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MASSACHUSETTS INSTITUTE OF TECHNOLOGY

**Departments of Electrical Engineering, Mechanical Engineering,
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6.022J/2.792J/HST542J: Quantitative Physiology: Organ Transport Systems

RENAL PHYSIOLOGY

Text Reference: Chapters 6 and 7

RENAL PHYSIOLOGY

These notes will present supplementary material, but are not meant to replace standard texts. Students are encouraged to read chapters 6 and 7 in the textbook by Costanzo.

I. INTRODUCTION

The kidneys are critical in regulating the internal environment of the body. In particular, they regulate the total body water, as well as a number of substances which are essential to life. We will focus on the following major topics:

- **Body Fluid Compartments**

- **The Functional Anatomy of the Kidney**

- **Basic Renal Mechanisms**
 - Glomerular Filtration
 - Tubular Absorption
 - Tubular Secretion
 - Overall Mass Balance for the Kidneys

- **Renal Regulation of:**
 - Sodium
 - Extracellular Volume and Osmolarity
 - pH

II. Body Fluid Compartments

Total body water (TBW) is approximately 60% of body weight. It is distributed as intracellular water (ICW) and extracellular water (ECW).

Intracellular water is the largest compartment, comprising approximately 40% of body weight. Extracellular water is about 20% of body weight. (Note the 20, 40, 60 rule for ECW, ICW, and TBW respectively.) Figure 1 shows the approximate sizes of the body fluid compartments.

Note that ECW is divided into interstitial fluid (16% of body weight), and blood *plasma* (4% of body weight).

Composition of the body fluid compartments differs markedly as shown in Figure 2. Extracellular fluid contains mostly sodium cations, and chloride anions. Interstitial fluid and plasma are very similar except for the higher concentration of protein in the plasma. On the other hand, intracellular fluid is rich in potassium cations and organic phosphate anions, with very little sodium and chloride.

Figure 1
(From Valtin 1983)

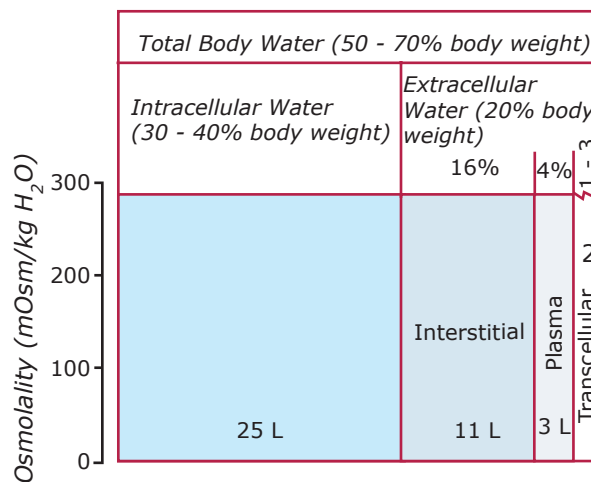


Figure by MIT OCW. After Valtin, Heinz. 1983. *Renal Function: Mechanisms Preserving Fluid and Solute Balance in Health*. Little, Brown.

Normal fluid compartments for a 70 kg man. Although there is considerable variation between individuals, a “20, 40, 60” rule is helpful for estimating the percentage of total body weight comprised of extracellular (ECW), intracellular (ICW), and total body water (TBW) respectively.

Figure 2
(From Valtin 1983)

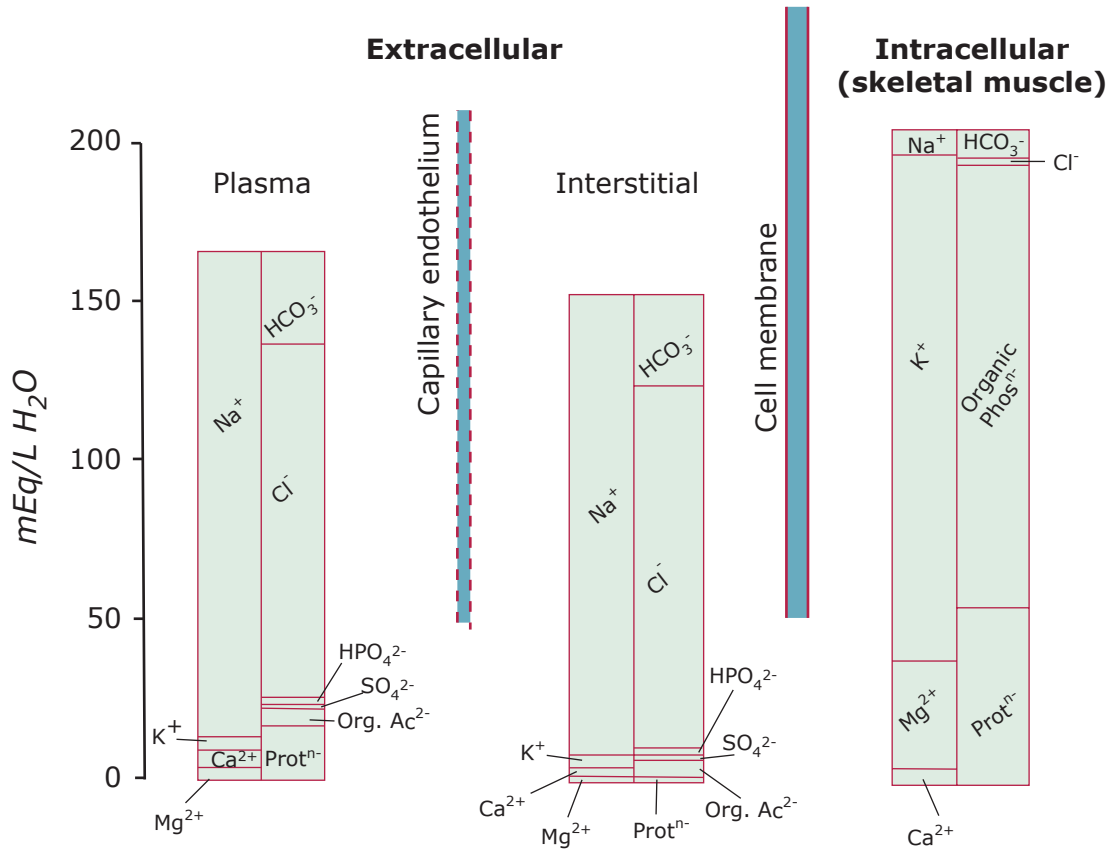


Figure by MIT OCW. After Valtin, Heinz. 1983. *Renal Function: Mechanisms Preserving Fluid and Solute Balance in Health*. Little, Brown.

Solute composition of the major body fluid compartments. Compartments are primarily composed of concentrations of electrolytes that balance charge such that each compartment is electrically neutral.

Why the difference? The intracellular compartment is separated from the extracellular compartment by cell membranes. This barrier is selectively permeable, and contains active sodium-potassium pumps which maintain the concentration differences. Plasma and interstitial fluid compartments are separated by capillary endothelium, which allows free passage of ions, but is not permeable to large protein molecules. *Water moves freely across all boundaries.*

Although the ionic compositions of the body fluid compartments are quite different, all compartments are in osmotic equilibrium. The normal osmolarity is about 300 milliosmoles/kg of H₂O. Adding solutes to any compartment will result in rapid movement of water so as to maintain osmotic equilibrium across compartments. In all compartments, cations constitute approximately half of the osmoles. Since there is osmotic equilibrium across compartments, it follows that the concentration of total cation is essentially equal throughout the body water.

Example:

A 70 Kg. man has a low serum sodium of 125 mEq per liter. How many mEq of sodium must be added to his body to bring the serum sodium concentration up to the normal 140 mEq/L?

Answer:

Total body water = approximately 42 liters (60% x 70 Kg.).

Total body cation content = 125 mEq/L x 42 = 5250 mEq.

New cation content 5,250 + x mEq.

New cation concentration = (5,250 + x)/42 mEq/L

New cation concentration in plasma = 140 mEq/L

For osmotic equilibrium:

$$(5,250 + x)/42 = 140 \text{ mEq/L}$$

$$5,250 + x = 5,880$$

$$x = 630 \text{ mEq.}$$

In the above example it is important to note that the sodium does not enter the intracellular compartment. Instead, water leaves the cells thereby raising the intracellular potassium concentration from 125 to 140 mEq/L.

Normal values for some common substances are shown in Table 1.

Table 1
(From Valtin 1983)

Substance	Range	Average Value Usually Quoted	Comments
Bicarbonate	24 to 30 mM/L ^a	24 mEq/L ^b	^a Venous plasma ^b Arterial plasma, which is commonly sampled in patients with problems of H ⁺ balance
Calcium	4.5 to 5.5 mEq/L	10 mg/100 ml	Approximately 50% is bound to serum proteins
Chloride	96 to 106 mEq/L	100 mEq/L	
Creatinine	0.7 to 1.5 mg/100 ml	1.2 mg/100 ml	
Glucose	70 to 100 mg/100 ml	80 mg/100 ml ^c	^c Determined in the fasting state; so-called fasting blood sugar (FBS)
Hematocrit (Hct)	40 to 50%	45%	Also called packed cell volume (PCV)
Hydrogen ion concentration [H ⁺] (arterial)		40 nEq/L	Note that units are nanoequivalents per liter
Osmolality	280 to 295 mOsm/kg H ₂ O	287 mOsm/kg H ₂ O ^d	^d A value of 300 is often used because it is a round figure that is easy to remember. This approximation does not introduce important quantitative error in most computations for evaluation of fluid and solute balance
Pco ₂ (arterial)	37 to 43 mm Hg	40 mm Hg	
Po ₂ (arterial)	75 to 100 mm Hg	—	While breathing room air. Value varies with age
pH (arterial)	7.37 to 7.42	7.40	
Phosphate ^e	2 to 3 mEq/L	3.5 mg/100 ml	^e Measured as phosphorus. The exact concentration of phosphate in milliequivalents per liter depends on pH of plasma
Potassium	3.5 to 5.5 mEq/L	4.5 mEq/L	
Protein (total)	6 to 8 g/100 ml	7 g/100 ml	
Sodium	136 to 146 mEq/L	140 mEq/L	
Urea nitrogen (BUN)	9 to 18 mg/100 ml	12 mg/100 ml ^f	^f Measured as the nitrogen contained in urea. Since urea diffuses freely into cells, values for serum, plasma, or whole blood are nearly identical (BUN = blood urea nitrogen). Average value varies with diet; BUN of 18 mg/100 ml may be normal or may reflect considerable reduction in renal function

Normal plasma, serum, or blood concentrations in adult humans.

Table by MIT OCW. After Valtin, Heinz. 1983. *Renal Function: Mechanisms Preserving Fluid and Solute Balance in Health*. Little, Brown.

III. FUNCTIONAL ANATOMY OF THE KIDNEY

This subject is well covered in the texts, and will not be repeated here. Students should be familiar with the anatomy of the kidney, ureters, bladder, and the detailed organization of the nephron, including tubular and vascular components. The anatomy of the juxtaglomerular apparatus is important.

IV. BASIC RENAL MECHANISMS

Urine formation begins with *filtration* of protein-free plasma into Bowman's capsule. The filtrate is modified as it passes through the nephron by *tubular reabsorption* and/or *tubular secretion*. Different substances are handled differently by the kidney. (See Figure 3.)

Figure 3
(From Valtin 1983)

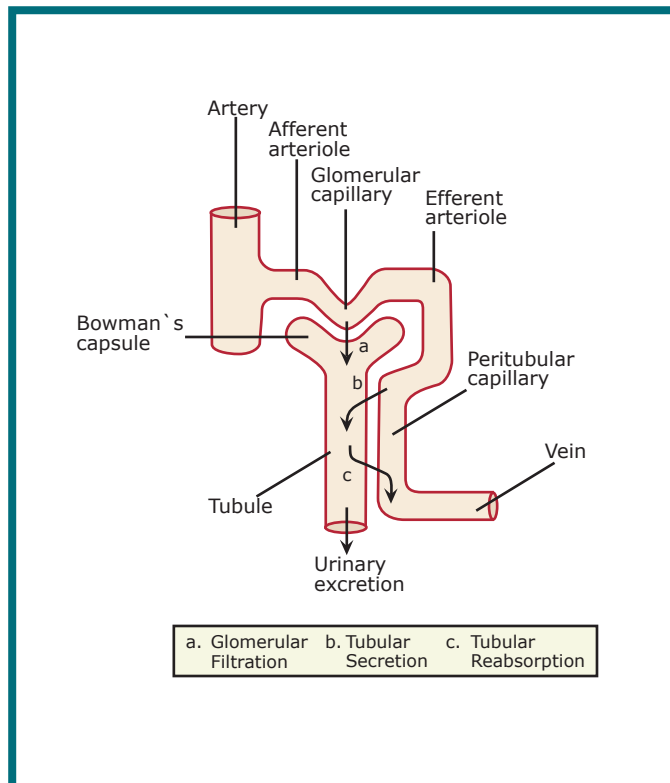


Figure by MIT OCW. After Valtin, Heinz. 1983. *Renal Function: Mechanisms Preserving Fluid and Solute Balance in Health*. Little, Brown.

Schematic of the three basic renal system functions: glomerular filtration, tubular secretion, and tubular reabsorption.

A. Glomerular Filtration

The formation of urine begins with a passive ultrafiltration process, in which the movement of water and associated dissolved small molecules is determined by hydrostatic and oncotic pressures. Glomerular capillaries are about 100 times more permeable to water and crystalloids than are muscle capillaries. Note that the plasma oncotic pressure rises as fluid moves along the capillary (due to net loss of water into Bowman's space). Typical Starling forces are shown diagrammatically in Figure 4.

Typical glomerular filtration rate (GFR) is ~ 180 liters per day, or 125 ml/min. Of this enormous amount, only 1-2 liters per day are excreted as urine, implying that 99% of the filtered volume is reabsorbed.

Important factors in determining GFR:

- Balance of “Starling Forces”:
 - resistance of afferent and efferent arterioles
 - arterial blood pressure
 - venous pressure
 - osmotic pressure
- Permeability of glomerular capillary
- Surface area of capillaries
- Plasma flow rate

In general, GFR can be *increased* by:

- increasing arterial BP
- decreasing afferent arteriolar tone
- increasing efferent arteriolar tone
- increasing plasma flow rate (in cases where filtration equilibrium exists).

Figure 4
(From Valtin 1983)

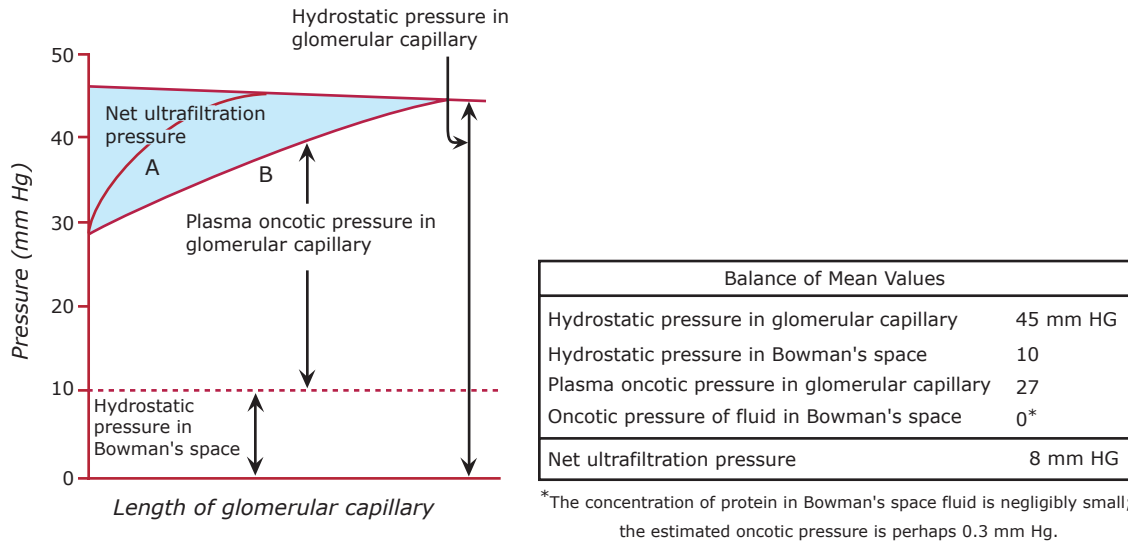


Figure by MIT OCW. After Valtin, Heinz. 1983. *Renal Function: Mechanisms Preserving Fluid and Solute Balance in Health*. Little, Brown.

Starling forces involved in glomerular ultrafiltration (rat). Ultrafiltration pressure declines in the glomerular capillaries due to plasma oncotic pressure increase. In contrast the decline of ultrafiltration pressure in extrarenal capillaries is mainly due to decreases in intracapillary hydrostatic pressure. The point at which the plasma oncotic pressure balances the hydrostatic pressure in the glomerular capillary is termed “filtration equilibrium.”

Autoregulation

The kidney exhibits dramatic autoregulation of renal blood flow and glomerular filtration rate over a wide range of perfusion pressures above 80 mmHg. (See Figure 5.)

Figure 5
(From Valtin 1983)

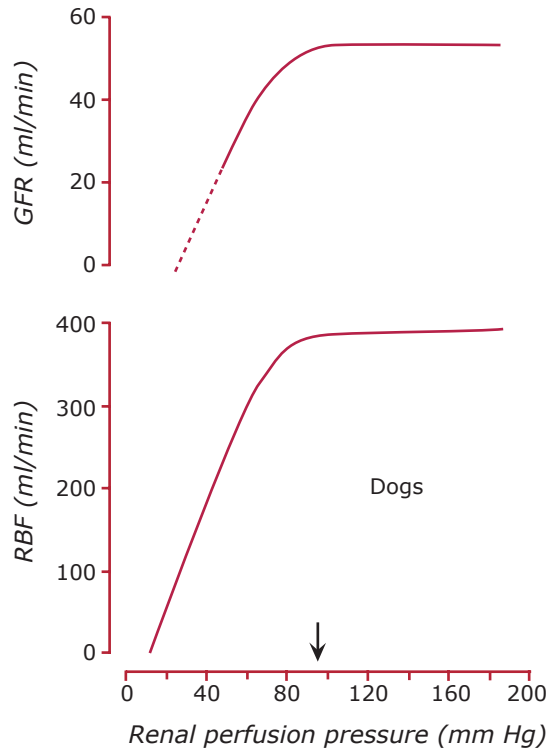


Figure by MIT OCW. After Valtin, Heinz. 1983. *Renal Function: Mechanisms Preserving Fluid and Solute Balance in Health*. Little, Brown.

Autoregulation of glomerular filtration rate (GFR) and renal blood flow (RBF) as a function of renal perfusion pressure. The normal mean renal artery pressure is indicated by the arrow. Since both GFR and RBF remain constant in the autoregulatory range (in this example, 80-180mmHg), the net change in resistance must occur in the afferent arterioles.

B. Tubular Reabsorption

Most substances filtered through the glomerulus are reabsorbed by the tubules of the kidney into interstitial fluid, and thence into the blood. Reabsorption conserves substances which are essential to normal function such as water, glucose, amino acids, and electrolytes. (See Table 2.)

Table 2
(From Valtin 1983)

Daily renal turnover of H₂O, Na⁺, HCO₃⁻, and Cl⁻ in an adult human					
		Filtered	Excreted	Reabsorbed	Proportion of Filtered Load That is Reabsorbed (%)
H ₂ O	L/day	180	1.5	178.5	99.2
Na ⁺	mEq/day	25,000	150	24,850	99.4
HCO ₃ ⁻	mEq/day	4,500	2	4,498	99.9+
Cl ⁻	mEq/day	18,000	150	17,850	99.2
Glucose	mM/day	800	≈ 0.5	799.5	99.9+

Table by MIT OCW. After Valtin, Heinz. 1983. *Renal Function: Mechanisms Preserving Fluid and Solute Balance in Health*. Little, Brown.

The reabsorptive process may be *active* or *passive*. Some reabsorption processes are characterized by a *transport maximum*, T_m . A good example is that of glucose. This molecule is actively reabsorbed, up to a maximum amount per unit time. When the filtered load is less than T_m , then no glucose appears in the urine. When the filtered load exceeds T_m , then glucose is excreted. (See Figure 6.)

Figure 6
(From Marsh 1983, p. 44)

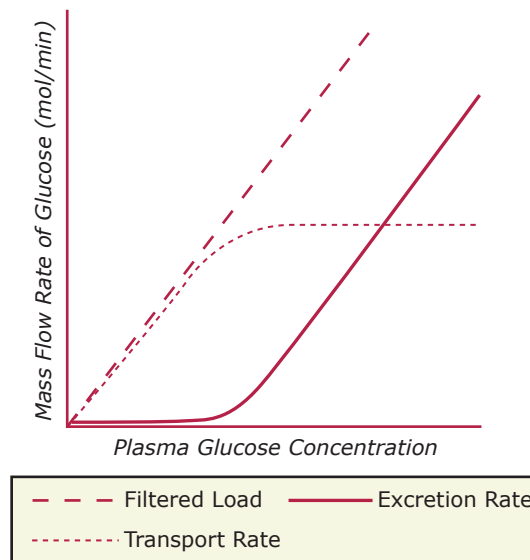


Figure by MIT OCW. After Marsh 1983, p. 44.

The filtered load of glucose, the excretion rate, and the transport rate are affected by the plasma glucose concentration. The rate of transport is the difference between the filtered load and the excretion rate. Note that the transport rate varies with concentration when the concentration of plasma glucose is low but not when it is high. This relationship suggests a saturable transport mechanism.

C. Tubular Secretion

The kidney can secrete certain substances from blood in the peritubular capillaries into the tubular lumen. Mechanisms may be either active or passive.

Probably of most importance to the regulatory function of the kidney is the ability to secrete hydrogen ion and potassium ion. This capability is central to pH regulation.

Most of the other substances secreted are foreign to the body, such as drugs. An important indicator substance used in measuring renal function is para-aminohippuric acid (PAH) which is actively secreted into the tubule, such that it is almost completely removed in a single pass through the nephron. This approximation holds only if PAH is present in low concentration. (See Figure 7.)

Figure 7
(From Marsh 1983, p. 45)

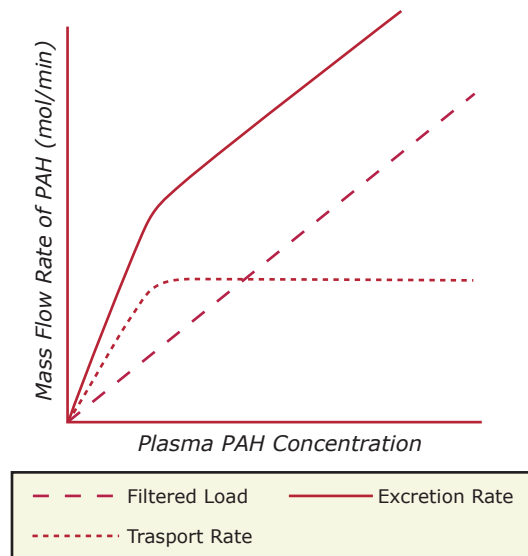


Figure by MIT OCW. After Marsh 1983, p. 45.

The excretion rate, transport rate, and the filtered load of *p*-aminohippuric acid (PAH) as affected by the plasma concentration. PAH is secreted.

D. Overall Mass Balance for the Kidneys

The following figure is a simplified schematic of the kidneys. It represents the function of both kidneys.

Figure 8

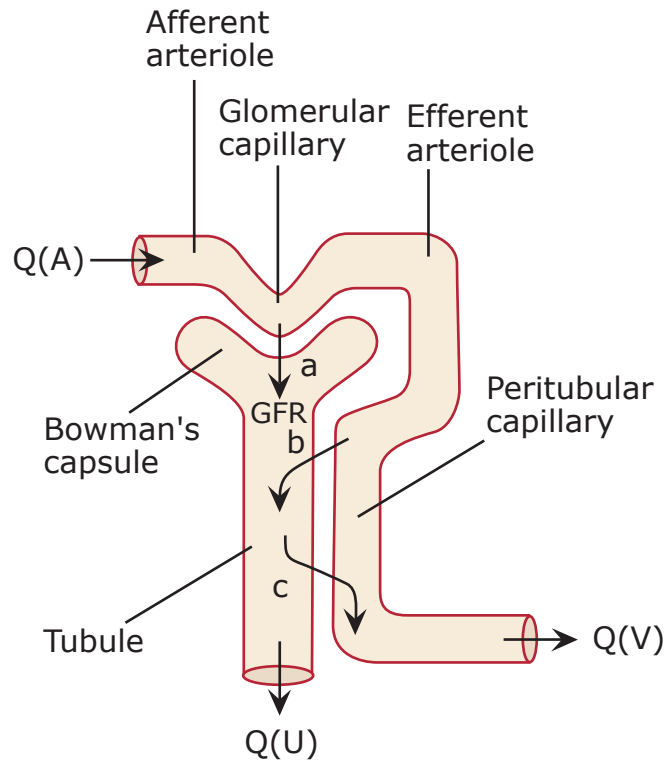


Figure by MIT OCW. After Valtin, Heinz. 1983. *Renal Function: Mechanisms Preserving Fluid and Solute Balance in Health*. Little, Brown.

Definitions:

$Q(A)$ = arterial flow rate (cc/min.)

$Q(V)$ = venous flow rate (cc/min.)

$Q(U)$ = urine flow rate (cc/min.)

$c(i,A)$ = concentration of the i -th molecular species in arterial blood

$c(i,V)$ = conc. of i -th species in venous blood

$c(i,U)$ = conc. of i -th species in urine.

The overall conservation of fluid in the control volume shown in the figure is:

$$Q(A) = Q(V) + Q(U) \quad (1)$$

For any particular molecular species, i , the conservation of mass would yield:

$$Q(A) * c(i,A) = Q(V) * c(i,V) + Q(U) * c(i,U) \quad (2)$$

Using equation (1) and combining with (2) to eliminate $Q(V)$, we get:

$$Q(A) = Q(U) * [c(i,U) - c(i,V)] / [c(i,A) - c(i,V)] \quad (3)$$

Equation (3) may be used to experimentally measure renal blood flow, $Q(A)$, if we can measure the concentration of the indicator, i , in urine and in both arterial and renal vein blood. It is relatively easy to measure arterial blood concentrations, but rather difficult to measure concentrations in renal venous blood (although it can be done). Fortunately there is a substance—para-aminohipuric acid (PAH)—which is almost completely removed from the blood in one pass through the kidney. Thus, for PAH the concentration in renal venous blood may be taken as zero - $c(\text{PAH},V) = 0$. Under these conditions:

$$Q(A) = Q(U) * c(\text{PAH},U) / c(\text{PAH},A) \quad (4)$$

This measurement yields the effective renal blood flow. It assumes that indicator concentrations in whole blood are given. If the more usual plasma concentrations are used, then equation (4) will yield renal plasma flow (RPF). RPF is approximately 600-700 cc/min. in the normal adult. Equation (4) is an approximation, since the concentration of PAH is not exactly zero in renal venous blood. Note that with the appropriate catheter techniques, $c(i,V)$ can be measured and exact values of RPF may be derived.

The glomerular filtration rate (GFR) is the flow rate of the ultrafiltrate into the nephron from the capillary bed. How might we measure the GFR?

If a substance could be found which is filtered freely, but is neither reabsorbed from nor secreted into the urine, then all the substance filtered will be excreted in the urine. Thus:

$$\text{GFR} * c(i,A) = Q(U) * c(i,U)$$

$$\text{GFR} = Q(U) * c(i,U) / c(i,A) \quad (5)$$

The indicator substance which fulfills our criteria is a sugar called INULIN. Inulin is not the only substance which can be used. Others include creatinine, vitamin B-12, and iothalamate. The normal GFR is 120-125 cc/min.

Clearance

The concept of “clearance” is commonly used in renal physiology. The term refers to the equivalent volume of plasma from which a substance is completely “cleared” per minute. Thus:

$$CL(i) \cdot c(i,A) = Q(u) \cdot c(i,U)$$

$$CL(i) = Q(u) \cdot c(i,U) / c(i,A) \quad (6)$$

where $CL(i)$ is the clearance of substance “i” in cc/min. It should be noted that in clinical practice the quantity $c(i,A)$ is taken to be the plasma concentration of the substance i, and is generally measured in systemic venous blood.

The PAH clearance $CL(\text{PAH})$ is the renal plasma flow.

The inulin clearance $CL(\text{inulin})$ is the GFR.

V. SODIUM AND WATER TRANSPORT

A. Sodium Balance

The volume and osmolarity of extracellular fluid are maintained within very narrow limits. The amount of H₂O and Na⁺ which are filtered each day exceed their daily intake by more than a factor of 100! Thus, fluid and sodium balance depend critically on tubular reabsorption.

$$\text{Sodium excretion} = \text{sodium filtered} - \text{sodium reabsorbed}$$

Sodium excretion may be adjusted by controlling one or both of the above mechanisms. Sodium excretion may be increased by increasing GFR, by decreasing reabsorption, or both. Conversely, sodium excretion may be decreased by decreasing GFR or increasing tubular reabsorption or both. (See Figure 9.)

Figure 9
(From Vander 1985, p. 436)

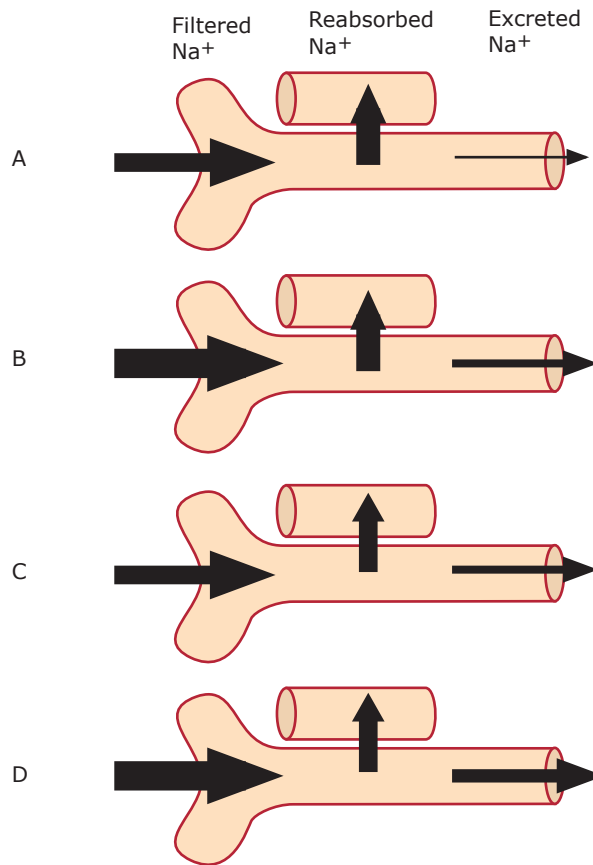


Figure by MIT OCW. After p. 436 in Vander, Arthur J., Sherman, James H., and Luciano, Dorothy S. 1985. *Human Physiology: The Mechanisms of Body Function*. 4th ed. McGraw-Hill.

Factors increasing sodium excretion. A) Normal sodium excretion. B) Increasing GFR C) decreasing reabsorption, or D) both, cause an increase in sodium excretion.

GFR is dynamically controlled largely by changes in the glomerular capillary pressure. This is a function of perfusion pressure, and the resistances of the afferent and efferent arterioles. The resistances are modified by sympathetic stimulation in response to baroreceptor and volume receptors. Figure 10 illustrates the mechanism by which GFR may respond to volume depletion.

Figure 10
(From Vander 1985, p. 437)

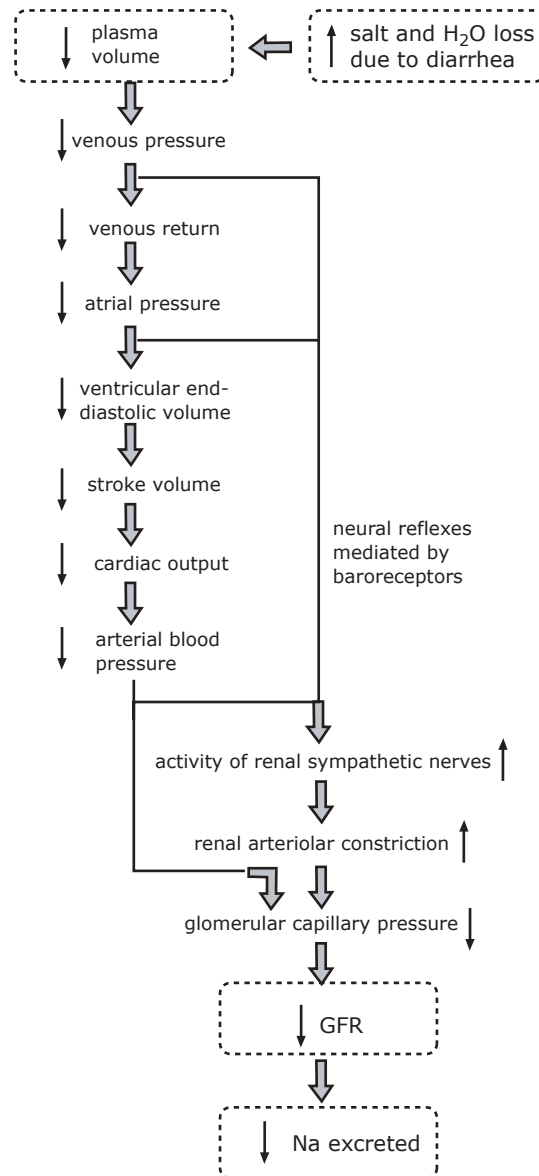


Figure by MIT OCW. After p. 437 in Vander, Arthur J., Sherman, James H., and Luciano, Dorothy S. 1985. *Human Physiology: The Mechanisms of Body Function*. 4th ed. McGraw-Hill.

Neural feedback and control decreases GFR when plasma volume is decreased. Baroreceptors in the heart walls, carotid sinuses, aortic arch, and large veins initiate a sympathetic reflex. This neural pathway is much more significant in lowering GFR than the direct effect of the lowered arterial pressure due to low plasma volume.

In general, sodium reabsorption is active, with passive reabsorption of H₂O. The approximate daily turnover of sodium in different portions of the nephron is shown in Figure 11.

Figure 11
(From Valtin 1983)

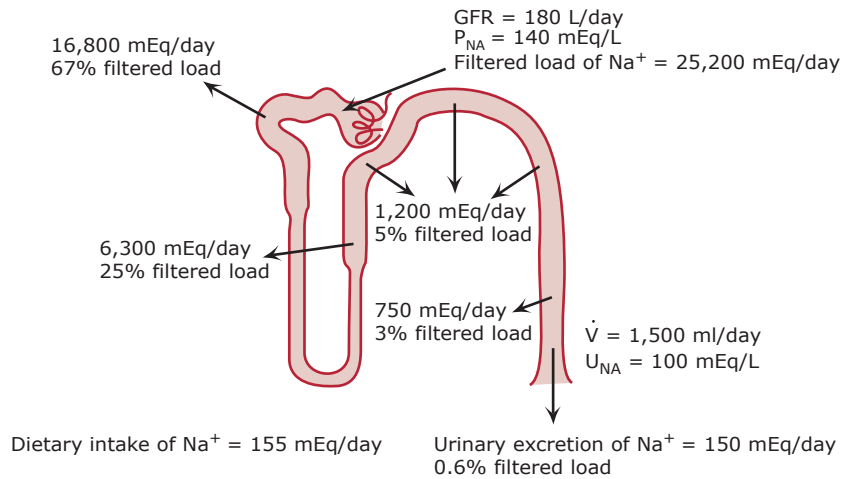


Figure by MIT OCW. After Valtin, Heinz. 1983. *Renal Function: Mechanisms Preserving Fluid and Solute Balance in Health*. Little, Brown.

Normal daily renal sodium turnover in the adult human. At steady state, the organism is “balanced,” such that the daily sodium output equals the daily sodium intake. Sodium output is comprised of renal excretion and extrarenal losses (sweat, saliva, and gastrointestinal secretions – negligible under normal conditions). P_{Na} and U_{Na} refer to the plasma and urinary concentrations of sodium respectively.

In the ascending limbs of the loop of Henle sodium transport is active, but water does not follow because this portion of the nephron is impermeable to water.

In the late distal tubules, and in the collecting ducts, the reabsorption of water varies directly with the blood concentration of anti-diuretic hormone (ADH), which permits the fine regulation of water balance.

B. The Renin-Angiotensin-Aldosterone System

Fine adjustments in sodium reabsorption in distal tubules and collecting ducts are mediated by aldosterone. Figure 12 diagrams the renin-angiotensin-aldosterone system.

Figure 12
(From Valtin 1983)

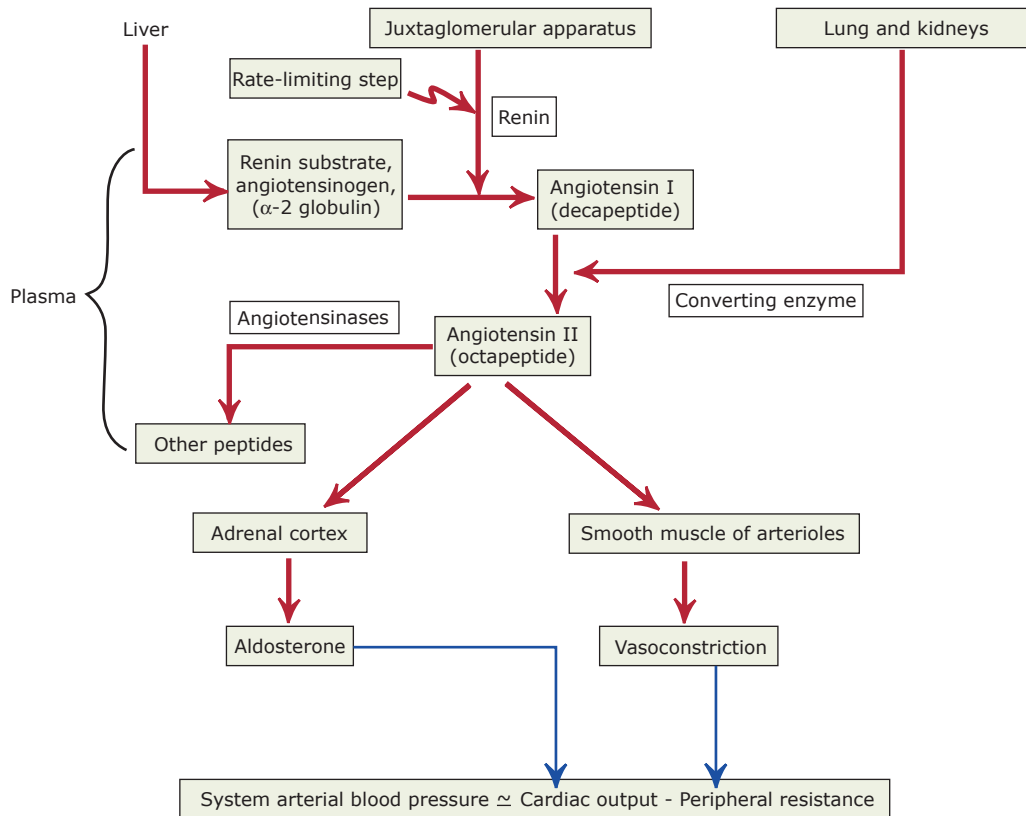


Figure by MIT OCW. After Valtin, Heinz. 1983. *Renal Function: Mechanisms Preserving Fluid and Solute Balance in Health*. Little, Brown.

Possible relationship between renin-angiotensin-aldosterone system dynamics and systemic arterial blood pressure.

Renin is secreted by the juxtaglomerular apparatus (JGA) in the kidney. Renin splits angiotensinogen to form the physiologically inactive angiotensin I. This is converted to an active substance, angiotensin II by a converting enzyme located in the lung. Angiotensin II is a potent vasoconstrictor, and also stimulates the adrenal cortex to secrete aldosterone. This hormone results in increased sodium reabsorption and hence increased extracellular volume.

How is renin release controlled? It is renin which is the rate-limiting step in producing aldosterone. There are several factors which may be important in controlling renin release. They include, but are probably not limited to:

- 1) A decrease in perfusion pressure of the renal artery (as would be expected when extracellular volume is depleted) results in an *increase* in renin production and vice-versa.

- 2) A change in NaCl in the vicinity of the macula densa modulates renin release. A decreased salt concentration in the tubular fluid leads to *increased* renin secretion. The precise mechanism is unclear.

- 3) Sympathetic nervous stimulation of the kidney *increases* the release of renin.

Figure 13 shows a sequence of events which would follow a decrease in plasma volume. (These events would occur in parallel to those illustrated in Figure 10.)

Figure 13
(From Vander 1990)

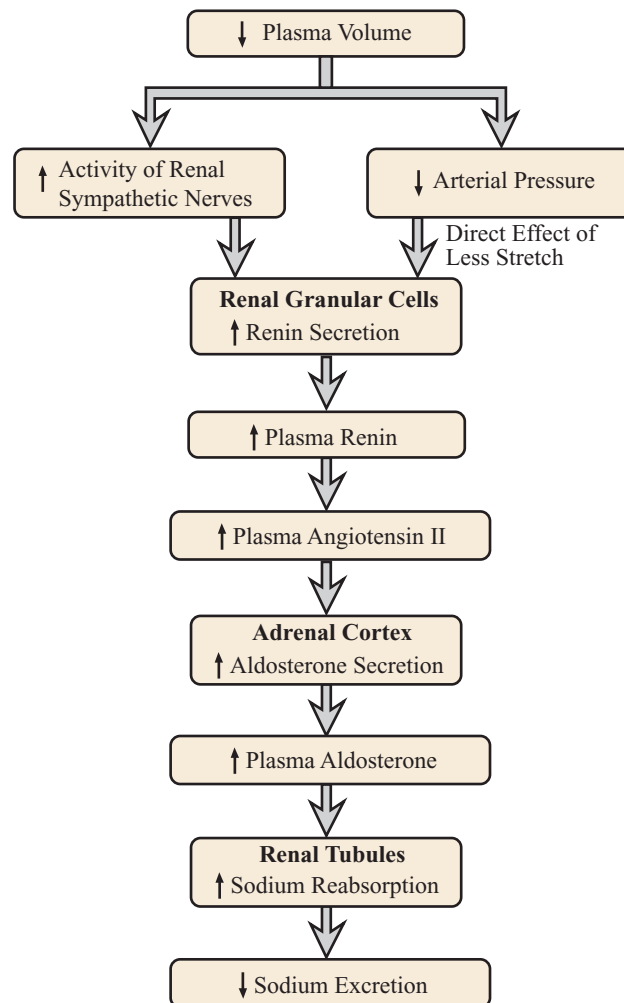


Figure by MIT OCW. After Vander, Arthur J., Sherman, James H., and Luciano, Dorothy S. 1990. *Human Physiology: The Mechanisms of Body Function*. 5th ed. McGraw-Hill.

Mechanism of increased reabsorption and decreased sodium excretion in response to plasma volume decrease. Granular cells function as intrarenal baroreceptors responding directly to decreased stretch due to the lowered arterial pressure. Renal sympathetic nerves can also stimulate granular cells. A third signal for stimulating renin secretion is via the macula densa (not shown).

C. Atrial Natriuretic Peptide

In 1981 Aldolfo de Bold and colleagues demonstrated that extracts derived from the cardiac atria caused a potent natriuresis and diuresis in rats. Since then, extensive research has focussed on this substance, known as atrial natriuretic peptide (ANP). It is now known to be a peptide hormone which is synthesized in atrial tissue, and stored as membrane-bound secretory granules.

ANP has been completely characterized: isolated, sequenced, and synthesized. It is released into the blood stream by *atrial stretch*, which generally results from increases in blood volume. The hormone has several different effects, all of which tend to diminish blood volume and blood pressure. Increased ANP leads to:

1. Increased excretion of sodium (natriuresis).

The mechanisms include increased GFR (caused by increased efferent arteriolar resistance), and also decreased tubular transport of sodium.

2. Increased excretion of water (diuresis).
3. Vasodilation (both arteriolar and venous).
4. Decreased production of aldosterone, and decreased secretion of aldosterone.
5. Decreased secretion of renin.
6. Decreased release of anti-diuretic hormone (ADH) from the posterior pituitary.

VI. REGULATION OF EXTRACELLULAR VOLUME AND OSMOLARITY

Regulation of extracellular volume depends not only on regulation of sodium, but also upon the control of free water. Thus, not only volume, but also osmolarity may be regulated by the kidney.

Anti-diuretic hormone, ADH, controls the permeability of the late distal tubules and collecting ducts to water. Thus, in these regions of the kidney, the reabsorption of salt and water can be controlled *independently*.

ADH is produced by specialized hypothalamic neurons and is transmitted via their axons to the posterior pituitary gland where it is released into the blood. How is ADH release controlled?

- Baroreceptors located in large veins and in the atria when stimulated by increased vascular volume, send inhibitory signals to increased secretion of H₂O. (See Figure 14.)
- Osmoreceptors in the hypothalamus stimulate *increased* ADH release in the presence of *increased* osmolarity. Thus, the permeability of distal tubules and collecting ducts is increased to H₂O, and water is retained.

It is easy to see how one can excrete excess water in a dilute urine. ADH is reduced, less H₂O is reabsorbed in the collecting ducts and distal tubules, and more H₂O was excreted. The most dilute urine possible is about 50 osmoles/liter. (See Figure 15.)

Figure 14
(From Vander 1985)

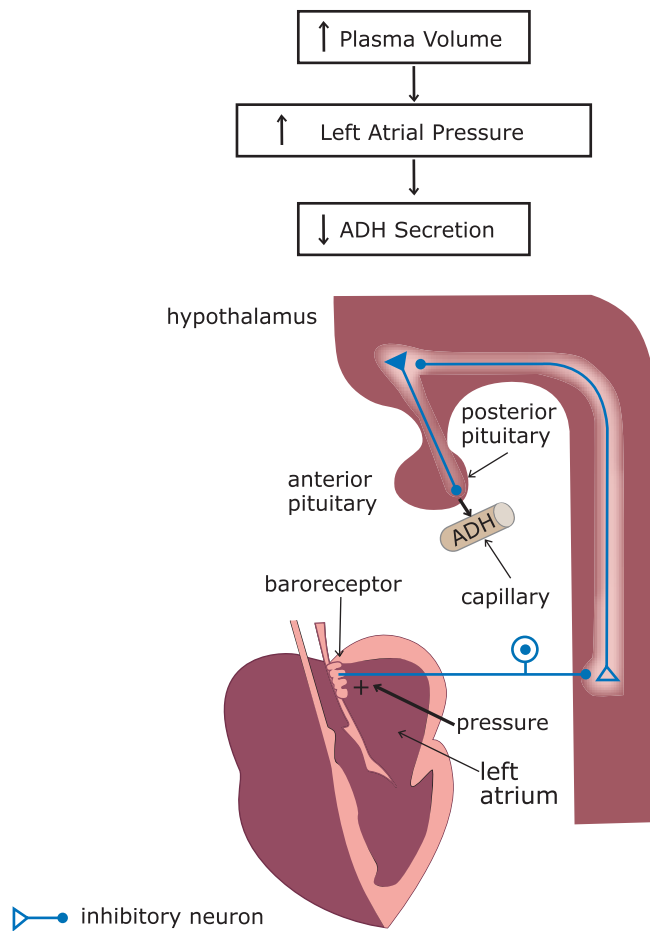


Figure by MIT OCW. After Vander, Arthur J., Sherman, James H., and Luciano, Dorothy S. 1985. *Human Physiology: The Mechanisms of Body Function*. 4th ed. McGraw-Hill.

Plasma volume regulation of ADH. Elevated plasma volume increases left atrial pressures, stimulating the atrial baroreceptors and inhibiting ADH secretion.

Figure 15
(From Vander 1990)

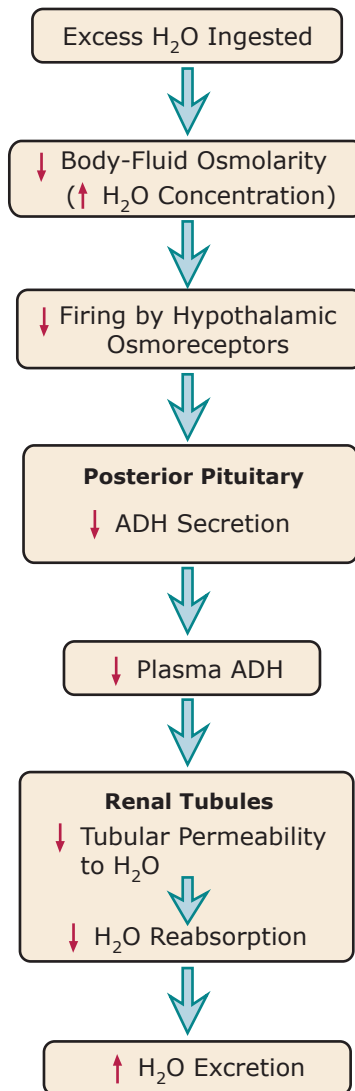


Figure by MIT OCW. After Vander, Arthur J., Sherman, James H., and Luciano, Dorothy S. 1990. *Human Physiology: The Mechanisms of Body Function*. 5th ed. McGraw-Hill.

Regulation of volume in response to excess water ingestion. Osmoreceptors in the hypothalamus detect the drop in osmolarity and decrease ADH secretion to allow excretion of excess water.

But how can the body conserve water and excrete a hyperosmotic urine? The answer is found in the countercurrent multiplier system which permits the renal medulla to become extremely hyperosmotic (osmolarity of about 1400). Figure 16 illustrates the end result of the counter current system, and reveals that in the presence of high ADH levels, urine may reach an osmolarity of

nearly 1400. Detailed description of the counter current system is found in standard texts and will not be given here.

Figure 16
(From Vander 1985)

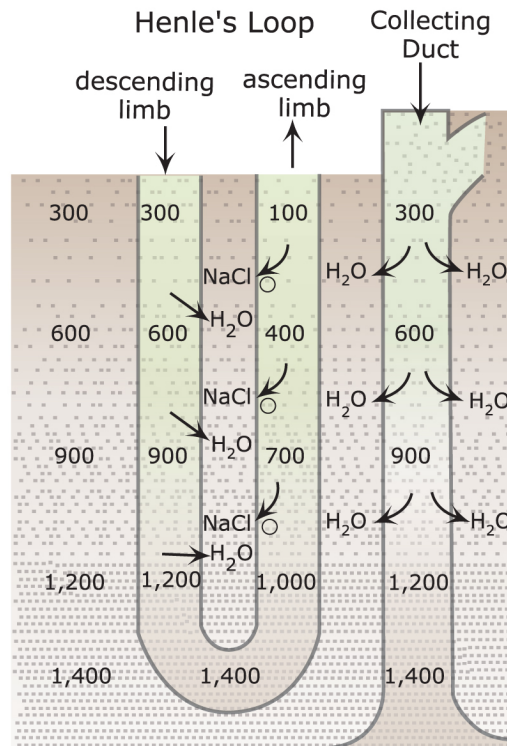
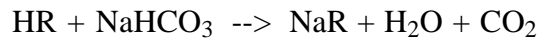


Figure by MIT OCW. After Vander, Arthur J., Sherman, James H., and Luciano, Dorothy S. 1985. *Human Physiology: The Mechanisms of Body Function*. 4th ed. McGraw-Hill.

Countercurrent multiplier responsible for the formation of hypertonic urine formation.

VII. pH REGULATION

The kidney is critical in regulation of the body's hydrogen ion concentration. During the metabolism of the average western diet, approximately 70-100 mEq of non-volatile (non-CO₂) acid is produced, and all of it must be excreted by the kidney in order to maintain body acid-base balance. The primary extracellular buffering system is the bicarbonate system:



Thus the production of 100 mEq of nonvolatile acid (HR) will be buffered by an equivalent amount of bicarbonate to form the sodium salt of the acid, plus carbon dioxide and water. The carbon dioxide is lost via the lungs, and if the process went on this way it would not be long before all the bicarbonate stores of the body would be gone. The kidney's task is to reverse the process by excreting 100 mEq of fixed acid each day, and regenerating the equivalent amount of bicarbonate. The kidney must also prevent the loss of bicarbonate in the urine—all bicarbonate filtered must be reabsorbed.

a. Reclamation of Filtered Bicarbonate

The proximal tubule reabsorbs 85-90% of filtered bicarbonate, which amounts to about 4,500 mEq (25 mEq/L X 180 L/day) per day. The mechanism is sketched in figure 17. The key process is thought to occur via a Na⁺/H⁺ coupled transport system (antiporter).

b. Bicarbonate Regeneration (excretion of titratable acid)

The distal nephron (predominantly the collecting duct) is the predominant site for bicarbonate regeneration and excretion of acid. The key mechanism is an electrogenic proton pump from the interior of the cell against an electrochemical gradient. This pump, requiring metabolic energy through ATP, is located on the luminal surface of the collecting duct epithelium. (See figure 18.) The epithelium can generate very large hydrogen ion concentration gradients (10³, or 3 pH units). Sodium reabsorption is not apparently coupled to the hydrogen ion pump in the collecting duct cells. The excreted hydrogen ions combine in the urine with either filtered anions such as phosphate, sulfate, or urate; or with ammonia which is produced by the epithelial cells. In either case, the hydrogen ion is “trapped” in the urine and is excreted as a weak acid or as the polar ammonium ion NH₄⁺. In order to maintain acid-base equilibrium, there must be a net acid secretion of 70-100 mEq per day through these mechanisms.

The body pH is established primarily via the bicarbonate buffer system, and is given by the Henderson-Hasselbalch equation:

$$\text{pH} = 6.1 + \log [\text{HCO}_3^-] / (0.03)(\text{P}_{\text{CO}_2})$$

The lungs are responsible for regulating the P_{CO_2} and the kidneys regulate the bicarbonate concentration. The former can act very quickly—in minutes, while the renal mechanisms are much slower—hours to days.

Figure 17
(From Seldin and Giebisch 1989)

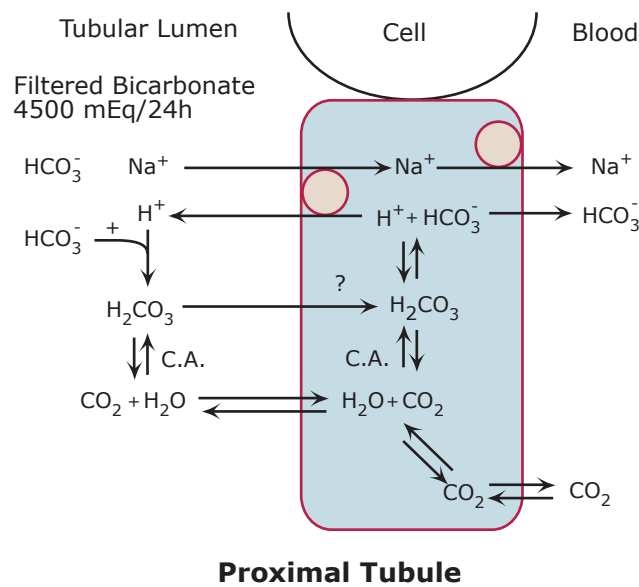


Figure by MIT OCW. After Seldin, Donald W., and Giebisch, Gerhard. 1989. *The Regulation of Acid-Base Balance*. Raven Press.

Figure 18
(From Seldin and Giebisch 1989)

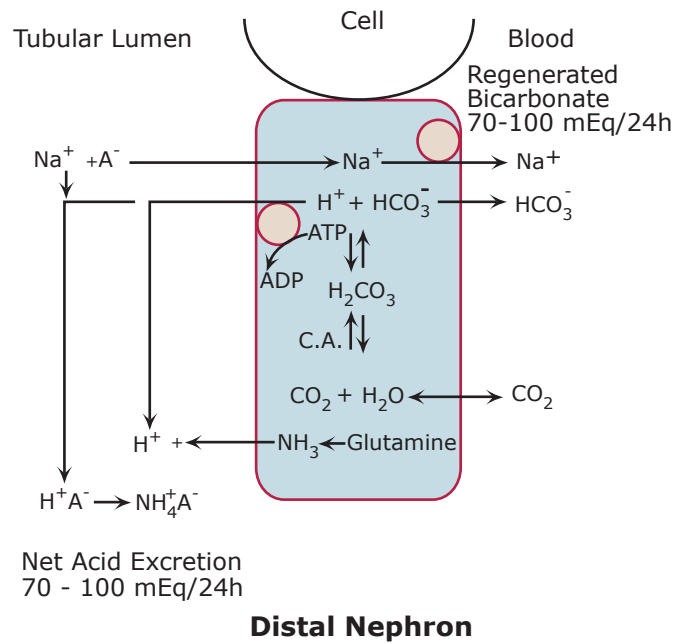


Figure by MIT OCW. After Seldin, Donald W., and Giebisch, Gerhard. 1989. *The Regulation of Acid-Base Balance*. Raven Press.

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