vascular compliance.
   b) high pressure –
      a. extrarenal - in aortic arch, carotid artery, sense pressure.
      b. intrarenal – senses pressure directly at afferent arteriole and via the JGA also senses pressure and urine flow at MD, which reflects pressure, to release renin.
   c) atria – myocytes in the heart synthesize atrial natriuretic factor (ANF) releasing it in response to increases in distension (volume). This is a different sensing than the low pressure atria sensor, which controls ANS activity, and is not really considered a baroreceptor.

Extra and intrarenal baroreceptors impinge upon the activity of the ANS (sympathetic nervous system branch).

Recall that ADH release is also sensitive to pressure and volume (sensed at the same sites), as well as afferent sympathetic signaling. Thus, increases in sympathetic signaling, and renin and ADH release often coincide.

12) The kidney is the primary effector for maintaining ECV. Variables regulated in this manner are RBF, GFR and Na reabsorption at the collecting duct. Also, the kidneys contribution to TPR is an effector site.

13) Signals: hormones (AngII, ADH, aldosterone, ANF) and nervous system (sympathetic NS).

   **Increased Na reabsorption** -
   1) AngII by aldosterone secretion
   2) Aldosterone (and ADH to a lesser degree) by affecting collecting duct

   **Decreased Na reabsorption** -
   1) ANF by increasing GFR to increase filtered load.
   Note that ANF negatively affects rennin, aldosterone and ADH release.

   Increased TPR and decreased RBF - 1) AngII, ADH, NE, Epi by affecting Ra and Re
   Decreased TPR and increased RBF and GFR - 1) ANP, NO by relaxing the afferent arteriole more than the efferent

14) **Case 1: decreased blood pressure:** Sensed by extrarenal and intrarenal baroreceptors, as well as the JGA. Causes increased sympathetic NS activity, resulting in contraction of the afferent and efferent arteriole (via alpha adrenergic receptors), release of ADH and renin (via beta adrenergic receptors; ultimately increasing AngII). Direct actions at the JGA also lead to increased renin release. Increased renin (AngII) release leads to increases in aldosterone. AngII (AT1 receptors), and ADH (via V1 receptors) increase TPR with aldosterone at the collecting duct increasing Na reabsorption. ADH (via V2 receptors) allows water to follow this Na in the collecting duct. The combined effect of this hormonal and neural input is to reestablish euvolemma and/or MAP with a major component being decreased Na excretion and shifting volume away from the kidney at the same time that TPR increases.

   **Case 2: increased blood pressure:** Decreased sympathetic signaling, and ADH and renin release. Increased ANF release. ANF relaxes arterioles to decrease TPR, and specifically relaxes the afferent more than efferent arteriole to increase RBF and GFR shifting volume into the kidney. The increase in GFR increases Na excretion.
You do not need to specifically memorize the following diseases, but you must know what happens to renal solute handling when certain tubular transport proteins are defective. For example, you don’t need to know Liddle’s syndrome, but do need to know that hyperactivation of the Na channel in Principal cells leads to hypertension.

15) Diseases involving aberrant salt handling by the kidney. The following diseases are monogenic, resulting from defects in a single gene. They demonstrate the importance of the kidney to maintenance of blood pressure and composition.

Hypertensive

a) Liddle’s syndrome – gain of function mutation in ENaC. Results in hypertension and hypernatremia associated with hypokalemia and decreased RAAS. Can treat with amiloride.

b) Glucocorticoid remediable aldosteronism – inappropriate crossover resulting in aldosterone synthase (the gene responsible for aldosterone production in the adrenal glomerulosa) becoming sensitive to ACTH. Thus, aldosterone secretion is under the control of physiological stimuli that usually control cortisol release. This results in hyperactive ENaC and avid Na reabsorption and K secretion. In addition to using genet screens, this can be distinguished from Liddle’s by the fact that aldosterone is high, but renin and AngII are low. Treated with cortisol to decrease ACTH.

c) Apparent mineralocorticoid excess – defective 11 beta-hydroxysteroid dehydrogenase (HSD). Glucocorticoids, such as cortisol, and the mineralocorticoid aldosterone can both affect the mineralocorticoid receptor (MR) in collecting duct principal cells to stimulate ENaC. Principal cells are usually protected from cortisol by the actions of 11beta HSD, which metabolizes cortisol but not aldosterone. A defect in this protein will result in cortisol inappropriately activating ENaC via MR leading to avid Na reabsorption. The RAAS is suppressed in this disease. It can be treated with amiloride. Nutrition can also cause this disease. Both black licorice and chewing tobacco contain a chemical that inhibits 11 beta HSD.

d) some forms of preeclampsia eclampsia – the mineralocorticoid receptor is usually inhibited by progesterone; however, in a recently identified disease, progesterone activates this receptor to stimulate avid Na reabsorption and K secretion. This is particularly noticeable during pregnancy when progesterone is high.

e) there are also a whole host of other disease that lead to primary and secondary hyperaldosteronism, hyperreninism and hypercortisolism (i.e. Cushing's Disease). All of these impinge upon Na handling by the kidney.

Hypotensive

a) Bartter’s syndrome – defect in the tri transporter, the TAL apical K channel or the TAL basolateral Cl channel. This disrupts the ability to reabsorb Na (and Mg) at the TAL and thus, destroys our ability to concentrate urine. One result is increased urine output and Na loss. Another is that since Na delivery to the collecting duct increases we also waste K. A further result is that since Na delivery to the DT is increased we also disrupt Ca reabsorption here and thus waste Ca. The hypersection of K at the collecting duct also affects H secretion (via the H/K exchanger) leading to also to alkalosis. This salt wasting leads to increased urine output and hypotension.

b) Gitelman’s syndrome – defect in the Na/Cl cotransporter in the DT. This disrupts the ability to reabsorb Na at the DT. The increased Na delivery to the collecting duct causes K wasting and alkalosis. However, Ca is avidly reabsorbed (distinguishing it from Bartter’s syndrome) at the DT due to a decrease in Na reabsorption here. Salt wasting leads to hypotension.

c) pseudohypoaldosteronism – results form either a defect in ENaC or the mineralocorticoid receptor in Principal cells. Cannot reabsorb Na and have no K secretion resulting in hyponatremia with hyperkalemia and a decrease in blood pressure. Can be associated with an acidosis.

d) As with monogenic hypertension, there are several other diseases that lead to hypotension and inappropriate salt wasting. Primary and secondary hypoaldosteronism, hyporeninism.....
Lecture 7 – April 7, 2014
Regulation of K⁺, Mg⁺⁺, Ca⁺⁺, PO₄²⁻, and Micturition

Objectives: Understand how the kidney handles K⁺, Mg⁺⁺, Ca⁺⁺ and P₀ and the process of micturition.

General Comments: After studying this material you should:
1) Understand where K is reabsorbed and secreted
2) Know the mechanism of action of hormones controlling K
3) Understand the role of PTH and calcitriol
4) Understand where and how Ca and P are reabsorbed
5) Understand where and how Mg is reabsorbed
6) Understand the process of micturition and regulation of this response
   a. recognize the control elements regulating bladder filling and emptying
   b. understand the mechanisms controlling filling and emptying
   c. understand reciprocal regulation of the bladder by sympathetic and parasympathetic innervation
   d. recognize the different types of muscles controlling bladder filling and emptying
   e. understand the micturition reflex
   f. understand voluntary and involuntary control of bladder emptying

Overview:
1) K and its associated anions are the major intracellular osmolytes. K plays a major role in determining membrane potential. Plasma K is held around 4 mEq. Movements away from this have profound effects on membrane potential and thus, muscle and neuron excitability. K in ECF is regulated by tissue buffering and a slower renal mechanism.

2) Tissue buffering – as plasma K increases it enters into the ICF due to the activity of the Na-K-ATPase. As K in the ECF decreases, the ICF serves as a buffer allowing some K leak. Aldosterone, insulin and catecholamines increase K uptake into the ICF.

K is released from the ICF as plasma osmolality increases and as cells die in some pathological conditions, such as rhabdomyolysis.

3) Renal regulation: Most of the filtered load of K is reabsorbed in the PT and TAL. In the PT it is due to the lumen positive charge. In the TAL, K enters the cell on the tritransport.

4) We fine tune the amount of K excreted by secretion at the collecting duct. Recall that K is secreted as the counter ion to Na reabsorption. This is under the control of aldosterone.

5) Factors that control aldosterone release: AngII and hyperkalemia. Thus, K secretion at the collecting duct is under negative feedback control.

6) K can also be reabsorbed in the collecting duct as the counter ion to H using the H/K-ATPase in alpha cells. This is influenced by systemic acid base balance.

7) Urine flow rate at the collecting duct also plays a major role in regulating K secretion. Increased urine flow (delivery of Na) increases K secretion.

In fact, this is why there is K wasting with most diuretics (excluding K sparing diuretics).

8) Ca and Phosphate enter the body across the gut together. They then enter and are released from bone together. The only place their movement is separated is in the kidney.

9) Ca is passively reabsorbed at the PT (60%) and at the TAL (30-40%) due to the lumen positive charges dependent on Na reabsorption. Ca excretion is fine tuned at the DT and inversely coupled to Na reabsorption here. At the DT, Ca enters the cell via the apical Ca channel and exists via the Na/Ca exchanger. If the DT is avidly reabsorbing Na, the Na/Ca exchanger is less efficient. Hormones regulated Ca reabsorption at the TAL and DT.

The TAL has a unique calcium sensor allowing Ca to regulate its own reabsorption!

10) Hormones that influence renal Ca and Phosphate handling are the parathyroid hormone (PTH) and calcitriol.

These hormones are themselves released in response to systemic Ca balance. Recall that the kidney activates calcitriol.
Decreased plasma Ca stimulates PTH release. PTH decreases the activity of NaPi in the PT to decrease renal reabsorption of phosphate. PTH induces bone resorption, activation of calcitriol, and renal tubular Ca reabsorption by affecting the DT. Calcitriol further increases bone resorption, Ca entry at the gut, and tubular Ca reabsorption (at the TAL).

11) Phosphate is reabsorbed mostly in the PT via a transcellular pathway coupled with Na using NaPi. Phosphate levels are fine tuned due to the negative actions of PTH on NaPi. In the absence of PTH, NaPi is functional and we reabsorb phosphate.

12) Magnesium is reabsorbed mostly at the TAL via the lumen positive charge due to K recycling. Its reabsorption is constitutive and not regulated directly but coupled to tritransporter activity and thus, urine flow. This is why loop acting diuretics often cause Mg wasting.

13) The kidneys also secreted erythropoietin. This hormone induces hyperplasia of reticulocytes in red bone marrow and matures reticulocytes to produce erythrocytes. Its release from the kidney is under the control of oxygen delivery. Decreased oxygen delivery results in increased EPO release.

**Micturition**

**Overview:**

1) After exciting the renal nephron urine spills into the renal pelvis and runs down the ureters to the bladder, where it is stored. Urine is moved from the pelvis to the bladder by peristalsis via the smooth muscle investing the pelvis and ureter. In humans, no further change occurs in urine composition and volume after it leaves the renal nephron (this is not true of all animals, particularly amphibians.)

2) The urinary bladder is made of a surrounding epithelial barrier surrounded itself by smooth muscle. The surrounding smooth muscle is called the **detrusor muscle**. Bladder epithelium is specialized capable of rapidly increasing (up to holding a volume of 0.5 L) and contracting surface area due to rapid trafficking of the apical plasma membrane. This epithelial, though, has only a barrier function it does not transport. The surrounding smooth muscle receives **reciprocal innervation** from the autonomic nervous system via lumbar L-L3 (sympathetic) and sacral S2-S4 (parasympathetic) segments of the spinal cord.

3) **Sympathetic signaling relaxes** the bladder allowing it to be flaccid capable of expanding and filling. **Parasympathetic signaling contracts** the bladder to void it. The process of voiding the bladder is called **micturition**. Bladder wall smooth muscle contracts in an organized fashion creating peristaltic waves pushing the urine out of the bladder into the urethra.

4) Emptying the bladder and allowing urine flow out of it are under both voluntary (input from the higher brain; specifically the pons and cerebral cortex) and involuntary (a local spinal cord reflex) control. This control arises from differential control of the sphincter muscles (musculature rings around the exit of the bladder/beginning of the urethra) and smooth muscle controlling bladder emptying, as well as the different muscle types of the internal and external sphincters controlling egress out of the bladder. The external urethral sphincter (termed the **urogenital diaphragm**) limiting egress out of the bladder is comprised of skeletal muscle, which is under voluntary control. However, the emptying of the bladder (as smooth muscle around the bladder contracts) is under reflex control by the autonomic nervous system with reciprocal innervation as noted above. Thus, the actual contraction of the bladder leading to voiding is an involuntary reflex but whether urine in the bladder is allowed to flow outwards or not is controlled by a voluntary (external, skeletal muscle) sphincter.

5) The micturition (voiding) reflex occurs when the bladder becomes full. This is a spinal reflex sometimes referred to as an autonomic (or visceral) reflex because it is mediated by the autonomic nervous system and controls the activity of an internal organ.

6) **Bladder filling.** When the bladder is not full but filling, sympathetic control predominates allowing the detrusor muscle to relax and become flaccid amenable to filling while the internal sphincter is kept contracted. The internal sphincter is smooth muscle and merely a specialized continuation of the detrusor muscle. Relaxation of the detrusor muscle is via **beta2 adrenergic receptors**, which are coupled to Gs and cAMP signaling. Contraction of the internal smooth muscle sphincter is via **alpha1 adrenergic receptors**. One neuronal transmitter (norepinephrine) controls both responses exerting opposite actions on these two smooth muscles because they have different adrenergic receptor types. Simultaneously, the external sphincter is tonically closed (until opened). Relaxation of the detrusor muscle serves two purposes. First is allows the bladder to be filled. It also, though, allows urine to flow from the ureters into the bladder in one direction only. When detrusor muscle is contracted, the ureters leading into the bladder across this muscle wall are normally pinched closed effectively creating **ureterovesical valves**, which impedes urine flow into the bladder but also prevents back flow into the kidney during bladder voiding. (This limits infection and facilitates unidirectional urine flow.) When the detrusor muscle is relaxed urine can now flow into the bladder from the ureter with the relaxed bladder posing no counter pressure to unidirectional urine flow into the empty bladder.
7) **Bladder emptying.** When the bladder becomes full, parasympathetic control predominates forcing the detrusor muscle to contract (via Ach and M3 muscarinic receptors coupled to Gq/11 and Ca signaling) whilst relaxing the internal sphincter (via Ach and M2/4 receptors coupled Go/i and activation of relaxing K channels) to eject urine from the bladder. Simultaneous relaxation of the external sphincter enables emptying flow out of the bladder. Most contractile Ach signaling is via M1 receptors coupled to Gq/11. It is interesting that the detrusor muscle uses M3. This recent finding sparked development of the latest drugs used to treat incontinence. The contractile state of the skeletal muscle external sphincter is controlled by somatic motor neurons under the voluntary control of the higher brain, which allows the sphincter to open. The external sphincter is defaulted to tonically contract (due to continuous stimulation from the CNS) and it is the voluntary decrease in tonic contraction that allows it to open. Voluntary control of the external sphincter more precisely actually modulates unconscious tonic control provided by the micturition reflex where sensing filling of the bladder inhibits tonic discharge of contractile signals to the external sphincter allowing it to relax. We can override this to some degree by consciously choosing to continue tonic contraction of the external sphincter.

8) **Sensing bladder fullness.** Bladder fullness is sensed by mechanoreceptors lining the bladder wall. Activation of these receptors by stretch sends a signal to the spinal cord eliciting reflex activation of parasympathetic signaling back to the bladder detrusor muscle. The micturition reflex is coordinated with voluntary (learned) control of the external sphincter muscle by modulating input from the higher brain via the midbrain. The micturition reflex involves a positive feedback component localized to the bladder and spinal cord where contraction leads to an increase in pressure which is sensed and causes a further increase in contraction with the micturition reflex occurring more frequently as the bladder fills ultimately leading to maximal contraction of the detrusor muscle and voiding of the bladder. (In contrast, an infrequent micturition reflex response allows relaxation of this reflex arc in a partially filled or empty bladder.)

9) Spontaneous filling and emptying of the bladder under the sole control of the micturition reflex, independent of any input from higher nervous centers, is referred to as the condition of automatic bladder - as apparent in infants. Input from higher brain centers then for the most part is inhibitory of the reflex promoting relaxation of the reflex arc tending to cause relaxation of the detrusor muscle. However, when urinating voluntarily, this input becomes facilitory, promoting the positive feedback cycle of the reflex arc.
Lecture 8 – April 7, 2014
Regulation of H⁺ and HCO₃⁻

Objectives: Understand how the kidney handles H⁺ and HCO₃⁻.

General Comments: After studying this material you should:
1) Understand the importance of the kidney and lungs in acid-base balance
2) Recognize where acid comes form
3) Understand how we buffer acid/base systemically
4) Understand where and how H and bicarb are secreted and reabsorbed in the kidney (i.e. proximal and distal acidification)
5) Know the cellular proteins involved in this transport
6) Recognize the role of glutamine and titratable acids in H and bicarb reabsorption
7) Understand the contribution of the ammonia/ammonium buffering system and ammonium recycling to urinary acidification

Overview:
1) Acid/base balance is accomplished by the coordinated function of the liver, lungs and kidney with the liver adding acid and/or base and the lungs and kidney riding the body of excess acid and/or base.

Acid and base are excreted purely as a consequence of mass action.

2) We maintain plasma pH within 0.02 of 7.4. This is despite continuous ingestion of acids and metabolic production of acid waste. pH of 7.4 = 0.4 x 10⁻⁷ Eq/L H⁺.

There are two types of physiologically relevant acids: H₂CO₃ (volatile) and noncarbonic acids (non-volatile). Volatile acids eventually breakdown into CO₂ and water! These can be exhaled through the lungs. The kidneys ultimately clear non-volatile acids.

3) Sources of acids: Acid (non-carbonic acid; non-volatile) is produced from metabolism (oxidation) of sulfur containing amino acids and cationic amino acids, and by metabolism (hydrolysis) of substances containing acidic phosphate. We also produce CO₂ during metabolism of lipids and carbohydrates, which combines with water to form acid (H₂CO₃; volatile acid). Similarly, we produce alkali by metabolizing anionic amino acids and other organic anions. The 50 to 100 mEq/day net H⁺ production from these reactions is handled by urinary excretion of acid in the form of ammonium and acid phosphate with expiration of CO₂ helping to maintain plasma pH. But we have to do this without plasma pH changing. We employ several buffering systems to limit plasma pH changes until the kidney (non-volatile) and lungs (volatile) can excrete the acid load. Thus, we simply hide the acid generated by metabolism with plasma buffer systems while the acid is in the plasma and uncover the acid at the kidney (or lung) to excrete it.

i.e. H₂SO₄ is created from metabolism of sulfur-containing amino acids. This strong acid is combined with 2 NaHCO₃ (the plasma buffer system) eventually leading to the generation of water and carbon dioxide: H₂SO₄ + 2 NaHCO₃ ⇔ Na₂SO₄ + 2 H₂CO₃ ⇔ 2 H₂O + CO₂ + Na₂SO₄. This rxn. minimizes the decrease in pH as carbon dioxide is exhaled (buffering the acid load), however, the excess (nonvolatile) H (initially from H₂SO₄) must eventually be excreted at the kidney to minimize loss of plasma bicarb.

4) The homeostatic response to these acid and base loads occurs in three stages:
   a. chemical buffering by ECF and ICF buffers
   b. changes in alveolar ventilation to control partial pressure of CO₂
   c. alteration in renal H excretion (and bicarb. reabsorption/regeneration) to regulate the plasma bicarbonate concentration.

Chemical buffering (in the ECF) and respiratory buffering are almost immediate, but have finite capacity. ICF buffering is slower and involves the transferring of H and/or bicarb. into and out of the ICF. Long term pH regulation occurs through the kidney’s ability to excrete acid and reabsorb bicarbonate, which is used to buffer the plasma.

5) What is Buffering?
Chemical buffering is due to the conversion of a strong acid (i.e. HCl) into a weak acid, such as H₂CO₃ or H₂NaPO₄, through a chemical reaction with a weak buffer base, such as NaHCO₃ or Na₂PO₄. The higher the concentration of the weak base, the better it buffers. The weaker the resulting acid, the better the buffering.

The strength of an acid depends upon its dissociation constant (Kₐ). A weak acid when dissolved yields few protons and has a small Kₐ. A strong acid, on the other hand, has a high Kₐ releasing many protons. pK is the negative log of Kₐ: pK = log (1/Kₐ). Thus, strong acids have a low pK.
Titration of buffers: when an acid dissociates into $H^+$ and buffer base ($A^-$), the mass action equilibrium is:

$$HA \rightleftharpoons H^+ + A^-,$$

where the dissociation constant $K_d = [H^+] [A^-] / [HA]$.

and thus, $[H^+] = K_d \times ([HA]/[A^-])$

When $[HA] = [A^-]$, then $[H^+] = K_d$

Since $pH = -\log [H^+]$, rearranging $K_d = [H^+] [A^-] / [HA]$ yields, $pH = pK + \log ([A^-]/[HA])$. When $[HA] = [A^-]$ (ie. at equilibrium), $\log ([A^-]/[HA]) = \log 1 = 0$, so $pH = pK$.

6) Isohydric principle: When a solution (or compartment) contains more than one buffer, all buffer pairs ($HA$ and $A^-$) in the system are in equilibrium with the same proton concentration.

7) Physiological buffer systems:
   a. $HCO_3^-/CO_2$ – most powerful buffer in the plasma and interstitial fluid
   b. bicarbonate from bone
   c. histidine groups of intracellular proteins (in particular on hemoglobin)
   d. intra and extracellular phosphates.

$$Hb + H^+ \rightleftharpoons HbH,$$
$$HCO_3^- + H^+ \rightleftharpoons H_2CO_3,$$
$$HPO_4^{2-} + H^+ \rightleftharpoons H_2PO_4^-,$$
$$Pr^- + H^+ \rightleftharpoons HPr$$

So in the ICF, $H^+ + Hb + Pr^- + HPO_4^{2-} \rightleftharpoons HbH + HPr + H_2PO_4^-$

And in the ECF, $H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons CO_2 + H_2O$, with bone contributing extra bicarb.

In the kidney, ammonia also becomes an important buffer with $H^+ + NH_3 \rightleftharpoons NH_4^+$

These buffers combine to maintain ECF and ICF pH within 0.3-0.4 units of their normal values as long as their capacity to bind protons is not exceeded. Since we are constantly generating acid (protons), we must have a mechanism to rid our body of this acid. This is where the kidney and lungs come into play.

8) Bicarbonate/CO2 system – involves both kidney and lung function.

Recall that dissolved $CO_2$ and water can form carbonic acid ($H_2CO_3$), which quickly dissociates into $H^+$ and $HCO_3^-$.

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

Since water is never limiting, its equilibrium with dissolved $CO_2$ and $H_2CO_3$, is a constant dependent on $[CO_2]$ level with $H_2CO_3 = K_1 \times [CO_2]$.

Carbonic anhydrase speeds up the formation/breakdown of carbonic acid. Thus,

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$$

From the mass action equilibrium then for dissociation: $K_d = ([H^+] \times [HCO_3^-])/[CO_2] \times K_1$

Because $[CO_2]$ dissolved in a solution is dependent on its partial gas pressure, where $[CO_2] = \alpha \times P_{CO_2}$ and $-\log K_d \times K_1 = 6.1$, and $\alpha = 0.03$, we get: $pH = 6.1 + \log ([HCO_3^-]/0.03 \times P_{CO_2})$.

If we assume carbon dioxide to be the conjugate acid, then $CO_2 \rightleftharpoons H^+ + HCO_3^-$. Recognize that this is not a true equilibrium, many intermediate steps are missing; however, it is useful when considering the two regulatory sites modulating acid-base balance: the lungs (controls $P_{CO_2}$) and kidney (controls bicarb.)

9) The $HCO_3^-/CO_2$ buffering system is an open system because one of its components $CO_2$ is volatile and thus, even though its effective $pK$ is much lower than 7.4, it is an effective buffer of plasma pH around 7.4. Simply put, we can control plasma $CO_2$ levels by modulating breathing and thus, $CO_2$ can be maintained constant as it is consumed or liberated in the buffering of protons.

Consider the following example: The ECF contains 24 mM Na$HCO_3$ and its partial pressure due to $CO_2$ is 40 mmHg. Then $pH = 6.1 + \log (24/0.03 \times 40) = 7.4$. 

As long as we can maintain partial pressures of CO₂ close to 40 mmHg, we can maintain pH. This is the respiratory component for controlling plasma pH. It is fast, dependent on changes in alveolar ventilation, but limited in its ability to buffer due to limitations of hypoxia and consumption of bicarb. Obviously, we also need to bring in oxygen, so we cannot just let respiration handle buffering, and we still must titrated protons generated from nonvolatile acids, which consume bicarb.

The conclusion from this is that the resulting pH change in an open system is much smaller than in a closed system where CO₂ sticks around. Thus, for a buffer pair where the weak acid (ultimately CO₂) is volatile, buffering is very efficient.

10) Add regulation: alveolar ventilation (and thus, inspiration and expiration) are under neuronal control. We have central and peripheral chemoreceptors that sense both PₐCO₂ and H⁺. Increases in alveolar ventilation reduces PₐCO₂ and thus, H⁺: (CO₂ ⇔ H⁺ + HCO₃⁻). Conversely, decreases in alveolar ventilation increase both PₐCO₂ and H⁺ to reduce pH. Obviously, this system then eventually becomes limited by the presence of HCO₃⁻ in the plasma.

Bicarbonate is an effective buffer of only noncarbonic acids, it however, cannot buffer carbonic acid, because bicarb. plus protons generate carbonic acid. This carbonic acid must be buffered by ICF buffers until exhaled.

12) The kidneys’ role in acid-base balance - The kidney secretes H and recclaims bicarb. to rid the body of non-volatile acids and maintain plasma bicarb levels and thus, pH. These processes are not directly regulated by hormones, but respond to plasma pH.

Summary: a. The kidneys excrete 50 to 100 mEq of noncarbonic acid generated each day.  
  b. This is achieved by H secretion, although mechanisms for this differ in proximal acidification at the PT, TAL (Na/H exchange), and distal acidification at the collecting duct (H-ATPases).  
  c. We cannot simply excrete free H⁺.  
  d. We also must reabsorb the filtered bicarb, because excreting bicarb is equivalent to adding acid to the blood.  
  e. We excrete H by binding it to other filtered, titratable buffers, such as HPO₄²⁻ and/or use an additional buffering system: NH₃/NH₄⁺. NH₄⁺ is generated by metabolizing glutamine at the PT.  
  f. ECF pH is the primary regulator of these kidney functions; however, in pathological states, volume, ECV, aldosterone and plasma K can affect acid excretion.

Metabolism of amino acids in the liver produces urea and glutamine (from NH₄⁺) consuming bicarb., as well as, producing strong acids, which also consumes bicarb. during buffering. In the blood, urea and glutamine do not affect pH, and the acid load is transferred back to the non-volatile, titratable acid bases, such as SO₄²⁻ and HPO₄²⁻ as we reabsorb bicarb. In addition the acid hidden in glutamate is uncovered as we regenerate bicarb. to excrete ammonium. Note, excreting titrated acids and ammonium keep the free H concentration in urine low. This is because we can generate urine only to a pH of 4.5. By maintaining urinary H low, this keeps the energy required for active H secretion low and also lowers the disruptive power of high, free H concentrations.

13) Renal hydrogen excretion: two steps 1) reabsorption of filtered bicarb. and 2) secretion of H⁺.

We have to reabsorb the entire filtered load of bicarb. If we don’t, this is like adding acid to the system. The filtered load of bicarb. is 180 L/day (GFR) x 24 mM (plasma [HCO₃⁻]) = 4300 mM/day.

Secretion of H and reabsorption of bicarb. are dependent on the activity of carbonic anhydrase!

a) If the secreted H combines with a filtered bicarb, we reabsorb the bicarb.

b) If the secreted H combines with a titratable acid base or ammonia we regenerate bicarb that was consumed at the liver buffering strong acids or producing urea/glutamate.

Net acid excretion = titratable acidity + NH₄⁺ - urinary HCO₃⁻

14) Secretion at the PT (proximal acidification). H is secreted in exchange with Na reabsorption. This is a secondary active process. H is generated from CO₂ and water through the actions of intracellular CA. The liberated bicarb. exits the cell on the basolateral Na/bicarb cotransporter or via the Cl/bicarbonate exchanger. The secreted hydrogen binds to filtered bicarb in the lumen and through the actions of CA generates carbon dioxide and water. The carbon dioxide diffuses back into the cell. The PT also can metabolize glutamine to yield bicarb and ammonium. This extra bicarb. enters the interstitium and the ammonium the urine (using the Na/H exchanger).

15) Secretion at the collecting duct (distal acidification). H is secreted through alpha intercalated cells by an active process either using the luminal H/K-ATPase or H-ATPase. Secreted H comes originally from carbon dioxide and water as in the PT. Bicarb exits through the basolateral membrane via the bicarb/Cl exchanger. Secreted H complexes with titratable acid.
bases in the urine or ammonia (there is little filtered bicarb. left in the urine by now). Since this is a primary active process, we can actually decrease urinary pH to ~ 4.5, which will titrate sulfuric and phosphoric acids and form ammonium. Recall that we can secrete bicarb. with beta intercalated cells if this becomes necessary during alkalosis.

16) Bicarbonate reabsorption: PT = 90%, TAL = 8%, collecting duct = 2%
Titration of acids happens mostly at the collecting duct and is dependent on urine pH decreasing.
Generation of ammonium happens at the PT.

17) Ammonium excretion/recycling. NH$_4^+$ is lipid insoluble and thus trapped in the urine. Note that NH$_3$ is freely diffusible. Since it is freely diffusible, as it is consumed by H to form ammonium, more diffuses into the lumen. Thus, it is quite a powerful buffer, and is almost an open system. There are actually 3 steps: a. ammonium is produced in the PT, b. ammonium is partially reabsorbed in the TAL and the ammonia recycled within the renal medulla (like urea but opposite direction), c. medullary ammonia diffuses into the collecting duct where it is trapped as ammonium.

18) Generation of ammonium at the PT. Glutamine $\rightarrow$ NH$_4^+$ + glutamate $\rightarrow$ NH$_4^+$ + $\alpha$-ketoglutarate $\rightarrow$ 2 HCO$_3^-$
Result is that two ammonium and two bicarb are generated. Ammonium exits on the luminal Na/H exchanger and the bicarb. on the serosal bicarb./Cl and Na/bicarb. transporters.

<table>
<thead>
<tr>
<th>Renal Excretion of Hydrogen Ion in Different States of Acid/Base Balance</th>
<th>Alkalosis</th>
<th>Normal</th>
<th>Acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titratable Acidity (mmol/day)</td>
<td>0</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>plus Urinary NH$_4^+$ (mmol/day)</td>
<td>0</td>
<td>40</td>
<td>160</td>
</tr>
<tr>
<td>minus Urinary Bicarbonate (mmol/day)</td>
<td>80</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total (mmol/day)</td>
<td>-80</td>
<td>59</td>
<td>200</td>
</tr>
<tr>
<td>H$^+$ added to blood</td>
<td>H$^+$ removed from blood</td>
<td>H$^+$ removed from blood</td>
<td></td>
</tr>
<tr>
<td>Urine pH</td>
<td>8.0</td>
<td>6.0</td>
<td>4.6</td>
</tr>
</tbody>
</table>
Lecture 9 – April 10, 2014
Acid-base challenges

**Objectives:** Understand acid-base regulation in humans.

**General Comments:** After studying this material you should:

1) Understand the kidney’s role in acid-base balance
2) Understand the lung’s role in acid-base balance
3) Know what acidosis and alkalosis mean
4) Understand simple acid base disorders
5) Recognize mixed acid-base disorders and understand dysfunction associated with them
6) Understand renal and lung compensation mechanism
8) Recognize the importance of anion gap
9) Understand how electrolyte and acid-base disorders are relate

**Overview:**

1) Processes that raise plasma pH are called alkalosis. If plasma pH is increased it is called alkalemia. Conversely, processes that decrease plasma pH are called acidosis and a decrease in pH is referred to as academia.

2) In general acidosis leads to academia and alkalosis leads to alkalemia; however, in mixed acid-base disorders, this is not always true with both existing at the same time.

3) Normal pH is 7.4 with plasma bicarbonate levels being 24 mM and plasma CO₂ contributing 40 mmHg of partial pressure. Recall the simplified equality: CO₂ ⇌ H⁺ + HCO₃⁻. Realize it’s the H that affects pH.

4) Alveolar ventilation (AV) modulates P_CO₂. Increased AV allows us to blow off more carbon dioxide, which decreases P_CO₂ leading to a decrease in H and thus, an increase in pH. Conversely, decreased AV leads to increases in H and decreases in pH. This is the respiratory component of acid base-balance.

5) Renal acid secretion and bicarbonate reabsorption/regeneration are interlinked. Any renal event that increases bicarbonate reabsorption will also increase pH. Conversely, decreased bicarbonate reabsorption decreases pH. This is the renal component of acid-base balance.

6) A defect in lung function can be compensated for by the kidneys. Alternatively, a defect in renal function can be compensated for by the lungs.

7) Acid-base disorders come in to varieties: acidosis and alkalosis. These can be further divided according to the primary cause:
   a. respiratory – dysfunction of the lung
   b. metabolic – dysfunction outside of the lung
      1. renal
      2. extrarenal

Respiratory acidosis/alkalosis is compensated by kidney function. Metabolic acidosis/alkalosis is compensated by both kidney and lung function, unless the dysfunction is a renal malady where only the lungs then compensate.

8) Simple acid base disorders: Easily understood by using the following equality and making the following table:

<table>
<thead>
<tr>
<th>Malady</th>
<th>P_CO₂ (in mmHg)</th>
<th>HCO₃⁻ (in mM)</th>
<th>pH</th>
<th>Compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>40</td>
<td>24</td>
<td>7.4</td>
<td>None</td>
</tr>
<tr>
<td>respiratory alkalosis</td>
<td>&lt; 38</td>
<td>24</td>
<td>&gt; 7.42</td>
<td>Renal increase in HCO₃⁻ excretion</td>
</tr>
<tr>
<td>respiratory acidosis</td>
<td>&gt; 42</td>
<td>&lt; 7.38</td>
<td>7.38</td>
<td>Renal increase in HCO₃⁻ reabsorption</td>
</tr>
<tr>
<td>metabolic alkalosis</td>
<td>≥ 26</td>
<td>&lt; 7.42</td>
<td>7.42</td>
<td>Decreased AV</td>
</tr>
<tr>
<td>metabolic acidosis</td>
<td>≤ 22</td>
<td>&gt; 7.38</td>
<td></td>
<td>Increased AV</td>
</tr>
</tbody>
</table>

Use the Henderson-Hasselbach equation to convince yourself of these number!

Note that compensation does not ameliorate the dysfunction but simply resists pH changes. The primary cause must be treated in any acid-base disorder to return to a normal steady state.
9) Until compensation can correct for the defect (it never does entirely), we must buffer the acid or base load. We do this with the bicarbonate buffer in plasma and ICF buffers, which are protein (i.e. Hb) and phosphates. Realize that an event that affects the plasma also eventually affects the ICF.

10) Speed of compensation: plasma buffering is fast (ECF), cellular buffering (ICF) and respiratory buffering are intermediate and renal buffering slow.

11) Simple acid-base disorders expanded.

Metabolic acidosis
Characterized by low plasma [HCO₃⁻] and low pH. Can develop through addition of non-volatile acids to the body (i.e. diabetic ketoacidosis), loss of non-volatile alkali (i.e. diarrhea), or with renal failure resulting in the inability to secrete H to titrated nonvolatile acids and reabsorb bicarbonate.

Most common imbalance.

Initial compensation is an increase in AV due to the fall in pH. This minimizes a further fall in pH. This happens quickly. The second phase of compensation is tissue buffering and the third (1-5 days) is renal compensation.

The kidney cannot compensate metabolic acidosis which results from a kidney defect.

When nonvolatile acid is added to the body, H increases and bicarb. decreases. In addition, the anion (base) associated with the nonvolatile acid increases. This presents a convenient way to analyze the cause of metabolic acidosis by calculating the anion gap.

$$\text{Anion gap} = [\text{Na}^+] - [\text{Cl}^-] - [\text{HCO}_3^-],$$

normally this anion gap is 8 to 16 mEq/L. If the anion of the nonvolatile acid is Cl⁻ (due bicarb. loss resulting in increases in Cl, as seen in diarrhea and renal tubular acidosis) the anion gap will be normal; however, if the nonvolatile acid is not associated with Cl, such as metabolic acids associated with diabetes the anion gap will increase.

Metabolic alkalosis:
Characterized by elevation of bicarb. and pH. Caused by addition of nonvolatile alkali to the body (i.e. ingestion of antacids), a decrease in ECV, or most commonly from a loss of nonvolatile acids, such as HCl during vomiting.

Initially response is a decrease in AV due to the pH rise, but this is limited to some extend by ensuing hypoxia. The intermediate response is ECF and ICF buffering. Finally the renal compensation is to excrete more bicarb., by reducing its reabsorption.

If metabolic alkalosis is associated with ECV decreases (ie. massive vomiting), we cannot have renal compensation due to decreased bicarb. reabsorption, because Na and bicarb. are reabsorbed together with volume depletion driving the reabsorption at the expense of acid-base balance.

Respiratory acidosis:  
Marked by decreased AV and increased P_{CO₂} and decreased pH.

Compensation is first to buffer in ICF (little ECF buffering) and then a renal component. Renal compensation is so slow that we divide this malady into an acute phase lasting 0-2 days where ICF buffering prevails, and a chronic phase after several days where renal compensation of increased bicarb. reabsorption and regeneration and ammonium excretion come into play.

Respiratory alkalosis:
Increased AV and reduced P_{CO₂}.

Buffering is mostly from ICF with long-term compensation coming from reduced renal reabsorption of bicarb. and ammonium excretion.

12) Realize that compensation just resists further changes in pH and does not fix the problem. The primary insult must be reversed to return to a normal steady state. Also realize that compensation is finite and saturatable. As a rule of thumb, respiratory compensation of metabolic alkalosis is limited due to hypoxia.

13) Mixed acid base disorders:
a. pH is near normal but $P_{CO_2}$ and/or HCO$_3^-$ are not. Opposite disorders.
b. pH is extreme and bicarb. and/or carbon dioxide appear relatively normal. Compounding disorders.

i.e. emphysema with vomiting: can result in respiratory acidosis and metabolic alkalosis. Acidosis would cause the $P_{CO_2}$ to increase with some increase in bicarb. Alkalosis would result in increased bicarb. and some increase in $P_{CO_2}$ but pH may remain near normal.

i.e. emphysema with diabetes: can result in respiratory acidosis and metabolic acidosis. Respiratory acidosis would cause an increase in $P_{CO_2}$ with some increase in bicarb. The metabolic acidosis would cause a decrease in bicarb. with some effect on $P_{CO_2}$ but both would result in a decrease in pH.

15) Effects on ECV. Bicarb. is reabsorbed in the PT in a Na dependent manner. Thus, ECV, which is dependent on Na and controls Na balance, can influence acid-base balance and visa-versa.

Example: Metabolic alkalosis associated with volume depletion results in increased AngII driving Na reabsorption in the PT. This is associated with an increase in bicarb. reabsorption; however, if volume depletion is associated with alkalosis, this will exacerbate the condition.