6. RENAL PHYSIOLOGY

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BODY FLUIDS

1. How much of the body is composed of water?

By weight, the body is composed of 50–70% water. This percentage varies depending on the individual body type because the water content of fat (approximately 20%) is much less than that of muscle (approximately 70%). In general, an average person has a total body water (TBW) of approximately 60% of body weight. The average 70-kg man would then have approximately 42 L of TBW (70 × 0.6 [1 L of water has a mass of 1 kg]). In contrast, an extremely lean, muscular individual would have a TBW that is close to 70% of total body weight, and an obese person would have a TBW that is nearer to 50% of total body weight.

2. Where in the body is the TBW located?

TBW is distributed between two major compartments, the **intracellular** and the **extracellular compartments,** which are separated by the cell membranes. The fluid volumes in these compartments are known as the **intracellular fluid** (ICF) and the **extracellular fluid** (ECF). The ICF is the fluid found within the cells, and the ECF is the fluid outside of cells, including the interstitial fluid, lymph, and plasma.

3. What proportion of TBW is in the intracellular and extracellular compartments?

In general, the ICF comprises two-thirds of TBW, whereas the ECF constitutes one-third of TBW. The average 70-kg man with approximately 42 L of TBW would then have approximately 28 L (42 L × ⅔) in the ICF and approximately 14 L (42 L × ⅓) in the ECF.

4. How is the ECF distributed?

The ECF is distributed into two major compartments, the **interstitial fluid** and the **plasma**. The barrier between these two compartments is composed of the highly permeable systemic capillaries. The interstitial fluid volume is approximately four-fifths of ECF, and the plasma volume is approximately one-fifth of ECF volume. The average 70-kg man with 14 L of ECF volume would therefore have approximately 11.2 L in the interstitial fluid (14 L × ⅘) and approximately 2.8 L of plasma (14 L × ⅕).

5. Calculate the normal blood volume.

The normal plasma volume is approximately 2.8 L, and the hematocrit (packed red blood cell fraction of blood) averages 0.38 to 0.42; therefore, the average individual has a blood volume of approximately 4.7 L (plasma volume/[1 – Hct] = 2.8 L/[1 – 0.4]).

6. What is osmolarity?

Osmolarity is a function of the total number of particles in solution, independent of mass, charge, or chemical composition. The dissolved particles (osmolytes) exert a force that tends to pull water across semipermeable membranes (osmotic pressure). Dissolved particles in biologic solutions are expressed in terms of milliosmoles (mOsm). For substances that do not dissociate into smaller particles when dissolved (i.e., urea, glucose, inulin), 1 mole = 1 osmole and 1 mmole = 1 mOsm. For substances that dissolve into two particles (sodium chloride [NaCl]) or three particles (calcium chloride [$CaCl_2$]), the osmolarity is double or triple the molarity (1 mmole NaCl = 2 mOsm). Osmolarity is therefore the concentration of osmotically active particles in solution and is expressed in terms of mOsm/L of water. In the body, the osmolarity of the ECF and ICF averages 280–300 mOsm/L.

7. What is osmolality?

An alternative notation used to express the concentration of dissolved particles is osmolality, which is expressed in terms of mOsm/kg of water. In relatively dilute solutions, such as those found in the body, the difference between osmolarity and osmolality is so small that the two terms are used interchangeably.

8. Define osmosis.

Osmosis is the movement of water across a semipermeable membrane owing to differences in osmolarity (an osmotic pressure gradient). Osmosis occurs from a fluid compartment in which the solute concentration is lower to a second compartment in which the solute concentration is higher until the osmolarity on each side of the membrane is equal. A semipermeable membrane (such as a cell membrane) is one that is permeable to water but not solutes. It is critical to recognize that a dissolved particle can exert an osmotic force only if it is not permeable in the membrane.

9. What is tonicity?

The total concentration of solutes in a solution that are not permeable in the cell membrane. Because these solutes exert an effective osmotic pressure in cells, the tonicity of a solution determines the effect of the solution on water movement into or out of cells.

10. Explain the influence of hypotonic, isotonic, and hypertonic solutions on cell volume.

- When a cell is placed in an **isotonic** solution, the cell volume will be unaltered.
- When a cell is placed in a **hypotonic** solution, the cell will swell.
- When a cell is placed in a **hypertonic** solution, the cell will shrink.

11. Is there a difference in the total osmolarity of the ICF and ECF?

No, under normal steady-state conditions, the total concentration of dissolved particles in the intracellular and extracellular compartments is equal because the cellular membranes are highly permeable to water, and any differences in osmolarity between these compartments are quickly corrected due to osmosis. Because the total concentration of substances that are osmotically active is the same in the ECF and ICF, the osmolarity of the ECF and ICF is equal (280–300 mOsm/kg).

12. Are there differences in the ionic composition of the fluid found in the ECF and ICF?

Over 90% of the ions in the extracellular fluid are sodium, chloride, and bicarbonate; the concentration of other ionic species in the ECF is relatively low. In contrast, the intracellular fluid is high in potassium and phosphate, whereas the ions abundant in the extracellular fluid (sodium and its anions) are relatively low within the cells.

Concentration of Selected Ions (mEq/L), pH, and Osmolarity (mOsm/L) in the ECF and ICF

	ECF	ICF (MUSCLE)
Sodium	145	10
Potassium	4	155
Calcium	5	0
Chloride	110	2
Bicarbonate	24	8
Phosphate	2	140
pH	7.4	7.15
Osmolality	290	290

13. Why are there differences in the concentration of the individual ions in the ECF and ICF?

The primary reason for the difference observed in the ECF and ICF is the cell membrane and the Na^+, K^+-ATPase pump which is found in the cell membranes. Cell membranes are highly per-

meable to water but the permeability to most electrolytes is relatively low. The Na^+, K^+-ATPase pump also plays a critical role in the regulation of intracellular concentration by actively transporting sodium out of cells (against this ion's electrochemical gradient) and pumping potassium into cells. Although sodium is driven by its electrochemical gradient into the cells, the sodium that diffuses into cells is actively extruded from the cells to maintain a low intracellular sodium concentration, whereas potassium is actively transported into cells.

14. Are there differences in the composition of the plasma and the interstitial fluid?

There is a slight difference in the ionic composition of plasma when compared to the interstitial fluid. This difference is due to plasma protein (approximately 6 g/dL), which is mostly in the form of albumin. The plasma proteins are effectively trapped in the plasma because the capillary membranes in most tissues are relatively impermeable to protein. The albumin carries a net negative charge, which tends to hold extra amounts of cations in the plasma. This property, known as the **Donnan effect,** slightly alters the distribution of other ions between the plasma and the interstitial space and leads to slightly greater concentration of cations (3–4 mEq/L) and slightly decreased concentration of anions in the plasma relative to the interstitial fluid.

15. Does water move from one body compartment to another?

Yes, as a result of differences in hydrostatic pressure, osmotic pressure, or both.

16. What regulates the distribution of water between the plasma and the interstitial fluid?

Fluid exchange between the plasma and the interstitial fluid is governed by **Starling's law** for capillary fluid exchange. That is, the net flux of fluid into or out of capillaries is determined by the algebraic sum of the hydrostatic and osmotic forces on either side of the capillaries. As a result of the pumping action of the heart, a systemic capillary has a relatively high hydrostatic pressure (25 mmHg) that favors movement of fluid out of the capillaries. Forces opposing movement of fluid out of the capillaries include the plasma oncotic pressure (the osmotic pressure exerted by proteins) and interstitial fluid hydrostatic pressure. Without forces opposing capillary hydrostatic pressure, primarily the plasma oncotic pressure, the plasma volume would rapidly be transferred to the interstitial fluid. These forces can be expressed in the simple equation:

$$\text{Flux} = K_f\,[(P_{cap} + \Pi_{int}) - (\Pi_{cap} + \Pi_{int})]$$

K_f = Ultrafiltration coefficient
P_{cap} = Capillary hydrostatic pressure
Π_{int} = Interstitial oncotic pressure
Π_{cap} = Plasma oncotic pressure
P_{int} = Interstitial hydrostatic pressure

In general, the forces favoring filtration slightly exceed those opposing filtration. This leads to a net filtration out of the capillaries, which is collected as lymph and returned to the circulation.

17. How is fluid exchanged between the ECF and ICF?

The movement of fluid between the ECF and ICF is governed by osmotic forces. The cell membranes are highly permeable to water and semipermeable to most solutes. Any change in ionic composition in one compartment is reflected in the osmolarity of that compartment (provided that the ion is not permeable in the cell membrane), and water quickly crosses the cell membranes until osmolarity is equal in both compartments.

18. How can the different body fluid compartments be measured?

The volume of different body compartments can be measured most easily by determining the volume of distribution of compounds known to be freely distributed within a certain compartment. In this technique, a known quantity of a substance that is distributed in the body fluid com-

partment of interest is administered. After a sufficient amount of time is allowed for equilibration, a sample of the fluid from that compartment is taken. By dividing the original amount injected (A_X) by the concentration of substance X at equilibrium (C_X), the volume of distribution (V_{DX}) is calculated ($V_{DX} = A_X/C_X$).

19. Describe the ideal substance for measuring volume of distribution.

- Nontoxic
- Mixes well in and is not removed from the targeted compartment
- Is not metabolized or synthesized in the body
- Rate of excretion easily quantified
- Easily and accurately measurable

Example: A 70-kg man is injected intravenously with 4×10^6 cpm of tritiated water (^3H_2O); 15 minutes later, a blood sample is taken, and the blood contains 100 cpm/mL ^3H_2O. The calculated volume of distribution of ^3H_2O in this individual is therefore 40 L (4×10^6 cpm/100 cpm/mL = 40,000 mL = 40 L). In cases in which compounds are excreted, the amount that has been excreted must be subtracted from the amount originally injected to determine an accurate volume of distribution.

20. Name some compounds used to measure volume of distribution of different body fluid compartments.

Body Fluid Compartment	Compound
Total body water	H_2O (^3H_2O)
Extracellular volume	Sodium (^{22}Na)
	Inulin (^{3}H-inulin)
	Iothalamate (^{125}I-iothalamate)
Plasma volume	Albumin (^{125}I-albumin)
	Evans blue dye

21. How can the volume of the interstitial fluid and ICF compartments be determined?

The ICF and interstitial fluid volumes can be calculated using the measured volumes of TBW, ECF volume, and plasma volume:

- The **ICF volume** can be determined by subtracting the ECF volume from TBW (ICF = TBW – ECF).
- **Interstitial fluid volume** can be calculated by subtracting plasma volume from extracellular volume (ISF = ECF – PV).

22. What will happen to the different body volume compartments after the intake of isotonic saline solution?

Isotonic NaCl (0.9%, 290 mOsm/L) has an osmolarity equal to that found in the ECF and ICF. Both NaCl and water are freely permeable throughout plasma and the interstitial space, so an isotonic NaCl load will be **equally distributed** throughout the ECF. Because sodium can enter the cells but is actively excluded by the Na^+, K^+-ATPase, any added sodium will be effectively trapped in the ECF. Since isotonic saline has the same osmolarity as the ECF and ICF, there will be no osmotic effect leading to a fluid shift between the ECF and ICF. The intake of isotonic NaCl will thus **increase TBW and ECF but will not appreciably alter ICF volume;** osmolarity of both the ECF and the ICF will be **unaltered** from the original value.

23. What will happen to the different body volume compartments after the intake of hypertonic saline solution?

A hypertonic NaCl load (osmolarity > 290 mOsm/L) will also initially be distributed equally throughout the ECF. The difference between the isotonic and hypertonic load is the final osmolarity that is attained in the ECF and ICF. Because the osmolarity will initially be increased in the ECF owing to the hypertonic saline, water will move freely down its concentration gradient out of the

partment of interest is administered. After a sufficient amount of time is allowed for equilibration, a sample of the fluid from that compartment is taken. By dividing the original amount injected (A_X) by the concentration of substance X at equilibrium (C_X), the volume of distribution (V_{DX}) is calculated ($V_{DX} = A_X/C_X$).

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cells until a new osmolarity is achieved. A hypertonic NaCl load will therefore **expand TBW, increase ECF, and decrease ICF volume**. A new level of osmolarity will be attained that will be equal throughout the ECF and ICF but will be **elevated from the value before the hypertonic load**.

24. What will happen to the different body volume compartments after the intake of hypotonic saline solution?

A hypotonic NaCl load (osmolarity < 290 mOsm/L) will also initially be distributed equally throughout the ECF. The major difference between the isotonic and hypotonic loads is the final osmolarity that is attained in the ECF and ICF. Because the ECF osmolarity initially will be decreased, water will move down its concentration gradient out of the ECF into the cells until a new osmolarity is achieved. A hypotonic NaCl load will therefore **expand TBW, increase ECF volume, and increase ICF volume**. The new level of osmolarity will be **equal** throughout the ECF and ICF and will be **decreased from the original value**.

25. How are clinical abnormalities in body fluid status evaluated?

The most commonly used clinical index of body fluid is the measurement of plasma or serum sodium. Because sodium and its anions are the major ionic species of the ECF, **plasma sodium** (P_{Na}) is used as a clinical indication of volume status. Under normal conditions, P_{Na} is 145 mEq/L. When P_{Na} exceeds this value, the patient is said to be **hypernatremic;** when a patient's P_{Na} is less than this value, the individual is **hyponatremic**.

26. What conditions lead to hypernatremia?

- Conditions in which thirst is impaired (coma, neurologic abnormality, or drug effects)
- Situations with no access to drinking water
- Loss of extracellular water (increased ECF sodium concentration with decreased ECF volume)
- Sodium retention or excess sodium intake (increased ECF sodium concentration with normal or elevated ECF volume)
- Selective loss of ECF fluid (e.g., owing to lack of secretion of antidiuretic hormone [ADH] or the inability of the kidneys to respond to ADH)
- Excessive evaporative losses (such as those that occur in individuals with extensive second-degree and third-degree burns)
- Conditions in which excessive amounts of sodium-retaining hormones (such as aldosterone) are secreted into the blood

It is important to distinguish the cause of hypernatremia in patients to select the correct therapeutic measures to be taken.

27. Name some conditions that lead to hyponatremia.

- Excess retention or intake of water (hyponatremia with increased ECF volume): Inappropriate or uncontrolled secretion of ADH (kidney retains excess amounts of water and leads to expansion of extracellular water and hyponatremia)
- Increased excretion or decreased intake of sodium (hyponatremia with reduced ECF volume)
  Kidney disease
  Inappropriate use of diuretics
  Conditions in which there is decreased secretion of sodium-retaining hormones (aldosterone)

28. What is edema?

Edema is a condition in which excess fluid accumulates in the body tissues, usually in the interstitial spaces. This condition occurs when an alteration in Starling's forces for systemic capillary exchange occurs.

29. List some causes of edema.

- Increased systemic capillary hydrostatic pressure
- Decreased plasma oncotic pressure (owing to decreased plasma protein)

- Increased systemic capillary permeability
- Blockade of lymphatic return to the venous circulation (leading to edematous build-up of fluid in the interstitial spaces)

30. Why is the kidney important in regulating the body volumes?

In the most basic terms, the primary function of the kidneys is to maintain the composition of the ECF and ICF. To understand the impact of altered renal function on body fluid volumes, it is critical to understand not only the processes by which the kidneys operate, but also the relationship between the different body fluid compartments. The kidneys regulate body fluid volume and composition by controlling the rate of excretion of various substances. This is accomplished through a complex and integrated relationship between the kidney, the endocrine system, the nervous system, and the cardiovascular system.

31. List the three main processes by which the kidneys maintain homeostasis of the body fluids.

1. **Bulk filtration:** The blood flow to the kidney is approximately 1200 mL/min or 20% of cardiac output. About 20% (100 mL/min) of the plasma that flows to the kidney is filtered out of the glomerular capillaries into the renal tubules in the process known as **glomerular filtration**. This is the initial step in the formation of urine.
2. **Reabsorption:** This is the mechanism whereby the renal tubules reabsorb the solutes and fluid that were filtered. This process is normally responsible for the return of approximately 99% of the glomerular filtrate to the ECF.
3. **Secretion:** This is a tubular transport process in which substances are transported by an individual tubular segment from the extracellular space into the tubular fluid to be excreted in the urine.

RENAL HEMODYNAMICS

32. Briefly describe the gross anatomy of the kidney.

The kidneys are paired organs found against the dorsal wall of the abdomen just beneath the diaphragm and behind the peritoneum. The renal tissue can be grossly divided into three major zones: cortex, outer medulla, and inner medulla.

33. What is a nephron?

A nephron is the basic unit of the kidney. Each normal human kidney has approximately 1 million nephrons. (See top figure on next page.)

34. Describe the path blood travels as it passes from the renal artery to the renal vein.

Blood enters the kidney through the renal artery; then flows through the interlobar artery, arcuate artery, interlobular artery, afferent arteriole, glomerular capillaries, efferent arteriole, peritubular capillaries, and interlobular, arcuate, and interlobar veins; and finally the renal vein. Of note, glomerular ultrafiltration occurs in the glomerular capillaries, and uptake of solute and water that has been reabsorbed by the epithelial cells occurs in the peritubular capillaries.

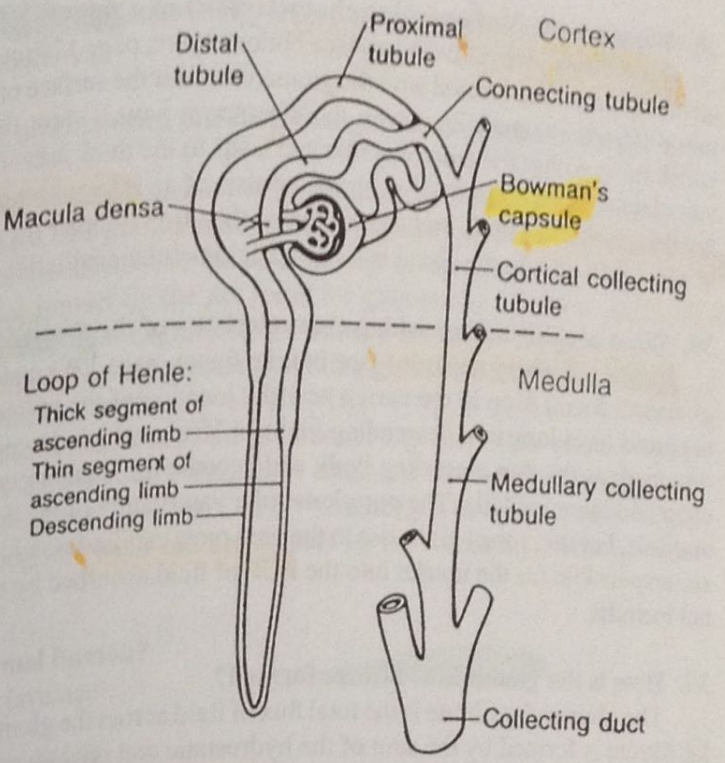
35. Are there different types of nephrons?

There are two general types of nephrons: **cortical** (superficial) and **juxtamedullary** (deep) nephrons. (See bottom figure on following page.)

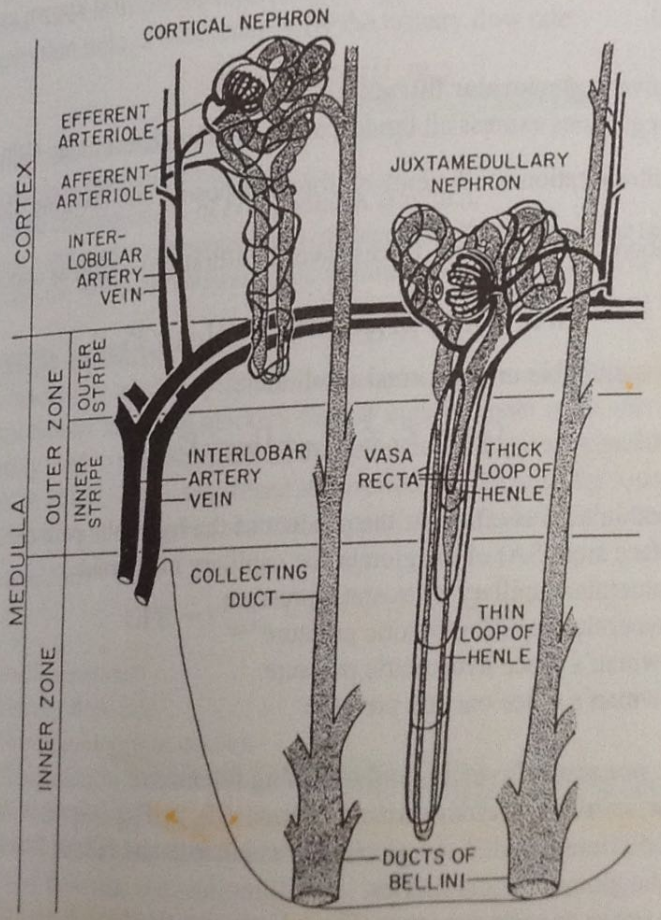
36. How are different types of nephrons distinguished?

Number — Tubular structure
Location — Vascular structure

(See bottom figure on page 129.)



Tubular segments of a nephron. (Reproduced with permission from Guyton AC, Hall JE: Textbook of Medical Physiology, 9th ed. Philadelphia, W.B. Saunders, 1996.)



Anatomy and vasculature of cortical (superficial) and juxtamedullary (deep) nephrons. (Reproduced with permission from Pitts RF: Physiology of the Kidneys and Body Fluids, 3rd ed. St. Louis, Mosby, 1974.)

37. What are the distinguishing characteristics of a superficial nephron?

Superficial cortical nephrons (see bottom figure, page 129) comprise approximately 90% of all nephrons and are located with the glomerulus near the surface of the kidney. The tubular structure differs in the medulla, where these nephrons have a short thin descending limb of Henle, which turns within the outer medulla and leads to the thick ascending limb. The postglomerular vasculature of the superficial nephron consists of an efferent arteriole, which gives rise to peritubular capillaries. Fluid and solutes reabsorbed from tubular segments located in the renal cortex are taken up into the blood in these postglomerular capillaries.

38. What are the distinguishing characteristics of the deep or juxtamedullary nephrons?

Juxtamedullary nephrons (see bottom figure, page 129) make up 10% of all nephrons with glomeruli found deep in the cortex near the junction of the cortex and medulla. Juxtamedullary nephrons have long thin descending limbs of Henle, which descend deep into the inner medulla, turn back as the thin ascending limb, and become the thick ascending limb at the border of the outer and inner medulla. The postglomerular vasculature of the deep nephrons is also an efferent arteriole, but this vessel gives rise to the vasa recta capillaries, which are found in the medulla and are responsible for the uptake into the ECF of fluid absorbed by the nephron segments in the renal medulla.

39. How is the glomerular filtrate formed?

The glomerular filtrate is the total flux of fluid across the glomerular capillaries. The glomerular filtrate is formed by the sum of the hydrostatic and oncotic pressures in the glomerular capillaries and Bowman's space. These forces, along with the hydraulic permeability and surface area of the glomerular capillary membranes, determine the net flux of fluid known as the glomerular filtration rate (GFR).

40. What forces govern glomerular filtration?

The following equations express all the forces involved in determining GFR:

$$\text{GFR} = (\text{ultrafiltration coefficient}) \times (\text{forces opposing and favoring filtration})$$

$$\text{GFR} = (\text{ultrafiltration coefficient}) \times [(\text{forces favoring filtration}) - (\text{forces opposing filtration})]$$

$$\text{GFR} = K_f \times [(P_{GC} + \Pi_{BS}) - (\Pi_{GC} + P_{BS})]$$

Because Π_{BS} is negligible under normal conditions:

$$G_{FR} = K_f \times (P_{GC} - \Pi_{GC} - P_{BS})$$

Where:

K_f = Ultrafiltration coefficient: the product of the hydraulic permeability (L_p) and the surface area (SA) of the glomerular capillary membranes
P_{GC} = Glomerular capillary hydrostatic pressure
Π_{GC} = Glomerular capillary oncotic pressure
P_{BS} = Bowman's space hydrostatic pressure
Π_{BS} = Bowman's space oncotic pressure

41. What are the pressures favoring and opposing filtration?

- **Glomerular capillary hydrostatic pressure (P_{GC}):** P_{GC} averages approximately 60 mmHg at the afferent end of the glomerular capillaries and falls to 58 mmHg at the efferent end of the glomerular capillaries.
- **Bowman's space oncotic pressure (Π_{BS}):** Normally, this force is negligible because minimal amounts of protein are filtered.
- **Hydrostatic pressure in Bowman's space (P_{BS}):** P_{BS} is approximately 20 mmHg and remains constant from the afferent to the efferent end of the glomerular capillaries.

- **Glomerular capillary oncotic pressure** (Π_{GC}): Π_{GC} averages 25 mmHg at the afferent end of the glomerular capillaries.

42. Do the pressures favoring and opposing filtration change over the length of the glomerular capillaries?

Because fluid is filtered out of the plasma in the glomerular capillaries while plasma proteins are left behind in the blood, the plasma protein concentration and oncotic pressure increase as blood proceeds from the afferent to the efferent end of the glomerular capillaries. The change in Π_{GC} has a major impact on the net force for glomerular filtration. At the beginning (afferent end) of the glomerular capillaries, the sum of the forces for glomerular filtration greatly favors net filtration. The net pressure favoring glomerular ultrafiltration (P_{UF}) can be approximated as follows: $P_{UF} = [(P_{GC} + \Pi_{BS}) - (\Pi_{GC} + P_{BS})] = [(60 + 0) - (25 + 18)] = 17$ mmHg. At the distal (efferent) end of the glomerular capillaries, the plasma oncotic pressure rises by as much as 15 mmHg, which drastically alters the forces for filtration: $P_{UF} = [(P_{GC} + \Pi_{BS}) - (\Pi_{GC} + P_{BS})] = [(58 + 0) - (40 + 18)] = 0$ mmHg. The concentration of protein in the glomerular blood therefore has a marked impact on the forces that favor glomerular filtration.

43. What is the GFR in a normal human?

120 mL/min (172.8 L/day) (average).

44. Explain the concept of clearance.

Clearance is the hypothetical volume of plasma from which the kidney removes all of a substance per unit time. The clearance of substance X (C_X) can be calculated by multiplying the urine-to-plasma concentration ratio of substance X by the urinary flow rate:

$$C_X = UF \times (U_X/P_X)$$

U_X = Urine concentration of compound X (mg/dL)
UF = Urine flow rate (mL/min)
P_X = Plasma concentration of compound X (mg/dL).

Because urinary and plasma concentration of substance X must be in the same units, the clearance value will have the same dimensions (i.e., volume/time) as urinary flow rate.

45. How can GFR be measured?

Ideally, substances that are freely filtered at the glomerulus and neither reabsorbed nor secreted by the renal tubules are ideal markers for the measurement of glomerular filtration. One substance commonly used to measure GFR in experimental situations is **inulin,** a polysaccharide (molecular weight = 5500), which is infused intravenously. Because the kidney removes inulin from the body by filtration and does not secrete, reabsorb, or metabolize this compound, the clearance of inulin (C_{inulin}) equals GFR:

$$GFR = C_{inulin} = UF \times U_{inulin}/P_{inulin}$$

C_{inulin} = Inulin clearance
UF = Urinary flow rate
U_{inulin} = Urine inulin concentration
P_{inulin} = Plasma inulin concentration

In this equation, the plasma and urine inulin concentrations must be expressed in the same units (i.e., mg/dL) and cancel each other out in the calculation. The units of GFR are then the same as the units of urinary flow rate (i.e., mL/min).

46. Can GFR be evaluated clinically?

Although inulin is the compound of choice for the measurement of GFR in experimental situations, this compound must be infused intravenously before any measurements can be made. In

the clinical setting, creatinine clearance is used to measure GFR. Creatinine is an endogenous substance formed by creatine metabolism in skeletal muscle; it is produced at a relatively constant rate, is freely filtered by the glomerulus, and is not appreciably reabsorbed or secreted.

47. How is creatinine clearance used to evaluate GFR clinically?

Creatinine clearance (C_{creat}) can be used as an index of GFR:

$$C_{creat} = GFR = UF \times (U_{creat}/P_{creat})$$

U_{creat} = Urine concentration of creatinine (mg/dL)
UF = Urine flow rate (mL/min)
P_{creat} = Plasma concentration of creatinine (mg/dL)

If we assume a state of constant creatinine production, urinary excretion of creatinine can be considered a constant K. Because creatinine is excreted only by the process of glomerular filtration, we can then say that:

$$\text{Creatine production} = \text{creatinine excretion} = K = (U_{creat} \times UF)$$

Because $GFR = (U_{creat} \times UF)/P_{creat}$, substituting K into the equation gives $GFR = K/P_{creat}$
Therefore, GFR α $1/P_{creat}$

Because P_{creat} normally equals 1 mg/dL, if we divide 100 by P_{creat}, we get an estimate of the percentage of normal GFR in this patient.

48. What are the possible concerns in the use of plasma creatinine to estimate GFR?

1. Creatinine can be secreted by the renal tubules, which leads to an overestimation of GFR even if creatinine clearance is determined.
2. The use of serum creatinine as an index of GFR assumes that all individuals have the same production rate of creatinine and therefore the same serum concentration.
3. Although changes in serum creatinine can indicate alterations in renal function, a relatively slight increase in serum creatinine from 1.0 mg/dL to 1.5 mg/dL would correspond to a decrease in GFR from 100% (1/1 × 100) to 67% (1/1.5 × 100) of normal.

49. What is contained in the glomerular ultrafiltrate?

The glomerulus is composed of the glomerular capillaries with endothelial cells covered by a basement membrane. The capillaries are surrounded by epithelial cells known as **podocytes**. Although the endothelial layer contains fenestrations of approximately 1000 Å diameter that are freely permeable to water and most small solutes, the podocytes have foot processes that form filtration slits (approximately 40 × 140 Å), which retard the filtration of macromolecules based on size. In addition, the surface of the endothelial cells, the basement membrane, and the podocytes all contain negatively charged glycoproteins, which inhibit filtration of negatively charged molecules (such as plasma protein). In general, the largest molecules that can be effectively filtered are less than 25 Å in diameter, although positively charged molecules can still be filtered at sizes as large as 40 Å.

50. Why isn't protein filtered in the glomerulus?

The glomerular ultrafiltrate is an ultrafiltrate of plasma excluding plasma protein and any substances bound to protein. Protein is excluded from the glomerular ultrafiltrate because of the specialized structure of the glomerular membranes.

51. What is the level of renal blood flow (RBF) in a normal human?

1.0–1.25 L/min to both kidneys (average).

52. Can renal blood flow be measured?

In experimental animals, RBF can be measured directly using electromagnetic flowmetry

of other devices used to measure blood flow invasively. This is not the case in patients, but a good index of RBF can be gained by determining the clearance of para-amino-hippuric acid (PAH). PAH clearance can be used to quantitate renal plasma flow (RPF) because this compound is freely filtered at the glomerulus and secreted by the organic acid transporter in the proximal tubule, but it is not reabsorbed by any nephron segments. The clearance of PAH can be calculated as:

$$C_{PAH} = RPF = UF \times (U_{PAH}/P_{PAH})$$

U_{PAH} = Urine concentration of PAH (mg/dL)
UF = Urine flow rate (mL/min)
P_{PAH} = Plasma concentration of PAH (mg/dL)

The value obtained for RPF can then be converted to RBF by dividing RPF by the fraction of blood that is plasma: RBF = RPF/(1 – Hct).

53. What is the filtration fraction?

The fraction of RPF that is filtered at the glomerulus.

54. How is the filtration fraction (FF) calculated?

FF = GFR/RPF.

55. How can RPF be calculated?

RPF is the fraction of RBF that is plasma. If RBF and the hematocrit (Hct) are known, RPF can be calculated as: RPF = RBF × (1 – Hct).

56. Describe what is meant by renal vascular resistance.

Resistance is generally defined by Poiseuille's law, in which resistance is proportional to $(8\eta l)/(\pi \times r^4)$, where r = the radius of the vessel, η = viscosity of the blood, and l = length of the vessel. Although Poiseuille's law is applicable only to steady flow of an ideal fluid through cylindrical tubes and is not correct for pulsatile flow of blood through blood vessels, it is a useful equation to understand the factors that can alter vascular resistance. Because the viscosity of the blood and the length of the renal vessels can be considered constant, alterations in resistance are generally attributed to changes in vessel radius. As the resistance is inversely proportional to the radius raised to the fourth power, small changes in vessel radius can have profound effects on vascular resistance.

57. What are the preglomerular blood vessels?

Those found before the glomerulus:

- Renal artery
- Interlobar artery
- Arcuate artery
- Interlobular artery
- Afferent arteriole

58. What are the postglomerular blood vessels?

Those found after the glomerulus:

- Efferent arteriole
- Peritubular (or vasa recta) capillaries
- Renal vein

59. Which blood vessels in the kidney provide for the greatest resistance to blood flow?

Efferent and afferent arterioles. This is indicated by a large decrease in intravessel pressure from the beginning to the end of these vessels. Intravascular hydrostatic pressure falls from ap-

proximately 100 mmHg to 60 mmHg from the beginning to the end of the afferent arteriole and from approximately 60 mmHg to 15 mmHg across the efferent arteriole.

60. Do selective changes in preglomerular and postglomerular renal vascular resistance lead to similar changes in RBF?

RBF is equal to the driving pressure (ΔP) divided by the renal vascular resistance (RVR): RBF = ΔP/RVR. An increased renal vascular resistance at any location in the renal vascular network leads to a decrease in RBF. Conversely, decreased renal vascular resistance at any location in the renal vascular tree leads to increased RBF. Increases or decreases in preglomerular or postglomerular resistance have the same general effect on renal blood flow.

61. How would selective changes in preglomerular or postglomerular renal vascular resistance alter GFR?

In general, GFR increases when the driving force for filtration (glomerular capillary pressure) is increased, and GFR decreases when glomerular capillary pressure is decreased. Because elevated resistance in preglomerular vessels leads to a decrease in pressure in all vessels downstream (including the glomerular capillaries), increased preglomerular resistance decreases GFR (as well as RBF). In contrast to the effects of increased preglomerular vascular resistance, increased postglomerular resistance leads to increased hydrostatic pressure in upstream segments (including the glomerular capillaries) causing an increase in GFR despite a decrease in RBF.

62. How do selective changes in renal preglomerular and postglomerular resistance alter filtration fraction?

In general, alterations in preglomerular resistance do not alter filtration fraction, whereas changes in postglomerular resistance do alter filtration fraction.

63. Summarize the influence of changes in preglomerular and postglomerular renal vascular resistance on RBF, GFR, and filtration fraction.

PREGLOMERULAR RESISTANCE	POSTGLOMERULAR RESISTANCE	RBF	GFR	FILTRATION FRACTION
⇑	=	⇓	⇓	=
=	⇑	⇓	⇑	⇑
⇓	=	⇑	⇑	=
=	⇓	⇑	⇓	⇓

64. Explain how fluid and solutes reabsorbed by the renal tubules are taken back up into the plasma.

The uptake of reabsorbed solute and water into the ECF is the primary role of the postglomerular peritubular and vasa recta capillaries. These capillaries are extremely effective for the uptake of reabsorbed substances for two reasons:

1. Hydrostatic pressure in these capillaries is fairly low—on the order of 15 mmHg in the peritubular capillaries and 6–10 mmHg in the vasa recta capillaries.
2. Oncotic pressure in these capillaries is relatively high.

Because 20% of the plasma is filtered at the glomerulus, the blood entering the efferent arteriole and continuing to the postglomerular capillaries has an elevated protein concentration and oncotic pressure (approximately 35–40 mmHg), which favors reabsorption. The balance of Starling forces for capillary exchange in these vessels is in favor (low capillary hydrostatic pressure and high capillary oncotic pressure) of net uptake of fluid back into the vasculature and the ECF.

65. Briefly describe the physiologic regulators of GFR and RBF.

A number of different systems are involved in the physiologic regulation of RBF and GFR. Hormones or autacoids that constrict the renal vasculature and **decrease RBF and GFR:**

- Endothelin
- Norepinephrine (released by sympathetic nerve stimulation)
- Angiotensin II

Factors that can **increase GFR and RBF:**

- Nitric oxide
- Bradykinin
- Prostaglandins

66. What is meant by autoregulation of GFR and RBF?

Autoregulation of GFR and RBF refers to the constancy of GFR and RBF when renal perfusion pressure is increased from 80 to 160 mmHg. To understand how autoregulation occurs, it is helpful to consider the response of tubes with a fixed resistance and those that are distensible during changes in perfusion pressure. If the renal vasculature functioned as a set of rigid tubes (fixed resistance), RBF would be predicted to increase directly with arterial pressure. Recall that blood flow (F) is directly proportional to perfusion pressure (P) and inversely proportional to resistance (R): $F \alpha P/R$. A direct increase in pressure with no change in resistance would thus lead to a proportional increase in flow. In contrast to the circumstance with rigid tubes, if the renal vasculature functioned as a set of distensible vessels, the increased perfusion pressure would dilate the vessels, and vascular resistance would decrease. Combined with the increased perfusion pressure, the fall in resistance would lead to even greater changes in flow than would be seen with rigid tubes. Instead of either of these two types of responses, RBF and GFR are maintained constant as perfusion pressure is increased.

67. How must vascular resistance change during autoregulation?

Renal vascular resistance must increase (vessel diameter must decrease) as pressure is increased to maintain GFR and RBF constant over the wide range of perfusion pressure.

68. Describe the mechanisms that lead to the autoregulation of GFR and RBF.

Autoregulation of GFR and RBF is thought to be mediated by two mechanisms:

- Myogenic response
- Tubuloglomerular feedback

The **myogenic response** is an intrinsic property of blood vessels whereby stretch of the vessel leads to a reflex contraction of the vascular smooth muscle. The myogenic response can also be observed in many vascular beds in addition to the renal vasculature. In **tubuloglomerular feedback**, increased tubular flow rate and increased NaCl transport rate in the macula densa cells initiate a feedback signal that is sent to the afferent arteriole to constrict in order to maintain a constant level of GFR and therefore tubular flow rate. In combination, the myogenic response and tubuloglomerular feedback are capable of maintaining GFR and RBF fairly constant over a wide range of arterial pressures.

69. Are GFR and RBF altered in pathologic conditions?

Any number of pathologic conditions can lead to alterations in GFR or RBF. GFR and RBF are usually decreased in both **acute** and **chronic renal failure**.

70. Define acute renal failure.

An abrupt impairment or interruption of renal function that is indicated by abnormally low or absent urinary excretion; this condition is often reversible. Acute renal failure can be caused by many conditions:

- Decreased blood supply to the kidney
- Acute injury to glomeruli or blood vessels

- Damage to renal tubules or the renal interstitium
- Obstruction of the lower urinary tract

71. Define chronic renal failure.

An irreversible and progressive loss of nephrons over an extended period of time.

72. What are the changes in GFR and RBF that occur in acute renal failure?

The rapid decrease in nephron function brought about acute renal failure is indicated by a fall in GFR, which can be determined clinically by increased serum or plasma creatinine.

73. List the types of renal vascular injury or abnormalities that can lead to acute renal failure.

Decreased blood flow to the kidney that leads to acute renal failure is known as **prerenal failure** or **acute ischemic renal failure**. Prerenal failure can be caused by the following:

- Hemorrhage
- Major surgery
- Diagnostic radiology techniques
- Severe vomiting, diarrhea, or other conditions that lead to severe dehydration, hypotension, or decreased blood volume

74. Describe glomerulonephrotic syndrome in acute renal failure.

Acute renal failure owing to glomerulonephrotic syndromes usually occurs 1–3 weeks after a **streptococcal** or **gram-negative infection**. This condition develops as a result of the deposition of antibody-antigen complexes in the glomerulus. These complexes, along with white blood cells, become entrapped in the glomeruli, reducing GFR and increasing the permeability of the glomerulus to protein. The glomerulonephrotic syndrome is therefore associated with decreased GFR and increased proteinuria. The acute glomerulonephrotic syndrome usually lasts 1–2 weeks, and renal function gradually returns to normal in the next few weeks to months.

75. Is GFR altered in chronic renal failure?

In chronic renal failure, the number of nephrons is progressively and irreversibly decreased. Although the remaining nephrons hypertrophy in an attempt to compensate for the loss of other nephrons, chronic renal failure eventually is associated with a reduction in GFR. This condition can be detected clinically as a gradual increase in serum or plasma creatinine that occurs over time (months to years).

TRANSPORT IN NEPHRON SEGMENTS

76. Name the different methods by which the kidney handles ions, nutrients, and water.

Normal renal function requires the movement of ions, essential nutrients, and water both into and out of the plasma compartment. These functions are accomplished by 3 major mechanisms:

1. Bulk filtration into the glomerulus
2. Reabsorption from the tubule into the plasma along nephron segments
3. Secretion from the plasma into the tubule at specific sites along the nephron

77. What different types of substances undergo these transport functions along the nephron?

The major **compounds** that must be transported along the nephron after filtration include glucose, proteins, and amino acids. Because ions are freely soluble in plasma, they are also freely filtered. All ions need to be reabsorbed along the nephron back into the plasma. The most critical of these **ions,** however, include Na^+, Cl^-, K^+, HCO_3^-, Ca^{++}, and Mg^{++}. Other nonessential waste products must predominantly remain in the tubular fluid, such as urea, uric acid, ammonia,

and creatinine. Most of these nonessential waste products are filtered freely, which is one of the mechanisms by which the kidneys clear the body of these compounds. In addition, **organic acids** and **bases** are transported (secreted) from the plasma into the tubular fluid as yet another mechanism for excreting substances into the urine. This function is particularly important for the removal of drugs and other pharmacologic substances from the plasma.

78. What is the filtered load of a substance?

The mass of any substance that is filtered at the glomerulus per unit time. This filtered load is critical to the tubular transport functions and ultimate renal handling of ions and filtered solutes. The **filtered load** is expressed simply as:

$$\text{Filtered load} = \text{GFR} \times [P]_x$$

where GFR = glomerular filtration rate and $[P]_x$ = the plasma concentration of any compound. (Theoretically, this equation should also factor a coefficient of filtration (k) for each compound, but for purposes of clinical use we can ignore this constant).

79. Give an example using the filtered load of Na^+ in humans.

Filtered load = GFR × $[P]_{Na^+}$

and GFR = 0.125 L/min; $[P]_{Na+}$ = 140 mM/L

Filtered Na^+ load = (0.125 L/min) × 140 mM/L

= 17.5 mM/min or approximately 25,200 mM Na^+/d

Therefore, it becomes readily apparent that the nephrons of the kidneys must have a large capacity to transport and reabsorb Na^+ because the daily filtered Na^+ load exceeds 10 times the total body Na^+.

80. Describe the filtered loads of some common plasma constituents and their percentages of tubular reabsorption into the plasma before urinary excretion.

*Quantities Involved in Urine Formation in the Human**

Fluid:
Renal blood flow (RBF) = 1200 mL/min (20–25% of cardiac output)
Renal plasma flow (RPF) = 660 mL/min
Glomerular filtration rate (GFR) = 125 mL/min
Fraction of plasma flow filtered (GFR/RPF) = 0.18–0.20

Solutes:

	PLASMA CONCENTRATION (MM)	FILTERED/DAY		EXCRETED/DAY		PERCENT REABSORBED
		mmoles	g	mmoles	g	
Sodium	140	25,200	570	103	2.3	99+
Chloride	105	18,900	660	103	3.7	99+
Bicarbonate	25	4,500	275	2	0.1	99+
Potassium	4	720	30	100	4.2	86+
Glucose	5	900	160	trace		100
Urea	5	900	50	360	20.0	60
Urate	0.3	54	9	4	0.7	93
Water		180L		1–1.5 L		99+

*Average values for a man weighing 70 kg.

81. What are the types of reabsorption that take place in the proximal convoluted tubules (PCT)?

Large amounts of fluid and solutes are reabsorbed by both passive and active mechanisms. It is the major segment of the nephron where reabsorption occurs.

82. How much of the filtered load is reabsorbed in the PCT?

The PCT is the nephron segment for **bulk** reabsorption of water and other substances back into the plasma. This segment reabsorbs approximately 67% of the filtered water, Na^+, Cl^-, K^+, and urea. Other important substances such as glucose, amino acids, and small filterable proteins are completely (100%) reabsorbed by the PCT.

67% REABSORBED	100% REABSORBED*
Filtered water	Glucose
Na^+	Amino acids
CL^-	Small filterable proteins
K^+	
Urea	

*To achieve 100% reabsorption, both passive and active processes must be involved.

83. If bulk reabsorption occurs in the PCT, is this nephron segment highly permeable to water and solute?

The PCT is often referred to as a **leaky** epithelium. In other words, both water and solutes easily cross this tubular segment, and the tight junctions between PCT cells do not afford much of a barrier to fluid movement either at the apical or at the basolateral membranes.

84. If the PCT is a leaky epithelium, what is the osmolality of tubular fluid at the end of this tubular segment?

The PCT undergoes isosmotic reabsorption, which is consistent with the leaky nature of the tubular cells in this nephron region. Thus, if the ultrafiltrate of the plasma at Bowman's capsule is isosmotic and provides tubular fluid with an osmolality of 290 mOsm/kg, the osmolality of the tubular fluid at the end of the PCT will also be 290 mOsm/kg. In other words, as solutes are reabsorbed in the PCT, water passively follows the solutes, thereby maintaining an isosmotic fluid in the tubular lumen.

85. Is filtration the only way the nephron gets substances into the tubular fluid?

No. Some substances enter the tubular fluid by active secretion from the basolateral cell membrane to the tubular lumen. These substances reach the basolateral membrane of the PCT by passive movement at the peritubular capillaries into the interstitial fluid surrounding the PCT and proximal straight tubules (PST). In addition to active secretion of substances, passive **back leak** of soluble ions is known to occur. This passive back leak from the basolateral to the apical sides of the PCT occurs only when either the concentration or electrochemical gradients favor movement in this direction. Because the PCT is leaky, water passively follows during ionic back leak, thereby maintaining isosmotic fluid in the tubular lumen.

86. What are the major classes of compounds secreted into the PCT and PST?

The major transport systems in this tubule segment for secretion are specific to organic anions and organic cations. These are the same systems that function for the secretion of PAH (organic acid). The active transport sites for these organic anions and cations are located on the basolateral membranes of the late PCT and throughout the PST.

87. What are the major mechanisms for Na^+ reabsorption in the PCT?

The most critical mechanism for reabsorbing Na^+ in the PCT is **active transport by Na^+, K^+-ATPase** located on the basolateral membrane of the tubular cell. This is the same active transport mechanism that is responsible for maintaining cell volume in cells throughout the body. The active removal of Na^+ from the cells establishes a low intracellular Na^+ and a negative intracellular electrical potential, which favors the facilitated movement of Na^+ down its electrochemical gradient from the tubular lumen into the cells. Na^+ enters the PCT cell on the apical membrane

through a number of facilitated transport processes. The PCT is particularly well suited for net reabsorption processes into the cell because of the large surface area on the brush border membrane of the apical surface. The active Na^+, K^+-ATPase extrusion of Na^+ from the cell into the interstitial compartment across the basolateral membrane produces the required concentration gradient for Na^+ between the tubular lumen and the intracellular compartment. Thus, despite the isotonic nature of the PCT tubular fluid, active transport of Na^+ out of the cell on the basolateral membrane establishes an effective concentration gradient for the movement of Na^+ from the tubular lumen into the cell across the apical membrane.

88. How important is Na^+, K^+-ATPase in the reabsorption of Na^+, Cl^-, and water in the PCT?

The active transport of Na^+ out of the cell at the basolateral membrane is essential to the reabsorption of Na^+ from the PCT. In the absence of active Na^+, K^+-ATPase at the PCT, delivery of Na^+ out of this nephron segment is approximately 65% of the filtered Na^+ load. Thus, at least two-thirds of the filtered Na^+ load is reabsorbed via mechanisms dependent on the Na^+, K^+-ATPase enzyme. This requirement is particularly important in clinical states in which severe damage is done to the proximal tubule, and the Na^+, K^+-ATPase no longer functions efficiently. These clinical manifestations are observed in conditions of renal ischemia or following exposure to certain nephrotoxic drugs that cause severe damage to PCT cells. Under these circumstances, delivery of Na^+ out of the PCT is greatly increased, and unless other tubular mechanisms downstream from the PCT are able to compensate in their reabsorption of Na^+, severe natriuresis and Na^+ loss occur.

89. What are the major anions that get reabsorbed across the PCT?

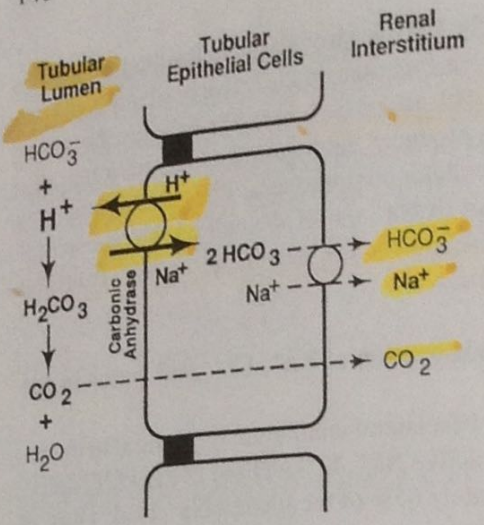
Cl^-
HCO_3^-
Anionic amino acids

90. Why is the reabsorption of these anions critically dependent on the active transport of Na^+, K^+-ATPase?

When the PCT no longer possesses the ability to extrude Na^+ from the inside of the cell, the reabsorption of major anions is greatly decreased. This is particularly noticed in various kidney diseases in which the PCT is damaged and the Na^+, K^+-ATPase activity is reduced, leading to natriuresis. This Na^+ loss is associated with significant proteinuria and increased excretion of HCO_3^- and Cl^-. These losses may lead to significant decreases in plasma oncotic pressure, hypochloremia, and alkalosis.

91. How are Na^+ and HCO_3^- reabsorption linked in the PCT?

The reabsorption of sodium bicarbonate ($NaHCO_3$) is critical to the net reabsorption of Na^+ in the proximal tubule as well as to the understanding of the regulation of urinary acidification. In addition to the Na^+, K^+-ATPase located on the basolateral membrane, the **apical** membrane possesses a Na^+-H^+ cotransporter which utilizes the electrochemical gradient favoring the movement of Na^+ into the cell from the tubular lumen in exchange for secretion of H^+ from inside the cell into the lumen. This electroneutral transporter is not only responsible for one-third of proximal tubule sodium reabsorption in the PCT, but also provides the driving force for coupled HCO_3^- reabsorption (see figure). The lumenal brush border of the PCT contains large amounts of carbonic anhydrase, which catalyze the production of carbonic acid (H_2CO_3). H_2CO_3 then dissociates into CO_2 and water, and the CO_2 diffuses into the cell down its concentration gradient. Inside the cell, an abundance of carbonic anhydrase catalyzes the synthesis of carbonic acid in the reverse direction, producing intracellular H^+ and HCO_3^-. The HCO_3^- is reabsorbed across the basolateral membrane and into the interstitium while the free H^+ becomes available to the Na^+-H^+ cotransporter for further secretion of H^+ into the tubular lumen. In this way, the PCT is able to reabsorb both Na^+ and HCO_3^-.



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92. Why is it necessary to reabsorb HCO_3^- in the form of CO_2 and water rather than by simply allowing passive HCO_3^- diffusion across the apical membrane down its concentration gradient?

Passive HCO_3- reabsorption across the apical membrane would certainly be the simplest mechanism for the dual reabsorption of $NaHCO_3$. To acidify the urine effectively, the apical membrane must maintain a relative impermeability to HCO_3-. (This process is best shown by the high reflection coefficient of the PCT apical membrane to HCO_3^-.) All cell membranes are highly permeable to dissolved gases such as CO_2. Thus, the brush border of the apical membrane of the PCT cell contains carbonic anhydrase, which helps catalyze the formation of CO_2 and H_2O from HCO_3-.

93. Does inhibition of HCO_3^- transport affect Na^+ reabsorption in the PCT?

Inhibition of HCO_3^- transport has been used as an effective "diuretic and natriuretic" agent for many years. Inhibition of carbonic anhydrase using acetazolamide (Diamox) effectively increases urinary Na^+ and HCO_3^- excretion and alkalinizes the urine. Other physiologic mechanisms of altering the PCT Na^+-H^+ exchanger may also affect tubular $NaHCO_3$ reabsorption. In this regard, metabolic or respiratory acidosis increases Na^+-H^+ exchange and increases secretion of H^+ in the PCT, whereas metabolic or respiratory alkalosis decreases the activity of the Na^+-H^+ exchange mechanism and thereby decreases urinary acidification.

94. Is Na^+ reabsorption linked to any other substances in the PCT?

A number of facilitated transport mechanisms are coupled with Na^+ in the reabsorptive process of the PCT. These Na^+-coupled transport mechanisms are located on the apical membrane of the PCT and include:

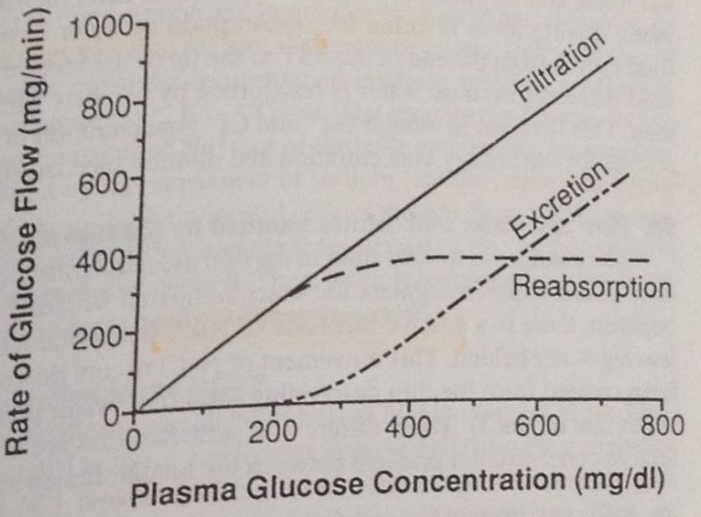
- Na^+–amino acid transporter
- Na^+–PO_4^- transporter
- Na^+–glucose transporter

Coupled Na^+-glucose Na^+–amino acid transport accounts for the complete reabsorption of the filtered load of glucose and amino acids in the PCT under normal physiologic conditions.

95. If glucose is 100% reabsorbed by the PCT, how does glucose get into the urine in diseases such as diabetes?

Because glucose undergoes a **facilitated** diffusion process, the glucose reabsorption is dependent on a fixed number of transport proteins located on the apical membrane. The relationship among plasma glucose and the rates of glucose filtration, reabsorption (via the facilitated diffusion transporter), and urinary excretion is shown in the figure. Under normal conditions, plasma glucose concentrations are less than 200 mg/dL. As plasma glucose concentrations increase, the filtration rate (or filtered load) of glucose also increases in a linear manner. The reabsorption capac-

ity of the glucose transport mechanism is able to match the filtered glucose load up to about 200 mg/dL plasma glucose concentration. At that point, the reabsorptive capacity of the glucose transporter can no longer equal the delivery of glucose from the filtered load, and glucose begins to spill into the urine. Urinary glucose excretion begins to rise such that at any plasma glucose concentration above 200 mg/dL, the sum of the excretion rate and reabsorption rate must equal the filtered load. This point where filtered load of glucose equals the reabsorptive rate of glucose is called the **transport maximum** (T_m). In pathologic conditions such as diabetes mellitus, plasma glucose often increases beyond the 200 mg/dL level because of an inability of cells throughout the body to transport glucose properly into the intracellular compartment. Under these conditions, glucose then appears in the urine as glucosuria because the filtered load of glucose exceeds the T_m for glucose.



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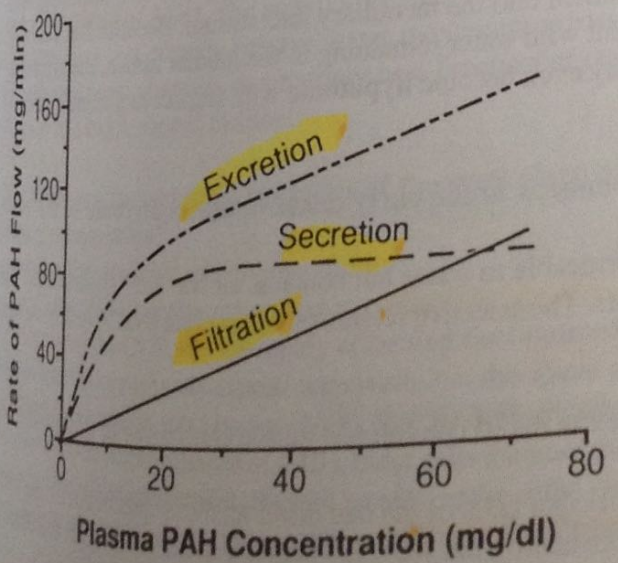
96. If a transport maximum (T_m) exists for facilitated glucose reabsorption, do similar types of T_m exist for the secretion of organic acids and bases into the tubular lumen?

All kidney transporters exhibit a T_m at a specific plasma concentration for their substrate, including transporters that are located on the basolateral membrane of the PCT such as the organic acid and organic base transporters. The relationships between plasma PAH concentrations (organic acid) and the rates of PAH excretion, secretion, and filtration are shown in the figure. Similar to glucose, as plasma concentrations of PAH are increased, the filtration rate or filtered load of PAH increases in a linear fashion. Similarly, the secretion rate of PAH increases as plasma PAH concentration increases. Because PAH is being transported from the blood into the nephron, the increase in the rate of excretion of PAH is rapid, and this excretion rate equals the sum of the secretion rate and the fil-



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tered load. Once the organic acid secretory capacity of the PCT is saturated (i.e., the T_m for organic acid secretion is reached), there is no further increase in the secretion rate of the compound, and any further elevations in plasma PAH concentration occur, the increases in excretion are equal to the rise in filtered load. In this example for the organic acid PAH, the T_m exists at a plasma PAH concentration of approximately 20 mg/dL, and the T_m for PAH secretion is approximately 80 mg/min.

97. What are the characteristics of the thin descending limb of the loop of Henle for water and solute movement?

The thin descending loop of Henle is relatively impermeable to Na^+, Cl^-, and urea but readily permeable to water. As the thin descending limb descends into the inner medulla, the interstitial solute concentration increases to as much as 1200 mOsm/L. There is, therefore, a strong osmotic driving force favoring the reabsorption of water in the thin descending limb. As tubular fluid moves from the end of the PST to the tip of the loop of Henle, the osmolality of the tubular fluid increases because water is reabsorbed by osmosis while NaCl is trapped in the tubular lumen. This increase in tubular Na^+ and Cl^- concentration in the thin descending loop of Henle is critical for the urinary concentration and dilution mechanism.

98. How are water and solutes handled by the thin ascending limb of the loop of Henle?

The changes in tubular fluid in the thin ascending limb are related to the relative impermeable state of this nephron segment for water compared with that of NaCl. Thus, in this segment of the nephron, there is a passive diffusion of NaCl out of the tubular lumen and into the interstitium, leaving water behind. This movement of NaCl occurs **down** its concentration gradient, which has been created from the thin descending limb (i.e., water permeability in thin descending limb exceeds that of NaCl). These differential permeabilities are important for helping to establish an effective concentration gradient between the tubular lumen and renal medullary interstitium.

99. Why are there no active transport mechanisms in the thin descending and ascending loops of Henle for reabsorption of ions?

The thin loops of Henle contain only simple squamous types of cells. These cells have few mitochondria, function primarily with anaerobic metabolism, and produce only small amounts of ATP required for active transport.

100. What are the most important transport characteristics of the thick ascending loops of Henle?

The medullary thick ascending limbs (MTAL) have two major functions in the reabsorption of water and solutes:

1. These cells are quite impermeable to water.
2. The cells contain a unique Na^+-K^+-$2Cl^-$ transporter that is capable of transporting large quantities of NaCl from the tubule lumen into the medullary interstitium. Because NaCl is being selectively reabsorbed in this segment with water remaining in the tubular lumen, the osmolality of the tubular fluid decreases and may even become **hypotonic** with respect to plasma by the end of the MTAL.

101. How do the transport mechanisms in the early distal tubule contribute to the reabsorption of NaCl?

The early distal tubule is impermeable to water but contains an Na^+/Cl^- cotransporter that is sensitive to thiazide diuretic agents. The selective reabsorption of solute (NaCl) in this segment further dilutes the tubular fluid.

102. How does the late portion of the distal convoluted tubule contribute to the tubular reabsorption of Na^+?

Reabsorption of Na^+ in the principal cells of the late distal tubule is dependent on the electrochemical gradient for Na^+ established by the Na^+, K^+-ATPase in the basolateral membrane.

luminal membrane Na^+ channels permit reabsorption down the electrochemical gradient and into the cells; the Na^+, K^+-ATPase in the basolateral membrane then removes the reabsorbed Na^+ from the cells. In addition to the reabsorption of Na^+, these cells are also important in the secretion of K^+. The Na^+, K^+-ATPase in the basolateral membrane moves K^+ into the cells and K^+ exits the cells through channels in the apical membrane.

103. How is Na^+ reabsorption controlled in the principal cells of the distal convoluted tubule (DCT) and cortical collecting duct?

Aldosterone (a steroid) affects distal convoluted tubules primarily by increasing Na^+, K^+-ATPase activity in the basolateral membrane and by increasing the apical membrane permeability for Na^+. After combining with its specific receptor in the cell cytoplasm, aldosterone moves to the nuclear membrane, where it activates the transcription and translation of specific apical membrane Na^+ channels. Insertion of these Na^+ channels into the apical membrane allows increased flux of Na^+ into the cell from the tubular lumen down the concentration gradient, which is continually maintained by the activity of the basolateral Na^+, K^+-ATPase. The increased substrate for the ATPase enzyme (Na^+) provides active transport of Na^+ out of the cells and into the interstitium. The reabsorption of sodium is completed by the movement of sodium into the peritubular capillaries and plasma. In contrast to the MTAL cells, the principal cells of the late distal tubule are water impermeable in the presence of antidiuretic hormone, and the reabsorption of Na^+ in this nephron segment can be associated with water reabsorption as well. Thus, water is reabsorbed in distal convoluted tubules under conditions when the body needs to conserve water.

104. Is Na^+ the only critical ion controlled at the DCT?

No. Because Na^+ reabsorption in the distal convoluted tubule is highly coupled to the Na^+, K^+-ATPase, Na^+ reabsorption is associated with K^+ movement into the cell from the extracellular space. In this regard, K^+ secretion (K^+ movement from basolateral to apical membranes) is heavily controlled in distal convoluted tubules by the presence or absence of aldosterone. Thus, although simultaneously stimulating Na^+ reabsorption at the basolateral membrane, the concentration gradient for K^+ is created, which favors K^+ movement from inside the cell into the tubular lumen. Aldosterone, therefore, is known not only for its critical ability to stimulate Na^+ reabsorption, but also for its direct effects to enhance K^+ removal from the plasma and excretion into the urine.

105. What are the functions of the cortical collecting tubule (CCT) in determining the final composition of the tubular fluid (urine)?

The CCT provides reabsorption of small amounts of remaining Na^+ in the tubular fluid. The primary function of the CCT is the **reabsorption of water**. These tubular cells specifically express a family of water channels called **aquaporins** at both the apical (aquaporin 2) and the basolateral (aquaporin 4) membranes. The insertion of the aquaporins in the apical membrane are under the control of ADH. The aquaporins are a unique family of proteins with selective and specific structures that provide passive water movement across cell membranes. Water movement through aquaporin channels occurs only as a function of osmotic gradients, and these channels function in a bidirectional fashion.

106. What are the primary purposes of the medullary collecting duct in the regulation of urinary composition?

- Regulate the final urinary osmolality
- Control water reabsorption and excretion

Similar to the CCT, the medullary collecting duct promotes water reabsorption by expressing aquaporins. These segments express aquaporin 2 in the apical membranes in the presence of ADH, also known as arginine vasopressin (AVP). The medullary collecting duct cells are normally impermeable to water. In the presence of ADH, these cells increase their expression and insertion of aquaporins into the apical membranes, thereby increasing the cells' permeability to water. During states of dehydration, the osmolality of the medullary and papillary interstitium is high, providing a strong os-

motic gradient for the movement of water across the cell membrane and into the interstitium. This **reabsorbed** water is then removed by the ascending vasa recta and returned to the circulation.

URINARY CONCENTRATION AND DILUTION

107. What are some of the different abilities of species to concentrate their urine?

The relative urinary concentrating capacity of different animals depends on the availability of water in their environments and habitats as well as the composition of the diet of each respective species. For example, humans exist in an environment of plentiful water availability and, therefore, concentrate their urine to a maximal level of only 1200 mOsm/kg. This degree of urinary concentrating ability in humans is contrasted to numerous desert-dwelling rodents that may concentrate their urine from 5000 to 7000 mOsm/kg during severe dehydration. Dilution of the urine (i.e., excretion of water loads) is effective in all species. The ability to excrete large quantities of water in a short period of time is provided by the rapid ability of animals to reduce their urine osmolality to 50 Osm/kg or less.

108. Is the excretion of a hypertonic or hypotonic urine necessary for the maintenance of homeostasis?

The ability of the mammalian kidney to produce a dilute or concentrated urine enables our bodies to excrete or conserve water while maintaining a relative constancy of solute excretion. In conditions when excess fluids have been ingested, the kidney can form a dilute or hypotonic urine to excrete excess water. In contrast, in conditions when total body water must be conserved, our kidneys produce a concentrated or hypertonic urine, which enables the conservation of water with the normal excretion of solute. Some examples of conditions that lead to a loss of total body water are listed in the table:

SECONDARY TO NORMAL FUNCTIONS (INSENSIBLE WATER LOSSES)	SECONDARY TO EXCESS WATER LOST AFTER ENVIRONMENTAL REINTUBATIONS
Breathing	Excessive heat exposure
Sweating	Prolonged exercise
	Fever
	Diarrhea

109. Does the kidney have a constant interstitial fluid osmolality from the cortex to the papilla?

Interstitial osmolalities range from 290 mOsm/kg in the cortex (essentially equivalent to plasma) to potentially high interstitial fluid osmolalities equivalent to the maximal urinary concentrating ability in the inner medulla. In humans, interstitial osmolality can increase to approximately 1200 mOsm/kg after 24 hours of water restriction.

110. How does the medullary interstitial concentration gradient contribute to the final concentration of the urine?

The concentration gradient found in the interstitial space from the cortex to the medulla of the kidney is absolutely essential for the production of both a concentrated and a dilute urine. Under normal circumstances, the body loses water because of respiration and sweat. Thus, the kidney is constantly being presented with a condition that requires the reabsorption and preservation of water. The presence of a hypertonic renal interstitium allows the appropriate movement of water **from** the tubular lumen **to** the interstitial fluid and back into the blood. Under these normal conditions in which water reabsorption is of primary importance, the final concentration of the urine is determined by the concentration of the renal interstitium within the deepest portions of the kidney (i.e., the inner medulla). As discussed below, the movement of water out of the late distal tubule and the cortical and medullary collecting duct is entirely dependent on the presence of ADH.

111. Does the PCT contribute to the final urinary concentration?

The PCT is responsible for the **bulk** reabsorption of water via isotonic transport mechanisms. Thus, in the PCT, the reabsorption of water is an **isosmotic** bulk flow of fluid. If the reabsorption in these segments is isosmotic, the osmolality of the tubular fluid is not changed and, therefore, is not concentrated further above that of plasma. Thus, although these nephron segments are extremely important for the bulk reabsorption of NaCl, water, and other ions, they do not contribute directly to producing a concentrated urine.

112. If the PCT provides bulk reabsorption, does urea get reabsorbed in the PCT as well?

Urea is reabsorbed in the PCT in the same bulk manner as all other filtered substances. Approximately 67% of the filtered urea in the PCT is reabsorbed back into the interstitium.

113. Is the PCT important in water reabsorption even though it does not participate in forming the final concentration of the urine?

The PCT is absolutely essential to the net reabsorption of water. Approximately two-thirds of the filtered load of water is reabsorbed in the PCT along with the other bulk reabsorbed filtered substances. In pathologic conditions in which the reabsorptive processes of the PCT are damaged (e.g., acute renal failure), there may be water loss via lack of the necessary reabsorption in this nephron segment. The contribution of the PCT to overall water reabsorption is therefore **critical to maintaining net water balance of the organism,** even though this nephron segment does not provide a mechanism for specifically changing the osmolality of the urine.

114. What are the major ionic components responsible for generating hypertonic urine?

A concentrated renal inner medullary interstitium is required to create an osmotic gradient for the reabsorption of water from the lumen of the collecting duct into the interstitial spaces. This concentration gradient is established by the excess concentration of NaCl and urea in the interstitial space of the inner medulla. This creates a hypertonic environment in the interstitial space surrounding the medullary collecting ducts and provides a driving force for water reabsorption in these distal tubular segments.

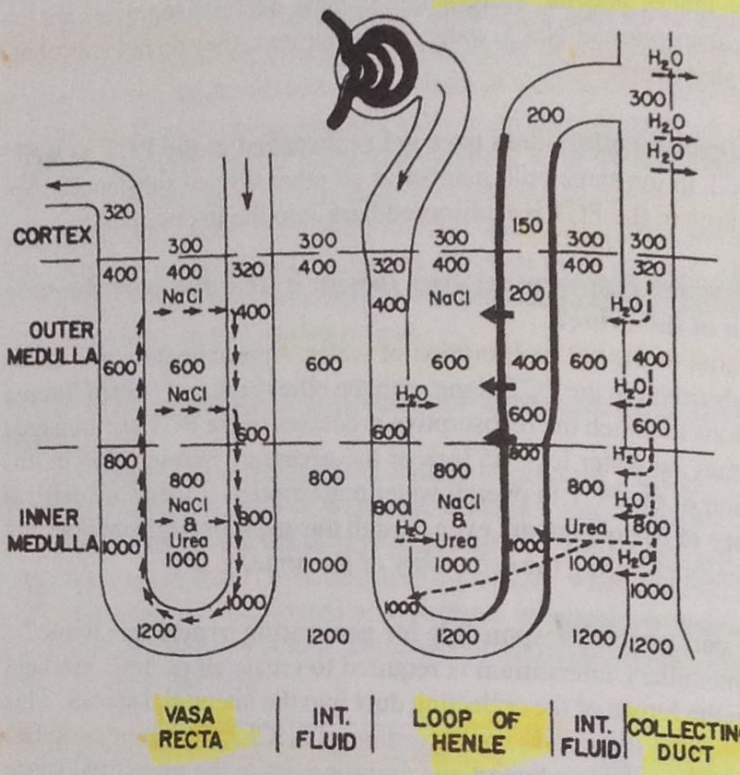
115. With the creation of a hypertonic inner medulla, how does water then get reabsorbed?

Under circumstances of water loading, the late distal tubule and collecting ducts are relatively **impermeable** to water. Therefore, the tubular fluid remaining within the nephron at the late distal tubule is excreted into the urine with an osmolality that is hypotonic to plasma. In the presence of ADH, the late distal tubule and collecting ducts become permeable to water; under these circumstances, water will be reabsorbed by osmosis from the tubular lumen into the interstitial space. Because the interstitial osmolality is hypertonic in the renal medulla, the urine excreted is hypertonic.

116. How does the kidney establish a differential concentration gradient from the cortex to the inner medulla during water deprivation?

The kidney generates a hypertonic inner medullary interstitium by both passive and active transport mechanisms. The degree of hypertonicity achieved is directly proportional to the length of the loop of Henle, such that the longer the loop of Henle, the greater the capacity to concentrate solutes in the inner medulla and consequently to concentrate the urine. The passive mechanisms reside primarily in the thin descending and ascending limbs of the loop of Henle. The thin descending limb is relatively impermeable to NaCl and urea with respect to water, whereas the thin ascending limb is relatively impermeable to water compared with the reabsorption of NaCl. Thus, in the thin descending limb, water is reabsorbed by osmosis leading to the concentration of solutes and the formation of hypertonic tubular fluid at the tip of the loop of Henle. In the thin ascending limb, the concentrated NaCl in the tubular lumen then moves out of the lumen down its concentration gradient. The active mechanism for creating a concentration of solutes in the renal medulla is the Na^+-K^+-Cl^- cotransporter of the thick ascending limb. The thick ascending limbs are impermeable to water. When Na^+ and Cl^- are actively reabsorbed in this segment in the ab-

sence of water reabsorption, the tubular fluid becomes dilute with osmolalities decreasing to levels as low as 100 mOsm/kg or less. The close proximity of the thin descending and ascending limbs provides the perfect juxtaposition of nephron segments for establishing a **countercurrent exchange** of solutes (see figure) and, in essence, for **trapping** the ions within the renal medulla and papilla.



(From Guyton AC, Hall JE: Textbook of Medical Physiology. 9th ed. Philadelphia, W.B. Saunders, 1996, with permission.)

117. What is the role of the vasa recta capillaries?

The function of the vasa recta capillaries is to deliver nutritive substances to the structures of the renal medulla and to reabsorb water and solutes reabsorbed in the loop of Henle and collecting ducts. The descending and ascending vasa recta are positioned within the inner medulla and papilla in close juxtaposition with the descending and ascending limbs of the loop of Henle as well as the medullary and papillary collecting ducts. These groups of tubules and capillaries are closely associated into bundles called **medullary rays**.

The vasa recta are capillaries that allow free exchange between the blood and interstitial compartments. In essence, they provide the conduit for returning reabsorbed water back to the renal vein and central circulation. When water is reabsorbed from the collecting duct (in the presence of ADH) down the concentration gradient that has been established in the hypertonic renal interstitium, the gradient may be lost because of dilution of the Na^+, Cl^-, and urea. Because the osmolarity of blood within the vasa recta equilibrates with the interstitial space, the reabsorbed water equilibrates with the blood in the ascending vasa recta. This is where the circuit of water reabsorption is then completed with water moving into the ascending vasa recta and returning to the central circulation.

118. Is urea absorption critical to the overall concentrating ability of the renal papilla?

Urea contributes to the medullary interstitial concentration gradient by being reabsorbed from the tubular fluid in the collecting duct. Reabsorption at the collecting duct is wholly dependent on the presence of ADH; this nephron segment remains impermeable to urea in the absence of ADH. Reabsorption of urea is important to the overall ability of the kidney to produce a concentrated urine. In the absence of urea reabsorption in the inner medulla, the ability of the kidney to reabsorb water and hence concentrate the urine is greatly impaired.

119. How does the MTAL contribute to the overall cortical-papillary concentration gradient?

The MTAL can be thought of as the engine that drives the concentration of urine. The reabsorption by the Na^+-K^+-$2Cl^-$ transporter on the apical membrane is driven by the electrochemical gradient for Na^+, which is established by the Na^+, K^+ ATPase on the basolateral membranes of this segment. The critical nature of this transporter in the generation of a concentrated urine is best demonstrated by the use of **loop diuretics,** such as furosemide and bumetanide. These diuretics block the MTAL cotransporter and prevent the reabsorption of NaCl in these segment of the nephron. These drugs not only cause profound natriuresis, but also prevent water reabsorption because the medullary interstitial concentration gradient is effectively abolished by these compounds. Thus, the urinary osmolality is not increased beyond that of plasma, even in the presence of sufficient ADH, because the medullary interstitial space no longer contains sufficient solutes to provide an adequate gradient for the reabsorption of water from the collecting ducts.

120. What is meant by countercurrent multiplication?

This general physiologic term describes the physical juxtaposition of fluids flowing in close proximity to one another but in opposite directions. In the case of the kidney, **countercurrent multiplication** is used in both the loop of Henle segment of the nephron and in the vasa recta capillaries, both of which descend deeply into the renal medulla. In each of these structures, there is flow of fluid in opposite directions and in close proximity to one another. In the case of the loop of Henle, the descending limb maintains different permeability properties compared with the ascending limb. This allows the creation of different concentration gradients in each of these limbs and creates the continual flow of ions out of the ascending limb, thereby effectively **concentrating** those ions secondary to the **countercurrents** of tubular fluid flow in close proximity to one another. Thus, the countercurrent multiplier is essential for the maintenance of an effective interstitial concentration gradient between the cortex and papilla.

121. How does the kidney produce a dilute urine?

Dilution of the urine is equally critical for the appropriate maintenance of plasma volume and water balance. Several factors account for the effective production of a dilute urine and **washout** of the cortical papillary concentration gradient.

1. Water ingestion decreases plasma ADH; therefore, the late distal tubule and collecting duct become relatively impermeable to water and urea. In the absence of ADH, water reabsorption in the distal segments of the tubule is minimal, and the final urine will have an osmolality similar to that of the hypotonic tubular fluid found in the early distal tubule.

2. The loss of urea reabsorption at the collecting duct decreases the osmotic concentration of the medullary interstitium. The dilution of the plasma by the ingested water creates a gradient in the ascending vasa recta for movement of NaCl and urea into the blood and out of the medullary interstitium. This loss of osmotic activity in the inner medulla effectively **washes out** the cortical-medullary concentration gradient. In the absence of a concentration gradient, any remaining permeability of the collecting duct cells does not result in the reabsorption of water because the medullary osmotic gradient has been diminished.

122. What is the time frame for washout of the cortical-papillary concentration gradient during the elimination of a water load?

After ingestion of 1 L of water in a normal adult over a 30-minute period, the concentration gradient is effectively eliminated within 20 minutes, and the urine osmolality decreases from concentrated values of 600–1000 mOsm/kg to 300 or less. Within 1 hour after ingestion of this load, urine osmolality can be as low as 50 mOsm/kg, which is significantly less than that of plasma. Thus, the kidney's osmotic gradient is effectively removed, the urine osmolality is more dilute than plasma, and the body is effectively eliminating free water from the circulation.

REGULATION OF PLASMA OSMOLALITY

123. What is the normal range of plasma osmolality (P_{osm}) in humans?

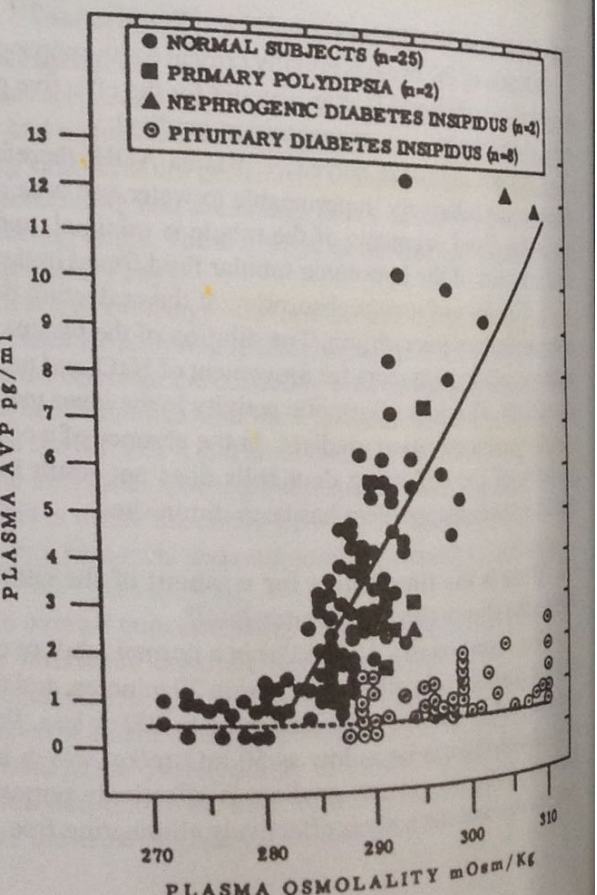
The normal range of P_{osm} in humans is 260–310 mOsm/kg. This range represents the extremes from overhydration (260 mOsm/kg) to severe dehydration (310 mOsm/kg). Under normal states of hydration, the P_{osm} is approximately 290 mOsm/kg.

124. What is the primary hormone responsible for the control of P_{osm}?

The regulation of water balance and P_{osm} is under unique control by ADH, which is synthesized in the hypothalamic regions of the brain by magnocellular neurons located predominantly in the supraoptic and paraventricular nuclei. These nuclei provide neural projections into the hypophyseal stalk with terminals located in the neurohypophysis.

125. How is ADH release from the neurohypophysis controlled?

The exact cellular mechanisms responsible for the control of ADH release remains unknown. What is known and well documented is that specialized cells within the anteroventral region of the hypothalamus, a portion of the brain that lacks the blood-brain barrier, sense the change in P_{osm} and function as an osmoreceptor. When P_{osm} is elevated, indicating relative dehydration, the cells shrink and send neural signals to the supraoptic and paraventricular nuclei, resulting in the release of ADH from granulated nerve terminals. When P_{osm} is reduced from normal values, the cell bodies of these neurons are thought to expand or swell and inhibit the release of ADH from their neuronal projections. The relationships between P_{osm} and plasma ADH concentrations are shown in the figure. These data show that the entire range of P_{osm} is essentially regulated over a narrow range of plasma concentrations of ADH (i.e., 0–12 pg/mL). (See figure.)



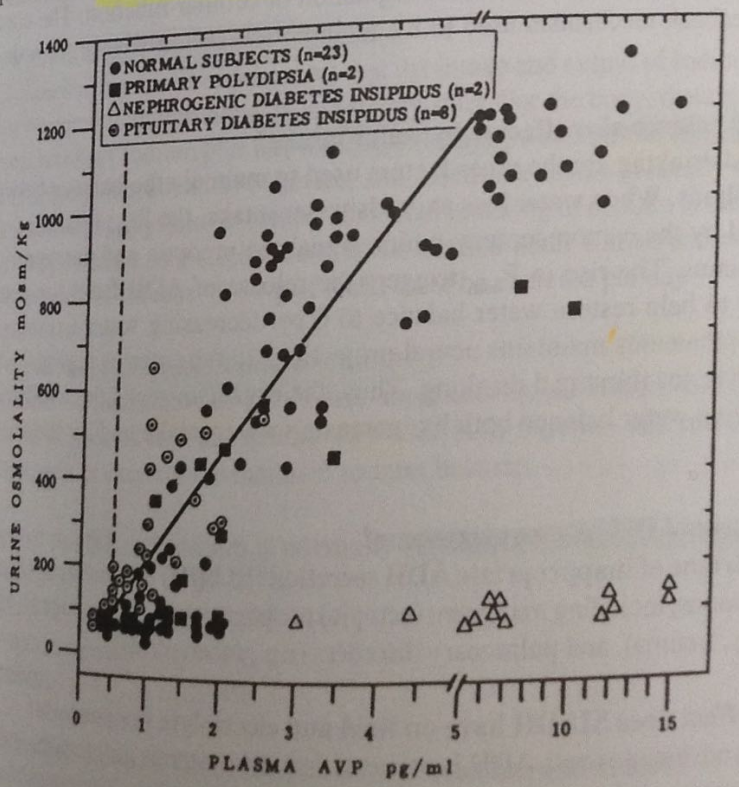
(From Robertson GL, Mahr EA, Athar S, Sinha T: Development and clinical application of a new method for the radioimmunoassay of arginine vasopressin in human plasma. J Clin Invest 52: 2340–2352, 1973, with permission.)

126. If regulation of total body water is critical for the maintenance of life, are there sensors for body fluid volumes that may also affect ADH release?

The other major sensors of body fluid volume are the low-pressure baroreceptors located in the right and left atria and in the vena cava just outside the right atrium. These are called **low-pressure baroreceptors** because they function in regions of the cardiovascular system where the vascular pressure is relatively low and does not undergo wide variations on a beat-to-beat basis. These baroreceptors sense the relative **stretch** or volume of blood entering the heart from the body and from the pulmonary circulation. The neural projections from these volume sensors enter the central nervous system via cranial nerve X (vagus) and reflexively regulate the release of ADH from the neurohypophysis. In this regard, when plasma volume is elevated (i.e., overhydration and low P_{osm}), stimulation of these receptors by excess stretch invokes an inhibitory reflex to decrease the release of ADH from the neurohypophysis. Conversely, when plasma volume is reduced (i.e., dehydration and increased P_{osm}), the reduced stretch on these low-pressure volume receptors decreases the inhibitory nerve fiber activity to the central nervous system and increases ADH release.

127. How does ADH increase or decrease plasma osmolality?

The release of ADH increases the permeability of the collecting duct to water and therefore increases water reabsorption and urine osmolality (see figure). The reabsorption of water from the collecting ducts directly enters the blood. ADH controls water independently of other ions and solutes. The nephron site of ADH's major effect is the late distal tubule and collecting duct. At this point in the nephron, nearly all of the solutes and osmotically active particles have already been reabsorbed. Thus, free water enters the bloodstream, diluting other ions and osmotically active particles, which decreases the P_{osm}. In contrast, when ADH release is decreased, the medullary and papillary collecting ducts remain relatively impermeable to water, and the net excretion of water is increased. Again, this water loss occurs in the absence of appreciable loss of ions; therefore, a net loss of free water occurs. This process provides a critical pathway for increasing the net concentration of ionic and osmotically active particles in the plasma compartment, thereby providing a net increase in P_{osm}.



(From Dunn FL, Brennan TJ, Nelson AE, Robertson GL: The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J Clin Invest 52:3212–3219, 1973, with permission.)

128. How is the relative clearance of water determined?

The clearance of water is termed **free water clearance** (C_{H_2O}) (i.e., the water that is cleared from the plasma that is free of osmotically active particles). C_{H_2O} must be equal to the urine flow less the osmolar clearance or clearance of osmotic substances:

$$C_{H_2O} = UF - C_{osm}$$

Because $C_{osm} = V \times U_{osm}/P_{osm}$, by simple substitution:

$$C_{H_2O} = UF - [V \times (U_{osm}/P_{osm})]$$

In most cases, the value for C_{H_2O} is a negative value. For example, during normal states of hydration:

U_{osm} = 700 mOsm/kg
UF = 1 mL/min
P_{osm} = 290 mOsm/kg

C_{H_2O} calculates to be –1.40 mL/min. This means that 1.40 mL/min of water that is free of osmotically active particles is being **reabsorbed** or returned from the tubular fluid back into the plasma every minute. When C_{H_2O} is positive, the organism is in a state of overhydration, and there is a net excretion of **free** water into the urine.

129. What is water balance?

The relationship between water intake and water loss. Although water loss is regulated primarily by controlling water excretion into the urine, it also includes the removal of water from the body as a result of other sources that are not easily regulated: respiration, sweating, and fecal water. On the average, water balance must always be equal to 0.

130. Why is water balance important for normal homeostasis?

When water balance does not equal 0, the organism is in a relative state of either dehydration (net water loss) or overhydration (water gain). Because the body is approximately 65% water, this delicate balance is critical for the overall regulation of cellular function. The control of C_{H_2O} is the body's feedback mechanism used to maintain normal water balance from the standpoint of water loss.

131. Is water balance also affected by water intake?

Thirst and drinking are the other factors used to maintain the balance between intake and excretion of fluids. When water loss exceeds water intake, the P_{osm} increases, and this rise in P_{osm} is sensed by the osmoreceptors, which signal the preoptic and paraventricular nuclei of the hypothalamus. The rise in P_{osm} triggers the release of ADH from the neurohypophysis, which serves to help restore water balance to 0 by decreasing water excretion. At the same time, the hypothalamus maintains neural projections to the anterior regions, which signal the desire and drive for thirst and drinking. Thus, the organism seeks the available water for resolving negative water balance both by increasing water intake and by reducing water excretion.

132. Does excess ADH release ever occur?

The **syndrome of inappropriate ADH secretion (SIADH)** is sometimes observed in patients for various reasons, including malignant (ectopic) neoplasms (e.g., bronchogenic carcinoma), CNS disorders (e.g., trauma), and pulmonary disorders (e.g., tuberculosis).

133. What effect does SIADH have on fluid and electrolyte homeostasis?

In this syndrome, excess ADH is released into the systemic circulation, and the hypothalamus no longer responds to normal changes in plasma osmolality. The elevated plasma concentrations of ADH maintain the kidneys in a constant state of water reabsorption leading to excess

retention of water. A number of electrolyte disturbances result from this syndrome, including hypokalemia, hyponatremia, and decreased plasma oncotic pressure.

134. What are the functional consequences of a lack of ADH release?

The lack of circulating ADH is the form of diabetes termed **diabetes insipidus**. In the absence of ADH, the organism tends to have excess urine flow and water excretion, because without ADH, the collecting ducts are relatively impermeable to water. Thus, individuals with diabetes insipidus are in a **permanent** state of water loss because of excess renal excretion of water. Under these circumstances, P_{osm} increases, causing continual thirst and drinking. These individuals seek water on a continual basis and maintain their normal water balance primarily through the thirst mechanism.

Diabetes insipidus may be caused by deficiencies in either **hypothalamic** or **renal** mechanisms. **Hypothalamic** diabetes insipidus is the lack of ADH secretion and release from the neurohypophysis. This form of diabetes insipidus can be treated easily with administration of ADH on a regular basis. In **nephrogenic** diabetes insipidus, the hypothalamopituitary axis secretes ADH normally, but the distal tubules and collecting ducts do not respond appropriately to the presence of the hormone. Effective treatment for nephrogenic diabetes insipidus has not yet been developed.

REGULATION OF SODIUM EXCRETION AND PLASMA VOLUME

135. Why is the regulation of sodium intake and excretion important in plasma volume regulation?

The regulation of sodium intake and output is extremely important in the regulation and maintenance of a normal plasma volume. The major cation found in the ECF is sodium with its accompanying anions (primarily chloride and bicarbonate). Together, these ions comprise greater than 90% of the osmolytes in the ECF. Because plasma osmolarity is tightly controlled by ADH, which regulates renal water handling, any changes in extracellular sodium lead to changes in ADH and the accompanying changes in plasma volume.

136. Explain what is meant by sodium balance.

The term *balance* refers to the requirement that the intake and output of sodium (or any other substance) must be equal if an individual is in a steady state. For the body, dietary sodium intake must equal the excretion of sodium plus any insensible losses, sweating, and fecal losses. Because sodium intake is largely dependent on behavior, and insensible losses generally are quite small and usually not under tight physiologic control, the renal handling of sodium is the critical link to ensure that the body remains in a steady state. If the normal adult human consumes 8–10 g of NaCl per day, to remain in balance, 8–10 g of NaCl must be excreted per day.

137. How do the kidneys normally handle sodium?

Kidneys handle sodium through two basic mechanisms: **filtration** and **reabsorption**. Changes in neural, hormonal, and physical factors alter both filtration and reabsorption to decrease or increase sodium excretion to maintain sodium balance.

138. How much of the filtered sodium is normally reabsorbed in each tubular segment?

Proximal tubule	60–70%
Loop of Henle	20–25%
Distal convoluted tubule	3–5%
Collecting duct	2–4%

139. Why does reabsorption of filtered sodium vary from normal values?

Values vary depending on the volume status of the individual. When excess sodium must be excreted, reabsorption decreases to increase excretion. In contrast, in cases of volume depletion

in which sodium must be conserved, sodium reabsorption is increased in the individually regulated nephron segments.

140. Summarize how changes in sodium intake and plasma volume can be sensed by the body.

Changes in plasma volume are sensed by the body at three main sites:

1. Low-pressure baroreceptors on the venous side of the systemic circulation
2. High-pressure baroreceptors on the arterial side of the systemic circulation
3. Intrarenal mechanisms (intrarenal baroreceptor and macula densa)

141. Where are the low-pressure baroreceptors?

Low-pressure baroreceptors are located within the **great veins**, the **atria**, and the **pulmonary vasculature**.

142. How do the low-pressure baroreceptors affect renal function?

Because they are located on the low-pressure side of the circulation, low-pressure baroreceptors respond to changes in fullness or central filling pressure by stretching and sending afferent signals via the vagus nerve to the cardiovascular control center in the hypothalamus and brain stem. In this region of the brain, the signals from the low-pressure and high-pressure baroreceptors are integrated, and reflex changes in renal nerve activity and arginine vasopressin release are mediated. In general, a change in venous volume of 5–10% is usually required before the low-pressure baroreceptors are activated.

143. Where are the high-pressure baroreceptors?

High-pressure baroreceptors are found in the **aortic arch** and **carotid artery**.

144. How do the high-pressure baroreceptors affect renal function?

These baroreceptors respond to changes in arterial pressure with afferent signals sent to the cardiovascular control center, where changes in renal sympathetic activity and arginine vasopressin release are regulated. These baroreceptors are fast acting and respond to a 5–10% change in arterial pressure. Despite the sensitivity of the arterial baroreceptors, much larger changes in volume occur in the highly compliant venous circulation before systemic arterial pressure is elevated 5–10%. The high-pressure baroreceptors therefore are not as sensitive to changes in plasma volume as the low-pressure baroreceptors.

145. What are the intrarenal mechanisms that sense changes in plasma volume?

Intrarenal baroreceptor
Macula densa

146. How do they function?

The **intrarenal baroreceptor** is a mechanism by which alterations in stretch of the afferent arteriole lead to changes in renin release. If increased intrarenal arterial pressure is sensed, renin release is inhibited. Conversely, renin release is stimulated when there is decreased stretch of the afferent arteriole.

The **macula densa** also alters renin release after changes in NaCl delivery. In response to increased NaCl delivery to this nephron segment, the macula densa signals the juxtaglomerular cells to release renin. When sodium chloride delivery to this segment is increased, the signal to the juxtaglomerular cells is to decrease renin release.

147. Explain how the signals from the high-pressure and low-pressure baroreceptors, the intrarenal baroreceptors, and the macula densa are integrated to regulate renal sodium handling.

The intrarenal and extrarenal mechanisms that sense the **fullness** of the extracellular space act in concert to regulate the renal handling of sodium. When volume is sensed to be high and

increased sodium is delivered to the macula densa, the systems involved in the conservation of sodium and water are suppressed or inactivated, depending on the degree of fullness of the system. In contrast, when the volume (pressure) is judged to be low and macula densa sodium delivery is decreased, the systems that favor the conservation of sodium and water are activated.

148. List the systems primarily involved in sodium and plasma volume regulation.

Renin-angiotensin
Aldosterone
Renal sympathetic nerves
Atrial natriuretic peptide
ADH
Physical factors

149. What is the renin-angiotensin system?

The renin-angiotensin system is a cascade of biochemical reactions that leads to increased levels of the biologically active octapeptide angiotensin II. Renin is an enzyme found in the juxtaglomerular cells of the renal afferent arteriole; when this enzyme is released into the circulation, it cleaves angiotensinogen, a circulating polypeptide produced by the liver, into the decapeptide angiotensin I. Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme, which is found in endothelial cells in the lung and the kidney. By themselves, renin, angiotensinogen, angiotensin I, and angiotensin-converting enzyme have little to no biologic activity. The active peptide is angiotensin II, which is a potent vasoconstrictor, stimulator of aldosterone release, and stimulator of tubular sodium reabsorption.

150. Name the stimuli that activate the renin-angiotensin system.

1. **Reductions in renal perfusion pressure** are sensed by intrarenal baroreceptors in the afferent arteriole, which leads to renin release.
2. **Decreased delivery of NaCl to the macula densa** also stimulates renin release from the juxtaglomerular cells.
3. **Stimulation of renal sympathetic nerves** directly increases renin release.

Each of these stimuli is activated when the body needs to conserve or retain sodium.

151. What are the principal effects of the renin-angiotensin system on renal function?

The overall effect of the renin-angiotensin system is to **decrease sodium and water excretion** by decreasing filtered load and increasing tubular sodium reabsorption. Angiotensin II is a potent systemic vasoconstrictor, and stimulation of the renin-angiotensin system also leads to **increased total peripheral resistance,** which tends to increase blood pressure by direct effects. The renin angiotensin system is activated in conditions when sodium needs to be conserved.

152. How does the renin-angiotensin system alter renal vascular function?

Angiotensin II increases renal vascular resistance. In the human kidney, this peptide appears to constrict the efferent arteriole preferentially at normal circulating levels. After hemorrhage or other insults that lead to hypovolemia or lowering of renal perfusion pressure, elevated levels of angiotensin II constrict the preglomerular vasculature as well as the postglomerular efferent arteriole, leading to a decrease in GFR and RBF.

153. Does the renin-angiotensin system influence tubular sodium transport?

Angiotensin II directly stimulates proximal tubule sodium reabsorption. Angiotensin II also acts at the level of the adrenal gland to increase aldosterone secretion; aldosterone then has potent effects to stimulate sodium reabsorption and potassium secretion in the distal portions of the nephron.

154. What is aldosterone?

A mineralocorticoid produced in the zona glomerulosa of the adrenal gland. In response to increased angiotensin II or increased extracellular potassium levels, the synthesis of aldosterone

and its release into the blood are increased. Of the two stimuli for aldosterone release, changes in extracellular potassium are the most potent.

155. How does aldosterone affect renal function?

The net effect of aldosterone on renal function is to **decrease sodium excretion** and **increase potassium excretion** without affecting renal hemodynamics (GFR and RBF). The mechanism of aldosterone action occurs at the level of the connecting tubule and collecting duct, where this steroid hormone binds to cytoplasmic receptors. This binding leads to increased synthesis and insertion of sodium channels into the tubular membranes to increase sodium reabsorption in exchange for potassium, which is secreted into the tubular lumen.

156. What is meant by *physical factors*, and how do physical factors affect renal sodium handling?

This a term used to describe collectively changes in hydrostatic and oncotic forces in the capillaries and renal interstitial space.

1. In the case of an expansion of ECF volume, plasma protein is diluted (plasma oncotic pressure decreases), and glomerular and peritubular capillary hydrostatic pressure increases. Increased glomerular capillary pressure increases the driving force for ultrafiltration, whereas dilution of plasma protein decreases the forces opposing filtration; for these reasons, the filtered load of sodium increases under volume-expanded conditions.
2. The increase in capillary hydrostatic pressure and decrease in plasma protein lead to less favorable conditions (elevated hydrostatic and reduced oncotic pressure) for reabsorption in the peritubular and vasa recta capillaries and tend to reduce the reabsorption of fluid from the tubules.

157. Explain how renal sympathetic nerves affect sodium handling.

In response to decreased volume and stretch from the low-pressure and high-pressure baroreceptors, renal sympathetic nerves are stimulated. The renal sympathetic nerves are activated in conditions of hypovolemia and serve to retain sodium. Renal sympathetic stimulation leads to sodium retention by three mechanisms:

- Decreasing filtered load
- Increasing tubular reabsorption
- Increasing renin release

158. What is atrial natriuretic factor?

A peptide found in the atria and great veins that is released in response to increased atrial stretch (increased ECF volume); also known as atrial natriuretic peptide.

159. What does atrial natriuretic factor do to affect renal function?

When atrial natriuretic factor is released, it increases sodium and water excretion by increasing GFR and decreasing collecting duct sodium reabsorption. Atrial natriuretic peptide is released in conditions of hypervolemia and acts to increase sodium excretion.

160. What is the pressure-natriuretic-diuretic mechanism?

The phenomenon by which increased renal perfusion pressure leads to an increase in sodium and water excretion owing to an intrinsic property of the kidney. The increased sodium and water excretion serves to decrease ECF volume and leads to a normalization of arterial pressure. Conversely, when arterial pressure is decreased, the pressure-natriuretic mechanism is shifted to a lower operating point, and the kidney tends to decrease sodium and water excretion to increase extracellular volume and return arterial pressure to control levels.

161. What is the importance of the pressure-natriuretic-diuretic mechanism?

This intrinsic feedback mechanism of the kidney is hypothesized by some scientists as one of the primary regulators of ECF volume and arterial blood pressure.

162. List other paracrine or autocrine systems or mechanisms that can alter renal sodium handling.

Natriuretic or Diuretic	*Antinatriuretic or Antidiuretic*
Prostaglandins	Thromboxane
Nitric oxide	Endothelin
Urodilatin	
Kinins	

163. How do all these systems act to regulate plasma volume?

The different neural, hormonal, and intrinsic mechanisms that regulate sodium and water excretion act in an integrated fashion in response to changes in sodium and water intake to maintain homeostasis. When dietary sodium is increased, output lags behind intake, and ECF space is expanded. The ECF expansion triggers a number of events:

- Activation of low-pressure baroreceptors, which inhibits sympathetic activity and vasopressin release
- Stretch of the atria, which leads to release of atrial natriuretic peptide
- A slight elevation of systemic arterial blood pressure, which shifts the pressure-natriuretic relationship to a higher level of pressure
- Inhibition of the renin-angiotensin-aldosterone axis by intrarenal mechanisms

These mechanisms operate in concert to maintain a constancy of the body's internal environment by excreting the excess sodium. In contrast to the changes that occur when sodium intake is elevated, these systems (sympathetic nerves, renin-angiotensin, vasopressin, aldosterone, pressure natriuresis-diuresis) are activated to conserve sodium in conditions of decreased dietary sodium intake or in other conditions in which the ECF is decreased.

164. How are these systems affected in disease states?

1. **Pathologic conditions:** In response to **hemorrhage, shock, severe vomiting,** or **severe diarrhea,** the mechanisms to conserve sodium and water are activated in the normal physiologic response to decreased ECF volume or decreased arterial pressure.

2. **Pathophysiologic conditions:** In **heart failure,** the inability of the heart to function adequately as a pump leads to a fall in cardiac output and mean arterial pressure. The fall in blood pressure leads to activation of sympathetic nerves, the renin-angiotensin system, vasopressin release, and aldosterone synthesis. These combined conditions lead to retention of fluid and water, which can actually exacerbate the heart condition by increasing the preload on the diseased heart.

3. It is also not uncommon to observe patients in which an **abnormality in one of the controlling systems** leads to alterations in renal sodium (and water) handling and the consequential effects on body fluids. In **hypoaldosteronism,** in which insufficient aldosterone is produced by the adrenal gland and large amounts of sodium are excreted, leading to decreased ECF volume, hypotension, and, if left untreated, circulatory shock and death.

ACID-BASE BALANCE AND EXCRETION OF POTASSIUM

165. Why is regulation of plasma K^+ concentration important?

The regulation of plasma K^+ concentration is critical to the overall function of the body because the K^+ concentration difference across cell membranes can dramatically influence the resting membrane potential of all cells. This resting membrane potential is particularly important for normal contraction of skeletal and cardiac muscle and function of nerve cells.

166. What is the normal range for plasma K^+ concentration?

3.0–5.0 mM/L.

167. How does the kidney participate in the control of K^+ balance?

The kidney and adrenal cortex work in concert as the primary organs that regulate plasma K^+

through the control of renal K^+ excretion. This regulation is accomplished by the release of aldosterone from the adrenal cortex, which regulates renal tubular K^+ handling.

168. Does aldosterone provide short-term or long-term control over Na^+ reabsorption and K^+ excretion?

Aldosterone should be considered a relatively **long-term** controller of Na^+ reabsorption and K^+ excretion. Aldosterone acts in the principal cells of the distal tubule and cortical collecting duct. It is a relatively long-term controller of Na^+ and K^+ balance because it is a steroid hormone, which activates transcription and translation of new protein.

169. How does aldosterone affect K^+ excretion and K^+ balance?

One mechanism by which aldosterone functions is to activate the tubular cell Na^+, K^+-ATPase. Stimulation of this basolateral cell enzyme not only increases Na^+ reabsorption into the interstitium, but also increases intracellular K^+ concentration. The increased intracellular K^+ promotes secretion of K^+ from inside the cell into the tubular lumen through apical channels and thereby promotes overall K^+ excretion. This gradient is under the complete influence of aldosterone, and for this reason aldosterone is often referred to as the **plasma K^+ controller**.

170. Does plasma K^+ concentration affect the secretion of aldosterone?

The concentration of K^+ in the plasma may be the most potent controller of aldosterone secretion from the adrenal zona glomerulosa cells. These cells are highly influenced by the circulating K^+ concentration. An elevation of plasma K^+ from 4.5 to 5.5 mEq/L provides near-maximum elevation of circulating aldosterone concentrations. Reduction of plasma K^+ below 3.0 mEq/L decreases aldosterone secretion and reduces plasma aldosterone to low values.

171. Do any other ions in the plasma affect plasma K^+?

The level of acidosis and plasma acidification can have a pronounced influence on the excretion of K^+ by the kidney. During chronic acidosis, elevation of extracellular H^+ ion greatly influences the plasma K^+ concentration. Both H^+ and K^+ are relatively permeable to movement into and out of cells. Thus, in the presence of excess H^+, the tendency is for H^+ to diffuse into cells and K^+ to diffuse out of cells to maintain electroneutrality.

172. How does acidosis affect plasma K^+?

Acute acidosis tends to decrease Na^+, K^+-ATPase and decrease the K^+ permeability of the apical membrane and thereby decrease potassium secretion and excretion. Chronic metabolic acidosis, however, induces **hyperkalemia,** which stimulates aldosterone release and has a net effect to increase potassium secretion and excretion.

173. What are the major mechanisms by which the kidney regulates acid-base balance?

Renal regulation of acid-base occurs via H^+ excretion and HCO_3^- reabsorption. Control of either H^+ excretion or the buffering capacity for H^+ with HCO_3^- has the net effect of controlling the overall state of extracellular fluid H^+ concentration.

174. What are the nephron segments responsible for regulating H^+ excretion?

Excretion of fixed acid (H^+) occurs in the proximal tubule, thick ascending limb, and intercalated cells of the distal tubule and collecting duct. In the proximal tubule and thick ascending limb, H^+ ion secretion occurs on the lumenal membrane in exchange for Na^+ ion. The intercalated cells contain specific proton pumps in the lumenal membrane that directly utilize ATP to secrete H^+. These proton pumps secrete H^+ into the tubular lumen of the distal tubule and collecting duct and assist in acidifying the urine.

175. How does HCO_3^- reabsorption contribute to the urine acidification process?

The removal of HCO_3^- from the tubular fluid is extremely important under normal conditions in which excess acid must be excreted from the body. The near complete reabsorption of fil-

tered HCO_3^- is necessary to maintain the body's acid-base status since the CO_2/HCO_3^- buffer system is extremely important in acid-base regulation. The reabsorption of HCO_3^- from the tubular fluid is highly effective in the proximal tubule, thick ascending limb of Henle, and intercalated cells of the collecting duct and under normal circumstances 99.9% of the filtered load is reabsorbed.

176. How is HCO_3^- reabsorbed in the PCT?

The lumenal membrane of the PCT is relatively impermeable to HCO_3^- ions. Therefore, all HCO_3^- must be reabsorbed in the form of CO_2. H^+ ion, which is secreted in exchange for Na^+, combines with HCO_3^- to form CO_2 and water, and this reaction is catalyzed by the presence of carbonic anhydrase on the PCT brush border membranes. CO_2 diffuses down its concentration gradient into the PCT cell because the lumenal membrane is permeable to this molecule (similar to all cells). Inside the cell, the CO_2 combines with water, again catalyzed by the presence of intracellular carbonic anhydrase, forming H^+ and HCO_3^-. From the inside of the cell, the HCO_3^- is able to diffuse down its concentration gradient into the blood and effectively complete the reabsorptive process.

177. How does acidosis increase the secretion of H^+ from the interstitial spaces into the tubular lumen?

Acidosis or increased plasma H^+ concentration is removed from the blood in a substrate-specific manner. As plasma H^+ concentration increases, the supply of substrate to the various transport processes in the kidneys also is increased. Therefore, H^+ secretion in the PCT and collecting duct is increased because of elevated substrate availability to the specific transporters in those sites.

178. What are the other mechanisms that the kidney uses to excrete H^+ ions and acidify the urine?

Other mechanisms include the excretion of PO_4^-, SO_4^-, and NH_3/NH_4^+. In the case of NH_3, acidosis increases ammoniagenesis through the deamination and metabolism of glutamine and glutamate. This deamination process in the PCT creates excess NH_3, which diffuses into the tubular lumen and combines with filtered H^+ ion to form NH_4^+. The NH_4^+ is then trapped in the tubular lumen and cannot diffuse back into the cell. Thus, the ammonia becomes an excellent carrier of excess H^+ into the excreted urine.

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