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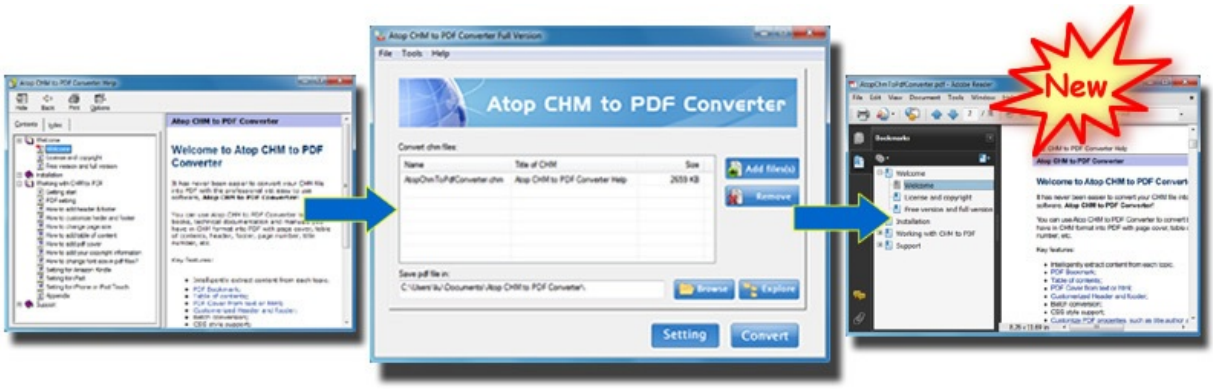

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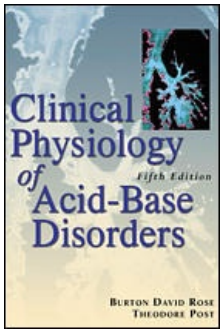
Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th edition



Editors: **Rose, Burton David; Post, Theodore W.**
Title: ***Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th E***

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DEDICATION

To Gloria, Emily, Anne, and Daniel and To Claire, Garrett, and Ian

Editors: Rose, Burton David; Post, Theodore W.
Title: *Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th E*

PREFACE

The fifth edition of *Clinical Physiology of Acid-Base and Electrolyte Disorders* has been largely rewritten to include the many important advances that have be and the controversies that have arisen in the past six years. As with the pr editions, this book attempts to integrate the essentials of renal and electro physiology with the common clinical disorders of acid-base and electrolyte Its underlying premise is that these clinical disturbances can be best appro from an understanding of basic physiologic principles. Chapters 2,3,4,5,6 review the physiology of normal renal function and the effects of hormones kidney. This is followed by a discussion of the extrarenal and renal factors in the internal distribution of the body water and in the normal regulation o (sodium), water, acid-base, and potassium balances (Chapters 7,8,9,10,11,12). In addition to providing the foundation for understanding how disease states c overcome these regulatory processes, the initial chapters can also be used year medical students studying renal physiology.

The material presented in these chapters presents the core of information t our opinion, the clinician should possess. Although relatively complete, it is meant to be an exhaustive review. In those areas where controversy exists, chosen to note the presence of uncertainty and to refer the interested read appropriate references, rather than extensively reviewing each theory. Sinc primary purpose of this book is to teach the reader how to approach clinica problems, the physiological discussions are correlated with situations in cli medicine wherever possible.

The last section of the book (Chapters 13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28) contains a separate chapter on each major acid-base and electrolyte disturbance. In addition to discussing symptoms, diagnosis, and treatment, each chapter begins with a short sumr the pathophysiology of the specific disorder with cross-references to more discussions in the earlier chapters. Although this leads to a certain amount repetition, it has the advantage of allowing each clinical chapter to be reac independently of the other parts of the book, making the book easier to use physician dealing with an acutely ill patient.

Problems are presented at the end of most of the chapters in both the phys and clinical sections. These problems are intended both to test understand emphasize important concepts frequently misunderstood by physicians deal these disorders. The answers to these problems are presented in Chapter 29 and Chapter 30 contains a summary of important equations and formulas that are in the clinical setting.

We are extremely grateful to Colin Sieff, Donald Kohan, Philip Marsden, Ev
Bruce Runyon, and Jess Mandel for contributing material to selected chapte
particularly 6, 16, 20, and 21.

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NOTICE

Medicine is an ever-changing science. As new research and clinical experie broaden our knowledge, changes in treatment and drug therapy are require authors and the publisher of this work have checked with sources believed reliable in their efforts to provide information that is complete and generall with the standards accepted at the time of publication. However, in view of possibility of human error or changes in medical sciences, neither the auth the publisher nor any other party who has been involved in the preparation publication of this work warrants that the information contained herein is in respect accurate or complete, and they disclaim all responsibility for any e omissions or for the results obtained from use of the information contained work. Readers are encouraged to confirm the information contained herein sources. For example and in particular, readers are advised to check the pr information sheet included in the package of each drug they plan to admini certain that the information contained in this work is accurate and that cha not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connecti new or infrequently used drugs

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Chapter one
Introduction to Renal Function

The kidney normally performs a number of essential functions:

1. It participates in the maintenance of the constant extracellular environm is required for adequate functioning of the cells. This is achieved by ex some of the waste products of metabolism (such as urea, creatinine, an acid) and by specifically adjusting the urinary excretion of water and el to match net intake and endogenous production. As will be seen, the kid able to *regulate individually* the excretion of water and solutes such as sodi potassium, and hydrogen largely by changes in tubular reabsorption or secretion.
2. It secretes hormones that participate in the regulation of systemic and r hemodynamics (renin, angiotensin II, prostaglandins, nitric oxide, endot and bradykinin), red blood cell production (erythropoietin), and calcium phosphorus, and bone metabolism (1,25-dihydroxyvitamin D[3] or calcitriol).
3. It performs such miscellaneous functions as catabolism of peptide horm[1,2] and synthesis of glucose (gluconeogenesis) in fasting condition.[3,4]

This chapter will review briefly the morphology of the kidney and the basic processes of reabsorption and secretion. The regulation of renal hemodyna

the specific functions of the different nephron segments, and the relationsh between hormones and the kidney will then be discussed in the ensuing cha

RENAL MORPHOLOGY

The basic unit of the kidney is the *nephron*, with each kidney in humans containing approximately 1.0 to 1.3 million nephrons.

Each nephron consists of a glomerulus, which is a tuft of capillaries interpo between two arterioles (the afferent and efferent arterioles), and a series o lined by a continuous layer of epithelial cells (Fig. 1-1). The glomeruli are located in the outer part of the kidney, called the *cortex*, whereas the tubules are presented ir both the cortex and the inner part of the kidney, called the *medulla* (Figs. 1-1 and 1-2).

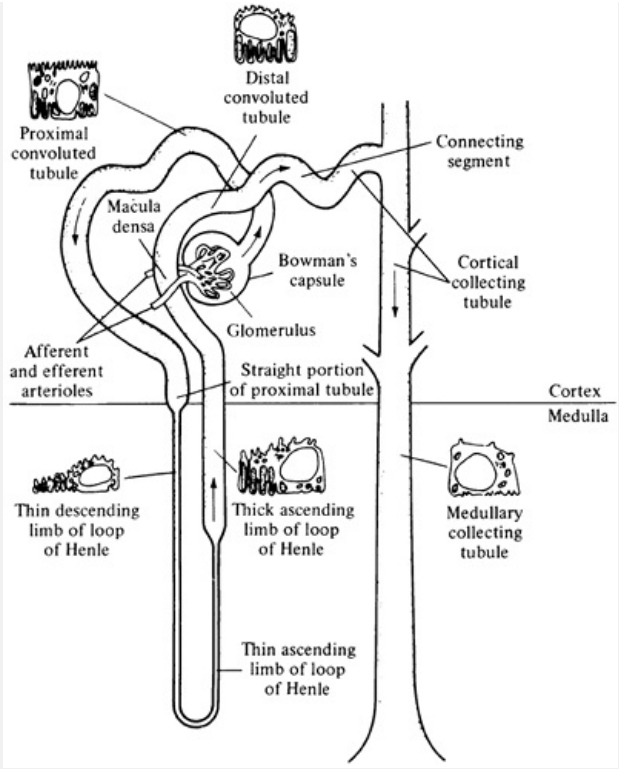

Figure 1-1 Anatomic relationships of the component parts of the nephron. (*Adapted from Vander R, Renal Physiology, 2d ed, McGraw-Hill, New York, 1980*)

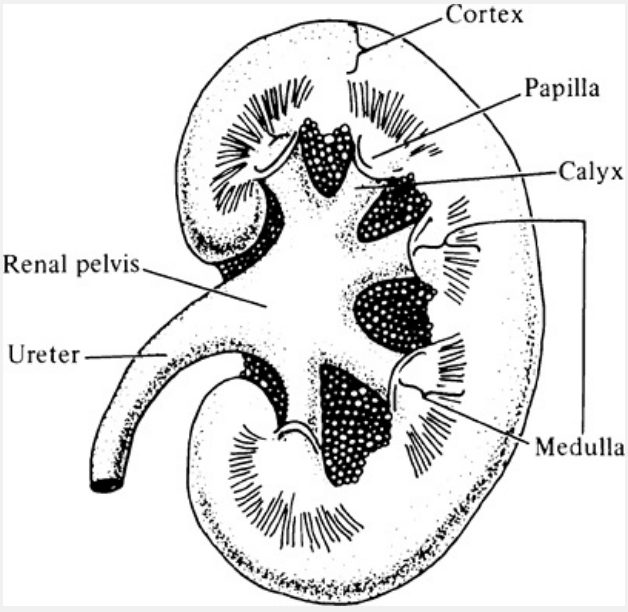

Figure 1-2 Section of a human kidney. The outer portion (the cortex) contai the glomeruli. The tubules are located in both the cortex and the medulla, the collecting tubules forming a large portion of the inner medulla (the pa Urine leaving the collecting tubules drains sequentially into the calyces, pelvis, ureter, and then the bladder. (*Adapted from Vander R, Renal Physiology, 2d ed, McGraw-Hill, New York, 1980*)

The initial step in the excretory function of the nephron is the formation of ultrafiltrate of plasma across the glomerulus. This fluid then passes throug tubules and is modified in two ways: by reabsorption and by secretion. *Reabsorption* refers to the removal of a substance from the filtrate, whereas *secretion* refers to the addition of a substance to the filtrate. As will be seen, the different tubular make varying contributions to these processes.

Fluid filtered across the glomerulus enters Bowman's space and then the pr tubule (Fig. 1-1). The *proximal tubule* is composed anatomically of an initial convoluted segment and a later straight segment, the pars recta, which ent outer medulla. The *loop of Henle* begins abruptly at the end of the pars recta. It generally includes a thin descending limb and thin and thick segments of th ascending limb. The hairpin configuration of the loop of Henle plays a majo the excretion of a hyperosmotic urine.

It is important to note that the length of the loops of Henle is not uniform (Fig. 1-3). Approximately 40 percent of nephrons have short loops that penetrate only medulla or may even turn around in the cortex; these short loops lack a thi ascending limb.[5] The remaining 60 percent have long loops that course throug medulla and may extend down to the papilla (the innermost portion of the m The length of the loops is largely determined by the cortical location of the glomerulus: Glomeruli in the outer cortex (about 30 percent) have only shor those in the juxtamedullary region (about 10 percent) have only long loops; those in the midcortex may have either short or long loops (Fig. 1-3).

The thick ascending limb also has a cortical segment that returns to the reg parent glomerulus. It is in this area, where the tubule approaches the affer glomerular arteriole, that the specialized tubular cells of the *macula densa* are located (Fig. 1-4). The juxtaglomerular cells of the afferent arteriole and the m densa compose the juxtaglomerular apparatus, which plays a central role in secretion (see Chap. 2).

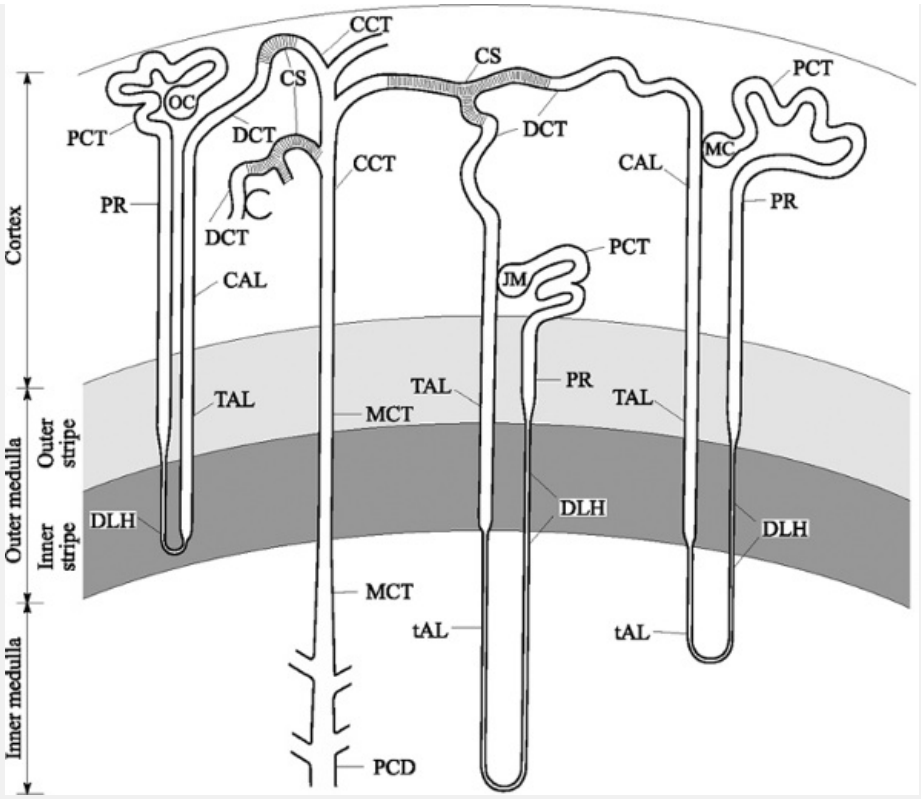

Figure 1-3 Anatomic relationships of the different nephron segments accord to location of the glomeruli in the outer cortex (OC), midcortex (MC), or juxtamedullary area (JM). The major nephron segments are labeled as foll PCT=proximal convoluted tubule; PR=pars recta, which ends in the S at the junction of the outer and inner stripes in the outer medulla; DLH=descending limb of the loop of Henle; tAL=thin ascending limb, whic present in outer cortical nephrons that have short loops of Henle; TAL=me thick ascending limb; CAL=cortical thick ascending limb, which ends in th macula densa adjacent to the parent glomerulus (see Figs. 1-4, 1-5, and 1-6); DCT=distal convoluted tubule; CS=connecting segment; CCT=cortical collecting tubul MCT=medullary collecting tubule; and PCD=papillary collecting duct, at th of the medullary collecting tubule. *Adapted from Jacobson, HR: Am J Physiol 241:F203, 1981. Used with permission.*

P. 6

After the macula densa, there are three cortical segments: the *distal convoluted tubule*, the *connecting segment* (previously considered part of the late distal tubule), and the *cortical collecting tubule*. The connecting segments of many nephrons drain into a single collecting tubule. Fluid leaving the cortic collecting tubule flows into the *medullary collecting tubule* and then drains sequentially into the calyces, the renal pelvis, the ureters, and the bladder (Fig. 1-2).

The segmental subdivision of the nephron is based upon different permeabi transport characteristics that translate into important differences in functio general, the proximal tubule and loop of Henle reabsorb the bulk of the filte solutes and water, while the collecting tubules make the final small change

urinary composition that permit solute and water excretion to vary appropri alterations in dietary intake.

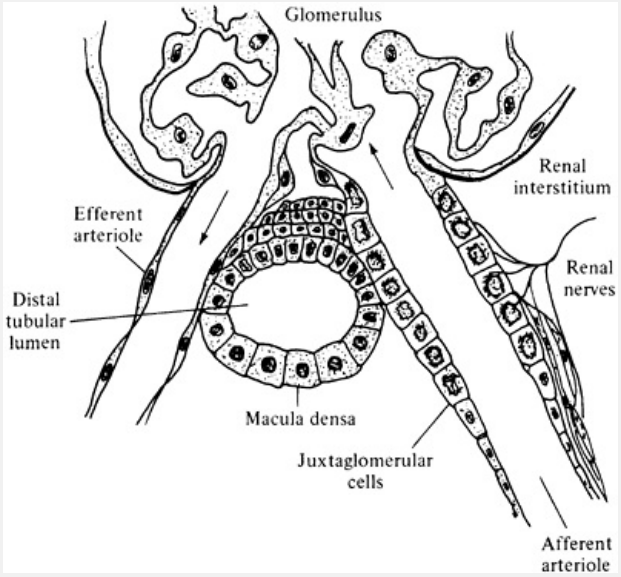

Figure 1-4 Diagram of the juxtaglomerular apparatus. The juxtaglomerular c in the wall of the afferent arteriole secrete renin into the lumen of the aff arteriole and the renal lymph. Stretch receptors in the afferent arteriole, sympathetic nerves ending in the juxtaglomerular cells, and the compositi the tubular fluid reaching the macula densa all contribute to the regulatio renin secretion. (*Adapted from Davis, JO: Am J Med 55:333, 1973. Used with permission.*)

There may also be significant heterogeneity within a given tubular segment particularly in the proximal tubule and cortical collecting tubule. In the latte for example, there are two cell types with very different functions. The *principal cells* reabsorb sodium and chloride and secrete potassium, in part under the influ aldosterone; and the *intercalated cells* secrete hydrogen or bicarbonate and reabsorb potassium, but play no role in sodium balance.[6]

REABSORPTION AND SECRETION

The rate of glomerular filtration averages 135 to 180 L/day in a normal adu this represents a volume that is more than 10 times that of the extracellular approximately 60 times that of the plasma, it is evident that almost all of th must be returned to the systemic circulation. This process is called *tubular reabsorption* and can occur either across the cell or via the paracellular route between the cells. With transcellular reabsorption, the substance to be rea first transported from the tubular lumen into the cell, usually across the lur aspect of the cell membrane; next, it moves across the basolateral (or perit

aspect of the cell membrane into the interstitium and then the capillaries th surround the tubules (Fig. 1-5). With paracellular reabsorption, the substance to

reabsorbed moves from the tubular lumen across the tight junction at the lu surface of adjacent cells (see below) into the interstitium and then into the peritubular capillaries.

Most reabsorbed solutes are returned to the systemic circulation intact. Ho some are metabolized within the cell, particularly low-molecular-weight prot the proximal tubule.

Solutes can also move in the opposite direction, from the peritubular capill through the cell and into the urine. This process is called *tubular secretion* (Fig. 1-5).

Filtered solutes and water may be transported by one or both of these mech For example, Na^+, Cl^-, and H_2O are reabsorbed; hydrogen ions are secreted; K^+ and uric acid are both reabsorbed and secreted; and filtered creatinine is e virtually unchanged, since it is not reabsorbed and only a small amount is r added to the urine by secretion.

The transcellular reabsorption or secretion of almost all solutes is facilitat *protein carriers* or *ion-specific channels*; these transport processes are essential, since free diffusion of ions is limited by the lipid bilayer of the cell membra spatial orientation of the cells is also important, because the luminal and b aspects of the cell membrane, which are separated by the *tight junction*, have different functional characteristics.

As an example, filtered sodium enters the cell passively down a favorable electrochemical gradient, since the active Na^+-K^+ ATPase pump in the basolateral membrane maintains the cell Na^+ concentration at a low level and makes the cell interior electronegative. Sodium entry occurs by a variety of mechanisms at nephron sites, such as Na^+-H^+ exchange and Na^+-glucose cotransport in the proximal tubule, a Na^+-K^+-$2Cl^-$ carrier protein in the cortical collecting tubule ar papillary collecting duct (Fig. 1-6). The sodium that enters the cells is then returr to the systemic circulation by the Na^+-K^+ ATPase pump in the basolateral membrane.[8] Removal of this Na^+ from the cell maintains the cell Na

concentration at a low level, thereby promoting further diffusion of luminal Na^+ into the cell and continued Na^+ reabsorption.

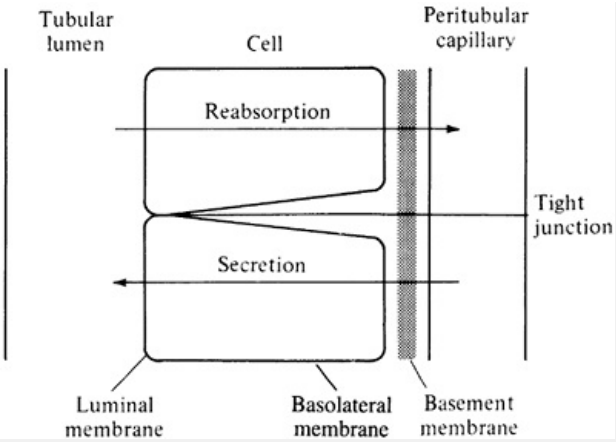

Figure 1-5 Schematic representation of reabsorption and secretion in the nephron.

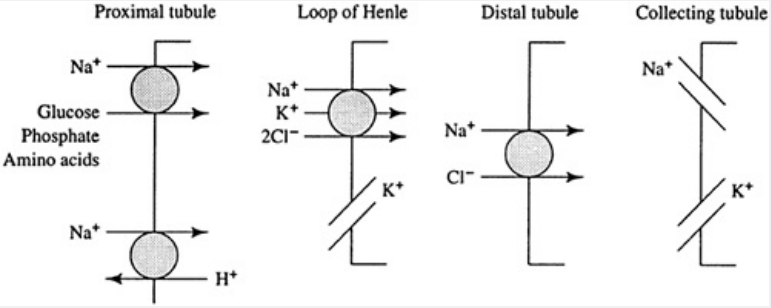

Figure 1-6 Major mechanisms of passive entry of Na^+ into the cells across the luminal (apical) membrane in the different nephron segments. With the ex of the selective Na^+ channels in the collecting tubules, Na^+ reabsorption in the more proximal segments is linked to the reabsorption or secretion of othe solutes. *(Adapted from Rose, BD: Kidney Int 39:336, 1991. Used with permission from Kidney International.)*

This simple summary of the mechanism of Na^+ transport illustrates that reabsorptic can involve both active and passive mechanisms. This is also true for tubul secretion. Potassium, for example, is secreted from the cortical collecting t into the lumen. The Na^+-K^+-ATPase pump in the basolateral membrane actively transports K^+ from the peritubular capillary into the cell; the ensuing rise in t K^+ concentration then promotes secretion into the lumen via K^+ channels in the luminal membrane.

The tubular cells perform these functions in an extremely efficient manner, reabsorbing almost all the filtrate to maintain the balance between intake a excretion. In an individual on a normal diet, more than 98 to 99 percent of t

H_2O, Na^+, Cl^-, and HCO_3^- is reabsorbed (Table 1-1). Although this process of filtration and almost complete reabsorption may seem inefficient, a high rat filtration is required for the excretion of those waste products of metabolis urea and creatinine) that enter the urine primarily by glomerular filtration.

Role of the Tight Junction

The tight junction is composed primarily of the zona occludens, which is a s structure on the luminal membrane that brings adjacent cells into appositio luminal surface.[9,10] Within the kidney, the tight junction has two important effe segmental function:[9,11,12]

1. It serves as a relative barrier or gate to the passive diffusion of solutes water between the cells.

2. It serves as a boundary or fence between the luminal (or apical) and ba membranes.

Table 1-1 Summary of the net daily reabsorptive work performed by the kidney[a]

Substance	Filtered	Excreted	Percent net reabsorption
Water	180 liters	0.5–3 liters	98–99
Na^+	26,000 meq	100–250 meq	>99
Cl^-	21,000 meq	100–250 meq	>99
HCO_3^-	4800 meq	0	~ 100
K^+	800 meq	40–120 meq	85–95[b]
Urea	54 g	27–32 g	40–50

[a] These values are for a normal adult man on a typical Western diet. Th glomerular filtration rate and therefore the filtered load of solutes and w is approximately 25 percent lower in women.

[b] The net reabsorption of K^+ reflects the interplay of two processes: the reabsorption of almost all of the filtered K^+ in the proximal tubule and loop of Henle and the secretion of K^+ into the lumen, primarily in the cortical

collecting tubule under the influence of aldosterone. This latter process is the primary determinant of urinary K^+ excretion (see Chap. 12).

It has been proposed that these two functions—paracellular gate and fence polarity—are mediated by different kinds of molecular contacts between the junction strands: The gate function may be due to contact between strands apposing cells, while the fence function may be due to contact between the forming the strands within a single cell.[12]

The "leakiness" of the tight junction barrier to passive diffusion varies with nephron segment. The barrier is relatively leaky in the proximal tubule, with as one-third of proximal Na^+ reabsorption occurring via this paracellular route. leakiness is important, because it allows the proximal tubule to efficiently r 55 to 60 percent of the filtrate (or over 90 L/day).

In comparison, the collecting tubule is a relatively "tight" epithelium with a tight junction than the proximal tubule.[9] As a result, diffusion across the tight junc is limited. This relative impermeability to passive paracellular transport allo segment to *create and sustain* very large transepithelial concentration gradients an example, the medullary collecting tubule is able to lower the urine pH to which represents a H^+ concentration that is almost 1000 times greater than tha the plasma (where the pH is about 7.40). The proximal tubule, on the other only reduce the tubular fluid pH to about 6.8, which represents a H^+ concentration only four times higher than that in the plasma.

The boundary function of the tight junction is thought to play an important maintenance of the polarity of the two membranes, preventing lateral mover transporters or channels from one membrane to the other.[9,11,12] Membrane polarity is an essential component of reabsorption or secretion in the renal tubular each component of the cell membrane plays an important role:[13]

1. *Luminal membrane.* The luminal (or apical) membrane contains the channe carriers that allow filtered solutes to enter the cells or some cellular so be secreted into the lumen (Fig. 1-6).
2. *Basolateral membrane.* The basolateral membrane performs two major functions. That part of the membrane adjacent to the luminal membrane called the lateral membrane) contains the components of the tight junct the cell adhesion molecules that participate in cell-cell contact and communication. The more distal part of this membrane (also called the basolateral or basal-lateral membrane) plays an essential role in ion tra and hormone responsiveness, as it contains K^+-H^+-ATPase pumps, hormone receptors, and solute carriers and channels.
3. *Basal membrane.* The basal membrane contains the basement membrane receptors that allow the cell to be anchored to the basement membrane.

As an example of transcellular transport, filtered Na^+ enters the cells across the luminal membrane via specific transporters or channels; it is then returned systemic circulation by the Na^+-K^+-ATPase pump to the basolateral membrane. Disruption of this normal polarity, as with opening of the tight junctions due ischemia, is associated with an impairment in Na^+ reabsorption.[11] This may be mediated in part by the translocation of functioning Na^+-K^+-ATPase pumps onto the luminal membrane.[14]

The signals that govern the initial insertion of a protein into the luminal or basolateral membrane are incompletely understood. One signal appears to presence of cassettes of unique amino acids (located within the sequences proteins themselves) that relay localization information to cellular sorting m One such amino acid motif, contiguous leucines located in the cytoplasmic direct the vasopressin V_2 receptor to the basolateral membrane.[15]

Another mechanism may involve the type of membrane anchor: Studies in ki cells suggest that the presence of glycosyl-phosphatidylinositol (GPI) at th terminal end of the protein leads to specific insertion on the luminal membr perhaps because this membrane is rich in glycosphingolipids.[16,17] On the other hand, the localization of the Na^+-K^+-ATPase pump to the basolateral membrane m be mediated by specific attachment to basolateral cytoskeletal proteins, su actin microfilaments and ankyrin.[11,18] Disruption of the actin microfilaments following ischemia impairs this tethering function, allowing Na^+-K^+-ATPase pumps to diffuse onto the luminal membrane through the now open tight junctions, th impairing net Na^+ reabsorption.[11]

The attachment to actin and fodrin also may promote the basolateral localiz Na^+-K^+-ATPase pumps by preventing their endocytic removal. Pumps that do inserted into the luminal membrane are removed at a rate 40 times faster th inserted into the basolateral membrane.[19]

Aberrant localization of membrane proteins may contribute to the developme multiple disorders, such as autosomal dominant polycystic kidney disease (ADPKD is in most cases caused by mutations in a membrane protein termed polycystin,[20] which appears to be involved in cell adhesion.[21] Abnormal

apical polarity of the Na^+-K^+-ATPase pumps in these patients may cause sodium secretion into and fluid accumulation in epithelial cysts.[22] In addition, abnormal epithelial proliferation within the cysts may be due to apical mislocation of growth factor receptors. The correlation between polycystin mutations and polarity is unclear, but may result from the dampened expression of fetal ge

Membrane Recycling

In addition to proper polarity, normal functioning of transporting epithelia r delivery of newly synthesized and recycled membrane components to precis

locations in the cell membrane.[23] For example, antidiuretic hormone combines wi its receptor on the *basolateral membrane* of collecting tubular cells. This initiates sequence of events in which preformed water channels (called aquaporin-2) cytoplasmic vesicles are specifically inserted into the luminal membrane, th allowing the reabsorption of luminal water. The hormone-receptor complex i internalized by endocytosis in clathrin-coated pits and then enters acidic e where the hormone and receptor are split (Fig. 1-7).[23] The former is metabolized within the cell, while the receptor is returned to the basolateral membrane. Attenuation of the ADH effect is associated with endocytosis of only those the luminal membrane that contain water channels, thereby restoring the re water impermeability of the luminal membrane.

The signaling events that control membrane recycling are incompletely und but activation of adenylyl cyclase appears to be involved.[24] In addition, the structure of aquaporin-2 helps dictate cellular distribution and recycling. Mutations c aquaporin-2 gene can cause resistance to antidiuretic hormone

(called nephrogenic diabetes insipidus). In the families reported thus far, tl appears to involve misrouting and/or loss of function.[25,26]

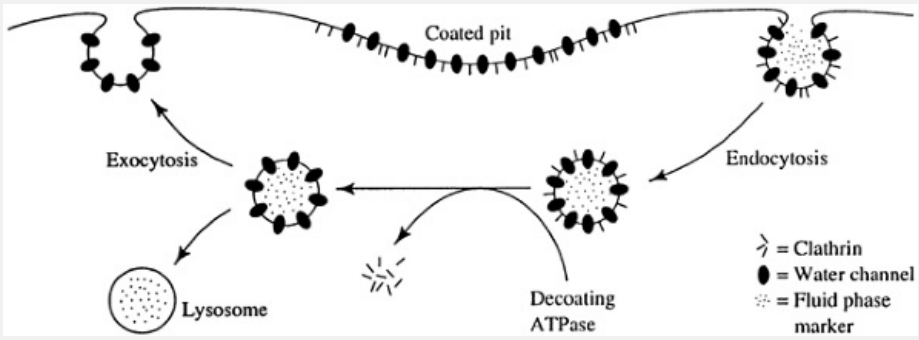

Figure 1-7 Proposed pathways of recycling of luminal membrane water char in principal cells in the collecting tubule. Water channels are concentrate clathrin-coated pits at the cell surface and are endocytosed in coated ves These vesicles are rapidly decoated; the water channels may escape degradation and be recycled to the luminal membrane in the presence of A (*From Brown, D.* Kidney Int. *35:F1, 1989. Used by permission from* Kidney International.)

Composition of Urine

The composition of the urine differs from that of the relatively constant ext fluid in two important ways. First, the quantity of solutes and water in the u highly variable, being dependent upon the intake of these substances. A no subject, for example, appropriately excretes more Na^+ on a high-salt diet than on a low-salt diet. In both instances, the steady-state and therefore the extracel

volume is maintained, as output equals intake. Similarly, the urine volume i after a water load than after water restriction, resulting in a stable plasma Na^+ concentration. This relation to intake means that there are no *absolute "normal" values for urinary solute or water excretion*. We can only describe a normal range which merely reflects the range of dietary intake, e.g., 100 to 250 meq/day K^+

Second, ions compose 95 percent of the extracellular fluid solutes; in comp the urine has high concentrations of uncharged molecules, particularly urea allows urea and other metabolic end products to be excreted, rather than accumulating in the body.

Summary of Nephron Function

The following chapters in Part One will describe the roles of the different n segments in the regulation of solute and water homeostasis. These functior summarized in Table 1-2.

As can be seen, there are marked differences in segmental function, a findi consistent with the differences in segmental histology (Fig. 1-4) and permeability and transport characteristics.[5] In addition, multiple sites participate in the regulatio the rates of excretion of the different substances in the filtrate. This divers provides the flexibility that allows the kidney to maintain solute and water l even in the presence of major changes in dietary intake.

ATOMIC WEIGHT AND MOLARITY

The efficacy of regulation of solute and water balance is estimated clinical measurement of the plasma concentrations of the appropriate substances. I therefore important to be aware of the different ways in which solute conce

can be measured—in milligrams per deciliter (mg/dL), millimoles per liter (n milliequivalents per liter (meq/L), or milliosmoles per liter or per kg (mosmo mosmol/kg). For sodium ion (Na^+), 23 mg/dL (or 23 mg/L), 1 mmol/L, 1 meq/L, ar mosmol/kg all refer to the same concentration of Na^+

Table 1-2 Contribution of the different nephron segments to solute and water homeostasis

Nephron segment	Major functions
Glomerulus	Forms an ultrafiltrate of plasma
Proximal tubule	Reabsorbs isosmotically 65 to 70 percent of the filtered NaCl and water Reabsorbs 90 percent of the filtered HCO_3^- (by H^+ secretion), mostly in early proximal tubule Major site of ammonia production in nephron

	Reabsorbs almost all of filtered glucose and amino acids Reabsorbs K^+, phosphate, calcium, magnesium, urea, and uric acid Secretes organic anions (such as urate) and cations, including many protein-bound drugs
Loop of Henle	Reabsorbs 15 to 25 percent of filtered NaCl Countercurrent multiplier, as NaCl reabsorbed in excess of water Major site of active regulation of magnesium excretio
Distal tubule	Reabsorbs a small fraction of filtered NaCl Major site, with connecting segment, of active regulation of calcium excretion
Connecting segment and cortical collecting tubule	Principal cells reabsorb Na^+ and Cl^- and secrete K^+, in part under influence of aldosterone Intercalated cells secrete H^+, reabsorb K^+, and, in metabolic alkalosis, secrete HCO_3^- Reabsorb water in presence of antidiuretic hormone
Medullary collecting tubule	Site of final modification of the urine Reabsorb NaCl; urine NaCl concentration can be reduced to less than 1 meq/L Reabsorb water and urea relative to amount of antidiuretic hormone present, allowing a dilute or concentrated urine to be excreted Secrete H^+ and NH_3; urine pH can be reduced to as low as 4.5 to 5.0 Can contribute to potassium balance by reabsorption or secretion of K^+

Table 1-3 lists the atomic weights of the most important elements in the body atomic weight is an assigned number that allows comparison of the relative of the different elements. By definition, one atom of oxygen is assigned a w 16, and the atomic weights of the other elements are determined in relation oxygen. In a molecule, i.e., a substance containing two or more atoms, the weight is equal to the sum of the atomic weights of the individual atoms. As example, the molecular weight of water (H_2O) is 18, since 2 and 1+16]=18.

Table 1-3 Atomic and molecular weights of

physiologically important substances

Substance	Symbol or formula	Atomic or molecular weight
Calcium ion	Ca^{2+}	40.1
Carbon	C	12.0
Chloride ion	Cl^-	35.5
Hydrogen ion	H^+	1.0
Magnesium ion	Mg^{2+}	24.3
Nitrogen	N	14.0
Oxygen	O	16.0
Phosphorus	P	31.0
Potassium ion	K^+	39.1
Sodium ion	Na^+	23.0
Sulfur	S	32.1
Ammonia	NH_3	17.0
Ammonium	NH^{+4}	18.0
Bicarbonate ion	HCO^-_3	61.0
Carbon dioxide	CO^2	44.0
Glucose	$C_6H_{12}O_6$	180.0
Phosphate ion	PO_{3-}^{4}	95.0
Sulfate ion	SO_{2-}^{4}	96.1

Urea	NH_2CONH_2	60.0
Water	H_2O	18.0

P.15

One mole (mol) of any substance is defined as the molecular (or atomic) we that substance in grams. Similarly, one millimole (mmol) is equal to one-tho of a mole or the molecular (or atomic) weight in milligrams. Since the atomi of Na^+ is 23, 23 mg is 1 mmol and 23 mg of Na^+ in 1 liter of water represents a Na concentration (written as $[Na^+]$) of 1 mmol/L. The concept of molarity is important because, from Avogadro's law, 1 mol of any nondissociable substance conta same number of particles (approximately 6.02×10^{23}). Thus, 1 mmol of Na^+ contains the same number of atoms as 1 mmol of Cl even though the former weighs 23 mg and the latter weights 35.5 mg. However, 1 mmol of NaCl (58.5 mg) largely dissociates into Na^+ and Cl^- ions and therefore contains *almost twice as many particles*. As will be seen, these relationships are important in understanding electrochemical equivalence and in the measurement of osmotic pressure.

Although the concentrations of uncharged molecules, e.g., glucose and ure can be measured in millimoles per liter, they are more commonly measured clinical laboratory as milligrams per deciliter. For example, the molecular w wt) of glucose is 180. Consequently, a glucose concentration of 180 mg/L (mg/dL) is equal to 1 mmol/L. To convert from milligrams per deciliter to mill liter, the following formula can be used:

$$\text{mmol/L} = \frac{\text{mg/dL} \times 10}{\text{mol wt}} \qquad (1\text{-}1)$$

P.16

(The multiple of 10 is used to convert milligrams per deciliter into milligram liter.)

Electrochemical Equivalence

Positively charged particles are called *cations*, and negatively charged particles are called *anions*. When cations and anions combine, they do so according to the charge (or valance), not according to their weight. Electrochemical equival refers to the combining power of an ion. One equivalent is defined as the w grams of an element that combines with or replaces 1 g of hydrogen (H^+) ion. Since 1 g of H^+ is equal to 1 mol of H^+ (containing approximately 6.02×10^{23} particles), 1 mol of any univalent anion (charge equal to 1) will combine with this and is equal to one equivalent (eq). Thus:

$$\underset{(1\,g)}{1\,\text{mol}\,H^+} + \underset{(35.5\,g)}{1\,\text{mol}\,Cl^-} \rightarrow \underset{(36.5\,g)}{1\,\text{mol}\,HCl}$$

By similar reasoning, 1 mol of a univalent cation (charge equal to 1) is equal to 1 eq, since it can replace and combine with 1 eq of H^+. For example,

$$1\,\text{mol}\,Na^{+} + 1\,\text{mol}\,Cl^{-} \rightarrow 1\,\text{mol}\,NaCl$$
$$(23\,\text{g}) \qquad (35.5\,\text{g}) \qquad (58.5\,\text{g})$$

In contrast, ionized calcium (Ca^{2+}) is a divalent cation (charge equals 2 $+$). Consequently, 1 mol of Ca^{2+} will combine with 2 mol of Cl^{-} and 1 mol is equal to 2 eq:

$$1\,\text{mol}\,Ca^{2+} + 2\,\text{mol}\,Cl^{-} \rightarrow 1\,\text{mol}\,CaCl_2$$
$$(40\,\text{g}) \qquad (71\,\text{g}) \qquad (111\,\text{g})$$

The body fluids are relatively dilute, and most ions are present in milliequi quantities (one-thousandth of 1 eq equals 1 meq). To convert from units of per liter to milliequivalents per liter, the following formulas can be used:

$$\text{meq/L} = \text{mmol/L} \times \text{valence} \qquad (1\text{-}2)$$

or from Eq. 1-1,

$$\text{meq/L} = \frac{\text{mg/dL} \times 10}{\text{mol wt}} \times \text{valence} \qquad (1\text{-}3)$$

There are two advantages to measuring ionic concentrations in milliequival liter. First, it emphasizes the principle that *ions react or combine milliequivalent for milliequivalent*, not millimole for millimole or milligram for milligram. Second, maintain *electroneutrality*, there is an equal number of milliequivalents of cation and anions in the body fluids. As will be described in later chapters, the ne preserve electroneutrality is an important determinant of ion transport in th and ion movement between the cells and the extracellular fluid. This obliga relationship cannot be appreciated if the ionic concentrations are measured millimoles per liter or in milligrams per deciliter (Table 1-4).

Table 1-4 Normal plasma electrolyte concentration

Electrolyte	meq/L	mmol/L
Cations		
Na^{+}	142.0	142.0
K^{+}	4.3	4.3
Ca^{2+}	2.5	1.25
Mg^{2+}	1.1	0.55
Total	149.9	148.1
Anions		
Cl^{-}	104.0	104.0

HCO_3^-	24.0	24.0
$H_2PO_4^-$, HPO_4^{2-}	2.0	1.1
Proteins	14.0	0.9
Other[b]	5.9	5.5
Total	149.9	135.5

[a] The values of Ca^{2+} and Mg^{2+} include only the ionized (unbound) form of these ions.
[b] This includes SO_4^{2-} and organic anions such as lactate.

P.17

Despite these advantages, not all ions can be easily measured in milliequiv liter. The total calcium (Ca^{2+}) concentration in the blood is approximately 10 mg From Eq. 1-3,

$$\text{meq/L of phosphate} = \frac{3.5 \times 10}{31} \times 1.8 = 2\,\text{meq/L}$$

However, roughly 50 to 55 percent of plasma Ca^{2+} is bound by albumin and, to a much lesser degree, citrate, so that the physiologically important (*ionized* or unbound) Ca^{2+} concentration is only 2.0 to 2.5 meq/L.

There is a different problem with phosphate, since it can exist in different i —as $H_2PO_4^-$, HPO_4^{2-}, or PO_4^{3-}—and an exact valence cannot be given. We can estimate an approximate valence of minus 1.8 because roughly 80 percent o extracellular phosphate exists as HPO_4^{2-} and 20 percent as $H_2PO_4^-$. If the normal serum phosphorus concentration is 3.5 mg/dL (phosphate in the blood is me as inorganic phosphorus), then

$$\text{meq/L of protein} = 0.9 \times 15 = 14\,\text{meq/L}$$

Similarly, only an average valence can be given for the polyvalent protein a the plasma protein concentration is 0.9 mmol/L and the average valance is then from Eq. 1-2,

$$\text{meq/L of protein} = 0.9 \times 15 = 14\,\text{meq/L}$$

P.18

Osmotic Pressure and Osmolality

Another unit of measurement is osmotic pressure, which determines the dis of water among the different fluid compartments, particularly between the extracellular and intracellular fluids (see Chapter 7). The osmotic pressure generated by a solution is proportional to the *number of particles* per unit volume of solvent,

not to the type, valence, or weight of the particles.

The unit of measurement of osmotic pressure is the osmole. One osmole (os defined as 1 g molecular weight (1 mol) of any nondissociable substance (s glucose) and contains 6.02×10^{23} particles. In the relatively dilute fluids in the b the osmotic pressure is measured in milliosmoles (one-thousandth of an osı kilogram of water (mosmol/kg). Since most solutes are measured in the labo units of millimoles per liter, milligrams per deciliter, or milliequivalents per following formulas must be used to convert into mosmol/kg:

$$\text{mosmol/kg} = n \times \text{mmol/L}$$

or, from Eqs. 1-1 and 1-2,

$$\text{mosmol/kg} = n \times \frac{\text{mg/dL} \times 10}{\text{mol wt}} \qquad (1\text{-}4)$$

$$\text{mosmol/kg} = n \times \frac{\text{meq/L}}{\text{valence}} \qquad (1\text{-}5)$$

where n is the number of dissociable particles per molecule. When $n = 1$, as for Na^+, Cl^-, Ca^{2+}, urea, and glucose, 1 mmol/L will generate a potential osmotic pres 1 mosmol/kg. If, however, a compound dissociates into two or more particle mmol/L will generate an osmotic pressure greater than 1 mosmol/kg. At the concentrations present in the body, for example, ionic interactions reduce t movement of NaCl so that it acts as if it were only 75 percent, rather than percent, dissociated. Thus, for each 1 mmol/L of NaCl, there will be 0.75 m each of Na^+ and Cl^- and 0.25 mmol/L of NaCl, or 1.75 mosmol/kg (Table 1-5).

Table 1-5 Relationship between various units of measurement

Substance	Atomic or molecular weight	mmol	meq	mosmol
Na^+	23	1	1	1
Cl^-	35.5	1	1	1
NaCl	58.5	1	2 (Na^+, Cl^-)	1.75[a]
$CaCl_2$	111	1	4 (Ca^{2+}, $2Cl^-$)	~ 3[a]
Glucose	180	1	...	1

[a] Both NaCl and $CaCl_2$ behave as if they are incompletely dissociated because ionic interactions limit the random movement or activity of the i

see text for details.

P.19

In the laboratory, the osmotic concentration of a solution is measured not a osmotic pressure but according to other properties of solutes, such as thei depress the freezing point or the vapor pressure of water. Solute-free wate at 0°C. If 1 osmol of any solute (or combination of solutes) is added to 1 kg the freezing point of this water will be depressed by 1.86°C. This observati used to calculate the osmotic concentration of a solution. As an example, th freezing point of the plasma water is normally about -0.521°C. This represe osmolality of 0.280 osmol/kg (0.521/1.86) or 280 mosmol/kg.

Only solutes that *cannot cross the membrane separating two compartments* generate an effective osmotic pressure. Thus, a lipid-soluble solute such a which can cross the lipid bilayer of cell membranes, does not contribute to pressure but will be measured as part of the plasma osmolality by freezing vapor pressure depression. There is therefore a difference between the tot osmolality and the effective osmolality of a solution, with the latter being d only by osmotically active solutes (such as Na^+ and K^+ across the cell membrane) (see Chap. 7).

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Footnote

* These changes in Na^+ and water excretion are relatively precise, so that increasing Na^+ intake from 100 to 200 meq/day, for example, results in a para in Na^+ excretion. If, as depicted in Table 1-1, 26,000 meq of Na^+ is filtered per day, then a 100-meq increase in excretion represents a change involving less th percent of the filtered load. This illustrates the high degree of efficiency re maintain salt and water balance.

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Chapter Two

Renal Circulation and Glomerular filtration rate

The blood flow to the kidneys averages 20 percent of the cardiac output. In flow per 100 g weight, the renal blood flow (RBF) is four times greater than flow to the liver or exercising muscle and eight times coronary blood flow.

Blood enters the kidney through the renal arteries and passes through seria branches (interlobar, arcuate, interlobular) before entering the glomeruli vi capillary wall then leaves the glomeruli via the efferent arterioles and ente postglomerular capillaries. In the cortex, these capillaries run in apposition adjacent tubules, although not necessarily to the tubule segments from the glomerulus.[1] In addition, branches from the efferent arterioles of the juxtame glomeruli enter the medulla and form the vasa recta capillaries. Blood returns to the systemic circulation through veins similar to the arteries in n location.

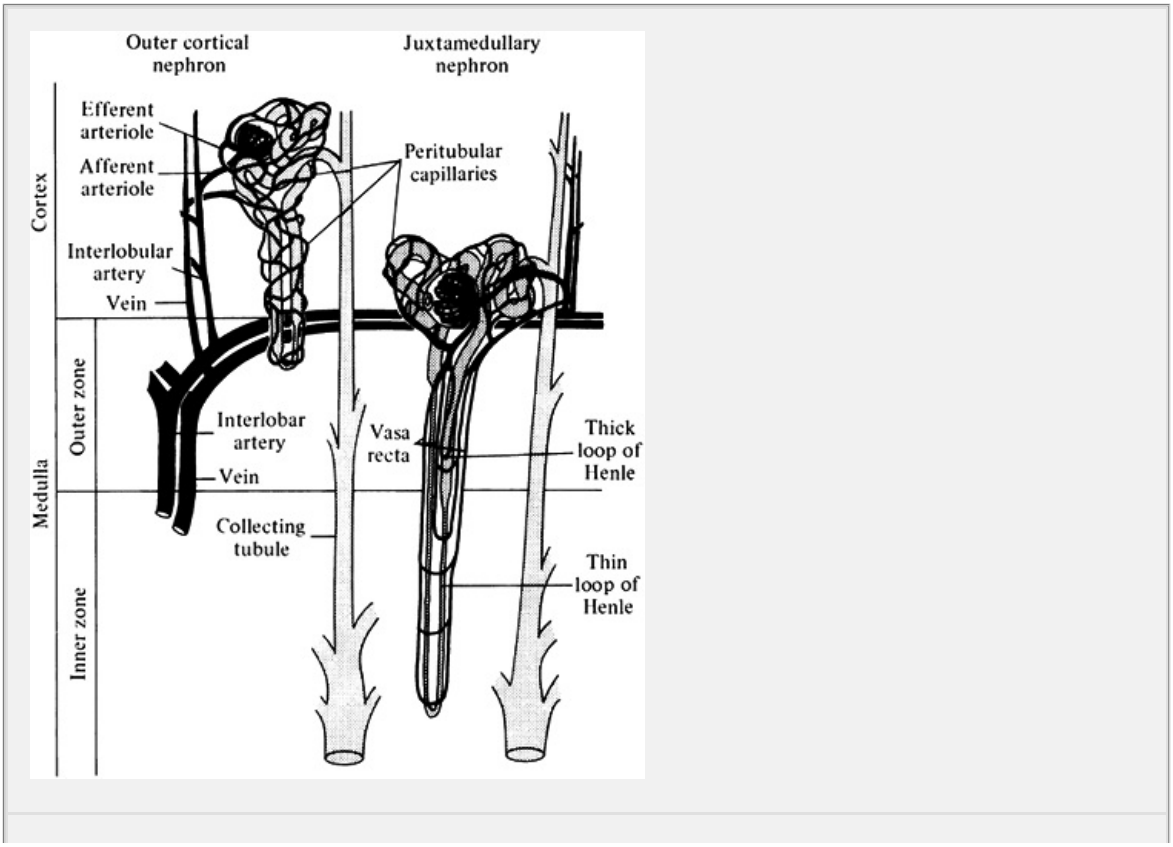

Fig. 2-1 Blood

Figure 2-1 Comparison of the anatomy and blood supplies of outer cortical juxtamedullary nephrons. Note that the efferent arterioles from the juxtam nephrons not only form peritubular capillaries around the convoluted tubu enter the medulla and form the vasa recta capillaries. *Adapted from Pitts, RF* Physiology of the Kidney and Body Fluids, *Copyright, 1974 by Year Book Medical Publishers, Inc, Chicago. Used by permission.*

The renal circulation affects urine formation in the following ways:

1. The rate of glomerular filtration is an important determinant of solute a excretion.
2. The peritubular capillaries in the cortex return reabsorbed solutes and the systemic circulation and can modulate the degree of proximal tubula reabsorption and secretion (see Chap. 3).
3. The vasa recta capillaries in the medulla return reabsorbed salt and wa systemic circulation and participate in the countercurrent mechanism, p the conservation of water by the excretion of a hyperosmotic urine (see Chapter 4).

The remainder of this chapter will review glomerular function, the factors r for the regulation of the glomerular filtration rate (GFR) and renal plasma f the clinical methods used to measure these parameters.

GLOMERULAR ANATOMY AND FUNCTION

The glomerulus consists of a tuft of capillaries that is interposed between t afferent and efferent arterioles. Each glomerulus is enclosed within an epit capsule (Bowman's capsule) that is continuous both with the epithelial cells surround the glomerular capillaries and with the cells of the proximal convo tubule (Fig. 2-2).[2] Thus, the glomerular capillary wall, through which the filtra pass, consists of three layers: the fenestrated endothelial cell, the *glomerular basement membrane* (GBM), and the epithelial cell. The epithelial cells are att to the GBM by discrete foot processes. The pores between the

foot processes (slit pores) are closed by a thin membrane called the *slit diaphragm* which functions as a modified adherent junction (Fig. 2-2).[3]

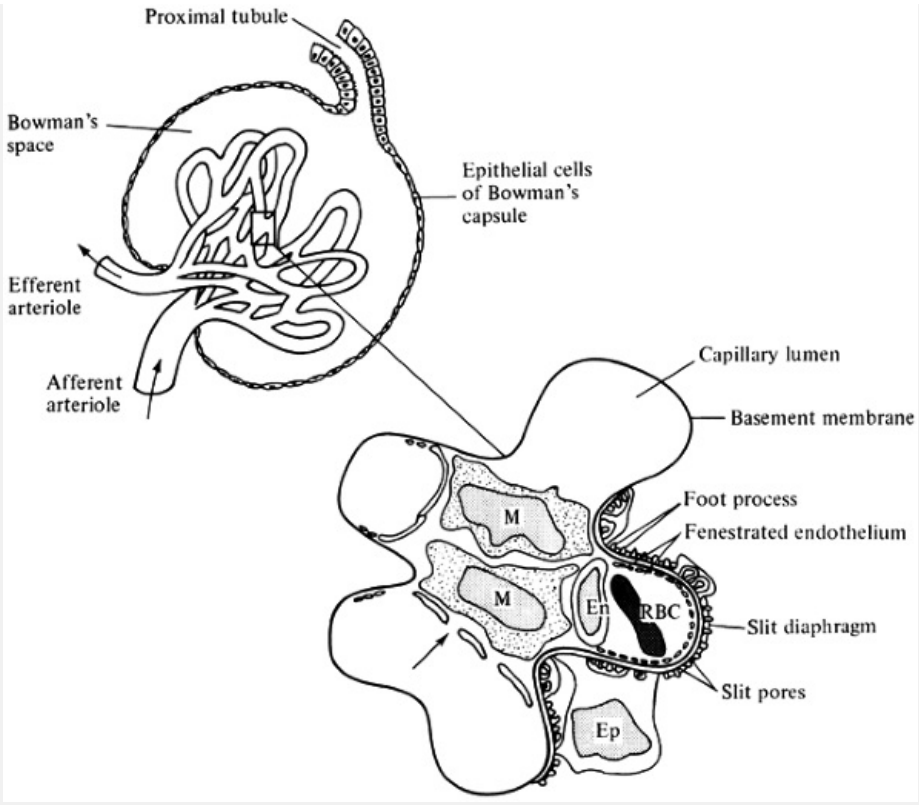

Figure 2-2 Anatomy of the glomerulus. The bottom drawing is a diagram of of a capillary tuft with the mesangial cells (M) in the middle surrounded b capillaries. The capillary wall has three layers composed of the fenestrat endothelial cells (En), the basement membrane, and the epithelial cells (E which attach to the basement membrane by discrete foot processes. Betw foot processes are slit pores which are closed by a thin membrane, the sl diaphragm. The glomerular basement surrounds the capillary loops, but m the mesangium is separated from the capillary lumen only by the relativel permeable fenestrated endothelium (*adapted from Vander R, Renal Physiology, 2d ed, McGraw-Hill, New York, 1980, and Landis EM, Handbook of Physiology, sec 8, Renal Physiology, vol I, Orloff J, Berliner RW, Geiger R, eds, American Physiological Society, Washington, DC, 1973 used with permission*).

The GBM is a fusion product of basement membrane material produced by t glomerular epithelial and endothelial cells.[4,5] It performs a variety of functions, including maintenance of normal glomerular architecture, anchoring of adja and acting as a barrier to the filtration of macromolecules. It consists of th major constituents:[4]

1. Type IV collagen, which forms cords that provide the basic superstructu GBM.
2. A variety of substances that fill the spaces between the cords, including nidogen, and heparan sulfate proteoglycans.[6] Laminin and nidogen form a tight complex, one of the major functions of which is cell adhesion to the GB

comparison, anionic heparan sulfate proteoglycans are largely responsi
the charge barrier to the filtration of anionic macromolecules (see belov

An abnormality in type IV collagen is responsible for the disorder hereditary
(Alport's syndrome), which is a progressive form of glomerular disease (at l
males) that is often associated with hearing loss and lenticular abnormaliti
primary defect in almost all patients appears to reside in the noncollagenou
of type IV collagen, involving the gene coding for the α_5 chain, which is located on
the X chromosome, the COL4A5 gene.[7,8] Abnormalities in the α_3 and α_4 chains of
type IV collagen may also cause hereditary nephritis, which is not surprisin
the α_3, α_4, and α_5 chains combine to form a novel collagen that is expressed
glomerulus and a few other tissues.[9]

Filtration Barrier and Protein Excretion

One of the major functions of the glomerulus is to allow the filtration of sma
(such as sodium and urea) and water, while restricting the passage of large
molecules (Fig. 2-3). Solutes up to the size of inulin (mol wt 5200) are freely f
On the other hand, myoglobin (mol wt 17,000) is filtered less completely tha
while albumin (mol wt 69,000) is filtered only to a minor degree. Filtration i
limited for ions or drugs that are bound to albumin, such as roughly 40 perc
circulating calcium.

This difference in filtration of solutes is important physiologically. The free
of sodium, potassium, and urea, for example, allows the kidney to maintain
steady state by excreting the load derived from dietary intake and endogen
metabolism. On the other hand, the restricted filtration of larger proteins pr
such potential problems as negative nitrogen balance, the development of
hypoalbuminemia, and infection due to the loss of immunoglobulin gamma (I

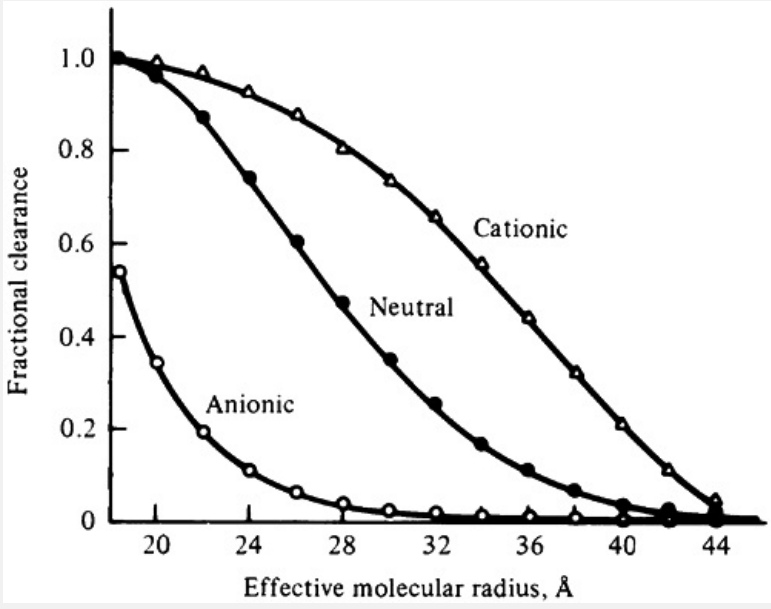

Figure 2-3 Fractional clearances (the ratio of the filtration of a substance t

of inulin, which is freely filtered) of anionic, neutral, and cationic dextran function of effective molecular radius. Both molecular size and charge are important determinants of filtration, as smaller or cationic dextrans are m easily filtered. As a reference, the effective molecular radius of albumin (anionic in the physiologic pH range) is 36 Å. *From Brenner BM, Hostetter TH, Olsen JL, Rennke HG, Ichikawa I, Hoyer MP, Baylis C, Humes HD, et al: J Clin Invest 1978; 61:72, by copyright permission of the American Society for Clinical Investigation.*

Size selectivity

As illustrated in Fig. 2-3, the GBM is both *size* and *charge* selective, as smaller and cationic molecules are more likely to be filtered. Both the GBM and the slit diaphragms between the foot processes of the epithelial cell contribute to s selectivity.[10,11]

The size limitation in the GBM represents functional pores in the spaces be tightly packed cords of type IV collagen.[12] In addition, the cellular components of t glomerular capillary wall are also important determinants of glomerular permeability.[13] This is illustrated by the following observations:

1. Macromolecules that pass through the GBM often accumulate below the diaphragms rather than passing into the urinary space.
2. In vitro studies of isolated GBM indicate that the GBM is much more per to macromolecules than the intact glomerulus; the net effect is that the glomerular cells may be responsible for as much as 90 percent of the ba filtration.[14]
3. Increased protein filtration in glomerular diseases may primarily occur i of focal foot process detachment.[15]
4. A mutation in the gene for nephrin, the first protein to be specifically lo the slit diaphragm, results in congenital nephrotic syndrome.[16]

Most of the pores in the glomerular capillary wall are relatively small (mean about 42 Å).[17]* They partially restrict the filtration of albumin (mean radius 3 allow the passage of smaller solutes and water.[18] The endothelial

cells, in comparison, do not contribute to size selectivity, since the endothe fenestrae are relatively wide open and do not begin to restrict the passage macromolecules until their radius is larger than 375 Å.[19] These cells do, however, contribute to charge selectivity.

There is also a much less numerous second population (less than 0.5 perce larger pores that permit the passage of macromolecules (including IgG) as 70 Å.[18] In normal subjects, however, only a very small amount of filtrate pas

through these pores.

Charge selectivity

Molecular charge is a second major determinant of filtration across the GBM.[10,11,20] As illustrated in Fig. 2-3, cationic and neutral dextrans are filtered to a greater degree than anionic dextran sulfates of similar molecular sizes. This inhibitory effect of charge is due in part to *electrostatic repulsion* by anionic sites both in the endothelial fenestrae and in the GBM. The negative charge is primarily composed of heparan sulfate proteoglycans (which are produced by the glomerular epithelial and endothelial cells).[2,21]

Albumin is a polyanion in the physiologic pH range. As with dextran sulfate, albumin filtration is only about 5 percent that of neutral dextran of the same molecular size. Thus, charge as well as size limits the filtration of albumin. However, the importance of charge selectivity may not be as great as previously thought.[23,24]

Dextran infusions have also been used in humans both to assess normal function and to determine the mechanism of the increase in protein excretion that typically occurs in glomerular diseases.[20,25] As illustrated in Fig. 2-4, for example, there is an increased number of larger pores, as evidenced by a selective elevation in clearance of neutral dextrans that are larger than 52 Å in diameter. Tunnels and cavities in the glomerular basement membrane appear to be the pathways for leakage.[26]

The net effect of loss of size selectivity is enhanced excretion of IgG (radius 55 Å) as well as albumin.[27] This pattern has been demonstrated in most glomerular diseases, including membranous nephropathy, minimal change disease, focal glomerulosclerosis, and diabetic nephropathy.[20,28,29] In these conditions, however, the size defect can account for all of the increase in albumin excretion in only one-half of cases, suggesting a concurrent defect in charge selectivity which is most prominent in minimal change disease.[25]

Figure 2-4 also illustrates an important clinical difference between the filtration of larger proteins and that of smaller solutes and water. The reduced clearance of smaller molecules in most proteinuric states reflects a decrease in surface area (due to fewer functioning pores) induced by the glomerular disease. At the same time, there is increased clearance of large proteins due to an enhanced number of pores (which still represent a very small fraction of the total

P.27

P.28

number of pores) and perhaps partial loss of the charge barrier (which does not affect the filtration of smaller molecules).

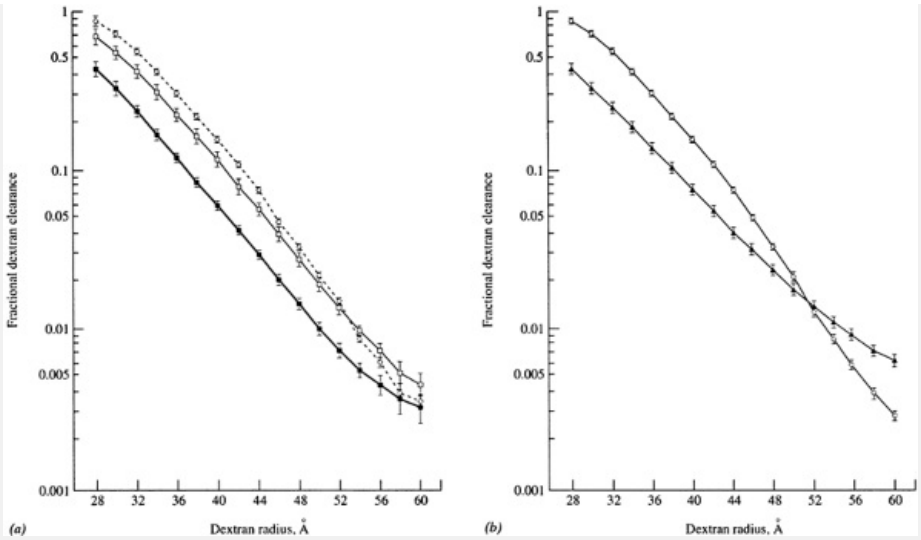

Figure 2-4 Dextran sieving profiles in patients with heavy proteinuria and t nephrotic syndrome. A fractional dextran clearance of 1 represents comple filtration. *a*) Profiles in patients with minimal change disease when nephrot (solid squares) and when in remission (open squares) compared to norma controls (open circles). Patients in remission are similar to controls, but d the active phase they have reduced clearance of dextrans of all sizes. Th proteinuria cannot be due primarily to defective size selectivity, suggestir primary role for loss of charge selectivity. *b*) Profiles in patients with focal glomerulosclerosis (triangles) compared to normal controls (circles). The have decreased clearance of smaller dextrans but increased clearance of dextrans with a radius above 52Å, suggesting an increased number of larg pores. *(From Guasch A, Hashimoto H, Sibley RK, et al: Am J Physiol 260:F728, 1991. Used with permission.)*

Other Functions

The glomerular cells also have synthetic, phagocytic, and endocrine functio epithelial cells, for example, are thought to be responsible for the synthesi GBM and for the removal of circulating macromolecules that are able to pas the GBM and enter the subepithelial space.[2,30] The endothelial cells, on the other hand, regulate vasomotor tone, in part via the release of prostacyclin, endo and nitric oxide. They may also play an important role in inflammatory diso involving the glomerulus by expressing adhesion molecules that promote th accumulation of inflammatory cells.[31]

The mesangium, in comparison, is composed of two different types of cells. the mesangial cell, which has microfilaments similar to those of smooth mus cells.[32,33] After glomerular injury or depopulation of resident mesangial cells mesangial cells may originate from cells that normally reside in the juxtaglo apparatus.[34] These cells do not appear to be macrophages or smooth muscle endothelial cells, or to excrete renin.

The intrinsic mesangial cells can respond to angiotensin II (which is locally

by the endothelial cells in the afferent arteriole) and can synthesize prosta
both of which play an important role in the regulation of

glomerular hemodynamics (see below and Chap. 6).[35] These cells also may be involved in immune-mediated glomerular diseases. They can both release a of cytokines (including interleukin-1, interleukin-6, chemokines, and epider growth factor) and proliferate in response to cytokines (such as platelet-de growth factor and epidermal growth factor).[33,36,37] These actions can contribute to the hypercellularity, mesangial matrix expansion, and glomerular injury that seen in these disorders.

The second cell type in the mesangium consists of circulating macrophages monocytes that move into and out of the mesangium. These cells may have phagocytic function, removing those macromolecules that enter the capillar are unable to cross the basement membrane and move into the urinary spac may also contribute to local inflammation in immune-mediated glomerular di[38] Macromolecule entry into and subsequent removal from the mesangium can because most of the mesangium is separated from the capillary lumen only relatively permeable fenestrated endothelium, not by basement membrane (Fig. 2-2).

RENIN-ANGIOTENSIN SYSTEM

Although the physiology of those hormones that importantly affect renal fun discussed in Chap. 6, angiotensin II plays such a central role in the regulation glomerular filtration rate that it is useful to review the renin-angiotensin sy this time.

The *afferent arteriole* of each glomerulus contains specialized cells, called the juxtaglomerular cells (Fig. 1-4). These cells synthesize the precursor prorenin which is cleaved into the active proteolytic enzyme renin. Active renin is th in and released from secretory granules.[39,40] More proximal cells in the interlobular artery can also be recruited for renin release when the stimulus prolonged.[41]

Renal hypoperfusion, produced by hypotension or volume depletion, and inc sympathetic activity are the major physiologic stimuli to renin secretion (Fig. 2-5). There is a gradient of response according to the location of the glomeruli: release is most prominent in the outer cortical (or superficial) glomeruli, wi response being seen in the midcortex and very little renin being secreted in juxtamedullary glomeruli.[44] This pattern may reflect changes in

glomerular perfusion pressure: The juxtamedullary glomeruli are closest to interlobular artery (Fig. 2-1), whereas the outer cortical glomeruli are furthest a and perfused at a lower pressure. The physiologic significance of these ob is unclear.

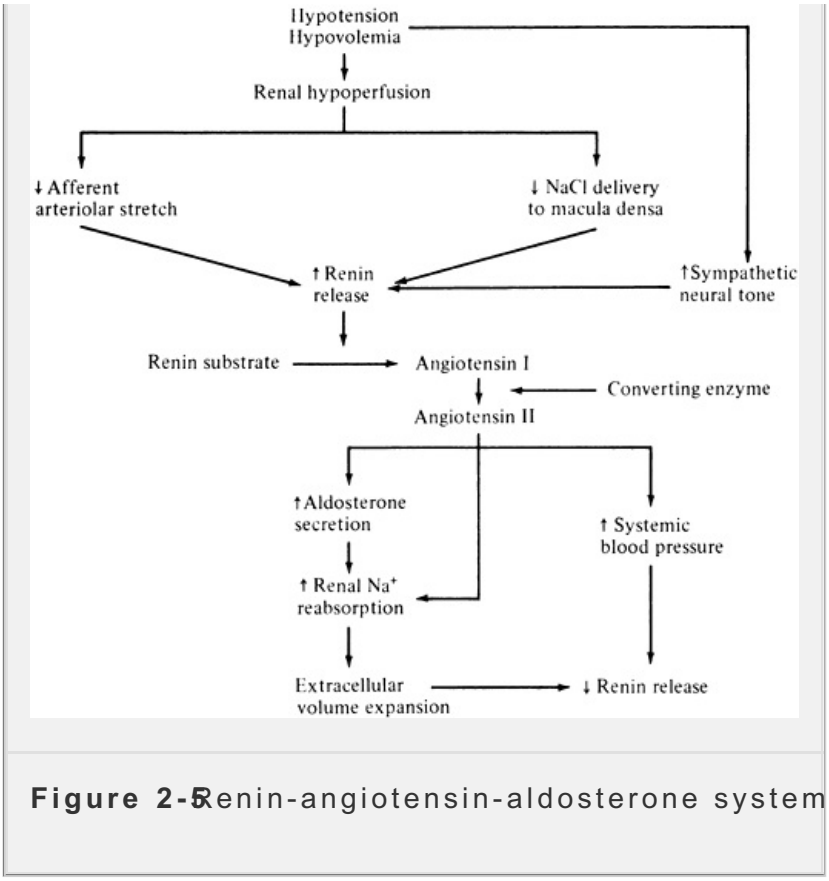

Figure 2-5 Renin-angiotensin-aldosterone system.

Renin initiates a sequence of steps that begins with cleavage of a decapep angiotensin I from renin substrate (angiotensinogen), an α2-globulin produced in the liver (and other organs including the kidney).[45,46] Angiotensin I is then converted into the octapeptide angiotensin II. This reaction is catalyzed by an enzyme angiotensin converting enzyme (ACE), which is located in the lung, the lum membrane of vascular endothelial cells, the glomerulus itself, and other org

Local Renin-Angiotensin Systems

The concentration of ACE is highest in the lung, and it had been thought th angiotensin II formation occurred in the pulmonary circulation. It is now cle however, that there are *extrarenal* renin-angiotensin systems and that angiotensi can be synthesized at a variety of sites, including the kidney, vascular end adrenal gland, and brain.[45,47,48] and[49] These extrarenal systems may account fo the persistent, although low, plasma levels of angiotensin II in anephric sub[50] It is presumed that local angiotensin II production is important for the regul local processes. Volume depletion, for example, leads to an increase in ren messenger ribonucleic acid (RNA) expression for both renin (in the glomeru angiotensinogen (in the proximal tubule).[51] Activation of the local renin system ma be mediated by local factors such as prostaglandins, nitric oxide, and endo[49] The proximal tubule also contains ACE and angiotensin II receptors, sugges local angiotensin II formation can occur and stimulate Na^+ reabsorption.[52] The observation that the concentration of angiotensin II in the peritubular capill proximal tubule is approximately *1000 times* higher than that in the systemic

circulation is consistent with the possibility of a local effect.[53] This effect can be achieved without releasing enough renin into the circulation to induce systemic vasoconstriction.

One clinical consequence of these observations is that measurement of the renin activity or angiotensin II concentration may be a misleading estimate tissue activity of this system. In some patients with essential hypertension, example, angiotensin II appears to be responsible for persistent renal vasoconstriction and sodium retention, even though the plasma levels of re angiotensin II are similar to those in hypertensives with normal renal perfus[54] These findings suggest a selective increase in the activity of the *intrarenal* renin-angiotensin system; the mechanism by which this occurs is not known. A sir selective activation of the intrarenal renin-angiotensin system may occur in congestive heart failure.[46]

Local generation of angiotensin II also can occur in vascular endothelium, may play an important role in the regulation of vascular tone and possibly i development of hypertension.[45,55] Volume depletion increases angiotensinogen messenger (mRNA) levels in aortic smooth muscle. If this results in enhanc release of angiotensinogen, then either locally produced or systemic renin initiate the sequential formation of angiotensin I and, via endothelial conve enzyme, angiotensin II.

These local effects could explain why ACE inhibitors are very useful antihy agents, even in patients with low plasma renin activity and low circulating l angiotensin II.[47,56] Although the findings in humans are only indirect, the pote importance of local renin-angiotensin systems in the genesis of hypertensio been more convincingly demonstrated in experiments in which a mouse reni was inserted into rats. The presence of this extra gene for renin led to sev hypertension that was largely corrected by an ACE inhibitor or an angiotens receptor antagonist.[57] Despite this evidence for angiotensin-mediated hyperter the plasma renin activity, plasma angiotensin II level, and renal renin conte below normal, while adrenal renin content and vascular angiotensin genera markedly elevated.[57,58] Thus, the elevation in blood pressure in this low (plas renin form of hypertension was mediated by local renin release in the adrer and perhaps vascular endothelium.

Actions of Angiotensin II

Angiotensin II has two major systemic effects: systemic vasoconstriction an and water retention. Both of these actions will tend to reverse the hypovole hypotension that is usually responsible for the stimulation of renin secretio (Fig. 2-5).[59,60]

The effects of angiotensin II are mediated by binding to specific angiotensi receptors: AT_1 and AT_2.[61] The vascular and renal tubular actions are primarily mediated by the AT_1 receptors.[61,62] The effects of the AT_2 receptors are less well

understood; they may contribute to the tubular actions of angiotensin II and regulation of cell proliferation in the arterial wall.[61,63,64]

Renal sodium and water retention

Angiotensin II promotes renal $NaCl$ and H_2O retention and therefore expansion of the plasma volume. This occurs by at least two mechanisms: by direct stimulation of Na^+ reabsorption in the early proximal tubule[60,65,66] and by increased secretion of aldosterone from the adrenal cortex, which enhances Na^+ transport in the cortical collecting tubule. Both systemic angiotensin II and angiotensin II generated in the adrenal gland contribute to the stimulation of aldosterone release.[51] (see Chapter 6).

The proximal effect of angiotensin II appears to result at least in part from stimulation of the Na^+-H^+ antiporter in the luminal membrane (see page 000).[67,68,69] This enhancement of Na^+-H^+ exchange appears to be mediated by two angiotensin II–dependent pathways (see Figs. 6-1 and 6-2): stimulation of an inhibitory G protein that decreases cyclic AMP generation, thereby minimizing the

normally suppressive effect of cyclic AMP on Na^+-H^+ exchange,[67] and, to a lesser degree, stimulation of phosphatidylinositol turnover, resulting in the generation of protein kinase C.[68]

Studies using a highly specific AT_1 receptor antagonist suggest that angiotensin II may be responsible for as much as 40 to 50 percent of Na^+ and HCO_3^- reabsorption in the initial segment of the proximal tubule.[64,70] The AT_2 receptors also appear to contribute to this response.[64] There is a much lesser effect in the more distal parts of the proximal tubule, where there are fewer angiotensin II receptors.

Systemic vasoconstriction

Angiotensin II produces arteriolar vasoconstriction, which, by elevating systemic vascular resistance, increases the systemic blood pressure. In addition to a direct action of angiotensin II on vascular smooth muscle (which appears to be mediated primarily by protein kinase C generation),[71] experimental observations suggest that enhanced sensitivity to and facilitated release of norepinephrine may also play a contributory role.[72,73] However, the applicability of the angiotensin II–norepinephrine relationship to humans is uncertain; it may be that only high angiotensin II levels, such as those seen with advanced congestive heart failure, are sufficient to stimulate norepinephrine release.[74]

The net effect is that angiotensin II plays *an important role in the maintenance of blood pressure* in all circumstances in which renin secretion is enhanced and circulating angiotensin II levels are high. This is true in the hypertension associated with renal artery stenosis (in which renal ischemia stimulates renin release) as in normotensive states associated with effective circulating volume depletion, such as true volume depletion, heart failure, and hepatic cirrhosis.[75,76,77] As

an example, the administration of an angiotensin II inhibitor to a normotens with hepatic cirrhosis can lower the blood pressure by as much as 25 mmHg possibly leading to symptomatic hypotension.[77]

The vascular action of angiotensin II involves enhanced phosphatidylinosito (see Fig. 6-2), rather than the generation of cyclic AMP, as in the proximal tub[78] The ensuing formation of diacylglycerol leads to the release of arachidonic which can then be converted into prostaglandins or, via the lipoxygenase p into metabolites of hydroxyeicosatetraenoic acid.[79] The latter compounds partially mediate angiotensin II-induced vasoconstriction (as well as aldosterone rel[79] whereas vasodilator prostaglandins tend to minimize the increase in vascul resistance.

Regulation of GFR

In addition to influencing systemic hemodynamics, angiotensin II plays an i role in the regulation of GFR and renal blood flow.[60] Although the clinical implications of these effects will be discussed below, it is helpful to review briefly at this time. Angiotensin II can affect renal blood

flow and the GFR by constricting the efferent and afferent glomerular arteri the interlobular artery.[80,81] and[82] These responses may be mediated at least in part by the local generation of the vasoconstrictor thromboxane A2.[83]

Although both afferent and efferent arterioles are constricted, the efferent has a smaller basal diameter; as a result, the increase in efferent resistanc as much as three times greater than that at the afferent arteriole.[84,85] The net effect is a reduction in renal blood flow (due to the increase in renal vascular res and an elevation in the hydraulic pressure in the glomerular capillary (P_{GC}), which tends to *maintain the GFR* when the renin-angiotensin system is activated by a systemic pressure.

The likelihood of excessive renal vasoconstriction is minimized because an II also stimulates the release of vasodilator prostaglandins from the glomer[86] The importance of this response can be illustrated by blocking the increase in prostaglandin synthesis with a nonsteroidal anti-inflammatory drug. In this low-sodium diet leads to more marked renal ischemia and, due to the declin perfusion, a substantial reduction in GFR (see Fig. 24-10 below).[87] Similarly, the degree of *systemic* vasoconstriction may also be minimized by the local angiot II-induced release of prostacyclin.[88]

Angiotensin II has two other effects that can influence the GFR. First, it co glomerular mesangium at higher concentrations, thereby lowering the surfa available for filtration. Second, angiotensin II sensitizes the afferent arteri constricting signal of tubuloglomerular feedback (see "Tubuloglomerular Feedback" below).[60]

The net result is that angiotensin II has counteracting effects on the regula

GFR: The increase in P_{glc} will tend to increase filtration, while the reduction in blood flow and mesangial contraction will tend to reduce filtration. The resu variable in different conditions, although how this occurs is incompletely ur When renal perfusion pressure is reduced, as in renal artery stenosis, angi acts to maintain the GFR, and the administration of an ACE inhibitor can ca renal failure. In comparison, the GFR may be reduced by angiotensin II in hypertension and congestive heart failure.[60,89]

Control of Renin Secretion

In normal subjects, the major determinant of renin secretion is Na^+ intake. A high intake expands the extracellular volume and decreases renin release, where intake (or fluid loss from any site) leads to a reduction in extracellular volu stimulation of renin secretion. Acute increases in renin secretion, as with v depletion, primarily reflect the release of preformed renin from secretory gr More chronic stimuli lead to increased synthesis of new prorenin and renin.[40]

The associated changes in angiotensin II and aldosterone production induc renin then allow Na^+ to be excreted with volume expansion or retained with vol depletion. Intrarenally formed angiotensin II probably plays at least a contr role in this response, as illustrated by the rise in mRNA for both renin and angiotensin substrate in the renal cortex following a low-sodium diet.[90]

These changes in volume are primarily sensed at one or more of three sites to the activation of effectors that govern the release of renin (Fig. 2-6).[39,91] baroreceptors (or stretch receptors) in the wall of the afferent arteriole; cardiac and arterial baroreceptors, which regulate sympathetic neural activ the level of circulating catecholamines, both of which enhance renin secret the β_1-adrenergic receptors,[92,93] and[3] the cells of the macula densa in the early distal tubule (see Fig. 1-4), which appear to be stimulated by a reduction in chlo delivery, particularly in the Cl^- concentration in the fluid delivered to this site.[94,95]

Baroreceptors

The baroreceptors respond to changes in stretch in the afferent arteriolar v ensuing alterations in renin release appear to be mediated by enhanced ca entry into the cells when renal perfusion pressure is reduced[96] and by the local release of prostanoids, particularly prostacyclin, when renal perfusion pres reduced.[92,97,98]

Macula densa

The macula densa dependence upon Cl^- is related to the characteristics of the Na^+-K^+-$2Cl^-$ cotransporter in the luminal membrane of the thick ascending limb a macula densa that promotes the entry of these ions into the cell (see Fig. 4-2).[94,99,100] The activity of this transporter is maximally stimulated at low

concentrations of Na^+ and K^+, but is regulated within the physiologic range by alterations in the concentration of Cl^- (see Fig. 4-3).[94] As an example, the decrease in proximal NaCl reabsorption that is seen with volume expansion will enha Cl^- concentration at the macula densa, thereby reducing renin secretion. In comparison, the administration of Na^+ with another anions (bicarbonate, acetate) ha little effect, since the tubular fluid Cl^- concentration will not rise.[94,95]

The importance of Na^+-K^+-$2Cl^-$ cotransport in the macula densa may explain the ability of loop diuretics to specifically enhance renin release. Although any can increase renin release by inducing volume depletion, the loop diuretics inhibit the Na^+-K^+-$2Cl^-$ transporter (see Chap. 15); as a result, less Cl^- is reabsorbed, thereby stimulating renin secretion.[94,101] The thiazide-type diuretics, on the other hand, inhibit Na^+-Cl^- cotransport primarily in the distal tubule and connecting segment; they do not directly affect the macula densa or renin release.[101]

Two factors may contribute to the mechanism by which the macula densa af renin secretion: adenosine and PGE_2.[92,96,102,103] As an example, adenosine may mediate at least part of the suppression of renin secretion with NaCl delive macula densa is increased.[102,103] The adenosine required to mediate this respo may be derived from the breakdown of adenosine triphosphate (ATP) that o the increase in delivery leads to enhanced local NaCl reabsorption.

On the other hand, the rise in renin release seen when NaCl delivery is red in hypovolemic states) may be mediated by increased production of PGE_2.[97,104] This effect may be related to enhanced activity of COX-2 (an isoform of cyclooxygenase) in epithelial cells located near the macula densa.[105]

The interaction between the renin-angiotensin system and prostaglandins m confusing, since each stimulates the secretion of the other,[86,87,92,98] and they induce opposing vascular actions—vasoconstriction with angiotensin II and vasodilation with most prostaglandins. However, angiotensin II is a systemi vasoconstrictor, whereas the prostaglandins act locally, because they are r metabolized when they enter the systemic circulation. Thus, the net effect simultaneous renal secretion of angiotensin II and prostaglandins is that ar II can cause systemic vasoconstriction and raise the blood pressure, while prostaglandins minimize the degree of renal vasoconstriction, thereby main renal blood flow and GFR.[87]

The contributions of the three major factors governing renin release can be appreciated from the response to hypovolemia (see Chap. 8). The decrease in volume initially lowers the blood pressure, which diminishes the stretch in t afferent arteriole, increases sympathetic activity, and reduces NaCl deliver macula densa (in part by enhancing proximal reabsorption).[94] Each of these changes then promotes renin secretion. This response can be largely aboli

inhibiting its mediators with a combination of indomethacin (which inhibits prostaglandin synthesis) and propranolol (a β -adrenergic blocker).[106]

On the other hand, renin release is diminished by volume expansion (as wit Na^+ intake). In addition to reversal of the above sequence, atrial natriuretic also may contribute by directly impairing the secretion of both renin and aldosterone.[107]

DETERMINANTS OF GLOBULAR FILTRATION RAT

The initial step in urine formation is the separation of an ultrafiltrate of pla across the wall of the glomerular capillary. As with other capillaries, fluid m across the glomerulus is governed by Starling's forces, being proportional t permeability of the membrane and to the balance between the hydraulic and pressure gradients (see Chap. 7):

$$\begin{aligned} GFR &= LpS\ (\Delta \text{ hydraulic pressure} - \Delta \text{ oncotic pressure}) \\ &= LpS\ [(P_{gc} - P_{bs}) - s(\pi_p - \pi_{bs})] \end{aligned} \qquad (2\text{-}1)$$

where Lp is the unit permeability (or porosity) of the capillary wall, S is the area available for filtration, and P_{gc} and P_{bs} are the hydraulic pressures in the glomerular capillary and Bowman's space, and π_p and π_{bs} are the oncotic pressures in the plasma entering the glomerulus and in Bowman's space, and s represen reflection coefficient of proteins across the capillary wall (with values rang if completely permeable to 1 if completely impermeable). Since the filtrate i essentially protein free, π_{bs} is 0 and s is 1. Thus,

$$GFR = LpS\ (P_{gc} - P_{bs} - \pi_p) \qquad (2\text{-}2)$$

The GFR in normal adults is approximately 95± 20 mL/min in women and 12 mL/min in men.[108] This degree of filtration is, per weight, more than 1000 tim in muscle capillaries. Two factors account for this difference:[1] The Lp S of the glomerulus is 50 to 100 times that of a muscle capillary, and[2] the capillary hydraulic pressure and therefore the mean gradient favoring filtration ($P_{gc} - P_{bs} - \pi_p$) is much greater in the glomerulus than in a muscle capillary (Table 2-1).[109,110] and [111] Although almost all of the filtered electrolytes and water are reabsorbed, th GFR is required to allow the filtration and subsequent excretion of a variet metabolic waste products such as urea and creatinine (see below).

Filtration Equilibrium

Changes in the GFR can be produced by alterations in any of the factors in Eq. 2-2 or in the rate of renal plasma flow (RPF). Before discussing the mechanism which these hemodynamic forces are regulated, it is important to first revie they change as fluid moves through the glomeruli. Experimental studies in r primates have demonstrated that the hydraulic pressures in the glomerulus Bowman's space remain relatively constant; the capillary oncotic pressure, *progressively rises* due to the filtration of protein-free fluid.

Table 2-1 Approximate values for Starling's forces in muscle and glomerulus[a]

		Glomerulus (primate)	
	Skeletal muscle (human)	Afferent arteriole	Efferent arteriole
Hydraulic pressure			
Capillary	17.3	46	45
Interstitium	-3.0	10	10
Mean gradient	20.3	36	35
Oncotic pressure			
Capillary	28	23	35[b]
Interstitium	8	0	0
Mean gradient	20	23	35
Net gradient favoring filtration	+0.3	+13	0
(ΔP-Δ π)			
+ = filtration			
- = absorption		Mean = + 6mmHg)	

[a] Units are mmHg. Values are from Rea[109] and Deen.[110]

[b] The capillary oncotic pressure rises in the glomerulus because of the filtration of relatively protein-free fluid.

P.37

The net result of these changes is depicted in Fig. 2-6.[110,111] and [112] The gradient favoring filtration normally averages about 13 mmHg at the afferent arteriol *falls to zero* before the efferent arteriole because of the elevation in plasma onco pressure (from 23 to 35 mmHg).

This phenomenon is called *filtration equilibrium* and, in the primate, occurs after th filtration of 20 percent of the RPF, a filtration fraction similar to that seen † (where approximate normal values for the GFR and RPF are 125 and 625 respectively). Further filtration *at the same RPF* cannot occur, i.e., the GFR cannot exceed 20 percent of the RPF, without an increase in P_{gc} or a reduction in π_p.

The presence of filtration equilibrium also means that the RPF becomes an determinant of the GFR.[111,114] If, for example, the RPF is diminished with no alteration in P_{gc}, then filtration equilibrium will still be reached after the filtra 20 percent of the RPF. Thus, *the GFR will fall in proportion to the decrement in RPF*, so that a 15 percent reduction in RPF will induce a 15 percent decline Conversely, a 15 percent elevation in RPF will lead to a 15 percent rise in

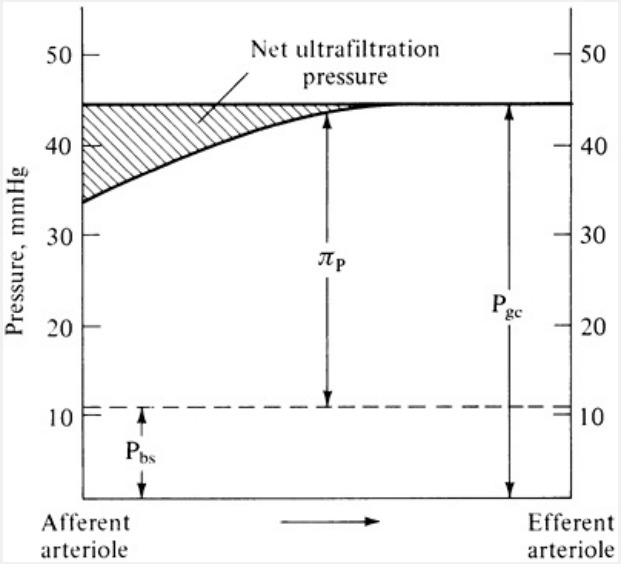

Figure 2-6 Depiction of the hemodynamic forces along the length of the pri glomerular capillary. The dotted line represents the hydraulic pressure in Bowman's space, P_{bs}. The plasma oncotic pressure is added to this so that t middle solid line represents the sum of the forces retarding filtration: $P_{bs} + \pi_p$. The upper solid line represents the glomerular hydrostatic pressure (P_{gc}), and the shaded area depicts the net gradient favoring filtration, which is $P_{gc} - P_{bs} - \pi_p$, +13 mmHg at the afferent arteriole. As a result of ultrafiltration of protein-f fluid, π_p increases until the filtration gradient is abolished and filtration ce This is in contrast to muscle capillaries, where filtration is limited by a de capillary hydraulic pressure. (*Adapted from Maddox DA, Deen WM, Brenner BM*, Kidney Int *5:271, 1974, and Deen WM, Robertson CR, Brenner BM*, Am J Physiol *223:1178, 1972. Used with permission from Kidney International.*)

P.38

Note that the oncotic pressure of the fluid leaving the efferent arteriole and the peritubular capillary is determined both by the protein concentration in plasma entering the glomerulus and by the degree to which the plasma prot

concentrated due to the removal of the protein-free filtrate, i.e., by the filtr fraction GFR/RPF. As will be seen, the filtration fraction and the peritubula oncotic pressure are important determinants of proximal tubular sodium and reabsorption (see page 84).

Capillary Hydraulic Pressure and Arteriolar Resistar

The glomerular capillaries are uniquely interposed between two arterioles. result, the P_{gc} is determined by three factors: the aortic pressure, the resista the afferent arteriole, and the resistance at the efferent arteriole. The abili regulate arteriolar resistances provides *rapid regulation of the GFR through change in the* P_{gc}. Constriction of the *afferent* arteriole, for example, reduces both P_{gc} and GFR, since less of the systemic pressure is transmitted to the glomerulus; the afferent arteriole, on the other hand, enhances both of these parameters (Figure 2-7). In comparison, constriction of the *efferent* arteriole retards fluid movement from the glomerulus into the efferent arteriole, increasing P_{gc} and GFR; dilation of the efferent arteriole facilitates fluid entry into the efferent arteriole, diminishing these parameters (Fig. 2-7).

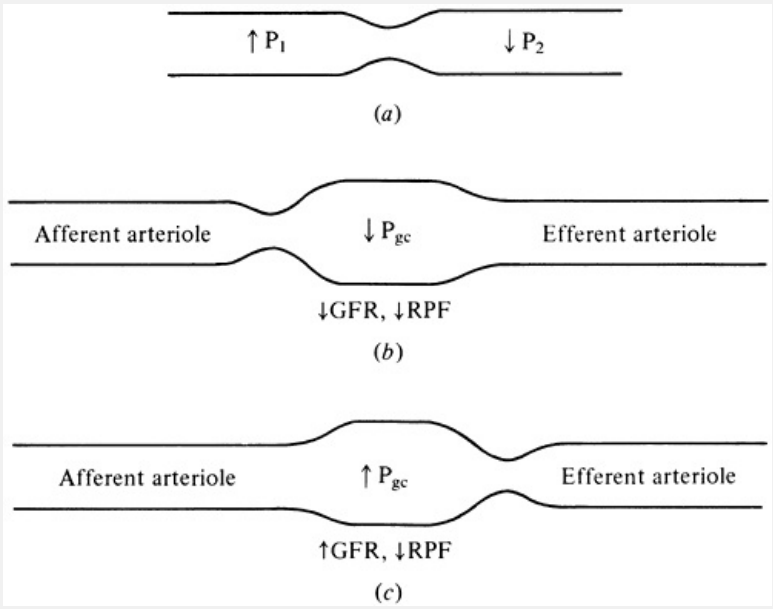

Figure 2-7 Relationship between arteriolar resistance, GFR, and RPF. (*a*) If flow is constant, constriction of a vessel results in a rise in pressure (↑) proximal and a fall distally (↓) (*b*). Constriction of the afferent arteriole reduces P_{gc} and GFR. (*c*) Constriction of the efferent arteriole, on the other hand, tends to increase P_{gc} and GFR. Since constriction of either arteriole also increases vascular resistance, RPF will fall in both (*b*) and (*c*). Arteriolar vasodilation has the opposite effects. For example, decreasing efferent arteriolar tone (as ACE inhibitor, which reduces the formation of angiotensin II) will lower P_{gc}.

Arteriolar tone also affects the RPF. In the kidney, the resistance to flow ac

arterioles constitutes 85 percent of renal vascular resistance, the remainin percent coming from the peritubular capillaries and renal veins.[115] The re between RPF, the Δ P across the renal circulation, and renal vascular resis be expressed by the following equation:

$$\text{RPF} = \frac{\text{aortic pressure} - \text{renal venous pressure}}{\text{renal vascular resistance}} \qquad (2\text{-}3)$$

This relation shows that an increase in tone at either end of the glomerulus elevate total renal resistance and reduce RPF. Thus, GFR and RPF are reg *in parallel* at the afferent arteriole, e.g., constriction decreases both, and *inversely* the efferent arteriole, e.g., constriction reduces RPF but may augment GFR. As a result, alterations in efferent (but not afferent) arteriolar tone affect t the GFR to the RPF (i.e., the filtration fraction), since these parameters wi change in opposite directions.

The opposing effects of efferent arteriolar tone on RPF also mean that the direct relationship between this resistance and the GFR (Fig. 2-7) must be modified, since the RPF is an independent determinant of GFR. As an example, althou efferent arteriolar constriction increases the concomitant elevation in renal vascular resistance will reduce RPF, which will tend to lower the GFR. Dep upon the magnitude of efferent constriction, the net effect may be an increa change, or, if RPF is sufficiently reduced, even a fall in GFR.

Arteriolar resistance is partially under intrinsic myogenic control, but also influenced by other factors, including angiotensin II, norepinephrine, renal prostaglandins, atrial natriuretic peptide, endothelin, and tubuloglomerular feedback (see below).

Role of Other Starling's Forces

The other determinants of glomerular filtration (Eq. 2-2) are of much lesser importance in the physiologic regulation of the GFR. The permeability of th glomerular capillary wall, for example, remains relatively constant in most r conditions.[110,111] Furthermore, *small changes in net permeability will not affec the GFR*, since the attainment of filtration equilibrium means that it is the ris capillary oncotic pressure, not permeability, that limits the filtration of sma and water.[111] A variety of hormones, including angiotensin II, antidiuretic hor and prostaglandins, can affect the LpS.[89,116] However, the physiologic significanc of these effects is uncertain, although high concentrations of angiotensin II to a net decline in GFR in some settings.[89] Similarly, a reduction in LpS in disease states such as glomerulonephritis can contribute to the fall in GFR that is observed; this problem is due primarily to a reduction in the surface area a for filtration.[117] The reduction in permeability becomes a limiting factor, becau now severe enough to prevent filtration equilibrium from being reached.

Alterations in P_{bs} or the plasma oncotic pressure also affect the GFR only in c states.[111] As an example, ureteral or intratubular obstruction leads to an inc

P_{bs}, thereby reducing the hemodynamic gradient favoring glomerular filtrati[118] On the other hand, volume depletion due to vomiting or diarrhea can result hemoconcentration and a rise in the plasma protein concentration. This inc π_p, contributing to the decrease in GFR that may be seen in this setting.

REGULATION OF GLOMERULAR FILTRATION RATE AND RENAL PLASMA FLOW

Regulation of renal hemodynamics is primarily achieved via changes in arte resistance, which can affect both RPF [Eq. 2-3] and GFR (by altering P_{gc} and RPF). In normal subjects, for example, changes in posture or diet can produ alterations in renal perfusion pressure. In this setting, two closely related *intrarenal* phenomena, autoregulation, and tubuloglomerular feedback, interact to mai GFR and RPF at a relatively constant level.[119] In comparison, pathophysiologic states, such as volume depletion, can lead to activation of systemic neuroh factors that can override these intrarenal effects.

Autoregulation

Since P_{gc} is an important determinant of GFR, it might be expected that sma variations in arterial pressure could induce large changes in GFR. However and RPF remain roughly constant over a wide range of arterial pressures ([Fig. 2-8]).[120,121] This phenomenon, which is also present in other capillaries,[122] intrinsic to the kidney, occurring in denervated, perfused kidneys, and has termed *autoregulation*.

Since the GFR and RPF are maintained in parallel, autoregulation must be in part by changes in afferent arteriolar resistance ([Fig. 2-7]).[119,123] As systemic pressure rises, for example, an increase in afferent arteriolar tone prevents elevation in pressure from being transmitted to the glomerulus, allowing P_{gc} and GFR to remain unchanged.[123] The enhanced arteriolar resistance also increase total renal vascular resistance, and [Eq. 2-3] this increase in vascular tone balances the rise in pressure and minimizes any change in RPF.

Conversely, as blood pressure decreases, *afferent arteriolar dilation* initially protect both GFR and RPF. However, the ability to maintain renal hemodyna becomes impaired at mean arterial pressures below 70 mmHg. In this settin and RPF fall in proportion to the drop in blood pressure, and the GFR ceas the systemic pressure reaches 40 to 50 mmHg.

The mechanism by which autoregulation is mediated is incompletely unders simplest hypothesis is that myogenic stretch receptors in the wall of the aff arteriole are of primary importance, similar to the role of the precapillary s the muscle capillary.[122] An elevation in renal perfusion pressure, for example, increase the degree of stretch, which will then promote arteriolar constricti[123] this effect is mediated in part by increased cell entry of calcium.[124]

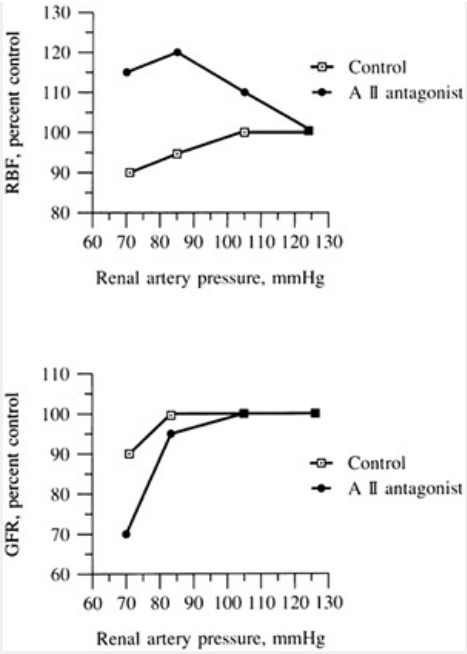

Figure 2-8 Effect of reducing renal artery pressure (from a baseline value o about 125 mmHg) on renal blood flow (RBF) and GFR, expressed as a percentage of control values in dogs fed a normal-sodium diet. The open squares represent control animals in which both RBF and GFR were maint until the pressure was markedly reduced. The closed symbols represent a given an intrarenal infusion of an angiotensin II antagonist; autoregulatio RBF was maintained (with an increase in the baseline level because of th renal vascular resistance), but the GFR was less well regulated. Although shown, autoregulation also applies when the renal artery pressure is initi raised. *(Adapted from Hall JE, Guyton AC, Jackson TE, Am J Physiol 233:F366, 1977. Used with permission.)*

P.41

The efferent arterioles, in comparison, have different characteristics: They seem to respond directly to changes in stretch and therefore do not contrib directly to the myogenic response.[125] Why this occurs is not clear, but the appare absence of voltage-gated Ca^{2+} channels in the efferent arterioles may play a contributory role.[126]

However, autoregulation of GFR is mediated by more than myogenic respon both angiotensin II (when the renal perfusion pressure is reduced) and tubuloglomerular feedback (especially when renal perfusion pressure is inc see below) can play an important role.[121,127] Other regulators of renal vascular resistance, such as the vasodilator nitric oxide (endothelium-dependent rel factor), do not appear to participate in autoregulation.[128]

As illustrated in Fig. 2-8, for example, the administration of an angiotensin II antagonist results in the dissociation of the autoregulation of RPF and GFR.[121] As described above, the renin-angiotensin system is activated as renal perfusi

pressure is lowered, resulting in both local and systemic generation of ang
II.[129] The preferential increase in efferent arteriolar resistance induced by
angiotensin II contributes to autoregulation of GFR by preventing any fall i
consequently, infusion of an angiotensin II antagonist or an ACE inhibitor le
less effective maintenance of the GFR. *Angiotensin II dependence is most
prominent when the renal perfusion pressure is substantially reduced* (Fig. 2-8).
Autoregulation of GFR with the initial decrease in renal artery pressure is p
mediated by TGF and the stretch receptors.[127]

Clinical Implications

Patients with bilateral renal artery stenosis, due most often to atherosclero
lesions, have an elevated pressure proximal to the stenosis but a normal or
pressure distal to the stenosis. As a result, the administration of antihypert
therapy to lower the systemic blood pressure is likely to diminish the distal
artery pressure (which includes that perfusing the glomeruli) to a level that
normal. In this setting, autoregulation plays an important role in maintainin
GFR, a response that can be partially impaired by diminishing the productio
angiotensin II with an ACE inhibitor. Up to one-half of such patients given a
inhibitor will have a usually mild decline in GFR, although severe (and reve
renal failure can occur.[130,131] Diuretic-induced volume depletion appears to be
important risk factor for this problem, since it makes maintenance of the GF
more angiotensin II-dependent.[121,132]

A similar decline in GFR can occur in the affected kidney in *unilateral* renal artery
stenosis,[133] a change that can lead to eventual ischemic atrophy.[134] This is not
easy to detect clinically, however, since the presence of the contralateral n
kidney prevents the development of acute renal failure (as would be eviden
rise in the plasma creatinine concentration; see below).

Other medications are less likely to produce this problem, since they do no
with autoregulation.[130,135] However, the ability of autoregulation to protect the
is impaired if the perfusion pressure is markedly reduced (Fig. 2-8). Thus, any
antihypertensive agent can produce acute renal failure when severe and
bilateral renovascular lesions (or a marked unilateral lesion in a solitary kid
[135]

The risk of acute renal failure after ACE inhibition is not limited to renovas
disease, but can occur in any condition in which renal perfusion pressure is
As an example, ACE inhibitors are standard therapy in heart failure, leading
increases in cardiac output, patient survival, and renal blood flow, as well
improvement in functional status. Despite all of these beneficial changes, t
falls in about one-third of cases, presumably due to a reduction in P
efferent arteriolar dilation.[136,137] This is most likely to occur in patients with a
diastolic pressure below 70 mmHg who are being treated with high doses of
diuretics.

Although the autoregulatory changes in arterial and arteriolar resistance ar

reversed when the renal perfusion pressure is elevated, angiotensin II leve in the basal state and it is unlikely that any further reduction is responsible maintenance of GFR. There is, however, substantial evidence for the role o tubuloglomerular feedback in this setting.

Tubuloglomerular Feedback

Tubuloglomerular feedback (TGF) refers to the alterations in GFR that can be induced by changes in tubular flow rate (Fig. 2-9). This phenomenon is mediated

by the specialized cells in the *macula densa* segment at the end of the cortical thic ascending limb of the loop of Henle; these cells sense changes in the deliv subsequent reabsorption of chloride.[94,99,100] The importance of chloride is, as described previously, probably related to the chloride dependence of the Na^+-K^+-2Cl^- carrier in the luminal membrane that promotes the entry of these ions i cell (see Fig. 4-3).[94,99,100]

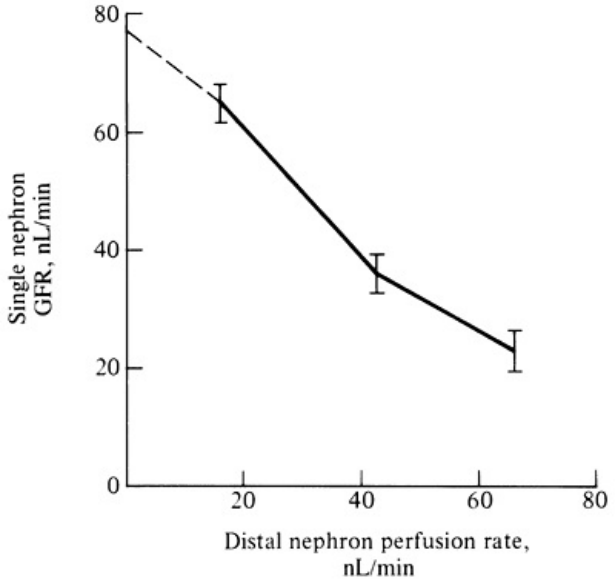

Figure 2-9 Relationship of single nephron GFR to distal nephron (macula d perfusion rate in dogs. As the perfusion rate increases (via the insertion micropipette into the late proximal tubule), there is a progressive reductio GFR to a minimum of about one-half the basal level. (*From Navar LG: Am J Physiol 234:F357, 1978. Used with permission.*)

TGF plays an important role in autoregulation.[127,141] An elevation in renal perfusion pressure can activate TGF via an initial rise in GFR; the ensuing in macula densa chloride delivery will then initiate a response that *returns both GFR and macula densa flow toward normal* (Fig. 2-9). This effect is mediated primarily b afferent arteriolar constriction, thereby decreasing the intraglomerular hydr pressure.[123,142]

If, on the other hand, the Na^+-$2Cl^-$ cotransporter in a single nephron is inhibit by a loop diuretic (such as furosemide), there is a marked impairment in autoregulation as renal perfusion pressure is increased.[142] Thus, part of the autoregulatory response that persists has been thought to reflect myogenic induced vasoconstriction.[124,142] There is, however, an alternative possibility: *cooperativity* among adjacent nephrons supplied by a common arterial branch.[143] The afferent vasoconstriction occurring in one nephron may be transmitted the artery and lead to vasoconstriction in adjacent nephrons. Thus, the in v of increasing distal Cl^- delivery in all nephrons will lead to a greater degree of afferent vasoconstriction in a single nephron than is induced by the macula that nephron.

Mediators

The factors that mediate TGF are incompletely understood.[140] The afferent site of constriction seen with increased distal flow involves the cells of the juxtagl apparatus that are responsible for renin secretion.[123] Although this observation suggests an important role for angiotensin II in tubuloglomerular

feedback, this hormone appears to play a permissive role, perhaps by sens afferent arteriole to the true mediators.[144] This action of angiotensin II appears to l relatively specific, since other vasopressors such as norepinephrine and ar hormone (ADH) do not have a similar effect.[145]

The sensitizing action on TGF is essential if angiotensin II is to contribute maintenance of the effective circulating volume by decreasing Na^+ excretion (see above).[146] The angiotensin II-mediated increase in proximal reabsorption wil diminish distal flow, which should, via a decrease in the TGF signal, raise return distal delivery to the baseline level. This response is minimized by t associated increase in sensitivity of the afferent arteriole to the mediator o thereby permitting the desired reduction in Na^+ excretion.[146]

Despite its modulating effect, angiotensin II is not the primary mediator of changes in renin release do not correlate with TGF. As an example, increas NaCl delivery will activate TGF at the same time that macula densa-mediate release is diminished.

There is suggestive evidence that the changes in arteriolar resistance assc with TGF may be mediated by alterations in the local release of *adenosine*,[102] which can induce the observed constriction of the afferent arteriole.[147] The TGF response to increased NaCl delivery is largely inhibited by blockade of the adenosine receptor and/or adenosine formation.[148,149] How adenosine secretion might be regulated in this setting is unknown. One possibility is that raising Na^+ and Cl^- will increase sequentially the filtered load, tubular sodium reabsorption, and t utilization of ATP, which results in the generation of adenosine.[102]

The adenosine hypothesis can also explain how the macula densa can conc perform two functions: regulating TGF and renin secretion. The increase in adenosine release with volume expansion can both activate TGF and inhibit renin release.[102,103]

Another vasoconstrictor that may participate in TGF is thromboxane. Throm production is increased when TGF is activated, the administration of a thro mimetic increases the sensitivity of TGF, and the TGF response is blunted thromboxane antagonist.[151] ATP itself is also a constrictor of the afferent arteri that may contribute to TGF.[152]

Vasodilator responses in TGF occur when macula densa flow is reduced. Th be mediated in part by reduced availability of the above vasoconstrictors.[153]

An additional significant regulator of TGF is *nitric oxide* (NO). NO, a molecular gas synthesized by cells in the macula densa, *blunts* the TGF response to increase sodium chloride delivery.[154]

NO release from the macula densa is increased in this setting, thereby cou the afferent arteriole constriction elicited in the TGF response. Thus, chan macula densa NO production may underlie the resetting of TGF that occurs salt intake is varied; the response is appropriately blunted with a high-salt maintenance of glomerular filtration promotes excretion of the excess salt.[155]

An alternative hypothesis suggests that changes in *interstitial* Cl^- *concentration or osmolality* constitute the signal for alterations in arteriolar resistance. The i region bordered by the early distal tubule (including the macula densa) and glomerular arterioles (see Fig. 1-4) is poorly perfused; as a result, solutes transported into this area from the luminal fluid are removed slowly, becaus must diffuse over a relatively long distance before they can enter the peritu capillaries.

Direct measurements in this region have demonstrated that, as distal flow r therefore macula densa Cl^- reabsorption are progressively increased, there is a in the local interstitial Cl^- concentration from about 150 meq/L (similar to that in plasma) to *over 600 meq/L*.[156] This increase in solute concentration or in osmol may then directly increase afferent arteriolar resistance.[150] In comparison, the interstitial Cl^- concentration remains relatively constant in areas that are further away juxtaglomerular region.[156] These sites are better perfused, and reabsorbed NaC rapidly removed by the peritubular capillaries.

Functions

A major function of autoregulation and TGF is to *prevent excessive salt and water losses*. To understand this concept, it is important to appreciate the differen function between the proximal and distal segments of the nephron. The bull filtrate (about 90 percent) is reabsorbed in the proximal tubule and loop of

with the final *qualitative* changes in urinary excretion (such as hydrogen and potassium secretion and maximum sodium and water reabsorption) being ma distal nephron, particularly in the collecting tubules. The collecting tubules have a relatively limited *total* reabsorptive capacity. Thus, the ability of the macu densa to decrease the GFR when distal delivery is enhanced prevents dista reabsorptive capacity from being overwhelmed, which could lead to potentia threatening losses of sodium and water. Viewed in this light, it may be that *macula densa flow itself, not the GFR*, is being maintained by autoregulation and TGF.[157]

A possible clinical example of TGF is the fall in GFR seen in acute tubular the most common form of acute renal failure developing in the hospital. In t disorder, proximal and loop sodium reabsorption are impaired by ischemic o tubular damage. Thus, the reduction of GFR (which is not easily explained histologic abnormality) may in part represent an *appropriate* TGF response to maintain sodium balance.[138,158] Similarly, TGF also mediates the reduction in G that occurs when proximal reabsorption is partially impaired by the adminis the carbonic anhydrase inhibitor acetazolamide, a proximally acting diuretic be useful in patients with edema and metabolic alkalosis (see pages 45 and 159).

On the other hand, glucosuria seems to *impair* TGF by an unknown mechanism that is in part mediated by the increase in tubular fluid glucose concentration.[138] This may play an important role in the marked fluid losses typically seen in diab ketoacidosis or nonketotic hyperglycemia (see Chap. 25). The osmotic diuresis induced by glucose reduces sodium and water transport in the proximal tub loop of Henle.[160] If TGF were normally active, the

ensuing increase in delivery to the macula densa would diminish the GFR, t minimizing the degree of fluid loss.

Neurohumoral Influences

The intrarenal effects of autoregulation and TGF are likely to be most impo the day-to-day regulation of renal hemodynamics in normal subjects. Autore also may help to maintain the GFR in patients with hypertension or with *selective* renal ischemia, as with bilateral renal artery stenosis. In fact, many of the experimental studies of autoregulation have been performed by using a sup aortic clamp to selectively alter renal perfusion pressure.[121,127]

In patients, however, renal artery pressure is most often reduced because o effective circulating volume depletion (as with true volume depletion, heart cirrhosis; see Chap. 8). In these disorders, there is marked stimulation of the vasoconstrictor sympathetic nervous and renin-angiotensin systems.[76,161] As described previously, angiotensin II increases the resistance in the efferen lesser degree the afferent arteriolen comparison, norepinephrine (either circulating or released from the renal sympathetic nerves) directly increase tone and indirectly, via stimulation of the release of renin and angiotensin enhances efferent resistance.[80,82,162]

Thus, a reduction in systemic prefusion pressure is associated with renal neurohumorally mediated vasoconstriction rather than autoregulation and T induced vasodilatation. The effect of these changes varies with the degree neurohumoral activation. A relatively mild increase in renal sympathetic ton produce no change in baseline renal perfusion, but may be sufficient to imp autoregulation (and therefore maintenance of GFR) as renal perfusion pres reduced.[163] In comparison, patients with advanced heart failure or severe vo depletion have more marked increments in norepinephrine and angiotensin setting, RPF is reduced at rest with a lesser fall or no change in GFR, sinc constriction increases the [80,162] This is a very effective adaptation because preferentially shunts perfusion to the critical coronary and cerebral circula maintaining GFR and therefore excretory capacity.

Renal vasodilator prostaglandins play an important role in modifying these vasoconstrictive effects. Both angiotensin II and norepinephrine stimulate g prostaglandin production.[86,164] The ensuing attenuation in the degree of arteric constriction prevents *excessive* renal ischemia, which might otherwise be induce the high local concentration of vasoconstrictors.[87,165] To a lesser degree, increased secretion of vasodilator kinins by the kidney also may act to pres renal perfusion in this setting.[165]

Clinical Implications

The clinical importance of these protective vasodilator responses has been demonstrated in humans by the administration of nonsteroidal anti-inflamma drugs, which inhibit prostaglandin synthesis.[167] These agents, which are widely used in the treatment of arthritis and other disorders, have little effect on r function when given to normovolemic

subjects in whom the baseline level of renal prostaglandin production is rel low.

The nonsteroidal anti-inflammatory drugs can, however, produce an acute d GFR and renal plasma flow when given to patients with high angiotensin II norepinephrine levels. This most often occurs with effective circulating volu depletion due, for example, to heart failure or cirrhosis. In these conditions prostaglandin synthesis is appropriately enhanced, and administration of a nonsteroidal anti-inflammatory drug can lead to unopposed action of the vasoconstrictors and acute renal failure (Figure 2-10).[167,168] Studies in animals indicate that both afferent and efferent resistance are increased in this set ensuing reduction in renal perfusion leads to a fall in GFR which, as mentic above, is flow-dependent.[165]

The decrease in renal perfusion seen with effective volume depletion is als associated with a marked alteration in the *distribution of intrarenal blood flow*. Under normal circumstances, approximately 80 percent of renal blood flow g the outer cortex (where most of the glomeruli are located), 10 to 15 percen

inner cortex (the site of the juxtamedullary nephrons), and the remaining 5 to 10 percent to the medulla. With hypovolemia, there marked reduction in outer cortical flow, with a preferential increase in perfu the inner cortex.[168,169,170] and[171] The mechanism by which these changes occ is unknown; angiotensin II, catecholamines, and prostaglandins have all be implicated, but their role is unproven.[171]

The physiologic significance of this intrarenal shunting of renal blood flow uncertain. It has been postulated that increasing inner cortical flow might p Na^+ retention in hypovolemic states because the juxtamedullary nephrons, v long loops of Henle, have a greater reabsorptive surface

than those in the outer cortex. However, redistribution of blood flow is not necessarily associated with redistribution of glomerular filtration, making th hypothesis less likely.[172]

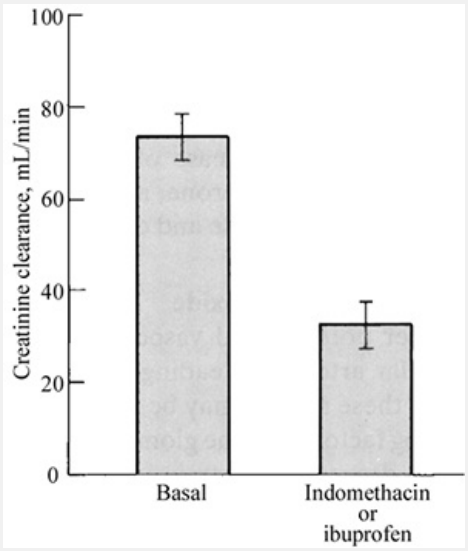

Figure 2-18 Reduction in GFR, as estimated from the creatinine clearance, a mean of 73 mL/min down to 32 mL/min after the administration of a nonsteroidal anti-inflammatory drug (indomethacin or ibuprofen) to 12 pat with stable hepatic cirrhosis and ascites. Urinary prostaglandin E_2 was substantially greater than normal in these subjects and was markedly redu following therapy. *From Zipse RD, Hoefs JC, Speckhart PF, et al: J Clin Endocrinol Metab 48:895, 1979. Copyright by The Endocrine Society, 1979. Used with permission.*

Volume expansion

In contrast to these hormonal changes with volume depletion, volume expan with a high-sodium diet) tends to be associated with increased renal perfus perhaps a mild rise in GFR.[54] Reduced secretion of angiotensin II and norepinephrine and enhanced release of dopamine and atrial natriuretic pe

may contribute to this response (see Chapter 8).[119]

1. Dopamine dilates both the afferent and efferent arterioles, thereby raising renal blood flow while producing a lesser increment or no change in GF
2. Atrial natriuretic peptide, on the other hand, appears to produce the un combination of afferent dilation and efferent constriction, both of which P_{GC} and therefore the GFR; there is a lesser alteration in RPF, since tot vascular resistance is relatively unchanged.[173]

These hormonal alterations also facilitate excretion of the excess sodium: release of those agents that enhance sodium reabsorption (angiotensin II, aldosterone, and norepinephrine) is diminished, whereas that of atrial natri peptide and dopamine is enhanced.

Endothelin and nitric oxide

Endothelin, released locally from endothelial cells, is another potent renal vasoconstrictor that affects both afferent and efferent glomerular arterioles to reductions in renal blood flow and GFR.[174,175] As with the other renal vasoconstrictors, the degree of ischemia is minimized by endothelin-induce of prostacyclin.[176,177]

Although endothelin is probably not an important regulator of renal hemody normal subjects, it may play a role in the reduction in GFR seen in postisch acute renal failure. In this setting, endothelial injury may lead to the releas endothelin and subsequent renal vasoconstriction.[178] A similar mechanism may contribute to the decrease in renal perfusion induced by cyclosporine.[179,180]

Another vasoactive factor released from the endothelial cells (in addition to prostacyclin and endothelin) is nitric oxide. Nitric oxide appears to be relea tonically in the renal circulation, thereby lowering renal vascular resistance contrast to the vasoconstrictive effect of endothelin).[174,181,182]

Glomerular hemodynamics and progressive renal failure

Arteriolar resistance and renal hemodynamics also may play an important ro patients with underlying chronic renal disease. A large body of experimenta clinical evidence suggests that *intraglomerular hypertension* is partially responsible for the progression of many disorders to end-stage renal failure.[183,184]

According to this theory, the loss of nephrons (due to almost any renal dise leads to a compensatory rise in filtration in the remaining more normal nepl This is an appropriate response in the short term, as it tends to maintain th GFR. It is driven by afferent arteriolar dilatation, which leads to a rise in b and plasma flow. The elevation in intraglomerular pressure, however, appea maladaptive in the long term, since it tends to lead to progressive glomerul damage. Similar findings are seen in diabetic nephropathy, except that the

vasodilatation is a primary event, induced in some way by hyperglycemia or deficiency.[185,186]

These observations are of potentially great clinical importance, since treat be aimed at reversing the hemodynamic adaptations. Both dietary protein re and antihypertensive therapy, perhaps preferentially with an ACE inhibitor, the intraglomerular pressure and diminish the degree of glomerular injury in experimental models of renal disease. Several clinical trials in chronic rena in humans suggest that administration of an ACE inhibitor can slow the rate of GFR, particularly in diabetic nephropathy.[187,188,189] and[190] The efficacy of dietary protein restriction remains controversial,[191,192,193] with evidence of benefit being best in patients with diabetic nephropathy.[194]

The apparent preferential benefit of ACE inhibition compared to other antihypertensive drugs is thought to be related to reversal of angiotensin II constriction of the efferent arteriole. Decreasing vascular resistance at this directly lower the intraglomerular pressure, independent of the reduction in systemic blood pressure (Fig. 2-8).

Summary

The GFR is normally maintained within relatively narrow limits to prevent inappropriate fluctuations in solute and water excretion. Regulation of the G primarily achieved by alterations in arteriolar tone that influence both the h pressure in the glomerular capillary and renal blood flow. In normal subject GFR is maintained by autoregulation, a phenomenon that is mediated by at three factors: stretch receptors in the afferent arteriole, angiotensin II, and tubuloglomerular feedback.[127] These responses, however, can be overridden by neurohumoral vasoconstiction in hypovolemic states, in an attempt to maxin coronary and cerebral perfusion.

CLINICAL EVALUATION OF RENAL CIRCULATION

Concept of Clearance and Measurement of GFR

Estimation of the GFR is an essential part of the evaluation of patients with disease. Since the total kidney GFR is equal to the sum of the filtration rat of the functioning nephrons, the total GFR can be used as an *index of functioning renal mass*. As an example, the loss of one-half of the functioning nephrons v to a significant decline in the GFR (which may be only 20 to

30 percent, not 50 percent, due to compensatory hyperfiltration in the rema nephrons). At this time, fluid and electrolyte balance may still be maintaine urinalysis may be normal. Thus, the fall in GFR may be the *earliest and only clinical sign of renal disease*.

Serial monitoring of the GFR can also be used to estimate the severity and the course of kidney disease. A reduction in GFR implies either progressior underlying disease or the development of a superimposed and potentially re problem, such as diminished renal perfusion due to volume depletion. An in

GFR, on the other hand, indicates improvement or possibly hypertrophy in t remaining nephrons.

Measurement of the GFR is also helpful in determining the proper dosage o drugs that are excreted by the kidney by glomerular filtration. When the GF drug excretion will be reduced, resulting in an increase in plasma drug leve potential drug toxicity. To prevent this, drug dosage must be lowered in pro the decrease in GFR.

How can the GFR be measured? Consider a compound, such as the fructose polysaccharide inulin (not insulin), with the following properties:

1. Able to achieve a stable plasma concentration
2. Freely filtered at the glomerulus
3. Not reabsorbed, secreted, synthesized, or metabolized by the kidney

In this situation,

Filtered inulin=excreted inulin

The filtered inulin is equal to the GFR times the plasma inulin concentratio (P_{in}), and the excreted inulin is equal to the product of the urine inulin concentra (U_{in}) and the urine volume (V, in milliliters per minute or liters per day). Therefo

$$GFR \times P_{in} = U_{in} \times V \qquad (2\text{-}4)$$

$$GFR = \frac{U_{in} \times V}{P_{in}} \qquad (2\text{-}5)$$

The term ($U_{in} \times V$)/P_{in} is called the clearance of inulin and is an accurate estim the GFR. The inulin clearance, in mL/min, refers to that volume of plasma c inulin by renal excretion. If, for example, 1 mg of inulin is excreted per min ($U_{in} \times V$) and the P_{in} is 1.0 mg/dL (or, to keep the units consistent, 0.01 mg/mL), the clearance of inulin is 100 mL/min; that is, 100 mL of plasma has been clear 1 mg of inulin that it contained.

Use and Limitations of Creatinine Clearance

Despite its accuracy, the inulin clearance is rarely performed clinically bec involves both an intravenous infusion of inulin and an assay for inulin that

available in most laboratories. The most widely used method to estimate th the endogenous *creatinine clearance*.

Creatinine is derived from the metabolism of creatine in skeletal muscle an released into the plasma at a relatively constant rate. As a result, the plasi creatinine concentration (P_{cr}) is very stable, varying less than 10 percent per da serial observations in normal subjects.

Like inulin, creatinine is freely filtered across the glomerulus and is neithe reabsorbed nor metabolized by the kidney. However, some creatinine enters by tubular secretion via the organic cation secretory pump in the proximal t resulting in creatinine excretion exceeding the amount filtered by 10 to 20

percent.[108] Thus, the creatinine clearance (C_{cr})

$$C_{cr} = \frac{U_{cr} \times V}{P_{cr}} \qquad (2\text{-}6)$$

will tend to exceed the inulin clearance by 10 to 20 percent. Fortuitously, t balanced by an error of almost equal magnitude in the measurement of P_{cr}. One of the method involves a colorimetric reaction after the addition of alkaline picrat plasma, but not the urine, contains noncreatinine chromogens (acetone, pro ascorbic acid, pyruvate), which account for approximately 10 to 20 percent normal P_{cr}.[108] Since both the U_{cr} and the P_{cr} are elevated to roughly the same degree, the errors tend to cancel out and the creatinine clearance is a reas accurate estimate of the GFR, particularly in the patient with relatively nor function. The normal values of the creatinine clearance are approximately 9 mL/min in women and 120± 25 mL/min in men.[108]

The creatinine clearance is usually determined in the following way. The pl creatinine concentration is measured in a venous blood sample, and the $U_{cr} \times V$ is concomitantly measured with a 24-h urine collection, since shorter collectio give less reliable results. Suppose, for example, that a 30-year-old woman weighs 60 kg is being evaluated for the possible presence of renal disease following results are obtained:

$$P_{cr} = 1.2\,\text{mg/dL}$$
$$U_{cr} = 100\,\text{mg/dL}$$
$$V = 1080\,\text{mL/day}$$

Since

$$1080\,\text{mL/day} \div 1440\,\text{min/day} = 0.75\,\text{mL/min}$$
$$C_{cr} = \frac{100 \times 0.75}{1.2} = 63\,\text{mL/min}$$

This finding suggests that the patient has lost about one-third of her GFR.

Limitations

Although the creatinine clearance is widely used in clinical medicine, there major problems that limit its accuracy as an estimate of the GFR: an incomp correction and increased tubular secretion of creatinine as renal

function declines. The relative constancy of creatinine production and subs excretion can be used to assess the completeness of the urine collection. I under the age of 50, daily creatinine excretion should be about 20 to 25 mg body weight in men and 15 to 20 mg/kg in women. Between the ages of 50 a there is a progressive 50 percent reduction in creatinine excretion (to abou in men), due primarily to a decrease in skeletal muscle mass. These relatio can be expressed by the following equations, which estimate daily creatinir excretion in mg/kg per day:[195]

$$\text{Creatinine excretion} = 28 - (\text{age in years}/6) \quad \text{(in men)}$$
$$= 22 - (\text{age in years}/9) \quad \text{(in women)}$$

Creatinine excretion that is much below these expected values suggests an

incomplete collection. In the above 30-year-old woman, for example, creatir excretion is 18 mg/kg per day (1080 mg÷ 60 kg), indicating that a complete has probably been obtained [22-(30/9)=18.7].

The second major error, enhanced creatinine secretion, begins early in the progressive renal disease. As the GFR falls, the initial rise in the plasma c concentration enhances creatinine delivery to the proximal secretory pump. leads to an elevation in creatinine secretion, since the pump is not yet satu[196] At a GFR of 40 to 80 mL/min, for example, the absolute amount of creatinin secreted may have risen *more than 50 percent*, with secretion accounting for as much as 35 percent of urinary creatinine.[196] As a result, the C_{Cr} is much higher than it would be if creatinine were excreted only by glomerular filtration, re a potentially marked *overestimation* of the true GFR.[196,197] and[198]

The net effect is that the creatinine clearance may be normal (>90 mL/min) one-half of patients with a true GFR (as measured by inulin clearance) of 6 mL/min and one-quarter of those with a GFR of 51 to 60 mL/min.[197] This difference may become proportionately more prominent in patients with more advanced disease, in whom the creatinine clearance can, in some cases, exceed the more than twofold.[198]

Thus, the creatinine clearance is not a predictably accurate measure of the that can be concluded is that the creatinine clearance (calculated from a co urine collection) *represents an upper limit of what the true GFR may be*. Furthermore, the degree of creatinine secretion appears to vary with time, the creatinine clearance independent of alterations in the GFR.[195,199,200] In some cases, the change in creatinine clearance is discordant with the change in As an example, the degree of creatinine secretion may fall (via an unknown mechanism) at a time when the GFR is actually increasing in treated patien lupus nephritis; this improvement, however, may be masked by no change o reduction in the creatinine clearance if the decrease in secretion is proport greater than the increase in creatinine filtration.[199,200]

The only way to determine the GFR accurately is to measure the clearance or a radiolabeled compound such as iothalamate or DTPA.[195,201] Unfortunately, determination of the inulin or iothalamate clearance is not

routinely available. There are, however, two alternatives that may provide a accurate estimate of the GFR: averaging the creatinine and urea clearance below) and measurement of the creatinine clearance during the administrati H_2 blocker cimetidine, which is another organic cation that competitively in creatinine secretion.

Cimetidine must be given in relatively high dose to predictably inhibit creat secretion in most patients.[202,203] As an example, one regimen used a single oral dose of 1200 mg plus a water load with urine collected between 3 and 6 ho both creatinine and inulin clearance. The ratio of the creatinine to inulin cl baseline was about 1.5 (range 1.14 to 2.27), indicating substantial creatini

secretion. The ratio fell to 1.02 in eight patients, but remained elevated (1. remaining patients, who had more efficient urinary cimetidine excretion.[202]

It is important to appreciate, however, that *exact knowledge of the GFR is not usually required*, particularly with the ability to measure plasma levels of man those potentially toxic drugs that are normally excreted by the kidney (such digoxin or an aminoglycoside antibiotic). What is important to know is whet GFR is changing (which can usually be determined from the plasma creatini concentration alone) and whether the GFR is reduced in a patient with kidn disease who has a normal or high-normal plasma creatinine concentration (below).

In addition to the potential errors involved in the use of the creatinine clea there is an additional problem: Progressive disease is not always associate significant reduction in GFR even if the latter is accurately measured. As n above, nephron loss is generally associated with compensatory hypertrophy hyperfiltration in the remaining normal or less affected nephrons. Thus, in such as lupus nephritis, progressive glomerular scarring can occur during t phase with little reduction in the total GFR.[200,204] In this setting, the patient must also be monitored for other signs of disease progression, such as an increa protein excretion or in the systemic blood pressure.

Plasma Creatinine and GFR

Changes in the GFR (rather than an exact measurement of the GFR) can ge be ascertained from measurement of the P_{cr}, a routine laboratory test. In a subject the steady state,

$$\text{Creatinine excretion} = \text{creatinine production} \qquad (2\text{-}7)$$

Creatinine excretion is roughly equal to the amount of creatinine filtered ($U_{cr} \times V$), whereas the rate of creatinine production is relatively constant. If these su are made in Eq. 2-3, 4, 5, 6 and 7, then

$$\text{GFR} \times P_{cr} = \text{constant} \qquad (2\text{-}8)$$

Thus, the *plasma creatinine concentration varies inversely with the GFR*. If, for example, the GFR falls by 50 percent, creatinine excretion will also be redu

As a result, newly produced creatinine will accumulate in the plasma until t load again equals the rate of production. Excluding changes in tubular secr will occur when the P_{cr} has doubled:

$$\text{GFR}/2 \times 2P_{cr} = \text{GFR} \times P_{cr} = \text{constant}$$

In adults, the range for the normal P_{cr} is 0.8 to 1.3 mg/dL in men and 0.6 to 1.0 mg/dL in women.[108]

Creatinine production and thus P_{cr} can be influenced by changes in diet. Creatinir production is determined by the total body creatine content, which itself is determined by the amount of creatine synthesized from amino acids and dir ingested in meat. As an example, creatine production can be enhanced by a protein or high-meat diet; this change, however, must persist over a period

to months before creatinine production (and therefore P_{cr}) is significantly enhanced, since only 1 to 2 percent of the extra creatine is converted to cr per day.[205] Furthermore, the increase in P_{cr} may be less than the increment in production because a high-protein diet also tends to raise the GFR and the rate of creatinine excretion.[206][207] On the other hand, switching to a meat-free d can lower the P_{cr} by as much as 15 percent without any change in the true GF[208]

A more acute effect may be seen with the ingestion of cooked meat, since h promotes the conversion of creatine to creatinine. As an example, eating a hamburger can raise creatinine excretion by as much as 350 to 450 mg (a 2 percent increase) and can acutely elevate the P_{cr} by as much as 1 mg/dL.[205][209] Thus, the P_{cr} should optimally be measured when the patient is fasting.

The idealized reciprocal relationship between the GFR and the P_{cr} is depicted in Fig. 2-11 There are three important points to note about this relationship. First, curve is *valid only in the steady state* when the P_{cr} is stable. If, for

example, a patient develops acute renal failure with a sudden drop in the G 120 to 12 mL/min, the P_{cr} on day 1 will be normal, since there will not have bee time for creatinine to accumulate in the plasma. After 7 to 10 days, the P_{cr} stabilize at roughly 10 mg/dL, a level consistent with the reduced GFR.

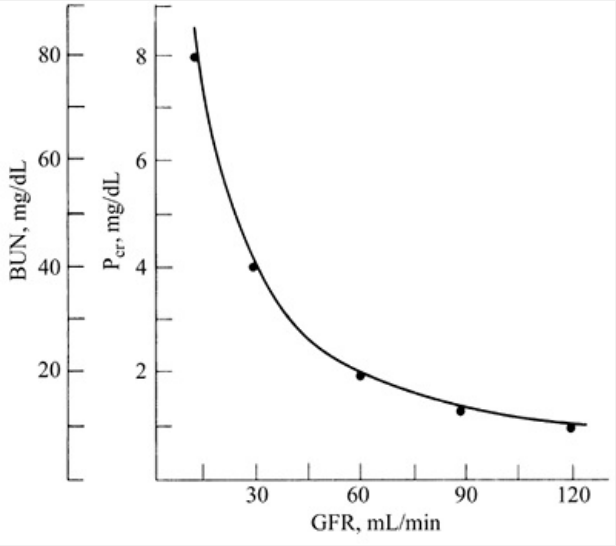

Figure 2-11 Idealized steady-state relationship between the plasma creatini concentration (P_{cr}), blood urea nitrogen (BUN), and the GFR.

The steady state can be disturbed by changes in creatinine production as v urinary excretion. Thus, a malnourished patient with reduced creatinine pro may have a stable P_{cr} despite a fall in GFR.

Second, it is important to appreciate the *shape* of the curve. In a patient with norma renal function, an apparently minor increase in the P_{cr} from 1.0 to 1.5 mg/dL can

represent a marked fall in the GFR from 120 to 80 mL/min. In contrast, in a with advanced renal failure, a marked increase from the P_{cr} of 6.0 to 12.0 mg/dL reflects a relatively small reduction in the GFR from 20 to 10 mL/min. Thus *initial elevation in the P_{cr} represents the major loss in GFR.* Furthermore, progressive reductions in GFR in patients with advanced disease are more detect by measurement of the P_{cr} (which may show a large increase) than by measurement of the GFR (which may fall by only a few mL/min, a change th be less than the sensitivity of the assay).[195]

Third, the relationship between the GFR and the P_{cr} is dependent upon the rate of creatinine production, which is largely a function of muscle mass and meat protein intake. Fig. 2-11 a normal GFR of 120 mL/min is associated with a P_{cr} of 1.0 g/dL. Although this may be true for a 70-kg man, a similar GFR in a 50- might be associated with a P_{cr} of only 0.6 mg/dL. In this setting, a P_{cr} of 1.0 mg/dL is not normal and reflects a 40 percent fall in GFR.

To account for the effects of body weight, age, and sex on muscle mass, th following formula has been derived to estimate the creatinine clearance (in from the P_{cr} in the steady state in adult men:[209,210]

$$C_{cr} = \frac{(140 - \text{age}) \times \text{lean body weight (in kg)}}{P_{cr} \times 72} \qquad (2\text{-}9)$$

This value should be multiplied by 0.85 in women, since a lower fraction of weight is composed of muscle.

The results obtained with this formula appear to correlate fairly well with a simultaneously measured creatinine clearance. Its usefulness can be illustr the observation that a P_{cr} of 1.4 mg/dL represents a creatinine clearance of 101 mL/min in an 85-kg, 20-year-old man:

$$C_{cr} = \frac{(140 - 20) \times 85}{1.4 \times 72}$$

but a creatinine clearance of only 20 mL/min in a 40-kg, 80-year-old woman

$$C_{cr} = \frac{(140 - 80) \times 40 \times 0.85}{1.4 \times 72}$$

The latter example calls attention to the danger of overdosing elderly patie have seriously impaired renal function despite a relatively normal P_{cr}. The use of this simple formula can help to avoid this problem but should not replace m of plasma drug levels when potentially toxic agents are given.

A similar decline in creatinine production can occur in malnourished patient those with cirrhosis. In addition to the loss of muscle mass, decreased mea and perhaps decreased hepatic production of creatine, the precursor of cre can also play a contributory role. The net effect is that some cirrhotic patie an apparently "normal" P_{cr} of 1 to 1.3 mg/dL have a GFR (as measured by inulir clearance) that can range from as low as 20 to 60 mL/min to a clearly norm above 100 mL/min.[211,212] The low protein intake and decreased production of (due to the hepatic disease) also limit the rise in blood urea nitrogen (BUN

should occur as the GFR falls (Fig. 2-11).

Thus, the presence of substantial renal dysfunction may be masked in cirrh patients if only the BUN and P_{cr} are measured. Calculation of the creatinine clearance will partially overcome this problem, since the reduction in creati production will be accounted for by a decline in creatinine excretion. Howe because of increased creatinine secretion, the clearance value obtained ma overestimate the true GFR by as much as 40 percent or more in patients wi insufficiency.[212]

In summary, the P_{cr} tends to vary inversely with the GFR in the steady state. Because of this relationship, serial measurements of the P_{cr} are typically used to monitor patients with kidney dysfunction. A rising P_{cr} indicates disease progression, whereas a fall in P_{cr} suggests recovery of renal function (if muscle mass and n intake are relatively constant). It is also presumed that a stable P_{cr} means stable disease, although this may not be an accurate assumption.

Limitations

It is now clear that significant disease progression can occur without *little change in the* P_{cr} in patients with a normal or near-normal GFR (>60 mL/min). Three can contribute to this problem, two of which prevent or minimize any fall in P_{cr} when the GFR does fall:

1. Loss of nephrons leads to compensatory hyperfiltration in the remaining normal nephrons, thereby maintaining the total GFR despite continued c activity.[184] As described above, in lupus nephritis, for example, progress glomerular scarring may be associated with no detectable change in glo filtration due to hypertrophy in normal or less affected glomeruli.[204]
2. Glomerular diseases damage the glomerular basement membrane, tendi lower the GFR by diminishing the effective surface area available for fil This effect, however, is counteracted by a rise in glomerular capillary p (P_{GC}) that tends to maintain the GFR despite progressive glomerular inju[117] The mechanism by which this occurs is not well understood; an initial re in GFR due to the fall in surface area could lead to diminished macula c flow and activation of TGF, which could then raise the GFR back to the level.
3. When the GFR does begin to fall, the rise in P_{cr} is hastened or prevented by an increase in tubular secretion, as described previously.[196] The potential result of this adaption is illustrated in Fig. 2-12. Although a fall in GFR from 120 to 60 mL/min should ideally induce a doubling of the P_{cr}, many patients have only a small increase in the P_{cr} (often as little as 0.1 to 0.2 mg/dL) because of enhanced tubular secretion. With more advanced disease (e.g., P_{cr} >1.5 to 2 mg/dL),

the P_{Cr} rises as expected, presumably due to saturation of the secretory mechanism.

The major clinical implication of these findings is that, in a patient with kno disease, *a P_{Cr} that is stable at a level under 1.5 mg/dL does not necessarily reflect stable disease.* As a result, it is important to look for other signs of dise progression, such as increased proteinuria, a more active urine sediment, o elevation in the systemic blood pressure. In addition, variations in the degr

of creatinine secretion can cause the P_{Cr} to vary independent of the GFR. Thus, an increase in GFR may not lead to a reduction in the P_{Cr} if it is associated with a proportionate decline in creatinine secretion.

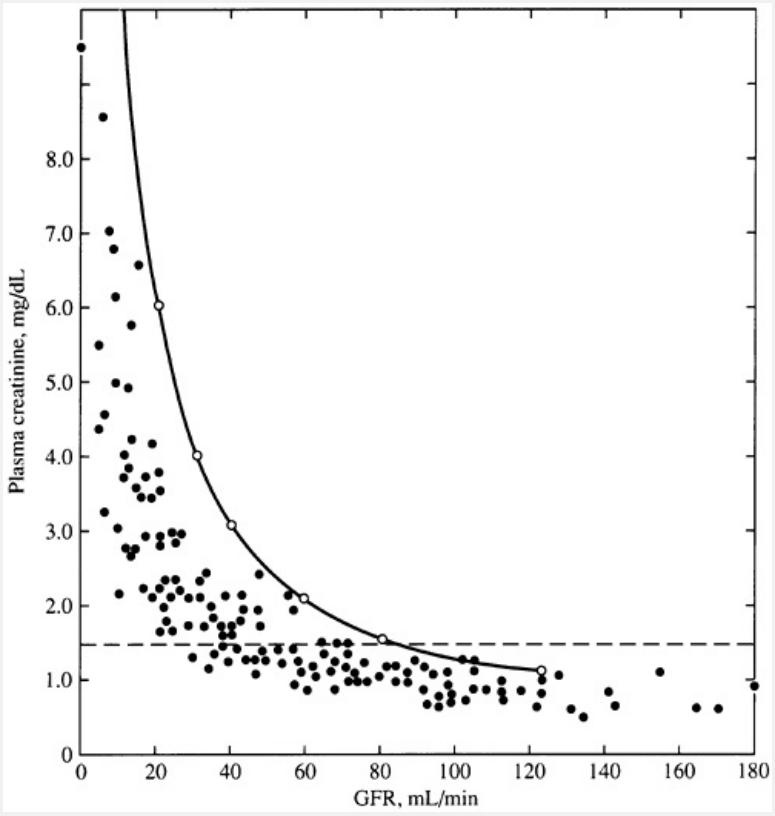

Figure 2-12 Relationship between the P_{Cr} and the true GFR (as measured by the inulin clearance) in 171 patients with glomerular disease. The open c joined by a continuous line represent the idealized relationship between t parameters if creatinine were excreted solely by glomerular filtration (see Figure 2-11); the dotted line represents the upper limit of "normal" for the P_{Cr} of 1.4 mg/dL. With the GFR varying between 120 and 60 mL/min in different pati there is often little elevation in the P_{Cr} due primarily to enhanced tubular secretion. Once the P_{Cr} is above 1.5 to 2 mg/dL (132 to 176 umuol/L), tubular secretion becomes saturated and the P_{Cr} rises as expected with further reductions in GFR. *(From Shemesh O, Golbetz H, Kriss JP, Myers BD: Kidney Int 28:830, 1985. Used with permission from* Kidney International.)

Less commonly, an error arises due to an elevation in the P_{cr} without any change in the GFR (or BUN). This is most often due to a large meat meal, ketoacidosis (in which acetoacetate can raise the P_{cr} by 0.5 to 2 mg/dL or more because it is measured as a noncreatinine chromogen), [208] or the administration of cimetidine or the antimicrobial trimethoprim (which is most often given in co with sulfamethoxazole), both of which competitively inhibit creatinine secretion. [203,214,215] In the last setting, the P_{cr} may increase by as much as 0.4 to 0.5 mg/dL. [215] Ranitidine, another commonly used H_2 blocker, has a less prominent effect on creatinine handling than cimetidine because it is given in much lo doses. [214]

Because of the variability in creatinine secretion and production, other end markers, such as cystatin C, have been evaluated for the estimation of GFR Cystatin C is a low-molecular-weight protein that is a member of the cystati superfamily of cysteine protease inhibitors. It is produced by all nucleated its rate of production is relatively constant, being unaltered by inflammator conditions or changes in diet. Preliminary studies suggest that the plasma concentration correlates more closely with the GFR than the plasma creatin concentration. [217] Whether the measurement of cystatin C levels will become available clinically is at present unknown.

Blood Urea Nitrogen and GFR

Changes in the GFR also can be detected by changes in the concentration the blood, measured as the BUN. Like creatinine, urea is excreted primarily glomerular filtration, and the BUN tends to vary inversely with the GFR (Fig. 2-10). However, two factors can alter the BUN without change in the GFR or P_{cr} in urea production and tubular urea reabsorption. Urea is formed by the he metabolism of amino acids that are not utilized for protein synthesis. As am are deaminated, ammonia is produced. The development of toxic levels of a in the blood is prevented by the conversion of ammonia (NH_3) into urea in a reaction that can be summarized by the following equation:

$$2NH_3 + CO_2 \rightarrow H_2N-CO-NH_2 + H_2O$$

Thus, urea production and the BUN are increased when more amino acids a metabolized in the liver. This may occur with a high-protein diet, enhanced breakdown (due to trauma, gastrointestinal bleeding, or the administration corticosteroids), or decreased tissue anabolism (due to tetracycline). [217] On the other hand, urea production and the BUN are reduced by severe liver disea low protein intake.

The second factor is that urea excretion is not determined solely by glomer filtration. Approximately 40 to 50 percent of the filtered urea is normally re

by the tubules. This process is passive, being driven by the rise in tubular

concentration that results from the reabsorption of sodium and water. Thus transport is enhanced in hypovolemic states due to the increase in sodium reabsorption. The net result is reduced urea excretion and an elevation in that is not due to a fall in GFR and therefore is not associated with a rise i P_{Cr}.[217] Under most conditions, the ratio of the BUN to P_{Cr} is 10 to 15 : 1. When this ratio exceeds 20 : 1, one of the conditions associated with enhanced u production or effective circulating volume depletion should be suspected.[217]

In summary, a reduction in the GFR results in elevation in both the BUN and P_{Cr}. Because of the variability in urea production and reabsorption, the BUN is a more reliable reflection of the GFR. For similar reasons, the urea clearance is no accurate estimate of the GFR. Since urea is reabsorbed and the degree of reabsorption is variable, the quantity of urea excreted is much less than th filtered. As a result, the urea clearance is only 50 to 70 percent that of inu[218]

The overestimation of the GFR with the creatinine clearance and the under with the urea clearance has led to the suggestion that the average of these values should be used:

$$GFR = \frac{C_{cr} + C_{urea}}{2} \qquad (2\text{-}10)$$

This equation may be most accurate in patients with moderate to advanced disease (P_{Cr} > 2.5 mg/dL).[219]

Change in GFR with Aging

An association between age and decreasing GFR, via several hypothetical unproven mechanisms, has been suggested by several studies.[220] In the Baltimore Longitudinal study, for example, the mean rate of decline in creatinine clea found to be 0.75 mL/min per year.[221] However, this and other studies may be flaw because of their reliance upon endogenous creatinine clearance measureme the presence of possible confounding conditions.

In an effort to obtain a more reliable correlation between GFR and age, anc study, which examined the GFR as measured via inulin clearance, found tha majority of elderly patients with normal cardiac function had measured clea within the normal range.[222] Thus, although the elderly appear to have lower clearance rates, comorbid conditions may significantly affect measurements function among such patients, and increased age is not invariably associat decreased GFR.[223]

Summary

Estimation of the GFR remains an important method of monitoring patients v disease. There is, however, no easily available way to do this accurately. T

increase in tubular secretion of creatinine as the GFR begins to fall serious the validity of the creatinine clearance. Since this test can overestimate th twofold or more in patients with moderate to advanced renal disease,[198] it is best

used as an *upper limit* of what the true GFR may be. P_{Cr}, on the other hand, is helpful in following the course of the disease, since changes in P_{Cr} vary inversely with the GFR (as long as muscle mass and meat intake are relatively consta However, enhanced creatinine secretion can minimize any rise in P_{Cr} as the GFR falls from the normal level of 120 mL/min down to 60 to 80 mL/min.

Thus, a stable P_{Cr} that is below 1.5 mg/dL does not necessarily mean that the disease is stable. In this setting, increases in systemic blood pressure and activity on the urinalysis may be the only clues to progressive disease (unl inulin or iothalamate clearance can be measured.[199] Once the P_{Cr} is above 1.5 to 2 mg/dL, however, tubular secretion is saturated, and a stable P_{Cr} makes it unlikely that progressive renal damage is occurring.

Variability in the production and tubular reabsorption of urea makes the BU useful reflection of the GFR than the P_{Cr}. The main clinical use of the BUN is in th calculation of the BUN-to-P_{Cr} ratio, which, if elevated, suggests that diminished renal perfusion contributes to the renal disease (assuming that none of the increased urea production is present).[217]

Measurement of Renal Plasma Flow

The principles of clearance have also been used to measure the RPF in exp conditions; this test has little clinical utility. Paraaminohippurate (PAH) is a measured indicator that enters the urine by glomerular filtration and by the anion secretory pathway in the proximal tubule. The combination of filtratio secretion results in the almost complete removal of PAH from the plasma in pass through the kidney. Therefore,

$$\text{PAH delivery to kidney} = \text{PAH excretion}$$

$$\text{RPF} \times P_{PAH} = U_{PAH} \times V \qquad (2\text{-}11)$$

$$\text{RPF} = \frac{U_{PAH} \times V}{P_{PAH}} = C_{PAH}$$

If the hematocrit (Hct) is known, then the renal blood flow (RBF) can be cal from

$$\text{RBF} = \frac{C_{PAH}}{1 - \text{Hct}} \qquad (2\text{-}12)$$

The normal RPF and RBF in humans are roughly 625 mL/min and 110 mL/mi respectively. Since only 85 to 90 percent of the PAH actually is removed fro circulation in a single pass, the PAH clearance will underestimate both RPF by 10 to 15 percent.

PROBLEMS

2-1A 68-year-old man is admitted to the hospital with acute renal failu following plasma creatinine concentrations are obtained:

Day	Plasma creatinine, mg/dL

1	1.0
2	3.0
3	4.9

If the patient weighs 70 kg, what would you estimate the GFR to be on

2-2 Dopamine dilates both the afferent and efferent arterioles. What ef this have on

a. **Renal blood flow**
b. **GFR (in relation to the change in renal blood flow)**
c. **The filtration fraction**
d. **The concentration of albumin in the peritubular capillary**

2-3 A patient with diabetic nephropathy has chronic renal failure (plasn creatinine concentration equals 2.1 mg/dL) and hypertension. He can b treated with an ACE inhibitor, which primarily dilates the efferent arte with other antihypertensive agents, which primarily dilate the afferent arteriole. Assuming that each form of therapy is equally effective in lo the systemic blood pressure:

a. **Compare the likely effects of the two regimens on the glomerular capillary hydraulic pressure, P_{GC}**
b. **Could this difference be clinically important?**

2-4 A creatinine clearance test is performed in an 80-kg man. The follo results are obtained:

P_{Cr}=3.5mg/dL

24-h urine volume=800 mL

U_{Cr}=125 mg/dL

a. **Calculate the creatinine clearance.**
b. **Is this an accurate estimate of the GFR?**

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Footnotes

* The data in Fig. 2-3 used dextrans of different sizes. However, dextrans are l and pliable and may underestimate the impermeability to round macromolec as albumin. Studies using ficoll, which behaves as an ideal solid sphere, ha estimated the pore radius to be 42 Å.

† A different anionic compound, podocalyxin, lines the sides of the epitheli processes and is probably responsible, again by electrostatic repulsion, fo maintaining the separation of adjacent foot processes.

‡ Prorenin is also secreted into the systemic circulation, accounting for 50

percent of circulating renin.[40] The physiological role of prorenin is unclear, since it has no direct effect on systemic hemodynamics and does not appear to be converted into active renin in the systemic circulation.[42] There is evidence, however, that the human uterus also secretes renin and prorenin, and that the latter may play a local role in the regulation of uterine function, particularly during pregnancy.[43]

¶ The concept of effective circulating volume depletion is defined in Chapter 8.

** The disparate afferent and efferent effects of angiotensin II may also be related to different mechanisms of constriction. Calcium channel blockers attenuate the afferent response while having little or no effect on the increase in efferent resistance.[85]

†† The applicability of this model of glomerular filtration to humans is speculative since only limited information is available.[112] Studies with glomeruli obtained from cadavers have revealed that the net permeability of the human glomerulus is much lower than that in most other animals.[113] As a result, the net gradient favoring filtration is estimated to be only about 4 mmHg, versus 6 mmHg in the primate, as in Table 2-1.

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Chapter Three
Proximal Tubule

Fluid filtered at the glomerulus enters the proximal tubule, where about 55 percent of the filtrate is normally reabsorbed.[1] The primary event in proximal tubula function is the active transport of Na^+, which then allows water and many of the other filtered solutes to be reabsorbed *passively* in a reabsorbate that is isosmotic plasma. In addition, some solutes are secreted rather than reabsorbed in th segment, including hydrogen ions (H^+) and organic anions and cations.

Although the proximal tubule plays a major role in solute transport, the deg reabsorption of individual solutes is not uniform. Almost all of the filtered g and amino acids are reabsorbed in this segment, but only about 90 percent HCO_3^-, 65 percent of the Na^+, and 55 percent of the Cl^- (Fig. 3-1).[1] This chapter will review the basic aspects of how the proximal tubule selectively perform functions as well as some of the clinical implications of the relationship be reabsorption of Na^+ and that of the other solutes in the filtrate.

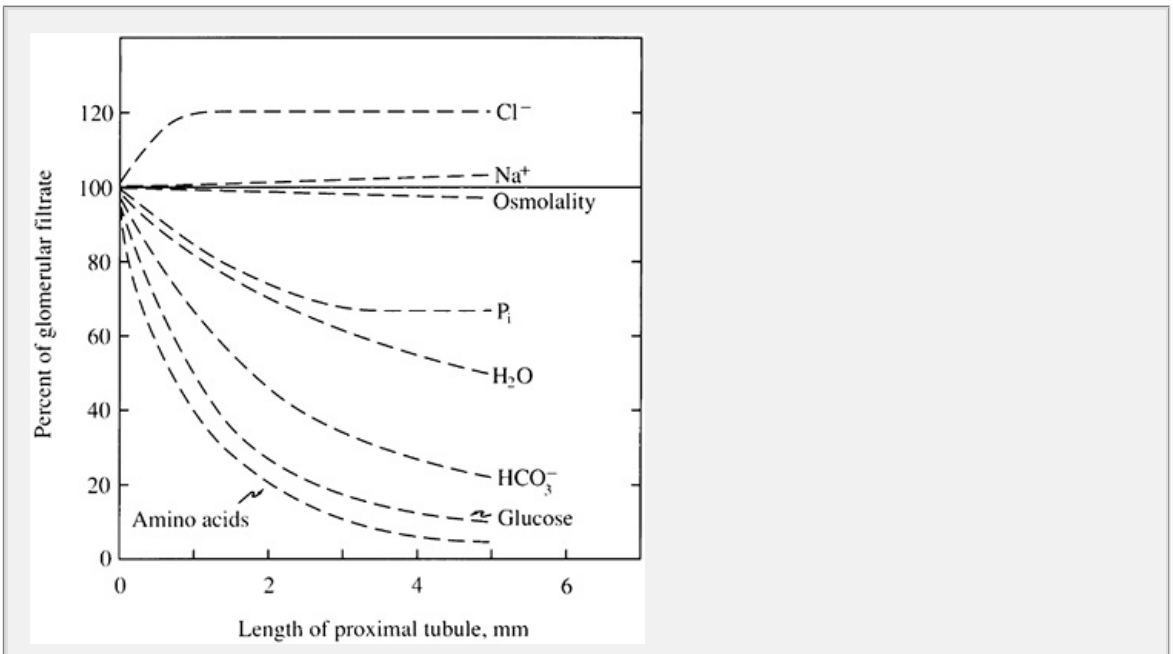

Figure 3-1 Changes in tubular fluid composition along the length of the pro tubule. For solutes, the lines represent the solute concentration as a perc that present in the glomerular filtrate. In comparison, the line for H

the percent of the filtered load remaining in the tubule. Some solutes, suc bicarbonate, glucose, and amino acids, are almost entirely reabsorbed in early proximal tubule, resulting in a marked reduction in their tubular fluic concentrations. Sodium, on the other hand, is reabsorbed to the same deg water, so that there is no change in the sodium concentration as fluid mov down the proximal tubule. However, the preferential reabsorption in the e proximal tubule of sodium with bicarbonate and glucose has an important secondary effect: The ensuing passive reabsorption of water leads to a ri the tubular fluid chloride concentration above that in the plasma. As will b this chloride gradient is sufficient to drive passive sodium chloride reabs in the later aspects of the proximal tubule. *Adapted from Rector FC, Am J Physiol 244:F461, 1983, and Maddox DA, Gennari FJ, Am J Physiol 252:F573, 1987. Used with permission.*

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ANATOMY

The proximal tubule has a convoluted segment, which begins at the glomeru then a straight segment (pars recta), which ends in the outer medulla in the descending limb of the loop of Henle (see Fig. 14–3). However, closer examination has revealed the presence of three distinct proximal segments with different cell type S_1 in the early convoluted segment; S_2 in the late convoluted segment and early pars recta; and S_3 in the remainder of the pars recta (Fig. 14–2).[2] These cell types can be isolated in relative purity via the use of monoclonal antibodies direc against cell surface peptidases uniquely expressed in each type, such as le aminopeptidase in the S_3 segment.[3]

The cells in the different proximal segments are, to some degree, associate different functional characteristics. The S_1 segment, for example, is a high-capacit site that plays a larger quantitative role in H^+ and HCO_3^- reabsorption than the later segments.[1] Both an increased number of transporters in the luminal

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membrane and a greater surface area available for reabsorption play a con role. In comparison, tubular secretion by the organic anion and cation secr pumps is most prominent in the S_2 segment.[2]

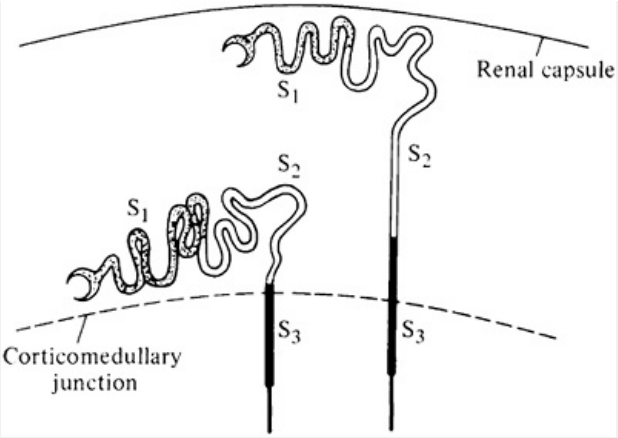

Figure 3-2 Distribution of the S_1, S_2, and S_3 segments defined by cell type in the proximal tubules from outer cortical (right) and juxtamedullary (left) n (*From Woodhall PB, Tisher CC, Simonton CA, Robinson RR, J Clin Invest 61:1320, 1978, by copyright permission of the American Society for Clinical Investigation*)

CELL MODEL FOR PROXIMAL TRANSPORT

The anatomy of the proximal tubule is similar to that of other transporting e (Fig. 3-3).[4,5] The cells have two membranes with different permeability and tr characteristics:

1. The *luminal* (or apical) membrane, which separates the cell from the tubu lumen, contains a variety of transmembrane protein carriers that facilita entry into the cell and, to a lesser degree, solute secretion into the lum[5]
2. The *basolateral* (or peritubular) membrane separates the cell from the interstitium and peritubular capillary. This membrane contains the Na^+-K^+-ATPase pump as well as transporters and channels that allow reabsorbe solutes to be returned to the systemic circulation. As will be seen, the Na^+-K^+-ATPase pump indirectly provides the energy that allows virtually all transport proteins to passively translocate filtered solutes.

The proximal tubular cells are separated by an intercellular space, which is both at the capillary end and to a lesser degree at the luminal end of the *tight* junction. The tight junction is composed of protein molecules that bring adj cells into apposition; it also serves as a boundary between the luminal and basolateral membranes, preventing the lateral diffusion of membrane protei one membrane to the other (see p. 96).[6]

The proximal tubule can reabsorb more than 100 L/day in subjects with nor function (55 to 60 percent of a daily filtration rate of 150 to 180 liters). It i suited for this task because of a series of adaptations, each of which facili reabsorption of the filtrate:

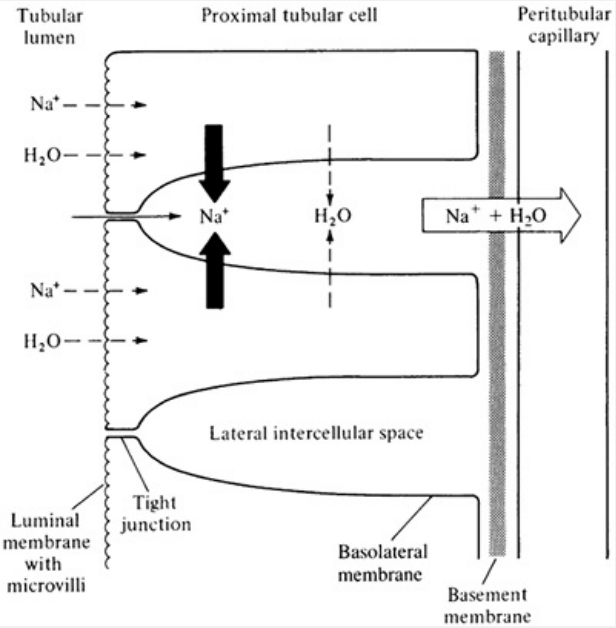

Figure 3-3 Schematic representation of active Na^+ and H_2O reabsorption in the proximal tubule. Na^+ enters the cell passively (dashed arrows) via carrier proteins in the luminal membrane; it is then actively transported into the intercellular space (dark solid arrow) by the Na^+-K^+-ATPase pump in the basolateral membrane. Water follows the movement of Na^+ down the osmotic gradient created by solute transport out of the lumen. Some of this may o through the tight junction as well as across the cell membranes. The Na^+ and H_2O that enter the intercellular space can either move into the peritubular capillary and be returned to the systemic circulation or leak back into the across the tight junction.

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1. The luminal membrane has microvilli which increase the surface area av for reabsorption. In addition, the microvilli have a brush border that cor specific carrier proteins as well as an enzyme, carbonic anhydrase, whi an important role in HCO_3^- reabsorption (see Chap. 11).
2. Solute reabsorption creates an osmotic gradient that allows water to be reabsorbed in part across the cells. This process can occur because bo luminal and basolateral membranes are relatively water permeable as a the presence of water channels within the membranes.[7,8,9] These water channels, called aquaporin-1, appear to be similar to those[9] in red cells. Targeted disruption of the genes for these channels results in the inabi reabsorb fluid within the proximal tubules.[10] In comparison, the luminal membranes of the ascending limb of the loop of Henle and the entire dis nephron largely lack water channels and do not allow osmotic water tra

the basal state (see Chaps. 4 and 5). Antidiuretic hormone, however, can increase the water permeability of the collecting tubule cells by causing different type of preformed water

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channels, called aquaporin-2, in the cytosol to move to and fuse with th membrane (see Chap. 6); this process is one of the essential steps both in water reabsorption and in the formation of a concentrated urine.

3. The preferential reabsorption of HCO_3^- in the early proximal tubule results in osmotic water transport and a subsequent rise in the tubular fluid Cl^- concentration (Fig. 3-1). As will be discussed below, this gradient is sufficient to allow as much as one-third of proximal NaCl and water reab to occur passively through the tight junction.[11,12] This capacity for passive transport is reflected in the observation that, despite the high rate of to reabsorption, Na^+-K^+-ATPase activity in the proximal tubule is much lower that in the thick ascending limb or distal tubule.[13]
4. Substantial passive reabsorption can occur because the tight junction o proximal tubule is relatively "leaky" in comparison to other nephron segm[6] On freeze-fracture electron microscopy, the tight junction has a strand-l appearance. The proximal tubule has only one strand, versus up to eight epithelia, such as the distal nephron.[6] Thus, transport through the paracellular pathway in the proximal tubule is a low-resistance route in comparison to traverse both the luminal and basolateral membranes.

In general, filtered Na^+ passively enters the cell across the luminal membrane a then actively transported by the Na^+-K^+-ATPase pump into the intercellular space. The removal of Na^+ and other solutes from the lumen initially lowers the lumin osmolality, creating an osmotic gradient of up to 15 mmHg that promotes th reabsorption of H_2O.[14,15] Water movement is also promoted by an additional fa The preferential reabsorption of $NaHCO_3$ in the early proximal tubule leads to an elevation in the tubular fluid Cl^- concentration; this makes the *effective* luminal osmolality even lower, since the tight junction is relatively permeable to Cl^-, which therefore functions as an ineffective osmole (see "Passive Transport" below).[15]

The reabsorbate that accumulates in the intercellular space can then enter peritubular capillary and be returned to the systemic circulation or can leak the lumen across the tight junction. As will be seen, net proximal tubular Na^+ reabsorption is affected by multiple factors, including filtered solutes that a reabsorbed with Na^+, peritubular capillary hemodynamics, and neurohumoral fa such as angiotensin II, norepinephrine, and dopamine.

Cell Entry

Luminal Na^+ must enter the cells before it can be reabsorbed. The primary st

this process is the *Na^+-K^+-ATPase pump in the basolateral membrane*, which has two functions that create a favorable electrochemical gradient for passive Na^+ entry into the cell (Fig. 3-4). First, the pump maintains the effective cell Na concentration at about 20 to 30 meq/L by transporting Na^+ out of the cell; this is

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well below the value of 145 meq/L in the tubular lumen.[16] Second, the pump contributes to the development of a *cell interior negative potential* by promoting the net loss of cations; this results both from the 2 K^+:3 Na^+ stoichiometry of the pump and from the subsequent back diffusion of some K^+ out of the cell through ATP-sensitive K^+ channels in the basolateral membrane.[17]

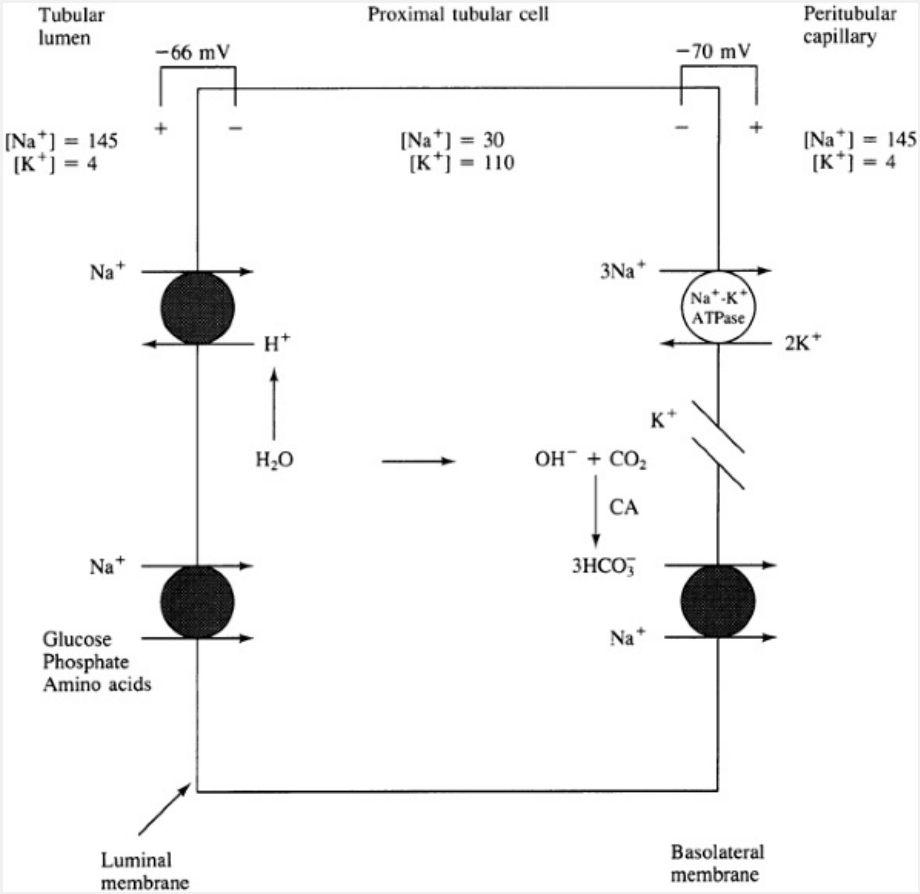

Figure 3-4 Schematic representation of the chemical and electrical gradien and some of the carrier-mediated mechanisms involved in proximal tubular transport. The low cell Na^+ concentration that is maintained by the Na^+-K^+ ATPase pump in the basolateral membrane permits secondary active trans which passive Na^+ entry into the cell is coupled by specific cotransporters t uphill reabsorption of glucose, phosphate, and amino acids, or to the sec of H^+. Units are meq/L; CA represents carbonic anhydrase.

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The net effect is a highly favorable electrochemical gradient that promotes Na^+ entry into the cells. This process, however, must occur via a transmem carrier or channel, since ions are unable to freely cross the lipid bilayer of membranes. In the proximal tubule, Na^+ movement across the luminal membrane is partially linked to the *cotransport* of other solutes, as specific Na^+-glucose, Na^+ amino acid, and Na^+-phosphate carrier proteins are present in the brush borde vesicles in the luminal membrane (Fig. 3-4).[19,20] and [21,22] Both sites must be occupied on the carrier for cotransport to occur.[19]

Na^+ entry also occurs by *countertransport* (or antiport) with H^+, as the carrier promotes both Na^+ reabsorption and H^+ secretion into the lumen (the latter step leading primarily to HCO_3^- reabsorption; see Chap. 11).[23,24]

As an example, one experiment used to document Na^+-dependent glucose reabsorption is illustrated by the study of proximal brush border vesicles in Fig. 3-5. The glucose concentration was the same in the bath and the vesicle, leading to glucose uptake into the vesicle in the absence of a transmembrane Na^+ gradient. However, glucose uptake was markedly stimulated when the bath Na^+ concentration was elevated to 10 times that in the vesicle.

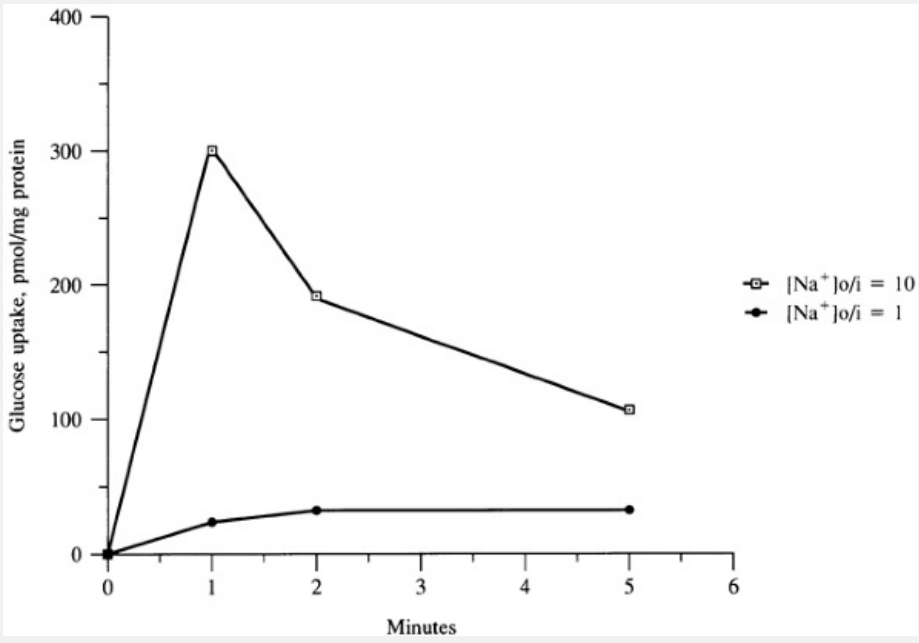

Figure 3-5 Time course of D-glucose uptake in response to changes in the electrochemical potential in proximal brush border luminal membrane vesi Vesicles were initially incubated so that K^+, Na^+, and glucose concentrations were the same in the medium and the vesicle. In this setting, there was m glucose uptake by the vesicles (closed circles). If, however, the vesicles bathed in a medium in which the Na^+ concentration ($[Na]_o$) was 10 times that inside the vesicle ($[Na]_i$), there was a marked stimulation of glucose uptake

(open squares) despite the absence of a transvesicle glucose gradient. T findings indicate the presence of a Na^+-glucose cotransporter. Although not shown, creation of a favorable glucose gradient was able to enhance the of Na^+. (*Adapted from Beck JC, Sackto rB Biol Chem 253:5531, 1978. Used with permission.*)

The mechanism by which coupled transport occurs is incompletely understo binding of the cotransported solute (as with glucose) appears to lead to a conformational change in the transport protein that results in opening of th a transmembrane Na^+ pathway. As a result, Na^+ crosses the membrane down its favorable inward gradient, and flow of the cotransported solute is in some v to that of Na^+.[25] the helical structure of these transporters appears to facilita process.[26] This passive process is called *secondary active transport*, since the energy is indirectly provided by the Na^+-K^+-ATPase pump.

In addition to this primary role for Na^+, there is also evidence that the other solute increase the reabsorption of Na^+. As an example, the removal of glucose, amino acids, and/or bicarbonate from the luminal fluid markedly impairs proximal Na^+ reabsorption.[27,28] Two factors may contribute to this effect.[1] Attachment of the cotransported solute to the carrier may increase its affinity for Na^+,[2] and glucose and bicarbonate are effective osmoles that, as they accumulate in the inter space, promote the passive reabsorption of H_2O and Na^+ across the tight junction (see "Passive Mechanisms of Proximal Transport" below).

Movement into the Intercellular Space

At the basolateral membrane, the Na^+ that has entered the cell must be transported i the intercellular space against electrical and concentration gradients (Fig. 3-4). The energy required for this process is derived from the hydrolysis of ATP by the Na^+-K^+-ATPase pump. This pump, which is also essential for Na^+ reabsorption in other nephron segments,[13] transports Na^+ out of the cell and K^+ into the cell in a 3 : 2, not a 1 : 1, ratio (Fig. 3-4).[29]

Solutes other than Na^+ move passively across the basolateral membrane, again carrier-mediated transport. As depicted in Fig. 3-4, for example, carbonic acid (H_2CO_3) within the cell dissociates into H^+ and HCO_3^- ions. The former is secreted into the lumen by the Na^+-H^+ antiporter, whereas HCO_3^- is returned to the systemic circulation by a HCO_3^-/Na^+ carrier in the basolateral membrane.[30]

The energy for this process is derived from a more complex form of second transport. The central step is again the Na^+-K^+-ATPase pump, which pumps K^+ into the cell, thereby raising the cell K^+ concentration. The latter change promotes

passive K^+ exit from the cell via K^+ channels in the basolateral membrane, a proc that makes the cell interior *negative* with respect to the interstitium; this potential then drives the net transfer of negative charge out of the cell via Na^+-$3HCO_3^-$ carrier.

Note that K^+ entry into the cells via the Na^+-K^+-ATPase pump and the backleak of this K^+ out of the cells varies in parallel with Na^+ transport. The link between these processes appears to be ATP, which normally inhibits the basolateral K^+ channels.[31] If, for example, Na^+ reabsorption rises, the associated elevation in Na^+-K^+-ATPase activity will lower cell ATP stores, thereby removing the inhibitory effect of increasing the number of open K^+ channels in the basolateral membrane. Thus, t extra K^+ that has been pumped into the cells can diffuse back out.

These reabsorptive processes are dependent upon the maintenance of norm membrane polarity in which the transporters, channels, and pumps Na^+-K^+-ATPase are correctly located. Both experimental animals and humans often have de recovery of tubular Na^+ reabsorption after a period of renal ischemia.[32,33] Studies in animals suggest that this defect may result from the loss of membrane po an ischemia-induced increase in the permeability of the tight junction allow lateral movement of Na^+-K^+-ATPase pumps from the basolateral to the luminal membrane.[34,35] and[36] Loss of Na^+-K^+-ATPase pumps from the proximal tubule basolateral membrane has also been demonstrated in renal transplant recip whom there is a delay in graft reperfusion.[37]

Mechanisms of Chloride Reabsorption

After Na^+, Cl^- is the most prevalent ion in the filtrate. Both active and passiv processes contribute to proximal Cl^- reabsorption, each of which is indirectly link to active Na^+ transport.[38] Active Cl^- reabsorption appears to occur via an anion exchanger in the luminal membrane, in which Cl^- is exchanged at least in part for cellular *formate*. Although the formate concentration is only about 0.25 to 0 meq/L in the filtrate, this anion is able to promote Cl^- reabsorption because it is recycled across the luminal membrane (Fig. 3-6).[38,39] and[40] Filtered formate initially combines with secreted H^+ to form formic acid (HF). The latter is uncharged and able to freely diffuse across the luminal The cell, however, has a lower H^+ concentration than the lumen, due to the secre of H^+. As a result, the reaction

$$HF \leftrightarrow H^+ + \text{formate}$$

within the cell is driven to the right. The H^+ is then secreted again, while the forma returns to the lumen via a *formate-chloride exchanger*.[40,41] and[42] Formic acid is reformed in the lumen, and the process can be repeated. The energy for th

exchangers is again provided indirectly by the Na^+-K^+-ATPase pump. By maintaining a low cell Na^+ concentration, this pump allows the continued Na^+-H^+ exchange that is essential for formate recycling. If, on the other hand, the proximal Na^+-H^+ exchanger is inhibited, there is a parallel inhibition of almost all of active transcellular chloride transport.[42,43]

The quantitative role of formate in HCO_3^- reabsorption is uncertain. As a result, it has been speculated that other anion exchangers, such as chloride-hydroxyl or oxalate exchangers, also play a contributory role.[40,41,42,44,45] Regardless of the mechanism, the reabsorbed HCO_3^- is returned to the systemic circulation across basolateral membrane. Both a selective Cl^- channel and a KCl cotransporter appear to contribute to Cl^- exit,[40,46] but other transporters also may play a role.[47] The energy of these transport processes is respectively provided by the cell interior negative potential and by the high cell K^+ concentration in relation to that in the interstitium.

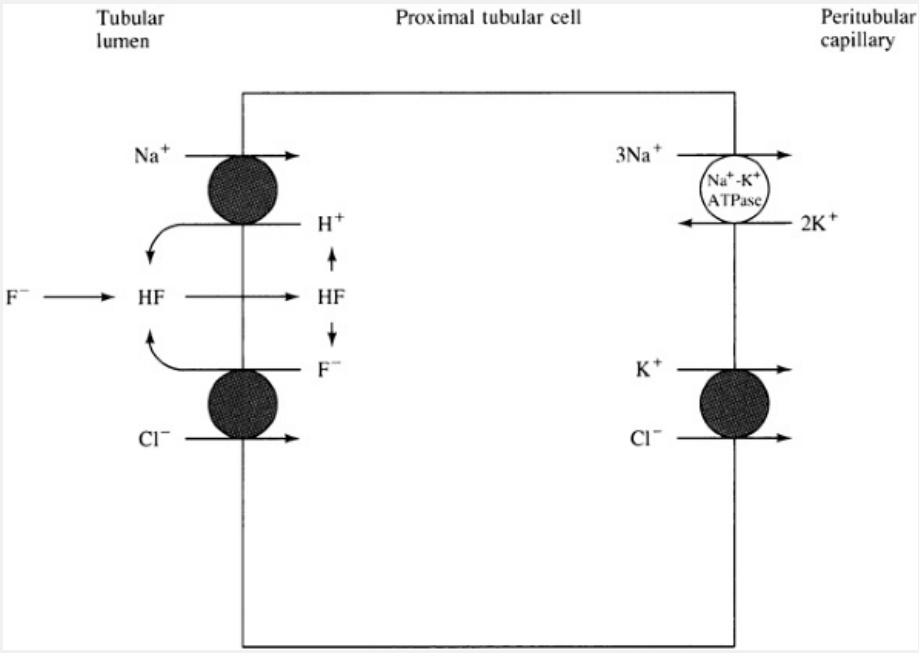

Figure 3-6 Role of filtered formate ($HCOO^-$) in active HCO_3^- reabsorption in the proximal tubule. The essential steps are transport of uncharged formic acid (HF) into the cell, formate secretion and HCO_3^- reabsorption via a formate-chloride exchanger, and recycling of formate into the cell as formic acid. Reabsorbed HCO_3^- is returned to the peritubular capillary by a KCl cotransporter in the basolateral membrane.

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Passive Mechanisms of Proximal Transport

Passive mechanisms appear to account for about one-third of proximal fluid reabsorption.[11,12,14] The mechanism by which this occurs is as follows: The e

proximal convoluted tubule reabsorbs most of the filtered glucose, amino ac
HCO_3^-, but a lesser amount of Cl$^-$ (Fig. 3-1). Water is then reabsorbed down an osmotic gradient.[14]

The net effect is that the tubular fluid has an osmolality similar to that of t
a *higher chloride concentration* and relatively little glucose, bicarbonate, or am
acids. In contrast, the intercellular spaces in the later segments of the prox
tubule have solute concentrations similar to that of the plasma, since they
equilibrium with fluid in the peritubular capillary (Fig. 3-7). If the tight junction were
equally permeable to all solutes, there would be no net fluid movement, sin
effective osmolalities of the two solutions would be similar. However, the p
to Cl$^-$ exceeds that to the other solutes, particularly HCO_3^-.[14,48]

In this setting, passive fluid reabsorption can occur across the tight junctio
intercellular space by two mechanisms:

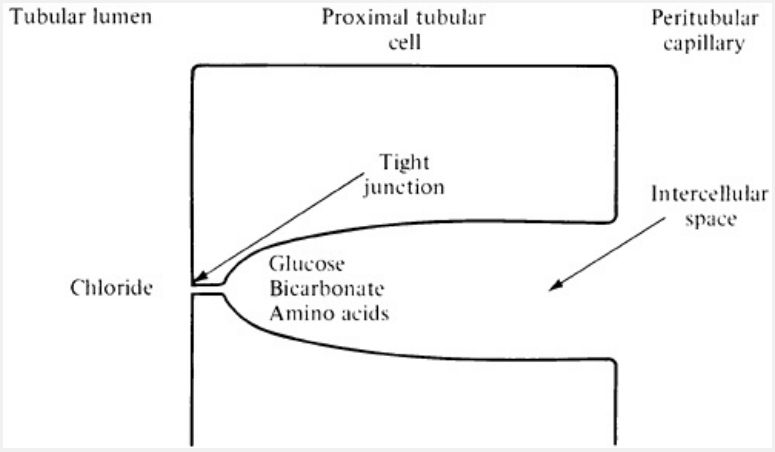

Figure 3-7 Schematic representation of the differences in solute compositio
between the lumen and the intercellular space in the later segments of th
proximal tubule. In comparison to the plasma and intercellular space, the
has a very low concentration of bicarbonate, glucose, and amino acids bu
relatively high chloride concentration.

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1. Chloride can traverse the tight junction down its concentration gradient
sodium and water then following down respective electrical and osmotic
gradients. (Bicarbonate, glucose, and amino acids do not move in the o
direction to the same degree, since the tight junction is much less perm
these solutes.) The presence of primary Cl$^-$ transport has been demonstrated b
the finding of a transepithelial potential difference that is *lumen-positive* (due to
the reabsorption of the anion Cl$^-$ in the late proximal tubule).[12] The potential
difference would be lumen-negative if Na$^+$ transport were the primary event.
2. Water can move across the tight junction down an osmotic gradient, wit

chloride following both by solvent drag and by diffusion, since the loss raises the solute concentrations in the tubule.[4] This movement of water occurs because the tight junction is preferentially permeable to Cl^- ions,[48] as a result, Cl^- is a relatively *ineffective* osmole (see Chap. 1). Thus, the *effective osmolality* in the intercellular space exceeds that in the lumen (thereby promoting water reabsorption), even though the total osmolality is the same in both compartments.[15]

It is likely that HCO_3^- is the most important of the solutes that promote passive transport, since it is present in the highest concentration [24 mmol/L versus 5 mmol/L (90 mg/dL) for glucose]. A clinical example of the effects of HCO_3^- is seen in the response to the administration of acetazolamide. This proximally acting diuretic is a carbonic anhydrase inhibitor that diminishes the reabsorption of bicarbonate and also produces a substantial reduction in proximal NaCl reabsorption, even though it has no known direct action on Cl^- transport.[49] This chloruresis presumably reflects the diminished passive reabsorption, resulting from the decreased transport of HCO_3^-

P.82

A similar reduction in proximal NaCl reabsorption occurs in metabolic acidosis, a disorder in which the plasma HCO_3^- concentration is decreased (see Chap. 19).[50] In this setting, less HCO_3^- is filtered (because of the low plasma level), and therefore less is available for proximal reabsorption.

In summary, other than the Na^+-K^+-ATPase pump, the *Na^+-H^+ antiporter is the main determinant of proximal Na^+ and water reabsorption*. It has three major effects on proximal transport: (1) it directly promotes HCO_3^- reabsorption, particularly in the early proximal tubule; (2) the preferential reabsorption of HCO_3^- and water creates the gradient for the passive reabsorption of Cl^-; and (3) it promotes active Cl^- reabsorption by operating in parallel with the Cl^-/formate and other Cl^-/anion exchangers. It is not surprising, therefore, that activity of the Na^+-H^+ exchanger varies appropriately with salt intake, increasing on a low-salt diet (when enhanced proximal reabsorption will tend to prevent volume depletion) and decreasing on a high-salt diet.[51]

Neurohumoral influences

These diet-induced changes in proximal Na^+-H^+ exchange and NaCl and water reabsorption are mediated at least in part by angiotensin II and norepinephrine:[51,52,53] and[54] The secretion of these hormones varies inversely with the effective circulating volume (see Chap. 8). Thus, volume depletion increases angiotensin II and norepinephrine release, leading to enhanced proximal transport and an appropriate reduction in urinary sodium excretion.

Although angiotensin II increases the activity of the Na^+-H^+ exchanger and

enhances HCO_3^- reabsorption in the early (S1 segment) proximal tubule, it does no induce an important change in net proximal HCO_3^- transport. This finding is related to the flow dependence of HCO_3^- but not Cl^- reabsorption in the later (S2 segment. Thus, the increase in HCO_3^- reabsorption in the initial proximal tubule leads to reduction in HCO_3^- delivery to (and therefore a fall in reabsorption in) the later proximal segments.[52,55] The net effect is no net change in delivery of HCO_3^- out of the proximal tubule. There is, however, decreased delivery of Cl^-, since there is no adaptive decrease in late proximal Cl^- transport.[55]

Thus, angiotensin II has an overall stimulatory effect on proximal NaCl and H_2O reabsorption, but not usually on net acidification. Angiotensin II may be res for as much as 40 to 50 percent of $NaCl$ and H_2O transport in the S1 segment.[56] There is a much smaller effect in the more distal proximal tubule, where the fewer angiotensin II receptors.

Dopamine is another hormone that regulates proximal transport, *diminishing* to Na^+ reabsorption. This effect is associated with partial inhibition of both of steps involved in transtubular Na^+ transport: decreased activity of the Na^+-H^+ exchanger, thereby reducing the entry of luminal Na^+ into the cell;[54,57] and reduced activity of the basolateral Na^+-K^+ ATPase pump,

perhaps due to phosphorylation of the pump by a dopamine-dependent phosphoprotein.[58,59]

These actions of dopamine may be physiologically important, since dopamir production is enhanced by volume expansion. Furthermore, blocking the eff dopamine with a receptor antagonist attenuates the natriuretic response to expansion.[60]

Capillary Uptake

The movement of the reabsorbate from the intercellular space into the perit capillary (derived from the efferent arteriole) is governed by Starling forc (Fig. 3-8):

$$\text{Capillary uptake} = \text{LpS}\,(\Delta\ \text{oncotic pressure} - \Delta\ \text{hydraulic pressure})$$
$$= \text{LpS}\left(s\left[\pi_{ptc} - \pi_{if}\right] - \left[P_{ptc} - P_{if}\right]\right)$$

where Lp is the unit porosity of the capillary wall, S is the surface area ava absorption, s is the reflection coefficient of proteins across the capillary w (ranging from 0 if freely permeable to 1 if completely impermeable), π_{ptc} and π_{if} are the oncotic pressures in the peritubular capillary and interstitium, and P_{ptc} and P_{if} are the hydraulic pressures in the capillary and interstitium.

The approximate normal values for the hydraulic and oncotic pressures in t peritubular capillary are depicted in Fig. 3-8. The mean hydraulic pressure is much less than arterial pressure due to the resistances at the glomerular arteriol

contrast, the oncotic pressure is higher than that in the systemic circulatio of the removal of protein-free filtrate in the glomerulus. Although the exact somewhat controversial, the net approximate effect is a relatively large gra π_{ptc}-P_{ptc}=13 mmHg) within the capillary that favors fluid

uptake from the intercellular space.[61] This gradient will be somewhat dissipated along the length of the proximal tubule, since uptake of the reabsorbate wil the π_{ptc} by dilution. In comparison, the hydraulic and oncotic pressures in th interstitial fluid are of lesser magnitude (less than 5 mmHg) and generally r smaller contribution to net fluid movement.[61]

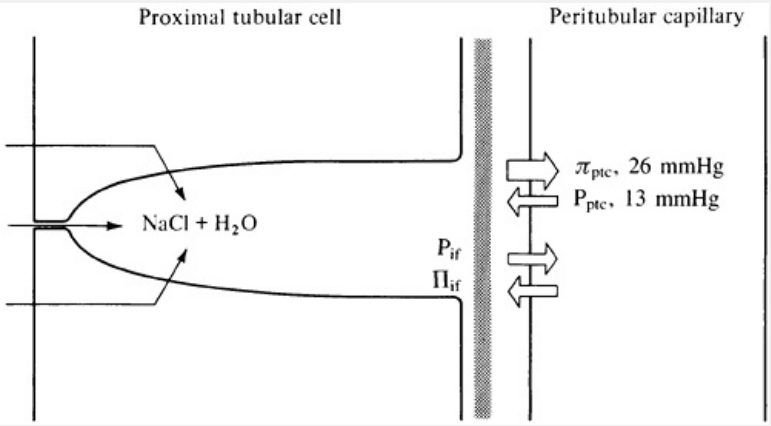

Figure 3-8 Role of Starling's forces in the uptake of the reabsorbate by the peritubular capillary. Approximate values for the capillary hydraulic and o pressures are included and show a relatively large gradient favoring fluid movement into the capillary. The interstitial pressures are of lesser magn and tend to balance out, thereby making a smaller contribution to net flui movement.

One way that net fluid reabsorption can be regulated is by alterations in th capillary hemodynamic forces, which are influenced by glomerular arteriola an example, the degree to which the systemic blood pressure is transmitted peritubular capillary is dependent upon glomerular arteriolar resistance. Ar constriction increases the pressure drop across the glomerulus, thereby re peritubular capillary hydraulic pressure; arteriolar dilation, in comparison, peritubular capillary pressure to rise toward that in the systemic circulatior

The capillary oncotic pressure, on the other hand, is determined by two fac baseline plasma protein concentration and the fraction of the renal plasma (RPF) that is filtered across the glomerulus (called the *filtration fraction*, or GFR/RPF). If relatively more fluid is filtered, i.e., if the filtration fraction is increased, be a greater than usual elevation in the protein concentration in the fluid le glomerulus and entering the peritubular capillary. Changes in the filtration are primarily induced by changes in resistance of the *efferent* arteriole. Efferent arteriolar constriction will tend to raise the GFR (by increasing glomerular

pressure) and lower the RPF (because of the elevation in renal vascular re thereby increasing the filtration fraction and the peritubular capillary oncot pressure (see page 38).

Thus, alterations in peritubular capillary hemodynamics induced by efferent constriction—increased oncotic pressure, reduced hydraulic pressure—pron capillary uptake and net proximal reabsorption. This becomes clinically imp because both angiotensin II and norepinephrine, released in response to ef circulating volume depletion, increase the resistance at the efferent and, to degree, the afferent arterioles, thereby raising the filtration fraction.[62] In congestive heart failure, for example, angiotensin II and norepinephrine levels, the filt fraction, and proximal reabsorption are all frequently elevated, thereby con to the low rate of Na^+ and water excretion that is commonly seen (see Chapter 16).[63] (As described above, angiotensin II and norepinephrine also promote proxin reabsorption via stimulation of Na^+-H^+ exchange.[52,54,56])

Backflux across the Tight Junction

The mechanism by which changes in peritubular capillary hemodynamics inf proximal reabsorption is incompletely understood.[4] It has been suggested that fluid transported into the intercellular space can either move into the peritubular or leak back into the lumen across the tight junction. This choice is influen by the balance of Starling's forces across the capillary wall. In volume expa example, enhanced movement of raffinose or sucrose from the peritubular c into the tubular lumen has been demonstrated.[64] Since these sugars do not enter cells, this movement must reflect increased permeability of the tight junctio suggests

that the associated reduction in proximal reabsorption may be mediated by backflux from the intercellular space into the lumen.

Changes in capillary hemodynamics may play an important role in this respo Both angiotensin II and norepinephrine release are diminished by hypervole ensuing efferent arteriolar dilation could lower the filtration fraction and im capillary uptake, thereby promoting backleak across the tight junction.

There is, however, a major problem with this passive backflux theory. Micro studies have demonstrated that lowering the oncotic pressure in the peritub capillary reduces the reabsorption of NaCl, but not that of glucose or HCO_3^-.[65] Although this could be explained by the known higher permeability of the tig junction to Cl^-,[14,48] it is the active, not passive reabsorption of NaCl that is impaired.[66]

Glomerulotubular Balance

The efficiency with which proximal transport is regulated can be appreciate phenomenon of glomerulotubular balance. The urinary excretion of Na^+ and water is equal to the difference between the amount filtered across the glomerulus a

amount reabsorbed by the tubules. To maintain the extracellular fluid volum important that tubular reabsorption varies with the spontaneous changes (s which are diet-induced) that can occur in the GFR.

As an example, a normal adult male filters approximately 180 L/day (125 mL urine output, however, is usually only 1 to 2 liters, as over 98 percent of th reabsorbed. If there were a slight elevation in GFR to 183 L/day but no cha tubular reabsorption, the result would be a 3-liter increase in urine output serious reduction in the extracellular fluid volume. Fortunately, this does n since, over a wide range of spontaneous and experimental variations in the there is a proportional change in tubular reabsorption.[67,68,69] Thus, a 1.5 percent increase in the GFR (from 180 to 183 L/day) is associated with a si increment in tubular reabsorption, resulting in only a small elevation in the output.

This response, in which the absolute level of tubular reabsorption is direct to the filtration rate, is called *glomerulotubular balance*. Notice that at all levels of GFR in Fig. 3-9, approximately 60 percent of the filtrate is reabsorbed in the p tubule. Similarly, the more distal nephron segments reabsorb a constant fra the load delivered to them from the proximal tubules.[68,69] This is another way to define glomerulotubular balance: that the fractional tubular reabsorption re roughly constant despite changes in the GFR.

The mechanism by which glomerulotubular balance is mediated in the proxi is incompletely understood, but both peritubular and luminal factors are tho contribute.[67,70,71] If, for example, the GFR increases while RPF remains cons the protein concentration in the plasma leaving the glomerulus will rise due loss of more protein-free filtrate. The ensuing elevation in the oncotic pres peritubular capillary can then enhance net proximal reabsorption.[70,71]

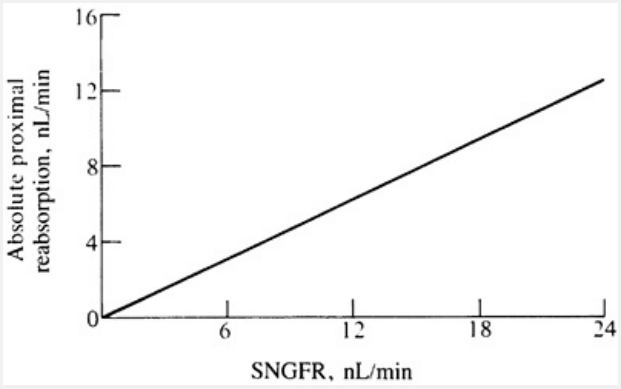

Figure 3-9 Glomerulotubular balance in the proximal tubule. Since fractiona and water reabsorption remains constant, absolute proximal reabsorption nephron is directly proportional to the single nephron glomerular filtration (SNGFR). A similar relationship between absolute Na^+ reabsorption and the amount of Na^+ delivered to the segment is present in the loop of Henle and distal tubule. (*Adapted from Spitzer A, Brandis M: J Clin Invest 53:279, 1974, by*

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It is likely that the presence of factors in the filtrate that enhance Na^+ and H_2O reabsorption also play a major role in glomerulotubular balance in the proxi tubule.[67] As described above, bicarbonate, glucose, and amino acids augmer reabsorption both by cotransporting carriers in the luminal membrane (Fig. 3-4) and by the subsequent creation of chloride and osmotic gradients for passive reabsorption (Fig. 3-7). An elevation in GFR will augment the filtered load of th (and other) solutes, and their subsequent reabsorption can contribute to glomerulotubular balance for Na^+ and H_2O.[67]

Glomerulotubular balance in the proximal tubule, loop of Henle, and distal t one of three intrarenal mechanisms that act to prevent fluid delivery from e the limited total reabsorptive capacity of the collecting tubules.[69] The others are *autoregulation*, which keeps the GFR relatively constant despite variations in arterial pressure, and *tubuloglomerular feedback*, which lowers the GFR if the load to the macula densa segment of the early distal tubule is increased (see Chap. 2). Thus, one view of nephron function is that the proximal tubule and loop of responsible for the reabsorption of the bulk of the filtrate, with the distal n (particularly the collecting tubules) making small variations in electrolyte a excretion in accordance with changes in intake.[69] This process operates most efficiently if the distal delivery of filtrate is kept at a nearly constant level.

The relationship between glomerular filtration and tubular reabsorption is n and may be reset at a different level when there are changes in the effectiv circulating volume (see Chap. 8). The fraction of the filtered Na^+ and water reabsorbed in the proximal tubule tends to be *increased by volume depletion and decreased by volume expansion*.[73,74] These changes are appropriate, however, since the maintenance of constant fractional Na^+ reabsorption is not desirable in these conditions. Enhanced reabsorption leading to Na^+ and water retention is a proper response to volume depletion. As mentioned previously, these chang mediated at least in part by angiotensin II and norepinephrine (either circu released from the renal sympathetic nerves).[52,54,55] and[56]

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Summary

The proximal tubule reabsorbs isosmotically about 55 to 60 percent of the f This process occurs in three steps: entry into the cell across the luminal m movement across the basolateral membrane into the intercellular space, an by the peritubular capillary. Despite the large amount of reabsorption that only major active (energy-requiring) step is mediated by Na^+-K^+-ATPase pump in the basolateral membrane. In addition to directly promoting Na^+ reabsorption, this pump maintains the low cell Na^+ concentration that allows passive entry of Na^+ into the

cell.

The reabsorption of many other solutes (such as glucose, phosphate, amino and bicarbonate) occurs by carrier-mediated coupled transport with Na^+ across the luminal membrane. Furthermore, the preferential reabsorption of these solu Na^+ in the early proximal tubule creates osmotic and concentration gradient permit about one-third of total proximal Na^+ and H_2O reabsorption to occur passively through the tight junction (see Figure 3-7).

Uptake by the peritubular capillary of fluid transported into the intercellula regulated by Starling's forces. Depending upon the magnitude of these forc can be influenced by vasoactive hormones, the reabsorbate either enters th capillary and is returned to the systemic circulation or leaks back into the l across the tight junction. Modulations in net proximal tubular reabsorption be influenced by luminal, peritubular capillary, and neurohumoral factors.

The data upon which the above conclusions are based were primarily obtai studies in experimental animals. Human studies are, of course, more limited However, the importance of luminal membrane cotransporters in humans wa suggested by findings in an infant who was born without the proximal tubula border and presumably without the carrier proteins that it normally contains child had *no tubular reabsorption* of glucose, amino acids, or phosphate, as evidenced by a rate of excretion for these compounds that was essentially the filtered load (determined from the GFR times the plasma concentration). The plasma bicarbonate concentration was 11 meq/L (normal equals about 24 me assuming that proximal bicarbonate reabsorption by the Na^+-H^+ antiporter was also negligible, this value of 11 meq/L presumably reflects the bicarbonate reabs capacity of the more distal segments. This distal contribution probably expl patients with type 2 (or proximal) renal tubular acidosis, who have an impai proximal bicarbonate reabsorption, usually are able to maintain their plasm bicarbonate concentration at or above 12 meq/L (see Chap. 19).

PRIMACY OF SODIUM TRANSPORT IN PROXIMAL TUBULAR FUNCTION

The relationship between the proximal reabsorption of sodium and that of m filtered solutes is often important clinically. This is particularly true in hypo states, in which the increase in proximal Na^+ transport is associated

with a *parallel rise in the reabsorption of bicarbonate, urea, calcium, and u* The remainder of this chapter will review the different transport systems fo solutes (both in the proximal tubule and in other nephron segments) and th clinical relevance of their relationship to Na^+ reabsorption. In many cases, the changes that occur are at the expense of the homeostatic requirements for solutes.

Bicarbonate

Approximately 80 percent of the filtered HCO_3^- is absorbed in the proximal tubule

and the remainder in the distal tubule and collecting tubules. HCO_3^- reabsorption is accomplished by the active transport of H^+ from the cell into the lumen; this process is mediated primarily by the H^+-Na^+ antiporter in the proximal tubule and by a H^+ ATPase pump in the distal nephron (see Chapter 1).

Relation of T_{mHCO_3} to sodium transport

The term HCO_3^- refers to the maximum tubular reabsorptive capacity for HCO_3^- per unit time. To measure this parameter, $NaHCO_3$ is used intravenously to raise the plasma HCO_3^- concentration and, therefore, the filtered load. Tubular reabsorption, measured in milliequivalents of HCO_3^- reabsorbed per minute, can then be calculated from

$$\text{Tubular reabsorption} = \text{filtered load} - \text{urinary excretion}$$
$$= \text{GFR} \times \text{plasma}\,[HCO_3^-] - \text{urine}\,[HCO_3^-] \times \text{volume}$$

The results of such an experiment are illustrated in Figure 3-10. There appears to be a maximum HCO_3^- reabsorption of 26 to 28 meq/L of glomerular filtrate. This would be an appropriate mechanism by which the kidney prevents the plasma HCO_3^- concentration from exceeding the normal value of 22 to 26 meq/L, since the HCO_3^- would be excreted in the urine. However, the proximal reabsorption of HCO_3^- is linked (by the H^+-Na^+ antiporter) to Na^+ transport, and the infusion of $NaHCO_3$ expands the extracellular volume, a stimulus known to diminish proximal Na^+ and perhaps HCO_3^- reabsorption.[73,76]

Figure 3-11 depicts the results of two HCO_3^- infusion experiments in a patient with moderate renal failure. When $NaHCO_3$-induced volume expansion was allowed to occur, HCO_3^- reabsorption reached a plateau when the plasma HCO_3^- concentration was 28 meq/L. In comparison, when volume expansion was minimized by prior depletion, HCO_3^- reabsorption continued to rise even when the plasma HCO_3^- concentration reached 36 meq/L. In the rat, a T_{mHCO_3} can be demonstrated if hypervolemia is prevented, even if the plasma HCO_3^- concentration is greater than 60 meq/L.[76]

These observations demonstrate that there is a *true* T_{mHCO_3}, since the reabsorptive capacity varies directly with the fractional reabsorption of

Na^+.[76,77] This assumes clinical importance in patients with volume depletion metabolic alkalosis (high plasma HCO_3^- concentration, elevated arterial pH). The normal response to an increase in the plasma HCO_3^- concentration is to excrete the excess HCO_3^- in the urine. However, hypovolemia and the associated hypoch

enhance HCO_3^- reabsorption, resulting in the retention of the excess HCO_3^- and perpetuation of the alkalosis (see Chapter 18). HCO_3^- excretion will rise only if the stimulus to Na^+ and Cl^- retention is removed by the restoration of normovolemia.

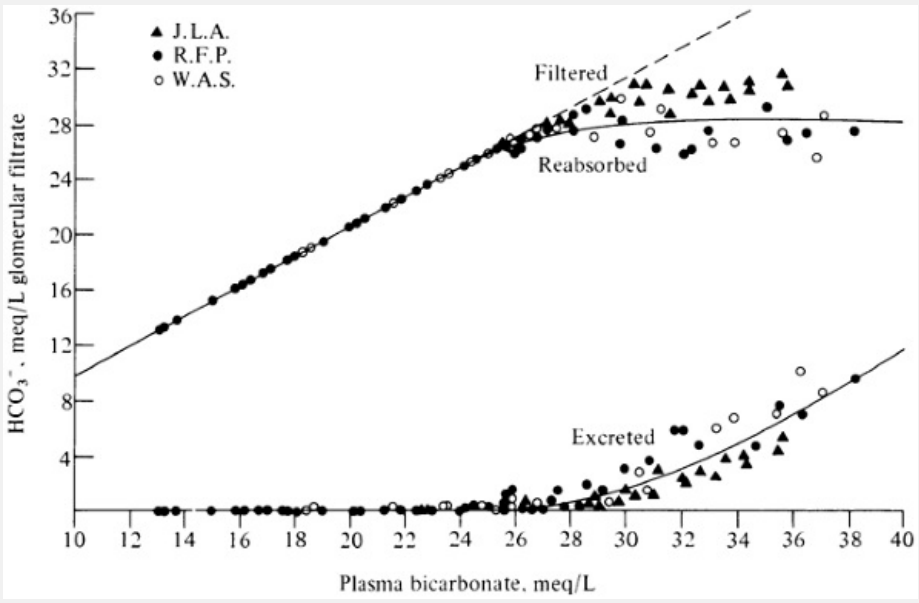

Figure 3-15 Filtration, reabsorption, and excretion of bicarbonate as a function of plasma concentration in normal humans. *From Pitts RF, Ayer J, Shiess W, J Clin Invest 28:35, 1949, by copyright permission of the American Society for Clinical Investigation.*

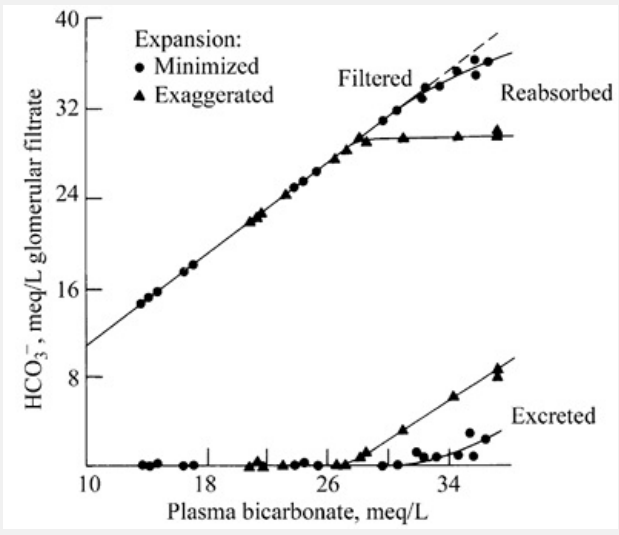

Figure 3-16 Bicarbonate titration curves obtained from a patient with a GFR of 37 mL/min studied under conditions of minimized and exag-gerated expansion of extracellular fluid volume. *From Slatopolsky E, Hoffsten P, Purkerson M, Bricker NS, J Clin Invest 49:988, 1970, by copyright permission of the American Society for Clinical Investigation.*

Glucose

Under normal conditions, all the filtered glucose is reabsorbed in the proxi and returned to the systemic circulation via the peritubular capillaries. This occurs in two steps. Filtered glucose enters the cell by passive cotransport (even though glucose moves uphill against a concentration gradient) (see Fig. 3-5);[19,20] it then leaves the cell at the basolateral membrane, probably by diff via specific glucose transporters that are Na^+-independent and that are limited to t basolateral membrane.[78,79]

The Na^+-glucose cotransporters have different characteristics in the differer proximal segments.[20] The S_1 and S_2 segments have a high-capacity, low-affinity carrier that is able to remove most of the filtered glucose. (This glucose is returned to the systemic circulation, since these segments do not primarily glucose for oxidative metabolism.[80])

The high degree of early proximal reabsorption results in relatively little gl being delivered to the S_3 segment. To reabsorb the remaining glucose, the carri this site has a higher affinity and a 2 : 1 binding ratio, i.e., 1 glucose : 2 Na^+. Thus, the additive effect of the favorable inward gradient of two Na^+ ions is used to drive the uphill transport of glucose against an increasing concentration gradient.[19] Similar differences are present in the glucose transporters in the basolater membrane that return reabsorbed glucose to the systemic circulation: low-a the S_1 segment; and high-affinity in the later parts of the proximal tubule.[78]

The cDNAs for the high-capacity, low-affinity carrier, termed SGLT2, and the low capacity high-affinity carrier, termed SGLT1, have both been cloned and sequenced.[81,82] Both transporters are highly homologous at the amino acid le and are able to transport sodium and glucose via transmembrane pores. SG found exclusively in the proximal tubule, while SGLT1 is also expressed in the gastrointestinal tract.

Studies in normovolemic subjects have shown a T_m for glucose of approximately 375 mg/min (Fig. 3-12).[2] Thus, glucose should not appear in the urine until the filte load exceeds this value. If the GFR is 125 mL/min, glucosuria should not be the plasma glucose concentration is greater than 300 mg/dL [125 mL/min × 3 (or 300 mg/dL) equals 375 mg/min]. (The normal plasma glucose concentrat to 100 mg/dL, fasting.)

However, glucose can usually be detected in the urine when the plasma glu concentration exceeds 180 to 200 mg/dL. This deviation from the *true* T_m is called *splay* and has been ascribed to heterogeneity in the relationship between glomeru and proximal tubular length within individual nephrons.[83] A nephron with a large glomerulus (i.e., high filtered load) or a relatively short proximal tubule (i.e

reabsorptive capacity) will spill glucose in the urine at a lower plasma gluc concentration than predicted from the T_m for the whole kidney.

Clinically, glucosuria is most commonly seen when the filtered load is incre to hyperglycemia in uncontrolled diabetes mellitus. Less often, there is a d proximal reabsorption that may be selective, as in renal glucosuria,[84] or part of a generalized abnormality in proximal transport, as in

the Fanconi syndrome.[85] In renal glucosuria, the appearance of glucose in the at a normal plasma glucose concentration is thought to be due either to a d number of glucose carriers or to a reduction in the affinity of the carriers fo glucose.[86]

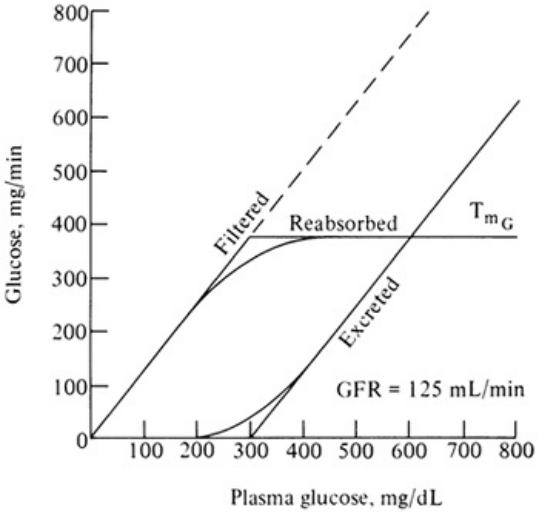

Figure 3-12 Filtration, reabsorption, and excretion of glucose as a function plasma concentration in normal humans. The curves for reabsorption and secretion are drawn in two ways: (1) as idealized, sharply breaking curves; and (2) as rounded curves more descriptive of the true relationships for T_ms. With a T_m glucose of 375 mg/min and a GFR of 125 mL/min, glucose excretion shoul begin until the plasma glucose concentration is greater than 300 mg/dL (s breaking curve). However, due to tubular heterogeneity (see text), there i "splay" in the glucose titration curve (rounded curves) and glucosuria bei when then the plasma glucose concentration exceeds 180 to 200 mg/dL, w before the saturation of tubular reabsorptive capacity. The relative lack o in the HCO_3 titration curve (Fig. 3-10) may be due to the ability of distal HCO_3 reabsorption to compensate for variations in proximal transport. This is in contrast to glucose, which is reabsorbed entirely in the proximal tubule. (From *Pitts RF*: Physiology of the Kidney and Body Fluids, 3d ed. Copyright ©197 Year Book Medical Publishers, Inc, Chicago. Used by permission. Adapted Wright HR, Russo HF, Sheggs HR, et al, Am J Physiol 149:130, 1947.)

Urea

Urea, which is an end product of protein metabolism, is lipid-soluble and ab cross most cell membranes by passive diffusion. The reabsorption of water proximal tubule increases the tubular fluid urea concentration, thereby allo to be reabsorbed passively down a concentration gradient. This may be fac a constitutive transporter. Urea also is reabsorbed in the more distal nephr segments, the importance of which will be discussed in Chapter 4. The net effect is that only 50 to 60 percent of the filtered urea is normally excreted.

The urea concentration in the blood is measured as the blood urea nitrogen The BUN tends to vary inversely with the GFR, a reflection of the importan glomerular filtration in urea excretion (see Chapter 2). Thus, an elevation in the BUN i often due to a fall in GFR. There are, however, two

important exceptions: conditions associated with enhanced urea production gastrointestinal bleeding, corticosteroid therapy, or a high-protein diet; and depletion, in which the increase in proximal Na^+ and H_2O reabsorption results in enhanced urea reabsorption and consequently a rise in the BUN. This is re as *prerenal azotemia*, since the elevation in BUN is not due to renal disease a associated with no or a lesser elevation in the plasma creatinine concentra[87]

Calcium

Dietary Na^+, K^+, and Cl are almost completely absorbed in the gastrointestinal tract, and their steady-state concentrations in the extracellular fluid are ma primarily by changes in urinary excretion. In contrast, calcium and phospha absorption are incomplete, and variations in intestinal absorption and calci phosphate release from bone, as well as in urinary excretion, contribute to regulation of calcium and phosphate balance.

Approximately 40 percent of the plasma Ca^{2+} is bound to albumin and is not filtere at the glomerulus. Of the remaining 60 percent, 50 percent is physiological important ionic (free) Ca^{2+}, and 10 percent is bound to citrate, bicarbonate, or phosphate. The filtered Ca^{2+} is reabsorbed throughout the nephron, with about percent being excreted on a regular diet.[88] Approximately 80 to 85 percent of the filtered Ca^{2+} is reabsorbed in the proximal tubule and medullary loop of Henl but not all, of this transport is passive, following gradients established by water reabsorption.[89,90] and[91] Passive calcium reabsorption in the thick ascen limb occurs via the paracellular pathway, a process that appears to be facil a tight junction protein called paracellin-1.[92]

The regulation of Ca^{2+} excretion according to physiologic needs appears to oc primarily in the cortical distal nephron, including the distal tubule and the a cortical thick ascending limb of the loop of Henle and the connecting segme Fig. 1-3).[89,91,93] In these segments, parathyroid hormone (PTH) and to a less degree vitamin D stimulate Ca^{2+} reabsorption. PTH activates a hormone-specific

adenylate cyclase system.[93,94,95,96,97] and[98] while vitamin D induces the production of calcium-binding proteins (calbindins)[99] and by enhancing the effect of PTH.[100]

Luminal Ca^{2+} appears to enter the cells through Ca^{2+} channels in the apical membrane, down a favorable electrochemical gradient (cell interior negativ Ca^{2+} concentration of less than 200 nanomol/l).[95,97] PTH increases Ca^{2+} entry, although the mechanism by which this occurs is incompletely understood. It suggested that the primary effect of PTH is to increase the number of open channels in the basolateral membrane; the ensuing loss of anionic chloride cell will hyperpolarize the cell membrane, thereby enhancing both the activ voltage-dependent Ca^{2+} channels in the luminal membrane and the gradient for passive Ca^{2+} entry into the cell.[93,97] A vitamin D-dependent calcium-binding prot also appears to facilitate Ca^{2+} uptake at the luminal membrane.[99]

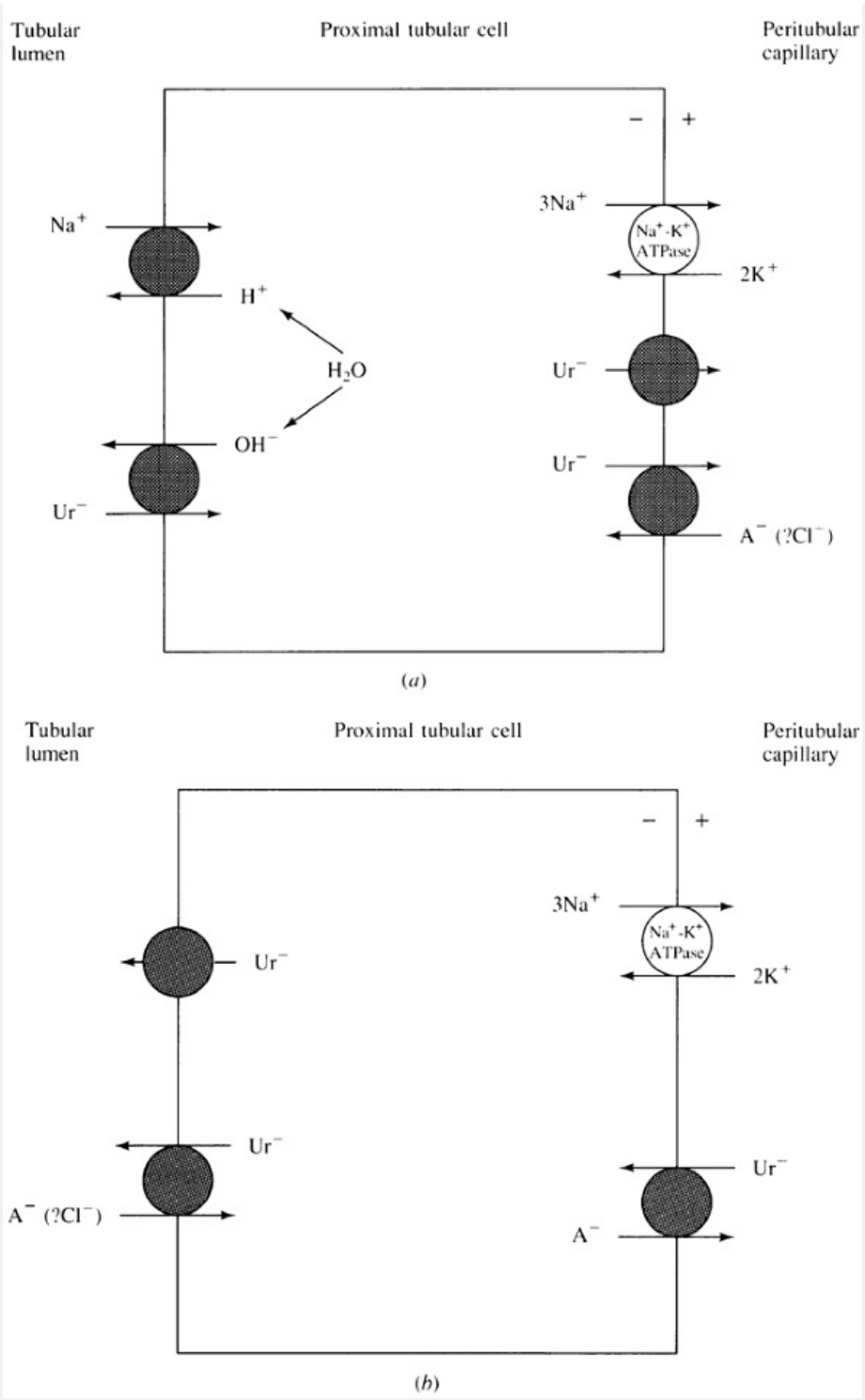

Figure 3-13 Model for urate (Ur⁻) reabsorption (*a*) and secretion (*b*) in the proximal tubule. (*a*) Urate reabsorption begins with entry into the cell via a urate–OH⁻-exchanger that is driven by the pH gradient created by the Na^+-H^+ antiporter. The reabsorbed urate then leaves the cell by carrier-mediated diffusion or possibly by anion exchange with an anion such as Cl^-. (*b*) Urate secretion, on the other hand, begins with urate entry into the cell across basolateral membrane, probably in exchange for cell A^-, such as citric acid intermediates. Movement from cell to lumen can then occur by simple diffusion or by exchange with an anion which has a relatively high lumina

concentration, such as Cl^-

Extrusion of this Ca^{2+} into the peritubular interstitium may then occur at least via a basolateral Ca^{2+}-ATPase pump or a $3Na^+$-Ca^{2+} exchanger.[89,95,101] The latter transporter, which may be responsible for up to 70 percent of calcium extrusion, uses the favorable inward electrochemical gradient for Na^+ entry (in this setting occurring at the basolateral membrane) to drive the reabsorption of Ca^{2+}.[94,101] In addition to increasing the number of open Ca^{2+} channels in the basolateral membrane, PTH may also increase the number of $3Na^+$-Ca^{2+} exchangers, thereby enhancing Ca^{2+} extrusion from the cell.[102,103]

Clinical Implications

The interaction between these humoral factors can be illustrated by the res an increase in dietary calcium intake. The ensuing rise in Ca^{2+} absorption from the gut leads to a small elevation in the plasma Ca^{2+} concentration, which diminishes the release of both PTH and calcitriol (1,25-dihydroxycholecalciferol, the m form of vitamin D; see chap. 6). The net effect is reduced distal Ca^{2+} reabsorption and excretion of the excess Ca^{2+}.

The thick ascending limb also may contribute to the calciuric response afte calcium load. This effect appears to be mediated by the calcium-sensing re which is expressed on the basolateral membrane of these cells (see "Magnesium below).[104]

On the other hand, a reduction in the plasma Ca^{2+} concentration below 8.5 to 9 mg/dL (the lower limit of normal) usually results in a fall in urinary Ca^{2+} excretion to very low levels.[105] This response is mediated in part by hypocalcemia-induced stimulation of PTH and calcitriol secretion.

Let us now consider how these relationships are altered in patients with hypoparathyroidism.[105] Since PTH is the major stimulus to calcitriol synthesis, is a deficiency of both hormones in this disorder. As a result, the relationsh between the plasma Ca^{2+} concentration and urinary Ca^{2+} excretion is reset: The impairment in Ca^{2+} reabsorption leads to persistent calciuria even though the may have a plasma Ca^{2+} concentration below 7.5 mg/dL. If calcitriol is now giv correct the hypocalcemia, there will still be PTH deficiency and a persisten distal Ca^{2+} transport. Consequently, an elevation in the plasma Ca^{2+} concentration to a still low level of 8 mg/dL may be associated with a significant rise in u Ca^{2+} excretion. Any attempt at further correction of the hypocalcemia will le increasing hypercalciuria and possible calcium stone formation.[105,106] Thus, the development of hypercalciuria often limits the degree to which the plasma Ca^{2+}

concentration can be normalized.

The passive reabsorption of most of the filtered Ca^{2+} in the proximal tubule and loop of Henle also is important clinically, since it means that transport of Ca^{2+} in these segments will be affected by changes in net NaCl transport. Thus, on a constant Ca^{2+} intake, variations in net Na^+ reabsorption (due to diet, drugs, or changes in the effective circulating volume) will alter both Na^+ and Ca^{2+} excretion.[107]

These characteristics are useful in the therapy of hypercalcemia and of nephrolithiasis due to hypercalciuria.[88,107]

1. Hypercalcemia can be corrected by increasing excretion of Ca^{2+}. This can be achieved by decreasing net Na^+ reabsorption in the proximal tubule with a high NaCl intake, and in the loop of Henle by the use of a diuretic that inhibits NaCl reabsorption, such as furosemide.
2. Conversely, lowering calcium excretion may reduce the frequency of stone formation in patients with idiopathic hypercalciuria.[108] This can be achieved by increasing Na^+ and, secondarily, Ca^{2+} reabsorption in the proximal tubule and loop of Henle by inducing volume depletion with a low Na^+ intake and a diuretic.[107,108] and[109] However, the diuretic must act *distal to the medullary thick ascending* limb so that it can enhance the excretion of Ca^{2+} without also increasing that of Na^+. Both the thiazide diuretics, which act in the distal tubule and amiloride, which acts in the connecting segment, are useful in this

In addition to inducing volume depletion, these agents also lower Ca^{2+} excretion by directly stimulating distal Ca^{2+} reabsorption.[110,111] How this occurs is not well understood; it is likely to be indirect, since the two diuretics act by different mechanisms (see Chap. 15). One theory proposes a central role for enhanced Ca^{2+} uptake at the luminal membrane via a mechanisms similar to that noted above for parathyroid hormone.[111,112] According to this hypothesis, a diuretic-induced reduction in Cl^- entry across the luminal membrane combined with continued Cl^- exit through Cl^- channels in the basolateral membrane results in hyperpolarization of the cell.[111] The net effect is increased activity of the voltage-dependent Ca^{2+} luminal channels and an enhanced electrical gradient favoring Ca^{2+} uptake from the lumen.

The fall in the cell Na^+ concentration following diuretic-induced inhibition of Na^+ uptake also may play a contributory role.[95,103] This intracellular change will enhance the gradient for passive entry of Na^+ across the basolateral membrane and therefore for Ca^{2+} extrusion from the cell via the basolateral Na^+-Ca^{2+} exchanger.

Phosphate

Eighty to ninety-five percent of the filtered phosphate is normally reabsorb almost all of this occurring in the proximal tubule. Filtered phosphate initia from the lumen into the cell via specific Na^+–phosphate cotransporters in the lumina membrane.[22,113,114] These transporters generally have a 3 Na^+ : 1 HPO_4^{2-} stoichiometry; this allows the favorable inward gradient of the Na^+ ion to drive continued phosphate uptake despite a falling tubular fluid phosphate concentration.[115] High-affinity transporters in the late proximal tubule also co to the ability to reabsorb most of the filtered phosphate.[116] The phosphate that enters the cell then diffuses passively out across the basolateral membrane uncertain mechanism.[114]

There are three different Na^+–phosphate cotransporters.[22,117] Type II appears to be the most important Na^+–phosphate cotransporter within the proximal tubule, as evidenced by severe renal phosphate wasting in mice with targeted inactiva this protein.[118]

Proximal phosphate transport is primarily regulated by two factors, both of specifically affect the activity of the Na^+–phosphate carrier: *plasma phosphate concentration* and *parathyroid hormone*.[114,119,120] and [121] A low-phosphate diet or hypophosphatemia, for example, leads to virtual abolition of phosphate e in the urine, an effect that is primarily mediated by increased activity of the cotransporter.[22,113,114] In mice without type II transporter genes, proximal phosphate transport with chronic phosphate deprivation is only 15 percent wild-type mice.[83]

In contrast, Na^+–phosphate carrier activity is diminished after a phosphate loa resulting in an appropriate increase in urinary excretion. Although this in p represents a direct effect of the rise in plasma phosphate concentration,[120] increased secretion of PTH also plays a contributory role.[113,123] Enhanced PTH release in this setting occurs because phosphate loading can reduce the pl Ca^{2+} concentration by driving the following reaction to the right

$$Ca^{2+} + HPO_4^{2-} \leftrightarrow CaHPO_4$$

and can decrease the renal production of calcitriol, thereby removing the n inhibitory effect of this hormone on the parathyroid gland.[124,125]

Another factor that can affect proximal phosphate reabsorption is metabolic In this setting, transporter activity is diminished, leading to an increase in excretion.[114] The phosphaturia is in part beneficial in that it enhances buffer excretion, thereby allowing more acid to be excreted. Two factors may be ir this response: direct inhibition of the Na^+–phosphate cotransporter as the affinity f the Na^+ interaction is reduced,[115] and, due to the fall in tubular fluid pH, conver of HPO_4^{2-} to $H_2PO_4^-$, which has a lower affinity for the phosphate binding site

the cotransporter.[114,126]

Magnesium

Circulating Mg^{2+} is partially protein-bound, so that only about 70 to 80 percer filtered across the glomerulus. In general, about 3 percent of the filtered Mg^{2+} escapes reabsorption in humans and is excreted.[127,128] This value is appropriately increased after a Mg^{2+} load and falls to very low levels with depletion. In contrast to other solutes, however, most of the filtered Mg^{2+} (50 to 60 percent) is reabsorbed in the cortical thick ascending limb of the loop of Henle and dis convoluted tubule, not in the proximal tubule (20 to 30 percent).[127] Furthermore, alterations in Mg^{2+} excretion are primarily due to changes in loop transport. A example, a low-Mg^{2+} diet leads to a rapid fall in Mg^{2+} excretion that is due to enhanced loop Mg^{2+} reabsorption and that may occur even before there is a fa the plasma Mg^{2+} concentration or in the filtered load.[129]

The cellular mechanisms of Mg^{2+} transport in the thick ascending limb are incompletely understood. The bulk of Mg^{2+} transport appears to be passive, occurring by paracellular diffusion between the cells and being driven by th favorable electrical gradient resulting from the reabsorption of sodium chlo Fig. 4-2.[127,128,130] Paracellular magnesium reabsorption at this site appears facilitated by a tight junction protein called paracellin-1.[92]

Factors controlling Mg^{2+} transport act through changes on the voltage and/or permeability of the paracellular pathway. Thus, decreased reabsorption and wasting can be induced by the administration of a loop diuretic, which inhib sodium and chloride reabsorption, or by mutations in the paracellin-1 gene.[92] paracellin-1 appears to mediate the passive reabsorption of calcium as wel magnesium, patients with mutations present with renal magnesium and calc wasting.[92]

Magnesium transport in the cortical thick ascending limb is also influenced variations in the plasma magnesium and/or calcium concentrations in a man permits Mg^{2+} reabsorption to vary appropriately with intake. This regulatory process is mediated in part by a calcium (and magnesium) sensing receptor in the basolateral membrane of thick ascending limb cells.[104] Binding of calcium or magnesium to the extracellular domain of the receptor initiates a series of intracellular signals, which result in the inhibition of apical (luminal) potas channels.[104,131] The latter effect will inhibit sodium chloride reabsorption, th increasing Mg^{2+} excretion by preventing the generation of passive gradients f Mg^{2+} reabsorption. This process is reversed by hypomagnesemia, resulting marked increase in loop reabsorption and a reduction in urinary excretion.

In addition to paracellular transport in the thick ascending limb, Mg^{2+} also involves an active transcellular process in the distal convoluted tubule. Thus process may be activated by changes in the plasma Mg^{2+} concentration and may occur via a Na^+/Mg^{2+} exchanger.

A number of hormones, including ADH, parathyroid hormone, glucagon, calc and β -adrenergic agonists, can stimulate Mg^{2+} reabsorption in the cortical thick ascending limb and distal convoluted tubule via the generation of cyclic AM It is not likely, however, that these responses play an important role in Mg^{2+} regulation, since the secretion of these hormones is not affected by alterat Mg^{2+} balance.

Uric Acid

Uric acid is formed from metabolism of purine nucleotides, of which about 5 the reaction

$$\text{Uric acid} \leftrightarrow \text{Urate}^- + \text{H}^+$$

is shifted far to the right at the normal arterial pH of 7.40. As a result, mos circulates as the urate anion. Filtered urate is handled entirely in the proxi where three separate processes are involved:

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1. Reabsorption of most of the filtered urate in the early proximal tubule
2. Tubular secretion by the organic anion secretory pathway in the mid-pro tubule of an amount normally equal to about 50 percent of the filtered l
3. Postsecretory reabsorption of most of the secreted urate in the late pro tubule.

The net effect is the excretion of 6 to 12 percent of the amount filtered. Alt excretion according to urate homeostasis are thought to be mediated prima changes in the rate of tubular secretion.

The mechanisms by which these processes occur is incompletely understoo *anion exchangers* appear to play an important role in *urate reabsorption*. For example, may be mediated by a urate-OH^- (or urate-HCO_3^-) countertransporter in the lumina membrane that operates in parallel with a Na^+-H^+ exchanger (Fig. 3-13). The latter, which is driven by the low cell Na^+ concentration, creates a gradient in which the cell is more alkaline [and therefore has a high HCO_3^- concentration) than the lumen. This favorable gradient for OH^- exit can then drive urate reabsorption.

The subsequent exit of reabsorbed urate across the basolateral membrane occur by facilitated diffusion down a favorable electrochemical gradient. Ex with an interstitial anion, such as Cl^-, which has a much higher concentration in th

interstitium than in the cell), could also play a contributory role.[136] A urate transporter has been cloned that may play a role in urate excretion.[138]

The steps involved in urate *secretion* are less clear.[135,136] Urate may enter the cell at the basolateral membrane in exchange for a cell anion (see "Secretory Pathways" below) (Fig. 3-18). Secretion across the luminal membrane could then occur by simple diffusion or in exchange for an anion such as Cl^-, which has a high luminal concentration and therefore a favorable gradient for entry into the cell.[135]

Although these models explain how urate can be transported, it still remains uncertain why urate is reabsorbed in the early and late portions of the proximal tubule and is secreted in the midportion. The current prevailing hypothesis is that urate reabsorption or secretion within an anatomic segment is determined by the absolute number of reabsorption or secretion transporters located within the luminal membranes of these segments.[135]

Net urate reabsorption also varies directly with proximal Na^+ transport, and in the presence of volume depletion, both Na^+ and urate excretion are reduced.[139] The mechanism by which urate handling is affected in this setting is incompletely understood, although angiotensin II may play a role. This hormone, the release of which is enhanced by hypovolemia, increases proximal Na^+-H^+ antiporter activity,[53,54] a change that could promote a parallel rise in OH^--urate exchange. In addition, increased proximal water reabsorption will enhance the tubular fluid urate concentration, thereby promoting urate entry into the cell.

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Regardless of the mechanism, increased net proximal reabsorption is responsible for the elevation in the plasma urate concentration (hyperuricemia) frequently seen in patients on diuretic therapy. If, however, the diuretic-induced Na^+ and water losses are replaced, hyperuricemia does not develop, since there is no stimulus to urate retention.[140]

Proteins

Filtered proteins are almost entirely reabsorbed in the proximal tubule. Several mechanisms are involved in this process, as proteins of different sizes have different transport systems.[141,142,143]

Amino acids primarily enter the cell by cotransport with sodium and then are transported to the systemic circulation by facilitated diffusion across the basolateral membrane.[21] There are several different sodium-dependent amino acid carriers, each of which recognizes different groups of amino acids.

There are also sodium-independent transporters for neutral amino acids (such as leucine, isoleucine, and phenylalanine) and for cystine and other dibasic amino acids (ornithine, arginine, and lysine).[144,145] Mutations in the gene named SCL3A1, which encodes a protein that mediates sodium-independent transport of cystine

dibasic acids in the proximal tubule and small intestine, are responsible for cystinuria.[146,147] This disorder is characterized by diminished reabsorption o cystine and the formation of cystine stones, since cystine is poorly soluble

There are also Na^+-dependent cotransporters in the basolateral membrane tha allow some amino acids (such as glycine and glutamine) to enter the cell at membranes. The physiologic importance of this effect is incompletely under The increased entry of glutamine may play a role in acid-base balance, sin amino acid is the primary source of ammonium production in the proximal tu Chap. 11).

Larger proteins are handled differently.[141,142] Small peptides, such as angiotensin II, are hydrolyzed by brush-border peptidases, and the amino acids are ther reabsorbed. Larger compounds, such as insulin and lysozyme, enter the cel carrier-mediated endocytosis and are then transported into lysosomes, whe are metabolized to amino acids.[141,148] The efficiency of endocytosis is in part dependent upon molecular change, with proteins that are cationic (that is, that have an isoelectric point above that of the urine pH) being reabsorbed completely than those that are anionic.[141,148,149] This charge dependence may reflect more avid binding of cationic proteins to anionic phospholipids in th membrane.

In addition, albumin can be reabsorbed by a second, low-affinity, high-capa endocytic process, when it is filtered in greater than normal amounts.[150] This most commonly occurs in the nephrotic syndrome, in which enhanced reabsorptio subsequent catabolism of filtered albumin may contribute to the associated hypoalbuminemia.

The net effect of proximal reabsorption and catabolism of proteins is twofol preservation of nitrogen balance by minimizing urinary loss[1] and participation in hormonal homeostasis, since the kidney is a major site of metabolism for po hormones such as insulin, gastrin, and glucagon.[2,141]

Citrate

In normal subjects, 65 to 90 percent of the filtered citrate is reabsorbed by mostly metabolized in, the proximal tubule.[151] As with the uptake of most of the solutes, the entry of filtered citrate into the proximal tubular cells is depen the favorable electrochemical gradient for Na^+ and is mediated by a $3Na^+$-citrate^{2-}-cotransporter in the luminal membrane, also called the dicarboxylate cotransporter.[151,152] and[153]

An important determinant of net citrate reabsorption is the state of acid-bas balance.[151,154] Acidemia is associated with increased proximal citrate reabso This change may be appropriate from the viewpoint of acid-base balance. T metabolism of each milliequivalent of citrate generates 3 meq of bicarbonat increasing citrate reabsorption with acidemia is beneficial in that it prevent

of alkali in the urine, a change that would further lower the extracellular pH

The relationship between acid-base balance and citrate handling is in part fall in luminal pH, which promotes the conversion of citrate(3-), the major c form, into citrate(2-), which appears to be more easily reabsorbed.[154] The associated intracellular acidosis also enhances citrate entry into the mitoch (via an unknown mechanism); the ensuing reduction in the cytosolic citrate concentration creates a more favorable gradient for citrate reabsorption fro tubular lumen.[151] These changes are reversed by alkalemia, which diminishes citrate reabsorption and therefore increases urinary citrate excretion.

In addition to metabolic acidosis, hypokalemia is another condition in which citrate reabsorption is enhanced.[155] A somewhat similar mechanism may be involved, since the loss of K^+ leads to a transcellular cation exchange in which H^+ leaves the cells to replete the extracellular stores and, to maintain electror H^+ and Na^+ enter the cells. The ensuing intracellular acidosis may be respon for the increased citrate reabsorption.

Citrate handling becomes clinically important in some patients who form cal stones. Citrate is a potent inhibitor of calcium oxalate and calcium phospha precipitation by combining with free Ca^{2+} to form a nondissociable but soluble complex. Hypocitraturia is a risk factor for stone disease[108,156,157] and can be corrected by the administration of alkali. Potassium citrate has most often in this setting because it has two advantages.[157,158] First, citrate (which is rapidly metabolized to bicarbonate) is generally better tolerated than bicarbonate, cause gastrointestinal symptoms due to local gas formation. Second, the po salt is preferred because sodium citrate will produce volume expansion, wh described above, will increase Ca^{2+} and Na^+ secondarily

Ca^{2+} excretion.[158] The latter effect could negate any stone-preventing benefi derived from the rise in citrate excretion.

SECRETORY PATHWAYS

In addition to their reabsorptive functions, the proximal tubular cells secret hydrogen ions (see Chap. 11) and organic cations and anions.[159,160] and[161] The last two processes occur primarily in segment S2 (see Fig. 3-1), which has the highest number of secretory pumps.[2,162] In general, tubular secretion occurs in three steps: movement of the organic solute from the peritubular capillary i interstitium by diffusion; transport of the solute into the cell across the bas membrane; and secretion from the cell into the lumen across the luminal membrane.[161]

Organic Cation Secretion

The mechanism by which these processes may occur can be illustrated from with organic cations, examples of which include creatinine and drugs such

cimetidine, trimethoprim, and quinidine (Fig. 3-14).[163,164] It is likely that passive forces play a primary role in cell entry across the basolateral membrane, si cation concentration in the extracellular fluid is higher than that in the cell is a cell interior negative potential. This process appears to occur by facili diffusion via cation-cation countertransport proteins, with substantial intrac sequestration of organic cations.[161,165]

A large number of specific transporters expressed on the basolateral membr been isolated and cloned. These include a polyspecific cation transporter, OCT1.[166] This transporter is sodium-independent and can transport a wide v of cations, including choline, dopamine, and acetylcholine.

For most organic cations, subsequent secretion across the luminal membrar appears to occur in parallel with the Na^+-H^+ antiporter.[163] The latter leads to a rise in the tubular fluid hydrogen concentration that allows secretion of the orga to be linked to the favorable inward H^+ gradient by different *H^+-cation exchangers* (Fig. 3-14).[164,167,168] Notice that the energy for each of these steps is again provided indirectly by the Na^+-K^+ ATPase pump. The low cell Na^+ concentration drive the Na^+-H^+ antiporter, and the high cell K^+ concentration results in passive K^+ diffusion out of the cell and the generation of cell negativity.

P-glycoprotein, a plasma membrane constituent that mediates outward activ transport of toxic and nontoxic substances, also may play a role in proximal cation secretion. It is localized to the luminal membrane of the proximal tub increased expression leads to enhanced cation secretion.[169]

The organic cations tend to compete for common secretory mechanisms.[167,168] As a result, the presence of cimetidine, for example, can diminish the secretio creatinine, reversibly raising the plasma creatinine concentration without a

decline in the glomerular filtration rate.[170] This effect may also be useful clinically by making the creatinine clearance a more accurate estimate of the glomeru filtration rate.[171,172]

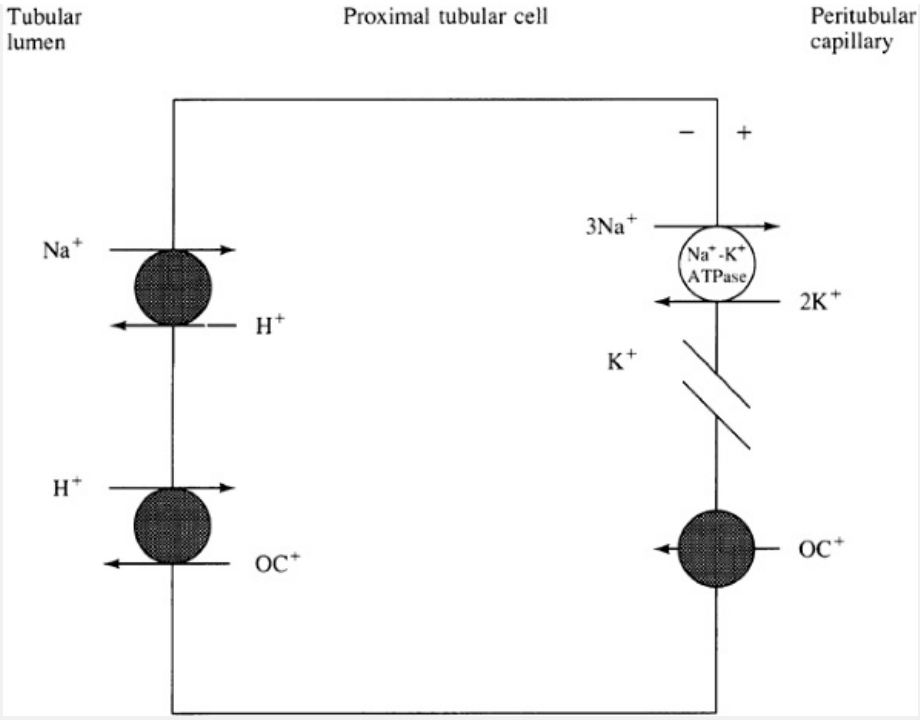

Figure 3-14 Model for organic cation (OC^+) secretion in the proximal tubule. Entry into the cell occurs in part by passive carrier-mediated diffusion ac basolateral membrane down favorable concentration and electrical gradie Secretion into the lumen occurs by OC^+-H^+ exchanger that is driven by the H^+ gradient created by the Na^+-H^+ antiporter.

Organic Anion Secretion

Organic anions, both endogenous (urate, hippurate, ketoacid anions) and e (penicillins, cephalosporins, salicylates, diuretics, radiocontrast media) co different secretory pathways. The mechanism by which this occurs is not w understood, but, as described above for urate, anion exchangers at the bas membrane and perhaps the luminal membrane appear to play an essential r (Fig. 3-13*b*).[160,161,163,173]

Citric acid cycle intermediates (particularly α-ketoglutarate) appear to be i the basolateral membrane. These compounds can enter the cell by cotransp sodium across the basolateral membrane and also are produced within the intracellular accumulation creates a favorable outward gradient that can th used to drive the uptake of organic anions via an intermediate-organic anio exchanger.[160,163] The number and distribution of negative charges seems to major determinant of the degree of binding to the anion exchanger.[173]

P. 10

A large number of organic anion transporters in the basolateral membrane h characterized and/or cloned. As an example, the organic anion transporter specificity for organic anions, including para-aminohippurate and α-ketoglu[174] Additional basolateral transporters include the multidrug resistance transpo

associated protein. Secretion of the organic anion into the lumen may then facilitated diffusion, since the cell interior negative potential creates a fav electrical gradient.[163]

Competition for these pathways can be important clinically. As an example, subjects frequently develop hyperuricemia. It is thought that this is second ketonemia of fasting, which could diminish urate secretion. Organic anion s can also be inhibited by the drug probenecid.[173] This property is useful in selected patients, as probenecid has been given in conjunction with penicillin therap reducing penicillin secretion (and excretion), higher blood levels of the ant be achieved.

The fact that these pathways are relatively nonspecific and are able to sec foreign substances make them well adapted for a *major role in the elimination of drugs and chemicals from the body*. This is particularly important for those agent that are highly albumin-bound and therefore cannot be excreted by glomeru filtration. Albumin binding promotes proximal secretion in two ways. First, b appears to be required for secretion, which does not occur with free organi anions.[175] Second, binding facilitates the urinary excretion of these compou maximizing the *rate of delivery to the secretory sites in the kidney*. Albumin and other large proteins cannot easily cross the peripheral capillary membranes result, protein-bound compounds are largely restricted to the vascular spac limited access to the interstitium or the cells.[176]

Other transport processes may be involved in the renal handling of organic In particular, these substances can undergo passive reabsorption or secret depending upon the urine pH. Salicylic acid, for example, exists both as the acid and the organic anion:

$$\text{Salicylic acid} \leftrightarrow H^+ + \text{salicylate}^-$$

The intact acid, but not the organic anion, can freely diffuse across cell me because it is nonpolar. This difference makes salicylate excretion *pH dependent*. Raising the urine pH (which lowers the H^+ concentration) will shift the above reaction to the right. The ensuing fall in the urinary salicylic acid concentr minimize the back-diffusion of secreted salicylic acid out of the tubular lum thereby increasing total drug excretion.[177] Thus, elevating the urine pH is an important component of the treatment of salicylate intoxication.

PROBLEMS

3-1 If there is no change in the extracellular volume, what effect will a increase in the GFR have on the following?

a. **Fractional Na^+ reabsorption**

b. **Absolute Na^+ reabsorption**

3-2 Parathyroid hormone acts in part by decreasing the activity of the Na^+-H^+

antiporter in the proximal tubule. What effect should this have on the reabsorption of the following?

a. **Bicarbonate**
b. **Chloride**
c. **Water**

3-3 A subject with a previous BUN of 10 mg/dL and plasma creatinine concentration of 1.0 mg/dL reports 3 days of diarrhea and poor appetit physical examination, the patient appears to be volume-depleted. Bloc at this time reveal a BUN of 40 mg/dL, creatinine concentration of 1.0 and plasma urate concentration of 10.1 mg/dL (normal is 4 to 8 mg/dL) Ketones (such as β-hydroxybutyrate) are noted in the urine and are be to reflect the ketosis associated with fasting.

a. **Why has the BUN increased?**
b. **Has there been a substantial change in the GFR?**
c. **What factors are responsible for the hyperuricemia?**

3-4 Patients with the distal form of renal tubular acidosis have a low p HCO_3^- concentration and a relatively high urine pH (see Chapter 21). What effect should this have on the following?

a. **Proximal NaCl reabsorption**
b. **Proximal citrate reabsorption**
c. **The likelihood of calcium phosphate stone formation**

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Footnotes

* The activity of the Na^+-K^+-ATP ase pump and the K^+ channel appropriately vary in parallel. A reduction in pump activity, due for example to decreased Na^+ reabsorption, results in ATP accumulation in the cell, which then downregul ATP-sensitive K^+ channels.[18] Less K^+ exit through these channels is required in setting, since there is less entry via the Na^+-K^+-ATPase pump.

† Passive fluid reabsorption appears to occur only in the outer cortical and midcortical nephrons. In contrast, active Na^+ transport appears to account for almo all NaCl reabsorption in the juxtamedullary proximal tubules, which are not preferentially permeable to chloride.[1248]

‡ Angiotensin II and norepinephrine also promote proximal transport by thei vasoconstrictive effects, which, by increasing the filtration fraction, increas of the reabsorbate by the peritubular capillary (see below).

¶ Since the $T_{mHCO_3^-}$ is measured in meq reabsorbed per minute, the maximum reabsorption of 28 meq/L of glomerular filtrate must be corrected for the GF GFR were 125 mL/min (or 0.125 L/min), then the $T_{mHCO_3^-}$ would be 3.5 meq/min (28 meq/L× 0.125 L/min).

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Chapter Four

Loop of Henle and the countercurrent mechanism

The 40 to 45 percent of the filtrate that is not reabsorbed in the proximal tu enters the loop of Henle, which has a characteristic hairpin configuration ir medulla. The loop of Henle consists of four different segments: the *descending thin limb*; the *thin ascending limb*; the *medullary thick ascending limb*; and the *cortical thick ascending limb*, which ends at the macula densa adjacent to the parent glom (Fig. 4-1). These segments perform two major functions: (1) They reabsorb approximately 25 to 35 percent of the filtered NaCl, primarily in the thick as limb, and (2) they reabsorb NaCl *in excess of water*, an effect that is essential for th excretion of urine with an osmolality different from that of the plasma. As w seen, this latter characteristic of loop function is dependent upon the varyi transport and permeability properties of the different loop segments.

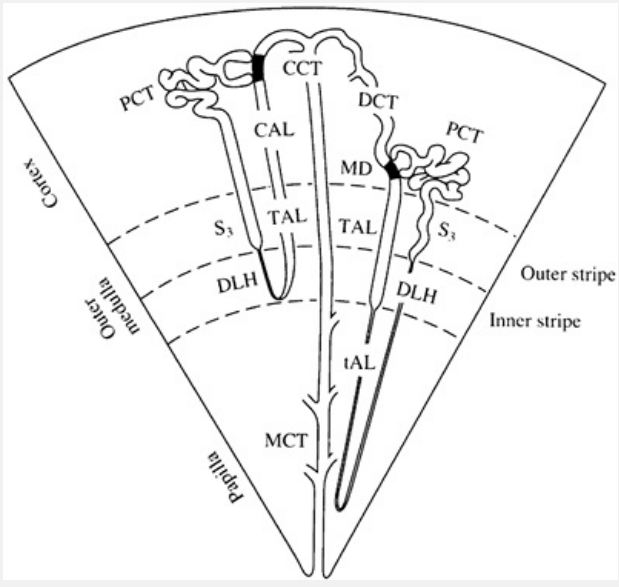

Figure 4-1 Representation of the anatomic relationships of the outer cortic juxtamedullary nephrons. PCT=proximal convoluted tubule; S_1 and S_2 (S segments); S_3=last segment of the proximal tubule, which ends at the junctio the outer and inner stripes in the outer medulla; DLH=descending limb of loop of Henle; tAL=thin ascending limb; TAL=medullary thick ascending lir

CAL=cortical thick ascending limb, which ends in the macula densa (MD, depicted as the shaded area adjacent to the glomerulus); DCT=distal con tubule; CCT = cortical collecting tubule; and MCT = medullary collecting Note that the outer cortical nephrons have no thin ascending limb, a shor that turns around in the outer medulla, and a relatively long cortical aspe thick ascending limb. The latter segment is very short in juxtamedullary nephrons, which have glomeruli that are near the corticomedullary junctio (*From Hogg RJ, Kokko JP, Rev Physiol Biochem Pharmacol 86:85, 1979. Used with permission.*)

CELL MODEL FOR SODIUM CHLORIDE TRANSPORT

Active NaCl transport in the thick ascending limb is driven by the basolater K^+-ATPase pump. The activity of this transporter is higher in the thick asce limb than in other nephron segments, indicating the importance of active Na reabsorption at the site[1,2] and[3]. The Na^+-K^+-ATPase pump has two major effects on Na^+ handling: It actively transports reabsorbed Na^+ out of the cell and back into the systemic circulation via the peritubular capillaries, and it maintains a lo Na^+ concentration that allows luminal Na^+ to continue to enter the cell down a concentration gradient[1].

Mechanism of NaCl Entry

Sodium chloride entry into the medullary and cortical aspects of the thick a limb (including the macula densa) primarily occurs via an electroneutral Na^+-K^+-$2Cl^-$ carrier in the luminal membrane (Fig. 4-2)[4,5,6,7,8] and[9]. Net transport into

the cell is seen only when all four sites on the carrier are occupied. Confir the 1 : 1 : 2 stoichiometry for this transporter in the thick ascending limb h from the following observations:

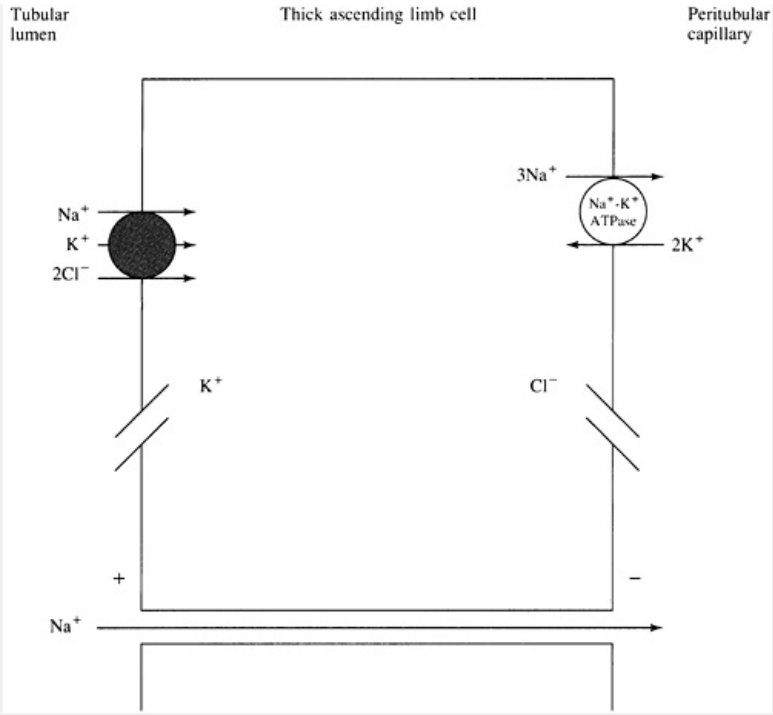

Figure 4-2 Schematic model of the major steps involved in NaCl transport i medullary thick ascending limb of the loop of Henle. Entry into the cell oc a passive Na^+-K^+-$2Cl^-$ carrier in the luminal membrane. The energy for this process is indirectly provided by the Na^+-K^+-ATPase pump in the basolateral membrane that maintains a relatively low cell Na^+ concentration. The return of reabsorbed Na^+ and Cl^- to the systemic circulation occurs via the Na^+-K^+ ATPase pump and a Cl^- channel, respectively. Recycling across the luminal membrane creates a lumen-positive potential that allows one-half Na^+ reabsorption, as well as Ca^{2+} and Mg^{2+} reabsorption, to occur passively via the paracellular route.

1. Na^+ is required, since removal of Na^+ from the lumen abolishes the reabsorption of Cl^-.
2. Cl^- is required, since removal of Cl^- abolishes the reabsorption of Na^+.
3. K^+ is required, since removal of K^+ prevents the reabsorption of both Na^+ and Cl^-.
4. The process is electroneutral, since changing the transepithelial electri potential is without effect on NaCl reabsorption.

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A number of Na^+-K^+-$2Cl^-$ cotransporters have been cloned and characterized. T cotransporter termed NKCC2 is principally responsible for Na^+-K^+-$2Cl^-$ transport in

the apical membrane of the thick ascending limb.[10] Mutations in this transporter cause classic Bartter's syndrome;[11] this disorder has clinical features (hypokalem metabolic alkalosis, and hypercalciuria) similar to those seen in patients gi diuretic, which inhibits the Na^+-K^+-$2Cl^-$ cotransporter of the thick ascending limb.

Sodium that enters the cells via the Na^+-K^+-$2Cl^-$ cotransport is returned to the system circulation by the active Na^+-K^+ ATPase pump in the basolateral membrane; chloride, on the other hand, exits through selective Cl^- channels (Fig. 4-2).[12] Mutations in the gene for these channels result in the same manifestations Bartter's syndrome.[13] In comparison, solute transport in the descending and th ascending limbs is passive, occurring down favorable concentration and os gradients (see below).

Loop transport is very different from that in the proximal tubule. Filtered gl amino acids, and phosphate are almost entirely removed in the proximal tub coupled transport with Na^+ (see Fig. 3-4). Thus, loop Na^+ reabsorption is not linked to organic solutes and must occur by coupled transport with H^+ or by Na^+-H^+ exchange, leading to HCO_3^- reabsorption.

Several important characteristics of the loop NaCl reabsorption deserve em

1. The affinity of the carrier for Na^+ and K^+ is very high, reaching near maximum activity at concentrations under 5 to 10 mEq/L (Fig. 4-3).[8] In comparison, it is Cl^- *delivery that is rate-limiting*, and net NaCl transport increases directly with tl tubular fluid Cl^- concentration. The loop diuretics, such as furosemide, ap inhibit loop NaCl reabsorption by competing for either the Cl^- or the K^+ on the carrier (see Chap. 15).

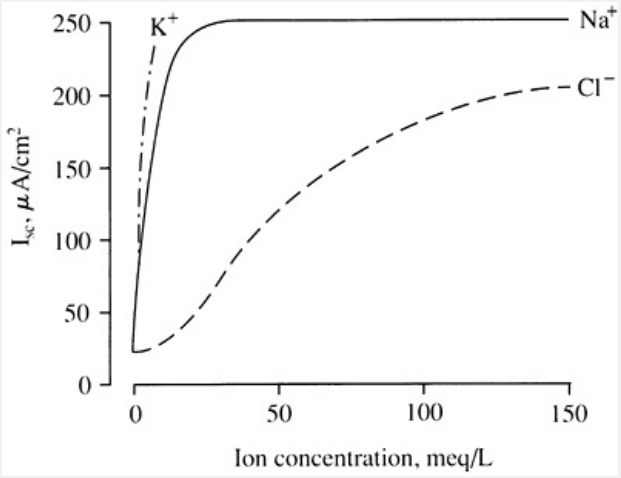

Figure 4-3 The dependence of the equivalent short circuit current (I_{sc}, a measure of active NaCl transport) on the luminal concentrations of K^+, Na^+, and Cl^- in the cortical thick ascending limb of the loop of Henle in the r

The carrier has a very high affinity for Na^+, reaching near maximum activity at concentrations under 10 meq/L; as a result, the luminal Cl^- concentration is normally the rate-limiting step in NaCl entry into the similar process occurs in the medullary thick ascending limb. (*From Greger R, Velazquez H: Kidney Int 31:590, 1987. Reprinted by permission from* Kidney International.)

2. It might appear that K^+ would also be limiting, since its concentration is so much lower than that of NaCl. This problem is overcome, however, by *recycling* of K^+ across the luminal membrane via specific K^+ channels.[6,15,16] Thus, reabsorbed K^+ is returned to the lumen for continued activation of th Na^+-K^+-$2Cl^-$ carrier. The activity of these K^+ channels is inhibited by adenosine triphosphate (ATP), which allows it to be appropriately linked to the lev reabsorption. As more Na^+ enters the cell, for example, transport of this Na^+ of the cell by the Na^+–K^+–ATPase pump lowers cell ATP levels. The latter change increases the activity of the luminal membrane K^+ channels, permitting the return of reabsorbed K^+ into the lumen and further reabsorption. Mutations in this channel cause another variant of Bartter's syndrome,[16] illustrating the requirement for the integrated function of multiple chann normal loop transport.

3. The backleak of cations (via K^+) across the luminal membrane (via Cl^- channel) into the peritubular capillary generates a net positive curre capillary to lumen, thereby creating a lumen-positive potential difference (Fig. 4-2). This potential is important because it can drive the *paracellular reabsorption* of cations, such as Na^+, Ca^{2+}, and Mg^{2+}.[6,17,18]

Role in Acid-Base Balance

In addition to the reabsorption of NaCl, the medullary thick limb also contri the regulation of acid-base balance. It reabsorbs most of the HCO_3^- delivered out of the proximal tubule.[19] This process is primarily mediated by a Na^+–H^+ exchanger in the luminal membrane (see Fig. 20-1).[19,20,21] Loop HCO_3^- reabsorption is appropriately stimulated by acidemia[20,21] and inhibited by alkalemia, thereby promoting the desired changes in HCO_3^- excretion.

The medullary thick limb also reabsorbs luminal NH_4^+, which substitutes for K^+ in the Na^+-K^+–$2Cl^-$ cotransporter.[22,23] and[24] The net effect is recycling of ammonia within the medulla, thereby maximizing urinary excretion in the presence of an acid load.[20] The physiologic significance of ammonia recycling is reviewed o

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Role in Urine Calcium Excretion

Although calcium is passively reabsorbed in the thick ascending limb, follov lumen-positive gradient created by sodium reabsorption, the loop of Henle participate in the regulation of calcium excretion with changes in calcium ir Cacium-sensing receptors expressed on the basolateral membrane on the c the thick ascending limb appear to mediate this process.[25,26]

When calcium intake is increased, some of the excess calcium is absorbed, the systemic circulation, and slightly raises the plasma calcium concentrati Binding of calcium to the calcium-sensing receptor leads to the generation arachidonic acid metabolite (which may be 20-HETE) inhibits the potassium

channel in the luminal membrane.[27] Inhibition of potassium recycling via the potassium channel reduces sodium chloride reabsorption via the Na^+-K^+-$2Cl^-$ cotransporter, thereby diminishing the generation of the lumen-positive ele gradient and the subsequent passive reabsorption of calcium.

Passive Na^+ Reabsorption and Medullary Hypoxia

Almost one-half of oxygen utilization by the thick ascending limb is involvec NaCl transport.[28] It is important to note in this regard that the Na^+-K^+-$2Cl^-$ stoichiometry of the luminal Na^+-K^+-$2Cl^-$ carrier *reduces the energy requirement for net Na^+ transport by 50 percent*. For every two Cl^- ions that are reabsorbed, one Na^+ ion is actively transported out of the cell by the Na^+-K^+-ATPase pump and one Na^+ ion is passively reabsorbed between the cells down the lumen-positive gradient (Fig. 4-2).[26]

This increase in efficiency is physiologically important because the renal m relatively poorly oxygenated. The medulla usually receives less than 10 pe the renal blood flow. Furthermore, the hairpin configuration of the vasa rec capillaries results in the exchange of oxygen between the oxygen-rich bloo the cortex and entering the descending capillary limb and the oxygen-poor draining the inner medulla in the ascending capillary limb (Fig. 4-4). The net effect is that the P_{O_2} bathing the thick limb cells in the outer medulla is as low as 10 mmHg.[29] Thus, the ability of the Na^+-K^+-$2Cl^-$ carrier to lower the energy requirement for Na^+ reabsorption may help to preserve the functional integrity tubular cells. A similar adaptation is present in the *thin* ascending limb, where Na^+ reabsorption appears to be entirely passive, occurring down a concentratio between the tubular fluid and the medullary interstitium (see "NaCl Reabsorption in the Thin Ascending Limb" below).

Clinical Implications

Hypoperfusion-induced acute tubular necrosis is one of the most common c

acute renal failure developing in the hospital. This finding is somewhat sur since the kidney is more highly perfused than most other organs yet cellula usually limited to the kidney.

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Experimental evidence suggests that this apparent paradox can be explaine by preferential injury to the thick ascending limb and the S3 segments of the proximal tubule, which ends in the outer medulla (Fig. 4-4). These cells normally function in a borderline ischemic environment and are therefore particularly susceptible when renal perfusion is impaired.[29]

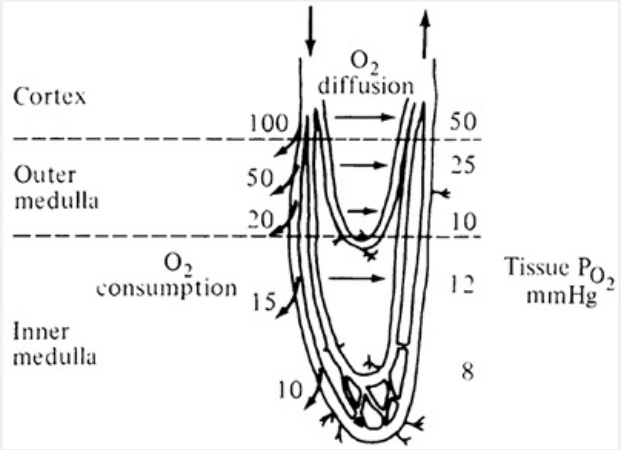

Figure 4-4 Development of medullary hypoxia due to the exchange of oxyge between the descending and ascending limbs of the vasa recta capillaries (straight arrows) and to oxygen consumption by the medullary cells (curve arrows). *(From Brezis M, Rosen S, Silva P, Epstein FH: Kidney Int 26:375, 1984. Reprinted by permission from* Kidney International.)

It is of potential interest in this regard that, in response to renal ischemia, ascending limb cells produce nonprostaglandin, cytochrome P450 arachidor metabolites that diminish NaCl transport;[30,31] this response is mediated at least in part by reduced activity of the luminal Na^+–K^+–2Cl transporter.[31] The inhibitory effect of ischemia could represent an appropriate or *protective* response, since reducing cellular transport and therefore energy requirement may preserve viability when there is inadequate energy delivery.[29,30] Adenosine, a breakdown product of ATP, also may contribute to this local adaptation. The release of adenosine from the thick limb is increased when renal perfusion is reduced the arachidonic acid metabolites, adenosine also reduces active NaCl reabsorption.[32]

Concentration and Flow Dependence of Loop Reabsorption

The loop of Henle, like the proximal tubule, tends to reabsorb a relatively c fraction of the load delivered to it (this is the phenomenon of glomerulotubu

balance; see page 85).[33] In the proximal tubule, total reabsorption is ultimately limited by the availability of luminal solutes (such as bicarbonate, glucose, amino acids) to be cotransported with Na^+ and by the balance of hemodynamic forces in the peritubular capillary that promotes or retards fluid uptake.

In comparison, *solute concentration* is the limiting factor in the thick ascending limb.[8,33,34] The ascending limb is essentially impermeable to water. As a res NaCl reabsorption leads to a reduction in the luminal concentration of thes this setting, two factors combine to restrict the level of net reabsorption:

1. The fall in the tubular fluid Cl^- concentration progressively decreases the activity of the Na^+–K^+–$2Cl^-$ carrier, thereby diminishing NaCl entry into the c (Fig. 4-3).
2. The reduction in NaCl concentration below that in the plasma promotes backleak of NaCl into the lumen across the tight junction.

Eventually, the reduced reabsorptive flux will be balanced by a backflux of magnitude. This steady state appears to occur at a luminal Cl^- concentration of 50 to 75 meq/L in the cortical aspect of the thick ascending limb.[8,34]

The limiting concentration gradient can explain the flow dependence of loop reabsorption. Suppose, for example, that more fluid is delivered to the asce limb because of an increase in glomerular filtration rate. If NaCl reabsorpti remains constant in the early part of the medullary thick ascending limb, th less of a reduction in the tubular fluid Cl^- concentration. Thus, the fluid in the

more distal parts of the ascending limb will have a *higher* Cl^- concentration, which will promote increased entry into the cell.[33]

Flow dependence also influences the *distribution* of NaCl reabsorption between the medullary and cortical aspects of the thick limb. As will be described below antidiuretic hormone (ADH) stimulates NaCl reabsorption in the medullary t by increasing entry via the Na^+–K^+–$2Cl^-$ carrier; this effect is mediated at least in part by enhanced generation of cyclic AMP.[6] This increase in reabsorption will reduce the Cl^- concentration, thereby limiting reabsorption in the cortical thic which can reabsorb only until the limiting gradient of 50 to 75 meq/L is reac The net effect is that NaCl reabsorption is increased in the medullary porti in the thick limb as a whole; this response permits increased efficiency of t countercurrent system and subsequent urinary concentration without affecti loop NaCl transport.[6]

Other peptide hormones also act to increase cyclic AMP generation and Na transport in the thick ascending limb.[35] These include glucagon in the medullary segment and glucagon, calcitonin, parathyroid hormone, and β -adrenergic in the cortical segment. The function of these responses is not clear. They

likely to be important regulators of NaCl balance, but parathyroid hormone perhaps calcitonin do contribute to the local regulation of Ca^{2+} and Mg^{2+} reabsorption, particularly in the cortical thick ascending limb.[35] (see Chap. 3).

Transport in Cortical Thick Ascending Limb

The cortical aspect of the thick ascending limb makes a variable contributio nephronal NaCl reabsorption. The juxtamedullary nephrons have long medu loops (which are essential for concentrating ability; see below) but short co segments. In comparison, the cortical aspect is more prominent in the outer nephrons, which are relatively far from the corticomedullary junction (Fig. 4-1).

The Na^+-K^+–2Cl^- carrier appears to mediate most of NaCl reabsorption in the cortex, as it does in the medullary thick limb.[8,36] In addition, the cortical thick ascending limb also plays a major role in Ca^{2+} and Mg^{2+} reabsorption. This segment is the site at which more than 50 percent of the filtered Mg^{2+} is reabsorbed, a level that changes appropriately with alterations in Mg^{2+} status in states of magnesium depletion due primarily to increased reabsorption in the thick as limb and distal convoluted tubule. Some of the Mg^{2+} transport is passive, occurring between the cells down the lumen positive gradient created by the Na^+-K^+-2Cl^- carrier (see Fig. 4-2) and being regulated in part by the calcium-sensing recep described above for calcium.[25] In addition, specific changes in Mg^{2+} handling are mediated by an active transcellular process in the distal convoluted tubule be activated by changes in the plasma Mg^{2+} concentration.[17,37]

The cortical thick ascending limb is also one of the sites (with the distal tu connecting segment) at which Ca^{2+} reabsorption is actively regulated according t the physiologic needs (see Chap. 3). Parathyroid hormone plays an important

role in this process, increasing Ca^{2+} reabsorption by activating a hormone-specifi adenylate cyclase.[38]

COUNTERCURRENT MECHANISM

Fluid leaving the proximal tubule is isosmotic to plasma. However, the excr isosmotic urine is usually not adequate to meet the homeostatic requiremen body. After a water load, for example, water must be excreted in excess of s This requires the excretion of urine that is hypoosmotic to plasma. Convers must be retained and a hyperosmotic urine excreted after a period of water restriction. The formation of a dilute (hypoosmotic to plasma) or concentrat (hyperosmotic to plasma) urine is achieved via the *countercurrent mechanism*, which includes the loop of Henle, the cortical and medullary collecting tubules, ar blood supply to these segments.

Before discussing these processes in detail, it is useful to summarize their aspects. The excretion of *concentrated* urine involves two major steps:

1. The medullary interstitium is made hyperosmotic by the reabsorption of without water in the medullary ascending limb of the loop of Henle. Ure into the interstitium from the medullary collecting tubule also contribute process.
2. As the urine enters the medullary collecting tubule, it equilibrates osmo with the interstitium, resulting in the formation of a concentrated urine. released from the posterior pituitary, plays an essential role in this pro increasing collecting tubule permeability to water, which is very low in t state. ADH appears to act by inserting aquaporin-2 *water channels* into the luminal membrane, thereby allowing transcellular water reabsorption to down an osmotic gradient (see Chap. 6).

In addition, two modifying factors are important for the *maintenance* of medullary hyperosmolality:

1. Water equilibrating in the medullary collecting tubule dilutes the interst change that would decrease maximum concentrating ability. To minimize effect, the volume of urine presented to this segment is markedly reduc cortex by ADH-sensitive water reabsorption in the cortical collecting tub
2. Medullary blood flow in the vasa recta is arranged in a hairpin configur minimize removal of the excess interstitial solute.

Urinary *dilution* also has two basic steps, the first of which is the same as in concentration:

1. NaCl reabsorption without water in the ascending limb of the loop of He decreases the osmolality of the tubular fluid at the same time as it incre osmolality of the interstitium.
2. The urine remains dilute if water reabsorption in the collecting tubules minimized by keeping these segments poorly permeable to water. This r the relative absence of ADH.

Countercurrent Multiplication: Loops of Henle

In humans, the maximum urine osmolality that can be attained is 900 to 140 mosmol/kg; the normal plasma osmolality is much lower, at about 285 mosm Since the urine becomes concentrated by equilibrating with the medullary interstitium, this means that a similar high osmolality must be achieved in t interstitium. The process by which the interstitial osmolality in the medulla increased from 285 mosmol/kg (isosmotic to plasma) to 900 to 1400 mosmol *called countercurrent multiplication*. (*Countercurrent* refers to the opposite directions of flow in the descending and ascending limbs that result from th configuration of the loop.)

The exact mechanism of countercurrent multiplication is incompletely understood.[39,40] and[41] The following discussion has been simplified by

emphasizing the generation of an interstitial osmotic gradient from the corticomedullary junction to the inner medulla. At any level, however, there likely to be variations in the interstitial osmolality with increasing distance vasa recta capillary bundles.[41]

One essential factor in countercurrent multiplication is the different permea transport characteristics of the descending and ascending limbs of the loop The descending limb is permeable to water and to a lesser degree NaCl and whereas both the thin and thick segments of the ascending limb are *impermeable to water*, but are able to transport NaCl into the interstitium (Table 4-1). These differences in water permeability are related to the presence (thin descend or absence (ascending limb) of water channels in the luminal membrane.[42,43] The water channels in the thin descending limb are called aquaporin-1,[43,44] which are similar to those in the luminal membrane of the proximal tubule but differen ADH-sensitive water channels (called aquaporin-2) in the collecting tubules Chap. 6).[45]

As will be seen, the *only active step* in countercurrent multiplication is NaCl reabsorption in the thick ascending limb, the mechanism for which is depict Fig. 4-2. In contrast, only passive solute transport appears to occur in the desce and *thin* ascending limbs.[39,41] The mechanism by which the thin ascending limb might reabsorb NaCl will be reviewed below; for the sake of simplicity, the discussion on the generation of the interstitial osmotic gradient will assume thin and thick ascending limbs function in a homogeneous manner.

The efficiency of countercurrent multiplication varies directly with the *length* of the thick ascending limb. Thus, this process primarily occurs in the 30 to 40

percent of nephrons that have long loops of Henle that descend into the inn medulla (Fig. 4-1). The glomeruli of these nephrons are located in the juxtame area and the midcortex. In contrast, there is little direct contribution from t cortical nephrons, which have short loops that turn around in the outer mec even the inner cortex (Fig. 4-1).

Table 4-1 Passive permeability of the loop of Henl and distal nephron segments to NaCl, urea, and water[a]

Segment	NaCl	Urea	Water	
			Basal	ADH
Descending limb	± to ++	± to +	++	++
Ascending limb				

Tshin segment	++	+	0	0
Thick segment	0	0	0	0
Distal tubule and connecting segment	0	0	0	0
Cortical collecting tubule	0	0	0	++
Medullary collecting tubule				
Outer	0	0	0	++
Inner	0	±*b*	±	++

a Data from Refs. 38 and 41. Symbols include: + +, highly permeable; + moderately permeable; ±, less permeable; 0, relatively impermeable.

b The urea permeability in the innermost part of the medullary collecting tubule is increased in the presence of ADH.

Generation of Medullary Interstitial Hyperosmolality

If one could start at a hypothetical time zero, the fluid in the descending ar ascending limbs and in the interstitium would be isosmotic to plasma, simila delivered into the descending limb from the proximal tubule (Fig. 4-5). The first and primary step in countercurrent multiplication is the transport of NaCl from t ascending limb of the loop of Henle into the interstitium; this process is lim maximum transtubular gradient that can be achieved, which in this example mosmol/kg. Since the ascending limb is impermeable to water, this results i increase in interstitial osmolality from 285 to 385 mosmol/kg. The fluid in tl descending limb then equilibrates osmotically with the interstitium, primaril movement out of the tubule. As water enters the interstitium, interstitial osr maintained by continued NaCl transport out of the ascending limb. The net the establishment of a 200-mosmol/kg gradient between the fluid in the asc limb (185 mosmol/kg) and that in the interstitium and descending limb (385 mosmol/kg).

As urine flows through the tubules, and NaCl transport in the ascending lim continues, the initial step in Fig. 4-5 is *multiplied*, resulting in the generation of a

much higher interstitial osmolality. An example of how this might occur is sh Fig. 4-6. For the sake of simplicity, steps 1 to 8 are depicted as discrete ins time, even though ion transport and urine flow occur simultaneously in the kidney. In steps 1 and 2, a gradient of 200 mosmol/kg is established betwe fluid in the ascending limb and that in the descending limb and interstitium. urine moves through the tubules, with the hyperosmotic fluid in the descend

flowing into the ascending limb. As NaCl is again pumped into the interstiti gradient of 200 mosmol/kg in step 4, the osmolality of the inner medullary i is now 485 mosmol/kg, as compared with 385 mosmol/kg in step 2.

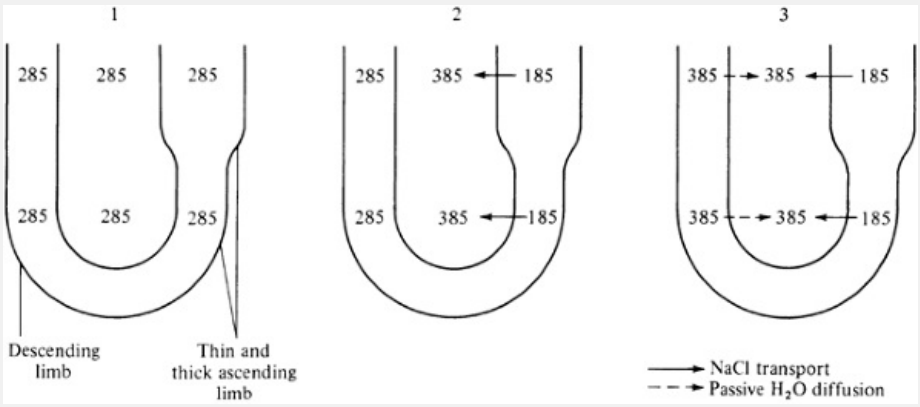

Figure 4-5 Role of active NaCl transport in initiating countercurrent multiplication. In step 1, at time zero, the fluid in the descending and asc limbs and the interstitium is isosmotic to plasma. In step 2, NaCl is transp out of the ascending limb into the interstitium to a gradient of 200 mosmo step 3, the fluid in the descending limb equilibrates osmotically with the hyperosmotic interstitium, primarily by water movement out of the tubule. of the interstitium by this water movement is prevented by continued NaC transport out of the ascending limb. The result is the creation of an osmo gradient between the ascending limb and the relatively hyperosmotic desc limb and interstitium.

These steps illustrate the basic aspects of countercurrent multiplication: N transport out of the ascending limb makes the interstitium and descending l hyperosmotic; the hyperosmotic fluid in the descending limb then flows in a countercurrent fashion into the ascending limb; the combination of a higher fluid osmolality in the inner medullary ascending limb (385 mosmol/kg in ste versus 285 mosmol/kg in step 1) and reestablishment of the 200 mosmol/kg between the ascending limb and interstitium results in a further elevation ir interstitial osmolality.

As the sequence in Fig. 4-6 goes on (steps 5 to 8), the osmolality continues to r being highest in the tubule at the hairpin turn and in the interstitium at the tip (the inner medulla). The osmolality at these sites is directly proportiona the length of the loops and to the gradient achieved between the ascending the interstitium. In humans, the maximum osmolality at the

papillary tip can reach 900 to 1400 mosmol/kg (Fig. 4-7). This is relatively inefficient in comparison with other mammals. As an example, the desert rat, which inf comes in contact with water, has relatively long loops of Henle and can atta interstitial and urine osmolalities in the range of 5000 mosmol/kg.

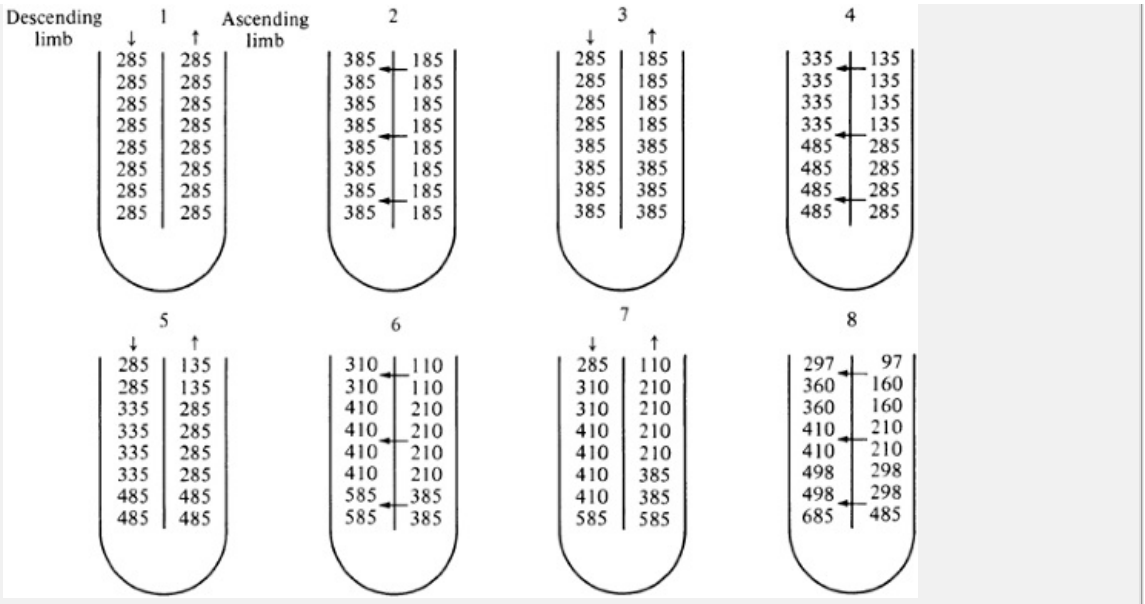

Figure 4-6 Principle of countercurrent multiplication based upon the assum that, at any level along the loop of Henle, a concentration gradient of 200 mosmol/kg can be established between ascending and descending limbs o loop of Henle by the transport of NaCl. The osmolality of the interstitium same as that in the descending limb and has been omitted from the diagra (*Adapted from Pitts, RF: Physiology of the Kidney and Body Fluids, Copyright* © *1974 by Year Book Medical Publishers, Inc, Chicago. Used by permission.*)

In addition to increased length of the loop of Henle, more efficient urinary concentration in some species is also due to stimulation of NaCl reabsorpti medullary thick ascending limb by ADH.[6,46,47] A cyclic adenosine monophosphate (AMP)–mediated rise in activity of the luminal Na^+-K^+-$2Cl^-$ carrier seems to be responsible for this effect.[46] The applicability of these findings to humans is uncertain, since studies in isolated human tubules have not demonstrated a induced increase in cyclic AMP activity in the thick ascending limb.[48]

Notice also that the osmolality of the tubular fluid leaving the ascending lir hypoosmotic to plasma (Fig. 4-7). This fluid is further diluted by NaCl reabsorpti without water in the cortical aspect of the thick ascending limb. As a result osmolality of the urine leaving the loop of Henle is approximately 100 mosm the collecting tubules are impermeable to water (ADH

absent), this dilute urine will be excreted relatively unchanged. In contrast, collecting tubules are permeable to water (ADH present), the urine will equ with the interstitium and a concentrated urine will be excreted (Fig. 4-7). Thus, the *final osmolality of the urine is mostly determined by the water permeabilit collecting tubules, not by events in the loop of Henle*

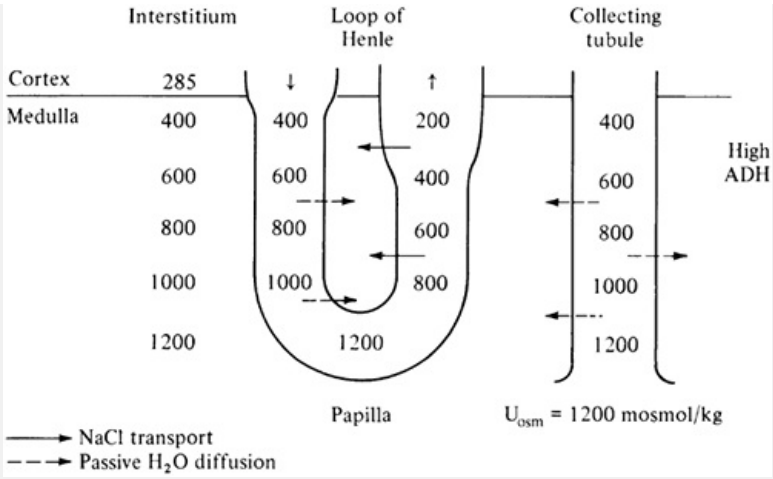

Figure 4-7 Countercurrent multiplication and the excretion of a concentrate urine. The transport of NaCl from the ascending limb results in the format an interstitial osmolal gradient from 285 mosmol/kg in the cortex to 1200 mosmol/kg at the papillary tip. In the presence of ADH, the urine becomes concentrated as it equilibrates with the interstitium in the medullary colle tubule. The contribution of urea to the concentrating process is discussed text and has been omitted from the diagram. The collecting tubule is also of active Na^+ transport, the importance of which is discussed in Chapter 5.

Collecting Tubules

As with the loops of Henle, the cortical and medullary collecting tubules po distinct permeability characteristics, being in the basal state relatively imp to the passive movement of NaCl, and, with the exception of the innermost the medullary collecting tubule, to urea and water (Table 4-1).[49,50] The impermeability to NaCl is essential, since it permits the high NaCl concentr the interstitium to act as an effective osmotic gradient between the tubular interstitium.

ADH promotes urinary concentration primarily by increasing the water perm the collecting tubules[40,49,50] via the insertion of unique water channels (called aquaporin-2) into the luminal membrane (see Chapter 6).[45,51] In the medullary collecting tubule, this allows the tubular fluid to reach osmotic equilibrium hyperosmotic interstitium.[40,52] The reabsorbed water then returns to the system circulation via the capillaries of the vasa recta.

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The *cortical* collecting tubule plays an equally important role in the concentra process. The maximum urine osmolality attained in the medulla cannot exce the interstitium at the papillary tip. As water leaves the medullary collecting decreases the interstitial osmolality by dilution, thereby reducing the maxin osmolality that can be achieved. This effect is minimized *because the volume of fluid present to the medullary collecting tubule is markedly reduced by AD induced water reabsorption in the cortical collecting tubule*.[49,52] In the presence

of ADH, the hypoosmotic fluid entering the cortical collecting tubule equilib
the cortical interstitium, which is isosmotic to plasma (Fig. 4-8).

If, for example, the osmolality of the tubular fluid entering the cortical colle
tubule is 100 mosmol/kg, then osmotic equilibration will result in the reabso
almost two-thirds of the water that has been delivered. Furthermore, additi
will be reabsorbed, down the osmotic gradient established by aldosterone-i
NaCl reabsorption in this segment (see Chap. 3). This marked reduction in tubular
fluid volume permits concentration of the urine to proceed in the medulla w
minimum dilution of the medullary interstitium. Since cortical blood flow is
10 times the maximum rate of urine flow, the water reabsorbed in the cortex
returned to the systemic circulation without dilution of the cortical interstiti

In the absence of ADH, the collecting tubules remain poorly permeable to w
result, much less water is reabsorbed and a dilute urine is excreted. Since
NaCl transport continues in these segments, the minimum urine osmolality
reduced from 100 mosmol/kg in the distal tubule to 50 to 75 mosmol/kg in th
urine.

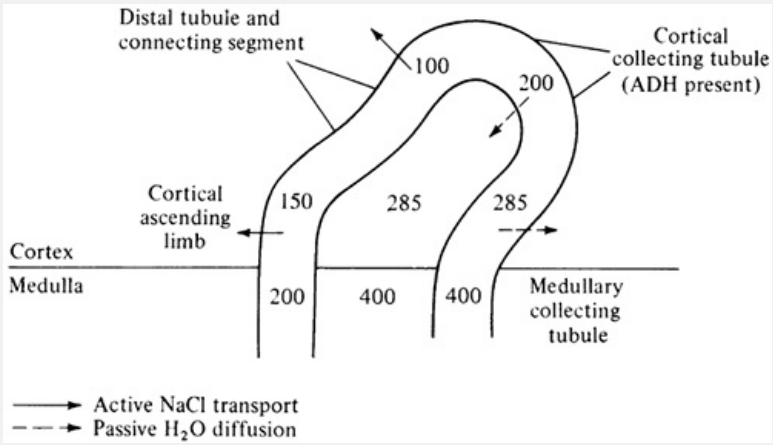

Figure 4-8 Representation of the role of the cortical collecting tubule in th
concentrating process. As a result of water reabsorption in this segment,
hypoosmotic urine formed in the ascending limb of the loop of Henle is ma
isosmotic to plasma and is much reduced in volume.

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ADH is able to play this central role in the regulation of water excretion be
release *varies directly with the plasma osmolality* (Fig. 4-9). Thus, a water load
sequentially lowers the plasma osmolality, ADH secretion, collecting tubule
permeability to water, and the urine osmolality. The net effect is excretion
excess water. These steps are reversed with water loss, as the increase in
osmolality stimulates the release of ADH, resulting in a rise in urine osmola
marked reduction in further water loss. Increased water intake due to a con
stimulation of thirst then returns water balance to normal.

Role of Urea

The discussion thus far has emphasized the importance of NaCl accumulati medullary interstitium in the concentrating process. However, almost one-ha approximately 1200 mosmol of solute per kilogram present at the papillary t antidiuresis is *urea*.[39] The high interstitial concentration of urea is produced b diffusion down a favorable concentration gradient from the inner medullary tubule into the interstitium (Fig. 4-10).[43,55]

ADH, acting in both the cortex and the medulla, plays a central role in this by increasing the water permeability of the collecting tubules. As water is r in the cortex and outer medulla, the *urea concentration in the tubular fluid rises markedly*, since these segments are essentially impermeable to urea.[49,50] In contrast, permeability to urea in the innermost part of the medullary collect is relatively high in the basal state (mediated by specific luminal membrane carriers)[56,57] and is increased further by ADH, apparently by insertion of nev transporters into the luminal membrane.[50,58,59] These effects allow urea to passively diffuse into the interstitium at this site.

The ADH-regulated urea transporter, UT1, that is responsible for urea trans the medullary collecting tubule has been identified and cloned.[57] As

expected, UT1 is principally expressed in the innermost part of the medulla collecting tubule.

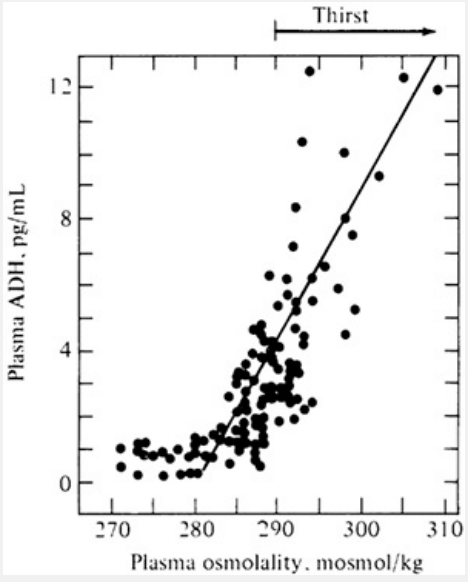

Figure 4-9 Relationship of plasma ADH concentration to plasma osmolality normal humans in whom the plasma osmolality was changed by varying the of hydration. Notice that the osmotic threshold for thirst is a few mosmol/ higher than that for ADH. *(Adapted from Robertson GL, Aycinena P, Zerbe RL,* Am J Med *72:339, 1982. Used with permission.)*

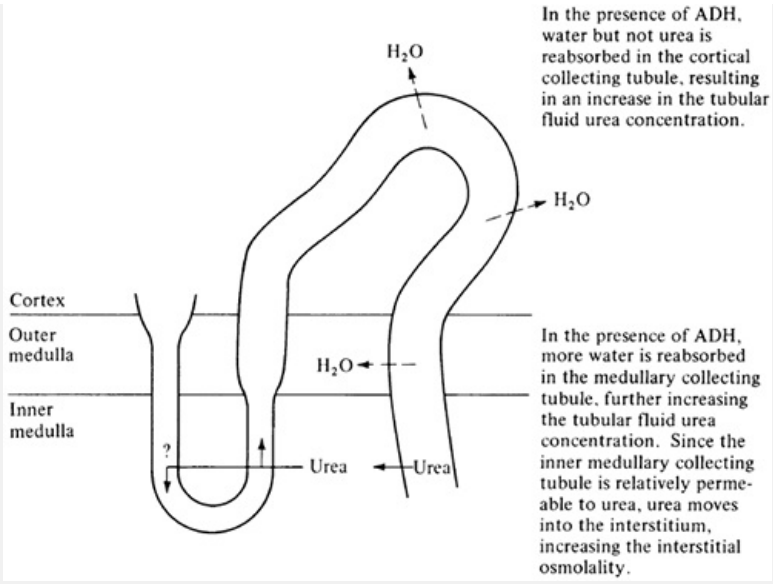

Figure 4-10 Mechanism by which urea achieves high concentrations in the medullary interstitium.

In addition to ADH, urea accumulation in the medulla is also indirectly depe upon active NaCl transport in the ascending limb. The ensuing increase in osmolality affects urea transport in two ways. First, it directly increases th of the inner medullary urea transporter via an effect that is independent of [60] Second, loop NaCl reabsorption makes the tubular fluid dilute and the inter concentrated, thereby creating the osmotic gradients that allow water reabs occur in the collecting tubules; the increase in water reabsorption raises th fluid urea concentration, enhancing the gradient for urea entry into the inte

Some of the urea that accumulates in the interstitium *reenters* the tubule in the thin ascending limb and the descending limb.[39,40,55] This recirculation of urea occurs via a second urea transporter, UT2.[57] The net effect of this *urea recycling* is that the quantity of urea in the early distal tubule is the same as or slightly exc amount filtered, even though 60 to 65 percent of the filtered urea has been reabsorbed in the proximal tubule.[61] Thus, both urinary and interstitial urea concentrations are maintained at high levels in the presence of ADH.

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The rise in medullary interstitial osmolality produced by urea allows the concentrating process to be more efficient in several ways. The most evide the higher interstitial osmolality maximizes concentrating ability and allows excretion of large quantities of urea without obligating concurrent water los[58] The interstitial accumulation of urea also promotes osmotic water movement out descending limb of the loop of Henle. This water flux leads to an elevation tubular fluid Na^+ concentration entering the ascending limb and to a reduction (by dilution) in the interstitial Na^+ concentration. Both of these changes promote passive Na^+ reabsorption in the thin ascending limb (see below). Thus, urea

indirectly plays an important role in primary step in the countercurrent mec

the transport of Na^+ out of the ascending limb into the medullary interstitium.

The overall importance of urea in the concentrating process can be appreci experimental studies in which ADH secretion is minimal because of a large load or hereditary diabetes insipidus.[62,63] In the absence of ADH, urea accumulation in the interstitium is virtually abolished, since the decline in reabsorption in the cortical and outer medullary collecting tubules prevents increase in the tubular fluid urea concentration that is necessary for urea (Fig. 4-11). NaCl accumulation is also reduced because, as just described, u accumulation indirectly promotes NaCl reabsorption in the thin ascending li

These findings demonstrate that *papillary osmolality is not constant but varies v the availability of ADH*. It is likely that a similar situation exists in humans. In

patients with central diabetes insipidus or those who shut off ADH secretio chronic water loading (see Chap. 24), the ability to concentrate the urine after th administration of ADH is impaired.[64] In one study, maintaining a high fluid intake normal subjects for only 3 days was sufficient to lower the maximum ADH-in urine osmolality by over 400 mosmol/kg (from approximately 1180 mosmol/k mosmol/kg).[65] Washout of medullary urea and NaCl was probably responsible this effect.

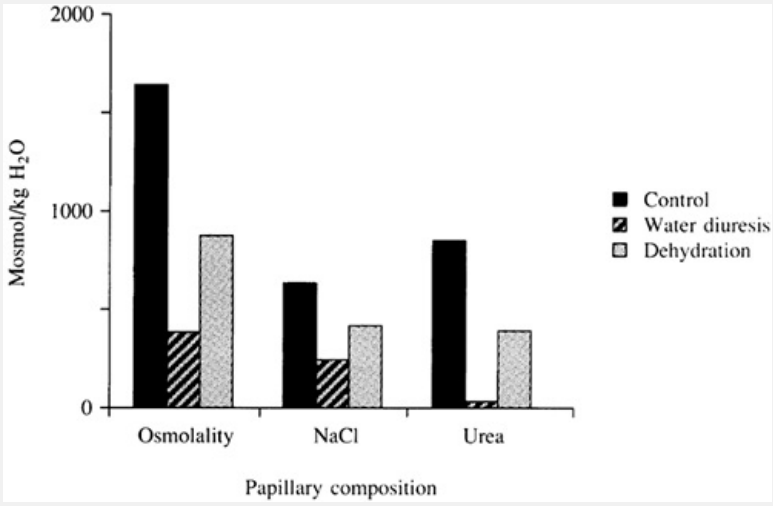

Figure 4-11 Simultaneous measurement of renal papillary osmolality, sodiur concentration, and urea concentration in rats in the control state, after a load, and 2 h after the reinstitution of fluid restriction plus the administra ADH. Water loading, which is associated with the inhibition of ADH releas to a marked reduction in papillary osmolality that was mostly due to the v abolition of urea accumulation. These changes rapidly returned toward no when ADH was given. (*Data from Levitin H, Goodman A, Pigeon G, Epstein FI J Clin Invest 41:1145, 1962, by permission from the American Society for Clinical Investigation.*)

NaCl Reabsorption in Thin Ascending Limb

NaCl reabsorption in the thin ascending limb appears to be primarily passiv
active as in the thick ascending limb. How a favorable concentration gradient
for NaCl diffusion might be created can be appreciated if we review the asp
countercurrent multiplication that have been discussed earlier (
Active NaCl reabsorption without water in the thick ascending limb makes tl
tubular fluid dilute and the interstitium concentrated (step 1). This dilute fl
presence of ADH, equilibrates osmotically with the isosmotic interstitium in
cortical collecting tubule (step 2) and then with the hyperosmotic interstitiu
medullary collecting tubule (step 3). The removal of water (but not urea) fr
tubular fluid in these segments results in a marked elevation in the urea
concentration, which diffuses into the interstitium in the inner medullary co
tubule (step 3).

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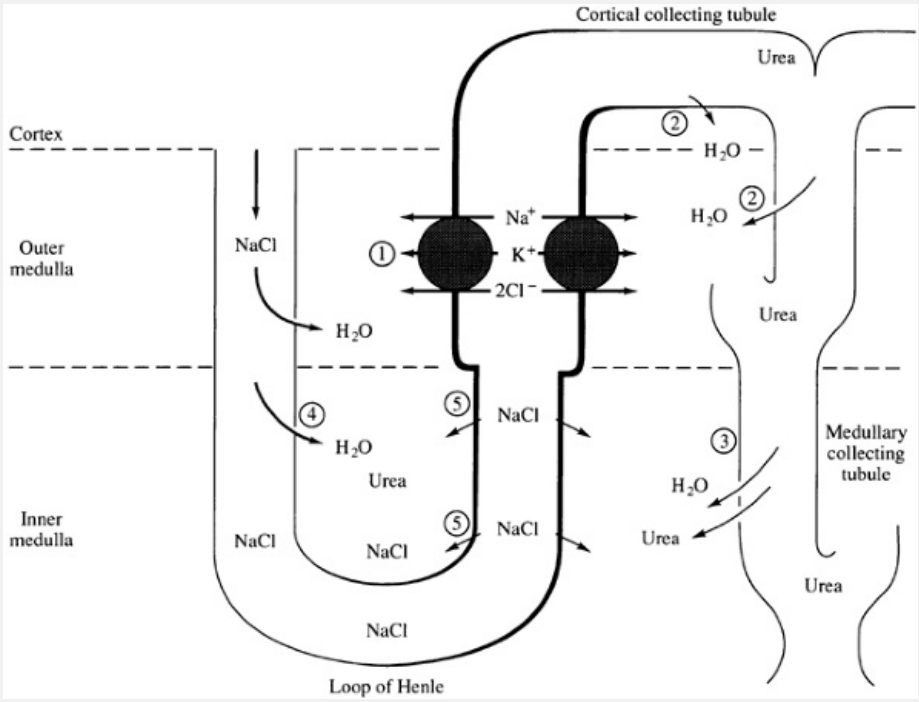

Figure 4-12 Summary of the steps involved in countercurrent multiplication which a concentration gradient is established that permits passive NaCl reabsorption in the thin ascending limb in the inner medulla. The thickene represent the water impermeability of the ascending limb. See text for det (*From Jamison RL, Maffly RH, N Engl J Med 295:1059, 1976. By permission from the* New England Journal of Medicine.)

At this point, let us suppose that the interstitial osmolality at the papillary mosmol/kg, half of which is NaCl (300 meq/L of both Na^+ and Cl^-) and half of which is urea. The fluid entering the descending limb from the proximal tubule has osmolality of about 300 mosmol/kg, a Na^+ concentration of 150 meq/L, and a urea

concentration below 10 mmol/L, similar to that in the plasma. If we assume equilibration with the hyperosmotic interstitium occurs entirely by water mo out of the tubule (step 4), then three-quarters of this fluid must be reabsor raise the tubular fluid osmolality to 1200 mosmol/kg, the value at the hairpi the interstitium (Fig. 4-7). If, however, osmotic equilibration is impaired because the absence of aquaporin-1, then concentrating ability is reduced.[44]

This elevation in osmolality will be accompanied by a fourfold increase in t fluid Na^+ concentration to about 600 meq/L, well above that in the interstitiu will promote passive NaCl diffusion out of the thin ascending limb, which is permeable to these ions (step 4).[41] Although there is a similar inward gradient fo urea in this segment (since the interstitial concentration is so high), the de urea entry into the tubule is much less because of a lower urea permeabilit (Table 4-1).[41] Thus, the net effect is NaCl reabsorption without water and a reduct tubular fluid osmolality, both of which are required for countercurrent multi

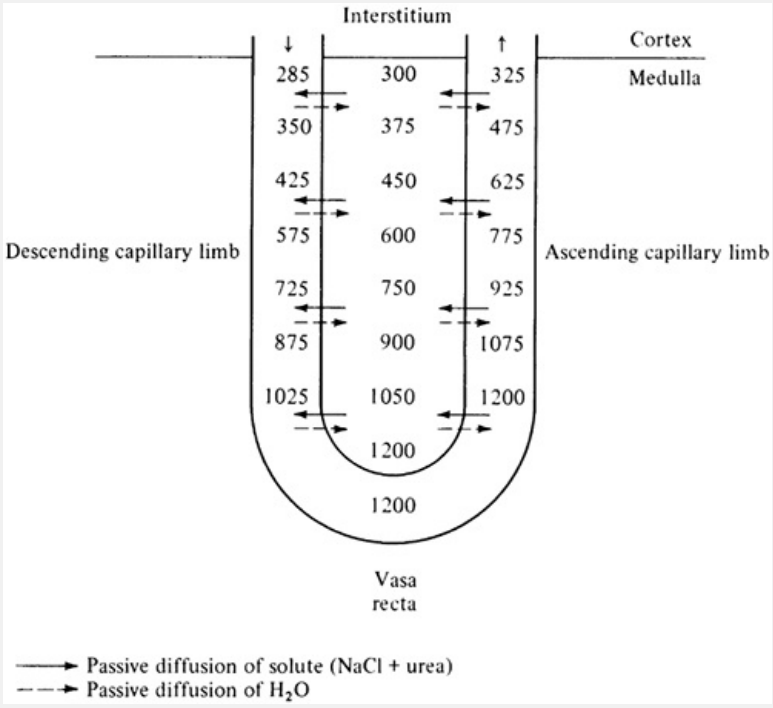

Figure 4-13 Principle of countercurrent exchange in the vasa recta capillar the descending capillary limb, solute enters and water leaves the capillar concentration gradients, tending to reduce interstitial osmolality. These processes are reversed in the ascending capillary limb, thereby preservin interstitial osmolal gradient. (*Adapted from Pitts, RF: Physiology of the Kidney and Body Fluids, 3d ed. Copyright ©1974 by Year Book Medical Publishers, Inc, Chicago. Used by permission.*)

The major problem with this model is that it is dependent upon osmotic equ in the descending limb occurring almost entirely by water removal, thereby a marked elevation in the transtubular NaCl concentration gradient. It is po

however, that the high interstitial concentration of urea could lead to passi diffusion of this solute into the tubule. This is likely to occur, since parts o descending limb have a relatively high urea permeability (Table 4-1).[40,41] To the degree that osmotic equilibration occurs by urea entry, there will be a lesse the tubular fluid NaCl concentration.

The net effect is that there does not appear to be a sufficient transtubular gradient established to support the degree of passive transport required fo countercurrent multiplication to proceed. Thus, the exact mechanism by whi ascending limb reabsorption occurs is at present incompletely understood.[40,41,66] It is possible that some component of active transport may be required in the of the thin ascending limb.[67]

This model also does not explain the mechanisms of transcellular NaCl reab in the thin ascending limb. Evidence suggests that Na^+ reabsorption primarily occurs via the paracellular pathway between the cells, Cl^- reabsorption

occurs via a kidney-specific Cl^- channel called CLC-K1.[69] How these processes are linked is not clear, but the importance of this Cl^- channel in urinary concentration ha been demonstrated by the finding of polyuria due to ADH resistance in mice this channel.[69]

Countercurrent Exchange: Vasa Recta

The capillaries of the vasa recta are derived from the efferent arterioles of juxtamedullary glomeruli and have a hairpin configuration, similar to the loo Henle (Fig. 4-13). They play an important role in the *maintenance of mass balance* in the medulla by returning the NaCl and water reabsorbed in the loop of Henl medullary collecting tubule to the systemic circulation. The ascending vasa well adapted for such a role, since Starling's forces in these vessels are m favor of fluid uptake: The oncotic pressure which promotes uptake is appro 26 mmHg, whereas the hydraulic pressure which pushes fluid out of the cap only about 9 mmHg at the papillary tip.[70,71] The net effect is that

the flow rate leaving the medulla in the ascending vasa recta is almost twic entering the medulla in the descending vasa recta.[72]

The vasa recta also play an integral role in the *maintenance* of the medullary osmotic gradient.[70] The vasa recta reach osmotic equilibrium with the interstit since they are permeable to solutes and water. In the descending vasa rect enters and water leaves as the plasma osmolality reaches a value similar to the interstitium at the papillary tip (Fig. 4-13). The very high interstitial sodium chloride and urea concentrations generate a sufficient osmotic pressure to free water loss, even though the direct effect of the intracapillary Starling's to promote water and solute movement into the capillary.[73]

If the vasa recta left the kidney at the papilla, the combination of solute re water addition would reduce medullary osmolality. However, the medullary o

gradient is maintained because the vasa recta turn around at the papillary return to the cortex. As a result, the solute removed from the interstitium in descending limb is returned to the interstitium, i.e., exchanged, in the asce down a favorable concentration gradient from the lumen to the interstitium. water added to the interstitium in the descending limb reenters the capillar ascending limb. Allowing for a lag in equilibration, the blood returning to th only slightly hyperosmotic to plasma (325 mosmol/kg).

Notice that this process of *countercurrent exchange* is driven by the preexisting transcapillary osmotic and concentration gradients. It is not dependent upo Starling's forces, which, as described above, are more important in the net of the solutes and water that have entered the interstitium by tubular reabs

The low rate of medullary blood flow (6 percent of renal blood flow), which partially under neurohumoral control,[74] also contributes to the maintenance of interstitial hyperosmolality. If medullary blood flow is increased, more blood mosmol/kg will leave the medulla, and a significant washout of medullary so occur, with a reduction in interstitial osmolality.[70]

Washout of medullary solute can alter loop NaCl and water handling via the sequence. It will diminish water reabsorption in the descending limb of the Henle, since there is now a lesser osmotic gradient between the tubular flu interstitium (step 4 in Fig. 4-12). This reduction in water removal will result in a lesser rise in the tubular fluid Na^+ concentration, thereby decreasing passive NaC reabsorption in the thin ascending limb (step 5 in Fig. 4-12).

A clinical example in which each of these changes in loop function occurs i an *osmotic diuresis* in which a large amount of nonreabsorbed solute is preser the urine. This may be seen with glucosuria in uncontrolled diabetes mellitu Chap. 25) or after an intravenous infusion of mannitol. In these settings, me blood flow is enhanced by an unknown mechanism,[75] resulting sequentially in a decrease in papillary osmolality,[76] and an elevation in both urine volume and Na^+ excretion, primarily due to a fall in descending limb water reabsorption and ascending limb Na^+ reabsorption.[77]

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Summary

The countercurrent mechanism permits the kidney to excrete urine with an o that varies in humans from a minimum of 50 mosmol/kg to a maximum of 900 mosmol/kg. The primary event in this process is active NaCl transport out o ascending limb of the loop of Henle into the medullary interstitium, produci of the tubular fluid and concentration of the interstitium. Because of the dif permeability characteristics of the descending and ascending limbs, this fir results in countercurrent multiplication in which a medullary osmotic gradie created that reaches its maximum at the papillary tip.

The osmolal changes that may occur as the tubular fluid moves through the are summarized in Fig. 4-14. The isosmotic urine delivered from the proximal tub becomes hyperosmotic in the descending limb as it equilibrates with the me

interstitium and then becomes hypoosmotic in the ascending limb as NaCl is reabsorbed without water. *Thus, the osmolality of the urine is determined in the final collecting tubules in a manner dependent upon ADH*

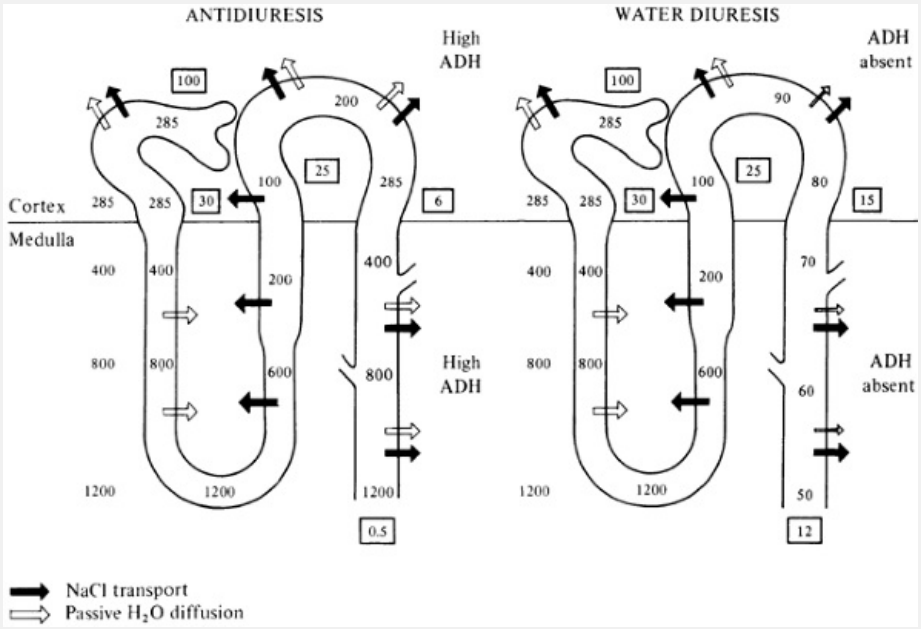

Figure 4-18 Summary of NaCl and H_2O transport throughout the nephron during an antidiuresis and a water diuresis. The tubular fluid and interstitial concentrations are expressed in milliosmoles per kilogram (mosmol/kg); th large, boxed numbers represent the percentage of the glomerular filtrate remaining in the tubule at each site. Note that the composition and volum tubular fluid are essentially the same at the end of the loop of Henle as t excretion of a concentrated or dilute urine is determined primarily in the collecting tubules.

1. In the presence of ADH, collecting tubule water permeability is increase allowing osmotic equilibration of the tubular fluid with the isosmotic int in the cortex and then the hyperosmotic interstitium in the medulla. The the excretion of a concentrated urine. ADH also contributes to the high medullary osmolality by permitting urea entry into the interstitium and, i species, by promoting NaCl reabsorption in the medullary thick ascendi
2. In the absence of ADH, the hypoosmotic urine leaving the loop of Henle not equilibrate with the interstitium, and a dilute urine is excreted.

These effects of ADH are dose-related. This is important because normal d usually do not require maximal dilution or concentration of the urine. A norr subject, for example, may need to excrete 800 mosmol of solute and 2 liters per day to remain in the steady state. The excretion of urine with an averag osmolality of 400 mosmol/kg requires a submaximal ADH response.

Clinical Example

This chapter has emphasized the importance of ADH in the production of a concentrated urine. However, other factors also can contribute, including th effective circulating volume (i.e., the rate of effective tissue perfusion). As example, the absence of ADH, as after a water load or with impaired produc to central diabetes insipidus, is generally associated with a urine osmolalit 100 mosmol/kg and a urine output that can exceed 10 L/day.

If, however, effective volume depletion is superimposed, the urine osmolalit to as high as 400 mosmol/kg or more.[78,79] In this setting, the associated reductio in glomerular filtration rate and increment in proximal Na^+ and water reabsorption can markedly diminish water delivery to the collecting tubules. The inner m collecting tubule is mildly permeable to water even in the absence of ADH.[50] As a result, the combination of a very lower rate of delivery and a small amount reabsorption at this site can substantially raise the urine osmolality.[79] The halt effect is that the presence of diabetes insipidus may be masked, since neither ma polyuria nor a very dilute urine is present. Volume repletion will reverse the changes and allow the correct diagnosis to be suspected.

MAINTENANCE OF CELL VOLUME

Maintenance of protein function within the cells generally requires a relativ constant cell volume, although it is possible that it is the concentration of intracellular proteins rather than volume itself that is being regulated.[80] This is an important issue for the cells in the medulla, such as those in the thick asce and inner medullary collecting tubule, since the interstitial milieu in which may undergo wide changes in osmolality, as illustrated in Figure 4-12.

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Although the luminal membrane of ascending limb cells is impermeable to w osmotic equilibration with the interstitium can occur across the basolateral membrane. As a result, the rise in interstitial osmolality induced by ADH wil water movement out of the tubular cells and cell shrinkage. This effect is tr however, because the cells are able to adapt by increasing their osmolality holding water within the cells.[81,82] This protective response is, at least acutely, mediated by ADH. Acting on the *basolateral* membrane, ADH promotes the entry of interstitial NaCl into the cells, apparently by activating Na^+-H^+ and Cl^-–HCO_3^- exchangers.[82] A similar process occurs in the inner medullary collec tubule, which is exposed to the same changes in interstitial osmolality[83] and has aquaporin-3 and aquaporin-4 water channels in the basolateral membra[84]

Another defense mechanism in the response to hypertonicity is the generati uptake of new organic solutes, which leads to the osmotic movement of wat the cell and the restoration of cell volume. These solutes include sorbitol, betaine, taurine, and glycerophosphocholine.[85,86,87,88] and[89] These solutes, which have been called *osmolytes*, have the advantage that changes in their

concentration within the cells do not appear to interfere with enzyme activi comparison, an elevation in the cell K^+ or Na^+ concentration may preserve cell volume at the expense of normal protein function.[85,86]

The mechanism by which osmolyte net production or uptake is enhanced in ascending limb and inner medullary collecting tubule is becoming better understood.[90] One possible signal is the cellular ionic strength ($Na^+ + K^+$ concentration).[87,91] With hyperosmolality, for example, the osmotic movement fluid out of the cells plus the initial K^+ and Na^+ uptake raises the cellular ionic strength. This appears to activate osmotic response elements on the genes regulate the activity of aldose reductase and the transporters for betaine a inositol.[90,92]

- The activity of aldose reductase, the enzyme that catalyzes the formatic sorbitol from glucose, is increased,[90,91,93] this change may be accompanied b reduced activity of sorbitol dehydrogenase, thereby diminishing sorbitol conversion to fructose.[93]
- There is also enhanced activity of Na^+-inositol and Na^+-betaine cotransporters, changes that will promote the cellular uptake of these solutes.[90,94] This increase in transport appears to occur across the basolateral membrane appropriate since the interstitial fluid (which is in equilibrium with the p likely to have a higher concentration of inositol and betaine than the lu to proximal reabsorption of most of the filtered osmolytes).[95]
- The accumulation of glycerophosphocholine (GPC) appears to result fro reduced degradation (a change that is mediated by diminished activity c enzyme GPC:choline phosphodiesterase)[96] as well as increased synthesis (fro phosphatidycholine, the precursor of GPC).[97]

The total osmolyte concentration within the cells is another important deter osmolyte accumulation. The administration of an aldose reductase inhibitor example, will prevent the generation of sorbitol; however, the net response hyperosmolality is not impaired since the reduction in sorbitol is balanced l increase in other osmolytes, particularly enhanced uptake of betaine.[98]

If, on the other hand, the interstitial osmolality falls (as with a water load), be a tendency for water to move into the cells, leading to cell swelling. In t the cell volume is maintained by reversing the above responses. Aldose red activity is reduced[93] and the excess intracellular sorbitol and other osmolytes leak out of the cell due to the expression of specific carriers or channels ir membrane.[85,95,99] Loss of ions, particularly K^+ and Cl^-, also occurs through specific channels in the luminal and peritubular membrane, respectively (se Fig. 4-2).[81]

TAMM-HORSFALL MUCOPROTEIN

The thick ascending limb secretes a protein called Tamm-Horsfall mucoprot (THMP) or uromodulin.[100101] THMP is a membrane protein that is principally located on the luminal surface of the cell membrane.[102]

The function of THMP is unclear. It may have some immunodulatory activity[100101] and is important clinically because it represents the *matrix of all urinary casts*[103] The casts may contain only the matrix (hyaline casts) or can include degen cells or filtered proteins (granular casts), or intact cells that are present in tubular fluid (red, white, or epithelial cell casts).[104] This type of cast that is present often has important diagnostic implications, e.g., red cell casts are virtuall pathognomonic of glomerulonephritis or vasculitis. In contrast, hyaline or g cast formation is not necessarily indicative of renal disease, since it can b physiologic states such as exercise or fever.[104]

THMP has been implicated in the pathogenesis of cast nephropathy, a form failure associated with multiple myeloma in which dense intratubular casts the flow of urine. Only some light chains appear to have this property, whic to require coaggregation with THMP.[105]

It has also been suggested that THMP plays an etiologic role in other disea such as the inflammatory response in interstitial nephritis. Tubular injury ir setting may lead to the release of THMP, which can then attract neutrophils binding to specific receptors on the cell surface.[106]

PROBLEMS

4-1 Explain the roles of the following in the production and maintenanc the hypertonicity of the medullary interstitium:

a. **NaCl reabsorption in the medullary ascending limb**

b. **Urea accumulation**

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c. **Flow in the vasa recta capillaries**

4-2 What is the role of NaCl reabsorption without water in the medullar ascending limb on:

a. **The excretion of a concentrated urine?**

b. **The excretion of a dilute urine?**

What is the contribution of NaCl reabsorption without water in the cort ascending limb and distal tubule to these processes?

4-3 In some species, ADH stimulates NaCl reabsorption in the medullar ascending limb. What effect would this have on:

a. **Concentrating ability?**

b. **NaCl delivery out of the *cortical* thick ascending limb into the distal tubule?**

4-4 In addition to osmotic diuretics, other diuretics are available which increase the urine output by inhibiting active NaCl reabsorption (see Chap. 17). What would be the likely site of action of a nonosmotic diuretic if

a. **Inhibited both concentration and dilution?**

b. **Inhibited dilution but not concentration?**

4-5 What is the mechanism by which water is reabsorbed in the descen limb of the loop of Henle? How might this change during:

a. **An osmotic diuresis?**

b. **A water diuresis due to central diabetes insipidus (absence of ADH**

4-6 What effect will a low-protein diet (urea is an end product of protei metabolism) have on concentrating ability?

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Footnotes

* Only about one-half of the papillary solute is NaCl, with urea accounting for most of the remainder (see "Role of Urea" below).

† Although the interstitial osmolal gradient is primarily created by those nephrons with long loops, urine from all nephrons drains into the collecting tubules (Fig. 4-1) and equilibrates osmotically with the interstitium in the presence of ADH.

‡ Water reabsorption is probably minimal in the distal tubule and connecting segment, which, like the ascending limb, are relatively impermeable to water in the basal state and in the presence of ADH.

¶ The volume of the medullary interstitium is relatively small. The weight o kidneys in humans is approximately 350 g, most of which is composed of ne segments, tubular fluid, and blood vessels. Thus, the attainment of high concentrations of urea in the medullary interstitium requires only small amc urea. Since approximately 27 to 32 g (about 500 mmol) of urea is excreted the interstitial accumulation of urea does not importantly affect total urea e

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Chapter Five
Functions of the Distal Nephron

INTRODUCTION

The distal nephron begins at the macula densa at the end of the cortical thi ascending limb and consists of four segments, each of which has one or mo distinct cell types: the distal tubule, the connecting segment (previously co part of the late distal tubule), the cortical collecting tubule, and the medulla collecting tubule (Fig. 1-3). These segments perform different functions and c be separated both by histologic appearance and by hormone responsiveness (Table 5-1).[1,2,3] and[4]

The distal nephron, particularly the collecting tubules, is the site at which t *final qualitative changes in urinary excretion* are made. Thus, maximal concentration of the urine, potassium secretion (which accounts for most of urinary potassiu excretion), maximal acidification of the urine, and sodium conservation all o the collecting tubules. As an example, the Na^+ concentration is about 75 meq/L in the fluid leaving the loop of Henle but can be appropriately reduced to less meq/L by the end of the medullary collecting tubule in states of volume depl

This steep concentration gradient between the tubular fluid and the plasma maintained because the distal nephron is relatively impermeable to the

passive transcellular or paracellular movement of both water (in the absenc antidiuretic hormone) and Na^+. Consequently, the gradient generated by active Na^+ transport is less likely to be dissipated by passive back-diffusion from the p into the tubular fluid. This impermeability to Na^+ and water movement is probably related to the thickness of the tight junction, which, on electron microscopy composed of up to eight strands in the distal nephron.[5] In comparison, the proximal tubule is a highly permeable epithelium, with only one strand demonstrable electron microscopy.[5] As a result, the proximal tubular fluid Na^+ concentration does not normally fall below that in the plasma, since back-flux of Na^+ down its concentration gradient can occur through the tight junction (see Chapter 3).

Table 5-1 Hormone responsiveness of distal neph segments

Segment	Antidiuretic hormone	Aldosterone	Parathyroid hormone	Calcitriol	Atrial natriuretic peptide
Distal convoluted tubule	0	0	+	+	0
Connecting segment	0	+	+	+	0
Cortical collecting tubule					
Principal cells	+	+	±	±	0
Intercalated cells	?	+	0	0	0
Medullary collecting tubule					
Outer	+	+	0	0	0
Inner	+	+	0	0	

Although the collecting tubules can generate and maintain large concentrati gradients, their *total* reabsorptive capacity is limited. In terms of active Na^+ transport, this is exemplified by a lower level of Na^+-K^+-ATPase activity than is present in other nephron segments (except for the descending and thin asce limbs of the loop of Henle, where transport is essentially passive).[6] As a result, the collecting tubules function most efficiently when the bulk of the filtrate is re in the proximal tubule and loop of Henle, and distal delivery is held relative constant. As described in Chaps. 2, 3, and 4, three intrarenal processes minimize changes in distal delivery in normal subjects:

1. *Autoregulation*, which maintains the glomerular filtration rate (GFR) in the presence of variations in renal arterial pressure
2. *Glomerulotubular balance*, in which proximal and loop reabsorption increase there is an elevation in the GFR
3. *Tubuloglomerular feedback*, which lowers the GFR in the load to the macula densa is enhanced

These processes are important, since an inappropriate increase in distal de

could overwhelm reabsorptive capacity, leading to potentially serious losses and water.

This chapter will briefly review the major functions of different cell types in nephron. In general, *cellular function correlates closely with hormonal responsiveness* (Table 5-1). As examples, Na^+ reabsorption and K^+ secretion occur in those Na^+ reabsorbing cells that respond to aldosterone; water reabsorptio occurs primarily when antidiuretic hormone (ADH) is present, and then only cells that respond to ADH; and calcium reabsorption is seen only in those c respond to parathyroid hormone (PTH) and calcitriol. In addition, the interca cells in the cortical collecting tubule plus the tubular cells in the outer med primarily secrete H^+, a response that is affected by changes in the extracellula and to a lesser degree by aldosterone. The role of each of these processes maintenance of ion and water balance will be discussed in chapters 8, 10, 11 and 12.

DISTAL TUBULE

Sodium and Water

The distal tubule normally reabsorbs about 5 percent of the filtered NaCl.[7] The mechanism by which this appears to occur is depicted in Figure 5-1. Na^+ entry into the cell is primarily mediated by electroneutral Na^+-Cl^- cotransport.[8,9] and[10] Two mechanisms contribute to this response: a Na^+-Cl^- cotransporter,[9,11,12] and, to a lesser degree, parallel Na^+-H^+ and Cl^--HCO_3^- exchangers.[13]

With the Na^+Cl^- cotransporter, the attachment of Na^+ to its site increases the affinity of the Cl^- site for its ligand; the transporter then undergoes a conforma change that translocates both Na^+ and Cl^- across the apical (or luminal) membrane.[9] The energy for this process is, as in other nephron segments, indirectly pro the basolateral Na^+-K^+-ATPase pump. This pump maintains a low cell Na^+ concentration, which promotes passive NaCl entry into the cell (page 75). (See also creates a cell interior negative potential, which is important for electrogenic (e.g., Na^+ reabsorption through the Na^+ channels in the cortical collecting tubule; see below) but not for electroneutral NaCl transport.

With parallel exchangers, on the other hand, intracellular water combines with CO_2 to form H^+ and HCO_3^- ions (see Fig. 3-3), which are then secreted into the lumen in exchange for Na^+ and Cl^-, respectively. The secreted H^+ and HCO_3^- then combine in the lumen to form carbonic acid, which, since it is uncharged and therefo soluble, can recycle into the cell and dissociate to regenerate H^+ and HCO_3^- to promote further NaCl reabsorption.

Notice that the mechanisms of entry in the distal tubule are different from th the loop of Henle, where there is also a requirement for the Na^+-K^+-$2Cl^-$ carrier in the apical membrane (see Fig. 4-2). This difference has some clinical

implications, since the latter carrier is inhibited by the loop diuretics, such

as furosemide.[7] The Na^+-Cl^- cotransporter in the distal tubule, on the other han relatively unresponsive to the loop diuretics but is impaired by the thiazide-diuretics, which produce their effect primarily by reducing NaCl reabsorptio segment.[7,8,10,14] Mutations in the Na^+-Cl^- cotransporter gene produce Gitelman's syndrome, a disorder characterized by hypokalemia, metabolic alkalosis, an hypocalciuria, findings similar to those induced by chronic thiazide therapy.[15]

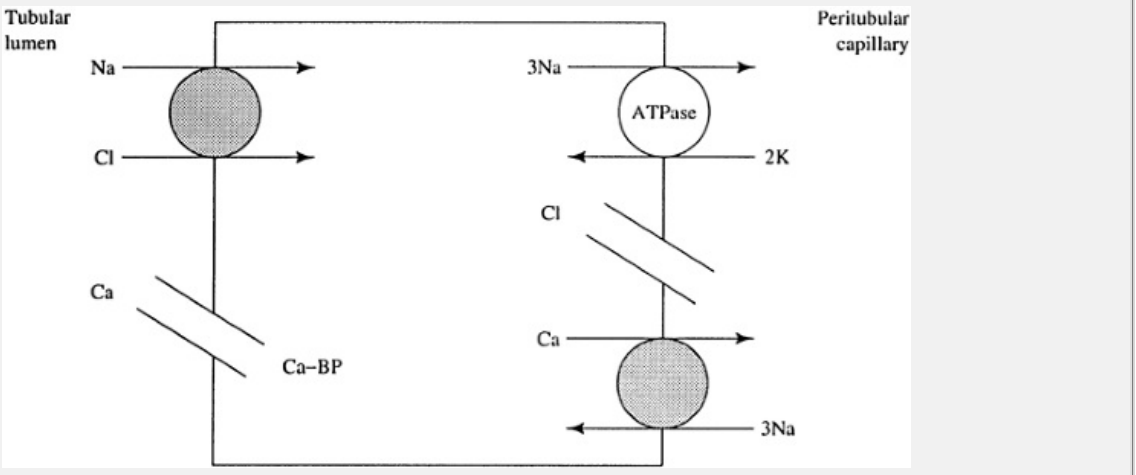

Figure 5-1 Schematic representation of the mechanisms of sodium chloride calcium reabsorption in the distal tubule. The entry of filtered sodium chlo into the cell is mediated by a neutral Na-Cl cotransporter in the luminal (a membrane; the energy for this process is provided by the favorable electrochemical gradient for sodium (low cell sodium concentration and ce interior electronegative). At the basolateral membrane, reabsorbed sodium pumped out of the cell by the Na^+-K^+-ATPase pump, while reabsorbed chloride exits via a chloride channel. Thiazide diuretics inhibit sodium chloride reabsorption by competing for the chloride site on apical Na-Cl cotranspor The distal tubule is also the major site of active calcium reabsorption. Cal enters the cell via a calcium transporter that is probably a voltage-depend calcium channel. Reabsorbed calcium combines with a vitamin D-induced c binding protein (Ca-BP), moves across the cell, and is then extruded at th basolateral membrane by a Ca-ATPase (now shown) and, to a greater degr 3Na : 1Ca exchanger which again uses the energy provided by the favorab inward gradient for sodium.

Like that in the loop of Henle, *distal tubular Na^+ reabsorption varies directly with Na^+ delivery* and therefore participates in glomerulotubular balance.[16] Thus, an increase in delivery results in a proportionate rise in segmental Na^+ reabsorption. This effect is independent of hormones such as aldosterone,[17] and, as in the loop of Henle, is probably related to changes in the Na^+ concentration in the tubular

fluid.[18,19] If more Na^+ is delivered to the distal tubule, the associated elevatio the luminal Na^+ concentration favors continued passive entry of Na^+ into the tubular cell. The degree to which this occurs is ultimately limited by the transtubular Na^+ concentration gradient between the tubular fluid and the plasma that the

distal tubule can maintain. The fluid entering the distal tubule normally has Na^+ concentration of about 75 meq/L; when this value is lowered to approximate meq/L by tubular reabsorption, further Na^+ transport essentially ceases as a result of both decreased binding to the Na^+-Cl^- cotransporter and backflux down a now very favorable concentration gradient through the tight junction.[8,9]

A common clinical example of this flow dependence occurs when distal deliv enhanced by the use of a loop diuretic. In this setting, distal tubular Na^+ reabsorption rises substantially,[7,20] a change that is accompanied by tubular hypertrophy[19,20] and by a necessary increase in Na^+-K^+-ATPase activity to return the extra Na^+ to the systemic circulation.[20,21] This distal adaptation can, in some edematous patients, severely limit the natriuretic response to a loop diureti problem can often be overcome by the addition of a thiazide diuretic to bloc transport in both segments (see page 437). If, on the other hand, distal Na^+ reabsorption is chronically diminished by the administration of a thiazide di inhibits the Na^+-Cl^- cotransporter, then tubular reabsorptive capacity and the Na^+-K^+-ATPase activity are reduced.[22]

These observations suggest that the cell Na^+ concentration is an important *chronic* determinant of transport capacity.[22] Reducing cell entry and therefore the cell Na^+ concentration with a thiazide diuretic diminishes NaCl reabsorptive capacity enhancing these parameters with a loop diuretic increases transport capacit

A similar distal tubular adaptation occurs when NaCl delivery is increased c by a high-salt diet.[23] This additional illustration shows that flow dependence do not necessarily result in appropriate changes in Na^+ excretion. At a time when tubular Na^+ reabsorption should be diminished to allow excretion of the exces intake, the distal tubule actually has a higher rate of Na^+ reabsorption. The proximal and collecting tubules, under the influence of angiotensin II, aldosterone, a natriuretic peptide, are the major sites at which Na^+ excretion is regulated in relation to needs (see Chap. 8).

In contrast to its role in NaCl handling, the distal tubule reabsorbs a minima of water. The water permeability of this segment is low in the basal state ar not appear to increase after the administration of ADH.[17] As a result, the distal tubule contributes to urinary dilution, since the reabsorption of NaCl withou will lower the tubular fluid osmolality.

Calcium

The early cortical distal nephron, including the cortical thick ascending limb as the distal tubule and connecting segment, is one major site at which urinary excretion is actively regulated (Fig. 5-1).[24,25] and [26] This process appears to be regulated primarily by parathyroid hormone and perhaps calcitriol (which increases production of a calcium-binding protein), both of which promote Ca^{2+} reabsorption.[27,28] and [29] The mechanism by which this occurs is reviewed in Chapter 3 (see page 92).

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When calcium intake is increased, some of the excess calcium is absorbed, enters the systemic circulation, and slightly raises the serum calcium concentration. It has traditionally been taught that suppression of PTH release with a subsequent reduction in distal tubular calcium reabsorption is responsible for the ensuing increase in calcium excretion. This appropriate change may be augmented by direct effects of hypercalcemia on the calcium-sensing receptor in the basolateral membrane of the ascending limb of Henle's loop.[30]

One characteristic of distal tubular function is that the reabsorption of Ca^{2+} can be dissociated from that of Na^+. PTH, for example, promotes the reabsorption of Ca^{2+} in this segment without changing that of Na^+, an effect that is mediated by the activation of adenylyl cyclase[31] and may involve facilitated entry of luminal Ca^{2+} into the cells.[28]

This ability to dissociate distal tubular Ca^{2+} and Na^+ handling may be important clinically in the treatment of recurrent calcium stone formation due to hypercalciuria. The thiazide diuretics are often beneficial in this setting because they impair reabsorption of NaCl *but increase that of* Ca^{2+}, leading to a desired reduction in Ca^{2+} excretion[32] and a lower rate of new stone formation.[33,34] How this might occur is discussed on page 92.[32]

Hydrogen and Potassium

The distal tubule may contribute to H^+ secretion and the reabsorption of HCO_3^-, although the collecting tubules are quantitatively much more important.[35,36] Some potassium secretion also may occur at this site, the physiologic significance of which is uncertain (see Chap. 12).[37,38]

CONNECTING SEGMENT

The connecting segment lies between the distal tubule and the initial portion of the cortical collecting tubule and shares characteristics of both segments. Like the distal tubule, it is impermeable to water, even in the presence of ADH; it participates in active Ca^{2+} reabsorption, being responsive to both PTH and calcitriol,[27,39] and it partially reabsorbs Na^+ by a thiazide-sensitive Na^+-Cl^- cotransporter in the apical membrane (in rabbits but apparently not in rats).[22,40,41] Like the cortical collecting tubule, however, it also reabsorbs Na^+ (via a Na^+ channel) and secretes K^+

response to aldosterone.[1,41,42]

CORTICAL COLLECTING TUBULE

The cortical collecting tubule has two cell types with very different function principal cells (about 65 percent) and intercalated cells.[1,43,44] The types of transport that occur in these cells are depicted in Figs. 5-2 and 5-3. The principal cells have Na^+ and K^+ channels in the luminal membrane[45,46] and[47] and, as in all Na^+-reabsorbing

cells, Na^+-K^+-ATPase pumps in the basolateral membrane. The intercalated ce comparison, do not transport NaCl, since they have a lower K^+-ATPase activity and have few if any apical membrane Na^+ channels, which are required for the entry of luminal Na^+ into the cell.[1,6,46] These cells appear to play an important role in H^+ and HCO_3^- handling and in K^+ reabsorption in states of K^+ depletion.

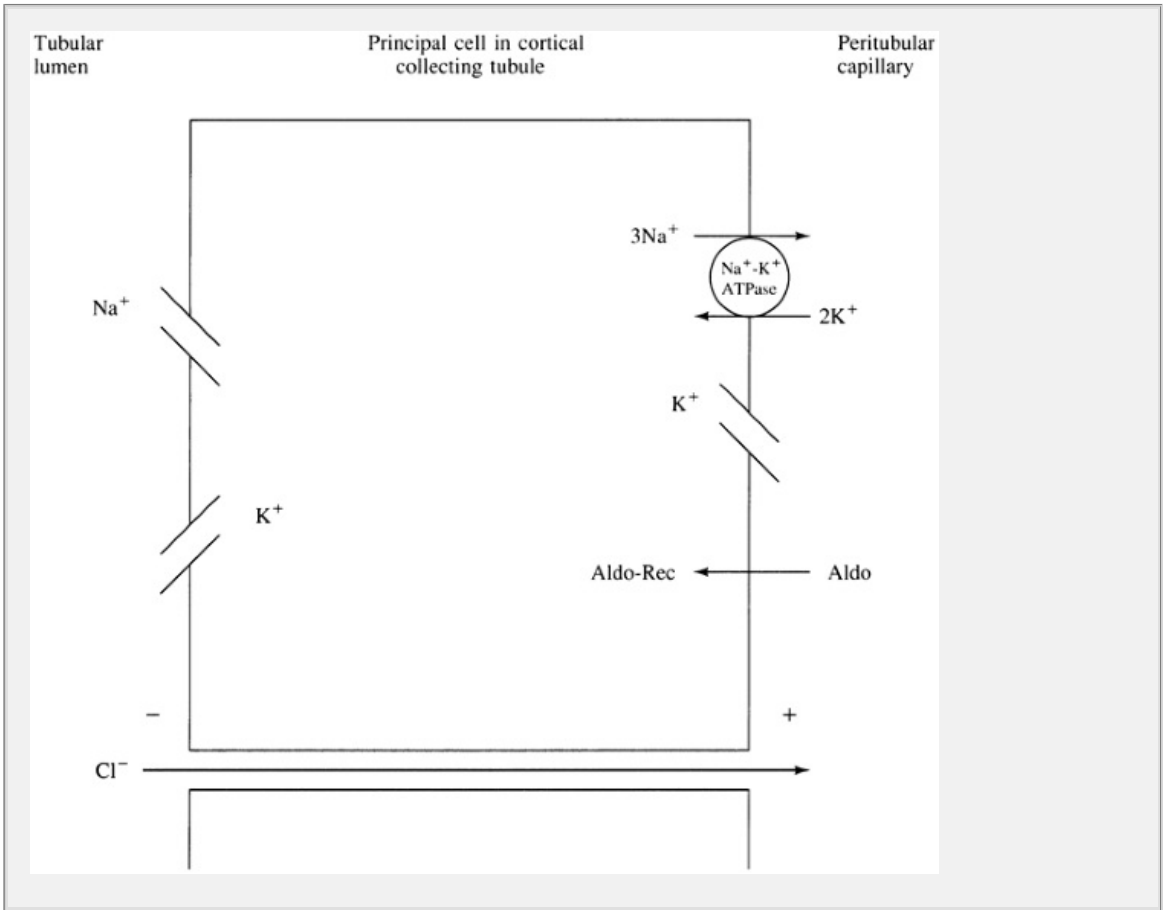

Figure 5-2 Ion transport in the principal cell in the cortical collecting tubule Luminal Na^+ enters the cell through a Na^+ channel in the luminal membrane. The lumen-negative voltage created by this movement of Na^+ promotes either the secretion of K^+ or the reabsorption of Cl^- via the paracellular route. These processes are promoted by aldosterone (Aldo), which enters the ce combines with its cytoslic receptor (Rec). These cells also can reabsorb w the presence of ADH.

Principal Cells

Sodium and potassium

The principal cells contribute to net Na^+ reabsorption and are the primary site of K^+ secretion. The entry of luminal Na^+ into these cells primarily occurs down a concentration gradient through ion-specific Na^+ channels[48,49] in the apical membrane.[45,46]

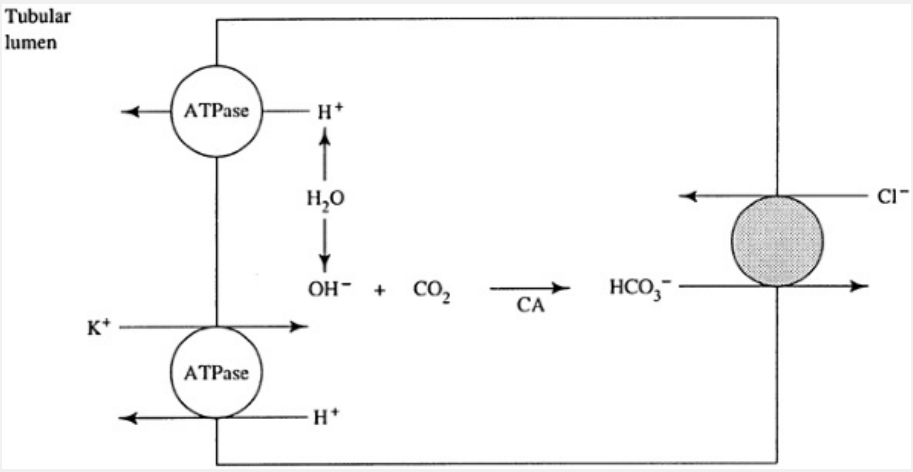

Figure 5-3 Transport mechanisms involved in hydrogen secretion and bicarbonate and potassium reabsorption in type A intercalated cells in the cortical collecting tubule and in the medullary collecting tubule cells. Wat within the cell dissociates into hydrogen and hydroxyl anions. The former secreted into the lumen by H^+-ATPase pumps in the luminal membrane; chloride may be cosecreted with hydrogen to maintain electroneutrality. The hydrox anions in the cell combine with carbon dioxide to form bicarbonate in a rea catalyzed by carbonic anhydrase (CA). Bicarbonate is then returned to the systemic circulation via chloride-bicarbonate exchangers in the basolatera membrane. The favorable inward concentration gradient for chloride (plasi interstitial concentration greater than that in the cell) provides the energy bicarbonate reabsorption. H^+-K^+-ATPase pumps, which lead to both hydrogen secretion and potassium reabsorption, may also be present in the luminal membrane. The number of these pumps increases with potassium depletion suggesting that their main function is to promote potassium conservation.

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In comparison to the *electroneutral* Na^+-K^+-$2Cl^-$ and Na^+-Cl^- entry mechanisms in the thick ascending limb and distal tubule, movement through the Na^+ channel is electrogenic in that it creates a lumen-negative potential difference. It is im consider why a Na^+ channel rather than a cotransporter *must be present* in the later

part of the collecting tubules. These segments can lower the urine Na^+ concentration to below 5 meq/L in states of volume depletion. This value is that in the cells; thus, an electroneutral cotransporter that depends upon a concentration gradient for Na^+ would not work in this setting. Rather, it is t cell electronegativity (generated largely by the Na^+-K^+-ATPase pump and subsequent leakage of K^+ back out of the cell; see page 92) that provides the entry into the cell; this negative potential can affect *electrogenic* Na^+ transport.

The relative lumen-negative potential created by Na^+ reabsorption then promotes either passive Cl^- reabsorption via the paracellular pathway (the major route of Cl^- transport in this segment)[43,50] or K^+ secretion from the cell into the lumen[51,52] through aldosterone-sensitive K^+ channels in the apical membrane.[47]

Na^+ reabsorption in this segment also enhances K^+ secretion by a second mechanism: The transport of reabsorbed Na^+ out of the cell by the Na^+-K^+-ATPase pump increases K^+ entry across the basolateral membrane. The ensuing rise in K^+ concentration and therefore in the K^+ transport pool permits continued K^+ secretion, which is the *primary determinant of urinary* K^+ excretion (see Chap. 12). Aldosterone plays a central role in these transport processes, primarily by i the number of open Na^+ channels in the apical membrane (see page 179)[52,53,54] and[55] As an example, going from a high- to a low-sodium diet (which is assc with enhanced aldosterone release and increased Na^+ reabsorption in the cortical collecting tubule) can increase the number of channels per cell from less than 100 to approximately 3000.[45]

There is also a later increase in Na^+-K^+-ATPase activity and in the number of oper luminal K^+ channels. These changes can at least initially be prevented by blo the Na^+ channel with the diuretic amiloride, suggesting that they are in part secondary to enhanced Na^+ flux through the cell.[52] As an example, increasing cell Na^+ concentration directly and rapidly stimulates Na^+-K^+-ATPase activity.[56] This initial response may be then sustained by a later increase in Na^+-K^+-ATPase synthesis mediated by aldosterone.[57]

Two different types of mutations in the luminal Na^+ channel have been described. The first is an activating mutation in Liddle's syndrome, a disorder with clin characteristics similar to those of a high-aldosterone state: excessive sodiu reabsorption and potassium secretion.[58] The second is an inactivating mutation in the autosomal recessive form of pseudohypoaldosteronism that produces sig low-aldosterone state: hyperkalemia and a tendency to hypovolemia due to Na^+ wasting.[59]

The cortical and medullary collecting tubules usually reabsorb 5 to 7 percer

filtered Na^+, and variations in Na^+ reabsorption in these segments are probably th *major determinant of diet-induced fluctuations in daily* Na^+ *excretion*.[60,61] For example, a reduction in Na^+ intake enhances aldosterone release via activation o the renin-angiotensin system (see Chap. 6). This results in increased Na^+ reabsorption both in the cortical collecting tubule and, to a lesser degree, i papillary (or innermost) segment of the medullary collecting tubule[43,62] (see bel leading to an appropriate fall in Na^+ excretion. The opposite sequence occurs with Na^+ load as aldosterone secretion is diminished. Enhanced release of atrial natriuretic peptide also may contribute to the natriuresis in this setting, in p diminishing Na^+ reabsorption (via a reduction in the number of open Na^+ channels) in the papillary and perhaps the cortical segment of the collecting tubule (see Chap. 6).[63]

In addition to these effects of regulating hormones, Na^+ reabsorption in the cortical collecting tubule may also be influenced by alterations in Na^+ delivery, locally produced prostaglandin E_2, and perhaps antidiuretic hormone:

1. Decreasing Na^+ delivery, as might occur with volume depletion, leads to an increase in the number of open Na^+ channels in the apical membrane.[64]

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   This response appears to be mediated by an initial fall in cell Na^+ concentration (due to the decline in delivery) and a subsequent reduction in the cell le protein kinase C (see Fig. 6-2). This enzyme normally diminishes Na^+ reabsorption; thus, a decrease in its activity is associated with an increa number of open Na^+ channels in an appropriate effort to conserve volume b preventing further Na^+ loss. The physiologic role of this effect remains to b determined.

2. By activating the EP1 receptor, prostaglandin E_2 inhibits Na^+ transport in the cortical collecting tubule.[65,66] and[67] ADH, on the other hand, may increase Na^+ reabsorption, perhaps by inserting new Na^+ channels in the apical membrane.[53] The importance of these hormonal effects in the regulation o balance is uncertain, particularly since they appear to be present in onl species.[53,66]

Water

The water permeability of the apical membrane of the principal cells is relat in the basal state (in contrast to the highly permeable proximal tubule, whic water channels in both the apical and basolateral membranes).[68] However, collecting tubule water permeability can be increased substantially by ADH, inserts cytosolic vesicles containing preformed water channels into the apic

membrane (see Chap. 6).[68,69,70] and[71] These water channels, termed *aquaporin-2*, are different from those in the proximal tubule, which are called aquaporin-[68,72]

The increase in luminal membrane water permeability induced by the inserti these water channels allows the dilute fluid entering the cortical collecting (about 100 mosmol/kg) to equilibrate osmotically with the isosmotic cortical interstitium. As described in the preceding chapter, this ADH-mediated wate reabsorption plays an important role in urinary concentration by markedly di the volume of fluid delivered to the hyperosmotic medulla (see Fig. 4-8).

The increase in water reabsorption induced by ADH might also be expected diminish K^+ secretion, since the latter process varies directly with urinary flo Chap. 12).[42] This does not occur, however, because the inhibitory effect of th decline in flow is counterbalanced by direct stimulation of K^+ secretion by ADH.[73] This response may be mediated by insertion of luminal K^+ channels into the apical membrane[74,75] or by stimulation of local Na^+ reabsorption, which will enhance the electrical gradient favoring K^+ secretion.[76]

Clinical Implications

Lithium therapy can lead to polyuria and polydipsia in 20 to 30 percent of p[77] This toxic effect results from interference with the ability of ADH to increas water permeability of the collecting tubules, thereby reducing water reabsor (see Chap. 24). For this problem to occur, filtered lithium must first gain acce the collecting tubular cells, apparently by entering the cell through the apic membrane Na^+ channels. This observation is important clinically, since blocki Na^+ channel with the potassium-sparing diuretic amiloride can minimize the and possibly prevent the development of this defect in urinary concentration[78]

Intercalated Cells

Hydrogen and bicarbonate

The intercalated cells are primarily involved in the independent regulation of H^+ and HCO_3^- acid-base balance.[1,35,79,80] As depicted in Fig. 5-3, intracellular water and carbon dioxide can, in the presence of carbonic anhydrase, lead to the formation of H^+ and HCO_3^- ions. The former is then secreted into the lumen by an H^+-ATPase pump or a H^+-K^+-ATPase pump,[81,82] whereas the latter returns to the systemic circulation across the basolateral membrane via a Cl^--HCO_3^- exchanger.[79,83] The Cl^--HCO_3^- exchanger is structurally similar to, but not identical with, the band 3 excha found on red cells. The bicarbonate exchanger is the product of transcriptio initiation on a *kidney-specific* site of the AE1 gene. Mutations in this gene can im urinary acidification and produce a picture of distal renal tubular acidosis (below).[84]

The net effect of these processes is loss of H^+ in the urine and an elevation in the plasma bicarbonate concentration. This process is appropriately stimulated by acidemia, since the ensuing urinary changes will result in an increase in the extracellular pH toward normal (see Chapter 11).[85]

Aldosterone appears to contribute to this process by enhancing the activity of H^+-ATPase pump.[86] In normal subjects, this effect is probably permissive, since there is little evidence that changes in acid-base balance alter the release of aldosterone. However, changes in aldosterone secretion can affect acid-base balance. Disease states associated with hyperaldosteronism usually lead to increased urinary H^+ loss and metabolitic alkalosis, while hypoaldosteronism is associated with H^+ retention and metabolic acidosis (see pages 846 and 900).

The homeostatic needs are reversed in the presence of an alkaline load. In this setting, loss of HCO_3^- in the urine is required. Although this can be achieved by reabsorbing less of the filtered HCO_3^- in the proximal and distal nephron, the cortical collecting tubule contributes to this process by *secreting* HCO_3^- form the cell into the lumen.[87,88] and[89] This is achieved by *reversing the polarity* of the transporters (Fig. 5-3) in a second population of intercalated cells, called the type B intercalated cells as opposite to the hydrogen-secreting type A intercalated cells (Fig. 5-4).[87,88]

In the type B intercalated cells, H^+ and HCO_3^- ions are again formed within the cell; however, the H^+ ions are now secreted into the peritubular capillary by the H^+-ATPase pump, which is located in the basolateral, rather than the apical, membrane. The HCO_3^- ions, on the other hand, are secreted into the lumen by an anion exchanger in the apical membrane. The identity of this transporter is uncertain; however, as it does not appear to represent the Cl^--HCO_3^- exchanger that is present in the basolateral membrane of stone-forming intercalated cells.[85]

The importance of these proteins in the maintenance of acid balance is illustrated by the observation that mutations in the H^+-ATPase proton pump result in distal renal tubular acidosis, a disorder characterized by diminished acid

secretion.[90] These individuals also have sensorineural deafness, suggesting that the proton pump also maintains the proper concentration of H^+ in the inner ear.

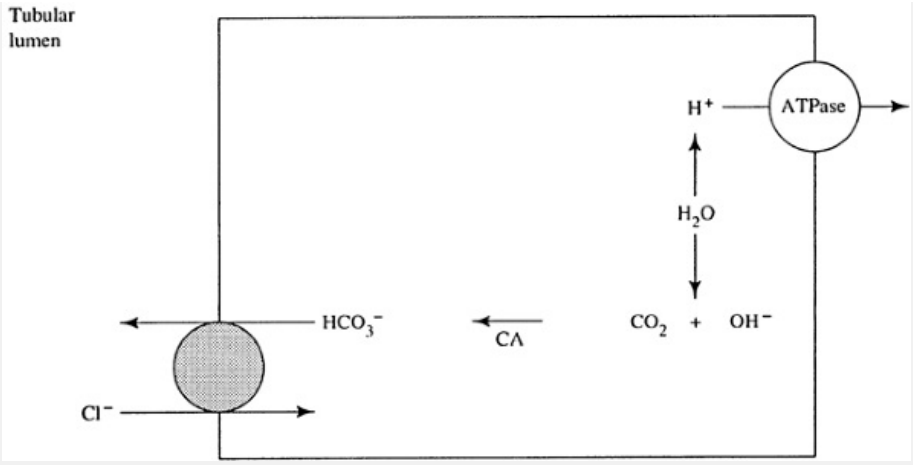

Figure 5-4 Transport mechanisms involved in the secretion of bicarbonate i the tubular lumen in the type B intercalated cells in the cortical collecting Water within the cell dissociates into hydrogen and hydroxyl anions. The f are secreted into the peritubular capillary by H^+-ATPase pumps in the basolateral membrane. The hydroxyl anions combine with carbon dioxide t bicarbonate in a reaction catalyzed by carbonic anhydrase (CA). Bicarbon then secreted into the tubular lumen via chloride-bicarbonate exchangers luminal membrane. The favorable inward concentration gradient for chloric (lumen concentration greater than that in the cell) provides the energy for bicarbonate secretion.

Potassium

Although the cortical collecting tubule normally secretes K^+, there can be *net reabsorption* in this segment in the presence of K^+ depletion.[91] This process occurs in the types A and B intercalated cells and appears to be mediated by an ac K^+-ATPase pump in the apical membrane that reabsorbs K^+ and secretes H^+ (Fig. 5-3).[92,93] The activity of this transporter is increased with hypokalemia, an eff may be mediated by the associated reduction in the cell K^+ concentration. In addition to maintenance of K^+ balance, this transporter also contributes to the increase acid secretion in metabolic acidosis.[92,94]

Within the type B intercalated cell, potassium reabsorption is also linked wi reabsorption via the luminal Cl^--HCO_3^- exchanger.[93] Concurrent activity of this exchanger and the H^+-K^+-ATPase pump may result in active KCl reabsorption.[95]

Water

The intercalated cells are relatively impermeable to water in the basal state appear to be minimally responsive to ADH, which primarily affects the adjac principal cells.[96,97]

MEDULLARY COLLECTING TUBULE

The distinction between the outer and inner medullary collecting tubules is based upon location, with the dividing point being the level at which the thi ascending limbs of the loop of Henle beginFig. (1 3). Nevertheless, this differentiation is physiologically appropriate because the cells in these seg have some important differences in function and hormone responsiveness (Table 5-1).

Outer Medulla

Hydrogen

The transition between the cortical and outer medullary collecting tubules is abrupt; as a result, the early portion of the medullary segment has cells tha contribute to Na^+ reabsorption and K^+ secretion, similar to that seen in the cortica *principal* cells.[43,98] However, the majority of cells in the outer medullary colle tubule are comparable to the cortical *intercalated* cells (although there are variation between species), being involved in acid secretion by H^+-ATPase and H^+-K^+-ATPase pumps in the apical membrane (Fig. 5-3).[94,98,99] The activity of these pumps, which is much greater than that in the cortex,[35] is stimulated in part by acidemia and by aldosterone.[86,100] The net effect is that this segment plays an important role in acidifying the urine (i.e., in lowering the urine pH to its mi level) and in the excretion of ammonium, the major mechanism by which the excretes the dietary acid load (see Chapter 11).[101,102]

Potassium

The outer medullary cells are also capable of reabsorbing K^+,[103] perhaps via an apical membrane H^+-K^+-ATPase, similar to that in the cortical intercalated cells response can contribute to K^+ conservation in the states of K^+ depletion and also is essential for the recycling of K^+ within the medulla (see page 357).[103]

Water

The other major function of the outer medullary collecting tubule is its role concentration. This segment is impermeable to water in the[3] basal state. presence of ADH, however, water permeability rises markedly due to insertio aquaporin-2 water channels into the luminal membrane,[68] allowing equilibration with the hyperosmotic medullary interstitium (see Chapter 4).

Inner Medulla

The inner medullary collecting duct is composed of several cell types.[104] The initial one-third has cells similar in function to those of the principal and intercalated cells in th and outer medulla, while the inner two-thirds contains a decreasing number principal cells and is composed primarily of a distinct cell type that contribu Na^+ reabsorption and the production of a concentrated urine,[1,105,106] but plays a

lesser role in urinary acidification.[107]

Sodium

Na^+ entry into the inner medullary cells primarily occurs through an amilorid sensitive cation-selective channel.[108,109 and 110] The lumen-negative potential created by this movement of Na^+ may then promote passive Cl^- reabsorption via the paracellular route, similar to that in the cortical collecting tubule (see Fig. 5-12).

The factors that stimulate this reabsorptive process are incompletely unders aldosterone plays a contributory role.[43,62,106,108] The net effect is that the urine Na^+ concentration can be reduced to 5 meq/L or less in the presence of volu depletion, a setting in which aldosterone release is enhanced. As mentionec beginning of this chapter, passive Na^+ entry into the cells cannot be driven by a concentration gradient in this setting, since the lumen now has a lower Na^+ concentration than the cell. Rather the cell interior negative potential provi electrical gradient that promotes Na^+ movement into the cell.

In contrast, Na^+ reabsorption in the inner medulla falls with volume expansion, response that may be mediated both by the reduction in aldosterone secreti by increased release of atrial natriuretic peptide. The latter hormone activa guanylate cyclase, leading to the production of cyclic guanosine monophosp (GMP); this compound then appears to diminish Na^+ reabsorption by decreasing the number of open Na^+ channels in the apical membrane.[111,112 and 113]

Water

The inner medullary collecting tubule plays an important role in water reabs and the excretion of a concentrated urine. As in the other aspects of the col tubule, the water permeability of the inner medullary segment is increased b allowing osmotic equilibration with the hyperosmotic medullary interstitium.[3]

There is, however, one important difference from the response seen in the c outer medulla. The latter segments are impermeable to urea, both in the bas and in the presence of ADH. The inner medulla, on the other hand, has a re high basal urea permeability that is mediated by specific urea transporters i basolateral and, to a lesser degree, the apical membrane.[114,115] Furthermore, the net urea permeability is increased approximately fourfold by ADH, primarily increasing the number of luminal transporters.[114,116] These characteristics allow urea to accumulate in the medullary interstitium, where it accounts for abou of the interstitial solute and therefore limits urinary water loss by contributi excretion of a maximally concentrated urine (see Fig. 4-10).

Potassium

The inner medullary collecting tubule can contribute to the maintenance of K^+ balance. This segment usually reabsorbs K^+, an effect that is more pronounced witl

K^+ depletion. On the other hand, it can secrete K^+ after a K^+ load.[106] Tubular secretion presumably occurs through the cation-selective channels in the ap membrane.[109] These channels also may have a role in limiting the degree of maximum K^+ conservation. K^+-depleted subjects can only lower the urine K^+ concentration to a minimum of 5 to 15 meq/L; it may be that a lower

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luminal K^+ level is prevented by passive leakage out of K^+ from the cells through these channels.

Hydrogen

The inner medullary cells secrete hydrogen ions,[107,117] a response that is enhanced by stimuli similar to those in the other acid-secreting cells in the tubule: acidemia and aldosterone.[107]

Cell volume regulation

In addition to their transport functions, the inner medullary collecting tubule well as those in the thick ascending limb) must maintain their cell volume in of constantly changing osmotic pressure in the interstitium. Fluid restriction example, will sequentially raise ADH levels, increase interstitial osmolality, cell shrinkage by osmotic water movement out of the cells across the water-permeable basolateral membrane, which contains both aquaporin-3 and aqua water channels.[118] Fluid loading, on the other hand, will produce the opposite changes, leading to cell swelling.

Despite this changing environment, the tubular cells are able to maintain th volume by altering the concentration both of ions (sodium and potassium) ar organic solutes (called osmolytes) that have the advantage of not interferin protein function.[119] These processes are reviewed on page 135.

RENAL PELVIS, URETERS, AND BLADDER

Minor modifications in the composition of the urine can occur after the urine the tubules. The renal pelvis is modestly permeable to urea and water. As a urea may diffuse out of and water into the pelvis from the inner medulla.[120,121] Similar compositional changes of as much as 7 to 15 percent can occur in th and bladder, particularly in low-flow states when contact time is prolonged.[122,123]

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Chapter Six
Effects of hormones on renal function

The preceding chapters discussed the reabsorptive and secretory functions individual nephron segments. These processes are affected by a variety of hormones, some of which are synthesized within the kidney, such as renin (Chap. 2), calcitriol (the most active metabolite of vitamin D), protaglandins, kinins. As will be seen, these hormones play an important role in the mainte fluid and electrolyte balance, since they allow for *individual regulation* of the rate of excretion of the different solutes and water. The kidney also secretes eryth a hormone that promotes red cell production by the bone marrow.

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This chapter reviews the major mechanisms of action and the regulation of of those hormones that have important effects on renal function. How these hormones interact with other factors to permit the maintenance of fluid and electrolyte balance will then be discussed in Chaps. 8, 9, 10, 11 and 12.

MECHANISMS OF HORMONE ACTION

The hormones that influence renal function generally work by activating sp cellular proteins via phosphorylation or by inducing the synthesis of new pr hormone can initiate these events by affecting adenylyl cyclase, guanylyl c phosphatidylinositol turnover, or, with steroid hormones, ribonucleic acid (R transcription (Table 6-1).[1,2,3,4,5,6,7,8 and 9]

Adenylyl Cyclase

Some of the responses mediated by adenylyl cyclase begin by attachment o hormone to its specific receptor on the basolateral membrane of the tubular hormone-receptor complex then affects the activation state of a guanine nu regulatory protein, such as the stimulatory (G_s) or inhibitory (G_i) G proteins (Fig. 6-1).[1,2,7,8] G_s, for example, has three components, alpha (α), beta (β), and ga (γ), with the α subunit normally binding guanosine diphosphate (GDP) in th state. Binding of hormone to its receptor causes the α subunit to release G up intracellular guanosine triphosphate (GTP), and at least partially dissoc the β-γ subunit. This G_{α}-GTP complex is able to activate adenylyl cyclase, lead the conversion of adenosine triphosphates (ATP) into cyclic adenosine monophosphate (AMP).

The generation of cyclic AMP is followed sequentially by activation of a pro kinase (due to binding of cyclic AMP to a regulatory subunit of the kinase)[10] phosphorylation of specific cell proteins (by the transfer of phosphate from intracellular ATP to the protein), and the physiologic effects of the hormone Hormone activity is eventually shut off by a GTPase intrinsic to the α molec

that hydrolyzes bound GTP.[1] The β -γ subunit may also be an important regulato these processes.[11]

Table 6-1 Mechanism of action of major hormones affecting renal function

Adenylyl cyclase		Prosphatidylinositol turnover	RNA transcription (steroid hormones)
Stimulate	Inhibit		
Vasopressin (V_2) Parathyroid hormone β-Adrenergic Prostaglandins (vascular effect)	Prostaglandins alpha$_2$-Adrenergic Angiotensin II (tubular effect)	Vasopressin (V_1) Angiotensin II Norepinephrine (α_1-adrenergic) Parathyroid hormone	Aldosterone Calcitriol

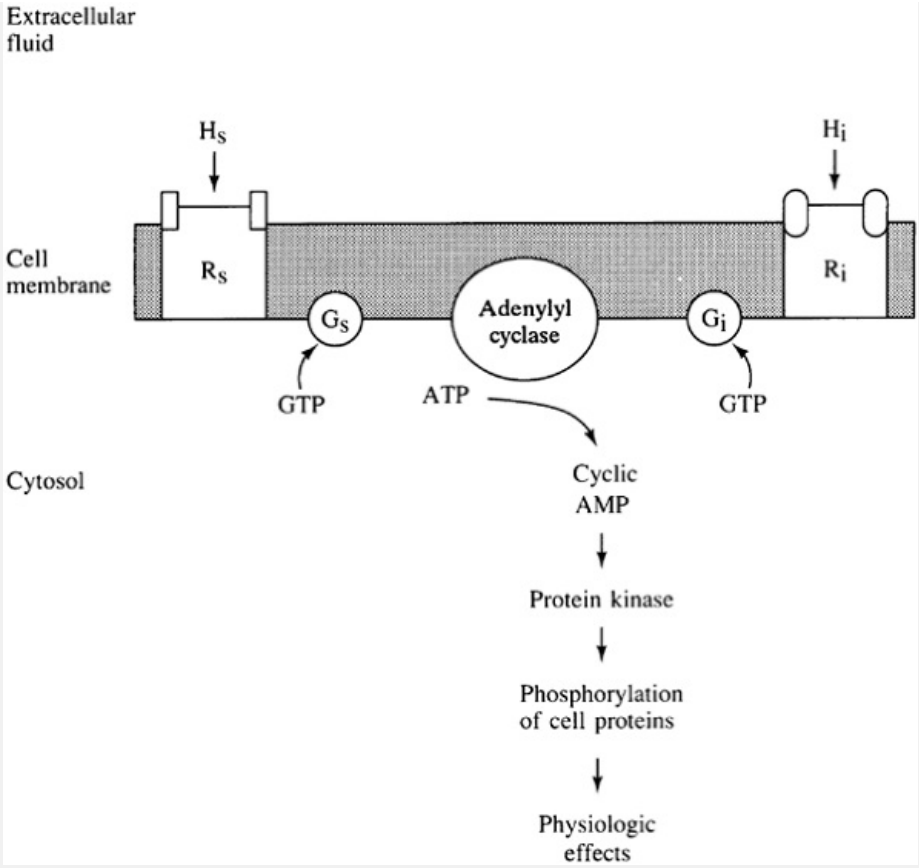

Figure 6-1 Schematic representation of the adenylyl cyclase–cyclic AMP sy
Activation begins when a stimulatory hormone (H_S) combines with its receptor (R_S). The hormone-receptor complex interacts with the regulatory protein (G_S), allowing it to take up guanosine triphosphate (GTP). This activated form then stimulates adenylyl cyclase. This step is followed sequentially by the formation of cyclic AMP, activation of a protein kinase, phosphorylation of proteins, and the physiologic effects of the hormone. Other hormones (H_i) inhibit adenylyl cyclase by binding to their receptors (R_i) and then activating an inhibitory regulatory protein (G_i).

On the other hand, activation of G_i results in diminished adenylyl cyclase activity and a reduction in cellular cyclic AMP levels.[1,2] Like G_S, G_i also dissociates into α, β, and γ subunits.

Guanylyl cyclase

An analogous but separate intracellular pathway involves the activation of *guanylyl cyclase*, leading to the subsequent formation of cyclic guanosine monophosphate (GMP) and phosphorylation of specific cell proteins.[3,9] This pathway appears to mediate the actions of atrial natriuretic peptide (ANP; see below) and of direct vasodilators, such as nitroprusside and nitroglycerine.

The initial event in this system is, for ANP, attachment to its extracellular r
the cell membrane. This transmembrane protein has a conserved intracellul

regulatory and cyclase catalytic domains.[9,12] Stimulatory and inhibitory regulatory proteins, as with adenylyl cyclase, do not seem to be involved.

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Binding of ANP to its receptor appears to induce a conformational change (dimerization) in the kinase domain, leading to activation of guanylyl cyclas and the generation of cyclic GMP.[3] In the kidney, this process leads to closing of Na^+ channels in the luminal membrane in the inner medullary collecting duc below), which is not well understood.[13]

Phosphatidylinositol Turnover

Another mechanism of hormone action involves the turnover of membrane li process is again initiated by binding of the hormone (e.g., angiotensin II ar norepinephrine) to its cell receptor, leading to the activation of a G protein G_q, as compared to G_s, which stimulates adenylyl cyclase) and the formation o GTP (Fig. 6-2).[1,4] In this setting, however, membrane-bound phospholipase C, rather than adenylyl cyclase, is activated.

Phospholipase C then promotes the breakdown of a membrane lipid, phosphatidylinositol 4,5-biphosphate, into two compounds: inositol 1,4,5-triphosphate (IP_3) and diacylglycerol. [1] mediates the acute effect of the hormone by increasing the release of calcium from stores in endoplasmic reticulum a enhancing the uptake of extracellular calcium. The net effect is an elevatio cytosolic calcium concentration. This calcium binds to calmodulin, leading t phosphorylation

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of specific cell proteins and the physiologic effects of the hormone. The ca effect, however, is short-lived, and sustained action of the hormone is med diacylglycerol, which activates protein kinase C. The latter compound then the desired changes in cell activity.

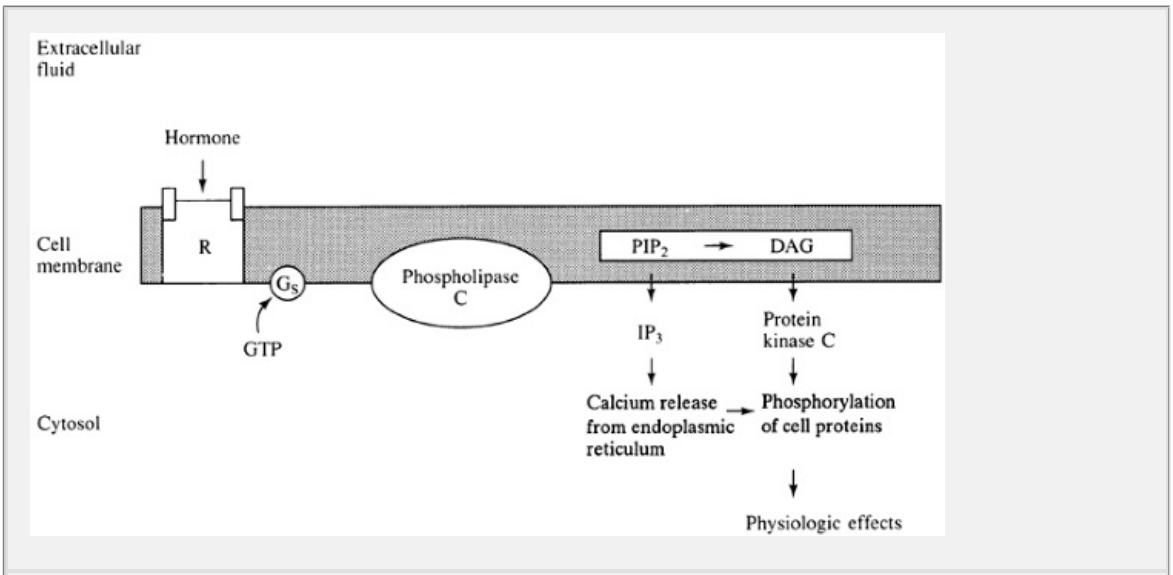

Figure 6-2 Schematic representation of the phosphatidylinositol pathway. T combination of a hormone with its receptor (R) leads to activation of a

stimulatory regulatory protein (G$_s$) with a subsequent increase in activity of membrane-bound phospholipase C. This enzyme results in the breakdown membrane lipid, phosphatidylinositol 4,5-biphosphate (PIP$_2$), into two compounds: inositol 1,4,5-triphosphate (IP$_3$) and diacylglycerol (DAG). The former mediates the acute action of the hormone by inducing the release calcium from stores in endoplasmic reticulum; the latter is responsible for sustained hormone effect by activating protein kinase C, leading to the phosphorylation of cell proteins.

The formation of diacylglycerol may also play an additional role, since the at position 2 is arachidonic acid, the precursor of the prostaglandins. Arach acid can be released from diacylglycerol by phospholipase A$_2$, an enzyme that can be hormonally activated. This may explain, for example, how antidiuretic ho (ADH) increases local prostaglandin production and, in part, how prostagla modulate the actions of ADH (see below).[14,15]

RNA Transcription

Steroid hormones, such as aldosterone, calcitriol, and cortisol, have a diffe mechanism of action, involving new protein synthesis (Fig. 6-3).[5,6] These hormones are lipid-soluble and therefore are able to diffuse across the cell membrane an with specific receptors that are located in the cytosol rather than the cell

membrane.[5,6] Attachment of hormone to its receptor results in unmasking of t DNA-binding site on the receptor.[5,6,16] As a result, the hormone-receptor complex able to migrate into the nucleus and to bind to specific sites near the gene responsible for the physiologic actions of the hormone. Subsequent steps i messenger RNA and ribosomal RNA transcription and the eventual synthesis proteins.

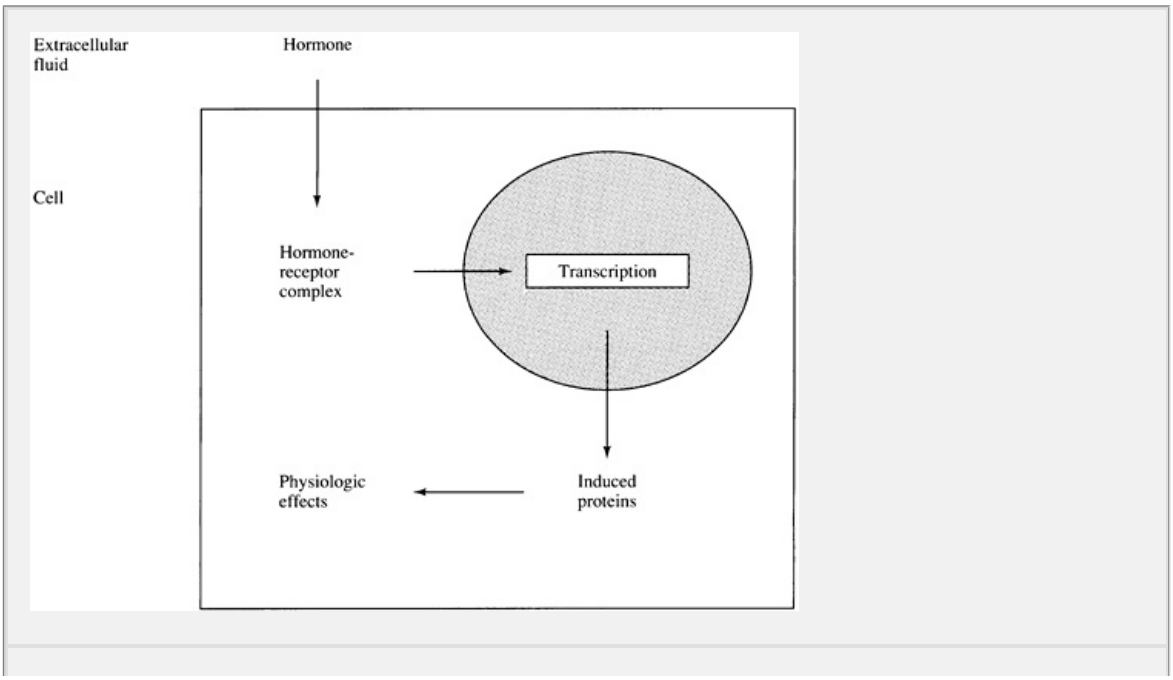

Figure 6-3 Model for the mechanism of action of steroid hormones, such as aldosterone and calcitriol. The hormone enters the cell by diffusion and combines with a specific receptor in the cytosol. The active hormone-rece complex, which unmasks the DNA binding site on the receptor, then migra the nucleus where it interacts with specific genes, leading to RNA transcr and the eventual production of new proteins that are responsible for the physiologic actions of the hormone.

The discovery of analogs of steroid hormones, which have receptor comple properties different from those of the endogenous hormones, may permit th administration of agents that possess the desirable properties of these hor circumvent their adverse effects. As an example, oxacalcitriol, a vitamin D analog, has a low affinity for vitamin D–binding protein; as a result, more o circulates in the free (unbound) form, allowing it to be metabolized more ra calcitriol.[17] This leads to a shorter half-life, which could explain the small an transient stimulation of intestinal calcium absorption and a lower likelihood inducing hypercalcemia than with calcitriol itself. The ability to minimize th hypercalcemia with a vitamin D analog may be important clinically when the given to suppress secondary hyperparathyroidism in patients with chronic r failure (see page 207).

A more important clinical example of tissue-selective activity occurs with se estrogen receptor modulators, such as raloxifene. In vitro experiments sugg raloxifene has different effects from estradiol at the estrogen receptor, incl differential modulation of DNA response elements,[18] causing a different conformational change in the transactivation domain of the ligand-binding d[19] In patients, raloxifene preserves the beneficial effects of estrogen on bone apparently the heart[20] without promoting endometrial hyperplasia or increasing risk of breast cancer.[21]

ANTIDIURETIC HORMONE AND WATER BALANCE

Antidiuretic hormone (the human form is called arginine vasopressin) is a p synthesized in the supraoptic and paraventricular nuclei in the hypothalamu (Fig. 6-4).[22] Secretory granules containing ADH migrate down the axons of the supraopticohypophyseal tract into the posterior lobe of the pituitary, where stored and subsequently released after appropriate stimuli. In addition, son secretory granules produced in the paraventricular nuclei enter the cerebro fluid or the portal capillaries in the median eminence[22] (The latter effect probably accounts for the observation that lesions of the posterior pituitary supraopticohypophyseal tract below the median eminence do not usually lea permanent diabetes insipidus (ADH lack), since ADH produced in the hypoth still has access to the systemic circulation.

ADH is rapidly metabolized in the liver and kidney, with a half-life in the cir only 15 to 20 min.

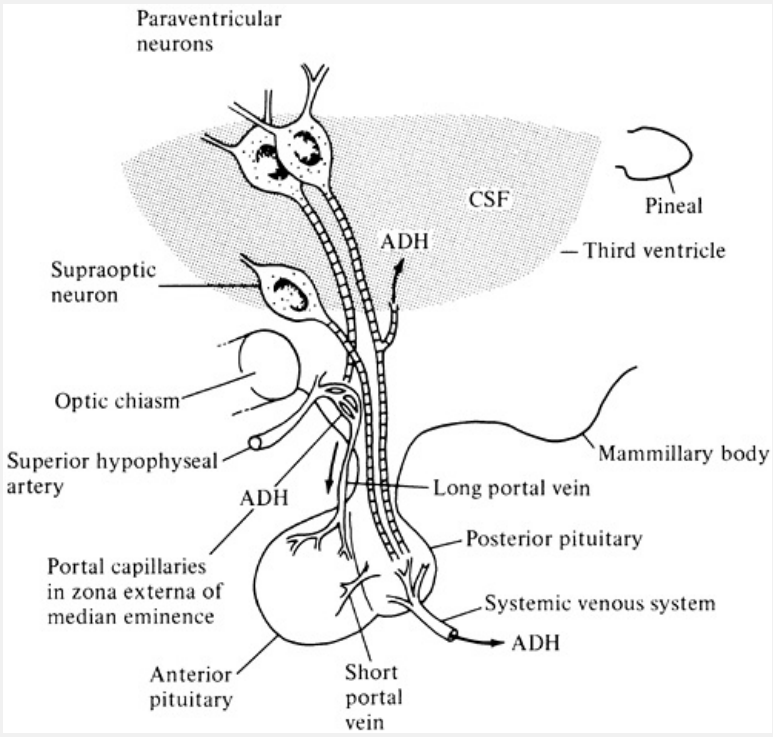

Figure 6-4 Diagram of the mammalian hypothalamus and pituitary gland sho pathways for the secretion of antidiuretic hormone (ADH). The hormone is formed in the supraoptic and paraventricular nuclei, transported in granul along their axons, and then secreted at three sites: the posterior pituitary the portal capillaries of the median eminence, and the cerebrospinal fluid of the third ventricle. (*Adapted from Zimmerman EA, Robinson AG, Kidney Int 10:12, 1976. Reprinted by permission from Kidney International.*)

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Actions

ADH is the primary physiologic determinant of the rate of free water excreti major renal effect is to augment the water permeability of the luminal memb the cortical and medullary collecting tubules, thereby promoting water reab via osmotic equilibration with the hypertonic interstitium (see Chapter 4 for a review of the countercurrent mechanism and of the other tubular mechanisms by whic can promote urinary concentration). The ADH-induced increase in collecting water permeability occurs primarily in the principal cells, as the adjacent ir cells are mostly involved in acid or bicarbonate secretion (see Chapters 23 and 24).

There are two major receptors for ADH: the V_1 and V_2 receptors. Activation of the V_1 receptors induces vasoconstriction and enhancement of prostaglandin relea below), while the V_2 receptors mediate the antidiuretic response as well as oth functions (see Fig. 6-5).[25] A third receptor, the V_3 or V_{1b} receptor, appears to mediate the effect of ADH on the pituitary, facilitating the release of ACTH.[26] Activation of adenylyl cyclase by ADH via the V_2 receptor initiates a sequence of

events in which a protein kinase is activated, leading to preformed cytoplas

vesicles that contain unique *water channels*.[27,28] and[29] The principal ADH-sensitive water channel, called *aquaporin-2*, is normally stored in the cytosol[29] and[30] under the influence of ADH, it moves to and fuses with the luminal membrane,[24,31] thereby allowing water to be reabsorbed down the favorable osmotic gradient.[32,33] This process results in the formation of intramembranou particle aggregates that are visible on electron microscopy (see Fig. 6-6).[31,34]

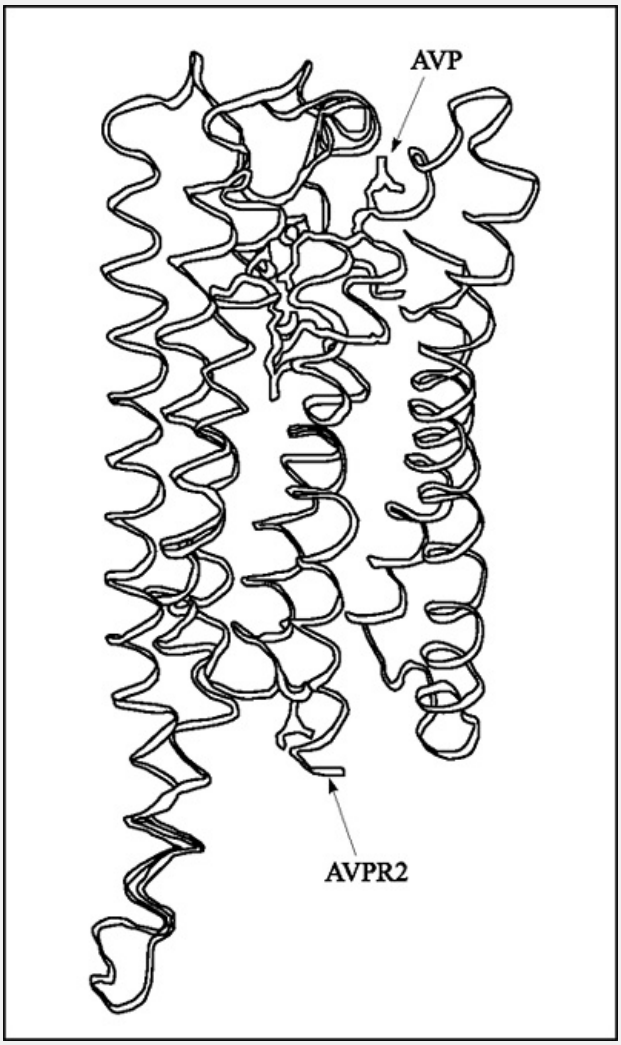

Figure 6-5 Interaction between AVP and its receptor. Schematic representat of the relation between arginine vasopressin (AVP, antidiuretic hormone) a AVP receptor 2 (AVPR2). The receptor is depicted as seven coiled red ribl AVP is nestled within a pocket formed by the transmembrane domains of A (*Adapted from Bochet DG, Oksche A, Rosenthal E, et al: Am J Soc Nephrol 8:1951, 1997. Used with permission.*)

Once the water channels span the luminal membrane and permit osmotic wa movement into the cell,[34] water is rapidly returned to the systemic circulation

across the basolateral membrane, which both is water permeable (even in t absence of ADH) and has a much greater surface area than the luminal men[35] When the ADH effect has worn off, the water channels aggregate within cla coated pits, from which they are removed from the luminal membrane by end and returned to the cytoplasm.[31,34]

A defect in any step in this pathway, such as attachment of ADH to its recep function of the water channel, can cause resistance to the action of ADH ar increase in urine output. This disorder is called nephrogenic diabetes insip (seepage 754) As examples:

Figure 6-8 ADH-induced intramembranous particle aggregates (arrows) on luminal membrane of the toad bladder, an epithelium similar to the mamma collecting tubule. Aggregates are seen between and near the bases of mic (MV). These changes correlate specifically with enhanced water permeabi (*From Kachadorian WA, Levin SD, Wade JB, et al: J Clin Invest 59:576, 1977, by copyright permission of the American Society for Clinical Investigatio*)

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1. Hereditary nephrogenic DI is usually transmitted in an X-linked fashion, genetic defect involving a number of different mutations (or deletions) i[2] receptor gene that can lead to decreased hormone binding, impaired intracellular transport or coupling to the adenylyl cyclase system, or di synthesis or accelerated degradation of the receptor.[36,37]
2. A second, autosomal recessive form of hereditary nephrogenic DI has b described in which there appears to be mutations in the aquaporin-2 gene.[30,38,39,40] These mutations may lead to impaired trafficking of the channels with lack of fusion with the luminal membrane and/or decrease

channel function.[30,39]

Electrolyte handling

In addition to increasing water permeability, ADH appears to affect a variet processes in the cortical collecting tubule, enhancing the reabsorption of Na^+ and the secretion of K^+.[23,24] and[25] The physiologic role of these effects is uncerta since ADH does not appear to be important in the maintenance of electrolyt base balance. However, the stimulation of K^+ secretion allows ADH to *regulate water transport without interfering with that of* K^+. The rate of distal urinary flow is normally an important determinant of the rate of K^+ secretion and subsequent excretion (see Chap. 12). ADH-stimulated water reabsorption should, by lowerin distal flow, inappropriately diminish K^+ secretion; this is prevented by the direct stimulatory effect of ADH on K^+ handling.[42]

Vascular resistance

As mentioned above, the antidiuretic effects of ADH are mediated by the V_2 receptors, which, in the kidney, stimulate adenylyl cyclase activity.[14] In comparison, the V_1 receptors promote phosphatidylinositol turnover and primarily act to i vascular resistance (hence the name *vasopressin*).[44] ADH release is markedly stimulated in the presence of effective circulating volume depletion (see be general, the vasopressor role of ADH is relatively minor,

as the blood pressure is maintained primarily by the renin-angiotensin and sympathetic nervous systems (see Chap. 8).[44]

Renal prostaglandins

ADH stimulates the production of prostaglandins (particularly prostaglandin E_2 and prostacyclin) in a variety of cells within the kidney, including those in the t ascending limb, collecting tubules, medullary interstitium, and glomerular mesangium.[45,46] and[47] The prostaglandins that are produced then impair both antidiuretic and vascular actions of ADH.[15,48,49] and[50] The former effect is in part due to a reduction in ADH-induced generation of cyclic AMP; stimulation of inhibitory regulatory protein (N_i) (see Fig. 6-1) and of protein kinase C formation (see Fig. 6-2) appears to contribute to this response.[15,48]

These findings have suggested that a *negative feedback loop* may be present in which ADH enhances local prostaglandin production, thereby preventing excessive antidiuretic response. It is of interest, however, that the effect o prostaglandin synthesis is mediated by not the antidiuretic V_2 receptors.[45,47] Activation of the V_1 receptors promotes phosphatidylinositol turnover, leading to the formation of diacylglycerol, from which arachidonic precursor of the prostaglandins, can be released via activation of phospholi

(see Fig. 6-2).[28,51]

The renal site of V_1-receptor stimulation of prostaglandin synthesis is uncertai collecting tubular cells have been found to contain 10 to 20 percent of the total ADH receptors in the cortical collecting tubule) and V_2 receptors,[52,53] and it is possible that a local negative feedback system is in place.[45] However, stimulation of these V_1 receptors appears to occur only at supraphysiologic concentrations of ADH.[54]

Alternatively, the major function of the ADH-prostaglandin relationship may the regulation of renal hemodynamics. ADH, acting via V_1 receptors, is a systemic and renal vasoconstrictor.[50] The local production of prostaglandins by tl kidney (particularly the glomeruli) minimizes the increase in renal vascular resistance, thereby maintaining renal perfusion.[50]

Other extrarenal effects

ADH has other renal effects of potential clinical importance, including a rol regulation of cortisol release and of factor VIII and von Willebrand's factor vascular endothelium.[25] ADH is cosecreted with corticotropin releasing hormon (CRH) from single neurons in the paraventricular and supraoptic nuclei[22] and promotes the secretion of ACTH by corticotropes in the pituitary via activation of V_3 receptors.[26] Cortisol has an inhibitory effect on the secretion of both CRH and ADH from paraventricular nuclei. Adrenal insufficiency (in which cortisol secretion is removes this inhibitory effect, leading to a persistent rise in ADH release.[22,55] The associated impairment in water excretion can result in water retention and hyponatremia, a common electrolyte disorder in patients with cortisol defici page 710).

ADH, acting through the V_2 receptors, also can stimulate the release of factor V and von Willebrand factor from vascular endothelium.[25] Although this response is of uncertain significance in normal subjects, the administration of ADH has be effective in transiently improving the bleeding tendencies in a

variety of disorders, including hemophilia, von Willebrand's disease, and ac renal failure.[25,56]

Control of ADH Secretion

The major stimuli to ADH secretion are hyperosmolality and effective circul volume depletion (Figs. 6-7 and 6-8).[57,58] These responses are appropriate, since the water retention induced by ADH will both lower the plasma osmolality (P_{osm}) and raise the extracellular volume toward normal. Conversely, lowering the P_{osm} by water loading will diminish ADH release. The ensuing reduction in collectin water reabsorption will decrease the urine osmolality (U_{osm}), thereby allowing the excess water to be excreted. Since the half-life of ADH in the circulation is min, the maximum diuresis after a water load is delayed for 90 to 120 min, t

required for the metabolism of the previously circulating ADH.

Osmoreceptors

The location of the osmoreceptors governing ADH release was demonstrate classic experiments of Verney.[59] These experiments utilized local infusions of hypertonic saline, which raised the P_{osm} locally without affecting the systemic P_{osm}. Such an infusion into the carotid artery, but not the femoral artery, resulted enhanced ADH secretion and an antidiuresis. These findings indicated that osmoreceptors, which are separate from the hormone-producing cells, are l the brain, not in the periphery.[55]

Studies in rats suggest that separate osmoreceptors are located in the upp bowel.[60] Thus, ingestion of a hypertonic NaCl solution leads to a rapid incre ADH release that is prevented by lesions in the splanchnic nerves. The phy role of these osmoreceptors is unclear; they may contribute to the regulatic water balance or participate in the sensation of satiety.

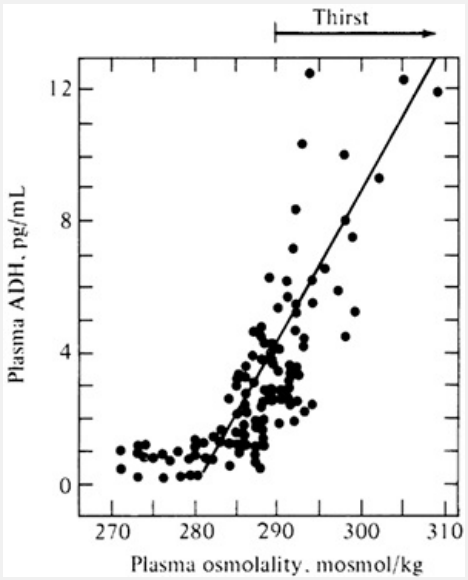

Figure 6-7 Relationship of plasma ADH concentration to plasma osmolality normal humans in whom the plasma osmolality was changed by varying the of hydration. Notice that the osmotic threshold for thirst is a few mosmol/ higher than that for ADH. (*Adapted from Robertson GL, Aycinena P, Zerbe RL, Am J Med 72:339, 1982. Used with permission.*)

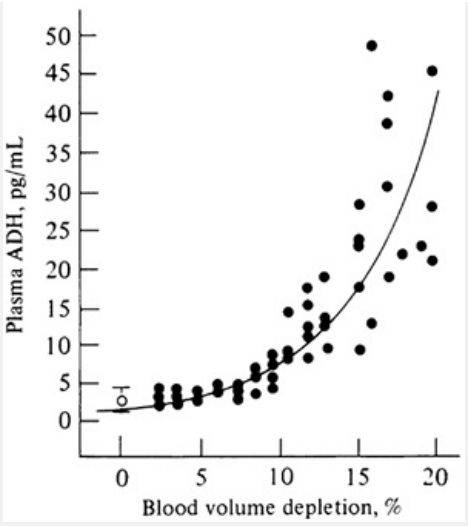

Figure 6-8 Relationship of ADH levels to isosmotic changes in blood volume the rat. Notice that much higher ADH levels can occur with hypovolemia th hyperosmolality, although a relatively large fall in blood volume is require this response is initiated. (*From Dunn FL, Brennan TJ, Nelson AE, Robertson GL*, J Clin Invest *52:3212, 1973, by copyright permission of the American Society for Clinical Investigation.*)

The increment in P_{osm} is perceived by the hypothalamic osmoreceptors as an effective osmotic gradient between the plasma and the receptor cell. It is p that the osmoreceptor is activated by changes in intracellular water conten altering intracellular osmolality. Water channels make the osmoreceptor cel membrane permeable to water, permitting water movement out of the cell wi hypernatremia (or other causes of hyperosmolality) and into the cell with hyponatremia. The ensuing reduction in cell volume in hypernatremia increa activity of stretch-inactivated cation channels,[6162] leading to depolarization of the cell, which in some way stimulates ADH secretion and synthesis. These ste reversed with hyponatremia.

In general, the *plasma sodium concentration is the primary osmotic determina ADH release*, since Na^+ salts are the major effective extracellular solutes (see page 246).[58] In contrast, increments in the plasma urea concentration (measured blood urea nitrogen, or BUN) do not affect ADH secretion, because urea is ineffective osmole that readily crosses cell membranes and will not induce movement out of the osmoreceptor cells.

The contribution of glucose, the other major extracellular solute, to ADH re somewhat more complicated.[63] In normal subjects, a rise in the plasma glucose concentration increases the release of insulin. Insulin can then promote glu entry into the osmoreceptor cells, making glucose an ineffective osmole tha affect the secretion of ADH. In uncontrolled diabetes mellitus, however, hyperglycemia is associated with insulin deficiency. In this setting, glucose

an effective osmole that can promote ADH release.[63]

The osmoreceptors are extremely sensitive, responding to alterations of P_{osm} in the as little as 1 percent.[57,58,64] In humans, the osmotic threshold for ADH release about 280 to 290 mosmol/kg (Fig. 6-7).[57,58] Below this level, there is little if any circulating ADH, and the urine should be maximally dilute, with an osmolalit 100 mosmol/kg. Above the osmotic threshold, there is a progressive and rel linear rise in ADH secretion. This system is so efficient that the P_{osm}

usually does not vary by more than 1 to 2 percent, despite wide fluctuation intake. As an example, a large water load will lower the P_{osm} and essentially shut off the release of ADH. The net effect is the excretion of more than 80 percent excess water within 4 h.

Role of thirst

The response to hyperosmolality, as can occur with water loss due to exerc induced sweating on a hot day, includes a second factor, as thirst as well a release is stimulated (Fig. 6-9). The net effect is that both increased water intak and reduced water excretion combine to return the P_{osm} toward normal (Fig. 6-9).[57] The osmotic threshold for thirst (which can be estimated only indirectly) has be reported to be either 2 to 5 mosmol/kg higher than or roughly equivalent to ADH release.[65,66] It is not clear whether these parameters are controlled by t same or by two different osmoreceptors.

Even though thirst is regulated centrally (including cortical areas that influ nonessential or social drinking), it is sensed peripherally as the sensation mouth.[55,67] The cessation of thirst (satiety) is also mediated initially in the periphery by *oropharyngeal mechanoreceptors* that are stimulated by swallowing relatively large volumes of fluid.[68,69,70]

It might be expected, for example, that the hyperosmotic stimulus to thirst a release would be attenuated as the P_{osm} returns toward normal. However, studies experimental animals and humans have demonstrated that drinking leads to marked, but transient, suppression of thirst and ADH within 10 to 20 min, *before there has been any appreciable reduction in the* P_{osm} *and*.[68,69,70] This

response can be considered to be appropriate, since there is a 30- to 60-m before ingested water is completely absorbed. Thus, water intake would be excessive if it continued until the P_{osm} were normalized, since there would still be substantial volume of nonabsorbed water remaining in the gastrointestinal t oropharyngeal receptors allow *repletion of the water deficit* to occur in discrete steps, as the suppression of thirst and ADH release will be transie as the P_{osm} remains elevated.

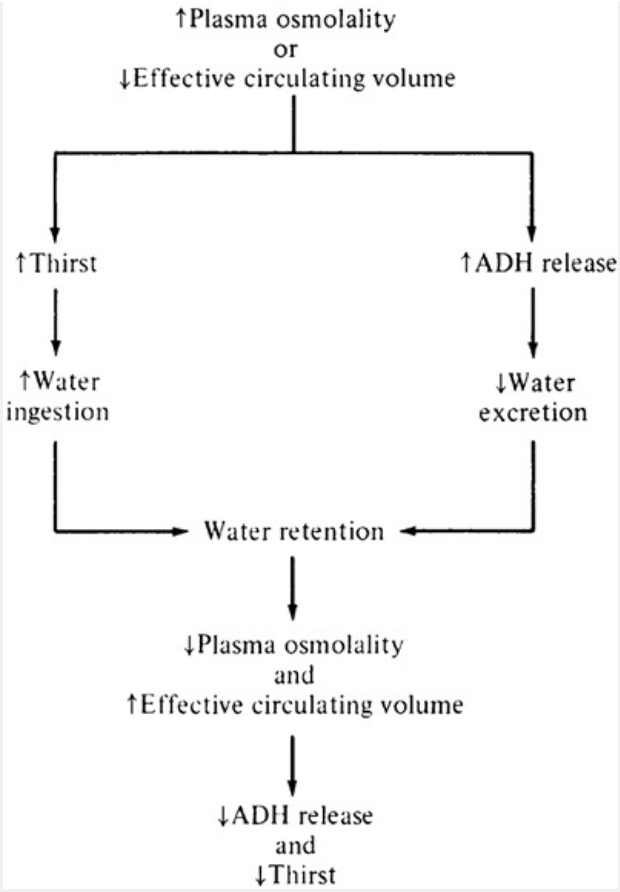

Figure 6-9 Feedback loop for the stimulation of ADH release and thirst.

Like ADH, thirst is also stimulated by volume depletion[67] however, how this occurs is incompletely understood.

Volume receptors

Patients with effective circulating volume depletion—as with vomiting, cirrhosis, heart failure (see Chap. 8)—may secrete ADH, even in the presence of a low plasma osmolality.[57,71,72] and[73] These findings indicate the existence of nonosmolal, volume-sensitive receptors for ADH release (see Fig. 6-8). Parasympathetic afferents in the carotid sinus baroreceptors are of primary importance in this response. Changes in the rate of afferent discharge from these neurons affect the activity of the vasomotor center in the medulla and subsequently the rate of ADH secretion.[14] The cells in the paraventricular nuclei. The supraoptic nuclei, in comparison, are important for osmoregulation but do not appear to participate in this volume response.[14])

Although low-pressure receptors in the left atrium play a contributory role in some animal species, they appear to be less important in humans, in whom a moderate reduction in intracardiac filling pressure does not stimulate ADH release unless there is a concomitant decline in systemic blood pressure.[74,75]

The carotid sinus baroreceptors, like other "volume" receptors, are actually

receptors. However, they are able to function indirectly as volume receptor this occurs can be appreciated from the formula relating pressure, cardiac and vascular resistance:

Mean arterial pressure=cardiac output × systemic vascular resistance

Thus, a fall in cardiac output due to volume depletion or primary cardiac di lead to an initial decline in mean arterial pressure, which can be sensed by carotid sinus baroreceptors. In experimental models of heart failure, for exa there is a fall in urine output and a rise in urine osmolality. These changes prevented by carotid baroreceptor denervation, indicating that the incremer release is governed by baroreceptor afferents.[76]

This product of cardiac output and systemic vascular resistance actually ec pressure drop across the circulation, i.e., mean arterial pressure minus me pressure. However, the latter is normally so much lower (1 to 7 mmHg) than former that ignoring the venous pressure produces only a small error.

The sensitivity of the volume receptors is different from that of the osmorec The latter respond to alterations in P_{osm} as little as 1 percent (Fig. 6-7); in comparison, small, acute reductions in volume that are sufficient to increas secretion of renin and norepinephrine *have little effect on the release of ADH*

Acutely, ADH is secreted nonosmotically in humans only if there is a large e change in the effective volume to produce a reduction in the systemic blood pressure.[75,76] Once hypotension occurs, there may be a marked rise in ADH secretion, resulting in circulating hormone levels that can substantially exc induced by hyperosmolality (compare Figs. 6-7 and 6-8).[57,75] Acute mild volume expansion generally has little effect on ADH release[77] in humans.

Interactions of the osmotic and volume stimuli

The hormone-producing cells in the supraoptic and paraventricular nuclei r input from both the osmotic and the volume receptors, resulting in positive negative interactions.[57,58] Thus, volume depletion potentiates the ADH respons hyperosmolality but can prevent the inhibition of ADH release normally indu fall in the P_{osm} (Fig. 6-10).[57,73,78]

These relationships are often clinically relevant. As an example, hypovolem are a common cause of water retention and hyponatremia (see Chap. 33). This occurs in part because the nonosmotic stimulation of ADH release prevents normal excretion of ingested water. On the other hand, chronic volume expa in primary hyperaldosteronism, can shift the osmotic threshold upward, lead mild elevation in the P_{osm} and plasma Na^+ concentration.[58]

Other factors affecting ADH secretion

ADH release can also be influenced by a variety of other factors that are n related to osmolal or volume balance (Table 6-2). Nausea is probably the most potent, potentially leading to as much as 500-fold rise in circulating ADH le

neither the physiologic role of this response nor the mechanism by which it well understood.[79]

In some circumstances, these additional stimuli to ADH release can become important. In surgical patients, for example, elevated levels of ADH may per several days after the operation,[80] a stress response that appears to be mediated pain afferents.[81] If a large amount of free water is given in this setting,

water retention, severe hyponatremia, and potentially irreversible neurolog may ensue.[82]

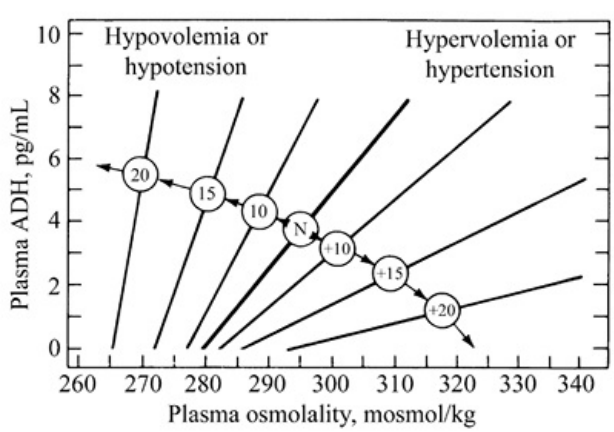

Figure 6-10 The influence of hemodynamic status on the osmoregulation of in otherwise healthy humans. The numbers in the center circles refer to tl percentage change in volume or pressure; N refers to the normovolemic n tensive subject. Notice that the hemo-dynamic status affects both the slo the relationship between the plasma ADH and osmolality and the osmotic threshold for ADH release. (*Adapted from Robertson GL, Shelton RL, Athar S, Kidney Int 10:25, 1976, Reprinted by permission from Kidney International.*)

Pregnancy, on the other hand, lowers the osmoregulatory threshold for ADH and thirst.[65] As a result, there is a downward resetting of the osmostat, leadi fall in the normal plasma Na^+ concentration by about 5 meq/L. This change, whic rapidly reversed after delivery, may be mediated by increased release of hu chorionic gonadotropin (hCG).[83] hCG may act indirectly via the release of relaxi[84]

Table 6-2 Factors influencing ADH secretion

Stimuli	Inhibitors
Hyperosmolality	Hypoosmolality
Hypovolemia	Hypervolemia
Stress, e.g., pain	Ethanol

Nausea Pregnancy Hypoglycemia Nicotine Morphine Other drugs (see Table 23-3)	Phenytoin

ALDOSTERONE

The steps involved in adrenal cortical steroid synthesis are illustrated in Fig. 6-11. The major adrenal hormones are synthesized in different areas of the adrer aldosterone in the zona glomerulosa, and glucocorticoids (particularly corti androgens, and estrogens in the zona fasciculata and reticularis. The zona glomerulosa is well adapted for the production of aldosterone.[85,86] It has a low concentration of 17α-hydroxylase, the enzyme necessary for cortisol and ar synthesis. More importantly, the final steps in the conversion of corticoster aldosterone, the addition of an hydroxyl group at the 18-carbon position an subsequent oxidation to an aldehyde, occur only in the zona glomerulosa.[85,86] These two reactions are mediated by a single multifunctional cytochrome P- enzyme called aldosterone synthase (or corticosterone methyl oxidase),[86,87 and 88] the activity of which is normally suppressed in the zona fasciculata. This s is important physiologically because it prevents aldosterone secretion from inappropriately regulated by ACTH.

Aldosterone synthase has over 95 percent homology with 11-hydroxylase (w converts deoxycortisol to cortisol in the zona fasciculata), and their genes located in the same region on chromosome 8.[89] This relationship becomes clinically important in the familial disorder glucocorticoid-remediable hyperaldosteror chimeric gene, containing the regulator portion of 11β-hydroxylase

and the synthetic region of aldosterone synthase, is formed in this conditio which the regulator portion of 11β-hydroxylase makes aldosterone synthesis dependent.[90]

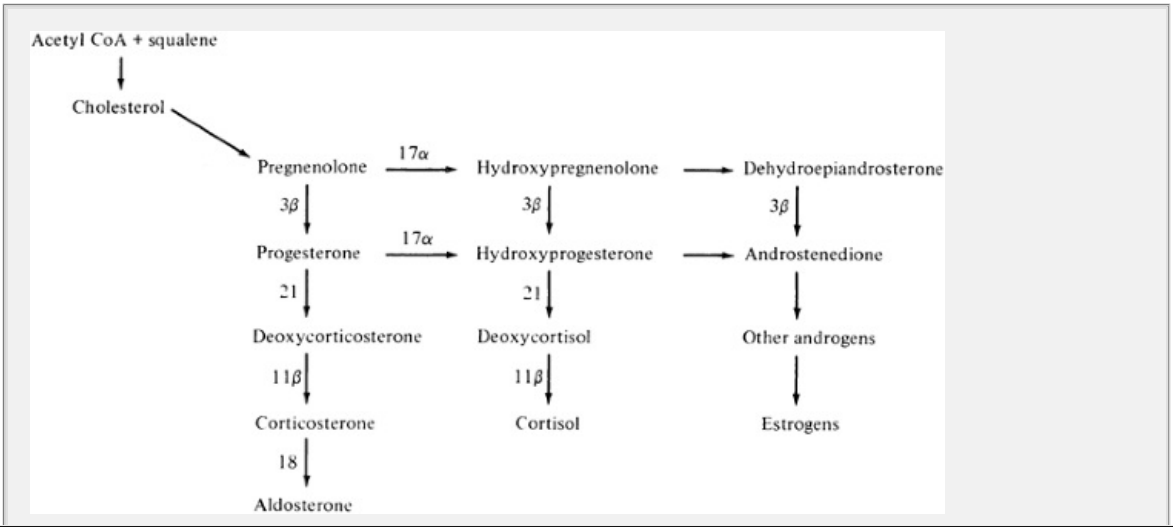

Figure 6-13 Schematic pathways of adrenal steroid biosynthesis. The numb at the arrows refer to specific enzymes: 17α equals 17α-hydroxylase; 3β e 3β-hydroxysteroid dehydrogenase; 21 equals 21-hydroxylase; 11β equals hydroxylase; 18 refers to a two-step process resulting in the addition of a aldehyde at the 18-carbon position. The last reactions occur only in the z glomerulosa, which is the site of aldosterone secretion.

Actions

Aldosterone acts primarily in the distal nephron to increase the reabsorpti and Cl^- and the secretion of K^+ and H^+ (Fig. 6-12).[2] Like other steroid hormones, aldosterone acts by diffusing into the tubular cell and then attaching to a s cytosolic receptor (Fig. 6-3).[5,91] The hormone-receptor complex then migrate to the nucleus, where it interacts with specific sites on the nuclear chromat enhance messenger RNA and ribosomal RNA transcription. This in turn is tr into the synthesis of new proteins called aldosterone-induced proteins (AIP [92,93] The time required for these processes to occur accounts for the 90-min late before electrolyte excretion is affected.

How these proteins act is not well understood. Aldosterone increases the a of the α subunit and promotes the phosphorylation of the β and γ subunits o luminal membrane Na^+ channel through which luminal Na^+ enters the cells.[94,95] One early AIP is a serine kinase that appears to regulate Na^+ channel activity.[96,97] Another AIP is a K-ras2, but its actions are not known.[98]

Cortisol as a mineralocorticoid

Cortisol, which circulates in much higher concentrations than aldosterone, equal affinity to the aldosterone receptor.[99]

However, cortisol does not act as a major mineralocorticoid because target such as the aldosterone-sensitive cells in the collecting tubules and saliva possess enzymes, such as 11β -hydroxysteroid dehydrogenase, that conver to cortisone and other inactive metabolites.[6,100,101] Thus, only aldosterone physiologically activates the receptor. If, however, 11β -hydroxysteroid dehydrogenase is inactivated, then cortisol can act as the primary endogen mineralocorticoid, leading to manifestations of primary hyperaldosteronism hypertension, hypokalemia, and metabolic alkalosis (see Chap. 27). One example is the chronic ingestion of licorice, which contains glycyrrhetinic acid, an inhi 11β-hydroxysteroid dehydrogenase.[101,102]

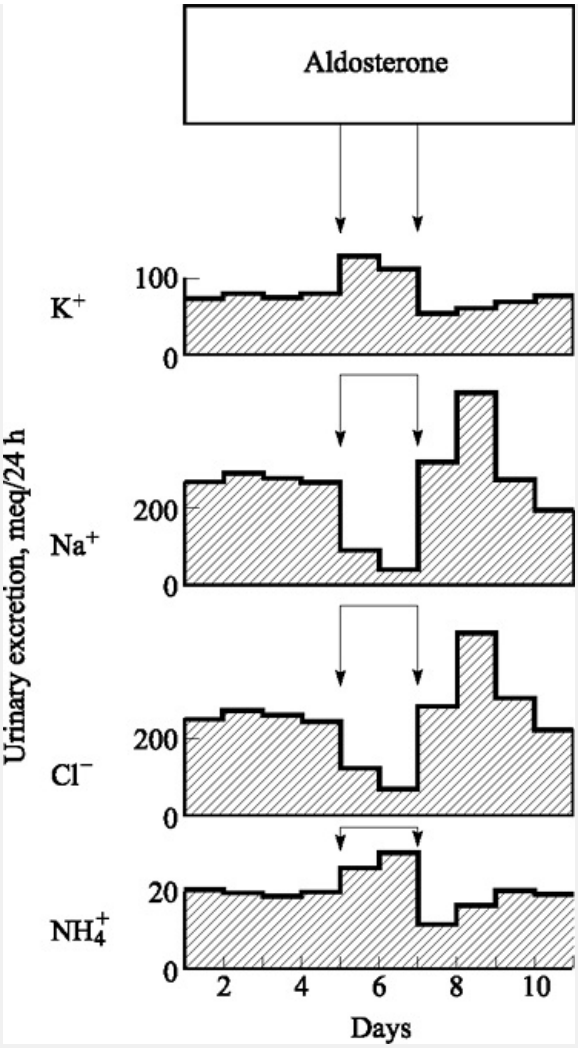

Figure 6-12 Effect of aldosterone on the daily urinary excretion of Na^+, Cl^-, K^+ and H^+ (as NH_4^+) in a normal subject maintained on a constant dietary intak Note that the quantit-atively most prominent effect is the marked reductio NaCl excretion. (*From Liddle GW: Arch Intern Med 102:998, 1958. By permission of the American Medical Association, copyright 1958*)

NaCl and potassium

The primary sites of action of aldosterone are in the connecting segment ai collecting tubules.[103][104] Its effects vary with the specific cell type that is affe Perhaps most important, aldosterone promotes the reabsorption of NaCl an secretion of K^+ in the connecting segment and in the principal cells in the cor collecting tubule,[105][106] and[107] it also appears to enhance Na^+ reabsorption but not K^+ secretion in the papillary (inner medullary) collecting

tubule.[108]

The cell model for how these processes occur is shown in Fig. 6-2. Aldosterone stimulates ionic transport in these cells by increasing the number and open N^+

K^+ channels in the luminal membrane as well as the activity of the Na^+-K^+-ATPase pump in the basolateral membrane.[5,91,94,106] As an example, going from a high- to a low-sodium diet (which is associated with enhanced aldosterone release) increase the number of open Na^+ channels per cell from less than 100 to approximately 3000.[109] Both opening of previously silent channels and insertion new channels in the luminal membrane appear to contribute to this response.[94,110]

The aldosterone-induced elevation in luminal Na^+ permeability promotes Na^+ diffusion into the tubular cell; this Na^+ is then returned to the systemic circulation the Na^+-K^+-ATPase pump.[5] The movement of Na^+ through its channel is electrogenic in that it creates a lumen-negative potential difference. Electr is maintained in this setting either by passive Cl^- reabsorption via the paracellular pathway or by K^+ secretion from the cell into the lumen. Na^+ reabsorption also enhances K^+ secretion by a second mechanism: The transport of reabsorbed Na^+ out of the cell by the Na^+-K^+-ATPase pump increases K^+ entry across the basolateral membrane. The ensuing rise in cell K^+ concentration permits continued K^+ secretion, which is the primary determinant of urinary K^+ excretion (see Chap. 12).

The increase in luminal Na^+ permeability represents a primary hormonal action, since blocking these channels with the diuretic amiloride at least transientl the aldosterone-induced increases in K^+ secretion, luminal K^+ permeability, and Na^+-K^+-ATPase activity.[106,111] Thus, the latter effects are in part secondary to rise in Na^+ entry; as an example, an elevation in cell Na^+ concentration directly and rapidly increases the number of active Na^+-K^+-ATPase pumps in the basolateral membrane.[112] However, the later increase in Na^+-K^+-ATPase activity is probably induced in part by aldosterone, as some aldosterone-induced proteins may subunits on the Na^+-K^+-ATPase pump.[5,113]

Hydrogen

The stimulatory effect of aldosterone on H^+ secretion occurs in different collecting tubular cells from those that transport Na^+: in the intercalated cells in the cortex a in the tubular cells in the outer medulla.[114,115] These cells, like the principal cells that reabsorb Na^+, are able to respond to aldosterone because they contain mineralocorticoid receptors.[116] Their main function in normal conditions is H^+ secretion via H^+-ATPase pumps in the apical membrane; they do not contribute net Na^+ reabsorption (see Fig. 5-3).

Aldosterone also indirectly stimulates H^+ secretion in the cortex via its effect on Na^+ reabsorption in the principal cells. The associated generation of a lumen-n potential creates a favorable electrical gradient for H^+ accumulation in the lumen.[117]

These effects of aldosterone are probably permissive, since there is little e that acid-base balance directly influences aldosterone release.

Extrarenal effects

Aldosterone reduces the concentration of Na^+ and raises that of K^+ in colonic and salivary secretions and in sweat.[5,118] These changes are generally of limited physiologic importance, although colonic secretion of K^+ can become an important route of K^+ elimination in patients with end-stage renal disease.[119]

Control of Aldosterone Secretion

Aldosterone plays an important role in the maintenance of volume and K^+ homeostasis via its effects on NaCl and K^+ excretion.[120] Thus, it is appropriate that angiotensin II (the production of which varies inversely with volume) and an elevation in plasma K^+ concentration are the major stimuli of aldosterone secretion.

Angiotensin II and hyperkalemia act on the zona glomerulosa, promoting the conversion of cholesterol to pregnenolone and, more importantly, of corticosterone to aldosterone via stimulation of aldosterone synthase (Fig. 6-11).[121,122] As an example, chronic sodium restriction leads to a tenfold increase in messenger RNA for aldosterone synthase and in aldosterone synthase activity (as estimated from the enhanced conversion of corticosterone to aldosterone).[122]

Aldosterone release can also be affected by other factors, being enhanced by adrenocorticotropic hormone (ACTH) and hyponatremia, and suppressed by atrial natriuretic peptide (see "Atrial Natriuretic Peptide," below).

Renin-angiotensin system

The volume stimulus to aldosterone secretion is primarily mediated by the renin-angiotensin system (see Chap. 2).[123,124] In normal subjects, both the plasma renin activity and aldosterone release vary inversely with dietary Na^+ intake (Fig. 6-13). An increase in Na^+ intake, for example, initially expands the extracellular volume, resulting in reductions in renin and aldosterone production. These changes allow excess Na^+ to be excreted by reducing renal Na^+ reabsorption in the proximal tubule (the site of action of angiotensin II) and in the cortical and papillary collecting tubules (the sites of action of aldosterone).[106,108,125] ANP, the secretion of which is increased by volume expansion, can contribute to the suppression of the aldosterone release in this setting (see below).

Conversely, a reduction in the effective circulating volume will enhance the secretion of renin and therefore that of aldosterone. The ensuing Na^+ retention returns the volume toward normal. The importance of renin in this sequence has been demonstrated by the loss of the hypovolemic stimulus to aldosterone release in nephrectomized patients.[126]

Plasma K^+ concentration

Aldosterone secretion is stimulated by increasing K^+ concentration, increasing linearly as the plasma K^+ concentration rises above 3.5 meq/L.[127,128] This represents a direct effect on the zona glomerulosa[129] and is extremely sensitive, as increments in the plasma K^+ concentration of as little as 0.1 to 0.2 meq/L can induce a significant elevation in aldosterone release.[127] The resultant increase in K^+ excretion then returns the plasma K^+ concentration toward normal (Fig. 6-14).[107,120]

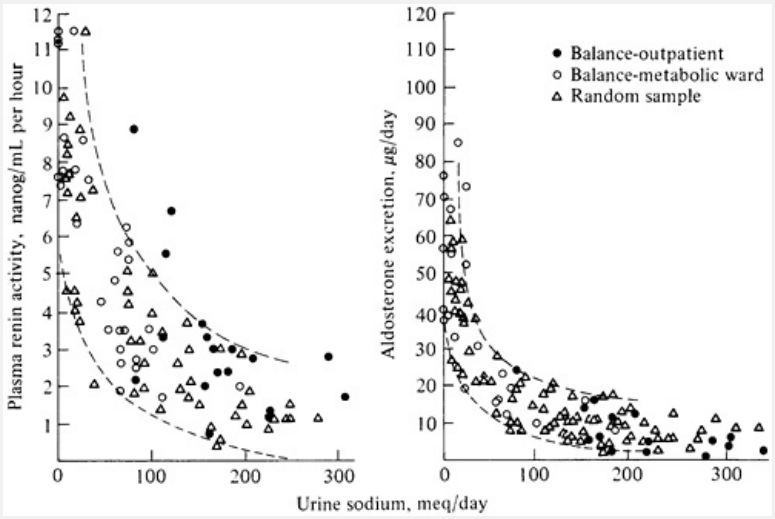

Figure 6-13 Relation of both plasma renin activity and 24-h urinary excretion of aldosterone to the concurrent daily rate of sodium excretion, used as an estimate of daily Na^+ intake. For these normal subjects, the data indicate an inverse relationship between dietary Na^+ intake and renin and aldosterone secretion. (*From Laragh JH, Baer I, Brunner HR, et al: Am J Med 52:633, 1972. Used with permission.*)

There appears to be a positive interaction between K^+ and angiotensin II, in that the presence of one stimulus to aldosterone production increases the response to the other.[128,130] This synergism may in part involve activation of an *intra-adrenal* renin-angiotensin system. In isolated zona glomerulosa cells, for example, an increased extracellular K^+ concentration enhances adrenal renin and angiotensin II release.[131,132] Furthermore, the associated increase in aldosterone secretion in this setting is impaired by the presence of an angiotensin converting enzyme inhibitor that reduces the local production of angiotensin II.[131,132]

ACTH

ACTH, released from the anterior pituitary, enhances adrenal glucocorticoid

androgen synthesis and release by increasing the gene expression for a nu adrenal enzymes, including 17α-hydroxylase, 21-hydroxylase, and 11β - hydroxylase.[86] It also causes a transient rise in aldosterone secretion that is mediated both by activation of adenylyl cyclase and by a small increase in Ca^{2+} entry.[133] The limitation in the ACTH response may be due to two factors:

1. Overproduction of deoxycorticosterone (Figure 6-11), an ACTH-dependent steroid with relatively potent mineralocorticoid activity. The ensuing fluid reten diminish the secretion of renin and secondarily that of aldosterone.

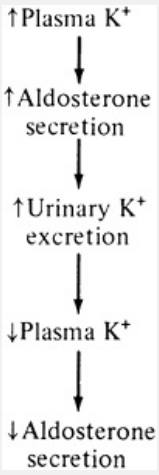

Figure 6-11 Role of aldosterone in potassium homeostasis.

2. The induction by ACTH of 17α-hydroxylase activity in the *zona glomerulosa* thereby converting this segment to cortisol production; this is an appro response when ACTH production is chronically stimulated in critically il patients.[134]

Plasma sodium concentration

Aldosterone secretion may be increased by hyponatremia and reduced by hypernatremia.[135,136] These changes can be seen with as little as a 4- to 5-m change in the plasma Na^+ concentration. However, the plasma Na^+ concentration does not play an important role in modulating aldo-sterone release in norma subjects, since it is normally held relatively constant (± 1 to 2 percent) by of ADH and thirst (see above). Even when hyponatremia is present, its effe aldosterone is frequently *overridden by concomitant changes in the effective circulating volume*. As an example, aldosterone secretion is increased in the hyponatremic patient who is volume-depleted but may be reduced in a patie volume-expanded, as in the syndrome of inappropriate ADH secretion.[137]

Maintenance of Sodium and Potassium Balance

Since aldosterone affects both Na^+ and K^+ handling, it might be expected that regulation of the excretion of one ion would interfere with that of the other. not occur because of two additional effects: (1) K^+ secretion is highly dependent upon the rate of sodium and water delivery to the cortical collecting tubule (see Chap. 12), and (2) K^+ balance can influence Na^+ reabsorption in the thick ascending limb of the loop of Henle (and perhaps the proximal tubule).[138,139]

How these factors interact to allow Na^+ and K^+ excretion to be regulated independently is summarized in Table 6-3. Effective circulating volume depletion, for example, activates the renin-angiotensin-aldosterone system. This response appropriately reduces Na^+ excretion by increasing reabsorption both in the proximal tubule (via angiotensin II) and in the distal nephron (via aldosterone). K^+ excretion, on the other hand, is not importantly affected in this setting,[140] since increase in proximal reabsorption reduces distal fluid delivery, thereby counteracting

the stimulatory effect of aldosterone. This explains why untreated patients failure or cirrhosis (who are effectively volume-depleted due to systemic vasodilatation; see Chap. 16) do not spontaneously develop K^+ wasting and hypokalemia, even though aldosterone secretion is frequently elevated.

Table 6-3 Interrelationships between aldosterone and Na^+ and K^+ balance

Clinical state	Aldosterone secretion	Proximal or loop reabsorption	Distal Na^+ delivery	Δ Urinary excretion	
				Na^+	K^+
Na^+ depletion	↑	↑	↓	↓	0
Na^+ load	↓	↓	↑	↑	0
K^+	↑	↓	↑	0	↑
K^+ depletion	↓	↑	↓	0	↓

Sodium loading reverses this sequence, and Na^+ excretion is increased, while K^+ balance is maintained due to the offsetting effects of increased distal deliv

reduced aldosterone secretion.[141] If, however, aldosterone release is not diminis because of a nonsuppressible adrenal adenoma, K^+ wasting and hypokalemia will ensue.[141] Thus, administration of a high-Na^+ load has been used as a screening test to unmask primary hyperaldosteronism.

A K^+ load, on the other hand, enhances aldosterone secretion and may redu Na^+ transport.[139] As a result, the aldosterone-induced increase in cortical co tubule Na^+ reabsorption is counteracted by the elevation in delivery of Na^+ from the more proximal segments. The net effect is an appropriate increase in the ex K^+ with little change in that of Na^+

Aldosterone Escape

If aldosterone is given to a normal subject on an adequate salt intake, NaC water retention and K^+ loss are seen initially, leading to a rise in blood pressu weight gain, and potassium depletion. However, after a weight gain of appr 3 kg, a spontaneous diuresis ensues, returning the plasma volume toward n (Fig. 6-15).[142,143]

This phenomenon has been called *aldosterone escape*.[144] It does not, however, represent aldosterone resistance, since urinary K^+ loss continues[142] and the cortical collecting tubule remains responsive to aldosterone.[145] Rather, the escape phenomenon appears to be due to decreased Na^+ reabsorption in some other nephron segment, perhaps the loop of Henle or the papillary collecting tubu[143] Two factors, which are induced by the initial volume expansion, are though major role in this response: increased secretion of ANP, which acts both by increasing the glomerular filtration rate and by diminishing Na^+ reabsorption in the inner medullary collecting duct (see "Atrial Natriuretic Peptide" below), and an elevation in systemic blood pressure (Fig. 6-15).[144] Both animals and humans demonstrate a close temporal relationship in which the rise in plasma ANP

precedes the onset of the natriuresis by 1 to 2 days.[146,147] The role of ANP, however, remains uncertain. Studies in animals made ANP-deficient by immu reveal no impairment in the escape phenomenon, indicating that ANP may c to the natriuresis but is not essential for it to occur.[148]

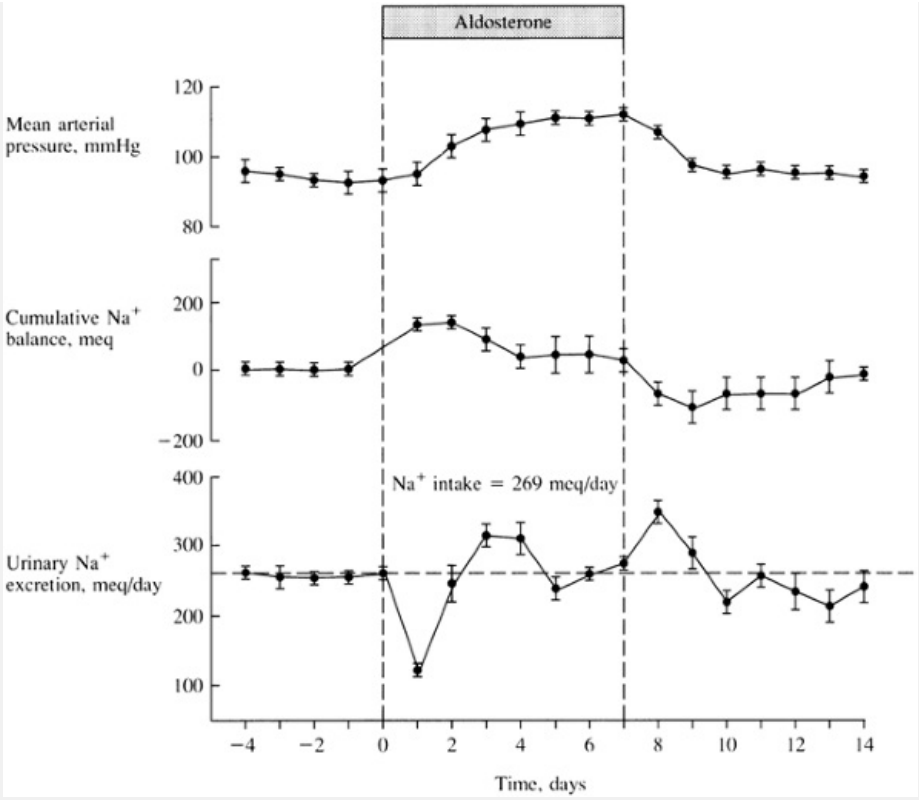

Figure 6-15 The phenomenon of aldosterone escape in dogs. The combinati of aldosterone administration and the ingestion of a diet high in Na^+ initially to Na^+ retention, volume expansion, and a rise in systemic blood pressure. several days, however, there is a spontaneous diuresis, resulting in the r Na^+ balance toward normal but persistent hypertension. Although it is not prevention of the rise in renal arterial pressure by use of a suprarenal cla prevents the natriuresis and is associated with progressive fluid retentior hypertension. [From Hall JE, Granger JP, Smith MJ Jr, Premen AJ Hypertension *6(suppl I):I-183, 1983. By permission of the American Heart Association, Inc.*]

On the other hand, escape can be prevented if a clamp is placed around th suprarenal aorta to *maintain renal arterial pressure at the baseline level* (see Fig. 8-9).[149] Furthermore, the continued volume expansion in this setting can lea pulmonary edema and a much more marked degree of hypertension.[149] This ab of the rise in renal perfusion pressure to limit the degree of Na^+ retention is called a *pressure natriuresis*. The site of action of this hemodynamic effect is unclear, variety of nephron segments may be involved (see page 272).[144,150]

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The clinical correlate of aldosterone escape occurs in patients with primary hyperaldosteronism, who have autonomous overproduction of aldosterone (s Chap. 27).[151] Hypokalemia and hypertension are typically seen in this setting not edema, since continued fluid retention is prevented.

ATRIAL NATRIURETIC PEPTIDE

Expansion of the extracellular volume with isotonic $NaCl$ results in an appropriate increase in Na^+ excretion. It was initially felt that this response could be expl by an increase in glomerular filtration rate (GFR) or a reduction in aldoster secretion. However, preventing a rise in GFR and administering high doses aldosterone may not impair the excretion of the Na^+ load.[152] Furthermore, cross-circulation experiments between volume-expanded and euvolemic animals s that the natriuretic response is mediated at least in part by some humoral f factors,[152] one of which is ANP.

ANP is released from myocardial cells in the atria and in some cases the ve and circulates primarily as a 28-amino-acid polypeptide consisting of amino –126 from the C-terminal end of pro-ANP.[153,154] and[155] Most of the physiologic actions of ANP appear to be mediated by attachment to specific receptors o membrane, with subsequent activation of guanylyl cyclase[3,12] and the formation of cyclic GMP.[3,156,157] and[158,159]

Actions

ANP has two major actions: It is a direct vasodilator, lowering the systemic pressure and it increases urinary Na^+ and water excretion.[154,157,159] The natriuretic and diuretic effects of this hormone may be mediated by a variet and extrarenal changes. In the kidney, for example, ANP directly increases and reduces Na^+ reabsorption; the natriuretic action appears to be primarily d the inhibition of sodium reabsorption in the medullary collecting tubule.(156 –162) In comparison, the outer medullary collecting tubule appears to be unaffected.[162]

Although this action is controversial, ANP also may diminish Na^+ reabsorption in the proximal tubule (primarily in the deep juxtaglomerular nephrons). This resp be mediated by an increase in peritubular capillary hydraulic pressure (see Chapter 3) and/or by the local release of dopamine.[163] There is indirect evidence in humans that ANP may have a proximal action, in that the excretion of phosphate an (which are almost entirely reabsorbed in the proximal tubule) is increased b ANP.[164]

The relative roles of the increased filtration and decreased reabsorption in natriuresis induced by ANP is uncertain. Some investigators believe that th in collecting tubule Na^+ reabsorption is the initial response, since the concentr of ANP required to achieve this effect is significantly lower than that requir affect the glomerulus.[165] With more marked volume expansion and

higher ANP levels, the increment in GFR may then contribute to the natriure the other hand, two lines of evidence suggest that the increase in filtered l be essential:[1] The natriuresis can be prevented if there is no rise in GFR, an[2]

simply blocking collecting tubule Na^+ channels without increasing the GFR (with t potassium-sparing diuretic amiloride) produces only a modest natriuresis.[166]

The rise in glomerular filtration rate induced by ANP is associated with littl change in renal blood flow, suggesting that ANP produces both afferent art dilation and efferent arteriolar constriction (see page 38).[157,167] The direct tubular effect, in comparison, appears to be mediated by a cyclic GMP-dependent p kinase, which closes the Na^+ channels through which luminal Na^+ normally enters the cell (see Fig. 5-4).[113,156]

In addition to these tubular and glomerular effects, ANP has a variety of otl actions that also promote increased secretion of Na^+ and water. It can reduce basal renin release, inhibit angiotensin II- and potassium-induced aldosterone se (the latter primarily via a direct action on the adrenal gland), inhibit the inc proximal Na^+ reabsorption and aldosterone release induced by angiotensin II, diminish the collecting tubular response to ADH.[168,169,170] and[171] Thus, the fall in activity of the renin-angiotensin-aldosterone system seen with volume ex may be mediated in part by ANP.

Other actions

ANP can be synthesized by a variety of tissues other than the atria, sugges autocrine or paracrine effects. As an example, ANP is produced in the vasc where it may diminish endothelial and vascular smooth muscle growth.[172]

Control of ANP Secretion

ANP is primarily released from the atria in response to volume expansion, v sensed as an increase in atrial stretch.[173,174] Although both atria appear to contribute,[175,176] there is suggestive evidence that the right atrium may be quantitatively more important.[176] Furthermore, chronic cardiac overload, as occu in congestive heart failure, can lead to recruitment of hormone production b myocardial cells in the ventricles[177,178] and, at least in animals, by the lungs.[179] There is also evidence that the carotid and renal baroreceptors contribute release by sending afferent signals back to the brain.[180]

Studies in humans and experimental animals have generally revealed that t release of ANP is increased in any hypervolemic state. This includes heart failure,[175,177] aldosterone escape,[146,147] renal failure,[181] and a salt-containing snack.[182] Furthermore, the rise in ANP secretion can be reversed by succes treatment of heart failure or, in renal failure, by removal of the excess fluid dialysis or restriction of Na^+ intake.[181,183]

Physiologic role

Despite the multiple sites at which ANP can affect Na^+ excretion and its appropriate release in response to changes in volume, the *physiologic*

role of ANP as a natriuretic agent remains uncertain.[166,184,185] Infusion studies in humans have revealed that ANP generally produces only a modest diuresis, because the concomitant fall in blood pressure induced by ANP counteracts natriuretic effects.[154,186] The following observations are compatible with a permissive role of hemodynamics in the renal response to ANP:

1. Lowering the renal arterial pressure blocks the natriuretic effect of ANP only slightly reducing that of the loop diuretic furosemide.[187]
2. Transgenic mice given an extra ANP gene have plasma ANP levels that times normal.[186] These animals have a reduced blood pressure and remain normal sodium balance. If, however, the blood pressure is elevated by v expansion, the natriuretic effect of ANP is unmasked resulting in a mark increase in sodium excretion.
3. Patients with heart failure and cirrhosis have high ANP levels, but avidl Na^+ (see Chap. 16). In experimental animals, this apparent resistance to A can be reversed by increasing the renal perfusion pressure to normal.[188,189]

In summary, the exact role of ANP as a natriuretic agent is unproven, and it possible that urodilatin and brain natriuretic peptide are more important na hormones (see below). The physiologic importance of most hormones has b demonstrated in part by removal of their site of production; unfortunately, t source of ANP limits the feasibility of this approach.

More complete definition of the role of ANP requires the availability of anta this hormone or its receptor. Injection of an antibody directed against ANP significantly diminishes baseline sodium excretion, attenuates the natriuret response to acute volume expansion, and further decreases the already low sodium excretion in congestive heart failure.[190,191] Similar observations have been made in animals made ANP-resistant by immunization.[148] Thus, ANP may play a contributory role in the day-to-day regulation of Na^+ excretion, although it is likely that changes in angiotensin II and aldosterone are of greater importance.[166]

Despite this acute role, *ANP resistance does not interfere with the response to chronic volume expansion* induced by oral salt loading or by mineralocortico escape (see "Aldosterone," above).[148] This finding, which is similar to the maintenance of Na^+ balance with aldosterone excess or deficiency, indicates t other factors (such as pressure natriuresis) can compensate if the normally role of ANP is impaired (see page 272).

Although of uncertain importance physiologically, ANP-induced diuresis may useful pharmacologically if its duration of action is prolonged. In both anim humans, the administration of an endopeptidase inhibitor (which slows the degradation of ANP) and/or a cyclic GMP phosphodiesterase inhibitor (whic the degradation of the second messenger) produces a relatively large natri

with little effect on the systemic blood pressure.[184,192,193] and[194]

The natriuretic response to endopeptidase inhibition can be enhanced by th concurrent administration of an angiotensin converting enzyme (ACE) inhibi reverses both the vasoconstriction and increased proximal reabsorption ind angiotensin II.[195] This interaction could be important in the treatment of edem patients with heart failure, since most patients are treated with an ACE inh reduce systemic afterload (see Chap. 16).[196]

Urodilatin

A separate ANP-like hormone has been identified in human urine and called urodilatin.[197,198] ANP is a 28-amino-acid peptide consisting of amino acids 9 from the C-terminal end of pro-ANP; urodilatin, in comparison, consists of a acids 95–126.

Urodilatin appears to be produced within the kidney, since plasma levels ar negligible. The distal tubule produces an ANP-like prohormone which, via a processing pathway that may be unique to the kidney, may be the precursor urodilatin.[199] Urodilatin does not seem to be catabolized by the endopeptidas metabolizes ANP.

The characteristics of urodilatin make it well adapted to regulate sodium ex since, unlike that of ANP, the effect of urodilatin is not limited by systemic hypotension or local catabolism. Its lack of catabolism by endopeptidases r in more urodilatin reaching its site of action in the distal nephron when con ANP.

Initial studies suggested that sodium excretion varies more closely with cha urodilatin excretion than with plasma ANP levels.[197,198] When given as an infusion, urodilatin appears to have natriuretic potency similar to that of ANP.[200] How urodilatin release might be regulated is uncertain.

Brain natriuretic peptide

Brain natriuretic peptide (BNP) is a natriuretic hormone that is homologous was initially identified in the brain but is also present in the heart, particul ventricles.[201] The circulating concentration of BNP is less than 20 percent of ANP in normal subjects but can equal or exceed that of ANP in patients with congestive heart failure.

The physiologic role of this hormone remains to be determined. The infusio to normal volunteers suggests that the compound has natriuretic activity sim that of ANP.[202] In addition, it may be responsible for the cerebral salt-wasting syndrome that can accompany severe neurologic injury, as with subarachno hemorrhage.[203]

C-type natriuretic peptide

C-type natriuretic peptide (CNP) is structurally similar to the other natriure

peptides. It activates cyclic GMP via a different receptor from ANP and BNP produced by vascular endothelial cells and in the kidney.[204,205] Initial studies have suggested that its major function may involve regulation of local blood flow.[204] However, its pathophysiologic role in humans is unclear, as the administrated doses has little effect on systemic hemodynamics, renal function, or the renin-angiotensin system.[206]

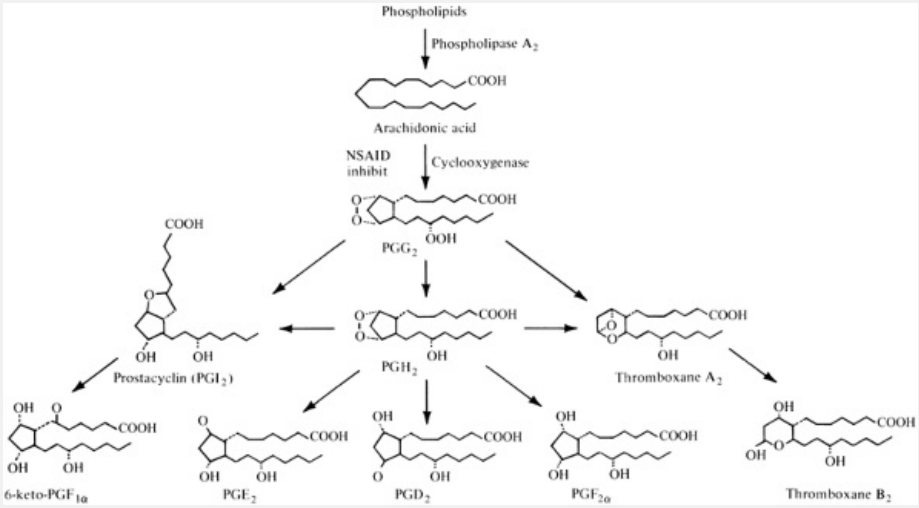

Figure 6-1 Biosynthesis of prostaglandins and thromboxane. All of the products shown in this figure have been found in kidney tissue. (From Dunn MJ, Zambraski EJ: Kidney Int 18:609, 1980. Reprinted by permission of Kidney International.)

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Marker for left ventricular dysfunction

Plasma levels of ANP and BNP may be useful as a marker for asymptomatic ventricular dysfunction in patients with heart disease.[207,208,209] The increase in cardiac filling pressure in this setting is the stimulus for the release of these natriuretic hormones.

PROSTAGLANDINS

Prostaglandins are derived from the metabolism of arachidonic acid, with the first step being catalyzed by the cyclooxygenase (COX) enzyme (Fig. 6-1).[6] These hormones are produced at a variety of sites within the kidney, including glomeruli and vascular endothelium, the medullary and to a lesser degree the cortical collecting tubule cells, and the renomedullary interstitial cells.[45,210] In general, the tubules primarily synthesize PGE_2, while the glomeruli produce both PGE_2 and prostacyclin.[45,210,211] The renal prostaglandins have important local functions but little systemic activity, since they are rapidly metabolized in the pulmonary circulation.

Two related isoforms of the COX enzyme have been described: COX-1, whic expressed in most tissues, but variably; and COX-2, which is usually undet most tissues but is increased during states of inflammation.[212]

This section will primarily review the known renal actions of PGE_2 and PGI_2, thromboxane B_2, and prostacyclin. Other arachidonic acid derivatives, such as thromboxane B_2, the leukotrienes (which are formed via the lipoxygenase pathway), and the epoxy- eicosatrienoic ac (which are cytochrome P450-dependent) also can affect renal function, but clinical significance is at present incompletely understood.[61,213,214,215] Thromboxane is similar to the prostaglandins in that its rate of production i relatively low in normal subjects and inhibition of its synthesis has little ef renal functions.[213] Thromboxane can, however, cause vasoconstriction and mesangial contraction, and may contribute to the fall in glomerular filtratior increase in protein excretion frequently seen in glomerular disease.[213]

The intrarenal effects have important clinical implications because of the w use of nonsteroidal anti-inflammatory drugs (NSAIDs).[216,217] Most traditional NSAIDs are nonselective inhibitors of both COX-1 and COX-2, ar the renal toxicities described below have been associated with these agent Selective COX-2 inhibitors are also available. Compared to the nonselectiv they provide similar analgesic and anti-inflammatory activity, but markedly gastroduodenal toxicity.[218,219]

COX-2 is constitutively expressed at low levels in the kidney.[220] Its effect on renal function in adults is unclear; however, it appears to have a major role in re development, as animals with deletion of the COX-2 gene have dysplastic t and immature glomeruli.[221] By comparison, mice without the COX-1 enzyme gen have minimal renal abnormalities.

Table 6-4 Renal actions of the prostaglandins and possible complications with nonsteroidal anti-inflammatory drugs

Effect of prostaglandins	Possible drug complication
Maintain renal blood flow and glomerular filtration rate by ameliorating angiotensin II and norepinephrine-induced renal vasoconstriction	Acute renal failure in conditions associated withincreased release of renal vasoconstrictors (Table 6-5)
Antagonize systemic vasoconstriction	May raise the blood pressure in hypertensive patients treated with a diuretic or β-adrenergic blocker; can worsen cardiac output in heart failure

	due to increased afterload
Increase the secretion of renin	Hyperkalemia due to hyporeninemic hypoaldosteronism, primarily in patients with renal insufficiency
Antagonize water-retaining effect of antidiuretic hormone (ADH)	Can potentiate effect of ADH, possibly promoting the development of hyponatremia
May increase sodium excretion in states of effective volume depletion	May promote more intense sodium retention; can impair response to diuretics

Actions

The renal prostaglandins have both vascular and tubular actions (Table 6-4). These effects result from the activation of distinct cell surface receptors, which are members of the G-protein-coupled family of seven-transmembrane receptors.[222] Different subtypes of these receptors exist, resulting in the varied actions of particular prostaglandin.[222]

Renal hemodynamics

Renal prostaglandins are primarily vasodilators (except for $PGF_{2\alpha}$ and thromboxane). They appear to play no role in the regulation of renal perfusion in the basal state when their secretion rate is relatively low. However, prostaglandin synthesis is increased (mostly within the glomeruli) by vasoconstrictors such as angiotensin II, norepinephrine, vasopressin (acting via V_1 receptors), and endothelin.[47,50,223,224] Each of these hormones activates phosphatidylinositol turnover (see Fig. 6-2), leading to the formation of diacylglycerol, which contains arachidonic acid at position 2.[51] The latter can then be released from diacylglycerol by the action of phospholipase A_2. The ensuing prostaglandin-induced vasodilation partially counteracts the neurohumoral vasoconstriction, thereby minimizing the degree of renal ischemia (see page 45).[223,225]

The net clinical effect is that nonselective NSAIDs do not impair renal perfusion in normal subjects, but can lead to *reversible renal ischemia and renal insufficiency* in a variety of disease states, particularly hypovolemic disorders in which angiotensin and norepinephrine secretion are increased (Table 6-5). These include true volume depletion and edematous states associated with effective circulating

volume depletion, such as cirrhosis and congestive heart failure (Fig. 6-17).[216,217,226] In both of the last two disorders, for example, increasing severity of the underlying disease is associated with increased secretion of the three

"hypovolemic" hormones—angiotensin II, norepinephrine, and ADH—and, at initially, of the renal prostaglandins.[72,73,227]

Table 6-5 Conditions associated with nonsteroida anti-inflammatory drug induced, hemodynamicall mediated acute renal failure

True volume depletion (vomiting, diarrhea, diuretic therapy)
Congestive heart failure
Hepatic cirrhosis
Glomerular diseases, including the nephotic syndrome and lupus nephrit
Hypercalcemia, which directly induces renal vasoconstriction

The likelihood of inducing acute renal failure with an NSAID is related to th of the underlying renal vasoconstriction. Patients with marked sodium reter higher levels of angiotensin II, norepinephrine, ADH, and renal prostagland have a relatively large reduction in the glomerular filtration rate if NSAIDs given.[228,229] This deleterious effect is usually rapidly reversible with discontinuation of the offending drug.

It is unclear whether the selective COX-2 inhibitors have a similar adverse Preliminary clinical trials did not demonstrate significant changes in renal f but most patients were not at risk for this complication.

Systemic hemodynamics

The vasodilator activity of the renal prostaglandins also acts to lower syste vascular resistance. Thus, the administration of a nonselective

NSAID to a hypertensive patient treated with a diuretic, β -adrenergic block inhibitor can raise the systemic blood pressure by an average of 3 to 5 mmH as much as 5 to 10 mmHg in some patients.[230,231,232] The NSAID-induced increment in vascular resistance can have an additional detrimental effect i with advanced heart failure. The associated increase in afterload in this se lead to a further reduction in cardiac contractibility and cardiac output.[233]

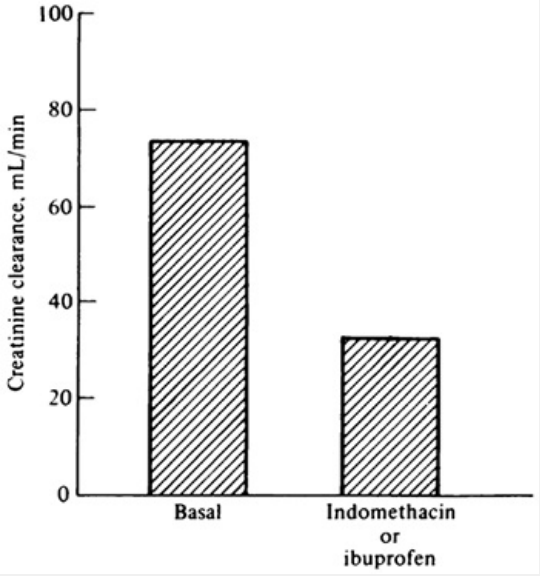

Figure 6-17 Reduction in GFR, as estimated from the creatinine clearance f a mean of 73 mL/min down to 32 mL/min, after the administration of a nonsteroidal anti-inflammatory drug (indomethacin or ibuprofen) to 12 pat with stable hepatic cirrhosis and ascites. Urinary prostaglandin E_2 excretion was substantially greater than normal in these subjects and was markedly redu following therapy. *From Zipser RD, Hoefs JC, Speckhart PF, et al, Endocrinol Metab 48:895, 1979. Copyright ©1979 by The Endocrine Society*

Renin secretion

The stimulation of renin secretion induced by baroreceptors in the afferent glomerular arteriole and by the macula densa cells in the early distal tubule to be mediated in part by locally produced prostaglandins.[234,235] These responses are blocked by an NSAID; as a result, prostaglandin synthesis inhibition ca *hyporeninemic hypoaldosteronism* (since angiotensin II is the major stimulus to aldosterone secretion) and an impairment in urinary K^+ excretion (see Chap. 28). The net effect is that the plasma K^+ concentration rises by a mean of 0.2 meq/L in normal subjects[236] and 0.6 meq/L in patients with renal insufficiency,[237] with the occasional development of overt hyperkalemia in the latter setting.[238]

Antagonism of ADH effect

ADH increases the production of renal prostaglandins, which then antagoni its hydroosmotic and vascular effects (see "Antidiuretic Hormone" above).[11,15,50] The clinical relevance of this relationship is uncertain. The administration to humans removes the inhibitory prostaglandin effect, possibly leading to i ADH-induced water reabsorption and an elevation in urine osmolality to a le can exceed 200 mosmol/kg.[239,240] The associated water retention can then caus reduction in the plasma Na^+ concentration. This is most likely to occur when the nonsuppressible ADH release, as a result of volume depletion or the syndro

inappropriate ADH secretion (see Chap. 25). In normal subjects, however, the initia fall in the plasma Na^+ concentration will diminish ADH secretion, thereby minim the likelihood of water retention.

Sodium excretion

The renal prostaglandins also may have a natriuretic effect, via reduced Na^+ reabsorption in the thick ascending limb and in the collecting tubules.[216,241,242] and[243] It is unclear how applicable these findings are to humans, since the major species differences in animals: As an example, prostaglandin E_2 inhibits cortical collecting tubular Na^+ absorption in rabbits but not in rats.[244]

If prostaglandins do promote Na^+ excretion, they will do so only when their rate o production is increased. Thus, prostaglandins have little effect in the basal may play a role in hypovolemic states, where they may moderate the rate of Na^+ retaining as well as the renal vasoconstrictive effects of angiotensin II, norepinephri possibly endothelin.[245] Consequently, inhibiting prostaglandin synthesis with a NSAID can promote further sodium retention in this setting, both by reducin glomerular filtration rate and by increasing tubular

reabsorption.[216] These effects also *can limit the responsiveness of edematous patients to diuretic therapy*.[236,246]

In addition to regulating net Na^+ excretion, the prostaglandins produced in the medulla may help to protect the thick ascending limb cells against ischemic when the patient is volume-depleted. The medulla normally has a very low P_{O_2}, in part to countercurrent exchange of oxygen (see page 147). This relative hypoxia is exacerbated when renal perfusion is diminished in hypovolemic states. By diminishing NaCl reabsorption in the thick ascending limb, prostaglandins r energy requirement of these cells, thereby allowing them to better tolerate decrease in oxygen delivery.[247]

HORMONAL REGULATION OF CALCIUM AND PHOSPHATE BALANCE

The maintenance of calcium and phosphate homeostasis involves changes i intestinal, bone, and renal function. Regulation of intestinal function is imp because, in contrast to the complete absorption of dietary NaCl and KCl, th absorption of Ca^{2+} and phosphate is incomplete. This limitation is due both to requirement for vitamin D and to the formation of insoluble salts such as ca phosphate, calcium oxalate, and magnesium phosphate in the intestinal lum example, a normal adult may ingest 1000 mg per day of Ca^{2+}, of which roughly 400 to 500 mg may be absorbed. However, 300 mg of calcium from digestive sec lost in the stool, resulting in the net absorption of only 100 to 200 mg.[248] In the steady state, this quantity of calcium is excreted in the urine.

Most of the body Ca^{2+} and much of the phosphate exist as hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, the main mineral component of bone. Phosphate also is pre in high concentration in the cells. Within the plasma, both Ca^{2+} and phosphate circulate in different forms. Of the plasma Ca^{2+}, roughly 40 percent is bound to albumin; 15 percent is complexed with citrate, sulfate, or phosphate; and 4 exist as the physiologically important ionized (or free) Ca^{2+}. Plasma phosphorus, in comparison, consists of phospholipids, ester phosphates, and inorganic pho The latter are completely ionized, circulating primarily as HPO_4^{2-} and $H_2PO_4^-$ in a ratio of 4 : 1 at a plasma pH of 7.40 (see page 305).

Although only a small fraction of the total body calcium and phosphate is lo the plasma, it is the *plasma concentrations of ionized* Ca^{2+} and *inorganic phosphate* that are under hormonal control. This function is mediated primari parathyroid hormone and vitamin D, which affect intestinal absorption, bone formation and resorption, and urinary excretion.[248,249,250,251,252] and [253] The physiologic roles of other hormones, such as calcitonin and estrogens, in t regulation of Ca^{2+} and phosphate balance are incompletely understood and wi be discussed further.[254]

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Parathyroid Hormone

Parathyroid hormone (PTH) is a polypeptide secreted from the parathyroid response to a decrease in the plasma concentration of ionized Ca^{2+}.[251] This change is sensed by a specific Ca^{2+}-sensing protein in the cell membrane of the parathyroid cells.[252,255] The receptor permits variations in the plasma Ca^{2+} concentration to be sensed by the parathyroid gland, leading to the desired in PTH secretion. Polymorphisms of this receptor may underlie a significant of the variability observed in the serum calcium concentrations in normal individuals,[256] while inactivating mutations lead to hypercalcemia because a plasma Ca^{2+} concentration is required to activate the receptor and suppress release.[257,258] and [259]

PTH acts to increase the plasma Ca^{2+} concentration in three ways (Fig. 6-18):

1. In the presence of permissive amounts of vitamin D, it stimulates bone resorption, resulting in the release of calcium phosphate.
2. It enhances intestinal Ca^{2+} and phosphate absorption by promoting the formation within the kidney of calcitriol (1,25-dihydroxycholecalciferol), active metabolite of vitamin D (see below).
3. It augments active renal Ca^{2+} reabsorption.

These effects are reversed by a small elevation in the plasma Ca^{2+} concentration,

which lowers PTH secretion.

PTH also influences phosphate balance, although its actions may be offset (Fig. 6-18). It tends to increase phosphate entry into the extracellular fluid by its bone and intestinal absorption. However, PTH also reduces proximal tubular phosphate reabsorption, resulting in enhanced excretion. The urinary effect predominates in patients with relatively normal renal function, as PTH tends the plasma phosphate concentration.

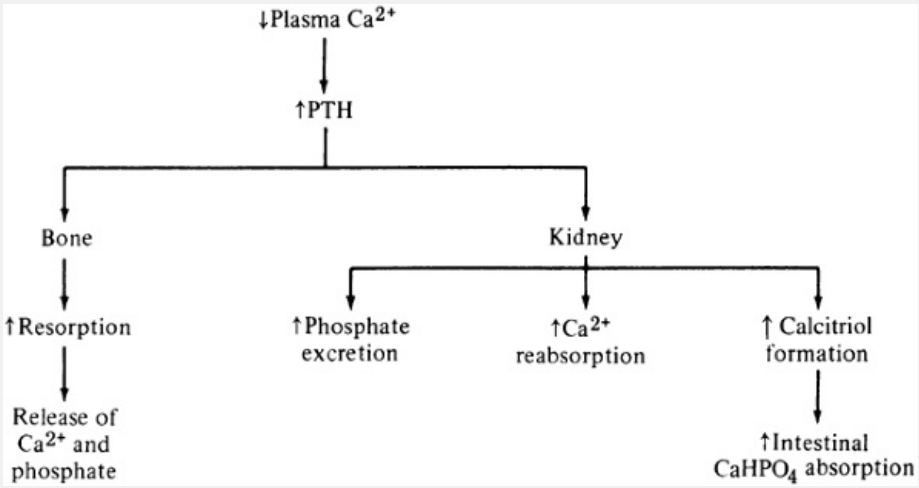

Figure 6-18 Effect of PTH on Ca^{2+} and phosphate metabolism. The net effect is an increase in the plasma Ca^{2+} concentration with no change or a decrease in the plasma phosphate concentration.

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Renal calcium and phosphate handling

The renal effects of PTH are in part mediated by activation of specific adenylyl cyclase systems (see Fig. 6-2) in the proximal tubule and the early cortical distal nephron, including the cortical thick ascending limb, the distal tubule, and connecting segment.[254,260] Activation of phospholipases C and A2 and the subsequent breakdown of phosphatidylinositol also mediates some of the actions of PTH, particularly the reduction in proximal phosphate reabsorption.[261,262,263] Stimulation of phospholipase C in the proximal tubule occurs at a lower and more physiologic concentration of PTH than stimulation of adenylyl cyclase.[264]

PTH diminishes the proximal reabsorption of phosphate by decreasing the activity of the type *Na^+-phosphate cotransporter* in the luminal membrane,[261,265,266] as a result, luminal phosphate is less able to enter the cells and be returned to the systemic circulation (see Chap. 3).

In comparison, the stimulatory effect of PTH on renal Ca^{2+} reabsorption occurs primarily in the early cortical distal nephron, particularly the distal tubule and connecting segment.[267,268] and[269] The mechanism by which PTH may enhance distal Ca^{2+}

transport is reviewed on page 92

A clinical example of the importance of the interaction between PTH and ca renal Ca^{2+} handling occurs in hypoparathyroidism, a disorder in which both P calcitriol levels are reduced.[254] The ensuing decrease in distal Ca^{2+} absorption results in persistent Ca^{2+} excretion, despite the presence of a plasma Ca^{2+} concentration that may be below 7.5 mg/dL (normal equals 8.5 to 10.5 mg/d calcitriol is given in this setting to raise the plasma Ca^{2+} concentration, there will still be PTH deficiency and a persistent partial defect in distal Ca^{2+} reabsorption. As a result, it may not be possible to safely raise the plasma Ca^{2+} concentration much above 8 mg/dL without inducing marked hypercalciuria, which can predispos calcium stone formation.

Acid-base balance

PTH also may contribute to the regulation of acid-base balance in the pres an acid load. A fall in extracellular pH stimulates PTH secretion, and the er increase in phosphate excretion can appropriately enhance net acid excreti buffering secreted H^+ ions.[43,270] PTH also minimizes the fall in pH by a second mechanism, promoting bone buffering of the excess acid (see page 319).

Vitamin D

Vitamin D_3 (cholecalciferol) is a fat-soluble steroid that is present in the diet also can be synthesized in the skin from 7-dehydrocholesterol in the preser ultraviolet light (Fig. 6-19).[248,253,271] The hepatic enzyme 25-hydroxylase places hydroxyl group in the 25 position of the vitamin D molecule, resulting in the of 25-hydroxyvitamin D or calcidiol.

Calcidiol produced by the liver enters the circulation and travels to the kidn to vitamin D-binding protein. In the kidney, tubular cells contain two enzym hydroxylase and 24α-hydroxylase) that can further hydroxylate calcidiol,

producing 1,25-dihydroxyvitamin D (calcitriol), the most active form of vitan 24,25-dihydroxyvitamin D, an inactive metabolite.[248,250,253,272] Studies in vitamin D-deficient animals suggest that the proximal tubule is the important site of synthesis. In contrast, studies in the normal human kidney under conditions vitamin D sufficiency indicate that the distal nephron is the predominant sit hydroxylase expression.[273]

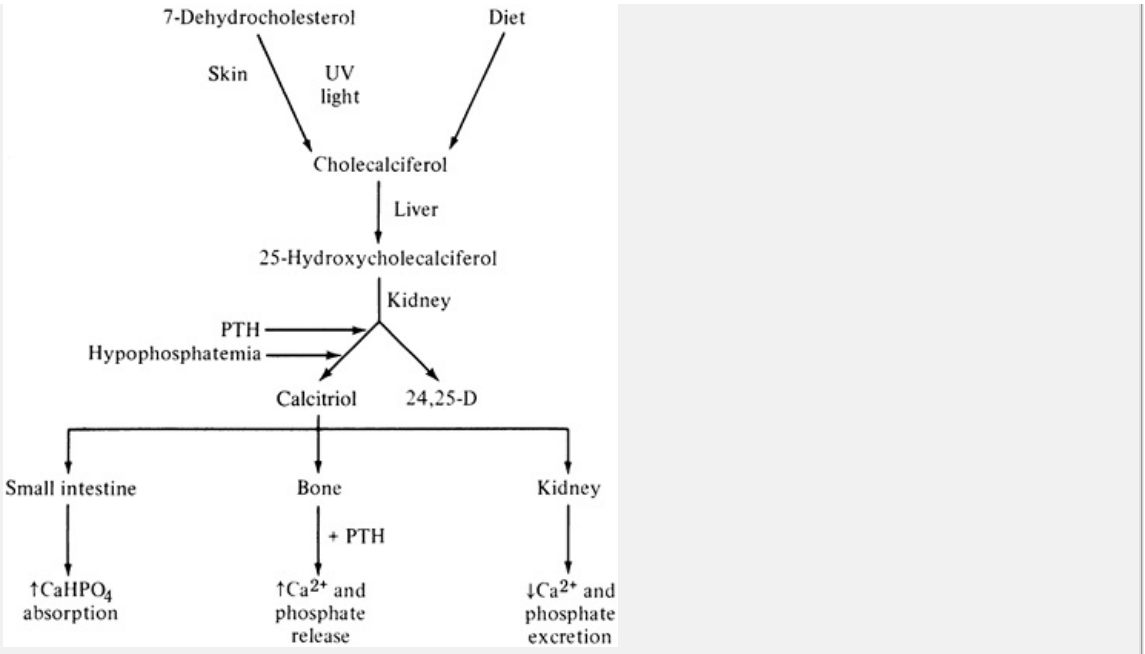

Figure 6-19 Metabolic activation of vitamin D and its effects on calcium and phosphate homeostasis. The result is an increase in the plasma Ca^{2+} and phosphate concentrations.

Calcitriol can also be synthesized in activated macrophages and thymic-derived lymphocytes.[274,275] and[276] This assumes importance in granulomatous diseases such as active pulmonary sarcoidosis and tuberculosis, and in lymphoma, in which overproduction of calcitriol can lead to increased intestinal calcium absorption, hypercalciuria, and hypercalcemia.[277,278,279,280] and[281] This effect appears to be mediated by interferon gamma[282] and, in tuberculosis, may have a physiologic role in promoting the ingestion and elimination of the tuberculous bacilli by macrophages and minimizing tissue destruction.[274]

The formation of calcitriol is primarily stimulated by *hypophosphatemia* and by PTH in an attempt to maintain Ca^{2+} and phosphate balance.[248,283] In comparison, the hepatic production of calcifediol is largely substrate-dependent and is not hormonally regulated.[249,250] The responsiveness of this system can be modulated by changes in the plasma Ca^{2+} concentration in that hypercalcemia impairs and hypocalcemia promotes PTH-induced calcitriol production.[284] This interaction is appropriate for the maintenance of Ca^{2+} balance; the facilitory action of hypocalcemia, for example, results in a greater increment in calcitriol release, thereby

promoting return of the plasma Ca^{2+} concentration toward normal. Excessive stimulation is prevented by the rise in plasma Ca^{2+} and by negative feedback regulation of the 1α-hydroxylase via binding of calcitriol to the vitamin D receptor.[272]

The regulatory role of phosphate is also important, since calcitriol is the pri

hormone that responds to changes in phosphate balance. Phosphate deplet
to raise and phosphate loading to lower renal calcitriol production.[283] Thus, in
calcitriol levels after a phosphate load protects against hyperphosphatemia
limiting further intestinal phosphate absorption. On the other hand, marked
increased levels of 1α-hydroxylase messenger RNA are found in mice with r
phosphate wasting and hypophosphatemia due to the targeted inactivation
sodium-phosphate wasting and hypophosphatemia due to the targeted inact
the sodium-phosphate cotransporter gene.[285]

Calcitriol is degraded in part by being hydroxylated at the 24-position by a
hydroxylase. The activity of the 24-hydroxylase gene is increased by calcit
therefore promotes its own inactivation) and reduced by PTH (thereby allow
active hormone to be formed).

Actions

The main action of calcitriol is to enhance the availability of calcium and p
both for new bone formation and for the *prevention of symptomatic hypocalcemia and hypophosphatemia*. This is primarily achieved by increases in bone resorp
intestinal absorption, and renal tubular reabsorption (Ca^{2+}) (Fig. 6-19).[249,250,254]
Some of the bone and renal actions of calcitriol are mediated by PTH, as ca
enhances the PTH-induced stimulation of both bone resorption and distal
reabsorption.[254,267,286]

Calcitriol regulates the plasma Ca^{2+} concentration in one other way—by binding t
receptors in the parathyroid gland, leading to a diminution in further PTH p
and release.[264,270,271,283,284,286,287,288,289] and [290] This modulating effect
prevents the development of an excessive PTH response. Its physiologic ro
normal subjects is uncertain. In patients with chronic renal failure, however
deficiency appears to be an important determinant of the associated secon
hyperparathyroidism (see below).[289,290]

Regulation of Plasma Calcium and Phosphate Concentrations

Figures 6-20 and 6-21 depict a model for the role of PTH and vitamin D in t
maintenance of the plasma Ca^{2+} and phosphate concentrations. The plasma Ca^{2+}
concentration, as routinely measured in the laboratory, includes all the Ca^{2+} in the
plasma, of which only about 45 percent circulates in the physiologically imp
ionized or unbound state. In general, measuring the total plasma Ca^{2+}
concentrations is sufficient, since changes in this parameter usually are as
with parallel changes in the ionized concentration. A common exception occ
patients with hypoalbuminemia, in whom the concomitant decrease in ion bi
leads to a reduction in the total plasma Ca^{2+} concentration without change in the
ionized form. To correct for this, the measured plasma Ca^{2+} concentration should

be increased by 0.8 mg/dL for each 1.0 g/dL fall in the plasma albumin conc

(normal plasma albumin concentration equals 4.0 to 5.0 g/dL). If, for examp plasma concentration of Ca^{2+} is 7.5 mg/dL and that of albumin is 2.0 g/dL (rougl 2.0 g/L less than normal), then the corrected plasma Ca^{2+} concentration would be 7.5+(2× 0.8) or 9.1 mg/dL, which is normal.

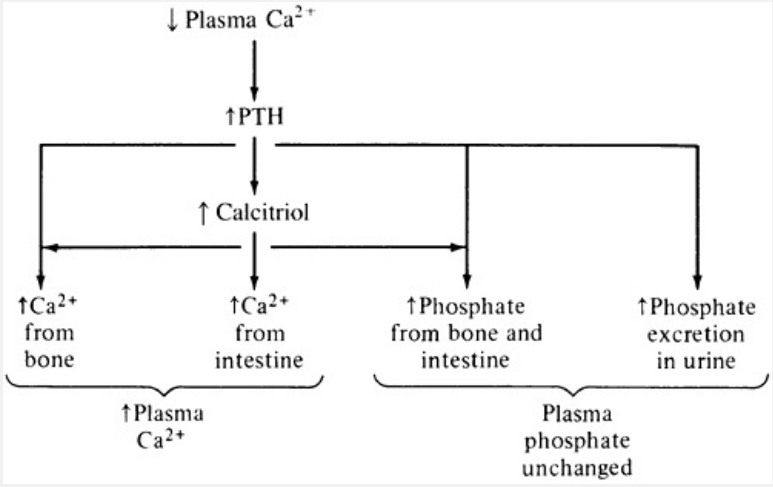

Figure 6-2 Physiologic sequence of events following the development of hypocalcemia. Because of the PTH interaction with vitamin D, the end res rise in the plasma Ca^{2+} concentration, with little or no change in the plasma phosphate concentration. *(Redrawn from deLuca, Am J Med 58:39, 1975. Used with permission.)*

PTH and calcitriol are essential for the maintenance of the plasma Ca^{2+} concentration, since their absence is associated with *progressive hypocalcemia* due to decreases in bone resorption and intestinal absorption and an increase i

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urinary Ca^{2+} excretion.[254] In addition to their individual effects, both hormones able to interact so that Ca^{2+} *and phosphate balance can be independently regulated*.

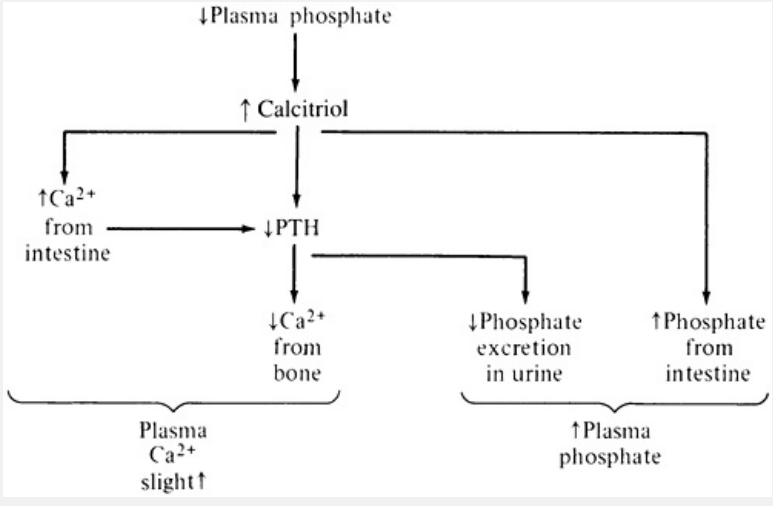

Figure 6-23 Sequence of events following the stimulation of calcitriol forma by hypophosphatemia. The net effect is an increase in the plasma phosph concentration with only a slight increase in the plasma Ca^{2+} concentration. Both the latter change and a direct inhibitory effect of calcitriol probably contr the decline in PTH release in this setting. *Redrawn from DeLuca, HF: Am J Med 58:39, 1975. Used with permission.*

If, for example, hypocalcemia does occur, there is a direct stimulus to PTH and the subsequent formation of calcitriol (Fig. 6-20). PTH increases calcium phosphate release from bone and urinary phosphate excretion, whereas cal augments intestinal calcium phosphate absorption. Both hormones also redu urinary Ca^{2+} excretion.[254] The net effect is an increase in the plasma Ca^{2+} concentration with little change in the plasma phosphate concentration. Thi sequence is reversed with hypercalcemia or a high Ca^{2+} intake, as both PTH secretion and calcitriol production are diminished.

The normal plasma phosphate concentration, measured in the laboratory as plasma inorganic phosphorus concentration (i.e., the concentration of phos contained in the inorganic phosphates), is 2.5 to 4.5 mg/dL. In the presenc dietary phosphate restriction or hypophosphatemia, there is increased gene expression and synthesis of renal Na^+-phosphate cotransporters, thereby enhancin proximal phosphate reabsorption.[291] In addition, calcitriol synthesis is directly enhanced,[283] increasing intestinal calcium phosphate absorption (Fig. 6-21). The ensuing small rise in the plasma Ca^{2+} concentration and perhaps a direct inhibito effect of calcitriol suppress PTH secretion, reducing calcium phosphate rel bone and further lowering urinary phosphate excretion. The net effect of th adaptations is virtual abolition of phosphate excretion in the urine (unless hypophosphatemia is due to phosphate wasting) and an increase in the plas phosphate concentration toward normal. This response is achieved with onl increment in the plasma Ca^{2+} concentration.

The hormonal response to hyperphosphatemia, which most often occurs in r failure, is discussed in the next section. The direct changes in proximal fur the opposite of those induced by phosphate depletion: decreased proximal phosphate reabsorption, due in part to reduced expression of the gene for t Na^+-phosphate cotransporter,[291] and diminished calcitriol synthesis.

Calcium and Phosphate Metabolism in Renal Failure

Although a complete discussion of the abnormalities in mineral metabolism in patients with chronic renal failure is beyond the scope of this chapter, it to review briefly how the homeostatic mechanisms governing calcium and pl balance can be impaired in this setting due to alterations in phosphate excr in PTH and calcitriol release.[292][293] and[294]

Phosphate balance and secondary hyperparathyroidism

Renal failure is characterized by a decrease in the functioning renal mass a therefore, in the total GFR. With the initial fall in GFR, there is a reduction filtered phosphate load and consequently in phosphate excretion. If intake constant, the net effect will be phosphate retention and a small increase in plasma phosphate concentration. This *phosphate retention is intimately relate to the common development*

of secondary hyperparathyroidism. As illustrated in Fig. 6-22, progressive renal failure is associated with a marked increase in circulating PTH levels that roughly with the degree of decline in GFR. If, however, phosphate retention prevented by restricting phosphate intake, *secondary hyperparathyroidism does no occur*.[295,296]

The mechanism by which phosphate retention leads to hyperparathyroidism incompletely understood. It was initially thought that excess phosphate will following reaction to the right:[297]

$$Ca^{2+} + HPO_4^{2-} \leftrightarrow CaHPO_4$$

The ensuing reduction in the plasma Ca^{2+} concentration can then stimulate the secretion of PTH, which, by increasing the Ca^{2+} release from bone and phosphate excretion in the urine, would *return both the plasma Ca^{2+} and phosphate concentrations to normal* (Fig. 6-23).

However, several observations are not compatible with this hypothesis. Firs initial minor degree of hyperphosphatemia may not be sufficient to cause a enough reduction in the plasma Ca^{2+} concentration to enhance PTH release.[298] Second, maintenance of normocalcemia by the administration of Ca^{2+} ions does prevent the development of hyperparathyroidism.[299]

An alternative and not mutually exclusive theory is that phosphate retention *diminishing the renal production of calcitriol*.[289,292] This will then lead to

hyperparathyroidism both by lowering the plasma Ca^{2+} concentration and by removing the inhibitory effect of calcitriol on PTH secretion.[289,290] The following observations are compatible with this hypothesis:

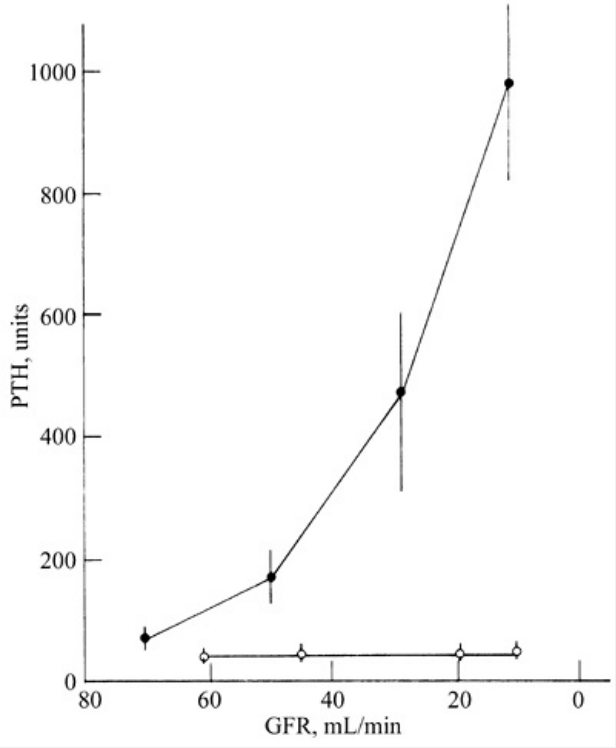

Figure 6-27 The relationship between PTH levels and GFR in two groups of dogs: those maintained on a 1200-mg/day phosphorus diet (closed circles) those maintained on a diet containing less than 100 mg of phos-phorus pe (open circles). (*From Slatopolsky E, Caglar S, Pennell JP, et al: J Clin Invest 50:492, 1971, by copyright permission of the American Society for Clinic Investigation.*)

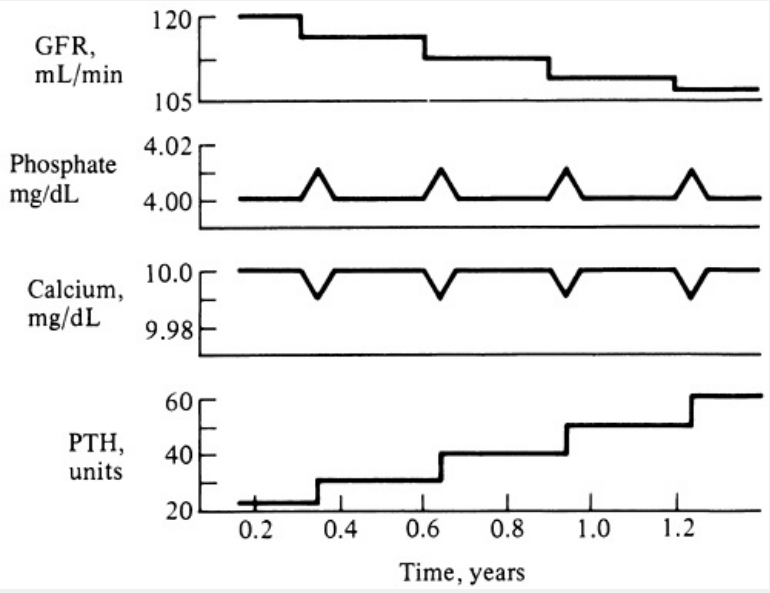

Figure 6-28 Hypothetical model for the development of secondary hyperparathyroidism in advancing chronic renal failure. Each decrement i promotes phosphate retention and a small reduction in the plasma Ca^{2+}

concentration. The latter change, plus a possible decline in calcitriol leve stimulates PTH secretion, which, at least initially, is able to return the pla Ca^{2+} and phosphate concentrations to normal. (*From Slatopolsky E, Bricker NS, Kidney Int* 4:14, 1973. Reprinted by permission from Kidney Internationa

1. Plasma calcitriol levels are often reduced in patients with mild to moder insufficiency, not elevated as would be expected from the presence of hyperparathyroidism.[300,301] Even the finding of normal or near-normal calci levels does not necessarily preclude a role for initial calcitriol deficien the secondary hyperparathyroidism will increase calcitriol synthesis.
2. The institution of dietary phosphate restriction is able to reverse many abnormalities in mineral metabolism: The plasma level of calcitriol is in while that of PTH is diminished,[302,303] and intestinal Ca^{2+} absorption is markedly improved.[302] In advanced renal failure, the decline in PTH secret can occur without change in the plasma levels of calcitriol (presumably the marked reduction in functioning renal mass) or in Ca^{2+} absorption. This observation suggests that hyperphosphatemia itself may contribute to the hyperparathyroidism, a theory that has been confirmed in both experime human studies.[304,305] and[306]
3. The administration of calcitriol to normalize the plasma calcitriol can pr[299] or reverse secondary hyperparathyroidism,[290,307] an effect that cannot be achieved by raising the plasma Ca^{2+} concentration with Ca^{2+} supplementation.[290,299]

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Partial resistance to the action of calcitriol also may play an important role pathogenesis of hyperparathyroidism. In particular, normal concentration of may be unable to suppress PTH secretion, perhaps due to a decreased num calcitriol receptors in the parathyroid glands.[308] This change can be demonstrated relatively early (when the plasma creatinine concentration has only doubled experimental animals; at a later stage, retained uremic toxins may contribut decreasing both receptor synthesis and hormone-receptor function.[309,310] This defect may also explain why supraphysiological levels of calcitriol (via intra intraperitoneal administration) can markedly diminish PTH release in patien maintenance dialysis, while physiologic oral doses are relatively ineffective.[290,311,312]

Regardless of the exact mechanism, the hypersecretion of PTH is initially appropriate, since it tends to normalize both the plasma Ca^{2+} and phosphate concentrations. This effect is not complete, as some patients may have a m elevation in the plasma phosphate concentration of less than 1 mg/dL; this degree of hyperphosphatemia may be sufficient to cause the persistent imp

calcitriol release and therefore the continued drive to PTH secretion.[301] In addition, each succeeding decrement in GFR will enhance the tendency toward phosphate retention, thereby requiring a further rise in PTH release (Fig. 6-23).[295]

In the long term, however, the development of hyperparathyroidism is in part *maladaptive*, because chronic exposure to high levels of PTH can lead to potentially serious bone disease, called osteitis fibrosa,[292,293] and[294] Furthermore, PTH loses its ability to maintain normophosphatemia when the GFR falls below 30 mL/min. Because of the inhibitory effect of PTH on proximal phosphate reabsorption, the fraction of the filtered phosphate that is reabsorbed can fall from the normal value of 80 to 95 percent to as low as 15 percent in severe renal failure.[313] At this point, PTH is unable to further increase phosphate excretion but continues to promote phosphate release from bone, resulting in persistent hyperphosphatemia if intake is not diminished. This may lead to the development of a vicious cycle as noted above, hyperphosphatemia in advanced renal failure can directly stimulate further PTH release.[304,305] and[306]

The combination of marked hyperphosphatemia and a normal or low-normal Ca^{2+} concentration will result in a very high calcium-phosphate product and a tendency for calcium phosphate precipitation into arteries, joints, soft tissues, and the viscera; this process is called *metastatic calcification*.[314] Total parathyroidectomy (usually with autotransplantation of some parathyroid tissue to the forearm) may be performed in this setting, since it will lower PTH levels as the plasma *calcium and phosphate* concentrations (Fig. 6-24).[314,315,316] and[317] The latter changes are due to diminished bone resorption and to the deposition of calcium phosphate in bones previously demineralized by chronic hyperparathyroidism.

Prevention of secondary hyperparathyroidism

In view of the deleterious consequences of prolonged hypersecretion of PTH, a variety of modalities have been tried in an attempt to prevent this complication. The most obvious is limiting net

phosphate absorption. Dietary restriction can be attempted, but compliance is a major problem. Furthermore, urinary phosphate excretion falls to such low levels in end-stage renal disease that limiting intake is not sufficient to prevent phosphate accumulation. In this setting, phosphate balance can be maintained only by binding dietary phosphate in the intestine, most frequently by using a phosphate binder such as calcium carbonate or calcium acetate.[318,319,320] and[321] This will lead to the formation of insoluble calcium phosphate precipitates in the gut and decrease intestinal phosphate absorption. Absorption of some of this calcium can also increase the plasma Ca^{2+} concentration, which may further lower PTH levels.

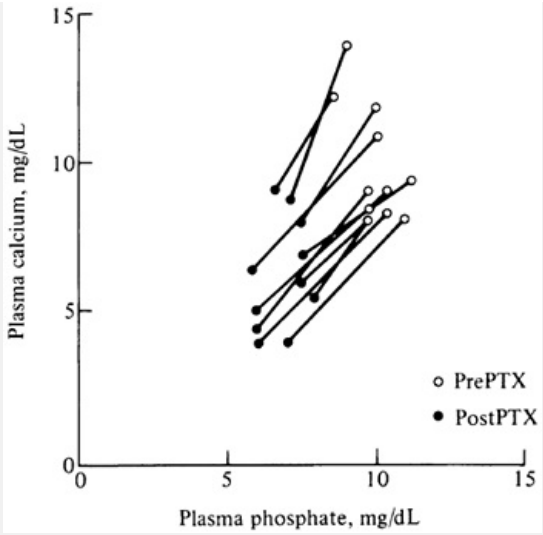

Figure 6-20 Changes in total plasma calcium and phosphate levels observe 11 uremic patients before and following subtotal parathyroidectomy (PTX) severe sec-ondary hyperparathyroidism. (*From Massry SG, Coburn JW, Popovtzer MM, Arch Intern Med 124:431, 1969. Copyright 1969, American Medical Association.*)

Aluminum-containing antacids

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were once widely used but created a major new problem: *aluminum intoxication* due to the gradual tissue accumulation of absorbed aluminum, particularly in bo the brain. The clinical manifestations of this syndrome include osteomalaci and muscle pain, microcytic anemia, and in selected cases dementia.[322] There is no safe dose that is also effective as a phosphate binder.[323]

Calcium citrate has also been used; however, this preparation is contraindi renal failure, since citrate can markedly increase intestinal aluminum absor predispose to aluminum toxicity.[321,324] Citrate appears to act in two ways: It combines with aluminum to form the soluble and absorbable aluminum citrat and it complexes with intestinal calcium. The ensuing decrease in free calc leads to increased permeability of the tight junctions between the cells, a c that can markedly enhance passive aluminum absorption.[324] Similar considerations apply to the concurrent administration of aluminum with sodium citrate (Bic which has been used to treat uremic acidosis.

The main problem with calcium carbonate or calcium acetate therapy is that hypercalcemia is a not infrequent complication with this therapy.[318,320] As a result, close monitoring is essential, particularly in patients who are also being tre a vitamin D metabolite such as calcitriol.[320] An aluminum-containing antacid or preferably sevelamer (RenaGel, see below) can be added if hyperphosphate persists or hypercalcemia limits the use of calcium.

Any phosphate binder should be given *with meals* to impair the absorption of dietary

phosphate.[325] Administration between meals, in comparison, binds only the phosphate in intestinal secretions, leading to a much lesser inhibition of ne phosphate uptake. The increased binding of calcium or aluminum to phosph second advantage in that cation absorption is also impaired. As a result, th both hypercalcemia and aluminum intoxication are reduced.[325]

The problems with phosphate binders containing calcium, aluminum, or mag has led to a search for different compounds that could bind phosphate. One compound is the nonabsorbable agent sevelamer (RenaGel), which contains calcium nor aluminum. It is a cationic polymer that binds phosphate through exchange. It is as effective as calcium antacids but, because of its expense currently used primarily in patients who develop hyperchloremia.[326,327] and hypercalcemia.[328]

Correction of calcitriol deficiency is another important component of therap patients with hyperparathyroidism. In patients already on dialysis, for exam intravenous or intraperitoneal administration of calcitriol can lead to a marl suppression in PTH release[290,311,312] and improvement in PTH-induced osteitis fibrosa.[312,329]

Calcitriol should not be given unless the plasma phosphate concentration h controlled, since the calcitriol-induced increase in intestinal phosphate abs can exacerbate underlying hyperphosphatemia. Careful monitoring for the development of hypercalcemia is also required. The risk of hypercalcemia n circumvented in the future by the administration of synthetic vitamin D anal as 22-oxacalcitriol, 1α-hydroxyvitamin D_2, or 19-nor) that have no or less calcemic phosphatemic effect but are still able to suppress PTH secretion.[330,331,332,333] and[334] The factors responsible for the selective actions of these analogs a incompletely understood.

Another factor that may be beneficial is correction of the metabolic acidosis commonly accompanies chronic renal failure. Buffering of the excess acid i leads to loss of bone mineral, possibly contributing to the development of hyperparathyroid bone disease.[335]

CATECHOLAMINES

Catecholamines, released from the sympathetic nerves and the adrenal mec (norepinephrine and epinephrine), play a central role in circulatory homeos their cardiac and vascular effects (see Chapter 8). They also can importantly influenc renal function, as adrenergic innervation has been identified in the renal va and in the proximal tubule, loop of Henle, and distal tubule.[336,337] and[338] Renal sympathetic activity tends to be increased in states of effective circulating depletion. In this setting, norepinephrine is a potent vasoconstrictor,

acting to reduce renal blood flow and therefore to preserve perfusion to the coronary and cerebral circulations.(336,337,339)

Enhanced sympathetic activity also increases Na^+ reabsorption, an effect that may

contribute to the compensatory renal retention of Na^+ seen with volume depletion.[337,340] At least three factors may participate in this response: stimulation of proximal and loop Na^+ transport,[340,341,342] and[343] which is primarily mediated by stimulation of α_1-adrenergic receptors,[3412] altered peritubular capillary hemodynamics, resulting from the increase in arteriola resistance (see page 83), and[3] activation of the renin-angiotensin-aldosterone system by the β_1-adrenergic receptors (see page 33).[341]

The α_2-adrenergic receptors produce an opposite response, increasing Na^+ and water excretion. These actions reflect at least in part a decrease in proxim transport and in collecting tubule water reabsorption.[343344] and[345] The diuretic effect appears to be mediated by activation of an inhibitory G protein, which impairs the ability of ADH to increase adenylyl cyclase activity and s water reabsorption (see Fig. 6-1).(344.345)

The ability of norepinephrine to increase Na^+ reabsorption at the same time that it tends to elevate the systemic blood pressure is important physiologically b prevents inappropriate urinary Na^+ wasting. The sympathetic nervous system is activated in states of volume depletion; the ensuing rise in blood pressure tend, via pressure natriuresis (see page 272), to increase Na^+ excretion if it were not for the concomitant stimulation of Na^+ reabsorption.[346] (Similar considerations apply to angiotensin II, which is also both a vasoconstrictor and a stimulato proximal Na^+ reabsorption; see Chap. 2)

Dopamine

Another catecholamine, dopamine, is primarily synthesized in the proximal t from circulating L-dopa, via the enzyme L-amino acid decarboxylase,[347,348] and,[349] dopaminergic nerves are also present in the kidney, but their physiologic si is unclear.[350] Dopamine generally has renal effects opposite to those of norepinephrine and epinephrine. At lower concentrations, it is a renal vaso acts at the interlobular arteries and both the afferent and efferent arteriole[351,352] Both a direct effect of dopamine and increased release of prostacyclin may contribute to this decrease in vascular resistance.[353]

The combined afferent and efferent dilation results in a marked increase in blood flow with *much lesser or no elevation in GFR*, since the reduction in efferent tone will tend to diminish the intraglomerular pressure (see page 38).[354,355] At higher concentrations, however, dopamine can induce vasoconstriction, a response that may be mediated by activation of α-adren receptors.[351]

Dopamine also tends to reduce proximal Na^+ reabsorption,[356] an effect that is mediated by partial inhibition of both of the major steps involved in Na^+ transu

reabsorption (see Chap. 3).[1] The activity of the Na^+-NH_4^+

exchanger in the luminal membrane is diminished via the formation of cyclic thereby reducing the entry of luminal Na^+ into the cell,[357] and[2] the activity of the Na^+-K^+-ATPase pump is decreased, thereby reducing the transport of Na^+ out of the cell into the peritubular interstitium and then the peritubular capillary.[348,358]

The net effect is that the administration of dopamine to patients can lead to natriuresis as well as an increase in renal perfusion.[355,356] It is not clear, however, whether endogenous dopamine is a physiologically important natriuretic hor The local production of dopamine in the proximal tubule is appropriately en volume expansion,[348,359] a response that is mediated at least in part by increa activity of L-amino acid decarboxylase.[348] This may contribute to the ensuing natriuresis, since the administration of a dopamine receptor inhibitor to exp animals impairs the response to modest volume expansion.[360]

The vasodilator and natriuretic properties of dopamine have led to the freq of low-dose, "renal-dose" dopamine (0.5 to 3 g/kg per minute) both to incre urine output and to preserve renal function in oliguric patients at risk for postischemic acute tubular necrosis.[349] Unfortunately, several clinical trials have failed to document the efficacy of dopamine in these settings.[361,362,363]

KININS

Kinins are another set of hormones produced in the kidney.[364,365] The process begins with the secretion of the enzyme kallikrein by the cells in the distal connecting segment (Fig. 6-25). This enzyme catalyzes the conversion of inactiv kininogen (a plasma protein that may also be produced locally) into lysyl-br and then, in the presence of an aminopeptidase, into bradykinin. Kinin gene probably occurs both in the tubular lumen and, since secreted kallikrein ap reach the vascular compartment, in the vascular space. On the other hand, kinins are rapidly metabolized by kininases in the proximal tubule and there not likely to have any intratubular effect.[364]

The physiologic role of the renal kinins is incompletely understood. Like th prostaglandins, they are vasodilators that may act to minimize renal ischem hypovolemic states in which angiotensin II and norepinephrine secretion ar

increased.[366,367] Their site of production in the distal nephron also suggests they may have an intraluminal effect on Na^+ and water handling in the collecting tubules. Compatible with this hypothesis are the observations that kinins di Na^+ reabsorption in the inner medulla (by closing Na^+ channels in the luminal membrane)[368] and impair the ability of ADH to increase local water reabsorpt[11] The latter effect appears to be indirect, being mediated by kinin-induced prostaglandin production.

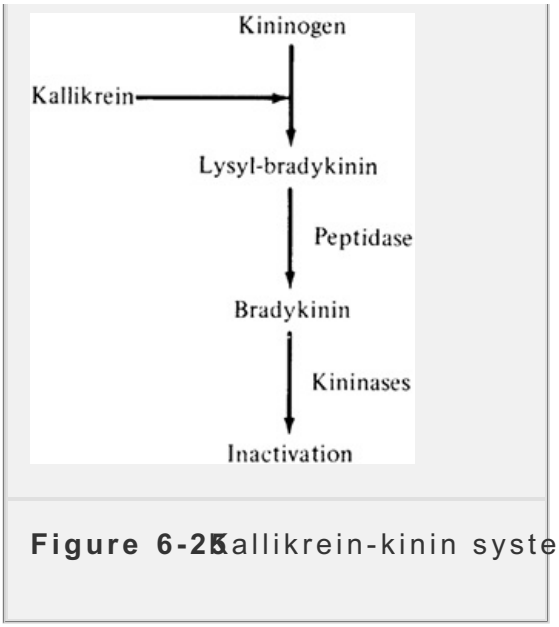

Figure 6-25 Kallikrein-kinin system.

Renal kinins appear to have a significant role in the developing kidney. The expression of bradykinin receptor mRNA is elevated 10- to 30-fold in neona as compared with adult kidney.[369] How kinins act in the maturing kidney is unkno

The kinins are probably not important circulating hormones, since they are metabolized in the circulation by kininases, one of which is angiotensin cor enzyme. This is the same enzyme that catalyzes the conversion of angioten angiotensin II.

ERYTHROPOIETIN

Erythropoietin (EPO) is a glycoprotein growth factor that is the primary stir erythropoiesis, promoting the terminal differentiation of erythroid colony-fo units (CFU-E) into normoblasts and then erythrocytes.[370] Mice with homozygous null mutations of EPO or the EPO receptor (EPOR) genes form erythroid burst-f units (BFU-E) and CFU-E normally but fail to differentiate into mature erythrocytes.[371]

Erythropoietin is produced by the kidney and to a much lesser degree (less percent) by the liver. A population of interstitial fibroblasts appears to be a source of renal EPO synthesis,[372,373] although some studies have suggested an important role for the proximal tubular cells.[374] Interstitial cells positive for EPO mRNA are limited to the deep cortex and outer medulla in the unstimulated With increasing anemia, the number of positive cells increases in number a spreads into the superficial cortex.[373]

Decreased oxygen delivery, most often due to anemia or hypoxemia, is the stimulus to erythropoietin release.[370] The oxygen sensor is probably a heme protein[375] that may be a cytochrome *b*-like flavohemoprotein (see Fig. 6-26).[376,377]

The following model has been proposed to explain the action of this sensor of oxygen to the sensor shifts its conformation from a deoxygenated (off) s oxygenated (on) state; the oxy form activates a series of events leading to

repression of EPO gene transcription.[378][379] This sequence is reversed with decreased oxygen delivery; activation as the deoxygenated state leads to s of a protein that binds to the active site on the enhancer region of the EPO resulting in increased EPO production.[380] The ensuing rise in red cell production will tend to return oxygen-carrying capacity toward normal.

Events downstream from the oxygen sensor involved in activation of EPO g expression require de novo protein synthesis, including the production of

specific transcription factors.[381] One of these is hypoxia-inducible factor-1, the activity of which is essential for enhanced EPO production.[382][383] Mice that lack this factor die at midgestation, while heterozygotes, although developmenta normal, fail to respond adequately to chronic hypoxia.[384]

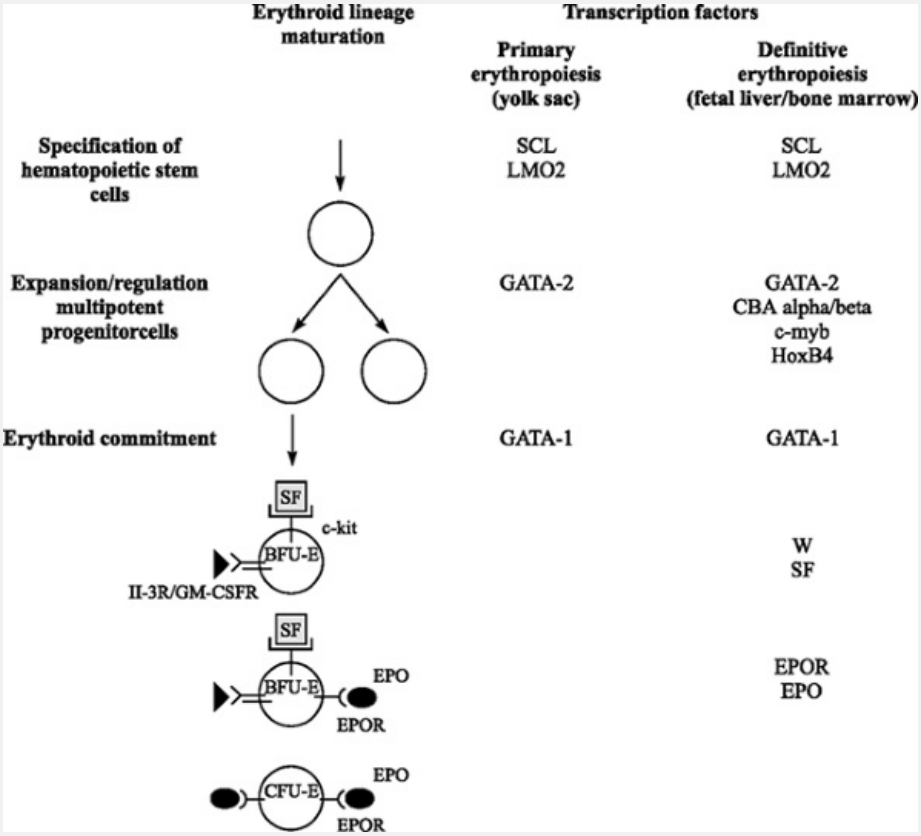

Figure 6-25 ormation of erythyroid progenitors. Schematic representation the formation of erythroid progenitors (BFU-E and CFU-E) from hematopoi stem cells and multipotent progenitor cells. The transcription factors impo for the maturation and differentiation of hematopoietic stem cells (HSC) a expansion of the stem/progenitor compartment are indicated on the right, according to whether they are important for primary erythropoiesis in the and/or definitive erythropoiesis in the fetal liver and/or bone marrow. Cer growth factors and their receptors, such as Steel factor (SF)/c-kit and erythropoietin (EPO/EPOR), are important or essential for erythropoiesis, respectively; by comparison, other growth factors, such as IL-3 or GM-CS synergistically but are not essential. Abbreviations include EPO and

EPOR=erythropoietin and its receptor, respectively; SF and W (c-kit)=Ste factor and its receptor, respectively; IL–3R=interleukin-3 receptor; BFU-E=erythroid blast-forming units; and CFU-E=erythroid colony-forming unit

The kidney is well suited to be the site of EPO production because it is abl dissociate changes in blood flow alone from those in oxygenation. Reducing

blood flow, for example, will also tend to diminish both the glomerular filtra and total tubular Na^+ reabsorption. Since active transport is responsible for mo renal oxygen consumption, the relation between oxygen delivery (reduced b hypoperfusion) and oxygen utilization (reduced by decreased reabsorption) relatively well maintained, thereby preventing an inappropriate increase in synthesis.[373]

EPO in Chronic Renal Failure

The importance of erythropoietin has been demonstrated in patients with ch renal failure. Anemia is common in this setting and is due primarily to reduc EPO production, a presumed reflection of the reduction in functioning renal mass.[370,385] This relationship has been convincingly demonstrated in studie which recombinant human EPO has been administered intravenously, subcutaneously, or intraperitoneally to anemic patients undergoing chronic (see Fig. 6-27).[370,386,387] Elevation of the hematocrit to the desired goal of 3 36 percent can be achieved in the majority of patients if an adequate dose given. Both lower and higher hematocrits have been associated with increa mortality.[388,389]

Correction of anemia with EPO in patients with end-stage renal disease is t associated with an often marked improvement in the sense of well-being.[370,386,387] This observation demonstrated that many symptoms previously

attributed to toxins retained because of the renal failure were due to anemi possibly to EPO deficiency).

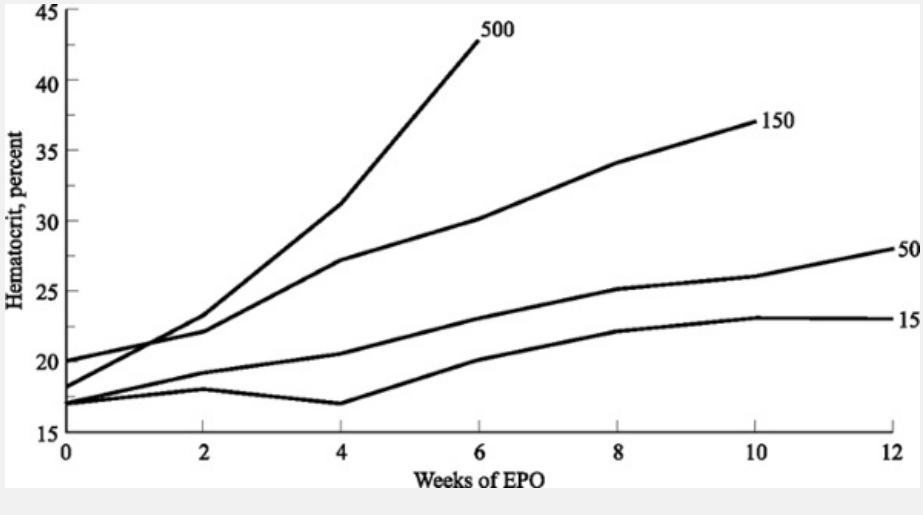

Figure 6-27 Dose response of EPO-induced correction of uremic anemia. Sl of the rate of increase in the hematocrit in patients on maintenance dialys given various doses (15 to 500 units/kg) of erythropoietin (EPO) three tim week. The response is fastest at the highest dose, but a gradual and ade rise in hematocrit is achieved in most patients with 50 units/kg. (*Data from Eschbach JW, Egrie JC, Downing MR, et al: N Engl J Med 316:73, 1987. Used with permission.*)

ENDOTHELIN

The endothelin (ET) family consists of three 21-amino-acid peptides (ET-1, and ET-3).[391] Each ET is formed as a propeptide known as big ET, which is converted to the mature peptide by endothelin converting enzymes located inside and outside of cells.[392][393]

Once secreted, ETs bind to two general classes of receptors: endothelin A endothelin B (ETB).[394][395] Two important features of ET-receptor interaction h explain the actions of ET:

1. ET remains bound to the receptor for several hours, imparting a sustain effect.
2. ET generally binds to receptors located on the same cell as, or on cells immediately adjacent to, the cells that secreted the peptide.

ETs are produced by most cell types in the kidney and have a wide variety biologic actions. The most important are:

1. Regulation of vascular resistance
2. Modulation of fluid and electrolyte transport
3. Regulation of cell proliferation and extracellular matrix accumulation.

Regulation of Vascular Tone

ETs, via stimulation of the ETA receptor, are extremely powerful vasoconstr[396] their effect is an order of magnitude greater than that of any other known vasoconstrictor. The renal vasculature is approximately an order of magnitu sensitive to ET than any other vascular bed.[397] Studies with nonselective ET receptor antagonists suggest that ET mediates part of the systemic and ren vasoconstrictive effects of angiotensin II.[398]

The use of selective receptor antagonists has helped clarify the individual the ETA and ETB receptors.[399] Administration of an ETA receptor antagonists produces local vasodilation that can be almost totally abolished by inhibitic oxide synthesis. In comparison, vascular resistance rises when an ETB rec

antagonist is given, either alone or after ETA receptor antagonism. Thus, th receptor appears to mediate vasodilation.

Most ETs in the renal vasculature are released by endothelial cells and act neighboring vascular smooth muscle. Endothelial cell ET-1 release is stimu other vasoconstrictors, thrombogenic agents, and inflammatory cytokines, a reduced by vasodilators (particularly nitric oxide) and anticoagulants.[400]

It is unlikely that ETs are involved in the minute-to-minute regulation of ren vascular resistance. Rather, ETs are released in substantial amounts by rel endothelial cells when a prolonged and severe decrease in renal blood flow This may be appropriate, as in marked prerenal states, in an attempt to ma coronary and cererbral perfusion. However, ET-induced vasoconstriction ca injurious, as with prolonged ET-mediated renal vasoconstriction following is renal injury or after renal exposure to nephrotoxins (such as cyclosporine, radiocontrast media, endotoxin, amphotericin B, and other agents).[400,401]

Modulation of Fluid and Electrolyte Transport

ETs are produced by most tubule segments, with the collecting duct being t predominant nephron site of synthesis. Once released, ETs bind to ETB rec found in most nephron segments.

Like that of the vasculature, the ET modulation of fluid and electrolyte tran involves the long-term, rather than instantaneous, regulation of fluid and el homeostasis. In general, ETs have an inhibitory effect (and may function as inhibitors) on tubular sodium and water reabsorption. At peptide concentrat likely to be present in the proximal tubule, ETs can suppress Na-K-ATPase[402,403] and Na-H antiporter activity. This effect is mediated, at least in part, via in levels of arachidonate metabolites.[404]

ETs also inhibit sodium and water reabsorption by the cortical collecting tu antagonizing the actions of ADH and aldosterone. These effects are mediat by reductions in cAMP accumulation and apical sodium channel activity.[405,406] ETs are potent inhibitors of ADH-stimulated cAMP accumulation in the inner med collecting duct; they also reduce Na-K-ATPase activity via stimulation of prostaglandin E_2 production.[404]

Enhanced nephron ET production may result in either physiologically appro toxic effects.[404] As an example, a prolonged increase in water intake enhance production of ET-1, which inhibits collecting duct water reabsorption, appro increasing water excretion. On the other hand, a sustained decrease in nep 1 production, as has been suggested to occur in essential hypertension, co enhance salt and water retention and contribute to the hypertensive state.

At first glance, it may appear confusing that ET raises blood pressure by co the renal vasculature, but also lowers blood pressure by promoting renal so water excretion. However, the actions of ET must be viewed in the context target cell and the activated receptor. Thus, the apparent paradox is explai

observation that the activation of ETA and ETB receptors raises and lowers blood pressure, respectively.

Regulation of Cell Proliferation and Extracellular Matrix Accumulation

Cell proliferation and extracellular matrix accumulation are altered by the endothelins, with ET-1 increasing the following parameters:[405,406]

1. The release of tissue inhibitor of metalloproteinase
2. The release of cytokines that stimulate matrix accumulation
3. The production of renal cell fibronectin and collagen

These peptides can also stimulate proliferation of a variety of renal cell typ

Although these effects may be important during normal development, they a relevant clinically in the development of pathophysiologic processes. In par ETs have a role in the gradual progression of glomerular sclerosis and inte fibrosis that occurs with irreversible renal injury. Inhibiting ET substantiall renal scarring in models of chronic renal failure, while humans with a varie diseases have increased renal ET-1 production.[400,407,408,409,410] and[411]

NITRIC OXIDE

Nitric oxide (NO) has a major role as a messenger molecule in most human systems.[412] In the blood vessel wall, basal and calcium-agonist-stimulated re of NO largely accounts for the bioactivity of endothelium-derived relaxing f (EDRF).[413] In the kidney, as well as in other solid organs, physiologic concentrations of NO function as a tonic vasodilator, working essentially instantaneously.[414] However, higher concentrations can be toxic, including damaging cellular constituents (such as DNA), and inducing hypotension in with sepsis.[415]

Basic Physiology

NO, a molecular gas, is formed by the action of one of three isoforms of nit synthase (NOS). The isoforms were named based upon the cell types in wh were first isolated: neuronal NOS (nNOS or NOS1), inducible or macrophag (iNOS, NOS2), and endothelial NOS (eNOS, NOS3). All three enzymes, whic cytochrome P450-like proteins, facilitate the addition of the guanidino nitro amino acid arginine to molecular oxygen, producing NO and water.

The expression of the three NOS isoforms differs, resulting in varying amou production. In general, eNOS and nNOS are constitutively active, producing relatively low levels of NO, with the output varying with changes in the intr calcium concentration. By comparison, the transcriptional regulation of iNO markedly induced, particularly by inflammatory cytokines, resulting in extre amounts of NO.

NO is a paracrine mediator that works differently from endocrine mediators, angiotensin II and ADH. NO, which is produced and released by individual c readily penetrates the biological membranes of neighboring cells, modulatir number of signaling cascades. Since it has an extremely short half-life, it e effects locally and transiently.

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The most recognized cellular target of NO is heme-containing soluble guany cyclase. The stimulation of this compound enhances the synthesis of cyclic (cGMP) from guanosine triphosphate (GTP), increasing the cytosolic levels The effects of NO can be enhanced by inhibiting the breakdown of cGMP, a catalyzed by a family of phosphodiesterases.

Other cellular targets for NO also exist:

1. NO interacts with thiol groups on proteins and small molecules, resultin formation of S-nitrosothiols.
2. NO can target Fe/S groups at the catalytic centers of proteins, includin hemoglobin.[416]
3. The formation of peroxynitrite from NO and superoxide radical has been implicated in cellular toxicity via the propensity of peroxynitrite to induc posttranslational changes in the tyrosine residues of proteins.[417]

Thus, the biologic effects of NO depend upon the concentration of NO prod well as upon features specific to the local environment, particularly the pre production of thiols and superoxide.

Expression of nitric oxide in the kidney

All three NOS isoforms can be expressed in the kidney. The renal pattern o expression (whether in normal individuals or in certain disorders) may be c important, as perturbations in NO bioactivity have been described in a num kidney-dependent pathologic states.[418]

Inconsistencies and controversies concerning the expression of NOS isofor due in part to variations in the methods of detection and/or the product bei detected (such as mRNA and/or protein).[419,420]

1. nNOS is principally expressed in the macula densa and the inner medul collecting duct.
2. Although this is somewhat controversial, iNOS has been localized to se tubule segments (principally the thick medullary ascending limb but also distal convoluted tubule and proximal tubule), the glomerulus, and the interlobular and arcuate arteries.
3. eNOS is expressed in the endothelium of glomerular capillaries, afferen efferent arterioles, and intrarenal arteries.

The greatest enzymatic activity for NO production in the kidney is found in medullary collecting duct (IMCD). IMCD NOS activity is three- to sixfold hig that observed in the glomeruli.[421]

Nitric Oxide and the Kidney

Insight into the role of NO in the kidney is primarily derived from experimer examining the altered expression of the NOS isoforms, the effects of inhibit

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NOS (thereby lowering levels of NO), or the administration of NO donors. T important actions of NO in the kidney are

1. Regulation of renal hemodynamics
2. Modulation of fluid and electrolyte transport
3. Regulation of damage in response to injury

Renal hemodynamics

As mentioned above, eNOS is expressed to a variable extent in endothelial the afferent arteriole, glomerulus, and efferent arteriole.[422] Endothelial-derived NO plays a major role in maintaining arteriolar dilation by participating in the p control of renal glomerular vascular resistance and mesangial cell tone. In acute systemic NOS inhibition causes marked increases in afferent and effe arteriolar resistances and a fall in glomerular capillary ultrafiltration coeffi[423] addition, chronic systemic blockade of NO bioactivity in rats induced by pharmacologic inhibition of NOS enzyme activity results in significant glome capillary hypertension.[424] In these models, the marked increases in efferent arteriolar resistance also reflected important contributions from both angiot and endothelin-1.[425]

The systemic blood pressure is significantly affected by NO. In animal mod hypertension results from deletion of the genes for eNOS[426,427] or from chronic inhibition of NO synthesis,[424,428] while hypotension occurs in transgenic mice th overexpress eNOS.[429] With inhibition of NO synthesis or deletion of eNOS ger significant reductions in renal plasma flow and glomerular filtration rate pa development of the hypertension.[426,428]

In some clinical settings, enhanced eNOS activity may be deleterious; it ma example, contribute to the renal vasodilation and glomerular hyperfiltration in diabetic nephropathy. In a diabetic rat model, enhanced glomerular filtra renal plasma were blocked by the administration of a nonselective NOS blo[430] Increased protein levels of eNOS, but not of iNOS, were observed in the gl these animals, suggesting that the hemodynamic effects were due to enhan eNOS activity.[430]

Solute and water transport

Although many renal responses to NOS blockade are mediated by actions o microcirculation, NO also affects solute and water transport by directly alte function of specific segments of the nephron. In particular, NO appears to p in the moment-to-moment homeostatic control of renal sodium excretion and extracellular fluid volume.

1. Intrarenal NO synthesis is increased during periods of enhanced salt in thereby facilitating renal sodium excretion. The administration of NO dc augments sodium elimination.
2. By comparison, acute or chronic blockade of NO synthesis (with NOS in impairs urinary sodium excretion, even at concentrations that do not aff glomerular or systemic hemodynamics. As an example,

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chronic administration of a NOS inhibitor in humans results in a 40 perc reduction in the fractional excretion of sodium.[431]

Thus, increased and decreased levels of NO enhance and impair the urinar excretion of sodium, respectively. This is due to effects on epithelial transp located in specific nephronal segments. Specifically, NO inhibits sodium en cortical collecting duct, Na-H exchange in the proximal tubule, and Na-K-AT activity in varied nephronal segments.[432,433] NO also impairs the responsiveness of the collecting tubule to ADH, facilitating the excretion of water.[434]

Tubuloglomerular feedback

Some of the effects of NOS inhibition on body fluid homeostasis are though mediated by changes in nNOS function expressed in the macula densa. NO synthesized by nNOS in the macula densa blunts the tubuloglomerular feed (TGF) response in which increasing sodium chloride delivery to the macula lowers the glomerular filtration rate to maintain distal flow at a relatively c level.[435]

However, micropuncture experiments using NOS antagonists indicate that N not mediate TGF. Rather, NO release from the macula densa is a modulatin that is augmented during increased sodium chloride delivery, thereby count afferent arteriole constriction elicited in the TGF response. Thus, changes densa NO production may underlie the resetting of TGF that occurs when s is varied; the response is appropriately blunted with a high-salt diet, as ma of glomerular filtration promotes excretion of the excess salt.[436]

Role in renal injury

The role of NO in the response to renal injury varies based upon the cell ty NO isoform. The function of endothelial-derived NO as a tonic vasodilator a its ability to inhibit platelet activation and adhesion may help minimize inju glomerulonephritis. This has been illustrated in studies in mice in which tar inactivation of the eNOS gene increases the sensitivity to glomerular injury[426,437]

However, NO generated by mesangial and tubular epithelial cells may exace damage, due in part to the ability of these cells to induce the expression of response to inflammatory stimuli.[438] Although mesangial cells do not express appreciable amounts of any of the NOS isoforms under basal conditions, th induced to express iNOS, a feature that has been documented in human glomerulonephritis, animal models of glomerular injury, and in vitro experim inflammatory cytokines.[439][440] and[441] As an example, exposure of mesangial cel to tumor necrosis factor-α (TNF-α) causes a 30-fold increase in cGMP cont first evident at 8 h and is maximal by 24 h.[442]

With inflammatory stimuli, increased levels of NO may enhance injury by su eNOS (resulting in vasoconstriction) and directly causing epithelial cell dar[439] Cellular injury is most likely due to the formation of peroxynitrite from NO a superoxide radical.

SUMMARY

Variations in hormone secretion are referred to as primary, i.e., nonphysiol secondary, i.e., physiologic. As an example, aldosterone release is appropr increased by volume depletion; this is called secondary hyperaldosteronism Conversely, the autonomous hypersecretion of aldosterone due to an adren adenoma is referred to as primary hyperaldosteronism. A brief review of the characteristics of these primary disorders can be helpful at this time by illu the role of the particular hormone in the regulation of water and electrolyte homeostasis. Most of these conditions will be discussed in detail in the rel clinical chapters in Part Two.

Primary excessive secretion of ADH results in increased water reabsorption collecting tubules. This is called *syndrome of inappropriate ADH secretion* and is characterized by water retention, hypoosmolality, and hyponatremia. Volu expansion and edema do not occur in this disorder because, similar to the f aldosterone escape, the initial fluid retention leads to a spontaneous diure may be mediated in part by a rise in renal perfusion pressure and perhaps increased release of ANP (Fig. 6-15).

In contrast, water reabsorption is reduced in the absence of ADH, as large (up to 10 to 20 L/day) of dilute urine are produced. This may be due to defi hormone secretion (central diabetes insipidus) or to renal resistance to the ADH (nephrogenic diabetes insipidus). Despite the polyuria, patients with e of diabetes insipidus tend to remain in near normal water balance, because stimulation of thirst leads to an increase in fluid intake to match the higher output.

Primary hyperaldosteronism is associated with enhanced H^+ and K^+ secretion in the cortical collecting tubule, resulting in hypokalemia and metabolic alkalosis. Na^+ and water retention also promote the development of hypertension; how fluid retention lasts for only a few days, due to aldosterone escape.

Hypoaldosteronism, in comparison, is characterized by variable degrees of

hyperkalemia, metabolic acidosis, and Na^+ wasting. The most prominent change is the rise in the plasma K^+ concentration, since aldosterone is the primary hormo affecting urinary K^+ excretion. Marked loss of Na^+, on the other hand, is usually not a major feature of this disorder in adults, because other antinatriuretic fact as angiotensin II and a reduction in renal perfusion pressure) are activated initial volume depletion (Chap. 8).

PTH increases bone resorption, the urinary excretion of phosphate, and ren calcitriol synthesis. As a result, hypercalcemia and a normal or diminished phosphate concentration are produced by the primary hypersecretion of PT contrast, hypoparathyroidism leads to hypocalcemia (which is in part due to associated calcitriol deficiency) and hyperphosphatemia.

Calcitriol increases the availability of calcium and phosphate primarily by i their rate of intestinal absorption and their release from bone. Consequentl calcitriol deficiency is characterized by hypocalcemia and hypophosphatem

lack of calcitriol may also be associated with rickets in children and osteon adults, since adequate levels of calcitriol, calcium, and phosphate are nece normal bone mineralization.

Vitamin D excess (due to the chronic intake of high doses of vitamin D or to granulomatous disease such as sarcoidosis) typically leads to increased in Ca^{2+} absorption, enhanced bone resorption, hypercalciuria, and, in some ca hypercalcemia.[277,278,281,390] The changes in Ca^{2+} balance induced by prolonged ingestion of vitamin D are primarily due to calcifediol, the 25-hydroxylated of calcitriol. The hepatic synthesis of calcifediol is substrate-dependent an physiologically regulated;[249] as a result, increased vitamin D intake can lead to marked increase in calcifediol production.[390] This compound is less active but, in this setting, is able to promote the development of hypercalcemia. In compa there is no large increase in calcitriol synthesis, because of the inhibitory the rise in the plasma Ca^{2+} concentration and the associated reduction in PTH release.[390]

PROBLEMS

6-1 Aldosterone secretion can be increased by an autonomous adrenal adenoma or in the presence of volume depletion. What will the plasma activity be in these two conditions?

6-2 Patients with renal failure have an elevated plasma osmolality due increase in the BUN, but do not have persistent ADH release. Why?

6-3 Thirst protects against the development of hypernatremia. Why doe the ability to shut off osmotic thirst protect against hyponatremia?

6-4 What effect will the following have on renal calcitriol synthesis?

a. **Ingestion of a high-phosphate diet**

b. **Hypoparathyroidism**

c. **Ingestion of a high-calcium diet**

d. **Renal disease in which phosphate intake is restricted to prevent phosphate retention**

6-5 What effect will each of the following have on the release of aldost ANP, and ADH?

a. **Ingestion of a Na^+ load (potato chips, for example) without water**

b. **Ingestion of a water load, which is normally rapidly excreted witho change in extracellular volume**

c. **An intravenous infusion of isotonic saline**

d. **Marked diarrhea in which the plasma Na^+ concentration remains normal**

6-6 Loop diuretics cause hypercalciuria by diminishing Ca^{2+} reabsorption in the thick ascending limb of the loop of Henle. They do not, however, c hypocalcemia. Why?

6-7 Aldosterone increases Na^+ reabsorption. Why doesn't the retained Na^+ result in an elevation in the plasma Na^+ concentration?

6-8 Patients with which of the following conditions are likely to develo decline in renal function following the administration of a nonsteroida inflammatory drug?

a. **Low-salt diet**

b. **High-salt diet**

c. **Untreated hypertension**

d. **Heart failure**

e. **Severe vomiting**

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Chapter Seven

The Total Body Water and the Plasma Sodiur Concentration

The body water is distributed among three major compartments: the intrace space; the interstitium, which constitutes the extracellular environment of t and the vascular space. Regulation of the intracellular volume, which is es normal cellular function, is achieved in part by regulation of the plasma osr through changes in *water* balance. In comparison, maintenance of the plasma volume, which is essential for adequate tissue perfusion, is closely related regulation of *sodium* balance. Sodium and water homeostasis will be reviewed detail in the following two chapters. It is useful, however, to first discuss tl involved in the distribution of water across the cell membrane (between the intracellular and extracellular fluids) and across the capillary wall (betweer vascular space and the interstitium).

EXCHANGE OF WATER BETWEEN CELLULAR AND EXTRACELLULAR FLUIDS

Osmotic forces are the prime determinant of water distribution in the body. freely cross almost all cell membranes; as a result, the body fluids are in o equilibrium, as the osmolalities of the intracellular and extracellular fluids same.[1]

The concept of osmotic pressure can be easily understood from the simple experiment in Fig. 7-1. Suppose distilled water in a beaker is separated into tw compartments by a membrane that is permeable to water but not to solutes, glucose is added to the fluid on one side of the membrane. Water molecules

random motion and can diffuse across a membrane by a mechanism similar diffusion of solutes. When solutes are added to water, however, the intermc cohesive forces lead to a reduction in the random movement (or activity) of molecules.[2,3] Since water moves from an area of high activity to one of low a water will flow into the compartment containing glucose.

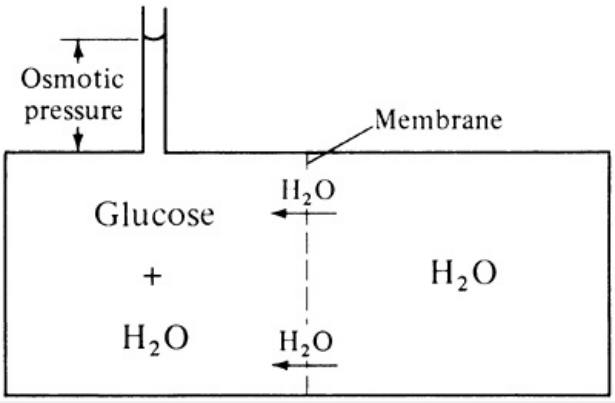

Figure 7-1 Effect of adding an impermeable solute such as glucose to the f on one side of a membrane. As water moves into the glucose compartment hydraulic pressure is generated (measured by the height of the column of above the glucose compartment) which at equilibrium will be equal to the pressure of the solution.

In theory, this movement of water, called *osmosis*, should continue indefinitely, because the activity of water will always be lower in the glucose compartme However, since the compartment is rigid, the increase in volume will result elevation in hydrostatic pressure, causing the fluid column above the comp rise. This hydrostatic pressure tends to push water back into the solute-fre compartment. Equilibrium will be reached when the hydrostatic pressure (as measured by the height of the column) is equal to the forces pulling water a membrane. This hydrostatic pressure that opposes the osmotic movement o called the *osmotic pressure* of the solution.

The osmotic pressure that is generated is proportional to the *number of particles* per unit volume of solvent, not to the type, valence, or weight of the particl solute, however, must be unable to cross the cell membrane. Let us now co what would happen in a beaker similar to that in Fig. 7-1 if a lipid-soluble and freely diffusible solute such as urea were added to one compartment (Fig. 7-2). The added urea would move down a concentration gradient into the solute-free compar The new equilibrium state would be characterized by equal urea concentrat each compartment, not by water movement into the urea compartment. As a osmotic pressure is generated by urea at equilibrium and urea is considere *ineffective osmole*.

Osmotic pressure is important in vivo because it determines the distributior between the extracellular and intracellular spaces. Each of these compartm one solute that is primarily limited to that compartment and therefore is the determinant of its osmotic pressure. Na^+ salts are the principal extracellular osmo and act to hold water in the extracellular space; conversely, K^+ salts account for almost all the intracellular osmoles (most of the other major cation, Mg^{2+}, is bound and osmotically inactive) and act to hold water within the cells.

Although the cell membrane is permeable to both Na^+ and K^+, these ions are able to

act as effective osmoles because they are restricted to their respective

compartments by the Na^+-K^+-ATPase pump in the cell membrane. The net effect that the volumes of the extracellular and intracellular fluids are determined amount of water present and by the extent of exchangeable Na^+ to exchangeable K^+.*

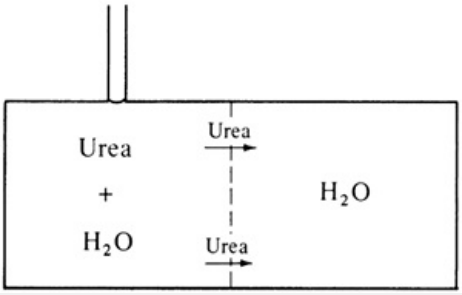

Figure 7-2 Effect of adding a permeable solute such as urea to the fluid on side of a membrane. In this setting, equilibrium is reached by urea equilib across the membrane rather than by water movement into the urea compar Consequently, no osmotic pressure is generated.

Under normal circumstances, the water and electrolyte content in the body maintained within relatively narrow limits, as variations in dietary intake ar by appropriate changes in urinary excretion. Nevertheless, it is important t understand the potential physiologic effects of alterations in solute or wate since these disturbances often occur in the clinical setting.

If, for example, the osmolality of one fluid compartment is changed, water w across the cell membrane to reestablish osmotic equilibrium. How this affec distribution and solute concentration can be appreciated from the following (Fig. 7-3). For the sake of simplicity, let us assume that the osmolality of the fluids is 280 mosmol/kg and is due entirely to 140 meq/L of Na^+ salts in the extracellular fluid and to 140 meq/L of K^+ salts in the cells; i.e., we are assuming that Na^+ and K^+ salts dissociate completely into cations and anions. As depic Fig. 7-3*a*, an average 70-kg man might have a total body water (TBW) of 42 l 42 kg) of which 25 liters (60 percent) is intracellular and 17 liters (40 perc extracellular.

What will happen if 420 meq of NaCl (420 mosmol) without water is added t extracellular fluid (Fig. 7-3*b*)? Since the NaCl remains extracellular, there will be increase in the extracellular fluid osmolality, resulting in *water movement out of the cells* down an osmotic gradient. The following calculations can be used to e the characteristics of the total body water in the new equilibrium state:

1. Initial total body solute = 280 mosmol/kg × 42 kg = 11,760 mosmol

2. Initial extracellular solute=280 mosmol/kg× 17 kg=4760 mosmol
3. New total body solute=11,760+420=12,180 mosmol

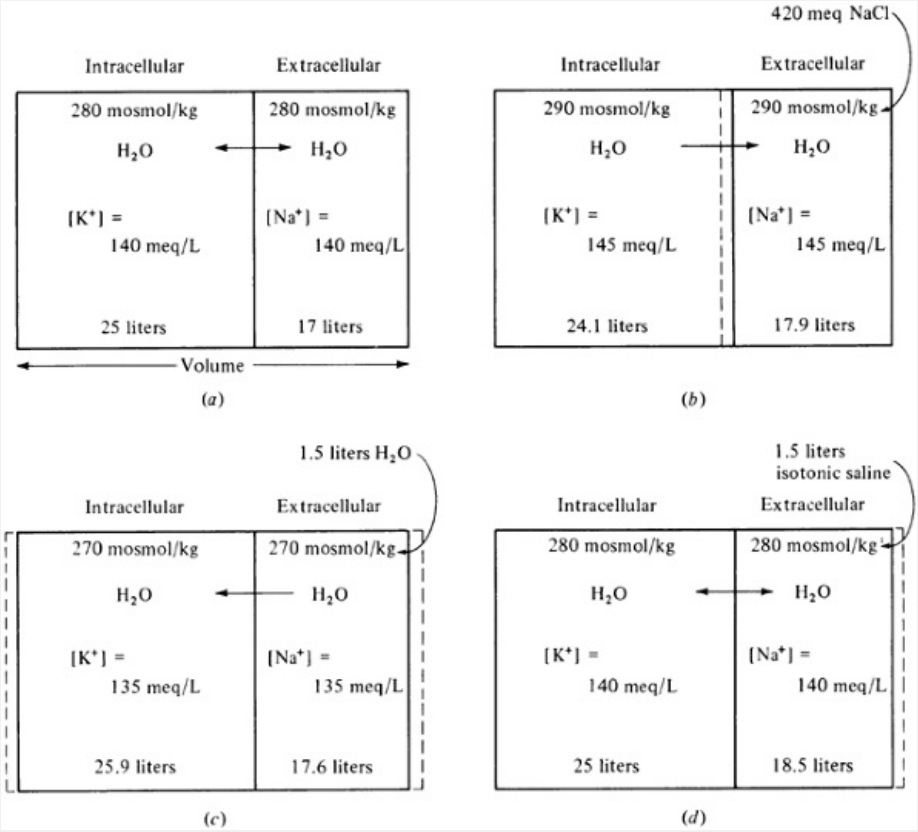

Figure 7-8 Osmolality of the body fluids and the distribution of the total body water between the intracellular and extracellular fluids (*a*) in the control state and after the addition of NaCl (*b*), H_2O (*c*), or (*d*) isotonic NaCl and H_2O to the extracellular fluid. For simplicity, it is assumed that Na^+ salts account for all the extracellular osmoles and K^+ salts for all the intracellular osmoles. See text for details. *(Adapted from Earley LE, in Maxwell MH, Kleeman CR (eds): Clinical Disorders of Fluid and Electrolyte Metabolism, 2d ed. New York: McGraw-Hill, 1972. Used with permission.)*

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4. New body water osmolality=12,180 mosmol÷42 kg=290 mosmol/kg
5. New extracellular solute=4760+420=5180 mosmol
6. New extracellular volume=5180 mosmol÷ 290 mosmol/kg=17.9 kg
7. New intracellular volume=42-17.9=24.1 kg
8. New extracellular or plasma $[Na^+]$=osmolality÷ 2=145 meq/L

Thus, increasing the quantity of extracellular solute results in the movement of mL of water from the cells into the extracellular fluid. The net effect is an increase in *the osmolality of both compartments* even though the added solute is restricted t

the extracellular space. This illustrates why the total body water (50 to

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60 percent of lean body weight) must be used when calculating the volume distribution of changes in plasma osmolality.

A different sequence occurs if 1.5 liters of solute-free water is added to the extracellular fluid, e.g., by ingestion. This reduces the extracellular fluid o creating an osmotic gradient favoring the *entry of water into the cells* (Fig. 7-3*B*). In estimating the new steady state, steps 1 and 2 are the same as those abov

1. Initial total body solute=11,760 mosmol
2. Initial extracellular solute=4760 mosmol
3. Initial intracellular solute=11,760-4760=7000 mosmol
4. New total body water=42+1.5=43.5 kg
5. New body water osmolality=11,760 mosmol÷ 43.5 kg=270 mosmol/kg
6. New extracellular volume=4760 mosmol÷ 270 mosmol/kg=17.6 kg
7. New intracellular volume=7000 mosmol÷ 270 mosmol/kg=25.9 kg
8. Ratio of intracellular volume to TBW=25.9÷ 43.5=60 percent
9. New extracellular or plasma $[Na^+]$=Na osmolality÷ 2=135 meq/L

Since there is no change in the ratio of intracellular to extracellular solute example, the fractional composition of the TBW is unchanged (cell water is percent of TBW). However, the TBW is increased, resulting in an *expansion* and *dilution* of both compartments.

Finally, if both NaCl and water are given as 1.5 liters of isotonic NaCl, ther no change in osmolality and consequently no water movement across the ce membrane (Fig. 7-3*C*). Since the administered NaCl remains in the extracellula space, the *only effect* is a 1.5-liter increase in the extracellular fluid volume.

The results of these experiments are summarized in Table 7-1 and illustrate an important and often misunderstood concept, that *the plasma Na^+ concentration is a measure of concentration and not of volume*. In each instance, the extracellular flu volume is increased because of an elevation in the TBW and/or the total exchangeable Na^+; despite this uniform change in volume, however, the plasm concentration is, respectively, increased, decreased, and unchanged. This because the plasma Na^+ concentration reflects the *ratio* of the amounts of solute and water present, not the absolute amount of either solute or water. Thus, *no necessary correlation between the plasma Na^+ concentration and the extracellular fluid volume*. These parameters change in a parallel direction whe Na^+ is administered (Fig. 7-3*B*) but in an opposite direction (low plasma Na^+ concentration, high extracellular fluid volume) when water retention occurs (Fig. 7-3*C*). Furthermore, since the extracellular volume is the primary determinant

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urinary sodium excretion (Chap. 8), there is also a *relationship* between the plasma Na^+ concentration and the rate of sodium excretion (Table 7-1). When water is retained, for example, the plasma Na^+ concentration falls by dilution, but urinary sodium excretion will rise because of the increase in extracellular volume.

One final point deserves emphasis in these experiments. The intracellular volume varies inversely with the plasma Na^+ concentration, decreasing with hypernatremia and increasing with hyponatremia. These changes are important clinically because the neurologic symptoms associated with acute changes in the plasma Na^+ concentration are primarily related to these alterations in cell volume in the brain (see Chaps. 23 and 24).

Table 7-1 Osmotic and volume effects of addition of NaCl, water, and isotonic saline

Substance added	Plasma osmolality	Plasma sodium	Extracellular volume	Intracellular volume	Urine sodium
NaCl	↑	↑	↑	↓	↓
Water	↓	↓	↑	↑	↑
Isotonic NaCl	0	0	↑	0	↑

Relation of Plasma Sodium Concentration to Osmolality

The osmolality of the plasma (P_{osm}) is equal to the sum of the osmolalities of the individual solutes in the plasma. Most of the plasma osmoles are Na^+ salts, with lesser contributions from other ions, glucose, and urea. The osmotic effect of plasma ions can usually be estimated from 2× plasma Na^+ *concentration*. The validity of this approximation results from the interplay of several factors:

1. Ionic interactions in plasma *reduce the random movement* of NaCl so that it acts osmotically as if it were only 75 percent, not 100 percent, dissociated. As a result, 1 mmol of NaCl behaves as if it dissociates into roughly 1.75 particles (0.75 Na^+, 0.75 Cl^-, and 0.25 NaCl); thus, the plasma Na^+ concentration must be multiplied by 1.75 to estimate the osmotic effect of sodium salts.
2. Only 93 percent of the plasma is normally composed of water, with fat and proteins making up the remaining 7 percent. In most laboratories, the plasma Na^+ concentration is measured per liter of plasma. This value must be divided by 0.93 to arrive at the physiologically important plasma Na^+ concentration in the

plasma water (Na^+ being present only in the aqueous phase of plasma). Th

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$$\text{Osmolality of } Na^+ \text{ salts} = (1.75 \div 0.93) \times \text{plasma } [Na^+]$$
$$= 1.88 \times \text{plasma } [Na^+]$$

3. The remaining 0.12× plasma Na^+ concentration is equal to 17 mosmol/kg (0.1 140), which happens to be the approximate osmotic pressure generated K^+, Ca^{2+}, and Mg^{2+} salts.

The osmotic contributions of glucose and urea, both of which are measured milligrams per deciliter, can be calculated from Eq. 7-1:

$$\text{mosmol/kg} = (\text{mg/dL} \times 10) \div \text{mol wt} \qquad (7\text{-}1)$$

The molecular weight of glucose is 180 and that of the two nitrogen atoms (since urea is measured as the blood urea nitrogen, or BUN) is 28. Therefo P_{osm} can be estimated from

$$P_{osm} \cong 2 \times \text{plasma } [Na^+] + \frac{[\text{glucose}]}{18} + \frac{\text{BUN}}{2.8} \qquad (7\text{-}2)$$

The *effective* plasma (and extracellular fluid) osmolality is determined by thos osmoles that act to hold water within the extracellular space. Since urea is ineffective osmole,

$$\text{Effective } P_{osm} \cong 2 \times \text{plasma } [Na^+] + \frac{[\text{glucose}]}{18} \qquad (7\text{-}3)$$

The normal values for these parameters are

$$\text{Plasma } [Na^+] = 137\text{–}145 \text{ meq/L}$$
$$[\text{Glucose}] = 60\text{–}100 \text{ mg/dL, fasting}$$
$$\text{BUN} = 10\text{–}20 \text{ mg/dL}$$
$$P_{osm} = 275\text{–}290 \text{ mosmol/kg}$$
$$\text{Effective } P_{osm} = 270\text{–}285 \text{ mosmol/kg}$$

Under normal circumstances, glucose accounts for only 5 mosmol/kg or Eq. 7-3, and can be simplified to

$$\text{Effective } P_{osm} = 2 \times \text{plasma } [Na^+] \qquad (7\text{-}4)$$

Thus, in most conditions, the plasma Na^+ concentration is a reflection of the P_{osm}, finding consistent with the fact that Na^+ salts are the principal extracellular osmol

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Determinants of the Plasma Sodium Concentration

Since the body fluids are in osmotic equilibrium,

$$\text{Effective } P_{osm} = \text{effective osmolality of total body water}$$
$$= \frac{\text{extracellular solute} + \text{intracellular solute}}{\text{total body water}}$$

As described above, exchangeable (Na^+ + K^+) salts are the primary effective extracellular solutes, and exchangeable (K^+) salts are the primary effective

intracellular solutes. Thus

$$\text{Effective } P_{osm} \cong \frac{2 \times Na_e^+ + 2 \times K_e^+}{TBW} \qquad (7\text{-}5)$$

(The multiple 2 is used to account for the osmotic contribution of the anion accompanying Na^+ and K^+.) If we now combine Eq. 7-4 and 7-5, both of which are formulas for the effective P_{osm}, we get

$$\text{Plasma } [Na^+] \cong \frac{Na_e^+ + K_e^+}{TBW} \qquad (7\text{-}6)$$

As illustrated in Fig. 7-4, this relationship holds over a wide range of plasma Na^+ concentrations in humans.

The importance of these variables for the plasma Na^+ concentration can be appreciated from the examples in Fig. 7-3. Increasing the Na_e^+ elevates the plasma Na^+ concentration (Fig. 7-3*B*); increasing the TBW decreases the plasma Na^+ concentration (Fig. 7-3*C*); and increasing the Na_e^+ and TBW proportionately has no effect on the plasma Na^+ concentration (Fig. 7-3*D*).

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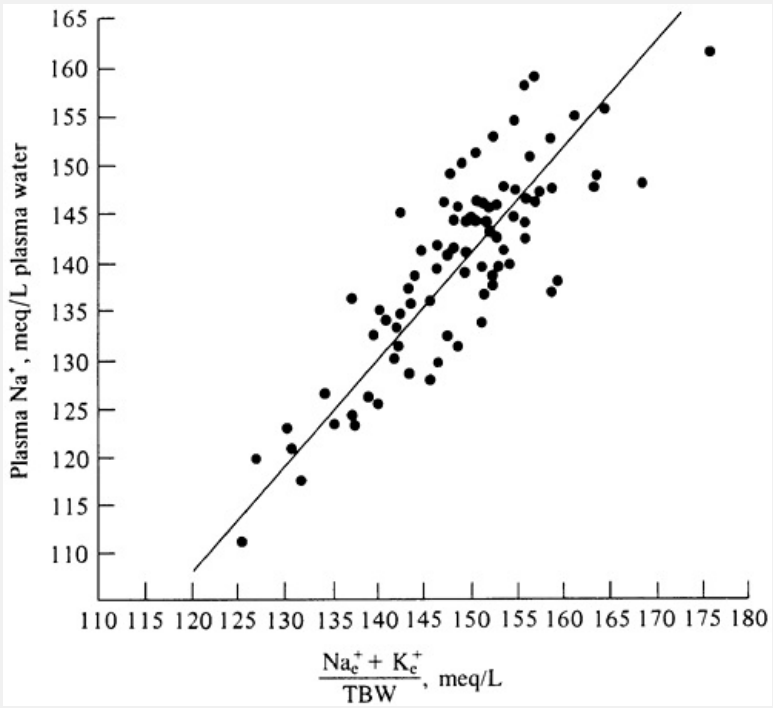

Figure 7-4 Relation between the plasma water Na^+ concentration and the ratio of $(Na^+_e + K^+_e)/TBW$. *(Adapted from Edelman I, Leibman J, O'Meara MP, Birkenfeld LW: J Clin Invest 37:1236, 1958, by copyright permission of The American Society for Clinical Investigation.)*

The effect of changes in potassium balance is less apparent but can be important clinically.[6,7] Suppose, for example, that K^+ is lost from the extracellular fluid

because of diarrhea, leading to a fall in the plasma K^+ concentration. This will create a concentration gradient favoring the movement of K^+ from the cells into the extracellular fluid. Since large proteins and organic phosphates are the ma intracellular anions and cannot easily leave the cells, electroneutrality is p by Na^+ (and H^+) entry into the cells, thereby lowering the plasma Na^+ concentration.

The major clinical application of these concepts occurs in patients with hyp (low plasma Na^+ concentration) or hypernatremia (high plasma Na^+ concentration) (see Chaps. 22, 23 and 24). From the relationships in Eqs. 7-4 and 7-6 we can see that hyponatremia usually represents hypoosmolality and can be produced b and K^+ loss or, most commonly, by water retention. Excretion of the excess w the urine is normally a very effective defense against the development of hyponatremia. Thus, a fall in the plasma Na^+ concentration is almost always associated with a defect in urinary water excretion, due most often to the p of antidiuretic hormone.

On the other hand, hypernatremia represents hyperosmolality and can be pr by Na^+ gain or water loss. The toxicity of hyperkalemia (high plasma K^+ concentration) prevents the retention of enough K^+ to cause an important elevation in the plasma Na^+ concentration. The primary protective mechanism against hypernatremia is the stimulation of thirst, thereby increasing water intake a lowering the plasma Na^+ concentration to normal. Thus, hypernatremia generall occurs in infants or comatose adults who cannot express a normal thirst res

Notice that the regulation of the plasma Na^+ concentration and therefore the plasm osmolality occurs by changing *water balance* (see Chap. 9). Although it is tempting to assume that maintenance of the plasma Na^+ concentration must be related to Na balance, this is not the case. Alterations in sodium balance are used to mai plasma volume and tissue perfusion, not the plasma Na^+ concentration (see Chap. 8). Too much sodium is manifested as edema, and too little sodium results i hypovolemia.

EXCHANGE OF WATER BETWEEN PLASMA AND INTERSTITIAL FLUID

The supply of nutrients to the cells and the removal of waste products from occur in the capillaries and postcapillary venules by the diffusion of solute gases (O_2 and CO_2) between the plasma and the interstitial fluid. Equally imp is the maintenance of a proper distribution of water between these compart

Although osmotic forces contribute to the distribution of water across the c wall, the situation differs from that across the cell membrane. Since

the capillary is permeable to small Na^+ and glucose, these substances do not beh as effective osmoles. It is only the *plasma proteins*, which move across the capillary wall to a limited degree, that act as effective osmoles and therefore hold w vascular space. This osmotic pressure generated by the plasma proteins is

the colloid osmotic pressure of the *plasma oncotic pressure*

Fluid does not continuously move into the capillary because the oncotic pre largely balanced by the capillary hydraulic (or hydrostatic) pressure. This p generated by the propulsion of blood from the heart and tends to push wate the vessels into the interstitium. Although less important, oncotic and hydra pressures present in the interstitium also contribute to the regulation of flu exchange between the plasma and the interstitial fluid (Fig. 7-5).

The relationship between net filtration from the vascular space into the inte and the hydraulic and oncotic pressure gradients across the capillary wall expressed by Starling's law[8,9,10] and[11]:

$$\text{Net filtration} = \text{LpS}\ (\Delta\ \text{hydraulic pressure} - \Delta\ \text{oncotic pressure})$$
$$= \text{LpS}\ [(P_{cap} - P_{if}) - s(\pi_{cap} - \pi_{if})] \qquad (7\text{-}7)$$

where Lp is the unit permeability (or porosity) of the capillary wall, S is the area available for fluid movement, and P_{cap} and P_{if} are the capillary and interstitial flui hydraulic pressures, π_{cap} and π_{if} are the capillary and interstitial fluid oncotic pressures, and s represents the reflection coefficient of proteins across the wall (with values ranging from 0 if completely permeable to 1 if completely impermeable). The interstitial oncotic pressure is derived primarily from filt plasma proteins and to a lesser degree from proteoglycans in the interstitiu

The normal values for these parameters in experimental animals and human resting state is uncertain, largely because of difficulties in measurement of the parameters, with the exception of the capillary oncotic pressure. Furthe capillary hemodynamics are not necessarily uniform within an organ, as bot and closed capillaries may be present.

What is clear, however, is that capillaries in different organs have different hemodynamic and permeability characteristics (Table 7-2). In skeletal muscle, for example, capillary pressure is much lower than systemic pressure (because high precapillary resistance) and the capillary wall is relatively impermeabl

proteins,[9,10] the interstitial hydraulic pressure, in comparison, has a negativ that appears to be generated by the lymphatic removal of interstitial fluid.

Table 7-2 Approximate values for Starling's force in muscle, lung, and kidney[3]

	Skeletal muscle	Alveoli	Glomeruli
Hydraulic pressure			
Capillary (mean)	17.3	8	45

Interstitium	-3.0	-2	10
Mean gradient	20.3	10	35
Oncotic pressure			
Capillary (mean)	28	26	29[b]
Interstitium	8	18	0
Mean gradient	20	8	29
Net gradient favoring filtration (δP-δpi)	0.3	2	6

[a] Units are mmHg. Values are from Refs. 9, 10, 12, and 13.

[b] The mean capillary oncotic pressure rises in the glomerulus because o filtration of relatively protein-free fluid.

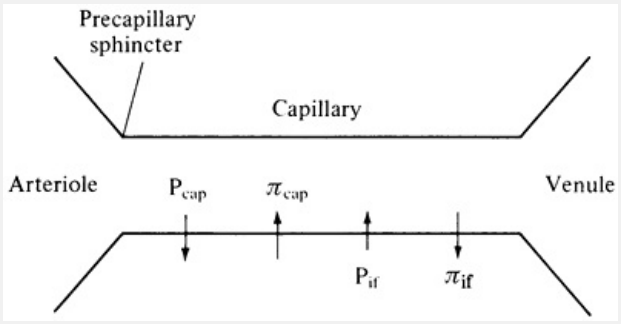

Figure 7-5 Schematic representation of the factors controlling fluid moveme across the capillary wall between the plasma and the interstitial fluid.

The net effect is a 0.3- to 0.5-mmHg gradient favoring filtration, with the fi returned to the systemic circulation by the lymphatic vessels. This gradient uniform within the capillary circulation. Although the *mean* hydraulic pressure is about 17 mmHg,[9,11,12] the pressure within most of the capillary is higher at 25 to mmHg; thus, filtration occurs throughout the capillary.[11] Most of this filtrate then reenters the vascular space in the highly permeable *postcapillary venules* where the hydraulic pressure falls to 10 mmHg, a level below the oncotic pr gradient.[11]

In comparison to those in skeletal muscle, the alveolar capillaries have bot

capillary hydraulic pressure (due to perfusion from the low-pressure right v and a lower transcapillary oncotic pressure gradient (because of a higher permeability to proteins).[10,13] The result is a small gradient favoring filtration, v is slightly larger than that in skeletal muscle. Once again, the fluid that is normally removed by the lymphatic vessels.[10]

The smaller transcapillary oncotic pressure gradient across the alveolar ca wall has important clinical implications, because it means that the rate of fi relatively unaffected by changes in the plasma oncotic pressures. As an exa fall in the plasma albumin concentration (called hypoalbuminemia) might be to promote fluid movement into the interstitium as a result of the associated reduction in the plasma oncotic pressure. However, the interstitial oncotic p will undergo *a parallel decline*, due in part to less albumin movement from the vascular space into the interstitium. The net effect with mild to moderate hypoalbuminemia is *no change in the transcapillary oncotic pressure gradient*. As a result, a low plasma albumin concentration alone is not likely to

produce pulmonary edema, which is a potentially life-threatening condition "Safety Factors" below).[14]

Finally, the glomerular capillaries are unique in that they have a much high hydraulic pressure, due in part to a *low* precapillary resistance.[15] This is physiologically important because the high pressure gradient plus a 50- to increase in net permeability allow the glomeruli to maintain a very high rate filtration (see Chap. 2).

Capillary Hydraulic Pressure and Autoregulation

The average capillary hydraulic pressure is determined by the interplay of factors: the arterial pressure, which has a normal mean value of 85 to 95 m humans; the resistance at the precapillary sphincter (Fig. 7-5); and the postcapillary resistance in the venules and veins. The precapillary sphincter resistance determines the degree to which the arterial pressure is transmitted to the c This is important physiologically because the ability to vary sphincter tone capillary hydraulic pressure and therefore the rate of capillary filtration to *relatively constant in the presence of changes in arterial pressure*.[16] How this occurs can be appreciated from the relationship between resistance (R), th pressure drop across the resistance (ΔP), and the blood flow (Q):

$$\Delta P = Q \times R \qquad (7\text{-}8)$$

Thus, an increase in resistance elevates the ΔP, and a decrease in resistar reduces the ΔP. If, for example, the arterial pressure is increased, a rise in precapillary resistance by constriction of the sphincter will increase the ΔP preventing an increment in the capillary pressure (and in capillary blood flo the elevations in pressure and resistance balance out). If this did not occu every patient with high blood pressure would tend to develop edema (define palpable swelling due to expansion of the interstitial fluid volume), since th in capillary hydraulic pressure would act to push water out of the vascular the interstitium. Although neural and humoral factors may contribute, capill

resistance is largely under local control, e.g., by stretch receptors in the s
wall and local metabolic factors, a process that is called *autoregulation*. (16)
(Autoregulation of the glomerular filtration rate is a more complex process t
involves the efferent glomerular arteriole.)

In contrast to these events at the arterial end of the capillary, the resistanc
venous end is less well regulated by local factors. Consequently, alteration
venous pressure produce parallel changes in capillary hydraulic pressure (
below).

Plasma Oncotic Pressure

The relationship between the protein concentration and the oncotic pressur
generates can be estimated from van't Hoff's law:

$$\text{Oncotic pressure} = cRT \qquad (7\text{-}9)$$

where c is the solute concentration in moles per unit volume of water, R is
with the same value as the gas constant per mole, and T is the absolute te
in kelvins. Since R and T are constants, the oncotic pressure should be a l
function of protein concentration.

This expectation, however, does not hold true. As depicted in Fig. 7-6, the oncotic
pressure generated by the plasma proteins is greater than that predicted o
basis of protein concentration from van't Hoff's law. This difference is due
the Gibbs-Donnan equilibrium, since more particles are present in the prote
containing compartment. According to the Gibbs-Donnan equilibrium, the pr
the concentrations of the major cations and anions in one compartment is e
the product in the other compartment, assuming free diffusibility across the
membrane. If, for example, Na^+ and Cl^- are the only diffusable ions in the plasma
and interstitial fluid, then

$$[Na^+]_p \times [Cl^-]_p = [Na^+]_{if} \times [Cl^-]_{if}$$

The Na^+ and Cl^- concentrations in the interstitium will be equal at about 145
In comparison, the plasma water Na^+ concentration will exceed that of Cl^- by about
15 meq/L ($[Na^+]=[Cl^-]+15$), which is the approximate negative charge on the p
proteins. Thus

$$([Cl^-]_p + 15) \times [Cl^-]_p = 145 \times 145$$
$$[Cl^-]_p = 137.7\ \text{meq/L}$$
$$[Na^+]_p = 152.7\ \text{meq/L}$$

The net effect is that the total number of milliequivalents of Na^+ and Cl^- in a liter in
the plasma water (137.7+152.7=290.4) exceeds that in the interstitial fluid
(145+145=290) by 0.4 meq/L or 0.4 mmol/L. Although this difference appear
the normal plasma protein concentration is only 0.9 to 1 mmol/L.

Consequently, the total osmotic effect of the plasma proteins is increased f
mosmol/kg (0.9 mmol/L equals 0.9 mosmol/kg)) to 1.3 mosmol/kg by the Gib
Donnan effect. Since 1 mosmol/kg generates an osmotic pressure of 19.3 m

effect increases the capillary oncotic pressure from 17.4 mmHg (0.9× 19.3) concentration alone to 25 to 26 mmHg (1.3× 19.3). (Other, poorly understoc also contribute to this discrepancy between the predicted and actual values oncotic pressure produced by the plasma proteins).[17]

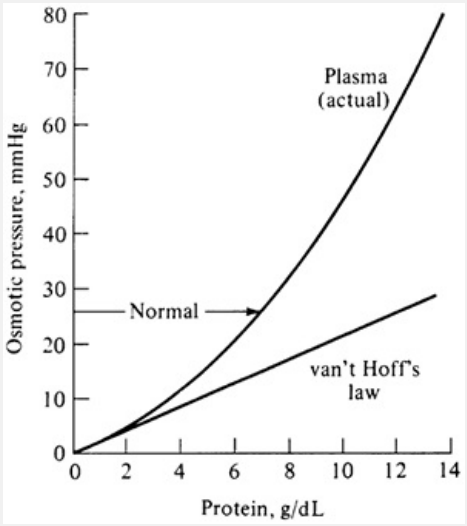

Figure 7-6 Relationship between protein con-centration and osmotic pressu predicted from van't Hoff's law and as actually occurs with plasma. (*Adapted from Landis E, Pappenheimer JR, in Hamilton WF, Dow P (eds): Handbook of Physiology, sec 2, Circulation, vol II. American Physiological Society, Washington, D.C., 1963. Used with permission.*)

Safety Factors

Since the mean gradient only slightly favors filtration, it might be assumed small increase in capillary hydraulic pressure (due to an elevated venous p or a small decrease in plasma oncotic pressure (due to hypoproteinemia) w to fluid movement into the interstitium and ultimately to clinically apparent However, experimental and clinical observations indicate that edema does n until there is a relatively large change in one or both of these parameters.

Three factors contribute to this protective response[9,10]

1. Lymphatic flow is able to increase, so that the excess filtrate can initial carried away.
2. As fluid initially moves into the interstitium, the oncotic pressure will fa dilution and by the lymphatic removal of interstitial proteins), thereby m the gradient for further entry into the interstitium.
3. The increase in interstitial fluid volume will cause the interstitial hydra pressure to rise; edema cannot occur until the normally negative value positive.[9]

The importance of these safety factors varies from organ to organ. In skele muscle, for example, all three contribute. In comparison, the hepatic sinusc relatively open and freely permeable to proteins.[10] As a result, there is normally *oncotic pressure* gradient across the sinusoids, since the plasma and interstit oncotic pressures are roughly equal. Thus, the hydraulic pressure gradient unopposed, although the intrasinusoidal pressure is relatively low because the hepatic perfusion derives from the low-pressure portal venous system. setting, it is hepatic lymph flow that is primarily responsible for preventing accumulation of excess interstitial fluid.

Although estimated values for Starling's forces in different organs are Table 7-2, methodologic difficulties make the accuracy of these measurements unc subcutaneous tissue, for example, where clinically evident peripheral edem usually detected, studies in humans suggest that the interstitial oncotic pre be as high as 12 to 15 mmHg, rather than only 8 mmHg.[18,19]

The potential clinical relevance of this issue can be appreciated from the m of edema formation in patients who have hypoalbuminemia due to urinary pr losses in the nephrotic syndrome.[20,21] In this setting, the fall in the plasma albur concentration leads to less entry of albumin into the interstitium

and a parallel decline in the interstitial protein concentration minimizes the change in the *transcapillary oncotic pressure gradient* from near normal value and therefore minimizes the degree of fluid loss into the interstitium (Fig. 7-7). If, for example, the respective plasma and interstitial oncotic pressures were 28 and 8 mmHg (a Table 7-2) then loss of interstitial proteins to balance the decrease in plasm oncotic pressure could account for a maximum safety factor of only 8 mmHg comparison, protection against fluid movement into the interstitium would b increased up to twofold if the true interstitial value were 12 to 15 mmHg; as hypoalbuminemia would be less likely to produce edema.

Studies in both humans and experimental animals with the nephrotic syndro consistent with the latter hypothesis, since primary renal sodium retention by the underlying renal disease) often plays a major role in edema formatio[20,22] animals with the unilateral nephrotic syndrome, for example, there is unilat retention, indicating that intrarenal rather than systemic factors are of prim importance (see page 481).[22] Increased collecting tubule reabsorption appears responsible for the Na^+ retention in this setting, although how this occurs is nc understood.[21,23,24]

The relative importance of underfilling (due to hypoalbuminemia-induced pl volume depletion) and overflow (due to primary renal sodium retention) in t generation of edema associated with hypoalbuminemia appears to be variab different patients.[20,25,26] Two settings have been identified in which underfillir clearly occurs: acute hypoalbuminemia, in which there is not time for the

interstitial oncotic pressure to fall; and severe hypoalbuminemia (plasma al

concentration less than 1.0 g/dL), in which the transcapillary oncotic gradie
be maintained because the interstitial value cannot be further reduced.[27] An example
of underfilling edema due to acute hypoalbuminemia is saline resuscitation
massive bleeding, lowering the plasma albumin concentration by dilution. It
be present in acute onset nephrotic syndrome,[26] but is less common in stable
disease.[27]

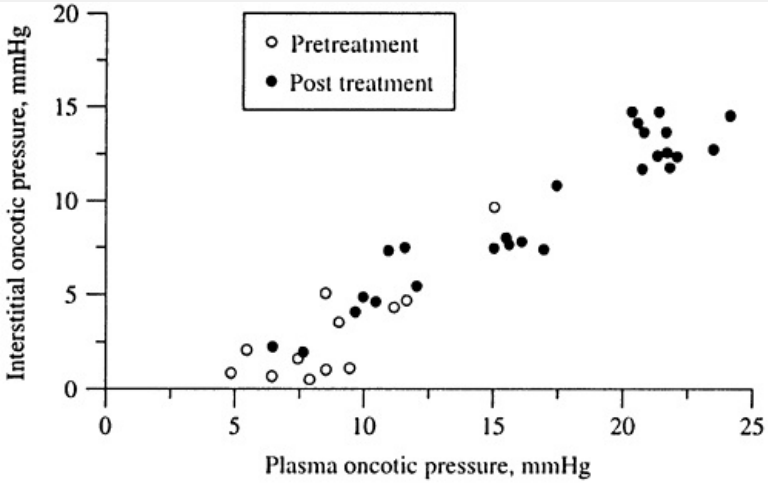

Figure 7-7 Relationship between plasma and interstitial oncotic pressures i
nephrotic patients with minimal change disease before (open circles) and
(closed circles) corticosteroid-induced remission of the proteinuria. These
are reduced in parallel during active disease with little change in the
transcapillary oncotic pressure gradient and therefore little tendency to p
edema formation. (*Adapted from Koomans HA, Kortlandt W, Geers AB, Dorho
Mees EJ*, Nephron *40:391, 1985. Used with permission.*)

PROBLEMS

7-1 What is the relationship between the plasma Na^+ concentration and the plasma osmolality? Between the plasma Na^+ concentration and the extracellular volume?

7-2 If glucose is added to the extracellular fluid, what will happen to th following?

a. **The plasma osmolality**
b. **The extracellular volume**
c. **The intracellular volume**
d. **The plasma Na^+ concentration**

7-3 Laboratory tests for a patient provide the following plasma values:

Osmolality=290 mosmol/kg

Sodium=125 meq/L

Urea nitrogen=28mg/dL

If glucose is the only other osmole in the extracellular fluid, calculate plasma glucose concentration in mg/dL.

7-4 What effect will the following have on the plasma volume?

a. **An elevation in arterial blood pressure**
b. **A decrease in venous pressure**
c. **A reduction in the plasma albumin concentration to 3 g/dL (normal 4 to 5 g/dL)**

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Footnotes

* The exchangeable portion is used because about 30 percent of the body N and a smaller fraction of the body K are bound in areas such as bone, where they are “nonexchangeable” and therefore osmotically inactive. These ions also may be partially bound in intracellular organelles such as the nucleus and lysosom[4].

† In this example, it is assumed that the administered water is retained. In subjects, however, excess water is excreted so rapidly that there is little ch volume or sodium excretion (see Chap. 9). Increases in extracellular volume and sodium excretion after a water load occur only if there is some defect in wa excretion, as with persistent secretion of antidiuretic hormone (see Chap. 23).

‡ The units and the methods used to measure the plasma osmolality are rev Chap. 1.

¶ This response is similar to that described above for the alveolar capillari the protection is even more prominent because the interstitial oncotic pres higher, at 18 mmHg (Table 7-2).

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Title: *Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th E*

Chapter Eight
Regulation of the effective circulating volum

The maintenance of adequate tissue perfusion is essential for normal cellul metabolism by providing nutrients and by removing waste products. It is not surprising, therefore, that multiple sensors and multiple effectors are involv process. The presence of several levels of control illustrates an important between the regulation of volume and the regulation of osmolality or the concentration of a particular solute. Maintenance of concentration can ofte achieved with only a single sensor (such as the hypothalamic osmoreceptor all tissues are perfused by the same arterial blood. In comparison, there ma marked variability in regional perfusion, necessitating the presence of loca

A simple example is changing from the sitting to the standing position, whic gravity, tends to result in hyperperfusion of and fluid accumulation in the lo extremities and hypoperfusion of the brain.[1] In this setting, activation of the caroti sinus baroreceptors with a subsequent increase in sympathetic activity help preserve cerebral perfusion (see below).

This chapter will review how the effective circulating volume is regulated, b face of changes in dietary intake and in disease states in which tissue perfu is altered. In particular, it will show how the neurohumoral influences and t reabsorptive characteristics of the different nephron segments that have be discussed in Chaps. 2, 3, 4, 5 and 6 are integrated in an appropriate fashion to maintain the steady state. The physiologic and clinical importance of the st state will also be reviewed.

DEFINITION

The *effective circulating volume* refers to that part of the extracellular fluid (ECF that is in the arterial system (normally about 700 mL in a 70-kg man) and is effectively perfusing the tissues.[2] However, a better physiological definition is th *pressure perfusing the arterial baroreceptors* in the carotid sinus and glomerular afferent arterioles, since it is changes in pressure (or stretch) rather than flow that is generally sensed at these sites.

The effective circulating volume usually varies directly with the ECF volume these parameters are typically proportional to total body Na^+, since Na^+ salts are the primary extracellular solutes that act to hold water within the extrac

space (see page 241). As a result, the *regulation of Na^+ balance (by alterations in urinary Na^+ excretion) and the maintenance of the effective circulating volu closely related functions*. Na^+ loading will tend to produce volume expansion, whereas Na^+ loss will lead to volume depletion.

In some settings, however, the effective circulating volume may be *independent of the ECF volume, the plasma volume, or even the cardiac output* (Table 8-1). In congestive heart failure, for example, the effective circulating volume is re because a primary decrease in cardiac output lowers the pressure at the baroreceptors.[2,3] As will be discussed below, this decline in pressure and flow induces compensatory fluid retention by the kidney, leading to expansion of extracellular fluid. The net result is effective volume depletion in associati increases in both the plasma and total ECF volumes.

The increase in volume in this setting is *appropriate* because the associated rise in intracardiac filling pressure can, by increasing cardiac stretch, impr cardiac contractibility and raise the cardiac output and systemic blood pres toward normal (see Chap. 16). On the other hand, the elevation in intravascular pressure can also be maladaptive in that it promotes fluid movement out of vascular space, potentially leading to both pulmonary and peripheral edema

The effective circulating volume may also, in some cases, be *independent of the cardiac output*. As well as in connection with a reduction in cardiac output, ef volume depletion can occur when perfusion pressure is reduced by a fall in

systemic vascular resistance (peripheral vasodilation).[2] In the presence of an arteriovenous fistula, for example, the cardiac output is elevated by an amo to the flow through the fistula.[4] However, this fluid can be considered to be circulating *ineffectively*, since it bypasses the capillary circulation. Thus, the p is normovolemic, despite the presence of a cardiac output that may be subs elevated.

Table 8-1 Potential independence of effective circulating volume from other measurable hemodynamic parameters

Clinical condition	Effective circulating volume	ECF volume	Plasma volume	Cardiac output
Na^+-depleted normal subjects	↓	↓	↓	↓
Heart failure	↓	↑	↑	↓
Arteriovenous	0	↑	↑	↑

fistula				
Advanced hepatic cirrhosis	↓	↑	↑	N/↑

The potential dissociation between the effective circulating volume and the output can also be illustrated by the hemodynamic volume and the cardiac also be illustrated by the hemodynamic changes seen in patients with adva cirrhosis and ascites (Table 8-1).[2,3] In this disorder, the ECF volume is expanded because of the ascites; the plasma volume is increased, in part as a result accumulation in the markedly dilated but slowly circulating splanchnic veno circulation;[5] and the cardiac output is often elevated because of multiple arteriovenous fistulas throughout the body, such as the spider angiomas on skin.[6]

Despite all of these signs suggesting volume expansion, most of the excess hemodynamically ineffective, and these patients *behave as if they were volume-depleted* as a result of marked peripheral vasodilatation. This is exemplified reductions in systemic vascular resistance and blood pressure, a very low urinary Na^+ excretion (often below 10 meq/day),[7] reduction in the blood volume in the cardiopulmonary circulation,[8] and a progressive increase in the secretion of hormones typically released in response to hypovolemia: renin, norepineph antidiuretic hormone (ADH),[7,8] and.[9] (The hemodynamic changes in cirrhosis are discussed in more detail in Chap. 10.)

In summary, the effective circulating volume is an unmeasured entity that re tissue perfusion and may be independent of other hemodynamic parameters.[2] The diagnosis of effective volume depletion is usually made by demonstrating re retention, as evidenced by *urine Na^+ concentration below 15 to 20 mmol/L*. This relationship is generally true as long as there is neither renal Na^+ wasting (most often due to diuretic therapy or underlying renal disease) nor selective ren glomerular ischemia (as with bilateral renovascular disease or acute glome disease). In the latter setting, urinary Na^+ excretion may be low without systemic hypoperfusion, whereas obligatory Na^+ wasting can prevent the renal retention that is normally associated with volume depletion.[10]

EFFECTIVE CIRCULATING VOLUME, RENAL SODIUM EXCRETION, AND THE STEADY STATE

The kidney is the primary regulatory organ of Na^+ volume balance, as urinary Na^+ excretion responds in an appropriate manner to changes in the effective cir volume. When there is an increase in volume, as after the acute closure of an arteriovenous fistula,[4] Na^+ excretion rises in an attempt to lower the volume tov normal. Conversely, the kidney retains Na^+ in the presence of effective volume

depletion. This system of volume regulation must be very efficient, since

small alterations in Na^+ intake necessitate parallel changes in Na^+ excretion that involve less than 1 percent of the filtered Na^+ load (see "Day-to-Day Regulation," below).

The time course of the response to variations in Na^+ intake is illustrated in Fig. 8-1.[11] If dietary intake is abruptly increased in a patient on a low-sodium diet about one-half of the excess intake is excreted on the first day. The remain retained, augmenting body Na^+ stores. This elevates the plasma osmolality, whic stimulates both thirst and the secretion of ADH (see page 178). The increments in water intake and renal water reabsorption produce water retention, resultin increases in the effective circulating volume and body weight and the retur plasma osmolality to normal. (This process of osmoregulation is discussed in Chap. 9.)

On subsequent days, a progressively greater fraction of the excess intake i excreted (and less retained) until by 3 to 4 days, a new steady state is ach which renal Na^+ excretion matches intake.[12] This new steady state is characterize by a mild increase in the effective circulating volume resulting from the Na^+ and water retained on the first 4 days.[12,13,14] and[15] The total quantity of Na^+ retained is directly related to the increment in Na^+ intake above the previous baseline. Thus, *the greater the increase in intake, the greater the increase in steady-state extracellular volume* (Fig. 8-2).

The same sequence occurs in reverse if Na^+ intake is reduced. Negative Na^+ balance occurs until there has been enough loss of volume to lower Na^+ excretion to the reduced level of intake.

Thus, a high-sodium diet is characterized by increases in volume and Na^+ excretion, and a low-sodium diet by decrease in volume and Na^+ excretion. The changes in volume are essential, since they *constitute the signal that allows urinary Na^+ excretion to vary appropriately with fluctuations in Na^+ intake*. Let us assume, for the sake of simplicity, that Na^+ excretion in normal subjects is primarily determin by the Na^+-retaining hormone aldosterone and the Na^+-losing hormone atrial natriuretic peptide (ANP). As Na^+ intake rises from 10 to a higher

than normal value of 350 meq/day, there must be a fall in the secretion of aldosterone and a rise in that of ANP to result in the necessary reduction in Na^+ reabsorption.[15] Furthermore, the rate of release of these hormones must *stay at this new level* if Na^+ excretion is to remain at 350 meq/day (Fig. 8-3). The signal for the continued suppression of aldosterone and stimulation of ANP is the volume expansion.

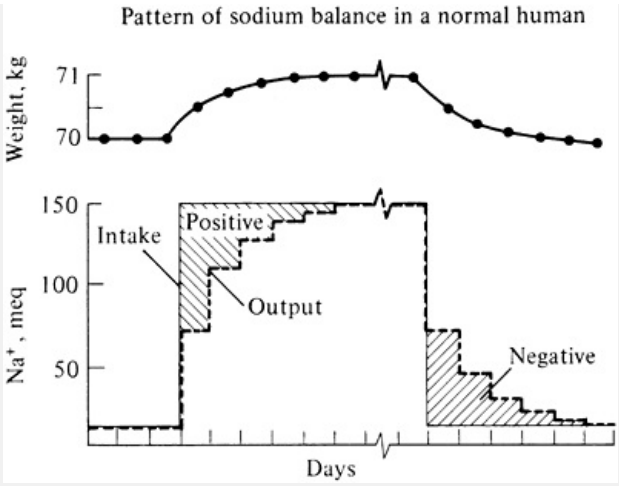

Figure 8-1 Effect of abrupt changes in Na^+ intake on body weight and renal Na^+ excretion in a normal human. The shaded areas refer to changes in total b Na^+ stores due to the difference between intake and excretion. See text fo details. *(From Earley LE: In Maxwell MH, Kleeman CR (eds): Clinical Disorders of Fluid and Electrolyte Metabolism. New York, McGraw-Hill, 1972. Used with permission).*

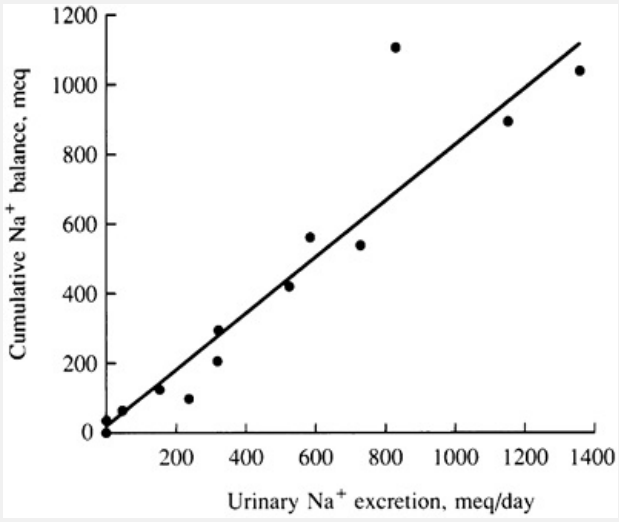

Figure 8-2 Urinary Na^+ excretion (an indicator of dietary intake in the steady state) as a function of cumulative Na^+ balance in 14 normal subjects studied at different levels of Na^+ intake. As can be seen, net Na^+ balance increases in proportion to the rise in intake, resulting in a progressively greater degre volume expansion. *(From Walser M: Kidney Int 27:837, 1985. Reprinted by permission from Kidney International).*

Clinical Implications

In addition to its role in volume regulation in normal subjects, the steady st

has important implications in the pathogenesis

and treatment of disease states. As an example, diuretics reabsorption at Na^+ different sites in the nephron; they are most often given to patients with ed hypertension to lower the ECF volume. The initial volume loss activates Na^+ retaining mechanisms, such as the renin-angiotensin system, which act to l further losses. These counterregulatory forces are so efficient that, assumi diuretic dose is constant, all of the fluid and electrolyte losses occur in the 14 days of therapy, with the *maximum* natriuretic response being induced by the f dose (see page 455).

A steady state is also achieved with changes in intake of other electrolytes example, if K^+ intake is increased, the new steady state will be characterized b limited elevation in body stores of K^+ and a small rise in the plasma K^+ concentration.[16] The latter change will be the stimulus to maintain an increas of K^+ excretion, a response that is mediated in part by enhanced secretion o aldosterone (see Chap. 12).

These observations have important implications for the development of man and electrolyte disorders. The capacity to excrete Na^+, K^+, HCO_3^-, and H_2O is so great in normal subjects that too much Na^+ (sodium), too much K^+ (hyperkalemia), too much HCO_3^- (metabolic alkalosis), or too much H_2O (hyponatremia) will *persist unless there is an abnormality in the renal excretion of the substa* The excretion of H_2O, for example, occurs via the suppression of the release of antidiuretic hormone, resulting in the formation of a dilute urine. Volume (see "Regulation versus Osmoregulation" below). Thus, the differential diagnosis of hyponatremia primarily consists of those disorders in which ingested water excreted normally, usually because of an inability to suppress the release o antidiuretic hormone (see Chap. 23).

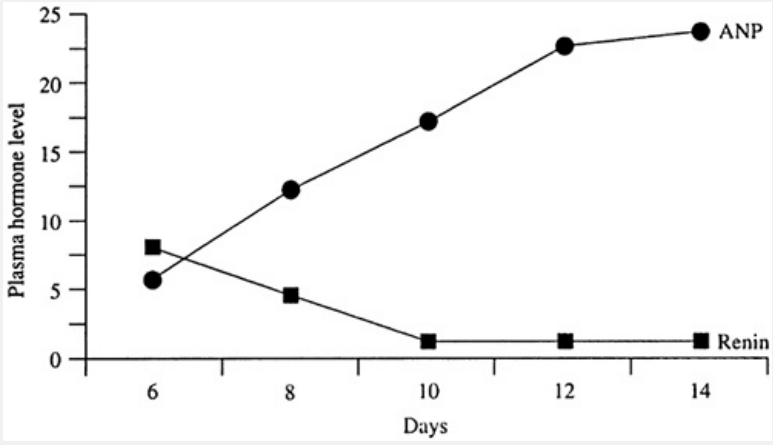

Figure 8-3 Increasing plasma levels of atrial natriuretic peptide (ANP) and plasma renin activity in normal subjects given a progressively increasing intake from 10 to 350 meq/day after a 5-day equilibration period. These h

responses promote urinary excretion of the excess sodium. Data from (*Sagnella GA, Markandu ND, Buckley MG, et al: Am J Physiol 256:R1171, 1989. Used with permission*).

REGULATION OF THE EFFECTIVE CIRCULATING VOLUME

The body responds to variations in the effective circulating volume[1] in two s The change is sensed by the volume receptors,[2] and receptors then activate a series of effectors that restore normovolemia by varying vascular resistar cardiac output, and renal Na^+ and water excretion.

Volume Receptors

The primary volume receptors are in the cardiopulmonary circulation, the ca sinuses and aortic arch, and the afferent glomerular arterioles in the kidne[2,17,18] Although it is volume that is being regulated, it is difficult to conceive of re that sense total extracellular, plasma, or capillary volume. What is actually sensed at most of the renal and extrarenal volume receptors is pressure (o stretch).[18] This allows effective volume control, since pressure and volume a usually directly related. For example, volume depletion induced by vomiting

sequentially associated with reductions in venous return to the heart, intra filling pressures, cardiac output, and systemic blood pressure.

In the kidney, the major volume receptors are the stretch receptors in the juxtaglomerular apparatus of the afferent arteriole and, to a lesser degree, macula densa cells in the early distal tubule. These receptors affect volum by influencing the activity of the renin-angiotensin-aldosterone system and endothelin and nitric oxide (see Chaps. 2 and 6).

In contrast, the extrarenal receptors (such as those in the atria and the car primarily govern the activity of the sympathetic nervous system and ANP.[2,17] Volume depletion, for example, can diminish both the intracardiac and systemic blo pressures, resulting in an increase in sympathetic tone and a reduction in t release of ANP, the consequences of which will be discussed below. These are reversed with volume expansion.

The role of cardiopulmonary receptors has been demonstrated in humans by response to immersion to the neck in warm water.[19,20] In this setting, the hydrostatic pressure of the water on the lower extremities results in the rec of intravascular fluid from the legs to the chest. The ensuing increase in ce blood volume (and subsequently in cardiac output) is associated with a mar increase in Na^+ and water excretion in an attempt to restore normovolemia (Figure 8-4*a*). Although aldosterone secretion is decreased in this setting, the natriur response shows a better temporal correlation with the associated

increase in ANP release.[19,20]

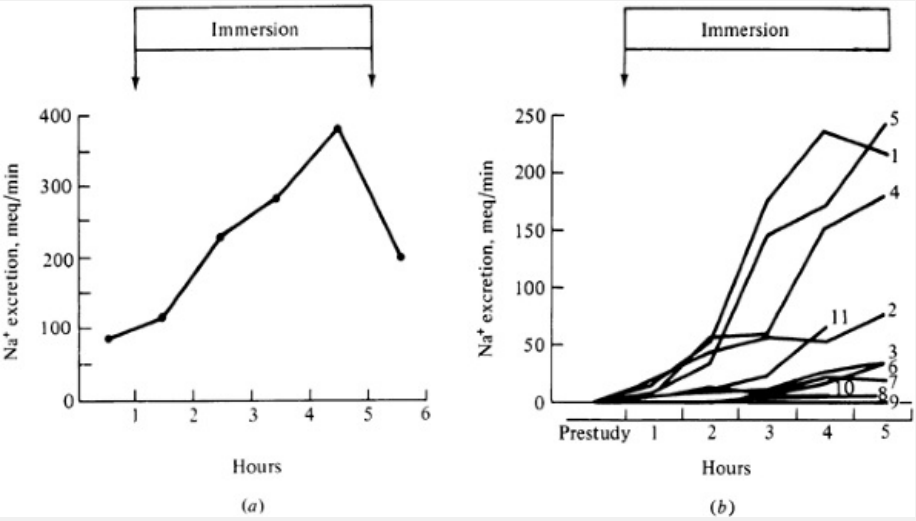

Figure 8-4 Effect of water immersion to the neck on sodium excretion in (*a*) six normal subjects ingesting 150 meq of Na^+ per day and (*b*) eleven patients with cirrhosis who excrete little Na^+ in the basal state. Sodium excretion tends to be increased in both settings, mediated at least in part by cardiopulmonary receptors sensing the associated expansion of the central blood volume. (*Adapted from Epstein, Circ Res 39:619, 1976, and Epstein M, Pins DS, Schneider N, Levinson, J Lab Clin Med 87:822, 1976. By permission of the American Heart Association, Inc*)

A similar natriuretic response to immersion to the neck can be demonstrated in patients with cirrhosis and ascites who excrete little Na^+ in the basal state (Fig. 8-4*b*).[3,21] This observation supports the view that the reduced excretion of Na^+ in cirrhosis is due to effective volume depletion, even though these patients have, as described above, elevations in the plasma volume and cardiac output.[2]

Although multiple receptors are involved in the regulation of the effective circulating volume, *no single receptor appears to be of primary importance*. For example, Na^+ balance is generally well maintained in the presence of cardiac or renal denervation[22,23,24] or the chronic administration of aldosterone (see below),[25] indicating that although these factors may be important in normal subjects, other receptors are capable of maintaining volume homeostasis. As an example, volume changes have direct mechanical effects on cardiac output and blood pressure, and the latter can influence NaCl and water excretion when other regulatory systems have failed ("Pressure Natriuresis," see below).[24]

Effectors

Multiple effectors are involved in volume control, influencing both systemic hemodynamics and urinary Na^+ excretion (Table 8-2). Since these regulatory

systems (except for the sympathetic nervous system) have been discussed previously (Chaps. 2 and 6), their effects will be only briefly reviewed in this section.

Sympathetic nervous system

Sympathetic neural tone and the secretion of catecholamines (norepinephri epinephrine) from the adrenal medulla are reduced by volume expansion an enhanced by volume depletion.[26,27,28] Thus, effective volume depletion, due fluid losses or to reduced tissue perfusion in cirrhosis or heart failure, is a with increased systemic and renal sympathetic

activity.[2,8,9,29]

Table 8-2 Principal effectors involved in volume rsegulation

Systemic hemodynamics
Sympathetic nervous system
Angiotensin II
Renal Na^+ excretion
Glomerular filtration rate
Angiotensin II
Peritubular capillary hemodynamics
Aldosterone
Sympathetic nervous system
Atrial natriuretic peptide
Pressure natriuresis
Plasma Na^+ concentration

Activation of sympathetic function in this setting is presumably related to a fall in effective cardiac output, due to decreased venous return, vasodilata cirrhosis), or primary cardiac disease. From the formula relating pressure, and resistance,

Mean arterial pressure = cardiac output × systemic vascular resistance

the reduction in cardiac output lowers the systemic blood pressure. This de pressure is sensed by the cardiac and arterial baroreceptors, resulting in a baroreceptor afferent discharge to the vasomotor centers in the brainstem.[18,26] These centers then induce an increase in peripheral sympathetic tone, initi series of events that act to restore normal tissue perfusion (Fig. 8-5):

1. Venous constriction increases blood delivery to the heart, since about 7 percent of the vascular volume is normally contained within the venous

2. Myocardial contractility and heart rate are increased, which, in combina the enhanced venous return, raises the cardiac output.
3. Direct arteriolar constriction increases systemic vascular resistance, th elevating the systemic blood pressure toward normal.
4. Renal tubular Na^+ reabsorption is enhanced because of both a direct adre effect (see Chap. 6) and increases in angiotensin II and aldosterone secretion.[26,31,32]

These cardiovascular changes are reversed by volume expansion, as sympa activity is reduced, thereby minimizing the elevations in cardiac output and pressure and facilitating the excretion of the excess Na^+.[27]

The importance of this regulatory system is illustrated in Figure 8-6. Although normal subjects easily tolerate the removal of 500 mL of blood (the equivalent of d one unit of blood), patients with autonomic insufficiency can develop sever hypotension. These patients also have both postural hypotension, since the compensate for the pooling of blood in the legs that occurs when one assur erect position, and an impaired ability to maximally conserve Na^+, presumably due to removal of the adrenergic stimulus to tubular Na^+ reabsorption.[26,33,34]

Angiotensin II

The physiology of the renin-angiotensin system is discussed in Chapter 27. To review briefly, renin secretion is enhanced in hypovolemic disorders, result generation of angiotensin II, which has two major

actions: It raises the blood pressure by arterial vasoconstriction, both direc enhancing the release and effect of norepinephrine, and it induces renal Na^+ retention, both directly and by increasing the secretion of aldosterone.[35,36] Like sympathetic blockade, inhibition of the renin-angiotensin system in hypovol subjects can lead to marked hypotension.[37,38]

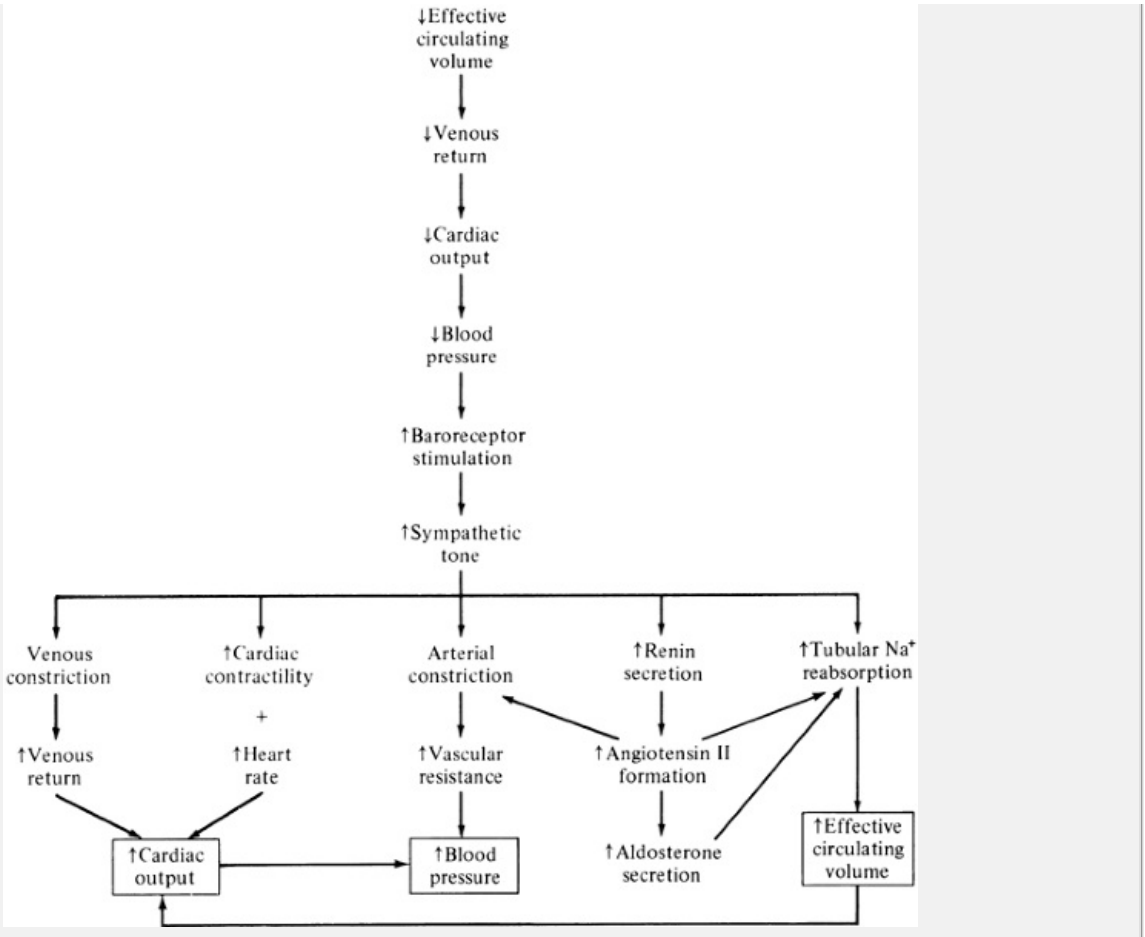

Figure 8-5 Hemodynamic responses induced by the sympathetic nervous sy after effective circulating volume depletion.

The vasoconstriction induced by angiotensin II and norepinephrine in the p of hypovolemia is compensatory in that it tends to maintain the systemic blo pressure; however, *renal Na^+ retention is usually required for the restoration o normovolemia*. As an example, a decrease in volume due to fluid loss can be corrected only by the ingestion and subsequent retention of exogenous Na^+ and water.

The situation is different when effective volume depletion is due to heart fa cirrhosis with ascites. In this setting, the effect of the fluid retention

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is dependent upon the severity of the underlying disorder. This concept is i in Fig. 8-7, which depicts the response to decreasing venous return as a resu partial constriction of the thoracic inferior vena cava.[37] There is an initial rapid decline in mean aortic pressure that is returned toward normal within 1 day by activation of the renin-angiotensin-aldosterone system. This is accompa marked reduction in Na^+ excretion, leading to a progressive increase in the pla volume and the development of ascites due to an elevation in hepatic venou pressure. By day 7, however, the degree of volume expansion is sufficient t normalize venous return. As a result, a *new steady state* is achieved in which

systemic hemodynamics are normal and the plasma renin activity and aldos
level fall and urinary Na^+ excretion rises toward the level of intake.

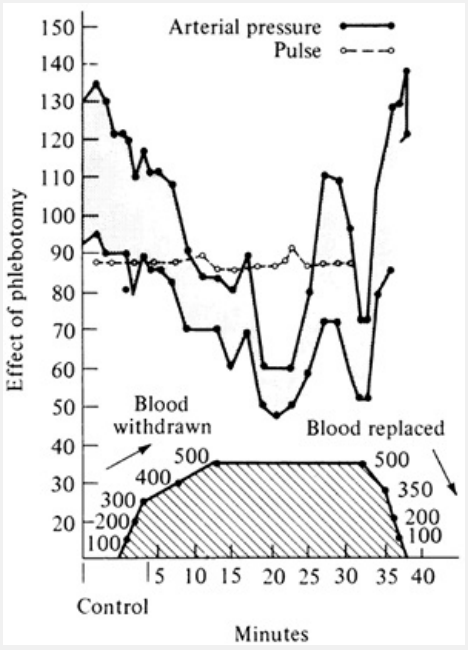

Figure 8-6 Effect of rapid removal and replacement of whole blood on the arterial blood pressure during recumbency in a patient with idiopathic aut insufficiency. (*From Wagner HN, Jr: J Clin Invest 36:1319, 1967, by copyright permission of the American Society for Clinical Investigation.*)

However, it is not always possible to reach a new steady state. If the vena constriction is very severe, then marked Na^+ retention and activation of the renin-angiotensin system persist, because fluid retention is unable to sufficiently venous return. A similar sequence can occur in humans with heart failure. F who are clinically stable may have a normal blood pressure and a normal pl renin activity, whereas patients with decompensated heart failure tend to b relatively hypotensive with high plasma renin levels.[39] Even those with relatively normal plasma renin activity may still have increased activity of the renin-angiotensin system.[40] *in vivo*

Regulation of renal Na^+ excretion

Renal Na^+ excretion varies directly with the effective circulating volume. Wh effective volume is expanded, the urine Na^+ concentration can exceed 100 meq/L. I contrast, the urine can be rendered virtually

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Na^+-free (urine Na^+ concentration as low as 1 meq/L) in the presence of volume depletion and normal renal function. These homeostatic changes in Na^+ excretion can result from alterations both in the filtered load, determined primarily by

glomerular filtration rate (GFR), and in tubular reabsorption, which is affec multiple factors. As will be seen, *an abnormality in any one factor does not precl the maintenance of* Na^+ *balance*, a finding indicative of the substantial overlap involved in volume regulation.

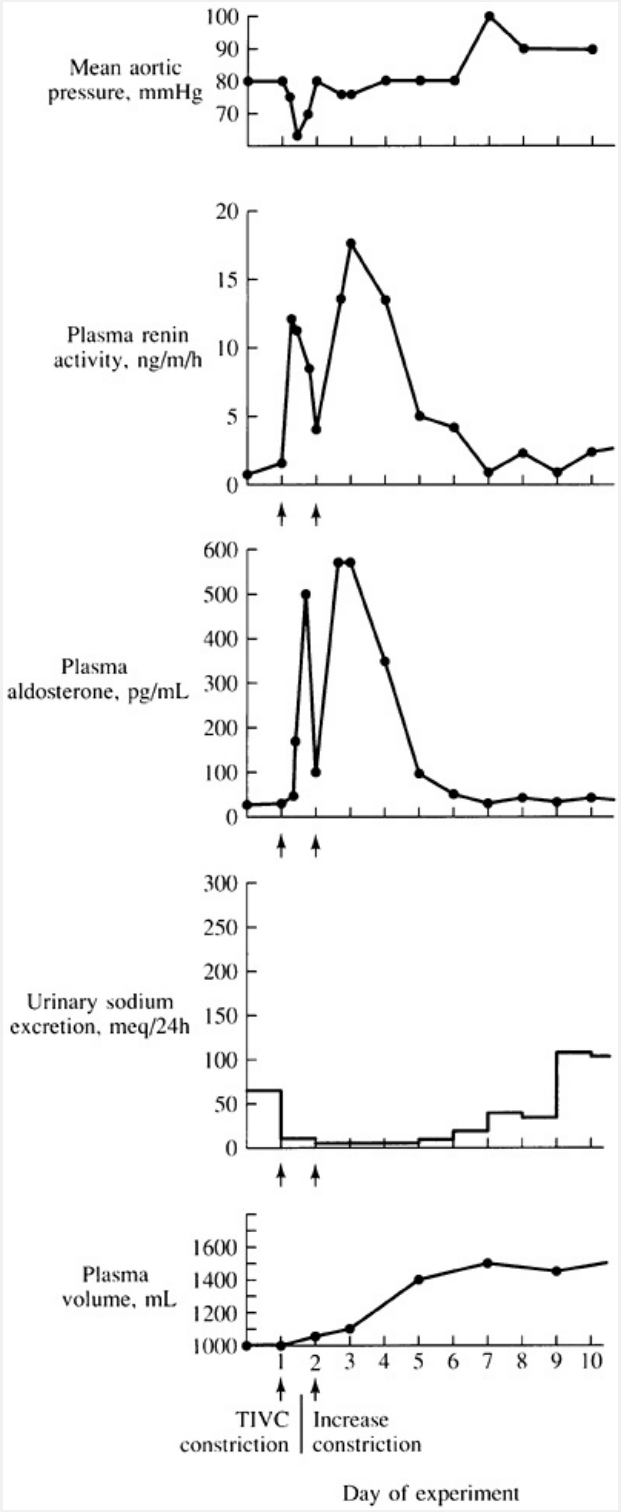

Figure 8-3 Sequential changes in mean aortic pressure, plasma renin activi plasma aldosterone concentration, urinary sodium excretion, and plasma v in a dog with moderate thoracic inferior vena cava constriction. There is i hypotension, activation of the renin-angiotensin-aldosterone system, and

marked reduction in urinary Na^+ excretion. By day 7, however, a new steady state is achieved in which renin and aldosterone levels and Na^+ excretion have returned to baseline levels. The associated plasma volume expansion is responsible for restoring venous return to the heart, thereby allowing sys hemodynamics to be normalized. *From (Watkins L Jr, Burton JA, Haber E, et al, J Clin Invest 57:1606, 1976, by copyright permission of the American Socie for Clinical Investigation)*

Glomerular filtration rate

The GFR tends to increase with volume expansion and to fall with volume d both of which can contribute to the associated change in Na^+ excretion.[41] However, alterations in the GFR are not required for the maintenance of Na^+ balance. As an example, patients with less than end-stage renal disease ma substantial reduction in GFR. Nevertheless, they are usually able (in the al the nephrotic syndrome) to adjust Na^+ excretion to match intake by decreasing the rate of tubular reabsorption.[42] The importance of tubular reabsorption is also illustrated by the phenomenon of *glomerulotubular balance*, in which a primary alteration in GFR leads to a parallel change in tubular reabsorption and, th relatively little variation in urinary Na^+ excretion (see page 85).[41]

Tubular reabsorption

In general, it is changes in tubular reabsorption that constitute the main ad response to fluctuations in the effective circulating volume. How this occur appreciated from Table 8-3, which gives the sites and determinants of segmenta Na^+ reabsorption. Although the loop of Henle and the distal tubule make an important overall contribution to net Na^+ handling, transport in these segments primarily varies with the amount of Na^+ delivered, i.e., reabsorption is flow-dependent (see page 113).[43,44] In comparison, the *neurohumoral regulation of Na^+ reabsorption according to body needs occurs primarily in the proximal and collecting tubules*

As an example, mild volume depletion in the rat results in a decrease in Na^+ excretion that is mostly due to enhanced collecting tubule reabsorption;[45] this effect is mediated at least in part by an increase in the secretion of aldosterone. reabsorption may also be enhanced, especially with greater degrees of hypovolemia.[45,46] This response is associated with increased activity of the l membrane Na^+H^+ exchanger that is responsible for both $Na^+HCO_3^-$ and NaCl reabsorption (see page 113).[47] Increased secretion of angiotensin II and norepinephrine probably plays an important role in this stimulation of proxi transport.[47] Reabsorption in the loop of Henle may also be increased in this an effect that may be mediated by a reduction in medullary interstitial pres "Pressure Natriuresis," below).[48,49]

These changes are reversed with volume expansion, as collecting tubule ar necessary, proximal and loop NaCl and water reabsorption all may be

reduced.[50,51] and[52] Decreased activity of the renin-angiotensin-aldosterone system and increased secretion of ANP (which can also raise the GFR) may particularly important in this setting.[14,53,54]

Table 8-3 Anatomic distribution and determinants of segmental NaCl reabsorption[a]

Tubule segment	Percent filtered NaCl reabsorbed	Determinants of reabsorption
Proximal tubule	60–65	Na^+-H^+ exchange Na^+-glucose cotransport Angiotensin II Norepinephrine Peritubular capillary hemodynamics
Loop of Henle	25–30	Flow-dependent
Distal tubule	5	Flow-dependent
Collecting tubules	4	Aldosterone Atrial natriuretic peptide

[a] Data from Bennett CM, Brenner BM, Berl T, *J Clin Invest* 47:203, 1968, by copyright permission of the American Society for Clinical Investigatio

Day-to-day regulation

The above findings were obtained from experiments in which relatively larg in volume were induced. In normal humans, however, variations in daily Na^+ intake require very small percentage changes in Na^+ excretion for balance to be maintained. Suppose, for example, that an adult man has a GFR of 160 L/da plasma water Na^+ concentration of 150 meq/L. The daily filtered load of Na^+ in this setting is 24,000 meq. If intake is normally 120 meq per day, then only 0.5 the filtered load has to be excreted. An increase in intake to 180 meq will r minimal rise in fractional excretion to only 0.67 percent.

It is likely that aldosterone plays an important role as the fine modular of Na^+ excretion.[15] As illustrated in Fig. 6-13, renin and aldosterone release vary inverse with relatively minor changes in Na^+ intake. There is also evidence that the natriuretic response to a relatively small increase in Na^+ intake is associated with a rise in ANP release,[15,55] although the physiologic role of ANP remains to be pr (see page 173).[56,57] Since aldosterone and ANP affect Na^+ reabsorption in the collecting tubules, this segment may be the primary site at which volume re achieved in normal humans.

Although proximal function cannot be measured directly in humans, studies monitoring changes in urate excretion suggest that changes in volume may associated with alterations in proximal reabsorption. Net urate reabsorptior the proximal tubule by a process that appears to be mediated by

parallel Na^+-H^+ and urate-anion exchangers (see Fig. 6-13). Volume depletion, as occurs with diuretic therapy, for example, is often associated with decrease excretion and hyperuricemia, suggesting that there has been an increase in proximal Na^+ and urate transport.[58] On the other hand, the urate wasting and hypouricemia commonly seen in the syndrome of inappropriate ADH secretio related in part to the associated water retention and volume expansion.[59]

Redundancy of control systems

Despite the probable importance of aldosterone in Na^+ excretion, abnormalities in the secretion of this hormone are not usually associated with disturbances Na^+ balance because other factors are able to compensate. As an example, adrenalectomized patients treated with replacement doses of a mineralocor able to maintain Na^+ balance, even though they are unable to vary the level of mineralocorticoid secretion.[60] Similarly, subjects given aldosterone or patients v an autonomous, aldosterone-secreting adrenal adenoma retain fluid for only days and then undergo a spontaneous diuresis that returns the volume stat normal. This phenomenon, called *aldosterone escape* (see Fig. 6-15), is due to decreased Na^+ reabsorption at some other site in the nephron, a response that may be mediated in part by ANP[25,61] and by a direct effect of the rise in renal perfusio pressure.[24]

Similar considerations in terms of the redundant regulation of Na^+ balance appear to apply to ANP. Studies in animals made ANP-deficient by immunization or by of the renal action of ANP have demonstrated an impairment in the natriure response to acute volume expansion but not to chronic hypervolemia as ind high salt intake with or without a mineralocorticoid.[57,61] On the other hand, transgenic mice given an extra ANP gene have plasma ANP levels that are normal.[62] Nevertheless, Na^+ excretion is still equal to intake, perhaps due in pa the concurrent fall in blood pressure that limits the natriuretic response to

ANP may contribute to but is not necessary for the maintenance of Na^+ balance.

Pressure natriuresis

An essential "backup" feature of the volume regulatory system that can com
for an abnormality in the humoral control of Na^+ excretion is the phenomenon of *pressure natriuresis* (Fig. 8-8). In normal subjects, a small elevation in blood pressure results in a relatively large increase in the urinary excretion of Na^+ and water.[63,64] and[65] In contrast to the other mediators of tubular Na^+ transport, this *pressure natriuresis* phenomenon does not require neurally or humorally media sensor mechanisms, since changes in volume directly affect the cardiac out therefore the systemic blood pressure.[63]

The mechanism by which pressure natriuresis occurs is incompletely unders decreased reabsorption appears to occur in the proximal tubule and loop of Henle.[49,66,67] and[68] It is possible, for example, that the increase in systemic pressure is transmitted, via the vasa recta capillaries, to the medullary interstitium.[49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67] and[68] This rise in interstitial pressure can impair NaCl transport in at least two ways[67,68]

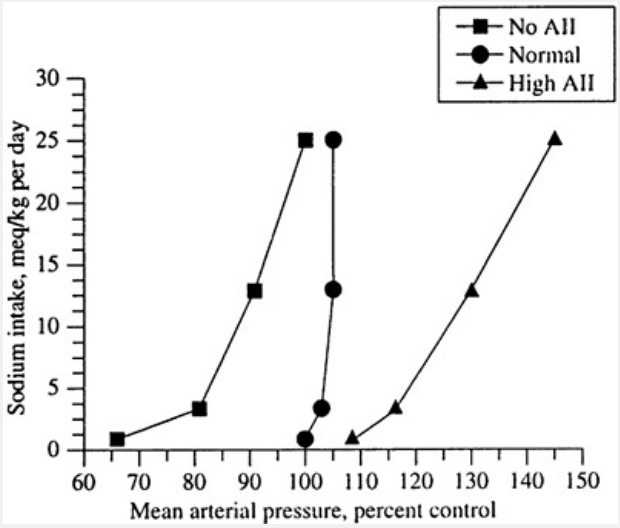

Figure 8-8 Relationship between increasing sodium intake and mean arteria pressure in normals, in the absence of angiotensin II (AII), and with an angiotensin II infusion. The inability to regulate angiotensin II and aldost the last two settings necessitates an elevation in blood pressure to excre extra sodium. (*From Guyton AC: Science 252:1813, 1991. Used with permission.*)

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1. The increase in capillary pressure can diminish the movement of reabsc solutes and water from the interstitium into the capillary, thereby preve return to the systemic circulation.

2. The elevation in interstitial pressure will tend to push fluid into the wat permeable *descending* limb of the loop of Henle, counteracting the osmotic gradient favoring water movement out of this segment into the hyperosm interstitium. The ensuring decline in descending limb water reabsorptio *minimize the rise in the tubular fluid* Na^+ *concentration* that is required for subsequent passive NaCl transport in the *thin* ascending limb (see page 130). The net effect is decreased loop NaCl reabsorption.

Increased release of renal prostaglandins and, more importantly, nitric oxid contribute to pressure natriuresis.[66,69,70] and[71] It is unclear whether this represents a direct hormonal effect on tubular Na^+ transport or is mediated by renal vasodilatation with a subsequent increase in intracapillary pressure. These are reversed with a fall in renal perfusion pressure, as tubular sodium and reabsorption are enhanced.[67,72]

Nitric oxide (NO) release from the macula densa is a modulating factor that augmented during increased sodium chloride delivery, thereby countering th afferent arteriole constriction elicited in the tubuloglomerular feedback (TG response. It has been suggested that enhanced macula densa NO productio

may underlie the resetting of TGF that occurs when salt intake is increased response is appropriately blunted in this setting, as maintenance of glomer filtration promotes excretion of the excess salt.[73]

Regardless of the mechanism, pressure natriuresis can, in certain circumst play an important role in the maintenance of volume balance. It is not likely contribute significantly to the day-to-day regulation of Na^+ excretion, since changes in aldosterone and perhaps ANP release are sufficient to accomplish this g example, a 50-fold increase in Na^+ intake and subsequent excretion (from very lo to high levels) is associated with only a 4-mmHg elevation in systemic bloo pressure in normal subjects (as shown in the middle curves in Fig. 8-3).[63] In this setting, the decline in angiotensin II and aldosterone and the increase in AN sufficient to markedly increase Na^+ excretion without requiring a large rise in blo pressure.

If, however, there is an impairment in one or more of the neurohumoral med volume regulation, then pressure natriuresis may be required to maintain Na^+ balance. This concept can be illustrated by the changes induced by increas sodium intake when the ability to regulate angiotensin II and aldosterone a to Na^+ intake is impaired, either by very low or by very high angiotensin II le and right curves in Fig. 8-3). In both cases, tubular Na^+ reabsorption cannot be decreased by diminishing the production of angiotensin II and aldosterone; result, a greater than normal increase in blood pressure is required to mair balance as intake is increased.

These experiments illustrate the role of pressure natriuresis in the regulati

blood pressure as well as that of Na^+ excretion. This can also be illustrated by th phenomenon of aldosterone escape.[25] The initial Na^+ retention and elevation in systemic blood pressure induced by aldosterone are followed by a spontane natriuresis that minimizes the degree of volume expansion and hypertensior Fig. 6-1).[5] Although the diuresis in this setting may in part be mediated by ir release of ANP,[74,75] pressure natriuresis also appears to play an important ro shown in Fig. 8-9, use of a suprarenal aortic clamp to maintain a constant ren perfusion pressure prevents aldosterone escape from occurring. The net ef continued Na^+ retention and the eventual development of pulmonary edema o malignant hypertension. Release of the clamp is rapidly followed by increas urinary Na^+ loss and a reduction in the systemic blood pressure.

This observation can be extended to any form of hypertension: The rise in pressure, whether induced by aldosterone, norepinephrine, or underlying re disease, is eventually limited by fluid loss induced by pressure natriuresis.[63,64] In terms of Fig. 8-8, the pressure natriuresis curve is shifted to the right in hype patients; that is, Na^+ balance is maintained, but at a higher than normal systen blood pressure to overcome, for example, the Na^+-retaining effect of aldosterone.

Pressure natriuresis can also limit net Na^+ retention when renal perfusion pressure is reduced by effective volume depletion due, for example, to diuretic therapy.[65] The sodium-retaining effect in this setting is normally mediated by

angiotensin II and norepinephrine as described above. If, however, both sys blocked, sodium retention still occurs in association with a fall in blood pre Fig. 15-1).[76] This fall in blood pressure, which can enhance Na^+ reabsorption by pressure natriuresis, is due to the absence of angiotensin II– and norepine mediated vasoconstriction, which maintains the blood pressure in hypovole subjects.

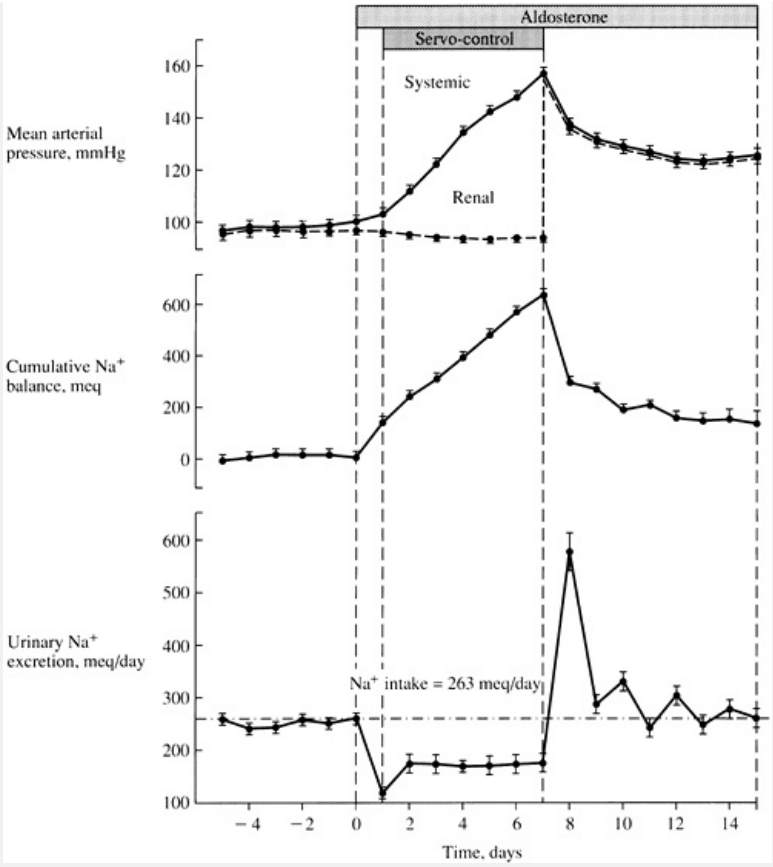

Figure 8-9 The effect of the administration of aldosterone and a high-Na+ diet on mean arterial pressure, cumulative balance, and urinary Na+ excretion in dogs. If renal perfusion pressure is held constant by use of a suprarenal clamp, Na+ excretion remains at low levels and aldosterone escape does not occur. The net result is progressive retention of Na+ and a marked elevation in systemic blood pressure. When, however, renal perfusion pressure is allowed to rise by release of the clamp, there is a spontaneous diuresis, leading to a return in Na+ balance toward normal and much less severe hypertension. *From Hall JE, Granger JP, Smith MJ Jr, Premen AJ, Hypertension 6(suppl 1):I-183, 1984. By permission of the American Heart Association, Inc.*

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Sympathetic nervous system

Pressure natriuresis can also explain the variable effects of sympathetic blockade on renal Na+ handling. As described above, increased sympathetic activity raises systemic blood pressure and enhances proximal tubular Na+ reabsorption.[26,31,32] The net effect on Na+ excretion, however, is not predictable, since the elevation in renal perfusion pressure will tend to counteract the direct tubular effect.[77] In effective volume depletion, for example, the increase in adrenergic tone appropriately raises the systemic blood pressure; this would also lead to inappropriate urinary Na+ wasting if it were not for the concurrent increase in Na+ reabsorption.[77]

The interaction between the pressure and reabsorptive effective of the sym nervous system can also be illustrated by the response to the sympatholyti guanethidine (a now rarely used antihypertensive drug). When given in dos not reduce the systemic pressure, guanethidine can inhibit the adrenergic a the kidney, resulting in an increase in Na^+ excretion.[34] However, when guanethidine is used to lower the blood pressure in patients with hypertension, the hypo effect predominates and Na^+ retention is likely to occur.[78,79] This constitutes the rationale for the use of diuretics in combination with sympathetic blockers i treatment of hypertension, since the increase in volume produced by the la to minimize the hypotensive response.[78]

Also complicating the evaluation of the sympathetic effect on Na^+ excretion is the demonstration that renal sympathetic tone may occasionally be regulated independent of that in other organs. This phenomenon appears to be media volume receptors in the left side of the heart, as an increase in left-sided p results in a *reduction in renal sympathetic tone*[80,81] and[82] even though total sympathetic activity may be enhanced.[82]

The potential importance of this cardiorenal reflex is illustrated by the follo animal experiment.[82] The induction of hypotensive hemorrhage (which lowers l sided pressures) resulted in a decrease in renal blood flow of as much as 9 and a cessation of urine output, both of which were due in large part to a hypotension-induced increase in sympathetic activity and subsequent marke vasoconstriction. In contrast, a similar reduction in systemic blood pressure an acute myocardial infarction (which raises left-sided pressures) was asso with only a 25 percent fall in renal blood flow and persistence of an adequa output. This relative maintenance of renal perfusion and urine flow presuma due in part to reduced renal sympathetic tone, resulting from the evaluation sided intracardiac pressure. It is also possible that increased secretion of A contributed to the relative renal vasodilation in this setting.

Although it is uncertain how important the left-sided cardiac receptors are i humans,[83] a cardiorenal reflex can explain the clinical observation that post acute tubular necrosis frequently follows hypotension due to sepsis, surger hemorrhage, but is rare when renal hypoperfusion is due to heart failure.[84]

Plasma Na^+ concentrations

Urinary Na^+ excretion also may be affected by the plasma Na^+ concentration, tending to increase with hypernatremia and to fall with hyponatremia.[85,86,] and[87] This effect may be mediated by changes in both the

filtered Na^+ load (GFR times plasma Na^+ concentration) and the rate of tubular reabsorption. These responses can be viewed as appropriate from the view maintenance of the plasma Na^+ concentration. Increasing Na^+ excretion with hypernatremia, for example, will tend to lower the plasma Na^+ concentration toward

normal.

However, the *plasma Na^+ concentration does not play an important role in the regulation of Na^+ excretion*, since it is normally maintained within narrow limits ADH and thirst (see Chap. 9). Furthermore, even in patients who are hyponatremi hypernatremic, the effective circulating volume is a *more important determinant* of Na^+ excretion than the plasma Na^+ concentration (see "Volume Regulation versus Osmoregulation," below). For example, the syndrome of inappropriate ADH sec is characterized by water retention, which leads to both hyponatremia and v expansion. As a result, this disorder is initially associated with enhanced N excretion, although the increase may be somewhat less than that seen with equivalent degree of volume expansion in a patient with a normal plasma N concentration.[88] Similarly, urinary Na^+ excretion is reduced in hypernatremic patients who are volume-depleted due, for example, to lack of replacement insensible water losses from the skin and respiratory tract (see Chap. 24).

Summary

It is clear that multiple factors affect renal Na^+ excretion and therefore the regulatic of the effective circulating volume. It seems likely that aldosterone and pos natriuretic peptide (or related peptides such as urodilatin) are responsible day variations in Na^+ excretion through their respective ability to augment and diminish Na^+ reabsorption in the collecting tubules. As the Na^+ is reduced, for example, the ensuing decrease in volume enhances the activity of the renin angiotensin-aldosterone system and reduces the secretion of ANP. The net enhanced Na^+ reabsorption in the collecting tubules, which seems to account appropriate fall in Na^+ excretion in this setting. With more marked hypovolemia decrease in GFR and an increase in proximal and thin ascending limb Na^+ reabsorption also contribute to the Na^+ retention. Both angiotensin II and norepineph may contribute to this response, which is clinically important because the s of proximal transport also increases the reabsorption of bicarbonate and ur Chap. 13). Consequently, hypovolemia can lead to the maintenance of metabo alkalosis (because the excess bicarbonate cannot be excreted) and to hype and gout, all of which commonly occur in patients receiving diuretic therapy

This sequence is reversed with volume expansion, as an increase in the se ANP and a reduction in that of aldosterone (Figure 8-3) allow excretion of the excess Na^+ by diminishing collecting tubule Na^+ reabsorption. With more pronounced hypervolemia, reabsorption may also fall in the proximal tubule, often leadi enhanced urate secretion and hypouricemia.[59]

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The pressure natriuresis phenomenon may be the *final defense* against changes in the effective circulating volume.[63,64] In normal subjects, it probably plays a relatively minor role, because the other regulatory systems are sufficiently to maintain Na^+ balance without a large change in extracellular volume or blo

pressure.[63] If, however, there is an abnormality in one of more of these factc with renal disease or excess angiotensin II or aldosterone), the degree of Na^+ retention that will occur is ultimately limited, since the ensuing volume exp raises the blood pressure, which then enhances Na^+ excretion. Eventually, a new steady state is reestablished in which intake and excretion are equal and tl pressure is higher than normal.

Sodium reabsorption in the distal tubule and the *thick* ascending limb of the loop of Henle is primarily flow-dependent and not influenced by hormones involved regulation (see Chaps. 4 and 5). As a result, changes in transport in these segm usually do not play an important role in regulating Na^+ excretion. One exception to this general rule occurs in patients treated with a loop diuretic, such as fur The reduction in loop reabsorption in this setting increases fluid delivery tc tubule, leading to an enhanced rate of distal Na^+ reabsorption (and the requisite ris in activity of the Na^+-K^+-ATPase pump that returns reabsorbed Na^+ to the systemic circulation; see Fig. 5-1).[89,90] and [91] Similarly, blocking distal tubule Na^+ reabsorption with a thiazide-type diuretic leads to increased downstream Na^+ transport in the cortical collecting tubule, which also can respond to chang flow.[92]

These compensatory adaptations may be important because they limit the n response to the diuretic. In most cases, an adequate diuresis is still obtain However, increased distal reabsorption can contribute to *diuretic resistance* in some patients, who may require combined therapy with a loop and a thiazide diur inhibit transport at several sites in the nephron (see Chap. 15).

VOLUME REGULATION VERSUS OSMOREGULATION

This chapter has dealt with the factors involved in the maintenance of the e circulating volume. It is important, however, to be aware that these homeos mechanisms are very different from those involved in the maintenance of th osmolality (Table 8-4). The plasma osmolality is determined by the *ratio* of the solutes (Na^+ and K^+ salts) and water, whereas the extracellular volume is determined by the *absolute amounts* of Na^+ and water that are present (see page 248). A few simple examples can illustrate the difference between these par

1. Exercising on a hot day leads to the loss of dilute fluid as sweat. The n is a *rise* in the plasma osmolality and Na^+ concentration but a *fall* in the extracellular volume. Similar changes can be seen in a nursing home pa who develops viral gastroenteritis, characterized by fever, profuse diarı decreased fluid intake.

2. An infusion of isotonic saline will cause volume expansion, with no alte the plasma osmolality.
3. The administration of one-half isotonic saline will initially lower the pla

sodium concentration by dilution and raise the extracellular fluid volume

Table 8-4 Difference between osmoregulation and volume regulation

	Osmoregulation	Volume regulation
What is being sensed	Plasma osmolality	Effective circulating volume
Sensors	Hypothalamic osmoreceptors	Carotid sinus Afferent arteriole Atria
Effectors	Antidiuretic hormone Thirst	Renin-angiotensin-aldosterone system Sympathetic nervous system Atrial natriuretic peptide Pressure natriuresis Antidiuretic hormone
What is affected	Water excretion and, via thirst, water intake	Urine sodium excretion

Changes in the plasma osmolality, which is primarily determined by the plasma Na^+ concentration, are sensed by osmoreceptors in the hypothalamus (see Chap. 6). These receptors affect both water intake and water excretion by influencing thirst and the release of ADH, respectively (Table 8-4). The latter increases the urine osmolality and causes water retention by enhancing the permeability of the collecting tubules to water. Notice that osmoregulation is activated by *alterations in water balance; Na^+ handling is not directly affected unless there are concurrent changes in volume.* Although it is tempting to assume that regulation of the plasma Na^+ concentration has something to do with Na^+, it is actually water intake and excretion that are affected.

Volume regulation, on the other hand, attempts to maintain tissue perfusion. Various sensors and effectors are involved in this process, as it is urinary Na^+ excretion, not osmolality, that is primarily monitored and altered (Table 8-4). The only major area of overlap involves the hypovolemic stimulus to ADH release; the ensuing water retention will then help to restore normovolemia.

The independent roles of the osmoregulatory and volume regulatory pathways can be appreciated by returning to the examples described above.

1. The rise in plasma osmolality following exercise on a hot day will stimu ADH release and thirst; the ensuing increase in urine osmolality and su water retention will eventually return the plasma Na^+ concentration toward normal. This subject is also volume-depleted; consequently,

there will be activation of the renin-angiotensin-aldosterone system, res a fall in urinary Na^+ excretion. The net effect is that the urine will initially highly concentrated and contain relatively little Na^+.
2. Similar hormonal changes occur in the nursing home patient with gastro However, the degree of extracellular fluid volume depletion is likely to b as a result of salt loss in the diarrheal fluid.
3. ADH release and thirst are not altered with an infusion of isotonic salin there is no change in the plasma osmolality. In this setting, only volume regulation is activated, as the associated volume expansion diminishes release of aldosterone and increases that of ANP. The net effect is excr the excess Na^+ and water in a relatively isosmotic urine.
4. Half-isotonic saline causes both hypoosmolality and volume expansion. ADH and renin release will be reduced and ANP secretion enhanced, the allowing the excess NaCl to be excreted in an appropriately dilute fluid.

Thus, the person who exercises on a hot day is dehydrated with a small deg volume depletion, the nursing home patient with gastroenteritis is also dehy with a greater degree of volume depletion, and a patient with diarrhea who a normal plasma Na^+ concentration is volume-depleted but not dehydrated.

Dehydration versus Volume Depletion

The preceding observations permit an understanding of the difference betw terms that are often used synonymously but actually refer to different phen dehydration and volume depletion (also called hypovolemia). *Dehydration* refers to water loss that leads to an elevation in plasma sodium concentration and a intracellular water deficit as a result of the osmotic movement of water from into the extracellular fluid. In comparison, *volume depletion* refers to a decrease in the extracellular fluid volume as a result of the loss of sodium and water. It produced by salt and water loss (as with vomitting, diarrhea, diuretics, blee third space sequestration) or by water loss alone (i.e., dehydration).

PROBLEMS

8-1 In what direction would the plasma volume, the total extracellular f volume, the effective circulating volume, and urinary Na^+ excretion change in the following conditions?

a. **An acute myocardial infarction producing a decrease in the cardiac**
b. **A high-Na^+ diet**

c. **The retention of ingested water due to inappropriate secretion of A**

8-2 What effect would you expect the administration of diuretics (whic increase urinary NaCl and water loss) to have on the secretion of reni Diuretics are used in the treatment of hypertension. Would this effect secretion influence the degree to which the blood pressure is lowered

8-3 Assuming that renal function is normal and that there is no obstruc renal blood flow, which of the following offers the most accurate asse of the effective circulating volume?

a. **Cardiac output**
b. **Plasma volume**
c. **Systemic blood pressure**
d. **Urinary Na^+ excretion**

8-4 In a stable patient chronically taking diuretics for hypertension, wh be the relationship between Na^+ intake and urinary Na^+ excretion?

8-5 What effect will each of the following have on the secretion of aldosterone, ANP, and ADH and on the urine osmolality and Na^+ excretion?

a. **An infusion of isotonic saline**
b. **The intake of 1000 mL of water, which is normally excreted very ra so that there is little change in extracellular volume**
c. **Eating potato chips (which are very salty) while ingesting no wate**
d. **An infusion of half-isotonic saline**

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Footnotes

* The product of cardiac output and systemic vascular resistance actually e change in pressure across the circulation, i.e., mean arterial pressure minu venous pressure. However, since the venous pressure is so much lower (no equals 1 to 7 mmHg) than the mean arterial pressure, only a small error res ignoring it.

† How Na^+ can enter the cell to be reabsorbed when its luminal concentratio below that of the cell is described on page 147.

‡ As described in Chap. 6, prostaglandins appear to inhibit Na^+ reabsorption in the thick ascending limb and in the cortical collecting tubule. This effect is not important in the day-to-day regulation of Na^+ excretion, since there is a low basal rate of prostaglandin production. The major stimuli to renal prostaglandin synthesis are the vasoconstrictors angiotensin II and norepinephrine, which are released in states of effective volume depletion. In this setting, the prostaglandins minimize both renal ischemia and the associated retention of Na^+.

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Chapter Nine
Regulation of Plasma Osmolality

Hypoosmolality and hyperosmolality can produce serious neurologic sympto death, primarily as a result of water movement into and out of the brain, re (see Chaps. 23 and 24).[1,2,3,4] and [5] To prevent this, the plasma osmolality (P_{osm}), which is primarily determined by the plasma Na^+ concentration (see Chap. 7), is normally maintained within narrow limits by appropriate variations in *water intake* and *water excretion*. This regulatory system is governed by osmoreceptors in t hypothalamus that influence both thirst and the secretion of antidiuretic ho (ADH).

Although it may seem that regulation of the plasma Na^+ concentration must have something to do with Na^+ balance, osmoregulation is almost entirely mediated b changes in *water balance*. Thus, the effectors for osmoregulation (ADH and thir affecting water excretion and water intake) are very different from those inv volume regulation (the renin-angiotensin-aldosterone system and atrial natr peptide, affecting Na^+ excretion) (see Table 8-4). This chapter will describe the sources of water intake, the sites of water loss from the body, and the roles thirst, and renal water excretion in the maintenance of the P_{osm}.

WATER BALANCE

Obligatory Water Output

In the steady state, water intake (including that generated from endogenous metabolism) must equal water output (Table 9-1). Much of the water output involves obligatory losses in the urine and stool, and, by evaporation, from the mois of the skin and respiratory tract. The evaporative losses play an important *thermoregulation*; the heat required for evaporation, 0.58 kcal/1.0 mL of water normally accounts for 20 to 25 percent of the heat lost from the body, with remainder occurring by radiation and conduction.[6] The net effect is the elimination o the heat produced by body metabolism, thereby preventing the development hyperthermia.

In contrast to these *insensible* losses, sweat can be called *sensible* loss. Sweat is a hypotonic fluid (Na^+ concentration equals 30 to 65 meq/L) secreted by the sw

glands in the skin. It also contributes to thermoregulation, as the secretion subsequent evaporation of sweat result in the loss of heat from the body. In basal state, sweat production is low, but it can increase markedly in the pr high external temperatures or when endogenous heat production is enhance with exercise, fever, or hyperthyroidism.[6] As an example, a subject exercising in a hot, dry climate can lose as much as 1500 mL/h[7] as sweat.

The obligatory renal water loss is directly related to solute excretion. If a s to excrete 800 mosmol of solute per day (mostly Na^+ and K^+ salts and urea) to remain in the steady state, and the maximum U_{osm} is 1200 mosmol/kg, then the excretion of the 800 mosmol will require a minimum urine volume of 670 mL.

Only small amounts of water, averaging 100 to 200 mL/day, are normally los stool. However, gastrointestinal losses are increased to a variable degree i with vomiting or diarrhea. The effect of these losses on the plasma Na^+ concentration depends on the sum of the Na^+ and K^+ concentrations in the fluid that is lost (see "Measurement of Renal Water Excretion," below).

Table 9-1 Typically daily water balance in a norma human[a]

	Water intake, mL/day			Water output, mL/day	
Source	Obligatory	Elective	Source	Obligatory	Elective
Ingested water	400	1000	Urine	500	1000
Water content of food	850		Skin	500	
Water of oxidation	350		Respiratory tract	400	
			Stool	200	
Total	1600	1000		1600	1000

[a] These values assume a low rate of sweat production. When exercise and/or hot weather stimulates sweat production, water losses from the s can increase markedly, occasionally exceeding 5 L/day. In this setting, t ensuing rise in plasma osmolality enhances thirst, resulting in an appro

increase in water intake.

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Water Intake

To maintain water balance, water must be taken in (or generated) to replac losses (Table 9-1). Net water intake is derived from three sources: (1) ingested water, (2) water contained in foods (e.g., meat is roughly 70 percent water and cert and vegetables are almost 100 percent water), and (3) water produced from the oxidation of carbohydrates, proteins, and fats. If the latter two sources acc 1200 mL/day and the obligatory water loss (from the skin, from the gastroin tract, and in the urine) is 1600 mL/day, then at least 400 mL must be ingest drinking to maintain balance. Humans drink more than this minimum require social and cultural reasons, and the extra water is excreted in the urine.

REGULATION OF PLASMA OSMOLALITY

The normal plasma osmolality (P_{osm}) is 275 to 290 mosmol/kg. It usually is held within narrow limits, as variations of only 1 to 2 percent initiate mechanism the P_{osm} to normal. These alterations in osmolality are sensed by receptor c the hypothalamus that affect water intake (via thirst) and water excretion (v which increases water reabsorption in the collecting tubules).

In terms of water balance, a water load decreases the P_{osm} and water loss (as with exercise on a hot day) increases the P_{osm}. In both of these settings, there is a parallel change in the plasma Na^+ concentration. These alterations in water bala must be differentiated from conditions of *isosmotic* fluid loss (such as bleeding or some cases of diarrhea), in which solute and water may be lost proportiona producing no direct change in the P_{osm} or the plasma Na^+ concentration.

The body responds to a water load by suppressing ADH secretion, resulting decreased collecting tubule water reabsorption and excretion of the excess The peak diuresis is delayed for 90 to 120 min, the time necessary for the metabolism of previously circulating ADH. As will be seen, the kidneys can to 10 to 20 L/day of water, well above any normal level of water intake. *Therefore, water retention resulting in hypoosmolality and hyponatremia occurs, with exceptions, only in patients with an impairment in renal water excretion* (see Chapter 23).

The correction of a water deficit (hyperosmolality) requires the intake and of exogenous water. This is achieved by increases in thirst and ADH releas are induced by the elevation in the P_{osm}. In contrast to the response to hypoosmolality, in which renal water excretion is of primary importance,

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increased thirst is the major defense against hyperosmolality and hypernat Although the kidney can minimize water excretion via the effect of ADH, a w deficit can be corrected only by increased dietary intake.

An example of the efficiency of the thirst mechanism occurs in patients with central diabetes insipidus, who, because they secrete little or no ADH, may more than 10 L/day or urine. Despite this, the P_{osm} remains near normal because the thirst mechanism augments water intake to match output. Thus, *symptomatic hypernatremia generally will not occur in a patient with a normal thirst mechanism and access to water* (see Chap. 24).

Excretion of a water load generally occurs so rapidly that there is little change in volume and no activation of the volume regulatory pathways. There are, however, settings in which both the volume and osmoregulatory systems come into play. For example, the intake of NaCl without water (as with a large quantity of potato chips) results in an elevation in the P_{osm} and, because of the rise in extracellular Na^+ stores, expansion of the effective circulating volume. The latter change promotes renal excretion of the excess Na^+, a response that is mediated at least in part by a reduction in the release of aldosterone and an increase in that of atrial natriuretic peptide (ANP). ADH secretion and thirst also are stimulated (by the rise in P_{osm}), and the ensuing increment in water intake both lowers the P_{osm} toward normal and further expands the volume, thereby enhancing the stimulus to excretion of Na^+. The end result is that the urine has a high osmolality and a relatively high concentration of Na^+, a composition that is similar to net intake.

In comparison, an infusion of isotonic saline causes volume expansion but does not change the P_{osm}. Consequently, ADH release and thirst are not directly affected, and the steady state is restored by the volume regulatory pathways.

RENAL WATER EXCRETION AND REABSORPTION

In the kidney, the bulk of the filtered water is reabsorbed passively in the proximal tubule and descending limb of the loop of Henle down an osmotic gradient created by NaCl transport (see Chaps. 3 and 4). This serves to maintain the volume of the extracellular fluid. In addition, the kidney contributes to the stability of the P_{osm} by excreting or reabsorbing water without solute. This function is primarily mediated by the presence [water conservation, high urine osmolality (U_{osm})] or absence (water excretion, low U_{osm}) of ADH. In normal adults, the U_{osm} can vary from a minimum of 40 to 100 mosmol/kg H_2O to a maximum of 900 to 1400 mosmol/kg.

The quantitative importance of ADH for water excretion is depicted in Table 9-2. In a subject excreting 800 mosmol of solute per day, the urine volume can vary widely depending upon the availability of ADH. In the absence of ADH, for

example, the minimum U_{osm} may be 80 mosmol/kg, resulting in the excretion of the 800 mosmol of solute in 10 liters of water. In a normal subject, this degree of polyuria is rarely seen and occurs only after a massive water load. More commonly, there is a moderate amount of ADH present, and the U_{osm} is somewhere between the extremes of 80 mosmol/kg (no ADH) and 1200 mosmol/kg (maximum ADH). If the subject had to excrete 2000 mL of water to remain in water balance, the average U_{osm} would be 400 mosmol/kg, that is, 800 mosmol of solute in 2000 mL. The

require a submaximal ADH effect.

Table 9-2 Effect of ADH on urine volume in a subject excreting 800 mosmol of solute per day

ADH	U_{osm}, mosmol/kg	Urine volume, L/day
0	80	10
++	400	2
+++	1200	0.67

The *urine output is also affected by solute excretion*, which is equal to net solute intake in the steady state. This is particularly important in disorders in whi of ADH secretion is relatively constant (Fig. 9-1). In a patient with complete central diabetes insipidus, for example, there is little or no ADH and the maximum U_{osm} may be only 80 mosmol/kg. In this setting, the daily urine volume will be 10 liter mosmol of solute is excreted, but only 5 liters if 400 mosmol of solute is ex (400 mosmol of solutes at 80 mosmol/kg equals 5 liters of urine). Thus, one therapy is to restrict the intake of sodium and protein (which is metabolized the ensuing reduction in solute excretion will then limit the degree of polyu Dietary modification may be especially important in patients

with *nephrogenic* diabetes insipidus, who are resistant to the action of ADH ar therefore will not respond to hormone administration. (See Chap. 24)

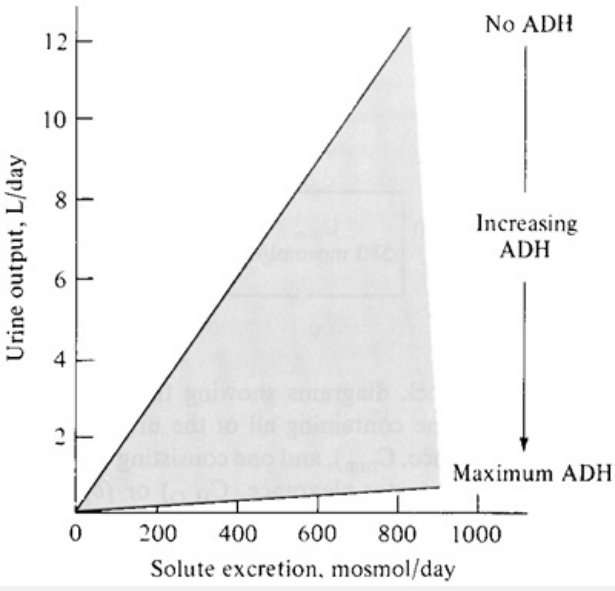

Figure 9-1 Effects of ADH and solute excretion on water excretion. It is ass

that the U_{osm} is 70 mosmol/kg in the absence of ADH and 1400 mosmol/kg w maximum ADH effect.

Measurement of Renal Water Excretion

This simple example of the effect of solute excretion demonstrates that wat excretion can vary widely without changes in the U_{osm}. Thus, *the U_{osm}, which reflects the kidney's ability to dilute or concentrate the urine, is not an ac estimate of its quantitative ability to excrete or retain water*

To measure the amount of solute-free water that the kidney can excrete per one can calculate the *free-water clearance*, C_{H_2O}. If the urine is hypoosmotic to plasma, the total urine volume (V, in milliliters per minute or liters per day) viewed as having two components: one that contains all the urinary solute i solution that is isosmotic to plasma (the osmolal clearance, or C_{osm}), and one that contains the solute-free water that makes the urine dilute (the free-water c (Fig. 9-2)[11]:

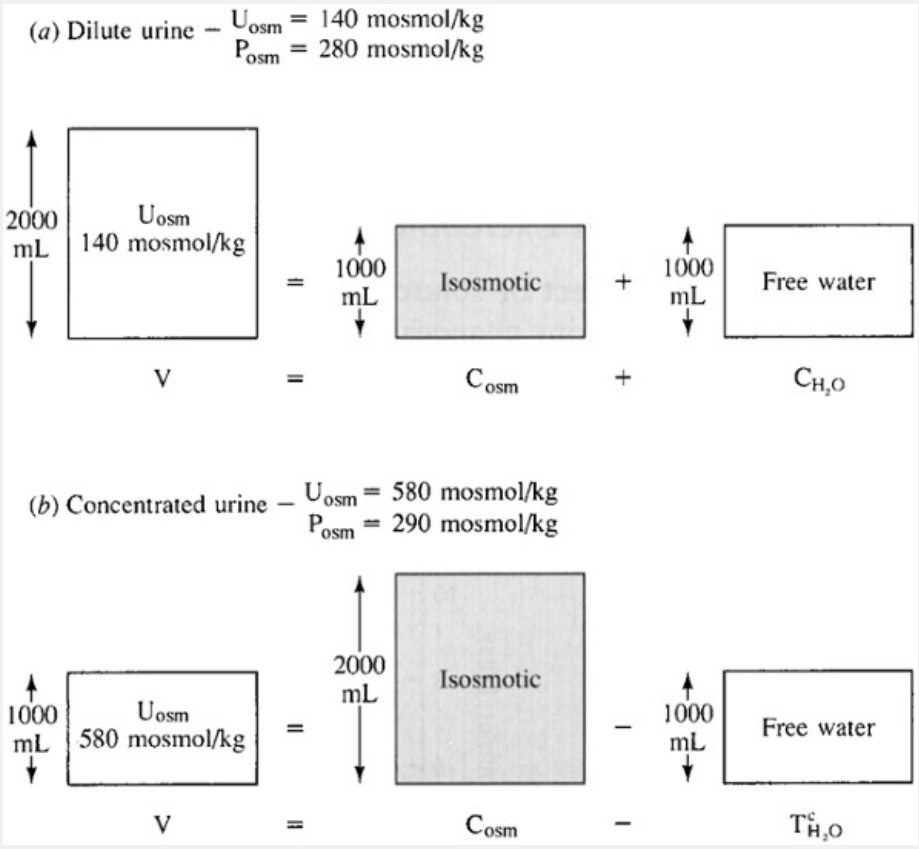

Figure 9-2 Block diagrams showing the relationship between the urine volu (V) and its two components: one containing all of the urinary solute in a s that is isosmotic to plasma (the osmolal clearance, C_{osm}), and one consisting of free water that has either been (a) generated in a dilute urine (the free-water clearance, C_{H_2O}) or (b) reabsorbed in a concentrated urine (the free water

reabsorption, C_{H_2O}). In these simple examples, the urine osmolality is one- and twice the plasma osmolality, respectively. (*From Rose BD: Am J Med 81:1033, 1986. Used with permission*)

$$V = C_{osm} + C_{H_2O} \quad (9\text{-}1)$$

The C_{osm} can be calculated from the general formula for clearance, C=UV/P page 49):

$$C_{osm} = \frac{U_{osm} \times V}{P_{osm}} \quad (9\text{-}2)$$

If Eq. 9-1 is now solved for C_{H_2O},

$$C_{H_2O} = V - C_{osm} = V\left(1 - \frac{U_{osm}}{P_{osm}}\right) \quad (9\text{-}3)$$

The manner in which this formula is used can be illustrated if we return to with central diabetes insipidus who is excreting a maximally dilute urine. If

$$P_{osm} = 280\,\text{mosmol/kg}$$
$$U_{osm} = 80\,\text{mosmol/kg}$$
$$V = 10\,\text{L/day}$$

then

$$C_{H_2O} = 10\left(1 - \frac{80}{280}\right) = 7.2\,\text{L/day}$$

Thus, of the 10 liters of urine being excreted, 7.2 liters exists as free wate (C_{H_2O}) and 2.8 liters as an isosmotic solution containing all of the urinary solute (U_{osm}).

In the clinical setting, the excretion of large volumes of dilute urine may be *appropriate* if it follows a water load or *inappropriate* if it is due to a primary deficiency of ADH or renal resistance to its effects. In either case, the loss free water tends to raise the P_{osm} and plasma $[Na^+]$ concentration unless it is accompanied by an equivalent increase in water intake.

Physiologic factors affecting C_{H_2O}

The excretion of free water by the kidney occurs in two basic steps (see Chapter 4):

1. Solute-free water is generated by NaCl reabsorption without water in th medullary and cortical aspects of the ascending limb of the loop of Hen a lesser degree in the distal nephron.
2. This water is then excreted by keeping the collecting tubules relatively impermeable to water.

In normal subjects, the volume of free water generated in the loop of Henle is primarily dependent upon the volume of water presented to that segment. Collecting tubular impermeability to water (step 2), on the other hand, requ

absence of ADH.

An understanding of the factors that influence C_{H_2O} has important clinical implications in patients with hyponatremia and hypoosmolality. Since the ca water excretion is normally so great (as much as 10 to 20 L/day), water ret leading to hyponatremia will occur only if there is a defect in water excretio rarely if the amount of water ingested exceeds excretory capacity (see Chap. 23). Diminished water excretion requires that one or both of the steps describec impaired. This can occur in three settings:

1. If less free water is generated because the rate of fluid delivery to the Henle is reduced, as with renal failure (where less water is filtered) or depletion (where less water may be filtered and more is reabsorbed in t proximal tubule)
2. If less free water is generated because NaCl reabsorption is inhibited b diuretics, particularly the thiazide-type diuretics (see page 702)
3. If ADH is present, as with effective volume depletion, the syndrome of inappropriate ADH secretion, or adreneal insufficiency

These disorders, along with primary polydipsia, in which there is a primary in water intake, constitute the *differential diagnosis of true hyponatremia* (see Chap. 23).

Measurement of Renal Water Reabsorption

In addition to the formation of a dilute urine, the kidney is also able to excr with an osmolality exceeding that of the plasma. If the urine is hyperosmoti urine volume can again be viewed as having two components: one containir urinary solute in an isosmotic solution and one containing the amount of fre that must have been removed from the urine by tubular reabsorption to rais U_{osm} to the observed hyperosmotic value (the free-water reabsorption, $T^c_{H_2O}$; T this setting (Fig. 9-2),

$$\begin{aligned} V &= C_{osm} - T^c_{H_2O} \\ T^c_{H_2O} &= C_{osm} - V \\ &= V\left(\frac{U_{osm}}{P_{osm}} - 1\right) \end{aligned} \qquad (9\text{-}4)$$

In contrast to the C_{H_2O}, which is equal to the volume of free water *excreted* per unit time, the $T^c_{H_2O}$ is equal to the volume of free water *reabsorbed* per unit time.

Suppose, for example, that a subject who has developed a mild water defici a concentrated urine and has the following values (Fig. 9-2):

$$P_{osm} = 290\ \text{mosmol/kg}$$
$$U_{osm} = 580\ \text{mosmol/kg}$$
$$V = 1\ \text{L/day}$$

In this setting,

$$T^{e}_{H_2O} = 1\left(\frac{580}{290} - 1\right) = 1\ L/day^{*} \qquad (9\text{-}5)$$

These results suggest that 1 L of free water is being added to plasma, whic appropriate in that it tends to lower the plasma osmolality back toward norr net effect, however, is different if the elevation in ADH release responsible high U_{osm} is due to the syndrome of inappropriate ADH secretion. In this set retention of 1 liter of water *would normally have been excreted* will lead to hypoosmolality and hyponatremia. This illustrates the importance of thinkin of $T^{e}_{H_2O}$ rather than of only the U_{osm}. The latter merely indicates the presence a concentrated urine; the former tells exactly how much water is being reta the kidney.

Electrolyte–free-water reabsorption

The formulas presented above described urinary water excretion in relation urinary solutes. This concept, however, must be amended when it is viewed of the plasma Na^+ concentration.[11] As described in chap. 7, the plasma Na^+ concentration is usually determined by the relationship between total excha extracellular solutes (primarily with Na^+ salts), total exchangeable intracellular solutes (primarily K^+ salts), and the total body water:

$$\text{Plasma } [Na^+] \cong \frac{Na^+_e + K^+_e}{TBW} \qquad (9\text{-}6)$$

Urea does not contribute to this relationship because it freely equilibrates cell membrane and therefore does not influence the effective P_{osm} or the distribution

of water between the cells and the extracellular fluid. However, urea is one major urinary solutes that can account for a large part of the U_{osm}. The loss of urea in the urine will cause the plasma urea concentration to fall but will not aff plasma Na^+ concentration. Similar considerations apply to the urinary excreti ammonium.

To more accurately assess the effect of the urine output on osmoregulation above formula for the C_{H_2O} or $T^{e}_{H_2O}$ must be amended in the following ways:[1] $U_{Na^+ + K^+}$ is substituted for the total U_{osm} and[2] the plasma Na^+ concentration is substituted for the P_{osm} (see page 249).[11,12] This new quantity is called the *electrolyte–free-water reabsorption* or $T^{e}_{CH_2O}$:**

$$T^{e}_{C_{H_2O}} = V\left(\frac{U_{Na^+ + K^+}}{P_{Na^+}} - 1\right) \qquad (9\text{-}7)$$

Suppose that the above patient with a fluid deficit and a urine osmolality of mosmol/kg had 5 meq/L of Na^+ and 43 meq/L of K^+ in the urine and had a plasma Na^+ concentration of 144 meq/L. In this setting,

$$T^{e}_{C_{H_2O}} = 1\left(\frac{48}{144} - 1\right) \qquad (9\text{-}8)$$
$$= -670\,\text{mL/day}$$

Thus, instead of retaining 1 L of free water as calculated in Eq. 9-5, this subject actually has a negative value for $T^{e}_{C_{H_2O}}$ and is *losing 670 mL of free water per day*

This concept is extremely important, because it illustrates again the differe between the U_{osm} and exact measurement of how much water is actually being excreted or reabsorbed. The U_{osm} of 580 mosmol/kg in this patient indicates that ADH is present and is producing a relatively concentrated urine. This respo appropriate, since it limits further water loss, which would aggravate the al present water deficit. Use of the traditional formula for free-water reabsorp Eq. 9-5 suggests that this concentrated urine also results in the addition of 1 li water to the body, directly correcting the mildly hyperosmolal state. Howeve sum of Na^+ plus K^+ in the urine is less than that in the plasma. Thus, from the viewpoint of regulation of the plasma Na^+ concentration, the urine output in this patient leads to the loss of 670 mL of free water (Eq. 9-8), producing *a further tendency to hypernatremia*. This finding should not suggest that ADH is ineffect since the U_{osm} would be under 100 mosmol/kg and the urine volume above 5 l in its absence.

Clinical Example

A 78-year-old partially demented man is admitted to the hospital because o pneumonia. Hyperalimentation with high-protein supplements (containing 30

meq/L each of Na^+ and K^+) is begun in an attempt to improve the patient's some poor nutritional status. Over the ensuing 5 days, it is noted that the urine o averaging 4 L/day, the blood urea nitrogen (BUN) has risen from 20 mg/dL t mg/dL, the plasma creatinine concentration is relatively stable at 1.4 mg/dL plasma Na^+ concentration has risen from 140 meq/L up to 156 meq/L despite relatively high fluid intake. The following additional findings are obtained:

$$P_{osm} = 342\,\text{mosmol/kg}$$
$$U_{osm} = 510\,\text{mosmol/kg}$$
$$U_{Na^+} = 10\,\text{meq/L}$$
$$U_{K^+} = 42\,\text{meq/L}$$

Comment

It is not initially clear how the hypernatremia developed in this patient, sin intake was relatively dilute and the urine concentrated. Using the traditiona for free-water reabsorption in Eq. 9-4, it appears that the kidney in this polyuric patient is actually adding 2 L/day of free water to the body, thereby protect against the development of hypernatremia:

$$T^{e}_{H_2O} = 4\left(\frac{510}{342} - 1\right)$$
$$= 2\,L/day$$

However, this patient is polyuric because of a urea osmotic diuresis, in whi excretion of large quantities of urea (derived from the catabolism of the ext protein) both raises the BUN and obligates the excretion of a large volume

Once again, the urine contains relatively large amounts of K^+ and Na^+. From the formula for the electrolyte–free-water reabsorption,

$$T^{e}_{C_{H_2O}} = 4\left(\frac{52}{156} - 1\right)$$
$$= -2.7\,L/day$$

The etiology of the hypernatremia is now apparent: The patient is losing approximately 2.7 L of free water per day in the urine.

Physiologic factors affecting free-water reabsorption

Renal water conservation is dependent upon two basic steps (see Chapter 4):

1. The formation and maintenance of the medulllary osmotic gradient
2. Equilibration of the urine in the collecting tubules with the hyperosmoti medullary interstitium

ADH plays an important role in both steps by promoting the medullary accu of urea and by increasing the water permeability of the collecting tubules. I hyperosmolality is also dependent upon NaCl reabsorption without water in ascending limb of the loop of Henle, a process that in humans is probably independent of ADH.

The concentrating process can be impaired by a defect in ADH release, dec responsiveness of the collecting tubule epithelium to ADH (most often due t use or hypercalcemia in adults), or a primary abnormality in countercurrent preventing the maintenance of the hyperosmotic interstitium. When one of t disturbances is present, water excretion increases and the patient may com polyuria and polydipsia (see page 767). Stimulation of thirst is an important protective response, since it can counteract the increased urinary losses, t preventing negative water balance and the eventual development of hypern

Summary and Clinical Implications

The ability to excrete urine with an osmolality different from that of the pla a central role in the regulation of water balance and maintenance of the P_{osm} and the plasma Na^+ concentration. If the P_{osm} is decreased—e.g., after a water load —ADH secretion is inhibited. This results in the excretion of a dilute urine, permits excretion of the excess water and return of the P_{osm} to normal. If the P_{osm} is elevated—e.g., because of sweat loss—both ADH release and thirst are stimulated. The combination of diminished urinary water loss and enhanced intake results in water retention and a decrease in the P_{osm} to normal.

In addition to the urine osmolality, solute excretion also determines how mu can be excreted (Fig. 9-1). Thus, the quantity of free water excreted or reabsor best measured directly as C_{H_2O} or $T^c_{H_2O}$, rather than being inferred from the urine osmolality.

Although the role of solute excretion may at first glance appear to be of int to the physiologist, it becomes clinically important in several situations. In subjects, water intake is the major determinant of the urine volume through on ADH release. However, when ADH secretion or responsiveness is relativ (as in the syndrome of inappropriate ADH secretion or diabetes insipidus), *water intake no longer directly affects the urine volume* and the rate of solute excretion assumes primary importance. As described above, restricting dietary NaCl a protein intake is one way to diminish the urine output and the secondary pc in patients with nephrogenic diabetes insipidus, who are resistant to the ef ADH.

On the other hand, the syndrome of inappropriate ADH secretion is charact a reduction in the urine output and a tendency to water retention and hypor (see Chap. 23). In this setting, a high-sodium, high-protein diet or the direct administration of urea in refractory cases can increase the urine output and plasma Na^+ concentration toward normal.[13]

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PROBLEMS

9-1 Diarrheal fluid usually is isosmotic to plasma even though its ionic composition differs from that of the plasma. Assuming that all of the d solute consists of Na^+ and K^+ salts, what effect will the loss of 2 liters of t fluid have on the following:

a. **Effective circulating volume**

b. **Urinary Na^+ excretion**

c. **Plasma osmolality**

d. **Plasma Na^+ concentration**

e. **ADH release**

f. **Urine osmolality**

If this patient drank a large quantity of water to prevent volume deple what would happen to the plasma Na^+ concentration?

9-2 Although secretory diarrheas, such as cholera, result in the loss of Na^+ and K^+ salts, an osmotic diarrhea (as with malabsorption or the administration of lactulose for hepatic encephalopathy) may be associ with the loss of isosmotic fluid with a Na^+ concentration of under 100 meq/L. What direct effect would the loss of this fluid have on the plas

concentration?

9-3 What is the relationship between the plasma Na^+ concentration and urinary Na^+ excretion?

9-4 A patient with volume depletion due to vomiting has hyponatremia hypoosmolality. What are the factors that may contribute to the inabili restore normal osmolality by excreting the excess water in the urine?

9-5 A subject switches from a regular diet to one consisting primarily o (which contains little or no K^+, Na^+, or protein) and is then given a water loa What will be the effect of this dietary change on the minimum U_{osm} that can be achieved and on the maximum C_{H_2O}?

9-6 Two patients, one with heart failure via the hypovolemic stimulus a with the syndrome of inappropriate ADH secretion, have an elevation i release. Both patients have a U_{osm} of 540 mosmol/kg, a urine output of 1 L/day, and, because of water retention, a low plasma Na^+ concentration of 130 meq/L. However, the patient with inappropriate ADH secretion has no c Na^+ handling (since volume regulation is intact) and has urine Na^+ and K^+ concentrations of 80 and 50 meq/L, respectively. The comparable valu the patient with heart failure are 10 and 50 meq/L because of the avid Na^+ retention induced by the low cardiac output.

a. **Is there a difference between the amount of free water excreted or reabsorbed by these two patients?**
b. **Can this difference affect the tendency to become hyponatremic?**

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Footnotes

* The physiology of the release and actions of ADH are discussed in detail in Chap. 8.

† Concentrating ability tends to fall with age, and so the maximum U_{osm} of an elderly patient may be only 500 to 700 mosmol/kg H_2O. Why this occurs is not well understood.

‡ It is important to emphasize again that *hyponatremia is a disorder of water imbalance, not Na^+ imbalance*. It is usually characterized by impaired water excretion, which lowers the plasma Na^+ concentration by dilution. Urinary loss of Na^+, on the other hand, directly causes effective circulating volume depletion. It can be associated with hyponatremia if there is both a hypovolemic stimulus to ADH release and some water intake to allow water retention to occur.

¶ These values can also be used to calculate the C_{H_2O}:

$$C_{H_2O} = 1\left(1 - \frac{580}{290}\right)$$
$$= -1\ \text{L/day}$$

Thus, -1 L/day of free water is being excreted; this is another way of statin L/day is being reabsorbed. This illustrates the inverse relationship betwee C_{H_2O}, which measures free-water excretion, and $T^c_{H_2O}$, which represents free-water reabsorption:

$$C_{H_2O} = -T^c_{H_2O}$$

** This correction should also be applied to the formula for free-water clea Eq. (9-3) to calculate the electrolyte–free-water clearance, $C^e_{H_2O}$

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Chapter Ten
Acid-base physiology

INTRODUCTION

Like the other components of the extracellular fluid, the H^+ concentration is maintained within narrow limits. The normal extracellular H^+ concentration is approximately 40 nanomol/L (1 nanomol/L equals 10^{-6} mmol/L), roughly one-*millionth* the millimole per liter concentrations of K^+, Ca^{++}, Na^+, and HCO_3^-.

Regulation of the H^+ concentration at this low level is essential for normal cell function because of the high reactivity of H^+ ions, particularly with proteins.[1,2] This property is related to the relatively small size of hydronium ions, the hydrated H^+,* in comparison with that of Na^+ and K^+ ions. As a result, H^+ ions are more strongly attracted to negatively charged portions of molecules and are more bound than Na^+ or K^+.

When there is a change in the H^+ concentration, proteins gain or lose H^+ ions, resulting in alterations in charge distribution, molecular configuration, and consequently protein function. As an example, the rate of glycolysis (as measured by the rate of lactate production) varies inversely with the H^+ concentration, increasing as the latter is reduced (Fig. 10-1).[1] This change in cellular

metabolism is mediated by a similar inverse relationship between the H^+ concentration and the activity of several glycolytic enzymes, particularly phosphofructokinase.[1]

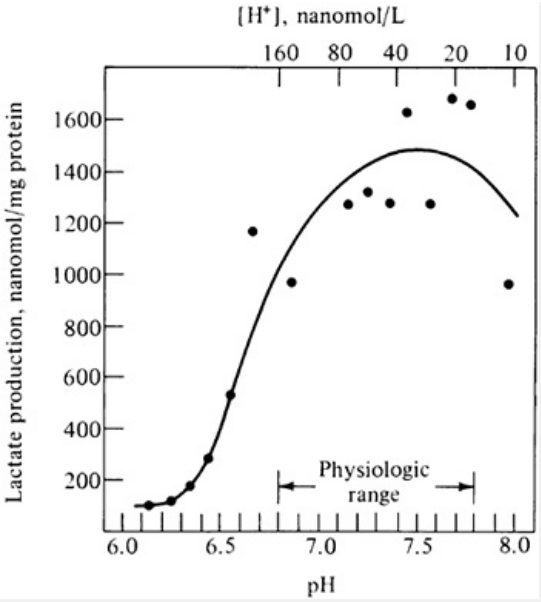

Figure 10-1 Influence of H^+ concentration and pH on lactate production by leukocytes. *(From Halperin ML, Connors HP, Relman AS, Karnovsky MJ: Biochem J Biol Chem, 244:384, 1969, with permission.)*

Under normal conditions, the H^+ concentration varies little from the normal value of approximately 40 nanomol/L. This occurs even though acids and bases are continually being added to the extracellular fluid. The precise regulation of H^+ involves three basic steps:

1. Chemical buffering by the extracellular and intracellular buffers
2. Control of the partial pressure of carbon dioxide in the blood by alterations in the rate of alveolar ventilation
3. Control of the plasma bicarbonate concentration by changes in renal H^+ excretion

This chapter will review the basic principles of acid-base physiology, including the efficacy of buffers in preventing large changes in the H^+ concentration. The roles of ventilation and renal H^+ excretion in acid-base homeostasis are discussed in Chapter 11.

ACIDS AND BASES

Using the definitions proposed by Bronsted, an acid is a substance that can release H^+ ions and a base is a substance that can accept H^+ ions.[4,5] These properties are independent of charge. Thus H_2CO_3, HCl, NH_4^+, and HPO_4^- all can act as acids:

$$\begin{array}{lcl} H_2CO_3 & \leftrightarrow & H^+ + HCO_3^- \\ HCl & \leftrightarrow & H^+ + Cl^- \\ NH_4^+ & \leftrightarrow & H^+ + NH_3 \\ H_2PO_4^- & \leftrightarrow & H^+ + HPO_4^{2-} \\ \text{Acid} & & \text{Base} \end{array}$$

There are two classes of acids that are physiologically important: carbonic (H_2CO_3) and noncarbonic acids. This distinction is important because of the different rates of production and routes of elimination of these acids. Each metabolism of carbohydrates and fats results in the generation of approxim 15,000 mmol of CO_2. Although CO_2 is not an acid, it combines with water to form H_2CO_3 (see below). Thus, there would be progressive accumulation of acid endogenously produced CO_2 were not excreted. This is prevented by the loss of CO_2 via respiration.

Noncarbonic acids, in comparison, are primarily derived from the metabolis proteins. As an example, the oxidation of sulfur-containing amino acids resu generation of H_2SO_4.[6] Only 50 to 100 meq/day of acid is produced from these sources;[3,6] these H^+ ions are then excreted in the urine.

Law of Mass Action

The law of mass action states that the velocity of a reaction is proportional product of the concentrations of the reactants. For example, water can diss into hydrogen and hydroxyl ionsraise4pt*:

$$H_2O \leftrightarrow H^+ + OH^-$$

The velocity with which this reaction moves to the right is equal to

$$v_1 = k_1[H_2O]$$

where k_1 is the rate constant for this reaction. Similarly, the velocity with wh reaction moves to the left can be expressed by

$$v_2 = k_2[H^+]\,[OH^-]$$

At equilibrium, $v_1 = v_2$. Therefore,

$$k_1[H_2O] = k_2[H^+]\,[OH^-]$$

$$K' = \frac{k_1}{k_2} = \frac{[H^+]\,[OH^-]}{[H_2O]} \qquad (10\text{-}1)$$

Since the H_2O concentration is relatively constant in the body fluids, this equ can be rearranged, so that

$$K_w = [H^+]\,[OH^-] \qquad (10\text{-}2)$$

where K_w is equal to the product of the two constants, K' and $[H_2O]$. At body temperature, $K_w = 2.4 \times 10^{-14}$. Thus, for distilled water,

$$[H^+]\,[OH^-] = 2.4 \times 10^{-14}$$

$$[H^+] = 1.55 \times 10^{-7}\ \text{mol/L}$$

$$[OH^-] = 1.55 \times 10^{-7}\ \text{mol/L}$$

Since the normal H^+ concentration in the extracellular fluid is 40 nanomol/L, w see that the extracellular fluid is slightly less acid than water (where the H^+ concentration is 155 nanomol/L).

The law of mass action can be written for the dissociation of all the acids a in the body. For example, for the dissociation of an acid, HA, into H^+ and A^-,

$$K_a = \frac{[H^+]\,[A^-]}{[HA]} \qquad (10\text{-}3)$$

where K_a is the apparent *ionization* or *dissociation constant* for this acid. In the body, K_a has a single value for the dissociation of each acid. Although K_a slightly with changes in temperature, solute concentration, and ionic strength, these parameters are held relatively constant under normal conditions. Since the same principles can be applied to the dissociation of a base,

$$BOH \leftrightarrow B^+ + OH^-$$

the behavior of bases will not be discussed separately.

Acids and bases may be strong or weak. Strong acids are those that are es completely ionized in the body. Since most of the acid exists as H^+ and A^-, a strong acid, from Eq. 10-3, has a relatively high K_a. HCl and NaOH are examples of a strong acid and a strong base, respectively. In comparison, $H_2PO_4^-$ is only 80 percent dissociated at the normal extracellular H^+ concentration and is considered a weak acid. As we will see, weak acids are the principal buffers in the body.

pH

The pH of a solution can be defined by the following relationship:

$$pH = -\log[H^+] \qquad (10\text{-}4)$$

In the laboratory, the H^+ concentration of the blood can be measured with a gla membrane electrode that is permeable only to H^+. The diffusion of H^+ ions between the blood and the fluid in the electrode results in the generation of a meas electrical potential (E_m) across the membrane. The magnitude of this potential is proportional to the logarithm of the ratio of the H^+ concentration in the two compartments according to the Nernst equation:

$$E_m = 61 \log \frac{[H^+]_e}{[H^+]_b}$$

where the subscripts e and b refer to the fluid within the electrode and the respectively. Since $[H^+]_e$ has a known value,

$$E_m \sim \log \frac{1}{[H^+]_b}$$

The log(1/a) is equal to -log a. Thus,

$$E_m \sim -\log[H^+]_b$$

Since pH = -log $[H^+]$,

$$E_m \sim pH^*$$

Since the *pH varies inversely with the* H^+ *concentration*, an increase in the H^+ concentration reduces the pH, and a decrease in the H^+ concentration elevates the pH. The relationship between the H^+ concentration and the pH within the physiolc range is depicted in Table 10-1. In general, the range of H^+ concentration that is compatible with life is 16 to 160 nanomol/L (pH equals 7.80 to 6.80). The n arterial pH is approximately 7.40; thus, the normal H^+ concentration can be calculated from

$$pH = -\log[H^+]$$

$$\log[H^+] = -7.40$$

Taking the antilogarithm of both sides,

$$[H^+] = \text{antilog}(-7.40)$$

$$= \text{antilog}(0.60 - 8)$$

The antilogarithm of 0.60 is 4, and that of -8 is 10^{-8}. Thus,

$$[H^+] = 4 \times 10^{-8}\ \text{mol/L}$$

$$= 40\ \text{nanomol/L}$$

Table 10-1 Relationship between the arterial pH ar H^+ concentration in the physiologic range

pH	$[H^+]$, nanomol/L
7.80	16
7.70	20
7.60	26
7.50	32
7.40	40
7.30	50
7.20	63
7.10	80
7.00	100

6.90	125
6.80	160

The relative merits of measuring the acidity of a solution in terms of pH or H^+ concentration have been the subject of much debate.[11] Since this issue is not likely to be important in the clinical setting, the following discussion will use both pH and H^+ concentration to familiarize the reader with these concepts.

Henderson-Hasselbalch Equation

Equation 10-3 can be rearranged in the following manner:

$$[H^+] = K_a \frac{[HA]}{[A^-]} \qquad (10\text{-}5)$$

If we take the negative logarithm of both sides,

$$-\log[H^+] = -\log K_a - \log\frac{[HA]}{[A^-]}$$

Substituting pH for $-\log [H^+]$ and $+\log ([A^-]/[HA])$ for $-\log ([HA]/[A^-])$, and defining pK_a as $-\log K_a$ (the H^+ concentration and K_a being expressed in units of moles per liter),

$$pH = pK_a + \log\frac{[A^-]}{[HA]} \qquad (10\text{-}6)$$

This is the Henderson-Hasselbalch equation, which can be written for the dissociation of any weak acid. Using the Bronsted definition, this is valid with A^- as a base and HA as an acid, this equation becomes

$$pH = pK_a + \log\frac{\text{base}}{\text{acid}} \qquad (10\text{-}7)$$

For example, for the reaction

$$H_2PO_4^- \leftrightarrow H^+ + HPO_4^{2-}$$

the relationship between the concentrations of the reactants can be expressed by the law of mass action or by the Henderson-Hasselbalch equation:

$$[H^+] = K_a \frac{[H_2PO_4^-]}{[HPO_4^{2-}]} \qquad (10\text{-}8)$$

$$pH = pK_a + \log\frac{[HPO_4^{2-}]}{[H_2PO_4^-]} \qquad (10\text{-}9)$$

The K_a for this reaction is 1.6×10^{-7} mol/L (or 160 nanomol/L), and thus the pK_a is 6.80.

To show how these equations can be used, let us calculate the HPO_4^{2-} and $H_2PO_4^-$ concentrations in the extracellular fluid if the total phosphate concentration is 1 mmol/L and the H^+ concentration equals 40 nanomol/L (pH is 7.40). From the law of mass action,

$$40 = 160\frac{[H_2PO_4^-]}{[HPO_4^{2-}]}$$

or

$$\frac{[HPO_4^{2-}]}{[H_2PO_4^-]} = 4$$

Since the total phosphate concentration is 1 mmol/L,

$$[HPO_4^{2-}] = 0.8\,\text{mmol/L}$$

$$[H_2PO_4^-] = 0.2\,\text{mmol/L}$$

The same results can be obtained from the Henderson-Hasselbalch equatio

$$7.40 = 6.80 + \log\frac{[HPO_4^{2-}]}{[H_2PO_4^-]}$$

Since the antilogarithm of 0.60 (7.40-6.80) is 4,

$$\frac{[HPO_4^{2-}]}{[H_2PO_4^-]} = 4$$

The phosphate system is somewhat more complicated, since phosphate alsc exist as PO_4^{3-} and H_3PO_4:

$$PO_4^{3-} + H^+ \overset{1}{\leftrightarrow} HPO_4^{2-} + H^+ \overset{2}{\leftrightarrow} H_2PO_4^- + H^+ \overset{3}{\leftrightarrow} H_3PO_4$$

However, only trace amounts of PO_4^{3-} and H_3PO_4 are present in the body, since th pK_a of reaction 1 ($pK_{a1} = 12.4$) is much higher than that of reaction 3 ($pK_{a3} = 2.0$), much lower than the extracellular pH of 7.40. For example, for reaction 1,

$$7.40 = 12.40 + \log\frac{[PO_4^{3-}]}{[HPO_4^{2-}]}$$

$$\frac{[PO_4^{3-}]}{[HPO_4^{2-}]} = \text{antilog}(-5) = 10^{-5}$$

Thus, at a pH of 7.40, there is only one molecule of PO_4^{3-} present for every 10^5 molecules of HPO_4^{2-}.

BUFFERS

One of the major ways in which large changes in H^+ concentration are prevented is by *buffering*. The body buffers, which are primarily weak acids, are able to ta or release H^+ so that changes in the free H^+ concentration are minimized. As an example, phosphate is an effective buffer, via the following reaction:

$$HPO_4^{2-} + H^+ \leftrightarrow H_2PO_4^-$$

If H^+ ions are added to the extracellular fluid, they will drive this reaction t by combining with HPO_4^{2-} to form $H_2PO_4^-$. Conversely, if H^+ ions are lost from the extracellular fluid, the reaction will move to the left as H^+ is released from $H_2PO_4^-$. In contrast, strong acids, such as HCl, are poor buffers at the body since they are *almost completely ionized and cannot bind* H^+ ions.

The efficiency of phosphate buffering can be appreciated from the following
Let us assume that in 1 liter of solution there are 10 mmol each of HPO_4^{2-}
$H_2PO_4^-$ as the Na^+ salts. From Eq. 10-8,

$$[H^+] = K_a \frac{H_2PO_4^-}{HPO_4^{2-}}$$

$$= 160 \times \frac{10}{10}$$

$$= 160 \text{ nanomol/L} \qquad (pH = 6.80)$$

Note that when the concentrations of acid ($H_2PO_4^-$) and base (HPO_4^{2-}) are the same, the H^+ concentration equals K_a and the pH equals pK$_a$.

If 2 mmol of HCl is added to this solution, the excess H^+ ions combine with HPO_4^{2-}:

$$HCl + Na_2HPO_4 \rightarrow NaCl + NaH_2PO_4$$

If we assume that virtually all the added H^+ is taken up by HPO_4^{2-}, then the HPO_4^{2-} concentration will fall to 8 mmol/L and the $H_2PO_4^-$ concentration will rise to 12 mmol/L. The new H^+ concentration will be

P.307

$$[H^+] = 160 \times \frac{12}{8}$$

$$= 240 \text{ nanomol/L} \qquad (pH = 6.62)$$

Thus, even though 2 mmol/L or 2 million nanomol/L of H^+ ions were added to the solution, the H^+ concentration has increased by only 80 nanomol/L. As a result *more than 99.99 percent of the excess H^+ ions has been taken up or buffered by HPO_4^{2-}*. If no buffers had been present, the H^+ concentration would have been 2 million nanomol/L, with a pH of 2.70.

If more H^+ ions are added or if H^+ ions are removed by adding NaOH,

$$NaOH + NaH_2PO_4 \rightarrow Na_2HPO_4 + H_2O$$

the change in pH (or H^+ concentration) can be calculated in a similar manner. I new pH is plotted against the amount of acid or base added, the result is th curve in Fig. 10-2. Although the shape of the curve is sigmoidal, there is a line midregion (pH equals 5.80 to 7.80) in which relatively large amounts of aci can be added without much change in pH. *Thus, a buffer is most efficient when the pH of the solution is within ± 1.0 pH unit of the pK$_a$.* If the pH is outside these limits, buffering will still occur, but a small amount of acid or base can proc relatively large change in pH.

Bicarbonate/Carbon Dioxide Buffer System

Carbonic acid can dissociate into a hydrogen ion and a bicarbonate ion:

$$H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

the pK_a of this reaction is 3.57 (equals 2.72×10^{-4}). Since this is far from the normal pH of 7.40, it seems as if HCO_3^- would be an ineffective buffer in the body. However, H_2CO_3 is formed from the hydration of carbon dioxide (CO_2), and this

buffer system can be more accurately described by the following series of reactions:

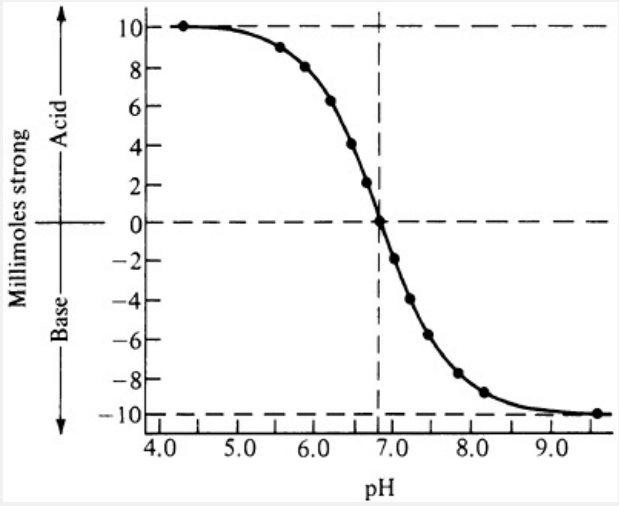

Figure 10-2 Titration curve of 1 liter of a 20 mmol $H_2PO_4^-$ and HPO_4^{2-} solution. Initially, the concentration of HPO_4^{2-} equals that of $H_2PO_4^-$ at 10 mmol/L, and the concentration of H^+ equals 160 nanomol/L (pH equals 6.80). The different points represent the effects on the pH of the solution of the addition of a strong acid or base. (*From Woodbury JW, Ruch TC, Patton HC (eds): Physiology and Bio-physics, 20th ed. Philadelphia, Saunders, 1974, with permission.*)

$$\underset{\text{gas phase}}{CO_2} \leftrightarrow \underset{\text{aqueous phase}}{CO_2 + H_2O} \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \qquad (10\text{-}10)$$

Dissolved carbon dioxide

All gases partially dissolve in water (that is, they enter the aqueous phase) degree to which this occurs is proportional to the partial pressure of the ga solution. In humans, the partial pressure of CO_2 (P_{CO_2}) in the arterial blood is in equilibrium with that in the alveolar air and normally is approximately 40 mm 37°C (normal body temperature), the amount of CO_2 dissolved in the plasma is

$$[CO_2]_{dis} = 0.03\, P_{CO_2}$$
$$= 0.03 \times 40 = 1.2\,\text{mmol/L} \qquad (10\text{-}11)$$

where 0.03 is the solubility constant for CO_2 in plasma.

Hydration of carbon dioxide

The equilibrium of the reaction

$$[CO_2]_{dis} + H_2O \leftrightarrow H_2CO_3$$

normally is far to the left, so that there are approximately 340 molecules of CO_2 in the solution for each molecule of H_2CO_3. Nevertheless, an increase in the P_{CO_2} increases the $[CO_2]_{dis}$ and, therefore, the H_2CO_3 concentration. Thus, CO_2, which is not an acid, increases the acidity of the solution through the formation of H_2CO_3.

In certain tissues, such as red blood cells and the renal tubular epithelium, the hydration and dehydration reactions is enhanced by the enzyme carbonic anhydrase. The importance of this enzyme for renal H^+ secretion and HCO_3^- reabsorption will be discussed in Chapter 11.

Dissociation of carbonic acid

The degree to which H_2CO_3 dissociates into H^+ and HCO_3^- [Eq. 10-10] can be appreciated from the law of mass action for this reaction:

$$K_a = \frac{[H^+]\,[HCO_3^-]}{[H_2CO_3]}$$

Since the K_a is 2.72×10^{-4} and the normal H^+ concentration is 40×10^{-9} mol/L,

$$2.72 \times 10^{-4} = \frac{40 \times 10^{-9} \times [HCO_3^-]}{[H_2CO_3]}$$

$$\frac{[HCO_3^-]}{[H_2CO_3]} = 6.8 \times 10^3$$

Thus, there are approximately 6800 molecules of HCO_3^- for each molecule of H_2CO_3.

Law of mass action for bicarbonate/carbon dioxide buffer system

Since the concentration of H_2CO_3 is so low in relation to the $[CO_2]_{dis}$ (1 : 340) and the HCO_3 concentration (1 : 6800), the reactions

$$[CO_2]_{dis} + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

can be simplified to

$$[CO_2]_{dis} + H_2O \leftrightarrow H^+ + HCO_3^- \qquad (10\text{-}12)$$

The law of mass action for this reaction is

$$K_a = \frac{[H^+]\,[HCO_3^-]}{[CO_2]_{dis}\,[H_2O]}$$

Since the concentration of water is constant, ($K_a \times [H_2O]$) can be replaced by K'_a:

$$K'_a = \frac{[H^+]\,[HCO_3^-]}{[CO_2]_{dis}} \qquad (10\text{-}13)$$

If we solve this equation for $[H^+]$,

$$[H^+] = \frac{K'_a \times [CO_2]_{dis}}{[HCO_3^-]}$$

In plasma at 37°C, K'_a is equal to 800 nanomol/L (800×10^{-9} mol/L, pK'_a equals 6.10). Thus,

$$[H^+] = 800 \times \frac{[CO_2]_{dis}}{[HCO_3^-]} \qquad (10\text{-}14)$$

Substituting $0.03P_{CO_2}$ for $[CO_2]_{dis}$:

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]} \qquad (10\text{-}15)$$

Since the normal H^+ concentration is 40 nanomol/L and this is P_{CO_2} 40 mmHg, the normal HCO_3^- concentration can be calculated from Eq. 10-15:

$$40 = 24 \times \frac{40}{[HCO_3^-]}$$

$$[HCO_3^-] = 24\,\text{mmol/L}^*$$

These relationships also can be expressed by the Henderson-Hasselbalch equation:

$$pH = 6.10 + \log\frac{[HCO_3^-]}{0.03P_{CO_2}} \qquad (10\text{-}16)$$

where 6.10 is the pK'_a.

The HCO_3^- concentration usually is measured in the laboratory in one of two ways. The first way is indirect: The arterial pH and P_{CO_2} are measured, and the HCO_3^- concentration is then calculated using the Henderson-Hasselbalch equation. The second method involves adding a strong acid to a venous blood sample and measuring the amount of CO_2 generated by a colorimetric reaction. As the added H^+ combines with plasma HCO_3^-, H_2CO_3 and then CO_2 are formed and Eq. 10-10 is driven to the left. This method, however, measures the *total CO_2 content*, which detects all the forms in which CO_2 is carried in the blood:

$$\text{Total } CO_2 \text{ content} = [HCO_3^-] + [CO_2]_{dis} + [H_2CO_3]$$

Since the H_2CO_3 concentration is very low, it can be omitted. If $0.03P_{CO_2}$ is substituted for $[CO_2]_{dis}$, then

$$[HCO_3^-] = \text{total } CO_2 \text{ content} - 0.03P_{CO_2} \qquad (10\text{-}17)$$

At a normal HCO_3^- concentration of 24 mmol/L and a normal P_{CO_2} of 40 mmHg, the total CO_2 content will be 24+(0.03× 40) or 25.2 mmol/L. Thus, when the total CO_2 content is measured, Eq. 10-11, 10-12, 10-13, 10-14, 10-15 and 10-16 must be modified in the following way:

$$pH = \log\frac{\text{total } CO_2 - 0.03P_{CO_2}}{0.03P_{CO_2}} \qquad (10\text{-}18)$$

For the sake of simplicity, only the HCO_3^- concentration will be used in this discussion.

Buffering by bicarbonate

As noted above, the most efficient buffering occurs within 1.0 pH unit of the pK_a (Fig. 10-2). Although the pK_a for the HCO_3^-/CO_2 system is 1.30 pH units less than the normal extracellular pH of 7.40, this system *buffers very effectively because the* P_{CO_2} *can be regulated by changes in alveolar ventilation* (see Chap. 11). An increase in ventilation augments CO_2 excretion and lowers the P_{CO_2}; a reduction in ventilation decreases CO_2 excretion, resulting in an elevation in the P_{CO_2}. Thus, as HCO_3^- is formed from the buffering of excess H^+ by HCO_3^-, a subsequent elevation in the P_{CO_2} [as Eq. 10-10

is driven to the left] can be prevented by an increase in alveolar ventilation enhancing the effectiveness of HCO_3^- buffering.

The importance of this ability to regulate ventilation can be illustrated by the following example. Let us assume that 1 liter of plasma, in which the only HCO_3^- buffer, has the following composition:

$$[H^+] = 40\,\text{nanomol/L} \qquad (\text{pH} = 7.40)$$
$$[HCO_3^-] = 24\,\text{mmol/L}$$
$$P_{CO_2} = 40\,\text{mmHg}$$
$$[CO_2]_{dis} = 1.2\,\text{mmol/L} \qquad (0.03 \times 40 = 1.2)$$

How many millimoles of HCl would have to be added to this solution to raise the H^+ concentration to 80 nanomol/L (pH equals 7.10)? As each millimole of H^+ combines with HCO_3^-, there will be an equimolar *decrease* in the HCO_3^- concentration and an *elevation* in the $[CO_2]_{dis}$ [from Eq. 10-10, 11 and 12]. Thus, the new HCO_3^- concentration will be 24-x and the new $[CO_2]_{dis}$ will be 1.2+x. From Eq. 10-11, 12, 13 and 14,

$$[H^+] = 800 \times \frac{[CO_2]_{dis}}{[HCO_3^-]}$$
$$80 = 800 \times \frac{1.2 + x}{24 - x}$$
$$x = 1.1\,\text{mmol/L}$$

This represents substantial buffering in that the H^+ concentration has increased only from 40 nanomol/L to 80 nanomol/L, even though 1.1 mmol/L (or 1.1 nanomol/L) has been added to the solution. However, this response would be physiologically inadequate, since the H^+ concentration has risen to a potentially dangerous level after the addition of only 1.1 mmol of H^+. The increase in the $[CO_2]_{dis}$ to 2.3 mmol/L in this setting is equivalent to an elevation in P_{CO_2} to 77 mmHg (0.03× 77=2.3).

If, however, ventilation could be increased so that the P_{CO_2} remained constant at 40

mmHg (and therefore the $[CO_2]_{dis}$ remained constant at 1.2 mmol/L), then

$$80 = 800 \times \frac{1.2}{24 - x}$$

$$x = 12\,\text{mmol/L}$$

Thus, the ability to maintain the P_{CO_2} at a constant level *increases the efficiency of HCO_3^- buffering 11-fold*. Furthermore, there will be an additional increase in th buffering capacity of the HCO_3^- if ventilation can be sufficiently enhanced to reduce P_{CO_2} below 40 mmHg. If, for example, the P_{CO_2} were lowered to 20 mmHg ($[CO_2]_{dis} = 0.03 \times 20 = 0.6$), then *18 mmol of H^+* could be added to each liter of plasma before the H^+ concentration increased to 80 nanomol/L:

$$80 = 800 \times \frac{0.6}{24 - x}$$

$$x = 18\,\text{mmol/L}$$

These changes in ventilation, which make the HCO_3^-/CO_2 buffering system so effective, occur in humans because the chemoreceptors controlling ventilat sensitive to alterations in the extracellular H^+ concentration (see Chap. 11). If the H^+ concentration is increased by the addition of HCl to the extracellular fluid,

there will be an increase in ventilation, resulting in a reduction in P_{CO_2}. This is an *appropriate compensatory response* since the decrease in P_{CO_2} will lower the H^+ concentration toward normal. Conversely, a decrease in the H^+ concentration (or an increase in the pH) will reduce ventilation.

The net effect is that the buffering capacity of the bicarbonate system diffe that of the nonbicarbonate buffers. The latter is determined by the quantity of buffer and the extracellular pH, as depicted in Fig. 10-2. In comparison, the capacity of the bicarbonate system is primarily determined by the plasma HCO_3^- concentration; the ability to vary the P_{CO_2} makes bicarbonate buffering capacity relatively independent of pH.

Isohydric Principle

From the law of mass action (Eqn. 10-5), the acid/base ratio of any weak acid is determined by its K_a and the H^+ concentration of the solution. Since the H^+ concentration affects each buffer, the following relationship is present:

$$[H^+] = K_{a1}\frac{0.03P_{CO_2}}{[HCO_3^-]} = K_{a2}\frac{[H_2PO_4^-]}{[HPO_4^{2-}]} = K_{a3}\frac{[HA]}{[A^-]} \qquad (10\text{-}19)$$

This is called the *isohydric principle*. If the H^+ concentration is altered, the acid/base ratio *of* the buffers in the solution is affected. This means that st the behavior of any one buffer is adequate to predict the behavior of the ot buffers in the solution. Clinically, the acid-base status of a patient is expre

terms of the principal extracellular buffer, the HCO_3^- system:

$$[H^+] = 24\frac{P_{CO_2}}{[HCO_3^-]}$$

Extracellular Buffers

The body buffers are located in the extracellular and intracellular fluids an
As described above, the ability of a particular buffer to protect the pH is pr
to its concentration and its pK relation to the ambient pH. In the transcellular
fluid, HCO_3^- is the most important buffer, as a result of both its relatively hig
concentration and the ability to vary the P_{CO_2} via changes in alveolar ventilation. I
for example, H_2SO_4 is added to the extracellular fluid from the metabolism of t
sulfur-containing amino acids methionine and cysteine, H^+ will be
buffered primarily by HCO_3^-

$$H_2SO_4 + 2NaHCO_3 \rightarrow Na_2SO_4 + 2H_2CO_3 \rightarrow 2CO_2 + 2H_2O \quad (10\text{-}20)$$

The CO_2 produced by this reaction is excreted by the lungs.

Although HCO_3^- is an effective buffer to noncarbonic acids, it buffers H_2CO_3,
because the combination of H^+ with HCO_3^- results in the regeneration of H_2CO_3:

$$H_2CO_3 + HCO_3^- \rightarrow HCO_3^- + H_2CO_3 \quad (10\text{-}21)$$

Consequently, CO_2 is buffered primarily by the intracellular buffers (see bel

There are other, quantitatively less important buffers in the extracellular fl
including inorganic phosphates (plasma phosphate concentration of 1 mmol
24 mmol/L of HCO_3^-) and the plasma proteins (Pr$^-$):

$$H^+ + Pr^- \leftrightarrow HPr \quad (10\text{-}22)$$

Intracellular and Bone Buffers

The primary intracellular buffers are proteins, organic and inorganic phosp
and, in the erythrocyte, hemoglobin (Hb$^-$):

$$H^+ + Hb^- \leftrightarrow HHb \quad (10\text{-}23)$$

In addition, bone represents an important site of buffering of acid and base
loads.[14,15,16] and[17] An acid load, for example, is associated with uptake of s
of the excess H^+ ions by bone. This can occur in exchange for surface K^+ and Na^+
and by the *dissolution of bone mineral*, resulting in the release of buffer
compounds, such as $NaHCO_3$ and $KHCO_3$ initially and then $CaCO_3$ and $CaHPO_4$,
into the extracellular fluid.[14,17,18] This buffering reaction appears to be initiated
part by the fall in the plasma HCO_3^- concentration, since a similar reduction in
extracellular pH induced by respiratory acidosis produces much less bone
dissolution.[17,18]

The loss of bone mineral with metabolic acidosis is not due simply to the
physiochemical release of calcium during the buffering reaction, since a sir
response is not seen in dead bone cells. This observation suggests that ce

must play a role and that both decreased osteoblastic and increased osteoc function have been demonstrated.[19] How this occurs is not known.

Although it is difficult to measure the exact contribution of bone buffering, estimated that as much as 40 percent of the buffering of an acute acid load place in bone.[20] The role of the bone buffers may be even greater in the pres of a chronic acid retention, as occurs in patients with chronic renal failure.[17,21,22] has been suggested that parathyroid hormone has a permissive effect on bo buffering,[23] but its physiologic importance remains uncertain.[17]

Bone and intracellular buffers also participate in the pH in the presence of loads. As an example, increased deposition of carbonate in bone has been

demonstrated after the administration of $NaHCO_3$.[20] In addition, the associated reduction in the H^+ concentration drives Eqs. (10-22) and (10-23) to the left, resulting in the release of H^+ from proteins and hemoglobin, and thereby tending raise the H^+ concentration toward normal.

Clinical Implications

One consequence of bone buffering is that *acid loading directly increases Ca^{2+} release from bone and urinary Ca^{2+} excretion*,[17,24,25] and[26] a relationship that may be an important contributing factor in some patients with calcium oxala disease. As described above, a normal diet results in the generation of app 50 to 100 meq of H^+ per day, most of which comes from the metabolism of sulfu containing amino acids. Increasing the acid load by increasing protein intak promote calcium stone formation via the following effects:[25,26] and[27]

- A significant rise in Ca^{2+} excretion.
- A reduction in the excretion of citrate by increasing its reabsorption in proximal tubule (see page 99). Urinary citrate is normally an important *inhibitor of stone formation, as it forms a dissociable but soluble complex with Ca^{2+}*, thereby decreasing the availability of free Ca^{2+} to precipitate with oxalate.[28]
- A reduction in urine pH. Although calcium oxalate precipitation is not pH dependent, the more acid urine promotes the conversion of urinary urat much less soluble uric acid ($urate + H^+ \rightarrow$ uric acid).[27,29] The possible subsequent precipitation of uric acid can then act as a nidus for calciur formation.[29]

Another significant clinical effect of bone buffering is the gradual reduction calcium stores in patients with end-stage renal disease, a disorder associa progressive acid retention due to impaired urinary acid excretion.[30] Another site of buffering in these patients is skeletal muscle, which can lead to protein bre

and muscle wasting.[31,32]

Chemical Buffering of Acids and Bases

Acidosis and Alkalosis

The arterial H^+ concentration is abnormal in a variety of clinical conditions (s Chaps. 17, 18, 19, 20 and 21). An increase in the H^+ concentration (or a decrease in the pH) is called *acidemia*; a decrease in the H^+ concentration (or an increase in th pH) is called *alkalemia*. Processes that tend to raise or lower the H^+ concentration are called acidosis and alkalosis, respectively.

In general, acidosis induces acidemia and alkalosis induces alkalemia. How difference between these phenomena becomes important in those patients v mixed acid-base disturbances in which both acidotic and alkalotic processe coexist. In this setting, the net pH may be acidemic, even though a disorde induces an alkalosis is also present (see Chap. 17).

From Eq. 10-11, 12-13, 14 and 15, a primary elevation in the P_{CO_2} causes acidemia, whereas a decrease in the P_{CO_2} causes alkalemia. Since the P_{CO_2} is regulated by the rate of

alveolar ventilation, these disturbances are referred to as *respiratory acidosis* and *respiratory alkalosis*.

The H^+ concentration also varies inversely with the plasma HCO_3^- concentration. Processes that primarily lower or raise the plasma HCO_3^- concentration are called *metabolic acidosis* and *metabolic alkalosis*, respectively.

Buffer responses to acid and base loads

The importance of the body buffers in protecting the pH can be appreciated data in Table 10-2. In these experiments, metabolic acidosis (with acidemia) w induced in dogs by the infusion of HCl. The dogs were nephrectomized to e the effect of changes in renal H^+ excretion. The total extracellular amounts of Na^+, K^+, HCO_3^-, and Cl^- were calculated from the product of the extracellular fluid (estimated from the volume of distribution of SO_4^{2-}, which is limited to the extracellular fluid) and the plasma electrolyte concentrations.

An average of 180 mmol of HCl was administered to each dog (the mean we being 18.9 kg). Let us assume that the total body water was 60 percent of t weight, or 11.3 liters. If 180 mmol of H^+ were distributed through 11.3 liters of distilled water, the H^+ concentration would be 16 mmol/L (pH of 1.80), a level t incompatible with life. In the intact animals, however, the arterial pH fell or 7.40 to 7.07 (H^+ concentration of 86 nanomol/L). This was associated with a reduction in the plasma HCO_3^- concentration from 24 to 7 mmol/L (by the

combination of extracellular HCO_3^- with the excess H^+ and with a compensatory increase in alveolar ventilation that lowered the P_{CO_2} to 25 mmHg. Thus, the body buffers were extremely effective in minimizing degree of acidemia.

Table 10-2 Summary of data from infusion of HCl into five nephrectomized dogs[a]

Weight, kg	18.9
HCl infused, mmol	180
Final arterial pH	7.07
Change in total extracellular quantity, mmol	
Na^+	+65
K^+	+28
HCO_3^-	-78
Cl^-	+170
Percent neutralized by Extracellular HCO_3^-	43
Intracellular buffers	57
Na^+ exchange	36
K^+ exchange	15
Cl^- entry	6

[a] Dat adapted from Swan RC, Pitts RF, *J Clin Invest* 34:215, 1955, by copyright permission of the American Society for Clinical Investigation.

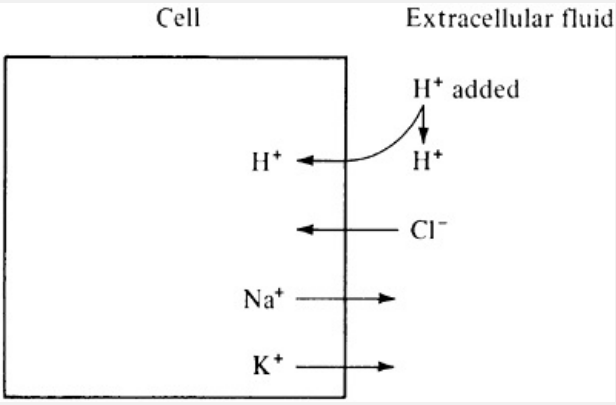

Figure 10-3 Effect of an HCl load on extracellular H^+, Na^+, Cl^-, and K^+. As H^+ enters the cells to be buffered, either Cl^- flows H^+ into the cells or intracellular Na^+ and K^+ leave the cells and move into the extracellular fluid. These ion are reversed when ions are removed from the extracellular fluid.

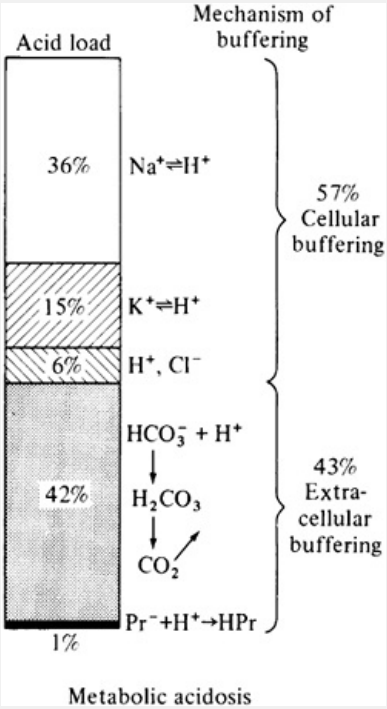

Figure 10-4 Mechanisms of buffering of strong acid infused intravenously in dog. (*From Pitts RF, Physiology of the Kidney and Body Fluids, 3rd ed, Copyright©1974 by Year Book Medical Publishers, Inc, Chicago. Used by permission. Adapted from Swan RC, Pitts RF, J Clin Invest 34:205, 1955, by copyright permission of the American Society for Clinical Investigation*)

The relative contributions of the intracellular and extracellular buffers to th can be estimated from the changes in the quantities of H^+, K^+, HCO_3^-, and Clin

the extracellular fluid. The administered H^+ ions either remain in the extracellular fluid or enter the cells (Fig. 10-3). The H^+ ions that stay in the extracellular fluid are buffered by HCO_3^- (and, to a much lesser degree, by the plasma proteins), resulting in a decrease in the amount of extracellular HCO_3^-. If HCO_3^- ions enter the cells, then, to maintain electroneutrality, either Cl^- will follow H^+ into the cells (a process that primarily occurs in red blood cells, where H^+ is buffered by Hb^-) or Na^+ and K^+ ions will leave the cells (and bone) and enter the extracellular fluid (Table 10-2). Of the 180 mmol of H^+ infused, 78 mmol has been buffered by HCO_3^-, 103 mmol has entered the cells: 65 mmol in exchange for Na^+, 28 mmol in exchange for K^+, and 10 mmol followed by Cl^-. (180 mmol of Cl^- was infused, but only 170 mmol remained in the extracellular fluid.) These results are depicted schematically in Fig. 10-4.

Buffering by the extracellular and intracellular buffers follows a characteristic course that is dependent upon the rapidity with which the administered H^+ ions move into the different fluid compartments. Buffering by plasma HCO_3^- occurs almost immediately, whereas approximately 15 min is required for H^+ to diffuse into the interstitial space to be buffered by interstitial HCO_3^-. Entry of H^+ into the cells occurs more slowly, as buffering by cell buffers is not complete until 2 to 4 h have elapsed.[33]

A potential serious complication of the transcellular exchange of H^+ for K^+ is that H^+ follows a H^+ load is an elevation in the plasma K^+ concentration, e.g., from the normal of 4 meq/L to as high as 6 to 7 meq/L in severe metabolic acidemia (see Chap. 12).[34] A similar increase may occur in the plasma Na^+ concentration, because Na^+ also leaves the cells. However, variations of several milliequivalents per liter are not physiologically important, since the normal plasma Na^+ concentration is approximately 140 meq/L.

The relative contribution of the HCO_3^- and nonbicarbonate buffers in the cells and bone to an acid load varies with the plasma HCO_3^- concentration.[13] In normal subjects, both buffer systems make roughly equivalent contributions. This does not apply, however, in metabolic acidosis or severe chronic respiratory alkalosis, disorders associated with a low plasma HCO_3^- concentration (see below). In these settings, the role of the nonbicarbonate buffers becomes increasingly important, since the cells and bone have a virtually limitless buffering capacity.[13]

Respiratory acidosis

The response to respiratory acidosis (high CO_2) differs from the response to metabolic acidosis in that there is virtually no extracellular buffering (as HCO_3^- is

not an effective buffer for H_2CO_3 [Eq. 10-11, 12, 13, 14, 15, 16, 17, 18, 19, 20 and 21]. As the P_{CO_2} increases, the elevation in H^+ concentration is initially minimized by a buffer-induced rise in the plasma HCO_3^- concentration. This HCO_3^- is derived from two major sources. Extracellular H_2CO_3 dissociates into HCO_3^- ions and H^+ ions, with the latter moving into the cells (and bone) in exchange for intracellular Na^+ and K^+, and HCO_3^- is released from erythrocytes in exchange for extracellular Cl^- (Fig. 10-5).

The latter process occurs in the following manner. CO_2 diffuses into the erythrocyte, where it combines with H_2O to form H_2CO_3. This reaction is catalyzed by the enzyme carbonic anhydrase. H_2CO_3 is then buffered by Hb:

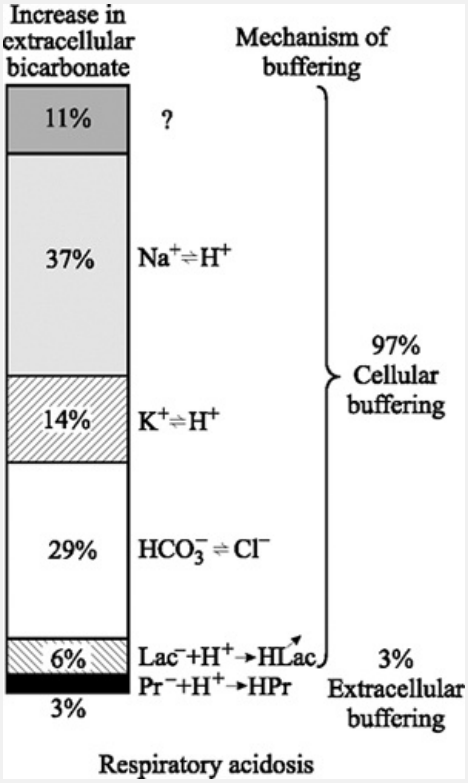

Figure 10-5 Mechanisms of buffering of CO_2 in respiratory acidosis in the dog. The source of approximately 11 percent of the increase in the extracellular HCO_3^- has not been identified. (From *Pitts RF: Physiology of the Kidney and Body Fluids, 3d ed. Copyright ©1974 by Year Book Medical Publishers, Inc, Chicago. Used by permission. Adapted from Giebisch G, Berger L, Pitts RF: J Clin Invest 34:231, 1955, by copyright permission of the American Society for Clinical Investigation.*)

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$$H_2CO_3 + Hb^- \rightarrow HHb + HCO_3^-$$

It is this HCO_3^- that moves into extracellular fluid. Of lesser importance is the

of H^+ by the plasma proteins and by extracellular lactate:

$$\text{Na lactate} + H_2CO_3 \rightarrow \text{lactic acid} + NaHCO_3$$

The lactic acid produced by this reaction is metabolized within the cells, ei
CO_2 and H_2O or via gluconeogenesis into glucose.

In humans, these buffers in the aggregate *increase the plasma HCO_3^- concentration approximately 1 mmol/L for each 10 mmHg elevation in P_{CO_2}* (see Chap. 20).

The degree to which this response protects the H^+ concentration can be appreciated if we calculate the effects of increasing the P_{CO_2} from 40 to 80 mmHg. If there is no buffering and the plasma HCO_3^- concentration remains constant, then the new H^+ concentration will be

$$[H^+] = 24 \times \frac{80}{24}$$
$$= 80 \text{ nanomol/L} \qquad (pH = 7.10)$$

However, a 40-mmHg elevation in the P_{CO_2} normally will induce roughly a 4 mmol/L increase in the plasma HCO_3^- concentration. In this setting,

$$[H^+] = 24 \times \frac{80}{28}$$
$$= 69 \text{ nanomol/L} \qquad (pH = 7.17)$$

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As illustrated by this example, the buffer-induced elevation in the plasma HCO_3^- concentration is not particularly effective in protecting the H^+ concentration in respiratory acidosis. The most effective defense against respiratory acidosis is a further increase in the plasma HCO_3^- concentration, produced by *enhanced renal H^+ excretion* (see Chap. 11). This response, which takes 4 to 5 days to reach completion, results in a *3.5 mmol/L elevation in the plasma HCO_3^- concentration for every 10 mmHg increase in the P_{CO_2}* (see Fig. 20-5). Thus, at a P_{CO_2} of 80 mmHg, the combined buffering and renal responses will raise the plasma HCO_3^- concentration from 24 to about 38 meq/L, resulting in much better protection of arterial H^+ concentration and pH:

$$[H^+] = 24 \times \frac{80}{38}$$
$$= 50 \text{ nanomol/L} \qquad (pH = 7.30)$$

The intracellular and extracellular buffers also protect the pH in metabolic or respiratory alkalosis, as the buffer reactions move in the opposite direction to those observed in the acidemic conditions. Thus, H^+ ions are released, not taken up, by the buffers. For example,

$$HPr \rightarrow H^+ + Pr^-$$
$$H_2PO_4^- \rightarrow H^+ + HPO_4^{2-}$$

These H^+ ions then react with HCO_3^-, resulting in an *appropriate reduction in the*

plasma HCO_3^- concentration, which tends to lower the elevated pH toward norm

To the degree that these H^+ ions are derived from cell buffers, their movement i the extracellular fluid occurs in exchange for extracellular K^+, which enters the cells. Thus, the plasma concentration of K^+ and Na^+, which tend to rise with acidemia, may fall with alkalemia.[34]

INTRACELLULAR PH

The intracellular pH can be measured using a variety of techniques, includi distribution of a weak acid or base, nuclear magnetic resonance spectrosco insertion of a H^+-sensitive microelectrode, and the use of fluorescent dyes.[35,36] In general, the cytosolic pH has been noted to be lower than that in the extrac fluid, although it varies from organ to organ. For example, at a normal extra pH of 7.40, the mean pH in skeletal or smooth muscle is about 7.06,[35] whereas that in the early proximal convoluted tubule is approximately 7.13.[37]

There is, however, one problem in interpretation of the intracellular pH. In *pH within the cell is not uniform* the value in the extracellular fluid, because of the presence of multiple compartments, including the cytosol, mitochondria,

endoplasmic reticulum, and nucleus.[2] As depicted in Fig. 10-6, a difference of approximately 0.5 pH unit is obtained when the cell pH of skeletal muscle is measured with both a weak acid, which is preferentially bound to the alkali in the cell, and a weak base, which is preferentially bound to the more acid the cell. At an extracellular pH of 7.40, for example, the respective values f intracellular pH are 7.17 and 6.69, respectively.

As a result of this heterogeneity, it is difficult to determine which pH reflec value that regulates the specific cellular function that is being studied. In t proximal tubular cell, for example, extracellular acidemia stimulates NH_4^+ production and secretion, primarily via the breakdown of glutamine (Chap. 11). It is thought that the initiating signal for this metabolic change is in part the parallel fal occurs in the intracellular pH.[38] However, studies using both nuclear magnetic resonance and the distribution of a weak acid suggest that although the cyt declines, the mitochondrial pH may remain relatively stable,[39,40] so that it may be that this increase in the transmitochondrial pH gradient, rather than the cytosolic pH, is the signal to alter the production of NH_4^+.

Several factors contribute to the regulation of intracellular pH, including th metabolic activity, tissue perfusion, and the extracellular pH. As

illustrated in Fig. 10-6, alterations in the pH of the extracellular fluid produce parallel, although lesser, changes within the cell.[36] The more efficient maintenance of intracellular pH is in part related to the greater buffering capacity within

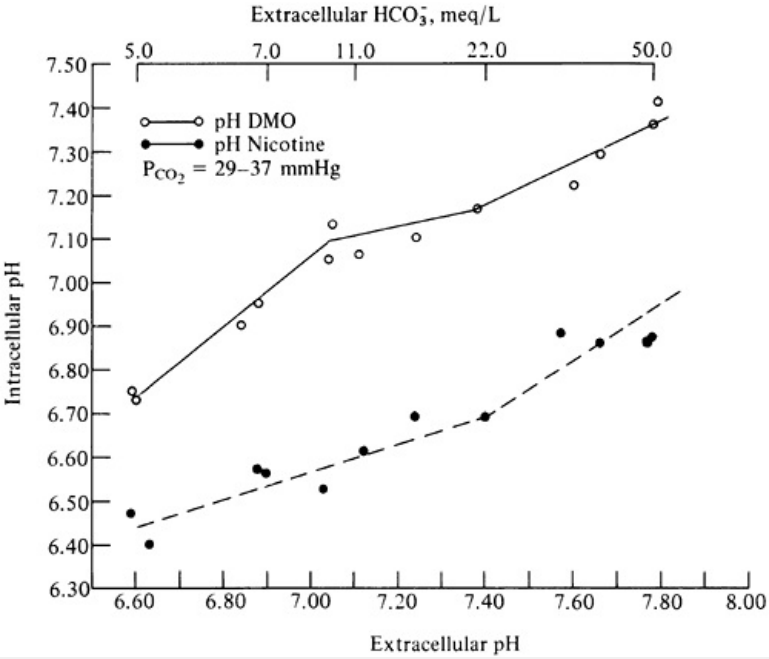

Figure 10-5 Relationship between skeletal muscle cell pH and the extracell pH in metabolic acidosis and alkalosis, in which the extracellular pH is ch by alterations in the plasma HCO_3^- concentration. A similar relationship is present in respiratory acidosis and alkalosis. The cell pH can be seen to heterogeneous, as evidenced by the difference between measuring the pH weak acid (DMO; 5,5-dimethyl-2,4-oxazolidinedione) or a weak base (nico (*From Adler, SJ Clin Invest 51:256, 1972, by copyright permission of the American Society for Clinical Investigation*)

This relationship between the pH in the two fluid compartments is extremely important in the clinical setting. The principal physiologic effect of changes on protein function. Since the cells are the functioning units in the body, it *intracellular pH that is of primary importance, yet it is only the extracellul (plasma) pH that can easily be measured in patients.* Fortunately, this still permits an accurate assessment of acid-base status, because of the direct relations between these two parameters.

The mechanism by which the cells sense alterations in extracellular pH is incompletely understood. Changes in the P_{CO_2} are presumably sensed directly, since CO_2 is lipid-soluble and can freely diffuse across the cell membranes. comparison, the effect of variations in the plasma HCO_3^- concentration is somewhat indirect. In the proximal convoluted tubule, for example, HCO_3^- enters the cell across the basolateral membrane via a Na^+-$3HCO_3^-$ carrier (see page 329). This process is stimulated in metabolic acidosis, since the associated reduction in the extr HCO_3^- concentration creates a favorable gradient for exit from the cell. The result is a fall in the intracellular pH, which, as will be described in th chapter, appears to be an important mediator of the appropriate increase in

NH^+_4 excretion that tends to raise the extracellular pH toward normal.

PROBLEMS

10-1 How do buffers minimize change in H^+ concentration? What factors determine how effective a buffer will be?

10-2 The sequential changes in the plasma HCO^-_3 concentration and arterial pH produced by the rapid intravenous administration of 90 meq of HCO^-_3 to a 70-kg man are depicted in the following table:

Time, min	HCO^-_3, meq/L	Arterial pH
0	24	7.40
10	32	7.51
20	29	7.48
180	27	7.45

a. **What accounts for the progressive fall in the plasma HCO^-_3 concentration between 10 and 180 min?**

b. **(b) How will acid-base balance be restored?**

10-3 If a patient has a PCO_2 that is fixed at 40 mmHg, what factors will determine how much the extracellular pH will fall after an acid load?

Appendix

Appendix: Measurement of intracellular pH

Newer techniques have largely replaced the indirect measurement of intrac
by determining the distribution of a weak acid or base between the extracel
the intracellular fluids. Fluorescent dyes, for example, permit continuous st
active, functioning cells under conditions in which the pH may be changing.
comparison, the weak acid method is somewhat limited in that continuous
measurements cannot be made. Nevertheless, a review of the latter techniq
useful at this time, because it demonstrates how the basic principles discus
this chapter can be applied.

The primary weak acid used has been DMO, which has a pK_a of 6.13 at the concentration and temperature of the body fluids—37°C. Thus, the Henderson-Hasselbalch equation for the reaction

$$HDMO \leftrightarrow H^+ + DMO^-$$

can be written as

$$pH = 6.13 + \log \frac{[DMO^-]}{[HDMO]} \qquad (10\text{-}24)$$

With DMO, two assumptions are made: (1) that the pK_a in the cell is the same as that in the extracellular fluid; and (2) that the undissociated acid (HDMO), being soluble, equilibrates across the cell membrane, whereas the polar compound DMO^- crosses the membrane very slowly if at all (Fig. 10-7). Using these assumptions, the intracellular pH can be estimated in the following way:

1. The extracellular pH is measured and, from Eq. (10-24), the $[DMO^-]/[HDMO]$ ratio is calculated. At the normal pH of 7.40, this ratio is approximately 1/1.
2. The total extracellular DMO concentration, that is, $[HDMO] + [DMO^-]$, is measured and, since the $[DMO^-]/[HDMO]$ ratio is known, the HDMO concentration in the extracellular fluid can be calculated; this value is assumed to be the same as that in the cell.
3. The extracellular and the intracellular volumes are measured by using substances limited to these compartments. For example, the distribution of

tritiated water (which equilibrates between the extracellular and intracellular compartments) and of sulfate or mannitol (which cannot enter cells) can be used to estimate the total water space and the extracellular fluid volume, respectively. The intracellular fluid volume is equal to the difference between these two measurements.

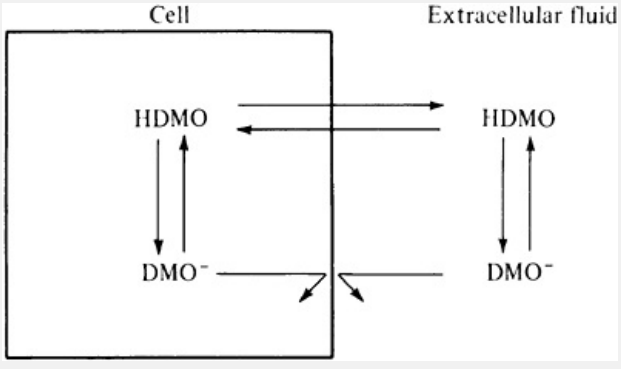

Figure 10-7 Distribution of HDMO and DMO^- between the cell and the extracellular fluid. Since HDMO is lipid-soluble, it is able to equilibrate across the cell membrane, reaching equal concentrations in both compartments. Once in the cell, HDMO dissociates into H^+ and DMO^- (the latter is polar and cannot freely diffuse across the cell membrane). The extr

this reaction is dependent upon the cell pH.

4. The total quantity of DMO in the extracellular fluid is calculated from th of the extracellular volume and the extracellular DMO concentration.
5. The total DMO in the cell is calculated from known amount of DMO adm minus the quantity in the extracellular fluid.
6. The cell DMO concentration is then calculated from the total DMO in th divided by the intracellular volume.
7. Since the DMO concentration in the cell equals the total DMO concentrati the cell minus the HDMO concentration in the cell (both of which are kn intracellular pH can be calculated by inserting these values into Eq. (1(

$$pH = 6.13 + \log \frac{[DMO]_{cell} - [HDMO]_{cell}}{[HDMO]_{cell}}$$

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Footnotes

* In the aqueous environment in the body, H^+ ions combine with H_2O and exist primarily as hydronium ions, H_3O^+. For simplicity, H^+ will be used in place of H_3O^+ for the remainder of this discussion.

† This reaction actually should be written

$$H_2O + H_2O \leftrightarrow H_3O^+ + OH^-$$

‡ The membrane potential and the pH are actually proportional to the *activity* of the H^+, that is, to the random movement of H^+ across the membrane, not to its molar concentration. Although the activity (aH+) of H^+ is directly proportional to the H^+ concentration,

$$a_{H^+} = \gamma[H^+]$$

the value of gamma is dependent upon the ionic strength of the solution. In concentrated ionic solutions, ionic interaction between H^+ ions can retard the random movement of H^+ so that its activity is significantly less than its concentration. However, the body fluids are relatively dilute, and it can be without much error that gamma is equal to 1 and therefore H^+ activity is equal to the H^+ concentration.[5]

¶ An additional reaction can occur, as HCO_3^- dissociate into hydrogen and carbonate ions

$$HCO_3^- \leftrightarrow H^+ + CO_3^{2-}$$

However, the pK of this reaction is 9.8, so that only trace elements of carbon present in the physiologic pH range.

** Since HCO_3 is a univalent anion, this value also represents a concentration meq/L.

†† An alternative explanation for the intracellular movement of Cl^- is that Cl^- enters the red cell in exchange for intracellular HCO_3^-. Thus HCO_3^- moves into the extracellular fluid and buffers the excess H^+. The net effect is the same as that of HCl entry into the cell.

‡‡‡ It is important to remember that the H^+ concentration is determined by the ratio between, not the absolute levels of, P_{CO_2} and HCO_3^-. Thus, the H^+ concentration can be maintained at or near normal when there are parallel changes in the P_{CO_2} and plasma HCO_3^- concentration.

¶¶ Although similar buffers are involved, the percentage contributions of the individual intracellular and extracellular buffers in alkalemia are somewhat different from those shown in Figs. 10-4 and 10-5 for acidemia.[10]

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Chapter Eleven
Regulation of Acid-Base Balance

INTRODUCTION

Acid-base homeostasis can be easily understood if it is viewed in terms of the HCO_3^-/CO_2 buffering system:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2 \qquad (11\text{-}1)$$

At equilibrium, the relationship between the reactants can be expressed by the mass action (see Chap. 10):

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]} \qquad (11\text{-}2)$$

or by the Henderson-Hasselbalch equation,

$$pH = 6.10 + \log \frac{[HCO_3^-]}{0.03 P_{CO_2}} \qquad (11\text{-}3)$$

This system plays a central role in the maintenance of acid-base balance, b the HCO_3 concentration and the P_{CO_2} can be *regulated independently*, the former

by changes in renal H^+ excretion and the latter by changes in the rate of alveo ventilation.

These processes are extremely important, because acids and to a lesser de bases are continually being added to the body through endogenous metabo processes. The metabolism of carbohydrates and fats (primarily derived fro diet) results in the production of approximately 15,000 mmol of CO_2 daily. Since CO_2 combines with H_2O to form H_2CO_3, severe acidemia would ensue if this CO_2 were not excreted by the lungs.

In addition, the metabolism of proteins and other substances results in the generation of noncarbonic acids and bases[1,2,3]. The H^+ ions are derived mostly from the oxidation of sulfur-containing (methionine and cysteine) an (arginine and lysine) amino acids, and the hydrolysis of that component of phosphate that exists as $R\text{-}H_2PO_4^-$:

$$\begin{aligned}
&\text{Methionine} && \rightarrow && \text{glucose} + \text{urea} + SO_4^{2-} + 2H^+ \\
&\text{Arginine}^+ && \rightarrow && \text{glucose (or } CO_2) + \text{urea} + H^+ \\
&R\text{-}H_2PO_4 + H_2O && \rightarrow && ROH + 0.8\,HPO_4^{2-}/0.2\,H_2PO_4^- + 1.8\,H^+
\end{aligned}$$

The major sources of alkali, on the other hand, are the metabolism of anior acids (glutamate and asparatate) and the oxidation or utilization for glucon of organic anions (such as citrate and lactate):

$$\begin{aligned} \text{Glutamate}^- + H^+ &\rightarrow \text{glucose} + \text{urea} \\ \text{Citrate}^- + 4.5O_2 &\rightarrow 5CO_2 + 3H_2O + HCO_3^- \\ \text{Lactate}^- + H^+ &\rightarrow \text{glucose} + CO_2 \end{aligned}$$

(The consumption of H^+ ions in the first and third reactions is equivalent to the generation of new HCO_3^- ions in the body.) On a normal western diet, the net e is the production of *50 to 100 meq of* H^+ *per day* in adults.[1,2] and[3]

The homeostatic response to these acid and base loads occurs in three sta

1. Chemical buffering by the extracellular and intracellular buffers (see Chapter 6)
2. Changes in alveolar ventilation to control the P_{CO_2}
3. Alterations in renal H^+ excretion to regulate the plasma HCO_3^- concentration

As an example, the H_2SO_4 produced from the oxidation of sulfur-containing ami acids is initially buffered in the extracellular fluid by HCO_3^-

$$H_2SO_4 + 2NaHCO_3 \rightarrow Na_2SO_4 + 2H_2CO_3 \rightarrow 2H_2O + CO_2 \quad (11\text{-}4)$$

Although this reaction minimizes the increase in the extracellular H^+ concentration, the excess H^+ ions must still be excreted by the kidney to prevent progressive depletion of HCO_3^- and the other body buffers and the development of metabo acidosis. The CO_2 generated by this reaction is excreted by the lungs.

Under normal conditions, the steady state is preserved, and renal H^+ excretion varies directly with the rate of H^+ production (Fig. 11-1).[1,3] If acid generation is enhanced, for example, some of the excess H^+ is initially retained, resulting in a slight redu in the plasma HCO_3^- concentration (which may be less than 1 meq/L) and pH. This minimal degree of acidemia, which may be too small to be detected clinicall least part of the stimulus to increase net renal acid excretion to a level sim new higher rate of acid generation.

The net effect is that the plasma H^+ concentration and pH are maintained within narrow limits. The normal values for these parameters are:

	pH	$[H^+]$, nanoeq/L	P_{CO_2}, mmHg	$[HCO_3^-]$, meq/L
Arterial	7.37–7.43	37–43	36–44	22–26
Venous	7.32–7.38	42–48	42–50	23–27

The decrease in pH (and increase in H^+ concentration) in venous blood is due to t uptake of metabolically produced CO_2 in the capillary circulation.

The remainder of this chapter will mostly discuss the general mechanisms i renal H^+ excretion and the factors responsible for the regulation of

these processes. It is useful to summarize the steps involved in this comple in advance:

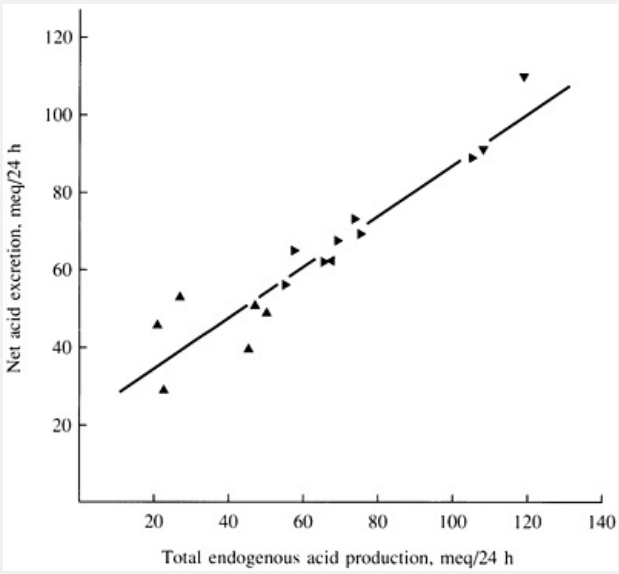

Figure 11-1 Relationship between net renal acid excretion and endogenous production in the steady state in normal subjects ingesting different diets varying acid content. (*From Kurtz I, Maher T, Hulter HN, et al: Kidney Int 24:670, 1983; and Lennon EJ, Lemann J Jr, Litzow JR: J Clin Invest 45:1601, 1966. Reprinted by permission from Kidney International and the American Society for Clinical Investigation.*)

1. The kidneys must excrete the 50 to 100 meq of noncarbonic acid genera each day.
2. This is achieved by H^+ secretion, although the major mechanisms are differ in the proximal tubule and thick ascending limb of the loop of Henle (Na^+-H^+ exchange) and in the collecting tubules (H^+-ATPase pump).
3. The daily acid load cannot be excreted as free acid, since the free H^+ concentration in the urine is extremely low (≤0.05 meq/L) in the physiol range.
4. The daily acid load also cannot be excreted *unless all of the filtered*

HCO_3^- has been reabsorbed because HCO_3^- loss in the urine is equivalent to adding H^+ ions to the body.

5. Secreted H^+ ions are excreted by binding either to filtered buffers, such as HPO_4^{2-} and creatinine, or to NH_3 to form NH_4^+. NH_4^+ is generated from the metabolism of glutamine in the proximal tubule; the rate at which this occurs can be varied according to physiologic needs.
6. The extracellular pH is the primary physiologic regulator of net acid excretion. In pathophysiologic states, however, the effective circulating volume, aldosterone, and the plasma K^+ concentration all can affect acid excretion, independent of changes in the systemic pH.

RENAL HYDROGEN EXCRETION

The kidneys contribute to acid-base balance by regulating H^+ excretion so that the plasma HCO_3^- concentration remains within appropriate limits. This involves two basic steps: (1) reabsorption of the filtered HCO_3^- and (2) excretion of the 50 to 100 meq of H^+ produced per day.

It is essential to appreciate that loss of filtered HCO_3^- in the urine is equivalent to the addition of H^+ to the body, since both are derived from the dissociation of H_2CO_3. As a result, virtually all of the filtered HCO_3^- must be reabsorbed before the dietary H^+ load can be excreted. The quantitative importance of this process cannot be underestimated. A normal subject with a glomerular filtration rate (GFR) of 180 L/day (125 mL/min) and a plasma HCO_3^- concentration of

24 meq/L filters and then must reabsorb approximately *4200 meq* of HCO_3^- each day.

The second step in renal acid-base regulation, excretion of the 50 to 100 meq H^+ load, is accomplished by the combination of H^+ ions either with urinary buffers such as HPO_4^{2-} (referred to as titratable acidity) or with ammonia to form ammonium ($NH_3 + H^+ \rightarrow NH_4^+$). These processes are important, because *excretion of free H^+ ions is minimal*. The lowest urine pH that can be achieved in humans is 4.5. Although this is almost 1000 times (3 log units) more acid than the extracellular fluid, it still represents an extremely low free H^+ concentration of less than 0.04 meq/L. Remember that the free H^+ concentration at an extracellular pH of 7.40 is only 40 nanomol/L, *one-millionth* the size of the daily acid load.

The reabsorption of HCO_3^- and the formation of titratable acidity and NH_4^+ all involve H^+ secretion from the tubular cell into the lumen (Figure 11-2).[4,5] Three initial points need to be emphasized:

1. The secreted H^+ ions are generated within the tubular cell from the dissoc of H_2O. This process also results in the equimolar production of OH^- ions
2. These OH^- ions bind to the active zinc-containing site of intracellular *anhydrase*; they then combine with CO_2 to form HCO_3^- ions, which are released into the cytosol and returned to the systemic circulation across the bas membrane.[4,6] The net effect is that *secretion of each H^+ ion is associated with the generation of one HCO_3^- ion in the plasma*. If the secreted H^+ combines with filtered HCO_3^-, the result is HCO_3^- reabsorption (Fig. 11-2). This maintains the plasma HCO_3^- concentration by preventing HCO_3^- loss in the urine. If, however, the secreted H^+ combines with HPO_4^{2-} or NH_3, a *new HCO_3^-* is added to the peritubular capillary blood (Figs. 11-3 and 11-4). This results in an increase in the plasma HCO_3^- concentration to *replace the HCO_3^- lost in buffering the daily H^+ load* (Eq. 11-4).
3. Different mechanisms are involved in proximal and distal acidification (s below).

Net Acid Excretion

Since the urinary concentration of free H^+ is negligible, the net quantity of H^+ excreted in the urine is equal to the amount excreted as titratable acidity and NH_4^+ minus any H^+ added to the body because of urinary loss of HCO_3^-:

$$\text{Net acid excretion} = \text{titratable acidity} + NH_4^- - \text{urinary } HCO_3^- \qquad (11\text{-}5)$$

In the steady state, the net amount of H^+ excreted is roughly equal to the normal H^+ load of 50 to 100 meq/day (Fig. 11-1). However, this value can exceed 300 meq/day (primarily through enhanced NH_4^+ excretion) if acid production is increased (see below). Net H^+ excretion also can have a negative value if a large amount of HCO_3^- is lost in the urine. This may appropriately occur after the ingestion of citra containing fruit juices, since the metabolism of citrate results in the genera HCO_3^-. How the kidney is able to make these homeostatic adjustments will b discussed below (see "Regulation of Renal Hydrogen Excretion: Extracellular p below).

Proximal Acidification

The primary step in proximal acidification is the secretion of H^+ by the Na^+-H^+ exchanger (or antiporter) in the luminal membrane.[7,8,9,10] This transport protein,

which also appears to mediate most of the HCO_3^- reabsorption in the thick ascending limb of the loop of Henle,[11,12] preferentially binds filtered Na^+ at its external site and intracellular H^+ at its internal site (Fig. 11-2).[10]

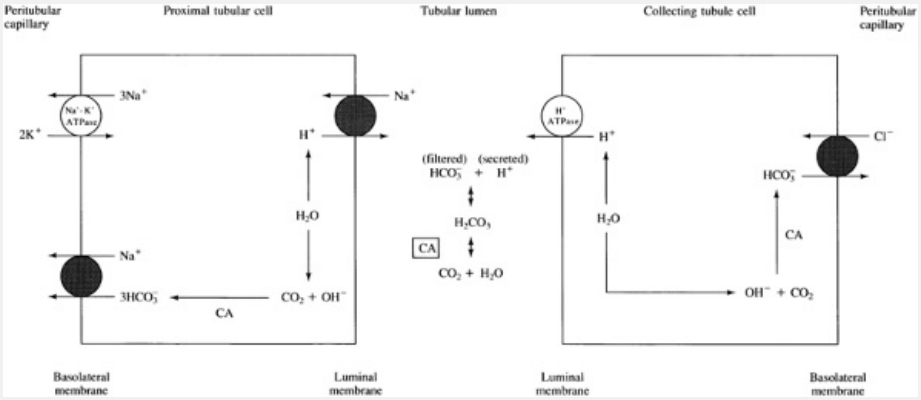

Figure 11-2 Major cellular and luminal events in bicarbonate reabsorption i proximal tubule and the collecting tubules. Intracellular CO_2 breaks down into a H^+ ion and a OH^- ion. The latter combines with CO_2 to form HCO_3^-, via a reaction catalyzed by carbonic anhydrase (CA). In the proximal tubule, the H^+ is secreted into the lumen by the Na^+-H^+ exchanger, whereas the HCO_3^- is returned to the systemic circulation primarily by the $3HCO_3^-$-Na^+ cotransporter. These same processes occur in the collecting tubules, although they are respectively mediated by an H^+-ATPase pump in the luminal membrane and a Cl^--HCO_3^- exchanger in the basolateral membrane. The secreted H^+ ions combine with filtered HCO_3^- to form carbonic acid (H_2CO_3) and then CO_2 + H_2O, which can be passively reabsorbed. This dissociation of carbonic acid is facilitated when luminal carbonic anhydrase (CA in box) is present, as occ the early proximal tubule (see text). The net effect is HCO_3^- reabsorption, even though the HCO_3^- ions returned to the systemic circulation are not the same those that were filtered. Although not shown, the collecting tubule cells a H^+-K^+-ATPase pumps in the luminal membrane that are primarily involved i reabsorption.

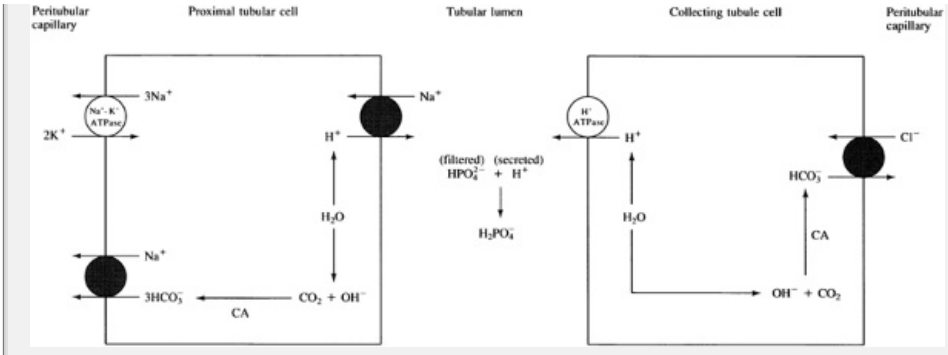

Figure 11-3 Formation of titratable acidity, which is primarily due to bufferi secreted H^+ by filtered HPO_4^{2-} and, to a lesser degree, other buffers such as creatinine. Note that a new HCO_3^- is returned to the peritubular capillary fo every H^+ ion that is secreted.

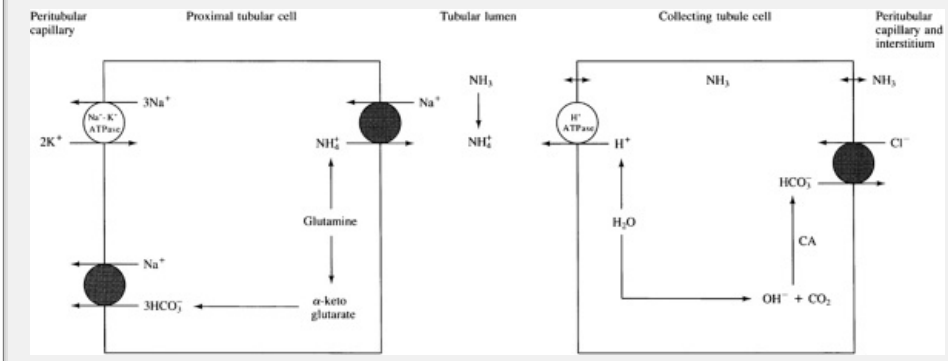

Figure 11-4 Formation of urinary ammonium (NH_4^+). In the proximal tubule, glutamine is taken up by the cells and metabolized into NH_4^+ and HCO_3^- ha-ketoglutarate. Utilization of the latter results in the generation of HCO_3^-, whereas NH_4^+ substitutes for H^+ on the Na^+-H^+ exchanger and is then secreted directly into the lumen. The mechanism is different in the collecting tubul nonpolar, lipid-soluble NH_3 diffused from the interstitial fluid into the lumen, where it combines with secreted H^+ to form NH_4^+. Ammonium is lipid-insoluble and is therefore unable to back-diffuse out of the lumen. Note that each NH_4^+ ion that is excreted is associated with the generation of a new HCO_3^- returned to the peritubular capillary.

A H^+-ATPase pump, similar to that in the distal nephron, is also present in t proximal tubule.[8,13] Via the use of different experimental methodologies, inclu genetic deletion, it appears that the Na^+-H^+ exchanger is responsible for

approximately two-thirds of proximal H^+ secretion, with the H^+-ATPase pump being responsible for the remainder.[9,14]

The *energy for Na^+–H^+ exchange is indirectly provided by the H^+–K^+-ATPase pump in the basolateral membrane.* As described in chap. 3, this pump transports reabsorbed Na^+ into the peritubular capillary and also has two other important effects: It maintains the effective cell Na^+ concentration at a relatively low level (10 to 30 meq/L), and it creates a negative electrical potential in the cell interior. The negative potential is induced by the loss of cation from the cell, because of the 3 Na^+ : 2 K^+ stoichiometry of the pump and the back-diffusion of most of the K^+ out of the cell through K^+ channels in the basolateral membrane. The low cell Na^+ concentration creates a favorable gradient for the passive diffusion of Na^+ into the cell that is large enough to drive H^+ secretion against a concentration gradient via electroneutral Na^+–H^+ exchange.

Proximal acidification also requires that the HCO_3^- formed within the cell be returned to the systemic circulation. As depicted in Fig. 11-2, this is primarily achieved by a Na^+–$3HCO_3^-$ cotransporter in the basolateral membrane, although a Cl–HCO_3 exchanger also is present, particularly in the S3 segment.[11,12,13,14,15,16] and [17] The Na^+–$3HCO_3^-$ transporter (which may actually function as a CO_3^{2-}:Na^+:HCO_3^- carrier)[17] results in the net movement of negative charge. The energy for this process is provided by the electronegative potential within the cell that is created by the Na^+–K^+-ATPase pump.[18]

Distal Acidification

H^+ secretion in the distal nephron primarily occurs in *intercalated cells* in the cortical collecting tubule and in the cells in the outer and inner medullary collecting tubules,[19,20,21] and [22] the distal tubule also may contribute but appears to be quantitatively less important.[23] As illustrated in Fig. 11-2, there are three main characteristics of distal acidification:

1. H^+ secretion is mediated by active secretory pumps in the luminal membrane.[24,25,26,27] and [28] Both H^+-ATPase and H^+–K^+-ATPase pumps are present.[24,29,30] The latter is an exchange pump, leading to H^+ secretion and K^+ reabsorption; its main role may be in minimizing urinary K^+ loss during hypokalemia rather than in regulating acid-base balance (see page 399).[24,27,31] Following appropriate

stimuli, such as systemic acidemia (see below), cytoplasmic vesicles containing the H^+-ATPase pumps move to fuse with the luminal membrane, resulting in H^+ secretion.[32] Electroneutrality is maintained in this setting by concurrent

secretion of Cl^- via voltage-dependent mechanisms.[19,21] Note that the Na^+-H^+ antiporter would not be an efficient mechanism of distal acidification, s activity of this carrier is limited by the transcellular gradient for Na^+ that provides the energy for H^+ secretion. This gradient is diminished in the collecting t as a result of the reduction in the tubular fluid Na^+ concentration, which can fall below 30 meq/L in the cortical collecting tubule and, in states of volume depletion, below 5 meq/L in the inner medullary collecting tubule. Furth the gradient against which H^+ must be secreted is markedly increased in the segments. A urine pH of 4.8, for example, represents an H^+ concentration that is 400 times (2.6 log units) greater than that in the extracellular fluid. The effect is that H^+ secretion by Na^+-H^+ exchange would require a nonphysiologi cell Na^+ concentration well below 1 meq/L. (There is evidence of a basol Na^+-H^+ exchanger in the medullary collecting duct; it is likely that this transporter is primarily involved in the regulation of cell pH rather than acid-base balance.[33,34])

2. The H^+ secretory cells in the distal nephron do not transport Na^+, since they have few if any of the luminal membrane Na^+ channels or transporters that are required for the entry of luminal Na^+ into the cell.[19,35] However, H^+ secretion by the intercalated cells in the cortical collecting tubule is indirectly in by Na^+ reabsorption in the adjacent *principal* cells. The transport of cationic Na^+ through Na^+ channels in the luminal membrane makes the tubular flui relatively electronegative. This electrical gradient can affect acid hand ways: It promotes H^+ accumulation in the lumen by minimizing the degree o back-diffusion,[36,37] and it facilitates the passive reabsorption of HCO_3^-.[23]

3. Bicarbonate exit is mediated by a Cl^-/HCO_3^- exchanger in the basolateral membrane, thereby returning HCO_3^- to the systemic circulation.[17,38] This protein is a truncated form of the Cl^-/HCO_3^- exchanger in red cells (which is also called band 3 protein).[39] The energy for Cl^-/HCO_3^- exchange is provided by the inward gradient for Cl^-, since the Cl^- concentration in the cells is relatively low.

Regulation of the H^+-ATPase secretory pumps appears to be mediated by a pro of membrane insertion and recycling that is similar to the effect of antidiure hormone on luminal membrane water channels (see Chapter 8).[32,40] In the medullary collecting tubule and many of the intercalated cells in the cortical collectin cytoplasmic H^+ pumps are inserted into the luminal membrane with an acid loa thereby facilitating excretion of the excess acid. On the other hand, an alka results in recycling of these transporters from the luminal membrane to cyto vesicles.[40]

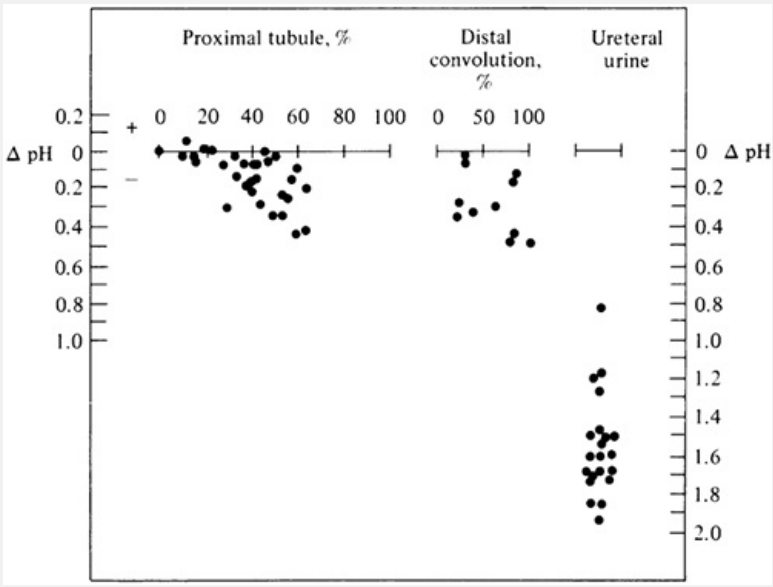

Figure 11-6 Change in pH (Delta pH) of the tubular fluid along the nephron the rat. *(From Gottschalk CW, Lassiter W, William E, , Myle M, J Physiol 198:581, 1960 with permission.)*

P.335

The net effect of H^+ secretion in the collecting tubules is illustrated in Fig. 11-5. The tubular fluid pH falls by about 0.6 units in the proximal tubule; is relatively the loop of Henle and distal tubule, which do not play a major role in urinar acidification; and then falls to its lowest level in the collecting tubules (rep in Fig. 11-5 as the difference between the distal tubule and the final urine).[41]

Impairment of this distal H^+ secretory process results in a reduced net acid excretion, metabolic acidosis, and urine pH that is inappropriately high; thi is called type 1 (distal) renal tubular acidosis. A number of different defect directly or indirectly cause this problem. Patients with Sjögren's syndrome described in whom there is complete absence of the H^+-ATPase pumps in the intercalated cells.[42,43] How immunologic injury leads to this change is not kno Another mechanism is a mutation in the basolateral Cl^-/HCO_3^- exchanger.[44]

The preceding discussion has emphasized the function of the type A interca cells. There is also a second type of intercalated cell (type B) in the cortic collecting tubule that can insert H^+ pumps into the luminal membrane with an acid load or into the basolateral membrane with an alkaline load.[40] The latter process allows HCO_3^- to be appropriately secreted rather than reabsorbed (se below).

Bicarbonate Reabsorption

Approximately 90 percent of the filtered HCO_3^- is reabsorbed in the proximal tubule

and most of this occurs in the first 1 to 2 mm of this segment.[45,46] The marked reabsorptive capacity of the early proximal tubule appears to be mediated

by an increased number of Na^+-H^+ exchangers and enhanced permeability to HCO_3^-.[47] The remaining 10 percent of the filtered HCO_3^- is reabsorbed in the more distal segments,[4] and most of this occurs in the thick ascending limb (primarily Na^+-H^+ exchange),[11,12] and in the outer medullary collecting tubule.[19,20,21]

Carbonic anhydrase and disequilibrium pH

Carbonic anhydrase within the tubular cells plays a central role in HCO_3^- reabsorption by facilitating the formation of HCO_3^- from the combination of OH^- ions with CO_2 (Fig. 11-2).[6,48,49,50] and[51] The role of *luminal* carbonic anhydrase in the proximal tubule is less well appreciated. As H^+ is secreted, two separate reactions occur in the tubular lumen (Fig. 11-2): 1 the combination of H^+ with filtered HCO_3^- to form H_2CO_3 and 2 the dehydration of H_2CO_3 into $CO_2 + H_2O$, which are then reabsorbed:

$$H^+ + HCO_3^- \overset{1}{\leftrightarrow} H_2CO_3 \overset{2}{\leftrightarrow} CO_2 + H_2O \qquad (11\text{-}6)$$

Step 2, the dehydration of H_2CO_3 into $CO_2 + H_2O$, normally proceeds relatively slowly. However, this reaction is accelerated in the early proximal tubule because brush border of the tubular cells contains carbonic anhydrase.[48,49] Consequently, there is no accumulation of H_2CO_3 in the proximal tubular fluid. From the law of mass action, the maintenance of a low H_2CO_3 concentration drives reaction 1 in Eq. 11-6 to the right, thereby keeping the H^+ concentration at a relatively low level. In general, the tubular fluid pH falls only 0.6 pH unit (from 7.40 in the filtrate to 6.80 by the end of the proximal convoluted tubule), despite the reabsorption of the majority of the filtered HCO_3^- (Fig. 11-5).[41]

This response is extremely important, since, as noted above, the gradient against which H^+ is secreted by the Na^+-H^+ antiporter cannot exceed the favorable inward gradient for Na^+. By minimizing the increase in the tubular fluid H^+ concentration, luminal carbonic anhydrase minimizes the gradient against which H^+ is secreted, thereby allowing continued H^+ secretion and HCO_3^- reabsorption.

The contribution of this system can be appreciated from the response to the administration of a carbonic anhydrase inhibitor that enters the cells to a limited degree and therefore inhibits the luminal but not the intracellular enzyme.[48,49] In this setting, the dehydration of H_2CO_3 in the lumen is slowed, resulting in increases in the H_2CO_3 and H^+ concentrations and thereby *impairing proximal HCO_3^- reabsorption by up to 80 percent*.[49] This ability to induce a HCO_3^- diuresis makes a carbonic anhydrase inhibitor useful in the treatment of some patients with r

alkalosis (see Chap. 18).

The role of luminal carbonic anhydrase can also be appreciated by comparing the function of the middle (S_2) and late (S_3) segments of the proximal tubule (Figure 11-2). Luminal carbonic anhydrase is present in the former, but absent in the latter.[51,52] As shown in the tubular perfusion experiments in Figure 11-6, both segments can lower the tubular fluid pH by 0.6 to 0.8 unit. This is associated with a marked reduction in the luminal HCO_3^- concentration in the early proximal tubule, as a result of a relatively high rate of HCO_3^- reabsorption. In

comparison, there is relatively little HCO_3^- transport in the S_3 segment, since, in the absence of luminal carbonic anhydrase, secreted H^+ and HCO_3^- accumulate in the tubular fluid, producing a rapid fall in luminal pH that limits further H^+ secretion.

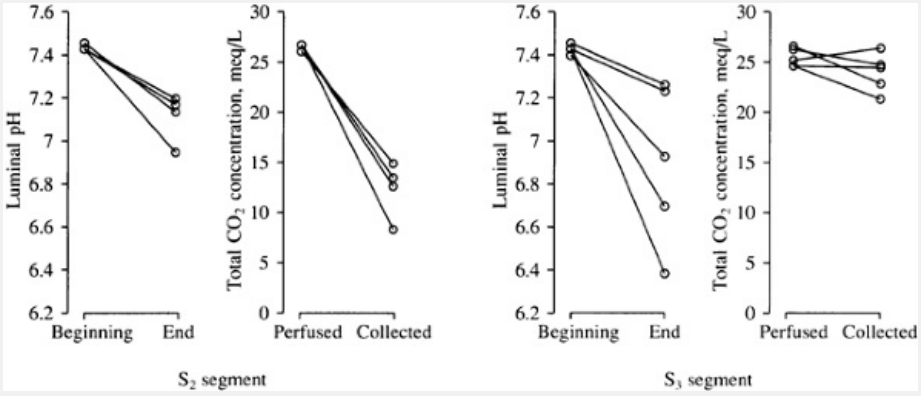

Figure 11-6 Changes in luminal (tubular fluid) pH and total CO_2 concentration as perfusion fluid flows through the S_2 (mid) and S_3 (late) segments of the proximal tubule. The total CO_2 concentration is equal to the sum of the concentrations of HCO_3^- and of dissolved CO_2 (equal to 0.03 times P_{CO_2}; see page 310). The S_2 segment contains carbonic anhydrase in the lumen; as a result, H^+ secretion results in a fall in luminal pH and in total CO_2 concentration, since a substantial amount of HCO_3^- reabsorption has occurred. In comparison, the S_3 segment lacks luminal carbonic anhydrase. Consequently, the luminal pH falls to a degree, even though there has been a relatively small amount of H^+ secretion that is insufficient to lower the total CO_2 concentration. This segment also demonstrates a disequilibrium pH, as the measured value is 6.89, while the calculated value is 7.35 (similar to that in the initial perfusate). The lack of change in the calculated pH from that in the perfusate is a reflection of the stable total CO_2 concentration, whereas the reduction in the measured pH is a reflection of the accumulation of CO_2. There is no disequilibrium pH in the S_2 segment, as the measured and calculated values are identical. (*Adapted from Kurtz I, Star R, Balaban RS, et al: J Clin Invest 78:989, 1986, by copyright permission of the American Society for Clinical Investigation.*)

It is also possible to demonstrate a *disequilibrium pH* in those segments that lack luminal carbonic anhydrase (the S3 segment, the cortical collecting tubule, and m of the medullary collecting tubule).[48,52,53] and[54] If, for example, the tubular fluid P_{CO_2} and HCO_3^- are measured in the late proximal tubule, the pH can be calc from the Henderson-Hasselbalch equation (Eq. 11-1). However, the *measured pH is almost 0.5 pH unit below the calculated value* (6.89 versus 7.35 in the S3 segment), a difference that is referred to as a *disequilibrium pH*.[48,52]

The error in the calculated pH results from the fact that the pK' of 6.1 cannot be applied to Eq. 11-6 only when the H_2CO_3 concentration is relatively low in relation the dissolved CO_2 and HCO_3^- concentrations (see page 308). The 0.5-unit pH difference in this setting is presumably due to the accumulation of excess a H_2CO_3. The disequilibrium pH can be dissipated by the addition of

carbonic anhydrase to the tubular fluid and is absent in those segments tha this enzyme.[52,54]

The uneven distribution of luminal carbonic anhydrase may play an importa urinary acidification. The early proximal tubule has this enzyme and is able reabsorb about 90 percent of the filtered HCO_3^-. The middle part of the outer medullary collecting tubule also contains luminal carbonic anhydrase and is the most important distal site of HCO_3^- reabsorption.[54] and[21] The other distal segments, in comparison, lack luminal carbonic anhydrase and are less able to reabsorb HCO_3^-; however, they play an *essential role in* NH_4^+ *excretion*, since the exaggerated reduction in tubular fluid pH promotes the diffusion of NH_3 into the lumen, where it combines with the excess H^+ and is trapped as NH_4^+ (see "Ammonium Excretion," below).[5,52,53] and[54]

Bicarbonate secretion

Virtually all of the filtered HCO_3^- is reabsorbed in normal subjects, in whom there a requirement to excrete the daily acid load. However, loss of the HCO_3^- in the urine is an appropriate response in patients with metabolic alkalosis (high arterial p plasma HCO_3^- concentration). Although this HCO_3^- diuresis can be achieved by reabsorbing less of the filtered HCO_3^-, it appears that *HCO_3^- secretion by the type B intercalated cells in the cortical collecting tubule* also contributes to this response.[20,40,55,56]

These cells differ from HCO_3^--reabsorbing type A intercalated cells in that the *polarity of the membrane transporters can be reversed* and HCO_3^- ions are still

produced within the cell; however, ions are secreted into the peritubular capillary by the H^+-ATPase pump, which is now inserted in the basolateral, rat than the luminal, membrane (Fig. 11-7).[40,56] The HCO_3^- ions, in comparison, are secreted into the tubular lumen by an anion exchanger in the luminal membrane.[55,56]

Titratable Acidity

Several weak acids are filtered at the glomerulus and may act as buffers in Their ability to do so is proportional to the quantity of the buffer present a pK_a. The latter is important, since maximum buffering occurs at ± 1.0 pH un the pK_a (see Fig. 10-2). Because of its favorable pK_a of 6.80 and its relatively high rate of urinary excretion, HPO_4^{2-} is the major urinary buffer (Fig. 11-3) with lesser contributions from other weak acids, such as creatinine (pK_a = 4.97) and uric acid (pK_a = 5.75).

This process is referred to as *titratable acidity*, since it is measured by the amount of NaOH that must be added to a 24-h urine collection to titrate the urine p the same pH as that in the plasma (approximately 7.40 in normal subjects). normal conditions, 10 to 40 meq/day of H^+ is buffered by these weak acids.

The ability of phosphate to buffer H^+ can be illustrated by the following example (Table 11-1). From the Henderson-Hasselbalch equation for the

$HPO_4^{2-}/H_2PO_4^-$ system,

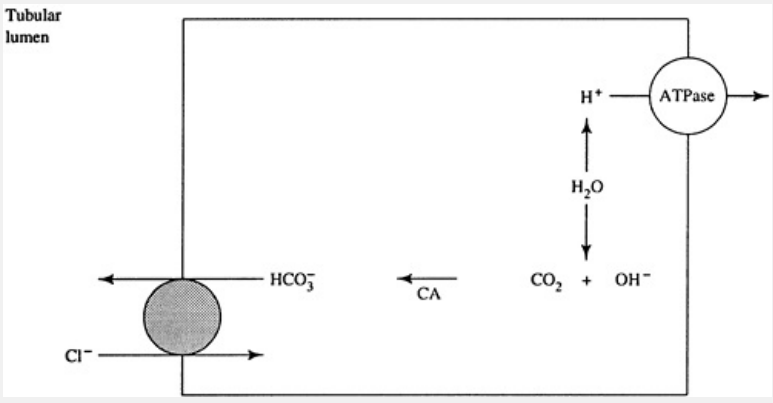

Figure 11-7 Transport mechanisms involved in the secretion of bicarbonate the tubular lumen in the type B intercalated cells in the cortical collecting Water within the cell dissociates into hydrogen and hydroxyl anions. The are secreted into the peritubular capillary by H^+-ATPase pumps in the basolateral membrane. The hydroxyl anions combine with carbon dioxide t bicarbonate in a reaction catalyzed by carbonic anhydrase (CA). Bicarbon then secreted into the tubular lumen via chloride-bicarbonate exchangers luminal membrane. The favorable inward concentration gradient for chlori (lumen concentration greater than that in the cell) provides the energy fo

bicarbonate secretion.

$$pH = 6.80 + \log \frac{[HPO_4^{2-}]}{[H_2PO_4^-]} \qquad (11\text{-}7)$$

the ratio of HPO_4^{2-} to $H_2PO_4^-$ is 4 : 1 at an arterial pH of 7.40. If 50 mmol of phosphate is excreted in the urine (the remainder of the filtered phosphate reabsorbed), then 40 mmol exists as HPO_4^{2-} and 10 mmol as $H_2PO_4^-$ in the glomerular filtrate. If the tubular fluid pH in the proximal tubule is lowered H^+ secretion, then, from Eq. 11-7, the ratio of HPO_4^{2-} to $H_2PO_4^-$ will fall to 1 : 1.

As a result, there will now be 25 mmol each of HPO_4^{2-} and $H_2PO_4^-$ in the tubule. This represents the buffering of 15 mmol (or 15 million nanomol) of H^+ by

HPO_4^{2-}, which an increase in the free H^+ concentration from 40 nanomol/L (pH of 7.40) to only 160 nanomol/L (pH of 6.80). Thus, over 99.99 percent of the s H^+ has been buffered. If the tubular fluid pH in the collecting tubules is low further to 4.8 (H^+ concentration of 0.016 mmol/L), essentially all the HPO_4^{2-} will be converted to $H_2PO_4^-$, as a total of 39.5 mmol of H^+ will have been buffered by the conversion of HPO_4^{2-} to $H_2PO_4^-$ (Table 11-1).

Table 11-1 Effects of a tubular fluid pH on bufferi by HPO_4^{2-} if 50 mmol of phosphate is excreted

Segment	pH	Quantity (in mmol) of HPO_4^{2-}	Quantity (in mmol) of $H_2PO_4^-$	Amount buffered by HPO_4^{2-} mmol
Filtrate	7.40	40	10	0
Proximal tubule	6.80	25	25	15
Final urine	4.80	0.5	49.5	39.5

In summary, *the amount of H^+ buffered by HPO_4^{2-} increases as the tubular fluid pH is reduced*. However, once the urine pH falls below 5.5, virtually all of the phosphate exists as $H_2PO_4^-$ and further buffering cannot occur unless there is a increase in phosphate excretion. To some degree, acid loading decreases p

phosphate reabsorption by decreasing the activity of the Na^+-phosphate cotransporter that is responsible for the entry of luminal phosphate into the cell.[59,60,61] This effect may be mediated both by decreased affinity for the inte with Na^+[61] and by conversion of HPO_4^{2-} to $H_2PO_4^-$, which binds less avidly to the cotransporter.[62] In addition, some of the excess H^+ ions may compete for the Na^+ site on the cotransporter, further decreasing phosphate reabsorption.[61]

Nevertheless, the ability to enhance net acid excretion by acidemia-induced phosphaturia is usually limited, and *increased NH_4^+ excretion that generally constitutes the major adaptation to an acid load*. An exception occurs in diabetic ketoacidosis, where large amounts of β -hydroxybutyrate ($pK_a = 4.8$) are excreted in the urine (see Chap. 25).[63] These ketoacid anions can act as urinary buffers, augmenting titratable acid excretion by as much as 50 mmol/day.[63] This effect is due both to the high concentration of ketoacid anions present and to the proxim pK_a of β -hydroxybutyrate to the acid urine pH.

Ammonium Excretion

The ability to excrete excess H^+ ions as ammonium adds an important degree of flexibil renal acid-base regulation, because the rate of NH_4^+ production and excretion can be varied according to physiologic needs. The mechanism by which this pro occurs has been considered to begin with ammonia (NH_3) production by the tubular cells.[64] Some of the excess NH_3 then freely diffuses into the tubular lumen, whe combines with secreted H^+ ions to form NH_4^+:

$$NH_3 + H^+ \rightarrow NH_4^+ \qquad (11\text{-}8)$$

These NH_4^+ ions are lipid-insoluble and are therefore "trapped" in the lumen back-diffusion cannot occur.

This sequence also explains how NH_3 can act as an effective buffer, even though the pK_a of this system is 9.0, well above that of the plasma or urine. At a uri 6.0, for example, the ratio of NH_3 to NH_4^+ is 1 : 1000. The combination of this sma amount of NH_3 with secreted H^+ ions should rapidly utilize all of the available bu This does not occur, however, since the ensuing reduction in the tubular flu NH_3 concentration results in the diffusion of more NH_3 into the lumen. This ability to replenish the quantity of buffer is not present with

titratable acidity; once HPO_4^{2-} has been converted to $H_2PO_4^-$, further buffering by this system cannot occur.

It is now clear that this model represents an oversimplification and that NH_4^+ excretion can be viewed as occurring in three major steps: (1) NH_4^+ is produced, primarily in the early proximal tubular cells; (2) luminal NH_4^+ is partially reabsorbed in

the thick ascending limb and then recycled within the renal medulla; a
the medullary interstitial NH_3 reaches high concentrations that allow NH_3 to diffuse into the tubular lumen in the medullary collecting tubule, where it is trapped by secreted H^+, as predicted from the classic theory.[64,65]

NH_4^+ production

The initial step in NH_4^+ excretion is the generation of NH_4^+ within the tubular cells from the metabolism of amino acids, particularly but not solely glutamine.[2,64,66]

$$\text{Glutamine} \rightarrow NH_4^+ + \text{glutamate} \rightarrow NH_4^+ + \alpha\text{-ketoglutarate}^{2-}$$

The first of these reactions is catalyzed by phosphate-dependent glutamina the second by glutamate dehydrogenase.[67] The subsequent metabolism of α-ketoglutarate results in the generation of two HCO_3^-, which are then returned to the systemic circulation by the Na^+-$3HCO_3^-$ cotransporter in the basolateral membrane (Fig. 11-4).

Notice that it is primarily NH_4^+, not NH_3, that is produced by these reactions, whic occur mostly in the proximal tubule.[68,69] Lipid-soluble NH_3 can freely diffuse out of the cell across both the luminal and basolateral membranes.[70] In comparison, lipid-insoluble NH_4^+ can be secreted only into the tubular lumen, since the require transmembrane transporters are present only in the luminal membrane.[70] This process of NH_4^+ secretion appears to be mediated at least in part by the Na^+-H^+ antiporter, which can also function as a Na^+-NH_4^+ exchanger (Fig. 11-4).[70,71] and 72

Medullary recycling

The NH_4^+ that is produced within the proximal tubule and secreted into the l exists in equilibrium with a much smaller quantity of NH_3. This NH_3 is capable of diffusing out of the lumen into the peritubular capillary, thereby reducing n excretion. This effect is minimized by the low urine pH, which can lower uri levels well below the level in the plasma. As depicted in Fig. 11-5, however, the urine does not become maximally acidified until the end of the collecting tubules. therefore possible that significant quantities of NH_3 could be lost from the lumen, particularly in the medullary collecting tubule, where progressively higher l concentrations of NH_4^+ and NH_3 are achieved.

These potential losses of luminal NH_3 are minimized because more than 75 percer of the tubular fluid NH_4^+ is *recycled within the medulla*, thereby maintaining a high interstitial NH_3 concentration (Fig. 11-6).[65,69,73] The primary step in this process i reabsorption in the thick ascending limb by substitution for K^+ both on the

Na^+-K^+–$2Cl^-$ carrier and, to a much lesser degree, through channels in the luminal membrane (see Fig. 4-2).[65,74] The movement of reabsorbed

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NH_4^+ into the less acid tubular cell drives Eq. 11-8 to the left, resulting in the formation of NH_3 and H^+. The H^+ ions are then resecreted into the lumen via a Na^+-H^+ exchanger, where they promote HCO_3^- reabsorption by combining with HCO_3^- that is delivered out of the proximal tubule.[75,76]

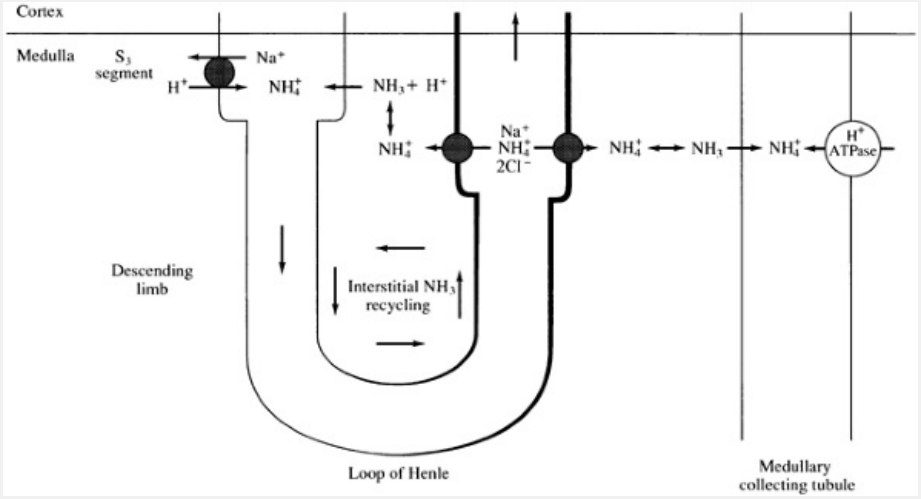

Figure 11-8 Schematic representation of ammonia recycling within the renal medulla. Although NH_4^+ production occurs predominantly in the proximal tubule, most of the NH_4^+ is then reabsorbed in the thick ascending limb, apparently by substitution for K^+ on the Na^+-K^+-$2Cl^-$ carrier in the luminal membrane. Partial dissociation into NH_3 and H^+ then occurs in the less acid tubular cells. The NH_3 diffuses into the medullary interstitium, where it reaches relatively high concentrations; it then diffuses back into those segments that have the lowest pH and therefore have the most favorable gradient: the S_3 segments of the late proximal tubule and, more importantly, the medullary collecting tubule, where secreted NH_3 is trapped as NH_4^+ and then excreted.

In comparison, the luminal membrane has the unusual characteristic of being impermeable to NH_3.[76] As a result, the NH_3 formed within the cell will diffuse out across the basolateral membrane into the medullary interstitium, and then into compartments that have the lowest NH_3 concentration, which in the tubules is a function of both delivery and the tubular fluid pH. As described above, a relatively small amount of H^+ secretion can lead to a large reduction in pH (and the generation of a disequilibrium pH) in those nephron segments that lack luminal carbonic anhydrase (Fig. 11-6). Thus, some of the NH_3 will diffuse into the S_3 segment of the

proximal tubule and then be recycled again in the thick ascending limb[52,74]. The net effect is the maintenance of a high medullary interstitial NH_3 concentration, which promotes secretion into the medullary collecting tubule.

Ammonium reabsorption in the thick limb is reduced by hyperkalemia (probably due to competition for the reabsorptive site on the Na^+-K^+-2Cl cotransporter, see "Plasma Potassium Concentration," below) and is enhanced by chronic metabolic acidosis due to increased NH_4^+ production in and delivery out of the proximal tubule.[73,77] The latter represents an appropriate response, since the ensuing increase in ammonia recycling will facilitate NH_4^+ excretion and therefore excretion of the acid load.

NH_3 secretion into the cortical and medullary collecting tubule

The fluid entering the collecting tubules has a relatively low NH_3 concentration because of removal in the loop of Henle. Furthermore, there is no luminal carbonic anhydrase in most of the collecting tubule segments[28,54]. As a result, continued H^+ secretion (by the H^+-ATPase pump) produces a maximally acid urine that further reduces the tubular fluid NH_3 levels. The net effect is that there is a relatively large gradient favoring the free diffusion of interstitial NH_3 into the tubular lumen, where it forms NH_4^+ (Fig. 11-8)[5,69].

For luminal NH_4^+ accumulation to occur with maximum efficiency, the NH_4^+ and NH_3 permeabilities must be different from those in the loop of Henle. In the latter segment, the luminal membrane is permeable to NH_4^+ but not to NH_3; these characteristics permit luminal NH_4^+ to be reabsorbed without back-diffusion of NH_3 into the lumen. In contrast, the cell membranes in the collecting tubules are highly permeable to NH_3 but have only a negligible permeability to NH_4^+[78]. As a result, interstitial NH_3 can passively diffuse into the tubular lumen, where it is then trapped as NH_4^+.

The net effect is that NH_3 is secreted into the lumen throughout the collecting tubules[65]. The gradient is greatest in the inner medulla, where the interstitial NH_3 concentration is highest. However, there is a roughly equivalent degree of NH_3 secretion in the cortex and outer medulla, which have a lower permeability, as a result of both an increase in unit permeability and a greater luminal surface area[65,67].

Response to changes in pH

According to this model, NH_4^+ excretion can be increased in one of two ways: by increasing proximal NH_4^+ production from glutamine and by lowering the urine pH

which will increase NH_3 diffusion into the lumen in the medullary collecting tub (Fig. 11-9).[65] In humans given an acid load, for example, NH_4^+ excretion begins to increase within 2 h, mostly as a result of the formation of a more acid urine that increases the efficiency of NH_3 secretion into the medullary collecting tubule.[79] Total NH_4^+ excretion reaches its maximum level at 5 to 6 days, a time at which there is an elevation in both glutamine uptake by the kidney and tubular NH_4^+ production (Fig. 11-10).[5,79,80] and [81]

Animal models provide confirmation of this sequence. Phosphate-dependent glutaminase activity increases on the first day and glutamate dehydrogenase by day 2 to 3 after an acid load.[82,83] However, NH_4^+ excretion begins to rise on the first day and is much greater than can be explained by the increase in enzyme activity; this response may reflect enhanced efficiency of trapping NH_3 or increased glutamine uptake by the cells.[82,83]

The adaptive increase in glutamine metabolism with acidemia begins with increased uptake by the proximal tubular cells. Under normal conditions, most of the filtered glutamine is reabsorbed by cotransport with Na^+, a process driven by the favorable electrochemical gradient for passive entry of Na^+ into the cells (see page 75). In the presence of acidemia, however, Na^+-dependent glutamine uptake also occurs from the peritubular capillary across the basolateral membrane.[84,85] The peritubular capillary is a fertile source of glutamine, since only 20 percent of the renal plasma flow and therefore only 20 percent of the glutamine presented to the kidney undergoes glomerular filtration.

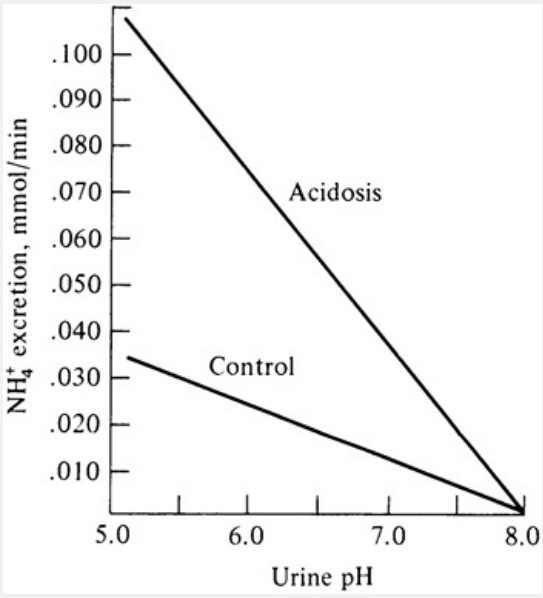

Figure 11-9 Effect of urinary and arterial pH on NH_4^+ excretion. Lowering the arterial pH (that is, acidemia) increases cellular production of NH_4^+ from glutamine.

Lowering the urine pH enhances the trapping of NH_3 as NH_4^+ in the medullary collecting tubules. (*Redrawn from Pitts, RF: Fed Proc 7:418, 1948, with permission.*)

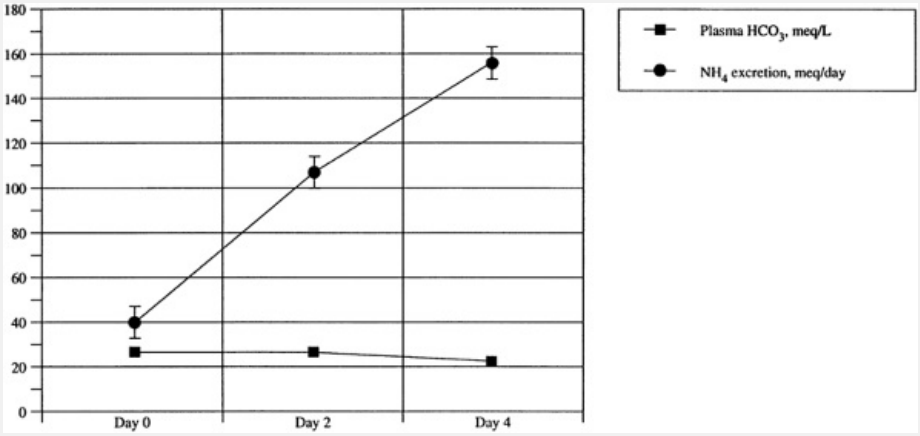

Figure 11-10 Effect of a dietary acid load on the plasma HCO_3^- concentration and urinary NH_4^+ excretion. The latter increases approximately fourfold with reduction of only a few milliequivalents per liter in the plasma HCO_3^- concentration. (*Data from Welbourne T, Weber M, Bank N: J Clin Invest 51:1852, 1972, with permission.*)

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Once glutamine is within the tubular cells, its proximal metabolism is pH-dependent, appropriately increasing with acidemia and decreasing with alkalemia.[68,69] How this occurs is incompletely understood, as several factors may play an important role. With acidemia, for example, the rise in NH_4^+ production may be largely mediated by enhanced activity of the enzymes involved in NH_4^+ production, including phosphate-dependent glutaminase (promoting the metabolism of glutamine to glutamate), glutamate dehydrogenase (promoting the metabolism of glutamate to α-ketoglutarate), and α-ketoglutarate dehydrogenase (promoting the metabolism of α-ketoglutarate).[66,82] These changes in enzyme activity are limited to the proximal tubule,[82] which is consistent with this segment being the site of increased NH_4^+ production in acidemic states.[68]

It is presumed that proximal glutamine metabolism responds to alterations in pH that parallel those in the extracellular fluid (see "Extracellular pH," below). In particular, it may be an alteration in the pH gradient between the cytosol and mitochondria that constitutes the signal to change the rate of NH_4^+ production.[66,86] Other, mostly unidentified circulating factors may also contribute, including

release of glucocorticoids.[87,88]

Regardless of the exact mechanisms involved, the net effect is that NH_4^+ excretion can increase from its normal value of 30 to 40 meq/day to over 300 meq/day in severe metabolic acidosis.[63,89] This response, which is in marked contrast to the limited ability to enhance titratable acid excretion, is appropriate; each NH_4^+ produced results in the equimolar generation of new HCO_3^- from the metabolism of α-ketoglutarate.[2] Return of this HCO_3^- to the systemic circulation then raises the plasma HCO_3^- concentration toward normal.

Urine pH

As depicted in Fig. 11-5, the tubular fluid pH falls progressively, reaching its lowest level in the medullary collecting tubule. In humans, the minimum urine pH that can be achieved is 4.5 to 5.0; this represents a maximum plasma-to-tubular fluid H^+ gradient of almost 1 : 1000 (3 log units). The inability to make the urine more acid may reflect a limit on the strength of the H^+-ATPase pump or on the impermeability of the tubular epithelium, which is required to prevent the passive backflux of secreted H^+ from the cell into the lumen.

This ability to lower the urine pH is important, because the formation of both titratable acidity and NH_4^+ is pH-dependent, with both increasing as the urine is made more acid (Table 11-1, Fig. 11-9). If the minimum urine pH were higher, at 5.5 to 6.0 (which is still less than that of the plasma), titratable acid and NH_4^+ excretion would fall, and excretion of the daily H^+ load might be prevented. This appears to be the mechanism responsible for the acidemia in patients with type 1 (distal) renal tubular acidosis (see Chap. 19).

The pH dependence of titratable acidity and NH_4^+ formation also means that these processes (as well as HCO_3^- reabsorption) occur throughout the nephron as the urine is made more acid. The sites at which they are most likely to occur can be

appreciated from the isohydric principle, which states that all three buffer systems must be in equilibrium:

$$pH = 6.1 + \log\frac{[HCO_3^-]}{0.03P_{CO_2}} = 6.8 + \log\frac{[HPO_4^{2-}]}{[H_2PO_4^-]} = 9.0 + \log\frac{[NH_3]}{[NH_4^+]}$$

Thus, a secreted H^+ ion will preferentially be buffered by that system with the highest concentration and/or the pK closest to that of the tubular fluid pH.[69] In the proximal tubule, most secreted H^+ ions are utilized for HCO_3^- reabsorption because of the high concentration of HCO_3^- and the ability to minimize the reduction in pH by the action of luminal carbonic anhydrase. This segment also represents the site at which most NH_4^+ is secreted into the lumen and in which about one-half of the

available HPO_4^{2-} is buffered (Table 11-1). In contrast, most H^+ ions secreted in the medullary collecting tubule (where the urine pH is reduced to its lowest val combine with secreted NH_3. Since virtually all the HCO_3^- has been reabsorbed and most of the HPO_4^{2-} has already been buffered (which occurs when the urine p below 5.8, that is, more than 1 pH unit from the pK$_a$ of the buffer).

REGULATION OF RENAL HYDROGEN EXCRETION

The preceding section discussed how the kidney excretes H^+. In this section, we will review the factors that determine exactly how much H^+ is excreted. The *extracellular pH* (which is most often measured clinically on a specimen of art blood) is the major physiologic regulator of this process, as it allows acid e to vary with day-to-day changes in the dietary acid load. In addition, the ra secretion also can be influenced by the effective circulating volume, aldost plasma K^+ concentration, and parathyroid hormone.

Extracellular pH

Net acid excretion tends to vary inversely with the extracellular pH. Acidem example, is characterized by a fall in extracellular pH (or increase in H^+ concentration) and is associated with an increase in both proximal and distal acidification.[90,91,92] and[93] This is manifested in the proximal tubule by four changes:

1. Enhanced luminal Na^+-H^+ exchange,[90,91,94] a response that may be mediated both by binding of excess intracellular H^+ ions to a modifier site on the exchanger[90] and by the synthesis of new exchangers, as evidenced by a mRNA for the Na^+-H^+ antiporter[95]
2. Enhanced activity of the luminal H^+-ATPase[13]
3. Increased activity of the Na^+:$3HCO_3^-$ cotransporter in the basolateral membrane, thereby allowing HCO_3^- formed within the cell to be returned to th systemic circulation[91,94,96]
4. Increased NH_4^+ production from glutamine[68]

In the collecting tubules, on the other hand, the increase in acidification ap involve the insertion of preformed cytoplasmic H^+-ATPase pumps into the luminal membrane of the acid-secreting cells,[40,57,97] particularly those in the outer medullary collecting duct.[97] The ensuing reduction in the tubular fluid pH in the segments will promote the diffusion of intracellular NH_3 into the lumen, where it will be trapped as NH_4^+ (Fig. 11-4).[79] The net effect of this increase in acid excretion i

enhanced generation of HCO_3^- by the tubules. Return of this HCO_3^- to the systemic circulation will then raise the extracellular pH toward normal.

The extracellular pH is thought to affect net acid excretion *primarily* by *although lesser, alterations in the renal tubular cell pH*.[98,99,100] The importance of this local effect, which is independent of other circulating fa been demonstrated in experiments with cultured renal proximal tubule cells. the pH of the bathing medium in this setting leads to a significant increase activity of the luminal Na^+-H^+ exchanger.[100] This effect is thought to be mediated by activation of pH-sensitive proteins.[101]

The mechanism by which the intracellular pH changes with the extracellular varies with the cause of the acid-base disorder. An elevation in the P_{CO_2}, for example, will lower the pH of the extracellular fluid; this will induce a simil rapid acidification in the cells, because CO_2 freely cross cell membranes.

The effect of alterations in the plasma HCO_3^- concentration are less direct, since transcellular diffusion of this anion is limited by the lipid bilayer of the cell membrane. However, the carrier-mediated HCO_3^- steps in the basolateral membrane of the proximal tubule (Na^+-$3HCO_3$ cotransport)[98,99] and the distal nephron (Cl-HCO_3 exchange)[102] are affected by the transmembrane HCO_3^- gradient. Lowering the extracellular pH by reducing the HCO_3^- concentration will make this gradient more favorable, thereby promoting exit of HCO_3^- from the cell and reducing the cell pH (Fig. 11-11).[98,99] The ensuing increase in acid excretion ther raises both the systemic and the intracellular pH toward normal; thus, it ma be the *intracellular pH* that is primarily being regulated.[102,103]

These adaptive changes in cell pH are determined by the extracellular pH i by the HCO_3^- concentration or P_{CO_2} alone. There is *no alteration in the cell pH* if both the HCO_3^- concentration and the P_{CO_2} are lowered or raised to a similar degree, so that the extracellular pH remains constant.[98] In this setting, there is also no change in net acid excretion.[92]

Metabolic acidosis

Metabolic acidosis is characterized by acidemia that is induced by a plasma HCO_3^- concentration. Net acid excretion is appropriately and often dramatic increased in this disorder, beginning within a day and reaching its maximun days (Fig. 11-10).[5,79,104] This response is mostly due to enhanced NH_4^+ excretion, which is mediated both by increased proximal tubule NH_4^+ metabolism[68,79] and by increased distal hydrogen secretion.[40,97]

In comparison, titratable acid excretion is generally limited by the amount o phosphate in the urine, which is modestly increased by an acidemia-induce

inhibition of proximal phosphate reabsorption.[59,60,61,62] An exception to this rule occurs in

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diabetic ketoacidosis, where urinary ketone anions (particularly β -hydroxyl can act as titratable acids. In this setting, net acid excretion can exceed 50 meq/day,[63,89] resulting in the generation of an equivalent quantity of HCO_3^- the extracellular fluid.

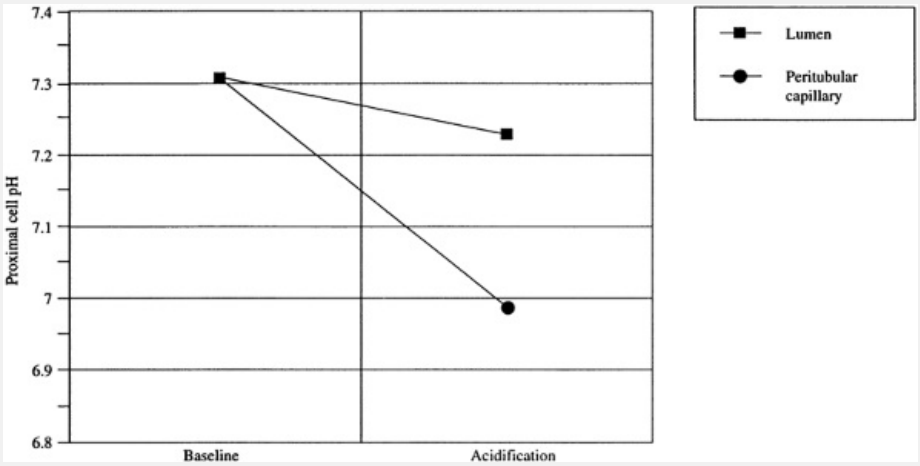

Figure 11-15 Effect of lowering the HCO_3^- concentration and pH in the fluid in the tubular lumen (squares) or in the peritubular capillary (circles) on the proximal tubular cell pH. Only the change in peritubular capillary pH signi lowers the cell pH, an effect that appears to be mediated by the Na^+-$3HCO_3^-$ cotransporter. (*Data from Alpern RJ, Chambers M: J Clin Invest 78:502, 1986, with permission.*)

The relationship between cell pH and net acid excretion can also be unders terms of the steady state. Suppose a normal subject increases acid generat going on a high-protein diet. Over a period of days, net acid excretion will meets the new level of acid production. At this time, the patient is back in a steady state, but the plasma HCO_3^- concentration must have fallen to provide the signal (lower cell pH) for the higher level of acid excretion. This process is reasonably efficient. As shown in Fig. 11-10, for example, lowering the plasma HCO_3^- concentration by 4 to 5 meq//L leads to a fourfold increase in NH_4^+ excretion.

Metabolic alkalosis

Metabolic alkalosis, on the other hand, is characterized by an alkaline extr pH that results from an *elevation* in the plasma HCO_3^- concentration. The normal response to a HCO_3^- load is to excrete the excess HCO_3^- in the urine, both by

diminishing its rate of reabsorption and by secretion in the cortical collecting tubule.[21,55,56] As described above, the latter process occurs in a subpopulation of cortical intercalated cells that are able, in the presence of an elevated pH, to pump H^+ into the basolateral rather than the luminal membrane (Figure 11-7).[40]

This protective bicarbonaturic response is extremely efficient. For example, administration of as much as 1000 meq of $NaHCO_3$ per day to normal subjects induces only a minor elevation in the plasma HCO_3^- concentration, as virtually all of the excess HCO_3^- is excreted in the urine.[105] Thus, maintenance of metabolic alkalosis requires the presence of a defect in HCO_3^- excretion, which is most often due to effective volume and chloride depletion (see below).

Respiratory acidosis and alkalosis

Disturbances in alveolar ventilation induce changes in CO_2 elimination and, consequently, in the P_{CO_2}. Primary hyperventilation, for example, enhances CO_2 loss, resulting in a fall in the P_{CO_2} (hypocapnia) and a rise in pH that is called *respiratory alkalosis*. Primary hypoventilation, on the other hand, impairs CO_2 elimination, producing an elevation in the P_{CO_2} (hypercapnia) and a reduction in pH that is called *respiratory acidosis*. Although correction of either of these conditions requires the restoration of normal alveolar ventilation, the kidney can minimize changes in arterial pH by varying H^+ excretion and HCO_3^- reabsorption.

From Eq. 11-3, the extracellular pH is a function of the HCO_3^-/P_{CO_2} ratio. Thus, the *pH may remain near normal in respiratory acid-base disorders if the P_{CO_2} and HCO_3^- concentration change in the same direction and to a similar degree.* Consequently, an elevation in the plasma HCO_3^- concentration is an appropriate response to hypercapnia, and a reduction in the plasma HCO_3^- concentration is an appropriate response to hypocapnia (see Chapters 20 and 21).

These changes occur because the P_{CO_2}, via its effect on intracellular pH, is an important determinant of H^+ secretion and HCO_3^- reabsorption (Fig. 11-12).[57,92,93] With chronic respiratory acidosis, for example, there is an increase in net acid excretion (primarily as NH_4^+), resulting in the generation of new HCO_3^- in the plasma.[106] The net effect in the steady state (which is achieved within 5 to 6 days) is that the rise in P_{CO_2} is partially offset by an increase in the plasma HCO_3^- concentration that *averages 3.5 meq/L for every 10-mmHg elevation* in P_{CO_2}.[107]

The renal response is reversed in chronic respiratory alkalosis. In this sett

concurrent rise in intracellular pH diminishes H^+ secretion, resulting in HCO_3^- loss in the urine and decreased NH_4^+ excretion.[108,109] These changes are manifested by a fall in the plasma HCO_3^- concentration that averages *5 meq/L for every 10-mmHg decline* in the PCO_2.[108]

Chronic metabolic acidosis versus chronic respiratory acidosis

Although chronic metabolic and respiratory acid-base disturbances can pro similar changes in extracellular pH, there are major differences in the rena that illustrate the role of the intracellular pH in determining the degree of acidification that occurs.[110,111] In chronic metabolic acidosis, for example, the d acid load must be increased to sustain the acidemia (as with chronic diarrh Consequently, net acid and NH_4^+ excretion are persistently above normal (Fig. 11-13).

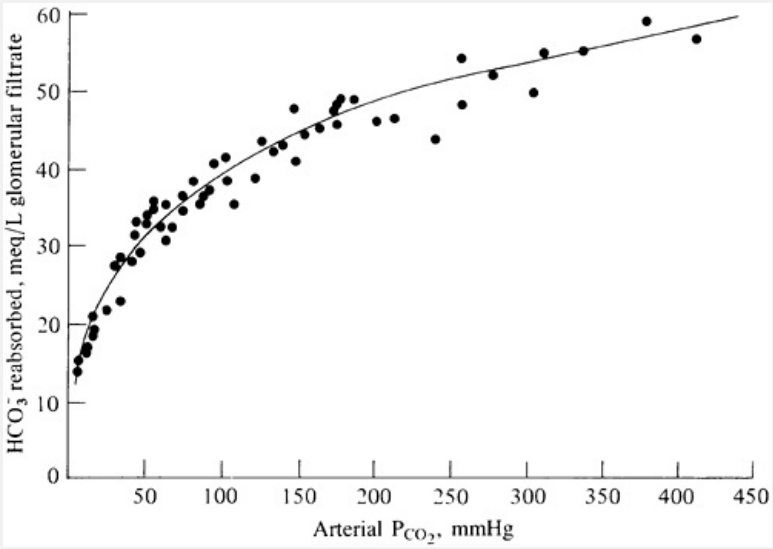

Figure 11-12 Relationship between arterial PCO_2 and HCO_3^- reabsorption. Note that the curve is steepest in the physiologic range of PCO_2 (35 to 90 mmHg). (*From Rector FC Jr, Seldin DW, Roberts AD Jr, J Clin Invest 39:1706, 1960, by copyright permission of the American Society for Clinical Investigation*)

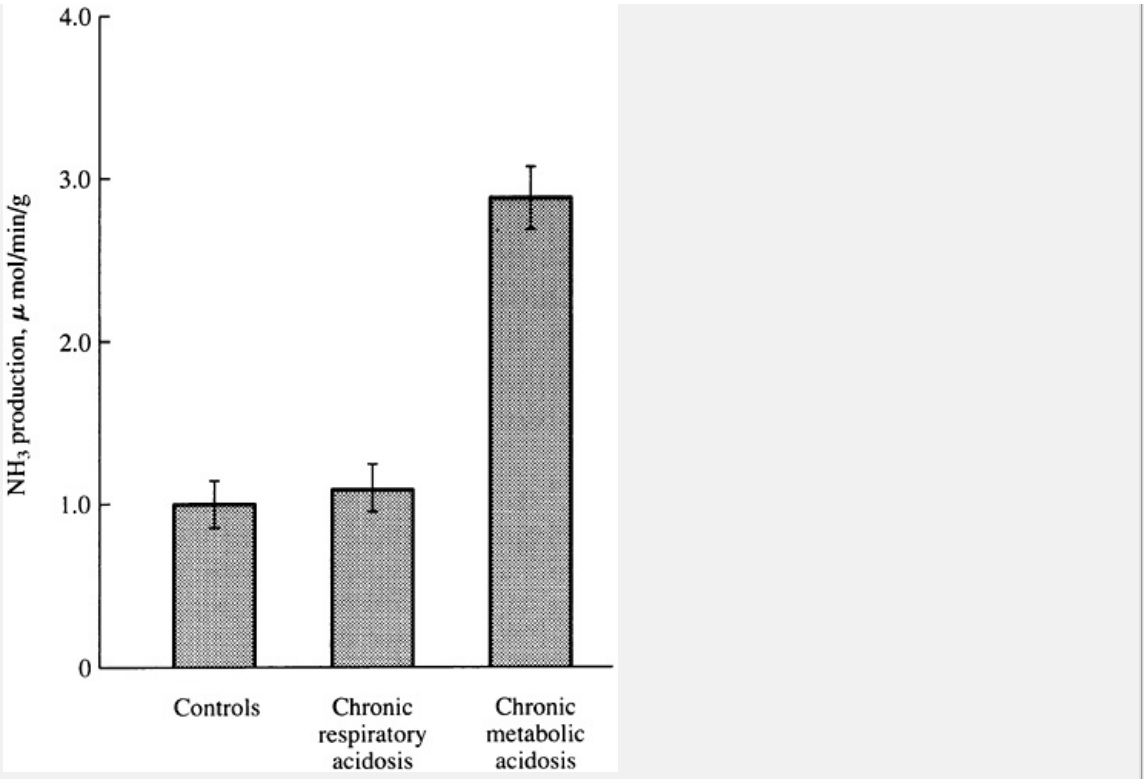

Figure 11-13 Ammonia production by the isolated perfused kidney from cont rats and those with chronic respiratory acidosis or chronic metabolic acid 3 days duration. Ammonia production is enhanced only in metabolic acidos despite a similar reduction in pH to about 7.30 in both acidotic groups. (*From Rodriguez-Nichols F, Laughrey E, Tannen RL: Am J Physiol 247:F896, 1984, with permission.*)

The same response is seen in respiratory acidosis, as new HCO_3^- must be generated to produce the compensatory rise in the plasma HCO_3^- concentration.[92,106] In the new steady state, the pH will be partially corrected the daily acid load generated from protein metabolism (assuming that there is no change in dietary intake). As a result, *there is a necessity for increased NH_4^+ excretion* in chronic respiratory acidosis, which returns to a level simila that in controls (Fig. 11-13).[110]

To summarize, net acid and NH_4^+ excretion are enhanced in chronic metabolic bu not respiratory acidosis, despite a similar degree of acidemia in both condi seemingly paradoxical finding may be *explained by differences in proximal tubula cell pH*.[111,112] Both metabolic and respiratory acidosis will produce a similar at the basolateral membrane: lowering the cell pH by lowering HCO_3^- will a more favorable gradient in metabolic acidosis and by increasing PCO_2 in respiratory acidosis.[98,99]

The responses are quite different, however, at the luminal membrane. The

HCO_3^- concentration and, therefore, the filtered load of HCO_3^- are reduced in metabolic acidosis. As a result, less HCO_3^- is reabsorbed in the proximal tubule by Na^+-H^+ exchange. In comparison, the plasma HCO_3^- concentration and filtered HCO_3^- load are elevated in chronic respiratory acidosis. This increase in the HCO_3^- concentration allows more HCO_3^- to be reabsorbed.[113] It is important to remember that proximal acidification is limited by the transcellular Na^+ gradient that provides the energy for the Na^+-H^+ antiporter. When more buffer (as HCO_3^-) is present, more H^+ secretion can occur without an excessive reduction in tubular pH.[113]

The net effect of this increase in H^+ extrusion from the cell is that *the proximal tubular cell pH returns toward normal in chronic respiratory acidosis*.[111][112] As a result, there is now no stimulus to increase proximal NH_4^+ excretion, in comparison to chronic metabolic acidosis, where the cell pH is persistently reduced.[112] Similar factors may explain why mRNA expression for the Na^+-H^+ exchanger is increased in metabolic acidosis but unchanged in chronic respiratory acidosis.[98]

Effective Circulating Volume

Bicarbonate reabsorption can be influenced by the effective circulating volume, the most important effect being an increase in HCO_3^- reabsorptive capacity with volume depletion.[113][114] and [115] As shown in Fig. 11-14, for example, raising the plasma HCO_3^- concentration by infusing $NaHCO_3$ leads to a plateau in HCO_3^- reabsorption at a level of about 26 meq/L (see *Fig. 8-8*). This is a proper response, since it allows virtually all of the filtered HCO_3^- to be reabsorbed as long as the plasma HCO_3^- concentration is within the normal range. Once the latter exceeds 26 meq/L, inappropriate HCO_3^- retention is prevented by excretion of the excess HCO_3^- in the urine.

In contrast, if hypovolemia is induced by the prior administration of a diuretic, net HCO_3^- reabsorption continues to increase, even at a level above 35 meq/L (see Fig. 11-14). This effect can be demonstrated in normals simply by the ingestion of a low-salt diet (10 meq/day), which is sufficient to increase HCO_3^- reabsorptive capacity by 4 meq/L even though the subject is clinically euvolemic.[116]

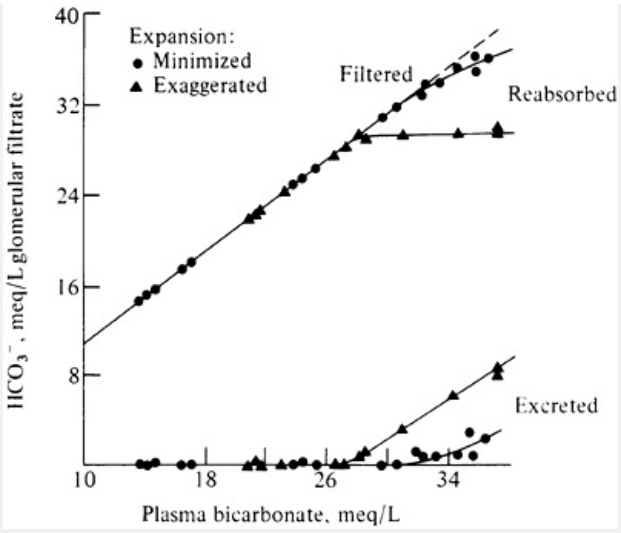

Figure 11-14 Relationship between arterial P_{CO_2} and HCO_3^- reabsorption. Note the curve is steepest in the physiologic range of P_{CO_2} (35 to 90 mmHg). *From Rector FC Jr, Seldin DW, Roberts AD Jr, Sudhir V: J Clin Invest 39:1706, 1960, by copyright permission of the American Society for Clinical Investigation.*

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The relationship between volume depletion and HCO_3^- transport becomes clinically important in patients with metabolic alkalosis, in whom the inability to excrete excess HCO_3^- prevents the spontaneous restoration of acid-base balance.[117] In this setting, *the attempt to maintain volume by preventing further loss of $NaHCO_3$ occurs at the expense of the systemic pH.*

At least four factors may contribute to this effect on HCO_3^- excretion: (1) a reduction in glomerular filtration rate, (2) activation of the renin-angiotensin-aldosterone system, (3) hypochloremia, and (4) concurrent hypokalemia due to urinary or gastrointestinal losses (see below).[114,127,128] and [129] A decline in GFR, for example, may play a permissive role in selected patients. It is not likely to be of primary importance, however, since the rise in the plasma HCO_3^- concentration results in a filtered load of HCO_3^- that is often not diminished. Furthermore, many patients maintain a P_{CO_2} that is relatively normal; in this setting, increased tubular reabsorption must be responsible for the absence of HCO_3^- excretion.[117,119]

Renin-angiotensin-aldosterone system

The hypovolemia-induced increase in renin release can enhance net H^+ secretion and therefore HCO_3^- reabsorption in several ways. Angiotensin II, acting in the proximal tubule, is a potent stimulator of HCO_3^- transport by increasing the activity of both the luminal Na^+-H^+ antiporter and the basolateral $3Na^+$-HCO_3^-

cotransporter.[120,121]

However, the physiologic significance of this response for acid-base balanc uncertain. Angiotensin II does increase HCO_3^- reabsorption in the early proximal tubule, but the ensuing decrease in delivery out of this segment may result equivalent delivery-dependent reduction in HCO_3^- transport in the late proximal tubule.[122,123] Thus, there may be a net neutral effect on HCO_3^- handling, as the major function of the proximal action of angiotensin II is to increase NaCl a reabsorption, thereby appropriately expanding the extracellular volume.[122]

Aldosterone may play a more important role by stimulating the Na^+-H^+ ATPase pump throughout the distal nephron, including the intercalated cells critical collecting tubule and the cells in the outer and inner medullary coll tubule.[124,125,126,127] and[128] ¶ Aldosterone also increases the activity of the second step in distal acidification, promoting HCO_3^- exit from the cell into the peritubular capillary via the basolateral Cl^--HCO_3^- exchanger.[102,127]

In addition, aldosterone can indirectly increase net H^+ secretion by the stimulation of Na^+ transport in a different cell population, the principal cells in the cortica collecting tubule (see chap. 6).[36,37,114] The reabsorption of cationic ions like Na^+ creates a lumen-negative potential difference; this electrical gradient then H^+ accumulation in the lumen by minimizing the degree of back- diffusion.

Chloride depletion

Hypochloremia is a common concomitant of metabolic alkalosis, since both Cl^- ions are lost in most patients, such as those with vomiting or diuretic th This reduction in the filtered Cl^- concentration can enhance H^+ secretion and HCO_3^- reabsorption through both *Na-dependent and Na-independent* factors. It has been proposed, for example, that the effect of hypochloremia is related to the hig Na^+ reabsorption seen in volume depletion, often leading to a urine Na^+ concentration below 5 to 10 meq/L. If, as in normal subjects, the filtrate Na^+ concentration is 145 meq/L and the filtrate Cl^- concentration is 115 meq/L, then only 115 meq/L of Na^+ can be reabsorbed with Cl^-. Since Cl^- is the only quantitatively important reabsorbable anion in the filtrate, *Na^+ reabsorption must be accompanied by H^+ or K^+ secretion to maintain electroneutrality.* This H^+ secretory processes, which primarily occur in the collecting tubules, become more im the presence of hypochloremia, a setting in which less of the filtered Na^+ can be reabsorbed with Cl^-. The net effect is enhanced H^+ secretion, increased HCO_3^- reabsorption, and persistence of the metabolic alkalosis.

The importance of both volume status and the reabsorbability of the anion

illustrated by the response to an infusion of Na_2SO_4 (SO_4^{2-} being a poorly reabsorbed anion). When given to a euvolemic subject, Na_2SO_4 is rapidly excreted in the urine. In a volume-depleted subject, however, the Na^+ will be retained (in part under the influence of aldosterone), and, since SO_4^{2-} cannot be reabsorbed, H^+ and K^+ secretion must be increased (Fig. 11-15).[129] In contrast, the administration of NaCl in this setting results in both Na^+ and Cl^- reabsorption without affecting H^+ and K^+ secretion.

The reabsorbability of the anion creates a paradoxical situation in patients hypovolemia and metabolic alkalosis in that the administration of acid will n necessarily correct the alkalemia. If, for example, given as HNO_3 (NO_3^- being relatively nonreabsorbable), it will be buffered by extracellular HCO_3^-

$$HNO_3 + NaHCO_3 \rightarrow NaNO_3 + H_2CO_3 \rightarrow CO_2 + H_2O$$

As the $NaNO_3$ is presented to the cortical collecting tubule, the Na^+ will be retained and H^+ excretion enhanced. This is similar to the Na_2SO_4 shown in Fig. 11-15. The net effect is the excretion of the administered acid (HNO_3).[130] As

a result, the arterial pH will be unchanged, since an acid urine is excreted the presence of systemic alkalemia.

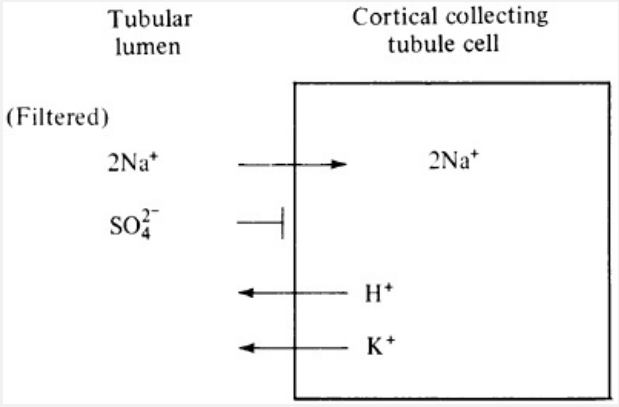

Figure 11-15 Events occurring after Na^+ reabsorption across the luminal membrane of the cortical collecting tubule cell. In a sodium-avid state, th presentation of Na^+ with a nonreabsorbable anion to the cortical collecting tubule enhances H^+ and K^+ secretion. In contrast, if NaCl is presented to this segment, Na^+ will be reabsorbed with Cl^-, with little effect on H^+ and K^+ secretion.

If, in comparison, acid is given as HCl, buffering by $NaHCO_3$ leads to the generation of NaCl. When this reaches the cortical collecting tubule, the Na^+ reabsorbed with Cl^- and not exchanged for H^+. Therefore, the administered H^+ will

be retained and the alkalemia will be corrected.

Rather than by giving HCl, the alkalemia can be reversed more easily by pr HCO_3^- excretion in the urine. This can be achieved by expanding the effecti circulating volume with NaCl, eventually allowing the excess HCO_3^- to be excreted as $NaHCO_3$. In comparison, the administration of Na^+ with a different, nonreabsorbable anion, such as SO_4^{2-}, will be ineffective. Thus, the correction o metabolic alkalosis in a volume-depleted, Cl^--avid subject requires the *administration of the only reabsorbable anion, Cl^-, either NaCl, HCl, or, if hypokalemia is present, KCl* (see Chap. 18).

The importance of Cl^- may also be related to direct effects on acid-base handli that are *independent of* Na^+.[118,131] In particular, both HCO_3^- secretion by the type B intercalated cells in the cortical collecting tubule and H^+ secretion in the distal nephron can be affected by the Cl^- concentration.

HCO_3^- secretion into the lumen in the type B intercalated cells appears to b mediated by a Cl-HCO_3 exchanger in the luminal membrane, the energy for whi provided by the favorable inward gradient for Cl^- (Fig. 11-7).[55,56] Lowering the tubular fluid Cl^- concentration will diminish this gradient, minimizing the abilit secrete HCO_3^-.

With H^+ secretion by the H-ATPase pump, Cl^- appears to be passively cosecreted to maintain electroneutrality.[25] The gradient for Cl^- secretion and therefore the ability to secrete H^+ may be enhanced when the tubular fluid Cl^- concentration is reduced.[131]

Both diminished HCO_3^- secretion and enhanced H^+ secretion will contribute to maintenance of the high plasma HCO_3^- concentration and persistence of the alkalemia.

In summary, the effects of hypochloremia on net HCO_3^- reabsorption are most prominent in the collecting tubules. Thus, the appropriate renal HCO_3^- retention induced by fluid and chloride repletion is mostly mediated by decreased net distal HCO_3^- reabsorption (which probably includes a component of HCO_3^- secretion).[132]

Plasma Potassium Concentration

Potassium is another potential influence on H^+ secretion, as a reciprocal relationship has been demonstrated between the plasma K^+ concentration and HCO_3^- reabsorption (Fig. 11-16).[133,134] and [135] The major proposed mechanism for this relationship is that alterations in K^+ balance lead to *transcellular cation*

shifts that affect the intracellular H^+ concentration (Fig. 11-17).

As an example, gastrointestinal or urinary losses of K^+ can lead to a reduction in the plasma K^+ concentration. As a result, intracellular K^+ moves out into the extracellular fluid (through K^+ channels in the cell membrane) down a favorable concentrati

gradient to replete the extracellular stores. To maintain electroneutrality, H^+ (and Na^+) enter the cell, resulting in an intracellular acidosis.[136] [112,137,138]

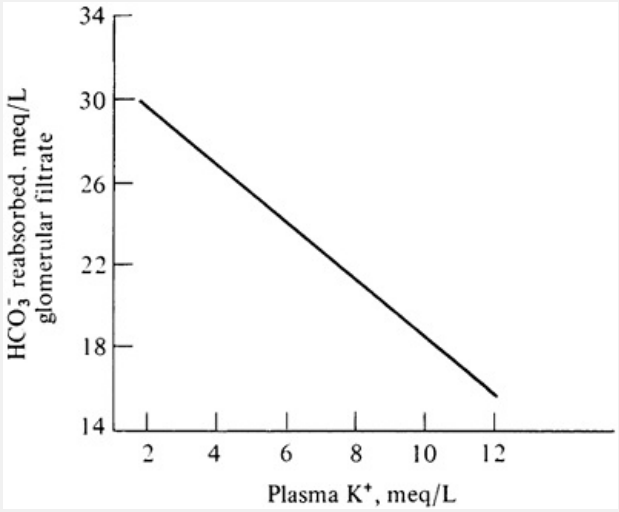

Figure 11-18 Renal tubular reabsorption of HCO_3^- as a function of the plasma K^+ concentration. *Adapted from Fuller GR, MacLeod MB, Pitts RF Jr: Am J Physiol 182:111, 1956, with permission.*

This increase in H^+ concentration in the renal tubular cells may account for th enhanced H^+ secretion, HCO_3^- reabsorption, and NH_4^+ excretion observed with K^+ depletion.[133,138,139] In the proximal tubule, for example, hypokalemia is asso with increased activity of both the luminal Na^+-H^+ antiporter and the basolateral Na^+-$3HCO_3^-$ cotransporter, which are required for the elevated rates of H^+ secretion and HCO_3^- reabsorption.[140]

These changes are reversed with a rise in the plasma K^+ concentration, as K^+ moves into and H^+ out of cells.[141] The ensuing intracellular alkalosis may then account for the associated reductions in HCO_3^- reabsorption and NH_4^+ excretion.[133,138,139]

Factors other than these transcellular shifts also may contribute to the pota induced changes in urinary acidification. For example, hyperkalemia reduces NH_4^+ excretion in rats; there is, however, no change in NH_4^+ delivery out of the

proximal tubule, suggesting that segments distal to the proximal tubule mus involved.[142] There are at least two mechanisms by which distal H^+ and K^+ handling might be related:

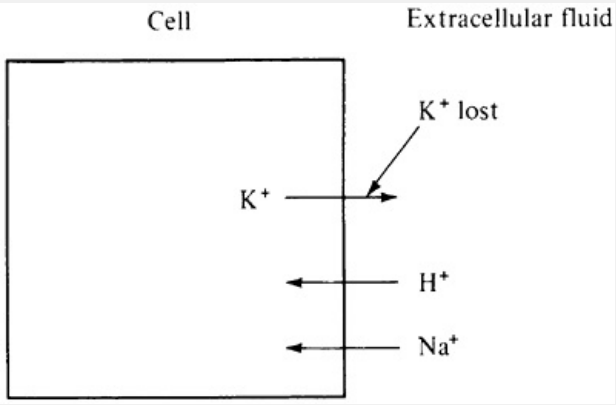

Figure 11-17 Reciprocal cation shifts of H^+, K^+, and Na^+ between the cells, including renal tubular cells, and the extracellular fluid. In the presence o hypokalemia, K^+ moves out of the cells down a concentration gradient. Since cell anions (primarily proteins and organic phosphates) are unable to cros cell membrane, electroneutrality is maintained by the entry of Na^+ and/or H^+ into the cell. The increase in cellular H^+ concentration may be responsible for the increased H^+ secretion and HCO_3^- reabsorption seen with hypokalemia. On the other hand, hyperkalemia causes K^+ and Na^+ to leave the cells, resulting in a fall in H^+ secretion and HCO_3^- reabsorption.

1. Medullary recycling of NH_4^+ is initiated by substitution of NH_4^+ for K^+ on the Na^+-K^+–$2Cl^-$ carrier in the luminal membrane of the thick ascending limb (Fig. 11-8).[74] Increased luminal K^+ in hyperkalemia could competitively inhibit this process, thereby limiting ammonia accumulation in the medullary interst subsequent secretion into the medullary collecting tubule, and total urin NH_4^+ excretion.[142,143]

2. H^+ secretion in the distal nephron is mediated in part by an electroneut K^+-ATPase that also actively reabsorbs K^+.[24,27,29] Active K^+ reabsorption by this pump appears to be stimulated by hypokalemia,[27,144,145] and[146] an effect that could in part explain the concurrent increase in H^+ secretion. The net result is that hypokalemia and aldosterone, which stimulate the H^+-K^+-ATPase and H^+-ATPase pumps, respectively, can have a potentiating effect on di hydrogen secretion and therefore on the development and maintenance metabolic alkalosis.[147] This synergism has potential clinical importance, si

many of the causes of metabolic alkalosis (such as diuretic therapy, vor and primary hyperaldosteronism) are associated with both a reduction i plasma K^+ concentration and increased aldosterone release (see Chap. 18).

In summary, hypokalemia tends to increase net acid excretion, which promo development of metabolic alkalosis. Hyperkalemia, via opposite mechanisms reduces net acid excretion, which, by causing H^+ retention, favors the development of metabolic acidosis. In some patients with hyperkalemia due to hypoaldos for example, the associated metabolic acidosis can be corrected solely by l the plasma K^+ concentration.[139]

Parathyroid Hormone

Parathyroid hormone (PTH) diminishes proximal tubule HCO_3^- reabsorption by reducing the activity of the Na^+–H^+ exchanger in the luminal membrane[148,149] and the Na^+–$3HCO_3^-$ cotransporter in the basolateral membrane.[150] However, the extra HCO_3^- delivered out of the proximal tubule is mostly picked up in the loop o and more distal segments. Although there may be a slight increase in HCO_3^- excretion, this is generally counteracted by enhanced excretion of phospha can increase net acid excretion by buffering secreted H^+ ions.[151]

This response may be physiologically important, since an acid load stimula secretion. PTH then minimizes the change in extracellular pH both by promo buffering and by increasing acid and phosphate excretion in the urine.[151,152]

The effect of a chronic excess of PTH on acid-base balance is less clear. P with primary hyperparathyroidism, who are also hypercalcemic, tend to

have a metabolic acidosis.[153] However, the chronic, continuous administration o PTH to normal humans increases net acid excretion and produces a small e not reduction, in the plasma HCO_3^- concentration.[154]

EFFECT OF ARTERIAL PH ON VENTILATION

Alveolar ventilation provides the oxygen necessary for oxidative metabolism eliminates the CO_2 produced by these metabolic processes. It is therefore appropriate that the main physiologic stimuli to respiration are an elevation P_{CO_2} and a reduction in the P_{O_2} (hypoxemia).[155,156] The CO_2 stimulus to ventilation primarily occurs in chemosensitive areas in the respiratory cent brain stem, which appear to respond to CO_2-induced changes in the cerebral interstitial pH.[157] This effect is extremely important in the maintenance of the base balance, since roughly 15,000 mmol of CO_2 is produced daily from endogenous metabolism, added to the capillary blood, and then eliminated via the lungs contrast, hypoxemia is primarily sensed by peripheral chemoreceptors in th bodies, which are located near the bifurcation of the carotid arteries.[156,158]

Respiratory Compensation in Metabolic Acidosis and Alkalosis

Alveolar ventilation also is affected by metabolic acid-base disorders.[159,160,161,162,163,164] and [165] In metabolic acidosis, for example, minute ventilation can increase from the normal of approximately 5 L/min to than 30 L/min as the arterial pH falls from 7.40 to 7.00 (Fig. 7-10). The initial rise in ventilation is mediated primarily by the peripheral chemoreceptors in the ca bodies, which immediately sense the reduction in pH. However, the ensuing P_{CO_2} produces an acute *elevation* in cerebrospinal fluid and cerebral interstitial since CO_2 but not HCO_3^- rapidly crosses the blood-brain barrier. As a result, th central chemoreceptors sense alkalemia and act to diminish ventilation, the limiting the ventilatory response.[159] If the acidemia persists for hours to days, however, the cerebral pH will fall, as a result of ionic diffusion or the forma new cerebrospinal fluid that reflects the change in systemic pH.[159,160] This cerebral adaptation allows the full degree of hyperventilation to be seen, u 12 to 24 h.[159,161]

The increase in ventilation with metabolic acidosis is an appropriate compe response, since the concomitant reduction in P_{CO_2} will return the extracellular pH toward normal.[162,163] Conversely, hypoventilation with a consequent elevation P_{CO_2} lowers the pH toward normal in metabolic alkalosis, where the HCO_3^- plasma concentration is increased.[164,165]

The potential importance of these respiratory compensations to metabolic a and alkalosis can be appreciated from the following hypothetical example. I ketoacidosis (see Chap. 25), the increased production of ketoacids is buffered i part in the extracellular fluid, resulting in a decline in the plasma

HCO_3^- concentration. If the latter were reduced to 6 meq/L and the P_{CO_2} remained at the normal 40 mmHg, then

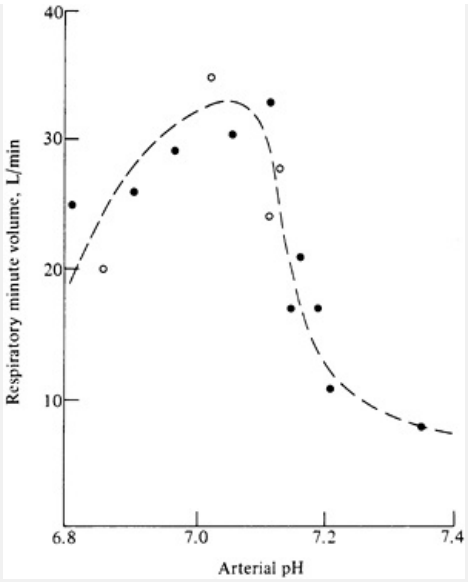

Figure 11-1 Relationship between respiratory minute volume and arterial p patients with diabetic ketoacidosis. (*Reproduced from Kety SS, Polis BD, Nadler CS, Schmidt CF: J Clin Invest 27:500, 1948, by copyright permission of the American Society for Clinical Investigation.*)

$$\text{pH} = 6.1 + \log\frac{6}{0.03 \times 40} = 6.80$$

However, if ventilation were stimulated by the acidemia and the P_{CO_2} fell to 15 mmHg, then

$$\text{pH} = 6.1 + \log\frac{6}{0.03 \times 15} = 7.22$$

Thus, the respiratory compensation has turned a life-threatening reduction one that is much less dangerous.

Limitation of Respiratory Compensation

Despite the effectiveness of the respiratory compensation, the pH is protec only a few days, since the initially beneficial change in P_{CO_2} alters renal HCO_3^- reabsorption. In metabolic acidosis, for example, the compensatory fa P_{CO_2} decreases HCO_3^- reabsorption (Fig. 11-1) and, therefore, the plasma HCO_3^- concentration. The net effect is that, after several days, *the extracellular pH is the same as it would have been if no respiratory compensation had occurred*, since the decline in P_{CO_2} is balanced by a further reduction in the HCO_3^- concentration (Table 11-2).[166] Fortunately, most forms of severe metabolic acidosis

are acute (ketoacidosis, lactic acidosis, ingestions), so that the associated hyperventilation does protect the pH.

Table 11-2 Arterial pH in chronic metabolic acidos with and without respiratory compensation

	Arterial		
Clinical state	pH	$[HCO_3^-]$, meq/L	P_{CO_2}, mmHg
Baseline	7.40	24	40
Metabolic acidosis			
No compensation	7.29	19	40
Compensation			
Acute	7.37	19	34
Chronic	7.29	16	34

Similar considerations apply to the compensatory hypoventilation seen with metabolic alkalosis. The rise in P_{CO_2} in this setting leads to increased H^+ secretion, a further elevation in the plasma HCO_3^- concentration, and no net improvement in the alkalemia.[167]

It is presumed that alterations in renal tubular cell pH are responsible for t changes in H^+ secretion. In metabolic acidosis, for example, the fall in plasma HCO_3^- concentration will produce a parallel reduction in the cell pH that is the signal to enhance H^+ secretion. Returning the extracellular pH toward norm increasing ventilation will also raise the cell pH, since reducing the P_{CO_2} will result in CO_2 diffusion out of the cell. This will lead to an initially lower level of n excretion and therefore a further reduction in the plasma HCO_3^- concentration.

These observations once again illustrate the importance of the steady state patient with chronic metabolic acidosis who produces an extra 100 meq of a day will enter the steady state only when daily acid excretion increases by The signal to maintain this increment in H^+ secretion is probably a reduction in the cell pH; furthermore, *the required level of cellular acidification to enhance acid excretion by 100 meq will be the same whether or not respiratory compens has occurred.* Thus, the extracellular pH will also be the same in both setting it is the primary determinant of changes in the cell pH.[98]

SUMMARY

From the Henderson-Hasselbalch equation, the arterial pH is a function of t $[HCO_3^-]/0.03P_{CO_2}$ ratio. Three processes are involved in the maintenance of arterial pH:[1] The extracellular and intracellular buffers act to minimize chang pH induced by an acid or base load,[2] and plasma HCO_3^- concentration

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is held within narrow limits by the regulation of renal H^+ excretion,[3] and the P_{CO_2} is controlled by variations in alveolar ventilation. How these processes inte protect the pH can be appreciated from the response to an HCl load (Fig. 11-19):

1. Extracellular buffering of the excess H^+ by HCO_3^- occurs almost immediately.
2. Within several minutes, the respiratory compensation begins, resulting hyperventilation, a decrease in the P_{CO_2}, and an increase in the pH toward normal.
3. Within 2 to 4 h, the intracellular buffers (primarily proteins and organic phosphates) and bone provide further buffering as H^+ ions enter the cells in exchange for intracellular K^+ and Na^+. These responses act to prevent wide swings in the arterial pH until acid-base homeostasis can be restored b renal excretion of the H^+ load as NH_4^+ and titratable acidity.
4. The corrective renal response begins on the first day and is complete w 6 days.[5,79,104]

This sequence tends to be reversed with a NaHCO$_3^-$ load. The corrective renal response tends to be more rapid than after an acid load, as the excess HCO_3^- is quickly excreted in the urine. Both decreased reabsorption and secretion of HCO_3^- in the cortical collecting tubule play a contributory role in this setting.[19,20] and [21,55] Alterations in pH induced by changes in the P_{CO_2} produce a somewhat different response. There is virtually no extracellular buffering since HCO_3^- and CO_2 effectively buffer each other (see page 313). Similarly, there is no compensatory chan in alveolar ventilation, since the primary disturbance is one of abnormal res Thus the intracellular buffers (including hemoglobin) and changes in renal H^+ excretion constitute the only protective mechanisms against respiratory aci alkalosis.

If, for example, the P_{CO_2} is increased, the intracellular buffers will act to incre the plasma HCO_3^- concentration, thereby minimizing the degree of acidemia (Fig. 11-20). This process is complete within 10 to 30 min.[168] This intracellular buffers increase the plasma HCO_3^- concentration by only 1 meq/L for each

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10-mmHg rise in the P_{CO_2} and are therefore relatively ineffective in protecting

pH.** If the hypercapnia persists, however, there will be an appropriate incr renal H^+ excretion, resulting in a further elevation in the plasma HCO_3^- concentration.

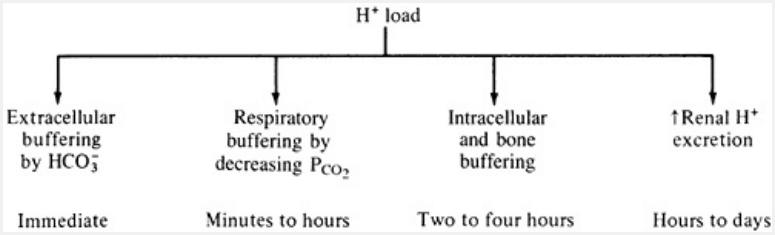

Figure 11-19 Sequential response to a H^+ load, culminating in the restoration of acid-base balance by the renal excretion of the excess H^+.

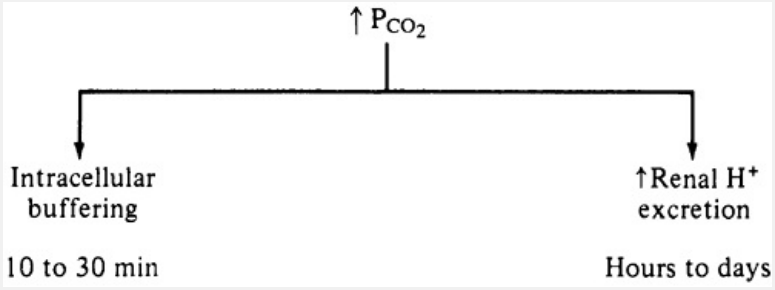

Figure 11-20 Response to an increase in the P_{CO_2}. Although these changes raise the pH toward normal, acid-base homeostasis will not be restored u ventilation is normalized.

It is this renal compensation, which begins within several hours but is not c for several days,[106] that constitutes the main defense against respiratory acid Even if the P_{CO_2} is chronically elevated at 80 mmHg, the pH usually is not mu lower than 7.30 because of the effectiveness of the renal compensation. Th sequence is reversed with respiratory alkalosis, as there is an appropriate in the plasma HCO_3^- concentration as a result of intracellular buffering and decreased net acid excretion.[108,109]

The renal responses to alterations in the P_{CO_2} are compensatory but not corrective Acid-base homeostasis will not be restored unless alveolar ventilation is nc

PROBLEMS

11-1 The daily H^+ load is excreted in the urine as titratable acidity and NH_4^+. Would H^+ retention leading to metabolic acidosis occur if there were:

a. a marked reduction in titratable acid excretion, as a result of a dec in the plasma phosphate concentration?

b. a marked reduction in NH_4^+ formation?

11-2 Equal amounts of H^+, as HCl or H_2SO_4, are given over several days to a volume-depleted subject. Which acid will produce the greater degree o acidemia?

11-3 Two patients with a normal GFR of 180 L/day are studied, one with acid-base balance and one with metabolic acidosis. The following labo data are obtained from the first patient:

$$\text{Plasma } [HCO_3^-] = 24 \text{ meq/L}$$
$$\text{Titratable acidity} = 30 \text{ meq/day}$$
$$NH_4^+ \text{ excretion} = 50 \text{ meq/day}$$
$$\text{Urine pH} = 5.5$$

Similar values in the second patient are

$$\text{Plasma } [HCO_3^-] = 6 \text{ meq/L}$$
$$\text{Titratable acidity} = 75 \text{ meq/day}$$
$$NH_4^+ \text{ excretion} = 140 \text{ meq/day}$$
$$\text{Urine pH} = 5.0$$

Assuming that all the filtered HCO_3^- is reabsorbed, which is indicated by the low urine pH, calculate:

a. net acid excretion

b. total H^+ secretion (which includes that utilized for reabsorption of t filtered HCO_3^-)

11-4 The following values are obtained on a 24-h urine collection:

$$\text{Phosphate} = 60 \text{ mmol}$$
$$\text{pH} = 5.8$$

If the arterial pH is 7.40 and the pK_a for phosphate is 6.80, how many millimoles of H^+ are excreted as titratable acidity using HPO_4^{2-} as a buffer? Is NH_4^+ excretion included in the measurement of titratable acidity?

11-5 A patient with persistent vomiting develops metabolic alkalosis as result of the loss of HCl in gastric juice. Why isn't the condition corre

spontaneously by excretion of the excess HCO_3^- in the urine?

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Footnotes

* The Na^+-$3HCO_3^-$ has an additional function in that it provides the major mechanism by which metabolic acid-base changes are sensed within the cell (see "Regulation of Renal Hydrogen Excretion: Extracellular Fluid (H^+) Concentration").

† The increment in renal glutamine uptake leads to an initial reduction in cell glutamine levels.[80] This is then followed by increased glutamine release from skeletal muscle, due in part to activation of glutamine synthetase.

‡ It seems likely that distal acidification is similar in metabolic and respiratory acidosis,[93] since the confounding effect of increased reabsorption of HCO_3^- is primarily limited to the proximal tubule. However, this preservation of distal H^+ in chronic respiratory acidosis does not lead to a significant increase in net H^+ excretion, since virtually all of the urinary NH_4^+ is produced proximally.[68,69] Thus, the absence of an elevation in proximal production of NH_4^+ limits[110] the degree to which distal H^+ secretion can enhance net acid excretion.

¶ This ability of aldosterone to increase urinary H^+ excretion can promote the development of metabolic alkalosis in disorders of primary mineralocorticoid excess such as primary hyperaldosteronism (see Chapter 18).

** The changes in the plasma HCO_3^- concentration seen with acute and chronic respiratory acidosis and alkalosis are presented in detail in Chapters 20 and 21.

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Chapter Twelve
Potassium Homeostasis

INTRODUCTION

The total body K^+ stores in a normal adult are approximately 3000 to 4000 me to 55 meq/kg body weight). In contrast, total Na^+ is restricted primarily to the extracellular fluid (ECF), K^+ is basically an intracellular cation, with 98 percent body K^+ being located in the cells. This can be appreciated from the disparit between the K^+ concentrations in the two compartments: cell K^+ concentration of 140 meq/L versus extracellular (and plasma) K^+ concentration of only 4 to 4.5 meq/l The location of Na^+ and K^+ in the different fluid compartments is maintained by active Na^+-K^+-ATPase pump in the cell membrane, which pumps out Na^+ and pumps K^+ into the cell in a 3 : 2 ratio (see page 75).[1,2]

Potassium has two major physiologic functions. First, it plays an important metabolism, participating in the regulation of such processes as protein an glycogen synthesis.[3] As a result, a variety of cell functions may become

impaired in conditions of K^+ imbalance. As an example, patients with marked K^+ depletion often complain of polyuria (increased urine output). This is due i reduced ability to concentrate the urine, resulting from decreased responsi antidiuretic hormone (ADH) (see page 172, Fig. 12-1).

Second, the *ratio* of the K^+ concentrations in the cell and the ECF is the major determinant of the resting membrane potential (E_m) across the cell membrane. This relationship can be expressed by the following formula:

$$E_m = -61 \log \frac{r[K^+]_{cell} + 0.01[Na^+]_{cell}}{r[K^+]_{ecf} + 0.01[Na^+]_{ecf}} \qquad (12\text{-}1)$$

where r is the Na^+-K^+ active transport ratio of 3 : 2 and 0.01 is the relative membrane permeability of the Na^+-K^+.[4] It is the resting potential that sets the stag for the generation of the action potential that is essential for normal neural muscular function. Thus, both hypokalemia (low plasma K^+ concentration) and hyperkalemia (high plasma K^+ concentration) can result in potentially fatal musc paralysis and cardiac arrhythmias, in part by altering conduction in skeleta

cardiac muscle.

The pathophysiologic effects of K^+ imbalance will be discussed in detail in Chapters 26, 27 and 28. The remainder of this chapter will deal with the two functions responsible for the maintenance of a normal plasma K^+ concentration: (1) the distribution of K^+ between the cells and the extracellular fluid and (2) the urinary excretion of the K^+ added to the extracellular fluid from the diet and endogenous cellular breakdown.

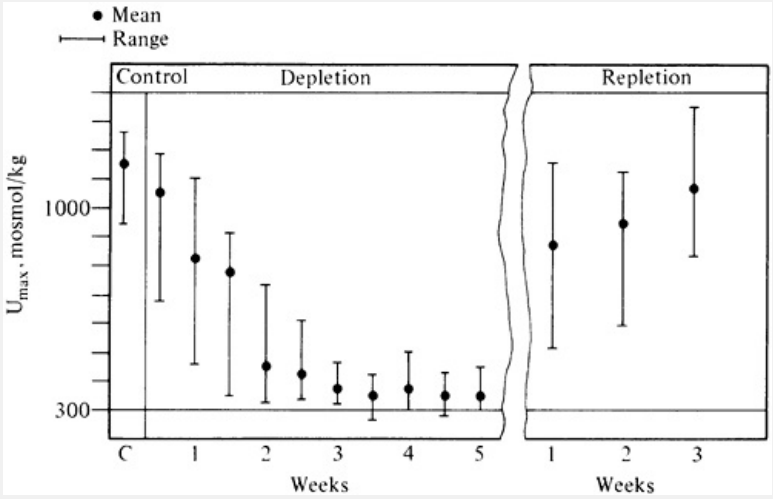

Figure 12-4 Ability to maximally concentrate the urine (U_{max}) in patients with progressive potassium depletion. The average daily K^+ deficit was 350 meq, or about 10 percent of the total body K^+. (*From Rubini, M: J Clin Invest 40:2215, 1961, by copyright permission of the American Society for Clinical Investigation.*)

DISTRIBUTION OF POTASSIUM BETWEEN CELLS AND EXTRACELLULAR FLUID

Regulation of the internal distribution of K^+ must be extremely efficient, since the movement of as little as 1.5 to 2 percent of the total body K^+ into the ECF can result in a potentially fatal increase in the plasma K^+ concentration to as high as 8 meq/L or more. A variety of factors, both physiologic and pathologic, can influence this process (Table 12-1).[5,6] The most important in the day-to-day regulation of K^+ balance are the Na^+-K^+-ATPase (the activity of which is increased by catecholamines and insulin) and the plasma K^+ concentration itself.

Sodium-Potassium-ATPase

Normal K^+ distribution is primarily determined by the Na^+-K^+-ATPase pump.[1] The activity of this pump is regulated by several factors, including thyroid hormone with regard to K^+ homeostasis, catecholamines, insulin, and the state of K^+

balance[1].

An example of the importance of this pump in humans can be seen when Na^+-K^+-ATPase is partially inhibited by a massive overdose of digitalis, a drug used in the treatment of heart disease. In this setting, marked hyperkalemia (plasma K^+ concentration of up to 13.5 meq/L) can occur, because of the relative inability of K^+ to enter the cells[7].

The result is somewhat different when the pump is impaired chronically, as in the case of chronic diseases such as renal failure and heart failure[1]. In these, Na^+-K^+-ATPase activity is often reduced as a result of an acquired defect in cell function[8,9]. As a result, K^+ leaves and Na^+ enters the cells down passive gradients. The net effect is as much as a 10 to 15 percent reduction in total body K^+ stores in association with

a high cell Na^+ concentration and a low cell K^+ concentration, but no change in the plasma K^+ concentration because the excess extracellular K^+ has nowhere to be excreted in the urine if renal function is adequate[8,9,10,and 11]. In patients with renal failure, however, the decrease in pump activity can contribute to the develc hyperkalemia.

Table 12-1 Factors influencing the distribution of K^+ between the cells and the extracellular fluid

Physiologic	
	Na^+-K^+-ATPase
	Catecholamines
	Insulin
	Plasma K^+ concentration
	Exercise
Pathologic	
	Chronic diseases
	Extracellular pH
	Hyperosmolality
	Rate of cell breakdown

In addition to the basal distribution of K^+, there is a frequent exchange of K^+ between the ECF and the cells because of variations in dietary intake. For example, three large glasses of orange juice contain approximately 40 meq of K^+. The normal extracellular fluid volume is roughly 17 liters in a 70-kg man. Thus, there would be a potentially dangerous 2.4 meq/L (40 meq÷17 L) increase in the plasma K^+ concentration if the ingested K^+ remained in the extracellular fluid. This is prevented

by the rapid entry of most of the K^+ load into the cells.[6] Within 6 to 8 h, K^+ balance is then restored by the urinary excretion of the excess K^+.[12,13] Although the initial elevation in the plasma K^+ concentration directly promotes the intracellular movement of K^+, both catecholamines and insulin also play an important role process.

Catecholamines

Catecholamines can affect internal K^+ distribution, with α-receptors impairing and β_2-receptors promoting the cellular entry of K^+.[14,15] The β_2-receptor-induced stimulation of K^+ uptake is mediated at least in part by activation of the Na^+-K^+-ATPase pump.[16,17] This appears to reflect *a permissive action of basal catecholamine levels*, since there is no evidence that a K^+ load increases the release of epinephrine or norepinephrine.[14]

The physiologic importance of catecholamines in humans can be illustrated observations. First, the increment in the plasma K^+ concentration after a K^+ load is greater and more prolonged if the subject has been pretreated with a β -ad blocker, such as propranolol (Fig. 12-2).[14,16,18,19] This difference is due to a substantial reduction in cellular K^+ uptake, most of which normally occurs in skele muscle and the liver.[14]

Second, the release of epinephrine during a stress response, such as coron ischemia, can acutely lower the plasma K^+ concentration by approximately 0.5 to 0 meq/L.[20] In this setting, the hypokalemic response also may be mediated by insulin release. Increased β_2-adrenergic activity enhances insulin secretion both direct stimulation of the pancreas and by enhancing glycolysis, leading to a the plasma glucose concentration.[21] The net effect can, in patients with preexiste mild diuretic-induced hypokalemia, result in an acute reduction in the plasm K^+ concentration to below 2.8 meq/L (Fig. 12-3).

A similar hypokalemic effect can be induced by the administration of a β_2-adrenergic agonist, such as albuterol, terbutaline, or dobutamine, to treat asthma or h or to prevent premature labor.[22,23] In heart failure, for example, the acute 0.4 me fall in the plasma potassium concentration can enhance the tendency to ver arrhythmias.[24]

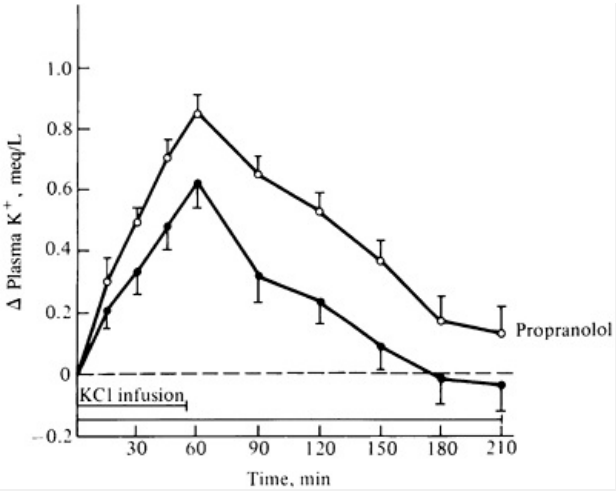

Figure 12-2 Changes in the plasma K^+ concentration after a K^+ load in the absence (solid circles) or presence (open circles) of the beta-adrenergic propranol. *(From Rosa RN, Silva P, Young JB, et al: N Engl J Med 302:431, 1980. Reprinted by permission from the New England Journal of Medicine.)*

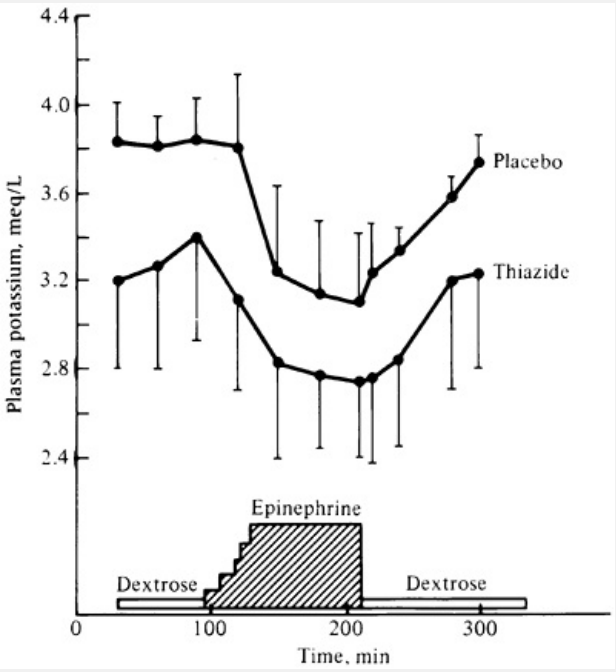

Figure 12-3 Plasma K^+ concentra-tion during an infusion of epine-phrine (in physiologic doses) in 6 patients pretreated with a placebo or a thiazide d for 7 days. The plasma K^+ concentration fell in both groups but reached potentially dangerous levels in the diuretic-treated patients, who had milc ine hypokalemia. *(From Struthers AD, Whitesmith R, Reid JL: Lancet 1:1358, 1983, with permission.)*

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Insulin

Insulin promotes the entry of K^+ into skeletal muscle and the liver[25,26] again by increasing Na^+-K^+-ATPase activity.[1,27] This property, which is independent of any effect on glucose transport,[25] plays a physiologic role in the regulation of the plasma K^+ concentration.[5,6,26,28] For example, the ingestion of glucose (which enhances endogenous insulin release) minimizes the rise in the plasma K^+ concentration induced by concurrent intake of K^+ (Fig. 12-4).[19]

On the other hand, the ability to handle a K^+ load is impaired with insulin deficiency (as might be induced by an infusion of somatostatin). In this setting, the basal plasma K^+ concentration rises (by 0.4 to 0.5 meq/L), and an K^+ load induces a greater than normal degree of hyperkalemia. These changes are reversed by infusion of insulin.[26] Furthermore, no alteration in K^+ balance is seen when somatostatin is used in type 1 (insulin-dependent) diabetes mellitus, since patients have little or no endogenous insulin and somatostatin is therefore effective.[26]

As with catecholamines, it appears that *basal insulin levels permissively allow K^+ entry into cells*. The possible presence of a positive feedback loop, in which K^+ stimulates the release of insulin, is uncertain. Initial studies demonstrated that the plasma insulin concentration after an increase in the plasma K^+ concentration of more than 1 meq/L,[28] in comparison, a more physiologic elevation of 0.3 to 0.7 meq/L is without apparent effect.[28,29] It is possible, however, that small elevations in the plasma K^+ concentration can increase insulin release into the portal vein, thereby promoting hepatic K^+ uptake without affecting the peripheral plasma insulin level.[30]

In addition to its physiologic role, the effect of insulin on K^+ distribution is useful in the treatment of *hyperkalemia*. Giving either glucose (to enhance endogenous insulin release) or insulin (with glucose to prevent hypoglycemia) can acutely lower the plasma K^+ concentration by driving K^+ into the cells (see Chap. 28).[31] On the other hand, treating *hypokalemia* by the administration of intravenous K^+-containing dextrose-containing solution can cause an initial further reduction in

the plasma K^+ concentration and the possible induction of ventricular arrhythmias.[32] This effect of insulin on K^+ distribution lasts only several hours, since other factors (including the plasma K^+ concentration itself) then cause K^+ to move back into the extracellular fluid.[31]

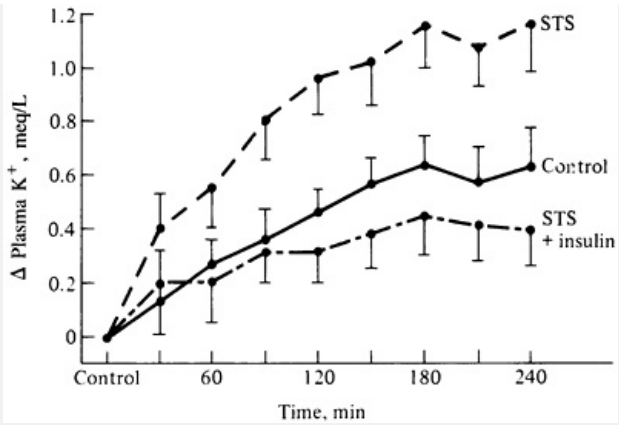

Figure 12-4 Peak increase in the plasma potassium concentration in normal subjects following the ingestion of 0.25 meq/kg of potassium alone (K) or glucose (K + G), a beta-blocker (K + β), or a beta blocker and glucose (K G). The degree of hyperkalemia was minimized by glucose (via enhanced release of insulin) and increased by a beta-blocker. (*Data from Allon M, Dansby L, Shanklin N:* Am J Med *94:475, 1993, with permission.*)

To summarize, the primary physiologic effect of insulin and catecholamines facilitate the disposition of an K^+ load. Although a deficiency of these hormones m initially elevate the baseline plasma K^+ concentration, this is usually transient, sir the excess K^+ is readily excreted in the urine. Thus, *in the fasting state, the plasma K^+ concentration is typically normal* in patients treated with β -adrenergic blockers in patients with type 1 diabetes mellitus given enough insulin to prevent ma hyperglycemia.[1,4,18,26]

Plasma Potassium Concentration

The combination of insulin deficiency and sympathetic blockade impairs but prevent the intracellular movement after a K^+ load, indicating that other factor must also be involved.[33] One of these is the plasma K^+ concentration itself. After a K^+ load, for example, the initial elevation in the plasma K^+ concentration promotes K^+ entry into the cells, perhaps by passive mechanisms. Conversely, the los from the ECF due to gastrointestinal or renal losses results first in a fall in plasma K^+ concentration and then in the movement of K^+ from the cells into the ECF to minimize the degree of hypokalemia.

The net effect is that, in most situations, the plasma K^+ concentration varies directly with body K^+ stores, decreasing with depletion and increasing with retention.[6] There are, however, some exceptions to this rule, including chronic disease described above (in which Na^+-K^+-ATPase activity appears to be reduced), exerc changes in the extracellular pH or rate of cell breakdown, and an increase effective plasma osmolality. In these disorders, clinically significant hyperk hypokalemia may result from redistribution of K^+ between the cells and the ECF

without change in body stores.

Exercise

Potassium is normally released from muscle cells during exercise. This resp
in part reflect a delay between exit of K^+ during depolarization and subsequent reuptake by the Na^+-K^+-ATPase pump.[1] With moderate to severe exercise, howev an additional factor may become important. Muscle cells have ATP-depende channels, in which ATP reduces the number of open channels. Thus, a redu ATP levels with marked exercise can open up more channels, thereby promo release of K^+ from the cells.[34]

The release of K^+ during exercise may have a physiologic function. The increase in the plasma K^+ concentration has a vasodilatory effect that contribut the enhanced blood flow (and therefore energy delivery) to the exercising muscle.[34,35] This response is impaired by K^+ depletion, an abnormality that may contribute to ischemic muscle injury.[35]

The elevation in the systemic plasma K^+ concentration (which is less than that in local circulation) is related to the degree of exercise: 0.3 to 0.4 meq/L with walking,[36] 0.7 to 1.2 meq/L with moderate exercise,[16,37,38] and as much as 2.0 meq/L with severe exercise to exhaustion.[39,40] These changes are reversed after several minutes of rest[37,40] and may be associated with a mild rebound hypokalemia of 0.4 to 0.5 meq/L below the baseline level.[39]

Exercise-induced hyperkalemia is attenuated by physical conditioning.[1,41] Conditioning enhances both the resting concentration and Na^+-K^+-ATPase activity (via an unknown mechanisms); the latter adaptation may be respons the lesser degree of K^+ release during exercise.

The hyperkalemia associated with exercise is generally mild and produces symptoms. However, it can lead to a potentially dangerous elevation in the K^+ concentration in the presence of some other abnormality affecting K^+ handling. As an example, severe exercise in patients taking a β-adrenergic blocker can acu the plasma K^+ concentration by 1.5 to as much as 4 meq/L.[16,40]

The effect of exercise can also affect the *measurement* of the plasma K^+ concentration. After a tourniquet is applied, the patient is frequently instru repeatedly clench and unclench his or her fist in an attempt to increase loc flow and make the veins more apparent for venipuncture. This can result in as a 1 to 2 meq/L elevation in the plasma K^+ concentration, leading to erroneous evaluation of the state of K^+ balance.[42]

Extracellular pH

Changes in acid-base balance may have important effects on the plasma K^+ concentration, particularly in those forms of metabolic acidosis (such as re that are not due to the accumulation of organic acids.[43] In this setting, 60 percent or more of the excess H^+ ions is buffered in the cells (see Fig. 12-4). Since the major extracellular anion (Cl^-) enters the cells only to a limited degree, electroneutralit maintained by the movement of cellular K^+ and Na^+ into the ECF (Fig. 12-5). The result is a *variable increase in the plasma K^+ concentration* of 0.2 to 1.7 meq/L for every 0.1-unit fall in the extracellular pH (the latter is usually measured cli an arterial blood specimen).[43,44] (The plasma Na^+ concentration may also rise, but an elevation of a few milliequivalents per liter is not physiologically importa the normal value is 140 meq/L, not 4 to 4.5 meq/L as with potassium.)

The wide variability in the degree of hyperkalemia is probably related in pa common presence of other factors that can influence K^+ homeostasis.[43,44] As examples, diarrhea and renal tubular acidosis are associated with increase gastrointestinal and urinary K^+ losses, respectively (page 623), the negative K^+ balance in these disorders often leads to hypokalemia despite the presence metabolic acidosis. It should be emphasized, however, that there is still *hyperkalemia* in this setting, since correction of the acidemia will lead to a fu reduction in the plasma K^+ concentration unless K^+ supplements are administered.

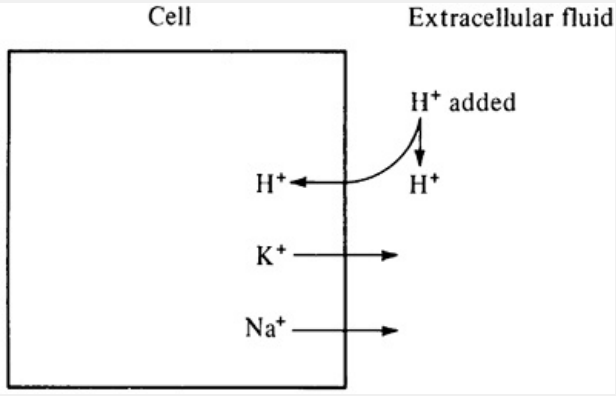

Figure 12-5 Reciprocal cation shifts of K^+, H^+, and Na^+ between the cells and the extracellular fluid. In the presence of a mineral acid load, H^+ moves into the cells, where it is buffered. To maintain electroneutrality, K^+ and Na^+ leave the cells, resulting in an increase in the plasma K^+ concentration.

The relationship between acidemia and K^+ distribution is also not predictable in th organic acidoses (lactic acidosis and ketoacidosis). In these conditions, th appears to be less likely to elevate the plasma K^+ concentration.[43,45,46] and[47]* As depicted in Fig. 12-6, for example, the administration of HCl, but not of lactic a causes hyperkalemia in dogs. The reason for this difference is not known.

possibility is that the organic anion (such as lactate or β -hydroxybutyrate ketoacidosis) is able to follow H^+ into the cell, thereby removing the necessity fo redistribution of K^+.[43,48] Alternatively, experimental studies suggest that organ anions may act as substrates for the pancreatic β cell, leading to the relea insulin.[49] Insulin then drives K^+ into the cells, counteracting the direct effect of acidemia. However, the applicability of these findings to humans remains tc proven, especially in diabetic ketoacidosis, where insulin deficiency is the abnormality.

The change in the plasma K^+ concentration is also much less prominent in metal alkalosis.[43] Although H^+ tends to move out of and K^+ into the cells in this disorder, there is generally only a small reduction in the plasma K^+ concentration (unless there are concomitant urinary or gastrointestinal losses of K^+). This relative lack of effect may result in part from less intracellular buffering (and therefore les transcellular H^+ movement) in metabolic alkalosis than in metabolic acidosis (percent versus 57 percent).[51] Large changes in the plasma K^+ concentration are also not seen in respiratory acidosis or alkalosis; why this occurs is not we understood.[43]

Hyperosmolality

The plasma K^+ concentration may rise by as much as 0.4 to 0.8 meq/L for eve mosmol/kg elevation in the effective plasma osmolality (due to hyperglycem hypernatremia, or the administration of hypertonic mannitol)[30,52,53,54] and[55] Hyper-osmolality results in the diffusion of water out of cells down an osmc gradient

(seepage 241). In this setting, two factors can contribute to the parallel move K^+ into the ECF:

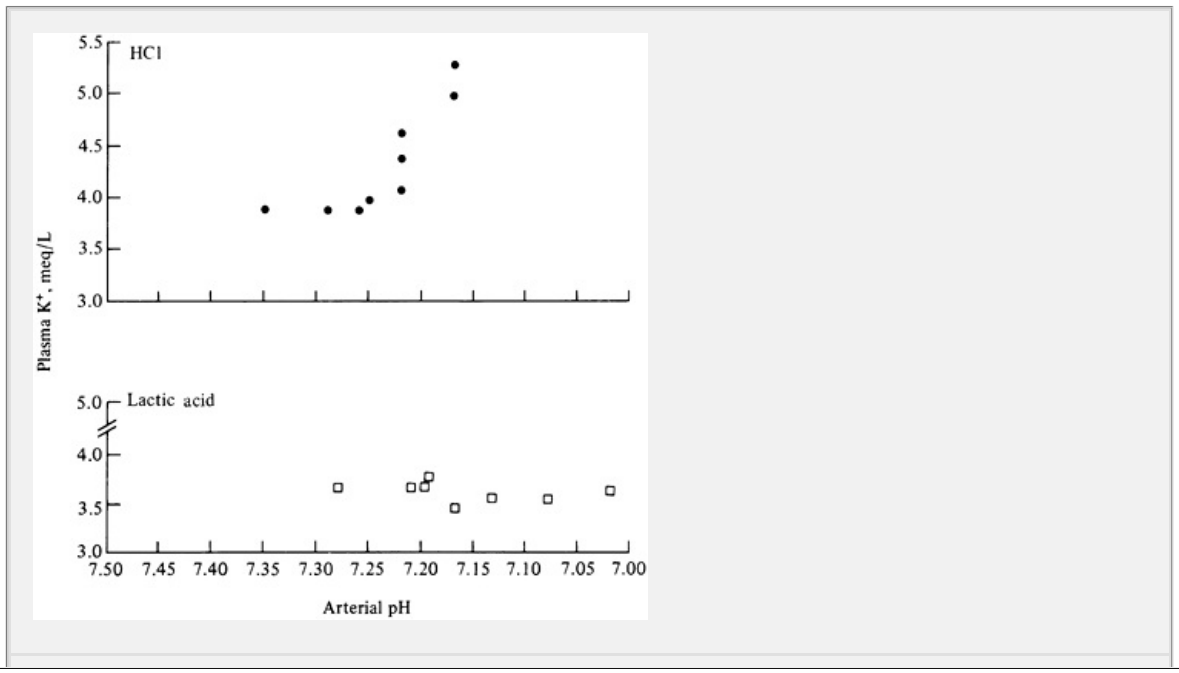

Figure 12-6 Change in the plasma K^+ concentration in relation to the arterial pH in experimentally induced hydrochloric acidosis (HCl is a mineral acid) and acidosis in dogs. *(From Perez GO, Oster JR, Vaamonde CA: Nephron 27:233, 1981, with permission.)*

1. The loss of water raises the K^+ concentration within the cell, thereby creating a favorable gradient for passive potassium exit through *potassium channels* in the cell membrane.
2. The frictional forces between the solvent (water) and solute can result in K^+ being carried along with water through the *water channels* in the cell membrane. This phenomenon, called *solvent drag*, is independent of concentration or electrical gradients for K^+ or other solutes.

A common clinical example of this phenomenon is the increase in the plasma K^+ concentration that commonly accompanies hyperglycemia in uncontrolled diabetes mellitus (Fig. 12-7).[50,52,53] The hyperkalemia partially dissipates with time, as some of the excess extracellular K^+ is excreted in the urine.

Rates of Cell Breakdown and Production

Any condition that enhances cell breakdown (such as severe trauma or the tumor lysis syndrome) results in the release of K^+ (and other intracellular solutes) into the ECF.[56,57] and[58] The degree to which this will elevate the plasma K^+ concentration is related to the ability of other cells to take up the excess K^+ and the ability of the kidney to augment K^+ excretion.

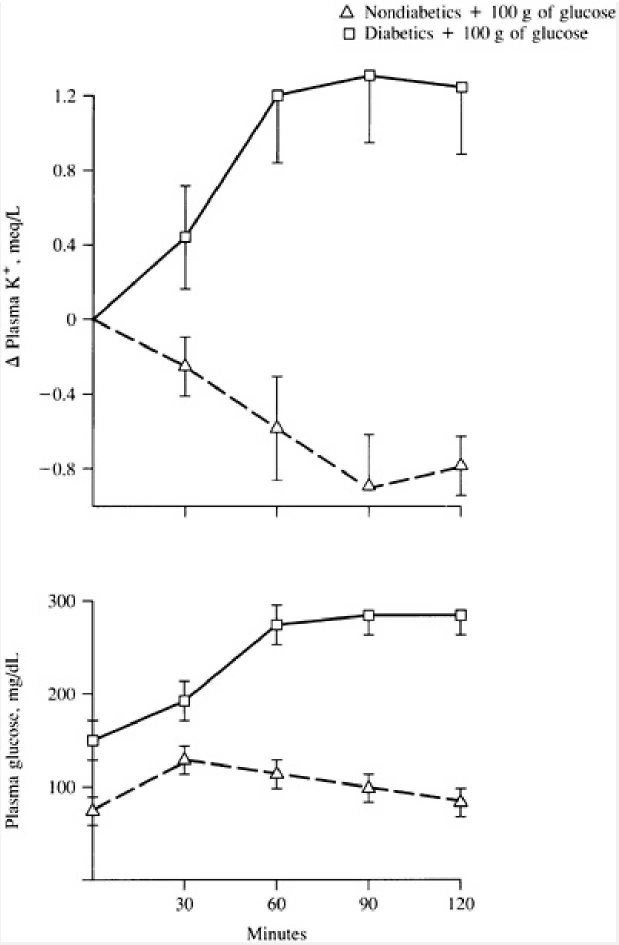

Figure 12- Effect of glucose infusion on the plasma K^+ and glucose concentrations in normal subjects (triangles) and in diabetics (squares). The plasma K^+ concentration falls in normals due to the release of insulin, but rises in diabetics because of the development of hyperglycemia and hyperosmo *(From Nicholis GL, Kahn T, Sanchez A, Gabriel JL,* Arch Intern Med *141:49, ©1981. Copyright 1981, American Medical Association, with permission.)*

On the other hand, conditions associated with a rapid *increase in cell production* can result in K^+ movement into the cells and hypokalemia. This sequence has observed after the administration of folic acid or vitamin B_{12} to patients with

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megaloblastic anemia, who typically respond with an acute and marked incr the production of red cells and platelets.[59]

Summary

In the basal state, the distribution of K^+ between the cells and the ECF is primarily governed by the Na^+-K^+-ATPase pump in the cell membrane. Although they are so important in the basal state, catecholamines and insulin play a major rol promoting the cellular uptake of K^+ after a dietary load. This prevents a potential serious elevation in the plasma K^+ concentration until the kidney can restore K

balance by excreting the excess K^+. These hormones appear to act permissively, since their rate of secretion is not enhanced by K^+.

The plasma K^+ concentration may also directly influence K^+ distribution, as K^+ moves into the cells with hyperkalemia and out of the cells with hypokalemi result, the plasma K^+ concentration generally reflects the state of total body K^+ stores. This relationship may be distributed, however, in a variety of condit as exercise, certain forms of metabolic acidosis, or hyperosmolality) in whi redistribution can alter the plasma K^+ concentration without a similar change in K^+ stores.

RENAL POTASSIUM EXCRETION

Although small amounts of K^+ are lost each day in stool (5 to 10 meq) and sweat to 10 meq), the kidney plays the major role in the maintenance of K^+ balance, appropriately varying K^+ excretion with changes in dietary intake (normal range to 120 meq/day). The primary event in urinary K^+ excretion is the *secretion of K^+ from the tubular cell into the lumen in the distal nephron*, particularly in the principal cells in the cortical collecting tubule and in the cells in the adjace connecting segment and outer medullary collecting tubule.[60,61,62]

Segmental Potassium Handling

The sequential handling of filtered K^+ by the different nephron segments is depict in the micropuncture experiments in Fig. 12-8.[60,63] The clearance of K^+ is compared to that of inulin, which is filtered and then is neither reabsorbed secreted. As a result, a fall in C_{K^+}/C_{in} ratio indicates that K^+ has been removed from the tubular fluid (or reabsorbed), and an elevation in the ratio indicate has been added to the tubular fluid (or secreted). Fig. 12-8 demonstrates that almost all of the filtered K^+ is reabsorbed in the proximal tubule and the loop of Henle, so that less than 10 percent of the filtered load is delivered to the e tubule ($C_{K^+}/C_{in} \leq 0.1$). Proximal K^+ transport appears to passively follow that of Na^+ and water,[64] whereas reabsorption in the thick ascending limb of the loop of is mediated by the Na^+-K^+-$2Cl^-$ carrier in the luminal membrane (see Fig. 4-2).[62]

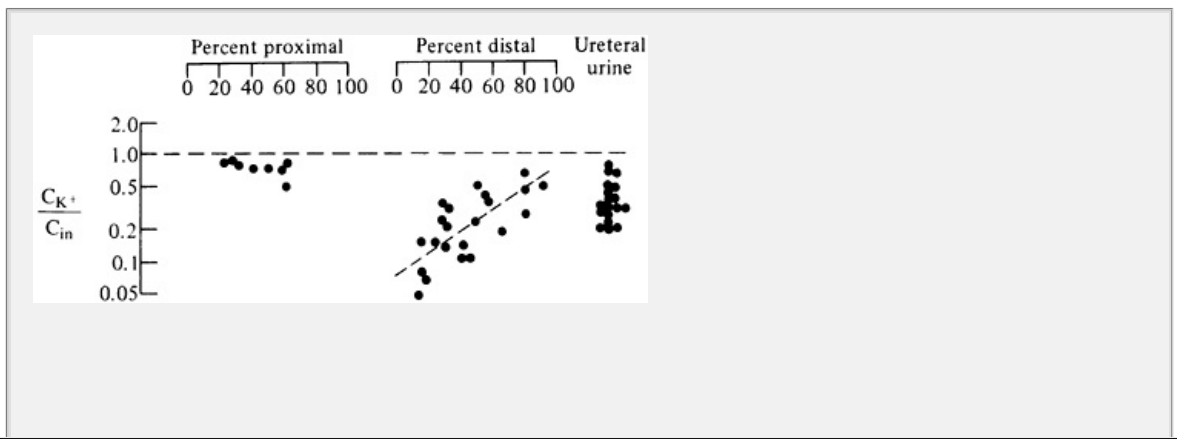

Figure 12-8 Summary of K^+ handling by the rat kidney as a function of the length of the proximal tubule and the cortical distal nephron (which includ late distal tubule, the connecting segment, and the cortical collecting tub Each point in these micropuncture experiments represents a separate sam reduction in the U_K/P_K ratio indicates reabsorption, whereas an elevation in the ratio indicates secretion. The function of the loop of Henle and the m collecting tubule can be estimated from the difference between late proxir early distal samples and the difference between late distal and ureteral u samples, respectively. *Adapted from Malnic G, Klose RM, Giebisch G* Am J Physiol *211:529, 1966, with permission.*

In comparison to these reabsorptive processes, K^+ is secreted by the connecting segment, the principal cells in the cortical and outer medullary collecting tu the papillary (or inner medullary) collecting duct (as shown by the rising U_K/P_K ratio in Fig. 12-8).[60,61,65] Secretion in these segments can be varied according physiologic needs and is generally responsible for most of the urinary K^+ excretion.

Distal K^+ secretion can be partially counteracted by *reabsorption* by the intercalated cells in the cortical and outer medullary collecting tubules.[66,67] This process may be mediated by an active H^+-K^+-ATPase pump in the luminal membrane, which resu in both H^+ secretion and K^+ reabsorption (see Fig. 5-3).[68,69] and [70] The activity of this pump is increased with K^+ depletion[68,70,71] and is reduced with K^+ loading.[72] The former adaptation is probably responsible for the observation that *net* K^+ *reabsorption, not secretion,* appropriately occurs in the distal nephron with K^+ depletion.[63,66,69] Selective inhibition of the H^+-K^+-ATPase pump in the setting of K^+ depletion abolishes distal K^+ reabsorption.[71]

Medullary recycling

The K^+ reabsorbed in the thick ascending limb initially enters the medullary interstitium. Some of this K^+ is then secreted into either the S3 segment of the late proximal tubule or the thin descending limb of the loop of Henle; this extra K^+ is reabsorbed again when it enters the outer medulla.[73] Thus, K^+ is *recycled* within the medulla, resulting in the attainment of a relatively high concentration in interstitium. The physiologic function of this phenomenon is uncertain. It is possible, for example, that K^+ accumulation in the interstitium promotes K^+ excretion by minimizing the degree of passive backlead out of the collecting tubular l (where the highest urine K^+ concentrations are

attained). The high interstitial K^+ concentration also may contribute to K^+ excretion

by a second mechanism, by diminishing the gradient for passive K^+ reabsorption via the Na^+-K^+–$2Cl^-$ carrier in the loop of Henle.[74]

Cell Model for Potassium Secretion

Potassium enters the principal cell across the basolateral membrane via the Na^+-K^+-ATPase pump; it is then secreted into the lumen down a favorable electrochemical gradient through K^+ channels in the luminal membrane (Fig. 12-9).[60,75,76] This final step, K^+ movement from the cell into the lumen, appears to be passive,[60,63] and therefore is primarily governed by those factors that affect passive transport:

1. The *concentration gradient* across the luminal membrane, which is equal to the difference between the cell and tubular fluid K^+ concentrations.

Although the total cell K^+ concentration is about 140 to 150 meq/L, ionic interactions with multivalent anions within the cell lower the random motion or activity of cytosolic K^+ to about 80 to 90 meq/L.[77,78] This value is still well above that in the tubular lumen; it is not clear, however, if all or only part of K^+ represents the transport pool that is available for secretion.[79] Regardless of its exact composition, the size of this pool is not constant but appropriately increases after load and decreases with depletion.[79] The plasma K^+ concentration and aldosterone appear to be the prime determinants of this response.

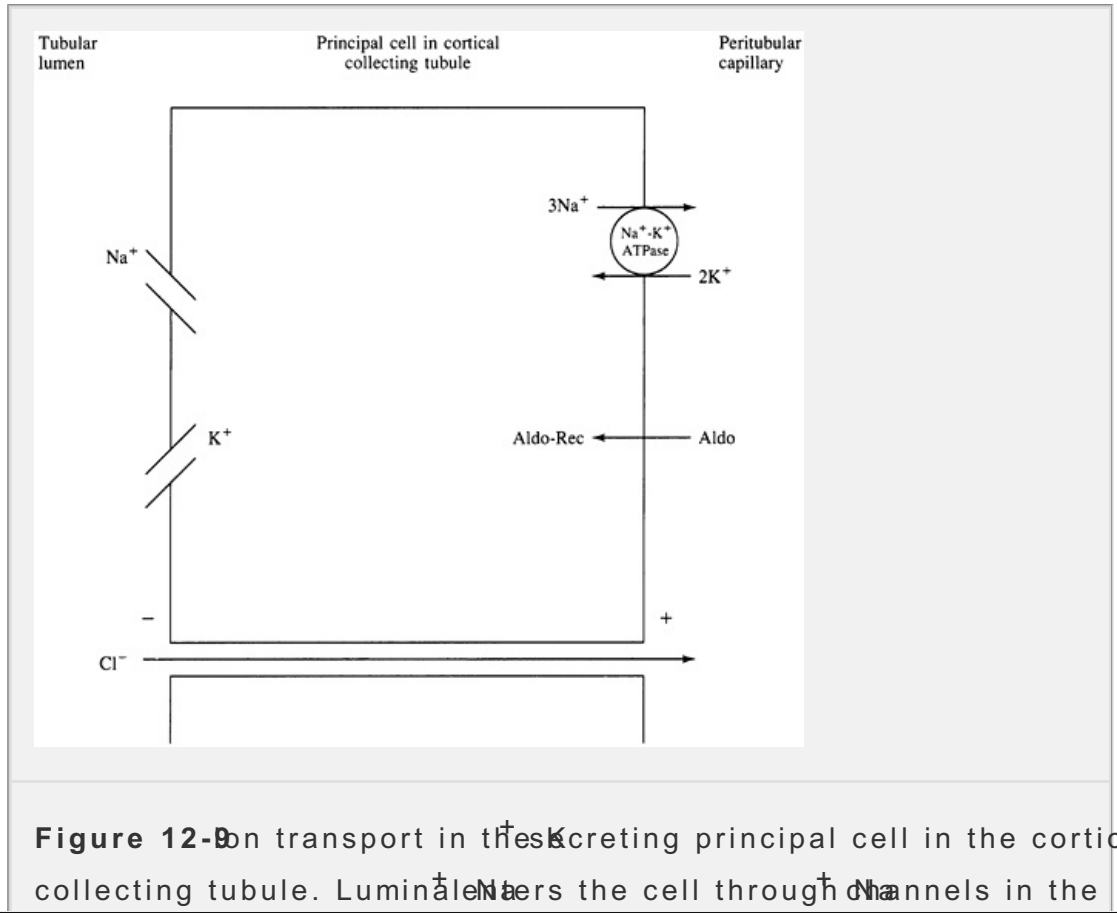

Figure 12-9 Ion transport in the K^+-secreting principal cell in the cortical collecting tubule. Luminal Na^+ enters the cell through Na^+ channels in the

luminal membrane, down a concentration gradient created by the Na^+-K^+-ATPase pump. The lumen-negative voltage created by this movement of K^+ then promotes both the secretion of K^+ (through K^+ channels in the luminal membrane) and the reabsorption of Cl^- (via the paracellular route). These processes are stimulated by aldosterone (Aldo), which enters the cell and combines with its cytosolic receptor (Rec).

2. The *electrical gradient*, which is primarily generated by the reabsorption of Na^+ through Na^+ channels in the luminal membrane.
3. The K^+ *permeability* of the luminal membrane, which is a reflection of the number of open K^+ channels.

As will be seen, *aldosterone* and the *plasma K^+ concentration*, acting in concert, are the major physiologic regulators of K^+ secretion.[80] The flow rate to the distal nephron and the potential difference generated by Na^+ absorption also are important, but they usually have a permissive rather than a regulatory effect.

Aldosterone

Aldosterone plays a major role in K^+ homeostasis by augmenting K^+ secretion in the principal cells in the cortical collecting tubule and in adjacent cells in the cortical segment and the outer part of the medullary collecting tubule.[81,82,83,84,85] After a K^+ load, for example, aldosterone secretion is directly enhanced, thereby promoting the excretion of the excess K^+ in the urine. This response is very efficient since a rise in the plasma K^+ concentration of as little as 0.1 to 0.2 meq/L can induce a significant elevation in aldosterone release.[86] Conversely, secretion of this hormone is reduced with K^+ depletion, a response that tends to preserve body K^+ by minimizing further urinary losses.

Aldosterone appears to result in stimulation of each of the major transport steps depicted in Fig. 12-9. It increases the number of open Na^+ and K^+ channels in the luminal membrane; and it enhances the activity of the Na^+-K^+-ATPase pump in the basolateral membrane (see page 180).[87,88] The *rise in luminal Na^+ permeability is the earliest change*; it promotes Na^+ entry into the cell, and this Na^+ is then returned to the systemic circulation by the Na^+-K^+-ATPase pump. These changes can enhance K^+ secretion by two mechanisms:

- The transport of Na^+ out of the cell by the Na^+-K^+-ATPase pump also results in K^+ movement into the cell, thereby increasing the size of the transportable K^+ pool.
- The reabsorption of cations makes the lumen relatively electronegative,

thereby increasing the electrical gradient favoring K^+ secretion.

Any persistent increase in K^+ secretion must be accompanied by enhanced Na^+-K^+-ATPase activity; if this did not occur; there would be eventual depletion of K^+ stores. It is of interest in this regard that the rate of Na^+ reabsorption

to K^+ secretion in the cortical collecting tubule is 3 : 2, similar to the stoich the Na^+-K^+-ATPase pump.[89] This observation suggests the following sequence: Na^+-K^+-ATPase pump transports reabsorbed cell Na^+ out of the cell in exchange for extracellular K^+; most of this K^+ is then secreted into the lumen, rather than leak back out across the basolateral membrane and being returned to the systen circulation.[89]

The primacy of the Na^+ reabsorptive effect is also suggested by the response t diuretic amiloride (See chap. 15). This agent closes the luminal Na^+ channels and at least transiently prevents the aldosterone-induced increase in K^+ secretion, luminal K^+ permeability, and Na^+-K^+-ATPase activity.[88,90]

Other hormones can also enhance distal K^+ secretion, including ADH, which appea to increase the number of luminal K^+ channels.[91,92] Although ADH is not a primary regulator of K^+ excretion, the elevation in luminal K^+ permeability may be physiologically important. It can counteract the associated reduction in dist due to ADH-induced water reabsorption, thereby preventing an undesired d in K^+ excretion.[91]

Plasma Potassium Concentration

The plasma K^+ concentration can directly affect K^+ excretion, independent of other factors such as aldosterone.[93] An example of this relationship is illustrated in Fig. 12-10. Dogs were adrenalectomized, given aldosterone replacement at differ doses, and then studied at different levels of K^+ intake. As intake was increased, there was a gradual elevation in the plasma K^+ concentration. When aldosterone replacement was at a normal level (50 µg/day, middle curve), urinary K^+ excretion remained at low levels until the plasma K^+ concentration exceeded 4.2 meq/L. At th point, K^+ excretion increased markedly in an attempt to maintain K^+ balance. This presumably reflected a direct effect of the plasma K^+ concentration, since aldosterone levels, Na^+ intake, and the urine output were relatively constant.

In intact animals, however, aldosterone secretion will rise and increase K^+ excretion, resulting in even more rapid excretion of K^+ (left curve, Fig. 12-10). The kidney is normally so efficient in excreting excess K^+ that *chronic hyperkalemia cannot occur unless the is an associated defect in urinary K^+ excretion*

Studies in adrenalectomized animals have also elucidated the mechanism b the plasma K^+ concentration affects distal K^+ secretion.[94,95] *Potassium alone replicates all of the changes in the principal cells that are induced by aldo* It increases Na^+ reabsorption and K^+ secretion, luminal membrane permeability to Na^+ and K^+ (by increasing the number of open channels),[75] and the activity of the Na^+-K^+-ATPase pump.[94] How these changes occur is not known. They are, however, less prominent that those seen when a K^+ load is appropriately accompanied by a rise in aldosterone secretion.[96]

The experiments in Fig. 12-10 also demonstrate the effect of chronic changes in aldosterone secretion on the *steady-state plasma* K^+ *concentration*.[80] If K^+ intake and excretion are normal at 50 meq/day, the plasma K^+ concentration

will be approximately 4.3 meq/L in dogs receiving physiologic levels of aldo (50 µg/day), 3.4 meq/L with hyperaldosteronism (250 µg/day), and 5.0 meq/ hypoaldosteronism (20 µg/day). When less aldosterone is available, for exa urinary K^+ excretion becomes less efficient; as a result, a higher plasma K^+ concentration is required to establish a new steady state in which intake a equals excretion. Thus, *hypo*aldosteronism is associated with hyperkalemia, whe primary *hyper*aldosteronism enhances urinary K^+ loss, often leading to a fall in the plasma K^+ concentration (see Chaps. 27 and 28).

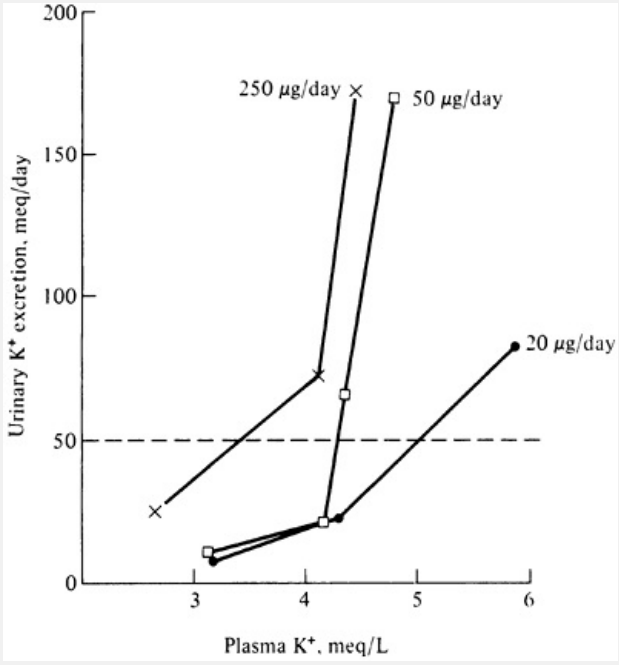

Figure 12-10 Mean values for plasma potassium concentration and steady-s urinary potassium excretion in adrenalectomized dogs given different leve aldosterone replacement and studied at increasing levels of K^+ intake. The dashed line represents the effects seen when K^+ excretion is 50 meq/day. (*From Young DB, Paulsen AW: Am J Physiol 244:F28, 1983, with permission.*)

Distal Flow Rate

Increasing distal flow rate is another potentially important stimulus of distal K^+ secretion (Fig. 12-11).[97,99] This response is most prominent in the presence of high-K^+ diet, since the concurrent elevations in aldosterone release and the K^+ concentration produce a high basal level of K^+ secretion. In comparison, K^+ depletion can lead to net reabsorption, not secretion, in the distal nephron.[66] It is not surprising, therefore, that distal flow has little or no effect on K^+ excretion in this setting.[97]

The mechanism by which distal flow affects K^+ handling is incompletely understood, but changes in the tubular fluid K^+ concentration appear to play an important role.[98] As described previously, almost all of the filtered K^+ is reabsorbed

in the proximal tubule and loop of Henle; as a result, the K^+ concentration in the fluid entering the distal nephron may be less than 1 meq/L.

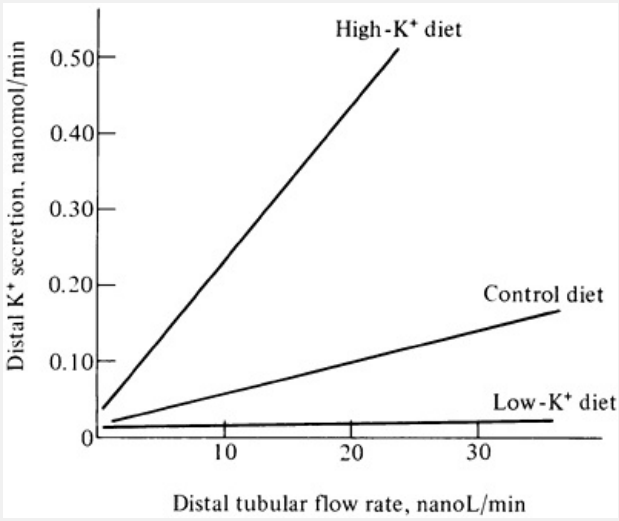

Figure 12-11 Combined effects of dietary intake and distal tubular flow rate on distal K^+ secretion. (*From Khuri RM, Wiederholt M, Strieder N, Giebisch G. Am J Physiol 228:1249, 1975, with permission.*)

The combination of K^+ secretion and, if ADH is present, water reabsorption in the cortical collecting tubule raises the tubular fluid K^+ concentration.[98] Increasing distal flow washes the secreted K^+ away and replaces it with relatively K^+-free fluid from the more proximal segments. Thus, the K^+ concentration in the lumen is kept at a relatively low level, maintaining a favorable gradient for secretion.[99]

The net effect is that the tubular fluid K^+ concentration remains nearly constant within the physiologic range of flow rate; increasing flow results in more K^+ being secreted without any elevation in the luminal K^+ concentration.[99] There may, however, be a rise in the tubular fluid K^+ concentration when distal flow is substantially diminished due, for example, to volume depletion.[99] In this setting, the high luminal concentration (due to less washout of K^+) and the low urine flow lead to a reduction in the absolute rate of K^+ secretion.

The flow dependence of K^+ secretion may also be related to changes in the deli of Na^+ to the distal secretory site.[99] Increased distal flow is generally associated with enhanced Na^+ delivery to and reabsorption in the cortical collecting tubu noted above, this elevation in Na^+ transport has two effects that favor K^+ secretion:

1 The entry of Na^+ into the cells through its channels in the luminal membrane makes the lumen relatively electronegative, creating an electrical gradient the movement of K^+ from the cells into the lumen (see below), and

2 subsequent transport of this Na^+ out of the cell by the Na^+-K^+ ATPase pump in the basolateral membrane results in the entry of new K^+ into the cells, thereby providing more K^+ for continued secretion. Thus, the flow dependence of K^+ secretion is probably mediated by the parallel changes in both water and Na^+ delivery.[98,100]

Physiologic role

The relationship between K^+ secretion and distal flow rate plays an important ro allowing aldosterone to regulate Na^+ and K^+ balance

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independently[80] and, as mentioned above, in allowing ADH to regulate water balance without affecting the secretion of K^+ (see page 184).[91,92] As an example, a Na^+ load expands the extracellular volume, resulting in a reduction in the secre renin and therefore that of aldosterone. Although the latter change promote excretion of the excess Na^+ (by decreasing cortical collecting tubule Na^+ reabsorption), it should also lead to K^+ retention and hyperkalemia. This does not happen, however, since volume expansion tends to increase the glomerular rate (GFR) and to diminish proximal Na^+ reabsorption (see Chap. 8), both of which augment the distal flow rate. The enhanced flow counteracts the fall in aldo release, resulting in little or no change in K^+ excretion.[80,101]

The outcome will be different if a Na^+ load is administered in the presence of nonsuppressible aldosterone secretion, as occurs in patients with primary hyperaldosteronism.[102] In this setting, the combination of increased distal flow normal or elevated aldosterone levels leads to enhanced K^+ excretion and a reduction in the plasma K^+ concentration.[102,103]

These changes are reversed with volume depletion, as the combination of i aldosterone release and reduced distal flow allows K^+ to be conserved without substantially affecting K^+ balance.[80,104] These observations explain why untreate patients with heart failure or cirrhosis are *typically normokalemic*, despite the common presence of secondary hyperaldosteronism and high ADH levels. If, however, distal flow is increased, then inappropriate wasting of K^+ is likely to ensue. This appears to be the *major mechanism by which the loop and thiazide diureti induce hypokalemia*.[105] These agents enhance distal delivery by diminishing Na^+ and water reabsorption in the loop of Henle and distal tubule, respectively Chap. 15). They also tend to stimulate aldosterone secretion, because of the concomitant reduction in extracellular volume.

Sodium Reabsorption and the Transepithelial Potent Difference

Since K^+ is a charged particle, its secretion is importantly affected by the transepithelial potential difference across the tubular cell. The normal pote difference in the K^+-secreting cells is approximately -15 to -50 mV (lumen negative).[89,106,107] This potential is generated by the transport of Na^+ from the lumen into the peritubular capillary (Fig. 12-12). Since Na^+ is positively charged, its reabsorption makes the lumen relatively electronegative, passively reabsorbed via the paracellular route down this electrical gradient; there is, however, a time lag, and it is this delay that is responsible for the observed potential

The importance of Na^+ in the generation of this potential can be illustrated by response to replacing luminal with Na^+ a nonreabsorbable cation, such as choline.[106] In this setting, the potential difference falls to zero (Fig. 12-12). On the other hand, replacing luminal Cl^- with a poorly reabsorbed anion, such as SO_4^{2-} increases the anion delay and augments the potential difference.

The central role of the Na^+-generated potential difference in K^+ secretion can be illustrated by the response to the diuretic amiloride.[79,105] This agent impairs the

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entry of luminal Na^+ into the cells of the distal nephron by closing channels in the luminal membrane.[108] The net effect is diminished Na^+ reabsorption and a reduction in the transepithelial potential difference, even in the presence o aldosterone.[79,88,105] There is also a marked fall in K^+ secretion; it is likely that thi effect is due to the decrease in potential difference, since amiloride has no direct influence on K^+ handling.[108]

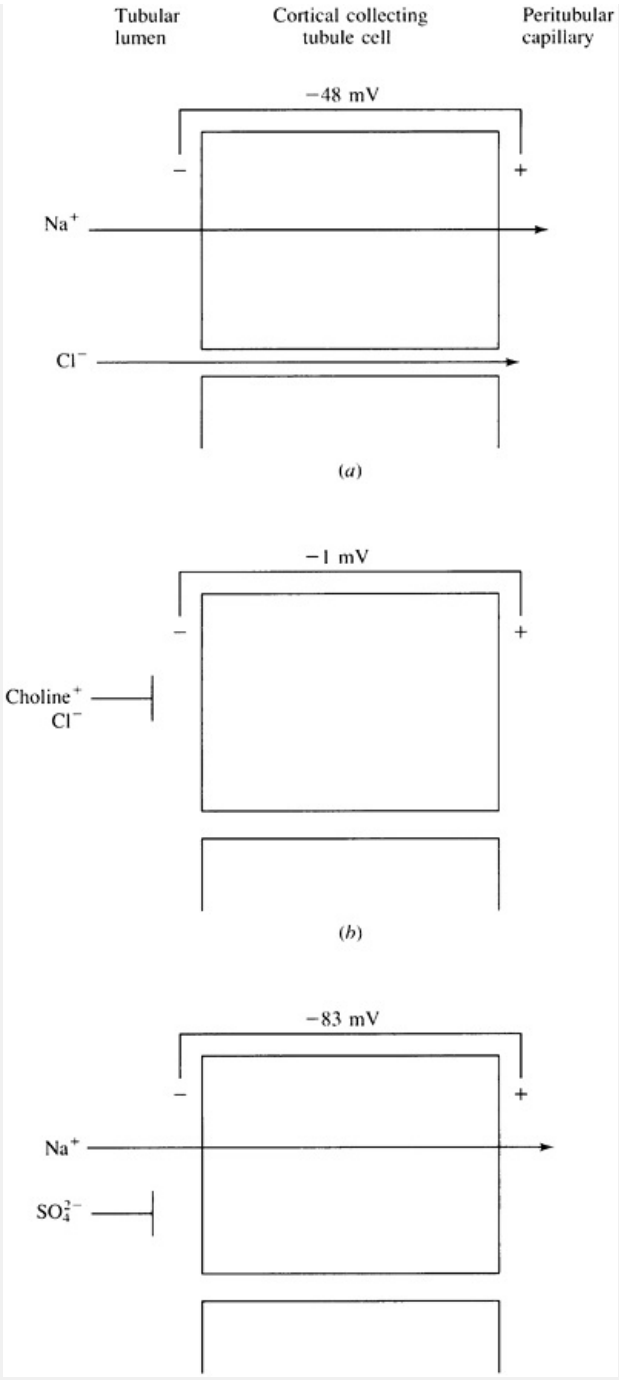

Figure 12-12 Schematic repre-sentation of the electrical events in a typical principal cell in the cortical collecting tubule. (*a*) Na^+ is actively transported from the lumen into the capillary; Cl^- follows via the paracellular route after a finite time lag; this delay is responsible for the trans-epithelial potential difference of 35 to -50 mV, lumen negative. (*b*) Replacing Na^+ in the lumen with the nonreabsorbable cation choline essentially eliminates the potential difference, illustrating the central role of trans-port. (*c*) Replacing Cl^- in the lumen with the non-reabsorbable anion SO_4^{2-} increases the anion delay and enhances the potential difference, thereby favoring the secretion of K^+ into the lumen. (*Data from Giebisch G, Malnic G, Klose RM, Windhager EE, Am J Physiol 211:560, 1966, with permission.*)

The stimulatory effect of Na^+ transport on K^+ secretion is more prominent if Na^+ is delivered with an *anion other than* Cl^- *that is nonreabsorbable*. In this setting, there will be less Cl^- available for reabsorption to dissipate the lumen-negative elec gradient created by Na^+ entry into the cell. As an example, a volume-depleted subject has a strong stimulus to Na^+ reabsorption in the cortical collecting tubule that is mediated by aldosterone. In this situation, the administration of Na_2SO_4 results in Na^+ reabsorption without SO_4^{2-} and, consequently, increases in the potential difference (Fig. 12-12) and K^+ secretion.[107,109,110] In contrast, if Na^+ balance and therefore both delivery and aldosterone secretion are normal, th is no stimulus to retain the excess Na^+, and Na_2SO_4 is excreted with only a small elevation in K^+ secretion.[109,110]

A clinical example of this phenomenon may follow the intravenous administr the antibiotic carbenicillin, which contains 4.7 meq of Na^+ per gram. Thirty grams of this compound contains approximately 140 meq of the carbenicillin anion; tl presence of this nonreabsorbable anion in the tubular fluid can, in some pa lead to enhanced urinary K^+ loss and hypokalemia.[111,112]

Studies in humans suggest that, in addition to volume status, the nonreabs anion itself may be a determinant of the effect on K^+ secretion.[110] Although the ability of sulfate to enhance K^+ loss is minimized by euvolemia, it is still able to promote K^+ secretion in this setting. How this might occur is not known.

Extracellular pH

As noted above, changes in the extracellular pH produce reciprocal shifts of K^+ between the cells and the ECF. As a result, K^+ tends to move into cells with alkalemia and out of cells with acidemia. These changes in the cellular K^+ concentration will tend to reduce K^+ secretion in acidemia and to increase K^+ secretion in alkalemia.[113,114] and[115]

These pH-induced effects, however, are *transient and are frequently overridden b concurrent variations in other factors that affect* K^+ *secretion*.[116,117] In type 2 renal tubular acidosis, for example, proximal HCO_3^- reabsorption is impaired (see Chap. 19). As a result, there is increased delivery of Na^+, of poorly reabsorbable anion HCO_3^-, and water to the distal secretory site. These changes overcome direct effect of acidosis, and K^+ loss ensues.[118,119] A similar sequence occurs in diabetic ketoacidosis, where Na^+ and water are delivered to the distal nephron w the ketoacid anions, β -hydroxybutyrate and acetoacetate.

Renal Response to Potassium Depletion and Potassium Loading

The regulation of K^+ excretion can be summarized by reviewing the renal respo to changes in K^+ balance.

Potassium depletion

K^+ excretion, for example, appropriately falls with K^+ depletion.[63,66,120] This response is initially mediated by diminished release of aldosterone, which represents a direct effect of K^+ on the adrenal zona glomerulosa cells.[120,121] Within several days, however, a decrease in the cortical K^+ concentration in the distal nephron probably assumes primary importance.[120] At this time, neither the administration of aldosterone[120,122] nor increasing distal flow rate (Fig. 12-11) substantially enhances urinary K^+ loss.

The fall in K^+ excretion in this setting is due both to reduced secretion and to K^+ reabsorption.[61,66] The latter process occurs in the intercalated cells in the cortex and outer medulla[66,67] and appears to be mediated by a luminal H^+-K^+ ATPase pump.[69,71] The activity of this pump, which reabsorbs K^+ and secretes H^+, increases with K^+ depletion.[70,71] This change is associated with an elevation in luminal membrane area in the intercalated cells,[66,67] due at least in part to insertion of new H^+-K^+-ATPase pumps in the luminal membrane.[61]

The net effect is that K^+ excretion can be lowered to 15 to 25 meq/day with a total K^+ deficit of 50 to 150 meq, and to 5 to 15 meq/day with more marked K^+ loss.[123] The inability to conserve K^+ more efficiently may be related to passive leakage of K^+ down a favorable concentration gradient from the tubular lumen through a relatively nonselective cation channel in the terminal nephron segment, the medullary collecting duct.[124]

Potassium loading

Urinary K^+ excretion increases after a K^+ load.[60] This response is so efficient that normal subjects can maintain K^+ balance even if K^+ intake is *slowly increased* from the normal level of 60 to 80 meq/day up to 500 meq/day or more.[125,126] This response is mediated both by aldosterone and by a rise in the plasma K^+ concentration.[80,126]

The ability to handle what might be a lethal K^+ load if given acutely is called K^+ *adaptation* and is due primarily to more rapid K^+ excretion in the urine.[127] Early adaptation can be induced by a single normal meal. As an example, rats fed K^+-containing meals were better able to excrete an intravenous K^+ load several hours later than fasted rats; more rapid urinary excretion meant that there was a small

elevation in the plasma K^+ concentration.[128]

In addition to increased urinary excretion, two other factors, both of which promoted by aldosterone, also may contribute to more chronic[1] adaptation: enhanced K^+ entry into extrarenal cells,[129,130] the importance of which is uncertain,[131] and[2] increased gastrointestinal losses due to colonic secretion K^+.[132,133]

The increase in urinary K^+ excretion during adaptation is due to *enhanced K^+ secretion throughout the late distal nephron*, including the short connecting segment, and the principal cells in the cortical and outer medullary collecti tubules.[66,84,95,96,134] The efficacy of this response is illustrated in Fig. 12-13,

which shows that distal K^+ secretion at a given plasma K^+ concentration is two to four times higher in K^+-adapted rats.[61] In addition to increased secretion, decreas reabsorption in the intercalated cells (mediated by a decrease in activity of H^+-ATPase pump) also may contribute to the kaliuresis.[72]

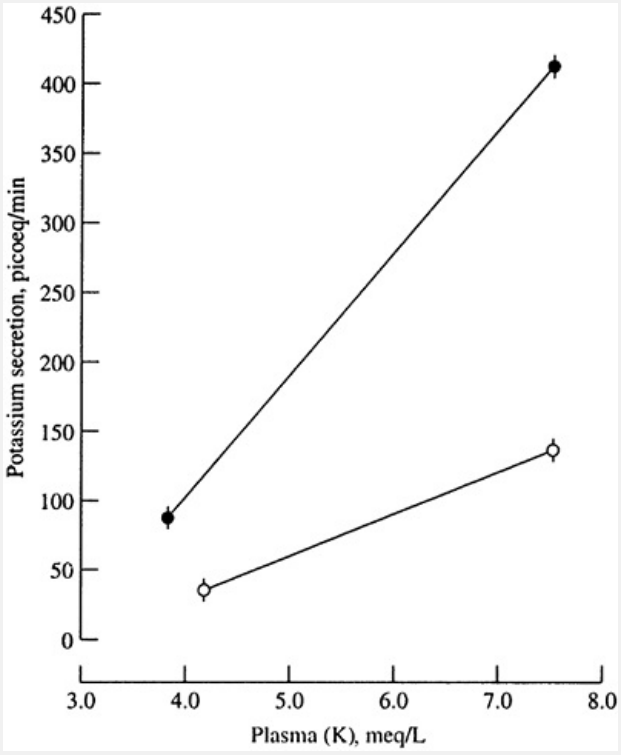

Figure 12-13 Relationship between plasma K^+ concentration (which is elevated by KCl infusion) and distal K^+ secretion in control animals (circles) and adapte animals (squares) given a high K^+ diet for 4 weeks. At any plasma K^+ concentration, K^+ secretion is two to four times higher in the adapted animal (*From Stanton BA: Am J Physiol 257:R989, 1989, with permission.*)

Both increased secretion of aldosterone and a small elevation in K^+ the plasma concentration are required for the complete expression of this response. [84,96] These act in part by enhancing Na^+-K^+-ATPase activity in these distal segments, [95,135] either directly or by increasing the entry of luminal Na^+ into the cell. [87,90,94] The morphologic correlate of this increased Na^+-K^+-ATPase activity is a marked increase in the area of the basolateral membrane, the site at which the Na^+-K^+-ATPase pumps are inserted. [61,7] This morphologic change begins within the first d of a high K^+ intake and does not reach a plateau until 2 weeks.

The role of these parameters in humans can be illustrated by the response K^+ loading (400 meq/day) in normal subjects (Fig. 12-14). [104,126] The plasma K^+ concentration rose from 3.8 to 4.8 meq/L and the plasma aldosterone conce increased 2.5-fold in the first 2 days. By 20 days, however, both the plasma K^+ concentration (4.2 meq/L) and the plasma aldosterone concentration had pa returned toward baseline levels, even though urinary K^+ excretion remained very high.

The increased efficiency of K^+ excretion at this time was probably related to the hyperkalemia-induced rise in Na^+-K^+-ATPase activity. [104,126] Indirect evidence in support of this hypothesis was the observation that discontinuation of the K^+ loading led

to transient Na^+ retention, which could have reflected the time required for di Na^+-K^+-ATPase activity to fall back to normal.

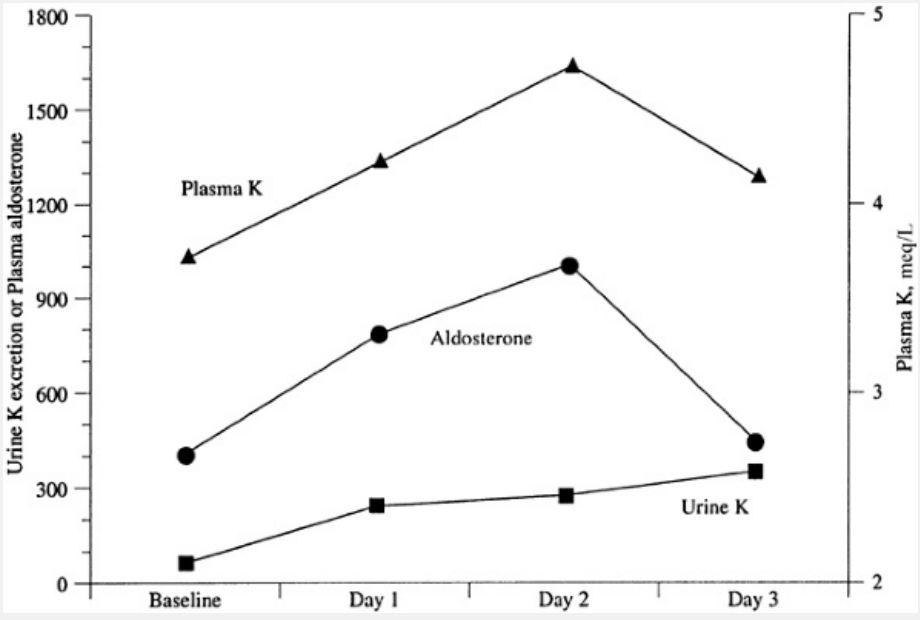

Figure 12-14 Response to increasing K^+ intake to 400 meq/day in normal subjects. Urinary K^+ excretion rises to this level within 2 days and is then maintained. This response is initially driven by elevations in the plasma K^+

aldosterone concentrations. By day 20, the efficiency of K^+ secretion has increased, resulting in a lesser elevation in the plasma K^+ concentration (to 4.2 meq/L) and normalization of the plasma aldosterone concentration. (*Adapted from Rabelink TJ, Koomans HA, Hené RJ, Dorhout Mees EJ: Kidney Int 38:942, 1990. Reprinted by permission from Kidney International.*)

The major clinical example of K^+ adaptation occurs in chronic renal failure, in wh the combination of a constant K^+ intake and fewer functioning nephrons requires increase in K^+ excretion per nephron.[136,137] This allows K^+ balance to be maintained even in advanced disease as long as intake is not excessive, th output and therefore the distal flow rate are adequate, and aldosterone sec be appropriately increased.[138,139]

Studies in experimental animals with renal failure have shown that Na^+-K^+-ATPase activity in the distal nephron is elevated, an expected correlate of enhance K^+ secretion per nephron.[140] However, this elevation in pump activity is seen only K^+ intake is normal, not when intake is restricted in proportion to the fall ir setting in which increased K^+ excretion per nephron is not required.[140] This finding suggests that the rise in Na^+-K^+-ATPase activity is *appropriate* and *specific*, not incidentally induced by renal insufficiency.

Enhanced colonic secretion of K^+ may play an important role in advanced re disease.[132,141] It has been estimated that increased stool losses

may account for the excretion of as much as 30 to 50 percent of dietary K^+ patients with end-stage renal failure on chronic dialysis.[5,142]

SUMMARY

The maintenance of a normal plasma K^+ concentration is dependent upon the abili of K^+ to enter the cells, where it achieves high concentrations, and upon th excretion of net dietary intake. After a load, most of the extra K^+ is initially taken up by the cells, a response that is facilitated by basal levels of catecholam insulin. This cell uptake minimizes the increase in the plasma K^+ concentration, pending the excretion of the excess K^+ in the urine.

Urinary K^+ excretion is largely a function of secretion in the distal nephron, in the principal cells in the cortical collecting tubule. The main factors mod this process are aldosterone and the plasma K^+ concentration itself. Distal flow rat and the transepithelial potential difference (which is generated primarily by reabsorption) play a *permissive* role: They do not change directly with K^+ balance, but relatively normal values are required for adequate K^+ secretion.

Understanding these principles can simplify the approach to patients with d of K^+ balance. Chronic hyperkalemia, for example, *must be associated with a defect in distal K^+ secretion*, since the adaptation response would normally permit excretion of the excess K^+ (Fig. 12-1).[4] From the preceding discussion, the two major mechanisms by which K^+ secretion might be impaired are *hypoaldosteronism* and *decreased distal flow* (due to a marked volume depletion or advanced renal failure). These conditions therefore constitute most of the differential diagn persistent hyperkalemia (see Chap. 28).

Urinary K^+ wasting and hypokalemia, on the other hand, are due to activation distal secretory process. This most often occurs with *hyperaldosteronism* (as long as distal flow is maintained), *increased distal flow* (as long as aldosterone secretion is normal or elevated, as with diuretic therapy), or the delivery to the distal nephron with *nonreabsorbable anions* (as is seen in ketoacidosis or type 2 renal tubular acidosis).[4,18,19]

PROBLEMS

12-1 What effect should aldosterone deficiency have on urinary K^+ excretion? What factor ultimately limits the changes that occur?

12-2 In a patient with primary hyperaldosteronism due to an adrenal ad what effect will increased dietary K^+ intake have on urinary K^+ excretion? How does this differ from the response in normal subjects?

12-3 K^+ depletion is most often due to urinary or gastrointestinal K^+ losse What test would be helpful in differentiating between these disorders?

12-4 Untreated patients with effective circulating volume depletion due heart failure or cirrhosis (see Chap. 10) are generally normokalemic even though the activity of the renin-angiotensin-aldosterone

system is frequently increased. Why doesn't aldosterone promote exc urinary K^+ loss in this setting? What would happen to K^+ excretion if a diuretic such as furosemide were then given to increase Na^+ and water excretion?

12-5 Which of the following drugs can raise the plasma K^+ concentration?

a. **A converting enzyme inhibitor, which limits the formation of angiot**
b. **A thiazide diuretic**
c. **A β -adrenergic blocker**
d. **An α-adrenergic blocker**
e. **An intravenous infusion of glucose**

12-6ADH increases water reabsorption in the collecting tubules. In pat with central diabetes insipidus, the urine output can exceed 10 L/day, of decreased collecting tubule water reabsorption. What effect will thi output state have on K^+ excretion?

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Footnotes

* Hyperkalemia is a common finding in ketoacidosis and lactic acidosis, but other than acidemia are probably of primary importance. In ketoacidosis, fo both insulin deficiency and hyperosmolality (see below) promote K^+ from the cells into the ECF. Thus, the incidence of hyperkalemia is similar in dia ketoacidosis and in nonketotic hyperglycemia, where the systemic pH is rel normal.[50]

† This process is similar to NH_4^+ recycling between the loop of Henle and the medullary collecting tubule that promotes net NH_4^+ excretion (see page 341).

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Chapter Thirteen
Meaning and Application of Urine Chemistrie

As is discussed in the ensuing chapters, measurement of the urinary electr concentrations, osmolality, and pH plays an important role in the diagnosis management of a variety of disorders. This chapter briefly reviews the mea these parameters and the settings in which they may be helpful (Table 13-1). It is important to emphasize that there are *no fixed normal values*, since the kidney varies the rate of excretion to match net dietary intake and endogenous pro Thus, interpretation of a given test requires knowledge of the patient's clin As an example, the urinary excretion of 125 meq per day Na^+ may be appropriate for a subject on a regular diet, but represents inappropriately increased Na^+ excretion in a patient who is volume-depleted.

In addition to being clinically useful, these tests are simple to perform and available. In most circumstances, a random urine specimen is sufficient, alt 24-h collection to determine the daily rate of solute excretion is occasional indicated. When K^+ depletion is due to extrarenal losses, for example, the K^+ urin excretion should fall below 25 meq/day. In some patients, however, random measurement may be confusing. If the urine output is only 500 mL/day beca associated volume depletion, then the appropriate excretion of only 20 meq K^+ per day will be associated with an apparently high urine K^+ concentration of 40 meq/L (20 meq/day ÷ 0.5 L/day = 40 meq/L).

Table 13-1 Clinical application of urine chemistrie

Parameter	Uses
Na^+ excretion	Assessment of volume status Diagnosis of hyponatremia and acute renal failure Dietary compliance in patients with hypertension Evaluation of calcium and uric acid excretion in stone formers
Cl^- excretion	Similar to that for Na^+ excretion

	Diagnosis of metabolic alkalosis Urine anion gap
K^+ excretion	Diagnosis of hypokalemia
Osmolality or specific gravity	Diagnosis of hyponatremia, hypernatremia, and gravity acute
pH	Diagnosis of renal tubular acidosis Efficacy of treatment in metabolic alkalosis and uric acid stone disease

SODIUM EXCRETION

The kidney varies the rate of Na^+ excretion to maintain the effective circulating volume, a response that is mediated by a variety of factors, including the r angiotensin-aldosterone system and perhaps atrial natriuretic peptide and r peptides (see Chap. 3). As a result, the urine Na^+ concentration can be used as an estimate of the patient's volume status. In particular, a urine Na^+ concentration below 20 meq/L is generally indicative of hypovolemia. This finding is espe useful in the differential diagnosis of *hyponatremia* and *acute renal failure*. The two major causes of hyponatremia are effective volume depletion and the sy of inappropriate antidiuretic hormone secretion (SIADH). The urine Na^+ concentration should be low in the former, but greater than 40 meq/L in the which is characterized by water retention but normal Na^+ handling (i.e., output equal to intake; see Chap. 23).

Similar considerations apply to acute renal failure, which is most often due depletion or acute tubular necrosis.[1] The urine Na^+ concentration usually exceeds 40 meq/L in the latter, in part because of the associated tubular damage an consequent inability to maximally reabsorb Na^+.[1,2,3] Measuring the fractional excretion of Na^+ and the urine osmolality also can help to differentiate betwee these conditions (see below).

In normal subjects, urinary Na^+ excretion roughly equals average dietary intake. Thus, measurement of urinary Na^+ excretion (by obtaining a 24-h collection) can used to check dietary compliance in patients with essential hypertension. R of Na^+ intake is frequently an important component of the therapeutic regime and adequate adherence should result in the excretion of less than 100 me[4,5]

The *concurrent use of diuretics does not interfere with the utility of this te* as long as drug dose and dietary intake are relatively constant. A thiazide diu example, initially increases Na^+ and water excretion by reducing transport in the

distal tubule. However, the diuresis is attenuated over a period of days, be ensuing volume depletion enhances renal Na^+ reabsorption both in the collecting tubule (via aldosterone) and in the proximal tubule (in part via angiotensin II).[6,7] The net effect is the establishment within 1 week of a new steady state in which the volume is somewhat diminished, but *Na^+ excretion is again equal to intake* (see Fig. 15-2).[8]

Measurement of urinary Na^+ excretion is also important when evaluating patient with recurrent kidney stones. A 24-h urine collection is typically obtained in setting to determine if calcium or uric acid excretion is increased, both of w predispose to stone formation.[9,10] However, the tubular reabsorption of both calcium and uric acid is indirectly linked to that of Na^+ (see Chap. 3). Thus, the increased Na^+ reabsorption in hypovolemia can mask the presence of underly hypercalciuria or hyperuricosuria.[11] In general, Na^+ excretion above 75 to 100 meq/day indicates that volume depletion is not a limiting factor for calcium acid excretion.

Limitations

Despite its usefulness, there are some pitfalls in relying upon the measurer Na^+ excretion as an index of volume status. A low urine Na^+ concentration, for example, may be seen in normovolemic patients who have *severe renal or glomerular ischemia* due to bilateral renal artery stenosis or acute glomerulonephritis.[2,12] On the other hand, a defect in tubular Na^+ reabsorption can lead to a high rate of Na^+ excretion, despite the presence of volume depletion. can occur with the use of diuretics, mineralocorticoid deficiency, or in advance renal failure.[13]

The urine Na^+ concentration can also be influenced by the rate of water reabsorption. This can be exemplified by central diabetes insipidus, a disor which a deficiency of antidiuretic hormone (ADH) can lead to a urine output exceeding 10 L/day. In this setting, the daily excretion of 1000 meq of Na^+ associated with a urine Na^+ concentration of 10 meq/L or less, incorrectly suggesting the presence of volume depletion. Conversely, a high rate of wa reabsorption can raise the urine Na^+ concentration and mask the presence of hypovolemia. To *remove the effect of water reabsorption*, the renal handling of Na^+ can be evaluated directly by calculating the fractional excretion of Na^+ (FE_{Na}).

Fractional Excretion of Sodium

The FE_{Na} can be calculated from a random urine specimen:[2,3,14]

$$FE_{Na}(\%) = \frac{\text{quantity of } Na^+ \text{ excreted}}{\text{quantity of } Na^+ \text{ filtered}} \times 100$$

The quantity of Na^+ excreted is equal to the product of the urine Na^+ concentration (U_{Na}) and the urine flow rate (V); the quantity filtered is equal to the product of the plasma Na^+ concentration (P_{Na}) and the glomerular filtration rate (or creatinine clearance, which is equal to $U_{cr} \times V/P_{cr}$). Thus,

$$FE_{Na} = \frac{U_{Na} \times V}{P_{Na} \times (U_{cr} \times V/P_{cr})} \times 100$$
$$= \frac{U_{Na} \times P_{cr}}{P_{Na} \times U_{cr}} \times 100$$

The primary use of the FE_{Na} is in patients with acute renal failure. As described above, a low urine Na^+ concentration favors the diagnosis of volume depletion, whereas a high value points toward acute tubular necrosis. However, a level between 20 and 40 meq/L may be seen with either disorder.[2,3] This overlap, which is due in part to variations in the rate of water reabsorption, can be minimized by calculating the FE_{Na}.[2,3,14] Na^+ reabsorption is appropriately enhanced in hypovolemic states, and the FE_{Na} is usually less than 1 percent; i.e., more than 99 percent of the filtered Na^+ has been reabsorbed. In contrast, tubular damage leads to a FE_{Na} in excess of 2 to 3 percent in most patients with acute tubular necrosis.

There are, however, exceptions to this general rule, as the FE_{Na} may be less than 1 percent when acute tubular necrosis is superimposed upon chronic effective volume depletion (as occurs in cirrhosis, heart failure, and burns) or when it is induced by radiocontrast media or heme pigment deposition.[1,15,16] and[17] The mechanism by which this occurs is uncertain, although tubular function may be better preserved in these disorders.[14]

Limitations

The major limitation in the use of this index is that it is dependent upon the amount of Na^+ filtered, and therefore the *dividing line between volume depletion and normovolemia is not always 1 percent*. This can be best appreciated in patients with normal renal function. If the glomerular filtration rate (GFR) is 180 L/day (125 mL/min) and the plasma Na^+ concentration is 150 meq/L, then 27,000 meq of Na^+ will be filtered each day. As a result, the FE_{Na} will always be under 1 percent as long as daily Na^+ intake is in the usual range of 125 to 250 meq. Since patients with relatively normal renal function should be able to lower daily Na^+ excretion to less than 20 meq/day in the presence of volume depletion, the FE_{Na} should be less than 0.2 percent in this setting. A FE_{Na} of 0.5 percent is indicative of normovolemia, not volume depletion, in such a patient unless there is renal salt wasting. In contrast, a FE_{Na} of 0.5 percent does reflect volume depletion in advanced renal failure, a condition in which the GFR and therefore

the filtered Na^+ load are markedly reduced. If, for example, the GFR is only 10 percent of normal, then the filtered load is 2700 meq/day; 0.5 percent of this

quantity is equal to only 14 meq of Na^+ excreted per day.

The FE_{Na} and the U_{Na} are difficult to interpret with concurrent diuretic therap since the ensuing natriuresis will raise these values even in patients who a hypovolemic. Although not widely available, measurement of the fractional e of endogenous lithium (which is present in trace amounts) may circumvent t problem. Lithium is primarily reabsorbed in the proximal tubule, which has t important consequences.[1] Proximal reabsorption is increased and therefore lith excretion is reduced in hypovolemic states,[2] and excretion is not significant increased by loop diuretics. The fractional excretion of lithium (FE_{Li}) is approximately 20 percent in healthy controls. In one report of patients with renal failure, a value below 15 percent (and usually below 10 percent) was suggestive of prerenal disease, independent of diuretic therapy.[18] In comparison, the

mean FE_{Li} was 26 percent in acute tubular necrosis (ATN).

Given the usual lack of ability to measure trace lithium, other markers for p function have been evaluated. Uric acid handling occurs almost entirely in proximal tubule, and the fractional excretion of uric acid is not affected by diuretic therapy. In the study noted above, values below 12 percent were su of prerenal disease (sensitivity 68 percent, specificity 78 percent), while va above 20 percent were suggestive of ATN (sensitivity 96 percent, specificit percent).[18]

CHLORIDE EXCRETION

Chloride is reabsorbed with sodium throughout the nephron (see Chaps. 3, 4, and 5). As a result, the rate of excretion of these ions is usually similar, and measu the urine Cl^- concentration generally adds little to the information obtained fr more routinely measured urine Na^+ concentration.

However, as many as 30 percent of hypovolemic patients have more than a difference between the urine Na^+ and Cl^- concentrations.[19] This is due to the excretion of Na^+ with another anion (such as HCO_3^- or carbenicillin) or to the excretion of Cl^- with another cation (such as NH_4^+ in metabolic acidosis.[19,20] Thus, it may be helpful to measure the urine Cl^- concentration in a patient who seems to volume-depleted but has a somewhat elevated urine Na^+ concentration.

This most often occurs in *metabolic alkalosis*, in which acid-base balance can be restored by urinary excretion of the excess HCO_3^- as NaHCO$_3$ (see Chap. 18). Many of these patients, however, are volume-depleted due to vomiting or diuretic the degree that the hypovolemic stimulus to Na^+ retention predominates, there will be low Na^+ and HCO_3^- levels in the urine and persistence of the alkalosis. If, other hand, there is a relatively mild volume deficit as compared to the sev

the alkalosis, some $NaHCO_3$ will be excreted, thereby elevating the urine Na^+ concentration (in some cases to over 100 meq/L). In comparison, the urine Cl^- concentration will remain appropriately low (unless some diuretic effect per since there is no defect in the reabsorption of NaCl.

Another setting in which measurement of the urine Cl^- concentration may be helpful is in patients with a normal anion gap metabolic acidosis (see Chap. 21).[21,22] In the absence of renal failure, this problem is most often due to diarrhea or to or forms of renal tubular acidosis (RTA). The normal response to acidemia is t increase urinary acid excretion, primarily as NH_4^+. When urine NH_4^+ levels are high, the *urine anion gap*

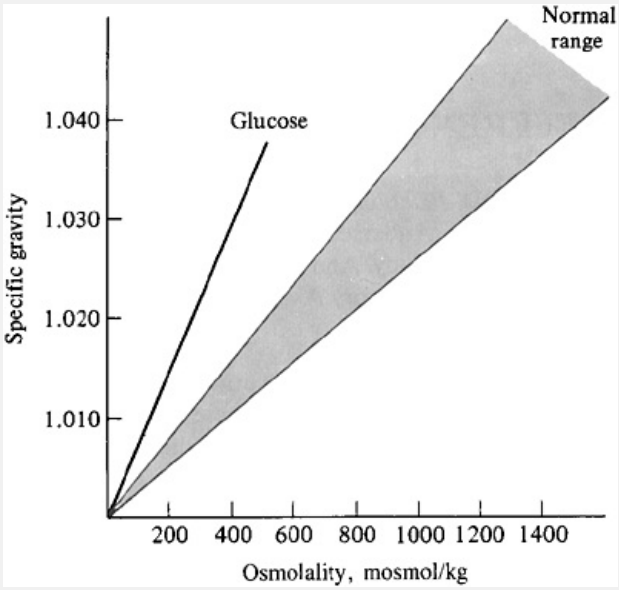

Figure 13-1 Relationship between the specific gravity and osmolality of the from normal subjects who have neither glucose nor protein in the urine. F comparison, the relationship between the specific gravity and osmolality f glucose solutions is included. (*Adapted from Miles B, Paton A, deWardener H* Br Med J *2:904, 1954. By permission of the British Medical Journal*)

$$\text{Urine anion gap} = ([Na^+] + [K^+]) - [Cl^-]$$

will have a negative value, since the Cl^- concentration will exceed the concentratic of Na^+ and K^+ by the approximate amount of NH_4^+ in the urine. Thus, the urine Cl concentration may be inappropriately high in diarrhea-induced hypovolemia of the need to maintain electroneutrality as NH_4^+ excretion is enhanced.[20]

In comparison, urinary acidification is impaired in RTA, leading to a low lev NH_4^+ excretion and a positive value for the urine anion gap.[21] The urine pH also will be inappropriately high (>5.3) in this setting.

POTASSIUM EXCRETION

Potassium excretion varies appropriately with intake, a response that is me primarily by aldosterone and a direct effect of the plasma K^+ concentration (see Chap. 12). If K^+ depletion occurs, urinary K^+ excretion can fall to a minimum of 5 to 25 meq/day.[23] As a result, measurement of K^+ excretion can aid in the diagnosis of unexplained hypokalemia. An appropriately low value suggests either extrar losses (usually from the gastrointestinal tract) or the use of diuretics (if th has been obtained after the diuretic effect has worn off). In comparison, th of more than 25 meq of K^+ per day indicates at least a component of renal K^+ wasting.

Measurement of K^+ excretion is less helpful in patients with hyperkalemia. If K^+ intake is increased slowly, normal subjects can take in and excrete more th of K^+ per day without a substantial elevation in the plasma K^+ concentration (normal daily intake is 40 to 120 meq).[24,25] Thus, chronic hyperkalemia *must be associated with a defect in urinary K^+ excretion*, since normal renal function would result in rapid excretion of the excess K^+. As a result, the urine K^+ concentration will be inappropriately low in this setting, most often as a result of renal failure or hypoaldosteronism (see Chap. 28).

URINE OSMOLALITY

Variations in the urine osmolality (U_{osm}) play a central role in the regulation of th plasma osmolality (P_{osm}) and Na^+ concentration. This response is mediated by

osmoreceptors in the hypothalamus that influence both thirst and the secre ADH (see Chap. 9). After a water load, for example, there is a transient reduct the P_{osm} leading to suppression of ADH release. This diminishes water reabsorption in the collecting tubules, resulting in the excretion of the exce in a dilute urine. Water restriction, on the other hand, sequentially raises U_{osm}, ADH secretion, and renal water reabsorption, resulting in water retention a excretion of a concentrated urine.

These relationships allow the U_{osm} to be helpful in the differential diagnosis of b *hyponatremia* and *hypernatremia* (see Chaps. 23 and 24). Hyponatremia with hypoosmolality should virtually abolish ADH release. As a result, a maximal urine should be excreted, with the U_{osm} falling below 100 mosmol/kg. If this is found, then the hyponatremia is probably due to excess water intake at a ra exceeds normal excretory capacity (a rare disorder called primary polydipsi more commonly, the U_{osm} is inappropriately high and *hyponatremia results from an inability of the kidneys to excrete water*. Lack of suppression of ADH release, due to volume depletion or the syndrome of inappropriate ADH sec the most common cause of this problem.

In contrast, hypernatremia should stimulate ADH secretion, and the U_{osm} should exceed 600 to 800 mosmol/kg. If a concentrated urine is found, then extrare loss (from the respiratory tract or skin) or the administration of excess Na^+

water is responsible for the elevation in the plasma Na^+ concentration. On the other hand, a U_{osm} below that of the plasma indicates primary renal water loss due of or resistance to ADH.

The U_{osm} (in addition to the FE_{Na}) also may be helpful in distinguishing volume depletion from postischemic ATN as the cause of the acute renal failure. AD tend to be elevated in both disorders, because hypovolemia is a potent stin the release of ADH (see page 176). However, tubular dysfunction in acute tubular necrosis impairs the response to ADH, leading to the excretion of urine with osmolality that is generally less than 400 mosmol/kg.[13] In comparison, the U_{osm} may exceed 500 mosmol/kg with hypovolemia alone if there is no underlying disease. Thus, a high U_{osm} essentially excludes the diagnosis of ATN. The find of an isosmotic urine, however, is less useful diagnostically. It is consisten but does not rule out volume depletion, since there may be a concomitant in in concentrating ability, a common finding in the elderly or in patients with reductions in glomerular filtration rate.[26,27]

Urine Specific Gravity

The solute concentration of the urine (or other solution) also can be estima measuring the urine specific gravity, which is defined as the weight of the s compared with that of an equal volume of distilled water. Plasma is approxi to 1.0 percent heavier than water and therefore has a specific gravity of 1. 1.010. Since the specific gravity is proportional to the *weight*, as well as the number, of particles in the solution, its relationship to osmolality is dependent upon molecular weights of the solutes.

As illustrated in Fig. 13-1, the specific gravity varies with osmolality in a relativ predictable way in normal urine, which contains primarily small solutes suc Na^+, Cl(-), K^+, NH_4^+, and HPO_4^-. In this setting, each 30 to 35 mosmol/kg raise the specific gravity by approximately 0.001. Thus, a specific gravity of 1.01 represents urine osmolality between 300 and 350 mosmol/kg.

However, there will be a disproportionate increase in the specific gravity as compared with the osmolality if larger molecules, such as glucose, are pres high concentrations. Clinical examples of this phenomenon include glucosu uncontrolled diabetes mellitus, and the administration of radiocontrast med approximately 550) or high doses of the antibiotic carbenicillin. In these se specific gravity can exceed 1.040 to 1.050, even though the urine osmolalit about 300 mosmol/kg, similar to that of the plasma.[28]

URINE PH

The urine pH generally reflects the degree of acidification of the urine and varies with systemic acid-base balance. The major clinical use of the urine occurs in patients with metabolic acidosis. The appropriate response to thi is to increase urinary acid excretion, so that the urine pH falls below 5.3 a below 5.6.[21] Values above 5.3* in adults and 5.6 in children usually indicate

abnormal urinary acidification and the presence of renal tubular acidosis;

the urine anion gap also tends to have a positive value in this setting, since NH_4^+ excretion is impaired.[21] Distinction between the various types of renal tubular acidosis can then be made by measurement of the urine pH and the fraction excretion of HCO_3^- at different plasma HCO_3^- concentrations (see chap. 19).

Monitoring the urine pH is also helpful in assessing the efficacy of treatme metabolic alkalosis and uric acid stone disease. As described above, HCO_3^- reabsorption is often increased in metabolic alkalosis due to concomitant v depletion. The net effect is that the urine pH is inappropriately acid (≤6.0), virtually all of the filtered HCO_3^- is reabsorbed. This defect can typically be reve by NaCl administration; as normovolemia is restored, the excess HCO_3^- can be excreted, resulting in an elevation in the urine pH to above 7.0. A persister urine pH usually indicates inadequate volume repletion.

A persistently acid urine is also an important factor in many patients with u stone disease. A high H^+ concentration will drive the reaction

$$H^+ + \text{urate}^- \leftrightarrow \text{uric acid}$$

to the right. The ensuing elevation in the uric acid concentration is physiol important, since uric acid is much less soluble than urate.[29] Administering alkali, on the other hand, can reverse this problem. The efficacy of therapy can be as by monitoring the urine pH, which should be above 6.0 to 6.5.

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Footnotes

* Although chronic diuretic use does not prevent attainment of a new steady urinary Na^+ excretion that is equal to intake is still inappropriately high in a hypovolemic patient.

† The diagnostic use of the urine pH requires that the urine be sterile. Infe any of the urinary pathogens that produce urease results in the metabolism urinary urea into ammonia (NH_3). The excess NH_3 directly elevates the urine pH according to the Henderson-Hasselbalch equation (see Chap. 4):

$$pH = 9.3 + \log \frac{NH_3}{NH_4^+}$$

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Chapter Fourteen
Hypovolemic states

In variety of clinical disorders, fluid losses lead to depletion of the extracellular fluid. This problem, if severe, can cause a potentially fatal decrease in tissue perfusion. Fortunately, early diagnosis and treatment can restore normovolemia in almost all cases.

ETIOLOGY

True volume depletion occurs when fluid is lost from the extracellular fluid at a rate exceeding net intake. These losses may occur from the gastrointestinal tract, skin, or lungs; in the urine; or by acute sequestration in the body in a "third space" that is not in equilibrium with the extracellular fluid (Table 14-1).

When these losses occur, two factors tend to protect against the development of hypovolemia. First, dietary Na^+ and water intake are generally far above basal needs. Thus, relatively large losses must occur unless intake is concomitantly reduced (as with anorexia or vomiting). Second, the kidney normally minimizes further urinary losses by enhancing Na^+ and water reabsorption.

The adaptive renal response explains why patients given a diuretic for hypertension do not develop progressive volume depletion. Although a thiazide diuretic

inhibits NaCl reabsorption in the distal tubule, the initial volume loss stimulates the renin-angiotensin-aldosterone system (and possibly other compensatory mechanisms), resulting in increased proximal and collecting tubule Na^+ reabsorption.[1,2] This balances the diuretic effect, resulting in the attainment within 1 to 2 weeks of a *new steady state in which there has been some fluid loss, but, in which Na^+ intake and excretion are again equal* (see Fig. 15-2).[3]

Table 14-1 Etiology of true volume depletion

A. Gastrointestinal losses
   1. Gastric: vomiting or nasogastric suction
   2. Intestinal, pancreatic, or biliary: diarrhea, fistulas, ostomies, or tube drainage
   3. Bleeding
B. Renal losses
   1. Salt and water: diuretics, osmotic diuresis, adrenal insufficiency, or salt-wasting nephropathies
   2. Water: central or nephrogenic diabetes insipidus
C. Skin and respiratory losses
   1. Insensible losses from skin and respiratory tract
   2. Sweat

3. Burns
4. Other: skin lesions, drainage and reformation of large pleural effusion, or bronchorrhea

D. Sequestration into a third space
1. Intestinal obstruction or peritonitis
2. Crush injury of skeletal fractures
3. Acute pancreatitis
4. Bleeding
5. Obstruction of a major venous system

Gastronintestinal Losses

Each day approximately 3 to 6 liters of fluid is secreted by the stomach, pancreas, gallbladder, and intestines into the lumen of the gastrointestinal tract. Almost all this fluid is reabsorbed, with only 100 to 200 mL being lost in the stool. However, volume depletion may ensue if reabsorption is decreased (as with external drainage) or secretion is increased (as with diarrhea).

Acid-base disturbances frequently occur with gastrointestinal losses, depending upon the site from which the fluid is lost. Secretions from the stomach contain high concentrations of H^+ and Cl^-. As a result, vomiting and nasogastric suction are generally associated with metabolic alkalosis. In contrast, intestinal, pancreatic, and biliary secretions are relatively alkaline, with high concentrations of HCO_3^-. Thus, the loss of these fluids due to diarrhea, laxative abuse, fistulas, ostomies, or tube drainage tends to cause metabolic acidosis. Hypokalemia is also commonly associated with these disorders, since K^+ is present in all gastrointestinal secretions.

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Acute bleeding from any site in the gastrointestinal tract is another common cause of volume depletion. Electrolyte disturbances usually do not occur in this setting (except for shock-induced lactic acidosis), since it is plasma, not gastrointestinal secretions, that is lost.

Renal Losses

Under normal conditions, renal Na^+ and water excretion is adjusted to match intake. In a normal adult, approximately 130 to 180 liters is filtered across the glomerular capillaries each day. More than 98 to 99 percent of the filtrate is then reabsorbed by the tubules, resulting in a urine output averaging 1 to 2 L/day. Thus, a small (1 to 2 percent) reduction in tubular reabsorption can lead to a 2- to 4-liter increase in Na^+ and water excretion, which, if not replaced, can result in severe volume depletion.

NaCl and water loss

A variety of conditions can lead to excessive urinary excretion of NaCl and water (Table 14-1). Diuretics, for example, inhibit active transport of Na^+ at different sites in the nephron, resulting in an increased rate of excretion (see Chap. 15). Although they are frequently given to remove fluid in edematous patients, diuretics can produce true hypovolemia if used in excess.

The presence of large amounts of nonreabsorbed solutes in the tubule also can inhibit Na^+ and water reabsorption, resulting in *osmotic diuresis*. The most common clinical example occurs in uncontrolled diabetes mellitus, in which glucose acts as the osmotic agent. With severe hyperglycemia, urinary losses can contribute to a net fluid deficit of as much as 8 to 10 liters (see Chap. 25).

Variable degrees of Na^+ wasting are also present in many renal diseases. Most patients with renal insufficiency [glomerular filtrate rate (GFR) less than 25 mL/min] are unable to maximally conserve Na^+ if acutely placed on a low-sodium diet. These patients may have *obligatory* Na^+ loss of 10 to 40 meq/day, in contrast to normal subjects, who can lower Na^+ excretion to less than 5 meq/day.[4,5] This degree of Na^+ wasting is usually not important, since normal Na^+ balance is maintained as long as the patient is on a regular diet.

In rare cases, a more severe degree of Na^+ wasting is present in which obligatory urinary losses may exceed 100 meq of Na^+ and 2 liters of water per day. In this setting, hypovolemia will ensue unless the patient maintains a high Na^+ intake. This picture of a severe *salt-wasting nephropathy* is most often seen in tubular and interstitial diseases, such as medullary cystic kidney disease.[6,7]

Three factors are thought to contribute to this variable salt wasting: the osmotic diuresis produced by increased urea excretion in the remaining functioning nephrons; direct damage to the tubular epithelium, which, in severe cases, can impair the response to aldosterone; and, probably most important in chronic renal disease, an inability to acutely shut off natriuretic forces.[5,6,8] Patients with renal insufficiency tend to have a decreased number of functioning nephrons. If Na^+ intake remains normal, they must be able to augment Na^+ excretion per functioning

nephron to maintain Na^+ balance. This requires a fall in tubular Na^+ reabsorption that may be mediated at least in part by a natriuretic hormone, such as atrial natriuretic peptide.

Thus, the salt wasting that occurs when Na^+ intake is abruptly lowered could represent persistent activation of these natriuretic forces. Consistent with this hypothesis is the observation that apparent salt wasters (with acute obligatory losses of as much as 300 meq/day) can maintain Na^+ balance on an intake of only 5 meq/day if intake is gradually reduced over a period of weeks rather than acutely.[5]

Therapy of renal salt wasting must be directed toward establishing the level of Na^+ intake required to maintain Na^+ balance. This can usually be determined empirically, as most patients will tolerate a daily intake above 1.5 to 2 g (60 to 80 meq). It should not be assumed, however, that a patient with salt wasting has a normal ability to excrete a Na^+ load. Some patients with renal insufficiency who become hypovolemic with Na^+ restriction may retain Na^+ and develop edema and hypertension if placed on a high-sodium diet. In these patients, the range of Na^+ intake compatible with the maintenance of Na^+ balance is relatively narrow.

The increase in urine output following relief of bilateral urinary tract obstruction is often considered to represent another example of renal salt wasting. This postobstructive diuresis, however, is in almost all cases *appropriate* in that it represents an attempt to excrete the fluid retained during the period of obstruction.[9,10] Thus, quantitative replacement of the urine output will lead to persistent volume expansion and a urine output that can exceed 10 L/day.

Although the diuresis is largely appropriate, some fluid therapy is required (e.g., 50 to 75 mL/h of half-isotonic saline), since there is often a mild sodium-wasting tendency, the severity of which is limited by the concurrent reduction in glomerular filtration rate and a modest concentrating defect due to downregulation of water channels.[11] Although the risk of volume depletion is minimal with this regimen, the

patient should be monitored for signs such as hypotension, decreased skin turgor, or a rise in the blood urea nitrogen (BUN).

Water loss

Volume depletion can also result from a selective increase in urinary water excretion. This is due to decreased water reabsorption in the collecting tubules, where antidiuretic hormone (ADH) promotes the reabsorption of water but not Na^+. As a result, an impairment in either ADH secretion (central diabetes insipidus) or the renal response to ADH (nephrogenic diabetes insipidus) may be associated with the excretion of relatively large volumes (over 10 L/day in severe cases) of dilute urine (see Chap. 24). This water loss is usually matched by an equivalent increase in water intake, since the initial elevation in the plasma osmolality and Na^+ concentration stimulates thirst. However, water loss, hypovolemia, and persistent hypernatremia will ensue in infants, comatose patients (neither of whom have ready access to water), or those with a defective thirst mechanism.

Skin and Respiratory Losses

Each day, approximately 700 to 1000 mL of water is lost by evaporation from the skin and respiratory tract (see Chap. 9). Since heat is required for the evaporation of water, these insensible losses play an important role in thermoregulation, allowing the dissipation of some of the heat generated from body metabolism. When external temperatures are high or metabolic heat production is increased (as with fever or exercise), further heat can be lost by the evaporation of sweat (a "sensible" loss) from the skin. Although sweat Na^+ concentration equals 30 to 50 meq/L) production is low in the basal state, it can exceed 1 to 2 L/h in a subject exercising in a hot, dry climate.[1,2]*

Negative water balance due to these insensible and sensible losses is usually prevented by the thirst mechanism, similar to that in diabetes insipidus. However, the cumulative sweat Na^+ losses can lead to hypovolemia.

In addition to its role in thermoregulation, the skin acts as a barrier that prevents the loss of interstitial fluid to the external environment. When this barrier is interrupted by burns or exudative skin lesions, a large volume of fluid can be lost. This fluid has an electrolyte composition similar to that of the plasma and contains a variable amount of protein. Thus, the replacement therapy in a burn patient differs from that in a patient with increased insensible or sweat losses.

Although rare, pulmonary losses other than those by evaporation can lead to volume depletion. This most often occurs in patients who have either continuous drainage of an active, usually malignant pleural effusion or an alveolar cell carcinoma with a marked increase in bronchial secretions (Bronchorrhea).

Sequestration into a Third Space

Volume depletion can be produced by the loss of interstitial and intravascular fluid into a third space that is not in equilibrium with the extracellular fluid. For example, a patient with a fractured hip may lose 1500 to 2000 mL of blood into the tissues adjacent to the fracture. Although this fluid will be resorbed back into the extracellular fluid over a period of days to weeks, the acute reduction in blood volume, if not replaced, can lead to severe volume depletion. Other examples of this phenomenon include intestinal obstruction, severe pancreatitis, crush injuries, bleeding (as with trauma or a ruptured abdominal aortic aneurysm), peritonitis, and obstruction of a major venous system.

The main difference between these disorders and, for example, the development of

ascites in cirrhosis is the *rate of fluid accumulation*. Cirrhotic ascites develops relatively slowly, allowing time for renal Na^+ and water retention

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to replenish the effective circulating volume (see Chap. 16). As a result, cirrhotic patients typically have symptoms of edema rather than those of hypovolemia.

HEMODYNAMIC RESPONSES TO VOLUME DEPLETION

Volume depletion induces a characteristic sequence of compensatory hemodynamic responses. The initial volume deficit results in decreases in the plasma volume and venous return to the heart. The latter is sensed by the cardiopulmonary receptors in the atria and pulmonary veins, leading to sympathetically mediated vasoconstriction in skin and skeletal muscle.[13] This effect, which shunts blood toward the more important cerebral and coronary circulations, is mediated by partial removal of the tonic inhibition of sympathetic tone normally induced by these receptors.

More marked volume depletion leads to a reduction in cardiac output. From the relationship between mean arterial pressure, cardiac output, and systemic vascular resistance,

Mean arterial pressure = cardiac output × systemic vascular resistance

the fall in cardiac output lowers the systemic blood pressure. This hemodynamic change is sensed by the carotid sinus and aortic arch baroreceptors, which induce a more generalized increase in sympathetic activity that now involves the splanchnic and renal circulations.

The net effect is relative maintenance of cerebral and coronary perfusion and return of the arterial pressure toward normal. The latter is mediated by increases in venous return (mediated in part by active venoconstriction), cardiac contractility, and heart rate (all of which act to elevate the cardiac output) and increases in vascular resistance due both to direct sympathetic effects and to enhanced secretion of renin from the kidney, resulting in the generation of angiotensin II.[13]

If the volume deficit is small (about 10 percent of the blood volume, which is equivalent to donating 500 mL of blood), these sympathetic effects return the cardiac output and blood pressure to normal or near normal, although the heart rate is likely to be increased.[14] In contrast, a marked fall in blood pressure will ensue if the sympathetic response does not occur—for example, because of autonomic insufficiency.[15,16]

With more severe hypovolemia (16 to 25 percent of the blood volume), there is more pronounced sympathetic and angiotensin II–mediated vasoconstriction. Although this may maintain the blood pressure when the patient is recumbent, hypotension can occur when the upright position is assumed, leading to postural dizziness. At this point, the compensatory sympathetic responses are maximal, and

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any further fluid loss will induce marked hypotension, even in recumbency, and eventually shock (see below).[14,17]

SYMPTOMS

Three sets of symptoms can occur in hypovolemic patients:[1] those related to the manner in which fluid loss occurs, such as vomiting, diarrhea,[2] or osmotic diuresis; those due to volume depletion;[3] and those due to the electrolyte and acid-base disorders that can accompany volume depletion.

The symptoms induced by hypovolemia are primarily related to the decrease in tissue perfusion. The earliest complaints include lassitude, easy fatigability, thirst, muscle

cramps, and postural dizziness. More severe fluid loss can lead to abdominal pain, chest pain, or lethargy and confusion as a result of mesenteric, coronary, or cerebral ischemia. These symptoms usually are reversible, although tissue necrosis may develop if the low-flow state is allowed to persist.

Symptomatic hypovolemia most often occurs in patients with isosmotic Na^+ and water depletion in whom most of the fluid deficit comes from the extracellular fluid. In contrast, in patients with pure water loss due to insensible losses or diabetes insipidus, the elevation in plasma osmolality (and Na^+ concentration) causes water to move down an osmotic gradient from the cells into the extracellular fluid. The net result is that about *two-thirds of the water lost comes from the intracellular fluid*.[18] Consequently, these patients are likely to exhibit the symptoms of hypernatremia (produced by the water deficit) before those of marked extracellular fluid depletion.

A variety of electrolyte and acid-base disorders also may occur, depending upon the composition of the fluid that is lost (see below). The more serious symptoms produced by these disturbances include muscle weakness (hypokalemia and hyperkalemia); polyuria and polydipsia (hypokalemia and hyperglycemia); and lethargy, confusion, seizures, and coma (hyponatremia, hypernatremia, and hyperglycemia).

An additional symptom that appears to occur only in primary adrenal insufficiency is extreme salt craving. Approximately 20 percent of patients with this disorder give a history of heavily salting all foods (including those not usually salted) and even eating salt that they have sprinkled on their hands.[18] The mechanism responsible for this appropriate increase in salt intake is not known.

EVALUATION OF THE HYPOVOLEMIC PATIENT

The evaluation of the patient with suspected hypovolemia includes a careful history for a source of fluid loss, the physical examination, and appropriate laboratory studies. In many patients in whom the history does not provide a clear etiology, a common presumption, particularly in the elderly, is that unreplaced

insensible losses are responsible. Evaporative and sweat losses are hypotonic and therefore must produce an elevation in the plasma Na^+ concentration if they are solely responsible for volume depletion. The presence of a normal plasma sodium indicates proportionate salt and water loss if the patient is truly hypovolemic.

These observations also help to avoid the common mistake of assuming that dehydration and volume depletion (or hypovolemia) are synonymous.[19] Volume depletion refers to extracellular volume depletion of any cause, most often due to salt and water loss. In contrast, dehydration refers to the presence of hypernatremia due to pure water loss; such patients are also hypovolemic.

Physical Examination

Although relatively insensitive and nonspecific,[20] certain findings on physical examination may suggest volume depletion. A decrease in the interstitial volume can be detected by examination of the skin and mucous membranes, while a decrease in the plasma volume can lead to reductions in systemic blood pressure and in venous pressure in the jugular veins.

Among patients with hypovolemia due to severe bleeding, the most sensitive and specific findings are severe postural dizziness (preventing measurement of upright vital signs) and/or a postural pulse increment of 30 beats/min or more.[20] Among patients with mild to moderate blood loss or other causes of hypovolemia (vomiting, diarrhea, decreased intake), few findings have proven predictive value, and

laboratory confirmation of the presence of volume depletion is typically required.[20]

Skin and mucous membranes

If the skin and subcutaneous tissue on the thigh, calf, or forearm is pinched in normal subjects, it will immediately return to its normally flat state when the pinch is released. This elastic property, called *turgor*, is partially dependent upon the interstitial volume of the skin and subcutaneous tissue. Interstitial fluid loss leads to diminished turgor, and the skin flattens more slowly after the pinch is released. In younger patients, the presence of decreased skin and subcutaneous tissue turgor is a reliable indicator of volume depletion. However, elasticity diminishes with age, so that reduced turgor does not necessarily reflect hypovolemia in older patients (more than 55 to 60 years old). In these patients, skin elasticity is usually best preserved on the inner aspect of the thighs and the skin overlying the sternum. Decreased turgor at these sites is suggestive of volume depletion.

Although reduced skin turgor is an important clinical finding, *a normal turgor does not exclude the presence of hypovolemia*.[20] This is particularly true with mild volume deficits, in young patients whose skin is very elastic, and in obese patients, since fat deposits under the skin prevent the changes in subcutaneous turgor from being appreciated.

In addition to having reduced turgor, the skin is usually dry; a dry axilla is particularly suggestive of the presence of hypovolemia.[20] The tongue and oral

mucosa may also be dry, since salivary secretions are commonly decreased in this setting.

Examination of the skin also may be helpful in the diagnosis of primary adrenal insufficiency. The impaired release of cortisol in this disorder leads to hypersecretion of adrenocorticotropic hormone (ACTH), which can result in increased pigmentation of the skin, especially in the palmar creases and buccal mucosa.

Arterial blood pressure

As described above, the arterial blood pressure changes from near normal with mild hypovolemia to low in the upright position and then, with progressive volume depletion, to persistently low regardless of posture. Postural hypotension leading to dizziness may be the patient's major complaint and is strongly suggestive of hypovolemia in the absence of an autonomic neuropathy or the use of sympatholytic drugs for hypertension, or in elderly subjects, in whom postural hypotension is common in the absence of hypovolemia.

An important change that can occur with marked fluid loss is that the secondary neurohumoral vasoconstriction leads to decreased intensity of both the Korotkoff sounds (when the blood pressure is being measured with a sphygmomanometer) and the radial pulse.[17,21] As a result, a very low blood pressure suggested by auscultation or palpation may actually be associated with a *near-normal pressure* when measured directly by an intraarterial catheter.

It is important to appreciate that the definition of normal blood pressure in this setting is dependent upon the patient's basal value. Although 120/80 is considered “normal,” it is actually low in a hypertensive patient whose usual blood pressure is 180/100.

Venous pressure

The reduction in the vascular volume seen with hypovolemia occurs primarily in the venous circulation (which normally contains 70 percent of the blood volume), leading to a decrease in venous pressure. As a result, measurement of the venous pressure

is useful both in the diagnosis of hypovolemia and in assessing the adequacy of volume replacement[22].

In most patients, the venous pressure can be estimated with sufficient accuracy by examination of the external jugular vein, which runs across the sternocleidomastoid muscle. The patient should initially be recumbent, with the trunk elevated at 15 to 30 degrees and the head turned slightly away from the side to be examined. The external jugular vein can be identified by placing the forefinger just above the clavicle and pressing lightly. This will occlude the vein, which will then distend as blood continues to enter from the cerebral circulation. The external jugular vein usually can be seen more easily by shining a beam of light obliquely across the neck.

At this point, the occlusion at the clavicle should be released and the vein occluded superiorly to prevent distention by continued blood flow. The venous pressure can now be measured, since it will be approximately equal to the *vertical distance* between the upper level of the fluid column within the vein and the level of the right atrium (estimated as being 5 to 6 cm posterior to the sternal angle of Louis). If the vein is distended throughout its length, the patient's trunk should be

elevated to 45 or even 90 degrees until an upper level can be seen. In a patient with a markedly increased venous pressure due to right ventricular failure, the external jugular vein may remain distended even when the patient is upright. The normal venous pressure is 1 to 8 cm H_2O or 1 to 6 mmHg (1.36 cm H_2O is equal to 1.00 mmHg).

There are some limitations to the use of this technique. For example, the external jugular vein may not become visible when it is occluded at the clavicle, particularly in those patients with a fat neck. If this occurs, it should not be reported that the venous pressure is very low. Rather, the venous pressure should be measured in some other way, such as by estimation of the *level of pulsations in the internal jugular vein* or directly by insertion of a catheter into the right atrium.

A much less common problem is kinking or obstruction of the external jugular vein at the base of the neck. In this setting, there is an increase in the external jugular venous pressure that does not reflect a similar change in right atrial pressure. This possibility should be suspected if an elevated venous pressure is found in a patient with no evidence or history of cardiac or pulmonary disease.

Relationship between right atrial and left atrial pressures

The filling pressures in the heart are important determinants of cardiac output, since the contractility of cardiac muscle and therefore the stroke volume increases as the filling pressure is increased (Fig. 14-1). If there is no obstruction to flow across the mitral valve, the left atrial pressure will be equal to the left ventricular end-diastolic pressure (LVEDP), that is, to the filling pressure in the left ventricle. The left atrial pressure can be estimated clinically by measurement of the pulmonary capillary wedge pressure with a flow-directed balloon catheter (such as a Swan-Ganz catheter).

In general, there is a predictable relationship between the right and left atrial pressures, with the latter being greater by approximately 5 mmHg (Fig. 14-2)[23]. When the right atrial (or central venous) pressure is reduced, the LVEDP also is decreased, and this tends to lower the cardiac output. Conversely, a high central venous pressure is associated with a high left atrial pressure, which predisposes toward the development of pulmonary edema.

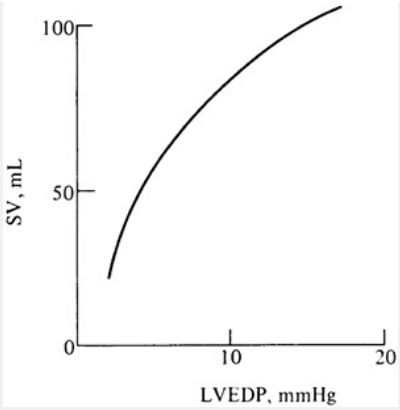

Figure 14-1 Frank-Starling curve relating stroke volume (SV) to left ventricular end-diastolic pressure (LVEDP). (*Adapted from Cohn, Am J Med 55:351, 1973, with permission.*)

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Although it is the LVEDP (not the right atrial pressure) that is the important determinant of left ventricular output and therefore tissue perfusion, measurement of the central venous pressure is useful because of its direct relationship to the LVEDP. There are, however, two clinical settings in which the central venous or right atrial pressure is not an accurate estimate of the LVEDP.[2] In patients with pure left-sided heart failure (as with an acute myocardial infarction), the wedge pressure is increased but the central venous pressure may remain unchanged if right ventricular function is normal. In this setting, treating a low central venous pressure with volume expanders can precipitate pulmonary edema. On the other hand, the central venous pressure tends to exceed the LVEDP in patients with pure right-sided heart failure (as with cor pulmonale). These patients may have high central venous pressures even in the presence of volume depletion; as a result, the central venous pressure cannot be used as a guide to therapy.

Shock

The symptoms and physical findings that have been described apply to patients with mild to moderate volume depletion who are still able to maintain an adequate level of tissue perfusion. However, as the degree of hypovolemia becomes more severe, due, for example, to the loss of 30 percent of the blood volume from a ruptured aortic aneurysm, there is a marked reduction in tissue perfusion, resulting in a clinical syndrome referred to as hypovolemic shock.[3] This syndrome is associated with a marked increase in sympathetic activity and is characterized by tachycardia; cold, clammy extremities; cyanosis; a low urine output

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(usually less than 15 mL/h); and agitation and confusion due to reduced cerebral blood flow. Although hypotension is generally present, it is not required for the diagnosis of shock, since some patients vasoconstrict enough to maintain a relatively normal blood pressure. Therapy to restore tissue perfusion must be begun immediately to prevent both ischemic tissue damage and irreversible shock (see below).

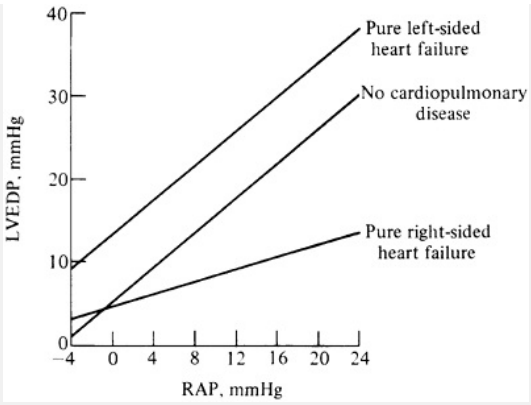

Figure 14-2 Relationship between left ventricular end-diastolic pressure (LVEDP) and mean right atrial pressure (RAP) in three groups of patients. In subjects without cardio-pulmonary disease, the LVEDP exceeds the RAP by about 5 mmHg and varies directly with the RAP. In patients with pure right-sided heart failure, e.g., due to chronic pulmon-ary disease, relatively large changes in the RAP can occur with little change in the LVEDP. In contrast, the LVEDP is much greater than the RAP in patients with pure left-sided heart failure, e.g., due to an acute myocardial infarction. This graph is somewhat simplified, since the stand-ard deviations within each group have been omitted. *Adapted from Cohn JN, Tristani FE, Khatri IM: J Clin Invest 48:2008, 1969, by copyright permission of the American Society for Clinical Investigation.*

Laboratory Data

Hypovolemia can produce a variety of changes in the composition of the urine and blood (Table 14-2). In addition to confirming the presence of volume depletion, these changes can give important clues to the pathogenesis of the fluid loss and to the appropriate replacement therapy.

Urine sodium concentration

The response of the kidney to volume depletion is to conserve Na^+ and water in an attempt to expand the extracellular volume. Except in those disorders in which Na^+ reabsorption is impaired, the urine Na^+ concentration in hypovolemic states should be less than 25 meq/L and may be as low as 1 meq/L (Table 14-3). This increase in tubular Na^+ reabsorption is mediated by several factors, including increased activity of the renin-angiotensin-aldosterone system, a fall in systemic blood pressure, and possibly reduced secretion of atrial natriuretic peptide (Chap. 8).

The urine Cl^- concentration is usually similar to that of Na^+ in hypovolemic states, since Na^+ and Cl^- are generally reabsorbed together. An exception occurs when Na^+ is excreted with another anion. This is most often seen in metabolic alkalosis, where the need to excrete the excess HCO_3^- (as NaHCO$_3$) may raise the urine Na^+ concentration despite the presence of volume depletion. In this setting, the urine Cl concentration remains low and is frequently a better index of volume status (see Chap. 18).[24,25] Thus, the urine Cl^- concentration should be measured when any apparently hypovolemic patient has what seems to be an inappropriately high urine Na^+ concentration.

Even if the physical examination is not diagnostic of hypovolemia, a low urine Na^+ concentration is virtually pathognomonic of reduced tissue perfusion. The main

exception to this rule occurs with *selective* renal or glomerular hypoperfusion, as with bilateral renal artery stenosis or acute glomerulonephritis.[26,27] In these settings, there is avid renal Na^+ retention independent of systemic fluid balance.

Table 14-2 Laboratory changes in hypovolemic states

Urine Na^+ concentration less than 20 meq/L
Urine osmolality greater than 450 mosmol/kg
BUN/plasma creatinine ratio greater than 20 : 1 with a normal urinalysis
Variable effects on plasma Na^+, K^+, and HCO_3^- concentrations
Occasional elevations in the hematocrit and plasma albumin concentration

Table 14-3 Urine Na^+ concentration in volume depletion

Less than 20 meq/L	Greater than 40 meq/L
Gastrointestinal losses	Underlying renal disease
Skin losses	Diuretics (while the drug is acting)
Third-space losses	Osmotic diuresis
Diuretics (late)	Hypoaldosteronism
	Some patients with metabolic alkalosis

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However, the presence of a low urine Na^+ concentration does not necessarily mean that the patient has true volume depletion, since edematous patients with heart failure or hepatic cirrhosis with ascites also avidly conserve Na^+. These disorders are characterized by *effective circulating volume depletion* due to a primary reduction in cardiac output (heart failure) or to splanchnic vasodilatation and sequestration of fluid in the peritoneal cavity (cirrhosis) (see Chaps. 16 and 17). The differentiation between edematous states and true volume depletion usually is made easily from the physical examination.

An alternative to measurement of the urine Na^+ concentration is calculation of the fractional excretion of Na^+ (FE_{Na}). The FE_{Na} is most useful in the differential diagnosis of acute renal failure with a very low glomerular filtration rate; in this setting, the FE_{Na} is usually under 1 percent in hypovolemic patients.[27,28] This FE_{Na} is more difficult to evaluate in patients with a normal glomerular filtration rate, since the filtered Na^+ load is so high in this setting that a differential value ($FE_{Na} \leq 0.1$ to 0.2 percent) must be used to diagnose volume depletion (see Chap. 13).

Urine osmolality

The renal retention of water in hypovolemic states is mediated in part by ADH, which is secreted in response to the decrease in tissue perfusion (Chap. 6). As a result, the urine is relatively concentrated, with an osmolality often exceeding 450 mosmol/kg.[27,28] and[29] This response may not be seen, however, if concentrating ability is impaired by renal disease, an osmotic diuresis, the administration of diuretics, or central or nephrogenic diabetes insipidus. For example, both severe volume depletion (which impairs urea accumulation in the renal medulla)[28] and hypokalemia (which induces ADH resistance; see Fig. 12-1) can limit the increase in the urine osmolality in some patients. Thus, a high urine osmolality is consistent with hypovolemia, but a relatively isosmotic value does not exclude this disorder.[29]

Urinary concentration can also be assessed by measuring the specific gravity.[30] This test, however, is less accurate than the osmolality, since it is dependent upon the size as well as the number of solute particles in the urine (see Fig. 18-1). As a result, it should be used only if the osmolality cannot be measured; a value above 1.015 is suggestive of a concentrated urine, as is usually seen with hypovolemia.

BUN and plasma creatinine concentration

In most circumstances, the blood urea nitrogen (BUN) and plasma creatinine concentration vary inversely with the GFR, increasing as the GFR falls (see Fig. 21-11). Thus, serial measurements of these parameters can be used to assess the course of renal disease. However, an elevation in the BUN can also be produced by an increase in the rate of urea production or tubular reabsorption. As a result, the plasma creatinine concentration is a more reliable estimate of the GFR, since it is produced at a relatively constant rate by skeletal muscle and is not reabsorbed by the renal tubules.

In normal subjects and those with uncomplicated renal disease, the BUN/plasma creatinine ratio is approximately 10 : 1. However, this value may be substantially elevated in hypovolemic states, because of the associated increase in tubular reabsorption.[31] In general, approximately 40 to 50 percent of filtered urea is reabsorbed, much of this occurring in the proximal tubule, where it is passively linked to the reabsorption of Na^+ and water (see Chap. 3). Thus, the increase in proximal Na^+ reabsorption in volume depletion produces a parallel rise in urea reabsorption. The net effect is a fall in urea excretion and elevations in the BUN and the BUN/plasma creatinine ratio, often to greater than 20 : 1. This selective rise in the BUN is called *prerenal azotemia*. The plasma creatinine concentration will increase in this setting only if the degree of hypovolemia is severe enough to lower the GFR.

Although the BUN/plasma creatinine ratio is helpful in the evaluation of hypovolemic patients, it is subject to misinterpretation, since it is also affected by the rate of urea production. A high ratio may be due solely to increased urea production (as with gastrointestinal bleeding), whereas a normal ratio may occur in some patients with hypovolemia if urea production is reduced. This can be illustrated by the following example:

Case History 14-1

A 40-year-old man with a history of peptic ulcer disease is seen after 2 weeks of persistent vomiting. On physical examination, the patient's blood pressure is normal, but his estimated jugular venous pressure is less than 5 cm H_2O and skin turgor is reduced. The laboratory data include

BUN	=	42 mg/dL
Plasma creatinine	=	3.6 mg/dL
Urine Na^+	=	7 meq/L
Urine osmolality	=	502 mosmol/kg

Comment

The low urine Na^+ concentration, the high urine osmolality, and the physical examination are all suggestive of hypovolemia. This diagnosis was subsequently confirmed by return of the BUN and plasma creatine concentration to normal levels with volume repletion. The failure of the initial BUN to increase out of proportion to the plasma creatinine concentration probably reflected the reduction in protein intake due to vomiting.

Urinalysis

Examination of the urine is an important diagnostic tool in patients with elevations in the BUN and plasma creatinine concentration. The urinalysis is generally normal in hypovolemic states, since the kidney is not diseased. This is in contrast to most of the other causes of renal insufficiency, in which the urinalysis reveals protein, cells, and/or casts.[29]

Hypovolemia and renal disease

The laboratory diagnosis of hypovolemia may be difficult to establish in patients with underlying renal disease. In this setting, the urine Na^+ concentration may exceed 25 meq/L and the urine osmolality may be less than 350 mosmol/kg, since renal insufficiency impairs the ability to maximally conserve Na^+ and to concentrate the urine.[29,32] In addition, the urinalysis may be abnormal as a result of the primary disease.

Despite these difficulties, making the correct diagnosis is important, since volume depletion is *a reversible* cause of worsening renal function, in contrast to progression of the underlying renal disease. The history and physical examination (possibly vomiting, diarrhea, use of diuretics, or decreased skin turgor) may be helpful in some patients, but these findings are not always present. As a result, a cautious trial of fluid repletion may be warranted in a patient whose renal function has deteriorated without obvious cause.

Plasma sodium concentration

A variety of factors can influence the plasma Na^+ concentration in hypovolemic states, and it is the interplay between them that determines the level seen in a given patient (Table 14-4). Volume depletion is a potent stimulus to both ADH release and thirst. The ensuing increases in renal water reabsorption and water intake can lead to water retention and the development of *hyponatremia*. On the other hand, *hypernatremia* can occur when water is lost in excess of solute. This can be seen with unreplaced insensible or sweat losses and with central or nephrogenic diabetes insipidus. Diminished thirst, usually due to impaired mentation, is essential for the plasma Na^+ concentration to rise in these disorders. The ability to increase water intake is normally an effective defense against the development of hypernatremia; patients with diabetes insipidus, for example, typically present with polyuria (that can exceed 10 L/day) and polydipsia, but a relatively normal plasma Na^+ concentration.

The osmotic effect of gastrointestinal losses is variable. Although the fluid lost is generally isosmotic to plasma, it is important to appreciate that the plasma Na^+ *concentration is normally determined by three factors: total exchangeable Na*$^+$,

total

exchangeable K^+ and total body water (see page 248). Secretory diarrheas, for example, tend to be pure electrolyte solutions, containing Na^+ and K^+ salts in a concentration similar to that in the plasma.[33] As a result, loss of this fluid will lead to volume depletion but no direct change in the plasma Na^+ concentration.

Table 14-4 Plasma Na^+ concentration in volume depletion

May be greater than 150 meq/L	May be less than 135 meq/L
Insensible and sweat losses Central or nephrogenic diabetes insipidus Uncontrolled diabetes mellitus	All other forms of volume depletion

In comparison, osmotic diarrheas (as seen with malabsorption, certain infections, and the administration of lactulose) contain nonreabsorbed solutes and tend to have Na^+ plus K^+ concentrations of 50 to 100 meq/L, well below that in the plasma.[33,34] Thus, water is lost in excess of Na^+ plus K^+, a change that will raise the plasma Na^+ concentration. Hypernatremia may not be seen, however, because of the possible counterbalancing effects of increased water intake and renal water retention. Thus, the *plasma Na^+ concentration may be low, normal, or elevated in patients with diarrhea*.

Similar principles apply to the osmotic diuresis seen with uncontrolled diabetes mellitus. In this setting, the urine is often hyperosmotic to plasma, because of the hypovolemia-induced stimulation of ADH release. Much of the urinary solute, however, is glucose, and the urine Na^+ plus K^+ concentration is typically less than that in the plasma. As a result, the plasma Na^+ concentration will tend to rise. However, this does not usually lead to hypernatremia, since the initial plasma Na^+ concentration is often below normal in these patients. The rise in plasma osmolality induced by hyperglycemia pulls water out of the cells, thereby lowering the plasma Na^+ concentration by dilution (see p. 215). Thus, the final plasma Na^+ concentration is variable, being determined by the degree of hyperglycemia, water intake, and the amount of water lost in the urine.

Plasma potassium concentration

Either hypokalemia or hyperkalemia can occur in hypovolemic patients. The former is much more common, because there is concurrent loss of K^+ from the gastrointestinal tract or in the urine. Hyperkalemia may be seen in several settings. First, the plasma K^+ concentration may be elevated in some forms of metabolic acidosis. As some of the excess H^+ ions enter the cells to be buffered, intracellular K^+ moves into the extracellular fluid to maintain electroneutrality (see p. 192). Thus, a patient may have an elevated plasma K^+ concentration even if total body K^+ stores are reduced. Second, there may be an inability to excrete the load of K^+ in the urine because

of renal failure, hypoaldosteronism, or volume depletion itself, since the delivery of Na^+ and water to the K^+ secretory site in the cortical collecting tubule will be reduced.[35]

Acid-base balance

The effect of fluid loss on acid-base balance also is variable. Although many patients maintain a normal extracellular pH, either metabolic alkalosis or metabolic acidosis can occur (Table 14-5). Patients with vomiting or nasogastric suction and those given diuretics tend to develop metabolic alkalosis because of K^+ loss and volume contraction (see chap. 18). On the other hand, HCO_3^- loss (due to diarrhea or intestinal fistulas) or reduced renal H^+ excretion (due to renal failure or hypoaldosteronism) can lead to metabolic acidosis. In addition, lactic acidosis can occur in shock and ketoacidosis in uncontrolled diabetes mellitus.

Table 14-5 Acid-base disorders that may occur in volume depletion

Metabolic acidosis	Metabolic alkalosis
Diarrhea or loss of other lower intestinal, pancreatic, or biliary secretions Renal failure Hypoaldosteronism Ketoacidosis in uncontrolled diabetes mellitus Lactic acidosis in shock	Vomiting or nasogastric suction Loop or thiazide diuretics

Hematocrit and plasma albumin concentration

Since the red blood cells and albumin are essentially limited to the vascular space, a reduction in the plasma volume due to volume depletion tends to elevate both the hematocrit and the plasma albumin concentration. These changes, however, are frequently absent because of underlying anemia and/or hypoalbuminemia, due, for example, to bleeding or renal disease.

Summary

An accurate history and physical examination can help to determine both the presence and the etiology of volume depletion. In the patient in whom the diagnosis cannot be made from the history, laboratory data can provide important clues to the correct diagnosis. This can be demonstrated by the following example.

Case History 14-2

A 38-year-old woman is admitted with a 2-day history of weakness and postural dizziness. She denies vomiting, diarrhea, melena, or drugs. On physical examination, the blood pressure is 110/60 recumbent and falls to 80/50 erect. The pulse is 100 and regular. The estimated jugular venous pressure is less than 5 cm H_2O, the skin turgor is poor, and the mucous membranes are dry. The laboratory data include

Plasma [Na^+]	=	140 meq/L	Arterial pH	=	7.25
[K^+]	=	3.2 meq/L	P_{CO_2}	=	28 mmHg
[Cl^-]	=	116 meq/L	Urine [Na^+]	=	9 meq/L
[HCO_3^-]	=	12 meq/L	Osmolality	=	584 mosmol/kg
BUN	=	40 mg/dL			
[Creatinine]	=	1.3 mg/dL			

Comment

Although the etiology is not apparent from the history, the physical examination is consistent with moderately severe volume depletion. The

low urine Na^+ concentration suggests that renal function is normal and that renal salt wasting and adrenal insufficiency are not responsible for the hypovolemia. The presence of metabolic acidosis and hypokalemia suggests that diarrhea is responsible for the fluid loss. Upon closer questioning, a history of laxative abuse with multiple bowel movements each day is obtained.

TREATMENT

Both oral and intravenous replacement fluids can be administered for volume replacement in the hypovolemic patient. The aims of therapy are to restore normovolemia and to correct any associated acid-base or electrolyte disorders that may be present.

Oral Therapy

In patients with mild volume depletion, increasing dietary Na^+ intake either by altering the diet or by using NaCl tablets may be sufficient to correct the volume deficit. Oral solutions containing glucose (or cereals that are composed of starch polymers such as rise) and electrolytes can also be used to treat persistent or severe diarrhea, as in cholera.[36,37] and[38] The addition of glucose both provides extra calories and promotes small intestinal Na^+ reabsorption, since there is coupled transport of Na^+ and glucose at this site, similar to that in the proximal tubule (see page 90). The rice-based solutions are generally more effective than glucose alone (particularly in cholera), since the digestion of rice provides both more glucose (50 to 80 g/L versus 20 g/L with glucose alone) and amino acids (which can also promote intestinal sodium absorption).[36]

Intravenous Solutions

With more severe hypovolemia or in patients unable to take oral fluids, volume repletion requires the administration of intravenous fluids. A wide variety of intravenous solutions are available. The compositions of the most commonly used solutions are listed in Table 14-6. The content of each solution determines the clinical situation in which it will be most useful.

Dextrose solutions

Since glucose is rapidly metabolized to $CO_2 + H_2O$, the administration of dextrose solutions is physiologically equivalent to administering distilled water. The main indication for the use of dextrose in water is to provide free water to replace insensible losses or to correct hypernatremia due to a water deficit. More concentrated dextrose solutions (20% and 50%) are available and

are used to provide extra calories (1 g of glucose equals 4 kcal). Hyperglycemia is a

potential risk with these solutions, and careful monitoring is warranted.

Table 14-6 Composition of commonly used intravenous solutions[3]

Solution	Solute	Concentrations g/100 mL	Ionic concentration, meq/L					
			$[Na^+]$	$[K^+]$	$[Ca^{2+}]$	$[Cl^-]$	$[HCO_3]$	Total mosmol/L
Dextrose in water								
5.0%	Glucose	5.0	—	—	—	—	—	278
10%	Glucose	10.0	—	—	—	—	—	556
Saline								
Hypotonic (0.45%, half-normal)	NaCl	0.45	77	—	—	77	—	154
Isotonic (0.9%, normal)	NaCl	0.90	154	—	—	154	—	308
Hypertonic	NaCl	3.0	513	—	—	513	—	1026
		5.0	855	—	—	855	—	1710
Dextrose in saline								
5% in 0.225%	Glucose	5.0	—	—	—	—	—	—
	NaCl	0.225	38.5	—	—	38.5	—	355
5% in 0.45%	Glucose	5.0	—	—	—	—	—	—
	NaCl	0.45	77	—	—	77		432
5% in 0.9%	Glucose	5.0	—	—	—	—	—	—
	NaCl	0.90	154	—	—	154	—	586
Alkalinizing solutions								
Hypertonic sodium bicarbonate (0.6M)	$NaHCO_3$	5.0	595	—	—	—	595	1190

Hypertonic sodium bicarbonate (0.9*M*)[b]	$NaHCO_3$	7.5	893	—	—	—	893	1786
Polyionic solutions								
Ringer's	NaCl	0.86	—	—	—	—	—	—
	KCl	0.03	147	4	5	156	—	309
	$CaCl_2$	0.03	—	—	—	—	—	—
Lactated Ringer's	NaCl	0.60	—	—	—	—	—	—
	KCl	0.03	—	—	—	—	—	—
	$CaCl_2$	0.02	130	4	3	109	28[c]	274
	Na lactate	0.31	—	—	—	—	—	—
Potassium chloride[d]	KCl	14.85	—	2	—	2	—	—

[a] Adapted from A. Arieff, *Clinical Disorders of Fluid and Electrolyte Metabolism*, 2nd ed., Maxwell MH, Kleeman CR (eds). New York, McGraw-Hill, 1972.

[b] The 0.9M solution of $NaHCO_3$ usually is available in the clinical setting in 50-mL ampuls containing 44 meq of Na^+ and 44 meq of HCO_3^-. This solution can be infused intravenously o added to other solutions.

[c] Lactated Ringer's solution contains 28 meq/L of lactate, which is converted in the b HCO_3^-.

[d] The KCl solution is available in 20- to 50-mL ampuls, which can be added to other s provide K^+. The K^+ concentration in this solution is 2 meq/mL.

Saline solutions

Most hypovolemic patients are both Na^+- and water-depleted. In this situation, isotonic, hypotonic, or hypertonic saline solutions can be used to correct both deficits. Isotonic saline (0.9%) has a Na^+ concentration of 154 meq/L, similar to that in the plasma water (see page 000). Half-isotonic saline (0.45%, Na^+ concentration of 77 meq/L) is more dilute than the plasma, and each liter can be viewed as being composed of 550 mL of isotonic saline and 500 mL of free water. On the other hand, hypertonic saline (3%, Na^+ concentration of 513 meq/L) is more concentrated than the plasma, and each liter can be viewed as containing 1000 mL of isotonic saline plus 359 meq of extra Na^+.

The plasma Na^+ concentration can be used to help determine which solution should be given. For example, half-isotonic saline (or dextrose in quarter-isotonic saline)

contains free water and should be administered to patients with hypernatremia, who have a greater deficit of water than of solute. On the other hand, hypovolemic patients with hyponatremia have a greater deficit of solute than of water and should be treated with isotonic or hypertonic saline (see Chap. 28). If the plasma Na^+ concentration is normal, either half-isotonic or isotonic saline can be given. The former has the advantage of containing free water, which can replace continued insensible water losses.

Dextrose in saline solutions

The indications for the use of these solutions are the same as those for the saline solutions. The addition of glucose provides a small amount of calories (5% dextrose equals to 50 g/L of glucose or 200 kcal/L).

Alkalinizing solutions

The primary uses of $NaHCO_3$ are in the treatment of metabolic acidosis or severe hyperkalemia. $NaHCO_3$ is most commonly administered as a 7.5% solution in 50-mL ampules containing 44 meq of Na^+ and 44 meq of HCO_3^-. This can be given intravenously over 5 min or added to another intravenous solution. However, $NaHCO_3$ should not be added to solutions containing calcium, such as Ringer's lactate, since Ca^{2+} and HCO_3^- can combine to form the insoluble salt $CaCO_3$.

Polyionic solutions

Ringer's solution contains physiologic concentrations of Na^+, Ca^{2+}, and K^+ in addition to NaCl. Lactated Ringer's solution has a composition even closer to that of the extracellular fluid, containing 28 meq of lactate per liter, which is rapidly metabolized into HCO_3^- in the body. Although they may seem more physiologic, there is no evidence that these solutions offer any advantages when compared with isotonic saline. Furthermore, lactated Ringer's solution should not be used in lactic acidosis, since the ability to convert lactate into HCO_3^- is impaired in this disorder.

Potassium chloride

KCl is available in a highly concentrated solution containing 2 meq/mL of K^+. When used to repair a K^+ deficit, 10 to 60 meq of KCl (15 to

30 mL) can be added to 1 liter of any of the above solutions (see Chaps. 28 and 29). K^+ should never be given as an intravenous bolus, since it can produce a potentially fatal acute increase in the plasma K^+ concentration.

Plasma volume expanders

Since Na^+ salts freely cross the capillary wall, the administration of saline solutions expands both the intravascular and interstitial volumes. When free water is provided, as with dextrose or hypotonic saline solutions, there is also an increase in the intracellular volume, as two-thirds of the free water enters the cells. Thus, dextrose in water expands the extracellular volume only one-third as much as an equivalent volume of isotonic saline, which is limited to the extracellular fluid. In contrast, albumin, polygelatins, and hetastarch are primarily restricted to the vascular space and selectively expand the plasma volume.

Albumin, for example, is available as pooled human albumin that has been treated with heating and filtration to eliminate the risk of infection (such as hepatitis or HIV). When given as a 25% solution (25 g/dL), which is markedly hyperoncotic (normal

plasma albumin concentration is 4 to 5 g/dL), albumin increases the plasma oncotic pressure, thereby drawing several times its volume of fluid into the vascular space from the interstitium. Albumin also can be given as a 5% solution in isotonic saline, which is similar to administering plasma.

Blood

In patients with anemia, particularly those who are actively bleeding, the administration of blood may be necessary to maintain oxygen transport to the tissues. Blood is usually given as packed red cells, since saline or albumin can be administered in place of the plasma, the components of which (such as platelets and clotting factors) can be used for other purposes.

Which fluid should be used?

The composition of the appropriate replacement fluid varies from patient to patient. The type of fluid lost, the plasma $[K^+]$, the plasma $[Na^+]$ concentration, the plasma osmolality, and acid-base balance all must be taken into account. For example, relatively hypotonic solutions should be used in hyperosmolal patients with hypernatremia or hyperglycemia, and isotonic or hypertonic solutions should be used in hypoosmolal patients with hyponatremia. The one exception to these general rules is that isotonic saline should always be given initially to patients with hypovolemia and hemodynamic compromise (e.g., hypotension or shock).

All the solutes in an intravenous solution must be included when calculating its effective osmolality, since *potassium, the primary intracellular solute, is as osmotically active as sodium*. Thus, 1 liter of isotonic saline is osmotically equivalent to 1 liter of half-isotonic saline (a $[Na^+]$ concentration of 77 meq/L) to which 77 meq of K^+ has been added. The major exception is glucose, which is rapidly metabolized in the body to CO_2 and H_2O and therefore is only transiently osmotically active.

A patient with diabetes insipidus who develops hypernatremia due to water loss can be treated with dextrose solutions alone. In contrast, a patient who had

lost both solutes and water may require more complex replacement therapy. This can be illustrated by the following example.

Case History 14-3

A 37-year-old woman is seen after several days of severe diarrhea and poor oral intake. Findings on the physical examination are consistent with moderately severe volume depletion. The laboratory data include

Plasma $[Na^+]$	=	142 meq/L	Arterial pH	=	7.22
$[K^+]$	=	3.7 meq/L	P_{CO_2}	=	20 mmHg
$[Cl^-]$	=	114 meq/L	Urine $[Na^+]$	=	4 meq/L
$[HCO_3^-]$	=	8 meq/L			

Comment

In addition to volume depletion, this patient has metabolic acidosis and probably K^+ depletion, since the plasma $[K^+]$ concentration is low-normal in the presence of acidemia. In view of the normal plasma $[Na^+]$ concentration and osmolality, the replacement fluid should be mildly hypotonic to provide free water that will replace continuing insensible water losses. An appropriate intravenous solution for this patient would be 1 liter of dextrose in quarter-isotonic saline (a $[Na^+]$ concentration equal to 38.5 meq/L) to which 44 meq (as $NaHCO_3$) and 40 meq of K^+ (as

KCl) have been added. This solution contains Cl^- and K^+ to correct the acidemia and K^+ depletion and is slightly hypotonic to plasma, having a Na^+ concentration of 122 meq/L.

The primary indication for the use of albumin- or other colloid-containing solutions is in protein-losing states such as burns or occasionally the nephrotic syndrome.[39] Although these solutions have also been used in the treatment of shock or severe hypovolemia, they appear to offer little or no advantage over the pure electrolyte solutions (see below).

Blood may be required in addition to fluid and electrolytes if the patient is bleeding or has marked anemia. Volume repletion with solutions other than blood expands the plasma volume and lowers the hematocrit by dilution. Thus, the degree of anemia may be masked on admission and become apparent only with volume replacement.

A separate issue in patients with marked hypovolemia due to penetrating torso injuries is whether fluid resuscitation should be delayed until operative intervention to control the bleeding. Animal and some human studies suggest an improved outcome from delayed resuscitation.[40a,41,42] The presumed mechanism is that aggressive fluid administration might, via augmentation of blood pressure, dilution of clotting factors, and production of hypothermia, disrupt thrombus formation and enhance bleeding. This approach should be considered only if rapid surgical exploration can be performed.[41] In a controlled human trial showing benefit, the mean time from injury to operation was 2 h, results that are not attainable in most circumstances.[40]

Volume Deficit

It is usually difficult to estimate the volume deficit in a hypovolemic patient. Knowledge of the patient's normal weight is helpful, but this information is frequently not obtainable. If hyponatremia or hypernatremia is present, the respective Na^+ water deficits can be estimated from the following formulas:

$$Na^+ \text{ deficit (in meq)} = 0.6 \times \text{lean body weight (in kg)} \times (140 - \text{plasma } [Na^+])$$

$$\text{Water deficit (in liters)} = 0.5 \times \text{lean body weight (in kg)} \times \left(\frac{\text{plasma } [Na^+]}{140} - 1\right)$$

However, these formulas estimate only the amount of Na^+ in a hyponatremic patient and the volume of water in a hypernatremic patient that would have to be retained to return the plasma Na^+ concentration to the normal value of 140 meq/L. This ignores any isosmotic fluid deficit that may also be present. As an example, the formula for the water deficit is relatively accurate for a patient with diabetes insipidus who has lost only water, but it underestimates the deficit in a hypernatremic patient with diarrhea and increased insensible losses who has lost both water and Na^+.

The extracellular fluid normally comprises about 20 percent of the lean body weight. Loss of this fluid results in hemoconcentration and an increase in the hematocrit. As a result, the extracellular deficit can be estimated from the change in the hematocrit (Hct) according to a formula similar to that for the water deficit:

$$\text{Extracellular fluid deficit} = 0.2 \times \text{lean body weight} \times \left(\frac{\text{Hct}}{\text{normal Hct}} - 1\right)$$

This formula, however, is useful only if the patient's normal hematocrit is known and if bleeding has not occurred.

In summary, the fluid deficit in a hypovolemic patient usually cannot be calculated precisely. Thus, the adequacy of volume repletion must be evaluated from the findings on physical examination and laboratory data. As volume expansion occurs,

the skin turgor should improve and there should be increases in body weight, arterial pressure (if there has been a fall in blood pressure), venous pressure, urine output, and urine Na^+ concentration. For patients who start with a low urine Na^+ concentration, serial measurements of this parameter can be used as an index of the degree to which normovolemia has been restored. If the urine Na^+ concentration remains under 25 meq/L, the kidney is sensing persistent volume depletion, and more fluids should be given.

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Rate of Volume Replacement

As with other water and electrolyte disorders, the immediate aim of therapy in hypovolemia is to get the patient out of danger. With the exception of patients with hypotension, shock, or severe associated electrolyte disturbances, *standard* saline is preferable, since it will restore normovolemia while minimizing the risk of volume overload and pulmonary edema. The optimal rate of fluid replacement is somewhat arbitrary. A regimen that has been successful is the infusion of the appropriate replacement fluids at the rate of 50 to 100 mL/h *in excess of the sum* of the urine output, estimated insensible losses (approximately 30 to 50 mL/h), and any other losses that may be present (such as diarrhea or tube drainage).

The *aim of therapy is not to administer fluids but to induce positive fluid balance*. Suppose a patient with severe diarrhea has losses averaging 75 mL/h. If fluid is administered at the rate of 75 mL/h plus estimated insensible losses, there will be no positive fluid balance and no correction of the hypovolemic state. A similar problem with continuing losses can occur in central diabetes insipidus, where the urine volume can exceed 500 mL/h. In this setting, the administration of ADH will reduce the urine output and make volume repletion easier to achieve (see Chap. 24).

Hypovolemic Shock

Hypovolemic shock is most often due to bleeding or third-space sequestration, although a similar picture can be produced by any of the causes of true volume depletion. Before discussing the therapy of this disorder, it is important to first review its pathophysiology.[1743] As described above, progressive volume depletion is associated with increasing degrees of sympathetic and angiotensin II–mediated vasoconstriction. This response initially maintains the blood pressure and cerebral and coronary perfusion. However, the combination of a hypovolemia-induced decrease in cardiac output and intense vasoconstriction results in a marked reduction in splanchnic, renal, and musculocutaneous blood flow that can ultimately lead to ischemic tissue injury and lactic acidosis. The intense ischemia can also result in the release of intracellular contents (such as lysosomal enzymes) into the systemic circulation and to the absorption of endotoxin from the gut.

Early therapy is important to prevent hypovolemic shock from becoming *irreversible*. As depicted in Fig. 14-3, experimentally induced hemorrhagic shock in a dog can be successfully treated if the blood that has been removed is reinfused within 2 h. However, there is only a transient increase in blood pressure if the return of the shed blood is delayed for 4 h or longer (Fig. 14-3).[1744] A similar phenomenon appears to occur in humans, although substantially more than 4 h may be required before volume repletion becomes ineffective.[44]

Irreversible shock seems to be associated with *pooling of blood in the capillaries and tissues, leading to a further impairment in tissue perfusion*.[44,45] Several factors may contribute to this vasomotor paralysis, including the following:

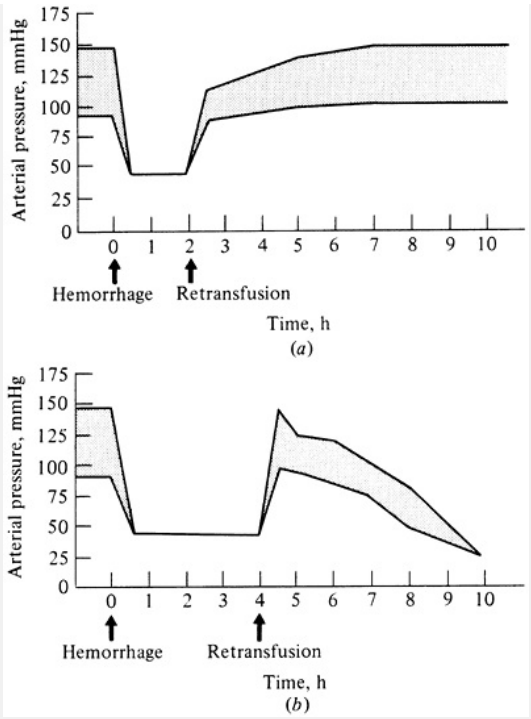

Figure 14-3 Reversibility of experi-mental hemorrhagic shock in the dog. (*a*) If the mean arterial pressure is reduced to 35 to 40 mmHg for less than 2 h, reinfusion of the shed blood will restore a normal blood pressure. (*b*) If the period of hypotension is extended to 4 h before the shed blood is returned, most of the dogs die within 24 h despite retransfusion. (*From Lillihei RC, Dietzman RH, in Schwartz SI, Lillihei RC, Shires GT, et al (eds): Principles of Surgery. New York, McGraw-Hill, 1974, with permission*)

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- Hyperpolarization of vascular smooth muscle cells as ATP depletion leads to opening of ATP-dependent K^+ channels, which are normally closed by ATP.[46] Hyperpolarization decreases Ca^{2+} entry through voltage-dependent Ca^{2+} channels, and the ensuing reduction in cellular Ca^{2+} concentration can lead to vasodilatation. In experimental models of shock, the administration of the sulfonylura glyburide, an inhibitor of the ATP-K^+ channel, led to both vasoconstriction and an elevation in systemic blood pressure.[46] The clinical applicability of this observation remains to be proven.
- Plugging of the capillaries by activated circulating neutrophils.[45]
- A cerebral ischemia–induced impairment in vasomotor regulation, resulting in reversal of the initial increase in peripheral sympathetic tone.[47]
- Increased generation of the vasodilator nitric oxide; in experimental animals, the vascular unresponsiveness in irreversible shock can be overcome by administration of an inhibitor of nitric oxide synthase.[48]
- Generation of iron-dependent, oxygen-derived free radicals.[49] Resuscitation with a free radical–scavenger conjugate of starch and deferoxamine may attenuate derangements in microvascular blood flow.

Regardless of the mechanism, the net effect is that administered fluid is sequestered

in the capillary circulation. The ensuing elevation in the capillary

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hydraulic pressure favors the movement of fluid out of the vascular space into the interstitium.[43,44] and[45,47] An increase in capillary permeability also may contribute to this process, as toxic products released from injured tissues or from the local accumulation of neutrophils can damage the capillary wall.[45]

In addition to sequestration in the capillaries, fluid may also be lost into the cells. Tissue ischemia diminishes cellular Na^+-K^+-ATPase activity, thereby reducing the active transport of Na^+ out of the cells. The ensuing rise in cellular Na^+ promotes osmotic water entry into the cells.[43] The net effect is more severe plasma volume depletion, hemoconcentration, increased viscosity, and red blood cell aggregation, all of which can further impair the capillary circulation.

With these potential hazards in mind, a rational therapeutic program can be begun. Patients with shock should have careful monitoring of their arterial pressure, central venous pressure (or, preferably, the pulmonary capillary wedge pressure), arterial pH, hematocrit, urine output, and mental status. In addition, therapy must be directed toward the underlying disease—for example, surgery in a patient with a ruptured abdominal aortic aneurysm.

The immediate aim of therapy in hypovolemic shock is to restore tissue perfusion by the administration of fluids. The use of vasopressors such as dopamine or norepinephrine will not correct the underlying volume deficit and may intensify the problem in the capillary circulation, further reducing tissue perfusion and predisposing toward ischemic damage.[50]

Which fluids should be given?

The choice of replacement fluid depends upon the type of fluid lost. Patients who are bleeding may require the administration of large amounts of blood. This can be given most rapidly under pressure through several intravenous catheters. In general, the hematocrit should not be raised over 35 percent. A higher level is not necessary for oxygen transport and may produce an increase in blood viscosity that can lead to stasis in the already impaired capillary circulation. The role of acellular, oxygen-carrying resuscitation fluids when blood is not available is uncertain. In one trial in which patients with traumatic hemorrhagic shock were randomized to receive either a diaspirin cross-linked hemoglobin solution or saline, the patients who received the oxygen-carrying blood substitute had a significantly *higher* mortality at 2 and 28 days (46 versus 17 percent at 28 days).[51]

The optimal form of fluid replacement other than blood is, in most cases, an electrolyte solution, such as isotonic saline or Ringer's lactate.[43] Some physicians have favored the use of a colloid-containing solution (such as albumin, polygelatins, or hetastarch), claiming that it has two advantages:[1] more effective plasma volume expansion, since it remains in the vascular space (in contrast to saline, two-thirds of which enters the interstitium),[2] and lesser risk of pulmonary edema, since the increase in plasma oncotic pressure favors fluid movement out of the interstitium into the vascular space.[14,52]

However, several controlled studies have *failed to confirm* either of these potential advantages,[53,54,55] and[56] and a review of randomized trails found that resuscitation

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with colloid solutions was associated with an increased absolute risk of mortality of 4 percent.[57] Albumin and electrolyte solutions are equally effective in producing

volume repletion, although 2.5 to 3 times as much saline must be given because of its extravascular distribution.[53] This is not a deleterious effect, however, since saline replaces the interstitial fluid deficit that is induced both by fluid loss and by fluid movement into the cells.

Colloid-containing solutions are also not more effective in preserving pulmonary function.[53,54,58] In general, the *pulmonary circulation is less sensitive than that in the periphery to changes in the plasma albumin concentration*. This difference reflects the normally higher permeability to proteins in the alveolar capillaries, which results in a higher baseline protein concentration and therefore oncotic pressure in the interstitium.[59,60] When the plasma albumin concentration is lowered due, for example, to saline-induced hemodilution, there will initially be a parallel reduction in the interstitial oncotic pressure, since less protein will now cross the capillary wall. The net effect is *maintenance of the balance between Starling's forces and relative resistance to interstitial fluid accumulation* in the absence of severe hypoalbuminemia (see page 485).[58,61]

Thus, the administration of saline to the patient with shock is unlikely to produce pulmonary edema unless there is an excessive elevation in the capillary hydraulic pressure.[61,62] Saline infusion can, however, induce peripheral edema, since the skeletal muscle and subcutaneous capillaries are less permeable to protein. They therefore have a lower baseline interstitial oncotic pressure and a lesser ability to protect against edema by diminishing the accumulation of interstitial proteins.[62] It is important to appreciate that *the development of peripheral edema does not necessarily indicate that fluid repletion should be discontinued* since it may result from dilutional hypoalbuminemia even though plasma volume depletion persists.[63]

In summary, electrolyte solutions seem to be preferable to colloid in the treatment of severe hypovolemia,[53,55,56] and[57] with the possible exception of patients with underlying hypoalbuminemia.[52]

In addition to fluid repletion, military antishock trousers have been used in the treatment of hypovolemic shock. They can rapidly raise the systemic blood pressure both by increasing vascular resistance (by mechanical compression of the legs) and by translocation of fluid from the lower extremities into the cardiopulmonary circulation.[63,64] Prolonged usage should be avoided, since it can lead to an ischemic compartment syndrome or impairment of venous return.[17,64]

Rate of fluid replacement

Approximately 1 to 2 liters of fluid should be given in the first hour in an attempt to restore adequate tissue perfusion as quickly as possible. It is impossible to predict what the total fluid deficit in a given patient will be, particularly if bleeding or third-space sequestration continues. Consequently, further fluids should be administered while monitoring the central venous or preferably the pulmonary capillary wedge pressure. Fluids should be given at the initial rapid rate as long as the cardiac filling pressures and the systemic blood pressure remain low.

Lactic acidosis

Marked tissue hypoperfusion in hypovolemic shock is often associated with lactic acidosis. The role of HCO_3^- therapy to raise the extracellular pH in this setting remains controversial. There is evidence that exogenous HCO_3^- can impair net lactate utilization, thereby preventing or minimizing correction of the acidemia.[65] Another potential problem is that measurement of the arterial pH may not give an

accurate assessment of the pH at the tissue level in this setting, necessitating evaluation of a mixed-venous blood sample ($P_{\bar{v}O_2}$).

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PROBLEMS

14-1A 75-year-old woman is admitted to the hospital with the acute onset of severe abdominal pain. When examined, the patient is agitated, her extremities are cold and clammy, and her blood pressure is 60/30. Her abdomen is distended, with diffuse tenderness. The results of the laboratory evaluation include a hematocrit of 53 percent. An arteriogram shows complete occlusion of one of the branches of the superior mesenteric artery.

a. **What is the etiology of the shock state in this patient?**

b. **What fluids would you administer?**

   Prior to surgery, a total of 7 liters of fluid is administered to maintain the blood pressure. Through this period, she is virtually anuric. At surgery, 40 cm of infarcted ileum is removed. Six hours after surgery, the patient is doing well when a marked increased in the urine output to nearly 1000 mL/h is noted. Her urine osmolality is 250 mosmol/kg; her urine Na^+ concentration is 95 meq/L.

c. **What might be responsible for this increase in output?**

d. **How would you treat the patient at this time?**

14-2Compare the effects of the loss of water (due to increased insensible losses or diabetes insipidus) and the loss of an equal volume of an isotonic Na^+ solution (due to diuretics or diarrhea) on the extracellular volume and the arterial blood pressure.

14-3What is the role of pure dextrose solutions in the treatment of hypovolemic shock?

14-4A 75-year-old woman develops volume depletion as a result of the excessive administration of diuretics. Prior to the administration of diuretics, the patient had a normal BUN and plasma creatinine concentration. After a 6-kg weight loss over 10 days, poor skin turgor is present, and the central venous pressure is 1 cm H_2O. The following laboratory data are obtained:

BUN	=	208 mg/dL
Plasma [creatinine]	=	5.7 mg/dL
Urine [Na^+]	=	5 meq/L
Urine output	=	25 mL/h
Urinalysis	=	normal

After the administration of 5 liters of half-isotonic saline over 18 h, the central venous pressure is 3 cm H_2O, the skin turgor has improved, and the results of repeat laboratory studies are

BUN	=	160 mg/dL
Urine [Na^+]	=	45 meq/L
Urine output	=	80 mL/h

a. **Why have the urine Na^+ concentration and urine output increased?**

b. **Does the repeat central venous pressure indicate persistent volume depletion?**

c. **Why is the repeat BUN still elevated despite volume repletion?**

14-5A 74-year-old man is admitted from a nursing home with a 3-day history

of recurrent vomiting and diarrhea. The results of the physical examination are consistent with volume depletion. The laboratory data reveal

Plasma $[Na^+]$	=	155 meq/L
$[K^+]$	=	3 meq/L
$[Cl^-]$	=	117 meq/L
$[HCO_3^-]$	=	25 meq/L

a. **What intravenous solution would you use for replacement therapy?**

b. **How rapidly should it be administered?**

14-6A 72-year-old woman is found confused on the floor of her apartment. No history is obtainable except that she has a history of hypertension. The physical examination reveals a blood pressure of 110/70, reduced skin turgor, and an estimated jugular venous pressure of less than 5 cm H_2O. The following laboratory data are obtained:

BUN	=	62 mg/dL
Plasma [creatinine]	=	1.8 mg/dL
$[Na^+]$	=	138 meq/L
$[K^+]$	=	3.1 meq/L
$[Cl^-]$	=	100 meq/L
$[HCO_3^-]$	=	29 meq/L

a. **Is the blood pressure normal?**

b. **Could this patient's volume depletion be due to the lack of replacement of insensible losses?**

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Footnotes

* These fluid losses represent only a small part of the hemodynamic stress induced by exercise in this setting. The required increases in muscle blood flow (to provide nutrients and remove waste products) and in cutaneous blood flow (to allow heat loss) can exceed 10 L/min in some cases.[12]

† The product of the cardiac output and systemic vascular resistance actually equals the *change in pressure* across the circulation—mean arterial pressure minus mean venous pressure. However, the venous pressure (normal equals 1 to 7 mmHg) is normally much lower than the arterial pressure. As a result, only a slight error results from ignoring the venous pressure.

‡ Distilled water cannot be given intravenously, because it will produce potentially fatal hemolysis due to water movement into red cells. This problem is prevented by the addition of an osmotically active solute such as dextrose.

¶ These formulas are derived in Chaps. 23 and 24. The formula for the Na^+ deficit assumes that the patient has true hyponatremia, not pseudohyponatremia due to hyperglycemia or hyperlipidemia (see page 712).

** This excludes edematous patients with heart failure or cirrhosis, in whom the low urine Na^+ concentration is an indication of effective circulating volume depletion but not of the need for more fluid.

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Chapter Fifteen
clinical use of diuretics

Diuretics are among the most commonly used drugs. They primarily act by diminishing NaCl reabsorption at different sites in the nephron, thereby inc urinary sodium and H_2O losses. This ability to induce negative fluid balance ha made diuretics useful in the treatment of a variety of conditions, particularl edematous states and hypertension. This chapter will review the mechanism action of diuretics, the time course of their action, the fluid and electrolyte complications that can occur, and an approach to the patient with refractory with particular emphasis on the problems that can occur in the patient with A more complete discussion of the different edematous states will then be p in the following chapter.

MECHANISM OF ACTION

The diuretics are generally divided into three major classes, which are dist by the site at which they impair renal Na^+ reabsorption: loop diuretics in the thick ascending limb of the loop of Henle; thiazide-type diuretics in the distal tub connecting segment (and perhaps the early cortical collecting tubule); and potassium-sparing diuretics in the aldosterone-sensitive principal cells in t collecting tubule (Table 15-1).[1,2,3]

To appreciate how this occurs, it is first necessary to review the general m by which Na^+ is reabsorbed. As was described in Chapters 3, 4, and 5, each of the Na^+-transporting cells contains Na^+-K^+-ATPase pumps in the basolateral membrane.[4] These pumps perform two major functions: They return reabsorbed Na^+ to the systemic circulation, and they maintain the cell Na^+ concentration at relatively low levels. The latter effect is particularly important, since it allows filtered Na^+ passively enter the cells down a favorable concentration gradient. This pro be mediated by a transmembrane carrier or channel, since charged particles cannot freely cross the lipid bilayer of the cell membrane. Each of the majo segments has a *unique Na^+ entry mechanism*, and the ability to specifically inhibit this step explains the nephron segment at which each of the different class diuretics acts.[3]

- The thick ascending limb of the loop of Henle has a Na^+-K^+-$2Cl^-$ cotransporter in the luminal membrane that is inhibited by loop diuretics.
- The distal tubule has a Na^+-Cl^- cotransporter in the luminal membrane that is inhibited by thiazide-type diuretics.
- The principal cells in the collecting tubules have Na^+ channels in the luminal membrane that are directly inhibited by amiloride or triamterene and indirectly inhibited by the aldosterone antagonist spironolactone.

Table 15-1 Physiologic characteristics of commonly used diuretics

Site of action	Carrier or channel inhibited	Percent filtered Na^+ excreted
Loop of Henle Furosemide Bumetanide Ethacrynic acid	Na^+-K^+-$2Cl^-$ carrier	Up to 25
Distal tubule and connecting segment Thiazides Chlorthalidone Metolazone	Na^+-Cl^- carrier	Up to 3 to 5
Cortical collecting tubule Spironolactone Amiloride Triamterene	Na^+ channel	Up to 1 to 2

The site of action within the nephron is a major determinant of diuretic potency. Of the filtered Na^+ load, 60 to 70 percent is reabsorbed in the proximal tubule (about 55 to 60 percent), the loop of Henle (25 to 35 percent), and the distal tubule (5 to 10 percent) (see Table 8-3). It might be expected, therefore, that a proximally acting diuretic, such as the carbonic anhydrase inhibitor acetazolamide, could induce relatively large losses of Na^+ and HCO_3^-. This does not occur, however, because most of the excess fluid delivered out of the proximal tubule can be reabsorbed more distally, particularly in the loop of Henle. Transport in the latter segment is primarily flow-dependent, varying directly with the delivered load (see Fig. 4-3).[5,6]

A similar process of distal compensation occurs with the loop diuretics. The

tubule is able to increase its rate of reabsorption, as evidenced by tubular hypertrophy and a rise in Na^+-K^+ ATPase activity with chronic loop diuretic administration.[7,8,9] and[10] However, the reabsorptive capacity of the distal and collecting tubules is relatively limited, and in most circumstances the natriu response to a loop diuretic is not seriously impaired.[2]

Loop Diuretics

The loop diuretics—furosemide, bumetanide, torsemide, and ethacrynic acic lead to the excretion of up to 20 to 25 percent of the filtered Na^+ load in maximum dosage.[1,11] They act in the medullary and cortical aspects of the thi ascending limb, including the macula densa cells in the early distal tubule. these sites, Na^+ entry is primarily mediated by a Na^+-K^+-$2Cl^-$ carrier in the luminal membrane that is activated when all four sites are occupied (see Chapter 4).[1,3,6,12,13] The loop diuretics appear to compete for the Cl^- site on this carrier, thereby diminishing net reabsorption.[13,14]

The loop diuretics also have important effects on renal Ca^{2+} handling. The reabsorption of Ca^{2+} in the loop of Henle is primarily passive, being driven by a gradient created by NaCl transport (see page 92).[15,16] As a result, inhibiting the reabsorption of NaCl leads to a parallel reduction in the reabsorption of Ca^{2+}, thereby increasing Ca^{2+} excretion. This effect is clinically important, because enhancing urinary Ca^{2+} losses with saline and a loop diuretic is a mainstay of therapy in patients with hypercalcemia.[17]

One potential concern is that the calciuric response can lead to kidney ston nephrocalcinosis. These complications have been primarily reported in prem infants, in whom a loop diuretic can induce more than a 10-fold rise in Ca^{2+} excretion.[18,19]

Thiazide-Type Diuretics

The thiazide-type diuretics primarily inhibit NaCl transport in the distal tubule,[1,2,3,20,21] the connecting segment at the end of the distal tubule,[22] and possibly the early cortical collecting tubule (although this finding is controversial).[23,24]

These segments normally reabsorb less of the filtered load than does the lo Henle; as a result, the thiazide-type diuretics are less potent and, when giv maximum dosage, inhibit the reabsorption of at most 3 to 5 percent of the fi Na^+.[1,2] Furthermore, the net diuresis may be partially limited by increased reabsorption in the cortical collecting tubules.[8,25] These responses make the thiazides less useful in the treatment of edematous states but are not a pro uncomplicated hypertension, where marked fluid loss is neither necessary r desirable.

Thiazide-sensitive Na^+ entry in the distal nephron is mediated by neutral Na^+–Cl^- *cotransport*.[3,26] Both a Na^+–Cl^- cotransporter[27,28] and[29] and, to a lesser degree, parallel Na^+–H^+ and Cl^-–HCO_3^- exchangers are responsible for NaCl reabsorptio these sites (see page 145).[22,26]

The thiazides inhibit NaCl reabsorption in these segments by competing for site on the Na^+–Cl^- cotransporter.[30] Some of these drugs (chlorothiazide but not bendroflumethazide, for example) also modestly impair HCO_3^- transport in the proximal tubule, due in part to partial inhibition of carbonic anhydrase.[21,31] This does not normally contribute to the net diuresis, however, since the excess fluid deli of the proximal tubule is reclaimed in the loop of Henle.[21]

Like the loop diuretics, the thiazides also can importantly affect Ca^{2+} handling.[32] The distal tubule is the major site of active Ca^{2+} reabsorption in the nephron, an effect that is independent of Na^+ transport.[15] Although the thiazides inhibit the reabsorption of Na^+ in this segment, they are able at the same time to *increase the reabsorption of* Ca^{2+}.[33] A similar response appears to occur in the cortical collecting tubule, as the K^+-sparing diuretic amiloride also can promote Ca^{2+} reabsorption.[33] The fall in Ca^{2+} excretion can be useful in the treatment of recu kidney stones due to hypercalciuria; this response is mediated by diuretic-induc alterations in intracellular composition and electrical potential[34,35] (see page 92).

Potassium-Sparing Diuretics

The three major K^+-sparing diuretics—amiloride, spironolactone, and triamtere —act in the principal cells in the cortical collecting tubule (and possibly in papillary or inner medullary collecting duct).[1,3,36,37] Na^+ entry in these segments occurs through aldosterone-sensitive Na^+ *channels*, rather than being carrier-mediated.[38,39] The reabsorption of cations with Na^+ without an anion creates a lumen-negative electrical gradient that then favors the secretion of K^+ (through K^+ channels) and H^+. Thus, inhibition of Na^+ reabsorption at this site can lead to hyperkalemia and metabolic acidosis as a result of the concurrent reduction and H^+ excretion.[1,2]

These drugs act by decreasing the number of open Na^+ channels, amiloride and triamterene directly and spironolactone by competitively inhibiting the effec aldosterone.[36,37] Another cation, the antibiotic trimethoprim, also can act as K^+-sparing diuretic when given in very high doses in patients with AIDS[40] and occasionally when given in conventional doses.[41]

The K^+-sparing diuretics have relatively weak natriuretic activity, leading to

maximum excretion of only 1 to 2 percent of the filtered Na^+ load.[1] Thus, they are primarily used in combination with a loop or thiazide diuretic, either to dimi degree of K^+ loss or to increase the net diuresis in patients with refractory edema.[1,2] In addition, spironolactone may have the surprising effect of being particularly potent in patients with cirrhosis and ascites (see Refractory Edema, below).

An additional use of amiloride has been demonstrated in patients with polyu polydipsia due to lithium-induced nephrogenic diabetes insipidus (see Chapter 24). The resistance to antidiuretic hormone (ADH) in this disorder appears to re lithium accumulation in the collecting tubule cells by movement through the Na^+ channels in the luminal membrane. Blocking these channels with amiloride h shown to partially reverse and may even prevent the concentrating defect, presumably by diminishing lithium entry into the tubular cells.[42]

Amiloride is generally the best tolerated of this diuretic class. It can be giv day and is associated with few side effects other than hyperkalemia. Triamt comparison, is a potential nephrotoxin,[43] possibly leading to crystalluria and cast formation (in up to one-half of patients)[44] and rarely to triamterene stones[45] or to acute renal failure due to either intratubular crystal deposition or the concu of a nonsteroidal anti-inflammatory drug.[46,47]

It is estimated, for example, that triamterene accounts for 1 in every 200 to stones.[45] These stones, which are more likely to occur in patients with a pri history of stone disease, are faintly radiopaque; their formation is pH-indep and they usually contain some calcium oxalate (although pure triamterene s occur).[45,48]

Acetazolamide

Acetazolamide inhibits the activity of carbonic anhydrase, which plays an ir role in proximal HCO_3^-, Na^+, and Cl^- reabsorption (see page 335). As a result, this agent produces both NaCl and $NaHCO_3$ loss.[49,50] The net diuresis, however, is relatively modest for two reasons.[1] Most of the excess fluid delivered out of the proximal tubule is reclaimed in the more distal segments, particularly the lo Henle; and[2] the diuretic action is progressively attenuated by the metabolic that results from the loss of HCO_3^- in the urine. The major indication for the use acetazolamide as a diuretic is in edematous patients with metabolic alkalos whom loss of the excess HCO_3^- in the urine will tend to restore acid-base balance.[50]

Mannitol

Mannitol is a nonreabsorbable polysaccharide that acts as an osmotic diure inhibiting Na^+ and water reabsorption in the proximal tubule and more importa

loop of Henle.[51,52] In contrast to other diuretics, mannitol produces a relative diuresis in which water is lost in excess and Na^+ and K^+.[57]

The major clinical use of mannitol as a diuretic has been in the early stage oliguric, postischemic acute renal failure in an attempt to prevent progress acute tubular necrosis.[53,54] The benefit of this approach is uncertain. Mannitol not generally used in edematous states, since initial retention of the hyper mannitol can induce further volume expansion, which, in heart failure, can pulmonary edema.

Mannitol can also produce a clinically important increase in the plasma osm two different mechanisms. First, the preferential water diuresis induced by repeated administration of mannitol can, if the losses are not replaced, lea water deficit and hypernatremia.[55] Second, hypertonic mannitol may be retained i patients with renal failure, directly increasing the plasma osmolality. In this water movement out of the cells down an osmotic gradient will lower the pla Na^+ concentration by dilution.[56,57] This is an important condition to recognize, since treatment must be aimed at the hyperosmolality, not the hyponatremia (see page 668).

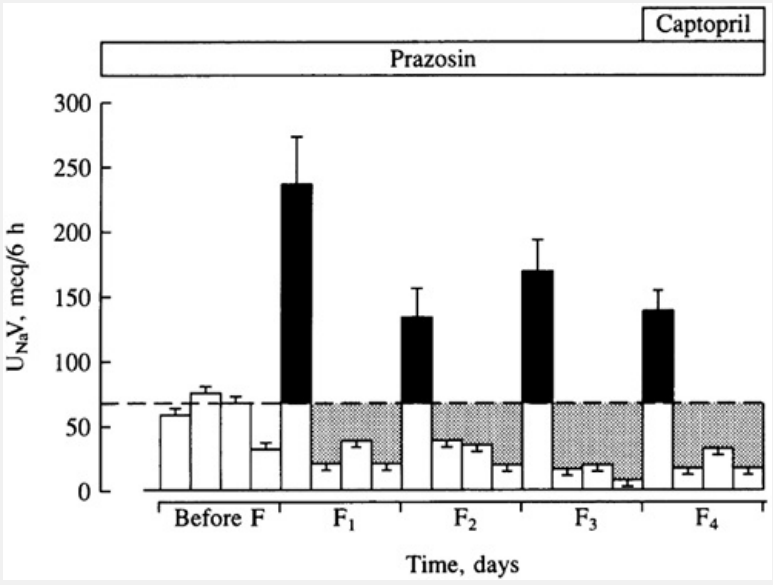

Figure 15-1 Values for 6-hourly rates of Na^+ excretion in normal subjects ingesting 270 meq of Na^+ per day after being given 40 mg of furosemide. The dashed horizontal line represents the level of Na^+ intake, which in the control period is roughly equal to the rate of Na^+ excretion. The latter rose markedly after the diuretic but fell below control levels (shaded areas) once the diu effect dissipated. The end result is no net diuresis at the end of the day. Blocking the renin-angiotensin-aldosterone system with captopril and the of norepinephrine with the alpha-adrenergic blocker prazosin did not alter this response. (*From Wilcox CS, Guzman NJ, Mitch WE, Kidney Int 31:135, 1987. Reprinted by permission from* Kidney International.)

TIME COURSE OF DIURESIS

The efficacy of a diuretic is related to a number of factors, including its site of action, its duration of action, and dietary Na^+ intake. The importance of the last two factors is illustrated in Fig. 15-1, which depicts the effect of a short-acting loop diuretic (furosemide) on the pattern of daily Na^+ excretion.[58,59] As expected, a significant natriuresis is noted during the 6-h period that the diuretic is active. However, Na^+ excretion falls to very low levels during the remaining 18 h of the day because the associated volume depletion leads to the activation of mechanisms for Na^+ retention.

The net result in these patients on a high Na^+ intake (270 meq/day) is that there is *no net Na^+ loss*. In this setting, one or more of the following changes must be present to induce negative Na^+ balance.

1. The patient can be placed on a low-Na^+ diet, thereby minimizing the degree of Na^+ retention once the diuretic has worn off.[59] This is the preferred method, since it can also limit concurrent losses of K^+ (see below).[60]
2. The diuretic can be given twice a day.
3. The dose of the diuretic can be increased, although the larger initial dose may induce symptomatic hypovolemia.

Several factors contribute to the compensatory antinatriuresis following the institution of diuretic therapy.[61] The initial fluid loss leads to activation of the renin-angiotensin-aldosterone and sympathetic nervous systems; angiotensin II, aldosterone, and norepinephrine can all promote tubular Na^+ reabsorption (see Chaps. 2 and 6).[62,63] and[64] However, blocking both of these pathways with prazosin (an α_1-adrenergic blocker) and captopril (an angiotensin converting enzyme inhibitor) does not prevent the secondary retention of Na^+ (Fig. 15-1).[13] In this setting, in which both vasoconstrictor hormones are inhibited, there is a mean *mmHg fall in the systemic blood pressure*.[58] Hypotension, in the absence of neurohumoral activation, directly promotes Na^+ retention via the pressure natriuresis phenomenon (see page 272).[64]

These observations permit a more complete understanding of the volume regulatory actions of angiotensin II and norepinephrine. In the presence of volume depletion, the combined vasoconstrictor and Na^+-retaining effects of these hormones result in both maintenance of the systemic blood pressure and an appropriate fall in Na^+ excretion. If, on the other hand, there were no stimulation of these hormones, then the persistent normotensin would, by pressure natriuresis, promote further Na^+ loss

and exacerbation of the hypovolemic state.

Reestablishment of the Steady State

Even if a net diuresis is induced, the response is short-lived, and a *new steady state is rapidly established, in which intake and output are again equal*, but the extracellular volume has fallen due to the initial period of negative Na^+ balance. In this

setting, the diuretic-induced losses are counterbalanced, as in Fig. 15-1, by several factors:[65]

1. Neurohumorally mediated increases in tubular reabsorption at non- diuretic-sensitive sites, such as the proximal tubule (angiotensin II and to a lesser degree norepinephrine) and the collecting tubules (aldosterone).[61,62]
2. Flow-mediated increases in tubular reabsorption distal to the site of action of the diuretic as distal Na^+ delivery is enhanced.[2,10] As mentioned above, administration of a loop diuretic leads to hypertrophy and increased Na^+-K^+-ATPase activity in both the distal and collecting tubules.[7,8,9] A thiazide diuretic, on the other hand, acts in the distal tubule and the more distal adaptations are limited to the Na^+-reabsorbing cells in the collecting tubules.[8,25]
3. Diminished diuretic entry into the urine also may contribute at a later stage if renal perfusion becomes impaired.[67]

The attainment and maintenance of the new steady state requires that both *diuretic dose and Na^+ intake be relatively constant*. This limitation on the net diuresis is physiologically appropriate, since progressive volume depletion and shock would eventually ensue if urinary Na^+ excretion were persistently greater than intake. What is generally underappreciated, however, is how rapidly the steady state is reestablished. Figure 15-2 illustrates the response of three normal subjects on a constant Na^+ and K^+ intake to the administration of 100 mg of hydrochlorothiazide per day, a relatively high initial dose.[68] As can be seen, *Na^+ is lost for only 3 days and K^+ for 6 to 9 days*; after this period, intake and output of these ions are again equal. A similar course in which there is a limited net diuresis also occurs in edematous states such as heart failure and cirrhosis. In heart failure, for example, the diuretic-induced reduction in cardiac filling pressures leads to a decline in cardiac output and activation of the renin-angiotensin system.[69]

These findings are very important clinically. As long as dose and dietary intake are stable, *all of the fluid and electrolyte complications associated with diuretic therapy occur within the first 2 to 3 weeks of drug administration*. Suppose, for example, that 25 mg of hydrochlorothiazide is given each day to a patient with essential hypertension. At 3 weeks, the blood pressure has fallen to the goal

and the blood urea nitrogen (BUN) and plasma creatinine, and K^+ and Na^+ concentrations remain within the normal range. In this setting, late hypokal hyponatremia is not likely to occur, and *repeated blood tests at every visit are not necessary* unless some new problem, such as vomiting or diarrhea, is superir

As an example, sequential evaluation of patients with hypertension has rev all of the fall in the plasma K^+ concentration following therapy with a thiazide diu occurs within the first 2 to 4 weeks, with subsequent stabilization at the ne[70] Similar considerations apply to the use of a K^+-sparing

diuretic to correct thiazide-induced hypokalemia; the plasma K^+ concentration rises during the first 2 to 3 weeks and then remains relatively constant.[71]

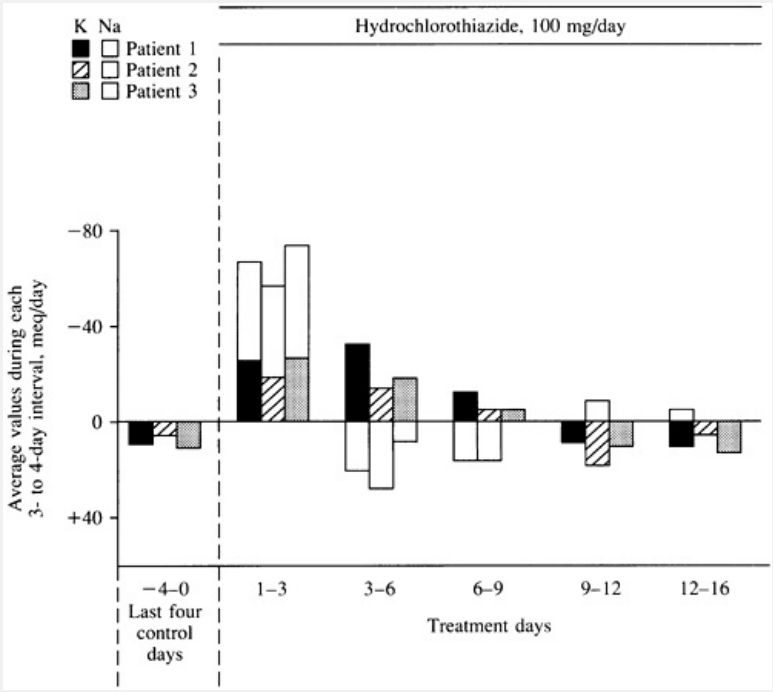

Figure 15-2 Sodium and potassium balance in three nonedematous patients treated with 100 mg of hydrochlorothiazide per day. Data for each patient the average balance for each 3- or 4-day period. Net loss of Na^+ occurs for only 3 days and of K^+ for 6 to 9 days before a new steady state is reestablished. (*Adapted from Maronde RF, Milgrom M, Vlachakis ND, JAMA 249:237, 1983. Copyright 1983, American Medical Association.*)

There is one other clinical correlate of these counterregulatory responses. no limitation in drug absorption and constant drug dosage, the *maximum diuresis will occur with the first dose of the diuretic.* As soon as fluid loss occurs, activatio of Na^+-retaining mechanisms limit the response to the second dose. This co illustrated by the findings in patients with stable chronic renal failure w treated with either intravenous boluses or a constant infusion of bumetanid[72] Figure 15-3

response to the second bolus was approximately one-third less than that to dose, whereas there is a gradually falling natriuresis with a constant infusi

The sequence is somewhat different in patients who are markedly volume-e as a result of renal sodium retention. In this setting, the renin-angiotensin suppressed and will not be activated by initial Na^+ loss, since hypervolemia persists Thus, the second and subsequent doses may produce as large a natriuresis original dose until most of the excess fluid has been removed. Even in this however, the first dose still represents the maximum response that will be s

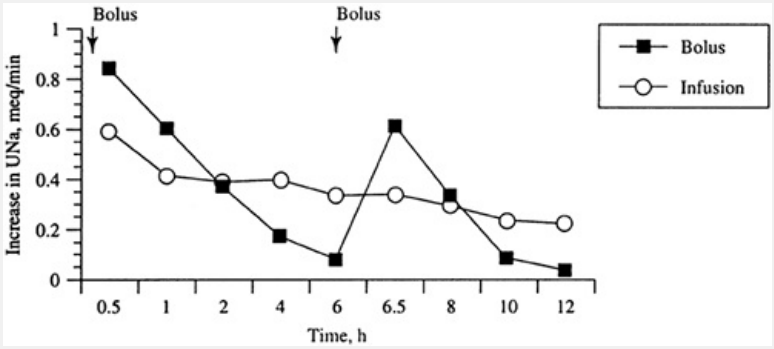

Figure 15-3 Maximum first-dose increase in urinary sodium excretion (UNa) intravenous bolus or infusion of bumetanide in patients with stable chroni failure. With an intravenous bolus (dark squares), the peak natriuretic res to the second dose is 25 percent less than that to the first. With a contin intravenous infusion (open circles), the natriuresis gradually declines ove 12-h period. The infusion produced a greater overall natriuresis, since an rate of diuretic excretion was maintained. *Adapted from Rudy DW, Voelker JR, Greene PK, et al: Ann Intern Med 115:360, 1991, with permission.*

FLUID AND ELECTROLYTE COMPLICATIONS

A review of the toxic and idiosyncratic side effects that can be induced by t different diuretics is beyond the scope of this discussion. It is important, h understand the pathogenesis and frequency of the major fluid and electroly disturbances that can occur (Table 15-2).

Volume Depletion

Although the duration of Na^+ loss is limited, some patients have a relatively larg initial diuretic response and develop true volume depletion. This problem c seen in patients with hypertension and also in those with mild edema who a

started on daily diuretic therapy, which is then continued even after the ed disappeared. Symptoms that can develop in this setting include weakness, muscle cramps, and postural dizziness.

Table 15-2 Fluid and electrolyte complications of diuretic therapy

Volume depletion
Azotemia
Hypokalemia
Metabolic alkalosis
Hyperkalemia and metabolic acidosis with K^+-sparing diuretics
Hyponatremia, especially with the thiazides
Hyperuricemia
Hypomagnesemia

Effective circulating volume depletion also can develop in patients who rem edematous. Although fluid overload persists, there may be a sufficient redu intracardiac filling pressures and cardiac output to produce a clinically imp reduction in tissue perfusion (see the sections on treatment of heart failure cirrhosis in the following chapter).

Azotemia

A reduction in the effective circulating volume with diuretic therapy also ca renal perfusion and secondarily the glomerular filtration rate. This problem manifested by elevations in the BUN and plasma creatinine concentration, i *prerenal azotemia*, since the defect is in renal perfusion, not in renal function there is a greater rise in the BUN than in the plasma creatinine concentrati page 92[73]

Increased passive reabsorption of urea, which follows the hypovolemia-indu increments in Na^+ and water reabsorption, plays a major role in the more pronounced elevation in BUN. In addition, as much as one-third of the rise BUN may reflect increased urea production; it is possible, for example, that perfusion to skeletal muscle leads to enhanced local proteolysis.[74] The amino acids that are released are then converted into urea in the liver.

Hypokalemia and Use of Diuretics in Hypertension

The loop and thiazide diuretics tend to increase urinary K^+ losses,[1,2,75] and often lead to the development of hypokalemia. For example, the administration of hydrochlorothiazide per day to treat hypertension is associated with a mean reduction in the plasma K^+ concentration of about 0.4 to 0.6 meq/L, with roughly percent of patients falling to or below 3.5 meq/L.[70,76] The degree of potassium wasting is even greater with 50 mg of the longer-acting chlorthalidone; in t setting, the mean fall in the plasma K^+ concentration is 0.8 to 0.9 meq/L.[76]

Two factors appear to be responsible for the kaliuresis in this setting: incre delivery of Na^+ and H_2O to the distal secretory site, as a result of inhibition of

reabsorption in the more proximal segments, and enhanced secretion of ald as a result of both the underlying disease (heart failure or cirrhosis) and th induction of volume depletion.[2,75]

The clinical significance of mild hypokalemia (K^+ concentration between 3.0 and 3.5 meq/L) remains controversial, particularly in the treatment of patie essential hypertension.[77] Some physicians have argued that mild K^+ depletion is usually a benign condition and that corrective therapy is not required in the of symptoms. Although this may be generally true, some patients appear to As an example, results from the Multiple Risk Factor Intervention Trial (MR other studies suggest that antihypertensive

therapy in selected patients might be associated with an *increase in the incidence of sudden death* (Fig. 15-4).[78,79] and[80]

The mechanism by which diuretics might increase coronary risk is uncertain agents produce a variety of metabolic abnormalities that could contribute to problem, including hypokalemia, hypomagnesemia (see below), hyperlipiden hyperglycemia.[81,82] and[83] The possible role of any of these factors is, of cour difficult to prove. Hypokalemia has been shown in some studies to be assoc with an increased incidence of ventricular arrhythmias.[84] In a report from the Framingham Heart Study, an association was noted between complex or frec 30/h) ventricular premature beats and hypokalemia.[85] It was estimated that the risk of these arrhythmias increased by 27 percent with each 0.5 meq/L reduction plasma potassium concentration.

In the basal state, the development of ventricular arrhythmias may not be s the plasma K^+ concentration falls to or below 3.0 meq/L.[76] However, mild hypokalemia can become severe hypokalemia during a stress response, with plasma K^+ concentration falling, for example, from 3.3 meq/L to below 2.8 me some patients (see Fig. 12-3). This response appears to be mediated by epinephrine, which drives K^+ into the cells via activation of β_2-adrenergic receptors.[86]

These observations suggest the following scenario: Coronary ischemia leac release of epinephrine, which exacerbates preexistent diuretic-induced hyp The combination of coronary ischemia and a marked reduction in the plasma K^+ concentration then facilitates the development of potentially fatal ventricula arrhythmias, particularly in patients with underlying left ventricular

hypertrophy. There is some evidence in support of this hypothesis, as the i of ventricular fibrillation following an acute myocardial infarction is increas than twofold in patients who are initially hypokalemic.[87]

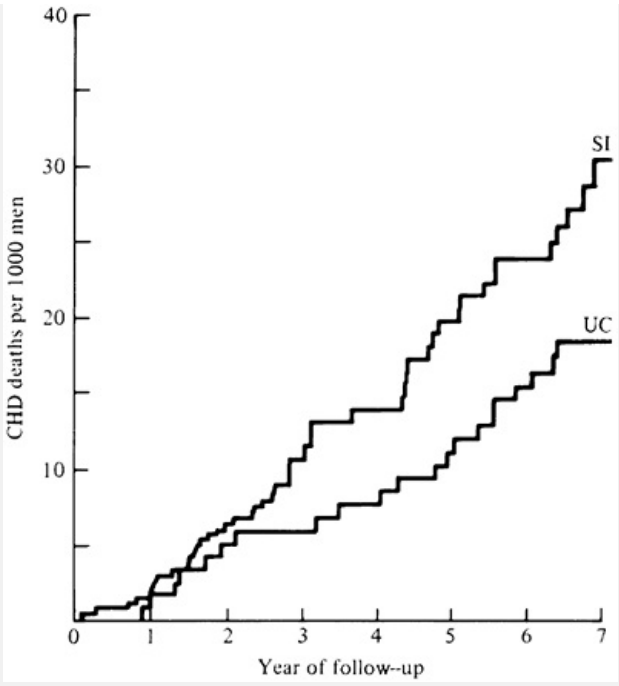

Figure 15-4 Cumulative coronary heart disease (CHD) mortality rates for hypertensive men with an abnormal resting electrocardiogram in the speci intervention (SI) and usual care (UC) groups at 7 years in the MRFIT trial mortality rate was 68 percent higher in the treated (SI) group. (*Adapted from Multiple Risk Factor Intervention Trial Research Group, Am J Cardiol 55:1, 1985, with permission.*)

The thiazide diuretic dose may be an important determinant of risk. Many p the studies in which diuretics were associated with an increased risk of suc death were treated with more than 50 mg/day of hydrochlorothiazide or chlorthalidone.[78,79] and[80] However, *lower and probably safer* doses can be used in many patients. As little as 12.5 mg of hydrochlorothiazide or 15 mg of chlorthalidone generally produce as large an antihypertensive effect as hig doses, with little or no change in the plasma concentration of K^+, glucose, or uric acid (Fig. 15-5).[88,89,90,91] and[92] No increase in ventricular ectopic activity is observed with these lower doses,[93] and low-dose thiazide therapy is one of the recommended first-line modalities for the treatment of hypertension.[99] The greater degree of volume depletion induced by higher diuretic doses may not lead t prominent fall in blood pressure because of increased activity of the renin-angiotensin system.

Metabolic Alkalosis

Loop or thiazide diuretic–induced hypokalemia is often accompanied by met alkalosis. Two factors contribute to this problem: increased loss of K^+ and, in part to secondary hyperaldosteronism, and, to a lesser degree, contraction extracellular volume around a constant amount of extracellular HCO_3^- (called

contraction alkalosis; see p. 1[95,96]). Aldosterone contributes to H^+ loss in this setting both by stimulating the distal H^+-ATPase pump and by

promoting the reabsorption of cation with Na^+. The latter effect creates a lumen-negative electrical potential that promotes H^+ secretion in the lumen by minimizing the degree of back-diffusion (see page 354).

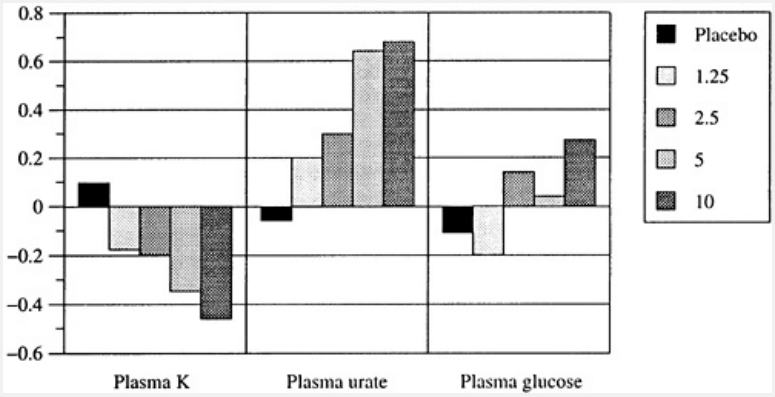

Figure 15-5 Metabolic complications induced by bendrofluazide in relation t dose (multiply by 10 to get equivalent doses of hydrochlorothiazide). Incr the dose led to progressive hypokalemia and hyperuricemia and a greater likelihood of a mild elevation in the plasma glucose concentration, all wit further reduction in the systemic blood pressure. Each treatment group co approximately 52 patients. *Data from Carlsen JE, Kober L, Torp-Pedersen C, Johannsen P, Br Med J 300:975, 1990, with permission.*

The loop diuretics can also increase loss of H^+ by increased H^+ secretion in the cortical aspect of the thick ascending limb[97]. This segment has two luminal mechanisms for Na^+ entry: via Na^+-K^+-$2Cl^-$ transport and Na^+-H^+ exchange. Inhibition of the former with a loop diuretic will tend to increase Na^+ reabsorption in exchange for H^+.

Although NaCl will reverse the alkalemia, this is not desirable in patients w In this setting, acetazolamide may restore acid-base balance by promoting HCO_3^- loss in the urine.

Hyperkalemia and Metabolic Acidosis

The K^+-sparing diuretics reduce both K^+ and H^+ secretion in the collecting tubules. As a result, their use can result in both hyperkalemia and metabolic acidos[98,99]. Prevention is the best therapy, as these drugs should be used with great ca at all, in patients with renal failure or those being treated with either an an converting enzyme inhibitor (which diminishes the release of aldosterone) c supplement.

Hyponatremia

Hyponatremia is a relatively common abnormality in edematous patients wit failure or cirrhosis. This problem can be exacerbated or produced de novo hypertensives by diuretic therapy. The mechanism by which hyponatremia is is related both to effective volume depletion, leading to enhanced secretion and to an increase in water intake.[100,101] The net effect is that ingested water is retained, lowering the plasma Na^+ concentration by dilution.

Almost all cases are due to therapy with a thiazide-type diuretic[57,100,101]

Although loop diuretics also induce volume depletion, they do so by impairi reabsorption in the thick ascending limb, thereby decreasing the generation medullary osmolal gradient (see Chap. 4). As a result, the ability of ADH to increas water reabsorption and promote the development of hyponatremia is limited thiazides, in comparison, act in the cortex and do not interfere with concen ability.[102]

Hyperuricemia

Hyperuricemia is a relatively common finding in patients on diuretic therapy[103,104] In general, this problem reflects increased urate reabsorption in the proxim

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tubule, a process that appears to be mediated by parallel Na^+-H^+ and $Urate^-$-OH^- exchangers in the luminal membrane (see Fig. 8-13).[103,105] Net urate reabsorption varies directly with proximal Na^+ transport, and in patients with diuretic-induced volume depletion, both Na^+ and urate excretion are reduced.[106] If, on the other hand, the fluid losses are replaced, there is no stimulus to compensatory Na^+ retention and no hyperuricemia.[107]

The mechanism by which urate reabsorption is increased in this setting is incompletely understood. Angiotensin II, released in response to hypovolem play a role by enhancing the activity of the Na^+-H^+ exchanger, which can then lead to a parallel increase in $Urate^-$-OH^- exchange. In addition, enhanced proximal wat reabsorption will elevate the tubular fluid urate concentration, thereby pror passive urate reabsorption.

Treatment of diuretic-induced hyperuricemia is *rarely necessary in asymptomatic patients*, even though the plasma urate concentration may exceed 12 mg/dL.[104,108] Goutly arthritis is uncommon in this setting, occurring primarily in patients personal or family history of gout. Renal damage due to the intratubular pre of uric acid is also not a problem, since the hyperuricemia is due to an initi decrease in the distal delivery and subsequent excretion or uric acid.

Hypomagnesemia

Magnesium depletion, which is generally mild, can be induced by diuretic therapy.[109,110] and[111] Most of the filtered magnesium is reabsorbed in the loo

Henle, a process that can be inhibited directly with loop diuretics.[112] Thiazides, in comparison, have little acute effect on magnesium handling but may be a with chronic magnesium depletion, perhaps because of the effects of hypok secondary hyperaldosteronism. Hypokalemia may directly inhibit distal tubu magnesium uptake, thereby increasing magnesium excretion.[112]

How aldosterone enhances urinary magnesium excretion is not clear, but th following mechanisms may contribute. The extrusion of reabsorbed magnesi across the basolateral membrane in the cortical collecting tubule may be m a Na^+-Mg^{2+} exchanger that relies on the favorable inward gradient for Na^+ to enter the cell. Increasing Na^+ reabsorption with aldosterone raises the cell Na^+ concentration, thereby diminishing the gradient for Na^+ entry across the basolateral membrane and therefore the degree of Mg^{2+} extrusion.[113] The observation that decreasing the aldosterone effect with a K^+-sparing diuretic tends to diminish urina magnesium losses is compatible with this hypothesis.[111,114]

DETERMINANTS OF DIURETIC RESPONSE

Before discussing the problem of resistant edema, it is important to first re factors that influence the natriuretic response to a given diuretic. As descr above, two important determinants are the site of action of the diuretic and possible presence of counterbalancing antinatriuretic forces, such as angio aldosterone, and a fall in the systemic blood pressure. In addition, *drug excretion* also plays a major role, particularly with the loop diuretics.[115,116,117]

Almost all of the commonly used diuretics, particularly the loop diuretics, a protein-bound.[118] As a result, they are not well filtered and enter the urine pr via the organic anion or organic cation secretory pump in the proximal tubu Fig. 3-13).[116,119] Their subsequent ability to inhibit Na^+ reabsorption is in part dose-dependent, being influenced by the rate at which the diuretic is delive tubular site of action (Fig. 15-6). Thus, higher doses of a loop diuretic will in ger produce a greater rate of both diuretic and Na^+ excretion. On the other hand, impaired diuretic entry into the lumen is one of the causes of diuretic resis below).

It should be noted, however, that the natriuretic response tends to plateau rates of diuretic excretion, presumably because of complete inhibition of th sensitive carrier or channel. In normal subjects, for example, *maximum diuresis is seen with 40 mg of furosemide or 1 mg of bumetanide given intravenous* The oral dose equivalent is similar for bumetanide, which is almost completely a but is increased to 80 mg for furosemide, only about one-half of which unde intestinal absorption. These doses often must be adjusted upward in edema patients as a result of decreased net drug entry into the lumen.

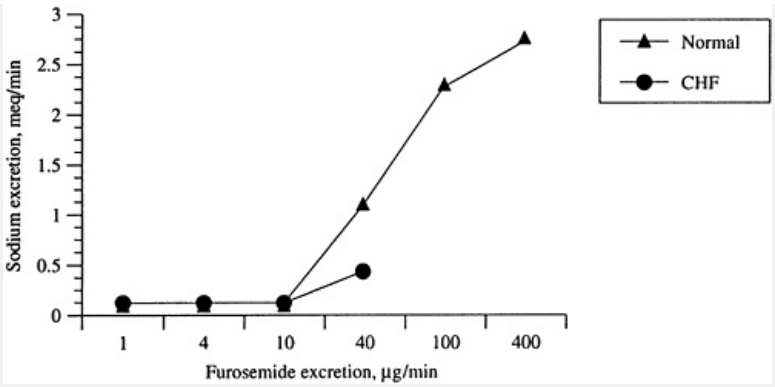

Figure 15-5 Relation between the rate of furosemide excretion and the incr in sodium excretion in normals and in patients with congestive heart failu (CHF). A diuresis is not seen until a threshold rate of furosemide excretio reached; at this point, sodium excretion increases in a dose-dependent m until a maximum effect is seen. Patients with CHF show relative resistanc given rate of diuretic excretion as a result of increased sodium reabsorpti other nephron segments. (*Data from Brater DC, Day B, Burdette A, Anderson S et al*, Kidney Int 26:183, 1984, *with permission*)

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REFRACTORY EDEMA

Although the treatment of the different edematous states will be discussed following chapter, the same principles apply to all patients who are resistar conventional diuretic therapy. The causes of this problem and possible corr measures are depicted in Table 15-3.[1,3,120] In general, therapy is begun with a lo diuretic, since these agents are the most potent and give the most predicta response. The initial aim is to find the *effective single dose*. In patients with advanced renal insufficiency or congestive heart failure, for example, 40 m intravenous furosemide may not induce a diuresis because of a reduction ir entry into the tubular lumen. In this setting, giving 40 mg twice a day will a ineffective, since adequate urinary levels are never achieved.[115] A more appropriate regimen is to *double the individual dose* until a diuresis is obtained or a maximum dose of 160 to 200 mg (or 320 to 400 mg of oral furosemide due to incomple intestinal absorption) is reached.[115,116]

Excess Sodium Intake

Assuming that the patient is taking the diuretic, maintenance of a high Na^+ diet, as shown in Fig. 15-1, will prevent net fluid loss even though an adequate diuresis is achieved. This possibility can be confirmed by a 24-h urine collection. A va 100 to 150 meq/day indicates the necessity for either better dietary compli the use of higher doses or more frequent drug administration.

This problem with diet is often seen after patients are discharged from the when Na^+ intake may be less carefully regulated. As a result, a previously

well-controlled patient may develop recurrent edema in the absence of any exacerbation of his or her underlying disease. Enhanced activity in the outp setting also may play a role. With congestive heart failure, for example, the output may be relatively normal at rest but unable to increase appropriately exertion (see "Decreased Loop Sodium Delivery" below). This low-output state will exacerbate the tendency toward Na^+ retention.

Table 15-3 Pathogenesis and treatment of refracto edema

Problem	Treatment
Excess sodium intake	Measure urine sodium excretion; attempt more rigorous dietary restriction if greater than 100 meq/day
Decreased or delayed intestinal drug absorption	Bowel wall edema can reversibly impair oral drug absorption; switch to intravenous loop diuretic if high dose oral therapy is ineffective
Decreased drug entry into the tubular lumen	Increase to maximum effective dose of a loop diuretic (160 to 200 mg of intravenous furosemide or 4 to 5 mg of bumetanide); use of spironolactone in cirrhosis mixture of albumin and loop diuretic if marked hypoalbuminemia
Increased distal reabsorption	Multiple daily doses if partial diuretic response; add thiazidetype and/or K^+-sparing diuretic
Decreased loop sodium delivery due to low GFR and/or enhanced proximal reabsorption	Attempt to increase delivery out of proximal tubule with acetazolamide or corticosteroids; diuretic administration in supine posture or head-down tilt; dialysis or hemofiltration if severe renal or heart failure

Decreased or Delayed Intestinal Drug Absorption

Some edematous patients who are resistant to as much as 240 mg of oral fu respond to as little as 40 mg given intravenously. This problem, which has been described in advanced heart failure and cirrhosis, reflects a delay in intest absorption, leading to urinary excretion of the drug at suboptimal levels.

[123] Decreased intestinal perfusion, reduced intestinal motility, and perhaps edema all may contribute to the delay in absorption.[122,123] Both removal of edema with intravenous diuretic therapy and, in heart failure, stabilization of card function may at least partially correct this absorptive defect, thereby restor efficacy of oral therapy.

Decreased Drug Entry into the Tubular Lumen

Decreased drug excretion can limit the diuretic response in patients with ac heart failure, renal failure, cirrhosis, or hypoalbuminemia.[120,124] For example, thiazide-type diuretics generally produce little effect once the glomerular fi rate is below 20 mL/min[125] unless either a loop diuretic is given concurrently[126] or very high doses of the thiazide are used.[127] The loop diuretics, on the other hand, may be effective even in advanced renal failure (Fig. 15-3).[72,119,128] As will be described below, there may be advantages to the use of intravenous infusio than bolus injections of loop diuretics in some patients.

Renal failure

Diuretic excretion is often limited in renal failure, in part because of the re organic anions such as hippurate that compete for secretion by the proxima secretory pump.[116,119] In this setting, a higher than normal dose is often requ produce the desired diuretic effect.

Studies with furosemide indicate that the peak response can usually be ach increasing the single intravenous dose from 40 mg up to a maximum of 160 mg.[107,128] This dose can be given two or even three times a day if necessar there is a relatively short-lived diuretic response. Similar considerations ap bumetanide, which is usually 40 times more potent than furosemide on a we and is therefore given in one-fortieth the dose. In renal failure, however, th relative increase in the extrarenal clearance of bumetanide; as a result, the must be increased to one-twentieth that of furosemide, or a maximum of 8 t mg.[116]

Some studies have advocated the use of extremely high doses of furosemid 2400 mg per day) in resistant patients. Although this may increase the urin

output in selected cases, it is also associated with an enhanced risk of oto and possible permanent deafness, particularly if given as an intravenous bo the attendant very high peak plasma levels) rather than being infused slowl to 60 min.[129,130] Observations in animals suggest that this complication may to inhibition of a Na^+-K^+-$2Cl^-$ carrier (similar to that in the thick ascending limb) the endolymph-producing cells.[131] Ethacrynic acid appears to have the highest ototoxic potential; its use is generally limited to patients allergic to one of agents, since it is the *only loop or thiazide diuretic that is not a sulfonamide derivative*.

Cirrhosis

Spironolactone is the diuretic of choice for the initial treatment of fluid ove the setting of cirrhosis. It may be more effective than loop diuretics alone[132,133] and does not induce hypokalemia, which may precipitate hepatic encephalo

One possible explanation for the surprising efficacy of spironolactone comp loop diuretics is that patients with cirrhotic ascites have marked hyperaldos and therefore reclaim the excess fluid delivered out of the loop of Henle in cortical collecting tubule. As depicted in Fig. 15-7, however, the slope of the relationship between the rate of furosemide excretion and the diuretic resp cirrhotic patients may be similar to that in normals, suggesting that there is minor intraluminal resistance to furosemide.

As mentioned above, most loop diuretics are highly protein-bound; as a res enter the tubular lumen by secretion in the proximal tubule, not by glomerul filtration. In many cases, the resistance to loop diuretics in cirrhosis result decreased rate of drug secretion into the lumen (≤20 mg/h), perhaps as a r competition from other organic anions such as bile salts for the organic ani secretory pump.[117] Spironolactone may be uniquely effective in this setting be it is the only *diuretic that does not require access to the tubular lumen*[37] It enters the tubular cell from the plasma across the basolateral membrane and then with aldosterone for its cytosolic receptor.

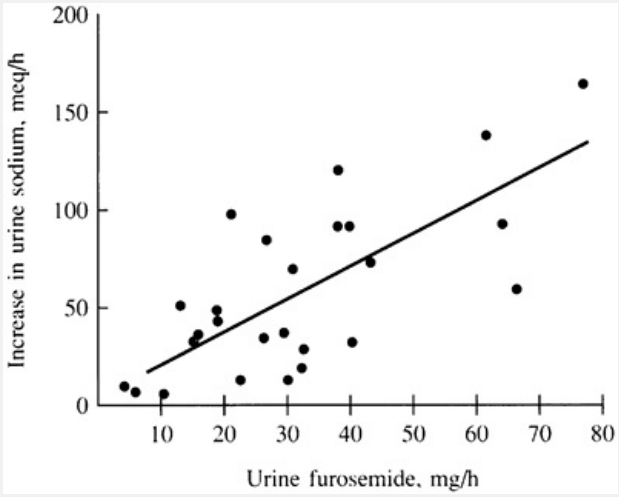

Figure 15-7 Relationship between the rate of furosemide excretion and the increase in the rate of Na^+ excretion in patients with alcoholic liver disease. T slope of this line is similar to that in normal subjects, with the natriuresis limited in those patients with a low rate of furosemide excretion. *From Pinzani M, Daskalopoulos G, Laffi G, et al: Gastroenterology 92:294, 1987. Copyright 1987 by The American Gastroenterological Association. Used with permis*

For patients who do not respond to dietary Na^+ restriction and spironolactone alone the most successful therapeutic regimen is the combination of single morni doses of spironolactone and furosemide, beginning with 100 mg and 40 mg,

respectively.[133,134] This combination in this ratio usually maintains normokale
The doses can be doubled if a clinical response is not evident. The maximu
recommended doses are spironolactone 400 mg/day and furosemide 160 mg

Hypoalbuminemia

Marked hypoalbuminemia (plasmin albumin concentration usually under 2 g/
another condition that may be associated with decreased diuretic entry into
lumen.[135] The protein-binding of drugs and toxins largely restricts the volum
distribution to the vascular space. This has two potentially protective effec
access to the cells, and it maximizes the rate of delivery to the kidney, whe
excretion can occur. When binding of a loop diuretic is diminished because
reduction in the plasma albumin concentration, however, there is increased
the interstitial space and a slower rate of drug excretion.

A second mechanism may be operative when hypoalbuminemia is due to hea
proteinuria in the nephrotic syndrome. In this setting, free drug that is secr
the tubular lumen may be bound to filtered albumin, thereby becoming
inactive.[136,137] In experimental animals, for example, nephrotic-range albumi
can diminish the response to intraluminal furosemide by about 50 percent.[137]
Filtered IgG, in comparison, does not bind furosemide or interfere with its e[137]

Some patients with the nephrotic syndrome and severe hypoalbuminemia ar
resistant to conventional diuretic therapy. Some of these patients have bee
with 40 to 80 mg of furosemide added to 6.25 to 12.5 g of salt-poor albumir
of the furosemide-albumin complex is thought to act by increasing diuretic
the kidney and can, in some cases, lead to a modest increase in sodium
excretion.[138]

Intravenous infusion of loop diuretics

A possibly safer and more effective alternative to bolus injections in patien
requiring high-dose therapy is to administer the loop diuretic as a continuo
intravenous infusion. Studies in patients with stable chronic renal failure s
a constant infusion of bumetanide (1 mg bolus followed by 1 mg per hour) c
produce as much as a 33 percent greater increment in sodium excretion cor
standard bolus therapy (6 mg every 6 h) (Fig. 15-5).[72] This difference is
probably related to differences in the rate of drug excretion. Bolus therapy
transiently associated with periods of both supramaximal and submaximal e
resulting in some of the drug being excreted ineffectively. In comparison, a
infusion maintains an optimal rate of drug excretion on the ascending portic
curve in Fig. 15-6. Similar findings have been demonstrated in normal subject
mg of intravenous furosemide per hour produces a greater diuresis than a 4
bolus.[139]

The main utility of continuous intravenous loop diuretics is in hospitalized
the intensive care unit with marked edema who show a response to a stand

intravenous bolus that is not sustained. Patients who show no response to bolus (such as 240 to 320 mg of furosemide) *are likely to respond to an infusion* since bolus therapy results in higher initial plasma and urinary diuretic leve

After the initial bolus, we generally begin with furosemide at a dose of 20 r diuresis is not sustained, a second bolus is given followed by a higher infu of 40 mg/h. The risk associated with still higher infusion rates of 80 to 160 must be weighed against those of alternative strategies such as the additio thiazide-type diuretic or fluid removal via hemofiltration (see below). Equiv doses are 1 mg/h increasing to 2 mg/h for bumetanide and 10 mg/h increasi mg/h for torsemide.

Increased Distal Reabsorption

The effect of a loop or thiazide diuretic is in part blunted by increased Na^+ reabsorption in the more distal segments, because of both the direct effect increase in Na^+ delivery and the action of aldosterone in the collecting tubules.[3,8,10,25] As an example, patients with moderate to advanced heart fai typically have a lower maximal diuretic response even if there is adequate into the lumen (Fig. 15-6).[115] In this setting, *a single response may be insufficien and drug administration two or even three times a day may be required* comparison, there is little to be gained from increasing the single dose abo 160 mg of intravenous furosemide (or 3 to 4 mg of bumetanide), since there already maximal inhibition of the Na^+-K^+-$2Cl^-$ carrier.[115]

In some patients, however, the increase in distal reabsorption results in res loop diuretic therapy. This problem can often be overcome by the addition c thiazide with or without a K^+-sparing diuretic to block Na^+ transport at multiple sites in the nephron.[120,126,140,141] and[142] The K^+-sparing diuretic is usually given to minimize K^+ loss, since it induces only a minor increment in Na^+ excretion.[120]

The efficacy of the addition of a thiazide may be related to both *proximal* and *distal* actions of the drug. The former normally plays a minor role, because t excess fluid delivered out of the proximal tubule is reabsorbed in the loop c Henle;[21] concurrent use of a loop diuretic, however, blocks this compensato response and can unmask the proximal effect. Furthermore, there is a comp rise in distal tubule Na^+ reabsorption induced by the increase in delivery out of loop of Henle; as a result, blocking this response with a thiazide will now p larger than normal increment in Na^+ excretion.[2,10] In one study of patients pretreated with furosemide or placebo, for example, the natriuretic respons addition of a thiazide was approximately 20 percent greater in the furosemi suggesting increased reabsorption at a thiazide-sensitive site (Fig. 15-8).[10]

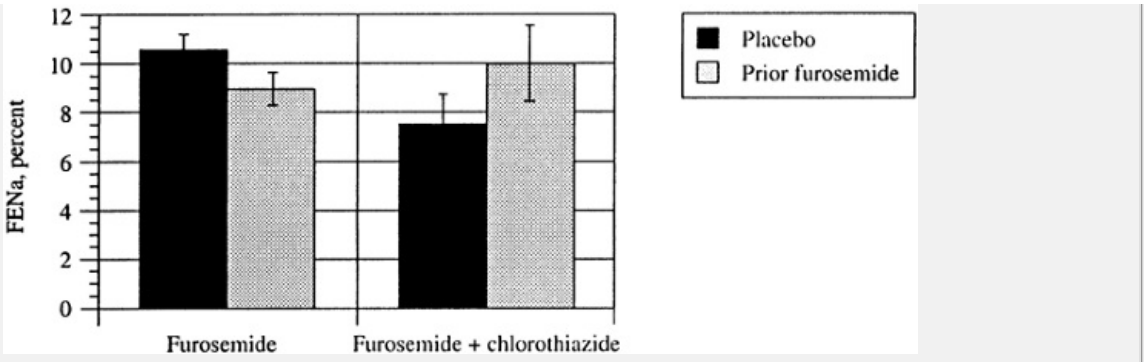

Figure 15-3 Diuretic responsiveness in patients previously treated for 1 mo with placebo or the loop diuretic furosemide. The subjects who had been with furosemide had a lesser increase in the fractional excretion of sodiu (FENa) after the administration of furosemide (left panel) but a greater na response to the addition of chlorothiazide (right panel). These findings ar compatible with increased tubular sodium reabsorption at the thiazide-ser site in the distal tubule when distal sodium delivery is chronically increas furosemide. (*Data from Loon NR, Wilcox CS, Unwin RJ, Kidney Int 36:682, 1989, with permission.*)

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The beneficial effect of adding a thiazide can be demonstrated even in pati advanced renal failure. One study, for example, evaluated patients with a m creatinine clearance of 13 mL/min.[142] The addition of the equivalent of 30 mg of hydrochlorothiazide almost doubled the increase in $U_{Na}V$ induced by the equivalent of 150 to 200 mg of furosemide alone.

It had been proposed that metolazone is more effective than other thiazides setting.[127] However, this study used very large doses; at equivalent doses, t little evidence of a response different from that to other thiazide-type diuretics.[3,126,142]

Careful monitoring is required when combination therapy is initiated, becau excessive diuretic response may be seen. Some previously refractory patie example, can lose as much as 5 liters of fluid and 200 mEq of K^+ per day.[140] It is prudent, therefore, to begin with low doses of a thiazide (such as 250 mg o chlorothiazide, 25 mg of hydrochlorothiazide, or 1.25 to 5 mg of metolazone probably to add a K^+-sparing diuretic unless the patient has baseline hyperkal As described above, monitoring is most important on the first day, when the response is likely to be greatest (Fig. 15-3).

Decreased Loop Sodium Delivery

In some patients with severe heart failure or cirrhosis, the combination of a in glomerular filtration rate (as a result of the decline in renal perfusion) a increase in proximal reabsorption (mediated in part by angiotensin II) marke reduces the delivery of fluid to the diuretic-sensitive sites in the more dista

segments.[124,143] In this setting, the addition of acetazolamide may substanti enhance the diuretic response by diminishing proximal reabsorption.[144]

Improving renal perfusion by changing *posture* is an additional modality that may be successful in selected cases. Patients with heart failure and cirrhosis te have effective volume depletion and renal vasoconstriction, mediated in pa associated increases in angiotensin II and norepinephrine. These changes prominent in the upright position, because of the effects of gravity and an i heart failure to appropriately increase cardiac output with exercise.[145] On the other hand, assumption of the supine position or a 10-degree head-down tilt maxi cardiac output in relation to needs and may enhance venous return to the h net effect is a rise in creatinine clearance of as much as 40 percent and a doubling of Na^+ excretion both in the basal state and after the administration loop diuretic.[146,147]

Some patients with advanced heart failure or renal failure will not respond the above modalities. In this setting, either dialysis or hemofiltration can b remove the excess fluid.[148,149] and[150] With continuous arteriovenous hemofiltration, for example, catheters are inserted into an artery and a veir pressure is used to perfuse a hemofilter (similar to a dialysis cartridge); th leaving the filter then returns to the patient through the venous catheter. C monitoring is essential, since the rate of filtration can exceed 500 to 1000 this procedure.[148,150]

OTHER USES OF DIURETICS

The preceding discussion has reviewed the use of diuretics in edematous s hypertension, hypercalcemia, and hypercalciuria. These agents are also us treatment of a variety of other conditions, including metabolic alkalosis, re acidosis, diabetes insipidus, hyponatremia due to the syndrome of inappro secretion, and hypokalemia due to primary hyperaldosteronism (see the rel chapters elsewhere in the book).

DIURETICS AND PROSTAGLANDINS

The loop diuretics and to a lesser degree the thiazides increase the renal p of prostaglandins.[151,152] and[153] The local release of vasodilator prostaglandin may have important hemodynamic actions, leading to an acute increase in r blood flow,[151,152] venodilation, and a rise in venous capacitance.[154,155] The last effect is helpful in the treatment of acute pulmonary edema, since the asso pooling of blood in the venous system will diminish fluid delivery to the hea lowering the cardiac filling pressures prior to the onset of the diuresis.[156]

Nonsteroidal anti-inflammatory drugs, which impair prostaglandin synthesis the diuresis induced by furosemide in humans.[157,158] It is not clear, however, whether this reflects reversal of a natriuetic effect of the prostaglandins (w inhibit Na^+ reabsorption in the thick ascending limb and cortical

collecting tubule) or renal ischemia due to the unopposed vasoconstrictor a angiotensin II and norepinephrine.[159]

Inhibition of vasodilator prostaglandin synthesis by nonsteroidal anti-inflam drugs may have two additional deleterious effects in patients treated with d an elevation in blood pressure in hypertensives[160,161] and a further reduction in cardiac output in severe heart failure due to the rise in vascular resistance[1,2,162]

Vasoconstrictor Response to Loop Diuretics

Loop diuretics are one of the initial mainstays of therapy in severe heart fa because of the combination of venodilation (in acute pulmonary edema) and enhanced urine output. However, there may be an acute deleterious effect i patients with chronic heart failure. This maladaptive response, which lasts h, is characterized by arteriolar vasoconstriction and a rise in systemic blo pressure; the ensuing increase in afterload then induces an elevation in pu capillary wedge pressure and a reduction in cardiac output.[163] The plasma renin activity and plasma norepinephrine levels are increased in this setting and presumably responsible for the rise in vascular resistance. By 4 h, in comp there is an improvement in cardiac function as the vasoconstrictor hormone to the basal levels and the diuretic effect lowers the cardiac filling pressur

Early vasoconstriction also occurs in some patients with cirrhosis, in whom furosemide can acutely lower both renal plasma flow and the glomerular filt rate by 30 to 40 percent.[164]

PROBLEMS

15-1Match the clinical setting with the preferred form of diuretic thera

a. **Acetazolamide**

b. **Loop diuretic**

c. **Thiazide-type diuretic**

d. **Spironolactone**

1. **Recurrent nephrolithiasis due to hypercalciuria**
2. **Cirrhosis with ascites**
3. **Metabolic alkalosis following diuretic therapy for heart failure**
4. **Hypercalcemia**
5. **Hyponatremia due to the syndrome of inappropriate ADH secretion**

15-2What are the mechanisms by which the following can limit the res to a diuretic?

a. **Hypoalbuminemia**

b. **Activation of the renin-angiotensin system**

c. **Hypotension**

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Footnotes

* The loop diuretics are generally ineffective in this segment, although furo may have a small inhibitory effect.[29]

† The reduction in the urine osmolality induced by a loop diuretic actually i free water excretion, making these agents useful *in the treatment of hyponatremia* in the syndrome of inappropriate ADH secretion (see page 729).

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Chapter Sixteen
Edematous states

Edema is defined as a palpable swelling produced by expansion of the inter fluid volume. A variety of clinical conditions are associated with the develo edema, including heart failure, cirrhosis, and the nephrotic syndrome. This will review the basic principles governing the pathophysiology of edema for and the treatment of the different edematous states. The review of the clini diuretics presented in Chap. 15 should be read before proceeding with this discussion, since these agents constitute the mainstay of therapy for most generalized edematous states.

PATHOPHYSIOLOGY OF EDEMA FORMATION

There are two basic steps involved in edema formation:

1. There is an *alteration in capillary hemodynamics* that favors the movement of fluid from the vascular space into the interstitium.
2. *Dietary Na^+ and water are retained by the kidney.*

The importance of the kidneys in the development of edema should not be underestimated. Edema does not become clinically apparent until the inters volume

has increased by at least 2.5 to 3 liters. Since the normal plasma volume is about 3 liters, edematous patients would develop marked hemoconcentratio shock if the edema fluid were derived only from the plasma.

These complications do not occur because of the sequence depicted in Fig. 16-1. The initial movement of fluid from the vascular space into the interstitium r plasma volume and consequently tissue perfusion. In response to these cha kidney retains Na^+ and water (see Chap. 8). Some of this fluid stays in the vascula space, returning the plasma volume toward normal. However, the alteration capillary hemodynamics results in most of the retained fluid entering the in and eventually becoming apparent as edema. The net effect is a marked ex of the total extracellular volume (as edema) with maintenance of the plasma at close to normal levels.

This example illustrates an important point to which we will return in the se

therapy: In most edematous states, renal Na^+ and water retention is *appropriate* compensation in that it restores tissue perfusion, even though it also augm degree of edema. On the other hand, removing the edema fluid with diuretic will improve symptoms but may diminish tissue perfusion, occasionally to cl significant levels.

The hemodynamic effects are somewhat different when the primary abnorma *inappropriate* renal fluid retention. In this setting, both the plasma and

interstitial volumes are expanded and there are no deleterious hemodynami from removal of the excess fluid. This is an example of the vascular *overfilling* tree, in contrast to the *underfilling* described above. It occurs most often with primary renal disease but may also be seen in early cirrhosis and with the certain drugs.

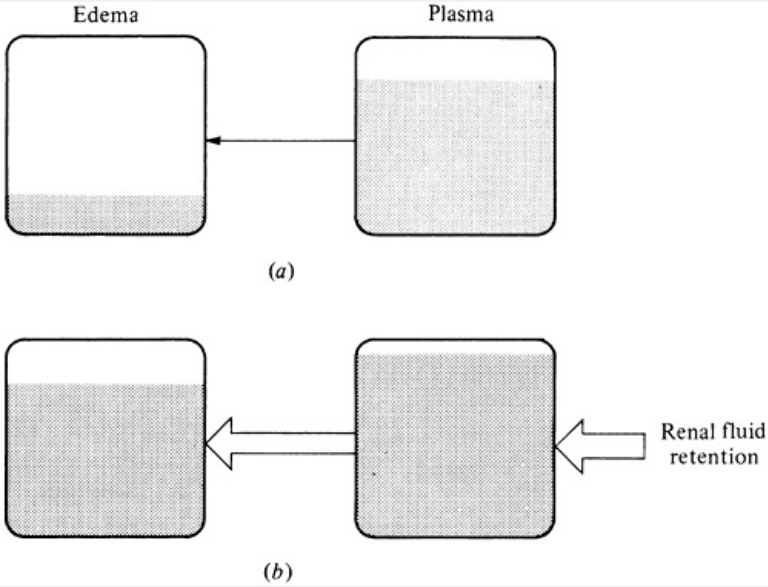

Figure 16-1 Pathophysiology of edema formation when there is an alteratio capillary hemodynamics, such as an elevated capillary hydraulic pressure favors the movement of fluid out of the vascular space into the interstitiu normal plasma volume is depicted as the full size of the plasma square. T shaded area in the edema square refers to the increase in the interstitial volume as edema. The initial reduction in the plasma volume produced by loss of fluid into the interstitium (*a*) stimulates renal Na^+ and water retention (*b*). This appropriately restores the plasma volume toward normal, but, becaus the altered capillary hemodynamics, much of the retained fluid enters the interstitium and becomes apparent as edema.

Capillary Hemodynamics

The exchange of fluid between the plasma and the interstitium is determine hydraulic and oncotic pressures in each compartment. The relationship betv these parameters can be expressed by Starling's law (see Chap. 7[1,2] and[3]

$$\text{Net filtration} = \text{LpS}\,(\Delta\ \text{hydraulic pressure} - \Delta\ \text{oncotic pressure})$$
$$= \text{LpS}\,\left[(P_{cap} - P_{if}) - \sigma(\pi_{cap} - \pi_{if})\right] \qquad (16\text{-}1)$$

where Lp is the unit permeability or porosity of the capillary wall, S is the s area available for filtration, and P_{cap} and P_{if} are the capillary and interstitial fluid hydraulic pressures, π_{cap} and π_{if} are the capillary and interstitial fluid oncotic pressures, and sigma represents the reflection coefficient of proteins acros capillary wall (with values ranging from 0 if completely permeable to 1 if co impermeable).

The normal values for Starling's forces in experimental animals and humans uncertain, largely because of difficulties in the measurement of these parar (with the exception of the capillary oncotic pressure). Furthermore, capillar hemodynamics are not necessarily uniform within an organ (as both open ar capillaries may be present), and capillaries in different organs have unique hemodynamic and permeability characteristics.

Despite these difficulties, important differences in the magnitude of Starlin have been identified in skeletal muscle and subcutaneous tissue (the sites peripheral edema), the liver, and the lung (Table 16-1).[2,4,5] Approximate normal values in a skeletal muscle capillary are shown in Fig. 16-2. As can be seen, the mean capillary hydraulic pressure (17 mmHg), which pushes fluid out of the and the plasma oncotic pressure (28 mmHg), which pulls fluid into the vasc space, are quantitatively the most important. There is normally a small mea of about 0.3 mmHg favoring filtration out of the vascular space,* and that is filtered is then returned to the systemic circulation by the lymphatics so tha accumulation in the interstitium is prevented.

Starling's forces are substantially different in the liver. The hepatic sinuso highly permeable to proteins; as a result, the capillary and interstitial onco pressures are roughly equal, and there is little transcapillary oncotic press

gradient.[2] The net effect is that the *hydraulic pressure gradient favoring filtration essentially unopposed*. To some degree, filtration is minimized by a lower capil hydraulic pressure than in skeletal muscle, since approximately two-thirds blood flow is derived from the portal vein, a low-pressure system. Neverthe there is still a larger gradient favoring filtration; however, edema does not occur, because the filtered fluid is again removed by the lymphatics.

Table 16-1 Approximate normal values for Starling forces in skeletal muscle and lung[2]

	Skeletal muscle	Alveoli
Hydraulic pressure		
Capillary (mean)	17.3	8

Interstitium	-3.0	-2
Mean gradient	20.3	10
Oncotic pressure		
Capillary (mean)	28	26
Interstitium	8	18
Mean gradient	20	8
Net gradient favoring filtration (δP-δpi)	0.3	2

[a] Units are millimeters of mercury. Values are from Refs. 1, 2, and 4.

The alveolar capillaries are somewhat similar to the hepatic sinusoids. The relatively low capillary hydraulic pressure (due to perfusion from the low-pr system in the right ventricle), but they are also more permeable to proteins skeletal muscle, resulting in a lesser transcapillary oncotic pressure gradie (Table 16-1).[4,5] The clinical significance of this difference will be discussed below.

Edema formation

The development of edema requires an alteration in one or more of Starling in a direction that favors an increase in net filtration.

This can be produced by an elevation in capillary hydraulic pressure, capil permeability, or interstitial oncotic pressure, or by a reduction in the plasm pressure (Table 16-2). Edema can also be induced by lymphatic obstruction, si the fluid that is normally filtered is not returned to the systemic circulation

Table 16-2 Major causes of edematous states

Increased capillary hydraulic pressure

A. Increased plasma volume due to renal Na^+ retention
   1. Heart failure, including cor pulmonale
   2. Primary renal Na^+ retention
      a. Renal disease, including the nephrotic syndrome
      b. Drugs: minoxidil, diazoxide, calcium channel blockers (?), nonsteroidal anti-inflammatory drugs, fludrocortisone, estrog
      c. Refeeding edema

d. Early hepatic cirrhosis
3. Pregnancy and premenstrual edema
4. Idiopathic edema, when diuretic-induced

B. Venous obstruction
1. Hepatic cirrhosis or hepatic venous obstruction
2. Acute pulmonary edema
3. Local venous obstruction

C. Decreased arteriolar resistance
1. Calcium channel blockers (?)
2. Idiopathic edema (?)

Decreased plasma oncotic pressure (primarily when plasma albumin concentration < 1.5 to 2g/dL)

A. Protein loss
1. Nephrotic syndrome
2. Protein-losing enteropathy

B. Reduced albumin synthesis
1. Liver disease
2. Malnutrition

Increased capillary permeability

A. Idiopathic edema (?)
B. Burns
C. Trauma
D. Inflammation or sepsis
E. Allergic reactions, including certain forms of angioedema
F. Adult respiratory distress syndrome
G. Diabetes mellitus
H. Interleukin 2 therapy
I. Malignant ascites

Lymphatic obstruction or increased interstitial oncotic pressure

A. Nodal enlargement due to malignancy
B. Hypothyroidism
C. Malignant ascites

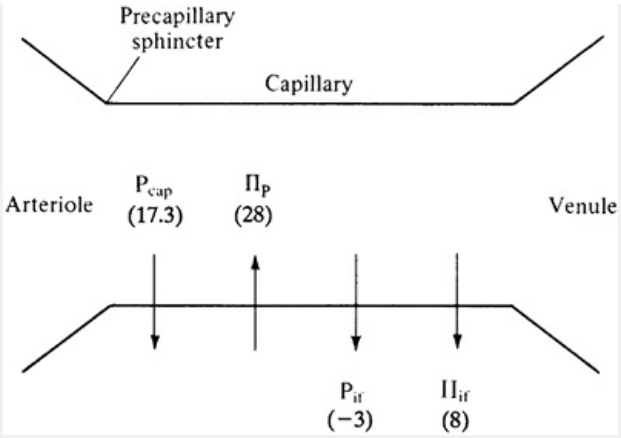

Figure 16-2 Schematic representation of the hemodynamic factors controllir fluid movement across the capillary wall in subcutaneous tissue. The num parentheses represent the approximate normal values, in millimeters of m for each of the factors. The negative value for P_{if} is probably generated by the removal of interstitial fluid by the lymphatic vessels. The net effect is a s gradient favoring filtration of 0.3 mmHg.

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Increased capillary hydraulic pressure

Capillary hydraulic pressure, although generated by cardiac contraction, is insensitive to alterations in arterial pressure. This stability is due to autore changes in resistance at the precapillary sphincter (Fig. 16-2), which determine the extent to which the arterial pressure is transmitted to the capillary (see the arterial pressure is increased, for example, the sphincter constricts, mi the elevation in capillary hydraulic pressure. This explains why patients wi hypertension do not develop edema. Conversely, the sphincter dilates when arterial pressure is reduced. This decreases the pressure drop across the s allowing the capillary pressure (as well as blood flow) to be maintained.

In contrast, the resistance at the venous end of the capillary is not well reg Consequently, changes in venous pressure result in parallel alterations in c hydraulic pressure. The venous pressure is increased in two settings: (1) when blood volume is expanded, augmenting the volume in the venous system, and (2) there is venous obstruction. Examples of edema due to volume expansion ir heart failure and renal disease; edema due to venous obstruction, on the o is commonly seen with cirrhosis, in which there is a marked increase in hep sinusoidal pressure, and with deep venous thrombosis in the lower extremit

Decreased plasma oncotic pressure

Hypoalbuminemia due to albumin loss in the urine in the nephrotic syndrom decreased hepatic albumin synthesis is another potential cause of edema. I hypoalbuminemia alone may be a less common cause of edema than was pre suspected (see "Safety Factors" below).

Increased capillary permeability

An increase in capillary permeability due to vascular injury promotes the development of edema both directly and by permitting albumin to move into interstitium, thereby diminishing the oncotic pressure gradient. This proble operative in the following clinical settings:

1. Burns, in which both histamine and oxygen free radicals can induce microvascular injury.[7]
2. Therapy with interleukin-2, which appears to directly increase capillary permeability.[8,9]
3. Episodic idiopathic capillary leak syndromes, which may be mediated by increased expression of interleukin-2 receptors on circulating mononucl or by increased generation of kinins.[10,11,12] and[13] Affected patients often have an associated monoclonal gammopathy and, during episodes, have massive leak of proteins and fluids out of the vascular space, with the hematocrit rising acutely to as high as 70 to 80 percent.[12] The mortality rate is high in this disorder. Preliminary evidence suggests that the combinatic aminophylline (an inhibitor of phosphodiesterase) and terbutaline (a rel selective β_2-adrenergic agonist) may prevent episodes.[12] It is not clear, however, why these drugs are effective.

4. Any of the conditions associated with the adult respiratory distress syn (Table 16-2) In this disorder, ischemia- or sepsis-induced release of cyto such as interleukin 1, interleukin 8, or tumor necrosis factor, may play a important role in the increase in pulmonary capillary permeability, at lea via the recruitment of neutrophils[14,15] and[16]

Capillary permeability is also moderately increased in patients with diabete mellitus.[17,18] This abnormality may be mediated in part by hyperglycemia-ind accumulation of both diacylglycerol (with subsequent activation of protein k see Fig. 6-3) and advanced glycosylation end products derived from the comb of glucose with circulating proteins.[19,20] The net effect is to enhance the severity edema, which, in these patients, is usually due to heart failure or the neph syndrome.

Lymphatic obstruction or increased interstitial oncotic pressure

Lymphatic obstruction is an unusual cause of edema that is most often seer nodal enlargement due to malignancy. This process is called lymphedema.[21] With hypothyroidism (myxedema), on the other hand, there is a marked increase interstitial accumulation of albumin and other proteins.[22] Although this may be due in part to an elevation in capillary permeability, the excess interstitial protein would normally be returned to the systemic circulation by the lymphatics. H

lymphatic flow is low or normal in myxedema,[22] not increased as in other edematous states.[23] This may be due to binding of the filtered proteins to excess interstitial mucopolysaccharides, thereby preventing their removal by the lymphatics.[22]

Establishing the diagnosis of these forms of edema is important, since they should not be treated with diuretics. When diuretics are given to treat the usual form of peripheral edema, the initial fluid loss comes from the intravascular space. The ensuing reduction in venous and therefore intracapillary pressure allows the interstitial fluid to be mobilized and the plasma volume to be maintained. However, this sequence does not occur with lymphatic obstruction or myxedema, since edema fluid cannot be easily mobilized into the vascular space. Similar considerations apply to peripheral edema due to localized venous disease of the lower extremities.

Safety factors

Since there is normally a small gradient favoring filtration, it might be expected that even a minor change in these hemodynamic forces would lead to edema. However, experimental and clinical observations indicate that there must be at least a *5 mmHg increase in the gradient favoring filtration before edema can be detected*.[1,2,5] Three factors contribute to this protective response:

1. Increased lymphatic flow can initially remove the excess filtrate.
2. Fluid entry into the interstitium lowers the interstitial oncotic pressure, by dilution and by lymphatic-mediated removal of interstitial proteins. For

example, interstitial oncotic pressure falls to very low levels in congestive heart failure, while the plasma oncotic pressure is relatively normal.[24] The associated increase in the transcapillary oncotic pressure gradient ($\pi_{cap} - \pi_{if}$) counterbalances the rise in capillary hydraulic pressure, thereby minimizing the degree of edema formation.
3. The increase in interstitial fluid volume will raise the hydraulic pressure, but this cannot occur until the normally negative value (generated by lymphatic pumping and removal) becomes positive.[1]

As an example, two safety factors limit the degree of ascites formation in patients with cirrhosis. Increased lymph flow (which can rise more than 10-fold as the intrasinusoidal hypertension augments the rate of filtration) provides the initial protection. However, once the rate of fluid movement out of the sinusoids is sufficient to overcome the ability of the lymphatics to remove the excess fluid, the ensuing elevation in intraperitoneal pressure eventually limits continued fluid accumulation in the peritoneum.[25,26]

Hypoalbuminemia and edema

The magnitude of the reduction that can occur in interstitial oncotic pressure is related to the baseline level. If, as listed in Table 16-1, the normal value in skeletal muscle and subcutaneous tissue is only 8 mmHg, then loss of interstitial pr

could account for a maximum safety factor of only 8 mmHg. However, more studies suggest that the normal level in humans may be as high as 12 to 15 mmHg.[27,28] and[29]

The potential clinical relevance of this observation can be illustrated by stu patients with heavy proteinuria due to the nephrotic syndrome. The fall in t albumin concentration in this disorder leads to a parallel decline in the inte oncotic pressure as a result of less entry of albumin into the interstitium (Fig. 16-3). As a result, the *transcapillary oncotic pressure gradient is initially maintaine* a protective factor that is increased up to twofold if the interstitial oncotic 12 to 15 mmHg rather than 8 mmHg.

The relative roles of hypoalbuminemia and primary renal sodium retention (by the underlying disease) in individual patients with the nephrotic syndron to be variable.[30] Some findings in both animals and humans with the nephrotic syndrome are compatible with the hypothesis that renal Na^+ retention, not hypoalbuminemia, is primarily responsible for edema formation.[29,30,31,32,33,34] and[35]

1. Minimal change disease is a common cause of the nephrotic syndrome. remission is induced by corticosteroids, there is an increase in glomeru filtration rate and a substantial rise in sodium excretion (with partial re the edema) *before any significant elevation in the plasma albumin concentration* (Fig. 16-4).[35] This finding suggests that the renal disease, ra than hypoalbuminemia, is responsible for the initial Na^+ retention.
2. If underfilling due to hypoalbuminemia were the primary initiating factor formation, then removal of the edema with diuretics should lead to

plasma volume depletion and azotemia. However, the plasma volume ap remain relatively constant in this setting unless there is excessive fluid removal.[31]

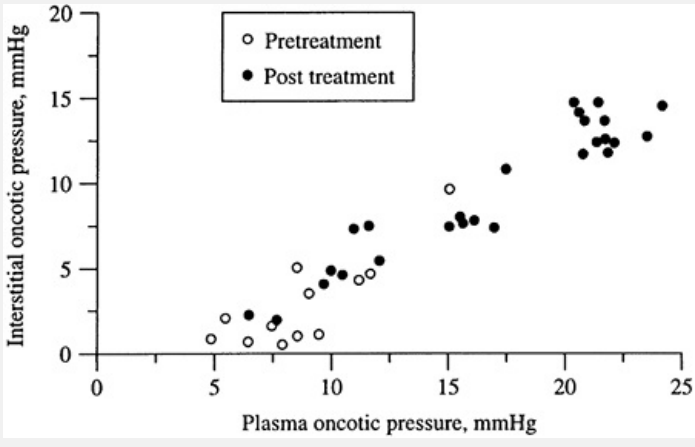

Figure 16-3 Relationship between plasma and interstitial oncotic pressures

nephrotic patients with minimal change disease before (open circles) and (closed circles) corticosteroid-induced remission of the proteinuria. These are reduced in parallel during active disease with little change in the transcapillary oncotic pressure gradient. (*Adapted from Koomans HA, Kortlandt W, Geers AB, Dorhout Mees EJ, Nephron 40:391, 1985, with permission*)

Experimental models of glomerular disease show a primary increase in Na^+ reabsorption that appears to occur in the collecting tubules.[33,36] How this might occur

is not well understood.[34,37] Other studies, however, suggest an important role for hypoalbuminemia in at least some patients:[38]

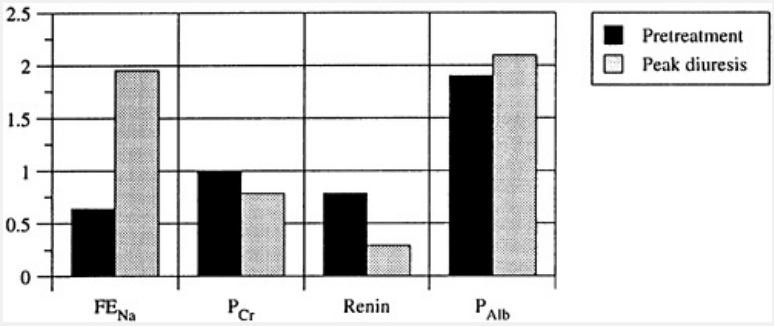

Figure 16-4 Changes in the fractional excretion of Na^+ (percent), plasma creatinine concentration (mg/dL), plasma renin activity (ng/mL/h), and plasma albumin concentration (g/dL) before corticosteroid therapy, during the peak diuresis, and after remission has been induced. The peak diuresis is associated with a fall in the plasma creatinine concentration and plasma renin activity toward normal, but occurs before there has been any significant rise in the plasma albumin concentration. (*From Koomans HA, Boer WH, Dorhout Mees EJ, Nephron 47:173, 1987, with permission*)

1. The administration of albumin to raise the plasma oncotic pressure can increase sodium excretion and lead to resolution of edema in some patients.[39,40]
2. Some patients have very low rates of sodium excretion, elevated plasma renin activity, and symptoms of hypovolemia.[41,42]

Severe and acute hypoalbuminemia are settings in which underfilling edema can occur. In patients with severe hypoalbuminemia (plasma albumin less than 1 g/dL), washout of the interstitial oncotic pressure would eventually be complete, leading to a reduction in the transcapillary oncotic pressure gradient and a tendency toward underfilling.[42] On the other hand, the rapid administration of large volumes of

to patients with marked hypovolemia leads to acute hypoalbuminemia, with for the interstitial albumin concentration.[43] As a result, the transcapillary oncotic pressure gradient is reduced and peripheral edema can occur befor restoration of normal intracardiac filling pressures.

In summary, the relative roles of primary renal sodium retention and hypoalbuminemia in individual patients with the nephrotic syndrome appear variable.[38,41,42] A study in children with minimal change disease sheds some on the often conflicting findings.[41] Thirty children with minimal change disease in remission were monitored carefully and studied within a few days of the ons relapse as indicated by persistent 3+ findings on the urine dipstick for protein. Wl the children were first evaluated, three different groups were noted:

1. Nine children were relatively normoalbuminemic [mean plasma albumin concentration 3.7 g/dL (37 g/L)]. They had a reduced fractional excretic sodium and signs of modest volume expansion (weight gain, increased b volume) but no overt edema. These findings appear to represent primar sodium retention.
2. Eight children had edema, overt nephrotic syndrome, and a mean plasm albumin concentration of 1.8 g/dL (18 g/L), but no signs of hypovolemia
3. Thirteen children had edema, overt nephrotic syndrome, a mean plasma concentration of 1.6 g/dL (16 g/L), and clear evidence of hypovolemia, by one or more symptoms suggestive of volume depletion (tachycardia, peripheral vasoconstriction, oliguria) and marked elevation in the plasm activity and concentrations of aldosterone and norepinephrine. These c also had a low glomerular filtration rate. In one child, the symptoms and neurohumoral activation were transiently improved by albumin infusion.

Pulmonary edema

As mentioned above, the pulmonary circulation has a greater baseline perm albumin and therefore a higher interstitial oncotic pressure of about 8 mm Table 16-1).[2,4,5] As a result, there is a larger safety factor

against edema due to hypoalbuminemia than that seen in skeletal muscle, s there can be a greater parallel decline in the interstitial oncotic pressure. the absence of a concurrent rise in left atrial and pulmonary capillary press pulmonary edema is not usually seen with hypoalbuminemia, even at a plas albumin concentration acutely low enough to induce peripheral edema.[43]

Kwashiorkor

Edema is common in the malnutrition syndrome kwashiorkor. This complicat been ascribed to hypoalbuminemia, but the preceding discussion casts doul hypothesis. As an alternative, it has been suggested that increased genera cysteinyl leukotrienes may be of primary importance in the edema of kwash

increasing capillary permeability.[44]

Renal Sodium Retention

The retention of fluid by the kidney in edematous states results from one o basic mechanisms. In some patients, the primary problem is an inability to e the Na^+ and water that have been ingested. This most often occurs in patien renal disease, such as the nephrotic syndrome or glomerulonephritis, as no above.[33,36,37] More commonly, renal fluid retention is an *appropriate compensatory response* to effective arterial or circulating volume depletion, with the urine Na^+ concentration often being less than 25 mEq/L (Fig. 16-1).[45,46] As reviewed in detail in Chap. 8, the effective circulating volume is an unmeasurable entity that re the pressure that is perfusing the arterial baroreceptors, such as those in t sinus and glomerular afferent arterioles.[46] In most instances, the effective circulati volume is directly proportional to the cardiac output. Thus, when the cardia is reduced because of underlying cardiac disease, the kidney attempts to re effective circulating volume by retaining Na^+ and water.

However, effective tissue perfusion and the cardiac output are not always r since the former can also be reduced by a decrease in peripheral vascular resistance.[46] For example, creation of an arteriovenous fistula is associated initial change in cardiac output, yet tissue perfusion is reduced since the b flowing through the fistula is bypassing the capillary circulation. In respons hemodynamic change, the kidney retains Na^+ and water, thereby increasing the blood volume and cardiac output.[47] The new steady state is characterized by a cardiac output that exceeds the baseline level by an amount equal to the fl through the fistula.

A common clinical correlate of this experiment occurs in patients with cirrho ascites, who frequently have an elevated cardiac output.[48] Despite this, they behave as if they were volume-depleted, as evidenced by avid renal Na^+ retention[49] and a progressive rise in secretion of the *hypovolemic hormones* renin, norepinephrine, and antidiuretic hormone (ADH)[46,50,51] and K^+.[52]

The disparity between the high cardiac output and the renal and neurohumo responses in cirrhosis is due both to splanchnic vasodilatation and to the p of multiple arteriovenous fistulas throughout the body, such as spider angio the skin; the net effect is a marked fall in systemic vascular resistance

and a reduction in systemic blood pressure.[46,53] Much of the cardiac output is circulating ineffectively, as there is a progressive reduction in renal and ev musculocutaneous perfusion.[53] (See "Cirrhosis," below, for a discussion of the possible pathogenesis of these hemodynamic changes.)

The renal Na^+ and water retention seen in heart failure or advanced cirrhosis from both a hypovolemia-induced fall in glomerular filtration rate (GFR) and more importantly, an increase in tubular reabsorption. The latter may occur

throughout the nephron, as enhanced proximal, loop, and collecting tubular reabsorption all may occur with effective volume depletion.[54,55,56,57,58,59] and[60] The initial decline in effective circulating volume primarily affects the distal as collecting tubular Na^+ reabsorption is enhanced, a response that is largely mediated by an increase in the secretion of aldosterone (and perhaps a reduced the release of natriuretic peptides).[54,61] As the disease progresses, proximal reabsorption is also stimulated,[54] probably as a result of increased levels of angiotensin II and renal sympathetic neural tone.[61,62]

The compensated state

Although the renin-angiotensin-aldosterone system undoubtedly contributes to Na^+ retention in disorders such as heart failure and cirrhosis, the plasma renin is normal in some patients with these disorders.[63,64] A partial explanation for this seemingly paradoxical finding is that the patient has entered a *compensated state* in which the initial fluid retention has increased venous return to the heart, thus allowing systemic hemodynamics to be stabilized (at least in the resting state) by removing the stimulus for continued renin release.[61,63]

This sequence is depicted in Fig. 16-5, which shows the changes that occur with chronic thoracic inferior vena cava constriction, an experimental model that mimics the changes seen in heart failure in humans.[61] The new steady state seen after 6 to 7 days is characterized by plasma volume expansion but normalization of the systemic blood pressure, urinary Na^+ excretion, and renin and aldosterone release.

In many patients, however, stable heart failure is associated with a persistent reduction in cardiac output, and it is not clear why the plasma renin activity is not to be normal.[63] One possible explanation is that circulating renin may not reflect the degree of activation of tissue renin-angiotensin systems (see Chapter 30). Studies in animals with congestive heart failure, for example, have shown that there is persistent, hypoperfusion-induced activation of the *intrarenal* renin-angiotensin system even though the plasma concentrations of renin and angiotensin II are elevated.[65]

Summary

The development of edema requires both an alteration in capillary hemodynamics (favoring fluid movement into the interstitium) and renal Na^+ and water retention. When the former predominates (as with major venous obstruction), there is a fall in the plasma volume. Edema then occurs because the compensatory retention of Na^+ and water by the kidney permits the plasma volume to be

maintained at near normal levels, while much of the excess fluid accumulates in the interstitium (Fig. 16-1).

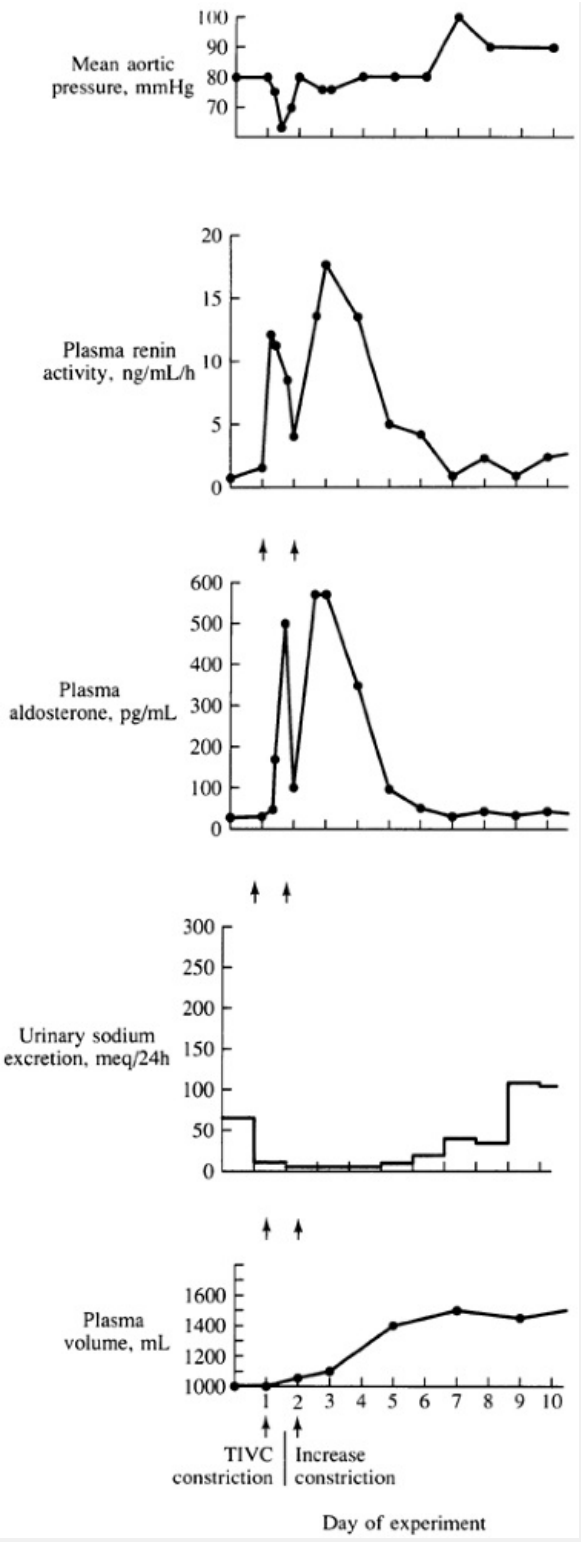

Figure 16-Sequential changes in mean aortic pressure, plasma renin activ plasma aldosterone concen-tration, urinary sodium excretion, and plasma in a dog with moderate thoracic inferior vena cava constriction. There is i hypotension, activation of the renin-angiotensin-aldosterone system, and marked reduction in urinary Na^+ excretion. By day 7, how-ever, a new steady state is achieved in which renin and aldosterone levels and Na^+ excretion have returned to baseline levels. The associated plasma volume expansion is responsible for restoring venous return to the heart, thereby allowing sys

hemodynamics to be normalized. *From (Watkins L Jr, Burton JA, Haber E, et al J Clin Invest 57:1606, 1976, by copyright permission of the American Societ for Clinical Investigation.)*

However, *generalized edema will not develop if Na+ retention is prevented by eliminating Na+ from the diet.* In this setting, the initial movement of fluid into t interstitium will significantly reduce the plasma volume. This will decrease arterial and venous pressures and consequently the capillary hydraulic pre thereby diminishing further fluid entry into the interstitium.

Similar considerations apply to heart failure and cirrhosis, which also repre conditions of effective circulating volume depletion. In these disorders, hov there is plasma volume expansion, because fluid retention is stimulated not in plasma volume but by a primary reduction in either cardiac output or sys vascular resistance (due primarily to splanchnic vasodilatation), respective

SYMPTOMS AND DIAGNOSIS

A complete discussion of the many diseases that can produce heart failure, or the nephrotic syndrome and the methods used in their diagnosis is beyor scope of this chapter. The mechanism of edema formation and treatment of individual disorders will be discussed in the next section. It is useful, howe review the general findings of physical examination that can aid in establis proper diagnosis. Three factors are of particular importance (Table 16-3):

- The *pattern of distribution of edema*, which reflects those capillaries with altered hemodynamic forces
- The *central venous pressure*
- The presence or absence of *pulmonary edema*

Pulmonary Edema

Patients with pulmonary edema complain primarily of shortness of breath ar orthopnea. Chest pain also may be a prominent symptom when pulmonary e

is due to an acute myocardial infarction. Physical examination usually reve tachypneic, diaphoretic patient with wet rales on auscultation of the chest possibly gallop rhythms and heart murmurs. The diagnosis should be confir chest x-ray, since other disorders that require different therapy may produc findings.

Table 16-3 Physical findings in major edematous states

Disorder	Pulmonary	Central venous	Ascites and/or

	edema	pressure	pedal edema
Left-sided heart failure	+	Variable	—
Right-sided heart failure	—	↑	+
Hepatic cirrhosis	—	↓-N1	+
Renal disease	Variable	↑	+
Nephrotic syndrome	—	Variable	+
Idiopathic edema	—	↓-N1	+

Although cardiac disease is the most common cause of pulmonary edema, it be produced by those disorders associated with primary retention or the acute respiratory distress syndrome (ARDS). If the correct diagnosis canno established from the history, physical examination, and laboratory data, me of the pulmonary capillary wedge pressure can be extremely helpful. The w pressure exceeds 18 to 20 mmHG when pulmonary edema is due to heart di primary renal Na^+ retention,[66] but is relatively normal in the setting of increased capillary permeability in the acute respiratory distress syndrome.[67]

In contrast to cardiac and renal disease, uncomplicated cirrhosis is not ass with pulmonary edema. The postsinusoidal obstruction in this disorder lead selective increases in venous and capillary pressures *below the hepatic vein* and to a normal or reduced blood volume in the cardiopulmonary circulation.[68,51]

Peripheral Edema and Ascites

In comparison to the potentially life-threatening nature of pulmonary edema peripheral edema and ascites are cosmetically undesirable but produce less symptoms. These include swollen legs, difficulty in walking, increased abdo girth, and shortness of breath due to pressure on the diaphragm in patients tense ascites.

Peripheral edema can be detected by the presence of pitting after pressure applied to the edematous area. Since peripheral edema locates preferential dependent areas, it is primarily found in the lower extremities in ambulatory and over the sacrum in patients at bed rest. Ascites, on the other hand, is with abdominal distention and shifting dullness and a fluid wave on percuss abdomen. Patients with the nephrotic syndrome may also have prominent pe

edema due to the low tissue pressure in this area.

The distribution of edema and estimation of the central venous pressure ca the differential diagnosis of heart failure, cirrhosis, primary renal Na^+ retention, a the nephrotic syndrome (Table 16-3).[69] This is particularly important in some patier with chronic right-sided heart failure, in whom the cardiac disease can leac cirrhosis (due to chronic passive congestion of the liver) and hemodynamic mediated proteinuria, which on rare occasions can approach the nephrotic r

Heart failure

Patients with right-sided heart failure have peripheral edema and, in severe ascites and edema of the abdominal wall. Shortness of breath is commonly and may be due to underlying pulmonary disease or coexistent

left ventricular failure. The edema in these disorders is due to an increase pressure behind the right side of the heart. Thus, the pressures in the righ and subclavian vein are elevated, changes that can be detected by estimati jugular venous pressure or by direct measurement with a central venous pr catheter.[51,68]

Cirrhosis

Cirrhotic patients can develop ascites and then edema in the lower extremit because of an increase in venous pressure below the diseased liver. As a r venous pressure above the hepatic vein—i.e., in the vena cava, jugular vei right atrium—usually is reduced or normal, not elevated as in right-sided heart failure. One exception to this general rule can occur in patients with tense whom upward pressure on the diaphragm can increase the intrathoracic pre Although elevated initially in this setting, the central venous pressure rapic normal following the removal of a small amount of ascitic fluid, which subst reduces the intraperitoneal pressure.[68]

A portal pressure >12 mmHg appears to be required for fluid retention in pa with cirrhosis; neither ascites nor edema is seen in patients without portal hypertension.[70,71] The presence of other signs of portal hypertension, such a distended abdominal wall veins and splenomegaly, also is suggestive of pri hepatic disease. However, these findings are not necessarily specific, sinc right-sided heart failure can produce hepatic injury.

The potential difficulties in distinguishing between primary hepatic and car disease can be illustrated by the following example.

Case History 16-1

A 56-year-old man has a 3-year history of ascites, which now requires remo to 4 liters of ascitic fluid by paracentesis every 3 weeks. The patient has b that he has cirrhosis, although a liver biopsy has not been performed. He h history of hepatic disease and is only a social drinker. The physical examin reveals no acute distress, a soft abdomen with marked ascites, and modera

edema. The heartbeat is irregularly irregular. The heart sounds are distant murmurs are heard. Several spider angiomata are present. The estimated ju venous pressure is greater than 15 cm H_2O.

The electrocardiogram shows arterial fibrillation and low voltage. There is proteinuria by dipstick; the plasma albumin concentration is 2.9 g/dL; and t function tests are mildly abnormal.

Comment

Despite the features suggestive of cirrhosis, the elevated jugular venous p the absence of tense ascites pointed toward right-sided heart failure. The c venous pressure was measured directly and found to be 21 cm H_2O (normal is 1 to 7 cm H_2O). Further evaluation confirmed the diagnosis of constrictive pericard pericardiectomy, the patient had a

complete recovery, including reversal of the liver function abnormalities an proteinuria.

Primary renal sodium retention

The physical findings associated with primary renal Na^+ retention are similar to those seen with biventricular failure: Both pulmonary and peripheral edema present and the jugular venous pressure should be elevated, since these pa are truly *volume-expanded*. An abnormal urinalysis (particularly if there are sign active renal disease, such as red cell casts) will usually distinguish underl disease from heart failure. However, this differentiation may be difficult in patients, since cardiac disease can produce both renal insufficiency (due t diminished renal perfusion) and proteinuria.[69] In this setting, the diagnosis may be established by the presence of normal cardiac function by echocardiograph

Nephrotic syndrome

Patients with the nephrotic syndrome typically present with periorbital and edema and occasionally ascites. The central venous pressure is usually no high-normal in the nephrotic syndrome, a reflection of the primary role of re Na^+ retention in most patients. However, as described above, some patients hav underfilling, which should be associated with a low central venous pressure.[38,41,42]

The diagnosis of the nephrotic syndrome can be confirmed by documenting presence of both heavy proteinuria (usually greater than 3 g/day) and hypoalbuminemia. Lipiduria and hyperlipidemia are also seen in many patie former reflects the abnormal glomerular filtration of large lipoprotein molec the latter reflects both increased hepatic lipoprotein synthesis (induced by plasma oncotic pressure) and decreased clearance of triglycerides.[72]

Other

Patients with idiopathic edema behave as if they were volume-depleted bec the exaggerated fall in the plasma volume in the erect position and the con

use of diuretics (see "Idiopathic Edema," below). As a result, they have peripheral edema, but the central venous pressure is normal or low-normal and pulmonary edema does not occur.

In addition to the above disorders, edema may result from local changes in hemodynamics. For example, a patient with a postphlebitic syndrome after an episode of thrombophlebitis may develop *unilateral* pedal edema due to an increase in venous pressure that is limited to that extremely. This is different from the generalized edematous states, in which bilateral edema should be present.

ETIOLOGY AND TREATMENT

General Principles of Treatment

Before discussing the therapy of the specific edematous disorders, it is important to consider the following questions that apply to all edematous states:

1. When must edema be treated?
2. What are the consequences of the removal of edema fluid?
3. How rapidly should edema fluid be removed?

When must edema be treated?

Pulmonary edema is the only form of generalized edema that is life-threatening and demands immediate treatment. In all other edematous states, the removal of the excess fluid can proceed more slowly, since it is of no danger to the patient. This is particularly true in cirrhosis, where hypokalemia, metabolic alkalosis, and renal shifts induced by diuretics can precipitate hepatic coma or the hepatorenal syndrome (see "Cirrhosis and Ascites," below).

What are the consequences of the removal of edema flu

As described above, the retention of Na^+ and water by the kidney in heart failure, cirrhosis, and capillary leak syndromes is *compensatory* in that it acts to raise the effective circulating volume toward normal (Fig. 16-1). In comparison, fluid accumulation is *inappropriate* with primary renal Na^+ retention, where the effective circulating volume as well as the total extracellular volume is expanded.

If the retention of edema fluid is compensatory, *removal of the fluid with diuretics should diminish the effective circulating volume.* To the degree that the fluid lost by diuresis comes from the plasma volume, there will be a decrease in venous return to the heart and therefore in the cardiac filling pressures. From the Frank-Starling relationship (Fig. 16-6), this reduction in the left ventricular end-diastolic filling pressure (LVEDP) should lower the stroke volume in both normal and failing hearts, possibly resulting in a fall in cardiac output and consequently in perfusion.

There is a great deal of evidence that this sequence occurs commonly in edematous states. First, the administration of diuretics to patients with either acute or

heart failure frequently leads to a reduction in cardiac output.[73,74] and[75] A similar sequence can occur in cirrhosis, particularly in patients who are rapidly diuresed.[76,77] Second, diuretic-induced fluid removal decreases *increased secretion of the three "hypovolemic" hormones*—renin, norepinephrine, and ADH—in many patients with heart failure or cirrhosis.[49,77,78]

Despite the reduction that may occur in the effective circulating volume, *most patients benefit from the appropriate use of diuretics.* As an example, the diminished exercise tolerance and symptoms of pulmonary congestion in patients with l failure are often improved by diuretic therapy, even though the cardiac outp fall by an average of 20 percent.[74] This observation suggests that small reductio in the cardiac output can be well tolerated. Similarly, relief of symptoms of and bloating are common in patients with noncardiac causes of edema.

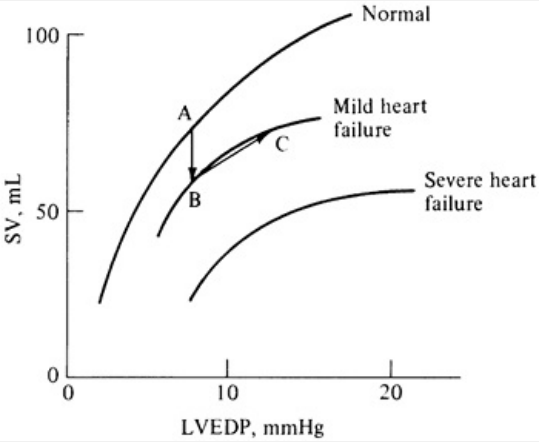

Figure 16-5 Frank-Starling curves relating stroke volume (SV) to left ventri end-diastolic pressure (LVEDP) in normal subjects and patients with heart failure. The onset of mild heart failure results in an initial reduction in ca function (middle curve, point B), a change that can initially be normalized raising the LVEDP via renal fluid retention (point C). In comparison, norm of stroke volume is not attainable with severe heart failure. (*Adapted from Cohn JN*, Am J Med *55:131, 1973, with permission*)

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However, the decrease in the effective circulating volume is sufficient to si impair tissue perfusion in selected cases. This occurs most commonly in tw settings:

1. When there is a low baseline effective circulating volume, as in severe failure
2. After the excessive or overly rapidly use of diuretics[76]

The adequacy of tissue perfusion can be estimated simply by monitoring th urea nitrogen (BUN) and plasma creatinine concentrations. *Although these*

parameters remain constant, it can be assumed that diuretic therapy has n
a significant impairment in perfusion to the kidney or, therefore, to other c

Otherwise unexplained significant elevations in the BUN and plasma creatir concentration after diuretic therapy indicate that *further fluid removal should be avoided* and that other therapeutic measures aimed at improving the underly disease should be attempted. The decline in tissue perfusion in this setting lead to weakness, fatigue, postural dizziness, and lethargy and confusion d decreased cerebral blood flow. These problems can be illustrated by the fo example.

Case History 16-2

A previously well 46-year-old man is admitted to the hospital with pulmonar due to an acute myocardial infarction. As part of his initial therapy, he is gi intravenous furosemide and then continued on an oral furosemide dose of 4 The pulmonary edema rapidly clears, and the patient is having an uneventfu recovery when it is noted on the tenth hospital day that his BUN has risen mg/dL on admission to 110 mg/dL and his plasma creatinine concentration h increased from 1 to 4.5 mg/dL. There has been a 6-kg weight loss since ad

The physical examination reveals that the patient is in no acute distress. T signs show a small reduction in blood pressure since admission. The

chest is clear to percussion and auscultation, and there are no murmurs or on cardiac examination. Estimated jugular venous pressure is less than 5 c H_2O, there is no peripheral edema, and the skin turgor is diminished.

Examination of the urine reveals a normal sediment, no proteinuria, a urine Na^+ concentration of 2 meq/L, and a urine osmolality of 550 mosmol/kg.

Comment

There are many signs in this patient pointing toward volume depletion seco *excessive diuresis* as the cause of the acute renal failure. These include weig loss, decreased skin turgor, low central venous pressure, a low urine Na^+ concentration and high urine osmolality, and an increase in BUN out of prop the elevation in the plasma creatinine concentration. This previously well p presented with a normal extracellular volume, a small quantity of which had translocated into the alveoli. Thus, continued fluid removal in this setting r to extracellular volume depletion.

Diuretic therapy was discontinued and the patient was given a high-sodium being carefully observed for the recurrence of heart failure. After 6 days of regimen, his skin turgor, BUN, and plasma creatinine concentration had ret normal.

However, a reduction in the effective circulating volume in response to diur therapy is not always due to overdiuresis. This can be illustrated by the fol case history.

Case History 16-3

A 64-year-old woman with chronic congestive heart failure due to atherosc heart disease is admitted to the hospital. In addition to pulmonary edema, s has signs of right-sided heart failure, including distended neck veins and p edema. After 3 days of diuretic therapy, there has been a 5-kg weight loss marked clinical improvement, although a mild degree of pulmonary congesti persists. During this period, the BUN has risen from 20 to 60 mg/dL, with a in the plasma creatinine concentration from 1.2 to 2.3 mg/dL. The urinary fi are similar to those in Case History 16-2.

Comment

This case represents another example of reduced tissue perfusion due to d therapy. However, edema persists. Thus, this patient has such severe heart that she cannot both be edema-free and have a stable plasma creatinine concentration on diuretic therapy alone. As shown in Fig. 16-6, the stroke volume can vary directly with the LVEDP even in severe heart failure. In this patien cardiac output was better maintained only at filling pressures so high that t caused both pulmonary and peripheral edema. When the filling pressures w reduced to a degree sufficient to diminish the edema, the cardiac output an perfusion were sacrificed.

In contrast to the adverse hemodynamic changes that may be seen in heart cirrhosis, or some cases of the nephrotic syndrome, impaired renal perfusio not occur after the appropriate use of diuretics in patients with primary ren retention (Table 16-2). In these conditions, the effective circulating volume is increased by fluid retention. Although diuretics reduce the effective circula volume, it will be from an initially high level back toward normal.

As noted above, localized edema due to lymphatic obstruction, deep vein th or hypothyroidism should *not* be treated with diuretics. Edema in these settings cannot be mobilized by a diuresis-induced reduction in venous pressure. As diuretic therapy will predictably lead to volume depletion. Similar considera apply to malignant ascites due to peritoneal carcinomatosis.[79]

How rapidly should edema fluid be removed?

When diuretics are administered, the fluid that is lost initially comes from t This results in a reduction in the venous pressure and consequently in cap hydraulic pressure, thereby promoting restoration of the plasma volume by mobilization of edema fluid into the vascular space. The rapidity with which occurs is variable. In patients with generalized edema due to heart failure, nephrotic syndrome, or primary renal Na^+ retention, the edema fluid can be mobilized rapidly, since most capillary beds are involved. Thus, removal of 2 to 3 lite edema fluid or more in 24 h can often be accomplished in such patients wit edema without much reduction in the plasma volume.

One important exception occurs in patients with cirrhosis and ascites but *no* *peripheral edema*.[76,77] In this setting, the excess ascitic fluid can be mobilize

via the peritoneal capillaries. Direct measurements have indicated that 500 mL/day is the maximum level that can be safely achieved by most patients. If diuresis proceeds more rapidly, the ascitic fluid will be unable to completel the plasma volume, resulting in azotemia and the possible precipitation of t hepatorenal syndrome (Fig. 16-7). This limitation does not apply to patients who have peripheral edema, since the rate of fluid mobilization is again relative unlimited in this setting.

Heart Failure

Heart failure can be produced by a variety of disorders, including coronary disease, hypertension, the cardiomyopathies, valvular disease, and cor pul The edema in the different causes of heart failure is due to an increase in pressure that produces a parallel rise in capillary hydraulic pressure. Desp similarity in pathogenesis, the *site of edema accumulation* is variable and is dependent upon the nature of the cardiac disease.

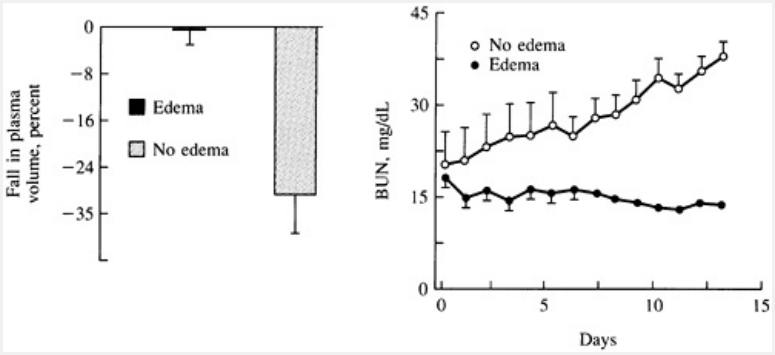

Figure 16-7 Change in plasma volume (left panel) and BUN (right panel) following diuretic-induced fluid loss of over 1 L/day in patients with cirrho or without peripheral edema. A limited rate of ascites mobilization in the l patients resulted in plasma volume depletion and progressive azotemia. T problems did not occur when peripheral edema was present. (*From Pockros PJ, Reynolds TJ, Gastroenterology 90:1827, 1986. Copyright 1986 by The America Gastroenterological Association*)

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- Coronary or hypertensive heart disease tends to preferentially impair le ventricular function. As a result, patients with one of these disorders ty present with pulmonary but not peripheral edema.
- Cor pulmonale, in comparison, is initially associated with pure right ver failure, resulting in prominent edema in the lower extremities and perha ascites.
- Cardiomyopathies tend to produce equivalent involvement of both the ri left ventricles, often leading to the *simultaneous onset* of pulmonary and peripheral edema.

In acute pulmonary edema due to a myocardial infarction or ischemia, the le ventricular disease results in elevation in left ventricular end-diastolic and pressures, which are transmitted *backward* through the pulmonary veins to the pulmona capillaries. In general, the pulmonary capillary pressure must exceed 18 to (normal equals 5 to 12 mmHg) before pulmonary edema occurs.[66,81]

The pathogenesis of edema formation is somewhat different in chronic hear In this setting, the increase in capillary pressure is a result of plasma volu expansion, not solely the obstructive effect of a diseased heart. This is cal *forward hypothesis* of heart failure, in which the primary event is a reduction i cardiac output (Fig. 16-8).[46,82,83] This decrease in tissue perfusion leads to activation of the sympathetic and renin-angiotensin systems, which have a cardiovascular and renal effects (see Chaps. 2 and 8).[84,85] Catecholamines, for example, stimulate both heart rate and cardiac contractility, changes that c return the cardiac output to normal, at least at rest. Norepinephrine and an II also cause both arteriolar constriction, which

can normalize the systemic blood pressure, and enhanced renal Na^+ reabsorption (which is in part due to angiotensin II–induced secretion of aldosterone).

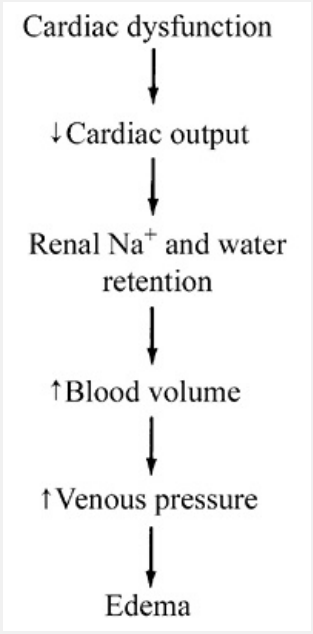

Figure 16-8 Forward hypothesis of heart failure in which a primary reductio cardiac output leads to fluid retention and edema.

The net effect in patients with relatively well-preserved cardiac function is mild impairment in Na^+ excretory ability. Edema is often absent at this time, un there is a high level of Na^+ intake.[88] With more advanced disease, however, forward output can be restored only by plasma volume expansion and intrac

filling pressures that are high enough to promote edema formation.

The effect of fluid retention on cardiac function is illustrated in Fig. 16-6. The upper curve represents the normal Frank-Starling relationship between stroke vol LVEDP, in which *increasing cardiac stretch enhances cardiac contractility*.[73,89,90] The development of mild cardiac failure (middle curve) will, if the sympathe stimulation of cardiac function is insufficient, lower both stroke volume and output (line AB). The ensuing retention of Na^+ and water retention can reverse these abnormalities, since the increments in plasma volume and LVEDP will augm cardiac contractility (line BC).

At this point, the patient is in a new steady state of *compensated heart failure* in which the stroke volume and cardiac output are normal, renal Na^+ excretion matches Na^+ intake, and the activity of the renin-angiotensin-aldosterone system has ret normal (Fig. 16-5).[61,63] The restoration of tissue perfusion in this setting has occurred only after there has been an elevation in the LVEDP, perhaps to a sufficient to produce pulmonary edema.

There are several points that deserve emphasis in this simple example of m moderate heart failure:

1. It demonstrates again the dual effects of fluid retention in edematous st beneficial increment in cardiac output and a potentially harmful elevatic venous pressure. The major increase in cardiac output occurs as the LV rises to 12 to 15 mmHg. There is little further effect on cardiac functior this level, but pulmonary edema becomes more likely.[81] These relationships have important implications for therapy (see "Treatment," below).
2. It illustrates that vascular congestion (that is, an elevated LVEDP) and cardiac output do not have to occur together in patients with heart dise point B, the patient is in a low-output state, but there is no congestion; C, the patient is congested but has a normal cardiac output.
3. The Frank-Starling relationship in Fig. 16-6 varies with exercise. Patients with moderate heart disease may have a normal cardiac output at rest but ma unable to increase the output adequately with even mild exertion.[91] This relative decrease in tissue perfusion can lead sequentially to further neurohumo activation, renal vasoconstriction and ischemia, Na^+ retention, and ultimately edema.[92,93] In this setting, limiting physical activity may produce substa improvement. Simply assuming the supine position for 1 to 2 h, for exan maximizes the cardiac output in relation to tissue needs. This can induc much as a 40 percent rise in glomerular filtration rate and a doubling of natriuretic response to a diuretic.[94]
4. Patients with mild to moderate heart disease may have no edema with d Na^+ restriction but may retain Na^+ and possibly become edematous if given a Na^+ load.[88] Suppose points A and C in Fig. 16-6 reflect the hemodynamic state

on a low-Na^+ diet. An increase in Na^+ intake will initially expand the intravascular volume and raise the LVEDP. In the normal subject (point A still on the ascending limb of the Frank-Starling curve, the increase in pressure will enhance stroke volume and cardiac output, which will ther the excretion of the excess Na^+. In contrast, a similar elevation in the LVEDP the patient with heart failure (point C), who is on a flatter part of the cu produce less of an increment both in cardiac output and consequently in excretion. Limiting dietary Na^+ intake in this setting may be sufficient to alle the edema.

The situation is somewhat different with severe heart failure (Fig. 16-6, flower curve). In this case, the plateau in stroke volume occurs earlier and at a lower leve mild heart failure, and increasing the LVEDP cannot normalize the stroke vo Two factors appear to account for this plateau. First, the heart may simply reached its maximum capacity to increase contractility in response to increa stretch.[95] Second, the Frank-Starling relationship actually applies to left ver end-diastolic *volume*, since it is the stretching of cardiac muscle that is respon for the enhanced contractility.[90] The more easily measured LVEDP is used clinica since, in relatively normal hearts, pressure and volume vary in

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parallel. However, cardiac compliance may be greatly reduced with severe l disease.[96] As a result, *a small increase in volume produces a large elevation i LVEDP* but no substantial stretching of the cardiac muscle and therefore litt change in cardiac output.[97]

Systolic versus diastolic dysfunction

The decrease in cardiac output that is initially seen in heart failure can occ of two mechanisms: *systolic dysfunction*, in which impaired cardiac contractility is the primary abnormality; and *diastolic dysfunction*, in which there is a limitation in diastolic filling and therefore in forward output due to increased ventricular Two factors may contribute to the latter problem: delayed postsystolic relax which may reflect impaired calcium efflux from the myocardial cells, and de ventricular compliance, which impairs ventricular filling during rate diastole.[93,94] Diastolic dysfunction is most often seen with hypertensive and less commor ischemic heart disease.[98,100]

The distinction between these two, not mutually exclusive types of heart fa be made by measurement of the ejection fraction with ultrasonography or radionuclide scanning. The ejection fraction will be normal (55 to 70 percen isolated diastolic dysfunction, since contractility is not impaired.[98,99,100] Establishing the correct diagnosis is important clinically, because each mec requires a different approach to therapy (see below).

Decreased diastolic compliance can also explain the development of "flash" pulmonary edema during an episode of ischemia. In this setting, lack of car distensibility during diastolic filling can result in a marked elevation in left

pressures and subsequent fluid movement into the alveoli. Some of these p not require chronic therapy for heart failure, since spontaneous or anatomi correction of the ischemic lesion can lead to restoration of normal cardiac function.[101,102 and 103] Recovery, however, may not be complete for several c to as long as 2 weeks, due to the phenomenon of the "stunned" postischem myocardium.[101,103,104]

Neurohumoral adaptation: initial benefit but long-term adverse effects

The reduction in tissue perfusion associated with progressive cardiac dysfu leads to increasing release of norepinephrine, renin, and ADH, all of which systemic and renal vasoconstrictors.[84,85,105,106 and 107] These neurohumoral changes, which begin before the onset of clinically evident congestion,[106] are initially beneficial, since they raise the cardiac output and systemic blood p toward normal. *Excessive* vasoconstriction is prevented in this setting by increa secretion of both renal vasodilator prostaglandins and atrial natriuretic pep (ANP);[85,107,108,109 and 110] renal ischemia and the elevation in atrial and ventricular pressures are the respective stimuli for the release of these hor (see Chap. 6).

The physiologic significance of prostaglandins in heart failure can be illust the response to a nonsteroidal anti-inflammatory drug, which blocks prosta synthesis. Removal of prostaglandin-induced vasodilation can lead to two deleterious effects in these patients: a decline in glomerular filtration rate,

since the vasoconstrictor actions of angiotensin II and norepinephrine are r unopposed; and a fall in cardiac output, due to the association rise in syste vascular resistance and therefore in cardiac afterload.[107]

An adverse response to a nonsteroidal anti-inflammatory drug is most likely when prostaglandin synthesis is enhanced—namely, in those patients with a heart failure in whom circulating angiotensin II and norepinephrine levels a likely to be elevated. The presence of *otherwise unexplained hyponatremia* is a good marker for patients at risk, since the combination of decreased renal and the associated rise in ADH release impairs the ability to excrete ingest water.[107]

The function of ANP in heart failure is less well defined. The chronic increa cardiac filling pressures leads to the release of ANP and brain natriuretic p (BNP) from the atria and, to a lesser degree, the ventricles (see Chaps. 6).[111,112,113 and 114] Both the cardiac and circulating levels of these hormone rise in parallel with the severity of the heart disease, even though the patie remain Na^+-avid and vasoconstricted.[112,113 and 114] It is possible that ANP and BNP play a modulating role in this setting, minimizing but not preventing th and renal effects, such as the degree of sodium retention and vasoconstric[109]

In addition to these peptides' possible physiologic role, measurement of pla

levels of ANP and BNP may be useful as a noninvasive marker of the prese mild left ventricular dysfunction, which is usually estimated by echocardiog radionuclide scanning.[112,113,114,115] and[116]

Long-term effects

Although neurohumoral vasoconstriction initially maintains circulatory hemo this response is clearly *maladaptive in the long term* because the failing heart has to pump against a higher resistance. The slowing of disease progression ar improvement in patient survival observed with use of angiotensin converting (ACE) inhibitors in patients with systolic dysfunction suggest that there is, a net negative effect of the neurohumoral adaptations of ventricular functio below).

Treatment: acute pulmonary edema

An extensive discussion of the treatment of acute pulmonary edema and chr heart failure is beyond the scope of this chapter. It is useful, however, to r those therapeutic modalities directed toward preventing edema accumulatio preserving normal renal function.

Acute pulmonary edema is a medical emergency requiring immediate therap restore tissue oxygenation and perfusion.[117] The initial regimen generally includes the administration of humidified oxygen via a face mask; intravenous morph which allays anxiety and induces venodilation, thereby diminishing venous lowering cardiac filling pressures; and an intravenous loop diuretic (such a furosemide) for fluid removal and for possible venodilation.[118] If these modalities are ineffective, intravenous nitroglycerin or intravenous nitroprusside can be a further reduce venous return.[119] The initial aim of therapy is to lower the pulmor capillary wedge pressure (if it is

being measured) to 15 to 18 mmHg, a level that is low enough to alleviate p edema but not so low as to further reduce the cardiac output.[81,120]

Patients with systolic dysfunction who remain in pulmonary edema despite t modalities may benefit from intravenous inotropic support to improve cardia performance and systemic perfusion. This is usually achieved by beta-agon therapy (e.g., dobutamine), a phosphodiesterase inhibitor (e.g., milrinone), both.[121,122]

Patients with acute pulmonary edema may also have severe acid-base distu such as respiratory and metabolic acidosis (primarily lactic acidosis).[123,124] Specific therapy may not be necessary, since reversal of the pulmonary ede usually sufficient to restore acid-base balance by improving gas exchange a allowing metabolism of the excess lactate into bicarbonate.[123,124]

Treatment: chronic heart failure

There are now five drugs that are often used in the treatment of chronic he due to systolic dysfunction. Two improve symptoms (digoxin and loop diuret

three improve survival (ACE inhibitors, beta blockers, if tolerated, and, in a heart failure, spironolactone). Important adjunctive measures include dietar restriction (1 to 2 g/day of sodium) and periods of rest. Some patients have output that is relatively normal at rest but does not increase adequately wit exertion.[91] It is during this latter period that renal Na^+ retention is most intense.[92,93] Thus, limiting physical activity may produce substantial clinical improvement, since maximizing tissue perfusion in relation to needs will ma Na^+ excretion.[94]

Loop diuretics

Diuretics (loop diuretics are usually used) have the advantage of directly r the excess fluid, thereby controlling the congestive symptoms (e.g., pulmon peripheral edema.[125,126] and[127] However, they do not reverse the impairment i cardiac function.

Other potential difficulties with diuretic therapy in heart failure are reviewe Chapter 15.[128] In some patients with marked edema, for example, impaired gastroint function (due to decreased perfusion or mucosal edema) can delay the abs and thereby minimize the efficacy of an oral loop diuretic; this defect can o reversed after a period of intravenous diuretic therapy. Even if drug deliver kidney is adequate, the associated increases in angiotensin II and aldoster enhance Na^+ reabsorption, thus diminishing the maximum diuretic response. I setting, the effective single dose [up to a maximum oral dose of 160 to 240 furosemide (only about one-half of which is absorbed) or 2 to 3 mg of oral intravenous bumetanide] may have to be given twice a day to induce an ade net diuresis.[128]

Loop diuretic therapy alone can also induce hypokalemia and hypomagnese which can predispose to serious arrhythmias. There is evidence that loop d may increase arrhythmic mortality, an effect that can be prevented by the c administration of a potassium-sparing diuretic.[129]

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Spironolactone

Administration of the potassium-sparing diuretic spironolactone, which com aldosterone for the mineralocorticoid receptor, significantly reduces mortal patients with advanced heart failure (Figure 16-9).[130] Two possible explanations for this benefit are that aldosterone has a deleterious effect on the failing hea maintaining a higher plasma potassium concentration is beneficial. The obs that non-potassium-sparing diuretics increase arrhythmic mortality in patien mild to moderate heart failure, an effect that can be prevented by a potassi sparing diuretic, suggests that hypokalemia plays at least a contributory ro[129] Based upon these findings, it has been suggested that spironolactone (25 t mg/day) may have a role in any stage of heart failure requiring diuretic the

Digoxin

Digoxin can improve cardiac performance, especially in patients with rapid fibrillation, in whom slowing of the ventricular rate allows better ventricular[131] Its long-term efficacy in patients with normal sinus rhythm is less predictab studies showed that stable patients treated with digoxin are much more like deteriorate if they are switched to placebo than if they are maintained on digoxin.[132,133] This symptomatic benefit (5 versus 27 percent worsening with placebo in one study) occurs even in patients already receiving an ACE inh[132]

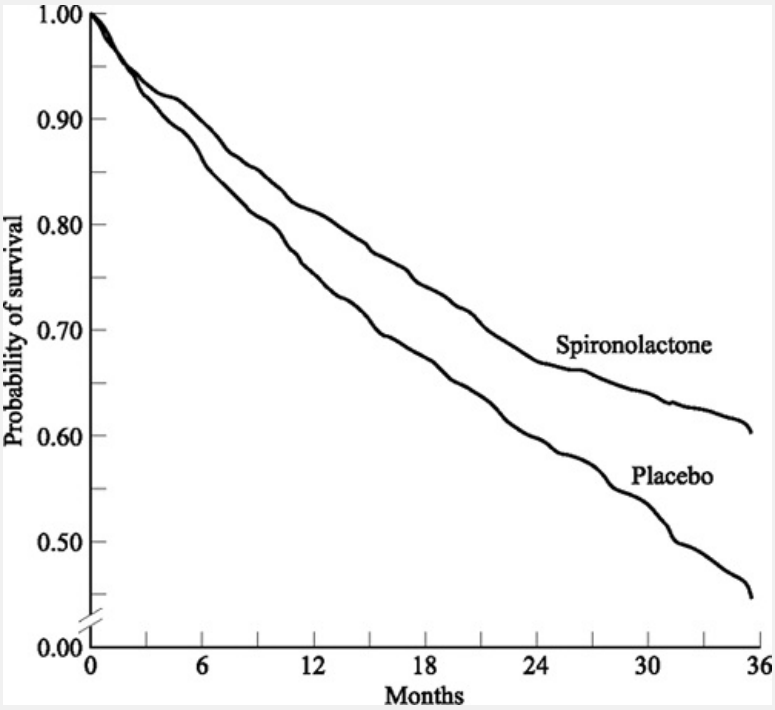

Figure 16-9 Spironolactone reduces mortality in heart failure. Kaplan-Meier analysis of survival among 1663 patients with advanced heart failure in th RALES trial shows that spironolactone reduces mortality by 30 percent (3 versus 46 percent for placebo, $p < 0.001$). *Redrawn from Pitt B, Zannad F, Remme WJ, et al, N Engl J Med 341:709, 1999, with permission.*

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The DIG (Digoxin Investigation Group) trial of almost 6800 patients is the d study of the effectiveness of digoxin.[134] Digoxin therapy was associated with symptomatic improvement, as shown by a reduction in the combined endpoi hospitalization for worsening chronic heart failure and mortality due to chro failure. However, there was no improvement in total survival with digoxin th (Fig. 16-10); the small improvement in death from worsening heart failure was counterbalanced by an apparent increase in arrhythmic death.

Digoxin is generally ineffective in those patients with heart failure who hav ventricular contractility. This problem may be seen with isolated diastolic d or with obstruction to flow in severe mitral stenosis.[100,135,136]

Vasodilators

Vasodilator therapy with an ACE inhibitor or the combination of hydralazine isosorbide dinitrate (HI) was the first pharmacologic approach shown to imp survival in patients with heart failure due to systolic dysfunction. Both can patient survival by decreasing progressive cardiac dysfunction and, in mild by diminishing the incidence of sudden death,[137,138] although a comparative study suggests that the benefit is more pronounced with the ACE inhibitors.[138]

The benefit of ACE inhibition has been demonstrated in the entire spectrum patients with heart failure, ranging from asymptomatic left ventricular dysfu[139] to mild to moderate heart failure,[137,138,140] to severe disease.[141] The selective angiotensin II–receptor antagonists appear to have an efficacy similar to th ACE inhibitors.[142]

Since ACE inhibitors produce more benefit than the direct vasodilators hydr and isosorbide dinitrate and since other oral vasodilators are less effective[143] mechanism of action of ACE inhibition probably involves more

than simply reducing afterload. One possibility is inhibition of the local intr renin-angiotensin system.[144] Such an effect may more efficiently reverse delete actions of angiotensin II on cardiac function. In addition, vasodilation-induc increases in the release of the vasoconstrictors angiotensin II and norepine are seen with HI but not with the ACE inhibitors.[145]

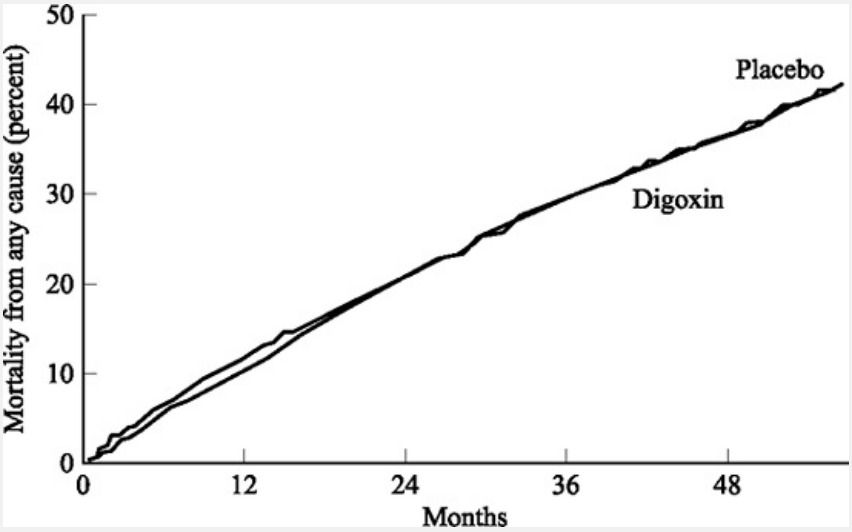

Figure 16-10 Digoxin has no effect on survival in heart failure. No differenc mortality was observed in patients with symptomatic congestive heart failu a low left ventricular ejection fraction (le 45 percent) who were randomize either digoxin or placebo. (*Redrawn from the Digitalis Investigation Group* Engl J Med *336:525, 1997, with permission*.)

Since ACE inhibitors increase cardiac output and renal blood flow, it might assumed that they would improve the glomerular filtration rate as well. How occurs in less than 10 percent of cases, while the plasma creatinine concer actually rises in about 30 percent of patients[146,147,148]. The latter complication is generally seen in the first week of therapy as angiotensin II acutely reduced.[146] It is most likely to occur in those settings in which mainte of the glomerular filtration rate is dependent upon high ambient angiotensir levels:[146,147,149] when there has been an excessive diuretic response, with LVEDP falling below 15 mmHg,[2] when the mean arterial pressure falls below 65 mmHg, and[3] when the pretreatment plasma $[Na^+]$ concentration is below 137 meq/L, which is a marker for marked neurohumoral activation.[107]

Thus, the mechanism of reversible renal insufficiency in this setting is simi seen in some patients with bilateral renal artery stenosis[42] or renovascular hypertension. Restoration of baseline renal function can often be achieved by lowering the diuretic do long-acting agent is used, possibly switching to captopril.[147,150] If this is unsuccessful, HI should be used, since these agents do not interfere with angiotensin II production and therefore are less likely to impair glomerular filtration.[47]

Beta blockers

Since beta blockers have negative inotropic activity, the presence of heart has been considered a contraindication to their use. However, an increasin of studies have demonstrated that at least some beta blockers (e.g., carved metoprolol, and bisoprolol) can lead to symptomatic improvement and impro survival in patients with heart failure.[151,152,153] and[154] Compared to those treated with placebo, patients treated with a beta blocker had an app 30 percent reduction in mortality during an average follow-up of 18 months.[154] Most patients in these trials were treated with ACE inhibitors, suggesting that be blockers provide an additive survival benefit.[151,152,153]

How beta blockers might act in this setting is not well understood. Among t proposed mechanisms are prevention of a toxic effect of the increased concentrations of circulating norepinephrine on the heart, a reduction in th concentration of vasoconstrictors, and upregulation of β-adrenergic receptors.[3]

It has been recommended that the beta blockers used in the above studies (carvedilol, metoprolol, and bisoprolol) be considered in patients with New Heart Association class II and III congestive heart failure (CHF) who have b stabilized on an ACE inhibitor, digoxin, and diuretics. An important concern many patients have a substantial period of worsening heart failure, often la 4 months, after the initiation of beta-blocker therapy.[155] This is more likely to occur in patients with advanced disease.

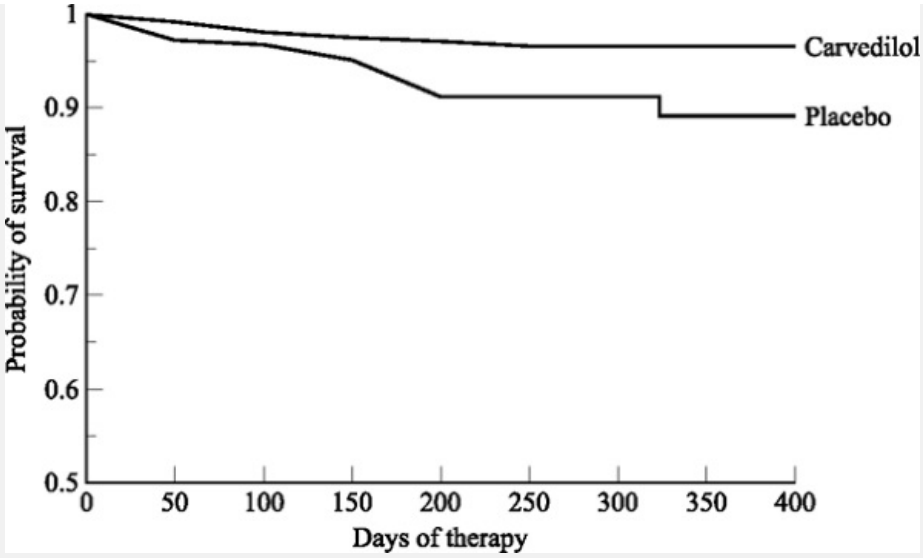

Figure 16-10 Carvedilol improves survival in heart failure. Among patients w CHF who were treated with digoxin, diuretics, and an angiotensin convert enzyme inhibitor, those randomized to carvedilol had significantly improve survival compared to individuals given placebo. (*Redrawn from Packer M, Bristow MR, Cohn JN, et al for the US Carvedilol Heart Failure Study Gro* Engl J Med *334:1349, 1996, with permission.*)

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Guidelines have been published for the safe initiation of this therapy.[156] It is particularly important that therapy be begun in *very low doses* and the dose doubled at weekly intervals until the target dose is reached or symptoms become limiting. Initi target doses are 3.125 mg bid and 25 to 50 mg bid (the higher doses being subjects over 85 kg) for carvedilol, 6.25 mg bid and 50 to 75 mg bid for me 12.5 or 25 mg daily and titrated up to 200 mg/day for therapy with extended metoprolol, and 1.25 mg qd and 5 to 10 mg qd for bisoprolol. Dose increase generally made at 2-week intervals. Even lower starting doses should be gi patients with recent decompensation of a systolic pressure below 85 mmHg effort should be made to achieve the target dose, since the improvement ap be dose-dependent. It is recommended that such therapy be initiated under consultative guidance of a heart failure center that has experience with this

Cor Pulmonale

The pathogenesis of edema in cor pulmonale due to chronic obstructive pul disease is different from that in other forms of heart failure. In this disorde cardiac output and GFR are usually normal or near normal both in the resti and with exercise,[157,158] and[159]

Edema seems to occur almost exclusively in patients with hypercapnia, sug that the high P_{CO_2} rather than cardiac dysfunction may be responsible for Na^+ retention in this disorder.[159] Hypercapnia is associated with an appropriate incr in proximal HCO_3^- reabsorption, which serves to minimize the fall in arterial pl

Chap. 21). This increase in proximal HCO_3^- transport, which occurs via Na^+-H^+ exchange, may be responsible for edema formation in cor

pulmonale, since it also promotes the reabsorption of NaCl and H_2O (see page 783).

Another contributing factor to sodium retention may be hypoxemia. Hypoxen cause renal vasoconstriction, leading to a reduction in urinary sodium excr[160]

Therapy of edema in cor pulmonale consists of improving pulmonary functio possible) and the use of diuretics. Correction of hypoxemia, with continuou oxygen if necessary, also may be helpful. As in other edematous states, the plasma creatinine concentration should be monitored during diuretic therap further fluid removal being deferred if renal function deteriorates. In additi diuretic-induced metabolic alkalosis should be avoided, since the rise in ex pH can further depress net alveolar ventilation.[161] The carbonic anhydrase inhibitor acetazolamide may be particularly effective in this setting; it tends to produ $NaHCO_3$ diuresis, thereby correcting both the fluid overload and the alkalos Chap. 15).

Cirrhosis and Ascites

Ascites refers to the accumulation of fluid in the peritoneal cavity. It can be variety of conditions, including severe acute or chronic hepatic disease (pa cirrhosis), heart failure, the nephrotic syndrome, and with tumor implants o peritoneum. In the last condition, both lymphatic obstruction and increased permeability contribute to ascites formation.[79]

In patients with liver disease, the ascitic fluid is derived from the hepatic s and enters the peritoneum by moving across the hepatic capsule. The princ factor in the development of hepatic ascites is *sinusoidal obstruction* (du to fibrosis or hepatic venous occlusion), leading to an increase in the hydraulic press sinusoids.[70,162] A portal pressure >12 mmHg appears to be required for fluid retention in patients with cirrhosis; neither ascites nor edema is seen in pa without portal hypertension[70,71] or in those without sinusoidal hypertension (e.g portal vein thrombosis).

Hypoalbuminemia due to increased hepatic synthesis may also be present; not, however, play an important role in hepatic ascites, since the sinusoids normally freely permeable to albumin. Thus, the transcapillary oncotic pres gradient is normally very low and does not act to hold fluid in the vascular space.[2,25]

Mechanisms of ascites formation

The possible mechanisms responsible for fluid retention and ascites format cirrhosis are illustrated in Fig. 16-12. Impaired Na^+ excretion can be demonstrated early in the course of the disease, prior to the presence of clinically evider and despite normal renal function and appropriate suppression of renin secretion.[163,164] Similar findings can be demonstrated in experimental model

hepatic disease in which renal Na^+ retention precedes the development

of ascites.[165]

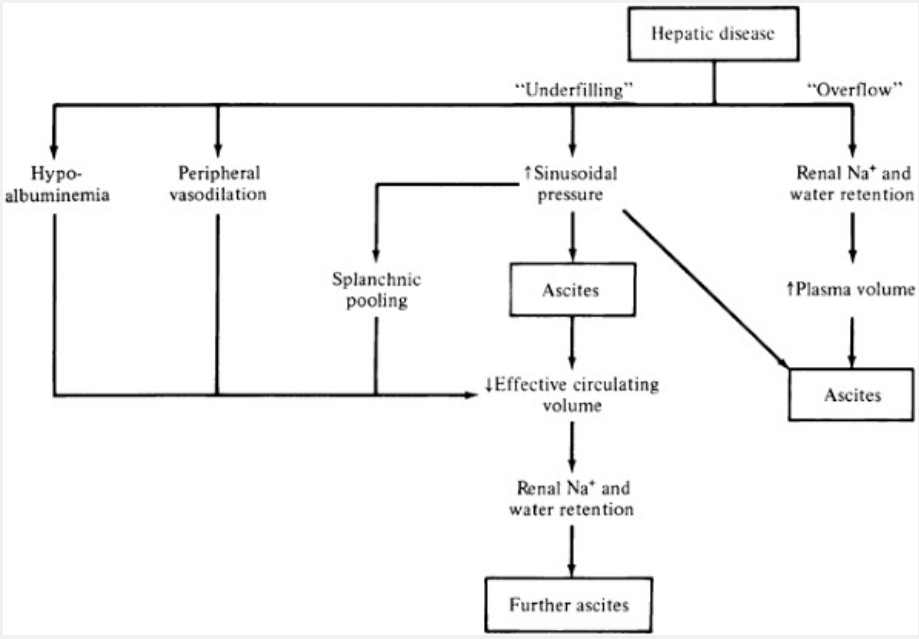

Figure 16-12 Underfilling and overflow theories of the pathogenesis of fluid retention and ascites formation in hepatic disease. In some patients, both mechanisms may be operative. In addition, the combination of increased f venous pressure (resulting from an ascites-induced elevation in intraperit pressure) and perhaps marked hypoalbuminemia can lead to peripheral ed

These observations have suggested that there might be an *overflow* initial phenomenon in which hepatic disease directly stimulates renal Na^+ retention independent of any change in systemic hemodynamics.[166,167] How this might occur is incompletely understood. Studies in experimental animals indicate that ir intrasinusoidal pressure, rather than portal venous pressure, is required.[167] This hemodynamic change may then activate a hepatorenal reflex, resulting in a elevation in renal sympathetic nerve activity.[168,169] The ensuing combination of a diminished renal perfusion and enhanced renal Na^+ reabsorption can then promote fluid retention.[168] The elevation in intrasinusoidal pressure promotes the accumul most of this excess fluid in the peritoneum.

It is likely, however, that effective circulating volume *underfilling* of the arterial circulation (rather than overflow) is primarily responsible for the sc retention in cirrhosis.[46,170] The earliest change appears to be a decrease in systemic vascular resistance due primarily to splanchnic vasodilatation.[46,170] In some experimental models, vasodilatation clearly precedes the onset of ren retention.[171]

A similar finding may occur in humans. When patients with cirrhosis and no edema are volume-expanded with a high-salt diet plus a mineralocorticoid, patients become progressively edematous and do not undergo aldosterone

escape (see page 185).[169] These patients, when compared to those who excret sodium normally, where already vasodilated, as evidenced by a much lower vascular resistance and a higher cardiac output.

The role of increasing splanchnic vasodilation in humans with progressive can be illustrated by the sequential changes in systemic and renal hemodyr that are seen in this disorder. Early in the course of the disease—stable ci ascites—the vasodilatory substances that affect the portal circulation also the kidney, and the glomerular filtration

rate may be as high as 50 percent above normal.[172] In addition to nitric oxide, vasodilator prostaglandins also may contribute to the glomerular hyperfiltra[173]

As the hepatic disease and splanchnic vasodilation become more severe, a progressive fall in systemic vascular resistance and blood pressure ensues alterations lead to increased renal and femoral vascular resistance (and re flow to these sites) that results in part from the hypotension-induced activa renin-angiotensin system.[53] The observation that the central blood volume (that volume present in the cardiopulmonary circulation and the arterial tree) is progressively reduced in cirrhosis is also consistent with a reduction in extrasplanchnic perfusion.[57]

The mechanism responsible for vasodilatation and the hyperdynamic circula cirrhosis are not well understood. Research has focused on *nitric oxide* (*NO*) and its role in splanchnic vasodilation in cirrhosis.[174] In cirrhotic rats, for example, inhibition of the synthesis of NO significantly increases the arterial pressu systemic vascular resistance, decreases the cardiac index,[175,176] and reverses the impaired response to vasopressors.[177,178] Although human studies are limited, th observation that serum levels of nitrite and nitrate, an index of in vivo NO are significantly higher in cirrhotic patients than in controls is also compat the NO hypothesis.[179]

The reason for enhanced NO production in cirrhosis is unclear. One mecha be that endotoxin absorbed from the gut is not normally inactivated in the l because of portal-systemic shunting. The ensuing endotoxinemia is a known to nitric oxide synthesis; increased release of cytokines also may play a co role.[174,180,181] Among patients with cirrhosis, support for this hypothesis is provided by the following observations:[180]

- Blood in the portal veins contains higher NO concentrations than blood peripheral veins.
- The oral administration of an antibiotic significantly reduces plasma lev

endotoxin, nitrite, and nitrate.

The importance of splanchnic vasodilatation–induced underfilling for the im in renal function in cirrhosis can also be demonstrated by the response to ornipressin, an analog of ADH. This vasoconstrictor acutely raises splanchr resistance, leading sequentially to an elevation in mean arterial pressure; r in the plasma renin activity and norepinephrine concentration; a decrease i vascular resistance; and elevations in renal blood flow, glomerular filtratior (from 18 to 29 mL/min in this study), and Na^+ excretion.[182] The therapeutic significance of this observation remains to be determined.

Indirect evidence of underfilling in cirrhosis has also come from studies of who are acutely volume-expanded by immersion to the neck in warm water (the hydrostatic pressure of the water on the lower extremities results in the translocation of fluid to the central cardiopulmonary circulation, as evidenced by the insertion of a peritoneovenous shut (in which ascitic fluid is reinfused internal jugular vein) or a transjugular intrahepatic portosystemic shunt (in low-resistance channel is created between the hepatic vein and the intrahe portion of the portal vein).[183,184,185] and[186] These modalities are often able to induce a marked natriuresis and a reduction in the plasma renin activity an norepinephrine concentration, all of which suggest improved tissue perfusic

The net effect, as described earlier, is that patients with advanced cirrhosi very low rates of Na^+ excretion (≤10 meq/day in some cases),[49] systemic blood pressure that is often below normal,[187] increased secretion of the three hypovolemic hormones (renin, norepinephrine, and ADH),[50,51,183] and a progressive decline in the glomerular filtration rate.[50,188]

Hepatorenal syndrome

The progressive hemodynamically mediated fall in GFR is, when clinically a called the hepatorenal syndrome.[190,191] and[192] This disorder is induced by intense renal vasoconstriction that is thought to reflect an imbalance betwe high level of vasoconstrictors and a relatively low level of protective renal vasodilators (such as prostaglandins and perhaps kinins). Studies in nonaz cirrhotics with ascites suggest that the approximate incidence of the hepatc syndrome is 18 percent at 1 year and 39 percent at 5 years.[193] An episode of gastrointestinal bleeding or infection may be a precipitating event, and pat highest risk are those with hyponatremia and a high plasma renin activity, s marked neurohumoral activation that reflect more severe effective circulatir depletion.[193] Progression to renal failure is typically associated with a fall ir arterial pressure, another indicator of increasing systemic vasodilatation.

The decline in GFR in patients with cirrhosis is usually *masked* because both urea and creatinine production are often markedly reduced due to the liver disea decreased muscle mass, respectively. As a result, some cirrhotic patients w plasma creatinine concentration within the “normal” range (1.0 to 1.3 mg/dL

glomerular filtration rate as low as 20 to 60 mL/min.[194,195] Recalculation of the creatinine clearance will partially overcome this problem, since the reductio creatinine production will be accounted for by a decline in creatinine excre However, the clearance value obtained will, because of

increased creatinine secretion, tend to overestimate the true GFR by as mu percent or more in patients with renal insufficiency.[195]

These renal manifestations of underfilling progress in parallel to the severi hepatic disease and may be prognostically important. For example, patients excretion below 10 meq/day or a plasma Na^+ concentration below 125 to 130 meq/L (indicative of impaired water excretion due in part to higher levels of ADH) mean survival time as low as 5 to 6 months, in comparison to over 2 years i with ascites but without these findings.[49,183] Mean survival in the hepatorenal syndrome is only a few weeks, with 90 percent of patients dying within 3 m[193]

In summary, underfilling appears to be of primary importance in the sodium seen in cirrhosis in humans.[46,170] Splanchnic vasodilatation, lowering both syste vascular resistance and the systemic blood pressure, may be the primary cl with increased hepatic sinusoidal pressure resulting in the preferential acc of the excess fluid in the peritoneum.

Vasodilator hormones

As in heart failure, the degree of renal vasoconstriction induced by angiote norepinephrine is initially minimized in cirrhosis by increased renal secretio vasodilator prostaglandins and kinins.[50,196,197] These hormones also may limit the degree of Na^+ retention, since prostaglandin E_2 and perhaps bradykinin appear to decrease tubular Na^+ reabsorption (see Chap. 6).

Treatment

The treatment of edema in cirrhosis varies with the severity of the disease.[162] Patients with mild to moderate disease usually have *a relative rate of Na^+ excretion of at least 40 meq/day and a relatively normal plasma Na^+ concentration*.[49,50,183] These findings are a reflection of the less severe state underfilling and therefore lower levels of renin and ADH. In this setting, the is restriction of sodium intake. An 88 meq (2000 mg) per day sodium diet is practical yet successful level of sodium restriction[198,199] that can be followed in an outpatient setting without the purchase of special food.

Water intake also may need to be restricted to about 1000 mL/day. As noted reduction in the plasma Na^+ concentration is a common problem in advanced disease, since the combination of progressive renal ischemia and increasin levels markedly limits the ability to excrete water.[50,183,200] These changes parallel the severity of the hepatic disease, and, as in congestive heart failure,[149]

hyponatremia is a marker for decreased patient survival.[200]

However, this diet alone will be effective only in the small subset of patien urinary sodium excretion is more than 78 meq/day (88 meq intake minus 10 nonurinary losses). Thus, most patients with cirrhosis and ascites will requ diuretic therapy. However, the use of diuretics in patients with cirrhosis is with several relatively unusual concerns, including the rate of fluid removal potential risk from the development of diuretic-induced hypokalemia and me alkalosis.

Rate of fluid loss

As described previously, the presence or absence of peripheral edema is ar important determinant of the rate at which fluid can be safely removed in ci After induction of fluid loss with a diuretic, peripheral edema can be mobili protect the plasma volume in a relatively rate-unlimited fashion; in compari patients can safely mobilize only about 300 to 500 mL of ascitic fluid per day.[76,77,80] As a result, more rapid fluid loss should be avoided in those pat who have *only ascites*, since it can lead to plasma volume depletion and azoter (Fig. 16-7). Furthermore, rapid diuresis is not necessary in this setting becau the absence of very tense ascites, the excess fluid is of no immediate dang patient.

The issue of fluid mobilization is even more important in patients with malig ascites due to peritoneal carcinomatosis or chylous malignant ascites. The induced lymphatic obstruction in this setting largely prevents mobilization o ascitic fluid.[79] Thus, even slow diuresis is likely to produce plasma volume de and azotemia unless the patient also has peripheral edema. Patients with m hepatic metastases appear to represent an exception to this general rule. T ascites in this condition is due to intrahepatic hypertension and can be trea similar fashion to cirrhotic ascites.[79]

Avoidance of hypokalemic alkalosis

Therapy with loop diuretics alone should be avoided in cirrhosis because s patients have *developed hepatic coma coincident with the onset of hypokalem alkalosis* and then awakened following no therapy other than KCl replacement.[201,202] Hypokalemia may promote the development of hepatic cor increasing ammonia (NH_3) production by the renal tubular cells,[203,204] thereby adding to the already high blood ammonia levels that are often present in s liver disease. This renal effect of hypokalemia appears to be mediated by a *transcellular cation exchange* in which K^+ leaves the cell (to replete the extracellular stores) and electroneutrality is maintained in part by the move extracellular H^+ ions into the cell; the ensuing intracellular acidosis is a poter stimulus to ammonia production (see page 341).

Concomitant metabolic alkalosis may also contribute to this problem. From Henderson-Hasselbalch equation for the ammonia/ammonium buffer system,

$$pH = 9.0 + \log \frac{[NH_3]}{[NH_4^+]}$$

an elevation in extracellular pH will tend to convert NH_4^+ into NH_3. The latter is lipid-soluble and can therefore diffuse down its concentration gradient into cells, thereby increasing the degree of cerebral dysfunction.

Diuretic regimen

Spironolactone, an aldosterone antagonist, is the diuretic of choice for the treatment of fluid overload in the setting of cirrhosis. It is more effective th furosemide alone in patients with more severe disease,[205,206] and it does not induce hypokalemia; to the contrary, this potassium-sparing diuretic

may induce hyperkalemia. Spironolactone, which can cause painful gynecor often more effective than amiloride, another potassium-sparing diuretic tha closes the aldosterone-sensitive luminal sodium channels in the collecting but produces a lesser diuresis in patients with marked hyperaldosteronism.[207]

The surprising finding that the normally weak diuretic spironolactone may b effective than a loop diuretic in cirrhotic ascites seems to be related to a s of drug excretion in the urine.[208] Most diuretics are highly protein-bound in the plasma and therefore enter the tubular lumen by secretion in the proximal t by glomerular filtration. This process appears to be impaired in cirrhosis as of the retention of substances such as bile salts, which may have a compet toxic effect on tubular secretion.[208] Spironolactone, in comparison, is the only commonly used diuretic that does not require access to the tubular lumen. I passively diffuses from the plasma into the cell across the basolateral mem then competitively inhibits the aldosterone receptor.[209]

The most successful therapeutic regimen is the combination of single morni doses of spironolactone and furosemide, beginning with 100 mg and 40 mg, respectively.[199,206] This combination in this ratio usually maintains normokale The doses can be doubled if a clinical response is not evident.

Massive ascites

Patients with ascites that is massive or symptomatic (such as shortness of impending rupture of an umbilical hernia) cannot easily be treated with diur therapy, given the recommendation of a maximum 300 to 500 mL/day net flu the absence of peripheral edema. Such patients are often treated with total paracentesis.

Paracentesis differs from diuretic therapy in three important ways: Fluid re easier to achieve, fluid is removed more quickly, and the risk of plasma vol depletion is related to the *rate of ascites reaccumulation* rather than the rate of fluid loss. It may also reduce intravariceal pressure and variceal wall tension, p reducing the risk of variceal bleeding.[210]

Total (or large-volume) paracentesis can be safely performed in patients wi

massive or tense ascites, resulting in *a shorter period of hospitalization and a lesser incidence of azotemia and electrolyte disturbances* when compared to therapy with diuretics alone.[211,212,213] and[214]

The need for colloid replacement after total paracentesis in an attempt to s ascites reaccumulation and therefore minimize effective circulating volume remains a controversial issue.[211,212,215] In a randomized trial, patients with tens ascites undergoing total paracentesis who received albumin (10 g/L of asci removed) were less likely to show signs of hemodynamic deterioration such increase in the plasma renin activity, worsening renal function, and/or seve hyponatremia.[212]

However, improved survival has not been proven, and it has not been possi identify patients in advance who may benefit.[215,216] In addition, the groups that use plasma expanders administer one-half of the expander at the end of the par and the remainder 6 h later; this converts an otherwise simple outpatient pr into an all-day visit or an overnight stay in the hospital. These factors,

as well as the cost and current shortage of albumin, make its routine use c difficult to justify.

Resistant ascites

A patient is not considered to be diuretic-resistant unless the individual is less than 78 meq of sodium (88 meq dietary intake minus 10 meq nonurinary excretion) per day while being administered diuretics at the doses recomme above.[216] Patients excreting more than 78 meq of sodium per day should be weight. If they are not, they are noncompliant with the diet and should visit dietitian again. Patients may also be considered diuretic-resistant if they d significant diuretic-related complications, such as progressive azotemia, he encephalopathy, or progressive electrolyte imbalance.

Diuretic-resistant ascites commonly occurs in association with advanced ci enhanced neurohumoral activation, and extremely low sodium excretion.[217,218] Neurohumoral activation causes renal vasoconstriction and enhanced sodiu reabsorption (in the proximal tubule and collecting tubules). Even in those resistant to diuretics, a greater degree of neurohumoral activation occurs i with diminished diuretic responsiveness.[205]

Progressive liver disease is the most common cause of the development of diuretic resistance in a patient previously sensitive to diuretics.[191,219] Two other complications of cirrhosis, hepatocellular carcinoma and portal vein thromb also underlie this development.

Three options exist for fluid control in diuretic-resistant patients: paracent insertion of a transjugular intrahepatic portosystemic shunt, and liver transplantation.[198,199,220] If there are no contraindications, the development c ascites in a previously compensated cirrhotic patient is an accepted indicat listing for liver transplantation. Patients who are first listed only after the

development of diuretic resistance may not live long enough to receive a ne
because of the organ shortage and long waiting times in the United States.

The role of serial total paracenteses in the treatment of recurrent tense as
less clear than that of paracentesis used as initial therapy. Most of these p
are noncompliant with their sodium-restricted diet and/or medications and a
masquerading as diuretic-resistant, preferring to have their ascites remove
than follow the diet and take their medications. The problem with this appro
that repeated paracentesis can cause protein and complement depletion co
diet/diuretic therapy and may indirectly predispose to ascitic fluid infection[216]

Intrahepatic and portal pressures can be lowered by insertion of a transjug
intrahepatic portosystemic shunt (TIPS). In approximately 75 percent of pat
refractory ascites, uncontrolled observations suggest that this modality lea
increase in urine output, a marked or complete reduction in ascites, and ce
diuretic therapy or the use of much lower diuretic doses.[221,222] However, a
randomized controlled trial that compared TIPS to paracentesis found a hig
mortality in the TIPS group (33 percent versus 17 percent).[223]

TIPS placement is also associated with a variety of complications, includin
encephalopathy (approximately 30 percent of patients).[224,225] Another

significant problem is early thrombosis or delayed shunt stenosis. Thus, en
for this technique has waned.

A peritoneovenous shunt, which drains into the internal jugular vein, reinfu
ascites into the vascular space and was popularized as a “physiologic” trea
resistant ascites (and of the hepatorenal syndrome). However, because of a
excessive rate of complications and no survival advantage compared with m
therapy, this procedure has been virtually abandoned.[226,227] Probably the only
indication for this technique is the rare patient with diuretic-resistant cirrh
who is not a candidate for transplantation and who has too many abdominal
scars to permit safe, successful paracentesis.[216]

Primary Renal Sodium Retention

Patients with normal cardiac and hepatic function may develop edema if the
primary renal abnormality preventing the excretion of Na^+ and water (Fig. 16-13).
This is most frequently seen with acute or chronic renal failure in which the
favors Na^+ retention. Patients with acute glomerulonephritis or the nephrotic
syndrome, for example, are particularly prone to develop edema. In these d
the glomeruli are diseased and the filtration rate is reduced, but tubular fu
initially normal. Thus, the kidney behaves as if it is underperfused and avid
reabsorbs Na^+,[228,229] particularly in the collecting tubules.[33,36,37] The net effect
is edema formation, suppression of renin release, high ANP levels, and frec
hypertension that is directly induced by volume expansion.[230,231] At a similar
degree of weight gain, patients with nephrotic syndrome have less suppres
renin release and less stimulation of ANP secretion than patients with acut

glomerulonephritis.[231] These observations suggest a smaller increase in plasm volume in the nephrotic syndrome, perhaps due to the low oncotic pressure "Nephrotic Syndrome," below).

Renal Na^+ handling may be somewhat different with chronic disease, as the glomerular injury is associated with secondary tubular dysfunction. As a res tendency to edema formation is reduced in some patients, because of an im in tubular Na^+ reabsorption.[228] Similar considerations apply to

primary tubulointerstitial diseases such as chronic pyelonephritis, in which Na^+ retention is unusual due to the predominant tubular damage.

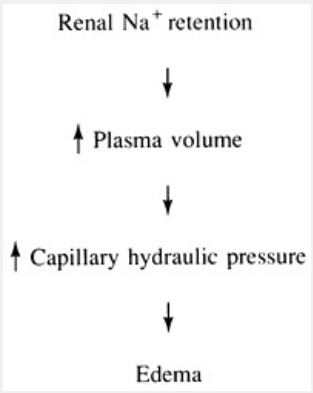

Figure 16-13 Pathogenesis of edema in primary renal Na^+ retention, which is most often due to glomerular disease, advanced renal failure, or the use potent vasodilators in the treatment of hypertension.

With advanced renal failure, however, the glomerular filtration rate falls to levels and Na^+ retention again becomes a problem. In this setting, there may very *narrow range in which Na+ balance can be maintained*, since the ability to acutely conserve Na^+ on a low-Na^+ diet is also impaired.[232] Thus, the optimal Na^+ intake to prevent both volume depletion and volume expansion must be emp determined.

Drugs

Certain drugs can enhance renal Na^+ reabsorption (Table 16-2). This is most likely to occur in patients with hypertension who are treated with *direct vasodilators*, such as minoxidil and diazoxide.[233][234] Patients treated with minoxidil, for example, o require therapy with high doses of a loop diuretic (such as 160 to 240 mg o furosemide) to prevent edema formation. Edema can also be induced by cal channel blockers, particularly the dihydropyridines. It is unclear, however, leakage out of the capillary due to dilatation of the precapillary sphincter o renal Na^+ retention is responsible for the edema.[235]

The mechanism by which these agents stimulate renal Na^+ retention is uncertain. The fall in blood pressure itself probably plays an important role via the pressure n phenomenon (see page 272). In addition, direct vasodilators also activate the re angiotensin-aldosterone and sympathetic nervous systems, both of which st Na^+ retention.[233,236] The ability of sympathetic agents to directly diminish re release and of ACE inhibitors to diminish angiotensin II production may ther explain why these drugs do not produce edema even though they lead to an equivalent reduction in blood pressure.

It has also been suggested that vasodilators may directly enhance Na^+ reabsorption.[233] However, two observations make this unlikely. First, the tenc to edema formation is directly related to vasodilator potency, with the effec minoxidil being greater than that of hydralazine and the effect of nifedipine greater than that of other calcium channel blockers.[234] Second, diazoxide produces Na^+ retention only if it is given systemically and lowers the blood pressure, is infused directly into the renal artery.[237]

Nonsteroidal anti-inflammatory drugs are widely used in the treatment of rheumatologic disorders and primarily act by inhibiting renal prostaglandin Since protaglandins maintain renal perfusion and may promote Na^+ excretion (see Chap. 6), decreasing their production can lead to Na^+ retention and edema.[238] Fluid retention is particularly likely to occur in patients with underling heart failu cirrhosis—conditions of effective hypovolemia in which the effect of prostag enhanced because high angiotensin II levels stimulate prostaglandin synthe

Fludrocortisone is a synthetic mineralocorticoid used in the treatment of hypoaldosteronism. Although this drug initially causes fluid retention, edem unusual because of the phenomenon of mineralocorticoid escape (see page 185). Estrogens (alone or in oral contraceptives) also may promote Na^+ retention,

primarily in patients with impaired estrogen metabolism due to hepatic disease.[239,240]

Pregnancy

Normal pregnancy is associated with the retention of 900 to 1000 mEq of Na^+ and 6 to 8 L of water.[241] This is commonly associated with mild peripheral edema, particularly in the third trimester, a time at which partial obstruction of the vena cava by the enlarged uterus also may play a contributory role.

The degree of fluid retention in pregnancy is generally independent of alter Na^+ intake, suggesting that Na^+ balance is being strictly regulated. It is possible example, that Na^+ retention reflects an *appropriate* response to systemic vasodilatation (which increases vascular capacity) and relative hypotension than a defect in renal function.[46,242]

Refeeding edema

Another example of primary renal Na^+ retention occurs in refeeding edema. Patients who have fasted for as little as 3 days display marked renal Na^+ retention and possibly edema after refeeding with carbohydrates.[243] A similar phenomenon may be seen during the treatment of diabetic ketoacidosis[244] and in some women with idiopathic edema (see "Idiopathic Edema," below).[245]

The mechanism by which these changes in renal Na^+ handling are mediated is incompletely understood, but increased availability of insulin is thought to play a major role. Insulin indirectly stimulates renal Na^+ reabsorption in the proximal tubule and perhaps in the loop of Henle and distal tubule as well.[246][247] and[248] In addition, fluid losses occur during fasting, driven in part by the excretion of ketoacids with Na^+ to maintain electroneutrality. This leads to the activation of the renin-angiotensin system, which, when combined with increased intake of Na^+ during refeeding, can lead to rebound fluid overload.[245]

Treatment

Nonpregnant patients with primary renal sodium retention can be safely treated with diuretics. Unless an excessive diuresis is induced, there is no risk of effective volume depletion, since these patients are truly volume-expanded. However, large doses of a loop diuretic (such as a maximum of 160 to 200 mg of intravenous furosemide, or twice this amount orally due to incomplete absorption[128]) without a thiazide are often required with advanced renal failure or with minimal diazoxide therapy for severe hypertension.[234][249] Either dialysis or hemofiltration is an effective alternative for refractory edema in patients with renal failure.

In comparison, edema during pregnancy is considered to be a physiologic rather than a pathologic event. As a result, diuretic therapy is not required and may actually have a deleterious effect by diminishing uterine perfusion.

Refeeding or insulin-induced edema is usually a transient phenomenon. In some cases, however, the edema persists, and patients may be treated as if they have idiopathic edema (see below).

P.520

Nephrotic Syndrome

The nephrotic syndrome can be produced by a variety of renal disorders and is characterized by an increase in the permeability of the glomerular capillary wall to proteins, leading to an increase in protein excretion. As described previously, renal Na^+ retention (and consequent volume expansion) appears to be a major factor in nephrotic edema.[29][30,31,32,33,34,35] and[36,35] This has important implications for treatment, since appropriate removal of the edema fluid with diuretics usually does not lead to either plasma volume depletion or azotemia.[31]

The second, not mutually exclusive mechanism of nephrotic edema is under

due to hypoalbuminemia.[38,41,42] This is most likely to occur with the acute onse nephrosis or in patients with severe hypoalbuminemia (plasma albumin conc below 1.5 g/dL).[41,42] To the degree that underfilling is present, diuretic therap lead to signs of volume depletion.

Treatment

The main aim of therapy in the nephrotic syndrome is, if possible, to revers glomerular disease, as with corticosteroids in minimal change disease.[29,250] Pending this potential response, a loop diuretic and dietary Na^+ restriction can be used to control the edema.[30] Diuretic resistance can occur, particularly in patie with marked hypoalbuminemia (plasma albumin concentration below 2 g/dL) advanced renal insufficiency. This problem is in part due to binding of free the tubular lumen by filtered albumin, thereby rendering the diuretic inactiv[251,252] In addition, marked hypoalbuminemia can lead sequentially to diminished pl binding of the diuretic, increased diffusion of unbound drug out of the vasc space, and a decreased rate of drug delivery to and subsequent excretion i urine.[252] In this setting, mixing the loop diuretic with albumin prior to infusio partially overcome the diuretic resistance, leading to an increase in Na^+ excretion.[253,254]

Other therapeutic options include higher doses of the loop diuretic (to a ma similar to that in primary renal Na^+ retention above) and combination therapy with loop and a thiazide diuretic.[249] Tight wrapping of the legs and periodic elevation the lower extremities also may be helpful by maximizing venous return to th heart.[255]

Idiopathic Edema

Idiopathic edema refers to a disorder occurring in young, menstruating women absence of cardiac, hepatic, or renal disease.[245,256,257] and[258] Fluid retention may initial occur premenstrually but often becomes persistent. Emotional pr (including depression and neurotic symptoms) and obesity are commonly pa syndrome.[259]

Role of capillary leak

The etiology of idiopathic edema is uncertain. Many women with this disord an *abnormal response to assumption of the upright posture*. Normal subjects develop a mild degree of plasma volume depletion in this

setting because of pooling of fluid in the lower extremities. As a result, the in urinary Na^+ excretion[240] and a daytime weight gain that averages 0.5 to 1.5 kg.[256,257] In comparison, women with idiopathic edema lose much more fluid the vascular space with standing,[257,261] leading to often marked elevations in the release of renin, norepinephrine, and ADH and to a larger morning-to eveni

gain that can exceed 5 kg in severe cases.[256,257] and[258]

These observations suggest that idiopathic edema may represent a *capillary leak* syndrome, in which increased capillary permeability favors the movement of of the vascular space, particularly when standing.[256,261] This primary tendency to plasma volume depletion also explains why the jugular venous pressure is i normal range and pulmonary edema does not occur, even in the presence of peripheral edema.

The factors responsible for fluid leakage out of the capillaries are not well understood: Either primary capillary injury[262] or altered capillary hemodynamics could be responsible. It is possible, for example, that dilatation of the prec sphincter plays a central role by permitting more of the systemic pressure t transmitted to the capillary, thereby increasing the capillary hydraulic press Women with idiopathic edema often have impaired hypothalamic function, re abnormal release of prolactin, luteinizing hormone, and perhaps other horm[263] These changes might then affect control of the capillary circulation.

Refeeding

Women with idiopathic edema are typically very conscious of their weight a drastically cut down on food intake for days at a time in an effort to lose w subsequent end of this fast can lead to rapid weight gain via the phenomen refeeding edema (see above).[245]

Diuretic-induced edema

Another theory postulates that idiopathic edema may be produced by *the chronic administration of diuretics*.[245,264] According to this hypothesis, patients are initially begun on a diuretic for a minor degree of fluid retention. As the continued, persistent diuretic-induced hypovolemia results in the activation retaining mechanisms, particularly the renin-angiotensin-aldosterone syste diuretic is then stopped, the patient may be unable to *promptly* shut off these Na^+ retaining mechanisms, resulting in rapid edema formation. *Mistaken* the assumption that chronic diuretic therapy is indicated. If, however, the patie maintained without diuretics for 1 to 3 weeks, a spontaneous diuresis will f ensue, with resolution of the edema (Fig. 16-14).

The frequency with which diuretics are responsible for idiopathic edema is Some investigators have proposed that most cases are diuretic-induced,[245,264] while others have found that most patients have no history or signs (volume depletion, hypokalemia, positive urine assay) of diuretic use.[265]

Diagnosis

The diagnosis of idiopathic edema is one of exclusion and should be consic in menstruating women who have a normal plasma albumin concentration, n jugular venous pressure, and no evidence of cardiac, hepatic, or renal dise Idiopathic edema should also be differentiated from premenstrual

edema. The latter disorder occurs in many women; it is mild and self-limited diuresis beginning with or shortly after the onset of menses. The fluid retention this setting is thought to be humorally mediated, as estrogens or possibly p may be responsible for the fluid retention.

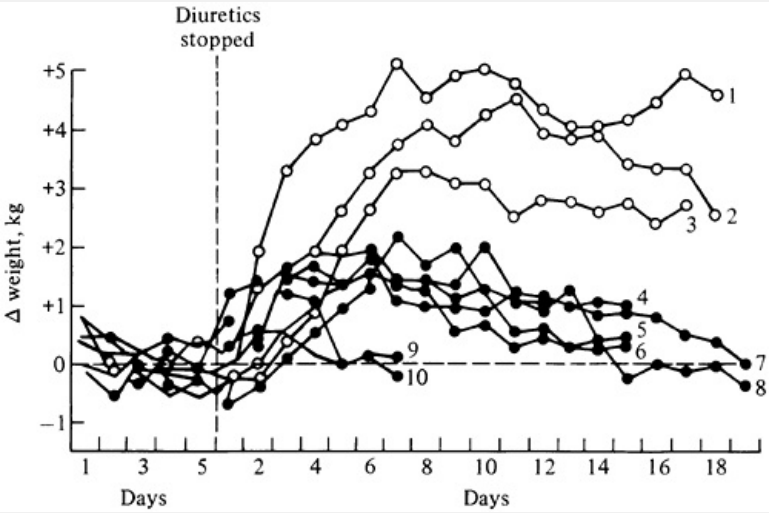

Figure 16-14 Changes in weight before and after stopping diuretics in 10 patients with idiopathic edema. Patients 4 to 10 returned to their baseline within 20 days. Patients 1 to 3 maintained their weight gain but eventuall the extra weight after the institution of a low-sodium diet. (*From MacGregor GA, Roulston JE, Markandu ND, Jones JC, deWardener HE: Lancet 1:397, 1979, with permission.*)

Some women are already receiving diuretic therapy at the initial evaluation physician, sometimes in massive doses that can exceed 600 mg of furosemi day.[266] As a result, hypokalemia is a common problem, with the plasma K^+ concentration in severe cases being persistently below 3 meq/L. This uncon therapy can lead to two potential complications: rhabdomyolysis (which may in part to K^+ depletion; see page 859) and chronic renal insufficiency that, on ren biopsy, is characterized by prominent tubulointerstitial scarring and atrophy intimal thickening of the interlobular arteries.[266,267] Both chronic hypokalemia and, rarely, an interstitial nephritis secondary to the diuretic may contribute to t injury. Discontinuation of diuretic therapy generally leads to at least partia of renal function.[266]

Treatment

Since diuretic-induced edema appears to be operative in at least some pati initial therapy should consist of a low Na^+ diet and *cessation of diuretic therapy* for 3 to 4 weeks (Fig. 16-14). The patient should be advised that this will initially l weight gain and reassured that diuretics can be always be reinstituted if a spontaneous diuresis does not ensue. If it becomes evident that a diuretic

required, the lowest effective dose should be used and it should be given i evening, since the edema primarily accumulates during the daytime, when t is erect.[257]

In patients who are not taking diuretics and those who fail to respond to di withdrawal, it has been suggested that a diet restricted in sodium and carb (approximately 90 g/day) leads to resolution of edema in many cases.[265] It is presumed that this effect is the reverse of the sodium retention seen with r

Patients who are resistant to this conservative regimen are often difficult t effectively. High-dose loop diuretic therapy can be used with careful monito the plasma K^+ and creatinine concentrations.[266] An alternative that has been effective in some cases is blockade of the renin-angiotensin system with ar inhibitor.[261,268] Minimizing the degree of secondary hyperaldosteronism may diminish the quantity of fluid retained during the day. It does not, however, the capillary leak or plasma volume depletion. As a result, these agents oft the systemic blood pressure by 5 to 10 mmHg, producing symptoms of hypo some patients.[261]

Two additional modalities have been tried in refractory idiopathic edema. S patients have responded to therapy aimed at reversing a possible dopamine deficiency by the administration of the dopamine agonist bromocriptine or a levodopa-carbidopa combination.[256,269,270] The efficacy of these agents, howeve remains unproven, and their use may be associated with unacceptable side

Increasing sympathetic activity with low-dose amphetamines or the sympath agonist ephedrine (15 to 60 mg TID) also has had some success.[257,271,272] These drugs may act by constricting the precapillary sphincter, thereby lowering t capillary hydraulic pressure and retarding fluid movement out of the capilla Ephedrine has been given successfully with an ACE inhibitor.[272] Side effects can be minimized by using lower ephedrine doses.

PROBLEMS

16-1The appropriate use of diuretics may induce or exacerbate effecti circulating volume depletion in which of the following edematous stat

a. **Congestive heart failure**
b. **Nephrotic syndrome with a plasma albumin concentration of 2.8 g/d**
c. **Renal failure**
d. **Cirrhosis and ascites**

What is the simplest way to detect this change?

a. **Measurement of the urine Na^+ concentration**
b. **Measurement of the BUN**

c. **Estimation of the jugular venous pressure**

d. **Measurement of the systemic blood pressure**

16-2A previously well 45-year-old man is admitted with the acute onse crushing chest pain and dyspnea. Medical evaluation confirms the diag of acute myocardial infarction with pulmonary edema. After treatment oxygen, intermittent positive-pressure breathing, and diuretics, he be edema-free. Because of the diuresis, his weight has fallen by 3 kg wit after admission and his estimated jugular venous pressure is less tha cmH_2O. At this time, he is noted to be oliguric with a urine Na^+ concentration of 4 meq/L. His BUN has increased from 10 to 28 mg/dL.

P.524

a. **What are two most likely causes of the oliguria and increase in BU**

b. **Would a normal ejection reaction necessarily distinguish between possibilities?**

c. **Does the low jugular venous pressure exclude the presence of car dysfunction?**

d. **Is his total extracellular volume greater than, equal to, or less tha normal?**

e. **What modes of therapy might return his BUN and urine output to no**

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Footnotes

* This gradient is not uniform within the capillary circulation. The hydraulic within most of the capillary is relatively high at 25 to 30 mmHg, resulting in throughout the capillary.[1,3,6] Most of this excess fluid is then returned to the vascular space in the highly permeable postcapillary venules, where the hy pressure falls to 10 mmHg, a level below the oncotic pressure gradient.[3]

† The technique for evaluating jugular venous pressure is discussed on pag

‡ Laryngeal edema, due to an allergic reaction, and angioedema also are p fatal. However, these conditions are special forms of localized edema requi epinephrine, corticosteroids, and, if needed, tracheostomy, not fluid remova

¶ This hypothesis is also applicable to high-output heart failure due, for ex hyperthyroidism (where the hypermetabolic state leads to an increase in en requirements) or to arteriovenous fistulas (where blood flowing through the bypassing the capillary circulation). In these conditions, the patients still b they are effectively volume-depleted, since the cardiac output is inappropri in relation to tissue needs.[4,78,87]

** Sodium retention and ascites formation are not prominent in all liver dise being relatively late events in primary biliary cirrhosis.[190] The renal vasodilator and natriuretic effects of retained bile salts may be responsible for the relative

preservation of renal function in this disorder.

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Chapter Seventeen

Introduction to Simple and Mixed Acid-Base Disorders

Disturbances of acid-base homeostasis are common clinical problems that w discussed in detail in Chaps. 18, 19, 20 and 21. This chapter will first review the bas principles of acid-base physiology, the general mechanisms by which abnor can occur, and an approach to evaluating patients with simple and mixed ac disorders.

ACID-BASE PHYSIOLOGY

Free H^+ ions are present in the body fluids in extremely low concentrations. normal H^+ concentration in the extracellular fluid is roughly 40 nanoeq/L, approximately *one-millionth* the milliequivalent-per-liter concentrations of Na^+, K^+, Cl$^-$, and HCO_3^-.* However, H^+ ions are small and highly reactive, allowing them bind more strongly to negatively charged portions of molecules than do Na^+ As result, maintenance of a stable H^+ ion level is required for normal cellular functio since small fluctuations in the H^+ concentration have important

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effects on the activity of cellular enzymes (Fig. 17-1). There is a relatively narrow range of extracellular H^+ concentration that is compatible with life, from 1 160 nanoeq/L (pH equals 7.80 to 6.80).

Under normal conditions, the H^+ concentration varies little from the normal value 40 nanoeq/L. The body buffers play an important role in this regulatory pro they are able to take up or release H^+ ions to prevent large changes in the H^+ concentration. There are a variety of buffers in the extracellular and intrac fluids, most of which are weak acids (which can release H^+ ions) and their ionized salts (which can take up H^+ ions) (see Chap. 10). The most important extracellular buffer is HCO_3^-, which combines with H^+ according to the following reaction:

$$\underset{\text{salt}}{H^+ + HCO_3^-} \leftrightarrow \underset{\text{weak acid}}{H_2CO_3} \leftrightarrow H_2O + CO_2 \qquad (17\text{-}1)$$

In most circumstances, the concentration of H_2CO_3 is very low in relation to that of

HCO_3^- and CO_2. As a result, the law of mass action for Eq. 17-1 can be expressed solely in terms of the concentrations of H^+, HCO_3^-, and CO_2 (see page 308):

$$[H^+] = \frac{K_a' \times 0.03P_{CO_2}}{[HCO_3^-]} \qquad (17\text{-}2)$$

where K_a' is the dissociation constant for this reaction and 0.03 P_{CO_2} represents the solubility of CO_2 in the plasma. If the H^+ concentration is measured in nanomoles per liter (nanomol/L), the value of K_a' is approximately 800 nanomol/L. If this is substituted in Eq. 17-2, then

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]} \qquad (17\text{-}3)$$

Equations 17-1 and 17-2 can also be expressed in logarithmic terms as the Henderson-Hasselbalch equation:

$$pH = 6.10 + \log \frac{[HCO_3^-]}{0.03P_{CO_2}} \qquad (17\text{-}4)$$

where pH equals $-\log [H^+]$ (the H^+ concentration being measured in moles per liter) and 6.10 equals $-\log K_a'$ ($-\log 800 \times 10^{-9}$ mol/L). At the normal H^+ concentration of 40 nanomol/L (or 40×10^{-9} mol/L),

$$\begin{aligned} pH &= -\log (40 \times 10^{-9}) \\ &= -(\log 40 + \log 10^{-9}) \end{aligned}$$

Since log 40 equals 1.6 and $\log 10^{-9}$ equals -9,

$$\begin{aligned} pH &= -(1.6 - 9) \\ &= 7.40 \end{aligned}$$

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Although the acidity of the extracellular fluid is measured as the pH, it is fr easier to think in terms of the H^+ concentration and Eq. 17-3. As a result, the following chapters will use both the pH and H^+ concentration to permit the reader to become familiar with these concepts. It is important to recognize the inverse relationship between the pH and the H^+ concentration. An increase in the H^+ concentration reduces the pH, and a decrease in the H^+ concentration raises the pH (Table 17-1).

Measurement of pH

The pH and PCO_2 are determined on blood drawn anaerobically (to prevent the loss of CO_2 from the blood into the air) into a heparinized syringe.[1,2] The pH is measured by an electrode permeable only to H^+ ions (see page 302), and the PCO_2 by a CO_2 electrode. The HCO_3^- concentration can then be calculated from the Henderson-Hasselbalch equation or measured directly. The latter procedure is the addition of a strong acid to the plasma sample and measurement by a colorimetric reaction of the amount of CO_2 generated.[1] The added H^+ ions will

combine with plasma H_2O, leading to the formation of H_2CO_3 and then CO_2 as Eq. 17-1 is driven to the right. Thus, this method measures *total* CO_2 *content*, since it also includes the dissolved CO_2 (equals to 0.03 PCO_2, which in the physiologic range adds 1 to 2 meq/L to the HCO_3^- concentration). For the sake of simplicity, the following discussion will refer only to the HCO_3^- concentration, since it is this parameter that is directly affected by changes in renal H^+ secretion and by the addition of acid or alkaline loads to the extracellular fluid.

Although the calculated and measured values for the plasma HCO_3^- concentration are generally similar, they may occasionally differ by as much as 7 to 8 meq/L. Some observers have suggested that the measured value is likely to be

more accurate in this setting, since calculation of the HCO_3^- level assumes, perhaps incorrectly, that the pK_a of 6.10 and the solubility constant for CO_2 of 0.03 are unchanged in acute acid-base disturbances.[3] On the other hand, other investigators claim that the calculated value is usually a better estimate, since there may be errors in the automated test used to directly measure the CO_2 content[4] and since the pK_a seems to vary little in most clinical conditions.[5] This issue is at present unresolved. Fortunately, the difference is usually small, and the only clinical problem may occur with calculation of the anion gap, where accurate determination of the plasma bicarbonate concentration is important (see Chap. 19).[6]

Table 17-1 Relationship between the arterial pH and H^+ concentration in the physiologic range

pH	$[H^+]$, nanomol/L
7.80	16
7.70	20
7.60	26
7.50	32
7.40	40
7.30	50
7.20	63

7.10	80
7.00	100
6.90	125
6.80	160

The normal values for the major acid-base variables in arterial and venous

	pH	$[H^+]$, nanoeq/L	PCO_2, mmHg	$[HCO_3^-]$, meq/L
Arterial	7.37–7.43	37–43	36–44	22–26
Venous	7.32–7.38	42–48	42–50	23–27

The decrease in pH (and increase in H^+ ion concentration) in venous blood is due to t uptake of metabolically produced CO_2 in the capillary circulation.

In general, arterial rather than venous blood is used to measure the extrace Arterial blood allows concurrent measurement of arterial oxygenation and is influenced by local changes in tissue perfusion. However, venous blood is obtain and just as accurate for pH determination if drawn without a tourniqu well-perfused area.

Pitfalls

There are several pitfalls that can lead to inaccurate results when the extra pH is measured. In addition to preventing loss of CO_2 to the air by drawing the bloo sample anaerobically, rapid measurement or cooling to 4°C is required. At roo temperature, continued anaerobic glycolysis by red cells and white cells le production of organic acids that can induce small reductions in the pH and plasma HCO_3^- concentration.[1]

If air bubbles occupy more than 1 to 2 percent of the blood volume in the s artifactually high arterial P_{O_2} and an underestimation of the true arterial P_{CO_2} result from equilibration of these gases between air bubbles and the specir magnitude of this error is greatest when the difference in gas tensions betv blood and air are high, when the surface area of bubbles is maximized by a and when the time between specimen collection and analysis is prolonged.[6,7,8]

Dilution of the blood specimen with heparin is another potential problem. F

example, patients in an intensive care unit often have their pH measured us arterial blood drawn from an indwelling intraarterial catheter that is routine with heparin. To minimize contamination of the blood sample, the first 8 to should be discarded. Use of the first 2 mL (which mostly contains

heparin) can lead to erroneous values for pH and P_{CO_2} as low as 6.50 and 3.5 mmHg, respectively.[9]

A similar error can occur with the use of a heparinized syringe.[10] There should be enough heparin to coat the sides of the syringe, but the volume of anticoag solution should be less than 5 percent of the volume of the blood sample.

Lastly, it is not always correct to assume that the arterial pH reflects the p tissue level. This is a particular problem in patients with severe circulatory cardiac arrest, in whom pulmonary blood flow is often substantially reduced setting, blood that is delivered to the lungs may be adequately cleared of CO_2, resulting in a relatively normal or even diminished arterial P_{CO_2}. However, the low cardiac output slows the return of containing blood from the periphery. As a result, the *mixed venous* P_{CO_2}, which represents blood that has not yet entered pulmonary circulation, may be markedly higher than the arterial blood.[11,12] In one study, for example, patients with a mean arterial pH of 7.42 and P_{CO_2} 32 mmHg during cardiopulmonary resuscitation had respective mixed venous va 7.14 and 74 mmHg.[11] If the latter results more closely reflect the pH at the cel level, then arterial measurements can lead to the misleading assumption th base balance is being maintained.

In addition to testing of mixed venous blood samples, the presence of dimin pulmonary blood flow may be suggested from measurement of the *end-tidal* CO_2 *concentration*.[13] A value above 1.5 percent suggests adequate pulmonary perf and the likelihood that arterial and mixed venous blood have a similar pH a P_{CO_2}. A value below 1 percent, however, is often indicative of a significant impair venous return.

Regulation of Hydrogen Concentration

The HCO_3/CO_2 system is the principal buffer in the extracellular fluid, becau both the high concentration of HCO_3^- and the ability to control the plasma HCO_3^- concentration and the P_{CO_2} independently (see Chap. 11). The former is regulated by *changes in the rate of* H^+ *secretion from the renal tubular cell into the tubul lumen*. Most of the secreted H^+ ions combine with filtered HCO_3^-, so that the final urine is virtually HCO_3^- free. Reabsorption of the filtered HCO_3^- is essential if acid-base balance is to be maintained, since loss of HCO_3^- in the urine is equivalent to the retention of H^+ (both H^+ and HCO_3^- being derived from the dissociation of

H_2CO_3).

In addition, some secreted H^+ ions combine either with HPO_4^{2-} (to form $H_2PO_4^-$) or with NH_3 (to form NH_4^+). These processes play a central regulatory role, since they result in the generation of new HCO_3^- ions in the extracellular fluid (see Figs. 11-3 and 11-4). Thus, an increase in net H^+ excretion (as $H_2PO_4^-$ and NH_4^+) leads to a rise in the plasma HCO_3^- concentration, whereas a reduction in net H^+ excretion results in H^+ retention and a fall in the plasma HCO_3^- concentration.

CO_2, on the other hand, is eliminated by the lungs. Thus, the P_{CO_2} is regulated by the *rate of alveolar ventilation*. Hyperventilation enhances CO_2 excretion and

lowers the P_{CO_2}; hypoventilation reduces CO_2 excretion and raises the P_{CO_2}.

Although CO_2 is not an acid, since it contains no H^+ ions, it acts as an acid in the body by combining with water to form H_2CO_3 (Eq. 17-1).

The kidneys and lungs play a central role in the maintenance of acid-base balance because they can adjust the rate of acid excretion to meet homeostatic needs. Each day, approximately 15,000 mmol of CO_2 is produced by endogenous metabolism and is then excreted by the lungs. Similarly, a normal diet generates 50 to 100 mEq of H^+ per day, derived mostly from the metabolism of sulfur- containing amino acids with the subsequent generation of H_2SO_4.[14,15] These H^+ ions are initially buffered by HCO_3^- and the cellular and bone buffers to minimize the fall in extracellular pH (see page 315). Acid-base balance is then restored by urinary H^+ excretion, which regenerates the HCO_3^- lost in the original buffering reaction.

When acid-base disturbances do occur, renal and respiratory function changes attempt to normalize the pH. From the law of mass action,

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]}$$

it can be seen that the H^+ concentration is related to the $P_{CO_2}/[HCO_3^-]$ *ratio*, not to the absolute value of either compound. If the H^+ concentration is increased, regardless of cause, it can be reduced toward normal by a decrease in the P_{CO_2} and/or an elevation in the plasma HCO_3^- concentration. Both of these changes occur, as both alveolar ventilation and urinary H^+ excretion are enhanced in this setting. At least part of the signal for these adaptations appears to be a pH increase in H^+ concentration (or reduction in pH) in the cerebral interstitium surrounding the central respiratory centers and in the renal tubular cells.[16,17,18]

Conversely, alveolar ventilation and H^+ excretion are diminished when the H^+

concentration is reduced. The resultant increase in the P_{CO_2} and decline in the plasma HCO_3^- concentration raise the H^+ concentration toward normal.

ACID-BASE DISORDERS

Definitions

A change in the extracellular pH may be seen when renal or respiratory fun abnormal or when an acid or base load overwhelms excretory capacity. *Acidemia* defined as a decrease in the blood pH (or an increase in the H^+ concentration), and *alkalemia* as an elevation in the blood pH (or a reduction in the H^+ concentration). On the other hand, *acidosis* and *alkalosis* refer to processes that tend to lower an raise the pH, respectively. In most conditions, an acidotic process leads to and an alkalotic process to alkalemia. However, this may not be true in

patients with mixed acid-base disturbances, in whom the final pH depends u balance between the different disorders that are present (see below).

Changes in the plasma H^+ concentration and pH can be induced by alterations i P_{CO_2} or plasma HCO_3^- concentration [Eqs. 17-3 and 17-4]. Since the P_{CO_2} is regulated by respiration, primary abnormalities in the P_{CO_2} are called *respiratory acidosis* (high P_{CO_2}) and *respiratory alkalosis* (low P_{CO_2}). In contrast, primary changes in the plasma HCO_3^- concentration are referred to as *metabolic acidosis* (low HCO_3^-) and *metabolic alkalosis* (high HCO_3^-).

In each of these disorders, compensatory renal or respiratory responses ac minimize the change in the H^+ concentration by minimizing the alteration in the $P_{CO_2}/[HCO_3^-]$ ratio (Table 17-2). To achieve this, the compensatory response always *changes in the same direction* as the primary disturbance. Thus, a high P_{CO_2} in respiratory acidosis results in enhanced renal H^+ excretion and an appropriate elevation in the plasma HCO_3^- concentration.

Table 17-2 also demonstrates that the diagnosis of an acid-base disorder req *measurement of the extracellular pH*. Simply looking at the plasma HCO_3^- concentration (which is routinely measured with the plasma K^+, and Na^+ and Cl^- concentrations) is not sufficient. A high value, for example, can be seen bo metabolic alkalosis (where it is the primary problem) and in respiratory acid (where it represents the appropriate renal compensation). These disorders differentiated by measurement of the pH.

Metabolic Acidosis

Metabolic acidosis is characterized by a fall in the plasma HCO_3^- concentration and a low pH (or high H^+ concentration). It can be induced either by loss of HCO_3^- (as with

diarrhea) or by the buffering of a noncarbonic acid, such as lactic acid or r diet-generated sulfuric acid (as occurs in renal failure):

$$H_2SO_4 + 2NaHCO_3 \rightarrow Na_2SO_4 + 2H_2CO_3 \rightarrow 2CO_2 + 2H_2O$$

The reduction in pH stimulates ventilation, resulting in a compensatory dec the P_{CO_2}.[19,20] Ultimate restoration of the pH usually depends upon renal ex of the excess acid, a process that takes several days.

Table 17-2 Characteristics of the primary acid-bas disturbances

Disorder	pH	$[H^+]$	Primary disturbance	Compensatory response
Metabolic acidosis	↓	↑	↓$[HCO_3]$	↓P_{CO_2}
Metabolic alkalosis	↑	↓	↑$[HCO_3]$	↑P_{CO_2}
Respiratory acidosis	↓	↑	↑P_{CO_2}	↑$[HCO_3]$
Respiratory alkalosis	↑	↓	↓P_{CO_2}	↓$[HCO_3]$

Metabolic Alkalosis

Metabolic alkalosis results from an elevation in the plasma HCO_3^- concentration and is associated with a high pH (or low H^+ concentration). This disorder can be produced by HCO_3^- administration or, more commonly, by H^+ loss, as with vomiting or the use of diuretics. The respiratory compensation consists of hypoventi an elevation in the P_{CO_2}.[21,22]

Renal excretion of the excess HCO_3^- (as $NaHCO_3$) should rapidly correct the pH. However, this does not occur in patients with metabolic alkalosis because HCO_3^- reabsorptive capacity is enhanced, usually because of concomitant volume and chloride (see Chap. 18).

Respiratory Acidosis

Respiratory acidosis is due to decreased effective alveolar ventilation, resu reduced pulmonary excretion of CO_2 and an increase in the extracellular P_{CO_2}

(hypercapnia). The renal compensation consists of enhanced H^+ secretion, which raises the plasma HCO_3^- concentration.[23,24] This response takes 3 to 5 days to reach completion.[23] As a result, two different acid-base disorders may occur: *acute* respiratory acidosis, in which there may be a dramatic fall in pH, and *chronic* respiratory acidosis, in which the pH is relatively well protected as a result of renal compensation (see Chap. 20). Similar considerations apply to respiratory alkalosis but not to metabolic acidosis or alkalosis, since the respiratory compensation in these disorders is rapid, beginning within minutes and being complete within 12 to 24 h.[20]

Respiratory Alkalosis

The primary disturbance in respiratory alkalosis is hyperventilation, resulting in the extracellular P_{CO_2} (hypocapnia) and an increase in pH (or reduction in H^+ concentration). The compensatory response consists of diminished renal H^+ secretion, producing HCO_3^- loss in the urine and an appropriate decrease in the plasma HCO_3^- concentration. As with respiratory acidosis, the renal compensation is time-dependent, so that both acute and chronic respiratory alkalosis can occur.[25,26] and[27]

Mixed Acid-Base Disorders

It is not uncommon for more than one of the above primary disorders to be present. Suppose a patient has a low arterial pH and is therefore acidemic. In this setting a low plasma HCO_3^- concentration indicates metabolic acidosis and a high P_{CO_2} indicates respiratory acidosis. If both are present, then the patient has a *combined* metabolic and respiratory acidosis. Similar reasoning can lead to the diagnosis of combined metabolic and respiratory alkalosis in a patient with an elevated plasma HCO_3^- concentration, and a low P_{CO_2}.

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Knowledge of the extent of the renal and respiratory compensations allows complex disturbances to be diagnosed.[1] The responses listed in Table 17-3 have been empirically derived from observations in humans with different acid-base disorders.[19,20,21,22,23,24,25] and[26] A simple example can illustrate how this information can be utilized. A patient with a salicylate overdose is found to following arterial blood values:

$$pH = 7.45$$
$$P_{CO_2} = 20\ mmHg$$
$$[HCO_3^-] = 13\ meq/L$$

Evaluation of acid-base status begins with the pH. The slightly high pH indicates that the patient is alkalemic. This can be due to a high HCO_3^- concentration or a low P_{CO_2}. Since only the latter is present, the primary diagnosis is respiratory alkalosis, most likely acute given the history. In this disorder, the body buffers will re

plasma HCO_3^- concentration by 2 meq/L for every 10 mmHg decrease in the P_{CO_2} (Table 17-3).[25,26] Thus, the $[HCO_3^-]$ should fall from 24 to 20 meq/L as the P_{CO_2} drops acutely from 40 to 20 mmHg. The actual $[HCO_3^-]$ of 13 meq/L is lower than expected, suggesting that the patient has a combined respiratory alkalosis and metabolic acidosis, a common finding with salicylate intoxication.[27]

Table 17-3 Renal and respiratory compensation to primary acid-base disturbances in humans

Disorder	Primary change	Compensatory response
Metabolic acidosis	$\downarrow[HCO_3^-]$	1.2 mmHg decrease in P_{CO_2} for every 1 meq/L fall in $[HCO_3^-]$
Metabolic alkalosis	$\uparrow[HCO_3^-]$	0.7 mmHg elevation in P_{CO_2} for every 1 meq/L rise in $[HCO_3^-]$
Respiratory acidosis	$\uparrow P_{CO_2}$	
Acute		1 meq/L increases in $[HCO_3^-]$ for every 10 mmHg rise in P_{CO_2}
Chronic		3.5 meq/L elevation in $[HCO_3^-]$ for every 10 mmHg rise in P_{CO_2}
Respiratory alkalosis	$\downarrow P_{CO_2}$	
Acute		2 meq/L reduction in $[HCO_3^-]$ for every 10 mmHg fall in P_{CO_2}
Chronic		4 meq/L decrease in $[HCO_3^-]$ for every 10 mmHg reduction in P_{CO_2}

The renal and respiratory compensations return the pH toward but rarely to normal.

Thus, a normal pH in the presence of changes in and plasma HCO_3^- concentration immediately suggests a mixed disorder. For example, the follo arterial blood values:

$$pH = 7.40$$
$$P_{CO_2} = 60\,mmHg$$
$$[HCO_3^-] = 36\,meq/L$$

are due to a combination of respiratory acidosis (elevated) and metabolic alkalosis (high plasma concentration). This disorder is most often due to diuretic therapy in a patient with severe chronic lung disease.

Finally, an arterial of 40 mmHg or a plasma concentration of 24 meq/L is not always normal. A patient with metabolic acidosis should hyperventilat minimize the reduction in pH. On the average, the will fall 1.2 mmHg for every 1 meq/L fall in the plasma concentration. Thus, a 16-meq/L reduction in the plasma HCO_3^- concentration from 24 to 8 meq/L should lower the about 19 mmHg (16× 1.2), from 40 to 21 mmHg. In this setting, the new pH will be 7.1 however, the remains at 40 mmHg, then the degree of acidemia will be m severe,

$$pH = 6.10 + \frac{8}{0.03 \times 40}$$
$$= 6.92$$

Since the of 40 mmHg is *inappropriately high* by 19 mmHg, this patient has a combined metabolic and respiratory acidosis.

Acid-Base Map

If the relationship between the arterial pH (or concentration), , and HCO_3^- concentration in the different acid-base disorders is plotted, the *acid* result is t *base map* in Fig. 17-1. The stippled areas represent the responses of otherwis normal subjects to metabolic and respiratory acidosis and alkalosis, includi appropriate compensations that should be present. Thus, a given increase is associated with a greater reduction in pH in acute, as compared to respiratory acidosis. This difference is due to the compensatory elevation i plasma HCO_3^- concentration seen with chronic hypercapnia.

Values between the stippled areas, on the other hand, represent mixed acid disturbances. This can be appreciated by plotting the three mixed disorders described above: Point A lies between respiratory alkalosis and metabolic a point B between respiratory acidosis and metabolic alkalosis (even though normal), and point C between metabolic and respiratory acidosis.

As mentioned above, the diagnostic approach used in this and the following chapters is based upon the observed in vivo compensatory responses of

patients with the different acid-base disorders.[19,20,21,22,23,24,25] and[26] In vitro measurements such as the base deficit, whole blood buffer base, and stand bicarbonate offer no advantages and frequently are confusing.[28] Consequently, they will not be used in this text.

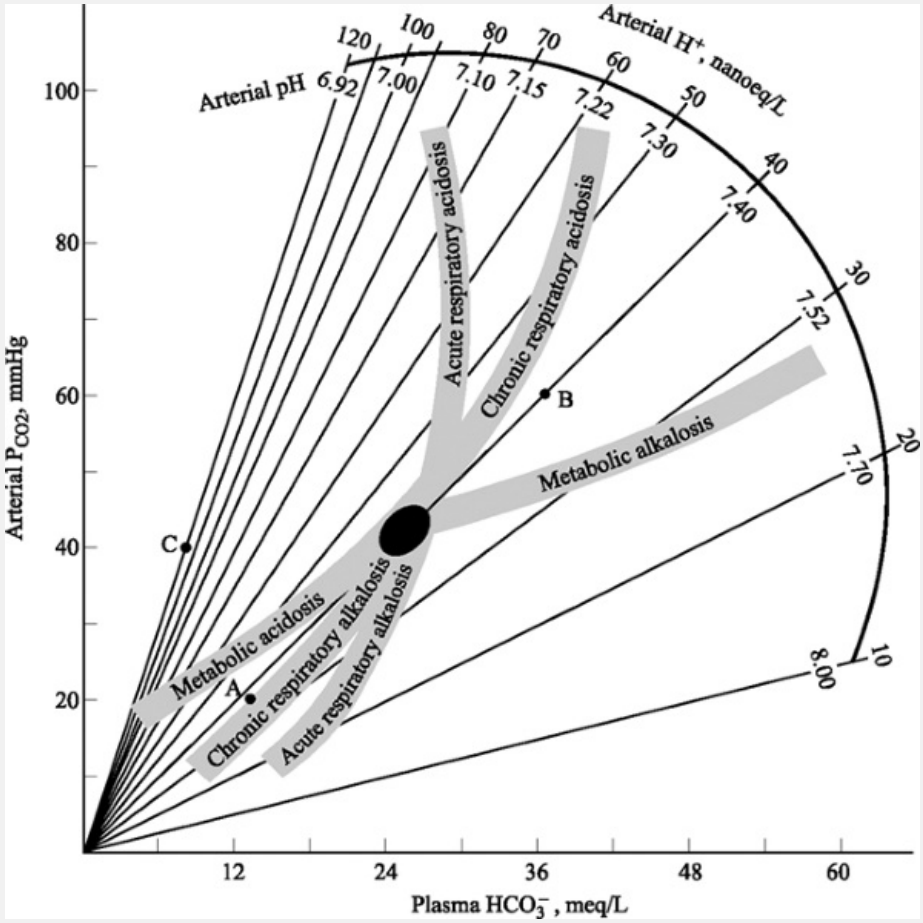

Figure 17-4 Acid-base map describing the relationships between the arterial H^+ concentration, P_{CO_2}, and HCO_3^- concentration. The dark area in the center represents the range of normal values for these parameters; the stippled areas represent the different simple acid-base disturbances. Points A, B, and C indicate the three mixed acid-base disorders discussed in the text. (*From Harrington JT, Cohen JJ, Kassirer JP, Mixed acid-base disturbances, in Cohen JJ, Kassirer JP (eds): Acid/Base. Little, Brown, Boston, 1982, with permission.*)

CLINICAL USE OF HYDROGEN CONCENTRATION

Although the acidity of the blood is measured in terms of pH, it is somewhat awkward to use logarithms at the bedside. In contrast, the calculation of the H^+ concentration is much easier. As stated in Eq. 17-3,

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]}$$

If the normal arterial P_{CO_2} is 40 mmHg and the HCO_3^- concentration is 24 meq/L, then the normal H^+ concentration is 40 nanoeq/L. To use this formula, one only to know how to convert the measured pH into H^+ concentration, a process involving a few simple calculations (Table 17-1).[29] If one begins at a pH of 7.40 and a H^+ concentration of 40 nanoeq/L, then for every 0.10 increase in pH, the H^+ concentration must be multiplied by 0.8; for every 0.10 decrease in pH, the concentration must be multiplied by 1.25. For example,

$$\text{pH} = 7.30 \quad [H^+] = 40 \times 1.25 = 50\,\text{nanoeq/L}$$
$$\text{pH} = 7.20 \quad [H^+] = 40 \times 1.25 \times 1.25 = 63\,\text{nanoeq/L}$$
$$\text{pH} = 7.50 \quad [H^+] = 40 \times 0.8 = 32\,\text{nanoeq/L}$$

Values at less than 0.10-unit steps can be estimated from interpolation. A p is three-tenths of the way between 7.30 and 7.20. Since the H^+ concentration increases by 13 nanoeq/L (from 50 to 63 nanoeq/L) as the pH falls from 7.3 the H^+ concentration at a pH of 7.27 can be calculated from

$$[H^+] = 50 + (0.3 \times 13) = 54\,\text{nanoeq/L}$$

The following example illustrates how this equation can be used in the clini setting. Suppose a patient with salicylate intoxication is found to have the arterial values, which are consistent with a mild metabolic acidosis:

$$\text{pH} = 7.32$$
$$P_{CO_2} = 30\,\text{mmHg}$$
$$[HCO_3^-] = 15\,\text{meq/L}$$

An important facet of therapy in this disorder is to alkalinize the blood, whi decrease the concentration of salicylate in the tissues (see Chaps. 19 and 39). Thus, the initial aim of therapy is to raise the arterial pH to 7.45 (H$^+$ concentration equal to 36 nanoeq/L). Assuming that the P_{CO_2} remains constant, the level to which the plas HCO_3^- concentration has to be raised to achieve this goal can be estimated

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]}$$
$$36 = 24 \times \frac{30}{[HCO_3^-]}$$
$$[HCO_3^-] = 20\,\text{meq/L}$$

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POTASSIUM BALANCE IN ACID-BASE DISORDERS

There are important interactions between potassium and acid-base balance involve both transcellular cation exchanges and alterations in renal functio

Metabolic Acid-Base Disorders

In metabolic acidosis, more than one-half of the excess hydrogen ions are b in the cells. In this setting, electroneutrality is maintained in part by the mo intracellular potassium into the extracellular fluid. Thus, metabolic acidosis a plasma potassium concentration that is elevated in relation to total body

The net effect in some cases is overt hyperkalemia; in other patients, who potassium-depleted due to urinary or gastrointestinal losses, the plasma po concentration is normal or even reduced.[30] There is still relative hyperkalemia, however, as evidenced by a further fall in the plasma potassium concentrat acidemia is corrected.

On average, the plasma potassium concentration will rise by 0.6 meq/L (the 0.2 to 1.7 meq/L) for every 0.1-unit reduction in extracellular pH.[31] The wide range, however, means that the degree to which the plasma potassium concentrati with treatment of the acidemia cannot be accurately predicted. Thus, carefu monitoring is required.

A fall in pH is much less likely to raise the plasma potassium concentration patients with lactic acidosis or ketoacidosis.[31,32] The hyperkalemia that is commonly seen in diabetic ketoacidosis, for example, is more closely relate insulin deficiency and hyperosmolality than to the degree of acidemia.[31,32] Why this occurs is not well understood.

Just as metabolic acidosis can cause hyperkalemia, a rise in the plasma po concentration can induce a mild metabolic acidosis. Two factors contribute phenomenon. First, a transcellular exchange occurs, as the entry of most o excess potassium into the cells is balanced in part by intracellular hydroge moving into the extracellular fluid.[33] The net effect is an extracellular acidosis an an intracellular alkalosis. Second, the rise in cell pH within the renal tubul reduces ammonium and therefore net acid excretion. In patients with hypoaldosteronism, for example, the mild metabolic acidosis is primarily du associated hyperkalemia.

The net effect of these changes in cation distribution and renal function is metabolic acidosis and relative hyperkalemia are often seen together. For s reasons, when the above ionic changes are reversed, hypokalemia and met alkalosis are also a common combination.[12,13]

Respiratory Acid-Base Disorders

Respiratory acidosis and alkalosis induce relatively small changes in potas balance. The reason for this minor effect is not well understood.

Concurrent Disorders of Potassium Balance

The preceding discussion has emphasized the effect of pH on potassium dis between the cells and extracellular fluid. However, some patients have con disorders of potassium balance that can affect this relationship. In particul although metabolic acidosis typically produces relative hyperkalemia, patie be hypokalemic at presentation if there is a source of potassium loss. Exam include diarrhea and renal tubular acidosis. On the other hand, true hyperk (i.e., associated with increased body potassium stores) is present in patien hypoaldosteronism (type 4 renal tubular acidosis) as a result of impaired u potassium excretion.

The situation may be more complicated in patients with diabetic ketoacidos patients are often markedly potassium-depleted because of urinary and gastrointestinal losses; however, hyperkalemia is found in approximately or patients at presentation because of the hyperosmolality and insulin deficie as noted above, the metabolic acidosis. The administration of insulin typica to hypokalemia, unmasking the true state of potassium balance. (See Chapter 25)

PROBLEMS

17-1 Convert the following values for arterial pH to H^+ concentration:

a. **7.60**

b. **7.15**

c. **7.24**

17-2 What acid-base disorders are represented by the following sets of arterial blood tests:

	pH	P_{CO_2}, mmHg	$[HCO_3^-]$, meq/L
(a)	7.32	28	14
(b)	7.47	20	14
(c)	7.08	49	14
(d)	7.51	49	38

17-3 A patient with severe diarrhea has the following laboratory tests:

$$\text{Arterial pH} = 6.98$$
$$P_{CO_2} = 13 \text{ mmHg}$$
$$[HCO_3^-] = 3 \text{ meq/L}$$

a. **What is the acid-base disorder?**

To get the patient out of danger, the initial aim of therapy is to inc the pH to 7.20 by the administration of $NaHCO_3$. Assuming that the P_{CO_2} remains constant:

b. **To what level must the plasma HCO_3^- concentration be raised to reach a pH of 7.20?**

c. **If the P_{CO_2} increased to 18 mmHg with therapy, due to partial remov the acidemic stimulus to hyperventilation:**

d. **To what level must the plasma HCO_3^- concentration now be increased to achieve a pH of 7.20?**

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Footnotes

* These concentrations can also be expressed in terms of molarity. Since th of H^+ is 1, 40 nanoeq/L equals 40 nanomol/L.

† Calculation of the anion gap and the ratio of the rise in the anion gap to the plasma HCO_3^- concentration also may be diagnostically important in patie with metabolic acidosis (see chap. 19).

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Chapter Eighteen
Metabolic alkalosis

The introduction to acid-base disorders presented in Chapter 17 should be read before proceeding with this discussion. Primary metabolic alkalosis is characterized by an elevation in the arterial pH (or a reduction in the H^+ ion concentration), an increase in the plasma HCO_3^- concentration, and compensatory hypoventilation, resulting in a rise in the PCO_2. A high HCO_3^- concentration, however, is not diagnostic of metabolic alkalosis, since it can also represent the renal compensation to chronic respiratory acidosis. These disorders can be differentiated by measurement of extracellular pH, which is reduced in chronic respiratory acidosis. In addition, a plasma HCO_3^- concentration of 40 meq/L or more indicates at least some degree of metabolic alkalosis, since this level is greater than that generally achieved by renal compensation to severe chronic hypercapnia.

PATHOPHYSIOLOGY

The pathophysiology of metabolic alkalosis is most easily understood by asking separate questions:

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1. How do patients become alkalotic?
2. Why do they remain alkalotic, since renal excretion of the excess HCO_3^- should rapidly restore normal acid-base balance?

Generation of Metabolic Alkalosis

A primary elevation in the plasma HCO_3^- concentration is usually induced by loss of H^+ from the gastrointestinal tract (as with vomiting or nasogastric suction) or the kidneys (as with the diuretic therapy) (Table 18-1). These H^+ ions are derived from the intracellular dissociation of H_2CO_3:

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

Thus, there will be an *equimolar generation of HCO_3^- for each milliequivalent of H^+ that is lost*.

Metabolic alkalosis can also be produced by the administration of HCO_3^-, by an H^+ movement into the cells, and by certain forms of volume contraction. A transcellular H^+ shift typically occurs with hypokalemia. As the plasma K^+ concentration falls, K^+ moves out of the cells down a favorable concentration gradient to partially correct the extracellular stores. Electroneutrality is maintained

in this setting by a reciprocal shift of H^+ (and Na^+) into the cells.[1,2] The net effect is an *extracellular alkalosis with a paradoxical intracellular acidosis*.[3,4] K^+ repletion can reverse the H^+ shift and lower the extracellular pH toward normal.[1,2]

Table 18-1 Causes of metabolic alkalosis

Loss of hydrogen

A. Gastrointestinal loss
   1. Removal of gastric secretions—vomiting or nasogastric suction[a]
   2. Antacid therapy, particularly with cation-exchange resin
   3. Chloride-losing diarrhea

B. Renal loss
   1. Loop or thiazide-type diuretics[a]
   2. Mineralocorticoid excess[a]
   3. Postchronic hypercapnia
   4. Low chloride intake
   5. High-dose carbenicillin or other penicillin derivative
   6. Hypercalcemia, including the milk-alkali syndrome

C. H^+ movement into cells
   1. Hypokalemia[a]
   2. Refeeding (?)

Retention of bicarbonate

A. Massive blood transfusion
B. Administration of $NaHCO_3$
C. Milk-alkali syndrome

Contraction alkalosis

A. Loop or thiazide-type diuretics
B. Gastric losses in patients with achlorhydria
C. Sweat losses in cystic fibrosis

[a] Most common causes.

A *contraction alkalosis* occurs when the fluid that is lost contains little or no HCO_3^-. In this setting, which is most commonly due to diuretics, the extracellular volume contracts around a relatively constant quantity of extracellular HCO_3^-. As a result, the plasma HCO_3^- concentration rises (Fig. 18-15).[5] The severity of this process is generally limited by buffering of the excess extracellular HCO_3^- by cellular and bone buffers.[6]

Patients with metabolic alkalosis are almost always *hypochloremic*, usually because of chloride loss with H^+ with gastrointestinal or renal losses. As described in this section, hypochloremia is thought to play a major role in the maintenance of metabolic alkalosis by limiting HCO_3^- excretion.

Maintenance of Metabolic Alkalosis

The kidney possesses the ability to correct a metabolic alkalosis by excreting excess HCO_3^- in the urine. For example, normal subjects given 1000 meq of $NaHCO_3$ per day for 2 weeks excrete virtually all of the excess HCO_3^- and develop only a minor increase in the plasma HCO_3^- concentration.[7] Since the disorders that cause metabolic alkalosis are associated with a much smaller, the *perpetuation of metabolic alkalosis requires an impairment in renal HCO_3^- excretion* (Table 18-2).*

Both a reduction in glomerular filtration rate (and therefore in the filtered HCO_3^- load) and an elevation in tubular reabsorption contribute to this process.[8,9,10,11] It is likely that the latter is more important, since a low filtration rate alone, as in chronic renal insufficiency, does not appear to predispose to metabolic alkalosis.

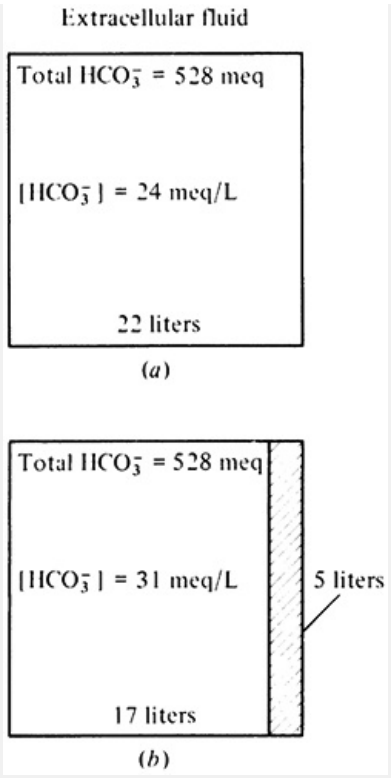

Figure 18-1 Mechanism of contraction alkalosis. (*a*) The volume and HCO_3^- concentration of the extracellular fluid in an as yet untreated 70-kg man w extracellular volume has increased from 17 to 22 liters because of conges heart failure. (*b*) If the excess NaCl is lost isotonically after the administrati diuretic, there will be a reduction in the extracellular volume. Since the q of extracellular HCO_3^- is initially unchanged, the HCO_3^- concentration in the extracellular fluid will increase from 24 to 31 meq/L.

As was reviewed in Chap. 11, HCO_3^- reabsorption occurs by secretion of H^+ from the tubular cell into the lumen. The proximal tubule plays the major role in this reabsorbing approximately 90 percent of the filtered HCO_3^-, mostly via Na^+–H^+ exchange. The remaining HCO_3^- is primarily reabsorbed in the loop of Henle via Na^+–H^+ exchange and in the collecting tubules via an H^+-ATPase pump in the luminal membrane.

A variety of factors may contribute to the increased HCO_3^- reabsorption that is seen in metabolic alkalosis, including volume and chloride depletion, hyperaldosteronism, and hypokalemia.

Effective circulating volume depletion

The increase in net HCO_3^- reabsorption in effective volume depletion (which includes edematous states such as heart failure and cirrhosis; page 258) can be viewed as an appropriate response from the viewpoint of volume regulation

excess HCO_3^- were excreted in the urine, it would obligate concurrent loss of Na^+ to maintain electroneutrality, further diminishing tissue perfusion.

The effect of volume status on HCO_3^- reabsorption is dependent upon the degree of volume depletion. As an example, a 4-meq/L increase in serum HCO_3^- (from 25 to 29 meq/L of glomerular filtration rate) can be seen with the ingestion of a very low Na^+ diet (10 meq/day), even though the patient is clinically euvolemic.[12] On the other hand, HCO_3^- reabsorptive capacity can exceed 35 meq/L with marked reductions in tissue perfusion, thereby allowing a relatively severe metabolic alkalosis to persist.[9,10]

Table 18-2 Causes of impaired HCO_3^- excretion that allow metabolic alkalosis to persist

Decreased glomerular filtration rate

A. Effective circulating volume depletion
B. Renal failure (usually associated with metabolic acidosis)

Increased tubular reabsorption

A. Effective circulating volume depletion
B. Chloride depletion (also decreases bicarbonate secretion)
C. Hypokalemia
D. Hyperaldosteronism

Despite the clear relationship between hypovolemia and increased HCO_3^- reabsorption, the mechanism by which this occurs is incompletely understood. Micropuncture studies in experimental animals suggest that increased proximal reabsorption, if it occurs, cannot quantitatively explain the reduction in HCO_3^- excretion.[13,14] and[15] It is probable that this relative lack of change reflects the interaction of several counterbalancing factors.[16] Both angiotensin II, released in response to hypovolemia, and the elevated tubular fluid HCO_3^- concentration increase proximal HCO_3^- reabsorption—the former by enhancing the activity of Na^+-H^+-exchanger,[17] and the latter by allowing more H^+ ions to be secreted before approaching the minimum pH that the proximal tubule can achieve.(15.16) On the other hand, metabolic alkalosis itself decreases the activity of the Na^+-H^+ antiporter, an effect that is probably mediated in part by a parallel rise in renal tubular

pH.[18]

The net effect is that the decrease in net HCO_3^- excretion in metabolic alkalosis associated with volume depletion is primarily due to enhanced net HCO_3^- reabsorption in the distal nephron.[14,15] Secondary hyperaldosteronism may contribute to this response. Aldosterone directly stimulates the H^+-ATPase pump in the cortical and medullary collecting tubules.[19,20] In addition, aldosterone can indirectly increase net H^+ secretion (and therefore HCO_3^- reabsorption) by promoting Na^+ transport in the cortical collecting tubule.[21,22] The reabsorption of cationic Na^+ creates a lumen-negative potential difference; this electrical gradient then promotes H^+ accumulation in the lumen by minimizing the rate of passive diffusion.

Concurrent Cl^- depletion (induced by vomiting or diuretics) and hypokalemia also appear to play an important role in the increase in distal HCO_3^- reabsorption. To the degree that *Na^+ is reabsorbed but Cl^- cannot follow to dissipate the electrical gradient*, there will be a greater increase in luminal negativity and therefore greater stimulus to H^+ secretion.[23] The net effect of the almost complete reabsorption of filtered HCO_3^- is the paradoxical finding of *an acid urine despite the presence of extracellular alkalemia*.[23]

These changes are reversed with correction of the fluid and chloride deficit; setting, reversal of the metabolic alkalosis requires increased HCO_3^- excretion, a change that is primarily mediated by decreased net HCO_3^- reabsorption in the distal nephron.[24]

Chloride depletion

The above discussion has suggested a central role for volume depletion in maintenance of metabolic alkalosis. It has been suggested, however, that it is *depletion*, rather than decreased tissue perfusion, that is actually of primary importance.[13,14,25] Consistent with this hypothesis is the observation that repletion of the volume deficit by the administration of albumin does not reverse the increase in distal HCO_3^- reabsorption and does not correct the alkalosis.[14] On the other hand, the administration of non-Na^+-containing Cl^- salts (such as potassium or choline chloride) does not restore normovolemia but does result in decreased net acid excretion and a reduction in the plasma HCO_3^- to normal.[13,14,25]

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There are three mechanisms by which Cl^- depletion could perpetuate a metabolic alkalosis, independent of balance[13]:

1. The activity of the Na^+–K^+–$2Cl^-$ carrier in the luminal membrane

of the macula densa cell is primarily determined by the availability of Cl^- (see Fig. 4-3). Thus, hypochloremia will decrease delivery of Cl^- to the macula densa, resulting in less NaCl reabsorption. The latter change will promote the release of renin, leading to secondary hyperaldosteronism[26] and increased distal H^+ secretion.

2. The luminal H^+-ATPase pump in the intercalated cells in the collecting tubule is probably associated with passive cosecretion of Cl^- to maintain electroneutrality.[27] A decline in the tubular fluid Cl^- concentration will facilitate this process by maximizing the transtubular gradient for Cl^- secretion.

3. It has been assumed that the appropriate response in metabolic alkalosis results from diminished reabsorption of filtered HCO_3^-. It now appears, however, that at least some of the urinary HCO_3^- is derived from HCO_3^- *secretion* by a subpopulation of intercalated cells in the cortical collecting tubule in which H^+-ATPase pump is located on the basolateral rather than the luminal membrane (see page 338 and Fig. 18-2).[28,29] The final step in this process seems to involve Cl^-/HCO_3^- exchange across the luminal membrane. The energy for this transport is supplied by the highly favorable inward gradient for Cl^- since the cell Cl^- concentration is very low. Lowering the tubular fluid Cl^- concentration in metabolic alkalosis will diminish this gradient, thereby minimizing the ability to secrete HCO_3^-.

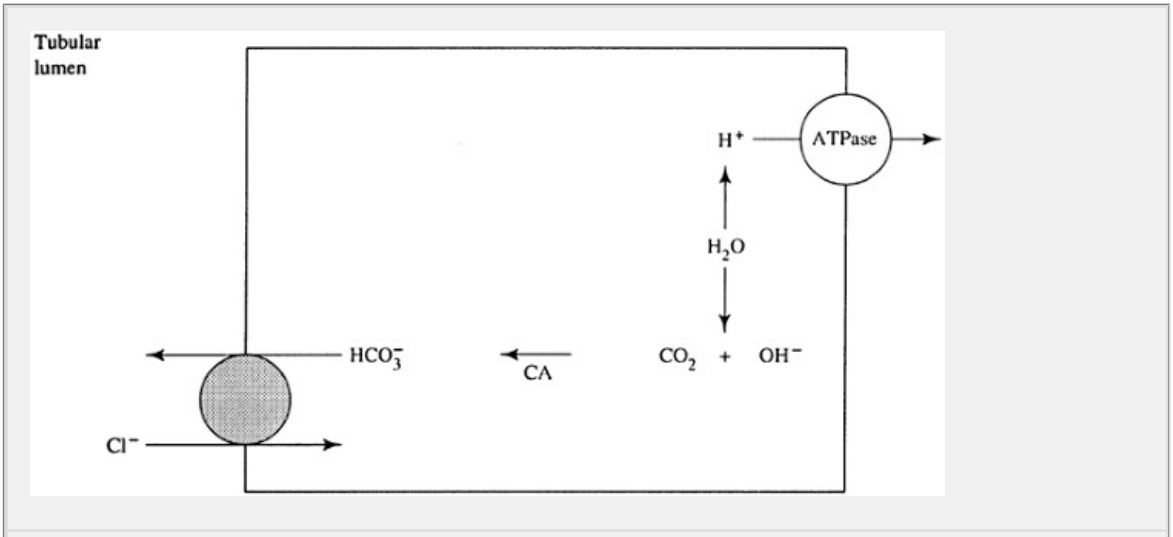

Figure 18-2 Transport mechanisms involved in the secretion of bicarbonate into the tubular lumen in the type B intercalated cells in the cortical collecting tubule. Water within the cell dissociates into hydrogen and hydroxyl anions. The hydrogen ions are secreted into the peritubular capillary by H-ATPase pumps in the basolateral membrane. The hydroxyl anions combine with carbon dioxide to form bicar

in a reaction catalyzed by carbonic anhydrase (CA). Bicarbonate is then s into the tubular lumen via chloride-bicarbonate exchangers in the luminal membrane. The favorable inward concentration gradient for chloride (lume concentration greater than that in the cell) provides the energy for bicarb secretion.

In summary, the relative roles of volume depletion and Cl^- depletion are unresolved. This issu is not of great clinical importance, however, since the administration of NaCl simultaneously correct both problems and allow the excess HCO_3^- to be excreted in the urine (see "Treatment," below).[9,29,30] This HCO_3^- diuresis is primarily due to diminished distal HCO_3^- reabsorption and/or enhanced distal HCO_3^- secretion.[13,24,28,29]

It is important to emphasize that hypovolemia and Cl^- depletion have *separate and independent effects* in metabolic alkalosis. To the degree that renal HCO_3^- reabsorption is enhanced, volume and chloride depletion from any cause will tend to perpe alkalosis. However, hypovolemia *per se* can produce an alkalosis only when the fluid lost contains an excess of H^+ ions or an excess of Cl^- in relation to HCO_3^-, thereby raising the plasma HCO_3^- concentration by contraction (Fig. 18-1). Thus, the vomiting or diuretic therapy often induce a metabolic alkalosis, but bleedin associated with the loss of NaCl and HCO_3^- in concentrations similar to those in the plasma, does not.

Hypokalemia

Hypokalemia is a potent stimulus to H^+ secretion and HCO_3^- reabsorption (see Fig. 11-16).[31,32] At least three factors may contribute to this relationship:

1. The concurrent intracellular acidosis, induced by transcellular K^+/H^+ exchange,[1,2] will tend to increase H^+ secretion.
2. There is a second proton pump in the distal nephron, a H^+-K^+-ATPase that actively reabsorbs K^+ as well as secreting H^+,[33,34] and[35] Electroneutrality is maintained by H^+ and K^+ movement in opposite directions across the lumina membrane. Active K^+ reabsorption by this pump appears to be appropriately stimulated by hypokalemia, an effect that could also enhance H^+ secretion.[33,35,36] and[37] Thus, hypokalemia and aldosterone, which stimul the H^+-K^+-ATPase and H^+-ATPase pumps, respectively, appear to have a potentiating effect on distal hydrogen secretion and therefore on the development and maintenance of metabolic alkalosis.[38] It is of interest in this regard that many of the causes of metabolic alkalosis (such as diuretic vomiting, and primary hyperaldosteronism) are associated with both a re

in the plasma K^+ concentration and increased aldosterone release.

3. Severe hypokalemia may cause, by an unknown mechanism, a reduction chloride reabsorption in the distal nephron.[39,40] As a result, Na^+ reabsorption at this site is associated with a greater luminal electronegativity and th greater tendency for H^+ secretion.[40]

The effect of hypokalemia is relatively small when HCO_3^- reabsorption is already stimulated by volume depletion (Fig. 18-3).[41] It appears to be of primary importanc however, in states of primary mineralocorticoid excess, as with an aldoster producing adrenal adenoma,[40,41] and[42] In this setting, aldosterone-induced Na^+ retention is transient, with marked volume expansion and edema being prev the phenomenon of aldosterone escape (see page 185). As a result, Na^+ intake and excretion are roughly equal, and it is hypokalemia, not volume depletion, th responsible for perpetuation of the alkalosis. Correction of the K^+ deficit returns the plasma HCO_3^- concentration toward normal in this setting, both by decreasing acid excretion in the urine[9,40,41] and[42] and, as most of the exogenous K^+ enters the cells to replete cellular stores, by movement of H^+ from cells back into the extracellular fluids.[1,2]

Respiratory Compensation

The development of alkalemia is sensed by the respiratory chemoreceptors, in a decline in ventilation and an *appropriate* elevation in the P_{CO_2}. On average, the P_{CO_2} rises 0.7 mmHg for every 1.0-meq/L increment in the plasma HCO_3^- concentration.[43,49] Thus, if the plasma HCO_3^- concentration is 34 meq/L (or 10 meq/L greater than normal), there should be a 7 mmHg increase in the P_{CO_2} to approximately 47 mmHg.

Values significantly different from this predicted value represent superimpo respiratory acidosis or alkalosis.

The respiratory compensation may be partially or completely impaired in th presence of underlying respiratory alkalosis or hypoxemia. As an example, with heart failure or cirrhosis frequently develop metabolic alkalosis as a r diuretic therapy. However, both of these disorders are often associated wit primary respiratory alkalosis (see Chap. 21), which can prevent the appropriate compensatory hypoventilation.

Hypoxemia, on the other hand, is generally less likely to affect the ventilat response. Hypoventilation will lower the P_{O_2} at the same time as it raises the P_{CO_2}.[45] However, the hypoxemic stimulation to respiration in alkalemic pati does not become prominent until the P_{O_2} is below 50 mmHg (see page 649). Thus,

in the absence of underlying lung disease, the final P_{CO_2} in metabolic alkalosis will not usually be sufficient to impair the compensatory response. As a result, P_{CO_2} in a previously normal subject can exceed 60 mmHg in severe metabolic alk[36]

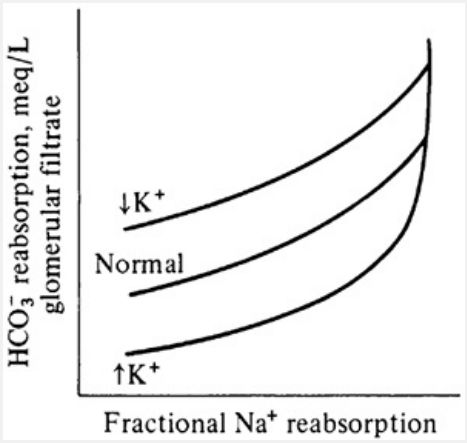

Figure 18-3 HCO_3^- reabsorption as a function of the fraction of the filtered Na^+ that is reabsorbed and the state of K^+ balance. HCO_3^- reabsorption is enhanced by both volume depletion (high fractional Na^+ reabsorption) and hypokalemia, conditions that therefore can perpetuate metabolic alkalosis. *Adapted from Kurtzman NA, White MG, Rogers PW: Arch Intern Med 131:702, 1973. By permission of the American Medical Association, copyright 1973*

What is less clear is the degree to which the change in respiration actually raises the extracellular pH. Studies in experimental animals indicate that this rise in P_{CO_2} in metabolic alkalosis increases net H^+ excretion and therefore *further elevates the plasma HCO_3^- concentration*.[47] These changes probably result from a reduction in renal tubular cell pH induced by the increment in the relative intracellular P_{CO_2}. The intracellular acidosis will stimulate H^+ secretion, thereby raising the plasma HCO_3^- concentration. The net effect is that, after several days, *the pH is the same as it would have been if no respiratory compensation had occurred*, because of equivalent elevations in the extracellular P_{CO_2} and HCO_3^- concentration (see page 580).[47]

ETIOLOGY

Metabolic alkalosis can be produced by a variety of disorders, most of which are characterized by enhanced HCO_3^- reabsorption due to volume, Cl^-, and/or K^+ depletion (Table 18-1).[11]

Gastrointestinal Hydrogen Loss

Removal of gastric secretions

Gastric juice contains high concentrations of HCl and lesser concentrations H^+. Each milliequivalent of H^+ secreted generates 1 meq of HCO_3^-. Under normal conditions, the increase in the plasma HCO_3^- concentration is only transient, since the entry of the acid into the duodenum stimulates an equal amount of panc HCO_3^- secretion.[48] However, there is no stimulus to HCO_3^- secretion if the gastric juice is removed, either by vomiting or by nasogastric suction. The net resu increase in the plasma HCO_3^- concentration and metabolic alkalosis.[23,49,50] The tendency toward alkalosis is enhanced by the concomitant volume and K^+ depl

Metabolic alkalosis also can occur after removal of gastric acid secretions with achlorhydria (little or no gastric acid secretion). In this setting, contra to the loss of a high Cl^-, low HCO_3^- fluid) rather than H^+ loss is responsible for the elevation in the plasma HCO_3^- concentration.

A somewhat similar sequence can be induced by chronic therapy with an an such as magnesium hydroxide. The hydroxide component buffers gastric H^+, while the magnesium combines with pancreatic HCO_3^- to form insoluble magnesium carbonate. If only these reactions occurred, there would be equivalent H^+ and HCO_3^- loss and no change in acid-base balance. However, some of the magn combines with other constituents in the intestinal lumen, such as fats and phosphates. As a result, some of the secreted HCO_3^- remains soluble and is

absorbed, leading to a mild alkaline load that produces no problems as long function is normal.[51]

The outcome may be different in patients with advanced renal failure who a treated with a cation-exchange resin (Kayexalate) for hyperkalemia.[49,52] In this setting, some of the magnesium binds to the resin, leaving more HCO_3^- in the form in the intestinal lumen and able to be absorbed. The renal failure is in perpetuating the alkalosis, since it prevents excretion of the excess HCO_3^-.

Congenital chloridorrhea

Since the enteric fluids below the stomach are alkaline, diarrhea usually le metabolic acidosis. However, a rare condition, *congenital chloridorrhea*, is associated with a specific intestinal defect in Cl^- reabsorption and HCO_3^- secretion, resulting in a high fecal Cl^- concentration that can reach 140 meq/L and a low fe pH.[49,53] Loss of this fluid tends to produce metabolic alkalosis; a similar pr can occur in some patients with a villous adenoma.[49]

Congenital chloridorrhea is induced by mutations in the down-regulated ade gene, which is presumably an intestinal anion transporter or a regulator of

transporter.[54] Treatment generally consists of a high chloride intake to preve volume depletion. However, such an approach also increases the severity o diarrhea because of the chloride malabsorption. Decreasing gastric chlorid secretion with a proton pump inhibitor such as omeprazole may produce 15 percent reductions in stool volume and Cl^- excretion.[55]

Factitious diarrhea

Factitious diarrhea due to laxative abuse is often associated with metabolic resulting from loss of HCO_3^--containing fluid.[49,56] However, many patients develop metabolic alkalosis.[49,56,57] How this occurs is not well understood, but hypokalemia may play an important role.

Renal Hydrogen Loss

Mineralocorticoid excess and hypokalemia

The conditions associated with primary mineralocorticoid excess, such as p hyperaldosteronism, are discussed in Chap. 27, since hypokalemia is typically the most prominent abnormality in these patients. As described above, aldoster promote H^+ secretion and the development of metabolic alkalosis by directly stimulating the distal H^+-ATPase pump and by making the lumen more electronegative via enhanced Na^+ reabsorption.[19,20,21] and[22] These transport processes involve different cells in the cortical and medullary collecting tul Na^+ reabsorption occurring in the principal cells and H^+ secretion occurring in the intercalated cells (see Chap. 5).

Hypokalemia due to concomitant urinary K^+ loss plays an essential role in the maintenance of the metabolic alkalosis in this setting.[9,40,41] and[42] If K^+ depletion is prevented, there is a lesser increment in H^+ excretion and only a minor elevation in the plasma HCO_3^- concentration.[42]

For these effects on H^+ and K^+ secretion to occur, there must be *adequate delivery of Na^+ and water to the distal secretory sites* (see page 184). This is not a

problem in primary hyperaldosteronism, in which the patient tends to be mil volume-expanded due to the stimulus to distal Na^+ reabsorption. However, distal delivery is reduced in patients with effective circulating volume depletion. A the associated secondary hyperaldosteronism does not lead to excessive H^+ and K^+ loss.[22,58] Thus, uncomplicated patients with heart failure or cirrhosis typica a normal K^+ concentration and are not alkalemic. However, hypokalemia and metabolic alkalosis may rapidly ensue if distal delivery is enhanced by the administration of diuretics.

Diuretics

The loop and thiazide-type diuretics are commonly associated with metabol

alkalosis, the severity of which varies directly with the degree of diuresis. volume contraction and, more importantly, increased H^+ loss may contribute to this problem.[5,6,59] The latter is primarily due to enhanced distal H^+ secretion, which results from the interplay of three factors: hypersecretion of aldosterone du associated hypovolemia; increased distal flow, since these agents inhibit N water reabsorption proximal to the H^+ secretory sites in the collecting tubules; an the concomitant development of hypokalemia.

Posthypercapnic alkalosis

Chronic respiratory acidosis is associated with a compensatory increase in H^+ secretion and therefore in renal HCO_3^- reabsorption (see chap. 20).[60] This represents an appropriate response, since the rise in the plasma HCO_3^- concentration returns the extracellular pH toward normal. The net effect is acidemia is not a major problem in uncomplicated patients.

Treatment with mechanical ventilation in this disorder can lead to a rapid r the P_{CO_2}. The plasma HCO_3^- concentration, however, will remain elevated, resulting in the development of metabolic alkalosis and, because of the fall P_{CO_2}, an acute rise in cerebral pH that can produce serious neurologic abnormali death.[61] As a result, the P_{CO_2} should be lowered slowly and carefully in patient with chronic hypercapnia; there is no need for rapid lowering, since the ext pH is generally well protected.[60]

Several factors may contribute to maintenance of the alkalosis in this settir Initially, there may be a "memory" effect, as the hypercapnia-induced stimu HCO_3^- reabsorption persists even though the P_{CO_2} has been returned toward normal.[62] How this occurs is not clear; however, the original increment in H^+ secretion takes 3 to 5 days to reach its maximum level,[60] and reversal of this process may be equally slow. Chronic respiratory acidosis is also associate both hypoxemia (which can lead to renal vasoconstriction)[63] and Cl^- loss in the urine, resulting in hypochloremia and volume depletion.[64] Increased cosecretion of Cl^- with the distal H^+-ATPase pump may be in part responsible for the chlorure[27] As a result, a posthypercapnic alkalosis will tend to persist until Cl^- balance is restored.[64]

Low chloride intake

Metabolic alkalosis may be induced in infants by the inadvertent administra formula containing Na^+ but almost no Cl^-.[65] The ensuing Cl^- depletion diminishes the amount of Cl^- in the tubular lumen, which can

promote the development of metabolic alkalosis by two mechanisms: Tubula H^+

reabsorption must occur in exchange for H^+, since less Cl^- is available,[22,23] and there is a more favorable gradient for CO_2 to be secreted into the lumen with H^+ by the H^+-ATPase pump.[27] Once the alkalosis has developed, the decrease in Cl^- delivery will, as noted above, contribute to perpetuation of the high plasma HCO_3^- concentration by impairing HCO_3^- excretion.[28,29]

High-dose carbenicillin or penicillin

A similar problem can occur with the intravenous administration of high dose carbenicillin or some other penicillin derivatives.[66,67] Intravenous carbenicillin, for example, contains 4.7 meq/g of Na^+, or 141 meq if 30 g is given. As the Na^+ carbenicillin is filtered, carbenicillin acts as a nonreabsorbable anion. Consequently some distal Na^+ reabsorption must occur in exchange for K^+ and H^+, resulting in hypokalemia and metabolic alkalosis.[68] The relatively low tubular fluid Cl^- concentration in this setting also may play a contributory role.

Hypercalcemia

Renal H^+ secretion and HCO_3^- reabsorption are increased by hypercalcemia,[69,70] possibly leading to a mild metabolic alkalosis.[71] Both the mechanism by which this might occur and the role of concurrent changes in parathyroid hormone (PTH) secretion are unclear. Patients with primary hyperparathyroidism tend to have a metabolic acidosis, a change that has been thought to result from a decrease in proximal HCO_3^- reabsorption.[72] However, some other factor may be important in this setting, since the chronic continuous administration of PTH to normal humans *increases* net acid excretion and produces a small elevation, not a reduction, in plasma HCO_3^- concentration.[73]

Regardless of the mechanism, similar factors probably contribute to the *milk-alkali syndrome*, in which the chronic ingestion of milk and/or calcium carbonate–containing antacids leads to hypercalcemia and metabolic alkalosis.[74,75,76] The carbonate load raises the plasma HCO_3^- concentration, while the combination of hypercalcemia and renal insufficiency (which is mostly due to the hypercalcemia) prevents the urinary excretion of the excess HCO_3^-.[75] The most common cause at present is the administration of calcium carbonate as a phosphate binder to patients with chronic renal failure.[76]

Intracellular Shift of Hydrogen

Hypokalemia

Hypokalemia is a frequent finding in patients with metabolic alkalosis. This association is due to several factors.[1] The common causes of metabolic alkalosis (vomiting, diuretics, mineralocorticoid excess) directly induce both K^+ loss and H^+ loss,[2] and hypokalemia causes a transcellular shift in which K^+ leaves and H^+ enters the cells,

thereby raising the extracellular pH,[1,2,3] hypokalemia increases net acid excretion and HCO_3^- reabsorption,[31,32,40,41] and[42] an effect that is probably due in part to the associated intracellular acidosis.

P.563

Refeeding

Patients who are refed carbohydrate after a prolonged fast can acutely dev metabolic alkalosis.[77] Since there is neither volume contraction nor a demonstr increase in urinary acid excretion, it has been proposed that an intracellula H^+ may be responsible. The mechanism by which this might occur is unknow

Refeeding is also associated with retention of Na^+, which may be responsible for perpetuation of the alkalosis.[77] Increased secretion of insulin, resulting from the carbohydrate ingestion, may contribute to this response.

Retention of Bicarbonate

Because of the ability of the kidney to excrete HCO_3^-, it is difficult to produce more than a small increment in the plasma HCO_3^- concentration by the chronic administration of as much as 1000 meq of HCO_3^- per day.[7] However, a significant alkalemia can be produced by the acute infusion of base or by the chronic administration of alkali in a patient in whom renal HCO_3^- excretion is impaired (as in the milk-alkali syndrome).

Administration of organic anions

Organic anions, such as lactate, are rapidly metabolized in the body to HCO_3^-.[78] For example,

$$CH_3CHOHCOO^-(\text{lactate}) + 3O_2 \rightarrow 2CO_2 + 2H_2O + HCO_3^-$$

The same is true for acetate, citrate, and, in the presence of insulin, the a the ketoacids.[79]

As a result, the administration of organic anions can lead to the developme metabolic alkalosis. Most bank blood, for example, is anticoagulated with a citrate-dextran. Each unit (500 mL) of blood contains 16.8 meq of citrate, w generates HCO_3^- as it is metabolized. Although citric acid also is present, it h a transient effect on the systemic pH, since it is rapidly converted to CO_2 and H_2O. In general, more than eight units of blood must be given acutely to produce significant elevation in the plasma HCO_3^- concentration.[80]

Citrate-induced alkalosis also may occur when citrate is used in place of he an anticoagulant in hemodialysis patients who are at high risk for bleeding.[81] In this setting, the rise in the plasma HCO_3^- concentration may persist for several days because of the absence of renal function.

A similar problem may occur after the administration of some human plasma fractions (Protenate, Plasmatein), which are used as volume expanders.[82] These solutions contain acetate (as a source of HCO_3^-) and citrate (as a preservative) in a total concentration of 40 to 50 meq/L. The metabolism of these anions can cause a significant elevation in the plasma HCO_3^- concentration.

Administration of sodium bicarbonate

The most common indication for $NaHCO_3$ therapy is in the treatment of metabolic acidosis. However, HCO_3^- therapy can result in metabolic alkalosis if given in excessive amounts. This is particularly true in lactic acidosis[83] and ketoacidosis,[79] in which endogenous HCO_3^- is replaced

during the initial buffering reaction by lactate or β -hydroxybutyrate. As a result, there is *no loss of potential* HCO_3^- (excluding those anions excreted in the urine), since the organic anion can be metabolized back to HCO_3^- once the underlying abnormality is corrected.

The net effect is that the administration of HCO_3^- in these disorders creates an excess of potential HCO_3^-, leading to a post-correction metabolic alkalosis. In extreme cases, the systemic pH has reached 7.90, with the plasma HCO_3^- concentration exceeding 60 to 70 meq/L, after the indiscriminate use of $NaHCO_3$ during cardiopulmonary resuscitation.[83] A similar problem can occur with massive $NaHCO_3$ ingestion as long as there is an underlying defect in HCO_3^- excretion, such as renal insufficiency.[84]

Contraction Alkalosis

The mechanism of a contraction alkalosis, in which NaCl and water are lost with HCO_3^-, is illustrated in Fig. 18-1.[5] This problem is most commonly seen with loop or thiazide-type diuretics; it can, however also occur with vomiting (even in patients with achlorhydria, in whom NaCl replaces HCl in the gastric secretions) or cystic fibrosis (where the sweat Cl^- concentration can exceed 70 to 100 meq/L, while the HCO_3^- concentration is well below that of the plasma).[85]

In the absence of massive fluid losses, the direct effect of contraction is largely minimized by the release of H^+ from cell buffers, thereby lowering the plasma HCO_3^- concentration toward normal:[6]

$$HCO_3^- + HBuf \rightarrow Buf^- + H_2CO_3 \rightarrow CO_2 + H_2O$$

Thus, with diuretic therapy or vomiting, it is the urinary or gastrointestinal losses of H^+ that are primarily responsible for the metabolic alkalosis.[6] The major contribution of volume contraction is in maintenance of the alkalosis by preventing excretion

the excess HCO_3^- in the urine.

SYMPTOMS

Patients with metabolic alkalosis may be asymptomatic or complain of symp related either to volume depletion (weakness, muscle cramps, postural dizz to hypokalemia (polyuria, polydipsia, muscle weakness). Complaints directl to alkalemia, however, are uncommon. Paresthesias, carpopedal spasm, an headedness occur in acute respiratory alkalosis but are seen much less fre metabolic alkalosis. This difference is probably related to the degree of alk the central nervous system: HCO_3^-, a polar compound, crosses the blood-brain barrier much more slowly than the lipid-soluble CO_2, thus producing a

lesser increase in the cerebrospinal fluid pH. Thus, the potentially severe neurologic abnormalities that may be seen in posthypercapnic alkalosis probably due to the sudden fall in PCO_2, not the persistent elevation in the plasma HCO_3^- concentration.

The physical examination is not usually helpful, revealing only signs of volu depletion, such as reduced skin turgor, low estimated jugular venous press postural hypotension, in selected cases. There may, however, be relatively findings in patients with self-induced vomiting. These include ulcers, callus scarring on the dorsum of the hand; dental erosions due to chronic exposur acid gastric secretions; and puffy cheeks resulting from hypertrophy of the glands.[50]

DIAGNOSIS

The etiology of metabolic alkalosis almost always is obtainable from the his there is no pertinent history, then the most likely diagnosis is *surreptitious vomiting or diuretic ingestion or one of the causes of mineralocorticoid ex*.

The urine Cl^- concentration can be helpful in differentiating between these conditions (Table 18-3).

Urine Chloride Concentration

The combination of hypovolemia and hypochloremia in patients with vomitin cystic fibrosis or those taking diuretics should induce maximum renal Cl^- conservation, usually lowering the urine Cl^- concentration to less than 25 meq/L. (This excludes the period during which the diuretic is active, when Cl^- excretion is elevated.) These patients may also show the physical findings of volume de of self-induced vomiting described above. In contrast, the signs of hypovole absent and the urine Cl^- concentration exceeds 40 meq/L in patients with mineralocorticoid excess or alkali loading, who are generally volume-expan in whom Cl^- excretion is equal to intake.

Metabolic alkalosis is the major clinical setting in which the *urine Cl concentration*

may be a more accurate estimate of volume status than is the urine Na^+

concentration[87] Although hypovolemia leads to renal Na^+ retention, this may be counteracted by the necessity for Na^+ to be excreted with the excess HCO_3^-. As depicted in Fig. 18-3, the maximum reabsorptive capacity for HCO_3^- may be markedly increased by volume depletion and the associated rise in Na^+. This response, however, takes 3 to 4 days to reach completion, leading to variable the urinary findings (Table 18-4).[23,49]

Table 18-3 Urine Cl^- concentration in patients with metabolic alkalosis

Less than 25 meq/L	Greater than 40 meq/L
Vomiting or nasogastric suction Diuretics (late) Factitious diarrhea Posthypercapnia Cystic fibrosis Low chloride intake	Primary mineralocorticoid excess Diuretics (early) Alkali load (bicarbonate or other organic anion) Bartter's or Gitelman's syndrome Severe hypokalemia (plasma K^+ < 2.0 meq/L

In the first few days of vomiting, there is a high filtered load of HCO_3^-, secondary to contraction alkalosis and hyperaldosteronism but an inability to maximally conserve HCO_3^-. As a result, some of the excess HCO_3^- is delivered out of the proximal tubule as Na^+ and HCO_3^-. Some of this Na^+ is then exchanged for K^+ in the cortical collecting tubule under the influence of aldosterone. The net effect is relatively high rates of Na^+ and K^+ excretion and HCO_3^- excretion, the latter leading to an alkaline urine pH. The urinary loss of potentially large amounts of K^+ during this early period is primarily responsible for the K^+ depletion that commonly occurs with persistent or massive vomiting; gastric losses play a lesser role, since K^+ concentration in gastric secretions is only 5 to 10 meq/L. The urine Cl^- concentration is appropriately reduced at this time, the only urinary sign pointing toward hypovolemia.

The urinary chemistries change dramatically once the HCO_3^- reabsorptive capacity increases sufficiently to reabsorb all of the filtered HCO_3^- load.[23] At this time, excretion of Na^+, K^+, HCO_3^-, and Cl^- are all reduced, and there is a paradoxically acid urine pH (Table 18-4). This late phase is dependent upon volume and Cl^- depletion being

severe enough to allow all of the filtered load of HCO_3^- to be reabsorbed. Some patients ingest enough NaCl so that the filtered load of HCO_3^- and the HCO_3^- concentration remains above reabsorptive capacity, leading to persistent urinary changes similar to those of the early phase. Again, it is the low urine Cl^- concentration that will point toward the correct diagnosis.

The urine Cl^- concentration may not be useful in patients who are unable to maximally conserve Cl^- because of a defect in tubular reabsorption. This abnormality may occur with renal insufficiency or with severe hypokalemia (plasma K^+ concentration below 2.0 meq/L), in which distal Cl^- reabsorption appears to be impaired.[39,40,88] In these settings, the urine Cl^- concentration may be elevated despite the presence of volume depletion.

Metabolic Alkalosis versus Respiratory Acidosis

An elevated plasma HCO_3^- concentration, hypercapnia, and hypoxemia all may be found in chronic respiratory acidosis as well as in metabolic alkalosis (see Chap. 20).

If uncomplicated, these disorders can be easily differentiated by measuring arterial pH. However, this distinction becomes more difficult when the patient with underlying chronic lung disease develops a superimposed metabolic alkalosis. For example, consider the following case history:

Table 18-4 Variation in urine electrolytes with vomiting

Time	$[Na^+]$	$[K^+]$	$[Cl^-]$	$[HCO_3^-]$	pH
Days 1–3	↑	↑	↓	↑	>6.5
Late	↓	↓	↓	↓	<5.5

Case History 18-1

A 45-year-old man with a long smoking history reports 1 week of recurrent v
and has the following arterial blood values on room air:

$$pH = 7.49$$
$$P_{CO_2} = 55 \text{ mmHg}$$
$$[HCO_3^-] = 40 \text{ meq/L}$$
$$P_{CO_2} = 68 \text{ mmHg}$$

Comment

The high P_{CO_2} is compatible with either an appropriate respiratory compensa metabolic alkalosis or underlying lung disease in this chronic smoker. The way to establish the correct diagnosis is to treat the metabolic alkalosis an the P_{CO_2}, which should return to normal if there is no impairment in pulmona function.

It also may be helpful in selected cases to calculate the alveolar-arterial ($A-a$) O_2 gradient (see page 663):[89]

$$(A\text{-}a)\ O_2 \text{ gradient} = P_{I_{O_2}} - 1.25P_{CO_2} - Pa_{O_2}$$
$$= 150 - (1.25 \times 55) - 68$$
$$= 13 \text{ mmHg}$$

where $P_{I_{O_2}}$ refers to the partial pressure of oxygen in the inspired air (150 r sea level) and Pa_{O_2} is the partial pressure of oxygen in arterial blood. A norma O_2 gradient suggests that pulmonary function is normal and that this patien pure metabolic alkalosis. However, the converse is not necessarily true. An increased gradient is not diagnostic of chronic respiratory acidosis, since i seen in many acute and chronic pulmonary diseases not associated with CO_2 retention.

TREATMENT

Metabolic alkalosis can be corrected most easily be the urinary excretion o excess HCO_3^-. This does not occur spontaneously because, in the patient wit relatively normal renal function, volume and/or K^+ depletion leads to enhanced net HCO_3^- reabsorption.[9,10] and[11] Therefore, the aim of therapy is to repair the deficits, which will have two beneficial effects: a decrease in HCO_3^- reabsorption, thereby allowing the excess HCO_3^- to be excreted, and, with K^+ depletion, a

direct reduction in the plasma HCO_3^- concentration because of the reciprocal shif K^+ into and H^+ out of the cells.[1,2] As will be seen, this requires the *administration of Cl, as NaCl, KCl, or HCl*.[30,90,91]

Treatment should also be directed at the underlying disease and at diminish further H^+ loss. In patients with continued vomiting or nasogastric suction, fo example, the administration of an H_2-blocker or proton pump inhibitor can marked reduce the rate of gastric H^+ secretion.[92]

Saline-Responsive Alkalosis

The most common causes of metabolic alkalosis are vomiting, nasogastric s and diuretic therapy. In these disorders (and with posthypercapnia and a lo intake), the increase in HCO_3^- reabsorption that maintains the alkalosis can be reversed by the oral or intravenous administration of NaCl and water, e.g., isotonic or isotonic saline (Table 18-5).[30,90,91] This regimen can lower the plasma HCO_3^- concentration in three ways:

1. By reversal of the contraction component.
2. By removing the stimulus to renal Na^+ retention, thereby permitting NaHCO$_3$ excretion in the urine.
3. By increasing distal Cl^- delivery, which will promote HCO_3^- secretion in the cortical collecting tubule. Studies in experimental animals suggest that HCO_3^- secretion is the primary factor responsible for the corrective bicarbonaturia following NaCl administration.[29]

The therapeutic effectiveness of this regimen can be followed at the bedsic measuring the *urine pH*. The urine pH is often below 5.5 prior to therapy as a r of enhanced H^+ secretion. However, when volume and Cl^- replacement are sufficient to allow the excess HCO_3^- to be excreted, the urine pH will exceed 7.0 and occasionally 8.0. The urine Cl^- concentration will remain below 25 meq/L until th is corrected.

The efficacy of fluid repletion is dependent upon the administration with the Na^+ only *reabsorbable* anion, Cl^-.[90,93] As this Na^+ enters the glomerular filtrate, it is reabsorbed with Cl^-, resulting in volume expansion. The outcome

is different if Na^+ is given with an impermeant anion, such as SO_4^{2-}. Reabsorption of this Na^+ in the distal nephron must now be accompanied by K^+ (or H^+) secretion to maintain electroneutrality.[93] The resulting increase in H^+ secretion will generate more HCO_3^- in the plasma, leading to exacerbation of the alkalosis.

Table 18-5 Causes of metabolic alkalosis accordin to saline responsiveness

Saline-responsive	Saline-resistant
Vomiting or nasogastric suction	Edematous states
Diuretics	Mineralocorticoid excess
Posthypercapnia	Severe hypokalemia

Low chloride intake	Renal failure

Although adequate NaCl repletion will usually normalize the plasma HCO_3^- concentration, it will not reverse any K^+ depletion that might be present. As with Na^+, the administration of K^+ with any anion other than Cl^- results in an increase in H^+ secretion, preventing correction of the alkalosis.[9094] This is important clinically, since many of the commercial K^+ supplements contain HCO_3^-, acetate, or citrate. Only KCl will be effective.

The requirement for Cl^- replacement also applies to those patients who are trea with an acid infusion (see below). HCl will be effective, because the initial of the excess acid will generate NaCl:

$$HCl + NaHCO_3 \rightarrow NaCl + H_2CO_3 \rightarrow CO_2 + H_2O \qquad (18\text{-}1)$$

In comparison, the administration of nitric acid will generate $NaNO_3$

$$HNO_3 + NaHCO_3 \rightarrow NaNO_3 + H_2CO_3 \rightarrow CO_2 + H_2O$$

The delivery of this Na^+ to the distal nephron with impermeant NO_3^- will again increase distal H^+ secretion.[95] The net effect is excretion of the administered ac and persistence of the alkalosis.

With the exception of patients with hypotension, shock, or severe associate electrolyte disturbances, *gradual* saline or half-isotonic saline repletion is prefer since it will restore normovolemia while minimizing the risk of volume overl pulmonary edema. The optimal rate of fluid replacement is somewhat arbitra regimen that has been successful is the infusion of the appropriate replace at the rate of 50 to 100 mL/h *in excess of the sum* of the urine output, estimated insensible losses (approximately 30 to 50 mL/h), and any other losses that present (such as diarrhea or tube drainage).

Saline-Resistant Alkalosis

The administration of saline is occasionally ineffective in correcting the alk This typically occurs in edematous states and in those disorders in which K^+ depletion, not hypovolemia, is responsible for perpetuation of the alkalosis. Table 18-5).

Edematous states

Patients with heart failure, cirrhosis, or the nephrotic syndrome often deve metabolic alkalosis following diuretic therapy. Both a reduction in the effec circulating volume, leading to avid Na^+ retention, and renal insufficiency can contribute the inability to excrete the excess HCO_3^- in these disorders. However, the administration of saline is not indicated, since it will increase the degree o perhaps precipitating pulmonary edema in the presence of heart failure. Co

therapy consists of withholding diuretics if possible, acetazolamide, HCl, o

Acetazolamide (250 to 375 mg, once or twice a day, given orally or intraven a carbonic anhydrase inhibitor that increases the renal excretion of $NaHCO_3$ (see Chap. 15).[96,97] This serves the dual purpose of treating both the edema and alkalosis. As with the use of saline in saline-responsive states, the efficacy acetazolamide can be assessed by monitoring the urine pH, which should e if HCO_3^- excretion is substantially enhanced. Balance must be carefully followed since acetazolamide increases urinary K^+ excretion.[96,97]

Acetazolamide can also be used in edematous patients with cor pulmonale a chronic hypercapnia.[98,99] Correction of the alkalemia may be particularly impor in this setting, since the rise in pH can further depress ventilation.[98] The latter, however, some potential problems, as acetazolamide can induce both a trar further elevation in the P_{CO_2} (usually 3 to 7 mmHg) and marked acidemia if ther an excessive reduction in the plasma HCO_3^- concentration.[100,101] The exacerbation of the hypercapnia, which is generally not clinically important partial inhibition of carbonic anhydrase in red cells. This enzyme catalyzes hydration of CO_2 to H_2CO_3, a reaction that is essential for CO_2 transport by the red cells and therefore for the elimination of CO_2 by the lungs.

If acetazolamide is ineffective and the alkalemia is moderately severe, HCl used to lower the plasma HCO_3^- concentration.[102,103] The amount of HCl required to normalize the plasma HCO_3^- concentration is equal to the HCO_3^- excess, which can be estimated from

$$HCO_3^- \text{ excess} = HCO_3^- \text{ space} \times HCO_3^- \text{ excess per liter}$$

In metabolic alkalosis, the HCO_3^- space is approximately 50 percent of the lean b weight.[104] If the normal plasma HCO_3^- concentration is 24 meq/L, then

$$HCO_3^- \text{ excess} = 0.5 \times \text{lean body weight (kg)} \times (\text{plasma } [HCO_3^-] - 24)$$

Thus, in a 60-kg patient with a plasma HCO_3^- concentration of 40 meq/L,

$$HCO_3^- \text{ excess} = 0.5 \times 60 \times (40 - 24)$$
$$= 480 \text{ meq}$$

It should be noted that this formula *underestimates* the acid requirement of a patient in a nonsteady state. As an example, continued losses from nasogastric suc be added on to the initial estimate of the HCO_3^- excess.

HCl is usually given as an isotonic solution (150 meq each of H^+ and Cl^- in 1 liter of distilled water) over 8 to 24 h.[11,102] Since HCl is very corrosive, it should be infused into a major vein, such as the subclavian or femoral vein. However, peripheral vein can be safely used if the HCl is buffered in an amino acid s and infused with a fat emulsion.[103]

Ammonium chloride and arginine hydrochloride, which result in the formatio should not be given, since they may lead to appreciable toxicity. Ammonium is converted into HCl and ammonia in the liver; the ensuing

accumulation of ammonia makes this drug contraindicated in patients with a liver disease. Furthermore, an ammonia-related metabolic encephalopathy, characterized by lethargy and coma, may occur even in patients with norma and renal function.[105] Arginine hydrochloride, on the other hand, can induce potentially life-threatening hyperkalemia.[106,107] This effect is thought to result fro the movement of cellular potassium into the extracellular fluid as the cation arginine enters the cells.

Mineralocorticoid excess

States of primary mineralocorticoid excess are characterized by mild volum expansion and a rate of urinary Na^+ excretion that is equal to intake (due to aldosterone escape; see page 185). The alkalosis in this setting is resistant to saline, since neither renal Na^+ avidity nor Cl^- depletion is the limiting factor in HCO_3^- excretion.[41] In contrast, it is the combination of hypokalemia and hypersecretion of aldosterone that is responsible for perpetuation of the alkalosis.[9,10,41,42] Correction of the hypokalemia tends to lower the plasma HCO_3^- concentration in two ways: by allowing increased HCO_3^- excretion and by causing H^+ ions to move out of the cells into the extracellular fluid.[41,42]

Successful treatment requires the restoration of normal mineralocorticoid a (see Chap. 27). This can be achieved by surgical removal of an adrenal aden by the use of a K^+-sparing diuretic, such as amiloride or the aldosterone anta spironolactone.[108]

Severe hypokalemia

Patients with metabolic alkalosis and hypovolemia may be resistant to salin in the presence of severe K^+ depletion.[88] In this setting, the total K^+ deficit usually is greater than 800 to 1000 meq, the plasma K^+ concentration generally is less than 2.0 meq/L, and the urine Cl^- concentration exceeds 15 meq/L despite the presen of volume depletion. This defect in Cl^- conservation, which appears to be due to diminished distal Cl^- reabsorption,[39,40] may explain the negative response to sali If Cl^- reabsorption is impaired and the availability of K^+ for exchange with Na^+ is limited, then Na^+ reabsorption must be accompanied by increased H^+ secretion and HCO_3^- reabsorption,[40] thereby preventing a HCO_3^- diuresis. Diminished Cl^- reabsorption could also impair correction by secretion of HCO_3^- in the cortical collecting tubule, a process that appears to be mediated by Cl^-/HCO_3^- exchange.

These effects of severe hypokalemia are readily reversible. The replaceme

one-half of the K^+ deficit will normalize Cl^- reabsorption and restore saline responsiveness, as the administration of saline will now correct the alkalosis.[88]

Renal failure

Rarely, a patient with renal failure develops metabolic alkalosis, usually as a result of marked gastric losses by nasogastric suction. In this setting, either HCl or NH4Cl can be used if the alkalemia is severe.[109] However, a special, low-buffer dialysis solution must be used, since normal solutions contain 35 to 40 meq/L of bicarbonate or an organic anion (such as acetate), which generates HCO_3^- when metabolized.[109]

PROBLEMS

18-1A patient with cirrhosis and ascites is admitted to the hospital with gastrointestinal bleeding due to ruptured esophageal varices. He is taken to surgery, where a portacaval shunt is performed. He is given a total of 6 units of blood before and during the surgery. Although the ascites was removed during the surgery, it begins to reaccumulate postoperatively. His laboratory tests were normal preoperatively, but the following values are obtained after surgery:

$$\text{arterial pH} = 7.53$$
$$P_{CO_2} = 50 \text{ mmHg}$$
$$[HCO_3^-] = 40 \text{ meq/L}$$

a. **What is responsible for the development of the metabolic alkalosis?**

b. **What would you expect the urine pH and Na^+ concentration to be?**

c. **How would you correct the alkalosis?**

18-2A 45-year-old woman with peptic ulcer disease reports 6 days of persistent vomiting. On physical examination, the blood pressure is found to be 100/60 without postural change, the skin turgor is decreased, and the jugular neck veins are flat. The initial laboratory data are

Plasma $[Na^+]$	=	140 meq/L	BUN	=	80 mg/dL
$[K^+]$	=	2.2 meq/L	[Creatinine]	=	1.9 mg/dL
$[Cl^-]$	=	86 meq/L	Urine pH	=	5.0
$[HCO_3^-]$	=	42 meq/L	$[Na^+]$	=	2 meq/L
Arterial pH	=	7.53	$[K^+]$	=	21 meq/L
P_{CO_2}	=	53 mmHg	$[Cl^-]$	=	3 meq/L

a. **How would you treat this patient?**

Twenty-four hours after appropriate therapy has been started, the HCO_3^- concentration is 30 meq/L. The following urinary values are obtained:

$$\text{Urine } [Na^+] = 100 \text{ meq/L}$$
$$[K^+] = 20 \text{ meq/L}$$
$$[Cl^-] = 3 \text{ meq/L}$$

b. **How do you account for the discrepancy between the high urine Na^+ concentration and the low urine Cl^- concentration?**

18-3A 22-year-old woman complains of easy fatigability and weakness year. She has no other symptoms. The physical examination is unrema including a normal blood pressure. The following laboratory tests have repeatedly present during this time:

$$\text{Plasma } [Na^+] = 141 \text{ meq/L}$$
$$[K^+] = 2.1 \text{ meq/L}$$
$$[Cl^-] = 85 \text{ meq/L}$$
$$[HCO_3^-] = 45 \text{ meq/L}$$
$$\text{Urine } [Na^+] = 80 \text{ meq/day}$$
$$[K^+] = 170 \text{ meq/day}$$

a. **What is the differential diagnosis?**

b. **What test would you order next?**

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Footnotes

* In this regard, metabolic alkalosis is similar to other “excess” disorders, s hyponatremia (too much water), hyperkalemia (too much K^+), and hypokalemia (too much Na^+). In each of these conditions, renal excretory capacity for the retained water is normally so high that a defect in renal excretion must be present f disorder to persist.

† The indications for the use of HCl, CO_2, lactic acidosis and ketoacidosis are discussed in Chaps. 19 and 25.

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Chapter Nineteen
Metabolic acidosis

The introduction to acid-base disorders in Chap. 17 should be read before proceeding with this discussion. Metabolic acidosis is a clinical disturbance characterized by a low arterial pH (or an increased H^+ concentration), a reduced plasma HCO_3^- concentration, and compensatory hyperventilation, resulting in a decrease in the PCO_2. A low plasma HCO_3^- concentration, however, is not diagnostic of metabolic acidosis, since it also results from the renal compensation to chronic respiratory alkalosis. These disorders can be easily differentiated by measurement of the arterial pH. In addition, a plasma HCO_3^- concentration of 10 meq/L or less is indicative of metabolic acidosis, as the renal compensation to chronic hypocapnia does not produce this degree of hypobicarbonatemia (see Chap. 21).

PATHOPHYSIOLOGY

From the reaction of H^+ with the primary extracellular buffer, HCO_3^-,

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O \qquad (19\text{-}1)$$

it can be appreciated that metabolic acidosis can be produced in two ways: by the addition of H^+ ions or by the loss of HCO_3^- ions. The latter increases the extracellular H^+ concentration by driving the buffering reaction to the left.

Response to an Acid Load

The response of the body to an increase in the arterial H^+ concentration involves four processes (see Chaps. 10 and 11): extracellular buffering, intracellular and bone buffering, respiratory compensation, and the renal excretion of the H^+ load. The first three act to minimize the increase in H^+ concentration until the kidneys restore acid-base balance by eliminating the excess H^+ in the urine. Since each of these processes has important clinical implications, they will be considered separately.

Extracellular buffering

Because of its high concentration, HCO_3^- is the most important buffer in the

extracellular fluid. The ability of the HCO_3^- to prevent large changes in the arterial pH (or H^+ concentration) can be appreciated if we use the law of mass action to the relationship between H^+, HCO_3^-, and P_{CO_2} (see page 308):

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]} \qquad (19\text{-}2)$$

If the normal P_{CO_2} is 40 mmHg and the plasma HCO_3^- concentration is 24 meq/L (equal to 24 mmol/L), then

$$[H^+] = 24 \times \frac{40}{24}$$
$$= 40 \text{ nanoeq/L} \qquad (pH = 7.40)$$

Let us assume that 12 meq of H^+ is added to each liter of the extracellular fluid. If this H^+ is buffered by HCO_3^-, the plasma HCO_3^- concentration will fall from 24 to 12 meq/L. If the P_{CO_2} remains constant,

$$[H^+] = 24 \times \frac{40}{12}$$
$$= 80 \text{ nanoeq/L} \qquad (pH = 7.10)$$

Even though 12 meq (or 12 million nanoeq) of H^+ has been added to each liter, the free H^+ concentration has increased by only 40 nanoeq/L or 40×10^{-6} meq/L. Thus, more than 99.99 percent of the extra H^+ ions has been taken up by HCO_3^-, thereby preventing the H^+ concentration from exceeding 160 nanoeq/L (pH equals 6.80), the highest level that is generally compatible with life.

Intracellular buffering and the plasma potassium concentration

H^+ ions also are able to enter the cells and be taken up by the cell and bone, including proteins, phosphates, and bone carbonate:

$$H^+ + Pr^- \leftrightarrow HPr$$

On the average, 55 to 60 percent of an acid load will eventually be buffered by cells and bone, although higher values may occur with severe acidemia when extracellular HCO_3^- stores are markedly reduced.[1,2,3] As a result, the addition of 12 meq of H^+ to each liter of extracellular fluid will lower the plasma HCO_3^- concentration by 5 meq/L or less, not by 12 meq/L. If the new plasma HCO_3^- concentration is 19 meq/L and the P_{CO_2} remains at 40 mmHg, then

$$[H^+] = 24 \times \frac{40}{19}$$
$$= 51 \text{ nanoeq/L} \qquad (pH = 7.29)$$

Thus, the contribution of cellular and bone buffers results in better maintenance of the extracellular H^+ concentration than was seen above when only extracellular HCO_3^- buffering was available (pH=7.10).

The intracellular entry of H^+ ions in metabolic acidosis is associated in part with movement of K^+ out of the cells to maintain electroneutrality.[4,5,6] This response leads to a variable rise in the plasma K^+ concentration that is most prominent in those forms of metabolic acidosis that are due to an excess of nonorganic acid and occurs with renal failure or diarrhea.[5] In the latter setting, the plasma K^+ concentration may be below normal as a result of concurrent intestinal loss but is still higher than it would have been in the absence of acidemia.[6]

For reasons that are incompletely understood, the fall in pH in the organic acidoses (such as ketoacidosis, lactic acidosis, or that following certain ingestions) have little effect on K^+ distribution (see page 372).[5,7,8] Hyperkalemia is often present in these disorders, but is primarily due to other factors. In diabetic ketoacidosis and nonketotic hyperglycemia, for example, the combination of insulin deficiency (which retards K^+ entry into cells) and hyperglycemia (which pulls water and, by solvent drag, K^+ out of the cells) frequently leads to hyperkalemia, despite usually marked K^+ depletion due to urinary and gastrointestinal losses.[7,9] Correction of these problems with insulin therapy results in a rapid fall in the K^+ concentration, thereby unmasking the true state of total body K^+ stores. Hyperkalemia can also occur in lactic acidosis, but it is due to hypoperfusion-induced tissue injury and renal failure, not to acidemia.

Respiratory compensation

Metabolic acidosis stimulates both the central and peripheral chemoreceptors controlling respiration, resulting in an increase in alveolar ventilation. The resulting fall in P_{CO_2} will then raise the extracellular pH toward normal. This increase in ventilation begins within 1 to 2 h and reaches its maximum level at 12 to 24 h.[10,11] It is characterized more by an increase in tidal volume than by an increase in respiratory rate, and may, if the acidemia is severe, reach a maximum of as much as 30 L/min (normal equals 5 to 6 L/min).[11] This degree of hyperventilation (called Kussmaul respiration) is usually apparent on physical examination and should alert the physician to a possible underlying metabolic acidosis.

Studies in otherwise normal patients with metabolic acidosis have revealed that, on the average, the P_{CO_2} *will fall 1.2 mmHg for every 1.0-meq/L reduction in the plasma* HCO_3^- *concentration* down to a minimum P_{CO_2} of 10 to 15 mmHg.[12]

Suppose, for example, that an acid load lowers the plasma HCO_3^- concentration to 9 meq/L. This decrease of 15 meq/L should be associated with an 18 mmHg (1.2 × 15) fall in the P_{CO_2} to approximately 22 mmHg (pH equals 7.23). Thus, in pure metabolic acidosis with a plasma HCO_3^- concentration of 9 meq/L, *the normal* P_{CO_2} *is roughly 22 mmHg, not 40 mmHg*

Values substantially different from the predicted P_{CO_2} represent mixed acid-base

disorders (Table 19-1). Thus, a "normal" P_{CO_2} of 40 mmHg (pH equals 6.98) in this setting is indicative of a combined metabolic and respiratory acidosis, as m in a patient with chronic lung disease. On the other hand, a lower than exp P_{CO_2} of 15 mmHg (pH equals 7.40) suggests a combined metabolic acidosis respiratory alkalosis, as might be seen with salicylate intoxication (see bel

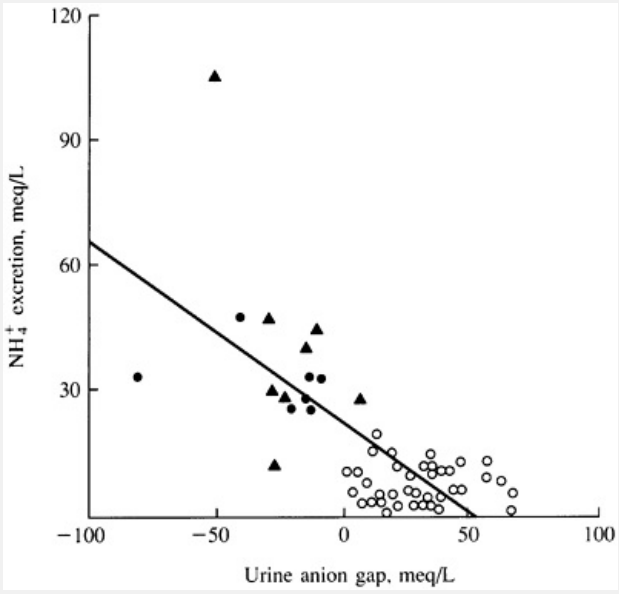

Figure 19-1 The relationship between the urine anion gap and the rate of NH_4^+ excretion in normal subjects receiving ammon-ium chloride (closed circles patients with metabolic acidosis due to diarrhea (closed triangles), and ir patients with impaired urinary acidification due to type 1 or 4 renal tubula acidosis (open circles). The urine anion gap has a positive value in the la group, indicative of the defect in NH_4^+ excretion. *(From Batlle DC, Hizon M, Cohen E, et al: N Engl J Med 318:594, 1988. By permission from the* New England Journal of Medicine.)

Although compensatory hyperventilation minimizes the degree of acidemia, *protective effect appears to last for only a few days.* This limitation occurs because the fall in P_{CO_2} directly lowers renal HCO_3^- reabsorption, resulting in HCO_3^- loss in the urine and a further reduction in the plasma HCO_3^- concentration.[13] It is thought that these changes reflect a hypocapnia-induced rise in renal tubular cell p diminishes H^+ secretion and HCO_3^- reabsorption (see page 360).

The net effect is that *the arterial pH in chronic metabolic acidosis is the same whether or not the respiratory compensation has occurred.*[13] As shown in the example in Table 19-2, for example, the arterial pH is 7.29 in uncompensated metabolic acidosis. The compensatory 6 mmHg decrease in the P_{CO_2} lowers the plasma HCO_3^- concentration from 19 to 16 meq/L, returning the arterial pH

7.29. Fortunately, severe metabolic acidosis is usually acute (lactic acidosi ketoacidosis, ingestions), and the hypocapnia is protective in this setting.

Renal hydrogen excretion

The metabolism of a normal adult diet results in the generation of 50 to 100 H^+ per day, which must then be excreted in the urine if acid-base balance is maintained.[14] This process involves two basic steps: reabsorption of the filte HCO_3^- and secretion of the dietary acid load.

The filtered HCO_3^- must be reabsorbed, since urinary loss of HCO_3^- will increase the net acid load and lower the plasma HCO_3^- concentration. Ninety percent of HCO_3^- reabsorption occurs in the proximal tubule and the remainder in the thick as limb and the distal nephron (see Chap. 11).

Table 19-1 Arterial measurements in hypothetical acid-base disorders

Acid-base status	Plasma $[HCO_3^-]$ meq/L	P_{CO_2} mmHg	Arterial pH
Normal	24	40	7.40
Pure metabolic acidosis	9	22	7.23
Combined metabolic and respiratory acidosis	9	40	6.98
Combined metabolic acidosis and respiratory alkalosis	9	15	7.40

The dietary acid load is excreted by the secretion of H^+ ions from the tubular cell into the lumen. These H^+ ions then combine either with the urinary buffers (particularly HPO_4^{2-}) in a process called titratable acidity) or with NH_3.[3,15]

$$H^+ + HPO_4^{2-} \rightarrow H_2PO_4^- \quad (19\text{-}3)$$

$$H^+ + NH_3 \rightarrow NH_4^+ \quad (19\text{-}4)$$

In general, 10 to 40 meq of H^+ is excreted each day as titratable acidity and 30 meq as NH_4^+. These processes are essential for the maintenance of acid-bas balance, because the rate of excretion of free H^+ ions is extremely low. At the minimum urine pH of 4.50, for example, the free H^+ concentration is less than 0.05 meq/L.

In the absence of therapy with $NaHCO_3$, the correction of metabolic acidosis usua requires the urinary excretion of the excess H^+. The kidney responds to this increased H^+ load by augmenting cellular NH_4^+ production and subsequent excretion,[15,16] changes that may be mediated by the extracellular acidemia producing a parallel reduction in the renal tubular cell pH (see page 345).[17,18] The net effect is that NH_4^+ excretion can exceed 250 meq/day with severe acidemia.[19,20]

In contrast, there generally is only a limited ability to enhance titratable ac phosphate excretion remains relatively constant.[15] One exception occurs in diabetic ketoacidosis, where excreted ketone anions (particularly β -hydroxybutyrate as urinary buffers, increasing titratable acid excretion by up to 50 meq/day.[19] The net effect is that total acid excretion can reach a maximum rate of 500 meq/ than five times normal) in patients with severe metabolic acidosis.[19,20]

Generation of Metabolic Acidosis

From this discussion, it can be seen that metabolic acidosis can be induced basic mechanisms: an inability of the kidney to excrete the daily load of H^+ an increase in the generation of H^+ as a result of either the addition of H^+ or the loss of HCO_3^- (Table 19-3). Decreased H^+ excretion produces a *slowly developing acidemia*, since only that fraction of the 50- to 100-meq daily load of H^+ that is not excreted will be retained. In comparison, an acute increase in H^+ load (as with lactic acidosis) can overwhelm renal excretory capacity, leading to the *rapid onset* of severe metabolic acidosis.

Anion Gap

Calculation of the anion gap is often helpful in the differential diagnosis of acidosis (Table 19-4).[21,22] and [23] The anion gap is equal to the difference betw the plasma concentrations of the major cation (Na^+) and the major measured anions ($Cl^- + HCO_3^-$):

Table 19-2 Arterial pH in chronic metabolic acidos with and without respiratory compensation

	Arterial		
Clinical state	pH	$[HCO_3^-]$, meq/L	P_{CO_2} mmHg
Baseline	7.40	24	40

Metabolic acidosis			
No compensation	7.29	19	40
Compensation			
Acute	7.37	19	34
Chronic	7.29	16	34

Table 19-3 Causes of metabolic acidosis

Inability to excrete the dietary acid load

A. Diminished NH_4^+ production
   1. Renal failure
   2. Hypoaldosteronism (type 4 renal tubular acidosis)
B. Diminished H^+ secretion
   1. Type 1 (distal) renal tubular acidosis

Increased H^+ load or HCO_3^- loss

A. Lactic acidosis
B. Ketoacidosis
C. Ingestions
   1. Salicylates
   2. Methanol or formaldehyde
   3. Ethylene glycol
   4. Paraldehyde
   5. Sulfur
   6. Toluene
   7. Ammonium chloride
   8. Hyperalimentation fluids
D. Massive rhabdomyolysis
E. Gastrointestinal HCO_3^- loss
   1. Diarrhea
   2. Pancreatic, biliary, or intestinal fistulas
   3. Ureterosigmoidostomy
   4. Cholestyramine

F. Renal HCO_3^- loss
    1. Type 2 (proximal) renal tubular acidosis

[a] Most common causes.

$$\text{Anion gap} = [Na^+] - ([Cl^-] + [HCO_3^-]) \qquad (19\text{-}5)$$

The approximate normal values for these ions are 140, 108, and 24 meq/L, respectively, leading to an anion gap of 5 to 11 meq/L. (This is lower than measured values, since a higher plasma Cl^- concentration is measured with the newer autoanalyzers.) As a result, knowing the normal range in a particular laboratory is often essential if the anion gap is to be interpreted properly.

Table 19-4 Anion gap in major causes of metaboli acidosis

High anion gap[a]

A. Lactic acidosis: lactate, D-lactate
B. Ketoacidosis: β-hydroxybutyrate
C. Renal failure: sulfate, phosphate, urate, hippurate
D. Ingestions
    1. Salicylate: ketones, lactate, salicylate
    2. Methanol or formaldehyde: formate
    3. Ethylene glycol: glycolate, oxalate
    4. Paraldehyde: organic anions
    5. Toluene: hippurate (usually presents with normal anion gap)
    6. Sulfur: SO_4^{2-}
E. Massive rhabdomyolysis

Normal anion gap (hyperchloremic acidosis)

A. Gastrointestinal loss of HCO_3^-
    1. Diarrhea
B. Renal HCO_3^- loss
    1. Type 2 (proximal) renal tubular acidosis
C. Renal dysfunction
    1. Some cases of renal failure
    2. Hypoaldosteronism (type 4 renal tubular acidosis)
    3. Type 1 (distal) renal tubular acidosis
D. Ingestions
    1. Ammonium chloride

2. Hyperalimentation fluids

E. Some cases of ketoacidosis, particularly during treatment with insuli

[a] The substances after the colon represent the major retained anions in high anion gap acidoses.

The negative charges on the plasma proteins account for most of the missi as the charges on the other cations (Ca^{2+}, K^+, and Mg^{2+}) and anions (phosphate, sulfate, and organic anions) tend to balance out. Thus, the normal value fo anion gap must be adjusted downward in patients with hypoalbuminemia; th approximate correction is a reduction in the anion gap of 2.5 meq/L for eve decline in the plasma albumin concentration.[22]

The factors that can affect the anion gap can be more easily appreciated if Eq. 19-5 is rewritten in the following way. In addition to being equal to the differenc

between measured cations and anions, the anion gap is also equal to the d between *unmeasured* anions and cations:

$$\text{Anion gap} = \text{unmeasured anions} - \text{unmeasured cations} \qquad (19\text{-}6)$$

Thus, an increase in anion gap can be produced by a fall in unmeasured ca (hypocalcemia, hypokalemia, or hypomagnesemia, where the change is only meq/L) or, more importantly, by an elevation in the amount of unmeasured a This can be induced by a high plasma albumin concentration (as with hypov induced hemoconcentration) or by the accumulation of a variety of different

These relationships can be applied to the different causes of metabolic aci which there is rapid extracellular buffering of the excess acid by HCO_3^-. If HCl is HCl, then

$$HCl + NaHCO_3 \rightarrow NaCl + H_2CO_3 \rightarrow CO_2 + H_2O \qquad (19\text{-}7)$$

In this setting, there is a milliequivalent-for-milliequivalent replacement of extracellular HCO_3^- by Cl^-; thus, there is no change in the anion gap, since the of $[Cl^-]+[HCO_3^-]$) remains constant. This disorder is called *hyperchloremic acidosis*, because of the associated increase in the plasma Cl^- concentration.

Gastrointestinal or renal loss of $NaHCO_3$ directly produces the same result. The kidney retains NaCl in this setting in an effort to preserve the extracellular leading to a net exchange of HCO_3^- for Cl^-.

Conversely, if H^+ accumulates with any anion other than Cl^-, extracellular HCO_3^- will be replaced by an unmeasured anion (A^-):

$$HA + NaHCO_3 \rightarrow NaA + H_2CO_3 \rightarrow CO_2 + H_2O \qquad (19\text{-}8)$$

The ensuing accumulation of A^- leads to an elevation in the anion gap. In this setting, identification of the specific disease process usually can be obtain measuring the plasma concentrations of creatinine, glucose, and lactate an

checking the plasma for the presence of ketones and intoxicants (particular salicylates, methanol, and ethylene glycol) (Table 19-4).

A simple example of how this approach can be used is illustrated by the following case history:

Case History 19-1

A 27-year-old man with insulin-dependent diabetes mellitus has not been taking insulin and is admitted to the hospital in a semicomatose condition. The following laboratory data are obtained:

Plasma $[Na^+]$	=	140 meq/L	Arterial pH	=	7.10
$[K^+]$	=	7.0 meq/L	P_{CO_2}	=	20 mmHg
$[Cl^-]$	=	105 meq/L	[Glucose]	=	800 mg/dL
$[HCO_3^-]$	=	6 meq/L	Plasma ketones	=	4+
Anion gap	=	29 meq/L			

Comment

The high anion gap, hyperglycemia, and ketonemia all point to the diagnosis of diabetic ketoacidosis. Note that the increase in the anion gap of approximately 18 meq/L (from 11 to 29) is the same as the fall in the plasma HCO_3^- concentration (from 24 to 6 meq/L).

Although a high anion gap is helpful in the differential diagnosis of metabolic acidosis, it is not always possible to identify the extra unmeasured anions.[22,23,24] and[25] This is particularly true when there is only a minor elevation in the anion gap (to less than 20 meq/L); in this setting, the correct diagnosis may not be evident since ketones, lactate, renal failure, and ingestions all may be missing. In comparison, one of these disorders is generally present when the anion gap is 25 meq/L.

Another potential problem is that the distinction between a high and a normal anion gap acidosis is not always absolute. Patients with diarrhea, for example, tend to develop a normal anion gap acidosis because of loss of HCO_3^- in the stool. If the fluid losses are severe, however, hemoconcentration (leading to hyperalbuminemia), acidosis (due to hypoperfusion), and hyperphosphatemia (resulting from acidosis-induced release of phosphate from the cells) all may combine to raise the anion gap.[26] This combination of normal and high anion gap acidosis can be detected by comparing the change (Δ) in anion gap to the change (Δ) in plasma HCO_3^- concentration.

Δ Anion gap/Δ plasma HCO_3^- Concentration

In addition to the level of the anion gap, the relationship between the increase in anion gap and the fall in the plasma HCO_3^- concentration may be helpful diagnostically. Use of this parameter is dependent upon an accurate assumption of the change in anion gap, which requires an estimate of the normal anion gap.

prior measurements are available. As described above, the normal value of approximately 8 meq/L must be adjusted downward in patients with hypoalbuminemia, with the approximate correction being a 2.5-meq/L fall in gap for every 1-g/dL reduction in the plasma albumin concentration.[22]

Failure to make this correction will underestimate the change in anion gap. for example, the anion gap is 15 meq/L in a patient with a plasma albumin concentration of 2 g/dL. The Δ anion gap is 7 meq/L using 8 meq/L as the b value; however, accounting for the hypoalbuminemia leads to a baseline an roughly 3 meq/L [8-(2.5× 2)], resulting in a higher Δ anion gap of 12 meq/L.

Although Eq. 19-8 seems to imply that there should be a 1 : 1 relationship betv the elevation in anion gap and the fall in plasma HCO_3^- concentration, this is usually not the case. As described above, more than 50 percent of this excess H^+ is buffered by the cells *not by* HCO_3^-. In contrast, *most of the excess anions remain in the extracellular fluid* since their distribution is pH-dependent. The extracellular has a slightly higher pH (and lower H^+ concentration) than the cells; as a result, t following reaction is driven to the left:

$$H^+ + BHB^- \leftrightarrow HBHB$$

where BHB^- refers to the β -hydroxybutyrate anion and HBHB refers to the undissociated β -hydroxybutryric acid. The net effect is that the extracellul has, in relation to the cells, a relatively high concentration of β -hydroxybu which is less able to enter the cells because anions cannot easily cross the bilayer of the cell membrane.

As a result, the *elevation in the anion gap usually exceeds the fall in the plas* HCO_3^- *concentration*; in lactic acidosis, for example, the Δ/Δ ratio averages ab 1.6 : 1.[27] It should be appreciated, however, that hydrogen buffering in cells bone takes several hours to reach completion. Thus, the ratio may be close with very acute lactic acidosis (as with seizures or exercise to exhaustion), there has not been time for nonextracellular buffering to occur.

Although the same principles apply to ketoacidosis, the ratio is often close this disorder because *loss of ketoacid anions in the* urine (which lowers the anion gap) tends to balance the effect of intracellular buffering of H^+.[27,28,29] and [30] The adequacy of renal function appears to be an important determinant o rise in anion gap in ketoacidosis. Patients in whom the glomerular filtration relatively normal have an elevation in filtered ketoacid load that exceeds tu reabsorptive capacity.[3,1] As a result, they can excrete a large quantity of ketoac anions in the urine,* thereby minimizing the rise in the anion gap and therefore Δ /Δ ratio.[28,30] In comparison, the anion gap will be higher when renal functi impaired, usually because of underlying renal disease or volume depletion by the glucose osmotic diuresis (see Chap. 25).[28,30] Anion loss in the urine is much less prominent in lactic acidosis, because the associated state of marked ti

hypoperfusion usually results in little or no urine output.

The loss of ketoacid anions in the urine also accounts for the observation t *normal anion gap acidosis typically occurs during the treatment phase of ketoacidosis*.[28,30] In the above case history, there is a 20-meq/L elevation in anion gap and a roughly equivalent decline in the plasma HCO_3^- concentration. After the administration of insulin, these ketoacid anions will be metabolized to H (see below). Thus, the anion gap will return to normal, but the plasma HCO_3^- concentration will increase by about 8 meq/L, not 20 meq/L, since the *generated HCO_3^- will effectively enter the cells to replenish the cell buffers*. At this time, the plasma HCO_3^- concentration will be 14 meq/L and the pH will still be but here will be no excess unmeasured anions (i.e., the patient will have a anion gap acidosis). The acidemia in this setting is due to two factors: the production of ketoacids and the excretion of the ketoacid anions, which, if could have been converted back into HCO_3^- by the administration of insulin; thu loss of these anions is physiologically equivalent to the loss of HCO_3^-.

In addition to this sequence during treatment, some patients with ketoacido excrete ketones in the urine so efficiently that the anion gap is relatively n *before* any therapy has been instituted.[29,30] A similar sequence, in which patients who overproduce organic acids can present with a normal anion gap, may o two other settings: lactic acidosis and toluene exposure (glue-sniffing). Filte lactate, the normal isomer produced in humans, is reabsorbed in the proxim via a Na^+-l-lactate cotransporter in the luminal membrane. This transporter is stereospecific and does not bind d-lactate, which may be overproduced in patient with a short bowel syndrome (see below). As a result, d-lactate is rapidly e the urine, lowering the anion gap toward normal. However, the acidosis per since the H^+ ion is still retained.

Anion loss is even more rapid with toluene ingestion, which is associated w overproduction of hippuric acid. Hippurate is both *filtered and secreted*, and a result, almost all of the hippurate delivered to the kidney enters the tubula and is then excreted, since there is little hippurate reabsorption. The net e that many patients present with a normal anion gap and are mistakenly thou have renal tubular acidosis.[32]

Summary

In summary, the Δ/Δ ratio is normally between 1 and 2 in patients with an uncomplicated high anion gap metabolic acidosis. A value below 1 : 1 sugge *combined high and normal anion gap acidosis* might occur when hemoconcentration and lactic acidosis are superimposed on severe diarrhea.[26] On the other hand, a value above 2 : 1 suggests that the fall in the plasma HCO_3^- concentration is less than expected because of a concurrent metabolic alka

Consider the following case history:

Case History 19-2

A previously well 55-year-old woman is admitted with a complaint of severe for 5 days. Physical examination reveals postural hypotension, tachycardia diminished skin turgor. The laboratory findings include the following:

Plasma [Na^+]	=	140 meq/L	Arterial pH	=	7.23
[K^+]	=	3.4 meq/L	P_{CO_2}	=	22 mmHg
[Cl^-]	=	77 meq/L	Plasma ketones	=	trace
HCO_3^-	=	9 meq/L	[Creatinine]	=	2.1 mg/dL
Anion gap	=	54 meq/L			

Comment

This patient has a high anion gap metabolic acidosis. Lactic acidosis is mo view of the physical findings and lack of significant ketonemia, renal failure history of an ingestion. However, the anion gap of 54 meq/L is markedly inc (45 meq/L above normal) while the reduction in the plasma HCO_3^- concentration is much smaller (15 meq/L, giving 9 meq/L), leading to a Δ /Δ ratio of 3 : 1. T disparity can be explained by a concomitant metabolic alkalosis due to vom which raised the plasma HCO_3^-

concentration without affecting the anion gap. Proof of this diagnosis came evaluating the response to fluid repletion. As tissue perfusion was restored metabolism of the excess lactate generated (see below), the plasma HCO_3^- concentration rose from 9 to 37 meq/L and the pH became alkalemic. Thus, meq/L elevation in the anion gap was actually associated with a 28-meq/L f plasma HCO_3^- concentration, a 1.7 : 1 ratio that is typical of lactic acidosis.[27]

Anion gap in renal failure

To understand the changes in the anion gap that can occur in renal failure, necessary to review the normal handling of acids. The dietary acid load is due to the generation of H_2SO_4 from the metabolism of sulfur-containing amino acids.[14,33,34] This acid is rapidly buffered by HCO_3^- and other buffers, leading to the formation of Na_2SO_4:

$$H_2SO_4 + 2NaHCO_3 \rightarrow Na_2SO_4 + 2H_2CO_3 \rightarrow 2CO_2 + 2H_2O$$

To maintain the steady state, both the H^+ and the SO_4^{2-} must be excreted in the urine. As described above, the excretion of H^+ primarily as NH_4^+ is a tubular function. In comparison, the excretion of SO_4^{2-} is determined by the difference between filtration and some degree of tubular reabsorption. In general, pro renal diseases lead to parallel impairments in glomerular filtration rate and function; as a result, both the H^+ and HSO_4^{2-} are retained, producing a high anion gap metabolic acidosis.[35,36] (Other retained anions in renal failure include

phosphate, urate, and hippurate.[37]

These findings are different, however, if there is more prominent impairmen tubular function. In this setting, both H^+ secretion and HPO_4^{2-} reabsorption will be diminished, with the latter maintaining the rate of SO_4^{2-} excretion (as Na_2SO_4) at near normal levels. Na^+ depletion is prevented by an equivalent increase in Na^+ reabsorption. The net effect is HCl retention, maintenance of HPO_4^{2-} balance, and a normal anion gap metabolic acidosis.[35,36]

Anion gap in other conditions

Small changes in the anion gap can occur in a variety of disorders other th metabolic acidosis.[21,22] and[23] A high anion gap, for example, can occur in nonketotic hyperglycemia with no or only mild metabolic acidosis as a resul release of phosphate and perhaps other anions from the cells.[9]

An elevation in unmeasured plasma anions is also a common finding in meta alkalosis.[22,38] Three factors may contribute to this finding:[1] a rise in the plasma albumin concentration as a result of extracellular volume depletion,[2] an increase in the number of negative charges per albumin molecule, since the pH is furth from the isoelectric point for albumin of approximately 5.4,[3] and appropriate alkalemia-induced increase in lactate production in an attempt to lower the toward normal. A high anion gap can also result from a reduction in unmeas cations; this effect, however, is generally of minor importance, since hypok hypocalcemia, or hypomagnesemia will raise the anion gap by only a few milliequivalents per liter.

There are also settings in which a low anion gap (less than 5 meq/L) may b From Eq. 19-6, this phenomenon can be induced by a fall in unmeasured anio (primarily hypoalbuminemia) or by a rise in unmeasured cations.[39] The latter can occur with hyperkalemia, hypercalcemia, hypermagnesemia, severe lithium intoxication, or some cases of multiple myeloma in which a cationic IgG par is produced.[22,40,41]

In rare cases, the anion gap has a negative value.[42] This is most often due to a laboratory artifact in severe hypernatremia (at levels above 170 meq/L, the concentration of sodium is underestimated), marked hyperlipidemia (where scattering in the colorimetric assay can result in marked overestimation of plasma chloride concentration, occasionally to above 200 meq/L), or bromic intoxication.[20,42,43] The last problem may be seen in patients taking pyridosti bromide for myasthenia gravis; it does not occur with Bromo-Seltzer, which contains bromide.[42] In several of the commonly used laboratory assays for chl there is a greater affinity for bromide; as a result, each milliequivalent of b may be measured as 2 meq of chloride, leading to overestimation of the pla chloride concentration and a low or even negative anion gap.

Urine anion gap

Calculation of the urine anion gap may be helpful diagnostically in some ca
normal anion gap metabolic acidosis.[4445] The major measured cations and anions
in the urine are Na^+, K^+, and Cl^-; thus, the urine anion gap is equal to

$$\text{Urine anion gap} = ([Na^+] + [K^+]) - [Cl^-] \quad (19\text{-}9)$$

$$\text{Urine anion gap} = \text{unmeasured anions} - \text{unmeasured cations} \quad (19\text{-}10)$$

In normal subjects excreting between 20 and 40 meq of NH_4^+ per liter (NH_4^+ being
the major unmeasured urinary cation), the urine anion gap generally has a
value or is near zero.[4446] In metabolic acidosis, however, the excretion of NH_4^+
(and of Cl^- to maintain electroneutrality) should increase markedly if renal
acidification is intact, resulting in a value that varies from -20 to more than
meq/L; the negative value in this setting

occurs because the Cl^- concentration now exceeds that of Na^+ plus K^+. In
comparison, the acidemia in renal failure and types 1 and 4 renal tubular a
primarily due to impaired H^+ and NH_4^+ excretion, and the urine

anion gap typically retains its normal positive value (Fig. 19-14).[44] Thus, use of the
urine anion gap in conjunction with the urine pH and plasma K^+ concentration can
help in arriving at the correct diagnosis (see "Renal Tubular Acidosis," below).

One simple example can illustrate the potential utility of the urine anion ga
Hypokalemia is a stimulus to renal NH_3 production, an effect that may be related t
an intracellular acidosis induced by the transcellular shift of K^+ and H^+ into
the cells (see page 356).[47] Diffusion of some of this excess NH_3 into the urine will
drive Eq. 19-4 to the right, thereby lowering the H^+ concentration and raising the
urine pH. Thus, a patient with diarrhea and hypokalemia may have metaboli
acidosis and, because of the effect of NH_3, an increase in urine pH similar to that
type 1 renal tubular acidosis. The correct diagnosis in this setting can be e
by calculation of the urine anion gap, which will have a positive value in re
acidosis but will be appropriately negative with diarrhea, since excretion of NH_4^+
is not impaired in this disorder.[44]

There are, however, two conditions in which the urine anion gap cannot be
The first is a high anion gap acidosis, such as ketoacidosis, where the exc
unmeasured ketoacid anions in the urine will counteract the effect of NH_4^+.[4445] As
a result, the urine anion gap may be positive even though there is an appro
increase in the rate of NH_4^+ excretion. The second is volume depletion with avi
Na^+ retention (urine Na^+ concentration ≤25 meq/L).[44] The associated decrease in
distal Na^+ delivery impairs distal acidification, resulting in a reversible form
renal tubular acidosis, even though diarrhea may be the primary abnormalit

in terms of the urine anion gap, the concurrent increase in Cl^- excretion prevents the excretion of NH_4^+ and the development of a negative anion gap.[40]

The decreased acid excretion with volume depletion may play an important the genesis of the metabolic acidosis that may be seen with severe or pers diarrhea.[45] Diarrheal fluid may contain as much as 50 meq/L of base. If renal function were normal, however, the fall in the plasma bicarbonate concentra would be limited by increased ammonium excretion, which can reach 150 to meq/day. Concurrent volume depletion will limit this adaptive response, the increasing the severity of the acidosis.

Urine osmolal gap

When the urine anion gap is positive and it is unclear whether increased ex unmeasured anions is responsible, the urine ammonium concentration can b estimated from calculation of the urine osmolal gap.[32,45] This calculation requires measurement of the urine osmolality and the urine sodium, potassium, urea and, if the dipstick is positive, glucose concentrations. The calculated urin osmolality can then be estimated from

$$\text{Calculated urine osmolality} = 2 \times ([Na^+ + K]) + \frac{[\text{urea nitrogen}]}{2.8} + \frac{[\text{glucose}]}{18}$$

The multiple of 2 accounts for the anions accompanying sodium and potass while the divisors 2.8 and 18 reflect adjustments required to convert from t routinely used units of mg/dL to mmol/L or mosmol/kg.

The gap between the measured and calculated urine osmolality should larg represent ammonium salts. This calculation is not affected by unmeasured a (such as β -hydroxybutyrate), since these anions will be accounted for by t sodium, potassium, and ammonium. Suppose, for example, that there is a 1(mosmol/kg difference between the measured and calculated urine osmolalit ammonium excretion in this setting should be approximately one-half this va (because of accompanying anions) or 50 meq/L, a level that is appropriate metabolic acidosis.[48]

One circumstance in which the urine gap will be inaccurate is when large q of an intact (undissociated) acid are excreted, as most often occurs with β hydroxybutyric acid in ketoacidosis. In this setting, the osmolal gap may be primarily to β -hydroxybutyric acid rather than to ammonium salts. This erro to be small, however, since β -hydroxybutyric acid is excreted primarily as ketoacid anion as a result of the relatively low pKa (4.7) of this acid. In on study of patients with diabetic ketoacidosis, the concentration of undissoci hydroxybutyric acid was less than 4 meq/L, while the concentration of keto anions was more than six times higher.[19] Furthermore, the diagnosis of ketoacidos is usually easily established from the history and routine laboratory data a not require calculation of the urine anion or osmolal gaps.

ETIOLOGY AND DIAGNOSIS

This section will review the pathogenesis, etiology, and diagnosis of the di disorders that can cause metabolic acidosis. It will also include some speci

aspects of therapy, although the general principles involved in the treatmer metabolic acidosis will be discussed separately later in the chapter.

Lactic Acidosis

Lactic acid is derived from the metabolism of pyruvic acid; this reaction is by lactate dehydrogenase and involves the conversion of $NADH + H^+$ to NAD^+ and oxidized nicotine adenine dinucleotide, respectively (Fig. 19-2). Normal subjects produce 15 to 20 mmol/kg of lactic acid per day, most of which is generated glucose via the glycolytic pathway or from the deamination of alanine.

Lactic acid is rapidly buffered, in part by extracellular HCO_3^-, resulting in the generation of lactate:

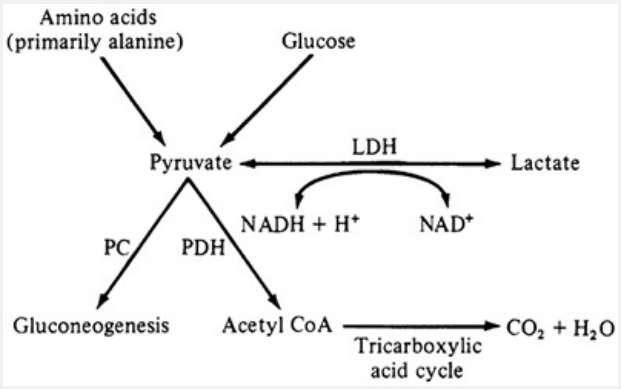

Figure 19-2 Major pathways of pyruvate and lactate metabolism. LDH is lac dehydrogenase, PDH is pyruvate dehydrogenase, PC is pyruvate carboxyl and NADH and NAD^+ are reduced and oxidized nico-tine adenine dinucleotide respectively.

$$CH_3-CHOH-COOH + NaHCO_3 \rightarrow Na^+lactate^- + H_2CO_3 \rightarrow CO_2 + H_2O \quad (19\text{-}11)$$

In the liver and, to a lesser degree, the kidney, lactate is metabolized back pyruvate, which is then converted into citrate and CO_2 (80 percent, catalyzed in part by pyruvate dehydrogenase) or glucose (20 percent, catalyzed in part pyruvate carboxylase; Fig. 19-2). Either of these processes results in the *regeneration of the* HCO_3^- lost in the initial buffering of lactic acid:

$$\text{Lactate} + 3O_2 \rightarrow HCO_3^- + 2CO_2 + 2H_2O \quad (19\text{-}12)$$

$$2\,\text{Lactate} + 2H_2O + 2CO_2 \rightarrow 2HCO_3^- + \text{glucose} \quad (19\text{-}13)$$

These reactions require both the entry of pyruvate into the mitochondria an oxidative metabolism. In comparison, pyruvate will be preferentially convert lactate in the cytosol in the presence of mitochondrial dysfunction or a mar reduction in tissue perfusion.

The normal plasma lactate concentration is 0.5 to 1.5 meq/L. Lactic acidosi

considered to be present if the plasma lactate level exceeds 4 to 5 meq/L in acidemic patient.

Pathogenesis and etiology

Excess lactate can accumulate when there is increased lactate production and diminished lactate utilization.[49,50,51] and[52] The former can occur by three mechanisms: enhanced pyruvate production, reduced pyruvate utilization, or commonly, an altered redox state within the cell in which pyruvate is preferentially converted into lactate (Table 19-5).[49,50] During glycolysis, NADH is generated and then reoxidized to NAD^+ in the mitochondria. If oxidation is impaired, however, pyruvate will accumulate, further promoting the conversion of pyruvate to lactate (Fig. 19-2). In this setting, the associated adenosine triphosphate (ATP) depletion may cause vasodilatation and a further decline in systemic blood pressure. ATP normally closes ATP-dependent K^+ channels. Thus, ATP depletion in lactic acidosis leads to opening of these channels, resulting

P.594
P.595

sequentially in K^+ movement out of the cells, hyperpolarization of vascular smooth muscle cells, and decreased Ca^{2+} entry into these cells through voltage-dependent Ca^{2+} channels.[86] The fall in cell Ca^{2+} concentration produces smooth muscle relaxation and a reduction in systemic vascular resistance.

In certain disorders, the primary role of lactate overproduction is clear. As an example, plasma lactate levels may transiently be as high as 15 meq/L during a grand mal seizure[60] and 20 to 25 meq/L with maximal exercise, with the systemic pH falling to as low as 6.80.[61,87] Studies in these patients have demonstrated rapid recovery of acid-base balance, with a maximum rate of lactate utilization that can reach 320 meq/h.[49]

This high rate of lactate metabolism suggests that there must be some component of *decreased utilization* in those disorders in which lactate overproduction occurs relatively slowly. In shock, for example, the reduction in perfusion to the liver and an associated intracellular acidosis may combine to substantially diminish hepatic lactate metabolism.[51,52,88] The importance of these events has been demonstrated experimentally by the observation that infusing lactic acid to otherwise normal animals is associated with increased hepatic utilization and relative difficulty in lowering the extracellular pH.[51,52]

Most cases of lactic acidosis are due to marked tissue hypoperfusion in shock or during a cariodpulmonary arrest.[49,50,89] The prognosis is generally poor unless tissue perfusion can be rapidly restored.

The association of lactic acidosis with *diabetes mellitus* is less certain, since many cases in the past were associated with the use of phenformin and some of these today with metformin.[83,84] Nevertheless, a moderate degree of lactic acidosis may be seen in some patients with diabetic ketoacidosis.[49,90] How this occurs is not

clear, although marked hypovolemia is likely to play an important role. Documentation of concurrent lactic acidosis may be clinically important, sir altered redox state in this setting also converts acetoacetate into β -hydrox Only the former is recognized by the nitroprusside tablet or dipstick used t the presence of ketones; as a result, a falsely negative result may be obtai the diagnosis of ketoacidosis obscured when there is preferential productic hydroxybutyrate.[90]

The pathogenesis of the lactic acidosis found with *malignancies* is also unclear.[79,80,81] and[82] Anaerobic metabolism due to dense clusters of tumor c and/or metastatic replacement of the hepatic parenchyma have been propos lactic acidosis has occurred in patients with relatively small tumor burdens.[79,81] Direct lactate production by the neoplastic cells has also been suggested, would not explain the rarity of tumor-induced lactic acidosis. Regardless of mechanism, removal of the tumor (or by chemotherapy, irradiation, or surge to correction of the acidosis.[79,81,82]

A mild degree of lactic acidosis also may be seen with *alcoholism*.[78] In this condition, lactate production is usually normal, but lactate utilization is dim because of impaired hepatic gluconeogenesis. Although lactate levels gene not exceed 3 meq/L in this setting, alcohol ingestion can potentiate the sev other disorders that are associated with the overproduction of lactate.

There are rare patients with the acquired immune deficiency syndrome (AID whom lactic acidosis is associated with drug-induced mitochondrial dysfunc absence of sepsis or hypotension. Such an association has been described patients with zidovudine-induced myopathy, characterized by elevated plasr creatine kinase concentrations and proximal muscle weakness,[91] and zidovudine- or stavudine-induced hepatic steatosis and hepatic failure.[69,70] The latter complication may, in some cases, be due to a concurrent deficiency of riboflavin, a precu number of cofactors necessary for mitochondrial energy production. In seve patients, nucleoside-induced lactic acidosis has been reversed by riboflavi therapy.[71,72] In addition, a seemingly idiopathic form of lactic acidosis can o the absence of zidovudine.[85]

D-lactic acidosis

A unique form of lactic acidosis can occur in patients with jejunoileal bypas commonly, small bowel resection or other cause of the short bowel syndrom these settings, glucose and starch are metabolized in the colon and d-lactic acid, which is then absorbed into the systemic circulation and[73,74,75,76] The ensuing acidemia tends to persist, since d-lactate is not recognized by l-lactate dehydrogenase, the enzyme that catalyzes the conversion of the physiologi occurring l-lactate into pyruvate.

Two factors tend to contribute to the overproduction of d-lactic acid in this

disorder.[74] First, there is overgrowth of gram-positive anaerobes, such as lactobacilli, which are most able to produce D-lactate. Second, there is usually relatively little glucose and starch delivered to the colon because of extens intestinal absorption. However, delivery of these substrates is markedly en when the small bowel is bypassed, removed, or diseased.

Patients with this disorder present with episodic metabolic acidosis (usuall occurring after high-carbohydrate meals) and characteristic neurologic abn including confusion, cerebellar ataxia, slurred speech, and loss of memory.[73,74] and [75] They may complain of feeling or appearing to be drunk in the absence of intake. It is not clear whether these symptoms are due to D-lactate itself or to some other toxin produced in the colon and then absorbed in parallel with D-lactate.

The classic neurologic findings plus the metabolic acidosis and the history intestinal disease should strongly suggest the presence of D-lactic acidosis. Confirmation of the diagnosis requires a special enzymatic assay that uses D-lactate dehydrogenase and measures the generation of NADH as lactate is convert pyruvate.[73,74] and [75] In contrast, the standard assay for lactate measures L-lactate dehydrogenase, which will not detect D-lactate.

An additional source of confusion may occur in D-lactic acidosis. Filtered D-lactate is *rapidly excreted* in the urine, being unable to bind to the Na^+-L-lactate cotransporter in the luminal membrane of the proximal tubule that normally promotes L-lactate reabsorption. As a result, patients with this disorder may have an anion gap normal or less than expected from the degree of reduction in the plasma HCO_3^- concentration.

Therapy in D-lactic acidosis consists of acute sodium bicarbonate administrat correct the acidemia and oral antimicrobial agents (such as metronidazole,

neomycin, or vancomycin) to decrease the number of D-lactate producing organisms.[74,75] and [76] A low-carbohydrate diet (or the use of starch polymers rather than simple sugars) also is helpful, by diminishing carboyhydrate de the colon.

Diagnosis

Although the diagnosis of lactate acidosis can be made definitively only by demonstration of an elevated plasma lactate concentration, there are often suggestive clues in the history, physical examination, laboratory data, and to therapy. These include a high anion gap; the presence of one of the disc can cause lactic acidosis; cool, clammy extremities and hypotension if shoc present; and continuing production of acid, as evidenced by an inability of exogenous HCO_3^- to raise the plasma HCO_3^- concentration.

The presence of an organic acidosis (primarily lactic acidosis or ketoacidos also be suspected if effective treatment of the underlying problem (such as

repletion in hypovolemic shock) leads to a *spontaneous elevation in the plasma HCO_3^- concentration*. This occurs because metabolism of the organic anion, in case lactate, results in the regeneration of HCO_3^- [Eqs. 19-12 and 19-13].

Treatment

Correction of the underlying disorder is the primary therapy in lactic acidos Reversal of circulatory failure, for example, will reduce further lactate prod allow metabolism of the excess lactate to HCO_3^-. (This spontaneous regeneration o HCO_3^- does not occur in D-lactic acidosis, since D-lactate cannot be metabolized.)

The role of $NaHCO_3$ administration in lactic acidosis has been a source of gre controversy.[92] Proponents argue that raising the arterial pH may improve tiss perfusion, by reversing acidemia-induced vasodilatation and impaired cardi contractility, and may diminish the risk of serious arrhythmias (see "Symptoms" below).[50,93] These potential benefits, however, must be weighed against the possible risks, which include volume overload, hypernatremia (a 5 percent $NaHCO_3$ solution contains almost 900 meq of Na^+ per liter), and overshoot metabolic alkalo after normal hemodynamics has been restored.[94] In addition, metabolic acidosis ma be in part protective during ischemia by minimizing hypoperfusion-induced t injury.[95]

In addition, both experimental[88,96,97] and human studies[80,97,98] have suggested that HCO_3^- therapy may be relatively ineffective, *producing only a transient elevation in the plasma HCO_3^- concentration* and possibly *worsening the intracellular acidosis*.[88,99,100] The seeming lack of efficacy of alkali therapy appears to be due in part to an associated *increase in net lactic acid production* (which also leads to a further rise in the anion gap).[88,96]

This unexpected change in lactate metabolism may be induced by the conti generation of CO_2 as a result of both cellular metabolic activity (including fib myocardial cells during cardiac arrest) and buffering of the excess H^+ ions by exogenous HCO_3^- [Eq. 19-11].[88,101] This CO_2 then accumulates in the tissues, since pulmonary blood flow is reduced as part of the shock state.[102,103,104] The ensuing local hypercapnia can exacerbate the intracellular acidosis, le

decreased lactate utilization in hepatic cells and a decline in contractility i cells.[82,96,99,101] The latter effect can reduce the cardiac output, a change th promote further lactic acid production.

It must also be emphasized that this problem of CO_2 accumulation may *not be detectable in arterial blood*.[103,104] Blood entering the pulmonary circulation may adequately cleared of CO_2, resulting in a relatively normal arterial P_{CO_2}. However, total CO_2 elimination is diminished because of the reduction in pulmonary blo

with severe circulatory failure or cardiac arrest. As a result, the tissue P_{CO_2} level may be markedly elevated, a change that can be detected by measuring *mixed venous blood*. In one study of patients undergoing cardiopulmonary resuscitation, the mean arterial pH and P_{CO_2} were 7.42 and 32 mmHg, respectively, whereas the mixed venous values were 7.14 and 74 mmHg.[103] This problem may be exacerbated by $NaHCO_3$ therapy, in part because buffering of H^+ ions in the blood by HCO_3^- increases the generation of CO_2.[103,104]

In summary, these findings make the optimal therapy of lactic acidosis uncertain at the present time. Some physicians have concluded that there is little indication for $NaHCO_3$ administration,[97] particularly during cardiac arrest.[100] However, most physicians give small amounts of $NaHCO_3$ to maintain the arterial pH above 7.10, since more severe acidemia can result in a deterioration in cardiovascular function. Careful monitoring, including measurement of mixed or central venous pH, is required to minimize side effects related to HCO_3^- administration.

There are three possible experimental alternatives to the therapy with HCO_3^-. One is the administration of Na_2CO_3 as a source of alkali: Buffering of excess H^+ ions by this compound will generate HCO_3^-, not CO_2, thereby minimizing the tendency to exacerbate the intracellular acidosis.[88,101] However, this agent has not been effective during cardiac arrest in experimental animals.[99,100] Although the extracellular pH may be increased, there is no improvement in the progressive decline in myocardial cell pH that results from continued production of CO_2 by the fibrillating cells.

The second alternative is the administration of dichloroacetate (DCA). This compound stimulates pyruvate dehydrogenase activity, thereby minimizing lactate production by allowing pyruvate to be oxidized to H_2O and CO_2 (Fig. 19-2). Although there is evidence of benefit in experimental models of lactic acidosis, a controlled trial in humans showed that DCA produced a minor increase in the plasma bicarbonate concentration and arterial pH but no improvement in systemic hemodynamics or mortality.[106]

The third option is tromethamine (THAM). THAM is an inert amino alcohol that buffers acids and CO_2 by virtue of its amine ($-NH_2$) moiety via the following reactions:[107]

$$\text{THAM}-\text{NH}_2 + \text{H}^+ = \text{THAM}-\text{NH}_3^+$$

$$\text{THAM}-\text{NH}_2 + \text{H}_2\text{O} + \text{CO}_2 = \text{THAM}-\text{NH}_3^+ + \text{HCO}_3^-$$

Protonated THAM is excreted in the urine at a slightly higher rate than creatinine clearance in conjunction with either chloride or bicarbonate. Thus, THAM supplements the buffering capacity of blood without generating carbon dioxide. It is less effective in patients with renal failure. Reported toxicities include hypo

hypoglycemia, and respiratory depression; the last complication probably re from the ability of THAM to rapidly increase the pH and decrease the P_{CO_2} in the central nervous system.

Published clinical experience with THAM is limited, but the drug has been u treat severe acidemia due to sepsis, hypercapnia, diabetic ketoacidosis, re tubular acidosis, gastroenteritis, and drug intoxication.[107] Its clinical efficacy compared to that of sodium bicarbonate in the treatment of metabolic acido remains unproven, and THAM is of uncertain safety.

These findings are consistent with the primary importance of reversing the underlying disorder. Patients generally die from tissue ischemia rather thar acidemia itself.

Ketoacidosis

The biochemistry of ketoacidosis is discussed in chapter 25. Briefly stated briefly, free fatty acids are converted in the liver into triglycerides and CO_2 or HCO_3^- into the ketoacids, acetoacetic acid and β -hydroxybutyric acid. Overproduction of k resulting in metabolic acidosis requires two factors: (1) increase in free fatty acid delivery to the liver due to enhanced lipolysis, and (2) resetting of hepatocyte function such that the free fatty acids are converted preferentially into keto not triglycerides.[108,109] and[110] *Both diminished activity of insulin and enhanc secretion of glucagon* (due in part to the insulin deficiency) contribute to these changes: the lack of insulin by increasing lipolysis, and the excess of gluca indirectly increasing fatty acyl CoA entry into the hepatic mitochondria, whe be converted into ketones.[108,109] and[110]

Etiology

Uncontrolled diabetes mellitus is the most common cause of ketoacidosis. Hyperglycemia is invariably present in this setting, with the plasma glucose concentration usually exceeding 400 mg/dL.

Fasting

Fasting can also result in ketosis, as the appropriate hormonal milieu (low high glucagon) is established by the lack of carbohydrate intake. In compar the potentially severe ketoacidosis that can occur in uncontrolled diabetes, levels do not exceed 10 meq/L with fasting. This limitation in the degree of formation may reflect the ability of ketonemia to promote insulin secretion, limiting the availability of free fatty acids.[111,112]

Alcoholic ketoacidosis

The combination of alcohol ingestion and poor dietary intake is another cau ketoacidosis.[113,114] and[115] The decrease in carbohydrate intake plus the inhib of gluconeogenesis by alcohol[49] result in the necessary changes in insulin and glucagon secretion. In addition, ethanol directly enhances lipolysis, further

increasing the supply of free fatty acids.[116]

The net effect may be a relatively severe acidosis that is often due to factc than ketoacidosis alone.[115,117] Concurrent hypovolemia can lead to enhanced la acid production, and some of the ethanol will be metabolized into acetic ac

These patients also frequently present with a mixed-base disturbance:[115]

1. Metabolic alkalosis may result from vomiting, which is a common compli problem. In some cases, the arterial pH may be relatively normal, and o elevated anion gap points toward the presence of ketoacidosis.
2. Patients with underlying chronic hepatic disease may have a chronic re alkalosis (see Chap. 21).
3. Urinary loss of the ketoacid anions can lead to a relatively normal anio comparison to the fall in the plasma bicarbonate concentration (see " Anion Gap," above).

Other

Increased ketoacid production can also occur in a variety of congenital org acidemias (such as methylmalonic or isovaleric acidemia)[118,119] and may contribute to the acidemia associated with salicylate intoxication.[22] The mechanisms responsible for the increased ketone synthesis in these disorders are not c understood.

Diagnosis

The presence of alcoholic ketoacidosis should be suspected in a patient wi history of alcohol abuse who is found to have an otherwise unexplained hig gap metabolic acidosis with a normal or only slightly elevated plasma gluco concentration. The osmolal gap—the difference between the measured and calculated plasma osmolality (see page 607)—also tends to be increased as a resu of the accumulation of glycerol (derived from fat breakdown) and acetone a possible presence of ethanol.[120] This finding, however, is of limited diagnostic utility, since the osmolal gap is also increased in other high anion gap acid as that due to methanol or ethylene glycol intoxication (see below).[121]

Confirmation of the presence of ketoacidosis requires the demonstration of ketonemia. This is generally done with nitroprusside (Acetest) tablets or re sticks. A 4+ reaction with serum diluted 1 : 1 is strongly suggestive of keto However, nitroprusside reacts with acetoacetate and acetone (produced by decarboxylation of acetoacetic acid), but not with β -hydroxybutyrate.[90] The latter ketoacid is formed from the reduction of the β -aldehyde group of acetoace reaction utilizing NADH. β -Hydroxybutyrate makes up about 75 percent of t circulating ketones in diabetic ketoacidosis, but this value can reach 90 pe when NADH levels are elevated with concurrent lactic

acidosis[90] or in alcoholic ketoacidosis (where NADH is generated from the ox of ethanol to acetic acid[113]).

In these settings, the nitroprusside test may underestimate the degree of k and ketonuria. Clinical awareness of the possibility of ketoacidosis is esse since an assay for β -hydroxybutyrate is not available in most hospitals. An method to circumvent this problem is to add a few drops of hydrogen peroxi urine specimen. This will nonenzymatically convert β -hydroxybutyrate into acetoacetate, which will then be detectable by nitroprusside.[122] An alternative, if available, is to directly measure β -hydroxybutyrate in the blood.

A different problem in diagnosis arises with sulfhydryl drugs, particularly ca which is widely used in the treatment of diabetic nephropathy and hyperten diabetics. These drugs can interact with the nitroprusside reagent to produ false-positive ketone test.[123] Thus, a positive nitroprusside test for ketonuria o ketonemia cannot be reliably interpreted in patients treated with captopril. setting, the diagnosis of diabetic ketoacidosis must be made on clinical gro (otherwise unexplained high anion gap metabolic acidosis in a patient with uncontrolled diabetes) or by direct measurement of β -hydroxybutyrate.

Treatment

Although insulin is the keystone to therapy in diabetic ketoacidosis, it may dangerous in alcoholism or fasting, where the baseline plasma glucose con may be low. In these conditions, the administration of glucose and saline w augment endogenous insulin secretion, diminish that of glucagon, normalize acid metabolism, and correct any fluid deficit that may be present.[114][115]

The role of HCO_3^- therapy is uncertain in ketoacidosis, as it is in lactic acido Most patients with ketoacidosis will derive no benefit from exogenous alkal insulin-induced metabolism of the ketoacid anions will result in the rapid regeneration of HCO_3^- and at least partial correction of the acidemia.[30][124][125]

There are, however, two settings in which HCO_3^- therapy may be beneficial: with marked acidemia (arterial pH≤7.00 to 7.10), and with a relatively normal an due to excretion of ketoacid anions in the urine.[30][93] In the latter condition, the quantity of HCO_3^- that can be generated from organic anion metabolism is minimized, and, in the absence of alkali therapy, restoration of acid-base b be a slow process, requiring renal excretion of the excess acid as NH_4^+.[30]

Hypophosphatemia is also a frequent complication of the treatment of ketoa since the rise in insulin levels promotes phosphate movement from the extra fluid into the cells. However, phosphate administration is generally not req unless marked hypophosphatemia occurs. When present, severe hypophosp may be associated with marked and possibly life-threatening complications patients, including myocardial dysfunction.[126]

Renal Failure

Metabolic acidosis is a common complication of advanced renal disease and from an inability of the diseased kidney to excrete the daily dietary acid

load.[35,36,127] The acidemia is generally not severe, although alkali therapy still have a variety of beneficial effects.

Pathogenesis

Renal insufficiency can affect all of the parameters involved in net acid exc With the initial reduction in glomerular filtration rate (GFR), hydrogen balan maintained by increased ammonium excretion per functioning nephron.[127,128,129] and[130] However, total ammonium excretion begins to fall when the GFR is l 40 to 50 mL/min (Fig. 19-3).[130,131] The net effect is the development of metabol acidosis, resulting from *inability to excrete all of the daily load*.[35,36,130] H^+

Both decreased titratable acidity (primarily as phosphate) and reduced HCO_3^- reabsorption also may contribute to the decline in net acid excretion. Phosp excretion is initially maintained in renal failure, in part by the associated s hyperparathyroidism (see page 202). However, net phosphorus absorption and therefore urinary excretion are diminished in patients with advanced diseas because of both dietary restriction and the use of oral phosphate binders, s calcium carbonate, to prevent hyperphosphatemia.[130]

The role of impaired HCO_3^- reabsorption is uncertain.[127] The need to increase Na^+ excretion per functioning nephron to maintain balance may lead to a modest increase in HCO_3^- excretion.[130,132,133] This defect, however, does not appear to play an important role in most cases.[133,134]

The fall in total ammonium excretion in renal failure usually does not repres tubular dysfunction per se. Ammonium excretion per total GFR (to account f reduction in functioning renal mass) is three to four times normal, a level s the maximum achieved in normal subjects following an acid load.[127,129] This suggests that the reduction in total ammonium excretion *reflects the number of functioning nephrons*, since ammonium production is already proceeding at a maximal rate.[129]

As the patient approaches end-stage renal failure, the plasma HCO_3^- concentration usually, but not always, falls and then stabilizes at 12 to 20 meq/L.[35,36,130,135] Although H^+ ions continue to be retained, a further reduction in the plasma H^+ concentration is prevented by buffering of the excess acid, primarily by bon buffers.[135,136] This process is manifested in part by the release of calcium f bone and its subsequent excretion in the urine. This negative calcium balan be reversed with alkali therapy;[135] if it is untreated, however, the calcium loss ca over a prolonged period, lead to osteopenia.[136]

A plasma HCO_3^- concentration below 10 to 12 meq/L is usually due to a superimposed abnormality, such as hypoaldosteronism (in which hyperkalem prominent finding; see Chap. 28), or another cause of metabolic acidosis, as with diarrhea. The latter problem can lead to a severe reduction in pH, since pa renal failure cannot compensate for the increased H^+ load by increasing renal acid excretion.

Treatment

Exogenous alkali therapy has not in the past been used to correct asymptor metabolic acidosis in adults with renal failure. The limited fall in the

plasma HCO_3^- concentration plus the respiratory compensation usually maint arterial pH near 7.30, a level that poses no danger to the patient. Furtherm raising the pH in the presence of hypocalcemia can precipitate tetany, and associated Na^+ load can increase the tendency toward volume expansion. As result, the major indications for alkali therapy have included a fall in the plasma HCO_3^- concentration below 12 meq/L; symptoms such as dyspnea, and

persistent hyperkalemia, since raising the pH will drive K^+ into the cells; and acidemia in children, which can impair growth.[137]

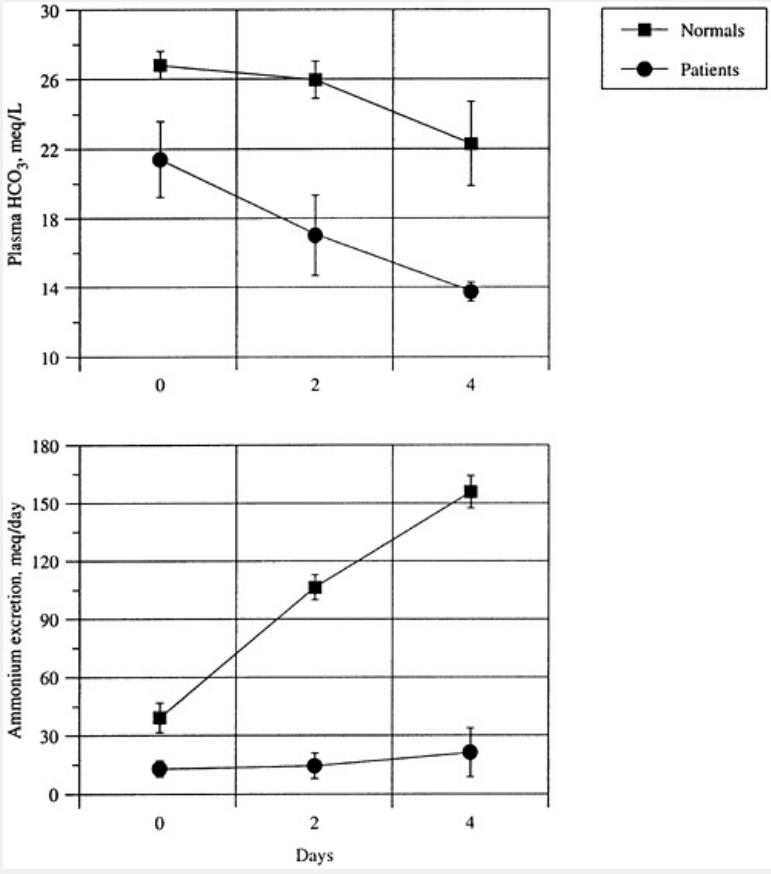

Figure 19-3 Effect of a dietary acid load on the plasma HCO_3^- concentration

and urinary NH_4^+ excretion in normals (squares) and patients with chronic re failure (circles). Normal subjects increase NH_4^+ excretion approximately fourfold with only a few meq/L reduction in the plasma HCO_3^- concentration. The patients with chronic renal disease had a low rate of NH_4^+ excretion at baseline (despite already having a mild metabolic acidosis) and showed no increme following the acid load. *Data from Welbourne T, Weber M, Bank N: J Clin Invest 51:1852, 1972, with permission.*

In adults, in whom growth is not an issue, there are least three potential re even mild metabolic acidosis should be treated in the patient with renal fail[138]

1. Minimizing bone buffering of excess H^+ ions may minimize the loss of bone calcium and possibly prevent or delay the development of osteopenia.[135,136] Correction of the acidosis also can prevent progression of hyperparathy bone disease,[139] an effect that may be related to a diminished stimulus to secondary hyperparathyroidism.[138]
2. Metabolic acidosis can lead to increased skeletal muscle breakdown an decreased albumin synthesis,[141,142,143,144] and[145] an effect that can be reversed by correction of the acidemia.[146,147] The catabolic state, which appears to be mediated in part by increased release of cortisol and dim release of insulin-like growth factor-I (IGF-I), may contribute to loss of mass and muscle weakness.[143,144] These problems may be exacerbated by t low-protein diet that may be prescribed in an attempt to slow the rate o progression of the renal failure (see p. 48).[142]
3. The adaptive increase in NH_3 production per nephron can lead to local complement activation and tubulointerstitial damage.[148] Preventing this response with alkali therapy may protect the kidney and slow the rate o progression of the underlying disease.[148]

Definitive studies on the treatment of metabolic acidosis in chronic renal fa humans have not yet been performed. Nevertheless, some physicians have advocated the earlier use of alkali therapy in this setting, particularly in vi observation that NaHCO$_3$ is better excreted (perhaps reflecting the impairment HCO_3^- reabsorption) and therefore less likely to produce fluid overload than equivalent quantity of NaCl.[148]

If alkali therapy is given, NaHCO$_3$ is the treatment of choice, while sodium citrate (citrate is rapidly metabolized to HCO_3^-) should be *avoided*. Citrate can markedly increase passive aluminum absorption, possibly predisposing to aluminum intoxication in patients with renal failure who are taking aluminum hydroxid

control hyperphosphatemia (see page 205).[150,151] Two factors are thought to contribute to this effect. Citrate combines with aluminum to form a nondissociable but soluble and absorbable complex, and oxalate combines with Ca^{2+} in the intestinal lumen, leading to a reduction in the free Ca^{2+} concentration that increases the permeability of tight junctions.[150]

Ingestions

Salicylates

Aspirin (acetylsalicylic acid) is rapidly converted into salicylic acid in the b
Although there is no absolute correlation between the plasma salicylate concentration and symptoms, most patients show signs of intoxication when

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plasma level exceeds 40 to 50 mg/dL (therapeutic range is 20 to 30 mg/dL).[156] Early symptoms include tinnitus, vertigo, nausea, vomiting, and diarrhea; more se intoxication can cause altered mental status, coma, noncardiac pulmonary e and death. Fatal overdosage can occur after the ingestion of 10 to 30 g by and as little as 3 g by children. The diagnosis can be made with certainty c measurement of the plasma salicylate concentration.

Increasing doses of aspirin cause a progressively greater risk of toxicity be *saturation of protective mechanisms*.[157] At therapeutic levels, 90 percent of salicylate is protein bound and therefore limited to the vascular space; the then partially glycinated in the liver to salicyluric acid, which is both less t more rapidly excreted by the kidney than salicylate. With salicylate toxicity the degree of protein binding falls to 50 percent and salicyluric acid format becomes saturated. Thus, more drug is now able to reach the tissues, and, of the decline in renal excretion, toxic levels persist for a longer period of

A variety of acid-base disturbances can occur with salicylate intoxication.[158] Salicylates stimulate the respiratory center directly,[159] resulting in a fall in the P_{CO_2} and respiratory alkalosis as the earliest abnormality.[156,158,160] Metabolic acidosis may then ensue, primarily because of the accumulation of organic acids, in lactate and ketoacids.[22,49,161] The respiratory alkalosis, which normally promot lactic acid production in an attempt to minimize the rise in pH,[54] appears to play a contributory role in this process. In experimental animals, lactate accumula seen if the initial fall in P_{CO_2} is prevented but gradually becomes more prominer hypocapnia is allowed to occur.[161] Salicylic acid itself (mol wt 180) has only a m effect, since a plasma level of 50 mg/dL represents a concentration that is 3 meq/L.

The net effect of these changes is that most adults have either a respirator alkalosis or a mixed respiratory alkalosis–metabolic acidosis; pure metabol is unusual.[158] In addition, approximately one-third of adults will also ingest o more other medications, many of which are respiratory depressants and car

concurrent respiratory acidosis.[158]

Treatment

The serious neurologic toxicity of salicylates, including death, is related to cerebral tissue salicylate concentration; thus, a reduction in this level mus first goal of therapy. This can in part be achieved by *alkalinization of the plasma* an arterial pH between 7.45 and 7.50. To appreciate how this works, it is ir to note that salicylic acid (HS) is a weak acid with a pK_a of 3.0. Thus, the Henderson-Hasselbalch equation for the reaction

$$H^+ + S^- \leftrightarrow HS \qquad (19\text{-}14)$$

can be expressed as

$$pH = 3.0 + \log\frac{[S^-]}{[HS]} \qquad (19\text{-}15)$$

where S represents the salicylate anion.

Table 19-5 Etiology of lactic acidosis

Increased lactate production

A. Increased pyruvate production
   1. Enzymatic defects in glycogenolysis of gluconeogenesis (as with type 1 glycogen storage disease)[53]
   2. Respiratory alkalosis, including salicylate intoxication[49,54]
   3. Pheochromocytoma[55,56]
B. Impaired pyruvate utilization
   1. Decreased activity of pyruvate dehydrogenase or pyruvate carboxylase
      a. Congenital[57]
      b. Possibly a role in diabetes mellitus, Reye's syndrome[58,59]
C. Altered redox state favoring pyruvate conversion to lactate
   1. Enhanced metabolic rate
      a. Grand mal seizure[60]
      b. Severe exercise[61,62]
      c. Hypothermic shivering[63]
      d. Severe asthma[64]
   2. Decreased oxygen delivery
      a. Shock[45]
      b. Cardiac arrest
      c. Acute pulmonary edema[56]
      d. Carbon monoxide poisoning ($\downarrow O_2$ uptake by hemoglobin)[65]
      e. Severe hypoxemia (P_{O_2} < 25 to 30 mmHg)[66]
      f. Pheochromocytoma[55,56]
   3. Reduced oxygen utilization
      a. Cyanide intoxication (↓ oxidative metabolism), which may res

from cyanide poisoning, during a fire, from smoke inhalation of vapors derived from the thermal decomposition of nitrogen-containing materials such as wool, silk, and polyurethane[67,68]

b. Drug-induced mitochondrial dysfunction due to zidovudine or stavudine[69,70,71,72]

D. D-Lactic acidosis[73,74,75,76]

Primary decrease in lactate utilization

A. Hypoperfusion and marked acidemia[51,52,77]
B. Alcoholism[78]
C. Liver disease[49]

Mechanism uncertain

A. Malignancy[79,80,81,82]
B. Diabetes mellitus, including metformin[48,83,84] in the absence of tissue hypoxia
C. Acquired immune deficiency syndrome[85]
D. Hypoglycemia[49]
E. Idiopathic

At the normal pH of 7.40, the ratio of HS^- to S is about 1 : 25,000; that is, only 0.00 percent of the total extracellular salicylate exists as HS. HS is nonpolar, lip soluble, and able to cross cell membranes; S^- is polar and crosses membranes poorly. As a result, the plasma and central nervous system (CNS) HS concentrations are in diffusion equilibrium, but not the S concentrations (Fig. 19-4).

If the systemic pH is increased, Eq. 19-14 will move to the left. As the plasma HS concentration falls, HS will leave the CNS (and other tissues) down a concentration gradient, where it will be trapped in the plasma as S^-. The fall in the CNS HS concentration then causes Eq. 19-14 to move to the right in the brain cell. This maintains the cellular HS concentration, thereby promoting further drug movement out of the CNS. For example, increasing the arterial pH from 7.20 to 7.50 will decrease the fractional concentration of HS from 0.006 to 0.003 percent. Although this change appears small, it will promote a significant reduction in tissue salicylate concentration. Note that alkalinization leads to an initial increment in the plasma salicylate concentration, but it is the tissue levels that are dangerous to the patient.

A second goal of treatment is rapid elimination of the drug from the body. Since salicylate is highly protein bound, it enters the urine primarily via secretion by the organic anion secretory pathway in the proximal tubule (Chap. 38) rather than by glomerular filtration. The rate of salicylate excretion can be markedly enhanced by alkalinization of the urine, which, by the same process of nonionic diffusion

urinary HS to S^-, thereby minimizing the back-diffusion of secreted HS out of t tubular lumen.[162] As an example, raising the urine pH from 6.5 to 8.1 by the administration of $NaHCO_3$ can increase total salicylate excretion more than fivefold.[163]

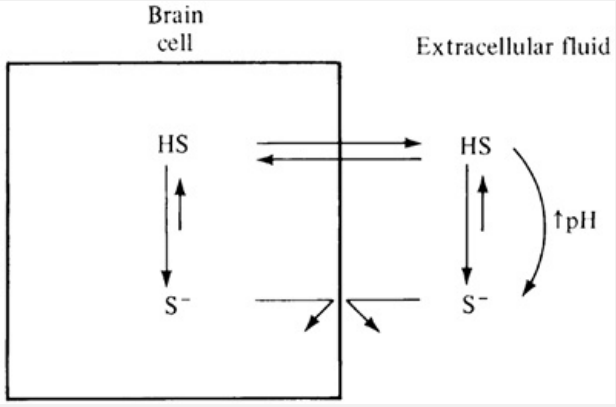

Figure 19-8 Schematic representation of the equilibrium distribution of sali (S^-) and salicylic acid (HS) between the extracellular fluid and the brain c is lipid-soluble and is in diffusion equilibrium, whereas S^- is not in equilibrium, since it is charged and cannot readily cross the cell membrane. Alkalinization of the extracellular fluid causes the reaction $S^- + H^+ \rightleftharpoons HS$, to move to the left, reducing the extracellular HS concentration. This allows cellular HS to di into the extracellular fluid down a concentration gradient. The decrease i cellular HS concentration then causes some cellular S^- to be converted to HS, thereby promoting continued HS diffusion out of the brain. Similar conside explain the increased movement of salicylate from the tubular cell into the when the urine is alkalinized.

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The efficiency of salicylate removal can also be enhanced by hemodialysis.[156,157,164] This procedure should be considered when the plasm salicylate concentration exceeds 80 mg/dL or the patient is comatose or ha renal function or fluid overload.

Another frequent problem of uncertain etiology is a low cerebrospinal fluid concentration, which may contribute to the neurologic abnormalities.[156] Thus, the administration of glucose should be part of the initial therapy in all patients salicylate intoxication.

In summary, the administration of alkali is an important component of therap patient with salicylate intoxication and metabolic acidosis. If, however, resp alkalosis is the primary disturbance, further alkalinization is not necessary.

Methanol

Methanol (wood alcohol, CH_3OH) is a component of shellac, varnish, deicing solutions, sterno, and other commercial preparations. It is metabolized to formaldehyde (in a reaction catalyzed by alcohol dehydrogenase) and then acid (Fig. 19-5). Symptoms and the high anion gap metabolic acidosis are usu delayed for 12 to 36 h after ingestion, since they are due to accumulation c metabolites, particularly formic acid.[1571,65,166] Early complaints include weakness nausea, headache, and decreased vision, which can then progress to blindn coma, and death. Funduscopic examination may reveal a retinal sheen due edema.

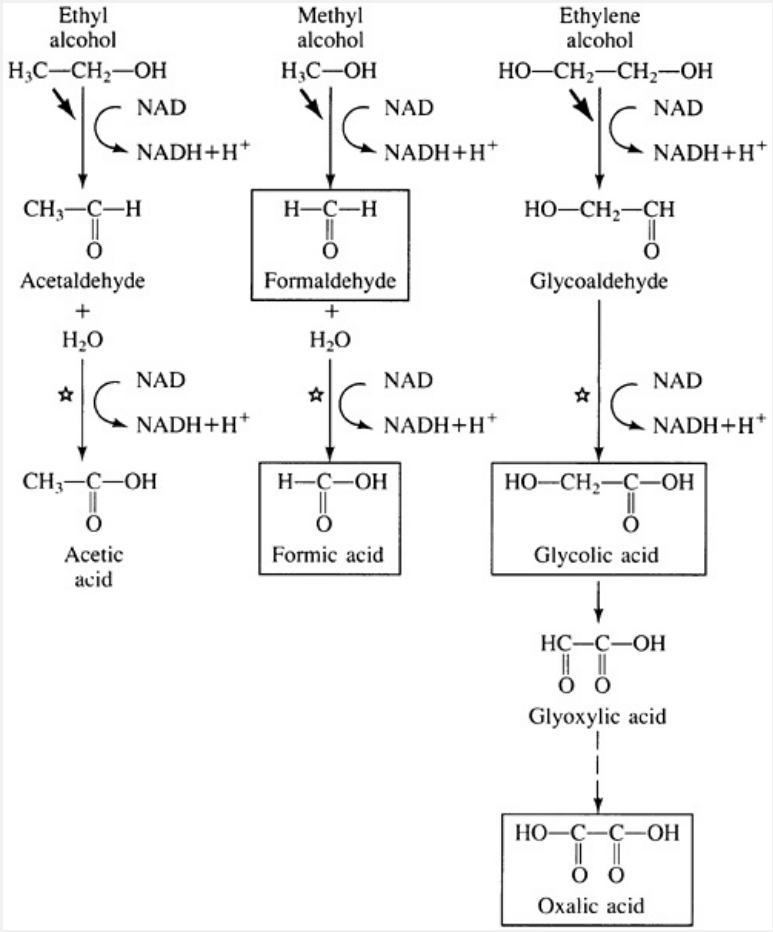

Figure 19-5 Pathways of metabolism of ethyl alcohol (ethanol), methyl alco (methanol), and ethylene glycol. Alcohol dehydrogenase (bold arrow) is a cytosolic enzyme that catalyzes the first oxidative step for each alcohol. Aldehyde dehydrogenase (star) is a mitochondrial enzyme that then cataly second oxidative step. The products in boxes are those responsible for th reactions associated with methanol or ethylene glycol intoxication. (*Adapted from Garella S: Kidney Int 33:735, 1988. Reprinted by permission of Kidney International.*)

The minimum lethal dose is 50 to 100 mL, although smaller amounts can lea permanent blindness. Similar clinical and acid-base disturbances may resul ingestion of formaldehyde.[167]

Osmolal gap

The diagnosis of methanol ingestion is made by a specific serum assay for
In addition, the presence of methanol intoxication may be suspected indirec
demonstration of an *osmolal gap* between the measured and calculated plasma
osmolality.[168,169]

$$\text{Calculated } P_{osm} = 2 \times \text{plasma } [Na^+] + \frac{[\text{glucose}]}{18} + \frac{\text{BUN}}{2.8} \qquad (19\text{-}16)$$

Methanol is a small molecule (mol wt 32) that can achieve high osmolal con
in the plasma. A level of 80 mg/dL, for example, is equivalent to 25 mosmol/
the measured plasma osmolality will exceed the calculated value by Eq. 19-16 in this
amount. A similar but less prominent effect can be induced by ethylene glyc
is a larger molecule (mol wt 62) that is present in lower molar concentratio
methanol. Salicylates, on the other hand, have only a minor effect, since th
level is almost always less than 5 mosmol/kg.[168]

Thus, a high osmolal gap in a patient with an *otherwise unexplained* high anion gap
metabolic acidosis has been thought to be suggestive of the presence of ei
methanol or ethylene glycol intoxication. However, an elevated osmolal gap
relatively nonspecific finding, since it is also seen in other high anion gap

such as diabetic or alcoholic ketoacidosis, lactic acidosis, and in chronic, l
acute, renal failure (due to the retention of unidentified small
solutes).[120,121,170,171] Furthermore, the osmolal gap must be correlated with
concomitant measurement of the plasma ethanol concentration, since patien
ingesting methanol or ethylene glycol often abuse alcohol[121] as well.

The factors responsible for the osmolal gap in ketoacidosis and lactic acido
not been defined. In one study of alcoholic ketoacidosis and lactic acidosis
example, the osmolal gap in these disorders averaged 27 and 17

mosmol/kg, respectively.[121] Although ethanol contributed in many of these patie
the gap remained at 10 to 11 mosmol/kg after the effect of ethanol was sub
Several possibilities can explain at least part of the persistent osmolal gap
setting:

1. The release from the cells of smaller products of glycogen breakdown (
than lactate) into the circulation
2. The accumulation of acetone in ketoacidosis

The net effect of these observations is that an elevated osmolal gap alone
diagnostic of a particular disorder in the patient with a high anion gap meta
acidosis. If, however, the history is not suggestive of either lactic acidosis
ketoacidosis, then a high osmolal gap (particularly if ≥25 mosmol/kg) strong
toward methanol or ethylene glycol intoxication.[121] In this setting, prophylactic
ethanol infusion can be initiated to prevent the formation of toxic metabolit

pending results of the assays for these toxins (see below).

An osmolal gap can also be found in a number of other conditions that are *not associated with metabolic acidosis*, including ethanol or isopropyl alcohol ingest or after the administration of intravenous glycine (during transurethral rese the bladder or prostate; see page 713) or mannitol.[170]

Treatment

Prompt treatment is required to prevent death or permanent residue such as blindness after a methanol overdose. In addition to correcting the acidemia $NaHCO_3$ and administering oral charcoal to minimize further drug absorption,[174] there are two basic aspects of therapy in the presence of severe poisoning:[1] administration of ethanol or fomepizole to prevent the formation of toxic me and[2] hemodialysis to remove both the parent compound and metabolites.[175,176] and[177]

Intravenous or oral ethanol is an effective therapy because alcohol dehydro the enzyme that is necessary for the metabolism of methanol and ethylene g their toxic metabolites (Fig. 19-5). It has more than a 10-fold greater affinity for eth than for other alcohols.[157,176,178] This effect is most prominent when the plasm ethanol concentration is about 100 to 200 mg/dL, a level that can generally achieved by the following regimen: a loading dose of 0.6 g/kg plus an hourl maintenance dose of 66 mg/kg in nondrinkers, 154 mg/kg in drinkers, and 2 once hemodialysis is started.[176,179] If oral ethanol is given, the dose may have t be doubled if charcoal has been administered.[179] Regardless of the mode of administration, the plasma ethanol concentration should be monitored, sinc adjustments in dosage will be required in some patients.

The effect of ethanol has also been demonstrated in selected patients who intoxicated with both methanol and ethanol.[180] In this setting, there may be very high plasma methanol levels, but no symptoms and no metabolic acidosis, s formaldehyde and formate production are minimized.

An alternative to ethanol is the administration of fomepizole (Antizol), whic and competitively inhibits alcohol dehydrogenase more potently than

ethanol.[181,182] and[183] Small studies or case series have documented dramati improvements in acidemia and prevention of renal injury when fomepizole is treat ethylene glycol intoxication.[184,185] Fomepizole also prolongs the half-life of ethanol; thus, the simultaneous use of both agents is recommended. Fomepizole is usually well tolerated but occasionally produces headache, nausea, brad dizziness, eosinophilia, or mild, transient elevation in liver enzymes.

Hemodialysis is used to remove both the parent compound and metabolites.[157] Sorbent-based hemodialysis systems should be avoided, since drug clearan be impaired because of rapid saturation of the cartridge.[186] Drug removal is also much slower with peritoneal dialysis,[177] which should not be used unless

hemodialysis is not available.

In general, ethanol is begun at the time of diagnosis and continued until th methanol concentration is below 20 mg/dL.[175] Hemodialysis should also be instituted if the plasma level is greater than 50 mg/dL, more than 30 mL ha ingested, acidemia is present, or visual acuity is decreased.[175]

Ethylene glycol

Ethylene glycol is a component of antifreeze and solvents that is metaboliz alcohol dehydrogenase into a variety of toxic metabolites (Fig. 19-5). The most important appear to be glycolic acid and oxalic acid, which are responsible the clinical symptoms and the metabolic acidosis.[157,187,188] After ingestion, there are three clinical stages of varying severity.[189,190] During the first 12 h, neurologic symptoms predominate, ranging from drunkenness to coma. This is followed onset of cardiopulmonary abnormalities, such as tachypnea and pulmonary and then flank pain and renal failure. The latter is primarily due to glycolat damage to the tubules, although plugging of the tubular lumen by precipitat oxalate crystals may also contribute.[188,191] The lethal dose of ethylene glycol is approximately 100 mL.

The diagnosis, suspected from the history and the possible presence of en and needle-shaped oxalate crystals in the urine,[191] can be confirmed by the demonstration of ethylene glycol in the serum. The standard assay using so periodate and Schiff's aldehyde reagent is generally accurate but can give positive result if mannitol has been given to induce a diuresis.[192] The diagnosis may also be suspected indirectly by the presence of an osmolal gap in the plasr although this is generally less prominent than with methanol, which is a sm molecule (see "Methanol," above).

Treatment

The specific treatment of ethylene glycol intoxication is identical to that fo ethanol or fomepizole and hemodialysis.[157,178,179,182,184,185,189] Other modalities that may be helpful include a forced diuresis to minimize tubular by oxalate crystals and the administration of pyridoxine and thiamine, whicl respectively promote the conversion of glyoxylate into glycine and α-hydrox ketoadipate, rather than the more toxic oxalate.[169]

Other toxins

A variety of other toxins can rarely lead to metabolic acidosis. Sniffing of *o*-toluene, a component of paint thinners, model glues, and transmission

fluid, can produce a metabolic acidosis, primarily via metabolism to hippuri[32] However, the hippurate anion is both filtered and secreted and is therefore excreted in the urine. As a result, the patient may present with a minimally or even normal anion gap, incorrectly suggesting the possible presence of

tubular acidosis.[32] The ingestion of *elemental sulfur*, used as a folk remedy, is associated with the generation of sulfuric acid.[193] The anion gap remains normal in this disorder, since the excess sulfate is rapidly excreted in the urine. Inhaled chlorine gas leads to the production of hydrochloric acid, producing a normal anion gap acidosis.[199]

Hyperalimentation fluids

The administration of hyperalimentation fluids can produce a metabolic acidosis by two mechanisms. First, some of these solutions contain an excess of cationic amino acids, such as arginine and lysine. When these amino acids are metabolized, H^+ ions are formed.[195]

$$R-NH_3^+ + O_2 \rightarrow \text{urea} + CO_2 + H_2O + H^+$$

This is in addition to the H^+ ions generated by the sulfur-containing amino acids in the solution. Second, starved patients may become hypophosphatemic when fed, resulting in a fall in phosphate and therefore titratable acid excretion. In this setting the H^+ load associated with the metabolism of the administered protein is not efficiently excreted, and metabolic acidosis is more likely to ensue.[196]

Gastrointestinal Loss of Bicarbonate

Diarrhea and fistulas

The intestinal fluids below the stomach, including pancreatic and biliary secretions, are relatively alkaline. The net base in these fluids, which may have a total HCO_3^- concentration of 50 to 70 meq/L,[197] consists of HCO_3^- as well as organic anions, which, if absorbed, would be metabolized to HCO_3^-.[198] As a result, diarrhea, a villous adenoma, or the removal of pancreatic, biliary, or intestinal secretions (by tube drainage, fistulas, or vomiting if there is intestinal obstruction) can lead to metabolic acidosis,[26,197] particularly if volume depletion or underlying renal disease limits the ability of the kidneys to adapt by increasing NH_4^+ excretion.[45]

The same sequence can occur in occult laxative abuse, which should be considered in any patient with a hyperchloremic metabolic acidosis and/or chronic diarrhea of unknown etiology.[199,200] As many as 15 percent of patients referred to tertiary referral centers for evaluation of chronic diarrhea are found to have laxative abuse as the cause of their diarrhea.[201] However, for reasons that are not well understood, many patients with laxative abuse present with metabolic alkalosis rather than acidosis.[197,202]

The increase in stool output in diarrheal states can result from either increased intestinal secretion or decreased absorption of fluids that have been secreted.[203] Secretion, for example, may be increased with cholera toxin, *Escherichia coli* or humoral substances released from tumors, such as vasoactive intestinal peptide

Ureterosigmoidostomy and other forms of urinary divisi

Implantation of the ureters into the sigmoid colon or, more recently, a short ileum that opens at the abdominal wall (ureteroileostomy) has been used to patients with obstructive uropathy due to locally invasive tumor, surgical re the bladder for carcinoma, or less often neurologic bladder dysfunction. A hyperchloremic metabolic acidosis is a relatively common complication of ureterosigmoidostomy (occurring in up to 80 percent of cases) and is due t factors.[197,204,205,206] and[207]

1. The colon has an anion exchange pump, with luminal Cl^- reabsorbed as HCO_3^- is secreted. Thus, when urine enters the colon, it will exchange fo HCO_3^-, which will then be lost in the stool.[208]
2. The colon can directly absorb NH_4^+, which is derived both from the urine and from urea-splitting bacteria in the colon.[197,204] In the liver, the NH_4^+ is metabolized into NH_3 and H^+. Hyperammonemic encephalopathy can occur in patients with underlying liver disease or a marked ammonia load due to tract infection with a urea-splitting organism.[209]

Metabolic acidosis is much less likely with a ureteroileostomy, since rapid of urine into an ileostomy bag means that contact time between the urine a intestine is normally too short for significant changes in urinary compositio However, metabolic acidosis can be seen if contact time is increased becau malfunction of the loop (most often due to stomal stenosis).[204,205,206] and[207] Thus, a loopogram should be performed when an otherwise unexplained me acidosis develops in a patient with a ureteroileostomy. Reabsorption of urin ammonium appears to be more important to the fall in the plasma bicarbona concentration in this setting than is secretion of bicarbonate in the ileum.[204,205]

Cholestyramine

Cholestyramine chloride is an orally administered resin used in the treatme hypercholesterolemia. It is nonreabsorbable and can act as an anion-excha exchanging its Cl^- for endogenous HCO_3^- and producing a metabolic acidosis.[210] This problem is most likely to occur if there is underlying renal disease, wh minimize renal excretion of the excess acid.

Renal Tubular Acidosis

Renal tubular acidosis (RTA) refers to those conditions in which metabolic results from diminished net tubular H^+ secretion.[211,212] There are three major types of RTA, the characteristics of which are summarized in Table 19-6. Although these disorders are relatively unusual in adults (with the exception of type 4 RTA provide interesting examples of the different ways in which the renal regula acid-base balance can be impaired.

The acidosis associated with renal failure could also be included in this gr
However, NH_4^+ excretion per total GFR in this disorder is equal to that achie
acidemic patients with normal renal function.[129] Thus, as mentioned above, the

major problem in renal failure is too few functioning nephrons, not diminish
function. In addition, the ability to maximally acidify the urine (urine pH ≤ 5.
usually maintained in renal failure, in contrast to type 1 and, in some circu
type 2 RTA.[127,130,131]

Table 19-6 Characteristics of different types of ren tubular acidosis

	Type 1 (distal)	Type 2 (proximal)	Type 4
Basic defect	Decreased distal acidification	Diminished proximal HCO_3^- reabsorption	Aldosterone deficiency or resistance
Urine pH during acidemia	>5.3	Variable: >5.3 if above reabsorptive threshold; <5.3 if below	Usually <5.3
Plasma $[HCO_3^-]$, untreated	May be below 10 meq/L	Usually 14 to 20 meq/L	Usually above 15 meq/L
Fractional excretion of HCO_3^- at normal plasma $[HCO_3^-]$	> 3% in adults, may reach 5%–10% in young children	>15%–20%	>3%
Diagnosis	Response to $NaHCO_3$ or NH_4Cl	Response to $NaHCO_3$	Measure plasma aldosterone concentration
Plasma $[K^+]$	Usually reduced or normal; elevated with voltage defect	Normal or reduced	Elevated

Dose of HCO_3^- to normalize plasma $[HCO_3^-]$, meq/kg per day	1–2 in adults, 4–14 in children	10–15	1–3; may require no alkali if hyperkalemia corrected
Nonelectrolyte complications	Nephrocalcinosis and renal stones	Rickets or osteomalacia	None

[a] What had been called type 3 RTA is actually a variant of type 1 RTA (s below).

Type 1 (distal) RTA

Type 1 RTA is characterized by a decrease in net H^+ secretion in the collecting tubules such that the urine pH, which can normally be lowered to a minimur 5.0 in these segments, remains above 5.3. This defect in acidification dimi NH_4^+ and titratable acid excretion, thereby preventing complete excretion o dietary acid load. As a result, there is continued net H^+ retention, leading to a progressive reduction in the plasma HCO_3^- concentration, which may fall below 10 meq/L.

Pathogenesis

Acidification in the collecting tubules is primarily achieved via net H^+ secretion by a luminal H^+-ATPase pump (see Fig. 5-3). This pump is located both

in the cortex (where it is present only in the *intercalated* cells) and in the medulla.[213,214] Although the H^+ secretory cells in the distal nephron do not transport Na^+,[213,215] net H^+ secretion in the cortical collecting tubule is indire influenced by Na^+ reabsorption in the adjacent *principal* cells (see Fig. 5-2). The removal of cationic Na^+ from the tubular fluid makes the lumen more electroneg thereby promoting the accumulation of H^+ in the lumen by minimizing the degr of passive back-diffusion.[213,216,217] In comparison, H^+ secretion in the medulla largely occurs in the absence of Na^+ reabsorption by adjacent cells and therefore essentially Na^+-*independent*.[213,218]

This brief review of distal acidification suggests that there are three mecha which type 1 RTA can occur.[211,212,217]

1. The most common problem is thought to be a defect in H^+-ATPase pump, which may be present in the cortex and/or the medulla. It is likely that a

of different defects can directly or indirectly cause this problem: Three with Sjögren's syndrome have been described in whom immunocytochem analysis of tissue obtained by renal biopsy showed complete absence o H^+-ATPase pumps in the intercalated cells.[219,220] How immunologic injury leads to this change is not known.

There are also genetic forms of type 1 RTA. In patients with autosomal disease, mutations in the gene for the chloride-bicarbonate exchanger (band 3) have often been described.[221,222] and[223] This exchanger is responsible for returning bicarbonate generated within the cell during h secretion to the systemic circulation. Mutations have also been describ gene encoding the B subunit of the H^+-ATPase pump; this disorder is associat with sensorineural deafness, suggesting that the pump is also required normal function of the inner ear.[224]

2. There can be a reduction in cortical Na^+ reabsorption, thereby diminishing the degree of luminal negativity and producing a *voltage-dependent defect*. This abnormality will lead to a concurrent impairment in K^+ secretion, which is also driven in part by the favorable electrical gradient (see Chap. 12).[225] Thus, hyperkalemia will accompany the metabolic acidosis; this problem has n often been described in patients with urinary tract obstruction and sickl disease.[217,226,227] and[228] In the former disorder, for example, a reductio Na^+-K^+-ATPase activity may be responsible for the reduction in Na^+ reabsorption; there may also be a concomitant decrease in H^+-ATPase activity in the outer medulla, further decreasing the ability to secrete hydrogen.[229] Impaired distal hydrogen and potassium secretion may also occur with a cause of marked volume depletion, where the diminished distal Na^+ delivery can induce a readily reversible form of type 1 RTA.[44,230]

An alternative mechanism may explain the development of hyperkalemic RTA in some cases.[231] These patients may have two different defects:

1 an impairment in the H^+-ATPase pump, which is responsible for the RTA, a

2 hypoaldosteronism or aldosterone resistance induced by tubular injury is responsible for the hyperkalemia.

3. There can be an increase in membrane permeability, which allows the b diffusion of H^+ ions (or possibly CO_2). A urine pH of 5.0, for example, is associated with a H^+ concentration that is *1000 times greater* than that in the extracellular fluid. This gradient can be maintained only if the luminal m and tight junction are relatively impermeable to H^+. A *gradient defect* has been documented only in patients treated with amphotericin B, which is a pot tubular toxin.[211,232]

The possible site and mechanism of the acidification defect in type 1 RTA h partially elucidated by the responses to furosemide and SO_4^{2-}.[217] Both agents enhance luminal electronegativity by increasing the delivery of Na^+ to and reabsorption in the cortical collecting tubule; in addition, the presence of the impermeant a SO_4^{2-} will tend to make the lumen more electronegative, since the gradient by Na^+ transport cannot be dissipated by SO_4^{2-} reabsorption.

The changes that these agents induce in H^+ and K^+ excretion in normal subjects an those with type 1 RTA are shown in Table 19-7.[217,228]

1. Normal subjects with metabolic acidosis will have an acid urine pH (≤5. can be further lowered with furosemide or SO_4^{2-}; the increase in electronegativity will also enhance K^+ excretion in this setting.

Table 19-7 Response to furosemide in normals different types of type 1 renal tubular acidos[a]

Type of defect	Site	Urine		K^+ excretion	
		Acidosis	Furosemide	Baseline	Furosemide
Normal		<5.3	Further decline	Normal	Increased
H^+-ATPase pump	Diffuse or CCT alone	>5.5	>5.5	Normal	Increased
H^+-ATPase pump	MCT	>5.5	<5.5	Normal	Increased
Voltage or Na^+ reabsorptive	CCT	>5.5	>5.5	Decreased	No response

[a] Similar responses will occur with SO_4^{2-}. CCT equals cortical collecting tubule; MCT equals medullary collecting tubule.

2. Patients with diffuse impairment in H^+-ATPase pump (due to decreased function or number) will have a persistently alkaline urine pH but a norr

K^+ excretion, since principal cell function is intact. A similar result will the pump dysfunction is limited to the cortical collecting tubule.

3. Patients with a pump defect that is *limited to the medulla* will have a relatively normal increase in both H^+ and K^+ excretion because cortical function is appropriately stimulated by the rise in luminal electronegativity.

4. Patients with a primary impairment in cortical Na^+ reabsorption (*voltage defect*) will have baseline hyperkalemia and no posttherapy increase in K^+ excretion, since there is no enhancement in luminal electronegativity. It is not possible to exclude the possibility that there is also a defect in H^+ function in this setting.

Although proximal HCO_3^- reabsorption is intact in this disorder, variable degree *fixed* bicarbonaturia are obligated by the high urine pH. If, for example, the P_{CO_2} is 46 mmHg (similar to that in venous blood), then, from the Henderso Hasselbalch equation, the urinary HCO_3^- concentration will vary with the urine pH

$$\text{Urine pH} = pK_a' + \log \frac{[HCO_3^-]}{0.03P_{CO_2}} \qquad (19\text{-}17)$$

At a urine pH below 6.0, the urinary HCO_3^- concentration is negligible. In adults w type 1 RTA, the urine pH is usually less than 6.5, resulting in a relatively n of urinary HCO_3^- loss with less than 3 percent of the filtered load of HCO_3^- excreted (Fig. 19-6). The latter can be calculated from a formula similar to that for the fractional excretion of Na^+ (see page 407), using a random urine specimen collecte under oil to minimize the evaporative loss of CO_2:

$$FE_{HCO_3^-}(\%) = \frac{\text{urine } [HCO_3^-] \times \text{plasma [creatinine]}}{\text{plasma } [HCO_3^-] \times \text{urine [creatinine]}} \times 100 \qquad (19\text{-}18)$$

In children, however, the minimum urine pH is generally higher and fixed HCO_3^- losses, which can be calculated from Eq. 19-17, are greater. When the urine pH exceeds 7.0, for example, the fractional excretion of HCO_3^- can reach 5 to 10 percent, thereby making an important contribution to the acidemia. This syn which has been called *type 3 RTA*, occurs in infants, who within a few years have lower urine pH and follow a course more typical of type 1 RTA.

Plasma K^+ concentration

The different types of acidification defects produce different changes in K^+ Those patients who have an impairment in ATPase H^+ pump or increased permeability to H^+ back-diffusion tend to have *urinary K^+ wasting and hypokalemia prior to therapy*. Three factors may contribute to this problem:

1. Single net distal H^+ secretion is diminished, more Na^+ reabsorption must now occur in exchange for K^+.

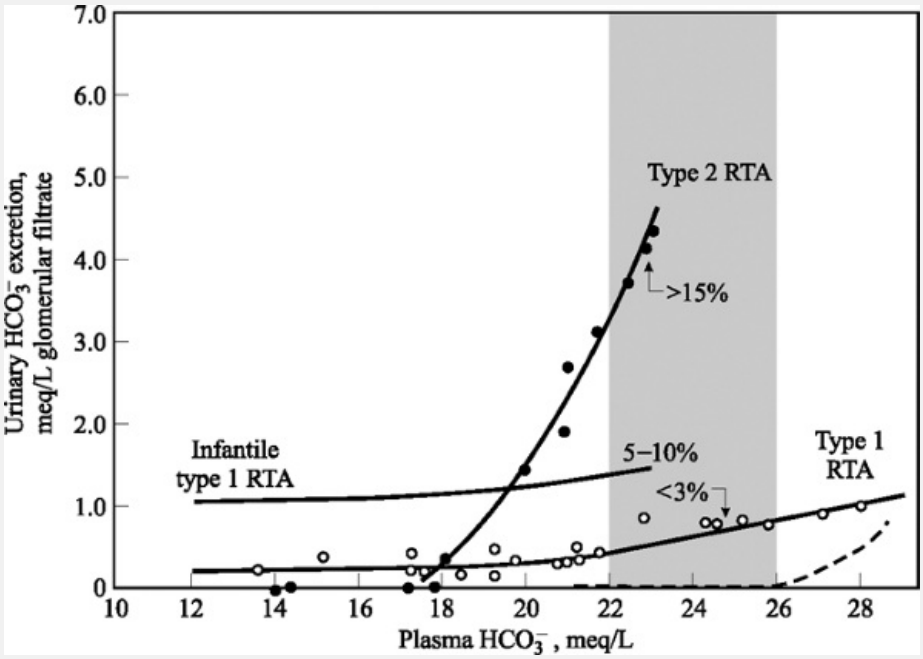

Figure 19-6 The relationship between urinary HCO_3^- excretion and the plasma HCO_3^- concentration in normal subjects (dashed line) and in patients with type 1 and type 2 RTA as $NaHCO_3$ is administered to raise the plasma HCO_3^- concentration toward normal. In the last condition, there is little urinary HCO_3^- and an acid urine pH when the plasma HCO_3^- concentration is below the maximal reabsorptive capacity. Above this l however, there is a rapid increase in HCO_3^- excretion such that more than 10 to 15 percent of the filtered HCO_3^- is excreted at a normal plasma HCO_3^- concentration (shaded area). Patients with type 1 RTA, on the other h are similar to normal subjects except that there is a fixed degree of bicarbonaturia obligated by the high urine pH. In adults, this is genera less than 3 percent of the filtered load, but it can reach 5 to 10 perce infantile type 1 RTA, in which there is a higher minimal urine pH. (*Adapted from Sebastian A, McSherry E, Morris RC Jr, in Brenner BM, Rector F (eds): The Kidney. Philadelphia, Saunders, 1976, chap 16, with permission.*)

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2. There may be a concurrent decrease in the activity of the second proto in the luminal membrane of the cortical and outer medullary collecting t the H^+-K^+-ATPase pump that reabsorbs K^+ as well as secreting H^+ (see Chap. 11).[214,238] The main function of this pump may be to reabsorb K^+ ions of

K^+ depletion, rather than to maintain acid-base balance. As a result, its inhibition may promote urinary K^+ wasting and hypokalemia as well as metabolic acidosis.[239]

3. Metabolic acidosis leads to increased NaCl and water delivery out of the proximal tubule; the ensuing volume contraction results in secondary hyperaldosteronism and increased loss of K^+. The latter defect in proximal tubule function is a probable reflection of the low plasma HCO_3^- concentration and therefore the less quantity of HCO_3^- reabsorption by Na^+-H^+ exchange in the proximal tubule. The Na^+-NH_4^+ exchanger plays an important role in proximal $NaCl$ reabsorption, both by creating a gradient for passive Cl^- transport and by promoting active Cl^- transport by operating in parallel with the apical Cl^--formate exchanger (see page 79).

Thus, any cause of metabolic acidosis will tend to diminish net proximal reabsorption.[240] Acidemia can also directly impair $NaCl$ transport (via an unknown mechanism) in the cortical aspect of the thick ascending limb.[241]

These abnormalities and most of the urinary K^+ wasting can be reversed by correction of the acidemia.[236,237] Some defect may persist, however, in those patients with impaired pump activity, since there will still be a requirement for more than normal amounts of K^+ in exchange for Na^+ in the cortical collecting tubule.[236,242]

In comparison, those patients with a voltage defect due to diminished distal H^+ transport will have a lesser degree of luminal electronegativity and therefore excrete less H^+ and K^+, resulting in *hyperkalemia* as well as metabolic acidosis.[211,217,226,227] and [228,243] These patients appear to have normal amounts of H^+-ATPase in the intercalated cells.[243] Although hyperkalemic acidosis is also found in type 4 RTA, this disorder is associated with low aldosterone and usually intact ability to reduce the urine pH below 5.3.[44,226]

Nephrocalcinosis

Hypercalciuria, hyperphosphaturia, nephrolithiasis (with calcium phosphate or struvite stones), and nephrocalcinosis are frequently associated with untreated 1 RTA.[244,245,246,247] and [248] In some families, hypercalciuria precedes the metabolic acidosis, suggesting that calcium-induced tubular damage is therefore responsible for the RTA.[244,245] In most cases, however, acidemia is directly responsible, both by increasing calcium phosphate release from

bone during buffering of the excess H^+,[135,249,250] and by directly reducing (via an

uncertain mechanism) the tubular reabsorption of these ions.[251,252] and [253] The degree of hypercalciuria is generally proportional to the fall in the plasma HCO_3^- concentration.[254]

In addition to hypercalciuria and hyperphosphaturia, two other factors incre tendency to stone formation in type 1 RTA: the persistently high urine pH, v promotes the precipitation of calcium phosphate, and low levels of citrate e Citrate normally inhibits crystallization by forming a nondissociable but sol complex with calcium, thereby decreasing the amount of free calcium availa stone formation.[245,246,247] and [248,255] Both metabolic acidosis and hypokalemia may contribute to the hypocitraturia by lowering the tubular cell pH in the p tubule, the former directly and the latter by transcellular Na^+/H^+ exchange (see page 356).[256,257] Intracellular acidosis promotes citrate utilization, leading seque to low citrate levels in the cell, a more favorable gradient for citrate reabs from the tubular lumen, and a decline in citrate excretion.[256] The acidemia-induced fall in luminal pH in the proximal tubule also may contribute to this respons converting filtered citrate(3-) into the more reabsorbable citrate(2-).[258]

Stone disease is less common in incomplete type 1 RTA.[248,260] this setting, low urinary citrate levels may be of primary importance (see below).

All of the above changes in complete type 1 RTA typically respond to early complete correction of the acidemia: less calcium phosphate release from b enhanced tubular reabsorption of these ions, an increase in urinary citrate (although not necessarily to normal),[246,248,255] and prevention of nephrocalcinosis and nephrolithiasis;[246,247] and [248,261] even in the incomplete form.[248]

In general, *potassium citrate* (citrate is rapidly metabolized to HCO_3^-) is the preferred therapy.[248] It is better tolerated than HCO_3^- solutions, correction of hypokalemia will further increase citrate excretion, and the natriuresis asso with *sodium* citrate leads to an undesirable increase in calcium excretion, sin and calcium handling are indirectly linked in the proximal tubule and loop o (see Chap. 3).[262,263]

In contrast, alkali therapy alone is less likely to prevent nephrocalcinosis i patients with hereditary RTA in whom hypercalciuria is the primary defect.[244,245] this setting, conventional therapy for calcium stones, such as a thiazide diu diminish calcium excretion and neutral phosphate to increase the excretion crystallization inhibitor pyrophosphate, may be effective.[264,265] and [266]

Incomplete type 1 RTA

Some patients with defective urinary acidification do not become acidemic, syndrome that is referred to as *incomplete* type 1 RTA.[131,267,268] Patients with the incomplete form have a normal rate of ammonium excretion despite a high u Why this occurs is not clear, but the observation that they also have a low

citrate excretion (similar to the complete form) suggests that there may be abnormality in the proximal tubule, such as an intracellular acidosis.[268] This wil promote proximal ammonium and H^+ secretion; by the mechanisms described abov both the intracellular and intraluminal acidosis can then enhance net citrat reabsorption.

The proposed increase in proximal ammonia production in combination with hypocitraturia can then explain the other findings in incomplete type 1 RTA.[268]

1. The increase in ammonia production will drive the reaction, $NH_3 + H^+ \leftrightarrows NH_4^+$, to the right, thereby lowering the free hydrogen concentration and raising the urine pH, even though total ammonium ex normal.
2. The combination of a high urine pH and low citrate excretion can promo precipitation of calcium phosphate in the tubules and the interstitium, p leading to kidney stones or nephrocalcinosis.
3. The direct toxic effect of NH_3 (which is freely diffusible and can accumulate the medulla) and perhaps calcium phosphate precipitation may explain t occasional progression of incomplete to complete type 1 RTA with metal acidosis. According to this hypothesis, the impairment in collecting tubu function is a secondary process induced by the primary abnormality in t proximal tubule.

Etiology

Many different conditions have been associated with type 1 RTA.[212] The most common identifiable causes in adults are autoimmune disorders, s Sjögren's syndrome and rheumatoid arthritis, hyper-calciuria which is the p defect in some families), toluene sniffing in

recreational drug users (although, as noted above, overproduction of hippu the probable mechanism in this setting),[32] and marked volume depletion;[219,220,230,244,245,269,270] in comparison, hereditary RTA is most common in children.[261] In selected patients with Sjögren's syndrome, the corre diagnosis is delayed because the renal tubular acidosis can precede the characteristic extrarenal manifestations by 5 years or more.[269,271]

Table 19-8 Major causes of type 1 renal tubular acidosis

Primary
A. Idiopathic or sporadic

Hereditary

A. Familial, including hypercalciuria as the primary abnormality
B. Marfan's syndrome
C. Wilson's disease
D. Ehlers-Danlos syndrome

Disorders of calcium metabolism and nephrocalcinosis

A. Idiopathic or familial hypercalciuria
B. Primary hyperparathyroidism
C. Hypervitaminosis D
D. Medullary sponge kidney

Autoimmune diseases

A. Sjögren's syndrome
B. Rheumatoid arthritis
C. Systemic lupus erythematosus
D. Chronic active hepatitis
E. Primary biliary cirrhosis
F. Hypergammaglobulinemia in cirrhosis
G. Thyroiditis

Drugs and toxins

A. Amphotericin B
B. Ifosfamide
C. Lithium carbonate
D. Analgesic abuse
E. Light chains in multiple myeloma
F. Toluene

Associated with hyperkalemia

A. Urinary tract obstruction
B. Sickle cell anemia
C. Renal transplant rejection
D. Systemic lupus erythematosus

Marked volume depletion of any cause

Clinical manifestations

Patients with type 1 RTA are often asymptomatic, although they may have c related to stone disease, to severe acidemia itself (see "Symptoms" below), or to hypokalemia (weakness, fatigue, polyuria, polydipsia). The situation is pote more serious in children, in whom failure

to thrive (in infants) and decreased linear growth are common and reversib findings.[137,261]

Diagnosis

The presence of type 1 RTA should be suspected in any patient with a norm gap metabolic acidosis and a urine pH greater than 5.3 in adults[44,131,132] or 5.6 in children.[242] In the absence of a high urine pH due to infection with a urea-sp organism, the only other conditions that can produce this combination are t RTA, volume depletion,[44,230] and hypokalemia (which increases urinary NH_4^+ production).[47] Measurement of the urine Na^+ concentration and the urine anion ga should be helpful in evaluating the contribution of the last two conditions:[1,2] a low urine Na^+ concentration (≤25 meq/L) can raise the urine pH by limiting distal H^+ delivery and reabsorption,[44,230] and the urine anion gap should be appropriate negative with hypokalemia alone, since there is no defect in NH_4^+ excretion in this setting.[44,272]

Types 1 and 2 RTA can be differentiated by the response to raising the plas HCO_3^- concentration with $NaHCO_3$ (infused at a rate of 0.5 to 1.0 meq/kg/h). The urine pH and fractional excretion of HCO_3^- will remain constant in type 1 disease b will rise markedly in type 2 RTA, since the reabsorptive threshold for HCO_3^- is excreted in this setting (Fig. 19-6).

A different approach is required in patients with incomplete type 1 RTA, in plasma HCO_3^- is normal. This disorder is usually suspected because the urin persistently above 5.5 in a patient with a positive family history of RTA or c stone disease.[131,248,260,267] The diagnosis can be established by giving an a load as NH_4Cl in a dose of 0.1 g/kg.[131,267] This should induce a 4- to 5-meq/L fal in the plasma HCO_3^- concentration within 4 to 6 h. The urine pH will remain ab 5.3 in type 1 RTA but will be less than this value and usually below 5.0 in r subjects, in whom acidemia stimulates maximal urinary acidification.

Treatment

Correction of the acidosis is generally indicated in type 1 RTA to allow nor to occur in children;[137,273] to minimize stone formation, nephrocalcinosis, and possible osteopenia due to calcium loss from bone;[246,247] and[248,254] and to diminish inappropriate urinary loss of K^+.[236,237] The alkali requirement in this

setting is variable, being equal to the fraction of the daily H^+ load that is not excreted *plus* the fixed HCO_3^- losses obligated by the high urine pH (Fig. 19-6). In adults, the latter are relatively small, and only 1 to 2 meq/kg per day of alk usually necessary. In children, however, the urine pH and HCO_3^- losses are higher, and as much as 4 to 14 meq/kg per day in divided doses may be required. Many patients can be treated only with sodium bicarbonate or sodium citrate (Bicitra), since K^+ wasting is markedly diminished when the acidemia is corrected.[137] However, potassium citrate, alone or with sodium citrate (Polycitra), is indicated for hypokalemia or for calcium stone disease or nephrocalcinosis.[236,237,248,262,263]

Type 2 (proximal) RTA

A different problem is present in type 2 RTA: decreased proximal tubular HCO_3^- reabsorption (Table 19-6).[212,261] Normal subjects who are euvolemic reabsorb essentially a filtered HCO_3^- until the HCO_3^- concentration in the plasma and, therefore, in the glomerular filtrate exceeds 26 to 28 meq/L (see Chap. 3). Above this level, the excess HCO_3^- is appropriately excreted in the urine. Approximately 90 percen HCO_3^- reabsorption occurs in the proximal tubule.

In type 2 RTA, proximal HCO_3^- reabsorption is reduced, as is total HCO_3^- reabsorptive capacity. If, for example, only 17 meq/L of glomerular filtrate c reabsorbed, then HCO_3^- will be lost in the urine until the plasma HCO_3^- concentration reaches 17 meq/L. At this point, all the filtered HCO_3^- can be reclaimed and a new steady state is achieved. Thus, type 2 RTA is a *self-limiting disorder* in which the plasma HCO_3^- concentration is usually between 14 and 20 meq/L.[261]

The absence of more severe acidemia in this condition is a probable reflect *intact reabsorptive capacity of the distal nephron*, particularly the outer medullary collecting tubule.[218] In experimental animals, for example, the administration c carbonic anhydrase inhibitor can block up to 80 percent of proximal HCO_3^- reabsorption, but only 30 percent of the filtered load appears in the urine as a result of enhanced distal reabsorption.[274] A similar effect probably occurs in humans, as the *total absence* of proximal reabsorption lowers the plasma HCO_3^- concentration to only 11 to 12 meq/L.[275]

The clinical difference between types 1 and 2 RTA can be appreciated by e the relationship between urinary HCO_3^- excretion and the plasma HCO_3^- concentration (Fig. 19-6). In normal subjects, HCO_3^- does not significantly appear in the urine until the plasma HCO_3^- concentration exceeds 26 meq/L. This relations is shifted to a lower level in type 2 RTA. If maximal reabsorptive capacity is

meq/L, then administering alkali to raise the plasma HCO_3^- concentration above this level will lead to the excretion of increasing amounts of HCO_3^-. By the time the plasma HCO_3^- concentration reaches the normal range, more than 15 percent of filtered HCO_3^- will appear in the urine, and the urine pH will exceed 7.5. In co the urine can be made maximally acid (pH≤5.3) if the plasma HCO_3^- concentration is below 17 meq/L, since all the filtered HCO_3^- can now be absorbed and distal acidification is normal.

In comparison, the curve relating urinary HCO_3^- excretion and the plasma HCO_3^- concentration in type 1 RTA is similar to that in normal subjects except that elevated urine pH obligates a fixed degree of bicarbonaturia. However, the defect prevents the excretion of all of the dietary acid load, and progressiv severe acidemia can occur.

The defect in HCO_3^- reabsorption in type 2 RTA may occur alone or as part of Fanconi syndrome, in which a variety of other proximal functions are impair including the reabsorption of phosphate, glucose, amino acids, and

urate.[265,266] In this setting, metabolic acidosis may be accompanied by hypophosphatemia, hypouricemia, aminoaciduria, and/or glucosuria at a nor plasma glucose concentration.

Pathogenesis

The factors responsible for the defects in proximal transport in type 2 RTA incompletely understood.[276] As described in chap. 11, three factors are of primary importance in proximal HCO_3^- reabsorption: (1) the Na^+-H^+ exchanger in the luminal membrane, (2) the Na^+-K^+-ATPase pump in the basolateral membrane that provid the energy of Na^+-H^+ exchange by maintaining a low cell Na^+ concentration and therefore a favorable gradient for passive entry of Na^+ into the cell, and (3) the enzyme carbonic anhydrase, which is located both in the cells, where it results in t generation of H^+ and HCO_3^-, and in the lumen, where it facilitates HCO_3^- reabsorption by catalyzing the dehydration of H_2CO_3 that is formed by the combination of filtered HCO_3^- with secreted H^+.

It is likely that one or more of these factors must be impaired to account fo HCO_3^- reabsorptive defect in type 2 RTA.[276] As examples, defective carbonic anhydrase activity and, in cystinosis, ATP depletion have been described ir patients.[277,278] and[279] In addition, the administration of a carbonic anhydras inhibitor, such as acetazolamide in glaucoma or a topical sulfonamide antib extensive burns, often results in a mild metabolic acidosis.[280,281]

Proximal tubular dysfunction can also be seen in multiple myeloma, which n most common cause of type 2 RTA in adults.[282,283] It is likely that toxic light chains

are reabsorbed by and then accumulate in the proximal tubular cells, leadir uncertain mechanism to impaired tubular function.[284]

Another cause of type 2 RTA is the anticancer drug ifosfamide,[285,286] it is unclear whether the tubular toxicity is mediated by the parent drug or by the metab chloracetaldehyde.[287] In addition to HCO_3^- loss, other findings that may occur include phosphate wasting and hypophosphatemia (possibly leading to ricke children), renal glucosuria, and aminoaciduria. Signs of distal damage also seen, including type 1 RTA and polyuria due to nephrogenic diabetes insipi[285]

K^+ balance

Urinary K^+ wasting and hypokalemia are common in type 2 RTA, although the to which this occurs is variable.[236,288] Prior to treatment, the patient is in a stea state in which virtually all of the filtered load of HCO_3^- is reabsorbed. In this setting, however, there is often persistent hyperaldosteronism and mild hypokalemia.[288] As described above, these changes are probably related to the decrease in pr transport of HCO_3^-, which leads to diminished active and passive proximal NaC reabsorption and a tendency toward Na^+ wasting.[240] An additional problem is added wit alkali therapy, as the elevation in the filtered load of HCO_3^- and the reabsorptive threshold results in a marked increase in HCO_3^- and water delivery to the cortical collecting tubule (Fig. 19-6). This elevation in distal flow with the relatively nonreabsorbable anion HCO_3^- plus persistent hyperaldosteronism combi to further enhance urinary K^+ loss (Fig. 19-7).[288]

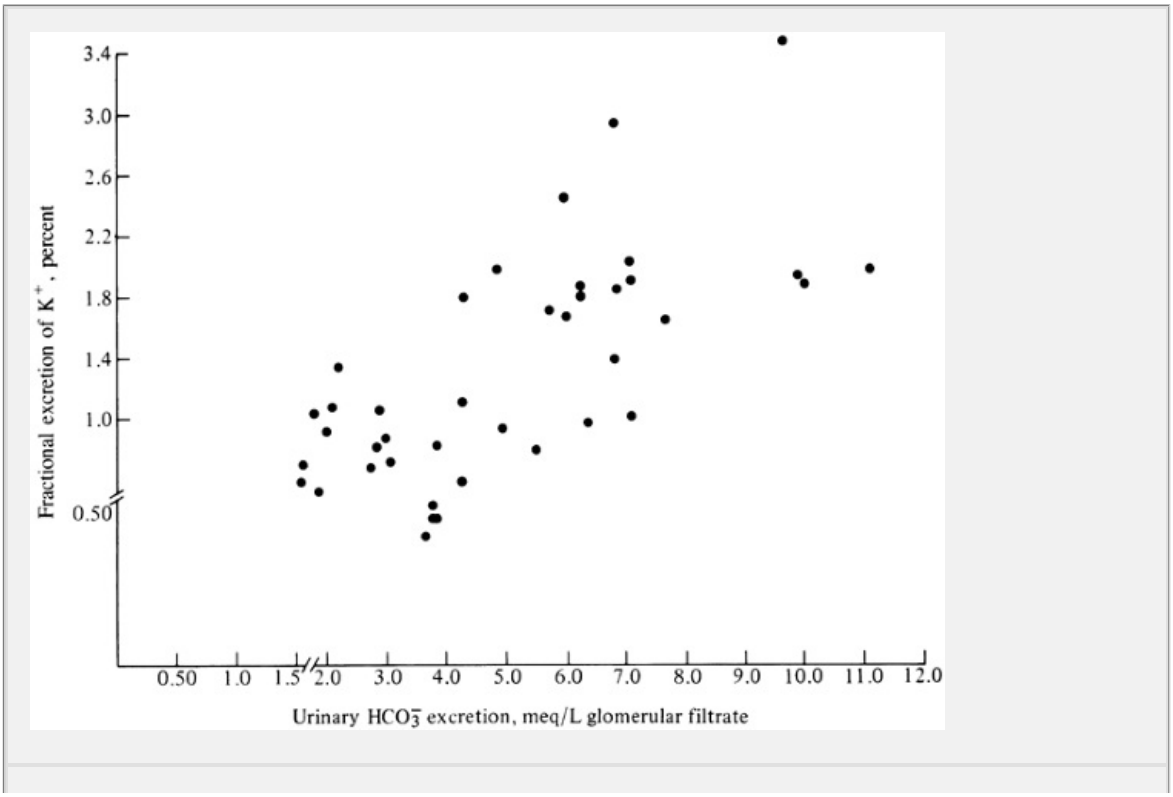

Figure 19-8 Relationship between the fractional excretion of filtered K^+ and urinary HCO_3^- excretion in patients with type 2 RTA in whom the plasma HCO_3^- concentration is maintained at normal levels (22 to 26 mEq/L). (*Adapted from Sebastian A, McSherry E, Morris RC Jr: J Clin Invest 50:231, 1971, by copyright permission of The American Society for Clinical Investigation.*)

Bone disease

Rickets in children and osteomalacia or osteopenia in adults are relatively common in type 2 RTA, occurring in up to 20 percent of cases.[247] Although these skeletal abnormalities may also be present in other acidemic states, their frequency is greater in RTA may be due in part to phosphate wasting and subsequent hypophosphatemia and to acquired vitamin D deficiency, since the proximal tubule is a major site of formation of calcitriol, the most active form of vitamin D (see Chap. 6). In addition, acidemia can directly impair growth in children.[261,273]

Nephrocalcinosis and nephrolithiasis do not occur in this disorder, in contrast to the high frequency in type 1 RTA.[247] Two factors may combine to protect against this complication: the ability to lower the urine pH, which increases the solubility of calcium phosphate, and the presence of nonreabsorbed amino acids and organic anions (including citrate), which can form soluble complexes with calcium, thereby limiting the amount of free calcium available to precipitate with phosphate or oxalate.[247]

Etiology

A variety of congenital and acquired disorders can cause type 2 RTA (Table 19-9). Idiopathic RTA and cystinosis are most common in children;

carbonic anhydrase inhibitors and multiple myeloma (which may be latent) are often responsible in adults.[238,282]

Table 19-9 Major causes of type 2 renal tubular acidosis

Primary

A. Idiopathic or sporadic, may be transient in children

Hereditary

A. Cystinosis
B. Hereditary fructose intolerance (during fructose administration)
C. Familial osteopetrosis (where there may be diminished carbonic

anhydrase activity)
D. Tyrosinemia
E. Glycogen storage disease, type 1
F. Wilson's disease
G. Pyruvate carboxylase deficiency
H. Lowe's syndrome
I. Galactosemia

Acquired disorders

A. Multiple myeloma, latent or fully expressed
B. Hypocalcemia and vitamin D deficiency
C. Drugs and toxins
    1. Ifosfamide
    2. Acetazolamide or other carbonic anhydrase inhibitor
    3. Streptozotocin
    4. Outdated tetracycline
    5. Lead
    6. Cadmium
    7. Mercury
D. Amyloidosis
E. Renal transplant rejection
F. Sjoögren's syndrome

Diagnosis

The presence of type 2 RTA should be suspected in any patient with an une normal anion gap metabolic acidosis, even if the urine pH is below 5.3. Oth findings suggestive of proximal tubule dysfunction may be very helpful in th including hypophosphatemia, hypouricemia, and renal glucosuria.

The diagnosis of type 2 RTA can be established by raising the plasma HCO_3^- concentration toward normal with an infusion of alkali (e.g., $NaHCO_3$ at a rate of 0.5 to 1.0 meq/kg/h). The urine pH, even if initially acid, will increase rapidly once th reabsorptive threshold for HCO_3^- is exceeded. As a result, the urine pH will be greater than 7.5 and the fractional excretion of HCO_3^- greater than 15 to 20 percent as the plasma HCO_3^- concentration approaches normal (Fig. 19-6).

Treatment

Correction of the acidemia will allow normal growth to occur in children and will promote healing of the bone disease (with phosphate and vitamin D supplementation if hypophosphatemia is also present). Even adequately treated patient should be asymptomatic (unless there is a complicating syst

disease) and able to lead a normal life. Furthermore, idiopathic type 2 RTA children may be transient, disappearing spontaneously after several years.[273]

Reversal of the acidemia is often difficult, however, because the exogenous rapidly excreted in the urine. As a result, 10 to 15 meq/kg/day of alkali is t required to stay ahead of urinary excretion. In addition, an empirically dete fraction must be given as the salt, since the associated bicarbonaturia leads increased urinary K^+ losses (Fig. 19-7).[288] Serial monitoring is also required in children, since growth can lead to substantial changes in alkali requiremen

Either HCO_3^- or citrate can be used as the source of alkali. In general, the la better tolerated and, when given in such high doses, may actually be slight The buffering of gastric H^+ ions by administered HCO_3^- can lead to the rapid formation of up to several hundred milliliters of CO_2 in the stomach. There are isolated case reports in which patients taking more than 20 meq of NaHCO eating a large meal developed gastric rupture due to the sudden increase i volume.[289]

When large doses of alkali are ineffective or not well tolerated, the additio thiazide diuretic may be helpful.[290] The ensuing mild volume depletion will increa the proximal reabsorption of Na^+ and secondarily that of HCO_3^- (see Chap. 3).

Type 4 RTA

Type 4 RTA refers to metabolic acidosis resulting from aldosterone deficien resistance. Aldosterone normally promotes distal H^+ and K^+ secretion as well as Na^+ reabsorption (see Chap. 6). The effect on H^+ secretion results both from direct stimulation of the H^+-ATPase pump[291] and from increased luminal electronegativi created by Na^+ reabsorption.[216] As a result, hypoaldosteronism impairs these processes, leading to hyperkalemia (which is generally more prominent) an metabolic acidosis (see Chap. 28).

In addition to the direct effect of aldosterone deficiency, hyperkalemia play important role in the metabolic acidosis by impairing NH_4^+ production and excretion.[292],[293] and[294] This effect may result in part from an increase in the tubular fluid K^+ concentration competitively inhibiting the binding of NH_4^+ to the K^+ site on the Na^+-K^+-$2Cl^-$ carrier in the loop of Henle. As a result, there will be sequential reductions in NH_4^+ recycling within the medulla and in NH_3 secretion into the medullary collecting tubule (see p. 341).[295] Reversing this process by correcting the hyperkalemia often leads to increased NH_4^+ excretion and correction of the metabolic acidosis.[294]

The metabolic acidosis seen with hypoaldosteronism is generally mild, with plasma HCO_3^- concentration usually remaining above 15 meq/L. The urine pH

disorder is generally but not always below 5.3,[44,296] distinguishing this disorder from the hyperkalemic form of type 1 RTA.[233] The low urine pH is also compatible with diminished NH_4^+ production as the primary abnormality, since total acid excretion is reduced because of the lack of available buffers, not impaired acidification.

The clinical characteristics of type 4 RTA are discussed in detail in Chapter 28 because of the general prominence of hyperkalemia in this disorder. Althou mineralocorticoid replacement may be effective in treating the hyperkalemia metabolic acidosis,[296,297] most patients have underlying renal insufficiency, ar associated Na^+ retention can exacerbate edema or hypertension. As a result, combination of a low-K^+ diet and a loop diuretic is often used.[298] The latter, by increasing distal Na^+ delivery, results in greater luminal electronegativity and increase in K^+ and H^+ secretion.[228]

Massive Rhabdomyolysis

A rare cause of a high anion gap metabolic acidosis is massive rhabdomyol[299] The presumed mechanism is the release of K^+ and organic anions from the damage cells. This diagnosis should be suspected if there is a marked elevation in plasma level of creatine kinase (as well as that of other muscle enzymes) a other apparent cause for the acidemia.

SYMPTOMS

Metabolic acidosis can result in changes in pulmonary cardiovascular, neur and musculoskeletal function. Since the respiratory compensation results ir as a four- to eightfold increase in minute ventilation (see Figure 11-6),[11,12] the patient may complain of dyspnea on exertion and, with severe acidemia, ev Furthermore, the observation of hyperpnea (affecting the depth more than t ventilation) on physical examination may be the only clue suggesting the pr an underlying acidemic state.

A fall in the arterial pH to less than 7.00 to 7.10 can predispose toward pot fatal ventricular arrhythmias and can reduce both cardiac contractility and inotropic response to catecholamines.[93,300,301] The last effect may be mediated ir part by decreased delivery of calcium to myofilaments and by decreased responsiveness of the myofilaments to calcium; how these changes might o not known.[301] This decrease in ventricular function may play an important ro perpetuation of shock-induced lactic acidosis, and partial correction of the may be required before tissue perfusion can be restored.[93] As noted above, however, alkali therapy may actually worsen the intracellular acidosis in pa circulatory failure.[99,100]

Neurologic symptoms ranging from lethargy to coma have been described in metabolic acidosis. These symptoms appear to be more closely related to t

pH in the cerebrospinal fluid (CSF) than to that in the plasma.[302] In general, neurologic abnormalities are much less prominent in metabolic acidosis tha respiratory acidosis. This may be due to the ability of lipid-soluble CO_2 to cross the blood-brain barrier much more rapidly than water-soluble HCO_3^-, thereby producing a greater fall in CSF pH.[303,304] When neurologic symptoms do occur in metaboli acidosis, a concurrent problem is more likely to be responsible, such

as the toxic effects of ingestions, diminished cerebral perfusion in shock, a hyperosmolality due to hyperglycemia in diabetic ketoacidosis.[305]

Chronic acidemia, as with renal failure or renal tubular acidosis, can lead t of skeletal problems that are probably due in part to release of Ca^{2+} and phosphate during bone buffering of the excess H^+ ions.[135,249,250,264,306] Of particular importance is impaired growth in children.[137,271,307] Other abnormalities that may occur include osteitis fibrosa (from secondary hyperparathyroidism), rickets children, and osteomalacia or osteopenia in adults.[247,308]

Correction of the acidemia may reverse these changes in patients without r failure.[308] Therapy is generally less successful with advanced renal disease other factors also contribute to the bone abnormalities, such as hyperparat vitamin D deficiency, and poor nutrition due to anorexia.[307,309,310] (The pathophysiology of renal osteodystrophy is reviewed in Chapter 16.)

In infants and young children, acidemia may also be associated with a varie nonspecific symptoms, such as anorexia, nausea, weight loss, muscle weak listlessness.[261] The last two symptoms may result in part from loss of lean bo mass as a result of alterations in muscle protein metabolism.[141,145,146] These changes are reversible with the restoration of acid-base balance.

TREATMENT

The specific aspects of therapy for individual disorders have been discusse appropriate sections above. It is important, however, to review the general particularly the type, quantity, and rate of alkali replacement.

General Principles

In most clinical situations, correction of the acidemia can be achieved by th administration of $NaHCO_3$. There are, however, some exceptions to this recommendation, since no alkali therapy may be required in lactic or ketoac (where metabolism of the organic anions will regenerate HCO_3^-), and sodium and/or potassium citrate may be preferable for chronic treatment in renal tubular a THAM and sodium lactate have also been used but offer no particular adva over $NaHCO_3$.[311,312]

The initial therapeutic goal in patients with severe acidemia is to raise the pH to about 7.20, a level at which arrhythmias become less likely and cardi

contractility and responsiveness to catecholamines will be restored. Attainr this pH usually requires only a small increment in the plasma HCO_3^- concentration. As an example, the following arterial blood values are obtained from a patie chronic diarrhea:

$$\text{Arterial pH} = 7.10$$
$$P_{CO_2} = 20 \text{ mmHg}$$
$$[HCO_3^-] = 6 \text{ meq/L}$$

The level to which the plasma HCO_3^- concentration must be raised for the pH to reach 7.20 can be calculated from the Henderson-Hasselbalch equation:

$$\text{pH} = 6.10 + \frac{[HCO_3^-]}{0.03P_{CO_2}}$$

If we assume that the P_{CO_2} will remain constant, then

$$7.20 = 6.10 + \frac{[HCO_3^-]}{0.03 \times 20}$$

Since this equation is difficult to solve at the bedside, it is easier to expres relationship between these parameters in nonlogarithmic terms [Eq. (19-12)]:

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]}$$

Since the H^+ concentration is 63 nanoeq/L at a pH of 7.20 (see Table 19-1),

$$63 = 24 \times \frac{20}{[HCO_3^-]}$$
$$[HCO_3^-] = 8 \text{ meq/L}$$

This calculation slightly underestimates the HCO_3^- requirement, since the drive to compensatory hyperventilation will diminish as the acidemia is corr resulting in an elevation in the P_{CO_2}. If we assume that the P_{CO_2} will rise from 20 to 25 mmHg, then

$$63 = 24 \times \frac{25}{[HCO_3^-]}$$
$$[HCO_3^-] = 10 \text{ meq/L}$$

Thus, *only a small increase in the plasma HCO_3^- concentration is necessary to get the patient out of danger if there is a normal respiratory compensation.*

Rapid administration of HCO_3^- is important only in patients with severe metaboli acidosis. In this setting, even a minimal additional reduction in the plasma HCO_3^- concentration can result in a large percentage change and therefore can in immediately life-threatening degree of acidemia. For example, lowering the HCO_3^- concentration from 24 to 22 meq/L in a patient with an initial pH of 7 P_{CO_2} of 40 mmHg will have only a minor effect on the H^+ concentration:

$$[H^+] = 24 \times \frac{40}{22}$$
$$= 44 \text{ nanoeq/L} \qquad (pH = 7.36)$$

However, a similar 2-meq/L reduction in a patient with an initial pH of 7.11, HCO_3^- concentration of 4 meq/L, and a P_{CO_2} of 13 mmHg will now decrease the pH to 6.81:

$$[H^+] = 24 \times \frac{13}{2}$$
$$= 156 \text{ nanoeq/L} \qquad (pH = 6.81)$$

Regardless of the initial severity, rapid correction of the pH to above 7.20 only is unnecessary but can induce potentially important reductions in the C and in tissue oxygen delivery. The administration of NaHCO$_3$ will lower minute ventilation and raise the P_{CO_2}. Since CO_2 crosses the blood-brain barrier much more rapidly than HCO_3^-, the brain will acutely sense only the elevation in P_{CO_2}. Thus, the CSF pH will become more acid, with possible aggravation o neurologic symptoms.[30,2] The increase in the arterial pH will also shift the hemoglobin dissociation curve to the left, increasing the affinity of hemoglo oxygen and possibly reducing tissue oxygen delivery.

Bicarbonate Deficit

The amount of HCO_3^- required to correct the acidemia can be estimated from t following formula:

$$HCO_3^- \text{ deficit} = HCO_3^- \text{ space} \times HCO_3^- \text{ deficit per liter} \qquad (19\text{-}19)$$

The apparent bicarbonate space is a reflection of total body buffering capa therefore determined both by the quantity of extracellular and by the intracellular (proteins and phosphates) and bone (carbonate) buffers. measured empirically by administering a HCO_3^- load and then observing the ensuing elevation in the plasma HCO_3^- concentration.[2] If, for example, 100 meq raises the plasma HCO_3^- concentration by 5 meq/L, then the apparent bicarbonate space L.

At a normal plasma HCO_3^- concentration of 24 meq/L, excess H^+ ions are buffered proportionately through the total body water, and the apparent HCO_3^- space is about 50 percent of lean body weight (Fig. 19-8). However, the HCO_3^- space rises in metabolic acidosis, since the fall in the plasma HCO_3^- concentration means that there is an ever-increasing contribution from the nonbicarbonate buffers. T bicarbonate space is approximately 60 percent of lean body weight in mild t moderate metabolic acidosis, but can reach 70 percent or more as the plasma HCO_3^- concentration falls below 8 to 10 meq/L (Fig. 19-8).[2,3]

The bicarbonate space can be estimated from:

$$\text{Bicarbonate space} = \left[0.4 + \left(2.6/P_{HCO_3^-}\right)\right] \times \text{lean body weight} \qquad (19\text{-}20)$$

It can exceed total body water or even lean body weight in severe metaboli acidosis, because almost all of the buffering is occurring within the cells a where there is a virtually inexhaustible supply of buffer.

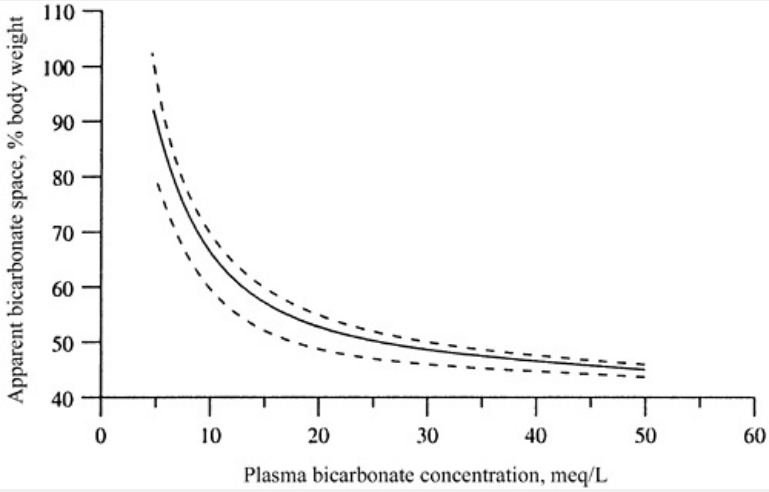

Figure 19-8 Variation in the apparent bicarbonate space according to the pl bicarbonate concentration. At values below 10 meq/L, most of the bufferin performed by the intracellular and bone buffers, leading to a marked rise space of distribution that can exceed 70 percent of lean body weight in se metabolic acidosis. (*From Fernandez PC, Cohen RM, Feldman GM, Kidney Int 36:747, 1989. Reprinted by permission of Kidney International.*)

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In the above patient with diarrhea, for example, the initial aim of therapy is the plasma HCO_3^- concentration from 6 to 10 meq/L. If this patient weighed 70 then

$$HCO_3^- \text{ deficit} = 0.7 \times 70 \times (10 - 6)$$
$$= 196 \text{ meq}$$

Thus, 196 meq of HCO_3^- can be given intravenously over the first several hour this is effective in raising the pH to a safe level, further HCO_3^- may be unnecessary, since increased renal H^+ excretion will slowly regenerate the lost HCO_3^-. Similarly, *exogenous alkali may not be required* if the initial arterial pH is greater than 7.20 the patient is asymptomatic, and the underlying process, such as diarrhea, controlled.

Needless to say, these are only rough guidelines and cannot replace serial measurements of the extracellular pH. In particular, the formula assumes a reasonably accurate estimate of lean body weight and assumes that the pat a steady state. If, for example, there is continuing acid production, as with

diarrhea, then the HCO_3^- requirements will increase with time.

The degree to which exogenous HCO_3^- will raise the plasma HCO_3^- concentration and pH is also dependent upon when the measurements are made. As descr above, excess H^+ ions are buffered first in the extracellular fluid and then in t cells. A similar sequence occurs when HCO_3^- is given to correct a metabolic acidosis. Acutely, the added HCO_3^- is limited to the vascular space, producing a large increase in the plasma HCO_3^- concentration. However, this change is attenuated as the exogenous HCO_3^- equilibrates through the total extracellular

fluid, which occurs within 15 min, and then equilibrates with the intracellula bone buffers, which occurs in 2 to 4 h.

If, for example, we assume that the extracellular volume is 15 liters and the HCO_3^- space is 49 liters in the above 70-kg patient with diarrhea, then the infusion of 100 meq of HCO_3^- will produce a 7-meq/L increase in the plasma HCO_3^- concentration at 15 min, but only a 2-meq/L increase at 2 to 4 h. Thus, the extracellular pH will be greater if it is measured at 15 min, before equilibra the intracellular buffers has occurred. As a result, it should be recognized measurement of the pH shortly after HCO_3^- has been given may overestimate the final effect of therapy.

Plasma Potassium Concentration

K^+ depletion is common in patients with metabolic acidosis associated with gastrointestinal and/or renal losses of K^+. Despite this, the initial plasma K^+ concentration may be relatively normal, since metabolic acidemia (except fo organic acidoses) causes K^+ to move out of the cells into the extracellular fluid (see page 379).[5,8]

A similar effect frequently occurs in diabetic ketoacidosis, in which the com of insulin deficiency and hyperglycemia (rather than acidemia) promotes K^+ movement into the extracellular fluid. Thus, patients with this disorder are hyperkalemic at presentation, despite moderate to marked total body K^+ depletion (see chap. 25).[9] The administration of insulin will reverse this sequence, redistributing K^+ into the cells and unmasking the true state of K^+ balance. As a result, careful monitorin of the plasma K^+ concentration is essential during the initial phases of therap

The potential risks of treatment are more immediate in the acidemic patient already hypokalemic at presentation. In this setting, there is a very large K^+ and the restoration of normal pH (or treatment with insulin in diabetic ketoa will further reduce the plasma K^+ concentration. Thus, initial therapy should cons of KCl alone (if the acidemia is not severe) or KCl with NaCl or $NaHCO_3$ with careful monitoring of the pH, the plasma K^+ concentration, muscle strength, and the

electrocardiogram. As much as 40 meq/h of KCl may be required to prevent threatening hypokalemia in some patients (see Chap. 27).

Metabolic Acidosis and Heart Failure

Sodium bicarbonate therapy is potentially dangerous in patients with left ve failure, since it can lead to increasing pulmonary congestion. Fortunately, a therapy is usually unnecessary when the underlying disorder is lactic acido acute pulmonary edema. In this setting, improvement in pulmonary function spontaneous resolution of the acidemia as a result of generation from the metabolism of lactate.[58]

However, specific therapy may be required in patients with severe acidemia pH≤7.10 to 7.15), particularly if the patient does not have a self-correcting

organic acidosis, such as lactic or ketoacidosis. Acutely, small doses (45 to 90 meq) can be cautiously administered. The risk of this regimen is relat small, since more than one-half of the will enter the cells to replenish the intracellular buffers.[1,2] Thus, there will be much less volume expansion than wi equivalent quantity of NaCl, which is restricted to the extracellular fluid.

Alternatively, peritoneal dialysis or hemodialysis can be used to correct bot overload and the acidemia. The former is generally preferred in patients wi heart disease, since it avoids the hemodynamic instability often associated hemodialysis. The dialysate should preferably contain as a source of alkali rather than lactate or acetate, which may not be normally metabolized in se failure.[3,13]

PROBLEMS

19-1 The following laboratory tests are obtained from two patients. Wo administer NaHCO to either one?

a.

(*a*) Plasma $[Na^+] = 140$ meq/L
$[K^+] = 4.2$ meq/L
$[Cl^-] = 114$ meq/L
$[HCO_3^-] = 16$ meq/L

b.

(*b*) Plasma $[Na^+] = 140$ meq/L
$[K^+] = 4.7$ meq/L
$[Cl^-] = 122$ meq/L
$[HCO_3^-] = 7$ meq/L
Arterial pH = 7.32
$P_{CO_2} = 14$ mmHg

19-2 A 31-year-old man with a history of epilepsy has a grand mal seizu Laboratory tests taken immediately after the seizure has stopped reve

Arterial pH = 7.14

P_{CO_2} = 45 mmHg

Plasma $[Na^+]$ = 140 meq/L

$[K^+]$ = 4.0 meq/L

$[Cl^-]$ = 98 meq/L

$[HCO_3^-]$ = 17 meq/L

a. **What is the acid-base disturbance?**

b. **Does the patient need $NaHCO_3$?**

c. **What will happen to his plasma K^+ concentration as the acidemia is corrected?**

19-3 If HCO_3^- therapy sufficient to normalize the plasma HCO_3^- concentration is suddenly stopped, match the subsequent course with the type of RT

a. **Type 1 RTA in adults (minimum urine pH=6.5)**

b. **Type 1 RTA in infants (minimum urine pH=7.2)**

c. **Type 2 RTA**

1. **Rapid fall in plasma HCO_3^- concentration, which stabilizes at 16 meq/L**
2. **Rapid decrease in plasma HCO_3^- concentration, which falls below 10 meq/L**
3. **Slowly progressive decrease in plasma HCO_3^- concentration to less than 10 meq/L**

If the plasma HCO_3^- concentration is raised to 22 meq/L with exogenous $NaHCO_3$, how would you distinguish among these three disorders?

19-4 Match the laboratory findings with the appropriate cause of a norm anion gap metabolic acidosis. The units in the table are meq/L.

	$[Na^+]$	$[K^+]$	$[Cl^-]$	$[HCO_3^-]$	Urine pH	Urine anion gap
1.	140	2.9	115	14	6.4	-45
2.	137	5.3	113	17	5.2	+18
3.	139	3.1	120	11	6.1	+23

a. **Hypoaldosteronism (type 4 RTA)**

b. **Diarrhea due to laxative abuse**

c. **Type 1 RTA**

19-5A 58-year-old man with a history of chronic bronchitis develops se diarrhea caused by pseudomembranous colitis. It is noted that the vol diarrheal fluid is approximately 1 L/h. Results of the initial laboratory

$$\begin{aligned}\text{Plasma } [Na^+] &= 138 \text{ meq/L}\\ [K^+] &= 3.8 \text{ meq/L}\\ [Cl^-] &= 115 \text{ meq/L}\\ [HCO_3^-] &= 9 \text{ meq/L}\\ \text{Arterial pH} &= 6.97\\ P_{CO_2} &= 40 \text{ mmHg}\end{aligned}$$

a. **What is the acid-base disorder?**

b. **(b) Assuming that the P_{CO_2} remains at 40 mmHg, to what level does the plasma HCO_3^- concentration have to be raised to increase the pH to**

c. **(c) How much HCO_3^- would be required to raise the plasma HCO_3^- concentration to the desired level, assuming that the patient has a body weight of 80 kg?**

d. **(d) After the administration of this amount of HCO_3^- for 4 h, the plasma HCO_3^- concentration is still 9 meq/L. What is responsible for this in to correct the acidemia?**

e. **(e) What would you estimate the total body K^+ stores in this patient to be?**

19-6A 50-year-old woman has severe chronic renal failure. The followi laboratory data are obtained:

$$\begin{aligned}\text{Plasma } [Na^+] &= 137 \text{ meq/L}\\ [K^+] &= 5.4 \text{ meq/L}\\ [Cl^-] &= 102 \text{ meq/L}\\ [HCO_3^-] &= 10 \text{ meq/L}\\ \text{Arterial pH} &= 7.22\\ P_{CO_2} &= 25 \text{ mmHg}\end{aligned}$$

a. **Why does metabolic acidosis develop in renal failure? Thirty minut after the administration of 88 meq of HCO_3^-, repeat blood tests reveal the following:**

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$$\begin{aligned}\text{Arterial pH} &= 7.38\\ P_{CO_2} &= 28 \text{ mmHg}\\ [HCO_3^-] &= 16 \text{ meq/L}\end{aligned}$$

In view of the improvement in the pH, no further therapy was given. However, on the next day, blood tests showed:

$$\text{Arterial pH} = 7.28$$
$$P_{CO_2} = 26 \text{ mmHg}$$
$$[HCO_3^-] = 12 \text{ meq/L}$$

b. **(b) What factors might have been responsible for this reduction in arterial pH?**

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Footnotes

* Only those ketones that are excreted as the K^+ or Na^+ salt will lower the Δ/Δ ratio. Both β-hydroxybutyrate and acetoacetate also may be excreted as the intac as the NH_4^+ salt. In these settings, H^+ is effectively lost with the anion, thereby correcting both the high anion gap and the fall in the plasma HCO_3^- concentration.

† Increased lactate accumulation following administration of HCO_3^- may also diminish cardiac function by a second mechanism. Patients who undergo prolonged cardiopulmonary resuscitation often have up to a 50 percent reduction in th Ca^{2+} concentration in the plasma, a change that can directly impair cardiac contractility.[105] The total plasma Ca^{2+} concentration, however, remains normal, indicating that increased binding of Ca^{2+} must be present. This effect is directly related to the severity of the acidemia and could represent binding of Ca^{2+} to lactate.

‡ Detection of an osmolal group with an alcohol intoxication can be achieve the plasma osmolality is measured by freezing-point depression. In compari osmotic contribution of volatile alcohols is not detected when a vapor press osmometer is used, since this technique assumes that only water is in the v phase.[172,173]

¶ The urine pK'_a varies with total electrolyte concentration and may be somew different from the plasma value of 6.10.[234]

** As described earlier, citrate should be avoided in patients who have dev renal failure, since it increases intestinal permeability and can lead to exce aluminum absorption and tissue accumulation.[150] This is most likely to occur in patients with renal failure who are taking aluminum-containing antacids to c hyperphosphatemia (page 206).

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Chapter Twenty
Respiratory acidosis

The introduction to acid-base disorders presented in Chapter 17 should be read before proceeding with this discussion. Respiratory acidosis is a clinical disorder characterized by a reduced arterial pH (or increased H^+ concentration), an elevation in the P_{CO_2} (hypercapnia), and a variable increase in the plasma HCO_3^- concentration. Hypercapnia also constitutes the respiratory compensation t metabolic alkalosis. However, the increase in the P_{CO_2} is appropriate in this setting, since it lowers the arterial pH toward normal.

PATHOPHYSIOLOGY AND ETIOLOGY

Endogenous metabolism results in the production of approximately 15,000 m CO_2 per day. Although CO_2 is not an acid, it combines with H_2O to form H_2CO_3 when it is added to the bloodstream, resulting in the formation of H^+ and HCO_3^-:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \qquad (20\text{-}1)$$

The ensuing elevation in the H^+ concentration is then minimized because most of excess H^+ ions combine with intracellular buffers, including hemoglobin (Hb) cells:

$$H_2CO_3 + Hb^- \leftrightarrow HHb + HCO_3^- \qquad (20\text{-}2)$$

The HCO_3^- generated by this reaction leaves the erythrocyte and enters the extracellular fluid in exchange for extracellular Cl^-.

The net effect is that metabolically generated CO_2 is primarily carried in the *bloodstream as HCO_3^-, with little change in the extracellular pH.* These processes are reversed in the alveoli. As HHb is oxygenated, it releases H^+ ions that combine with HCO_3^- to form H_2CO_3 and then CO_2, which is excreted.

Control of Ventilation

Before we discuss how hypercapnia can occur, it is helpful to review briefly aspects of ventilatory regulation. Alveolar ventilation provides the oxygen r for oxidative metabolism and eliminates the CO_2 produced by these metabolic processes. It is therefore appropriate that the *physiologic stimuli to respiratio*

are a reduction in the arterial P_{O_2} (hypoxemia) and an elevation in the arterial P_{CO_2} (Fig. 20-1)[1,2]

The CO_2 stimulus to ventilation occurs primarily in chemosensitive areas in respiratory center in the medulla, which respond to CO_2-induced changes in the cerebral interstitial pH and[1,2,3] In contrast, the initial hypoxemic enhancement o ventilation is mostly mediated by chemoreceptors in the carotid bodies, whi located near the bifurcation of the carotid arteries[1,4] In normal subjects, these regulatory processes permit adequate oxygenation to be maintained and the

P_{CO_2} to be held within narrow limits (40± 4 mmHg), despite the large daily O_2 and variability in the respiratory quotient and metabolic rate.

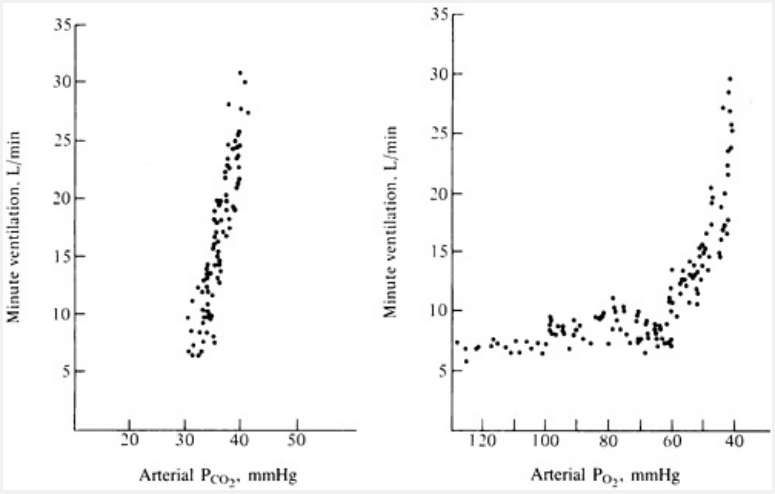

Figure 20-1 Relationship between arterial P_{CO_2} (left panel) and P_{O_2} (right panel) and the respiratory minute volume in normal adult subjects. (*Adapted from Hudgel DW, Control of breathing in asthma, in Weiss EB, Segal MS, Stein (eds): Bronchial Asthma: Mechanisms and Therapeutics, 2nd ed. Boston, Little, Brown, 1984, with permission.*)

Carbon dioxide is the major stimulus to respiration, and minute ventilation i enhanced by even minor elevations in the arterial P_{CO_2} (Fig. 20-1). For example, among most normal subjects in whom hypercapnia is induced by breathing a hypercapnic gas mixture, minute ventilation rises by 1 to 4 L for every 1 mm P_{CO_2}.[2,5]

In contrast, hypoxemia does not begin to substantially promote ventilation u arterial P_{O_2} is less than 50 to 60 mmHg (Fig. 20-1 and 20-2). Lesser degrees of hypoxemia initially increase ventilation; however, the ensuing fall in the CO_2-induced extracellular pH, which depresses respiration and blunts the hypoxemic stir The importance of pH in influencing the ventilatory response to hypoxemia

illustrated by the upper curve in Fig. 20-2. If the arterial P_{CO_2} is held at normal values (or is elevated because of intrinsic lung disease), then the limiting r alkalosis does not occur and ventilation begins to be enhanced at a much h arterial P_{O_2} of 70 to 80 mmHg (Fig. 20-2).[2] This relationship has important implications for the control of ventilation in patients with chronic respirator (see below).

Development of Hypercapnia

Since the CO_2 stimulus to ventilation is so strong, hypercapnia and respirator acidosis are almost always due to a reduction in effective alveolar ventilati

an increase in CO_2 production. Hypoventilation can occur when there is interfe with any step in the ventilatory process (Table 20-1).[5] In patients with reduced respiratory drive or neuromuscular dysfunction, for example, there tends to generalized fall in alveolar ventilation. In contrast, CO_2 retention in intrinsic pulmonary disease is thought to be due primarily to an *imbalance between ventilation and perfusion* (which is functionally equivalent to increasing the amo of dead space to tidal volume ratio).[6] The hypercapnia in this setting is

in part beneficial in that it allows the metabolically produced CO_2 to be excreted at a lower minute ventilation, thereby diminishing the work of breathing and ofte reducing the feeling of breathlessness.[5]

Table 20-1 Causes of acute and chronic respirator acidosis

Inhibition of the medullary respiratory center

A. Acute
   1. Drugs: opiates, anesthetics, sedatives
   2. Oxygen in chronic hypercapnia
   3. Cardiac arrest
   4. Central sleep apnea

B. Chronic
   1. Extreme obesity (Pickwickian syndrome)
   2. Central nervous system lesions (rare)
   3. Metabolic alkalosis (although hypercapnia is an appropriate response to the rise in pH in this setting)

Disorders of the respiratory muscles and chest wall

A. Acute
   1. Muscle weakness: crisis in myasthenia gravis, periodic paralysis

aminoglycosides, Guillain-Barré syndrome, severe hypokalemia o hypophosphatemia

B. Chronic
   1. Muscle weakness: spinal cord injury, poliomyelitis, amyotrophic lateral sclerosis, multiple sclerosis, myxedema
   2. Kyphoscoliosis
   3. Extreme obesity

Upper airway obstruction

A. Acute
   1. Aspiration of foreign body or vomitus
   2. Obstructive sleep apnea
   3. Laryngospasm

Disorders affecting gas exchange across the pulmonary capillary

A. Acute
   1. Exacerbation of underlying lung disease (including increased CO_2 production with high-carbohydrate diet)
   2. Adult respiratory distress syndrome
   3. Acute cardiogenic pulmonary edema
   4. Severe asthma or pneumonia
   5. Pneumothorax or hemothorax

B. Chronic
   1. Chronic obstructive pulmonary disease: bronchitis, emphysema
   2. Extreme obesity

Mechanical ventilation

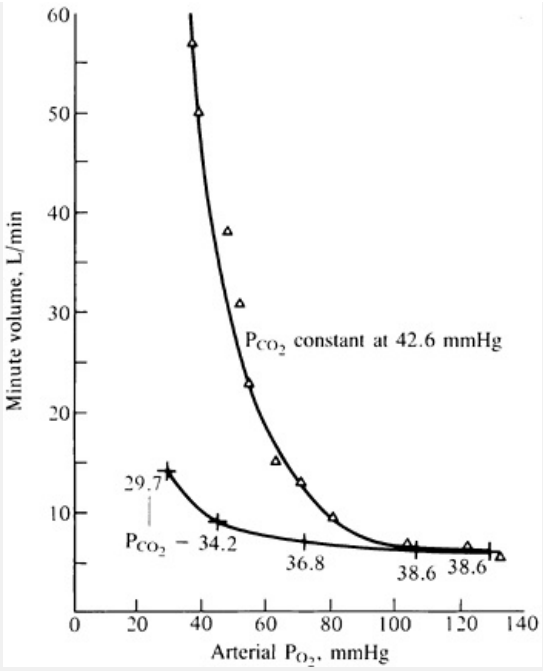

Figure 20-2 Influence of arterial P_{O_2} on the ventilatory response to hypoxemia. In normal subjects (lower curve), lowering the partial pressure oxygen in the inspired air increases ventilation and lowers the arterial P_{CO_2}. However, these changes are relatively minor until the arterial P_{O_2} falls below 50 mmHg. The earlier and greater degree of hyperventilation seen when the P_{CO_2} is held constant (upper curve) indicates that the development of mild hypocapnic alkalosis normally limits the ventilatory response to hypoxemia. (*Adapted from Loeschcke HH, Gertz KH: Arch Ges Physiol 267:460, 1958, with permission.*)

If ventilatory function is not restored, the decrease in pH produced by increased CO_2 is minimized by the cell buffers and by increased renal H^+ excretion, both of which result in an elevation in the plasma HCO_3^- concentration. Since the renal response occurs over several days, protection of the extracellular pH in acute respiratory acidosis is much less efficient than that in chronic respiratory acidosis (see Figs. 20-3 and 20-4).

Relationship between Hypercapnia and Hypoxemia

All patients with hypercapnia who are breathing room air experience a fall in arterial P_{O_2} because the sum of partial pressures of all gases in the alveoli must equal atmospheric pressure. In most cases, *hypoxemia occurs earlier and is more prominent than hypercapnia.* Two factors contribute to this difference:

1. CO_2 can diffuse across the alveolar capillary wall 20 times as quickly as O_2.
2. As patients attempt to increase ventilation in relatively normal segments of lung, more CO_2 can be excreted but *more O_2 cannot be taken up*, since the

saturation of hemoglobin already approaches 100 percent in these area

The clinical importance of this relationship between the arterial P_{O_2} and P_{CO_2} can be illustrated by the sequence seen in patients with acute asthma.[8] The combination of mucous plugs and bronchoconstriction initially induces hypoxemia; both P_{O_2} and activation of intrapulmonary mechanoreceptors then lead to enhanc ventilation.[8,9] Thus, a mild to moderate asthmatic attack is associated with hypocapnia and respiratory *alkalosis*. With increasing severity of the attack,

airway resistance rises, the maximal minute ventilation falls, and conseque P_{CO_2} rises, eventually to normal and even hypercapnic levels. Thus, the combination of hypoxemia and a "normal" P_{CO_2} of 40 mmHg represents severe disease in the acute asthmatic.[8] This principle can be applied generally to patien with intrinsic lung disease: Hypercapnia is a *late finding*, and even a small elevation in the P_{CO_2} of a few millimeters of mercury in the *advanced pulmonary dysfunction* or a concomitant insult to ventilatory drive (e.g., narcotic use), s CO_2 is normally such a powerful stimulus to ventilation (Fig. 20-1).

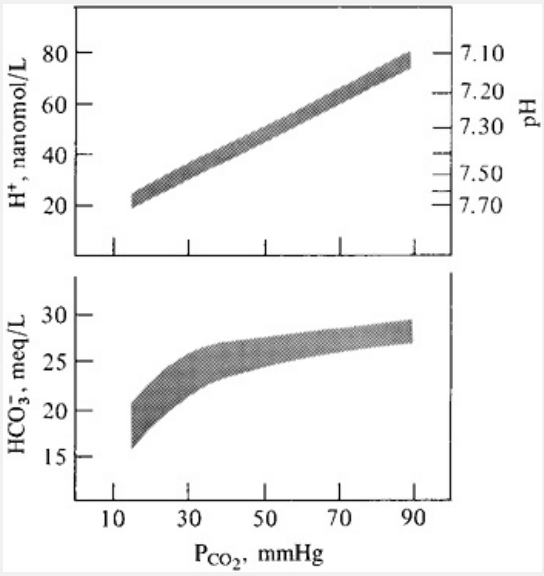

Figure 20-3 Combined significance bands for plasma pH and HCO_3^- concentration in acute hypocapnia and hypercapnia in humans. In uncomp acute respiratory acid-base disorders, values for H^+ and HCO_3^- concentrations will, with an estimated 95 percent probability, fall within th Observations lying outside the band indicate the presence of a complicati metabolic acid-base disturbance. (*From Arbus GS, Herbert LA, Levesque PR, et al*, N Engl J Med *280:117, 1969. By permission from* The New England Journal of Medicine.)

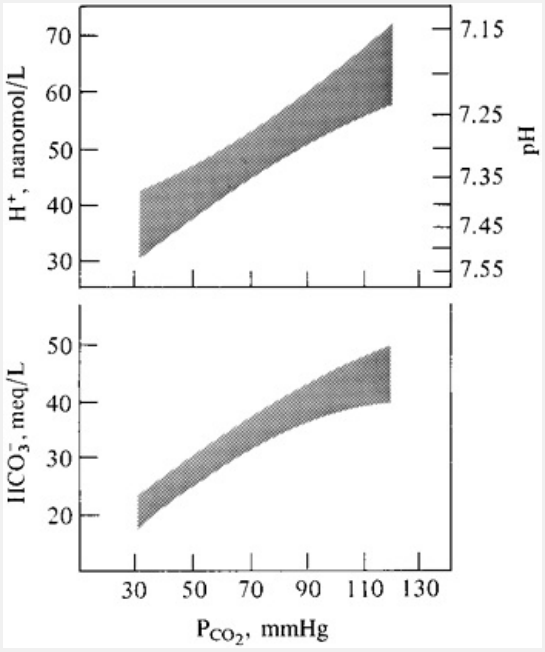

Figure 20-4 Ninety-five percent significance bands for plasma pH and H^+ and HCO_3^- concentrations in chronic hypercapnia. Note that, per change in P_{CO_2}, there is much less change in H^+ concentration and pH than in acute hypercapnia (Fig. 20-3). This reflects the effect of increased renal generation of HCO_3^-. *From Schwartz WB, Brackett NC Jr, Cohen JJ: J Clin Invest 44:291, 1965, by copyright permission of the American Society for Clinical Investigation.*

Although hypoxemia-induced hyperventilation helps to delay the onset or m the degree of hypercapnia, there is a 16-fold variability (probably inherited sensitivity to hypoxemic stimuli.[5,10,11] Those subjects who are less sensitive to hypoxemia will be more likely to develop respiratory acidosis in the presen appropriate cause, such as chronic bronchitis or marked obesity (see below

Regulation of Ventilation in Chronic Respiratory Acidosis

Two general statements are often made concerning ventilatory control in th with chronic hypercapnia:

1. The respiratory centers become less sensitive to CO_2 and to the acidemic drive to ventilation.
2. As a result, hypoxemia becomes the primary stimulus to respiration.

However, these conclusions are based upon observations that are subject t somewhat different interpretation.

Insensitivity to CO_2

Evidence for insensitivity to P_{CO_2} is based primarily upon experiments that showe that patients with chronic respiratory acidosis have *less increase in ventilation* than normals when the P_{CO_2} is raised by increasing the CO_2 content of inspired air (Fig. 20-5). This apparent insensitivity, however, may, at least in part, reflec plasma HCO_3^- concentration induced by the renal compensation in this settin[5,12] From the law of mass action,

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]} \qquad (20\text{-}3)$$

it can be seen that a given rise in P_{CO_2} will induce a smaller increase in the arterial H^+ concentration when the plasma HCO_3^- concentration is elevated. Thus, the lesser increment in ventilation in chronic respiratory acidosis and there apparent insensitivity to CO_2 may simply reflect the *lesser rise in H^+ concentration*.[12,13]

Consider, for example, the response to ammonium chloride, which is metabo hydrochloric acid and reverses the compensatory rise in the plasma HCO_3^- concentration. In this setting, the slope of the curve between alveolar venti the P_{CO_2} increases toward normal (Fig. 20-5), being limited by the mechanical properties of the diseased lung, not by the responsiveness of the[12] This enhanced sensitivity to CO_2 is directly related to the fall in the plasma HCO_3^- concentration, since the increase in ventilation per *increase in H^+ concentration* is the same in the control state and after the administration of ammonium chloride.[12,13]

In addition to normalizing the slope, reducing the plasma HCO_3^- concentration also leads to an increase in the baseline rate of ventilation, resulting in a fall ir

P_{CO_2} and a rise in P_{O_2} (Fig. 20-5).[12,13] and[14] These findings indicate that the renal compensation to chronic hypercapnia has two effects: *It restores the extracellular pH, but, in so doing, it limits the stimulus to respiration, agg the hypoxemia and hypercapnia.* Similarly, the induction of metabolic alkalosis w diuretic therapy also suppresses ventilation, further evidence that the pH s intact.[15]

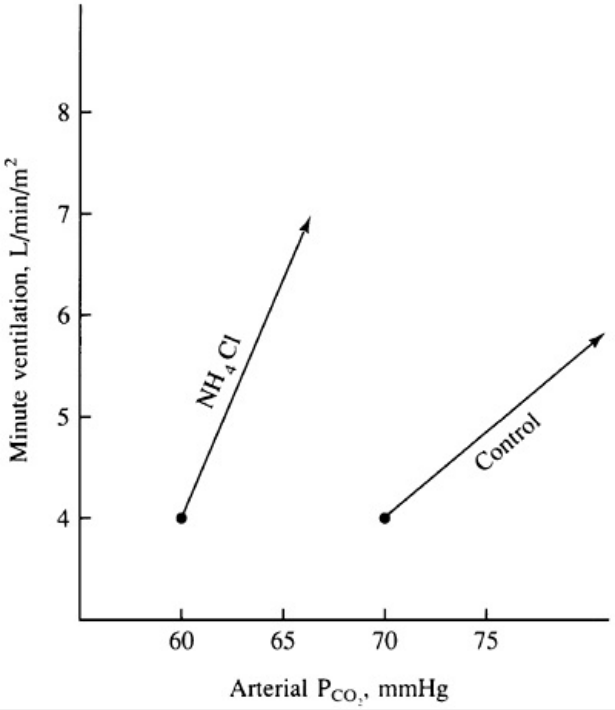

Figure 20-5 Ventilatory responses to inhalation of CO_2 in a patient with chronic hypercapnia in the control state and after the HCO_3^- concentration has been lowered by the administration of ammonium chloride. The latter therapy increases baseline ventilation (as evidenced by a lower initial P_{CO_2}) and increases the respiratory responsiveness toward CO_2 normal. *(From Goldring RM, Turino GM, Heinemann HO, Am J Med 51:772, 1971, with permission.)*

Dependence upon hypoxemia

Patients with chronic respiratory acidosis do rely upon hypoxemia to stimul ventilation.[16] This relationship, however, is based not upon insensitivity to pl upon two other factors. First, the renal compensation, plus the frequent cor use of diuretics for edema in cor pulmonale, results in a rise in the HCO_3^- plasma concentration that returns the extracellular pH toward or, in some cases, ab normal. Thus, there is little or no acidemic stimulus to ventilation in many p with chronic hypercapnia.

Second, the relationship between the P_{O_2} and ventilation is altered in the presenc of a high P_{CO_2}. As shown in Fig. 20-5, hypoxemia does not importantly stimulate respiration in normals until the P_{O_2} is below 50 to 60 mmHg, because of the poter suppressive effect of concurrent hypocapnia and respiratory alkalosis. In comparison, this fall in P_{O_2} does not occur in chronic respiratory acidosis; as a result, ventilation is enhanced as soon as the P_{O_2} falls below 80 mmHg.

Correction of hypoxemia is important clinically, since maintaining the P_{O_2} above 55 mmHg improves both survival and the quality of life in patients with chronic

disease (see "Treatment," below).[17,18] and[19] However, oxygen must be given carefully, because rapid and excessive correction can produce a further ele the P_{CO_2} that, if marked, can lead to neurologic symptoms.[11,16,17]

Interestingly, a reduction in minute ventilation is not the primary factor resp for the development of worsening hypercapnia.[11,20,21] In one study, for example, the administration of oxygen to patients with chronic lung disease and acut respiratory failure produced a 7 percent reduction in minute ventilation, wh accounted for only 5 mmHg of the 23 mmHg elevation in P_{CO_2}.[11] Of greater importance were worsening of ventilation/perfusion mismatching due to atte of hypoxemia-induced vasoconstriction (which will increase the dead space volume ratio by increasing blood flow to poorly ventilated areas) and decre affinity of hemoglobin for CO_2 (the Haldane effect).

Acute Respiratory Acidosis

The ability to acutely protect the extracellular pH is different in metabolic a respiratory acidosis. In the former, extracellular and intracellular buffering compensatory hyperventilation all minimize the fall in pH (see Chap. 19). In contrast, the body is not so well adapted to handle an acute elevation in P_{CO_2}. *There is virtually no extracellular buffering* because HCO_3^- cannot buffer CO_2:[22]

$$H_2CO_3 + HCO_3^- \rightarrow H_2CO_3 + HCO_3^- \qquad (20\text{-}4)$$

Since the renal response takes time to develop, the cell buffers, particularl hemoglobin (Eq. 20-2) and proteins, constitute the only protection against acut hypercapnia:

$$H_2CO_3 + Buf^- \rightarrow HBuf + HCO_3^- \qquad (20\text{-}5)$$

As a result of these buffering reactions, there is an increase in the plasma HCO_3^- concentration, averaging *1 meq/L for every 10 mmHg rise in the* P_{CO_2} (Fig. 20-4).[23,24] Thus, if the P_{CO_2} is acutely increased to 80 mmHg, there will be approximately a 4-meq/L elevation in the plasma HCO_3^- concentration to 28 meq/L and a potentially serious reduction in the extracellular pH to 7.17:

$$pH = 6.10 + \log \frac{28}{0.03(80)}$$

$$= 7.17$$

This is not very efficient, since the pH would have been only slightly lower there were no buffering and the plasma HCO_3^- concentration had remained at 24 meq/L. A more severe reduction in the pH to below 7.00 can occur when the combined respiratory and metabolic acidosis, as with acute pulmonary eden lactic acidosis due to severe heart failure.[25]

Etiology

Common causes of acute respiratory acidosis include acute exacerbations c

underlying lung disease, severe asthma or pneumonia, pulmonary edema, a suppression of the respiratory center following a cardiac arrest, a drug ove the administration of oxygen to a patient with chronic hypercapnia.[11,26]

In addition, an increasingly recognized cause of hypercapnia is the *sleep apnea syndrome*.[27,28] and[29] This disorder is characterized by multiple (up to severa hundred) apneic episodes per night associated with short periods of arousa are not apparent to the patient) due to hypoxemia and hypercapnia. Three types of sleep apnea have been recognized: in which rare cerebral disorder interfere with the medullary control of ventilation; *central*, in which there is abnormal passive collapse of the pharyngeal muscles during inspiration, su the airway becomes occluded from the apposition of the tongue and soft pa against the posterior oropharynx; and *obstructive*, in which there is a mixed central and obstructive picture.[28,29] and[30] Most patients have at least some obstructive component, which is typ manifested by loud snoring. Obesity, hypothyroidism, tonsillar enlargement, nasal obstruction also may contribute to the development of inspiratory obstruction.[31]

The sleep apnea syndrome is associated with a variety of occasionally subt manifestations, which are due both to the repeated episodes of hypoxemia hypercapnia and/or to the lack of uninterrupted sleep. These include headа daytime somnolence and fatigue, morning confusion with difficulty in conce personality changes, depression, persistent pulmonary and systemic hypert and potentially life-threatening cardiac arrhythmias.[28,29,32] Serious job-related and familial problems frequently ensue.

The diagnosis of sleep apnea should be suspected from the clinical history (particularly loud snoring and daytime somnolence) and can be confirmed b appropriate evaluation while the patient is asleep.[33] Cardiac monitoring is performed as part of the polysomnographic evaluation to check for the presence of se arrhythmias. Effective treatment can rapidly reverse almost all of the clinic findings.[34]

Chronic hypercapnia is unusual in the sleep apnea syndrome, since the CO_2 retained during apneic episodes can be excreted when the patient is awake ventilation is relatively normal.[5] In a minority of cases, the combination of underl lung disease, obesity, and repetitive apneic episodes (including those due somnolence) can lead to a low total daily alveolar ventilation and persisten CO_2 retention.[35,36] This disorder is called the obesity hypoventilation syndrome.[37]

Finally, mechanical ventilation may be associated with hypercapnia if the ra effective alveolar ventilation is inadequate. These patients, in whom ventila *fixed*, may also retain CO_2 if the rate of CO_2 production is increased. This sequen can occur either with the administration of NaHCO$_3$ to treat lactic acidosis during cardiopulmonary resuscitation[27,38,39] and[40] or with enteral or parenteral overfeeding.[41] In the former setting, the presence of marked hypercapnia may

missed if arterial blood is measured, since the lungs are capable of removi O_2 from the diminished amount of blood flow that is delivered. Use of mixed ve blood is required to more closely measure acid-base status at the tissue le page 59)[42]

Chronic Respiratory Acidosis

The acid-base picture is different with chronic hypercapnia because of the compensatory renal response. The persistent elevation in the P_{CO_2} stimulates renal H^+ secretion, resulting in the addition of HCO_3^- to the extracellular fluid (see page 348).[7] The net effect is that, after 3 to 5 days, a new steady state is attaine which there is roughly a *3.5 meq/L increase in the plasma HCO_3^- concentration for every 10 mmHg increment in the* P_{CO_2} (Fig. 20-4).[43,44]

If, for example, the P_{CO_2} were chronically increased to 80 mmHg, the plasma HCO_3^- concentration should rise by approximately 14 meq/L, up to a level of 38 me response is extremely effective, since the arterial pH falls only to 7.30, in 7.17, as seen above, with a similar degree of acute hypercapnia. The effici the renal compensation has allowed some patients to tolerate high P_{CO_2} as 90 to 110 mmHg without a fall in the arterial pH to less than 7.25 and without as long as adequate oxygenation is maintained.[45]

The extent of the rise in the plasma HCO_3^- concentration in chronic respiratory acidosis is determined *solely by the increase in renal H^+ secretion*, which is presumably mediated by a fall in renal tubular cell pH induced by the extrac acidemia. The net result is that maximal HCO_3^- reabsorptive capacity is enhanced and the plasma HCO_3^- concentration rises to a new steady state level as in Fig. 20-4.

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Exogenous alkali therapy is both unnecessary (since the pH is so well prote ineffective, as the excess HCO_3^- is rapidly excreted in the urine without raising t final plasma HCO_3^- concentration.[46]

Etiology

Chronic respiratory acidosis is a relatively common clinical disturbance tha often due to chronic obstructive lung disease (bronchitis and emphysema) i smokers. Despite the presence of severe intrinsic pulmonary dysfunction, it completely understood why some patients become hypercapnic and hypoxem relatively early ("blue bloaters"), whereas others do not ("pink puffers"). S *unaffected* family members of patients with chronic hypercapnia have a reduc ventilatory response to hypoxemia and, to a lesser degree, hypercapnia, pr because of genetic variation in the sensitivity of the respiratory center.[47]

Such genetic factors can lead to the following sequence: Lung disease initi

impairs net alveolar gas exchange, resulting in hypoxemia and eventually hypercapnia, both of which can stimulate ventilation and return the arterial O_2 and P_{CO_2} toward normal. Persistent hypercapnia will occur relatively early (as i bloaters) when the ventilatory response to these stimuli is impaired. If, on hand, the central control of respiration is normal, persistent hypercapnia w occur until pulmonary dysfunction is more severe (as in pink puffers).[5]

A similar problem may be present when chronic respiratory acidosis occurs extremely obese patients (called the obesity hyperventilation or Pickwickia syndrome).[36,37] and[38] It had been assumed that the primary problem in this disorder was increased weight of the chest wall, leading to enhanced work breathing and inspiratory muscle weakness.[48] Reversal of the hypercapnia with weight loss in some patients is consistent with this hypothesis. However, th following observations suggest that factors other than obesity also play a contributory role. First, most morbidly obese patients do not become hyperc and, in those who do, there is no correlation between the degree of obesity ventilatory abnormalities.[49] Second, a more normal ventilatory pattern can be produced in some patients with progesterone (a direct respiratory stimulant[29,50,51] this finding indicates that these patients can increase alveolar ventilation a the possibility of an associated central defect.

An abnormality in respiratory control is also suggested by the demonstratio obese hypoventilators have decreased respiratory responsiveness to both h and hypercapnia.[49,52,53] In contrast, obese patients with normal ventilation re normally to these stimuli.[53,54] Once again, an inherited defect in ventilatory regulation may select out those obese patients who will develop chronic hypercapnia.

Obese hypoventilators may also have a component of obstructive sleep apn[31] The symptoms are somewhat similar to these two conditions, as many Pickw patients complain of excessive daytime somnolence. However, there are als important differences, since obstructive sleep apnea alone is uncommonly a with chronic CO_2 retention.[35]

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SYMPTOMS

Severe *acute* respiratory acidosis can produce a variety of neurologic abnormalities.[55] The initial symptoms include headache, blurred vision, restlessness, and anxiety, which can progress to tremors, asterixis, deliriur somnolence (called CO_2 narcosis). The cerebrospinal fluid (CSF) pressure is o elevated, and papilledema may be seen. These latter effects may be mediat by an acidemia-induced elevation in cerebral blood flow.[56] This hemodynamic change can be viewed as an appropriate response, since the increase in ce perfusion will tend to wash away the excess CO_2, thereby returning the cerebral pH toward normal.[56]

Both the neurologic symptoms and the increase in cerebral blood flow appe related to changes in the CSF (or cerebral interstitial) pH, not to the arteri P_{CO_2}.[57,58] CO_2 is lipid-soluble and rapidly equilibrates across the blood-bra barrier; HCO_3^-, in comparison, is a polar compound that crosses this barrier v slowly. Thus, acute hypercapnia produces a greater fall in CSF pH than doe metabolic acidosis;[57] this probably explains why neurologic abnormalities are l prominent in the latter disorder. Symptoms are also less common with *chronic* hypercapnia, since the renal compensation returns the arterial pH and ultim CSF pH toward normal.

In addition to neurologic abnormalities, arrhythmias and peripheral vasodila combine to produce severe hypotension if the systemic pH is reduced to be In the patient with underlying lung disease, this problem is most often seen respiratory acidosis is complicated by a superimposed metabolic acidosis.

Chronic respiratory acidosis is also commonly associated with cor pulmonal peripheral edema. The cardiac output and glomerular filtration rate (GFR) a normal to near normal in this disorder, which generally occurs only in those with severe lung disease who are hypercapnic.[58] These findings suggest a direct role for CO_2 in the renal Na^+ retention in this setting, although marked hypoxem also may contribute (see page 509).[58,59]

DIAGNOSIS

The presence of an acid pH and hypercapnia is diagnostic of respiratory ac However, identifying the underlying acid-base disorder is more complicated metabolic acidosis or alkalosis, since the responses to acute and chronic r acidosis are different. The following examples will illustrate how the confid bands in Figs. 20-3 and 20-4 can be used in the evaluation of patients with respiratory acidosis. As will be demonstrated, these are *not substitute for an accurate and complete history*, since a given set of arterial blood values can be associa with several different disorders.

In acute hypercapnia, the plasma HCO_3^- concentration should be between 24 and meq/L (Fig. 20-3). Values above or below this range indicate superimposed me disorders. For example:

Case history 20-1

A previously well patient is brought into the emergency room in a moribund Physical examination and chest x-ray suggest acute pulmonary edema. The laboratory tests include the following:

$$\text{Arterial pH} = 7.02$$
$$P_{CO_2} = 60 \text{ mmHg}$$
$$[HCO_3^-] = 15 \text{ meq/L}$$
$$P_{O_2} = 40 \text{ mmHg}$$

Comment

Since the plasma HCO_3^- concentration should rise 1 meq/L for each 10 mmHg increment in P_{CO_2} in acute respiratory acidosis, an acute elevation of the P_{CO_2} to 60 mmHg should increase the plasma HCO_3^- concentration to 26 meq/L (pH of 7.24 Therefore, the findings in this patient represent a combined respiratory and metabolic acidosis, a life-threatening combination not infrequently seen in acute pulmonary edema in which lactic acidosis is superimposed upon the p dysfunction.[25]

The difficulties in interpretation in chronic respiratory acidosis are illustrat Figs. 20-6 to 20-8 Consider the following set of arterial blood tests:

$$\text{Arterial pH} = 7.27$$
$$P_{CO_2} = 70 \text{ mmHg}$$
$$[HCO_3^-] = 31 \text{ meq/L}$$
$$P_{O_2} = 35 \text{ mmHg}$$

The 30 mmHg increase in the P_{CO_2} should be associated with a 3-meq/L elevatio in the plasma HCO_3^- concentration to 27 meq/L in acute hypercapnia or an 11- increment (3.5 meq/L per 10 mmHg rise in the P_{CO_2}) to 35 meq/L in chronic hypercapnia. The observed value of 31 meq/L falls *between* the confidence bands for acute and chronic respiratory acidosis (Fig. 20-6, point A). This can represent metabolic acidosis complicating chronic hypercapnia (Fig. 20-6, [1] acute, superimposed on chronic, respiratory acidosis (Fig. 20-6, [2]; or metabolic alkalosis and acute hypercapnia (Fig. 20-6, [3]). *These possibilities cannot be distinguished without the respective histories*

1. A patient with chronic bronchitis develops persistent diarrhea.
2. A patient with chronic hypercapnia complains of fever and increased sp production. The chest x-ray is consistent with pneumonia.

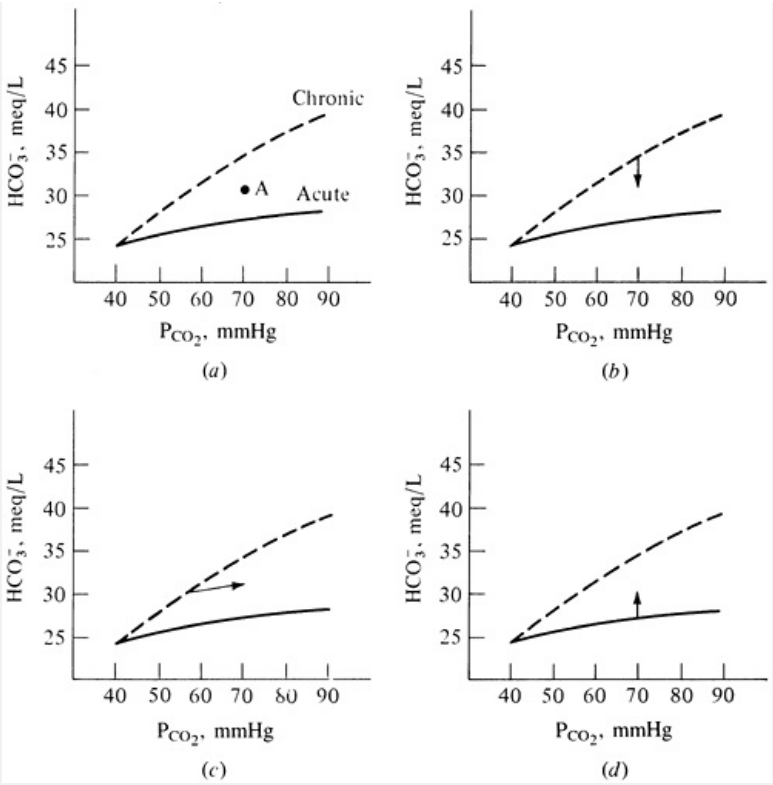

Figure 20-6 Confidence bands for acute and chronic hypercapnia have b transposed from Figs. 20-3 and 20-4 (a) Point A lies between the curves and can represent three different disorders. (b) Metabolic acidosis complicating chronic respiratory acidosis. (c) Acute, superimposed on chronic, hypercapnia. (d) Acute respiratory acidosis and metabolic alk (*Adapted from Cohen JJ, Schwartz WB: Am J Med 41:163, 1966, with permission.*)

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3. A patient with a history of extrinsic asthma has 5 days of vomiting as a theophylline toxicity and then develops an acute asthmatic attack after theophylline is discontinued.

A different problem in interpretation is present in the following example. Th laboratory data were as follows:

$$\text{Arterial pH} = 7.53$$

$$P_{CO_2} = 50 \text{ mmHg}$$

$$[HCO_3^-] = 40 \text{ meq/L}$$

$$P_{O_2} = 45 \text{ mmHg}$$

Oxygen was started and repeat tests were obtained:

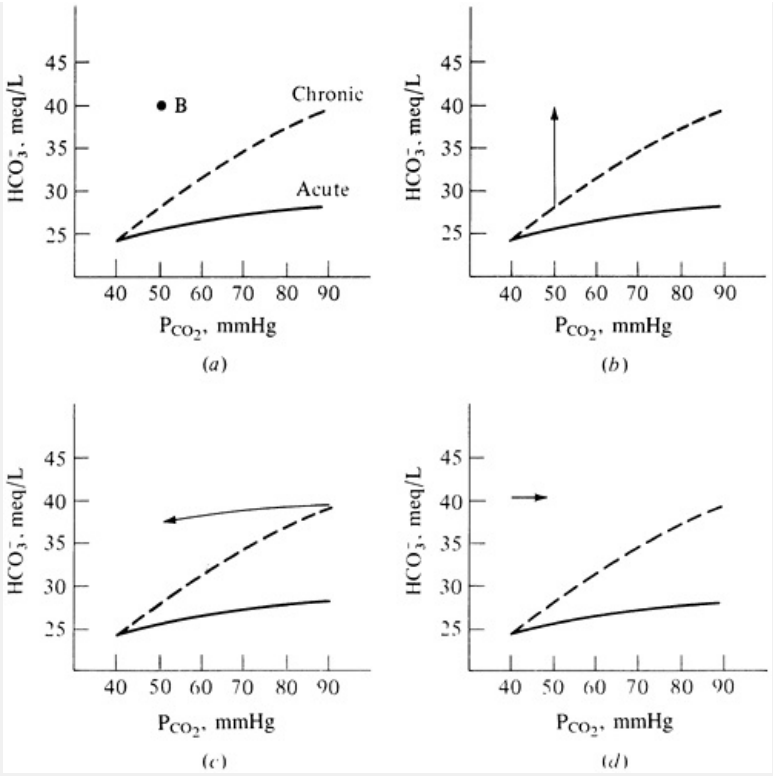

Figure 20-7 Confidence bands for acute and chronic respiratory acidosis. (a) Point B lies outside the confidence bands and can be due to one of three disorders. (b) Metabolic alkalosis complicating chronic (or acute) hypercapnia. (c) An acute reduction in the P_{CO_2} in a patient with chronic respiratory acidosis. (d) Primary metabolic alkalosis with compensatory retention of CO_2.

$$\text{Arterial pH} = 7.47$$
$$P_{CO_2} = 57 \text{ mmHg}$$
$$[HCO_3^-] = 40 \text{ meq/L}$$
$$P_{O_2} = 80 \text{ mmHg}$$

Because of the increase in P_{CO_2}, oxygen was discontinued for fear of further hypercapnia and CO_2 narcosis. After appropriate therapy with NaCl, the following values were noted:

$$\text{Arterial pH} = 7.41$$
$$P_{CO_2} = 39 \text{ mmHg}$$
$$[HCO_3^-] = 24 \text{ meq/L}$$
$$P_{O_2} = 68 \text{ mmHg}$$

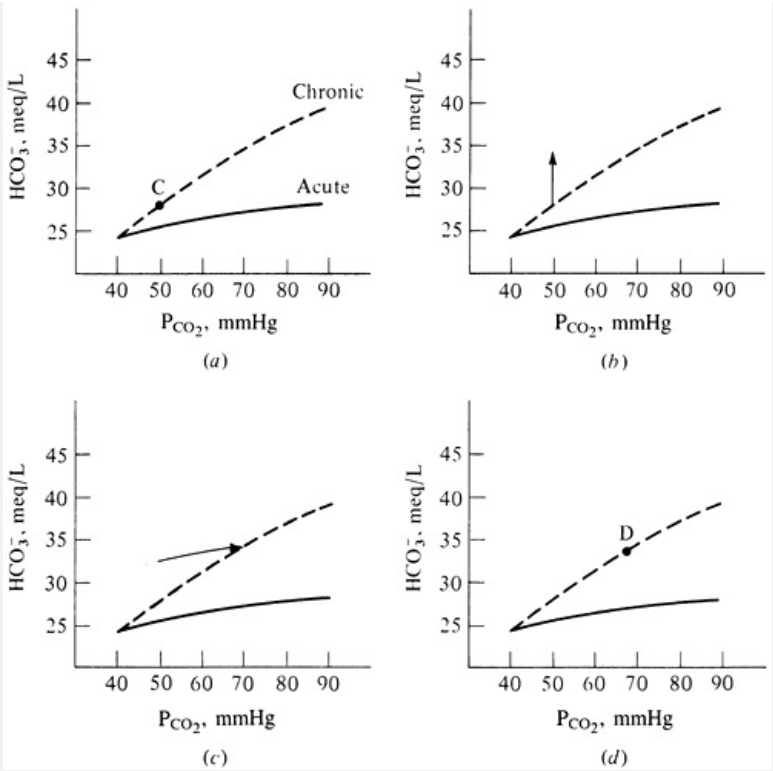

Figure 20-8 A patient with stable chronic hypercapnia (a, point C) develops metabolic alkalosis due to vomiting (b). During one episode, he aspirates vomitus and has an acute increase in P_{CO_2} (c). At this point, his blood values lie within the confidence band and are indistinguishable from those seen in uncomplicated chronic respiratory acidosis (d, point D).

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Despite the high P_{CO_2} on admission, the pH was alkaline. Most commonly, this degree of hypercapnia in an alkalemic patient is due to metabolic alkalosis complicating chronic hypercapnia (Fig. 20-7). However, this can also represent acute hypocapnia superimposed on chronic respiratory acidosis (Fig. 20-7) or hypercapnia as part of the normal respiratory compensation to metabolic al (Fig. 20-7). This specific diagnosis cannot be made directly from the labora data, and the respective clinical histories are required:

1. A patient with chronic obstructive pulmonary disease develops pedal ed to cor pulmonale and is started on diuretics.
2. Tracheal intubation and mechanical ventilation are begun in a patient w severe CO_2 retention. This entity is referred to as *posthypercapnic alkalosis*.
3. A patient has 5 days of persistent vomiting.

The correction of the alkalemia and hypercapnia with NaCl indicates that th patient's primary problem was metabolic alkalosis due to vomiting. Althoug

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high P_{CO_2} that increases after the administration of oxygen is most often se

chronic respiratory acidosis, it may also occur with metabolic alkalosis, sin development of severe hypoxemia can limit the degree of compensatory hypoventilation. This is most likely to occur in patients with underlying lun the postcorrection P_{O_2} of only 68 mmHg in this patient is compatible with this possibility.

It should also be noted that the further increment in P_{CO_2} after oxygen therapy is *beneficial*. In this setting, as the arterial pH decreased toward normal (from 7 7.47). There was no danger of CO$_2$ narcosis, and oxygen could safely have been continued.

Finally, one *cannot assume that values within the confidence bands connote uncomplicated disorders*. Suppose a patient with stable chronic hypercapnia (Fig. 20-8, point C) develops recurrent vomiting (Fig. 20-8) and then aspiration pneumonia (Fig. 20-8). Although this represents a triad of chronic respiratory acidosis, metabolic alkalosis, and acute respiratory acidosis, the final blood values l the confidence band and cannot be distinguished from pure, severe chronic hypercapnia (Fig. 20-8).

In summary, the confidence bands are useful guides in the interpretation of measurements. However, this interpretation cannot proceed in a vacuum an correlated with a complete history and physical examination.

Use of the Alveolar-Arterial Oxygen Gradient

Calculation of the alveolar-arterial (A-a) oxygen gradient may be helpful in differentiating intrinsic pulmonary disease from extrapulmonary disorders a cause of hypercapnia. The derivation of a formula that can be used to estin gradient requires a brief review of the physiology of alveolar gas exchange barometric pressure of 1 atm (Patm = 760 mmHg) in the inspired air at sea lev water vapor accounts for approximately 47 mmHg, nitrogen for 563 mmHg, a oxygen for the remaining 150 mmHg (Fig. 20-9). Since the pressure in the alveolus remains at 1 atm and there is no net movement of nitrogen or water vapor a alveolar capillary, the P_{N_2} and P_{H_2O} in the alveolus are the same as those in the inspired air and equal 610 mmHg. Thus, *the sum of the partial pressures of the other gases in the alveolus must be equal to 150 mmHg*, the partial pressure of oxygen in the inspired air (Fig. 20-9).

In the alveolus, inspired O$_2$ enters the blood, and CO$_2$ leaves the blood and enters the alveolus. If the amount of CO$_2$ added were equal to the amount taken up, then the alveolar P_{O_2} ($P_{A_{O_2}}$) would be less than the inspired P_{O_2} ($P_{I_{O_2}}$) by an amount equal to the alveolar P_{CO_2} ($P_{A_{CO_2}}$):

$$P_{A_{O_2}} = P_{I_{O_2}} - P_{A_{CO_2}} \qquad (20\text{-}6)$$

However, more O$_2$ is usually taken up than CO$_2$ produced, since, on a normal diet, each molecule of CO$_2$ generated represents the utilization of 1.25 molecules of i.e., the respiratory quotient is 0.8. To account for this, Eq. 20-6 can be rewritten:

$$P_{A_{O_2}} = P_{I_{O_2}} - 1.25P_{A_{CO_2}} \qquad (20\text{-}7)$$

Since CO_2 diffuses across the alveolar capillary rapidly (20 times as fast as O_2), the $P_{A_{CO_2}}$ is essentially equal to the arterial ($P_{a_{CO_2}}$). Therefore,

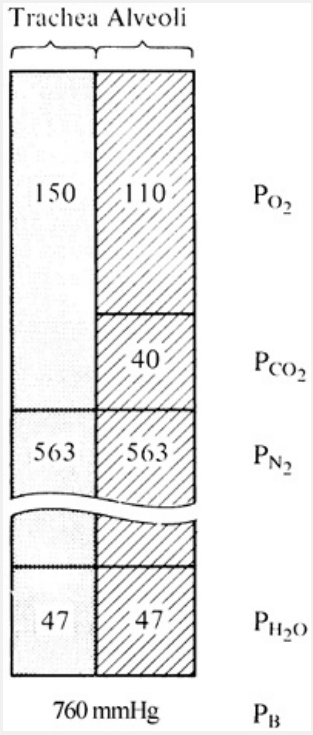

Figure 20-9 Composition of gas in the trachea at end inspiration (the same that in the inspired air) and composition of alveolar gas. The total pressu the partial pressures of nitrogen and water vapor are the same in both compartments; alveolar P_{O_2} goes down in proportion to the increase in alveola P_{CO_2}. It should be noted that these values are for a patient breathing roo If a patient is given supplemental oxygen, the alveolar P_{O_2} will be proportionately increased. *(Adapted from Snider, Chest 63:801, 1973, with permission.)*

$$P_{A_{O_2}} = P_{I_{O_2}} - 1.25P_{a_{CO_2}} \qquad (20\text{-}8)$$

In a subject inspiring room air ($P_{I_{O_2}}$ equals 150 mmHg) with a $P_{a_{CO_2}}$ of 40 mmHg,

$$P_{A_{O_2}} = 150 - (1.25 \times 40)$$
$$= 100\,\text{mmHg}$$

Not all of this oxygen enters the blood, however, since there is an alveolar- (A-a) oxygen gradient averaging, on room air, 5 to 10 mmHg in subjects unc age of 30 and gradually increasing to 15 to 20 mmHg in the elderly. This gr probably is due both to pulmonary arteriovenous shunts and to perfusion of underventilated areas of the lung. Since

$$\text{(A-a) } O_2 \text{ gradient} = P_{A_{O_2}} - P_{a_{O_2}} \qquad (20\text{-}9)$$

by substituting Eq. 20-8 for $P_{A_{O_2}}$, we have

$$(A\text{-}a)\ O_2 \text{ gradient} = P_{I_{O_2}} - 1.25P_{a_{CO_2}} - P_{a_{O_2}} \qquad (20\text{-}10)$$

The (A-a) oxygen gradient is always increased in hypercapnic patients with pulmonary disease and may be increased in some patients with extrapulmor disorders.[60] However, a normal gradient essentially excludes pulmonary dise suggests some form of central alveolar hypoventilation (including primary m alkalosis) or an abnormality of the chest wall or inspiratory muscles.

TREATMENT

A complete discussion of the treatment of all of the causes of acute and ch respiratory acidosis is beyond the scope of this chapter. Nevertheless, it is review some of the general principles that are involved, particularly those r acid-base balance.

Acute Respiratory Acidosis

Patients with acute respiratory acidosis are at risk from both hypercapnia a hypoxemia. Although the P_{O_2} can usually be raised by the administration of supplemental oxygen, reversal of the hypercapnia requires an increase in e alveolar ventilation. This can be achieved by control of the underlying dise with bronchodilators and corticosteroids in asthma) or by mechanical ventil delivered via either a tight-fitting mask or an endotracheal tube. Indications mechanical ventilation include refractory severe hypoxemia, symptomatic or progressive hypercapnia, and depression of the respiratory center due, for to a drug overdose.

Sodium bicarbonate

The role of $NaHCO_3$ in the treatment of acute respiratory acidosis (without concomitant metabolic acidosis) is not well defined. Although the primary a therapy is to restore normal ventilation, small doses (44 to 88 meq) can be infused over 5 to 10 min if the P_{CO_2} cannot be promptly controlled in a severel acidemic patient (pH less than 7.15). This regimen may be particularly bene patients with severe status asthmaticus requiring mechanical ventilation.[61] In this setting, elevating the plasma HCO_3^- concentration allows the pH to be controlled a high P_{CO_2} and, therefore, at a lower minute ventilation with lower transpul pressures. The latter change may minimize the incidence of potentially seri complications such as pneumothorax or pneumomediastinum.[61]

There are, however, several potential hazards with the use of $NaHCO_3$ in infants with respiratory acidosis:

1. The administration of $NaHCO_3$ should be avoided, if possible, in patients wit pulmonary edema, because it can increase the degree of pulmonary con In general, most of these patients can be managed without using $NaHCO_3$; correction of the pulmonary edema and hypoxemia is usually sufficient t

acid-base balance.[25,62]

2. Bicarbonate therapy does not protect against the central nervous syste of hypercapnia, since bicarbonate does not readily cross the blood-brai
3. The infusion of $NaHCO_3$ can result in an increase in CO_2 generation and therefore in the P_{CO_2} by the following reaction:

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

Normally, the CO_2 that is generated is rapidly eliminated by the lungs. Hov in patients with inadequate pulmonary blood flow (especially during a c arrest), the CO_2 may be retained, and the resultant elevation in the P_{CO_2} can exacerbate the tissue acidemia.[38,39] and[40,42] Thus, careful monitoring is required; furthermore, during cardiopulmonary resuscitation, measureme mixed venous pH may be the best indicator of the acid-base status at th level (see page 452).[42]

4. Metabolic alkalosis (due to the excess HCO_3^-) may ensue after the P_{CO_2} has returned to normal. This is usually not a major problem.

Tromethamine

The limitations and potential deleterious effects of bicarbonate therapy hav promoted investigation into the use of alternative buffering agents, such as tromethamine (THAM; trometamol). THAM is an inert amino alcohol that buf and CO_2 by virtue of its amine moiety via the following reactions:[63]

$$THAM-NH_2 + H^+ \rightarrow THAM-NH_3^+$$

$$THAM-NH_2 + H_2O + CO_2 \rightarrow THAM-NH_3^+ + HCO_3^-$$

Protonated THAM is excreted in the urine at a rate slightly higher than crea clearance in conjunction with either chloride or bicarbonate. Thus, THAM supplements the buffering capacity of blood without generating carbon diox less effective in patients with renal failure. Reported toxicities include hyp hypoglycemia, and respiratory depression; the last complication probably re from the ability of THAM to rapidly increase the pH and decrease the P_{CO_2} in the central nervous system.

Published clinical experience with THAM is limited, but the drug has been u treat severe acidemia due to sepsis, hypercapnia, diabetic ketoacidosis, ar disorders.[63] Its clinical efficacy compared to that of sodium bicarbonate in th treatment of respiratory acidosis remains unproven, and THAM is of uncerta

Chronic Respiratory Acidosis

The primary goals of therapy in patients with chronic respiratory acidosis a maintain adequate oxygenation and, if possible, to improve effective alveol ventilation. Because of the effectiveness of the renal compensation, it is us

necessary to treat the pH, even in patients with severe hypercapnia.[45] In addition, the frequent concurrent use of diuretics in patients with cor pulmonale can raise the pH, occasionally to normal or even alkalemic levels.

The appropriate treatment varies with the underlying disease.[26] As a general rule, excessive oxygen and sedatives should be avoided, since they can act as r depressants, producing further hypoventilation. For patients with

chronic obstructive lung disease, bronchodilators and, when infection is pr antimicrobials may ameliorate the airflow characteristics of the disease.[664] Dietary modification to reduce the respiratory quotient also may be helpful selected patients by reducing CO_2 production.[65] In obese patients, weight reductio can improve alveolar ventilation, leading to an elevation in the arterial P_{O_2} and reduction in the P_{CO_2} (of as much as 10 mmHg each).[48,66] Although the loss of weight may directly improve ventilatory mechanics, carbohydrate restriction about 200 g/day) can produce a similar improvement in the absence of any weight.[67] The beneficial effect seen in this setting appears to involve increa central stimulation of ventilation; how this occurs, however, is not clear. (T appropriate management of the obesity hypoventilation syndrome is beyond scope of this discussion.[34])

If severe hypoxemia persists (arterial P_{O_2} below 50 to 55 mmHg), continuous low-flow oxygen therapy is indicated to prolong survival, diminish the severity c pulmonale, and improve the quality of life.[17,18] and [19,26,68] The pulmonary benefits derived from correction of hypoxemia may result from improved per due to reversal of pulmonary vasoconstriction and of secondary polycythem increases blood viscosity. The aim of therapy is to raise the P_{O_2} to 60 to 65 mmHg (hemoglobin saturation above 90 percent), while carefully monitoring the P_{CO_2} to ascertain that ventilation has not been suppressed to a clinically important partial correction of the hypoxemia.

Mechanical ventilation may be required when there is an acute exacerbatio chronic hypercapnia (as with the development of pneumonia). In this setting must be taken to *lower the P_{CO_2} gradually*. Rapid correction of hypercapnia to ne normal levels can lead to an overshoot alkalemia and a marked rise in the p central nervous system (CNS), since CO_2 can easily diffuse out of the brain. The acute increase in CNS pH can, in selected cases, lead to severe neurologic abnormalities, such as seizures and coma.[69,70] These findings typically improve if the P_{CO_2} is allowed to rise toward its previous level.

Effect of superimposed metabolic alkalosis

As described above, the influence of pH on ventilation is maintained in chr respiratory acidosis.[12,13,14] and [15] Thus, the induction of metabolic alkalosis (usually due to diuretic therapy for cor pulmonale) will further depress vent

aggravating both the hypoxemia and the hypercapnia.[1571] In this setting, lowering the plasma HCO_3^- concentration can reverse these abnormalities and may imp the patient's sense of well-being.[15]

Correction of a superimposed metabolic alkalosis can be achieved by disco diuretic therapy and administering NaCl. This is not practical, however, in t who is still significantly edematous. In this circumstance, acetazolamide (25 mg once or twice a day) can both lower the plasma HCO_3^- concentration and increase the urine output by inhibiting proximal reabsorption of $NaHCO_3$ (see chap. 15). Monitoring the urine pH is a simple method of assessing the efficacy of regimen, since a HCO_3^- diuresis leads to an elevation in the urine pH to above

Despite its effectiveness in many patients, there are two potential problems use of acetazolamide. First, the plasma HCO_3^- concentration should be lowered to the level *appropriate for the degree of hypercapnia* (see Fig. 20-4). Returning the plasma HCO_3^- concentration to the normal value of 24 meq/L can lead to seve acidemia due to persistent marked hypercapnia.[1472] Second, acetazolamide can produce a *transient elevation* in the P_{CO_2} (usually 3 to 7 mmHg) prior to its diuret effect.[72] This complication, which is generally not clinically important, may b partial inhibition of carbonic anhydrase in the red blood cell.[1472] This enzyme catalyzes the hydration of CO_2 to H_2CO_3, a reaction that is essential for CO_2 transport by the red cell [see Eqs. 20-1 and 20-2] and, therefore, for the elimination of CO_2 by the lungs.

PROBLEMS

20-1 Match the clinical histories with the appropriate arterial blood val

	pH	P_{CO_2}, mmHg	$[HCO_3^-]$, meq/L
(a)	7.37	65	37
(b)	7.22	60	26
(c)	7.35	60	32

1. **A 60-year-old man with chronic bronchitis develops persistent diar**
2. **A 24-year-old man is markedly obese.**
3. **A 14-year-old girl has a severe acute asthmatic attack.**
4. **A 56-year-old woman with chronic bronchitis is started on diuretic**

for peripheral edema, resulting in a 3-kg weight loss.

20-2A 54-year-old man with a history of chronic obstructive lung disea a 2-day episode of increasing shortness of breath and sputum product chest radiograph reveals a left lower-lobe pneumonia. The following laboratory data are obtained with the patient breathing room air:

$$\text{Arterial pH} = 7.25$$
$$P_{CO_2} = 70 \text{ mmHg}$$
$$[HCO_3^-] = 30 \text{ meq/L}$$
$$P_{O_2} = 30 \text{ mmHg}$$
$$\text{Urine } [Na^+] = 4 \text{ meq/L}$$

The patient is started on intravenous aminophylline and nasal oxygen becomes less responsive. Repeat blood tests are obtained and show t following:

$$\text{Arterial pH} = 7.18$$
$$P_{CO_2} = 86 \text{ mmHg}$$
$$[HCO_3^-] = 31 \text{ meq/L}$$
$$P_{O_2} = 62 \text{ mmHg}$$

a. **What is the probable acid-base disturbance on admission?**
b. **What is responsible for the increase in P_{CO_2} in the hospital?**
c. **What further therapy would you recommend?**

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d. **If the P_{CO_2} is rapidly lowered to 40 mmHg, what will happen to the arterial pH?**
e. **If the patient is then maintained on a low-sodium diet, how long wi take for the plasma HCO_3^- concentration to return to normal?**

20-3A 65-year-old man has a history of smoking and hypertension, whi treated with a diuretic. The following arterial blood values are obtaine room air:

$$\text{Arterial pH} = 7.48$$
$$P_{CO_2} = 51 \text{ mmHg}$$
$$[HCO_3^-] = 36 \text{ meq/L}$$
$$P_{O_2} = 73 \text{ mmHg}$$

a. **What is the most likely acid-base disturbance?**
b. **Does the patient have significant underlying lung disease?**

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Chapter Twenty-One
Respiratory alkalosis

The introduction to acid-base disorders presented in Chapter 17 should be read before proceeding with this discussion. Respiratory alkalosis is a clinical disturbance characterized by an elevated arterial pH (or a decreased H^+ concentration), a low P_{CO_2} (hypocapnia), and a variable reduction in the plasma HCO_3^- concentration. It must be differentiated from metabolic acidosis, in which the plasma HCO_3^- concentration and P_{CO_2} also are diminished, but the pH is reduced rather than increased.

PATHOPHYSIOLOGY

A primary decrease in the P_{CO_2} occurs when effective alveolar ventilation is increased to a level beyond that needed to eliminate the daily load of metabolically produced CO_2. Before discussing the different disorders that can cause a respiratory alkalosis, it is helpful to first review how the body responds to hypocapnia. The law of mass action,

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]}$$

it can be seen that the reduction in the extracellular H^+ concentration induced by hypocapnia can be minimized by lowering the HCO_3^- concentration. This protective response involves two steps: rapid cell buffering and a later decrease in net acid excretion. As a result of the time differential between the cellular and renal effects, the changes in acute and chronic respiratory alkalosis are different.

Acute Respiratory Alkalosis

Within 10 min after the onset of respiratory alkalosis, H^+ ions move from the cells into the extracellular fluid; they then combine with HCO_3^-, resulting in an appropriate fall in the plasma HCO_3^- concentration:

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

These H^+ ions are primarily derived from the protein, phosphate, and hemoglobin buffers in the cells,

$$HBuf \rightarrow H^+ + Buf^-$$

and from an alkalemia-induced increase in cellular lactic acid[1] production.

In general, enough H^+ ions enter the extracellular fluid to lower the plasma HCO_3^- concentration 2 meq/L for each 10 mmHg decrease in P_{CO_2} (see Fig. 20-3).[2] If, for example, the P_{CO_2} were reduced to 20 mmHg (20 mmHg less than normal), the plasma HCO_3^- concentration should fall by 4 meq/L to 20 meq/L (pH equals 7.

$$\text{pH} = 6.10 + \log \frac{20}{0.03(20)}$$

$$= 7.63$$

This cellular response is not very efficient, since the pH would have been c slightly greater, at 7.70, if there were no cell buffering and the plasma HCO_3^- concentration had remained at 24 meq/L.

Chronic Respiratory Alkalosis

In the presence of persistent hypocapnia, there is a compensatory decrease H^+ secretion that begins within 2 h but is not complete for 2[3,4] to 3[5] days. This response, which is presumably mediated at least in part by a parallel rise in tubular cell pH, is manifested by HCO_3^- loss in the urine and by decreased urinary ammonium excretion.[4,5] Both of these effects lower the plasma HCO_3^- concentration, the latter by preventing the excretion of the daily H^+ load and the former by resulting in H^+ retention.

On average, the combined effects of the cell buffers and the renal compens result in a new steady state in which the plasma HCO_3^- concentration falls in humans approximately 4 meq/L for each 10 mmHg reduction in P_{CO_2} (Fig. 20-1).[6] Thus, if the P_{CO_2} were chronically reduced to 20 mmHg, the plasma HCO_3^- concentration should fall by 8 meq/L, to 16 meq/L. This response effectivel the extracellular pH, which is increased only to 7.53, as compared to 7.63 v similar degree of acute hypocapnia.

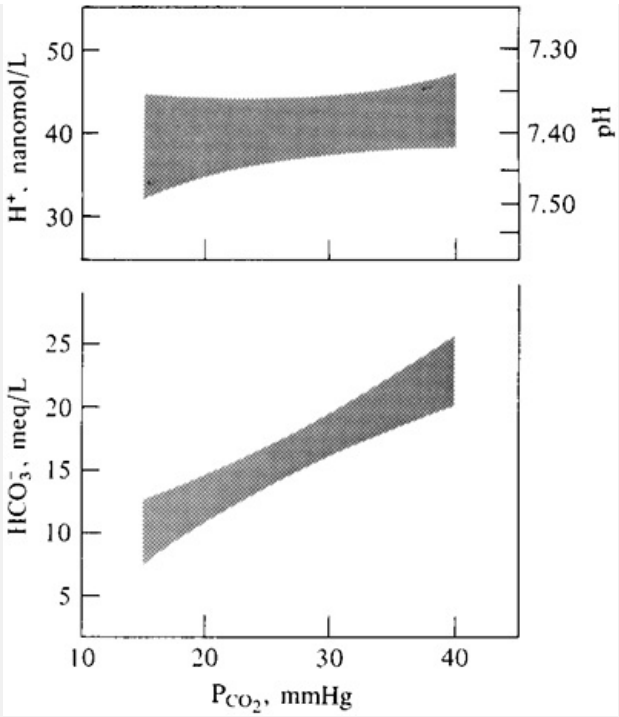

Figure 21-1 Significance bands of 95 percent probability for plasma pH and H^+ and HCO_3^- concentrations in chronic hypocapnia. Note that there is only a minimal change in the H^+ concentration and pH as the P_{CO_2} is reduced. *(From Gennari JF, Goldstein MB, Schwartz WB: J Clin Invest 51:1722, 1972, by copyright permission of the American Society for Clinical Investigations.)*

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ETIOLOGY

Respiration is physiologically governed by two sets of chemoreceptors: tho respiratory center in the brainstem and those in the carotid and aortic bodi located at the bifurcation of the carotid arteries and in the aortic arch, respectively.[7,8]

1. The central chemoreceptors are stimulated by an increase in the P_{CO_2} or the metabolic acidosis, both of which appear to be sensed as a fall in the p surrounding cerebral interstitial fluid.[9]

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2. The peripheral chemoreceptors are primarily stimulated by hypoxemia, a they also contribute to the acidemic response.[7,8,10]

Thus, *primary* hyperventilation resulting in respiratory alkalosis can be produ hypoxemia or anemia, a reduction in the cerebral pH (an apparently rare ev the cerebrospinal fluid pH is usually elevated in respiratory alkalosis) or ot for hyperventilation, such as pain, anxiety, stimulation of mechanoreceptors

the respiratory system, or direct stimulation of the central respiratory cente (Table 21-1).[11,12] and[13]

Hypoxemia

The respiratory response to hypoxemia (which includes reduced oxygen del to severe hypotension or anemia) occurs in two stages, which illustrate the interaction between the peripheral and central chemoreceptors (Fig. 21-2).[8,14,15] Hypoxemia initially activates the peripheral chemoreceptors, resulting in hyperventilation, hypocapnia, and mild increases in the arterial and cerebra However, the cerebral alkalosis inhibits the central respiratory center, ther limiting the degree of hyperventilation. Thus, hypoxemia does not significa stimulate respiration acutely unless the arterial P_{O_2} falls below 50 to 60 mmHg or hypocapnia does not occur because of underlying lung disease (Fig. 21-2). In the latter setting, ventilation begins to rise rapidly when the P_{O_2} is less than 70 to 80 mmHg.

Table 21-1 Causes of respiratory alkalosis

Hypoxemia

A. Pulmonary disease: pneumonia, interstitial fibrosis, emboli, edema
B. Congestive heart failure
C. Hypotension or severe anemia
D. High-altitude residence

Pulmonary disease

Direct stimulation of the medullary respiratory center

A. Psychogenic or voluntary hyperventilation
B. Hepatic failure
C. Gram-negative septicemia
D. Salicylate intoxication
E. Postcorrection of metabolic acidosis
F. Pregnancy and the luteal phase of the menstrual cycle (due to progesterone)
G. Neurologic disorders: cerebrovascular accidents, pontine tumors

Mechanical ventilation

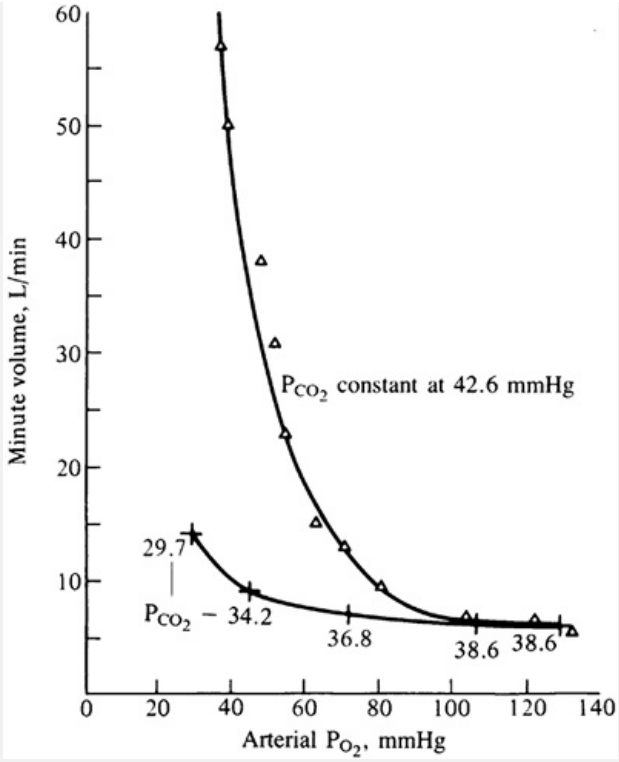

Figure 21-2 Influence of arterial P_{CO_2} on the ventilatory response to hypoxemia. In normal subjects (lower curve), lowering the partial pressure oxygen in the inspired air increases ventilation and lowers the arterial P_{CO_2}. However, these changes are relatively minor until the arterial P_{O_2} falls below 50 mmHg. The earlier and greater degree of hyperventilation seen when the P_{CO_2} is held constant (upper curve) indicates that the development of mil hypocapnic alkalosis normally limits the ventilatory response to hypoxemi (*Adapted from Loeschcke HH, Gertz KH, Arch Ges Physiol 267:460, 1958, with permission*).

Persistent hypoxemia, on the other hand, can lead to a greater degree of hyperventilation. The initial fall in P_{CO_2} induces a compensatory reduction in the plasma HCO_3^- concentration that lowers the extracellular pH toward normal (Fig. 21-1). This response partially removes the alkalemic inhibition of ventilation, t allowing a greater respiratory response to hypoxemia.

Pulmonary Disease

Respiratory alkalosis is a common finding in a variety of pulmonary disease including pneumonia, pulmonary embolism, and interstitial fibrosis[16,17,18] and it may also occur in pulmonary edema, but metabolic and respiratory acidosis more common in this disorder.[19]

Although hyperventilation in pulmonary disease may be due in part to hypo frequently not corrected by the administration of oxygen.[16,17] This observation indicates that other factors contribute to the increase in ventilation. The m

important appear to be mechanoreceptors located throughout the airways, l chest wall, which stimulate the respiratory center via afferent signals sent the vagus nerves.[16,17,20]

Several different receptors may participate in this response, including *juxtacapillary* receptors in the interstitium of the alveolar wall—which can be activated by interstitial edema, fibrosis, or pulmonary vascular congestion—and *irritant* receptors in the epithelial lining of the airways, which can be activated by the inhalat irritants and perhaps by local inflammatory processes such as pneumonia a asthma.[16,20] Although direct confirmation of the importance of these recepto humans is limited, vagal blockade can reverse the hyperventilation associa pulmonary disease in experimental animals.[16,20,21]

These receptors play little role in the control of ventilation in normal subje their effect in pulmonary disease can be somewhat maladaptive. For examp dyspnea and breathlessness are common complaints in diffuse pulmonary ir fibrosis, even in patients without severe hypoxemia. These symptoms are p due at least in part to increased ventilatory drive.[13,16]

Direct Stimulation of the Medullary Respiratory Center

Primary hyperventilation due to stimulation of the respiratory center may be a variety of disorders (Table 21-1). The possible mechanisms by which this occur are variable and include the primary effect of cortical centers in psychogen hyperventilation,[22] retained amines in hepatic failure,[23,24] bacterial toxins in gram-negative septicemias,[25] salicylates in salicylate intoxication,[26,27] progesterone in pregnancy and, to a lesser degree, the luteal phase of the menstrual cycle,[28,29] a persistently acid cerebrospinal fluid (CSF) pH following the rapid correct metabolic acidosis.[30,31]

In the last situation, the administration of $NaHCO_3$ raises the extracellular HCO_3^- concentration and pH. As the increase in pH is sensed by the peripheral chemoreceptors, there is a decrease in the degree of compensatory hyperv and a moderate elevation in the P_{CO_2}. Since CO_2 but not HCO_3^- rapidly crosses the blood-brain barrier, the brain initially senses only the higher P_{CO_2}. This produces a paradoxical fall in the CSF pH, which tends to prolong the hyperventilatory state.[30,31]

Respiratory alkalosis is also an occasional finding in neurologic disorders. pontine tumors, a reduction in the cerebral pH due to local lactic acid prod be responsible for increased ventilation.[32] Hypocapnia also may be seen with acut cerebrovascular accidents.

Mechanical Ventilation

The use of mechanical ventilation not uncommonly leads to respiratory alka
The imposition of forced hyperventilation often results from an attempt to c
hypoxemia. If necessary, the respiratory alkalosis can be reversed by incre
dead space or reducing either the tidal volume or the respiratory rate.

SYMPTOMS

The symptoms produced by respiratory alkalosis are related to increased ir
of the central and peripheral nervous systems and include light-headedness
consciousness, paresthesias of the extremities and circumoral area, cramps
carpopedal spasm that is indistinguishable from that seen with hypocalcemi
syncope.[22,33] A variety of supraventricular and ventricular arrhythmias also r
occur, particularly in critically ill patients.[34]

These abnormalities are thought to be related to the ability of alkalosis to
cerebral function and to increase membrane excitability. Respiratory alkalo
reduces cerebral blood flow (by as much as 35 to 40 percent if the P_{CO_2} falls by 20
mmHg),[35] which may contribute to the neurologic symptoms. In addition, som
complaints may be unrelated to the change in pH. Patients with psychogeni
hyperventilation, for example, frequently complain of headache, shortness
chest pain or tightness, and other somatic symptoms that may be emotional
and not caused by the alkalemia.

The above problems primarily occur in *acute* respiratory alkalosis when the P_{CO_2}
falls below 25 to 30 mmHg, a setting in which there is a substantial rise in
pH. They are much less likely to be seen in chronic respiratory alkalosis (s
pH is so well protected) or in metabolic alkalosis, where there is a lesser e
CSF pH because of the relative inability of HCO_3^- to cross the blood-brain
barrier.[11,36]

An additional finding in many patients with severe respiratory alkalosis is a
in the plasma phosphate concentration (measured in the laboratory as the p
concentration of inorganic phosphorus) to as low as 0.5 to 1.5 mg/dL

(normal equals 2.5 to 4.5 mg/dL).[37] This finding reflects a rapid shift of phosphat
from the extracellular fluid into the cells. It may be mediated by the stimula
glycolysis by intracellular alkalosis, resulting in increased formation of
phosphorylated compounds such as glucose 6-phosphate and fructose 1,6-
diphosphate.

DIAGNOSIS

The physical finding of tachypnea may be an important clue to the presence
hypocapnia, due either to primary respiratory alkalosis or to the respiratory
compensation to metabolic acidosis. Once the presence of respiratory alkal
been confirmed by measurement of the extracellular pH, P_{CO_2}, and HCO_3^-
concentration, the cause of this condition should be identified (Table 21-1). For
example, respiratory alkalosis is a relatively early finding in septicemia,[25]

diagnosis should be considered in the appropriate clinical setting when the other apparent cause for the hyperventilation.

Since the responses to acute and chronic hypocapnia are different, the det of the correct acid-base disorder is more difficult than in metabolic acidosi alkalosis. Suppose, for example, that a patient has the following arterial bl values:

$$\text{Arterial pH} = 7.48$$
$$P_{CO_2} = 20 \text{ mmHg}$$
$$[HCO_3^-] = 16 \text{ meq/L}$$

The alkaline pH and hypocapnia are diagnostic of respiratory alkalosis. Wit of 20 mmHg, the plasma HCO_3^- concentration should be roughly 20 meq/L in acu respiratory alkalosis (a reduction of 2 meq/L per 10 mmHg fall in the P_{CO_2}) and 16 meq/L in chronic respiratory alkalosis (a reduction of 4 meq/L per 10 mmHg P_{CO_2}).

Thus, 16 to 20 meq/L describes the approximate normal range for the plasm concentration in a patient with respiratory alkalosis and a P_{CO_2} of 20 mmHg. Values significantly above or below this range represent superimposed metabolic a or acidosis. In this patient, the plasma HCO_3^- concentration of 16 meq/L is consistent with uncomplicated chronic respiratory alkalosis. However, it is compatible with acute respiratory alkalosis combined with metabolic acidos produce the greater than expected reduction in the plasma HCO_3^- concentration. Thus, evaluation of the laboratory data must proceed in conjunction with th and physical examination, as illustrated by the following example:

Case History 21-1

A 5-year-old child is brought into the emergency room in a stuporous condit only pertinent history is that he had been playing with a bottle of aspirin ta earlier that day.

Comment

The most likely explanation for the above laboratory findings is a salicylate overdose. The acute respiratory alkalosis in this disorder is often complica salicylate-induced metabolic acidosis, leading to a reduction in the plasma HCO_3^- concentration (from the expected value of 20 meq/L down to 16 meq/L).

TREATMENT

In general, treatment of the alkalemia is not necessary, and therapy should at the diagnosis and correction of the underlying disorder. There is no ratio the use of respiratory depressants or for the administration of acid, such a an effort to normalize the pH. In severely symptomatic patients with acute r alkalosis, rebreathing into a paper bag—i.e., increasing the P_{CO_2} of the inspired air

—may partially correct the hypocapnia and relieve the symptoms. The extra pH should be monitored in this setting, since the compensatory decrease in plasma HCO_3^- concentration will persist and may result in metabolic acidosis P_{CO_2} is increased toward normal. This is usually mild but rarely may requir amounts of $NaHCO_3$.

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Chapter Twenty-Two
Introduction to disorders of osmolality

Hyponatremia and hypernatremia are common clinical problems. Although it plasma Na^+ concentration that is abnormal, these disorders reflect abnormali water balance that may or may not be accompanied by changes in body Na^+. The review presented below, which is essential for understanding the approach patients with hyponatremia or hypernatremia, is discussed in greater detail Chaps. 7 and 9.

WATER DISTRIBUTION AND OSMOTIC PRESSURE

The total body water (TBW) makes up about 60 percent of lean body weight and 50 percent in women. It is primarily distributed between the intracellula percent of body water) and extracellular (40 percent of body water) compar addition, roughly one-fifth of the extracellular fluid is confined to the intrav space (the plasma water). Thus, in an average 70-kg man, the total body w approximately 42 liters, of which 25 liters is intracellular and 17 liters is ex Within the extracellular compartments, 3 liters is in the vascular space.

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Osmotic forces are the primary determinants of the distribution of water bet these compartments. Each compartment has one major solute that, because restricted primarily to that compartment, acts to hold water within the comp Thus, Na^+ *salts* (extracellular osmoles), *K*$^+$*salts* (intracellular osmoles), and the *plasma proteins* (intravascular osmoles) help to maintain the volumes of the extracellular, intracellular, and intravascular spaces. In contrast, K^+ and urea rapidly crosses cell membranes and equilibrates throughout the total body w a result, urea does not affect the distribution of water between the cells an extracellular fluid and is therefore called an *ineffective* osmole.

The extracellular and intracellular fluids (ECF and ICF) are in *osmotic equilibrium* since the cell membranes are freely permeable to water. (The renal medulla exception.) If an osmotic gradient is established, *water will flow from the compartment of low osmolality to that of high osmolality until the osmotic pressures are equalized*

PHYSIOLOGIC EFFECTS OF CHANGES IN PLASMA

OSMOLALITY

The effects of variations in the effective plasma osmolality on internal wate distribution can be illustrated by the responses to NaCl, water, and an isot solution of NaCl and water (Fig. 22-1). (The methods used to calculate the new steady state are discussed on page 243.) Since Na^+ is essentially limited to the ECF the administration of NaCl without water augments ECF osmolality, resultin movement *out of* the cells (Fig. 22-*b*). Equilibrium is characterized by hypernatremia and equal increases in the osmolality of the ECF (due to the NaCl) and the ICF (due to water loss). In addition, the redistribution of wat enhances the extracellular volume and reduces the intracellular volume.

Thus, *the osmotic effect of the administered NaCl is distributed throughout total body water, even though NaCl itself is largely restricted to the ECF*. In this example, one might have expected the addition of 210 meq of Na^+ and 17 liters of ECF to increase the plasma Na^+ concentration by 12.5 meq/L (210÷17=12.5). However, the plasma Na^+ concentration rises by only 5 meq/L, because the osm water movement out of the cells lowers the plasma Na^+ concentration by dilution.

The results are different when only water is given. In this setting, there is fall in ECF osmolality, thereby promoting water *into* the cells (Fig. 22-c). The new steady state is characterized by a reduction in ECF and ICF osmol hyponatremia, and expansion of both the extracellular and intracellular volu

In contrast, the effect of an isotonic NaCl solution is limited to expansion o volume (Fig. 22-d). Since there is no change in osmolality, there is no shiftin water and the composition of the ICF is unchanged.

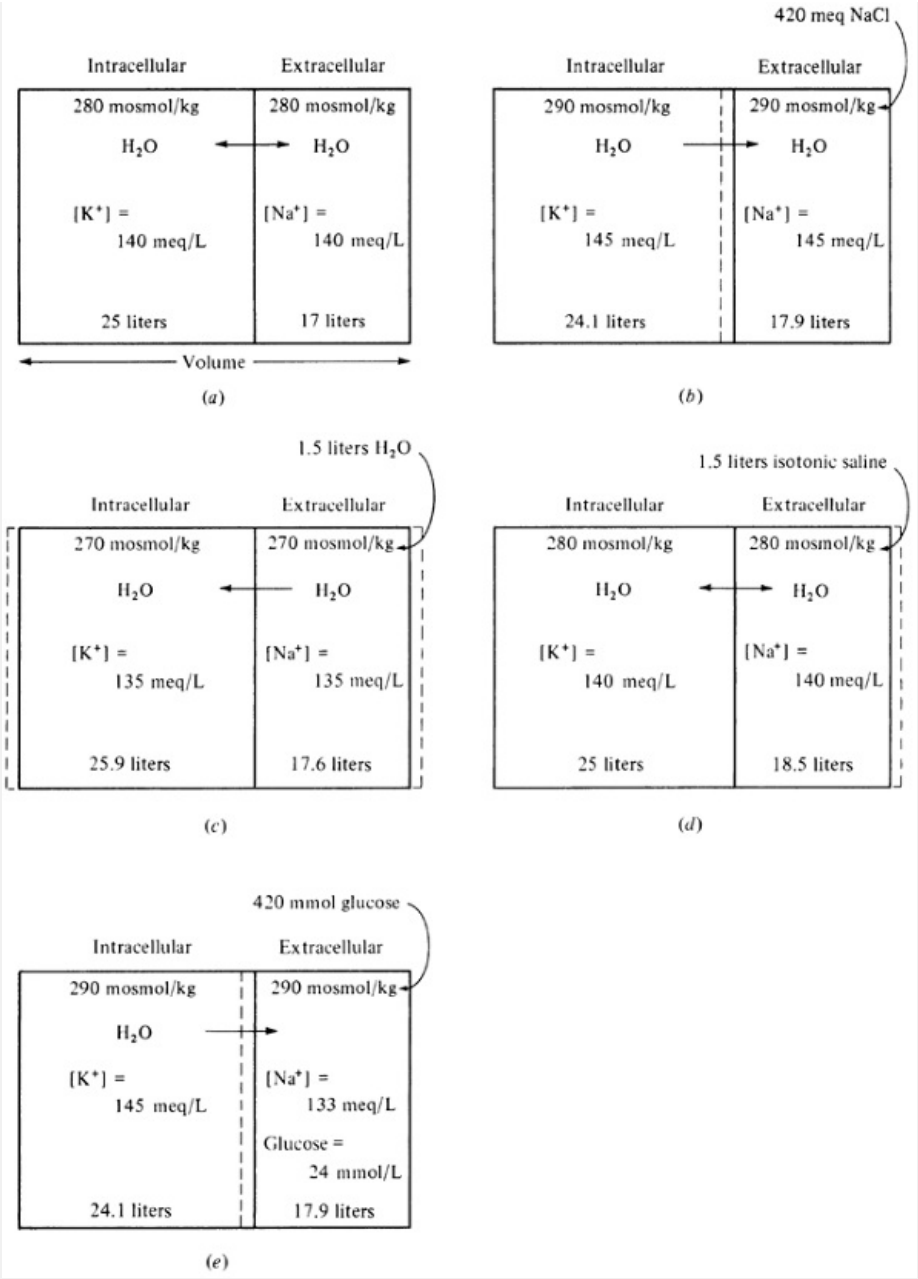

Figure 22-1 Osmolality of the body fluids and the distribution of water betw the intracellular fluid and the extracellular fluid in the control state (a) ar the addition of NaCl (b) (H_2O), isotonic NaCl and (H_2O), or glucose (e) to the extracellular fluid. For simplicity, it is assumed that the only extracell intracellular osmoles are Na^+ salts and K^+ salts, respectively.

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These examples illustrate two important clinical points. First, an increase i ECF osmolality results in cellular dehydration (Fig. 22-1*b*), and a decrease in effective ECF osmolality results in cellular overhydration (Fig. 22-1*d*). As will be seen, it is this flow of water out of and into brain cells that is primarily res for the symptoms that may be associated with hypernatremia and hyponatre respectively. These water shifts do not occur and the symptoms of hyperosı

are absent when the plasma osmolality is elevated by a gradual increase in Na^+ concentration, as occurs in renal failure. Urea, in contrast to Na^+, freely crosses the cell membrane, and osmotic equilibrium is reached by urea entry into ce than water movement out of cells.

Second, it can be seen that the plasma Na^+ concentration, which is a function of th *ratio* of the amounts of solute and water present, does not necessarily corre volume, which is a function of the *total* amount of Na^+ and water present. In each of the examples in Fig. 22-1, the extracellular volume is increased, yet the plasma Na^+ concentration is high, low, and normal, respectively. The different physiolo responses to these three states will be discussed below (see "Osmoregulation versus Volume Regulation").

MEANING OF PLASMA SODIUM CONCENTRATION

An understanding of what the plasma Na^+ concentration represents, including its differences from the extracellular volume, is essential in the approach to pa with hyponatremia or hypernatremia. Although it may appear logical to cons alterations in the plasma Na^+ concentration as indicating abnormal Na^+ balance, they are almost always a reflection of *abnormal water balance*.

Plasma Sodium Concentration and Plasma Osmolalit

The osmolality of a solution is determined by the number of solute particles kilogram of water. Since salts (particularly NaCl and $NaHCO_3$), glucose, and Na^+ urea (measured as the blood urea nitrogen, or BUN) are the primarily extra (and plasma) osmoles, the plasma osmolality (P_{osm}) can be approximated from

$$P_{osm} \cong 2 \times \text{plasma } [Na^+] + \frac{[\text{glucose}]}{18} + \frac{\text{BUN}}{2.8} \qquad (22\text{-}1)$$

where 2 reflects the osmotic contribution of the anion accompanying Na^+, and 18 and 2.8 represent the conversion of the plasma glucose concentration and the B units of milligrams per deciliter (mg/dL) into millimoles per liter (mmol/L).

Although urea contributes to the absolute value of the P_{osm}, it does not act to hold water within the extracellular space because of its membrane permeability. result, urea is an ineffective osmole and does not contribute to the effectiv P_{osm}.

$$\text{Effective } P_{osm} \cong 2 \times \text{plasma } [Na^+] + \frac{[\text{glucose}]}{18} \qquad (22\text{-}2)$$

In humans, the normal values for these parameters are

$$P_{osm} = 275\text{–}290 \text{ mosmol/kg}$$

$$\text{Effective } P_{osm} = 270\text{–}285 \text{ mosmol/kg}$$

$$\text{Plasma } [Na^+] = 137\text{–}143 \text{ meq/L}$$

$$\text{Plasma [glucose]} = 60\text{–}100 \text{ mg/dL (fasting)}$$

$$\text{BUN} = 10\text{–}20 \text{ mg/dL}$$

Under normal conditions, glucose and urea contribute less than 10 mosmol/

the plasma Na^+ concentration is the main determinant of the P_{osm}:

$$P_{osm} \cong 2 \times \text{plasma } [Na^+] \qquad (22\text{-}3)$$

Thus, *hypernatremia represents hyperosmolality and, in most instances, hyponatremia reflects hypoosmolality.* A common exception to this general relationship occurs with hyperglycemia due to uncontrolled diabetes mellitus. The elevation in the plasma glucose concentration raises the effective P_{osm} by pulling water out of the cells and lowering the plasma Na^+ concentration by dilution (Fig. 22-1*e*). This is clinically important, because therapy should be directed toward hyperosmolality and not, as suggested by the reduced plasma Na^+ concentration, hypoosmolality.

Plasma Sodium Concentration and Total Body Osmolality

If the plasma Na^+ concentration is a reflection of the P_{osm} and the P_{osm} is in equilibrium with the total body osmolality, then (see page 347)

$$\text{Plasma } [Na^+] \propto \text{total body osmolality} \qquad (22\text{-}4)$$

Since

$$\text{body osmolality} = \frac{\text{extracellular} + \text{intracellular solutes}}{\text{TBW}}$$

and Na^+ and K^+ salts (including the accompanying anions) are the primary extracellular and intracellular solutes, respectively, Eq. (22-4) can be converted to

$$\text{Plasma } [Na^+] \cong \frac{Na_e^+ + K_e^+}{\text{TBW}} \qquad (22\text{-}5)$$

where Na_e^+ and K_e^+ refer to the total "exchangeable" quantities of these ions (Fig. 22-2).[1] The exchangeable portion is used because about 30 percent of the body K^+ and a small fraction of the body Na^+ are bound in areas such as bone where they are "nonexchangeable" and therefore *osmotically inactive*.

The importance of the variables in Eq. (22-5) can be appreciated from the examples in Fig. 22-1. Increasing the Na_e^+ with NaCl elevates the plasma Na^+ concentration; raising the TBW lowers the plasma Na^+ concentration; and

increasing Na_e^+ and TBW proportionately with isotonic saline has no effect on plasma Na^+ concentration.

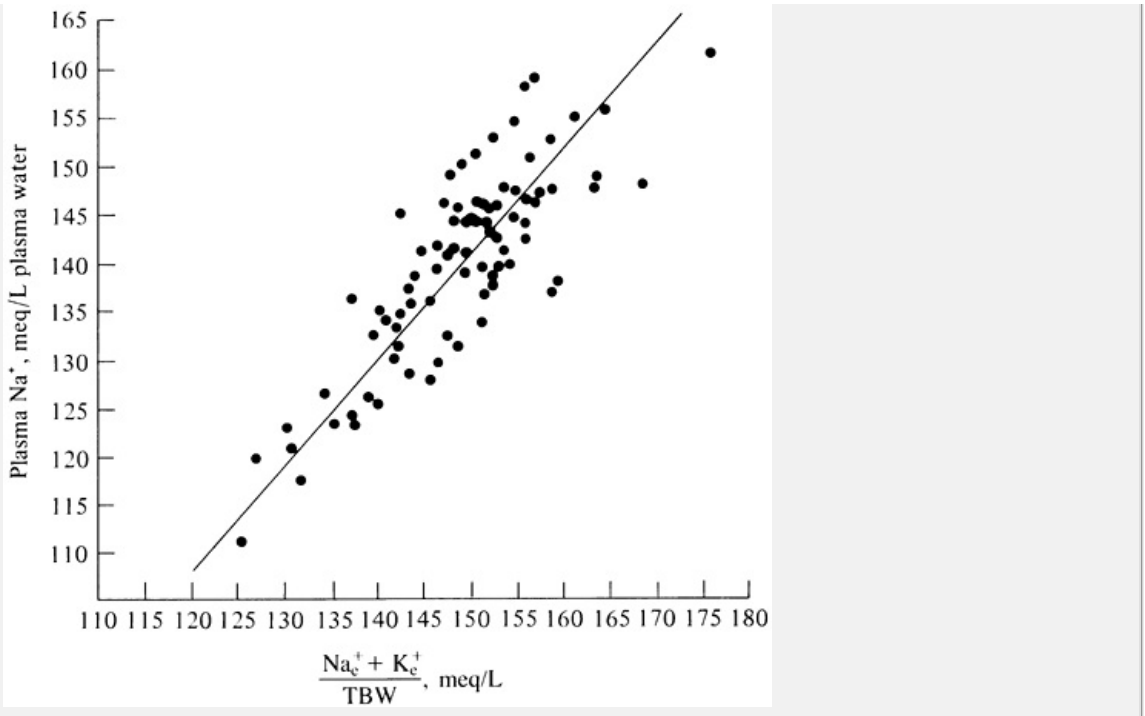

Figure 22-2 Relation between the plasma water Na^+ concentration and the ratio of $(Na^+_e + K^+_e)/TBW$ (*Adapted from Edelman I, Leibman J, O'Meara M, Birkenfeld L. J Clin Invest 37:1236, 1958, by copyright permission of the American Society for Clinical Investigation*)

The effect of K^+ is less apparent but can be clinically important. If, for example, K^+ is lost from the extracellular fluid (as a result of renal or gastrointestinal loss), extracellular K^+ concentration will fall. This will create a concentration gradient favoring the movement of K^+ out of the cells. Since large proteins and organic phosphates are the major intracellular anions and cannot easily leave the cells, electroneutrality is preserved in one of three ways, each of which will lower the plasma Na^+ concentration:

1. Extracellular Na^+ will enter the cells, directly lowering the plasma Na concentration.
2. Intracellular Cl^- will leave the cells (primarily red blood cells). The loss of Cl^- will lower the cell osmolality, resulting in movement out of the cells and H_2O thereby reducing the plasma Na^+ concentration by dilution.
3. Extracellular H^+ ions will dissociate from extracellular buffers and enter the cells, where they will combine with cell buffers. This movement of H^+ is osmotically neutral, but the loss of K^+ will lower the cell osmolality and induce osmotic H_2O movement out of the cells.

In some patients with diuretic-induced hyponatremia, for example, it is the

in exchangeable K^+, not Na^+, that is primarily responsible for the fall in the

plasma Na^+ concentration.[2] Furthermore, administration of KCl alone will raise the plasma K^+ and Na^+ concentrations.

A more common clinical example of the osmotic importance of K^+ is seen with fluid replacement for volume depletion. In diabetic ketoacidosis, for example, the in the plasma glucose concentration raises the effective P_{osm}. As a result, hypotonic fluids, such as half-isotonic saline, are often administered both to reexpand and to lower the P_{osm}. This solution, which contains 77 meq each of Na^+ and Cl^-, is essentially composed of two solutions: 500 mL of isotonic saline (77 meq of 500 mL or 154 meq/L) and 500 mL of free water. However, patients with diabetic ketoacidosis are also depleted of K^+, and 40 meq of KCl is frequently added to the replacement fluid. This raises the $(Na^+ + K^+)$ concentration to 117 meq/L. Consequently, each liter now contains 760 mL of isotonic fluid (117 meq in 154 meq/L) and only 240 mL of free water. Administration of this solution at will supply 50 mL/h of free water, which is roughly equivalent to the rate of insensible water losses from the skin and respiratory tract. Thus, there will free-water retention and no lowering of the P_{osm}.

Hyponatremia and Hypernatremia

From Eq. (22-5), it can be seen that hyponatremia or hypernatremia can be ind by alterations in Na^+, K^+, or water balance. In the clinical setting, however, the disorders are *almost always due to changes in water balance*. Hyponatremia, for example, almost always results from the retention of ingested or administer Although $(Na^+ + K^+)$ loss in excess of water also can lower the plasma Na^+ concentration, this is a rare event, occurring in some patients with thiazide induced hyponatremia (See Chap. 23).

Hypernatremia, on the other hand, usually results from water loss in excess and less often from the administration of a hypertonic solution of Na^+ (see Chap. 24). The toxicity of hyperkalemia (high plasma K^+ concentration) prevents the retention of enough K^+ to raise the plasma Na^+ concentration.

As will be described below, different protective mechanisms normally preve alterations in the plasma Na^+ concentration. Water retention leading to hyponatreamia does not usually occur because the excess water can be exc the urine via suppression of the secretion of antidiuretic hormone. Water lo to hypernatremia does not usually occur because stimulation of thirst will p water intake to replace the lost fluid.

Diarrheal states

A clinical illustration of the multiple factors that can influence the plasma Na^+ concentration occurs in patients with diarrhea. Although diarrheal fluid is r

isosmotic to plasma, the ionic composition is variable.[3,4] In secretory diarrheas (such as cholera), the ($Na^+ + K^+$) concentration of the diarrheal fluid is similar to of the plasma.[3] Thus, loss of this fluid will produce volume depletion but will not directly alter either the P_{osm} or the plasma Na^+ concentration.

The findings are different with osmotic diarrheas, as occur with lactulose t malabsorption, and some infectious enteritides. In this setting, the ($Na^+ + K^+$) fecal (N concentration is usually between 30 and 110 meq/L, with nonreabsorbed so (such as lactulose) accounting for most of the remaining osmoles.[3,4] As a result, the plasma Na^+ concentration will tend to rise, since water is lost in excess of N K^+ even though the fluid is isosmotic to plasma.[5]

Diarrheal syndromes also have other effects on water balance, as they may associated with fever, metabolic acidosis, and volume depletion. Fever incr water loss as sweat, and metabolic acidosis leads to compensatory hyperve which enhances water loss from the lungs. On the other hand, volume deple potent stimulus to thirst and antidiuretic hormone (ADH) secretion, resultin retention due to the combined effects of increased intake and reduced excr

In most patients with diarrhea, the increments in free-water loss and water are of roughly the same magnitude, resulting in little change in the plasma Na^+ concentration. In infants, however, water intake may not be increased, sinc to water is often limited. As a result, enteric infections with fever can lead water balance and hypernatremia, particularly when gastrointestinal water l is present as a result of an osmotic diarrhea.[6] Conversely, the hypovolemic adult is often able to satisfy thirst, possibly leading to positive water balance with consequent hyponatremia.

REGULATION OF PLASMA OSMOLALITY

The relationship of the plasma Na^+ concentration to water balance is also illustra by the manner in which the plasma Na^+ concentration and P_{osm} are normally regulated: namely, by alterations in the intake and excretion of water, not o

Each day, there is a variable degree of water intake and loss that can lead changes in the P_{osm} (see Chap. 9). Water intake is derived from three sources: drinking, the water content of food, and water of oxidation (e.g., carbohydr metabolized to CO_2 and water; Table 22-1). The retention of this water tends to lower the P_{osm}. On the other hand, water is lost in the urine and feces as we from the skin and respiratory tract as insensible and sweat losses. This los tends to raise the P_{osm}.

Under normal circumstances, there is a balance between net water intake a excretion such that the P_{osm} is maintained within narrow limits. This regulatory response is mediated by osmoreceptors in the hypothalamus which sense cl the P_{osm} of as little as 1 percent and which affect both water intake via thir

water excretion via the secretion of ADH from the posterior lobe of the pitu
Chap. 6). In the kidney, ADH augments the water permeability of the collecti
tubules, resulting in increased water reabsorption and the excretion of a
hyperosmotic urine (high U_{osm} and specific gravity). When ADH is absent, water
reabsorption falls, and a dilute urine is excreted (low U_{osm} and low U

specific gravity), since the collecting tubules are now relatively impermeab
water.

Table 22-1 Typical daily water balance in a norma human[a]

Source	Water intake, mL/day	Source	Water output, mL/day
Ingested water	1400	Urine	1500
Water content of food	850	Skin	500
Water of oxidation	350	Respiratory tract	400
		Stool	200
Total	2600		2600

[a] These values assume a low rate of sweat production. With exercise an hot weather, however, water losses from the skin as sweat can increase markedly, occasionally exceeding 5 L/day. In this setting, the ensuing ris plasma osmolality enhances thirst, resulting in an appropriate increase water intake.

The osmoreceptors regulate the P_{osm} in the following manner. After a water load, there is a fall in the P_{osm} which inhibits ADH secretion. This promotes the urin excretion of the excess water, thereby returning the P_{osm} toward normal. If, on the other hand, a patient becomes hyperosmolal (as with hypernatremia due to insens water losses), thirst and ADH release are stimulated. The combination of e water intake and renal water conservation results in water retention and an appropriate reduction in the P_{osm}. (In contrast, the osmoreceptors are not stimul by hyperosmolality due to an elevation in the BUN, since urea is an ineffec osmole.)

This regulatory system can be disrupted either by neurologic disorders, wh interfere with hypothalamic or posterior pituitary function, or by renal disor which can impair concentrating or diluting ability. In addition, there are nor factors that can influence hypothalamic function and the effects of *circulating* osmolality. In particular, volume depletion is a potent stimulus to ADH relea thirst (see Chap. 6).[7,8] and[9] As a result, patients who are hypovolemic may hav persistent thirst and ADH secretion, even in the presence of hyponatremia. setting, volume and tissue perfusion are maintained at the expense of the P_{osm}

Osmoregulation versus Volume Regulation

It is important to understand the differences between osmoregulation and v regulation (Table 22-2). As described above, the P_{osm} is determined by *the ratio* of solutes (primarily Na^+ and K^+ salts) and water, whereas the extracellular volume determined by *the absolute amounts* of Na^+ and water that are present. Two simple examples can illustrate the frequent dissociation between these parameters Exercising on a hot day leads to the loss of dilute fluid as sweat. The net e *rise* in the plasma Na^+ concentration but a *fall* in the extracellular volume. On the

other hand, water retention due to persistent ADH release will lead to a *dilution* of the plasma Na^+ concentration but an *increase* in volume. Thus, knowledge of the plasma Na^+ concentration gives *no predictable information* on volume status.

Table 22-2 Differences between osmoregulation an volume regulation

	Osmoregulation	Volume regulation
What is being sensed	Plasma osmolality	Effective circulating volume
Sensors	Hypothalamic osmoreceptors	Carotid sinus Afferent arteriole Atria
Effectors	Antidiuretic hormone	Renin-angiotensin-aldosterone system
	Thirst	Sympathetic nervous system Natriuretic peptides, including atrial natriuetic peptide and urodilatin Pressure natriuresis Antidiuretic hormone

What is affected	Water excretion and, via thirst, water intake	Urinary sodium excretion

The preceding discussion has emphasized the roles of the hypothalamic osmoreceptors, ADH, and thirst in the regulation of which P_{osm} is achieved primarily by changes in water balance. Volume regulation, on the other han attempts to maintain tissue perfusion. Different sensors and effectors are i this process, as it is urinary Na^+ excretion, not osmolality, that is being regulated (Table 22-2). The rate of Na^+ excretion is primarily regulated by aldosterone, angiotensin II, and perhaps natriuretic peptides; changes in the plasma Na^+ concentration have little effect unless there are associated changes in volu Chap. 8). Thus, the urine Na^+ concentration should be less than 25 meq/L when hyponatremia is due to net Na^+ loss (volume depletion) and greater than 40 meq/ when it is due to primary water retention (volume expansion). As a result, measurement of the urine Na^+ concentration is an important component of the diagnostic approach to hyponatremia (see page 23).

The independent roles of the osmoregulatory and volume regulatory pathwa be illustrated by the different responses elicited by NaCl, water, and isotor and water (as in Fig. 22-1).

- Isotonic saline enhances the extracellular volume without change in the P_{osm} (Fig. 22-1*d*). Thus, only the volume receptors are activated, resulting in N (and water) loss in the urine due to inhibition of the renin-angiotensin-aldosterone system and perhaps also to increased secretion of atrial na peptide (or related peptides; see page 190).

- A water load lowers the P_{osm} (Fig. 22-1*c*). This leads sequentially to the inhibition of ADH release, the formation of a dilute urine, and the rapid of the excess water. This response is normally so efficient that volume transiently increased and there is little change in the volume regulatory hormones (such as atrial natriuretic peptide) or in NaCl excretion.[10]
- The administration of NaCl without water increases the extracellular vo (Fig. 22-1*b*) and leads to renal NaCl loss. In addition, the increase in P_{osm} stimulates ADH release and thirst. These changes result in water retent which both reduces osmolality toward normal and augments volume, furt promoting the renal excretion of the NaCl load. The net effect is the ex the excess Na^+ in a relatively concentrated urine, a composition similar to intake.

Volume Depletion versus Dehydration

A common mistake in terms of terminology is the assumption that dehydratio

volume depletion (or hypovolemia) are synonymous. Volume depletion refers to extracellular volume depletion from any cause, most often due to salt and w In contrast, dehydration refers to the presence of hypernatremia due to pur loss; such patients are also hypovolemic.

URINE OSMOLALITY AND SPECIFIC GRAVITY

Estimating the ability to concentrate or dilute the urine can be helpful in th diagnosis of patients with hypernatremia or hyponatremia. This can be done measuring the urine osmolality or, if an osmometer is not available, the spe gravity of the urine. In general, the urinary specific gravity correlates reas with the U_{osm} according to the following approximate relationship:

Specific gravity	Osmolality
1.000	0
1.010	350
1.020	700
1.030	1050

However, this relationship is changed when larger molecules are present in urine, as occurs during a glucose osmotic diuresis or after the administrati radiocontrast media. In these settings, use of the specific gravity can be m since it will be elevated out of proportion to any change in the U_{osm}.

RELATION BETWEEN INTAKE AND OUTPUT

In the treatment of patients with hyponatremia or hypernatremia, attention i appropriately paid to comparing net fluid intake to urinary output, since cha state of water balance can return the plasma $[Na^+]$ toward normal. For example, hyponatremic patients who are not volume-depleted can be treate fluid restriction. If intake is kept below output, there will be a net loss of w an elevation in the plasma $[Na^+]$.

It must be emphasized, however, that *the composition of the fluids given and those excreted is often markedly different*. Therefore, merely comparing intake and output m be insufficient to accurately predict the effects of therapy. If, for example, NaCl and water loss is induced by a diuretic and the fluid losses are replac equal volume of water, the patient will be in water balance. However, loss o unreplaced solute will induce hypoosmolality and hyponatremia.

A more complex evaluation of fluid balance can be illustrated by the followi history:

Case history 22-1

A 58-year-old woman with an oat-cell carcinoma of the lung is admitted for progressive lethargy and confusion. The physical examination shows no foc neurologic findings and a weight of 60 kg. Laboratory data reveal

$$\text{Plasma } [Na^+] = 102 \text{ meq/L}$$

$$P_{osm} = 230 \text{ mosmol/kg}$$

$$\text{Urine } [Na^+] = 70 \text{ meq/L}$$

$$U_{osm} = 420 \text{ mosmol/kg}$$

A diagnosis of inappropriate ADH secretion due to the lung tumor is made (Chapter 23). In view of the severe hyponatremia, the patient is treated with water re hypertonic saline (Na^+ concentration equals 513 meq/L; osmolality equals 1026 mosmol/kg) and furosemide.

Overnight, the patient is given 1700 mL of hypertonic saline and excretes 3 urine with an osmolality of 300 mosmol/kg and Na^+ and K^+ concentrations of 95 and 35 meq/L, respectively. Repeat blood tests in the morning reveal a plasma Na^+ concentration of 123 meq/L and a plasma osmolality of 271 mosmol/kg.

Comment

At first glance, it seems unlikely that a negative fluid balance of only 1600 result in such a marked rise in the plasma Na^+ concentration and osmolality. However, a more complete evaluation of intake and

output shows how this change occurred.(4a*) The patient weighed 60 kg on admission, approximately one-half of which was water. Thus, her TBW on a was 30 liters. Since the osmolality in all fluid compartments is equal,

$$\text{Total body osmoles} = \text{TBW} \times P_{osm}$$

Since the effective P_{osm} is roughly equal to 2× plasma $[Na^+]$,

$$\begin{aligned}\text{Total effective osmoles} &= \text{TBW} \times 2 \times \text{plasma } [Na^+] \\ &= 30 \times 204 \\ &= 6120 \text{ mosmol} \end{aligned} \quad (22\text{-}6)$$

With the loss of 1600 mL of water, her TBW fell to 28.4 liters. If her total o were still 6120, then, by rearranging Eq. (22-6),

$$\begin{aligned}\text{Plasma } [Na^+] &= \text{total osmoles} \div (2 \times \text{TBW}) \\ &= 6120 \div 56.8 \\ &= 108 \text{ meq/L} \end{aligned} \quad (22\text{-}7)$$

This is clearly much different from the measured value of 123 mosmol/kg. T lies in the assumption that the patient's total osmoles were unchanged. The osmolar intake was 1745 mosmol (1700 mL at 1026 mosmol/kg) and total (Na^+ + K^+) loss was 860 mosmol [3.3 L× 130 meq/L × 2 (to account for accompanying a Thus, there was a 885-mosmol *increase* in total osmoles, from 6120 up to 6980

mosmol. As a result, from Eq. (22-7)

$$\text{Plasma } [Na^+] = 6980 \div 56.8$$
$$= 123 \text{ meq/L}$$

PROBLEMS

22-1A patient has the following laboratory data:

$$\text{Plasma } [Na^+] = 125 \text{ meq/L}$$
$$[\text{Glucose}] = 108 \text{ mg/dL}$$
$$\text{BUN} = 140 \text{ mg/dL}$$

a. **Calculate the plasma osmolality.**

b. **Would this patient have symptoms of hyperosmolality?**

22-2Suppose a patient can excrete only urine that is isosmotic to plas the patient's intake were limited to the administration of isotonic salii concentration equals 154 meq/L, the same as the Na^+ concentration in the plasma water):

a. **What would happen to the plasma osmolality and the Na^+ concentration?**

b. **Would the slow infusion of half-isotonic saline (a Na^+ concentration of 77 meq/L) supplemented with 77 meq/L (as KCl) have different effects on the plasma osmolality and the Na^+ concentration and on the extracellular volume?**

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Chapter Twenty-Three
Hypoosmolal states—hyponatremia

The introduction to disorders of water balance presented in Chapter 22 should be read before proceeding with this discussion.

PATHOPHYSIOLOGY

The plasma Na^+ concentration is the main determinant of the plasma osmolali (P_{osm}). As a result, hyponatremia, defined as a plasma Na^+ concentration below 135 meq/L, usually reflects hypoosmolality. This is an important relationship be low P_{osm} results in water movement into the cells; it is this cellular overhyd particularly in brain cells, that is primarily responsible for the symptoms th associated with this disorder (see "Symptoms," below).

The basic mechanisms by which hyponatremia and hypoosmolality occur ca easily understood if we ask two separate questions:

1. How do patients develop hyponatremia?
2. Why do they stay hyponatremic?

Generation of Hyponatremia

From the relationship between the plasma Na^+ concentration and the osmolality of the body fluids (see Fig. 22-2),

$$\text{Plasma } [Na^+] \cong \frac{Na_e^+ + K_e^+}{\text{total body water}} \qquad (23\text{-}1)$$

it can be seen that either solute (Na^+ and K^+) loss or water retention can produce hyponatremia. However, solute loss, as with vomiting or diarrhea, usually o fluid that is isosmotic to plasma. Thus, isosmotic fluid loss cannot directly lower the plasma Na^+ concentration, but hyponatremia will ensue if these losses are re with ingested or administered water. Thus, *retention leading to an excess of water in relation to solute is the common denominator in almost all hypoos states* The corollary of this relationship is that hypoosmolality generally ca produced if there is no water intake.

Perpetuation of Hyponatremia

The primary response to a fall in the P_{osm} occurs in normal subjects after the ingestion of a water load, is to diminish the secretion and synthesis of anti hormone (ADH; also called vasopressin), a response that is mediated in pa decreased ADH-specific messenger RNA (2,3 mRNA). This results sequentially in decreased water reabsorption in the collecting tubules, the production of a dilute urin rapid excretion of the excess water (more than 80 percent within 4 h). This dependent effect, so the final urine osmolality (U_{osm}) is determined by how much ADH release is inhibited.

As depicted in Fig. 23-1, ADH secretion essentially ceases when the P_{osm} falls below 275 mosmol/kg, a setting in which the plasma $[Na^+]$ concentration should be about 135 meq/L. In the absence of ADH, the U_{osm} can fall to 40 to 100 mosmol/kg (specific gravity equals 1.001 to 1.003), with a maximum water excretory ca that can exceed 10 L/day of solute-free water on a regular diet.

Since the capacity for water excretion is normally so great, water retention in hyponatremia typically occurs only when a *defect in renal water excretion*. A rare exception to this rule is seen in patients with primary polyd who drink such large volumes of fluid that they overwhelm even the normal capacity.

The excretion of free water is dependent upon two factors:

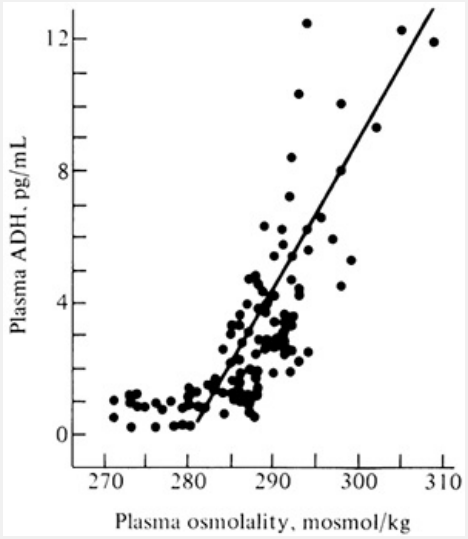

Figure 23-1 Relationship of plasma ADH concentration to plasma osmolality normal humans in whom the plasma osmolality was changed by varying the of hydration. ADH secretion is almost totally suppressed when the plasma osmolality falls below 275 to 280 mosmol/kg. *Adapted from Robertson GL, Aycinena P, Zerbe RL: Am J Med 72:339, 1982, with permission.*

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1. The generation of free water and a dilute urine by NaCl reabsorption wi

water in the diluting segments in the ascending limb of the loop of Henl
a lesser degree, the distal tubule.

2. The excretion of this water by keeping the collecting tubules impermeab
water (see Chap. 4).

Therefore, a reduction in free-water excretion, which is required for the de
of hyponatremia in most patients, must involve an abnormality in one or bot
steps (Table 23-1). Virtually all hyponatremic patients (except for those with r
failure and primary polydipsia) have an excess of ADH, most often due to th
syndrome of inappropriate ADH secretion (SIADH) or to effective circulating
depletion.[4,5]

This decrease in free-water excretion is manifested by a U_{osm} that is inappropriately high (U_{osm} greater than 100 mosmol/kg and usually greater than 300 mosmol considering the presence of hypoosmolality. The impairment in

water excretion does not have to be very severe. Suppose a patient has a c
solute intake of 400 mosmol and a net water intake (intake minus insensible
2 liters. To excrete this load and remain in the steady state, the average U_{osm} would be 200 mosmol/kg. If this patient were unable to reduce the U_{osm} below 222 mosmol/kg (a level still hypoosmotic to plasma), the 400 mosmol of solute w excreted in only 1800 mL of water, resulting in the daily retention of 200 ml and a gradual fall in the plasma $[Na^+]$ concentration.

Table 23-1 Pathophysiologic factors that diminish renal water excretion

Diminished generation of free water in the loop of Henle and distal tubu

A. Decreased fluid delivery to these segments
    1. Effective circulating volume depletion
    2. Renal failure
B. Inhibition of NaCl reabsorption by diuretics

Enhanced water permeability of the collecting tubules due to the presen
ADH

A. Syndrome of inappropriate ADH secretion
B. Effective circulating volume depletion
C. Adrenal insufficiency
D. Hypothyroidism

In theory, shutting off thirst should protect against progressive hyponatrem

setting. However, this does not occur, because most fluid is ingested out of for cultural reasons (e.g., coffee or soda with meals or as snacks), not bec osmotic stimulation of thirst (see Chapter 9).

ETIOLOGY

Since hyponatremia with hypoosmolality is caused by the retention of soluti water, the differential diagnosis of this disturbance consists primarily of th conditions that limit water excretion (Table 23-2).[5]

Table 23-2 Etiology of hyponatremia and hypoosmolality

Disorders in which renal water excretion is impaired

A. Effective circulating volume depletion
   1. Gastrointestinal losses: vomiting, diarrhea, tube drainage, bleed intestinal obstruction
   2. Renal losses: diuretics, hypoaldosteronism, salt-wasting nephropathy
   3. Skin losses: ultramarathon runners, burns, cystic fibrosis
   4. Edematous states: heart failure, hepatic cirrhosis, nephrotic syndrome with marked hypoalbuminemia
   5. K^+ depletion
B. Diuretics
   1. Thiazides in almost all cases
   2. Loop diuretics
C. Renal failure
D. Nonhypovolemic states of ADH excess
   1. Syndrome of inappropriate ADH secretion
   2. Cortisol deficiency
   3. Hypothyroidism
E. Decreased solute intake
F. Cerebral salt wasting

Disorders in which renal water excretion is normal

A. Primary polydipsia
B. Reset osmostat: effective volume depletion, pregnancy, psychosis, quadriplegia, malnutrition

Effective Circulating Volume Depletion

The term *effective circulating volume* refers to that fluid which is effectively

perfusing the tissues (see Chap. 8). Effective volume depletion may be associate with either reduction or expansion of the extracellular volume. True volume i.e., depletion of both the intravascular and interstitial compartments, can l produced by fluid loss from the gastrointestinal tract, kidneys, or skin (see Table 23-2). In addition, decreased tissue perfusion also may be present in some edematou —for example, as a result of a primary reduction in the cardiac output in he or decreased vascular resistance in cirrhosis (see Chap. 16).

Effective volume depletion predisposes toward the development of hyponatr through its effects on renal water excretion, thirst, and K^+ balance (Fig. 23-2). Regardless of the underlying disorder, volume depletion can impair water e in two ways:

- Hypovolemia, acting via the carotid sinus baroreceptors, is a potent sti ADH secretion (see Fig. 6-8), resulting in augmented water permeability in th collecting tubules. For example, almost all hyponatremic patients with a heart failure or cirrhosis have elevated circulating ADH levels.[5,6,7,8] This can be called *appropriate ADH secretion*, since the retained water attempts to restore normovolemia. Furthermore, the hypersecretion of ADH can be r if perfusion is increased, as with the administration of an angiotensin c enzyme (ACE) inhibitor to some patients with heart failure.[9]

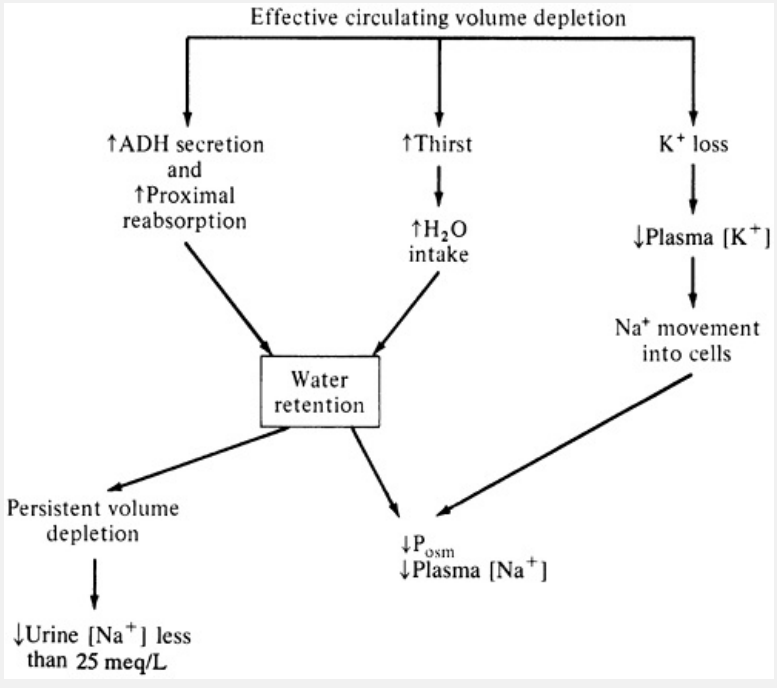

Figure 23-2 Pathophysiology of the development of hyponatremia in effective circulating volume depletion.

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- The combination of a fall in glomerular filtration rate (GFR) and an incr proximal tubular Na^+ and water reabsorption diminishes fluid delivery to th

diluting segments. As a result, the amount of free water that can be ger limited,[10] even if ADH release is suppressed.[11] It seems likely that this intrarenal effect is generally less important than the rise in ADH, since administration of an ADH antagonist largely reverses the defect in wate excretion in experimental heart failure, cirrhosis, and adrenal insufficie without improving tissue perfusion[12,13] and[14]

Not surprisingly, the tendency to increase ADH release and to reduce loop related to the degree of volume depletion. Thus, increasing severity of hea or cirrhosis is associated with a progressive rise in the release of ADH and two other "hypovolemic" hormones, renin and norepinephrine,[15,16,17] and[18] The net effect is that *hyponatremia does not occur in the absence of advanced disease*[15,16,17] and[18] Patients with heart failure who have a plasma Na^+ concentration below 137 meq/L have a significant reduction in survival com similar patients who are normonatremic.[19] It is important to remember in this regar that the capacity to excrete water is normally so great that *even a minor reduction in the plasma Na^+ concentration reflects a severe impairment in water excretio* (unless intake is markedly enhanced).

The *volume of water that is retained is related to both the severity of the r in water excretion and the intake of water*. Increased intake may contribute to the development of hyponatremia in this setting, since volume depletion can di stimulate thirst.[20] An interesting example of this relationship between intake a excretion has been described in ultramarathon runners, who have estimated losses of 10 to 14 liters of fluid containing 20 to 100 meq/L of Na^+ and K^+. These losses are almost entirely replaced by carbohydrate-containing solutions th much lower solute content. The net effect is water retention and, in some c symptomatic hyponatremia, with a fall in the plasma Na^+ concentration below 120 meq/L.[21]

Another example is the replacement of severe diarrheal losses due to chole is associated with a sodium concentration in stool of 120 to 140 meq/L) wit rehydration solution with reduced osmolarity. Compared with standard (i.e., sodium concentration) oral rehydration therapy, the use of a lower-solute s may result in an increased incidence of hyponatremia.[22]

Lastly, concurrent K^+ depletion also represents the loss of effective solute and contribute to the development of hyponatremia. This effect is due to a *transcellular cation exchange*, in which K^+ leaves the cells to replete the extracellular stores electroneutrality is in part maintained by the movement of Na^+ into the cells. In otherwise normal subjects, the fall in P_{osm} is transient, since ADH secretion is suppress (Fig. 23-1) leading to enhanced water excretion and normalization of the P_{osm} and Na^+ concentration. If ADH release is increased because of volume depletion however, the hyponatremia may persist. In this setting, the administration o alone can reverse the cation exchange and partially correct the fall in the p

Na^+ concentration.[23,24] and[25]

Diuretics

Hyponatremia is a relatively common, though usually mild, complication of c therapy. However, acute severe hyponatremia may occur as an idiosyncratic reaction,[24,25,26,27,28] and[29] particularly in patients who also drink large volu of water.[26,30] A careful analysis of 13 patients with a history of acute thiazid induced hyponatremia evaluated these patients and controls after rechallen 50 mg of hydrochlorothiazide.[26] Only those with prior hyponatremia developed a reduction in the plasma Na^+ concentration, which appeared to be due primarily t *increased water intake* rather than a greater natriuretic or diuretic response.

Three mechanisms in addition to fluid intake may also contribute to diuretic hyponatremia: volume depletion (by mechanisms similar to those in Fig. 23-2), K^+ depletion, and direct inhibition of urinary dilution by diminished NaCl reabs the loop of Henle and distal tubule.[29] Concurrent measurement of the blood urea nitrogen (BUN) and plasma uric acid concentration can help to distinguish b these mechanisms in an individual patient.[31] Increased water intake and transient volume expansion lead to increases in the urinary excretion of urea and uri the development of hypouremia (with the BUN often falling below 10 mg/dL) hypouricemia (with the plasma uric acid level often falling below 4 mg/dL). comparison, volume depletion leads to elevations in both of these paramete

One, at first surprising, observation is that *almost all cases of diuretic-induced hyponatremia are due to thiazide, not loop, diuretics*.[24,25,26,27,28,29] and[30] This difference in susceptibility may be related to the different sites of action of drugs within the nephron (see Chap. 15), which lead to varying effects on urinary concentrating ability.[32] A concentrated urine is produced by equilibration of the in the collecting tubules with the hyperosmotic medullary interstitium (see Chap. 14). The loop diuretics interfere with this process by inhibiting NaCl reabsorptio medullary thick ascending limb, thereby diminishing the interstitial osmolali[32] Thus, loop diuretics can induce volume depletion, leading to the release of a subsequent increase in the permeability of the collecting tubules to water however, the *degree of water retention and therefore the tendency to hyponat are limited by the lack of medullary hypertonicity*. As will be described below, this ability of the loop diuretics to diminish ADH-induced free-water reabsorptio actually be used to treat hyponatremia in SIADH.

The thiazides, in comparison, act in the cortex in the distal tubule and do n interfere with urinary concentration or the ability of ADH to promote water retention.[32] Furthermore, use of thiazide diuretics represents virtually the on clinical setting in which hyponatremia can be produced in part by the *loss of effective solute ($Na^+ + K^+$) in excess of water*. This effect results from the combination of diuretic-induced Na^+ plus K^+ loss and ADH-induced water retention.

In one study of seven patients, for example, the urine K^+ plus Na^+ concentration at presentation averaged 156 meq/L while the plasma levels were below 110 m[27] These losses will directly lower the plasma Na^+ concentration, independent of the level of water intake.

Rechallenge studies have shown that the plasma Na^+ concentration begins to fall within 6 to 24 h in susceptible subjects;[26,27] furthermore, the hyponatremia occurs within 2 weeks of the onset of therapy in most cases.[29] These findings are not surprising, since the maximum response to a given dose of a diuretic is see first dose, and all fluid and electrolyte complications begin to develop with few days (see page 453). After the first few weeks, a *new steady state* is established in which intake and excretion are again equal;[33] further change in the plasma Na^+ concentration will occur only if there is some superimposed problem, su vomiting, diarrhea, or an increase in water intake or drug dose.

Renal Failure

Progressive renal disease impairs urinary dilution, as manifested by an ina maximally lower the urine osmolality after a water load.[34,35] This defect is largely related to the associated osmotic diuresis; if dietary intake is similar to tha normals, then patients with fewer functioning nephrons must, to maintain ba increase the rate of solute excretion in the remaining nephrons. Neverthele relative water excretion (as measured by the rate of free-water excretion di the glomerular filtration rate) is not diminished in mild-to-moderate kidney disease.[34] Thus, nonoliguric patients are usually able to maintain a near normal plasma Na^+ concentration as long as water intake is not excessive. However, water rete hyponatremia are common when the GFR falls to very low levels.

Syndrome of Inappropriate ADH Secretion

SIADH is a common problem that can be seen in a wide variety of clinical s (Table 23-3).[3] It is characterized by the nonphysiologic release of ADH (i.e., n to the usual stimuli or hyperosmolality or hypovolemia) and by the relatively finding of *impaired water excretion at a time when Na^+ excretion is normal*. Understanding the implications of this relationship is essential if effective to be instituted (see "Treatment," below).[36]

Pathogenesis

The fluid and electrolyte consequences of persistent ADH activity are depic Fig. 23-3.[89] Because of the hormonal effect to enhance renal water reabsorp ingested water is retained, resulting in dilution (hyponatremia and hypoosm and expansion of the body fluids.[90] Edema does not occur, however, because the volume receptors become activated, leading to an appropriate increase in u Na^+ and water excretion that may be mediated in part by enhanced release

natriuetic peptide.[91]

The net effect is that the combination of water retention and secondary sol (sodium plus potassium) loss can account for essentially all of the fall in th sodium concentration in SIADH.[90-92] These changes occur in the following sequence.[90] The hyponatremia is initially mediated by ADH-induced water ret The ensuing volume expansion activates secondary natriuretic mechanisms, in sodium and water loss. The net effect is that, with

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chronic SIADH, sodium loss is as or more prominent than water retention. S hyponatremia may also be associated with potassium loss; since potassium osmotically active as sodium, the loss of potassium can contribute to the re in the plasma osmolality and sodium concentration.[90] This potassium is derived from the cells and probably represents part of the volume regulatory response. C increase in size as a result of water entry in hyponatremia lose potassium a solutes in an attempt to restore cell volume (see "Symptoms" below).

Table 23-3 Causes of SIADH according to probabl major mechanism of action

Increased hypothalmic production of ADH

A. Neuropsychiatric disorders[a]
   1. Infections: meningitis, encephalitis, abscess, herpes zoster
   2. Vascular: thrombosis, subarachnoid or subdural hemorrhage, temporal arteritis
   3. Neoplasma: primary or metastatic
   4. Psychosis[37]
   5. Other: human immunodeficiency virus infection,[38] Guillain-Barré syndrome, acute intermittent porphyria, autonomic neuropathy, hypothalamic sarcoidosis, post-transsphenoidal pituitary surgery[39,40]

B. Drugs
   1. Intravenous cyclophosphamide (increased sensitivity may also contribute)[41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56]
   2. Carbamazepine (though increased sensitivity is probably important)[41,44,45]
   3. Vincristine or vinblastine[46,47]
   4. Thiothixene[48]
   5. Thioridazine[49]
   6. Haloperidol[50]
   7. Amitriptyline[54]
   8. Fluoxetine or sertraline[52,53,54]
   9. Monoamine oxidase inhibitors[55]

10. Bromocriptine[56]
11. Lorcainide[57]

C. Pulmonary disease

1. Pneumonia[a] viral, bacterial, or fungal[58,59]
2. Tuberculosis[60,61]
3. Acute respiratory failure[62]
4. Other: asthma, atelectasis, pneumothorax[58,63]

D. Postoperative patients[58,64,65][a]

E. Severe nausea[66,67]

F. Idiopathic[68]

Ectopic (nonhypothalamic) production of ADH

A. Carcinoma: small cell of lung,[a] bronchogenic, duodenum, pancreas, thymus, olfactory neuroblastoma[69,70,71,72]

B. Potentiation of ADH effect

A. Chlorpropamide[73,74,75,76,77]
B. Carbamazepine[78,79,80,81]
C. Psychosis[3,7]
D. Intravenous cyclophosphamide[42]
E. Tolbutamide[63]

Exogenous administration of ADH

A. Vasopressin[82,83]
B. Oxytocin[84,85,86]

Possible production of another antidiuretic compound (or increased sensitivity to very low levels of ADH)

A. Prolactinoma[87]
B. Waldenstrom's macroglobulinemia[88]

[a] Most common causes.

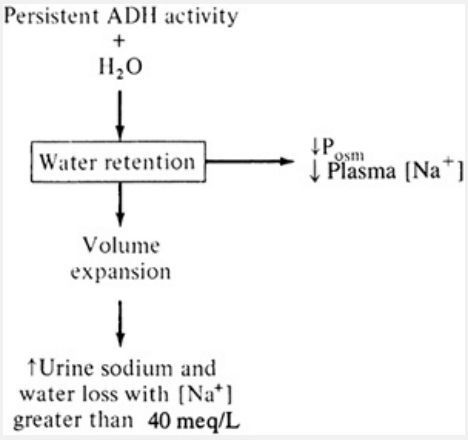

Figure 23-3 Pathophysiology of hyponatremia in the syndrome of inappropri ADH secretion.

If the levels of ADH release and Na^+ and water intake remain relatively constant, new steady state will be reached within 1 to 2 weeks in which *Na^+ excretion is equal to intake* (resulting in a urine Na^+ concentration that is typically above 40 meq/L) the *plasma Na^+ concentration is reduced, due both to water retention and to loss*,[90,92]* and the *degree of hyponatremia is stable* as water intake and excretion are also equal.[93,94] A further reduction in the plasma Na^+ concentration will occur only if there is an increase in either the secretion of ADH or water intake.

The stabilization of the plasma Na^+ concentration in this setting is associated wit reduction in the urine osmolality that appears to reflect partial resistance c collecting tubules to ADH.[93,94] This escape from ADH-induced antidiuresis appe to be mediated by decreased expression of aquaporin-2, the ADH-sensitive channel in the collecting tubules;[97,98] the regulation of aquaporin-2 in this settin appears to be unrelated to plasma or tissue osmolality.[98]

It is important to emphasize that the ingestion of water is an essential step development of hyponatremia in SIADH. If water intake is restricted, water and Na^+ loss do not occur, and *there is no fall in the plasma Na^+ concentration*.[89,93]

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ADH secretion

Although it might be thought that ADH is secreted at random in SIADH, this only a minority of patients, as four distinct patterns of ADH release have be identified (Fig. 23-4).[20] Furthermore, no correlation can be made between these patterns and the underlying cause of SIADH.

1. Type A is characterized by erratic changes in ADH secretion that are independent of the P_{osm}. In this setting, ADH release is occurring randomly in response to volume stimuli, as all osmotic regulation appears to be lo
2. Type B represents a "reset osmostat," in which ADH secretion varies appropriately with the P_{osm} but the curve is shifted leftward (see "Reset Osmostat" below). In this situation, the plasma Na^+ concentration is relatively stable (usually between 125 and 130 meq/L), the urine can be appropria diluted after a water load, and progressive hyponatremia does not occu
3. Type C is characterized by normal ADH release when the P_{osm} is normal or elevated but an inability to reduce ADH secretion below a certain level water load. This defect reflects selective loss of the ability of hypoosm suppress ADH release.

4. Type D is the least common, being associated with normal ADH secretio increased sensitivity to ADH (as occurs, for example, with chlorpropami [75][76] and [77] or some other antidiuretic factor must be present in these patient [87]

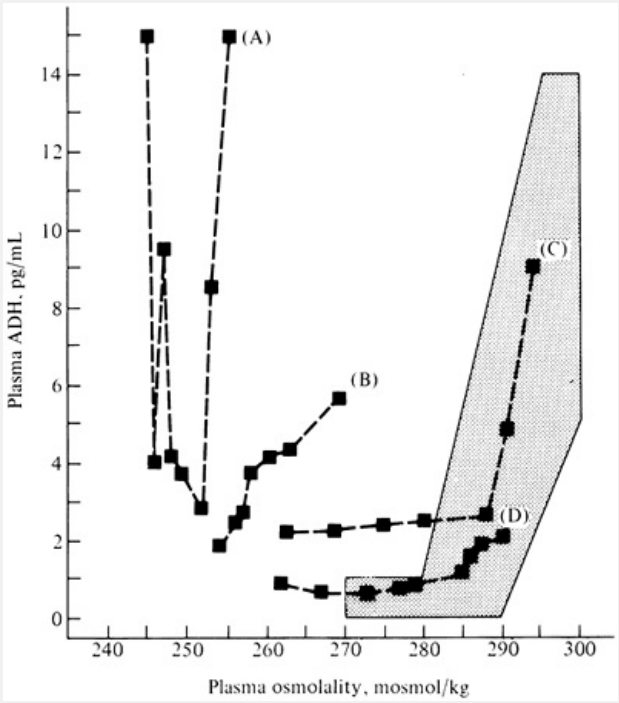

Figure 23-4 The relationship between plasma ADH levels and plasma osmol in patients with SIADH. The plasma osmolality is increased in these initia hypoosmolar patients by the administration of hyper-tonic saline. The sha area represents the normal range. (*From Robertson GL, Shelton RL, Athar S* Kidney Int *10:25, 1976. Reprinted by permission from* Kidney International.)

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Acid-base and K^+ balance

Although the retention of water lowers the plasma Na^+ concentration by dilution, it does not reduce either the plasma HCO_3^- concentration or, in most cases, the plasma K^+ concentration.[89] The maintenance of acid-base balance in the face o hypotonic volume expansion appears to be mediated both by the movement of H^+ ions into cells[99][100] and by increased renal excretion of H^+,[101] both of which prevent a dilutional fall in the plasma HCO_3^- concentration. To the degree that a dilutiona acidosis does at first occur, this effect will be minimized by the entry of ex H^+ ions into the cells, where they combine with the cell buffers.[99][100] The associated increase in urinary H^+ excretion[101] may reflect direct stimulation of distal H secretion by ADH.[102]

Dilutional hypokalemia is prevented in SIADH primarily by the movement of K^+ out of the cells. Some of this K^+ transport may reflect a transcellular cation exchange, since electroneutrality must be maintained as H^+ ions enter the cells to be buffered.[99] However, renal K^+ excretion may increase and mild hypokalemia may ensue if the P_{osm} falls below 240 mosmol/kg (plasma Na^+ concentration less than 115 meq/L).[101] A hyponatremia-induced elevation of aldosterone secretion may contribute to this process.[103,104]

Etiology

SIADH can be produced by enhanced hypothalamic secretion, ectopic (nonhypothalamic) hormone production, the potentiation of ADH effect, or the administration of exogenous ADH or oxytocin (Table 23-3). A variety of *neuropsychiatric disorders* can promote ADH release, either directly or by activation of cortical neurons that can stimulate the hypothalamus.[37,89,105] As examples, SIADH may occur in over 20 percent of patients with a subarachnoid hemorrhage[106] and in 20 to 35 percent of patients after transsphenoidal pituitary surgery [in which adrenal insufficiency due to impaired adrenocorticotropic hormone (ACTH) release may also contribute].[39,40] In psychotic patients, on the other hand, there is often a more complex derangement in water handling, as ADH release, the renal response to ADH, and water intake all may be increased.[37,107]

Hyponatremia is also seen in up to 40 percent of patients with human immunodeficiency virus infection.[38] Volume depletion and adrenal insufficiency are responsible in some cases, but most patients appear to have SIADH.[38,108] *Pneumocystis carinii* pneumonia, malignancy, and central nervous system disease all may play a role.

Although *drugs* can cause SIADH, most of the agents listed in Table 23-3 are only rarely associated with the development of hyponatremia.[109] There are, however, certain drugs that deserve emphasis. Particular care must be taken with cyclophosphamide, an alkylating agent that can increase the sensitivity to ADH and perhaps its release when given intravenously in high doses, but not when taken orally in low doses.[41,42] and[43] A high fluid intake is generally recommended in order to limit drug contact with the bladder and prevent the development of hemorrhagic cystitis. However, the combination of increased ADH effect and enhanced water intake can lead to *severe, occasionally fatal hyponatremia* within 24 h.[41,43] This complication can be minimized by using isotonic saline rather than water to maintain a high urine output.

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Chlorpropamide, an oral hypoglycemic agent that is now rarely used, is the most predictable cause of drug-induced SIADH. When used in diabetes mellitus, the plasma Na^+ concentration in roughly 4 to 6 percent of patients.[73,74] This problem is most likely to occur in patients over the age of 60 who are also

thiazide diuretic.[74] Some other hypoglycemic drugs, such as tolazamide and acetohexamide, have opposite effects, as they induce an *increase* in water excretion (by an unknown mechanism).[110]

Chlorpropamide appears to act primarily by potentiating the effect of ADH, enhancing its secretion.[75,76] and[77] How this occurs is incompletely understood. experimental animals, chlorpropamide directly increases NaCl reabsorption medullary thick ascending limb, an effect that would enhance medullary inte osmolality and therefore the ability of ADH to raise the U_{osm}.[76,77] It has also been proposed that chlorpropamide may act directly on the collecting tubule cells increasing water permeability via an effect that is independent of ADH; how might occur is not known.[111]

Although chlorpropamide increases the action of ADH, some circulating ADH present for this potentiation to occur.[77] As depicted in Fig. 23-1, some normal subjects maintain low basal levels of ADH (>2 pg/mL) despite the presence hypoosmolality; it is possible that it is these individuals who are most likely become hyponatremic with chlorpropamide.[73] The concurrent use of another drug that increases ADH secretion (such as a thiazide diuretic) will also increase of hyponatremia.[73,112]

Nonsteroidal anti-inflammatory drugs also can potentiate the effect of ADH. mediated by a reduction in renal prostaglandin synthesis, since prostaglandi normally antagonize the action of ADH (see page 172).[172] Despite this effect, spontaneous hyponatremia is a rare event, probably because ADH secretion reduced, either because of a direct effect of prostaglandin synthesis inhibi because of the initial fall in P_{osm}, some water is retained.[113] These agents may, however, exacerbate the tendency to hyponatremia in patients who are volu depleted or have SIADH.

Pulmonary diseases—particularly pneumonia but including acute asthma, atelectasis, empyema, pneumothorax, tuberculosis, and acute respiratory fa —can lead to SIADH.[58,59,60,61,62] and[63] The mechanism by which this occurs is uncertain, but a decrease in pulmonary venous return, leading to activation volume receptors, may be involved;[114] the finding of a low urine Na^+ concentration in some patients is compatible with this hypothesis.[59,115]

Pulmonary disease also may in some way increase central release of ADH. been best documented in tuberculosis, where many patients have a reset os pattern. Furthermore, ethanol has been shown to increase water excretion, presumably by inhibiting the hypothalamic secretion of ADH.[60,61]

In the patient who has undergone *major surgery*, inappropriate ADH secretion is common and persists for 2 to 5 days.[58,64] This response appears to be mediated b pain afferents that directly stimulate the hypothalamus.[65] An additional mechanism may also be operative in patients undergoing mitral commissurotomy to reli stenosis; in this setting, the acute reduction in left atrial

pressure may activate the atrial volume receptors and contribute to enhanc release.[116]

Ectopic tumor production of ADH has been reported with a variety of different neoplasms, particularly small cell (oat cell) carcinoma of the lung (Table 23-3). Direct evidence for tumor hormonal synthesis has come from the demonstration tha tumors contain and can synthesize both ADH and its carrier neurophysin, w derived from a common precursor.[69,70,71] and[72]

Oxytocin is a second hormone synthesized in the hypothalamus and released the neurohypophysis. Its primary effects are on uterine function and lactati oxytocin also possesses significantly antidiuretic activity. The use of intrav infusions of this hormone in dextrose and water to stimulate labor in pregna has resulted in water retention, severe hyponatremia, and seizures in both mother and the fetus.[84,85] and[86] This complication can be prevented by limiting amount of water given and using isotonic saline rather than dextrose and w Hyponatremia can also be induced by the administration of exogenous ADH control gastrointestinal bleeding or dDAVP for polyuria in central diabetes i or bleeding due to platelet dysfunction (see Chapter 24).[82,83]

Rarely, no cause for SIADH can be identified.[68] Although some of these patients have remained idiopathic for many years, careful and repeated monitoring f presence of an occult tumor (particularly pulmonary) is essential.[68,71] In addition, temporal arteritis should be considered in elderly patients with an otherwis unexplained elevation in the erythrocyte sedimentation rate.[117]

In summary, SIADH can be produced by a variety of disorders. It is characte the following features:[1] hyponatremia and hypoosmolality,[2] U_{osm} that is inappropriately high (greater than 100 mosmol/kg),[3] U_{Na} concentration greater than 40 meq/L, unless the patient is volume-depleted for some othe [4] normovolemia;[5] normal renal, adrenal, and thyroid function, and[6] normal acid-base and K^+ balance.

Another frequent, although not pathognomonic, finding is hypouricemia due enhanced urinary urate excretion.[118] The initial volume expansion induced by wat retention may reduce proximal Na^+ and urate reabsorption. In comparison, sodiun and urate reabsorption are enhanced and hyperuricemia is common in hypo patients who are effectively volume-depleted.

Cerebral Salt Wasting

Rarely, patients with cerebral disease (most often subarachnoid hemorrhag develop hyponatremia with all of the other associated findings of SIADH (in hypouricemia), except that they are volume-depleted and the high urine Na^+ concentration is due to urinary Na^+ wasting, not volume expansion.[119,120,121,122] and[123]

The etiology of this cerebral salt-wasting syndrome is incompletely underst possibility is the release of a hormone from the damaged brain that causes and urate wasting.[124] Brain natriuretic peptide may be such a hormone. One st prospectively evaluated 10 patients with aneurysmal subarachnoid

hemorrhage and compared them to 10 patients undergoing elective cranioto cerebral tumors and 40 controls.[123] The patients with subarachnoid hemorrhage h increases in the mean plasma concentration of brain natriuretic peptide. Th concentration of atrial natriuretic peptide was normal, while that of aldoste reduced in the patients with subarachnoid hemorrhage. The fall in aldoster have been mediated in part by the natriuretic peptides.

Adrenal Insufficiency

Hyponatremia is a common complication of adrenal insufficiency. Although v depletion due to diarrhea, vomiting, or renal loss (Na^+ and resulting from marked lack of aldosterone) may contribute to the fall in the plasma Na^+ concentration,[125] *cortisol deficiency* appears to play a major role, as cortisol replacement rapidly incre rate of water excretion and raises the plasma Na^+ concentration toward normal.[126],[127] and[128]

The deleterious effect of cortisol deficiency is largely related to increased ADH, as evidenced by the ability of an ADH antagonist to almost completely the defect in water excretion.[13] The hypersecretion of ADH in this setting is in p due to effective volume depletion, since the systemic blood pressure, cardi and ultimately renal blood flow are reduced by an unknown mechanism.[129] In addition, ADH is an important ACTH secretagogue that is cosecreted with corticotropin releasing hormone (CRH) by the cells in the paraventricular nucleus.[130],[131] and[132] Thus, cortisol feeds back negatively on both CRH and release, an inhibitory effect that is removed with cortisol insufficiency.[130],[133]

Hypothyroidism

Significant hyponatremia is an unusual complication of hypothyroidism. Why occurs is not well understood. The cardiac output and GFR are frequently r such patients,[134],[135] changes that can lead both to the release of ADH and to diminished delivery to the diluting segments.[134],[135],[136],[137] and[138] The latter may be particularly important in those patients in whom hyponatremia has led to appropriate suppression of ADH release.[137] Normal water balance can be restored by the administration of thyroid hormone.

Reset Osmostat

As described above, patients with a reset osmostat

have normal osmoreceptor responses to changes in the P_{osm}, but the threshold for ADH release (and usually thirst) is reduced (Fig. 23-4, pattern B).[20] As a result, the

plasma Na^+ concentration is below normal but stable (usually between 125 and 130 meq/L), since the ability to excrete water is maintained.

Patients with a reset osmostat fulfill all the criteria for SIADH, and the only the diagnosis is the presence of stable mild hyponatremia.[20] A reset osmostat has also been described in a number of particular settings. These include hypo states (in which the baroreceptor stimulus to ADH release is superimposed normal osmoreceptor function; see Fig. 6-10),[20] quadriplegia (in which effective volume depletion may be induced by venous pooling in the legs),[139] psychosis,[140] and chronic malnutrition.[141] In the last setting, defective cellular metabolism ma responsible for the abnormal osmoreceptor function. Correction of the unde problem and hyperaliminentation have been effective in returning the plasm Na^+ concentration toward normal.[141]

A reset osmostat is also present in almost all *pregnant women*, in whom the plasma Na^+ concentration falls by about 5 meq/L.[142,143] This change occurs within the firs 2 months of pregnancy and is then stable until delivery. Increased secretion human chronic gonadotropin (hCG) may play a central role in this response,[142,143] perhaps acting via the release of the ovarian hormone relaxin.[144]

It has been proposed that these hormonal changes may directly affect the osmoreceptor or may act directly by contributing to the systemic vasodilata pregnancy, thereby inducing relative volume depletion. Two observations in experimental animals and in women suggest a direct action on the osmorece[1] Persistent volume expansion during pregnancy does not raise the plasma Na^+ concentration, as would be expected if hypovolemia were involved;[2] and administration of hCG to normal women during the luteal phase of the mens cycle[145,146] or the chronic administration of relaxin to rats[144] can lower the plasma Na^+ concentration and reset the thresholds for ADH release and thirst desp maintenance of a high-Na^+ diet.

Primary Polydipsia

Patients with primary polydipsia have a primary increase in water intake an complain of polyuria or excessive thirst. This disorder is particularly preval psychosis, affecting as many as 7 percent of patients with schizophrenia.[37,147,148] Many of these patients have an exaggerated weight gain during the day (du transient retention of some of the excess water). In addition to the underlyi psychosis, the sensation of a dry mouth in patients taking phenothiazines m contribute to the increase in water intake.[149] Primarily polydipsia may also occur with hypothalamic disorders (such as sarcoidosis), in which the regulation may be directly affected.[150]

It is presumed that a *central defect in thirst regulation* plays an important role in the pathogenesis of polydipsia.[29,148] In some cases, for example, the osmotic thresh

for thirst is reduced *below* the threshold for the release of ADH.[151]

The plasma Na^+ concentration is usually normal or only slightly reduced in this disorder, since the excess water can be readily excreted.[147,152] In rare instances, however, water intake exceeds 10 to 15 L/day and overwhelms renal excretory capacity, resulting in potentially fatal hyponatremia.[147,148,149,153,154,155] and[156] One patient, for example, was able to lower her plasma Na^+ concentration to 84 meq/L, even though her GFR was normal and her urine was maximally (U_{osm} equal

to 74 mosmol/kg, specific gravity of 1.003).[153] Symptomatic hyponatremia can also be induced by an acute 3- to 4-liter water load in anxious patients, as has been rarely reported prior to a radiologic examination or urine drug testing.[157]

The tendency to hyponatremia in patients with primary polydipsia is increased if there is a concurrent impairment in water excretion. This combination can be seen in patients who are also taking a diuretic,[30,156] in psychotic patients, in whom the underlying cerebral dysfunction and, in selected cases, antipsychotic drugs (see Table 23–3) can lead to increased ADH release as well as enhanced water intake,[37,158] or with nausea- or stress-induced ADH secretion.[157]

Another interesting example of this phenomenon has been described in drinkers of beer in excessive amounts, in whom the ability to excrete water is reduced *not* by reduced *dietary intake*.[159] A normal subject may excrete 750 mosmol/day of solute, consisting mostly of NaCl, KCl, NH_4Cl, and urea (which is derived from the metabolism of proteins). If the minimum U_{osm} is 50 mosmol/kg, then the maximum daily urine volume will be 15 liters: 750 mosmol/day ÷ 50 mosmol/kg = 15 L. However, the daily solute load can fall to 250 mosmol or less in beer drinkers who may ingest only small amounts of K^+, Na^+, and protein. In this setting, the maximum urine volume is only 5 liters (250÷ 50=5 L/day), and hyponatremia will ensue if more than this amount of fluid (primarily as beer) is ingested.

Pseudohyponatremia

In some patients, a decrease in the plasma Na^+ concentration is associated with a normal or increased effective P_{osm} rather than with hypoosmolality. This has been called pseudohyponatremia (Table 23–4).[160] These disorders highlight the importance of measuring the P_{osm} in patients with hyponatremia, *since therapy should generally not be directed toward the fall in the plasma Na^+ concentration*

Hyponatremia with normal P_{osm}

A fall in the plasma Na^+ concentration without change in the P_{osm} can occur when there is a reduction in the fraction of plasma that is composed of the plasma

water; this is the classic form of pseudohyponatremia. Each liter of plasma

contains about 930 mL of water, with the plasma proteins and lipids occupy remaining 70 mL. However, the plasma water may fall to as low as 720 mL p plasma in states of severe hyperlipidemia (as in uncontrolled diabetes mell hyperproteinemia (as in multiple myeloma).[160,161] and[162] The P_{osm} will be unaffected in this setting, since the lipids exist in a separate phase and an osmometer measures only the activity of the plasma water. However, the plasma Na^+ concentration, *measured per liter of plasma, not of plasma water*, will be artifactually reduced to 110 meq/L (154 meq/L of plasma water × 0.72 liter o water per liter of plasma).

Table 23-4 Etiology of pseudohyponatremia

Low plasma Na^+ concentration with normal P_{osm}

A. Severe hyperlipidemia
B. Severe hyperproteinemia
C. Post-transurethral resection of prostate or bladder or ultrasonic lithotripsy

Low plasma Na^+ concentration with elevated P_{osm}

A. Hyperglycemia
B. Administration of hypertonic mannitol
C. Administration of intravenous immune globulin with maltose accumula in patients with renal failure

This form of pseudohyponatremia, which requires no therapy related to the hyponatremia, is easily diagnosed by the presence of lactescent serum (wit hyperlipidemia) and a normal P_{osm}. Use of an ion-selective electrode, rather than flame photometer, may confirm that the plasma water Na^+ concentration is normal. However, even this modality may not be accurate if the plasma or serum sp diluted, because a 1 : 100 dilution of the total plasma will produce more tha 100 dilution of the plasma water.[160] Suppose, for example, that the plasma water (with a Na^+ concentration of 150 meq/L) is 80 percent of the plasma; in this s each liter of plasma will have 120 meq of Na^+. If this is now diluted to a total volum of 100 liters, there will be only 120 meq of Na^+ present and, correcting for dilution, the true Na^+ concentration will appear to be 120 meq/L.

Isosmotic or slightly hypoosmotic reduction in the plasma Na^+ concentration also can occur in patients undergoing transurethral resection of the prostate or blad These procedures may be associated with the use of as much as 20 to 30 li

nonconductive flushing solutions containing glycine, sorbitol, or mannitol[163,164] [165] Variable quantities of this fluid are absorbed, both by entry into damage vessels and by leakage into the retroperitoneal space. Some patients absor or more, leading to a dilutional reduction in the plasma Na^+ concentration, which may fall below 100 meq/L. A similar problem can occur with the use of glyci containing irrigation solutions during hysteroscopic surgery in women.[166,167]

The incidence of hyponatremia following transurethral resection has been r to be approximately 7 percent.[168] Risk factors include prolonged surgery, large tissue resection, and excess height of the reservoir of the irrigant solution, therefore introduced under high pressure.[163,164]

The degree of hyponatremia is related to both the quantity of fluid absorbe rate of absorption. Severe hyponatremia generally requires a rate of fluid a in excess of 200 mL/10 min. The fall in the plasma sodium concentration is when the fluid is first absorbed and is limited to the extracellular

space. Within a few minutes, however, the plasma sodium concentration beg rise even before the fluid is excreted, probably because of glycine and wat into the cells.[166] At 2 to 4 h, glycine is almost equally distributed between the extracellular and intracellular compartments. At this time, glycine is acting ineffective osmole, raising the plasma osmolality (similar to the effect of ur failure) without affecting water distribution between the fluid compartments.[166] Thus, degree of hyponatremia represents true hyponatremia even though the plas osmolality is usually near normal.

The plasma osmolality in these patients is variable.[166] The mannitol solution is isosmotic, whereas both the glycine and sorbitol solutions have an osmolal between 165 and 200 mosmol/kg.[164] Thus, the initial plasma osmolality will be normal or only modestly reduced.[163,164] and[165] However, both glycine and sorbitc are rapidly metabolized and also may be excreted in the urine, leaving free behind. As a result, there will be a tendency for the plasma osmolality to fa the rate of excretion of the excess fluid is at least equal to the rate of solu metabolism and excretion.

Confusion, disorientation, twitching, seizures, and hypotension all may be s these patients, although why these symptoms occur is not clear. The very l plasma sodium concentration itself, the varying degree of hypoosmolality, g toxicity, and the accumulation of ammonia (from the metabolism of glycine) contribute in individual patients.[163,164] and[165,169] Experimental studies suggest that hypoosmolality may not be of primary importance, since the outcome is improved by preventing the fall in plasma osmolality with mannitol.[170]

The diagnosis of this disorder is strongly suggested from the clinical histor be confirmed early in the course by documenting the presence of an osmola which is the difference between the plasma osmolality measured in the labo and the plasma osmolality calculated from the following formula (see page 247)

$$\text{Calculated } P_{osm} = 2 \times \text{plasma Na} + \frac{[\text{glucose}]}{18} + \frac{\text{BUN}}{2.8}$$

There is little if any osmolal gap in normal subjects, as there is usually a c correlation between the measured and calculated values. In comparison, th gap can exceed 30 to 60 mosmol/kg following transurethral resection as a r the accumulation of glycine, sorbitol, or mannitol.[164,165] The osmolal gap is also increased when there is a disparity between the P_{osm} and the plasma Na^+ concentration with hyperlipidemia, hyperproteinemia, or the administration mannitol (see below). Other drugs, such as ethanol, methanol, and ethylene also can achieve significant osmolal concentrations in the blood, resulting osmolal gap (see page 607). However, these alcohols are ineffective osmoles (l urea) and do not affect water distribution or the plasma Na^+ concentration.[171]

Optimal therapy of *symptomatic* hyponatremia following transurethral resection o hysteroscopy is unclear. Hypertonic saline can be given if the

plasma osmolality is reduced, but it has an uncertain role when the plasma is in the normal range.[163] The benefits of raising the plasma Na^+ concentration in this setting may be counterbalanced by a rise in the plasma osmolality abo Hemodialysis has been used in patients with end-stage renal disease who h other means to excrete the excess solute and water.[165] In comparison, no specific therapy is necessary in the absence of symptoms. Renal excretion of the ex and metabolism and excretion of the excess solute will rapidly correct the hyponatremia as long as renal function is near normal.

Hyponatremia with increased P_{osm}

If a solute that penetrates cells poorly, such as glucose, is added to the ex fluid, the P_{osm} will rise. This will create a transcellular osmotic gradient, res water movement out of the cells and a reduction in the plasma Na^+ concentration by dilution (see Fig. 22-4). Conversely, as insulin therapy drives glucose into the water will follow, and the plasma Na^+ concentration will rise.

Physiologic calculations suggest that the plasma sodium concentration sho 1 meq/L for every 62-mg/dL (3.5-mmol/L) rise in the plasma concentration o or mannitol (which have the same molecular weight).[172] However, this standard correction factor was not verified experimentally. In an attempt to address t hyperglycemia was induced in six healthy subjects by the administration of somatostatin (to block endogenous insulin secretion) and a hypertonic dext solution.[173] A nonlinear relationship was observed between the changes in th glucose and sodium concentrations. The 1 : 62 ratio applied when the plasr glucose concentration was less than 400 mg/dL. At higher glucose concentr there was greater reduction in the plasma sodium concentration. An overall : 42 (a 2.4-meq/L reduction in the plasma sodium concentration for every 1(elevation in the plasma glucose) provided a better estimate of this associat the usual 1 : 62 ratio.

Two other causes of hyponatremia with an increased P_{osm} are the administration of hypertonic mannitol and of intravenous immune globulin.[174,175] Although measurement of the plasma mannitol concentration is not available in most laboratories, the presence of significant amounts of mannitol in the blood c estimated from calculation of the osmolal gap. Intravenous immune globulin given in a 10 percent maltose solution. Maltose is normally metabolized by the proximal tubule. In patients with renal failure, however, maltose can ac in the extracellular fluid, raising the plasma osmolality and lowering the pla sodium concentration by dilution.[175]

Hyponatremia and azotemia

Patients with renal failure have a high P_{osm} as a result of the increase in the BUN. However, urea is an ineffective osmole, and the effective P_{osm} ($2 \times$ plasma $[Na^+]+[glucose]/18$) is generally normal or reduced. As an example, consider a patient with the following plasma values:

$$\text{Plasma } [Na^+] = 115 \text{ meq/L}$$
$$[\text{Glucose}] = 90 \text{ mg/dL}$$
$$\text{BUN} = 140 \text{ mg/dL}$$
$$P_{osm} = 285 \text{ mosmol/kg}$$

Despite the normal P_{osm}, the effective P_{osm} is markedly reduced at 235 mosmol/kg Thus, this patient has true hyponatremia, not pseudohyponatremia, and may symptomatic.

SYMPTOMS

The symptoms directly attributable to true hyponatremia primarily reflect *neurologic dysfunction induced by hypoosmolality*.[176,177] and[178] As the P_{osm} falls, an osmolal gradient is created across the blood-brain barrier, resulting in wate movement into the brain (as well as into other cells). The degree of cerebra overhydration appears to correlate with the severity of symptoms. As depict Fig. 23-5, a rapid reduction in the plasma Na^+ concentration to 119 meq/L in rabbits produces a marked increase in brain water content, severe symptoms, and comparison, a similar degree of slowly developing hyponatremia results in a degree of cerebral edema and a lesser likelihood of neurologic symptoms.[176,178,179]

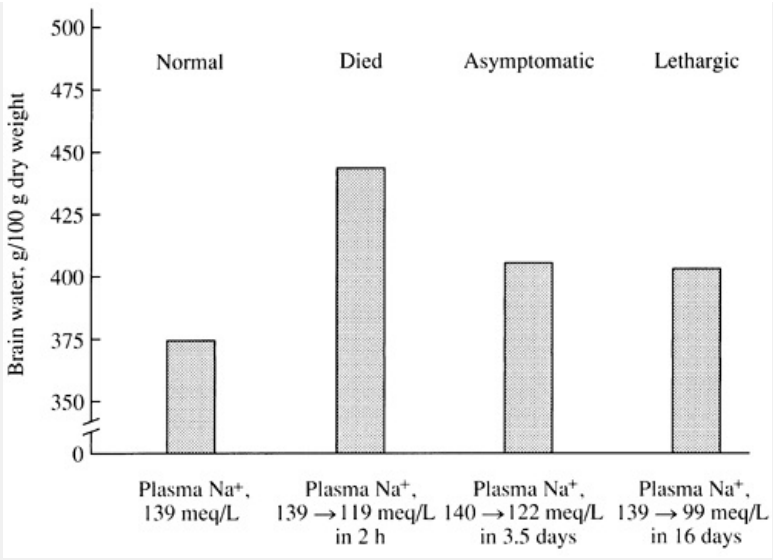

Figure 23-5 Brain water content in normal and three groups of hyponatremi rabbits. When the plasma Na^+ concentration is acutely lowered to 119 meq/L ir h, brain water content increases to 17 percent above normal and is assoc with severe symptoms and death. In contrast, slowly lowering the plasma Na^+ concentration to the same level over 31 over 2 days results in a smaller e in brain water (7 percent) and no symptoms. Finally, gradually reducing th plasma Na^+ concentration to extremely low levels (99 meq/L) produces a sn increment in brain water and only mild neurologic symptoms. (*From Arieff AI, Llach F, Massry SG: Medicine 55:121, 1976, with permission*)

The mechanism of osmotic water movement into the brain has been partially elucidated by studies in mice without the genes for aquaporin-4, a water ch expressed at the interface between the brain and blood, and between the b cerebrospinal fluid.[180] Compared with wild-type mice, knockout mice exhibit considerably less brain edema, morbidity, and mortality after the induction hyponatremia, suggesting that aquaporin-4 mediates a substantial portion c water transport into the brain.

Osmotic Adaptation

The adaptation to hyponatremia depicted in Fig. 23-5 involves two steps. First, the initial cerebral edema elevates the hydrostatic pressure in the cerebral inte fluid. This creates a favorable gradient for fluid movement from the cerebra interstitium into the cerebrospinal fluid, thereby decreasing the amount of c swelling.[178,181]

Second, solutes move out of the cells, since a net decrease in cell osmolal promotes osmotic water loss, thereby diminishing cell swelling and[178,182,183,184] The initial cellular adaptation consists of the loss of K^+ and Na^+, processes that occur quickly via the activation of quiescent channels in the cell membrane.[178] These

is followed over a period of hours to days by the loss of organic solutes su myoinositol and the amino acids glutamine, glutamate, and taurine.[182,183,184] A report in humans using proton nuclear magnetic resonance (NMR) spectrc found a somewhat different pattern, with myoinositol and choline compound the primary organic solutes lost.[185] (Myoinositol appears to be the primary osmol *taken up* by the brain as part of the protective response in patients with hypernatremia.)

As shown in Fig. 23-6, these solutes (called *osmolytes*) account for approximately one-third of the cell solute loss in chronic hyponatremia.[182,183,184] Furthermore, the degree of osmolyte loss is directly related to the severity of the hyponaterr Although there is a quantitatively greater loss of cation than of osmolyte, tl percentage loss of these solutes is very different: less than 10 percent for Na^+ versus approximately 60 percent for the osmolytes. This observation su specific function for the osmolytes. In addition to maintaining cell volume, (have the advantage of *not interfering* with protein function, in contrast to the potentially deleterious effects of large changes in the cellular Na^+ plus K^+ concentration.[186] Thus, osmolyte loss is a specific response of the cell that o more slowly than cation loss because the synthesis of new transporters is required.[178] (Similar changes, although in the opposite direction, occur in hypernatremia; see Chap. 24.)

The net effect of the osmotic adaptation is that the severity of neurologic s is related to the *rapidity as well as the degree of the reduction in the plasma* Na^+ *concentration*.[177,187,188] and [189] The changes induced by acute hyponatremia (developing over 1 to 3 days) may result in permanent neurologic damage a primarily due to cerebral overhydration. This problem is most likely to occu

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postoperative patients given large quantities of hypotonic fluid or those wit thiazide-induced hyponatremia.[27,177,190,191]

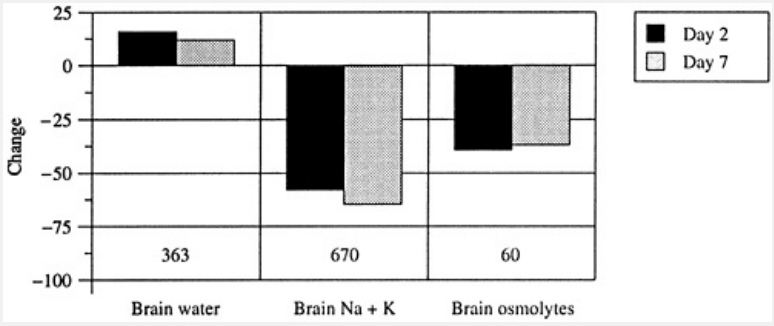

Figure 23-6 Changes in brain water, sodium plus potassium content, and th organic solutes—inositol, glutamine, and taurine—after onset of severe hyponatremia in rats (plasma sodium concentration less than 110 meq/L).

numbers at the bottom represent the baseline values. The return of brain toward normal at day 7 is due to loss of sodium, potassium, and the organ solutes (called osmolytes). Although the absolute osmolyte loss is less th of sodium plus potassium, the fractional loss is much greater—36 or 60, c percent, versus 60 or 670, or less than 10 percent. (*Data from Verbalis JG, Gullans SR: Brain Res 567:274, 1991, with permission.*)

In comparison, symptoms are unusual in chronic hyponatremia unless there marked reduction in the plasma Na^+ concentration. The findings in this setting appear to be mediated by the low plasma Na^+ concentration (rather than by cerebra edema), perhaps reflecting the importance of adequate Na^+ in neural function. This is illustrated in the far right panel in Fig. 23-5 and may also account for some of the neurologic findings in glycine-induced hyponatremia.[163]

Neurologic Abnormalities

The neurologic symptoms induced by hyponatremia are similar to those in o metabolic encephalopathies.[27,176,177,187] In general, the patient begins to complain of nausea and malaise as the plasma Na^+ concentration falls acutely belov 125 meq/L. Between 115 and 120 meq/L, headache, lethargy, and obtundati appear, although many patients with chronic hyponatremia will have few if a symptoms. The more severe changes of seizures and coma are not usually s the plasma Na^+ concentration is less than 110 to 115 meq/L.[27,177,184,185] Focal neurologic findings are uncommon but may occur in patients with an underl defect such as an old cerebral infarct.[193]

There is substantial interpatient variability in the susceptibility to symptom acute hyponatremia. For reasons that may be related to differences in cere metabolism,[194] *women, particularly premenopausal women*, appear to be at much greater risk of developing severe neurologic symptoms and of irreversible r damage than men.[190] The possibility that sex hormones are an important determinant of risk is also supported by the absence of a gender difference risk of symptomatic hyponatremia in prepubertal children.[195]

Acute, symptomatic hyponatremia can lead to permanent neurologic deficits death.[27,177,190] In one series, for example, 15 previously healthy young wom with postoperative SIADH were given an excessive quantity of intravenous The net result was a reduction in the plasma Na^+ concentration from 138 to 108 meq/L over a 48-h period; 4 of the women died, and the remainder had perm neurologic deficits (Fig. 23-7).[177] A more recent study suggests that the majority premenopausal women who develop symptomatic hyponatremia do not fully thus, prevention is of primary importance.[190] In comparison, the symptoms are mor often reversible in men.

There is an additional mechanism that may cause neurologic symptoms in tl with hyponatremia: *overly rapid elevation* of the plasma Na^+ concentration. This issue will be discussed below, in the section on treatment.

When volume depletion is present, patients may also complain of the sympt hypovolemia, such as weakness, fatigue, muscle cramps, and postural dizzi Chap. 14). In contrast, signs of extracellular volume expansion such as edem not seen in patients with water retention due to SIADH or primary polydipsi roughly two-thirds of the retained water is stored in the cells and persisten hypervolemia is prevented by increased Na^+ and water excretion, as long as Na^+ handling is intact.[89,90,92]

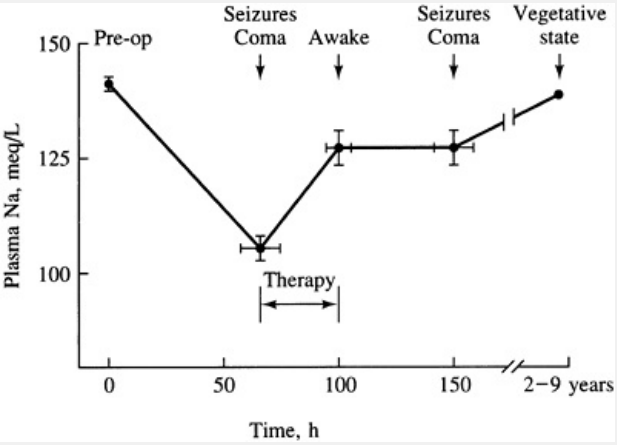

Figure 23-7 Clinical course in 7 women with acute, severe post-operative hyponatremia and sei-zures and coma. All of the women initially awoke wh plasma Na^+ concentration was raised from 105 to 131 meq/L in 41 h. After a further 58 h, seizures and recurrent coma developed despite maintenance plasma Na^+ concentration above 128 meq/L. (*From Arieff AI, New Engl J Med 314:1529, 1986. Reprinted by permission from* The New England Journal of Medicine.)

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DIAGNOSIS

As with other electrolyte and acid-base disturbances, the history (possibly diarrhea, diuretic therapy, or one of the causes of SIADH) and physical exa (perhaps findings of true volume depletion or edema) can provide important the correct diagnosis. In addition, the initial laboratory evaluation should in measurement of the P_{osm}; the plasma concentrations of Na^+, K^+, Cl^-, HCO_3^-, urea, and glucose; the urine Na^+ concentration and osmolality; and, if the HCO_3^- concentration is abnormal, the extracellular pH. Tables 23-5 and 23-6 illustrate how these tests can be used to identify the cause of the hyponatremia.

Plasma Osmolality

The first step in the approach to the patient with hyponatremia is to confirm presence of hypoosmolality (Table 23-5). If the effective P_{osm} (measured P_{osm} minus BUN/2.8) is normal or elevated, evaluation for one of the causes of pseudohyponatremia should be carried out.

Urine Osmolality

Once it is demonstrated that the patient is hypoosmolal, measurement of th U_{osm} can be used to determine whether water excretion is normal or impaired. A U_{osm} below 100 mosmol/kg (specific gravity ≤ 1.003) indicates that ADH secretio almost completely and appropriately suppressed, a finding seen with either polydipsia or a reset osmostat (if water intake has reduced the P_{osm} to the new threshold for ADH release). These disorders can be distinguished by the *response to water restriction*. The urine will remain dilute until the plasma

Na^+ concentration is normal in primary polydipsia (< 155 mM). In contrast, the U_{osm} will rise progressively with a reset osmostat, since a small elevation in the plasma Na^+ concentration will stimulate the release of ADH. By using these criteria, ma psychotic patients initially thought to have primarily polydipsia were shown reset osmostat.[140]

Table 23-5 Major steps in the initial evaluation of hyponatremia

Plasma osmolality

A. Low: true hyponatremia
B. Normal or elevated: pseudohyponatremia or renal failure

Urine osmolality

A. Less than 100 mosmol/kg: primary polydipsia or reset osmostat
B. Greater than 100 mosmol/kg: other causes of true hyponatremia in w water excretion is impaired

Urine sodium concentration

A. Less than 25 meq/L: effective circulating volume depletion (including heart failure and hepatic cirrhosis), by dilution in primary polydipsia the urine output is very high
B. Greater than 40 meq/L: SIADH, renal failure, reset osmostat, diuretic (when drug still acting), adrenal insufficiency, some patients with vomiting (in whom there is obligatory loss of $NaHCO_3$ in the urine; see page 565), osmotic diuretics (with pseudohyponatremia due to glucose or mannitol)

Table 23-6 Acid-base and potassium disturbances hyponatremia

Metabolic acidosis	Normal pH	Metabolic alkalosis
Plasma K^+ concentration may be normal or elevated	Plasma K^+ concentration usually normal	Plasma K^+ concentration may be normal or reduced
Renal failure	SIADH	Vomiting
Adrenal insufficiency	Primary polydipsia (maysee hypokalemia) Edematous states (no diuretics) Pure cortisol deficiency	Nasogastric suction Diuretics
Plasma K^+ concentration may be normal or reduced Diarrhea or drainage of intestinal secretions	Hypothyroidism	

In the vast majority of hyponatremic patients, however, water excretion is i
and the U_{osm} exceeds 100 mosmol/kg. It is important to emphasize that a U_{osm}
100 to 200 mosmol/kg may be hypoosmotic to plasma but is still inappropria
This can be illustrated by a simple example. Raising the U_{osm} from a maximally
dilute level of 60 mosmol/kg up to 180 mosmol/kg requires the removal of tv
of the water. Thus, a patient with a dilute U_{osm} of 180 mosmol/kg will be able to
excrete only one-third the normal amount of free water and, therefore, will
more likely to develop hyponatremia.

Urine Sodium Concentration

The differential diagnosis of hyponatremia, hypoosmolality, and an inappro
high U_{osm} usually narrows down to effective circulating volume depletion, SI
adrenal insufficiency, and rarely hypothyroidism. In addition to assessment
and thyroid function, the urine Na^+ concentration is usually helpful in differentiat
among these disorders (Table 23-5). The urine Na^+ concentration should be less

than 25 meq/L in hypovolemic states, but greater than 40 meq/L in SIADH (v Na^+ excretion is equal to intake), with a reset osmostat, wasting Na^+ conditions such as diuretic therapy, renal disease, and adrenal insufficienc inappropriate Na^+ losses in the last disorder are due to hypoaldosteronism. In contrast, renal Na^+ handling is normal in pure cortisol

deficiency (as seen in hypopituitarism), and the urine Na^+ concentration may be below 25 meq/L.[128]

In those patients in whom the findings are equivocal, the response of the U_{osm} and urine Na^+ concentration to the administration of NaCl can be used to establis correct diagnosis. This can be illustrated by the following case history:

Case history 23-1

A 49-year-old man with small cell carcinoma of the lung develops severe vo after the institution of chemotherapy. On admission, the estimated jugular v pressure is below 5 cm H_2O, the skin turgor is reduced, and the following labora tests are obtained:

$$\text{Plasma } [Na^+] = 114 \text{ meq/L}$$
$$P_{osm} = 243 \text{ mosmol/kg}$$
$$\text{Urine } [Na^+] = 6 \text{ meq/L}$$
$$U_{osm} = 498 \text{ mosmol/kg}$$

The clinical and laboratory findings are consistent with true volume depleti also possible, however, that the patient has underlying SIADH due to his m The patient is initially treated with isotonic NaCl, and the next morning the Na^+ concentration has increased to 122 meq/L. At this time, the urine Na concentration and osmolality can be used to distinguish among three possib

1. Hypovolemic alone was responsible for the hyponatremia, and the patie volume-depleted. As a result, the urine Na^+ concentration will still be low and the U_{osm} still elevated because of the nonosmotic release of ADH.
2. Hypovolemia alone was responsible for the hyponatremia, and the patie euvolemic. In this setting, the U_{osm} will be below 100 mosmol/kg, since there no longer any stimulus to ADH secretion. Urinary Na^+ excretion will be elevated, but the urine Na^+ concentration may, by dilution, still be less than 25 meq/
3. Both hypovolemia and SIADH contributed to the hyponatremia, and the p now euvolemic. This will be manifested by a urine Na^+ concentration above 40 meq/L and a persistently elevated U_{osm} since there is continued ADH release

Extracellular pH and Potassium Concentration

Abnormalities in acid-base and K^+ homeostasis are occasionally associated with

hyponatremic disorders, and their presence can be helpful in establishing t diagnosis (Table 23-6). For example, the presence of metabolic alkalosis and hypokalemia should lead one to suspect vomiting or diuretic therapy, where hyperkalemia and metabolic acidosis in a patient with relatively normal ren is highly suggestive of adrenal insufficiency.

Hypokalemia may also occur in patients with primary polydipsia by a mecha is directly related to the high urine output (>140 L/day). In the presence of K^+ depletion, normal subjects can lower the urine K^+ concentration to a minimum of 5 to 15 meq/L.[197] If, however, the urine output is 10 L/day or more, then there will b *obligatory* K^+ loss that can exceed 50 to 100 meq and promote the developme hypokalemia.

TREATMENT

There are two basic principles involved in the treatment of hyponatremia: r plasma Na^+ concentration at a safe rate and treating the underlying cause (s giving cortisol in adrenal insufficiency). In general, hyponatremia is correct by giving Na^+ to patients who are volume-depleted and by restricting water in patients who are normovolemic or edematous (Table 23-7). However, more vigorous therapy (usually requiring hypertonic saline) is indicated when symptoms a or the plasma Na^+ concentration is less than 110 meq/L, since these are the s in which irreversible neurologic damage and death can occur. Although the of acute, severe hyponatremia are (Fig. 23-7), attention must also be paid to the rate of correction, particularly in asymptomatic patients.

Sodium Deficit

The amount of Na^+ required to raise the plasma Na^+ concentration to a desired value can be estimated from the following formula:

$$Na^+ \text{ deficit} = \text{volume of distribution of plasma } [Na^+] \times Na^+ \text{ deficit per liter} \quad (23\text{-}2)$$

Although Na^+ itself is restricted to the extracellular fluid, changes in the plas concentration reflect changes in osmolality and are distributed through the water (see Fig. 22-1). The total body water is approximately 60 and 50 percent *lean* body weight in men and women, respectively. The (Eq. 23-2) the approximate amount of Na^+ (in milliequivalents) required to

raise the plasma Na^+ concentration to a safe level of 120 meq/L in women is rc equal to:

Table 23-7 Basic therapeutic regimen in the different causes of hyponatremia

NaCl	H_2O restriction
True volume depletion	SIADH
Diuretics	Edematous states
Adrenal insufficiency	Renal failure
	Primary polydipsia

$$Na^+ \text{ deficit} = 0.5 \times \text{lean body weight (kg)} \times (120 - \text{plasma } [Na^+]) \qquad (23\text{-}3)$$

Suppose a 60-kg woman is started on a thiazide diuretic and 5 days later p with lethargy, confusion, decreased skin turgor, and a plasma Na^+ concentration of 108 meq/L. The amount of Na^+ required to raise the plasma Na^+ concentration to 120 meq/L is approximately 360 meq:

$$\begin{aligned} Na^+ \text{ deficit} &= 0.5 \times 60 \times (120 - 108) \\ &= 360 \text{ meq} \end{aligned} \qquad (23\text{-}4)$$

Since 3 percent saline contains 513 meq of Na^+ per liter, 700 mL of this solution wi provide the required Na^+. The plasma Na^+ concentration will increase by one of tw mechanisms: retention of the Na^+ in patients who are hypovolemic, or initial retention of the Na^+ followed by the excretion of water in SIADH. In the latter disorder, volume regulation is intact, and the administered Na^+ will be excreted in the urine as a result of the associated volume expansion. It is the water los by excretion of the extra sodium that is responsible for the steady state ele the plasma sodium concentration (see below).

Three issues related to Eq. 23-3 deserve emphasis:

1. It applies only to the administration of Na^+ without or in marked excess of wate (i.e., hypertonic but not isotonic saline). Isotonic saline will, however, correct hyponatremia due to true volume depletion. In this setting, resto normovolemia will eliminate the hypovolemic stimulus to ADH release, th allowing the excess water to be excreted in a maximally dilute urine (see "True Volume Depletion," below).
2. It is only an estimate, and serial measurements of the plasma Na^+ concentration (beginning at 2 to 3 h are necessary to assess the efficiency of treatme
3. It does not include any isosmotic losses that may also be present. For e a patient with diarrhea may lose 5 liters of isosmotic fluid and then bec hyponatremic by drinking and retaining 3 liters of water. Equation 23-3 estimates the amount of Na^+ required to counteract the dilutional effect of th liters of free water; a 2-liter isosmotic Na^+ and water deficit will still remain.

The adequacy of *volume* repletion can be determined by following the skin turg jugular venous pressure, and urine Na^+ concentration. If, for example, this woman had an initial urine Na^+ concentration of 2 meq/L, and, after the administration 400 meq of NaCl, the urine Na^+ concentration were only 7 meq/L, then hypovoler persists and further replacement therapy is indicated. A urine Na^+ concentration above 40 meq/L usually indicates that normovolemia has been restored.

Rate of Correction

Despite the dangers of acute, severe hyponatremia, experimental and clinic suggest that overly rapid correction may also be harmful, leading within on several days to central demyelinating lesions, particularly in the pons (a di called central pontine myelinolysis or osmotic demyelination).[179,188,191,192,198,199,200,201,202,203,204] and [205] This severe neurologic disorder is characterized by paraparesis or quadriparesis, dysar dysphagia, and coma; seizures also may occur but are less common.[199,202,204,205] It may, for example, have contributed to the late deterioration in mental function in the women depicted in Fig. 23-7.

The diagnosis of osmotic demyelination is generally suspected from the clir findings and can usually be confirmed by computed tomography (CT) scann more accurately, by magnetic resonance imaging.[204,206] These lesions, however, may not be detectable radiologically for as long as 4 weeks; thus, an initial negative study in a patient who develops neurologic symptoms *after* the treatment of hyponatremia does not exclude the presence of osmotic demyelination.[199,206]

The mechanism by which rapid elevation in the plasma Na^+ concentration induces demyelinating lesions is unclear. The risk is greatest in patients with sever hyponatremia, a setting in which the cerebral adaptation has returned brair toward normal. In this setting, an acute elevation in the plasma Na^+ concentration may lead to osmotic shrinkage of axons, severing their connections with the surrounding myelin sheaths.[199] Brain cells adapted to hyponatremia may be at particular risk, since they have inserted transporters to lose osmolytes; the therefore be less able to switch to taking up these organic solutes.[178]

The net effect is that the adaptive loss of solutes from the cells *minimizes the early symptoms and creates a problem for therapy*. Rapid correction can now lead to cerebral dehydration and demyelination, changes that are not seen if chron asymptomatic hyponatremia is not corrected.[179,200] The risk of posttherapy osmotic demyelination is much less in patients with acute hyponatremia (developing 3 days) who still have cerebral edema.[179,188,208]

Although the incidence of osmotic demyelination is probably low,[203,209,210] those patients who develop this disorder generally have one or more of the follow factors:[1] more than a 12-meq/L elevation in the plasma Na^+ concentration in the

first day,[2] overcorrection of the plasma Na^+ concentration to above 140 meq/L within the first 2 days,[3] hypoxic or anoxic episodes prior to therapy.[188,200,201,202,203,204 and 205] Hypercatabolism or malnutrition due to burns or chronic alcoholism also appears to predispose to osmotic demyelin[207]

A definitive recommendation for the treatment of severe hyponatremia cann made with certainty. Experimental and clinical observations suggest that th *of correction over the first 24 h* (less than 10 to 12 meq/L being safest) is much more important than the rate over a given hour or period of

hours.[204,205,211,212] It therefore seems advisable to raise the plasma Na^+ concentration in *asymptomatic* patients by *less than 10 to 12 meq/L on the first da and less than 18 meq/L over the first 2 days*.[203,204,205] Even at this "safe" rate, however, an occasional patient will develop neurologic symptoms.[202,204] It is probably wise therefore to correct the hyponatremia at less than the maxim (less than 10 meq/day) in asymptomatic patients.

An exception to the above recommendation occurs in patients who already h seizures or other severe neurologic symptoms directly induced by the low p Na^+ concentration. In this setting, the risk of untreated hyponatremia and c edema is greater than the potential harm of overly rapid correction; as a re hypertonic saline should be given to raise the plasma Na^+ concentration more quickly (1.5 to 2 meq/L/h for 3 to 4 h or until the severe neurologic symptor abated).[188,191] Even with this initial rapid rate of correction, the elevation ir plasma Na^+ concentration should not exceed 10 to 12 meq in the first 24 h, s partial osmotic adaptation will already have occurred.[188,199,205] As noted previously, young women with symptomatic hyponatremia are at high risk fo irreversible symptoms, independent of the type of therapy given.[190]

As an example, the woman in the case described above requires initial ther approximately 700 mL of hypertonic saline to raise her plasma Na^+ concentration from 108 to 120 meq/L. Administration of this fluid over 24 h at a rate of 30 should achieve the desired goal: correcting the hyponatremia at a rate of 1 the first day. However, the initial infusion rate may be increased to 50 to 75 the first 3 to 4 h, since the patient does have mild neurologic symptoms. Ca monitoring is required during this period, however, since the calculations in Eqs. 23-3 and 23-4 are based on only a rough estimate of the total body water.[200]

Although rapid correction generally results from the administration of hyper saline, there are *two settings in which this problem can occur with water restr alone* primary polydipsia and volume depletion after euvolemia has been re each of these conditions, ADH release is appropriately suppressed by the hyponatremia, thereby allowing the excess water to be rapidly excreted in a urine.[213]

An unresolved and fortunately infrequent issue is the potential benefit of

administering water to lower the plasma Na^+ concentration in patients with severe hyponatremia who have been corrected too rapidly. One study in rats addre problem. A marked reduction in the incidence and severity of brain lesions if overly rapid correction (25 meq/L or more over several hours) was partial reversed after 12 h, so that the net daily elevation in the plasma sodium concentration was less than 20 meq/L.[212] This benefit was seen only if therapy wa begun before the onset of neurologic symptoms; improvement was much les animals with symptomatic demyelination.

The same authors described one patient with severe thiazide-induced hypo whose neurologic status deteriorated after the plasma Na^+ concentration had been increased from 106 to 127 meq/L in the first 24 h.[214] The plasma Na^+ concentration was then lowered by 16 meq/L over the ensuing 14 h by the administration

of dDAVP and hypotonic fluids. This maneuver was well tolerated, and the p Na^+ concentration was then gradually normalized, with complete neurologic More data are needed before this approach can be recommended.

True Volume Depletion

True volume depletion due to gastrointestinal or renal losses represents th indication for the use of NaCl in the treatment of hyponatremia. Isotonic sa oral NaCl and water can be used in patients with asymptomatic or mild redu the plasma Na^+ concentration. This regimen will correct the hyponatremia in t stages:

1. The plasma Na^+ concentration will initially rise slowly, since the administe fluid has a higher Na^+ concentration than the plasma. If, for example, the p Na^+ concentration is 114 meq/L (40 meq/L less than that in isotonic sali the total body water is 40 kg, then each liter of saline will supply 40 me Na^+, which will effectively be distributed through 40 L. The net result is *elevation in the plasma Na^+ concentration of only 1 meq/L*
2. Once the hypovolemia is corrected, ADH release will be suppressed, lea the production of a maximally dilute urine, rapid excretion of the excess and correction of the hyponatremia. Careful monitoring is required at th prevent overly rapid correction and possible osmotic demyelination.[213]

Hypertonic saline should be given only for symptomatic reductions in the pl Na^+ concentration. There is, however, little rationale for the administration of d solutions, such as half-isotonic saline. Although this solution will correct th deficit, it will also initially exacerbate the hyponatremia.

Effect of potassium

Correction of K^+ depletion, if present, is another important component of thera

The administration of K^+ in this setting will directly increase the P_{osm} and raise the plasma Na^+ concentration (unless given in an isosmotic solution [24,25,36]). The exogenous K^+ will primarily enter the cells, which contain 98 percent of the b In this setting, electroneutrality will be maintained in one of three ways, ea which will act to correct the hyponatremia:

1. Intracellular Na^+ will leave the cells, directly increasing the plasma Na^+ concentration.
2. Extracellular Cl^- will enter the cells (primarily red blood cells). The additio KCl will increase the cell osmolality, resulting in movement of H_2O into the cells, thereby raising the plasma Na^+ concentration.
3. Intracellular H^+ ions will dissociate from intracellular buffers and move int extracellular fluid, where they will combine with extracellular

buffers. This movement of H^+ is osmotically neutral, but the extra cell K^+ will raise the cell osmolality and induce osmotic movement of H_2O into the cells.

The net effect is that K^+ is *as effective as* Na^+ in correcting hyponatremia. Thus, administered K^+ must be included when calculating the amount of Na^+ to be given to increase the plasma Na^+ concentration at a safe rate. In some patients with sev hypokalemia, for example, the amount of K^+ given during the first day (200 to 400 meq) may be sufficient to raise the plasma Na^+ concentration by close to the maximum rate. In this setting, also giving Na^+ may lead to overly rapid correction.

Edematous States

Treatment is different in edematous patients with hyponatremia. Therapy m aimed at water removal, since the administration of Na^+ will increase the severity of the edema. If one assumes that the water content of food is approximately e the insensible water loss from the skin and respiratory tract (see Table 2-6) then negative water balance can be achieved by restricting water intake to a vol is *less* than the urine output. For example, the patient will continue to retain daily fluid intake is held to 800 mL but output is only 500 mL.

Although water restriction is the initial therapy of choice in edematous stat may be very difficult to achieve in patients with advanced heart failure. In t setting, the combination of the low cardiac output and the high circulating l angiotensin II often stimulates thirst. As a result, one of the major complair a patient is intense and persistent thirst; achieving effective water restricti extremely difficult. Fortunately, the plasma Na^+ concentration falls gradually in this setting, and symptomatic hyponatremia is a rare event.

Thus, it is reasonable to allow asymptomatic hyponatremia to persist in pat advanced heart failure and to limit the recommendations to preventing exce

intake. In patients who develop symptoms, the plasma $[Na^+]$ can be raised by the use of a loop diuretic in combination with hypertonic saline o extreme cases, by peritoneal dialysis or hemodialysis. With the former regi and water loss is induced by the diuretic, and only the Na^+ lost is then replaced; the net effect is negative water balance and a rise in the plasma $[Na^+]$.

Some hyponatremic patients with advanced heart failure benefit from the co of a loop diuretic and unloading therapy with an ACE inhibitor.[215,216,217] These agents, neither of which may be effective alone, appear to have a sy interaction. At least two factors contribute to this response.[1] The loop diuretic increases water delivery to the collecting tubules by impairing transport in ascending limb, and[2] ACE inhibitors can then diminish water reabsorption in th collecting tubules by reversing the excessive release of ADH (via the increa cardiac output)[9,217] and perhaps also by antagonizing the

tubular action of ADH, an effect that appears to be mediated by stimulation prostaglandin release.[218]

Other modalities

Given the often refractory nature of the hyponatremia in heart failure and c other therapies have been evaluated. Even if effective, however, these age only correct a laboratory abnormality without inducing any tangible benefit asymptomatic patients. The tetracycline derivative demeclocycline increase water excretion by inducing ADH resistance (see below).[219,220,221] and[222] The use of this agent has been limited, however, because hepatic drug metaboli reduced in heart failure and cirrhosis, resulting in increased plasma drug le frequent nephrotoxicity.[221,222]

A more direct form of therapy is the administration of a specific antagonist V_2 receptor, which mediates the antidiuretic effects of ADH. These agents are in a variety of animal models of hyponatremia,[12,13] and oral V_2 receptor antagonists are undergoing clinical trials.[223,224] and[225]

Syndrome of Inappropriate ADH Secretion

Treatment of SIADH is potentially more complicated than treatment of the o causes of hyponatremia and may be different in the acute and chronic setti (Table 23-8).

Acute

Hyponatremia in SIADH is due initially to water retention and then in part to Na^+ loss induced by the ensuing volume expansion.[90,92] The simplest therapy is restricting water intake while maintaining that of NaCl. If this is ineffective or if sever hyponatremia is present, the combination of hypertonic saline and a loop di be used to raise the plasma $[Na^+]$.[36,226]

A few simple calculations can demonstrate the general role of NaCl adminis and loop diuretics in the treatment of SIADH. It is essential to appreciate th excretion is impaired in this disorder as a result of the continued presence but that *Na^+ handling and therefore volume regulation are intact*. These principles can be illustrated by the following case history:

Table 23-8 Treatment of SIADH

Acute
Water restriction
Hypertonic saline or NaCl tablets
Loop diuretic
Chronic
Water restriction
High-salt, high-protein diet
Loop diuretic
Other: demeclocycline, lithium, or urea

Case history 23-2

A 58-year-old woman with a small cell carcinoma of the lung is admitted bec slight obtundation. Her weight is 60 kg. The following laboratory data are o which are consistent with SIADH:

$$\text{Plasma } [Na^+] = 115\,\text{meq/L}$$
$$P_{osm} = 240\,\text{mosmol/kg}$$
$$U_{osm} = 680\,\text{mosmol/kg}$$
$$\text{Urine volume} = 1000\,\text{mL/day}$$
$$\text{Urine } [Na^+] = 62\,\text{meq/L}$$

If this patient is given 1000 mL of isotonic saline (in which Na^+ and Cl concentration each equals 154 meq/L, osmolality equals 308 mosmol/kg), the plasma Na^+ concentration will initially increase because the solution has a higher osmolality than the However, the steady state effect will be different. The excess NaCl will be in the urine in a volume of only 453 mL (308 mosmol÷ 680 mosmol/kg =453 since the U_{osm} will be relatively constant (Table 23-9). As a result, all of the solute is excreted, more than one-half of the water is retained, and there will be a *further reduction in the plasma Na^+ concentration*.

The effect of this water retention can be estimated from the equations deriv page 694:

$$\text{Total body osmoles} = \text{total body water (TBW)} \times P_{osm}$$

Table 23-9 Effect of isotonic saline, hypertonic saline, and hypertonic saline with loop diuretic i SIADH with a urine osmolality of 680 mosmol/kg

	NaCl, mosmol	H_2O, mL
Isotonic saline		
In	308	1000
Out	308	453
Net	0	+547
Hypertonic saline		
In	1026	1000
Out	1026	1500
Net	0	-500
Hypertonic saline +loop diuretic (3	$_{osm}$	00 mosmol/kg)
In	1026	1000
Out	1026	3400
Net	0	-2400

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Since the effective R is roughly equal to 2× plasma [Na$^+$], [Na

$$\text{Total effective osmoles} = \text{TBW} \times 2 \times \text{plasma } [Na^+]$$
$$= 0.5 \times 60 \times 2 \times 115$$
$$= 6900 \text{ mosmol} \qquad (23\text{-}5)$$

The retention of 550 mL of water will raise the TBW to 30.55 L, while the to effective osmoles will be unchanged, since all of the excess solute is excre new plasma Na^+ concentration can be estimated from rearranging Eq. 23-5

$$\text{Plasma } [Na^+] = \text{total effective osmoles} \div (2 \times \text{TBW})$$
$$= 6900 \div 61.1$$
$$= 113 \text{ meq/L} \qquad (23\text{-}6)$$

Thus, each liter of isotonic saline will lower the plasma $[Na^+]$ concentration by about 2 meq/L in this setting. To correct the hyponatremia, the *effective osmolality of the fluid given must be greater than that of the urine*. Table 23-9 illustrates the effect of giving 1000 mL of 3% saline to this patient. Although the plasma $[Na^+]$ concentration will initially rise, because of the direct effect of the administered fluid, the steady state will be characterized by excretion of the administered NaCl and the net loss of 500 mL of water, resulting in a new TBW of 29.5 liters (Eq. 23-5), from

$$\text{Plasma } [Na^+] = 6900 \div 5$$
$$= 117 \text{ meq/L}$$

The net effect is that even hypertonic saline may not be so effective when U_{osm} is very high**.** What is required in this situation is a reduction in this U_{osm} which can be achieved by the administration of a loop diuretic, such as furosemide.[36226227] and[228] If, for example, the U_{osm} were lowered to 300 mosmol/kg (due to an impairment of NaCl reabsorption in the medullary thick ascending limb, the countercurrent multiplication, see Chap. 4), then the infused NaCl will now be excreted in 3400 mL of urine (Table 23-9), resulting in a reduction in the TBW to 27.6 liters. Thus,

$$\text{Plasma } [Na^+] = 6900 \div 55.2$$
$$= 125 \text{ meq/L}$$

The above calculations may underestimate the true effect, since unreplaced loss will lead to volume depletion. This will activate the volume regulatory (such as increased secretion of renin), resulting in retention of some of the administered Na^+ and a more prominent rise in the plasma $[Na^+]$ concentration.

Chronic

SIADH is frequently a transient phenomenon that resolves after discontinua the offending drug or recovery from the underlying disease process (such a meningitis, pneumonia, or active tuberculosis). However, normalization of t Na^+ concentration does not necessarily indicate recovery, since inducing ne water balance will raise the plasma $[Na^+]$ concentration independent of ADH levels. Thus, the simplest regimen is to slowly increase water intake once normona achieved, particularly if it appears that the causative factor has been corre hyponatremia recurs while the U_{osm} remains high, then SIADH persists and water restriction should be reintroduced.

Chronic SIADH can also occur, particularly in patients with ectopic hormone production. The mainstay of therapy in this setting is water restriction. If th ineffective, further treatment must be aimed at increasing water excretion, enhancing solute excretion or by antagonizing the effect of ADH (Table 23-8). In normal subjects, water intake is the major determinant of the urine volume, effect on ADH release. In SIADH, however, ADH secretion and therefore the U_{osm} are relatively fixed; as a result, *the urine output is primarily determined by the ra of solute excretion*. Thus, in the above patient with a U_{osm} that is relatively fixed at

680 mosmol/kg, the daily urine output will be 1000 mL if 680 mosmol of solu excreted, but 1500 mL if 1020 mosmol of solute is excreted. This increase i output can be achieved by putting the patient on a high-salt, high-protein d unused protein will be excreted as urea) or, if available, by giving 30 to 60 per day.[229,230] Urea has few side effects other than some gastroinestinal discomfort as long as renal function is normal; however, this modality is ra in the United States.

As an alternative, the U_{osm} can be lowered by antagonizing the effect of ADH. T can be achieved by the administration of 20 to 40 mg/day of furosemide in doses (with NaCl to prevent hypovolemia)[227,228] or of demeclocycline or lithium.[219,231,232] In contrast to furosemide, which acts in the loop of Henle, demeclocycline and lithium directly interfere with the effect of ADH on the tubules.[233,234] The mechanism by which this occurs is incompletely understo Lithium, for example, enters the collecting tubule cells through Na^+ channels in the luminal membrane (see page 75).[235] The ensuing intracellular accumulation presumably impairs the response to ADH, perhaps by reducing expression o aquaporin-2 water channel or by reducing ADH receptor density.[236,237]

In general, demeclocycline (in a dose of 300 to 600 mg twice a day) is more and better tolerated than lithium,[238] although the latter is preferred in children because tetracyclines can interfere with bone development.[239]

The choice of which regimen to use is in part dependent upon the U_{osm}. Patients with a U_{osm} below 400 mosmol/kg can usually be treated by dietary means al Once the U_{osm} exceeds 600 to 700 mosmol/kg, however, free-water excretion very low levels, and a loop diuretic (which is probably safer) or demeclocyc be required to maintain the plasma Na^+ concentration at a safe level.

A possible future alternative is the administration of a V_2 receptor antagonist to produce a selective water diuresis.[233,225] In one study, for example, 11 patien with SIADH were administered a vasopressin antagonist and underwent a w diuresis that was independent of urinary solute excretion.[224] The plasma Na^+ concentration rose by 3 meq/L over a 6-h period. There is, however, a pote if the ADH effect is completely eliminated: a marked increase in water excr resulting in overly rapid correction of the hyponatremia.

Reset osmostat

A reset osmostat is a variant of SIADH in which ADH secretion and thirst ar regulated normally around a lower plasma osmolality (Fig. 23-4). The new plasma Na^+ concentration is usually between 125 and 135 meq/L, and the patients asymptomatic. The presence of a reset osmostat should be suspected when measurements reveal stable hyponatremia; it can be confirmed by demonstr normal excretion of a water load.[141]

Correcting the hyponatremia in the reset osmostat is not necessary and, if attempted, is difficult to sustain. Raising the plasma $[Na^+]$ concentration above the new baseline will both stimulate ADH release and make the patient very thi the thirst threshold is also reset.[141] Treatment must be aimed at correcting the underlying disorder, such as tuberculosis or malnutrition.

Other Disorders

Somewhat different considerations may apply to the treatment of other caus hyponatremia. Patients with *primary adrenal insufficiency* are both cortisol- and aldosterone-deficient. The administration of cortisol will rapidly increase w excretion and return the plasma $[Na^+]$ concentration toward normal.[126,127] A mineralocorticoid (such as fludrocortisone) is frequently required to correct urinary Na^+ wasting and hyperkalemia that are commonly present. Mineralocc alone will not normalize renal water excretion and is not necessary in patie hypopituitarism in whom aldosterone secretion is relatively normal.[128] Hormone replacement will also correct the hyponatremia in patients with *hypothyroidism*[134,135,136] and[137]

The imposition of water restriction will rapidly return the plasma $[Na^+]$ concentration to normal in patients with *primary polydipsia*, since water excretory capacity is intact. However, hypertonic saline may be required initially in patients with neurologic symptoms.[208] These patients generally have acute hyponatremia an at less risk for osmotic demyelination;[208] nevertheless, careful monitoring of the plasma $[Na^+]$ concentration is still required, and allowing a controlled increase water intake may be necessary in selected cases. It may also be helpful to drug regimen when phenothiazines stimulate thirst by causing the sensation mouth.[149]

PROBLEMS

23-1A 45-year-old woman is started on hydrochlorothiazide and a low-s diet for the treatment of hypertension. After 1 week, she complains of weakness, muscle cramps, and postural dizziness. On physical examin the patient is found to be alert and oriented. The blood pressure is 13 pretreatment level was 150/100). The skin turgor is decreased, and the venous pressure is less than 5 cm H_2O. The laboratory data are

$$\begin{aligned}\text{Plasma } [Na^+] &= 119\ \text{meq/L}\\ [K^+] &= 2.1\ \text{meq/L}\\ [Cl^-] &= 71\ \text{meq/L}\\ [HCO_3^-] &= 34\ \text{meq/L}\\ P_{osm} &= 252\ \text{mosmol/kg}\\ U_{osm} &= 540\ \text{mosmol/kg}\\ \text{Urine } [Na^+] &= 4\ \text{meq/L}\end{aligned}$$

a. **Hydrochlorothiazide**

b. **Volume depletion**

c. **Increased ADH secretion**

d. **Water retention**

e. **K^+ depletion**

The appropriate therapy should include which of the following?

a. **Water restriction alone**

b. **Potassium citrate**

c. **Potassium chloride**

d. **Half-isotonic (0.45%) saline**

e. **Isotonic (0.9%) saline**

23-2A 52-year-old man with hypertension treated with unknown medica is admitted to the hospital in a comatose state, responding only to de On physical examination, the blood pressure is found to be 200/120. T turgor is reduced, and the neck veins are flat. After appropriate studie diagnosis of an intracerebral hemorrhage is made. To minimize the de brain swelling, the patient is given a total of 25 g of mannitol. Only 10 other fluids is given. The laboratory data at this time include

$$\begin{aligned}\text{Plasma } [Na^+] &= 120\ \text{meq/L}\\ [K^+] &= 3.3\ \text{meq/L}\\ [Cl^-] &= 78\ \text{meq/L}\\ [HCO_3^-] &= 29\ \text{meq/L}\\ P_{osm} &= 253\ \text{mosmol/kg}\\ U_{osm} &= 240\ \text{mosmol/kg}\\ \text{Urine } [Na^+] &= 46\ \text{meq/L}\end{aligned}$$

a. **Pseudohyponatremia due to mannitol**

b. **Volume depletion**

c. **SIADH**

23-3Match the correct therapy with the appropriate clinical setting:

P.735

1. **A 41-year-old man with end-stage renal failure, mild peripheral ede and a plasma Na^+ concentration of 125 meq/L**
2. **A 53-year-old woman with an oat cell carcinoma of the lung, a plas concentration of 107 meq/L, and a urine osmolality of 640 mosmol/**
3. **A 27-year-old woman with chronic diarrhea, decreased skin turgor, plasma Na^+ concentration of 126 meq/L**

4. **A 38-year-old man with multiple myeloma, a plasma Na^+ concentration of 127 meq/L, and a plasma osmolality of 286 mosmol/kg**
5. **A 58-year-old diabetic man with congestive heart failure, a plasma Na^+ concentration of 124 meq/L, and a plasma osmolality of 268 mosmo**
6. **A 49-year-old woman with carcinoma of the lung, a stable plasma Na^+ concentration of 118 meq/L, and a urine osmolality of 290 mosmol/l**

a. **Water restriction with normal sodium intake**
b. **(b) Water and sodium restriction**
c. **(c) No therapy required**
d. **(d) Isotonic saline**
e. **(e) Hypertonic saline**
f. **(f) Hypertonic saline plus a loop diuretic**

23-4A 60-year-old man weighing 70 kg has an oat cell carcinoma of the and is admitted to the hospital with a 2-week history of progressive le and obtundation. The physical examination is within normal limits exc the obtundation. The following laboratory studies are obtained

$$\begin{aligned}\text{Plasma } [Na^+] &= 105\ \text{meq/L}\\ [K^+] &= 4\ \text{meq/L}\\ [Cl^-] &= 72\ \text{meq/L}\\ [HCO_3^-] &= 21\ \text{meq/L}\\ P_{osm} &= 222\ \text{mosmol/kg}\\ U_{osm} &= 604\ \text{mosmol/kg}\\ \text{Urine } [Na^+] &= 78\ \text{meq/L}\end{aligned}$$

a. **What is the most likely diagnosis?**
b. **How and at what initial rate would you raise the plasma Na^+ concentration?**

23-5Uric acid reabsorption in the proximal tubule is related to Na^+ reabsorption (see Chap. 3). Considering the effects of volume on Na^+ reabsorption, how might the plasma uric acid concentration be used to differentiate between hyponatremia due to SIADH and volume depletio

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Footnotes

* It has been suggested that movement into the cells, where it becomes bour and osmotically inactive, might also contribute to the reduction in the plasm concentration in SIADH.[95] This hypothesis, however, is unproven, and it is likel water retention and Na^+ loss are sufficient to explain the hyponatremia in most cases.[92,96]

† Proteins make only a minimal contribution to the P_{osm} because they are very large molecules. The normal plasma protein concentration of 7 g/dL (or 70 example, represents only 1.3 mosmol/kg. Thus, doubling the plasma protein concentration will produce a minimal increase in osmolality but will reduce fraction of plasma that is water and therefore will lower the measured plasm concentration.

‡ When SIADH is due to a central nervous system disorder, it may be difficu determine whether the neurologic disease or the low plasma $[Na^+]$ concentration is reponsible for the symptoms. The inciting factor can be assessed more acc observing the response to correction of the hyponatremia.

¶ A similar neurologic lesion can be seen with severe and prolonged hyperc due to hypernatremia or hyperglycemia, particularly in patients with burns.[207] This observation is consistent with the central role of osmotic shrinkage during correction of hyponatremia.

** The assumption that the U_{osm} will remain constant in this setting is probably accurate, as the marked solute load will lead to an osmotic diuresis that sh the urine somewhat less concentrated. The basic principle, however, will st since the U_{osm} will not fall dramatically.

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Chapter Twenty-Four
Hyperosmolal states—hypernatremia

The introduction to disorders of water balance presented in Chapter 23 should be read before proceeding with this discussion.

PATHOPHYSIOLOGY

Hypernatremia represents hyperosmolality. Since Na^+ is an effective osmole, the increase in plasma osmolality (P_{osm}) induced by the rise in the plasma Na^+ concentration creates an osmotic gradient that results in water movement o cells into the extracellular fluid. It is this cellular dehydration in the brain t primarily responsible for the neurologic symptoms that may be seen with th (see "Symptoms," below).

A similar syndrome can be produced when the P_{osm} is elevated by hyperglycemia. Hyperosmolality can also result from the accumulation of a cell-permeable (osmotically *ineffective*) solute, such as urea (as in renal failure) or ethanol; in these settings, there is *no water shift* in the steady state, since osmotic equilibrium

is reached by solute entry into cells. As a result, symptoms of hyperosmola occur.

Since it is the effective P_{osm} that is clinically important, the contribution of urea (measured as blood urea nitrogen, or BUN) to the P_{osm} should be excluded. In general, the effective P_{osm} can be calculated from (page 247)

$$\text{Effective } P_{osm} = \text{measured } P_{osm} - \frac{BUN}{2.8} \qquad (24\text{-}1)$$

or estimated from

$$\text{Effective } P_{osm} \cong 2 \times \text{plasma } [Na^+] + \frac{[\text{glucose}]}{18} \qquad (24\text{-}2)$$

The normal value for the effective P_{osm} is 270 to 285 mosmol/kg. The BUN and glucose concentration are divided by 2.8 and 18 to convert from units of mg mmol/L.

Generation of Hypernatremia

From the relationship between the plasma Na^+ concentration and the osmolality of the body fluids (see Fig. 22-2),

$$\text{Plasma } [Na^+] \cong \frac{Na_e^+ + K_e^+}{\text{total body water}} \qquad (24\text{-}3)$$

it can be seen that hypernatremia can result from *water loss or Na^+ retention* (Table 24-1). The serious toxicity of hyperkalemia prevents the retention of enough K^+ to significantly raise the plasma Na^+ concentration.

To cause hypernatremia, water loss in excess of $Na^+ + K^+$ loss must occur. Free water can be lost from the skin and respiratory tract and in a dilute urine. The latter requires either decreased secretion of antidiuretic hormone [central diabetes insipidus (CDI)] or end-organ resistance to its effect [nephrogenic diabetes insipidus (NDI)].

The effect of gastrointestinal water loss, as occurs with diarrhea, is more variable and illustrates the importance of the relationship in Eq. 24-3. The fluid that is lost in secretory diarrheas, such as cholera, is isosmotic to plasma and is almost entirely composed of Na^+ and K^+ salts.[3] The loss of this fluid will produce volume depletion but will not directly affect the plasma Na^+ concentration. The findings are different, however, in osmotic diarrheas, such as those seen with lactulose (to treat hepatic encephalopathy), charcoal-sorbitol (to treat a drug overdose), malabsorption, and some infectious enterides. In these settings,

the diarrheal fluid is also isotonic to plasma, but has a $Na^+ + K^+$ concentration of only 30 to 110 meq/L, with the nonreabsorbed solute accounting for most of the remaining osmoles.[3,4,5] and[6] Thus, water is lost in excess of $Na^+ + K^+$, which will tend to raise the plasma Na^+ concentration.

Similar considerations apply to increased urinary solute losses induced by drugs or osmotic diuretics (such as glucose or mannitol). In these settings, plasma Na^+ concentration will tend to increase because the $Na^+ + K^+$ concentration is less than that of the plasma.[2]

Table 24-1 Etiology of hypernatremia

Water loss

A. Insensible loss
   1. Increased sweating: fever, exposure to high temperatures, exerci
   2. Burns
   3. Respiratory infections

B. Renal loss
   1. Central diabetes insipidus
   2. Nephrogenic diabetes insipidus
   3. Osmotic diuresis: glucose, urea, mannitol

C. Gastrointestinal loss
   1. Osmotic diarrhea: lactulose, malabsorption, some infectious

enteritides
D. Hypothalamic disorders
1. Primary hypodipsia
2. Reset osmostat due to volume expansion in primary mineralocorticoid excess
3. Essential hypernatremia with loss of osmoreceptor function
E. Water loss into cells
1. Seizures or severe exercise
2. Rhabdomyolysis

Sodium retention

A. Administration of hypertonic NaCl or $NaHCO_3$
B. Ingestion of sodium

Thirst and the Maintenance of Hypernatremia

The normal defense against the development of hypernatremia is the stimul both antidiuretic hormone (ADH) release and thirst by the hypothalamic osmoreceptors (see Chap. 6). The combination of decreased water excretion and increased water intake results in water retention and return of the plasma $[Na^+]$ concentration to normal. The secretion of ADH generally begins when the P_{osm} exceeds 275 to 285 mosmol/kg (see Fig. 23-1), whereas the threshold for thirst appears to be somewhat higher (approximately 2 to 5 mosmol/kg).[7,8] Osmoregulation is normally so efficient that P_{osm} is *maintained within a range of 1 to 2 perce* (usually between 280 and 290 mosmol/kg), despite wide variations in $[Na^+]$ and water intake.

Although ADH release may occur earlier, it is *thirst that provides the ultimate protection against hypernatremia*.[9] Thus, patients with CDI who secrete little or no A for example, renal water reabsorption falls, and the urine output can excee L/day. Nevertheless, water balance is maintained because water intake is a to match output. Conversely, even with maximum ADH secretion, the kidney unable to retain enough water to offset insensible losses from the

skin and respiratory tract in a patient with hypodipsia (diminished thirst).[10] Thus, hypernatremia due to water loss occurs only in patients who have hypodips extremely rare disorder), in adults with altered mental status, and in infants have an intact thirst mechanism but are unable to ask for water.[11,12] A plasma $[Na^+]$ concentration greater than 150 mEq/L is *virtually never seen in an alert adult with normal thirst mechanism and access to water*.

In adults, *hypernatremia developing outside the hospital most often occurs i patients over the age of 60*.[12,13] In addition to an increased frequency of concurrent illness and diminished mental status, increasing age is also ass

with diminished osmotic stimulation of thirst, even though the release of AD maintained.[14,15] Careful study of ADH-secreting neurons in the brain in elder subjects has actually shown an increase in activity, which may reflect a compensatory response to the age-related loss of ADH receptors in the kidn[16] Although most otherwise healthy older patients maintain normal water balar response to a given stress may be impaired, increasing the likelihood of th becoming hypernatremic. Mentally handicapped patients are also at increas negative water balance and hypernatremia.[17]

ETIOLOGY

The major causes of hypernatremia are listed in Table 24-1 according to their probable underlying mechanism.

Insensible and Gastrointestinal Water Loss

Insensible fluid losses from the skin and respiratory tract are hypoosmotic and average 800 to 1000 mL/day in adults. Any condition that increases the —such as fever, respiratory infections, burns, or exposure to high temperat —predisposes toward the development of hypernatremia. Gastrointestinal w losses, due to an osmotic diarrhea, can also produce a similar effect.[3,5,6] Lactulose, for example, is used to treat hepatic encephalopathy. It is given in a hyperc solution, resulting in the flow of water into the gastrointestinal tract. When losses are large, as manifested by water diarrhea, hypernatremia can ensu[5] The decreased thirst induced by the diminished mental status in these patients essential permissive role.

Hypernatremia following a diarrheal illness was once a relatively common p infants.[18,19] Increased insensible (due to fever) and gastrointestinal losses this setting, and the degree of dehydration does not have to be very large i infant to produce a substantial elevation in the plasma Na^+ concentration. Hyperglycemia may also be seen, further elevating the effective P_{osm}.[19] This increase in the plasma glucose concentration (to as high as 300 to 500 mg/ appears to be a stress response, perhaps mediated by catecholamines, and corrected with rehydration. In recent years, the incidence of hypernatremic dehydration following gastroenteritis in infants has fallen, primarily becaus

use of low-solute feedings (Na$^+$ plus K$^+$ concentration about 95 meq/L), which supply more free water to replace the insensible losses.[11,20,21]

Diabetes Insipidus

Diabetes insipidus is characterized by the complete or partial failure of ADH secretion (CDI) or of the renal response to ADH (NDI). As a result, renal wa reabsorption falls, and a diuresis of dilute urine ensues (3 to 20 L/day). It emphasized again that the majority of these patients maintain water balanc near normal plasma Na^+ concentration because their thirst mechanism is intact[22,23]

Their major complaints are polyuria and polydipsia, not the symptoms of hypernatremia.

The outcome is different, however, if the hypothalamic disorder producing C interferes with thirst. In this setting, even a partial defect in ADH release c water loss and potentially severe hypernatremia.[22,24] For example, a patient with partial CDI may be able to maximally concentrate his or her urine to 400 (U_{max}) mosmol/kg. This is hyperosmotic to plasma but less than the normal U_{max} of 800 to 1400 mosmol/kg. If this patient excreted 800 mosmol/day of solute (primaril K^+ salts and urea), the solute load would be excreted in the urine in a mini 2000 mL of water (800 mosmol of solute in 2000 mL of water equals 400 mo In contrast, the obligatory renal water loss would be only 800 mL if the U_{max} normal at 1000 mosmol/kg (800 mosmol in 800 mL of water equals 1000 mos Thus, the reduction in renal concentrating ability can result in an extra 120 water lost in the urine per day. In a hypodipsic patient, this added loss mig replaced, leading to the development of hypernatremia.

Central diabetes insipidus

ADH is synthesized in the supraoptic and paraventricular nuclei in the hypo It then streams down the axons of the supraopticohypophyseal tract and is and subsequently released from the posterior lobe of the pituitary (neurohy (Fig. 24-1).[25,26] Impaired secretion of ADH can be induced by a variety of cli disorders that disrupt the osmoreceptors, the hypothalamic nuclei, or the supraopticohypophyseal tract (Table 24-2).[27,28] In contrast, damage to the tract below the median eminence or removal of the posterior pituitary usually pro only a *transient* period of diabetes insipidus.[28] In these settings, ADH can still be secreted into the systemic circulation via the portal capillaries in the media eminence (Fig. 24-1).

Among the causes of CDI (Table 24-2), approximately 75 percent of cases are due idiopathic DI, neurosurgery (particularly for craniopharyngioma), head trau primary or secondary malignancies or infiltrative diseases, such as Langerh histiocytosis (histiocytosis X).[28,29,30] and[31] Idiopathic CDI accounts for approximately 30 percent of cases, being associated with destruction of the hormone-secreting cells in the hypothalamic nuclei. It has been suggested autoimmune process is involved in many, if not most, patients.[32]

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individuals, antibodies directed against the vasopressin-producing cells ma responsible for the progressive decline in ADH release.[33]

Table 24-2 Etiology of central diabetes insipidus

Idiopathic—may be familial	

Neurosurgery

A. Craniopharyngioma
B. Transsphenoidal surgery

Head trauma
Hypoxic or ischemic encephalopathy

A. Cardiopulmonary arrest
B. Shock
C. Sheehan's syndrome

Neoplastic

A. Primary: craniopharyngioma, pinealoma, cyst
B. Metastatic: breast, lung

Miscellaneous

A. Histiocytosis X
B. Sarcoidosis
C. Anorexia nervosa
D. Cerebral aneurysm
E. Encephalitis or meningitis

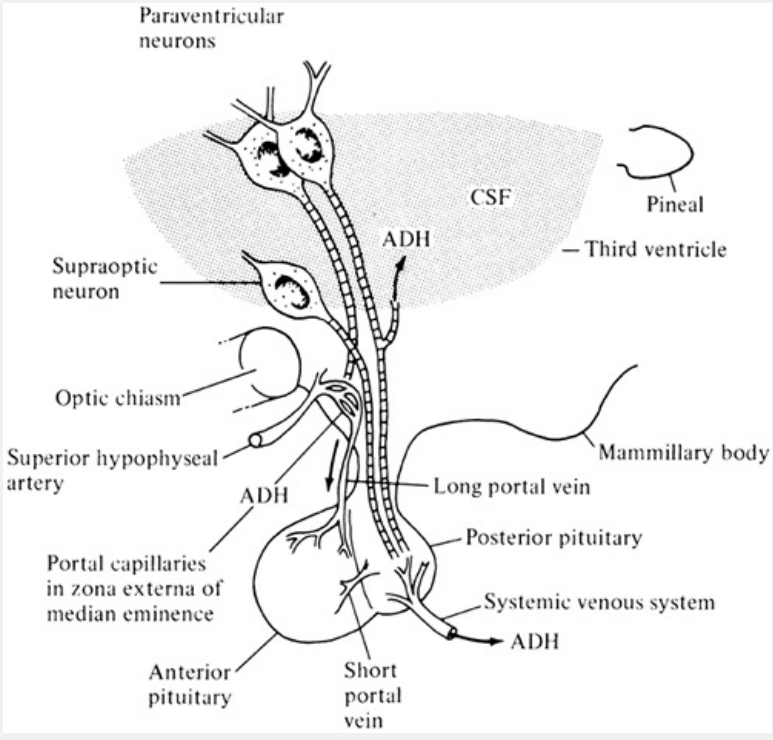

Figure 24-1 Diagram of the mammalian hypothalamus and pituitary gland

depicting pathways for the secretion of ADH. The hormone is formed in th supraoptic and paraventricular nuclei, transported in granules along their and then secreted at three sites: the posterior pituitary gland, the portal capillaries of the median eminence, and the cerebrospinal fluid (CSF) of t ventricle. (*Adapted from Zimmerman EA, Robinson AG, Kidney Int 10:12, 1976. Reprinted by permission from* Kidney International.)

The autoimmune process is characterized by lymphocytic inflammation of th pituitary stalk and posterior pituitary that resolves after destruction of the neurons.[32] Magnetic resonance imaging (MRI) performed when active inflamm is still present often reveals thickening and/or enlargement of these structu destructive process may also lead to concurrent abnormalities in anterior p function, with decreased release of growth hormone and adrenocorticotropi hormone (ACTH) in some cases.[34]

Rarely, idiopathic CDI is a familial disorder, usually with autosomal domina inheritance. The defect in at least some cases involves a point mutation in encoding for preprovasopressin-neurophysin II, the precursor of ADH.[35,36] The precursor that is produced cannot be normally cleaved or transported and accumulates locally, leading to death of the ADH-producing cells.[37] This sequence probably accounts for three characteristic findings in this disorder:[1] development of marked polyuria even though only one of the two hormone-p genes is defective,[2] delayed onset of polyuria for months to years, with an ag onset that ranges from 1 to 28 years,[38] and a bright spot visible on MRI (perhaps due to the accumulated precursor) that is not seen in patients with nonfami idiopathic CDI.[37]

Neurosurgery (usually transsphenoidal) or trauma to the hypothalamus or tr another common cause of central DI.[29,30,31,32,33,34,35,36,37,38] and[39] However, a somewhat different response has been detected with transfrontal surgery craniopharyngioma. In this setting, the polyuria appears to result from the r an ADH precursor from the hypothalamus that competes for but does not ac antidiuretic V_2 receptors.[39] These patients initially have high ADH levels by immunoassay but have little or no biological activity and a diminished respo exogenous hormone replacement. Thus, they behave as if they have nephro although the polyuria is typically transient.

Damage to the hypothalamus or tract can produce a *triphasic* response (Fig. 24-2).

1. There is an initial polyuric phase that typically begins within 24 h, lasts days, and probably represents inhibition of ADH release due to hypotha dysfunction.[29,40]
2. From days 6 to 11, however, there is an antidiuretic phase that represe release of stored hormone from the degenerating posterior pituitary. Du

time, excessive water intake can produce hyponatremia in a manner sim that in the syndrome of inappropriate ADH secretion (SIADH; see Chap. 28).

3. The second stage is often followed by permanent CDI once the neurohypophyseal stores are depleted, although some patients have on transient SIADH (also called isolated second phase) and then appear to without developing late polyuria.[41,42] Adrenal insufficiency due to ACTH deficiency may contribute to the hyponatremia in this setting.[41]

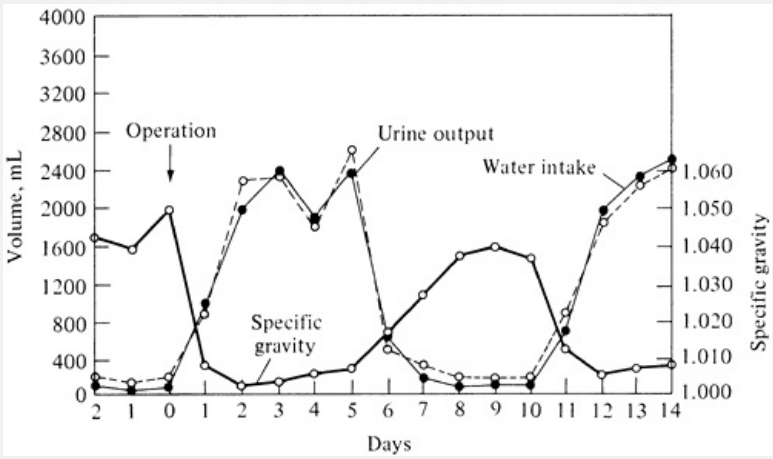

Figure 24-7 Typical triphasic cycle produced by section of the hypophyseal and damage to the median eminence. The interphase of excess ADH secre extends from day 6 to day 10 of illness. (*From Hollinshead WW: Mayo Clin Proc 39:92, 1964, with permission.*)

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It must be emphasized, however, that polyuria following neurosurgery is mo *not* due to CDI.[29] More common causes in this setting include excretion of exc fluid administered during surgery and an osmotic diuresis resulting from tre aimed at minimizing cerebral edema with mannitol or corticosteroids (which to hyperglycemia and glucosuria). These conditions can be distinguished b measuring the urine osmolality and the response to water restriction and th administration of exogenous ADH (see "Polyuria," below).

Hypoxic encephalopathy or severe ischemia, as occurs following cardiopuln arrest or shock, can also lead to diminished ADH release.[28,43] Although marked polyuria can occur in these settings, the functional impairment is mild and s in some cases. As an example, overt diabetes insipidus is unusual in patier Sheehan's syndrome (postpartum panhypopituitarism) despite frequent atro posterior pituitary and hypothalamic nuclei. Nevertheless, ADH secretion in to raising the P_{osm} is frequently subnormal.[44]

Hemodynamic factors can also lead to transient CDI by a second mechanisr Polyuria is occasionally seen after correction of a supraventricular tachyca this setting, both a natriuresis and a water diuresis occur, which may be du

enhanced release of atrial natriuretic peptide and diminished secretion of A respectively.[45] Increases in left atrial and systemic blood pressures may activ local volume receptors, thereby leading to these transient hormonal change

Patients with Langerhans cell histiocytosis (histiocytosis X) are at particula risk for CDI.[31] As many as 40 percent develop polyuria within the first 4 years especially if there is multisystem involvement and proptosis.

A similar infiltrative disease can occur with sarcoidosis, which can also cau polyuria due to NDI (induced by hypercalcemia) or primary polydipsia.[46] Other infiltrative disorders that may rarely cause CDI include Wegener's granulom

and autoimmune hypophysitis.[47,48] and[49]

Polyuria without hypernatremia is also a common finding in anorexia nervos release in response to an elevation in P_{osm} is erratic or subnormal in this disorder, which may also be associated with a primary increase in thirst.[50] These abnormalities are presumably due to the associated cerebral dysfunction.

Nephrogenic diabetes insipidus

Nephrogenic diabetes insipidus (NDI) is a congenital or acquired disorder i hypothalamic function and ADH release are normal, but the ability to conce urine is reduced because of diminished or absent renal responsiveness to A[51,52] Concentration of the urine normally involves two basic steps:[1] creation of a hyperosmotic medullary interstitium (to a maximum of 800 to 1400 mosmol/k primarily by NaCl reabsorption without water in the ascending limb of the lo Henle (a process called countercurrent multiplication),[2] and equilibration of the urine in the collecting tubules with the medullary interstitium (see Chapter 4). ADH is essential for the second step since it markedly increases the water perm the collecting tubules (see Chap. 6).

Thus, NDI must be associated with an abnormality in either countercurrent or the ability to respond to ADH. The various causes of NDI are listed in Table 24-3.

Hereditary NDI

Congenital NDI is an uncommon condition that is transmitted in an X-linked fashion with varying degrees of penetrance in heterozygous females.[53,54] and[55] Thus, males tend to have the complete disorder, whereas the

manifestations range from the carrier state to marked polyuria in females. T factors contribute to the variable manifestations in females: One-half the c normal by the Lyon hypothesis, and the genetic defect is of variable severit some women may be asymptomatic in day-to-day life but develop moderate polyuria during pregnancy when vasopressinases released from the placent increase the metabolic clearance of endogenous ADH (see below).

Table 24-3 Causes of nephrogenic diabetes insipidus

Congenital
Hypercalcemia
Hypokalemia
Drugs
1. Lithium 2. Demeclocycline 3. Streptozotocin
Sjoögren's syndrome
Amyloidosis
Osmotic diuresis: glucose, mannitol, urea
Loop diuretics
Acute and chronic renal failure
Hypercalcemia
Hypokalemia
Sickle cell anemia
Pregnancy
Ifosfamide
Propoxyphene overdose
Methoxyflurane

The defect in most patients with congenital NDI appears to involve differen mutations in the V_2-receptor gene.[54,55,56] and[57] These mutations can lead to decreased hormone binding, impaired intracellular transport or coupling to adenylyl cyclase system, or diminished synthesis or accelerated degradatio receptor.[54] The V_2 receptor mediates the antidiuretic response to ADH and als promotes peripheral vasodilation and the release from endothelial cells of f and von Willebrand's factor, all of which are impaired in congenital NDI.[58,59] In comparison, the V_1 receptor, which causes vasoconstriction and increased ren prostaglandin release, functions normally in this disorder.[58]

A second, autosomal recessive form of hereditary nephrogenic DI has been described that further elucidates our understanding of the mechanism of ac ADH. In this disorder, the V_2 receptor and vasodilator and coagulation responses ADH are intact. The defect lies in the genes for the aquaporin-2 water channels.[60,61] These channels are normally stored in the cytosol; under the influence of ADH, they move to and fuse with the luminal membrane, thereb water to be reabsorbed down the favorable concentration gradient.[62,63] The mutations may lead to either impaired trafficking of the water channels, whi fuse with the luminal membrane, or decreased channel function.[60,61]

The major causes of acquired NDI that are sufficiently severe to produce p adults are *lithium toxicity, hypercalcemia,* and the *osmotic diuresis* associated with uncontrolled diabetes mellitus. Polyuria is a common problem within lithium appearing as early as 8 to 12 weeks and ultimately occurring in approximat percent of patients.[64,65] and[66] In addition, a subclinical impairment in concentrating ability is present in another 30 percent of cases. Although ge reversible, the concentrating defect may be permanent after prolonged drug usage.[64,66]

Lithium appears to act by accumulating within the collecting tubule cells, a entering the cells through the Na^+ channels in the luminal membrane (see Figure 5-2).[67] It then interferes with the ability of ADH to increase water permeability this occurs is incompletely understood, but a number of different mechanisr involved: Decreased stimulation of adenylate cyclase (mediated in part by e activity of G_i, the inhibitory guanine regulatory protein that reduces the activi adenylate cyclase),[68] reduced density of ADH receptors,[69] and a post-cyclic AMP defect that may be mediated by downregulation of

aquaporin-2.[70]

A more predictable resistance to ADH occurs with the use of demeclocycline tetracycline derivative.[71] The duration of administration of this drug is usually t short for polyuria to be a serious problem. However, the increase in free-wa excretion induced by demeclocycline has led to its use in occasional patien refractory hyponatremia (see Chap. 23).[72]

Hypercalcemia and hypokalemia

Hypercalcemia and hypokalemia produce a form of NDI that is generally rev within 1 to 12 weeks after correction of the electrolyte disturbance.[73,74] and[75] With *hypercalcemia,* the concentrating defect may become clinically apparent wher plasma Ca^{2+} concentration exceeds 11 mg/dL.[74] It was originally suggested that calcium deposition in the medulla with secondary tubulointerstitial injury ma important role.[76] More recent studies suggest an important role for impaired regulation of aquaporin-2[77] and for activation of the normal calcium-sensing receptor by the elevation in the plasma calcium concentration.[78]

1. Calcium-sensing receptors are expressed on the *basolateral* membrane in the thick ascending limb of the loop of Henle. Activation of these receptors calcium reduces sodium chloride and calcium reabsorption in the thick ascending limb, an effect that appears to be mediated by the generation P450 arachidonic acid metabolite (possibly 20-HETE), which then induc closure of the luminal potassium channel.[79] Inhibition of loop reabsorption impairs generation of the medullary osmotic gradient that is essential fo concentration.

2. Calcium-sensing receptors are expressed on the *luminal* membrane of the cells of the inner medullary collecting duct. Diminished calcium reabsorption loop of Henle in hypercalcemia results in more calcium being delivered binding with calcium-sensing receptors in the collecting duct. Activation receptors reduces the antidiuretic hormone–induced increase in water permeability.[80]

The concentrating defect seen with *hypokalemia* requires a K^+ deficit of 300 to 400 meq, a setting in which the plasma K^+ concentration should be under 3.0 meq/L (s Fig. 12-1).[75] Collecting tubule responsiveness to ADH is diminished by hypokalemia,[81,82] an effect that may be mediated in part by a reduction in cyc AMP generation.[83] Hypokalemia may also impair countercurrent function by interfering with NaCl transport in the thick ascending limb.[84,85]

The polyuria seen with these electrolyte disorders has been largely attribut associated defects in concentrating ability. However, hypokalemia and perh hypercalcemia also may directly stimulate thirst,[86,87] and[88] How this might occur is not known.

Osmotic and nonosmotic diuretics

An osmotic diuresis refers to enhanced urinary water loss induced by the p of large amounts of nonreabsorbed solute in the tubular lumen.[89] The increase in urine output induced by the excess solutes

results in a dilutional fall in the urine $(Na^+ + K^+)$ concentration to a level below that the plasma.[90] From Eq. 24-3, this *loss of water in excess of* $(Na^+ + K^+)$ will directly raise the plasma Na^+ concentration unless there is a concomitant increase in f intake.

Uncontrolled diabetes mellitus with glucosuria is the most common cause of osmotic diuresis, although a similar problem can also occur in patients give high-protein tube feedings (resulting in the formation of urea from hepatic p metabolism) or prolonged infusions of hypertonic mannitol.[90,91] and[92] The plasma Na^+ concentration is variable at presentation in uncontrolled diabetes, sinc effect of the osmotic diuresis is counteracted by hyperglycemia-induced wa movement out of the cells (see Chap. 25).[93] However, hypernatremia is not uncommon after insulin therapy has been initiated, as both glucose and wat reenter the cells.

Loop diuretics, such as furosemide and bumetanide, impair urinary concent inhibiting NaCl reabsorption in the thick ascending limb. However, these ag short-acting, and the water losses can be replaced by oral intake. As a resu hypernatremia is an unusual consequence of diuretic therapy.

Other

An inability to concentrate the urine maximally is an early finding in most fo renal failure. Several factors contribute to this problem, including the osmo diuresis resulting from increased solute excretion in the remaining function nephrons,[94,95] decreased tubular responsiveness to ADH,[96] and interference with the countercurrent mechanism in disorders affecting the renal medulla, suc chronic pyelonephritis and analgesic abuse nephropathy.[97] The net effect is that, as the renal failure becomes more severe, the U_{max} falls, becoming isosmotic or even slightly hypoosmotic to plasma.[98] However, the degree of *polyuria is usually limited by the reduction in functioning renal mass*. A more severe concentrating defect (U_{max} less than 150 mosmol/kg) with marked polyuria may transiently follow relief of urinary tract obstruction, but this is clearly a rare[99] occurrence.

Diminished concentrating ability is an early and uniform finding in patients cell anemia.[100,101] The low partial pressure of oxygen and high osmolality of renal medulla favor sickling in the vasa recta, thereby impairing countercur function.[102] The net effect is that, by the age of 10, the U_{max} is usually 400 to 500 mosmol/kg, less than half the normal value.[103,104] These changes occur later and are less severe in patients with sickle cell (SC) trait or hemoglobin SC dise[100] Transfusions with hemoglobin A can initially reverse the concentrating defe presumably by restoring vasa recta flow.[103,104] However, this beneficial response lost by age 15, at which time chronic medullary ischemia has produced irre interstitial fibrosis and tubular atrophy.

On rare occasions, amyloidosis[105] and Sjögren's syndrome[106] are associated with NDI and polyuria. Biopsy specimens reveal, respectively, amyloid deposits lymphocytic infiltration around the collecting tubules. These changes presu interfere with tubular function and are responsible for the concentrating de

Another cause of NDI is the chemotherapeutic agent ifosfamide, which is a tubular toxin.[107] Both proximal and distal nephron injury are common problems this drug. Thus, in addition to decreased concentrating ability, one or more following tubular abnormalities also may be seen: type 1 or type 2 renal tub acidosis, phosphate wasting and hypophosphatemia (possibly leading to ric children), renal glucosuria, and aminoaciduria. Two other drugs that are int associated with NDI are cidofovir and foscarnet, which are used to treat cytomegalovirus infection in HIV-infected patients.[108,109]

Finally, an unusual form of NDI and polyuria has been described in selected during the second half of pregnancy.[110,111] Normal pregnancy is associated with high circulating levels of vasopressinase (probably released from the place leading to rapid degradation of endogenous or exogenous ADH.[112] In a great majority of patients, this change is not clinically important and leads to no Those women who develop polyuria may have higher than normal vasopress activity or, possibly, subclinical central or perhaps congenital NDI that is u during pregnancy. Although these patients are resistant to vasopressin, the

can be controlled by the administration of dDAVP, which appears to be resis the vasopressinase, perhaps because it has a different N-terminus.[111,112] Thus, polyuria is transient in all patients, resolving spontaneously within a few w delivery.

Polyuria in diabetes insipidus

Several factors contribute to the degree of polyuria in CDI and NDI, includi severity of the concentrating defect, the rate of solute excretion, and the p volume status. The interrelationship between the U_{max} and solute excretion can be illustrated by the following examples. Suppose the daily rate of solute excr 750 mosmol (composed mostly of Na^+ and K^+ salts and urea). If the U_{max} is 300 mosmol/kg (similar to the P_{osm}), then the minimum urine output will be 2.5 L/day (750 mosmol/day ÷ 300 mosmol/kg=2.5 L/day). In comparison, the minimum output will exceed 7.5 L/day if this U_{max} is 100 mosmol/kg or less. In general, such severe concentrating defect is seen only in complete CDI, congenital NDI, l nephrotoxicity, or occasional patients with hypercalcemia. Most other cases acquired NDI are associated with a U_{max} that is greater than 300 mosmol/kg. In th setting, *nocturia* may be the primary complaint, since the urine normally becon most concentrated overnight, when there is no fluid intake.

When the U_{osm} is relatively fixed, as it is in diabetes insipidus, the *rate of solute excretion* becomes the primary determinant of the urine output. For example, the U_{osm} is 100 mosmol/kg, then the daily urine volume will be 8 liters if 800 m excreted but only 4 liters if 400 mosmol is excreted. This has potential ther importance, since a low-sodium, low-protein diet can limit the degree of pol diminishing solute excretion.

Effective circulating volume depletion also can limit the urine volume. Sinc collecting tubule water reabsorption is diminished in diabetes insipidus, the output in this condition is directly related to the volume of water delivered segments. The kidney responds to volume depletion in part by lowering the glomerular filtration rate and by increasing proximal Na^+ and water reabsorption (see Chap. 3).[113] As a result, distal delivery and, consequently, the urine output v

This effect of hypovolemia constitutes the rationale for the use of diuretics low-sodium diet in the therapy of CDI or NDI (see "Treatment," below). It also explains why cortisol deficiency— which is associated with reductions in sy blood pressure, cardiac output, and renal blood flow and increased release of ADH from the paraventricular nuclei (see page 710)[114]—limits the urine output in diabetes insipidus. Thus, patients with coexistent anterior and posterior pit insufficiency may not initially complain of polyuria. However, the underlying be unmasked and polyuria will ensue when cortisol replacement is given.[115]

Hypothalamic Dysfunction

Chronic hypernatremia in an alert patient with access to water is indicative

hypothalamic disease affecting thirst. Two somewhat different syndromes h described which are most often due to tumors, granulomatous diseases suc sarcoidosis, and vascular disease.[7,9] In one disorder, there is a defect in thirst w or without concomitant CDI.[9,10,116,117] In general, *forced water intake* is sufficient to return the plasma Na^+ concentration to normal in this disorder, although part CDI, if present, may also have to be treated (see below).

In other hypodipsic patients, water loading is ineffective in lowering the pla concentration, as the administered water is excreted in the urine.[118,119] This diuretic response to water, presumably mediated by inhibition of ADH secre initially suggested that the osmoreceptors in the hypothalamus were reset t recognize the elevated plasma Na^+ concentration as normal. This syndrome has been called *essential hypernatremia*.

Although rare, essential hypernatremia affords an interesting clinical oppor study the independent effects of osmolality and volume of ADH secretion. If osmostat has been reset upward, its characteristics should be similar to tho normal osmostat:

1. Inhibition of ADH release and the excretion of a dilute urine after a wat
2. Stimulation of ADH release and the excretion of a concentrated urine af restriction
3. Maintenance of the new "normal" plasma Na^+ concentration within arrow limits (± 1 to 2 percent)

Patients with essential hypernatremia satisfy the first two criteria, but usua wide variations in the plasma Na^+ concentration, which can range between 150 a 180 meq/L.[118,119,120] and [121]

The latter findings suggests that the *osmoreceptors are relatively insensitive, rat than being reset at a higher level*. The appropriate responses to variations in wa intake in this setting might be mediated by the volume receptors, rather tha reflecting intact osmoreceptor function. As an example, water loading incre effective circulating volume, which could inhibit ADH secretion and allow th water to be excreted. Conversely, water restriction decreases volume, whic augment ADH secretion.

To test this hypothesis, hypertonic saline can be administered. This increas the P_{osm} and volume, respectively stimulating and inhibiting ADH release. In normal subject, the osmotic effect predominates, causing ADH secretion an increase in U_{osm}.[7,122] However, the U_{osm} typically falls in patients with essentia hypernatremia, indicating reduced ADH release despite the rise in P_{osm} (Fig. 24-3).

These findings suggest that essential hypernatremia represents selective d the osmoreceptors, resulting in hypodipsia, hypernatremia, and volume-mec

ADH release.[7,119,121] This hypothesis has been directly confirmed in at least patient, in whom plasma ADH levels increased normally with the induction o hypotension but showed little change with an elevation in P_{osm}.[121] The normal response to volume again illustrates that the osmoreceptor cells are distinc hormone-producing cells.

Hypernatremia due to true resetting of the osmostat has been reported only of *primary mineralocorticoid excess* such as primary hyperaldosteronism.[7] The chronic mild hypervolemia induced by the mineralocorticoid effect retards A secretion. This shifts the osmotic threshold for ADH release upward by 5 to

mosmol/kg (see Fig. 6-10).[7] As a result, the normal plasma $[Na^+]$ concentration in these disorders is slightly elevated at about 145 meq/L. Normal osmoregulation c restored by removing the source of hormone secretion or by lowering the ef circulating volume with diuretics.[7]

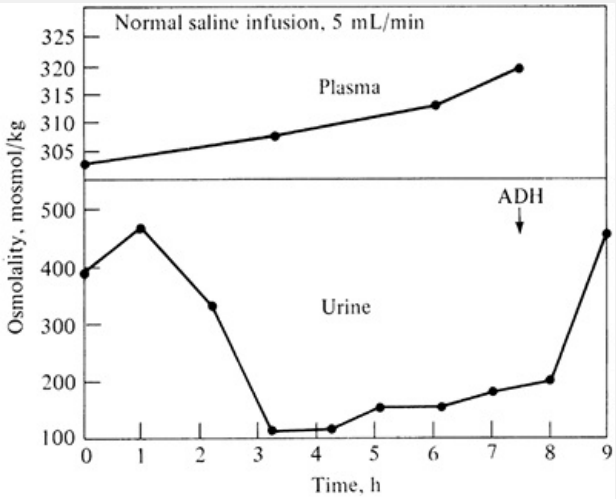

Figure 24-3 Response to saline infusion in a patient with essential hypernatremia. After overnight de-hydration, an infusion of approx-imately mL of saline results in urinary dilution (U_{osm} 102 mosmol/kg). With continued saline infusion, a sustained water diuresis is observed despite a rising pl osmolality (301 to 320 mosmol/kg). The ability of exogenous ADH to termi the water diuresis suggests that endogenous ADH release has been inhibi despite the rise in P_{osm}. (*From DeRubertis FR, Michelis MF, Beck N, et al, Clin Invest 50:97, 1971, by copyright permission of the American Society fo Clinical Investigation*)

Water Loss into Cells

Transient hypernatremia (in which the plasma $[Na^+]$ concentration can rise by as muc as 10 to 15 meq/L) can be induced by severe exertion, as with exercise or seizures.[123,124] This effect is presumed to result from an increase in intrace

osmolality, which promotes water movement into the cells. Lactic acidosis a occurs in this setting, and it may be the breakdown of glycogen into smalle molecules (such as lactate) that is responsible for the cellular hyperosmola similar effect can also be seen in rare cases of rhabdomyolysis.[123,125]

Sodium Overload

Although hypernatremia is generally a problem of water loss, it can also be by the ingestion or infusion of hypertonic Na^+ solutions. This problem can occur in infants given high-Na^+ feedings (either accidentally or purposefully) or hyperto $NaHCO_3$,[126,127,128] and[129] after the use of $NaHCO_3$ during cardiopulmonary resuscitation,[130] or after massive salt ingestion, as might occur with the inges a hypertonic saline emetic or gargle.[131] For example, the inadvertent administratio of only 1 tablespoon of NaCl to a newborn can raise the plasma Na^+ concentration by as much as 70 meq/L.[127] These patients are volume overloaded and generall have a high urine Na^+ concentration, in contrast to the low values seen with hypovolemia due to water loss.[129]

SYMPTOMS

The symptoms of hypernatremia (hyperosmolality) are primarily neurologic. weakness, and irritability are the earliest findings, which can then progress twitching, seizures, coma, and death in severe cases.[132,133] These symptoms are related less to the absolute level of the plasma Na^+ concentration than to the movement of water out of the brain cells down the osmotic gradient created rise in the effective P_{osm} (Fig. 24-4). Studies in experimental animals and in huma have revealed that this decrease in brain volume causes rupture of the cere veins, resulting in focal intracerebral and subarachnoid hemorrhages and n dysfunction that may be irreversible.[126,133,134,135] and[136] A lumbar puncture at this time may reveal blood in the cerebrospinal fluid.

A clinically significant acute water shift appears to require at least a 30- to mosmol/kg osmolal gradient between the plasma and the brain.[137,138] This gradient, which is derived from animal studies, correlates well with the find humans. In children with acute hypernatremia, for example, seizures and

potentially permanent neurologic damage are most likely to occur when the Na^+ concentration exceeds 158 meq/L.[135] This 17-meq/L elevation above normal represents, if the anion accompanying the Na^+ is included, approximately a 34-mosmol/kg rise in the P_{osm}. However, there is wide interpatient variability in th likelihood of irreversible neurologic dysfunction. For example, some infants apparently complete recovery from acute elevations in the plasma Na^+ concentration to above 200 meq/L.[129]

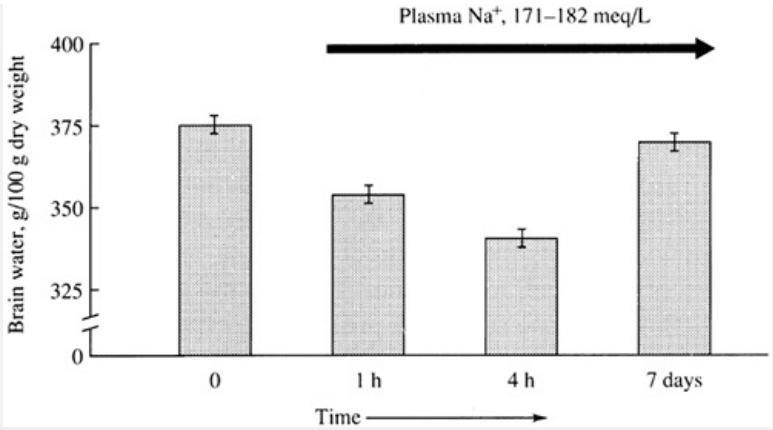

Figure 24-4 Effect of sustained hypernatremia on brain water content in rab Brain water was significantly reduced by 1 to 4 h but returned to normal v week. No values were obtained between 4 h and 1 week. (*From Pollock AS, Arieff AI,* Am J Physiol *239:F195, 1980, with permission.*)

Osmotic Adaptation

The cerebral dehydration induced by hypernatremia is transient. Within sev hours, the brain begins to adapt to the hyperosmolal state with an increase cell osmolality, resulting in water movement back into the brain and the retu brain volume toward normal (Fig. 24-4).[139,140] and [141] Two factors are involved in this initial protective response:

1. First, the cerebral contraction induced by hypernatremia lowers the hyd pressure in the cerebral interstitial fluid, creating a gradient that favors movement of fluid from the cerebrospinal fluid into the dehydrated brain increasing the interstitial volume.[142,143] and [144]
2. Second, the cells take up Na^+, K^+, Cl^-, and organic solutes, and this leads to elevation in cell osmolality that pulls water into the cells, thereby retur volume toward normal.[139,142]

Similar changes, but in the opposite direction, occur in hyponatremia (see page 669).

If uptake of Na^+ and K^+ were the only cell adaptation, the associated elevation cell cation concentration could have deleterious effects on the activity of

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cell proteins.[145] This is minimized by the accumulation of organic solutes call *osmolytes*, which do not interfere with protein function as their concentration rises.[145] Within the brain, increases in the amino acids glutamine and glutar in inositol appear to constitute most of the osmolyte response to hypernatre animals,[146,147] accounting for approximately 35 percent of the rise in brain o osmoles.[147]

Inositol accumulation is primarily mediated by uptake from the extracellular

an increased number of inositol transporters in the cell membranes.[139,148] It is not clear whether enhanced uptake or intracellular release from cell proteins is responsible for the accumulation of glutamine and glutamate. This requirem synthesis of new transporters explains why osmolyte uptake occurs more sl cation uptake, since the latter is probably mediated by the activation of qui channels in the cell membrane.[139]

One study of an infant with an initial plasma sodium concentration of 195 m confirmed the general applicability of these observations to human.[149] The patient was first studied, using proton nuclear magnetic resonance (NMR) spectros day 4, when the plasma sodium concentration had fallen to 156 meq/L. At th there was a 17-mosmol/kg increase in brain osmolyte concentration, due pr the accumulation of inositol. The excess brain osmolyte concentration fell t mosmol/kg on day 7 and was normal by day 36.

One question that remains unresolved in the process of osmotic adaptation hypernatremia is how the alterations in osmolality are sensed by the cells a lead to the desired changes in solute balance. There is evidence that hyperosmolality, perhaps via stress on the cytoskeleton as the cell volume activates a specific protein kinase.[150] This kinase, via protein phosphorylation, m then lead to activation of transporters, such as the sodium-inositol cotrans that promote solute uptake into the cells.

Clinical consequences

The near normalization of brain water content has two important clinical consequences. First, patients with chronic hypernatremia may be relatively asymptomatic, despite a plasma Na^+ concentration as high as 170 to 180 meq/L.[151] Thus, the severity of the neurologic symptoms is related to both the degree more importantly, *the rate of rise in the effective* P_{osm}. Symptoms appear to be primarily related to cerebral dehydration, which is more prominent with acu hypernatremia. Second, overly rapid correction of chronic hypernatremia ca the now near normal brain water to increase above normal, leading to *cerebral edema* and possible neurologic deterioration (see "Treatment," below).

Other Findings

Underlying neurologic disease frequently precedes the onset of hypernatrem it may be difficult to tell initially whether the neurologic abnormalities are,

in fact, due to the increase in the plasma Na^+ concentration. For example, patients with CDI, primary hypodipsia, and essential hypernatremia have hypothalam that may be due to tumors. Also, patients with decreased mentation due to or cerebrovascular disease are particularly prone to develop hypernatremia of their decreased access to water.[13] The relative roles of hyperosmolality and th underlying disease can be evaluated more accurately after the restoration o normal plasma Na^+ concentration.

In addition to the neurologic changes, hypernatremic patients may show sig volume expansion or volume depletion, depending upon the underlying dise mechanism. Patients with an Na^+ overload may have peripheral and/or pulmonary edema; in comparison, patients with an osmotic diuresis or enteric infectior have lost both Na^+ and water) may have marked extracellular volume depletion manifested by a jugular venous pressure below 5 cm H_2O, decreased skin turgor, and postural hypotension. These findings occur later when only water is lost (a diabetes insipidus or unreplaced insensible losses), since roughly two-thirc water deficit comes from the cells. The plasma Na^+ concentration usually exceeds 160 to 165 meq/L in these settings before signs of hypovolemia are detecte

As noted above, hypernatremia is uncommon in either form of diabetes insi because of the effectiveness of thirst. These patients complain of polyuria, and polydipsia rather than symptoms of hyperosmolality. Most normal subje highly concentrated urine only while sleeping at night, since no water is tal during this time. As a result, nocturia may be the only symptom in patients to moderate concentrating defect, as occurs, for example, with moderate re insufficiency. The underlying partial diabetes insipidus is usually masked d day, when there is no need form maximum ADH effect.

For reasons that are unclear, patients with central diabetes insipidus often predilection for iced water to satisfy their thirst.[152] It is possible that this represents activation of a cold-sensitive oropharyngeal receptor, since sucking ice chi acutely lower ADH levels in normal subjects—a response that is not seen w exposure to water at 25°C or to hypertonic saline.[152]

Untreated patients with chronic polyuria may also develop functional dilata bladder, hydroureter, and hydronephrosis because of voluntary suppression urination in an attempt to minimize urinary frequency. This can result in a n increase in bladder capacity such that the patient may void as much as 100 time.

DIAGNOSIS

Since polyuric states can, if accompanied by diminished thirst, lead to an e the plasma Na^+ concentration, the diagnostic approach to both hypernatremia polyuria will be considered in this section.

Hypernatremia

Hypernatremia generally occurs in adults with an altered mental status or i since there are the settings in which thirst is most often impaired. An awak patient with hypernatremia, on the other hand, can be assumed to have a hypothalamic lesion affecting the thirst center. Although the history may be (possibly polyuria, polydipsia, diabetes mellitus), neurologic abnormalities by the hyperosmolality or by underlying cerebral disease frequently limit th information that can be attained at presentation. In this setting, measureme U_{osm} can be particularly helpful.

To understand the meaning of this measurement, it is helpful to first review response of a normal subject to the induction of hypernatremia by water res or the administration of hypertonic saline. As the P_{osm} rises, ADH release is stimulated (Fig. 24-5), resulting in enhanced renal water reabsorption and an elevation in the U_{osm} to a maximum value of 800 to 1400 mosmol/kg (specific g equals 1.023 to 1.035). This limit represents *maximum ADH effect on the kidney* and is reached when the P_{osm} is 285 to 295 mosmol/kg. In this setting, the administ of *exogenous ADH will not induce a further increase in the* U_{osm}.[23]

Patients with hypernatremia (plasma Na^+ concentration above 150 meq/L) already have a P_{osm} greater than 295 mosmol/kg, the level at which the urine should maximally concentrated. Thus, two conclusions can be drawn from this U_{osm} setting:

- There is at least a partial defect in ADH release or effect if the U_{osm} is less than 800 mosmol/kg.

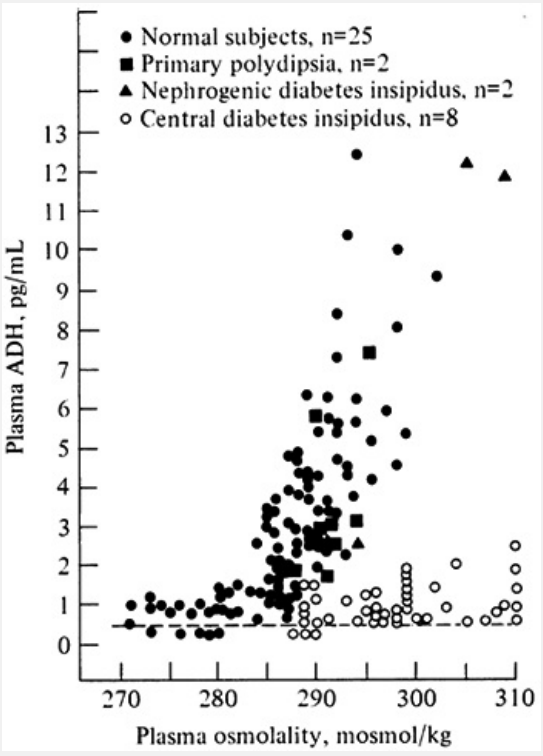

Figure 24-5 Relationship of plasma ADH levels to plasma osmolality in normal subjects and patients with polyuria of diverse etiologies. ADH secretion is reduced only in central diabetes insipidus. (*From Robertson GL, Mahr EA, Atkar S, Sinka J: J Clin Invest 52:2340, 1973, by copyright permission of the American Society for Clinical Investigation.*)

- Exogenous ADH (given as 5 units of aqueous vasopressin subcutaneous

μg of dDAVP by nasal insufflation) will increase only U_{osm} if endogenous secretion is impaired, as occurs in CDI.[23]

These responses can be used to evaluate the hypernatremia (Table 24-4):

1. Concentrating ability should be normal in subjects with Na^+ overload, enhanced insensible loss, and primary hypodipsia without CDI. In these conditions U_{osm} should exceed 800 mosmol/kg if there is no underlying concentrating defect, and will be unaffected by vasopressin. The urine Na^+ concentration is generally below 25 meq/L when hypernatremia is due to water loss but often well above 100 meq/L when hypernatremia is due to Na^+ overload.[129] Both the concentrated urine and the increased rate of Na^+ excretion contribute to the high urine Na^+ concentration in this setting.
2. Either severe CDI or NDI is present if the urine is hypoosmotic to plasma (U_{osm} less than 300 mosmol/kg, specific gravity less than 1.010). These disorders can be differentiated by the administration of ADH, which will produce at least a 50 percent increase in the U_{osm} and a marked fall in urine volume in CDI but will have little or no effect in NDI (see below).[23]
3. Many patients fall in an intermediate area, with the U_{osm} ranging from 300 to 800 mosmol/kg (specific gravity of 1.010 to 1.023). This can reflect volume depletion in severe CDI, partial CDI, partial NDI, or an osmotic diuresis. Exogenous ADH is effective only in the first two conditions, augmenting U_{osm} by at least 60 mosmol/kg and frequently by much more.[23]

Table 24-4 Urine osmolality and response to ADH in patients with hypernatremia

Urine osmolality	Response to vasopressin
Less than 300 mosmol/kg	
CDI	+
NDI	-
300 to 800 mosmol/kg	
Volume depletion in CDI	+
Partial CDI	+

Partial NDI	-
Osmotic diuresis	-
Greater than 800 mosmol/kg	
Insensible or gastrointestinal water losses	-
Primary hypodipsia	-
Na^+ overload	-
Variable	
Essential hypernatremia	Variable

Two factors need to be considered when evaluating the U_{osm} in patients with hypernatremia:[1] the effect of concurrent volume depletion,[2] and the frequently limited clinical utility of finding values in the intermediate range. Volume de alone can raise the U_{osm} in severe CDI to as high as 400 mosmol/kg or more.[113,153] The ability to concentrate the urine in this setting is related to factors: The distal nephron, particularly the inner medullary collecting tubu some permeability to water even in the absence of ADH,[154] and the combination of a fall in glomerular filtration rate and a rise in proximal reabsorption induced hypovolemia can markedly diminish distal water delivery. Since delivery is s reabsorption of even a small amount of water in the inner medulla can subs raise the U_{osm} and lower the urine volume. This effect is more prominent in p with partial CDI, since volume depletion can increase in ADH release (altho lesser degree than in normal subjects) (see Fig. 24-5).[5] This provides an additional mechanism for raising the U_{osm} and lowering the urine volume, possibly masking underlying polyuria. These changes are readily reversed with volume replet

Many individuals without hypernatremia have modest reductions in concentr ability (U_{max} between 350 and 700 mosmol/kg). Included in this group are pat with underlying renal disease and elderly subjects.[94,95,155] These patients are not polyuric, and loss of this mildly hyperosmotic urine will not substantially ra plasma Na^+ concentration. However, the ability of the kidney to conserve wat impaired in this setting, an abnormality that can play a contributory role in presence of some other insult, such as unreplaced insensible losses.

The U_{osm} in essential hypernatremia is variable and depends upon the state hydration: high if water-restricted, low if water-loaded. The presence of thi syndrome of selective osmoreceptor dysfunction should be suspected in a

persistently hypernatremic patient who is alert and in whom the administrat water is relatively ineffective in lowering the plasma $[Na^+]$ and Na^+ concentration.

Polyuria

Polyuria is a relatively common clinical problem. It is arbitrarily defined as volume above 3 liters per day and must be distinguished from urinary frequ more frequent complaint in which there are multiple voids of relatively smal and the urine volume is within the normal range.

The diagnostic approach to this problem can be simplified by considering p the outpatient and inpatient settings separately. The differential diagnosis outpatients includes *inappropriate* water loss due to CDI or NDI (particularly uncontrolled diabetes mellitus) and *appropriate* water loss due to increased water intake (primary polydipsia; see Chap. 23). (Table 24-5)[23]

The history may be helpful in identifying a possible cause for the polyuria. include NDI due to lithium or uncontrolled diabetes and CDI due to neurolo disease. Sarcoidosis can cause all three disorders associated with a

water diuresis: CDI or primary polydipsia due to granulomatous infiltration hypothalamus and NDI due to hypercalcemia.[46]

There are several other clues in the history and laboratory data that may p toward the correct diagnosis.

Table 24-5 Major causes of polyuria

	Appropriate	Inappropriate
Water diuresis	Primary polydipsia	Central diabetes insipidus
(U_{osm} < 250 mosmol/kg)	Intravenous infusion of dilute solutions	Nephrogenic diabetes insipidus
Solute diuresis		
(U_{osm} > 300 mosmol/kg)	Saline loading Postobstructive diuresis	Hyperglycemia High-protein tube feedings Na^+-wasting nephropathy (rare)

1. Patients with CDI frequently have a predilection for very cold or iced w

finding that does not seem to be present in other polyuric disorders.[152] In addition, CDI typically begins abruptly, so that the patient can date the onset of the disease. A more gradual onset suggests NDI or primary pol

2. Severe polyuria with a urine output exceeding 4 to 5 L/day is seen only primary polydipsia or a severe concentrating defect (U_{max} less than 200 to 250 mosmol/kg). In general, the latter occurs primarily with CDI, lithium toxi congenital NDI. Marked polyuria can occur but is unusual in the other c acquired NDI.

3. Measurement of the plasma Na^+ concentration may be helpful in selected cas Primary polydipsia is a disorder of water excess, so the plasma Na^+ concentration is typically in the low-normal range (135 to 140 meq/L) ar rare cases in which there is massive water intake, be associated with tr hyponatremia.[23,156] In comparison, diabetes insipidus is a disorder of wat loss, and the plasma Na^+ concentration tends to be in the high-normal rang (140 to 145 meq/L).[23] Although there is substantial overlap between the pla Na^+ concentrations in these conditions, a clearly high or low value can toward the likely diagnosis.

Water-restriction test

The definitive diagnosis can be made by inducing hyperosmolality with com water restriction, thereby stimulating endogenous ADH release and raising the U_{osm}.[23] The urine volume, U_{osm}, and body weight are measured hourly and the P_{osm} and plasma Na^+ concentration every 2 h. Water restriction is continued until the U_{osm} reaches a plateau (defined as less than a 30-mosmol/k increase in the U_{osm} in two consecutive hourly specimens) or

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until the P_{osm} reaches 295 to 300 mosmol/kg.[24] At the latter level, the plasma ADH concentration is usually greater than 3 to 5 pg/mL (Fig. 24-5), which should lead to maximum ADH effect on the kidney in subjects with normal renal function.[157] At this point, exogenous ADH [10 µg of desmopressin (dDAVP) by nasal insufflation or 1 µg subcutaneously or intravenously] is given and the hourly measurements continued. (The subcutaneous administration of aqueous vasopressin is now used.)

Accurate interpretation of the water-restriction test generally requires that desmopressin *not be given* before the U_{osm} has stabilized or the P_{osm} has reached 295 mosmol/kg. Below this level, maximum *endogenous* ADH effect may not be present and an antidiuretic response to desmopressin is of no diagnostic va since it will raise the U_{osm} even in normal subjects. One exception to this rule is the patient in whom NDI is strongly suspected (e.g., gradual onset of polyu patient on chronic lithium therapy). In this setting, simply giving desmopres without water restriction may be sufficient to establish the diagnosis if the shows little or no response using the criteria described in the next section.

The different patterns of response during the water-restriction test are illus
Fig. 24-6In normal subjects, the urine becomes maximally concentrated, the
volume falls to less than 0.5 mL/min, and the administration of desmopressi
without effect. Patients with complete or partial CDI or NDI respond to indu
hyperosmolality and desmopressin in the same manner as when endogenous
released in response to spontaneously developing hypernatremia and
hyperosmolality (Table 24-4). Urinary concentration is impaired; therefore, the u
osmolality does not rise to the level seen in normal subjects.

A major positive response to desmopressin is seen only with CDI. The eleva
urine osmolality ranges from 100 to 800 percent in complete and 15 to 50 p
partial CDI, typically to values above the plasma osmolality.[23,159] This increase in
urinary concentration is associated with an equivalent fall in urine output.

Many patients with NDI are partially, not completely, resistant to ADH. As a
administration of desmopressin (which produces a supraphysiologic antidiu
response) may result in a modest (up to 45 percent) elevation in urine
osmolality.[23,159] Although this value is similar to that seen with partial CDI, t
absolute numbers are quite different. Patients with partial CDI usually have
osmolality of 300 mosmol/kg or higher after water restriction, while patients
symptomatic NDI typically have a persistently dilute urine after water restri
an osmolality that rises, but remains well below isosmotic, after desmopres
noted above, the history may also be helpful in distinguishing

between these disorders. NDI is a rare cause of true polyuria in adults in tl
absence of lithium use, hypercalcemia, or rarely tubular damage in patients
amyloidosis or Sjögren's syndrome.

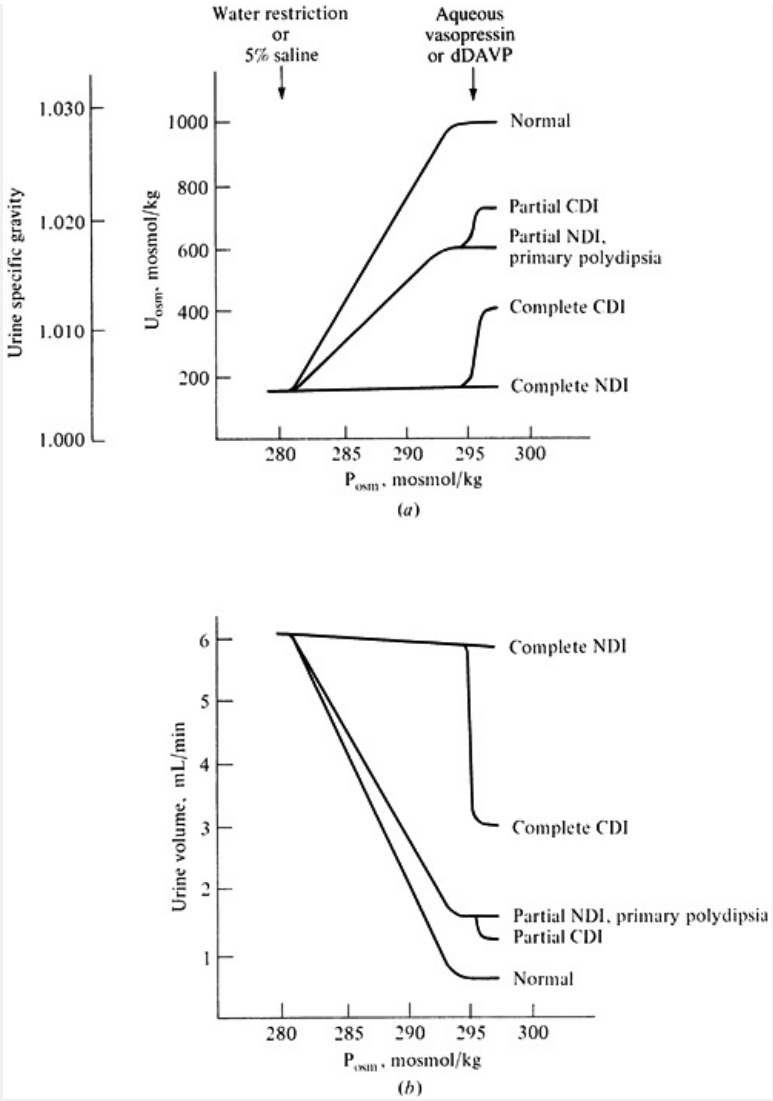

Figure 24-6 Effect of the induction of hyperosmolality, either by water restr or by hypertonic saline, and exogenous ADH (vasopressin) on (*a*) urine osmolality and (*b*) urine volume in normal subjects and in polyuric states. In normal subjects, there is maximum ADH effect on the kidney as the P_{osm} reaches 285 to 295 mosmol/kg, resulting in a U_{osm} greater than 800 mosmol/kg and a urine volume less than 0.5 mL/min. Exogenous ADH will be without In patients with complete central diabetes insipidus (CDI) or nephrogenic diabetes insipidus (NDI), the urine will remain hypoosmotic to plasma with urine volume. ADH will increase the U_{osm} and lower the urine volume only in CDI. Patients with partial CDI (or complete CDI with volume depletion) or show an intermediate response, and only the former will respond to ADH. primary polydipsia may induce a form of acquired NDI, these tests may no differentiate this condition from other mild forms of NDI.

As depicted in Fig. 24-6, the U_{max} achieved in CDI (after vasopressin) and prima polydipsia is less than that in normal subjects. In both of these disorders, A secretion is reduced (due, in primary polydipsia, to the chronic water loadi addition, chronic overhydration in primary polydipsia appears to downregul

release, so that plasma ADH levels in response to an elevation in the plasm osmolality are subnormal.[160] Since the lack of ADH impairs urea accumulation ir medullary interstitium, interstitial osmolality and, therefore, the U_{max}, are diminished (see page 127). This defect is readily correctible by the chronic administratio desmopressin in CDI or by the restriction of water intake in primary polydip both conditions represent *reversible forms of acquired NDI*.

Primary polydipsia can usually be differentiated from other causes of NDI b history and laboratory data and, since ADH secretion is normal (Fig. 24-5), from partial CDI by its lack of response to desmopressin.

Patients undergoing the water-restriction test must be monitored carefully, complications can occur. In some patients with complete CDI, for example, t output can reach 700 to 800 mL/h. In this setting, severe volume depletion vascular collapse can occur if water deprivation is allowed to continue bey above limits (stable U_{osm} or P_{osm} of 295 mosmol/kg). In general, the maximum weight loss should not exceed 3 to 5 percent of body weight. A loss of 1.0 t is usually sufficient, requiring 4 to 12 h of water restriction. A longer perio necessary in patients with primary polydipsia, who may be water-overloade start of the test. These patients must be observed carefully, since they can bizarre ways in which to ingest water, e.g., from a flower vase.

Results similar to those of the water-restriction test can be obtained by ind hyperosmolality with an intravenous infusion of hypertonic saline. This has called the Hickey-Hare test. Five percent saline (Na^+ concentration of 855 meq/L) is infused at the rate of 0.05 mL/kg/min for no more than 2 h, and the urine vo U_{osm} are followed.[122] This method is used less frequently than water restricti because of the danger of circulatory overload. It does, however, have the a of being shorter than the water-restriction test, and it may be particularly u essential hypernatremia, where hypertonic saline may produce a paradoxica the U_{osm} since ADH secretion is governed primarily by volume, not osmolali (Fig. 24-3).

Although the response to water restriction or hypertonic saline has been th standard approach to patients with polyuria, these tests are indirect, since P_{osm} is used as an index of ADH secretion or effect. The accuracy of the water r test has been evaluated directly by concomitant measurement of plasma AD levels.[159] The water-restriction test established the correct diagnosis in 80 of patients, with the *major error occurring in the distinction between the partia and primary polydipsia*. Some patients with partial CDI appear to have increase sensitivity to ADH,[159] possibly because of compensatory upregulation of hormo

receptors.[161] As a result, they are polyuric at the normal P_{osm} of 280 to 290 mosmol/kg, when ADH secretion is low, but have a maximally concentrated u P_{osm} of 295 mosmol/kg, when their ADH levels are higher but still subnorma administration of desmopressin will produce no further effect in this setting incorrect diagnosis of primary polydipsia will be made.

Distinguishing between partial CDI and primary polydipsia is essential from viewpoint of therapy: The administration of desmopressin will relieve the po and polydipsia in CDI but can produce *potentially life-threatening hyponatremia* primary polydipsia, since the excess water now cannot be excreted. Measur plasma ADH levels is less easily available and of variable utility. Normal va indicate primary polydipsia,[159] but, as noted above, there is frequent downregulation of ADH release in this disorder, so that subnormal values si those in partial CDI are often seen.[160]

Thus, when the results of the water-restriction test are not definitive, the c clues described previously (acute versus gradual onset, presence of psychi illness) can be used to suggest the correct diagnosis. In appropriate patien whom primary polydipsia seems less likely from the history, it is reasonable institute a trial of desmopressin (see "Treatment," below). Patients with CDI will not immediate relief of the polyuria and the polydipsia. The urine output will al primary polydipsia, but stimulation of thirst will persist and the excess wate may be retained. As a result, careful monitoring of the plasma $[Na^+]$ concentration is required if intake remains high.

Another possible error with the water-restriction test occurs in polyuria dev during pregnancy. As noted above, this disorder, which has been called ges diabetes insipidus, is typically due to the release of vasopressinases from placenta).[110,111] In this setting, the patient will be resistant to aqueous vaso (mistakenly suggesting NDI) but will respond to desmopressin.[112]

Polyuria in hospitalized patients

The approach to polyuria must be modified when it develops in the hospital setting, the increase in urine output frequently reflects a *solute (or osmotic) diuresis* due to the administration of large amounts of saline solutions, the use of h high-protein enteral feedings,[51] or the relief of urinary tract obstruction.[162,163] It is useful to evaluate such patients by asking two questions (Table 24-5):

- Does the polyuria reflect a solute or a water diuresis?
- Is the diuresis appropriate or inappropriate?

Water transport in the kidney occurs by two passive mechanisms: It follows reabsorption of NaCl in the proximal tubule and loop of Henle, and, in the p of ADH, it is reabsorbed down a favorable osmotic gradient in the collecting (see Chap. 4). Thus, polyuria, which represents an increase in water excretio occur during a solute diuresis, when NaCl reabsorption is reduced, or durin water diuresis due to diminished activity of ADH.

If polyuria is arbitrarily defined as a urine output exceeding 3 to 4 L/day, th distinction between a solute and a water diuresis can usually be made by m the U_{osm}. A U_{osm} below 250 mosmol/kg generally indicates a water diuresis, a the patient should undergo a water-restriction test to differentiate diabetes

from increased water intake (including fluids administered intravenously). C exception to this general rule occurs in patients given large volumes of hal saline. In this setting, there will be both a water diuresis (due to the dilute a Na^+ diuresis that will be apparent from the high rate of Na^+ excretion.

An isosmotic or hyperosmotic urine (U_{osm} greater than 300 mosmol/kg), on the oth hand, is generally indicative of a solute or osmotic diuresis. Although parti NDI can also result in a similar U_{osm}, such a moderate concentrating defect will n lead to marked polyuria if solute excretion is normal. The normal range of s excretion (composed primarily of Na^+ and K^+ salts and urea) on a typical western diet is 600 to 900 mosmol/day. If this U_{max} is 300 mosmol/kg, then the maximum uri output will be only 2 to 3 L/day (900 mosmol/day ÷ 300 mosmol/kg = 3 L/da value greater than this can be achieved only if solute excretion is increase U_{osm} is reduced.

In patients with a solute diuresis, hyperglycemia and high-protein feedings excluded by the history and laboratory data. In uncertain cases, measuring Na^+, glucose, and urea concentrations can be used to identify the major sol is being excreted. When Na^+ is the primary solute, the polyuria is *almost always appropriate*, being induced by volume expansion due to the administration of excessive amounts of saline or the release of bilateral urinary tract obstruc

Some patients, for example, may have a urine output in excess of 10 L/day of the initial infusion of 1 to 2 liters of saline followed by orders to replace output with an equivalent volume of saline. As a result, the urine output gra increases, since the patient remains volume-expanded. Similarly, a postobs diuresis is almost always appropriate, representing the excretion of fluid re during the period of obstruction.[162,163] The correct therapy in either of these settings is to limit fluid intake to a maintenance level, thereby allowing the develop negative fluid balance. The polyuria will cease when the excess flu been excreted.

An *inappropriate* sodium diuresis as a cause of polyuria is much less common should be suspected if the patient develops hypotension, reduced skin turg decreased renal function. Although Na^+ wasting can occur with renal insufficiency the uncommon disorder cerebral salt wasting, polyuria is an unusual compla these disorders, since the obligatory urine output is generally less than 2 L[164] The kidney has an important protective mechanism that prevents more seve wasting: tubuloglomerular feedback, which is mediated by the cells of the m densa. Through this phenomenon, increased sodium chloride delivery to the densa (due to decreased proximal and/or loop reabsorption) results in affer arteriolar constriction and a fall in the glomerular filtration rate, thereby lir degree of sodium chloride loss (see Chapter 2).

These observations imply that when severe salt wasting, appropriate or inappropriate, does occur, there must be an impairment in tubuloglomerular feedback. This can be achieved by volume expansion (which permits approp

wasting), the administration of loop diuretics (which prevents sensing of th in Cl^- delivery by blocking the Na^+-K^+-$2Cl^-$ cotransporter in the luminal membrane the macula densa cells), and glucosuria in uncontrolled diabetes mellitus (v uncertain mechanism).[165][166]

One rare setting in which inappropriate salt wasting can be severe enough produce polyuria is after the administration of dopamine to some hypotensi patients with sepsis.[167][168] The urine output can exceed 300 to 500 mL/h in thi setting. How sepsis might potentiate the normal natriuretic effect of dopami Chap. 6) and why it occurs so infrequently are not known.

Clinical Example

The sequential approach to the polyuric patient can be illustrated by the fo case history.

Case history 24-1

A 60-year-old man has a cardiac arrest and is resuscitated. Although circul function is restored, the patient remains comatose. The urine output is noti increase to 300 to 400 mL/h within the first day. At this time, the laboratory reveal the following:

$$\text{Plasma } [Na^+] = 144\ \text{meq/L}$$
$$P_{osm} = 290\ \text{mosmol/kg}$$
$$U_{osm} = 120\ \text{mosmol/kg}$$

A water-restriction test is begun. When this P_{osm} is 296 mosmol/kg, the U_{osm} is only 130 mosmol/kg, but it rises to 370 mosmol/kg after the administration of desmopressin. A diagnosis of CDI is made, and the patient is begun on desi therapy and enteral hyperalimentation. The urine output is initially well cor but it increases to over 150 mL/h on the fourth day and is now refractory to desmopressin. At this time, examination of the urine reveals the following:

$$U_{osm} = 500\ \text{mosmol/kg}$$
$$[Na^+] = 30\ \text{meq/L}$$
$$[K^+] = 33\ \text{meq/L}$$
$$[\text{Glucose}] = 0$$
$$[\text{Urea nitrogen}] = 840\ \text{mg/dL}$$

Comment

The low U_{osm} when the patient is initially polyuric indicates the presence of diuresis. The subsequent response to the water-restriction test is consistei CDI, presumably induced by hypoxic encephalopathy.

The recurrent polyuria, in comparison, is refractory to desmopressin, a find consistent with CDI. However, the high U_{osm} of 500 mosmol/kg indicates that this i a solute diuresis, probably due to the high-protein enteral alimentation. Th diagnosis was confirmed by analysis of the urine, which demonstrated that the major urinary osmole; a urea nitrogen concentration of 840 mg/dL repre

concentration of 300 mmol/L or 300 mosm/kg. Treatment of the polyuria now requires a decrease in protein intake, not administration of higher doses of vasopressin.

TREATMENT

General Principles

Rapid correction of hypernatremia can produce *cerebral edema, seizures, permanent neurologic damage, and death*[141169] This potential complication is a direct resu of the beneficial increase in brain volume toward normal that initially prote the symptoms of hypernatremia (see Fig. 24-4). In this setting, a rapid reduction in the P_{osm} results in water entry into the brain down an osmotic gradient, ther increasing brain volume to above normal levels. The brain cells can lose th K^+ and Na^+ taken up during osmotic adaptation relatively quickly, thereby mi the risk of cerebral edema. However, this protection is not complete, since of excess osmolytes occurs more slowly, perhaps because of the time requi stop synthesizing new transporters (such as the Na^+-H^+ cotransporter) and to remove previously inserted transporters from the cell membrane.[139148]

To minimize this risk, the current recommendation is that the *plasma [Na+] concentration be slowly lowered* unless the patient has symptomatic hypernatrem (see below). The potential danger of more rapid correction is illustrated by following example.

Case history 24-2

A slightly somnolent 19-year-old woman is found to have a plasma Na^+ concentration of 183 meq/L. Her past history reveals 3 years of progressive panhypopitui which was being treated with hydrocortisone and thyroid hormone replacem patient is given large volumes of dextrose and water in an attempt to correc hypernatremia. During the first 6 h, the plasma Na^+ concentration falls to 154 meq/L but the patient becomes unresponsive. A lumbar puncture reveals an openir pressure of 30 cm H_2O (normal is 10 to 20 cm H_2O), clear fluid, and no cells. Over the next 36 h, the patient's mental status gradually returns to normal.

Water Deficit

Most cases of hypernatremia are due to water loss. Gradual correction of tl problem with fluid replacement requires calculation of the water deficit. Th to estimate this deficit can be derived in the following way. The quantity of in the body is equal to the osmolal space [the total body water (TBW)] time osmolality of the body fluids:

$$\text{Total body osmoles} = \text{TBW} \times P_{osm}$$

Since the P_{osm} is primarily determined by the plasma Na^+ concentration,

$$\text{Total body osmoles} \propto \text{TBW} \times \text{plasma } [Na^+] \qquad (24\text{-}4)$$

If hypernatremia results only from water loss, then

$$\text{Current total body osmoles} = \text{normal total body osmoles}$$

or, if the normal plasma $[Na^+]$ concentration is 140 meq/L,

$$\text{Current body water (CBW)} \times \text{plasma } [Na^+] = \text{normal body water (NBW)} \times 140$$

Solving this equation for normal body water,

$$\text{NBW} = \text{CBW} \times \frac{\text{plasma } [Na^+]}{140} \qquad (24\text{-}5)$$

The water deficit can then be estimated from

$$\text{Water deficit} = \text{NBW} - \text{CBW}$$

or, by substituting for NBW from Eq. 24-5,

$$\text{Water deficit} = \left(\text{CBW} \times \frac{\text{plasma } [Na]^+}{140}\right) - \text{CBW}$$
$$= \text{CBW} \times \left(\frac{\text{plasma } [Na^+]}{140} - 1\right) \qquad (24\text{-}6)$$

The total body water is normally about 60 and 50 percent of lean body weig
and women, respectively. However, it is probably reasonable to use values
percent lower in hypernatremic patients who are water-depleted. Thus, in w
Eq. 24-6 becomes

$$\text{Water deficit} = 0.4 \times \text{lean body weight} \times \left(\frac{\text{plasma } [Na^+]}{140} - 1\right) \qquad (24\text{-}7)$$

This formula estimates the amount of positive water balance required to ret
plasma Na^+ concentration to 140 meq/L. It does not include any additional
fluid deficit, a condition that is frequently present when both Na^+ and wa
been lost, as occurs with an osmotic diuresis.

The patient described in Case History 24-2 can be used as an example of t
approach to therapy. If her lean body weight were 50 kg, then

$$\text{Water deficit} = 0.4 \times 50 \times \left(\frac{183}{140} - 1\right)$$
$$= 6 \text{ liters}$$

Although no definitive trials have been performed, observations in children
that the *maximum safe rate at which the plasma Na^+ concentration should be lowered (in the absence of hypernatremic symptoms) is 0.5 meq/L per hour* (12 meq/L per day),[170] a rate equivalent to that in severe hyponatremia (see page 725).

Thus, administration of 6 liters of free water to lower the plasma Na^+ concentration by 43 meq/L should occur over a minimum of 86 h, which represents a rate administration of 70 mL/h. Since the aim is to induce positive water balance estimated insensible losses (usually 30 to 50 mL/h) must be replaced raisin infusion rate of free water to about 110 mL/h.

Although not applicable to this patient, high levels of urinary or gastrointes losses must also be considered in the replacement calculations. It is import regard to return to the idea that the plasma Na^+ concentration is affected only by

Na^+, K^+, and the total body water. For example, a patient with hypernatremia lithium-induced nephrogenic diabetic insipidus may put out 150 mL/h of isos urine (urine osmolality equals 325 mosmol/kg) because, as noted above, vo depletion ameliorates the polyuria. At first glance, it may appear that there water in the urine and therefore that the urinary losses do not have to be r order to correct the hypernatremia (even though replacement is indicated fo prevention of volume and potassium depletion). However, as described in Chap. 9 urinary urea and ammonium may make up much of the urine osmolality even their loss does not affect the plasma Na^+ concentration. Thus, it is the urine (Na^++K^+) concentration that must be evaluated, not the total urine osmolalit value is 60 meq/L in a patient with a plasma (Na^++K^+) concentration of 150 meq/L, then the effective urine osmolality is basically 40 percent that of the plasm though the total urine output is free water and must be added to the above calculations to correct the hypernatremia. The polyuria and therefore the w replacement requirements are likely to increase as the hypovolemia is corre

The type of fluid administered to replace these losses is variable, dependir the patient's clinical state and the cause of the hypernatremia:

1. Free water can be given orally or intravenously (as dextrose in water) patients with hypernatremia due to pure water loss.

2. An infusion of quarter-isotonic saline is preferable if Na^+ depletion is also present, as typically occurs with concurrent vomiting, diarrhea, or diure One liter of this solution is a combination of 750 mL of free water and 2 isotonic saline. Thus, about 150 mL/h of quarter-isotonic saline must be administered to provide 110 mL/h of free water.
3. Isotonic saline should be used initially if the patient is hypotensive. In setting, restoration of tissue perfusion is the most urgent requirement; be best achieved with isotonic saline. This solution may also lower the Na^+ concentration, since it is hypoosmotic to the hypernatremic patient. dilute solutions can be substituted once tissue perfusion is adequate.
4. The contribution of K^+ salts must be taken into account when calculating th tonicity of the fluid that is to be given. As an example, quarter-isotonic which 40 meq of K^+ has been added is osmotically equivalent to half-isotor saline.

It must be emphasized that Eq. 24-7 is only an approximation of the water deficit that serial measurements of the plasma Na^+ concentration are required to ascertai that the desired rate of correction is being achieved. For example, the tota water may be substantially less than 40 to 50 percent of lean body weight i patients who are cachectic. In this setting, the calculated TBW and water d be falsely elevated, possibly leading to an overly rapid reduction in the pla Na^+ concentration.

Central Diabetes Insipidus

The most physiologic therapy of CDI is to give exogenous ADH (This is typically achieved by the administration of desmopressin (dDAVP), a two-an

Table 24-6

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substitute of arginine vasopressin. In contrast to older vasopressin prepara desmopressin has more antidiuretic activity, has no vasopressor effect, and taken only once or twice a day (in 5- to 20-µg doses by nasal insufflation) of a longer duration of action.[172] In addition, chronic use of the other ADH preparations, but not desmopressin, can lead to anti-vasopressin antibody production and a secondary increase in urine output that now appears to be ADH-resistant.[173]

Table 24-6 Drug therapy of central diabetes insipidus according to probable mechanism of action

ADH preparations
A. dDAVP nasal spray (desmopressin)
B. Aqueous vasopressin
C. Lysine-vasopressin nasal spray
D. Vasopressin tannate in oil
Drugs that potentiate ADH effect
A. Chlorpropamide
B. Carbamazepine
C. Nonsteroidal anti-inflammatory drugs
Drugs that increase ADH secretion
A. Clofibrate
Drugs not requiring ADH
A. Thiazide diuretics

An oral tablet preparation of desmopressin is available in 0.1- and 0.2-mg s absorption of desmopressin in normal persons is decreased by 40 to 50 per when taken with meals.[174] This usually has little effect on the antidiuretic actio administering the drug in the fasting state may be tried if there is a poor re the usual doses taken with meals.

The oral form has about one-tenth to one-twentieth the potency of the nasa because only about 5 percent is absorbed from the gut. Thus, a 0.1-mg tab equivalent of 2.5 to 5 µg of the nasal spray. However, because the oral dos be precisely predicted from a previous nasal dose, transferring from nasal therapy will usually require some retitration.

The oral form of desmopressin is typically preferred because of ease of administration. The initial dose is 0.05 mg (one-half a 0.1-mg tablet) at bec subsequent titration according to response. The usual daily maintenance do ranges from 0.1 to 0.8 mg in two or three divided doses but may be as high mg/day.

There are few long-term data on the use of oral desmopressin. In one study children with central DI were treated and followed for up to 3 years.[175] There was no attenuation of the antidiuretic effect, and no side effects or antibody for was noted. In another report, 10 adults had satisfactory maintenance of the antidiuretic effect over 1 year with doses of 0.3 to 0.6 mg/day given in two doses per day; doses larger than 0.2 mg—e.g., 0.4 versus 0.2 mg—had no g effect, but probably lasted longer.[176]

It is important to be aware that there is potential risk to the administration desmopressin in CDI. Patients with this disorder are polyuric but not in dan marked fluid loss and hypernatremia as long as their thirst mechanism is in However, once desmopressin is given, the patient has ADH activity *interrupted* and is at risk of developing water retention and hyponatremia. As a result, *minimum dose must be used to allow the maintenance of an adequate urine* This can be achieved by giving the first dose in the late evening to control troubling symptom, nocturia. The necessity for and size of a daytime dose c be determined from the effectiveness of the evening dose. If, for example, p does not recur until noon, then half the evening dose may be sufficient at t

Non-ADH therapy

Although desmopressin is the treatment of choice for CDI, other drugs can given to lower the urine output (Table 24-6).[176] For example, the induction of mild volume depletion with a low-sodium diet and a thiazide diuretic (such as hydrochlorothiazide, 12.5 to 25 mg once or twice daily) is often extremely e diabetes insipidus, being primarily used in patients

with NDI. Although it seems paradoxical to treat polyuria with a diuretic, as 1.0- to 1.5-kg weight loss can reduce the urine output by more than 50 perc for example, almost 10 L to below 3.5 L per day.[177] Addition of the K+-sparing diuretic amiloride can enhance the response, while also minimizing thiazide hypokalemia.[178]

This response is primarily due to diuretic-induced hypovolemia. Volume dep associated with enhanced proximal NaCl and water reabsorption (see Chap. 8).[113] As a result, less water is delivered to the collecting tubules (the site of ADH act and therefore less water is excreted (Note that a *loop diuretic should not be*

used in this setting, since it will further impair concentrating ability by inhib
first step in the countercurrent mechanism: The reabsorption of NaCl witho
in the thick ascending limb of the loop of Henle (see Chap. 4).

The addition of moderate dietary protein restriction can also contribute to
the polyuria. The combination of sodium and protein restriction reduces the
solute excretion, which, as described above, will diminish the urine output
diabetes insipidus.

The action of diuretics and diet is *independent* of ADH. In contrast, the other drugs
used in the treatment of CDI act by potentiating the effect of ADH or by inc
secretion (Table 24-6). These drugs generally require at least some ADH to be
present and are not effective in those patients who secrete no ADH, as may
after neurosurgery.[29]

Chlorpropamide is an oral hypoglycemic agent (now largely replaced by other
hypoglycemic drugs) that enhances the action of ADH.[179,180,181] Two different
mechanisms may contribute to this response: increased efficiency of the
countercurrent mechanism by enhanced NaCl reabsorption in the thick asce
limb of the loop of Henle[182,183] and a direct elevation in collecting tubule water
permeability.[184] These unique effects of chlorpropamide allow it to be given a
in conjunction with desmopressin, since it will potentiate the antidiuretic re

The usual dose of chlorpropamide is 125 to 250 mg, once or twice a day. H
doses (up to 1250 mg/day) can increase the antidiuresis,[180] but they also increase
the risk of hypoglycemia and should not be used. If hypoglycemia does dev
problem that is particularly likely to occur in patients with associated anter
pituitary insufficiency, the dose can be reduced or a thiazide can be added,
latter tends to raise the plasma glucose concentration (Fig. 24-7).[179,185]
Occasionally, chlorpropamide has to be discontinued because of severe or
hypoglycemia.

Both *clofibrate* (now rarely used in the treatment of hyperlipidemia; 500 mg ev
h)[186,187] and *carbamazepine* (used in the treatment of seizures and tic doulour
100 to 300 mg, twice daily) also can effectively lower the urine output in pa
CDI.[180,188,189] Clofibrate appears to enhance ADH secretion,[186] whereas
carbamazepine seems to increase the effect of ADH[189,190,191] and perhaps augment its
secretion cases.[191]

Like thiazide diuretics, carbamazepine and clofibrate can produce more tha
percent reduction in urine output in responsive patients. If, however, this

represents a decrease in output from 12 to 6 L/day, then the patient, althou
improved, will still complain of polyuria. In this setting, combination therap
used. Additive antidiuretic effects can often be achieved by choosing agent
have different mechanisms of action. For example, a thiazide diuretic and
chloropropamide can be used together or in conjunction with desmopressin
excellent results (Fig. 24-7).[179] Carbamazepine and chlorpropamide also can be

effective combination.[180]

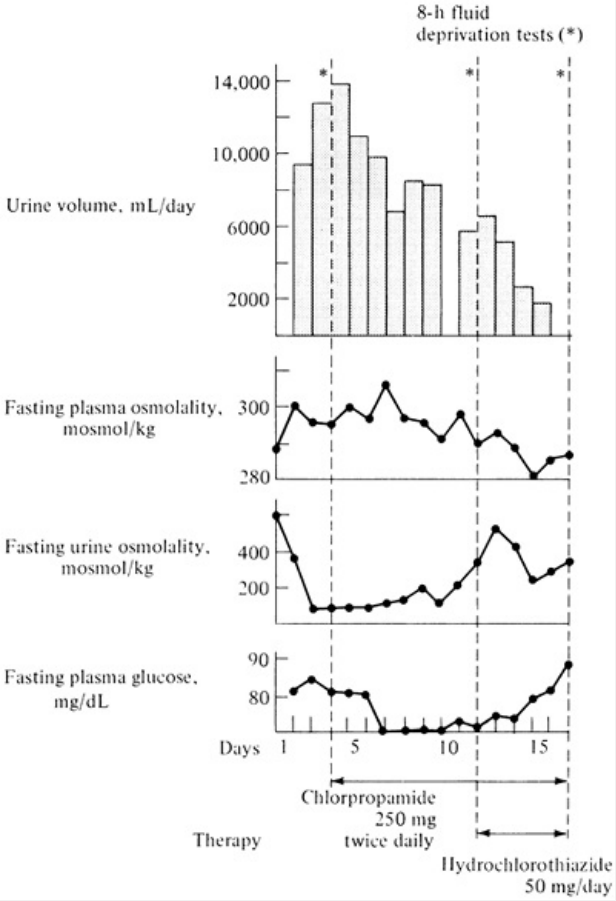

Figure 24-3 Serial observation in control and treatment periods in a patient partial CDI. Note the additive antidiuretic effects of chlorpropamide and hydrochlorothiazide, and the ability of the latter drug to protect against a the plasma glucose concentration induced by chlorpropamide. (*From Webster B, Bain J,* J Clin Endocrinol Metab *30:215, 1970. Used by permission from the Journal of Clinical Endocrinology and Metabolism and from*) Lippincott

As discussed in Chap. 23, the antidiuretic properties of thiazide diuretics, chlorpropamide, and carbamazepine can lead to water retention and hypona This is particularly true in patients with primary polydipsia. Thus, one must

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be certain to exclude the latter disorder as the cause of polyuria before be therapy for CDI. Less commonly, chloropropamide can induce symptomatic hyponatremia in patients with partial CDI.[179] Since the symptoms of hyponatremia can mimic those of hypernatremia and the therapy is diametrically opposite restriction versus water loading), it is important to establish the correct dia and not to assume the presence of hypernatremia (which does not occur in insipidus if thirst is intact) because of the history of CDI.

Administration of a nonsteroidal anti-inflammatory drug (NSAID) represents possible mechanism by which the ADH effect can be enhanced. Renal prost

normally impair the response to ADH, in part by diminishing the generation AMP (see page 172),[192,193] as a result, inhibiting prostaglandin synthesis with of these agents can lead to a significant potentiation of the response to AD[194] Because of the efficacy of the modalities described above, there is little ex with the use of NSAIDs in CDI; they have, however, been helpful in many pa with NDI.

Nephrogenic Diabetes Insipidus

Chronic therapy for NDI should be reserved for those patients with sympton polyuria in whom the renal defect is not rapidly correctable. This represent small group of patients, such as those with congenital NDI, lithium toxicity, amyloidosis or Sjögren's syndrome.[57,64,66] Specific treatment is not required whe the concentrating defect is reversible (drugs, osmotic diuresis, hypercalcer hypokalemia) or when polyuria is not a problem (renal failure, sickle cell ar

Since patients with NDI do not usually have a major response to ADH, desm or drugs depending upon ADH for their action are ineffective. The major for therapy in this disorder is the use of a *thiazide diuretic and a low-sodium, low-protein diet*, as described above in the treatment of CDI.[177,195] In addition, the K^+-sparing diuretic amiloride may produce additional benefit by two mechanism[1] can enhance the initial natriuresis by acting at a different site (cortical col tubule versus distal tubule and connecting segment with a thiazide),[178,2] and is specifically indicated in patients with mild to moderate lithium toxicity.[67] Fi lithium enters the collecting tubule cells through Na^+ channels in the luminal membrane; this pathway is blocked by amiloride. However, this effect of am will be beneficial only if the lithium is continued and only if the collecting t injury is at least partially reversible. (Reversibility is usually present if the urine osmolality that can be achieved is above 200 to 250 mosmol/kg.)

There is some risk, however, in using diuretics in patients who must contin lithium. Although the ensuing volume depletion can reduce the urine output,[66,67] also increases the proximal reabsorption of Na^+ and secondarily of lithium, resultin in decreased excretion and potential lithium toxicity.[196] Careful monitoring of the plasma lithium concentration is therefore required in this setting.

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One other modality that has been effective in some patients with congenital lithium toxicity is the administration of a NSAID, which increases urinary concentrating ability and lowers the urine volume[197,198,199] and[200] by impairing renal prostaglandin synthesis.[192] These agents can increase the U_{osm} even in the absence of ADH.[193]

In children with congenital NDI, for example, the administration of a NSAID the maximum U_{osm} by up to 100 percent, thereby reducing the urine volume by percent.[197,198,199] and[200] This beneficial effect is additive to that of a thiazi diuretic, potentially resulting in more than a two-thirds decline in urine out

the pretreatment level.[178,200] However, a similar response with fewer side effec can often be achieved with the combination of a thiazide and amiloride.[178]

It should not be assumed, however, that all NSAIDs are equally effective. In patients, ibuprofen has been without benefit despite a good antidiuretic res indomethacin.[198] In addition, sulindac may be less effective in this setting, si appears to relatively spare renal prostaglandin synthesis.[201]

There may be a role for desmopressin in patients with persistent symptoma polyuria after institution of the above regimen. Most patients with NDI have rather than complete resistance to ADH. Thus, attaining supraphysiologic h levels may increase the renal effect of ADH to a clinically important degree example, three patients described in two reports evaluating the water-restr in polyuric patients found that exogenous ADH raised the urine osmolality b percent, which should produce a similar decline in urine volume.[23,159]

Hypothalamic Dysfunction

The proper treatment of patients with hypothalamic dysfunction depends up pattern of ADH secretion. Patients with primary hypodipsia but without CDI simply treated with forced water intake.[9,10] The patient can be instructed to drink 1500 to 2000 mL of water per day, regardless of thirst. There is no risk of v overload in this setting, since the ability to excrete water is generally not i

Correction of the hypernatremia is somewhat more difficult in hypodipsic pa who also have partial CDI or essential hypernatremia. In these conditions, loading will diminish ADH secretion, resulting in polyuria, excretion of the i water, and persistent elevation of the plasma $[Na^+]$.[118,119,120] and [116,118,119,120,121] Chlorpropamide has been effective in many of these patients, and[121] probably by enhancing the action of the small amount of ADH being released.[118] There is, however, some risk of *hyponatremia* in this setting, since the osmoreceptor defect may prevent complete suppression of ADH release afte load.[7]

In addition to these regimens, an integral part of the therapeutic approach with CDI or hypothalamic disease is a neurologic evaluation to determine th underlying cause. Some tumors, for example, may respond to radiotherapy.

Sodium Overload

Therapy in patients with primary Na^+ overload is best aimed at removing the exce Na^+. When renal function is normal, the Na^+ will usually be excreted rapidly i the urine. This process can be facilitated by inducing a Na^+ and water diuresis with diuretics and replacing the urine output solely with water. Intravenous dext water can also be used in those patients who present with marked hypernat However, careful monitoring is necessary, since these patients are volume- and the excess fluid may lead to pulmonary congestion in susceptible cases

In patients with poor renal function or in infants, peritoneal dialysis with ar electrolyte-free, hypertonic (8%) dextrose and water solution can initially b remove the excess Na^+. Water retention is minimized, since the dialysis solu is hyperosmotic to plasma. The rate of dialysis should be adjusted to preve overly rapid fall in the plasma Na^+ concentration and the possible development of cerebral edema.

PROBLEMS

24-1A 45-year-old woman with sarcoidosis complains of drinking 8 to 1 of water per day. The results of laboratory studies are as follows:

$$\text{Plasma } [Na^+] = 134 \text{ meq/L}$$
$$P_{osm} = 274 \text{ mosmol/kg}$$
$$U_{osm} = 80 \text{ mosmol/kg}$$

a. **What is the most likely diagnosis?**

b. **How would you establish the correct diagnosis?**

24-2An 80-year-old partially senile woman treated with hydrochlorothi for hypertension is admitted from a nursing home with a 4-day history viral-like illness, diarrhea, and increasing confusion. Physical examin reveals a 50-kg woman with decreased skin turgor and mentation, but normal blood pressure. The laboratory findings include the following:

$$\text{Plasma } [Na^+] = 174 \text{ meq/L}$$
$$\text{Urine } [Na^+] = 5 \text{ meq/L}$$
$$U_{osm} = 606 \text{ mosmol/kg}$$

a. **Diarrhea**

b. **Decreased thirst**

c. **Diabetes insipidus**

d. **Diuretic therapy**

e. **Insensible losses**

Is the low urine Na^+ concentration surprising in a patient with hypernatre What is the most appropriate initial therapy for the hypernatremia?

a. **Isotonic saline at 100 mL/h**

b. **Five percent dextrose in water at 200 mL/h**

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c. **Quarter-isotonic saline at 100 mL/h**

d. **Quater-isotonic saline at 200 mL/h**

e. **Five percent dextrose in water at 500 mL/h**

24-3A 40-year-old male alcoholic is brought into the hospital in a coma

state. He is found to have a skull fracture. It is noted that his weight i and his urine output is 175 mL/h. The following laboratory data are obt

$$\text{Plasma } [Na^+] = 168\ \text{meq/L}$$
$$[K^+] = 4\ \text{meq/L}$$
$$[Cl^-] = 130\ \text{meq/L}$$
$$[HCO_3^-] = 25\ \text{meq/L}$$
$$P_{osm} = 350\ \text{mosmol/kg}$$
$$U_{osm} = 80\ \text{mosmol/kg}$$

a. **How would you confirm this diagnosis?**

b. **What is the approximate water deficit?**

c. **How much free water should be given and at what rate to lower the plasma Na^+ concentration to normal (assuming that the urine output fallen to low levels)?**

   The diagnosis of central diabetes insipidus is made, and the patier good response to vasopressin tannate in oil. Two days later, the pl Na^+ concentration has fallen to 124 meq/L.

d. **(d) What is responsible for the late development of hyponatremia?**

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Footnotes

* Some patients have a modest rise in U_{osm} after the administration of ADH, suggesting that a mild impairment in ADH release may also contribute to the polyuria.[64]

† This is in contrast to normal subjects, in whom the major factor affecting U_{osm} output is water intake via its effect on ADH secretion and subsequently the P_{osm}.

† Accurate measurement of the P_{osm} is an essential part of this test. A potential error of as much as 8 mosmol/kg can occur if the blood specimen is stored h after it has been obtained.[158] In this setting, persistent glycolytic activity in erythrocytes and leukocytes can result in the production of lactic acid and into the plasma. This problem can be prevented by refrigeration at 0°C or b separation of the plasma from the cells within 20 min.

‡ The urea nitrogen concentration in mg/dL must be divided by 2.8 to conve mmol/L or mosmol/kg (see page 15). Thus

$$[\text{Urea nitrogen}] = 840 \text{ mg/dL} \div 2.8$$
$$= 300 \text{ mosmol/kg}$$

¶ The osmotic contribution of dextrose usually can be ignored, since it is ra metabolized in nondiabetics to carbon dioxide and water. Thus, although 5 dextrose in water has an osmolality of 278 mosmol/kg, it is equivalent to fre the body. However, intravenous administration of large volumes of dextrose can, in some patients, lead to marked hyperglycemia, since the quantity of given can exceed the maximum amount that can normally be metabolized. This problem can be avoided by giving free water orally, by minimizing the urine CDI with desmopressin (see below), or by careful monitoring of the plasma concentration.

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Chapter Twenty-Five
Hyperosmolal states—hyperglycemia

PATHOPHYSIOLOGY

Hyperglycemia due to poorly controlled diabetes mellitus is a common clinic problem. In addition to producing a hyperosmolal state similar to hypernatre hyperglycemia may also be associated with severe metabolic acidosis (keto and volume depletion, both of which can jeopardize the life of the patient.

Although a complete discussion of the regulation of carbohydrate and fat m is beyond the scope of this chapter, a review of the roles of insulin, glucag other hormones is essential to understand the pathophysiology of this diso will be seen, both *insulin deficiency* and *glucagon excess* play a major role in the increases in glucose and ketoacid levels—glucagon by altering hepatic met to promote glucose and ketoacid production, and insulin deficiency by both hepatic function and increasing the supply of substrates to the liver to allo processes to occur.[1,2,3] and[4]

Glucose Metabolism

The glucose concentration in the extracellular fluid is determined by the re between production and utilization. Net glucose production is influenced by factors: dietary intake, glycogenolysis, and hepatic gluconeogenesis, using

P.795

lactate, amino acids (primarily alanine), and glycerol as substrates (Fig. 25-1). The glucose that is produced can then be utilized for energy or stored, for futur the liver and skeletal muscle as glycogen.

In the normal subject, the extracellular supply of glucose is carefully regula the plasma glucose concentration being maintained within narrow limits (60 mg/dL, fasting). Insulin and glucagon, which are secreted from the pancrea central role in this process by affecting both glucose production and glucos utilization (Fig. 25-1).[3,5,6] and[7] Following a glucose meal, the ensuing elevation the plasma glucose concentration produces a similar change in the pancrea cell as glucose enters the cell via GLUT2 and GLUT1 transporters in the ce membrane, the expression of which is increased by chronic exposure to hig concentration.[8,9]

The enzyme glucokinase, which phosphorylates glucose to glucose 6-phosp may act as the *glucose sensor* within the cell.[10] In mice, deletion of one of

the glucokinase genes reduces the glucose sensitivity of insulin secretion, deletion of both genes causes perinatal death due to severe hyperglycemia[11,12]. In humans, mutations in this enzyme can lead to one of the forms of maturity-o diabetes of the young[13].

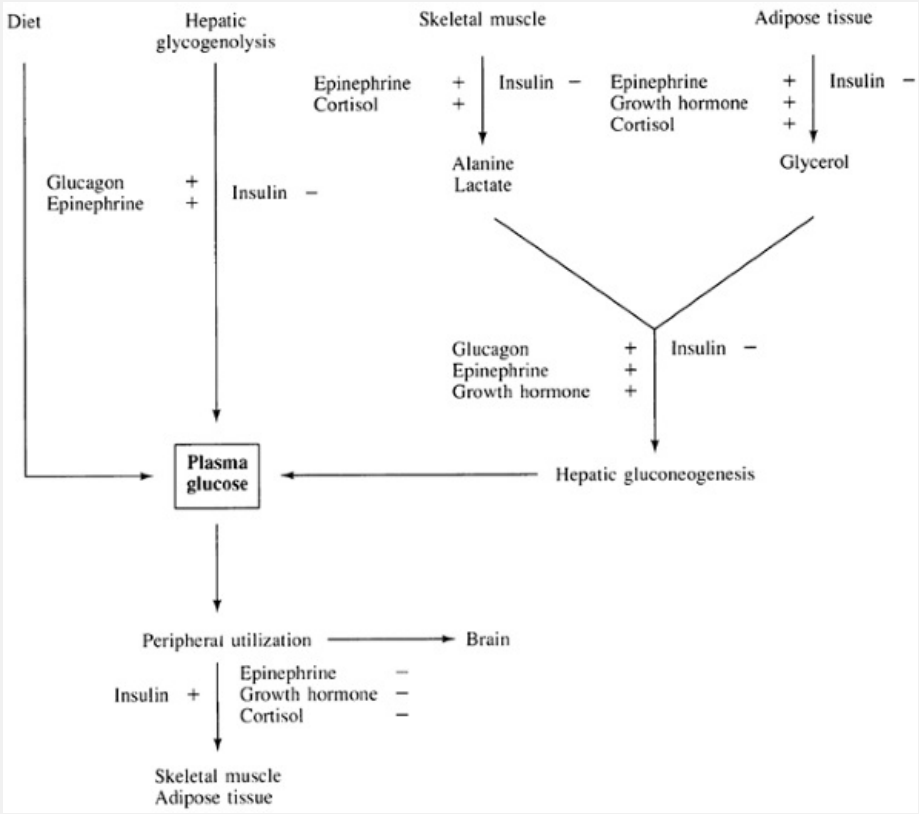

Figure 25-1 Hormonal regulation of carbohydrate and fat metabolism. Insuli glucagon are most important in this process: the former by increasing the utilization of glucose; the latter by increasing its rate of production.

The metabolism of glucose increases cellular adenosine triphosphate (ATP) concentrations and closes potassium-dependent ATP (KATP) channels in th cell membrane, causing membrane depolarization, an influx of calcium, and release[10]. The KATP channel plays an important role in this process. This ch a functional complex of the sulfonylurea 1 receptor (SUR1) and an inward r potassium channel subunit, Kir6.2[14,15]. The administration of a sulfonylurea is one the major therapies for treating type 2 diabetes, acting to increase insulin secretion. In addition, mutations in either the SUR1 gene or the Kir6.2 gen to the loss of KATP activity; thus, the cell is persistently depolarized, resul calcium influx and the release of insulin, producing a syndrome called pers hyperinsulinemic hypoglycemia of infancy[16].

Insulin acts to restore normoglycemia by three effects: It decreases hepatic production by diminishing both glycogenolysis and gluconeogenesis; it incr

glucose uptake by skeletal muscle and adipose tissue by translocating gluc transporters from an intracellular pool to the cell surface,[17] and it diminishes the hepatic delivery of the gluconeogenetic precursors, alanine and glycerol, b antiproteolytic and antilipolytic effects.[5,6,7] Insulin also inhibits glucagon secretion by direct inhibition of the glucagon gene in the pancreatic alpha [18] which further diminishes hepatic glucose production.[1,3]

Glucagon, in comparison, has a primary effect on hepatic glucose metabolism, altering the ratio between glycolysis and gluconeogenesis.[1,4] The major regulatory compound in this process is *fructose 2,6-bisphosphate* (fructose 2,6-P_2), which normally increases the activity of 6-phosphofructo-1-kinase (PF-1-K) and in activity of fructose 1,6-bisphosphatase; both of the latter enzymes are part bifunctional enzyme (Fig. 25-2).[1,19] PFK drives the reaction

$$\text{Fructose 6-phosphate} \leftrightarrow \text{fructose 1,6-bisphosphate} \qquad (25\text{-}1)$$

to the right, thereby promoting the conversion of glucose into pyruvate (glycolysis).[1,4] The last step in this sequence, the conversion of phosphoenolpyruvate to pyruvate, is further enhanced, since fructose 1,6-bisphosphate directly increases the activity of pyruvate kinase (Eq. 25-2).[19] In comparison, fructose 1,6-bisphosphatase (Eq. 25-1) is inhibited to the left, leading to gluconeogenesis, and pyruvate (derived in part from alanine and lactate) ca converted to glucose.

Glucagon, one of the counterregulatory hormones, is normally secreted in r to a fall in the plasma glucose concentration, which directly increases gluc expression.[20] After it reaches the liver via the portal vein, glucagon (acting v generation of cyclic adenosine monophosphate, or AMP (Fig. 25-2). *Pyruvate kinase* *fructose 2,6-P_2* Formation by decreasing the activity of 6-phosphofructo-2-kinas (PF-2-K), the enzyme that catalyzes the production of fructose 2,6-P_2 from fructose 6-phosphate (Fig. 25-2).[19] As a result, there is a concurrent inactivation of PFK disinhibition of fructose 1,6-bisphosphatase (Eq. 25-1),

moves to the left, a change that enhances gluconeogenesis, appropriately r plasma glucose concentration toward normal. Glucagon also promotes glycc breakdown, further increasing hepatic glucose production.[1]

Insulin tends to counteract the hepatic effect of glucagon, increasing PF-2-activity.[19] This leads to the formation of fructose 2,6-bisphosphate and the promotion of glycolysis.

Response to glucose load

In the fasting state, the liver produces glucose to meet basal energy requir process that is primarily mediated by glucagon.[3] Insulin levels are low at this time, and the glucose released from the liver is primarily taken up by the brain (a lesser degree by the red cells and the renal medulla), tissues that do not r insulin for glucose utilization.[6]

The subsequent ingestion of glucose leads to a rise in the plasma glucose concentration, which increases the secretion of insulin and reduces that of (which also falls because of the suppressive effect of hyperinsulinemia).[18-21] Arterial blood enters the core of each islet, delivering substrates and information first to cells, and then to the alpha and delta cells.[22] Thus, insulin released in response to a glucose load directly and appropriately suppresses glucagon release.

The degree of postprandial hyperglycemia is often minimized by concurrent induced release of cholecystokinin.[23] This hormone delays gastric emptying, there slowing the rate of glucose absorption.

In normal subjects, the glucose-induced changes in insulin and glucagon se produce two major changes: a 50 to 70 percent inhibition of hepatic glucos production and the peripheral utilization of the 70 percent of the glucose lo not taken up by the liver.[24,25] The net effect is that the plasma glucose concentration returns to baseline levels within several hours.

Response to hypoglycemia

These hormonal changes are reversed with hypoglycemia, as the secretion falls whereas that of glucagon rises.[6,26,27] The enhanced release of glucagon, which promotes both glycogenolysis and gluconeogenesis in the liver,[1,3] appears to be mediated by several factors, including the fall in insulin secretion, the d the plasma glucose concentration itself, and possibly a concurrent rise in epinephrine release.[28,29] In addition, glucose-sensing neurons in multiple brai areas appear to promote the release of glucagon and other counterregulato hormones.[30] These include epinephrine and, if the hypoglycemia is prolonge cortisol and growth hormone,[6,27] via both hepatic and peripheral effects (Fig. 25-1).[31,32] and[33]

Although less important than glucagon, other counterregulatory hormones t response to hypoglycemia are epinephrine, cortisol, and growth hormone:[27]

1. Epinephrine, acting via β -adrenergic receptors, has hepatic effects sim those of glucagon. It also increases the delivery of gluconeogenic subs from the periphery, inhibits glucose utilization by several tissues,[2] and v receptors, inhibits insulin secretion.
2. Cortisol and growth hormone contribute to increased glucose utilization the hypoglycemia is severe and persists for several hours. These hormo glucose utilization and enhance hepatic glucose production.

Studies in which hypoglycemia is induced by insulin infusion have demonst glucagon and epinephrine are of primary importance, as either hormone alo sufficient to protect against an excessive fall in the plasma glucose concentration.[6,27,28] Epinephrine also has a second major effect, producing

symptoms such as sweating, tremor, and tachycardia that provide an early v signal to the patient to ingest glucose to prevent progressive neuroglycope

Severe hypoglycemia can ensue if the ability to increase the secretion of th hormones is impaired, because of both diminished glucose generation and t of early warning symptoms.[6,34] This is of particular importance in diabetics, who may have such a combined hormonal defect resulting from concurrent pancr alpha cell dysfunction and autonomic neuropathy, respectively.[6,34] It is unclear why diabetics are unable to increase plasma glucagon levels in response to hypoglycemia, since they are able to respond to other stimuli such as amin ingestion.[26] One possible mechanism is the absence of the normal reduction insulin secretion that in nondiabetic subjects is partially responsible for th hypoglycemia-induced rise in glucagon release.[29]

As a result, intensive insulin therapy to correct the hyperglycemia and poss prevent diabetic microvascular complications[35] is associated with a much greater risk of symptomatic hypoglycemic episodes in patients with defective counterregulation.[34] This increase in risk is often enhanced by the attempt at glucose control that is associated with impairments in the threshold for the counterregulatory hormones and in the development of warning neurologic s in response to hypoglycemia.[34,36,37] It has been suggested that these maladapti changes result from recurrent episodes of hypoglycemia that are frequently by intensive insulin therapy. The combination of strict glycemic control plus prevention of hypoglycemia restores both the hormonal and the neurologic responses to or toward normal.[37]

In normal subjects, the following thresholds have been identified in the res hypoglycemia:[26,27,38]

1. Insulin secretion begins to fall when the plasma glucose concentration f below 80 mg/dL.
2. The release of glucagon and epinephrine rises when the plasma glucose concentration falls below 65 to 70 mg/dL.
3. Growth hormone and cortisol secretion are enhanced at a plasma glucos concentration below 60 mg/dL.

These hormonal responses begin well before overt neuroglycopenia is seen.[27] Early cognitive dysfunction is noted in normals at a plasma glucose concentration approximately *50 to 55 mg/dL*,[6,26,38,39] and[40] while more severe symptoms (such as lethargy and seizures) require a plasma glucose concentration below 45 mg/dL.[27] In comparison, the threshold for symptoms in poorly controlled diab may be higher, averaging about 80 mg/dL.[40] Chronic hyperglycemia may be responsible for this change by downregulating glucose transporters in the b thereby allowing neuroglycopenia to occur at a higher plasma glucose

concentration.[41]

Hyperglycemia

Hyperglycemia generally requires the presence of insulin deficiency with or insulin resistance, conditions that most often occur in patients with diabete mellitus.[5,42,43] In addition to its direct effects on glucose metabolism, the lac insulin also contributes to the development of hyperglycemia by promoting secretion of glucagon and, to a lesser degree, catecholamines and growth hormone,[3,33,44,45] and[46] How these secondary changes occur is incompletely understood.

A characteristic sequence is seen with increasing severity of the disease. T plasma glucose concentration is initially *normal in the fasting state*, since low insulin secretion is appropriate in this setting. However, the insulin response to a load is impaired (because of diminished secretion in type 1 and diminished and secretion in type 2 diabetes), resulting in *postprandial*

hyperglycemia.[5,47] This abnormality is mostly due to decreased peripheral glu utilization in skeletal muscle.[47] In comparison, hepatic glucose production is at f appropriately suppressed, as a result of two factors.[1] The liver is perfused by the portal vein, which has a much higher insulin concentration than arterial blo[48] and the hepatic effect requires only half as much insulin as the stimulation of p glucose uptake.[7]

More severe insulin deficiency is also associated with *fasting hyperglycemia* due to increased hepatic glucose production.[5,24,49] This problem is primarily due to enhanced gluconeogenesis, with the contribution of glycogenolysis being li rapid depletion of glycogen stores.[24,49] The increase in glucose production in this setting is in part derived from alanine released from skeletal muscle; thus, hyperglycemia may represent a catabolic state with loss of lean body mass. example, hepatic glucose production in patients with poorly controlled diab (fasting plasma glucose concentration greater than 250 mg/dL) rises to a le *more than twice that seen in normal fasting subjects, despite the presence of hyperglycemia*.[5,24,49] The magnitude of this abnormality becomes more appare when it is noted that even a minimal rise in the plasma glucose concentrati normal subjects increases insulin secretion and suppresses hepatic glucose production by 70 percent or more.[24,25]

Role of glucagon

In addition to the importance of insulin deficiency and/or resistance, the el hepatic gluconeogenesis in uncontrolled diabetes is strongly dependent up hypersecretion of glucagon.[1,4] As described above, glucagon promotes gluconeogenesis by decreasing the formation of fructose 2,6-bisphosphate, enhancing the conversion of fructose 1,6-bisphosphate into glucose (Fig. 25-2).[1,4,19] This effect interacts synergistically with insulin deficiency, since th

increases the delivery of gluconeogenetic precursors (alanine and glycerol) liver.

The importance of glucagon in this setting can be illustrated by the observa fasting hyperglycemia in insulin-deficient subjects can be markedly attenua glucagon release is prevented, either by infusing somatostatin or by the pr a somatostatin-producing tumor.[3,50] However, *excess glucagon alone does not lea to marked hyperglycemia*, since its effects are readily counteracted by normal i secretion.[51] Patients with glucagon-secreting tumors, for example, typically h mild hyperglycemia that is easily controlled by diet, oral agents, or insulin associated with diabetic ketoacidosis.

The increases in epinephrine and growth hormone release induced by insul deficiency[46] can also contribute to the development of hyperglycemia.[31,33] These hormones enhance gluconeogenesis, diminish peripheral glucose uptake, a increase the delivery of alanine and glycerol to the liver (Fig. 25-3).[31,32] and[33] In addition, the release of epinephrine and cortisol are further increased by s[33] This may explain why acute problems such as infection or volume depletion most common precipitating factors in patients with diabetic ketoacidosis or hyperglycemia.[52,53]

Ketoacidosis

When decreased insulin effect impairs glucose utilization (as with fasting o mellitus), ketones are produced by the liver from free fatty acids to supply alternative source of energy.[2,54] This adaptation also conserves body protein stores.[54] If ketones were not available, there would be a greater requiremen gluconeogenesis, much of which is derived from alanine that is released fr skeletal muscle proteins.[55]

Two basic steps are required for ketogenesis to occur (Fig. 25-3).[1,2,4] First, lipolysis must be increased to *enhance the delivery of free fatty acids to the live* This is achieved by hormonal changes that are similar to those responsible hyperglycemia—insulin deficiency[56] and, to a lesser degree, epinephrine, norepinephrine, growth hormone, and cortisol.[33,57,58]

Second, *hepatic metabolism must be altered* to allow ketone formation to occur. Excess fatty acids alone are insufficient, since they can be metabolized in into triglycerides.[1,2] The rate-limiting step in hepatic ketogenesis is the entry acyl CoA into the mitochondria, a process regulated by the cytosolic enzym *carnitine palmitoyl transferase* (CPT; Fig. 25-3). The activity of this enzyme appear to *vary inversely with the level of malonyl CoA*,[2,4,59] which may bind the regulatory subunit of CPT.[4] In the fed state, malonyl CoA is relatively abundant, activity is low, and ketone synthesis will not occur even if free fatty acids a available.

These changes are reversed in poorly controlled diabetes, as malonyl CoA low, CPT activity is increased, and ketogenesis can occur. *Glucagon excess* appears to play a major role in this hepatic response, lowering malonyl CoA product by diminishing the availability of pyruvate for acetyl CoA formation (since t production of pyruvate from glucose is impaired) (Fig. 25-2)[4] and by decreasing the activity of acetyl CoA carboxylase, the enzyme that converts acetyl CoA int CoA (Fig. 25-3).[2,4,60] In comparison, insulin has a relatively minor intrahepatic effect,[56,61] and epinephrine does not appear to stimulate hepatic ketogenesi at high concentrations.[57]

Acetoacetic acid is the initial ketone formed. It may then be reduced to β - hydroxybutyric acid or nonenzymatically decarboxylated to acetone.[62] Acetone is chemically neutral, but the other ketones are organic acids, and their accu will lead to metabolic acidosis. The degree of ketoacid accumulation is limi fasting, usually to less than 12 meq/L.[63,64] This limitation may be mediated in part by ketone-induced stimulation of insulin release,[65] thereby decreasing the availability of free fatty acids. In contrast, severe metabolic acidosis can o insulin-deficient patients with diabetes mellitus, since this secondary incre insulin secretion does not occur.[66,67]

It has been proposed that diminished ketone utilization may contribute to th acidemia in poorly controlled diabetes.[68] The importance of this problem is uncertain, however, as ketone utilization in diabetics is similar to that in fa least until plasma ketone levels exceed 12 meq/L.[64]

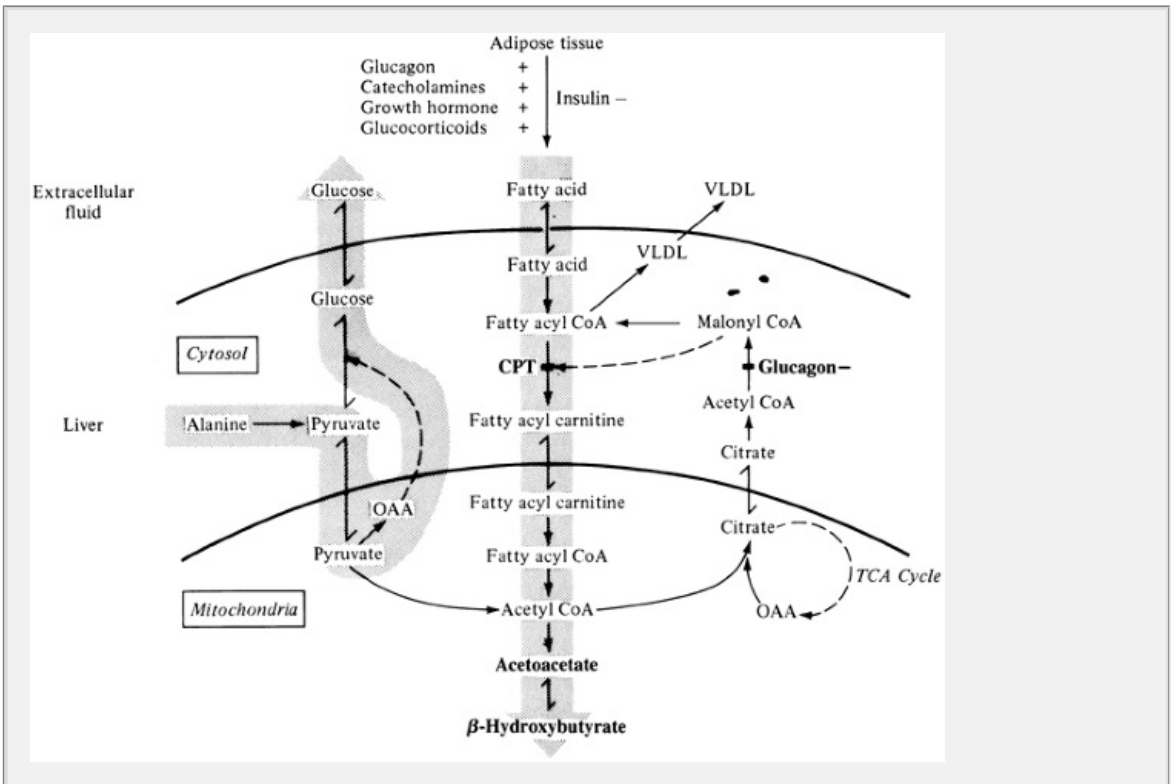

Figure 25-3 Summary of hepatic fatty acid and carbohydrate metabolism in uncontrolled diabetes mellitus, a low-insulin, high-glucagon state. In this

two changes occur: Free fatty acid delivery to the liver is enhanced, most because of insulin deficiency, and malonyl CoA levels in the hepatocyte a The latter effect is largely mediated by glucagon, which diminishes both a CoA formation (since pyruvate synthesis from glucose is diminished; Fig. 25-2 and the activity of acetyl CoA carboxylase, which normally converts acety into malonyl CoA. The net effect is enhanced activity of carnitine palmitoy transferase (CPT), because of removal of the inhibitory action of malonyl As a result, the increased quantity of free fatty acids presented to the he is able to enter the mitochondria and be metabolized to ketones. The meta pathways are different in the fed state, since glucagon secretion is reduc pyruvate and malonyl CoA are abundant, and CPT activity is low. In this s any free fatty acids delivered to the liver will remain in the cytosol and be converted to very low density lipoprotein (VLDL) triglycerides. (*Adapted from Cahill GF Jr: Kidney Int 20:461, 1982. Reprinted by permission of Kidney International.*)

Hypovolemia

Hypovolemia is an almost invariable finding with marked hyperglycemia and primarily induced by the associated glucosuria. As the filtered load of gluco (glomerular filtration rate, or GFR, times plasma glucose concentration) ris eventually exceeds tubular reabsorptive capacity (see Chap. 3). As a result, glucose remains in the tubular lumen and acts as an osmotic diuretic, increasing th loss of electrolytes and water.[66] In severely hyperglycemic patients, the

fluid loss may reach 8 to 10 liters (almost 25 percent of the total body wate produce circulatory insufficiency.[69]

In addition to producing volume depletion, the osmotic diuresis is also asso with water loss in excess of Na^+ and K^+.[70] This will further elevate the plasma osmolality,[52,71] frequently contributing to the development of neurologic dysf (see "Symptoms," below).

Renal Insufficiency

Hypovolemia also reduces renal function. This may be an extremely importa change, since the kidney can modify many of the metabolic abnormalities of ketoacidosis (Table 25-1).[3] The maintenance of relatively normal renal function i one sense beneficial, because both the hyperglycemia and the acidemia ca minimized by excretion of some of the excess glucose and acid in the urine. example, urinary β -hydroxybutyrate (the major ketoacid anion) can buffer s H^+ ions to form β -hydroxybutyric acid or can be excreted with NH_4^+ as the N source of acid excretion). In one study of patients with diabetic ketoacidosis, keto production averaged 51 meq/h, while net acid excretion with the ketoacid a averaged 15 meq/h.[72] Thus, 30 percent of the generated ketoacids were excre

the urine, limiting the severity of the metabolic acidosis. (A second protecti mechanism is the conversion of acetoacetic acid to acetone, which neutrali another 15 to 25 percent of the acid load.)[62,72]

On the other hand, loss of β -hydroxybutyrate with either K^+ or Na^+ is part detrimental. In most cases, *ketoacidosis is in part self-correcting*, since insulin-induced metabolism of the excess ketoacid anions results in the regenerati HCO_3^-.[67,73] However, the degree to which this will occur is diminished if the anions are lost in the urine.[67] Volume and K^+ depletion will also be exacerbated by the ketonuria.

Normal renal function in patients with diabetic ketoacidosis is detrimental f second reason: It maximizes the osmotic diuresis. This relationship can be by the response of patients with advanced underlying renal disease (includ already on dialysis) to uncontrolled diabetes.[71,74,75] The plasma glucose concentration can exceed 1000 to 1500 mg/dL in this setting, because the e

glucose cannot be excreted. Despite this severe hyperglycemia, volume dep and marked hyperosmolality are not usually seen because of the lack of a g osmotic diuresis. As a result, neurologic symptoms are often absent[71] unless there has been a very rapid rise in the plasma concentration.[74,76]

Table 25-1 Effects of intact renal function in diabetic ketoacidosis

Beneficial	Detrimental
Excretion of some excess glucose	Volume depletion
	Exacerbation of hyperosmolality
Excretion of some excess acid, as β-hydroxybutyric acid or NH_4^+ salt of β-hydroxybutyrate (or to a lesser degree, acetoacetate)	Loss of Na^+ and K^+ salts of β-hydroxybutyrate, leading to volume and K^+ depletion and to loss of potential HCO_3^-
K^+ loss protects against initial hyperkalemia	K^+ loss contributes to marked K^+ depletion

The kidney also plays an important role in K^+ balance in hyperglycemic patients. Th triad of enhanced distal flow (due to the osmotic diuresis), ketonuria, and hypovolemia-induced hyperaldosteronism leads to increased urinary K^+ loss,

which are largely responsible for the often marked K^+ deficit seen in these patients (see "Treatment," below).[42,69] In one sense, however, this effect is *protective*. At presentation, patients with diabetic ketoacidosis or nonketotic hyperglycemic often hyperkalemic,[69] both because of the rise in P_{osm} (which pulls water and K^+ out of the cells) and because of insulin deficiency (which impairs K^+ entry into the cells; see Chap. 12).[77,78] The degree to which this occurs is limited to the concurrent K^+ depletion. In dialysis patients, on the other hand, there is no r K^+ loss, and severe hyperglycemia can lead to life-threatening hyperkalemia (K^+ concentration above 8 to 9 meq/L).[79]

Plasma Sodium Concentration

Variable changes in the plasma sodium concentration occur with hyperglyce Since glucose penetrates cells slowly, an increase in the plasma glucose concentration raises the effective P_{osm} and causes water to move from the cells i the extracellular fluid (ECF; see Fig. 22-4).

Physiologic calculations suggest that the plasma sodium concentration sho 1 meq/L for every 62-mg/dL rise in the plasma concentration of glucose.[80] However, this standard correction factor was not verified experimentally. In an attemp address this issue, hyperglycemia was induced in six healthy subjects by th administration of somatostatin (to block endogenous insulin secretion) and hypertonic dextrose solution.[81] A nonlinear relationship was observed between th changes in the glucose and sodium concentrations. The 1 : 62 ratio applied plasma glucose concentration was less than 400 mg/dL. At higher glucose concentrations, there was a greater reduction in the plasma sodium concen An overall ratio of 1 : 42 (a 2.4-meq/L reduction in the plasma sodium conc for every 100-mg/dL elevation in the plasma glucose) provided a better esti this association than the usual 1 : 62 ratio.

If, for example, the plasma glucose concentration is 1000 mg/dL (930 mg/dL than normal), then the plasma Na^+ concentration should fall approximately 22 me from 140 to 118 meq/L. The effective P_{osm} in this setting can be estimated from (s page 247)

$$\text{Effective } P_{osm} \cong 2 \times \text{plasma } [Na^+] + \frac{[\text{glucose}]}{18}$$

$$\cong 292 \text{ mosmol/kg}$$

This again demonstrates that hyperglycemia alone, as might occur in a diab dialysis patient, does not produce marked hyperosmolality (P_{osm} > 330 mosmol/kg),

since the rise in the P_{osm} is in part counteracted by water movement out of the cells.[71,75,76] However, dialysis patients are typically volume-expanded betwe dialyses, and the osmotic shift of water out of the cells can precipitate pulm edema in some cases.[74]

In many patients, however, the plasma Na^+ concentration differs from the value predicted from the degree of hyperglycemia. Most commonly, the plasma Na^+ concentration and therefore the effective P_{osm} are higher than expected due to the free-water loss induced by the osmotic diuresis.[69] On the other hand, the measured plasma Na^+ concentration may be artifactually reduced in patients with marke hyperlipidemia. The presence of lactescent serum should alert the physicia possibility, which can be confirmed by measurement of the P_{osm} (see page 713). The latter will be substantially higher than predicted from the glucose, Na^+, and urea concentrations.

ETIOLOGY

There are two major symptomatic hyperglycemia syndromes in humans: *diabetic ketoacidosis* (DKA) and *nonketotic hyperglycemia* (NKH).[42,69,82] These disorders are most often due to type 1 or type 2 diabetes mellitus, but they can also the use of certain drugs or after total pancreatectomy (see below).

The factors responsible for the absence of ketoacidosis in NKH are incomp understood. One proposed factor is differential sensitivity of fat and glucos metabolism to the effects of insulin. Studies in humans indicate that the concentration of insulin necessary to suppress lipolysis is *one-tenth* that required to promote glucose utilization.[83] Consequently, with moderate insulin deficiency, there might be enough insulin available to block lipolysis but no to enhance glucose utilization. The result will be hyperglycemia without ket since even high levels of glucagon will not produce ketoacidosis if free fatt delivery is not increased. On the other hand, lipolysis will be enhanced wit severe insulin deficiency, and ketoacidosis will accompany the rise in the p glucose concentration.

Consistent with this model are the findings by some observers that patients tend to have higher plasma free fatty acid concentrations and lower plasma concentrations than those with NKH.[69,84,85] In addition, DKA tends to occur in patients with type 1 (insulin-dependent) diabetes mellitus, who produce litt endogenous insulin. In contrast, NKH is found primarily in older patients (a age 60 to 65) in whom insulin levels are reduced but not absent, and in wh is either no history or one of mild, type 2 (non-insulin-dependent) diabetes mellitus.[53,82,86]

However, some observers have been unable to demonstrate these differenc plasma insulin concentration,[87,88] and DKA can occur in patients with type 2 diabetes.[89] It is possible that these conflicting results represent an inconsis relationship between insulin secretion and plasma insulin concentrations, a measurement of C-peptide (rather than insulin) is a more accurate reflectio

hepatic insulin delivery.[85] Alternatively, ketone formation in DKA may be due to efficient hepatic synthesis (rather than increased free fatty acid delivery), resulting from an increase in the glucagon/insulin ratio in the portal vein.

Regardless of the mechanism, it should be emphasized that DKA and NKH a distinct disorders. They are best considered as part of a spectrum of findin patients with insulin deficiency.[85]

Both DKA and NKH are usually precipitated by various stresses (infection, hypovolemia, surgery, emotional trauma), which act in part by increasing th secretion of catecholamines, glucagon, and cortisol.[53,69,82] Omission of insulin or oral hypoglycemic therapy or failure to augment insulin dosage when the pl glucose concentration is poorly controlled is less often responsible. NKH c induced in diabetics by glucose loading, as occurs with peritoneal dialysis.[71–73] This complication is more common when hypertonic glucose solutions (such as 4 glucose) are used and can be prevented by careful monitoring of the plasm concentration and by the addition of insulin to the dialysis fluid.[90]

Both DKA and NKH can also be induced in patients who do not have primary diabetes mellitus. As examples, DKA can be induced by total pancreatectom[91] while NKH can result from marked glucose loading in acutely ill stressed patients[92,93] or from the administration of dextrose in water to replace the hi urine output in diabetes insipidus.[94] In the latter setting, the amount of glucose infused may be so large that it exceeds the normal maximum metabolic capa

SYMPTOMS

The patient with hyperglycemia may suffer from symptoms due to hyperosmo volume depletion, and, in DKA, metabolic acidosis. The severity of these sy is generally proportional to both the degree and the duration of the hypergl some patients, however, these findings may be masked by the symptoms as with the acute illness that precipitated the hyperglycemic state.

The earliest complaints associated with hyperglycemia are polyuria, polydi weight loss. This characteristic triad is due to the combination of the gluco diuresis and hypovolemia. In more severely affected patients, focal or gene neurologic abnormalities may be seen, including lethargy, twitching, obtund motor or sensory defects, seizures, and coma.[69,95,96]

These symptoms and the response of the brain are similar to those seen wh hyperosmolality is due to hypernatremia (see Chap. 24).[95] The increase in P_{osm} initially causes water movement out of the cells, leading to cellular dehydra importantly in the brain. Within 4 to 6 h, however, brain cell volume begins toward normal as a result of the generation of *new osmoles* that pull water back into the cells.[95]

The mechanisms underlying this response have been best studied with hypernatremia. Initially, there is movement of Na^+ and K^+ into the brain, in part from

newly formed cerebrospinal fluid.[95,97] If this were the only adaptation, however, t alterations in cell cation concentration could have deleterious effects on th

of cell proteins.[98] This is prevented by the generation of solutes called *osmolytes* (or idiogenic osmoles), which do not interfere with protein function as their concentration rises.[98,99] Within the brain, inositol and the amino acids glutamine and glutamate appear to constitute a major part of the protective response to elevation in the plasma Na^+ concentration.[100,101] New solutes are also generated in hyperglycemic states,[95] but it has not yet been determined if they are similar to those induced by hypernatremia.

Despite the relative preservation of brain volume, the severity of neurologic symptoms in DKA and NKH is roughly proportional to the degree of hyperosmolality.[96] Thus, coma is not usually seen unless the effective osmolality ($P_{osm(eff)}$ or P_{osm} minus the BUN/2.8, since urea is an ineffective osmole) is greater than 320 to 330 mosmol/kg.[75,96] In NKH, for example, the plasma glucose concentration frequently exceeds 1000 mg/dL, the effective plasma osmolality may reach 380 mosmol/kg, and neurologic abnormalities (including coma in 25 to 50 percent of cases) are often the reason that the patient is brought to medical care.[1,69,86,96] This degree of hyperosmolality occurs less often in DKA, where the plasma glucose concentration is generally below 800 mg/dL.[1,69]

The more severe hyperglycemia in NKH may reflect at least two factors. First, patients with NKH are older and frequently have impaired renal function. In contrast, DKA occurs primarily in young patients with type 1 diabetes mellitus who have a defect that, in the first 5 years of the disease, may be as much as 50 percent above normal.[102] As a result, these patients generally have a much greater capacity to excrete glucose than those with NKH—a mechanism that will limit the degree of hyperglycemia. Second, patients with DKA may present early with the symptoms of metabolic acidosis (such as shortness of breath), rather than late with those of hyperosmolality.

The symptoms and signs produced by hypovolemia and metabolic acidosis are discussed in Chaps. 14 and 19. Circulatory insufficiency with hypotension or shock is not uncommon in NKH or DKA as a result of the marked fluid losses and, in the latter disorder, possibly severe acidemia, since the arterial pH is often below 7.1.[66,67]

In addition to those symptoms that are present at initial evaluation, neurologic deterioration and cerebral edema may develop in selected cases after fluid and insulin therapy have been instituted (see "Treatment," below).[103,104]

DIAGNOSIS

The history and physical examination may provide important clues to the presence of uncontrolled diabetes mellitus. Hyperglycemia, for example, should be

suspected in any patient complaining of polyuria, polydipsia, and weight loss. The findings of hyperventilation and the fruity odor of acetone on the patient's breath suggest that ketoacidosis is also present. In addition, hyperglycemia (and rarely hypoglycemia) must be included in the differential diagnosis of any comatose

Once suspected, the diagnosis can be easily confirmed by measuring the pl glucose concentration directly or by using reagent sticks. Tablets or reager can also be used to detect glucosuria, ketonuria, and ketonemia. If serum c that is undiluted or diluted 1 : 1 with normal saline has a 4+ reaction for ke then at least some degree of ketoacidosis can be assumed to be present. H the nitroprusside tablets used in this test [105] react with acetoacetate and acetone but not with β -hydroxybutyrate. The ratio of β -hydroxybutyrate to acetoacetate is a 3 : 1 in DKA but may be as high as 8 : 1 with alcoholic ketoacidosis or whe coexistent lactic acidosis. In the latter disorder, for example, the altered redo state that promotes conversion of pyruvate to lactate also favors the reduc acetoacetate to β-hydroxybutyrate.

Thus, nitroprusside can underestimate the severity of the ketoacidosis. An way around this problem is to add a few drops of hydrogen peroxide to the specimen. This will convert β -hydroxybutyrate to acetoacetate, which will t detectable by nitroprusside.[106] An alternative is to directly measure β - hydroxybutyrate in the blood; the KetoSite system (GDS Diagnostics, Elkha one method by which this can be performed.

A different problem in diagnosis arises with sulfhydryl drugs, such as capto penicillamine. These drugs can interact with the nitroprusside reagent to pr false-positive ketone test.[107] Thus, a positive nitroprusside test for ketonuria or ketonemia cannot be reliably interpreted in patients treated with captopril. setting, the diagnosis of DKA must be made on clinical grounds (otherwise unexplained high anion gap metabolic acidosis in a patient with uncontrolle diabetes) or by direct measurement of β -hydroxybutyrate.

The presence of ketoacidosis should also be suspected in any patient with anion gap metabolic acidosis. As described on page 586, there is a variable relationship between the rise in the anion gap and the fall in the plasma HCO_3^- concentration in DKA. In particular, the loss of the K^+ and Na^+ salt of β - hydroxybutyrate (or acetoacetate) will *lower the anion gap without affecting H^+ excretion or, therefore, the severity of the acidosis.*[73,108] Thus, patients who maintain relatively normal renal function may have marked ketonuria and ca with the combination of severe metabolic acidosis and an only mildly elevat gap. Furthermore, a true normal anion gap (or hyperchloremic) metabolic ac commonly occurs after therapy with insulin is begun. In this setting, the exc gap disappears as the ketones are metabolized, but some degree of acidem persist because of the loss of potential HCO_3^- when the ketoacid anions were excreted in the urine.[73,108]

A more complicated acid-base disorder can be seen in those patients who a marked vomiting or have been treated with diuretics. The concurrent metab alkalosis in this setting will partially or even completely counteract the

ketoacidosis, and the extracellular pH will depend upon the relative severit two disorders.[109] Even if the patient is initially alkalemic, the high anion gap

presence of hyperglycemia should suggest the possibility of underlying keto

Although uncontrolled diabetes mellitus may be suggested by many of the a findings, hypoglycemic therapy with insulin should not be begun until the p hyperglycemia has been demonstrated. *The isolated finding of glucosuria or ketonemia does not necessarily mean that hyperglycemia is present, and t administration of insulin to such a patient may be dangerous.*[110] Diabetics, particularly those on insulin, can be in coma because of a low rather than a elevated plasma glucose concentration. If the patient has not emptied his o bladder for several hours, the urine may still contain glucose, reflecting a p hyperglycemia that may have existed several hours previously. The adminis insulin in this setting will further reduce the plasma glucose concentration produce neurologic deterioration and death.

Whenever there is a question as to the presence of hypoglycemia or hyperg it is always safer to give glucose (50 mL of 50% glucose intravenously) imn after blood has been drawn for measurement of the plasma glucose concent This will dramatically improve the status of the hypoglycemic patient but wi harmful to the patient with hyperglycemia.

In addition to diabetes mellitus, alcoholism (when accompanied by decrease carbohydrate intake) can also produce severe ketoacidosis (see pages 600, 607, 608, 609, 610).[111,112] In this condition, the plasma glucose concentration is less than 250 mg/dL be less than 100 mg/dL. Other causes of a high anion gap metabolic acidos must be excluded in an alcoholic are methanol and ethylene glycol intoxicat[113]

The treatment of alcoholic ketoacidosis is the administration of glucose, wh suppress the secretion of glucagon and stimulate that of insulin, thereby di both lipolysis and hepatic ketogenesis. Since the plasma glucose concentra frequently is normal, the administration of exogenous insulin is not indicate can precipitate severe hypoglycemia.

TREATMENT

Therapy must be directed toward each of the metabolic disturbances that m present in the hyperglycemic patient: hyperosmolality, ketoacidosis, hypovo and potassium and phosphate depletion.[1,42] Since absolute or relative insulin deficiency is responsible for most of these problems, the administration of and volume repletion are the mainstays of therapy. To assess the effect of the plasma glucose concentration should be measured every 2 h and the pl electrolytes and arterial pH every 2 to 4 h until the patient is out of danger

Insulin

Insulin acts to correct the hyperglycemia, to diminish ketone production (by diminishing both lipolysis and glucagon secretion), and perhaps to augment utilization. The major effect of insulin on glucose metabolism is to diminish glucose production (gluconeogenesis), with enhanced peripheral utilization

requires a higher concentration of insulin[7] but is quantitatively less important.[49,114] The net effect is that the plasma glucose concentration falls at a *maximum rate of 65 to 125 mg/dL/h*.[114,115,116] and[117]

Although more rapid correction is not necessarily desirable, this response s reflect significant *insulin resistance*. Normal subjects, for example, can be made hyperglycemic (plasma glucose concentration about 650 mg/dL) by the coml of somatostatin (to block insulin release) and glucose.[81,117] The subsequent administration of insulin can lower the plasma glucose level by up to 500 m difference that cannot be explained by more rapid urinary glucose excretion.[117] The mechanism of insulin resistance in diabetic patients is probably multifactor includes primary tissue resistance in type 2 diabetes,[5] the initially high levels of glucagon, and possibly hyperosmolality itself.[118] The normal subjects had acute hyperglycemia, little time for an osmotic diuresis, and therefore a lower P_{osm} than typically seen in DKA or NKH.

The effect of insulin on adipose tissue requires a much lower concentration required for glucose utilization;[83] as a result, any dose of insulin that corrects th hyperglycemia also will normalize ketone metabolism. Subsequent utilizatio excess ketones will tend to reverse the metabolic acidosis, since metabolis ketoacid anions results in the regeneration of HCO_3^-.[66] Although this occurs relatively rapidly over the first 5 to 10 h, acetone is cleared more slowly (i the lungs) and may remain in the blood for more than 36 h.[119] Thus, the persistence of ketonemia and ketonuria is not necessarily indicative of failure of insulir

Most patients with DKA or severe NKH are treated with a low-dose regular i regimen in which the total amount of insulin administration is usually betwe 100 units.[114,115] and[116,120,121] Insulin requirements do not appear to be substantially different in DKA and NKH.[69] A loading dose of 15 to 20 units should l given initially, followed by 8 to 15 units/h until the biochemical abnormalitie under reasonable control. Higher doses (such as 50 to 100 units/2 h) can b but do not usually lower the plasma glucose concentration more rapidly.[115,116,120] Although diabetics are frequently insulin-resistant,[117] the equivalent effectiveness o the low- and high-dose regimens suggests that both doses saturate the cell membrane receptors and that the insulin resistance is generally due to a postreceptor defect.[115] Some patients, however, do not respond to low-dose ins in this setting, the dose must be increased to a level adequate to control th glucose concentration.

Regular insulin can be given by the intravenous, subcutaneous, or intramus route; these appear to be equally effective in correcting the hyperglycemia ketoacidosis.[121] Hospitalized patients are usually treated initially with intrave insulin. A relatively concentrated solution should be used to

minimize insulin absorption onto the glass and plastic tubing. If, for exampl of regular insulin is added to 100 mL of isotonic saline, an infusion at 20 to

will deliver 8 to 12 units/h of insulin to the patient.

In patients who are markedly hypovolemic, insulin therapy is withheld *initially* for 30 to 60 min until 1 to 2 liters of fluid can be given. Insulin drives glucose because of the ensuing fall in P_{osm} water into the cells. As a result, insulin can exacerbate the degree of extracellular volume depletion if it is given before replacement has been begun.

Fluids

The average fluid loss is 3 to 6 liters in DKA, but it can reach 8 to 10 liters NKH.[1,69] With each liter of water, only about 70 meq of monovalent cation (Na^+ + K^+) is lost. This reflects the enhanced water loss relative to solute induced glucose osmotic diuresis. Fluid repletion is generally begun with *isotonic saline*. This solution will replace the fluid losses, correct the extracellular volume deple rapidly than half-isotonic saline, lower the P_{osm} (since it is still hypotonic to the patient), and reduce the plasma glucose concentration by as much as 35 to mg/dL/h.[122] The last effect results both from hemodilution and from increase urinary glucose losses as renal function is improved.

The optimal rate at which isotonic saline should be administered is depend the clinical state of the patient. For example, fluids should be infused as q possible in patients who are in shock. In comparison, patients who do not h extreme volume deficit may be effectively repleted at a rate of 500 mL/h for h followed by 250 mL/h for the next 4 h.[123] More rapid administration is not necessary and may actually delay correction of the acidemia, in part by a d induced reduction in the plasma HCO_3^- concentration.[123]

The increase in renal perfusion leads to reductions in the blood urea nitrog and plasma creatinine concentration. Although the plasma creatinine conce generally varies inversely with the GFR, this value may be misleading in DK acetoacetate is a noncreatinine chromogen that is *measured as creatinine* in the standard colorimetric assay. As a result, the plasma creatinine concentratio falsely elevated by as much as 2 mg/dL or more, leading to a marked underestimation of the glomerular filtration rate.[124] Metabolism of the acetoacetate following the administration of insulin will rapidly lower the measured plasn creatinine concentration toward its true value.

Although begun on isotonic saline, most patients are switched at some poin isotonic saline to replace the free-water loss induced by the osmotic diures this should occur, however, is uncertain, because of concern about the pos development of cerebral edema.

Cerebral edema is an unusual complication of therapy that occurs within 24 treatment has been initiated.[103,104,125] Headache is the earliest clinical manifestation; more severe neurologic symptoms (including brain herniatior death) can occur in up to 3 percent of children, particularly those treated w relatively dilute fluids.[125] Almost all cases occur in patients under the age of 2(

symptomatic cerebral edema appears to be a rare complication[103] in adults. However, *subclinical* brain swelling is much more common than symptomatic disease, as evidenced by computed tomography (CT) scanning and by an in cerebrospinal fluid pressure.[104,126,127]

The mechanisms responsible for cerebral edema are incompletely understoo combination of insulin and fluids can lower the plasma glucose concentratio maximum of 200 mg/dL/h or 11 mosmol/kg/h if there is no compensatory rise plasma Na^+ concentration as a result of the concurrent administration of rela dilute fluids. This rapid reduction in the P_{osm} of the ECF, as in hypernatremia (see page 762), promote osmotic water movement into the brain.[104,125] Studies in an animal model suggest a primary role for a rapid fall in the plasma glucose concent no contribution from ketoacidosis.[128] Other factors also may be important, includi a hyperglycemia-induced increase in blood-brain permeability,[129] and perhaps acute dilutional hypoalbuminemia.[130]

Studies in diabetic animals with marked hyperglycemia suggest that insulin play a role in the genesis of cerebral edema.[131] Lowering the plasma glucose concentration below 250 to 330 mg/dL with insulin can result in the generat new (idiogenic) osmoles within the brain cells. This increase in brain cell o can draw water into the brain and produce cerebral edema. The importance insulin in this phenomenon is suggested by the absence of new osmole form when the plasma glucose concentration is reduced without insulin via perito dialysis.[131] This model is not entirely applicable to humans, however, since edema has been described at a time when more marked hyperglycemia is st present.[103]

In summary, it is likely that rapid reduction in the plasma glucose concentra P_{osm} contribute to the common development of mild cerebral edema.[104,125,128] It is not clear, however, why only a small number of patients develop severe n symptoms.[103]

The optimal regimen for safe fluid repletion is uncertain. Nevertheless, the recommendations seem prudent:[104,125]

- Fluid repletion should be begun with isotonic saline, which is administe rate described above until tissue perfusion is adequate, as evidenced f systemic blood pressure, urine output (once glucosuria has disappeared physical examination. At this point, the patient is out of danger, and cor correction should occur slowly over several days.
- Therapy with regular insulin should be discontinued and dextrose-conta saline solutions should be used when the plasma glucose concentration below 300 mg/dL.[69] Further insulin can be given as necessary. It is import remember that persistent ketonemia or ketonuria frequently reflects the clearance of acetone and not persistent ketoacidosis.[119]

- Half-isotonic saline can be used once the phase of rapid fluid repletion completed, since slow administration of this dilute fluid will not lead to reduction in P_{osm}. It must be emphasized, however, that marked K^+ depletion is also typically present and therapy for K^+ depletion is usually begun when the plasma K^+ concentration is ≤ 4.5 meq/L (see below). As K^+ is osmotically

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active as Na^+ (see page 687), as a result, the addition of 40 meq of KCl to e liter of isotonic saline now represents a hypertonic solution with an effe osmolality of almost 400 mosmol/kg (using a K^+ concentration of 194 meq/L). Thus, K^+ should be given in half-isotonic (or even quarter-isotonic) salin unless the patient is still markedly hypovolemic.

- Patients should be observed for possible signs of cerebral edema, such severe headache, incontinence, or decreased mental status. Early treat with hypertonic mannitol in this setting may prevent irreversible neurolc damage.[103]

Bicarbonate

The indications for HCO_3^- therapy in the treatment of ketoacidosis are unclear. general, insulin leads to partial correction of this problem, since metabolisı ketoacid anions that have not been lost in the urine results in the regenera HCO_3^-.[66,67] Thus, several controlled trials in small numbers of patients hav unable to demonstrate that the use of $NaHCO_3$ leads to any clinical benefit or any important difference in the rate of rise in the plasma HCO_3^- concentration.[132,133] In addition, alkali therapy may increase hepatic ketone production, slowing th recovery from the ketosis.[134]

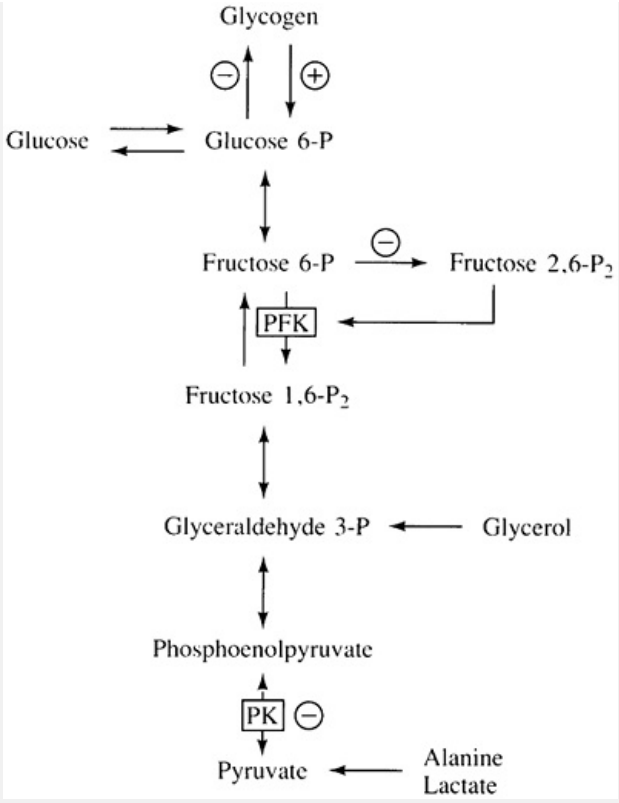

Figure 25-2 Schematic representation of the regulation of hepatic gluconeogenesis (arrows that point upward) and glycolysis (arrows that p downward). For simplicity, only the important regulatory reactions are sho Fructose 2,6-bisphosphate ($F-2,6-P_2$) plays a central role in this process by increasing the activity of phospho-fructokinase (PFK), thereby promoti glycolysis by enhancing the conversion of fructose 6-phosphate to fructos bisphosphate. The circles with positive or negative signs represent the re that are affected by glucagon. The most important is diminished formation fructose 2,6-P_2 thereby impairing glycolysis and facilitating gluconeogenes allowing pyruvate to be converted into glucose. Glucagon also induces a block in the glycolytic pathway, as the pyruvate kinase (PK)–mediated conversion of phosphoenolpyruvate to pyruvate is diminished. The sites o of the gluconeogenetic precursors, alanine, lactate, and glycerol, are als shown.

These findings, however, do not address the issue that there may be select patients who may benefit from cautious alkali therapy.[73,135] These include patients with severe acidemia (arterial pH ≤7.0 to 7.1), in whom decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusio Chap. 19),[135] and patients with a relatively normal anion gap due to excretio ketoacid anions in the urine.[73] In the latter setting, the quantity of HCO_3^- that can be generated from organic anion metabolism is minimized. As a result, there normal anion gap acidosis during the correction phase (see page 1858), and restoration of acid-base balance in the absence of alkali therapy will be a s

process, requiring renal excretion of the excess acid anions.[4,73] The aim of HCO_3^- administration in patients with one or both of these indications is to raise t pH above 7.15 to 7.20, a level at which the patient should be out of danger In addition, $NaHCO_3$ should also be given to patients with potentially life-threa hyperkalemia. Bicarbonate drives K^+ into the cells, thereby lowering the plasma K^+ concentration (see Chap. 28).

Potassium

Most patients with DKA or NKH are markedly K^+-depleted. The average K^+ deficit is 3 to 5 meq/kg, but it can exceed 10 meq/kg in some patients.[42] Several factors contribute to this problem, including vomiting, increased urinary losses due osmotic diuresis and to ketoacid anion excretion, and the loss of K^+ from cells due to glycogenolysis and proteolysis.[42,136]

Despite the K^+ deficit, the plasma K^+ concentration is usually normal or, in about one-third of patients, elevated.[42,69,136] This paradoxical finding results from a transcellular shift as K^+ moves from the cells into the extracellular fluid. Two fa appear to be of primary importance in this process: insulin deficiency (since insulin normally promotes K^+ uptake by the cells)[136] and, more importantly, hyperosmolality (see Fig. 12-7).[77,78,138] The elevation in P_{osm} results in the osmotic movement of water out of the cells. This can promote the movement of K^+ into the extracellular fluid via two mechanisms:

1. The loss of cell water raises the cell K^+ concentration, thereby promoting passive K^+ diffusion through K^+ *channels* in the cell membrane.
2. The frictional forces between solvent (water) and solute can result in K^+ being carried along with water through *water pores* in the cell membrane. This phenomenon, called solvent drag, is independent of the electrochemical for K^+.

In comparison, acidemia itself does not seem to play a major role, since org acids are much less likely to influence the internal distribution of K^+ (see page 379).[136,139] Thus, hyperkalemia is as prevalent in NKH, where the pH is rela normal, as it is in DKA.[69]

Although masked initially, the K^+ deficiency becomes rapidly apparent as insulin therapy drives K^+ into the cells (both directly and by reversing the hyperglyce To prevent the development of potentially severe hypokalemia, 20 to 40 me should be added to the intravenous infusions once the plasma K^+ concentration falls below 4.5 meq/L.

The need for K^+ repletion is more urgent in those patients who are *hypokalemic prior to therapy*. In this setting, K^+ replacement must be begun immediately, since insulin and fluids alone can produce a potentially dangerous reduction in the K^+ concentration. The rate of K^+ administration is variable, with doses of up to 20–40 meq/h being required if serious cardiac arrhythmias are present. These doses are generally safer if they can be given orally. Careful monitoring of plasma K^+ concentration and the electrocardiogram is important to determine the efficacy of therapy (see Chap. 27).

Phosphate

Cellular phosphate depletion with an initially elevated plasma phosphate concentration is another common finding in DKA or NKHH.[42,66,140] The loss of phosphate is primarily related to decreased intake and to increased urinary excretion resulting from the osmotic diuresis, the direct effect of acidemia, and the rise in plasma phosphate concentration.[42,140] The dissociation between phosphate stores and the plasma phosphate concentration again reflects a transcellular shift of phosphate out of the cells. Both the osmotic water shift induced by the rise in P_{osm} and the

direct effect of an organic acidosis (by an unknown mechanism) may contribute to this response.[140,141]

Like the rise in the plasma K^+ concentration, the hyperphosphatemia is also rapidly corrected with insulin therapy. In one study, for example, the mean plasma phosphate concentration fell from 9.2 mg/dL on admission to 2.8 mg/dL at 12 h.[140] Furthermore, values as low as 1.0 mg/dL may be seen in selected patients with severe phosphate depletion.[66,142]

Despite these findings, the routine use of phosphate supplements in DKA or NKHH has not been shown to improve morbidity or the rate of correction of the electrolyte disturbances.[143,144] In addition to lack of efficacy, phosphate administration is not without risk, since hyperphosphatemia and hypocalcemia may result.[145] It seems prudent, therefore, to reserve phosphate administration for the occasional patient who develops a severe, symptomatic reduction in the plasma phosphate concentration.

PROBLEMS

25-1A 68-year-old woman with adequately controlled diabetes mellitus and previously normal renal function presents with fever, dysuria, nausea, recurrent vomiting, flank pain, and polyuria that have become progressively more severe over 4 days. The physical examination reveals a temperature of 39.6°C, reduced skin turgor, estimated jugular venous pressure below 5 cmH_2O, postural hypotension, and marked tenderness over the right costovertebral angle. The urine shows pyuria and bacteriuria, and a diagnosis of acute pyelonephritis is made. Other laboratory data reveal the follo

Plasma [glucose]	=	570 mg/dL	BUN	=	32 mg/dL
$[Na^+]$	=	135 meq/L	[Creatinine]	=	4.0 mg/dL
$[K^+]$	=	2.6 meq/L	Serum ketones	=	4^+, diluted 1 : 1
$[Cl^-]$	=	87 meq/L	Arterial pH	=	7.36
$[HCO_3^-]$	=	20 meq/L	P_{CO_2}	=	37 mmHg

The electrocardiogram shows prominent U waves in the precordial lea occasional multifocal premature ventricular beats.

a. **What is the acid-base disturbance on admission?**

b. **What factors account for the elevations in the BUN and plasma crea concentration?**

c. **What would be your initial therapeutic regimen?**

25-2A 25-year-old woman with type 1, insulin-dependent diabetes is ad to the hospital with a soft-tissue infection of the palate. The initial lab data include the following:

Plasma [glucose] = 147 mg/dL
$[Na^+]$ = 140 meq/L
$[K^+]$ = 3.8 meq/L
$[Cl^-]$ = 110 meq/L
$[HCO_3^-]$ = 23 meq/L

The patient eats sparingly because of pain on swallowing. To minimize risk of hypoglycemia, her insulin is withheld. Repeat blood tests are d 36 h later:

Plasma [glucose]	=	270 mg/dL	Anion gap	=	15 meq/L
$[Na^+]$	=	135 meq/L	Serum ketones	=	4^+, diluted 1:1
$[K^+]$	=	5.0 meq/L	Arterial pH	=	7.32
$[Cl^-]$	=	105 meq/L	P_{CO_2}	=	30 mmHg
$[HCO_3^-]$	=	15 meq/L			

A diagnosis of diabetic ketoacidosis is made.

a. **Why is the anion gap only slightly elevated despite the presence o ketoacidosis?**

b. **How would you treat the patient at this time?**

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Chapter Twenty-Six

Introduction to disorders of potassium balance

The maintenance of K^+ balance is essential for a variety of cellular and neuromuscular functions. This chapter will review the physiologic effects of K^+ and the factors governing K^+ homeostasis, topics that are generally discussed in great detail in Chap. 12. The application of these principles to the common clinical problems of K^+ depletion and K^+ excess will then be presented in Chaps. 27 and 28.

PHYSIOLOGIC EFFECTS OF POTASSIUM

The total body K^+ stores in a normal adult are approximately 3000 to 4000 meq (40 to 55 meq/kg body weight). Roughly 98 percent of this body K^+ is located in the cells; this is in contrast to Na^+, which is primarily limited to the extracellular fluid. The localization of Na^+ and K^+ to the different fluid compartments is maintained by the Na^+-K^+-ATPase pump in the cell membrane, which transports Na^+ and K^+ into the cells in a 3 : 2 ratio.[1,2] The net effect is that the K^+ concentration is about 140 meq/L in the cells but only 4 to 5 meq/L in the extracellular fluid (including plasma).

Cell Function

Potassium plays an important role in cell function and in neuromuscular transmission. In the cells, K^+ participates in the regulation of such processes as protein and glycogen synthesis.[3] As a result, conditions of K^+ imbalance are associated with a variety of signs and symptoms. For example, patients with hypokalemia or K^+ depletion may complain of polyuria and polydipsia (increased urine output and thirst). These problems, which are reversed with K^+ repletion, are primarily due to diminished urinary concentrating ability, resulting from decreased tubular responsiveness to antidiuretic hormone.[4,5]

Resting Membrane Potential

In addition to the importance of the *absolute* amount of K^+ present, the *ratio* of the K^+ concentration in the cells to that in the extracellular fluid is the major d of the resting membrane potential (E_m) across the cell membrane. This relationshi can be expressed by the following formula:

$$E_m = -61 \log \frac{r[K^+]_c + 0.01[Na^+]_c}{r[K^+]_e + 0.01[Na^+]_e} \qquad (26\text{-}1)$$

where r is the 3 : 2 active transport ratio of the Na^+-K^+-ATPase pump, 0.01 is the relative membrane permeability of Na^+ to K^+, and the subscripts c and e refer to th cellular and extracellular concentrations, respectively.[6]

If the normal concentrations for K^+ and Na^+ are substituted in Eq. 26-1 (see Table 1-5),

$$E_m = -61 \log \frac{3/2\ (140) + 0.01\ (12)}{3/2\ (4.4) + 0.01\ (145)}$$
$$= -86 \text{ mV} \qquad \text{(cell interior negative)}$$

This resting potential is generated largely by the diffusion of the K^+ out of the cell down its concentration gradient; Na^+ diffusion in the opposite direction is much less prominent because of the lower membrane permeability to Na^+. The loss of positively charged K^+ ions makes the interior of the cell electrically negative w respect to the extracellular fluid. The steady state described in Eq. 26-1 is reached when this cell negative potential (which tends to hold the K^+ within the cell) is of the same magnitude as the concentration gradient that promotes K^+ diffusion out of the cell.

It is the resting membrane potential that sets the stage for the generation o *action potentials*[7,8] that is essential for normal neural and muscular function. During excitation, the steady state is altered, because the release of acetylcholine synapses and motor end plates produces an increase in the number of oper sensitive Na^+ channels (in which clusters of positively charged amino acid re constitute the site of voltage activation).[9,10] The ensuing progressive increase in net Na^+ permeability has three consequences:[8,9,11]

- Na^+ diffuses into the cell down its concentration gradient.
- This Na^+ movement causes the membrane potential to be depolarized, i.e declines toward zero.
- Depolarization results in the opening of voltage-sensitive K^+ channels,[12] both the increased K^+ permeability and decreased cell interior electronegativity promote K^+ movement out of the cell.

The net effect depends upon the *degree of depolarization*. When the depolarizing

stimulus is relatively small, there is only a minor increment in Na^+ permeability. As a result, the initial Na^+ movement into the cell is followed by a period in which K^+ exceeds further Na^+ entry, because of the greater K^+ permeability. This flux of K^+ raises the membrane potential back toward its baseline value, and generati action potential does not occur.

The *threshold potential* (E_t) is that potential at which the Na^+ permeability is sufficiently enhanced so that *the rate of Na^+ entry continues to exceed that of K^+ exit*. This induces a self-perpetuating cycle characterized by more depolariz (since the continued entry of Na^+ makes the cell interior less electronegative), a further increase in Na^+ permeability (up to 1000 times the basal value, as depolarization directly leads to continued activation of voltage-sensitive Na^+ channels), more Na^+ entry, more depolarization, etc.[8,9,11] The net effect is the generation of an action potential, in which the cell interior ultimately becon *electropositive* as a result of the massive influx of Na^+. The propagation of these changes to adjacent cells is responsible for the transmission of neural impu the initiation of muscle contraction.

The action potential is followed by *repolarization and recovery*.[8] During repolarization, the permeability to Na^+ returns to its low baseline value, whereas t to K^+ is slightly increased because of activation of voltage-sensitive K^+ channels.[7,9] In this setting, the high cell K^+ concentration, high K^+ permeability, and favorable electrical gradient (cell interior now positive) all favor the passive K^+ moveme out of the cell, returning the potential to its negative resting level. In the r phase, the Na^+-K^+-ATPase pump extrudes the Na^+ that entered the cell during depolarization and pumps in the K^+ that left the cell during repolarization, resulti the normalization of cell composition.

It should be noted that the quantity of ions that must cross the cell membra produce these changes is extremely small. The generation of a resting pote 86 mV, for example, requires the separation of only 10^{-7} eq/L of K^+ per cm^2 of membrane, or about one one-hundred-thousandth of the intracellular K^+ pool.[13]

Membrane excitability

The excitability (or irritability) of neuromuscular tissue is defined as the di between the resting and threshold potentials ($E_m - E_t$). Thus, any factor that alters either of these potentials affects excitability. In particular, small changes ir extracellular K^+ concentration (which is much lower than that in the cells) can produce relatively large changes in the $[K^+]_e/[K^+]_c$ ratio and consequently in the resting membrane potential.[14,15]

However, the effect of alterations in the plasma K^+ concentration on membrane

excitability cannot be directly predicted from the $[K^+]_c/[K^+]_e$ ratio. As an example, an elevation in the plasma potassium concentration will decrease this ratio an depolarize the cell membrane (that is, make the resting potential less electronegative). This change will initially increase membrane excitability, of a depolarizing stimulus is required to generate an action potential. Howe later effect that is seen in patients is different. Persistent depolarization *inactivates* Na^+ *channels* in the cell membrane, thereby producing a net reduction in mem excitability that may be manifested clinically by impaired cardiac conductio muscle weakness or paralysis.[7]

Similarly, hypokalemia will induce initial hyperpolarization of the cell memb (resting potential more electronegative), lowering membrane excitability. Th will remove the normal state of inactivation of Na^+ channels, thereby increasing neuromuscular excitability.[7] In the heart, these effects of hyperkalemia and hypokalemia can produce characteristic changes in the electrocardiogram a potentially fatal arrhythmias (see Chaps. 27 and 28).

The clinical manifestations of alterations in the plasma K^+ concentration are variable. One patient may have severe muscle weakness with a plasma K^+ concentration of 1.8 meq/L, whereas another may be relatively asymptomati same level. At least two factors appear to be responsible for this individual The effect of hypokalemia (or hyperkalemia) is dependent upon the degree there is a similar change in cell K^+ concentration, thereby minimizing the alteratic the $[K^+]_c/[K^+]_e$ ratio. In particular, *transcellular shifts of* K^+ *are more likely to produce symptoms than changes in external balance.* In hypokalemic periodic paralysis, for example, extracellular K^+ rapidly moves into the cells. Thus, the $[K^+]_c$ rises slightly, whereas the $[K^+]_e$ falls, resulting in a relatively large change in th $[K^+]_c/[K^+]_e$ ratio and the frequent development of muscle weakness or paraly Chap. 27). The findings are different with depletion of K^+ due to gastrointestinal or renal losses. In this setting, the fall in the plasma K^+ concentration creates a gradient that promotes passive movement of K^+ out of the cells not the extracellular fluid.[16] As a result, the K^+ concentration is diminished in both compartments, le to a smaller change in the $[K^+]_c/[K^+]_e$ ratio and therefore a lesser likelihood of symptoms. Similar principles apply to the risk of symptomatic hyperkalemia.

Membrane excitability is determined by factors other than K^+, including the plasma Ca^{2+} concentration and pH. The effect of Ca^{2+} becomes clinically important because it can counteract the membrane effects of hyperkalemia. How this not well understood, but the administration of calcium salts is the most rap for reversing the neuromuscular and cardiac symptoms of severe hyperkale Chap. 28). Membrane excitability is also influenced by changes in the extrac pH, being directly increased by alkalemia and decreased by acidemia. Thus metabolic acidosis will tend to counteract the membrane effects of hypocalc

since each abnormality has a different effect on membrane excitability.

In summary, the degree to which an increase or decrease in the plasma K^+ concentration affects neuromuscular excitability is dependent upon a variet factors. These include the mechanism of change (alteration in external bala versus transcellular shift) and the extracellular Ca^{2+} concentration and pH. As a result, the severity of symptoms does not necessarily correlate with the ma the change in the plasma K^+ concentration. Since the electrocardiogram and mu strength reflect the *functional consequences* of K^+ excess or depletion, monitoring of these parameters as well as the plasma K^+ concentration is essential in the management of patients with severe K^+ imbalance.

REGULATION OF POTASSIUM BALANCE

The maintenance of K^+ balance involves two functions: (1) the normal distribution of K^+ between the cells and extracellular fluid and (2) the renal excretion of the K^+ added to the extracellular fluid from dietary intake and endogenous cellular breakdown.

Distribution between Extracellular Fluid and Cells

Regulation of the internal distribution of K^+ must be extremely efficient, since the movement of as little as 1.5 to 2 percent of the total body K^+ into the extracellular fluid can result in a potentially fatal increase in the plasma K^+ concentration to as high as 8 meq/L or more. In the basal state, normal K^+ distribution is achieved primarily by the Na^+-K^+-ATPase pump.[1] In addition, the ability of K^+ to move between the cells and the extracellular fluid is also important.[16,17] As an example, K^+ enters the cells after a K^+ load. The importance of this response can be appreciated from a few s calculations. Suppose a normal 70-kg man drinks three glasses of orange ju containing 40 meq of K^+. If this K^+ remained in the extracellular fluid (the extracellular volume being approximately 17 liters), there would be a poten dangerous 2.4-meq/L increase in the plasma K^+ concentration. This is prevented by the rapid entry of most of the K^+ into the cells,[16] followed, within 6 to 8 h, by the urinary excretion of the excess K^+.[17,18]

The physiologic and pathologic factors that influence the distribution of K^+ are listed in Table 26-1. The role of these factors in hypokalemic and hyperkalemic stat be discussed in the following two chapters. Nevertheless, it is useful at thi briefly review the physiologic roles of catecholamines and insulin (both of v increase the activity of the Na^+-K^+-ATPase pump) and of the plasma K^+ concentration itself.[1]

Catecholamines and insulin

Catecholamines and insulin can affect K^+ distribution, as both β_2-adrenergic stimuli (due mostly to epinephrine) and insulin promote the cellular uptake of K^+ by skeletal muscle and liver.[17,20,21,22] and[23] These actions are primarily mediated by a hormone-induced increase in activity of the Na^+-K^+-ATPase pump.[1,23,24] The adrenergic effect may also be in part indirect, since, when

epinephrine levels are elevated, there is often a concurrent rise in insulin l due both to a direct β_2-adrenergic effect on the pancreas and to the stimulation glycolysis, leading to a rise in the plasma glucose concentration.[25]

Table 26-1 Factors influencing the distribution of K^+ between the cells and the extracellular fluid

Physiologic
Na^+-K^+-ATPase
Catecholamines
Insulin
Plasma K^+ concentration
Exercise
Pathologic
Chronic diseases
Extracellular pH
Hyperosmolality
Rate of cell breakdown

The physiologic importance of catecholamines and insulin has been demons the response to the administration of β -adrenergic blockers or somatostati impairs insulin secretion). In these settings, the increment in the plasma K^+ concentration after a K^+ load is greater and more prolonged than in normal sub (see Fig. 12-2).[22,26,27] On the other hand, glucose-induced insulin release in normal subjects limits the degree of hyperkalemia following a glucose- and K^+-containing meal (see Fig. 12-4).[28]

It appears that it is the *basal levels* of epinephrine and insulin that enhance K^+ uptake, since a physiologic load (with a rise in the plasma K^+ concentration of less than 1 meq/L) produces little or no change in the plasma levels of thes hormones.[20,29] It is possible, however, that there may be some release of ins into the portal vein, thereby promoting hepatic K^+ uptake without increasing the peripheral plasma insulin concentration.[30]

If, on the other hand, the availability of epinephrine or insulin is increased

glucose load for insulin), there will be a further tendency for K^+ to move into the cells.[26,31] This effect lasts for only several hours, because other factors (pe the plasma K^+ concentration itself) then cause K^+ to move back into the extracellula fluid.[31] This transient action of insulin is useful clinically, since the adminis insulin (with glucose to prevent hypoglycemia) is an important component o in patients with severe hyperkalemia.

In summary, the primary physiologic effect of epinephrine and insulin is to *facilitate the disposition of an acute K^+ load, not to regulate the baseline plasma K^+ concentration*. Although a deficiency of these hormones may cause mild hyperkalemia,[22] this effect is transient, since the excess K^+ can soon enter the cells or be excreted in the urine. As a result, the fasting plasma K^+ concentration is typically normal in patients treated with β -adrenergic blockers and in patients

with diabetes mellitus who are given enough insulin to prevent marked hyperglycemia.[20,26]

Plasma potassium concentration

The combination of insulin deficiency and β -adrenergic blockade impairs b not prevent the intracellular movement of K^+, indicating that other factors must als be involved.[32] One of these is probably the plasma K^+ concentration itself, which will rise after a K^+ load, thereby promoting the passive movement of some of th excess K^+ into the cells. Conversely, will K^+ leave the cells when hypokalemia is c to gastrointestinal or renal losses, an effect that will minimize the fall in th K^+ concentration.

As a result, the plasma K^+ concentration usually varies directly with total body K^+ stores, decreasing with K^+ depletion and increasing with K^+ retention. In general, a reduction in the plasma K^+ concentration from 4.0 to 3.0 meq/L is associated wi 200- to 400-meq deficit in total body K^+.[16] On the other hand, an elevation in the plasma K^+ concentration from 4.0 to 5.0 meq/L is usually associated with the retention of 100 to 200 meq of K^+.[16]

There are some exceptions to this rule, which occur with disorders that affe K^+ distribution. As examples, movement out of the cells is induced by insulin deficiency and hyperosmolality in uncontrolled diabetes mellitus, some form metabolic acidosis, severe exercise, and excess tissue breakdown. In these hyperkalemia may occur even though total body K^+ stores are normal or even reduced.

These problems are discussed in detail in the next two chapters. It is impor however, to note that the effect of exercise can interfere with the routine measurement of the plasma K^+ concentration. After a tourniquet is applied to ob a blood sample, the patient is frequently instructed to repeatedly clench an

unclench his or her fist in an attempt to increase local blood flow and make K^+ more prominent. This can result in movement of K^+ out of the cells and an elevation the plasma K^+ concentration of as much as 1 to 2 meq/L, leading to erroneous evaluation of the state of K^+ balance.[33]

Renal Excretion

Although small amounts of K^+ are lost each day in the feces and sweat, the urine the major route by which the K^+ derived from the diet and endogenous cellular breakdown is eliminated from the body. The primary event in urinary K^+ excretion is the *secretion* of K^+ from the tubular cell into the lumen in the distal nephron, particularly in the *principal cells in the cortical and outer medullary collecting tubule* (see Chap. 12).[34,35] and [36] Although a substantial amount of K^+ is filtered, almost all of this is reabsorbed prior to the distal secretory sites. The amou secreted varies appropriately with the state of K^+ balance: It is enhanced by a K^+ load and reduced by a low-K^+ diet. In addition, net distal reabsorption rather tha secretion can occur in states of K^+ depletion.[34,36]

The secretion of K^+ from the cell into the lumen is primarily passive and is the a function of luminal membrane permeability and the concentration and

electrical gradients across the luminal membrane.[34,35] *Aldosterone* and the *plasma K^+ concentration*, acting in concert, are the major physiologic determinants of K^+ secretion, as they vary directly with the state of K^+ balance (Fig. 26-1). The flow rate to the distal nephron and the lumen-negative potential difference gene Na^+ reabsorption are also important, but they generally play *a permissive rather than a regulatory role* in that they do not necessarily change with alterations in K^+ balance.

Aldosterone and the plasma K^+ Concentration

After a K^+ load, the small increase in the plasma K^+ concentration stimulates the release of aldosterone,[37] and both of these then promote distal K^+ secretion (see Fig. 12-10).[38,39,40] and [41] Aldosterone appears to enhance each of the major s involved in distal K^+ secretion.[1] It makes the lumen more electronegative by promoting Na^+ reabsorption (this is the earliest change),[2] subsequent transport of this Na^+ out of the cell by the Na^+-K^+-ATPase pump also results in movement into the cell, thereby raising the cell K^+ concentration; and[3] aldosterone increases the number of open K^+ channels in the luminal membrane, an additional change facilitates K^+ secretion.[38,39] and [40] The importance of aldosterone in maintainin K^+ homeostasis can be illustrated by the response to spironolactone: This competitive inhibitor of aldosterone produces a variable increase in the pla

potassium concentration as a result of a reduction in potassium excretion.[42] The small elevation in the plasma K^+ concentration after a K^+ load potentiates the effect of aldosterone.[41] Studies in adrenalectomized animals have demonstrated that K^+ loading alone replicates all of the changes in principal cell function induced by aldosterone, resulting in both enhanced Na^+ reabsorption and K^+ secretion.[43,44] How these changes occur is not known. They are, however, less prominent than those seen in the intact animal, in which a K^+ load is appropriately accompanied by a rise in aldosterone secretion.[45]

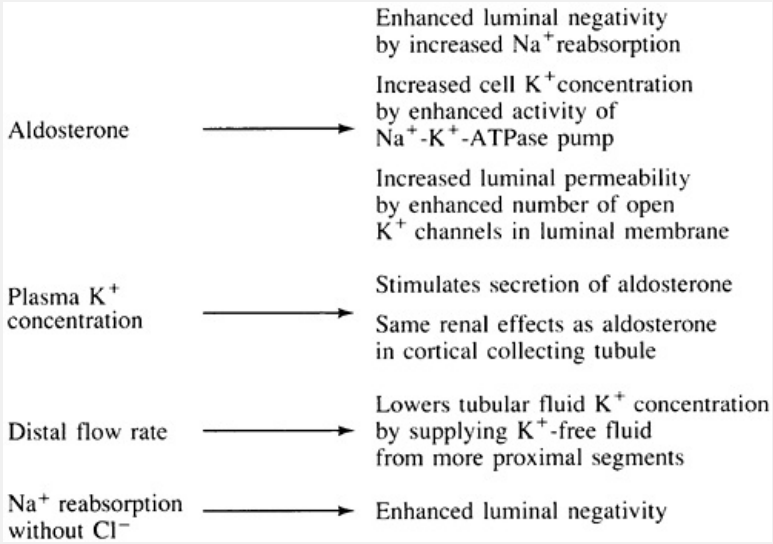

Figure 26-1 Major factors influencing K^+ secretion in the distal nephron, particularly the principal cells in the cortical collecting tubule. Aldosteron the plasma K^+ concentration are the most important physiologic regulators c this process, both increasing with a K^+ load and falling with K^+ depletion. In the latter setting, increased active K^+ reabsorption in the intercalated cells i the cortical and outer medullary collecting tubules also contributes to the app decline in K^+ excretion.

Potassium depletion

These changes in distal function are reversed with dietary K^+ depletion.[34,35] and[36,46] Both the reduction in the plasma K^+ concentration and the associated decrease in aldosterone secretion lead to a marked decline in d K^+ secretion. The ensuing fall in K^+ excretion is also due in part to *active K^+ reabsorption*.[47] This process appears to be mediated by H^+-K^+-ATPase pumps in the luminal membrane of the intercalated cells in the cortical and outer med collecting tubules.[47,48,49] and[50] The net effect is that urinary K^+ excretion can be

reduced to 15 to 25 meq/day with a moderate K^+ deficit and to as low as 5 to 15 meq/day with marked K^+ depletion.[51]

Distal flow rate

The distal flow rate affects K^+ secretion in a different manner, by influencing the *tubular fluid K^+ concentration not that of the cell*. The cell secretion of K^+ raises the tubular fluid K^+ concentration, thereby limiting the concentration gradient for diffusion out of the cell. Increasing distal flow minimizes this effect, since the secreted K^+ is washed away and replaced with relatively K^+-free fluid delivered out of the loop of Henle (Fig. 12-11).[52,53] Distal Na^+ delivery is also enhanced in this setting, and the associated increase in Na^+ reabsorption can contribute to the flow dependence of K^+ secretion.[54]

The distal flow rate plays an important role in both normal and disease states. In particular, *it allows aldosterone to regulate Na^+ balance and antidiuretic hormone (ADH) to regulate water balance without interfering with the control of K^+ balance*. In hypovolemic states such as congestive heart failure, enhanced secretion of aldosterone and ADH contribute to the retention of Na^+ and H_2O. These patients (if untreated) are not usually hypokalemic, however, since the associated increases in proximal Na^+ reabsorption and ADH-induced water reabsorption combine to reduce distal flow, thereby counteracting the direct stimulatory effects of aldosterone and ADH on K^+ secretion.[55,56] and [57] Conversely, an elevation in K^+ secretion does not occur in normal subjects if the distal flow rate is enhanced by intravenous Na^+ infusion.[58,59] In this setting, the ensuing volume expansion suppresses the secretion of aldosterone, allowing the excess Na^+ to be excreted without wasting K^+.

In comparison, inappropriate K^+ loss and hypokalemia will occur if distal flow is enhanced while aldosterone secretion is normal or elevated. This sequence can follow the administration of Na^+ to a patient with an aldosterone-producing adenoma (in whom aldosterone secretion is not suppressible by volume expansion)[59,60] or the use of a loop or thiazide-type diuretic.[61,62] In the latter setting, flow to the secretory site is increased because tubular reabsorption is impaired in the loop of Henle or distal tubule (see Chap. 15); this is frequently accompanied by hyperaldosteronism and high ADH levels due to the diuretic-induced volume loss and often to the underlying disease, such as heart failure or cirrhosis.

Sodium reabsorption and the transepithelial potential difference

Since K^+ is a charged particle, its secretion is also affected by the transepithelial potential difference across the tubular cell. The normal potential difference for K^+-secreting cells in the cortical collecting tubule is approximately -35 to -5

(lumen negative); this potential is generated by the reabsorption of Na^+ (which is positively charged) from the lumen into the peritubular capillary (see Fig. 12-10). This luminal negativity favors K^+ secretion into the lumen.[63]

The importance of Na^+ transport in this process can be illustrated by the response to the diuretic amiloride.[61,62,64] This drug impairs the entry of luminal Na^+ into the cells of the distal nephron by decreasing the number of open Na^+ channels in the luminal membrane.[65] The net effect is diminished Na^+ reabsorption, a reduction in the transepithelial potential difference, and a marked decrease in K^+ secretion. Since amiloride has no known direct effect on K^+ handling, it is likely that the decrease in the potential difference is responsible for the decrease in K^+ secretion.[64]

This stimulatory effect of Na^+ transport can, as noted above, contribute to the flow dependence of K^+ secretion.[54] This effect is most prominent if Na^+ is delivered to the distal nephron with an *anion other than* Cl^- *that is nonreabsorbable*.[63] For example, a volume-depleted subject has a strong stimulus to Na^+ reabsorption in the cortical collecting tubule that is mediated by aldosterone. Under normal conditions the potential generated by Na^+ transport in this segment is in part dissipated by reabsorption of Cl^-. However, if Na^+ is given with a nonreabsorbable anion such as SO_4^{2-}, there will be an increase in both the potential difference and K^+ secretion.[63,66]

Hypokalemia and Hyperkalemia

In summary, K^+ enters the body by dietary ingestion (normal K^+ intake is 40 to 120 meq/day) or intravenous infusion, is stored primarily in the cells, and is excreted in the urine and to a lesser degree in the feces and sweat (Fig. 26-2). An alteration in the plasma K^+ concentration must involve a change in one or more of these processes. For example, hypokalemia can be produced by increased K^+ entry into cells or by increased losses. Decreased dietary intake can contribute to these disorders; it will not, however, cause hypokalemia in normal subjects unless intake is severely restricted, since the kidney can reduce K^+ losses to less than 15 to 25 meq/day.[51] As the tubular fluid K^+ concentration is lowered, more efficient K^+ conservation (to less than 5 meq/L, as may be seen with Na^+ restriction) may be prevented by

leakage (down a favorable concentration gradient) from the cell into the lumen through a relatively nonselective cation channel in the luminal membrane of the medullary collecting duct.[67]

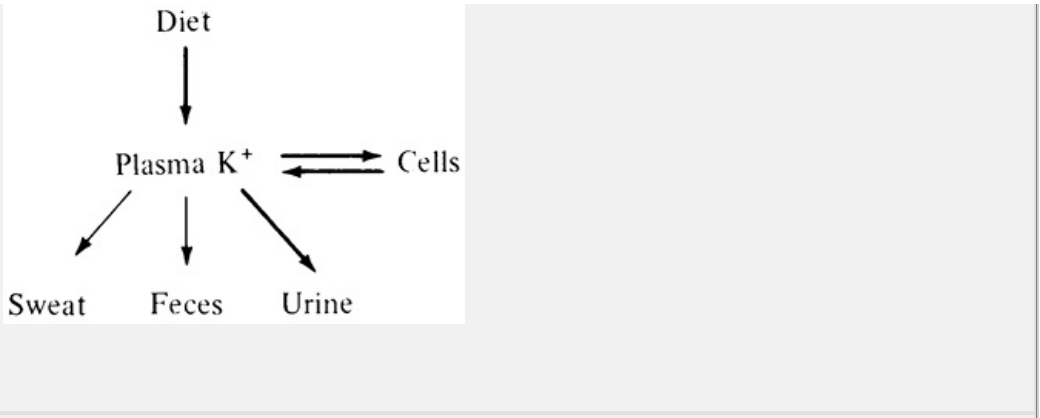

Figure 26-2 Schematic illusion of the factors involved in K^+ homeostasis.

Conversely, hyperkalemia is most often due acutely to enhanced release of K^+ from cells or chronically to decreased urinary excretion. Unless given acutely, ir intake alone will not lead to hyperkalemia if adrenal and renal function are since the excess K^+ will be excreted in the urine (a phenomenon called *potassium adaptation*, see page 889).[45,68,69] Normal subjects, for example, can slowly increase K^+ intake and excretion to over 400 meq/day (normal equals 40 to 1 meq/day) with only a small rise in the plasma K^+ concentration (see Fig. 26-3).[70]

PROBLEMS

26-1A patient with recurrent diarrhea complains of severe muscle wea There is no history, e.g., carpopedal spasm, or physical findings, e.g., Trousseau's or Chvostek's sign, consistent with hypocalcemia. The electrocardiogram reveals ST-segment and T-wave changes with prema

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ventricular beats, which are felt to be compatible with hypokalemia. T following laboratory data are obtained:

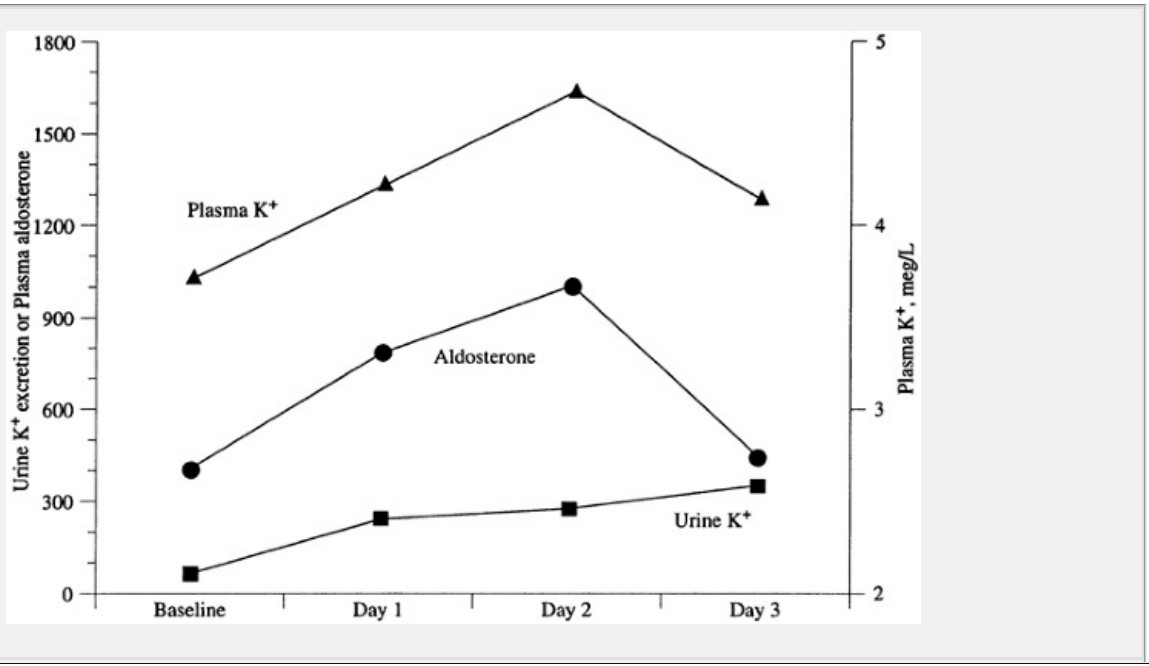

Figure 26-8 Response to increasing K^+ intake to 400 meq/day in normal subjects. Urinary K^+ excretion rises to this level within 2 days and is th maintained. This response is initially driven by elevations in the pla K^+ and aldosterone concentrations. By day 20, the efficiency of K^+ secretion has increased, resulting in a lesser elevation in the plasm concentration (to 4.2 meq/L) and normalization of the plasma aldoste concentration. (*Adapted from Rabelink TJ, Koomans HA, Hené RJ, Dorho Mees EJ,* Kidney Int *38:942, 1990. Reprinted by permission of* Kidney International.)

Plasma $[Na^+] = 140$ meq/L
$[K^+] = 1.3$ meq/L
$[Cl^-] = 117$ meq/L
$[HCO_3^-] = 10$ meq/L
[Albumin] = 4.1 g/dL (normal = 3.5–5.0 g/dL)
$[Ca^{2+}] = 6.3$ mg/dL (normal = 8.8–10.5 mg/dL)
Arterial pH = 7.26
$P_{CO_2} = 23$ mmHg

a. **What effect would correction of the metabolic acidosis have on the plasma K^+ concentration?**
b. **Would correction by hypocalcemia be part of your initial therapeut regimen?**

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Chapter Twenty-Seven
Hypokalemia

The introduction to disorders of potassium balance presented in Chapter 26 should be read before proceeding with this discussion.

ETIOLOGY

Potassium enters the body by dietary intake or intravenous infusion, is prin stored in the cells, and is then excreted in the urine and, to a lesser degre stool and in sweat. An abnormality in any one or more of these processes c hypokalemia (Table 27-1). This section will review the causes of K^+ depletion as well as some aspects of the diagnosis and treatment of certain disorders. T general principles involved in the approach to the hypokalemic patient will discussed separately later in the chapter.

Table 27-1 Etiology of hypokalemia

Decreased net intake

A. Low dietary intake of K^+-free intravenous fluids
B. Clay ingestion

Increased entry into cells, leading to transient hypokalemia

A. Elevation in extracellular pH
B. Increased availability of insulin
C. Elevated β-adrenergic activity—β_2 stress, coronary ischemia, delirium tremens, administration of β-adrenergic agonists for asthma or heart failure
D. Period paralysis—hypokalemic form
E. Treatment of megaloblastic anemias with vitamin B_{12} or folic acid, or of neutropenia with GM–CSF (granulocyte-macrophage colony-stimulati factor)
F. Pseudohypokalemia
G. Hypothermia
H. Chloroquine intoxication

Increased gastrointestinal losses[a] Increased urinary losses

A. Loop and thiazide-type diuretics[a]
B. Mineralcorticoid excess (see Table 27-2)
C. Liddle's syndrome
D. Bartter's or Gitelman's syndrome
E. Increased flow to the distal nephron
    1. Loop and thiazide-type diuretics
    2. Salt-wasting nephropathies
F. Sodium reabsorption with a nonreabsorbable anion
    1. Vomiting or nasogastric suction[a]
    2. Metabolic acidosis
    3. Penicillin derivatives
G. Amphotericin B
H. Hypomagnesemia[a]
I. Polyuria
J. L-dopa

Increased sweat losses
Dialysis
Potassium depletion without hypokalemia

[a] Most common causes.

Decreased Net Intake

The normal range of dietary K^+ intake is approximately 40 to 120 meq/day, with n of this K^+ then being excreted in the urine. If intake is diminished, urinary K^+ excretion can be appropriately reduced to a minimum of 5 to 25 meq/day.[1,2] This renal adaptation is associated with reabsorption rather than secretion of K^+ in the cortical and outer medullary collecting tubules. As described in Chapter 12, distal K^+ secretion occurs in the principal cells in these segments under the influenc aldosterone; active K^+ reabsorption, on the other hand, occurs in the

intercalated cells and is mediated by H^+-K^+-ATPase pumps in the luminal membran that reabsorb K^+ and secrete H^+; the activity of these pumps is increased by hypokalemia.[3,4,5,6] and[7]

The renal response to K^+ depletion is sufficiently effective that a diet (or a low K^+ content of intravenous feedings) will not lead to significant K^+ loss unless intake is severely limited. Since K^+ is present in meat, fruit, and some vegetables

marked K^+ restriction is difficult to sustain and is a rare cause of hypokalem otherwise normal subjects. However, reduced intake can contribute to other of K^+ depletion. For example, poor people living in rural areas may have an K^+ intake of only 25 meq/day, in part because of the relatively high cost of containing foods.[8] These patients are more likely to become hypokalemic if tre with diuretics for hypertension. Similarly, the hypocaloric liquid protein die rapid weight loss can lead to K^+ depletion unless K^+ supplements are given.[9]

Net K^+ intake can also be limited by chronic clay ingestion, a not uncommon in some rural areas in the southeastern United States.[10] The clay appears to bind dietary K^+ and iron directly, diminishing their ability to be absorbed. Hypokal and iron-deficiency anemia may ensue if the ingestion is continued for a pr period.

Increased Entry into Cells

Translocation of K^+ from the extracellular fluid into the cells can occur in a va conditions, leading to a transient reduction in the plasma K^+ concentration that can become clinically important.

Elevation in extracellular pH

Alkalemia, either metabolic or respiratory, can promote K^+ entry into the cells. In alkalemic states, H^+ ions are released from the cellular buffers and move into extracellular fluid to minimize the elevation in pH. To preserve electroneutr extracellular K^+ (and Na^+) enter the cells.[12,13] In general, the plasma K^+ concentration falls less than 0.4 meq/L per 0.1-unit increase in extracellula a result, the degree of hypokalemia induced by the alkalemia is typically mi[13]

A similar reduction in the plasma K^+ concentration can occur when $NaHCO_3$ is administered to correct a metabolic acidosis. In this setting, both the eleva and a direct effect of the increased plasma HCO_3^- concentration appear to contribute to the movement of K^+ into the cells.[14]

Although the effect of alkalemia alone is relatively small, *hypokalemia is a common finding in metabolic alkalosis*. Perhaps the major reason for this association is t the causative factor (diuretics, vomiting, hyperaldosteronism) induces both K^+ and H^+ loss. In addition, the development of hypokalemia may play an

important role in the genesis and maintenance of the metabolic alkalosis (s Chapter 18). In patients with primary hyperaldosteronism, for example, metabolic alk does not occur if hypokalemia is prevented by KCl replacement.[15]

At least three factors may contribute to this effect of K^+

1. A fall in the plasma K^+ concentration leads to a transcellular shift induced b

movement out of the cells to replete extracellular stores. Electroneutrality is maintained in this setting by an Na^+-H^+ entry into the cells, leading to an *intracellular acidosis* and an *extracellular alkalosis*.[16,17] Hypokalemia then contributes to *maintenance* of the metabolic alkalosis by increasing H^+ secretion and HCO_3^- reabsorption by the tubular cells, thereby preventing excretion of the excess HCO_3^-.[18,19] and [20] This response probably reflects the intracellular acidosis,[21] which is a potent stimulus to H^+ secretion (see Chap. 11).

2. Hypokalemia and aldosterone appear to have a potentiating effect on distal hydrogen secretion and therefore on the development and maintenance of metabolic alkalosis by stimulating H^+-K^+-ATPase and H^+-ATPase pumps, respectively.[22] It is of interest in this regard that many of the causes of hypokalemia (such as vomiting, diuretic therapy, and primary hyperaldosteronism) are associated with both a reduction in the plasma K^+ concentration and increased aldosterone release.

3. The lower luminal fluid K^+ concentration in hypokalemia may result in increased NH_4^+ attachment to the K^+ site on the Na^+-K^+-$2Cl^-$ carrier in the thick ascending limb of the loop of Henle. As a result, reabsorption of NH_4^+ and subsequent medullary recycling of NH_3 are enhanced, thereby raising the efficiency of NH_3 secretion into the medullary collecting tubule and increasing net acid excretion (see page 341). Although this hypothesis is unproven for hypokalemia, the reverse effect—decreased NH_4^+ reabsorption, recycling, and urinary NH_4^+ excretion—has been demonstrated with hyperkalemia.[23,24]

Increased availability of insulin

Insulin promotes the entry of K^+ into skeletal muscle and hepatic cells,[25,26] apparently by increasing the activity of H^+-K^+-ATPase pump.[27,28] The major setting in which this leads to hypokalemia is during the treatment of severe hyperglycemia due to uncontrolled diabetes mellitus. These patients are marked K^+-depleted, but the initial plasma K^+ concentration is usually normal or elevated because the combination of insulin deficiency and hyperosmolality promotes movement of intracellular K^+ to the extracellular fluid (see page 25).[29] These abnormalities are corrected by insulin, which then unmasks the underlying K^+ depletion.

Mild hypokalemia can also be induced by a carbohydrate load or by the administration of exogenous insulin.[26,30,31] This effect can become important if intravenous KCl is given in dextrose-containing solutions as part of the therapy for hypokalemia. In this setting, there may be a transient further reduction in the K^+ concentration and the possible induction of ventricular arrhythmias.[30]

Elevated β-adrenergic activity

Catecholamines promote K^+ entry into the cells, a response that is mediated by β_2-adrenergic receptors[32,33] and that also involves increased activity of the Na^+-K^+-ATPase pump.[28] As a result, transient hypokalemia can be induced when epinephrine release is enhanced by hypoglycemia or by the stress of an ac illness.[31,34] For example, diuretic therapy in mild hypertension is often asso with mild hypokalemia (see below); however, stress-induced release of epir (e.g., during an episode of coronary ischemia) can result in a potentially da further reduction in the plasma K^+ concentration to below 2.8 meq/L (Fig. 27-1).[35] The now severe hypokalemia may promote the development of serious ventr arrhythmias.[36]

Hypokalemia that presumably reflects stress-induced epinephrine release h described in a variety of other conditions, including post–cardiopulmonary resuscitation, delirium tremens, acute head trauma, and theophylline intoxi particularly if acute.[37,38,39] and[40] A similar effect, in which the plasma K^+ concentration can acutely fall by 0.5 to 1 meq/L, can also be induced by th administration of a β -adrenergic agonist (such as albuterol, terbutaline, do or ritodrine) to treat asthma, heart failure, and other disorders.[41,42,43,44] In heart failure, for example, a rapid 0.4-meq/L fall in the plasma K^+ concentration following the administration of dobutamine may cause an exacerbation of ve arrhythmias.[43]

On the other hand, β -adrenergic agonists have been used to *treat hyperkalemia* patients with advanced renal failure, since they can transiently lower the p K^+ concentration until the excess K^+ can be removed by a cation exchange resin or dialysis (see Chap. 28).[45]

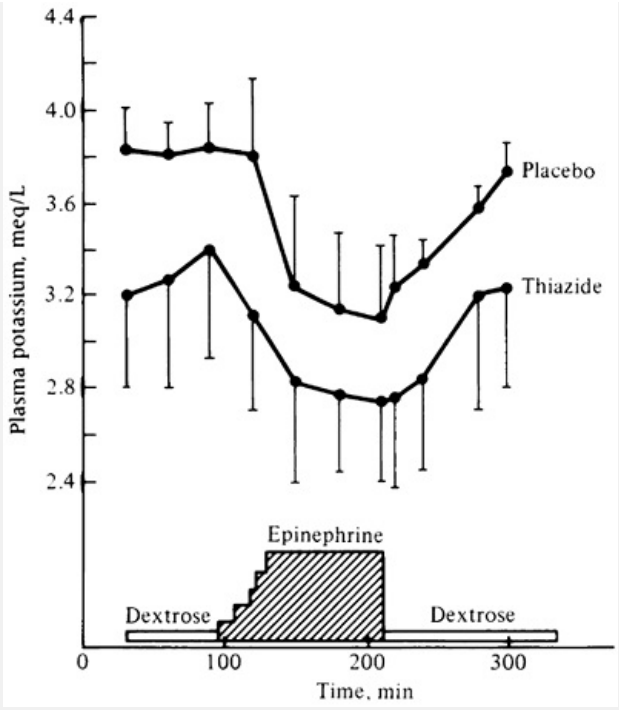

Figure 27-8 Plasma K^+ concentration during an infusion of epinephrine (in physiologic doses) in six patients pretreated with a placebo or a thiazide for 7 days. The plasma K^+ concentration fell in both groups but reached potentially dangerous levels in the diuretic-treated patients who had mild baseline hypokalemia. (*From Struthers AD, Whitesmith R, Reid JL, et al: Lancet 1:1358, 1983, with permission.*)

The effect of epinephrine on K^+ balance can be prevented by nonselective β-adrenergic blockers, such as propranolol.[46] In comparison, β1-selective agents such as atenolol are relatively ineffective,[46] since the epinephrine-induced shift in K^+ is mediated by the β2 receptors.[33] Although it protects the plasma K^+ concentration, propranolol may be associated with some risk in the presence of excess ep because the β2-mediated vasodilator response is also inhibited. As a result, t concurrent α-adrenergic vasoconstriction is now unopposed, leading to a ri diastolic pressure that can exceed 20[46] mmHg.

Periodic paralysis

Periodic paralysis is a rare disorder characterized by recurrent episodes of weakness or paralysis, which can be fatal if the respiratory muscles are inv[47] The severity of individual attacks is variable, ranging from weakness in a s muscle group to diffuse paralysis.

Hypokalemic, hyperkalemic, and normokalemic forms have been des-cribed.[47,48] The hypokalemic form may be familial with autosomal dominant inheritance

acquired as a result of thyrotoxicosis (particularly in Chinese males)[49,50,51,52] and
[53] In either disorder, episodes can be precipitated by rest after exercise, a carbohydrate meal, stress, or the administration of insulin or epinephrine. These attacks are associated with the sudden movement of K^+ into the cells, resulting in an acute reduction in the plasma K^+ concentration (which is normal between attacks) as low as 1.5 to 2.5 meq/L. The hypokalemia is often accompanied by hypophosphatemia and hypomagnesemia.[54] If the condition is untreated, muscle strength returns after 6 to 48 hours as K^+ moves back into the extracellular fluid.

The pathogenesis of familial disease is now better understood. The abnormality in most cases is located on chromosome 1q; the defect is found in the dihydropyridine-sensitive calcium channel in skeletal muscle.[55,56] However, a defect in the calcium channel might lead to episodic potassium movement into the cells, known. Intracellular calcium is increased in these patients, so the defect in the receptor may promote increased calcium entry into the cells.[55] However, the mechanism may not involve calcium movement; the dihydropyridine-sensitive channel also acts as a voltage sensor for excitation-contraction coupling,[57] and the defect in hypokalemic periodic paralysis is associated with a reduced sarcolemmal ATP-sensitive potassium current.[58] In vitro studies have shown that blockade of L-type calcium channels does not prevent membrane depolarization induced by K^+ in muscle fibers from patients with hypokalemic periodic paralysis.[59]

In thyrotoxicosis, there is an increased sensitivity to catecholamines, and the administration of β -adrenergic blockers can minimize the severity and number of attacks and, in some cases, the fall in the plasma K^+ concentration.[50,51] These findings suggest an important role for increased sympathetic activity, although

how it leads to the exaggerated fall in the plasma K^+ concentration is uncertain.[48]

In addition, thyroid hormone increases Na-K-ATPase activity (thereby tending to drive potassium into cells), and thyrotoxic patients with periodic paralysis have higher sodium pump activity than those without paralytic episodes.[60] Excessive thyroid hormone may therefore predispose to paralytic episodes by increasing the susceptibility to the hypokalemic action of epinephrine or insulin.[52] It is also possible that Asians who are susceptible to thyrotoxic periodic paralysis have a mutated calcium channel, which in the euthyroid state is not sufficient to produce symptoms.[47]

The diagnosis of hypokalemic periodic paralysis should be suspected from the history (including a possible familial incidence), the severity of the hypokalemia, the absence of any obvious cause, and the rapid normalization of the plasma K^+ concentration and relief of symptoms following the administration of KCl. Thyroid function studies should be obtained in patients with a negative family history.

A similar acute form of paralysis can be induced by barium poisoning, which

results from contaminated foods.[48] In this disorder, barium blocks the K^+ channels in the cell membrane that normally allow cellular K^+ to diffuse into the extracellular fluid. Patients undergoing radiographic procedures are not at risk for this p since the barium sulfate used in gastrointestinal studies is not absorbed in systemic circulation.

Treatment

Treatment of the acute episode in hypokalemic periodic paralysis involves t administration of 60 to 120 meq of KCl. This should lead to increased musc strength within 15 to 20 min. If no improvement is observed, another 60 me given. The presence of hypokalemia must be confirmed prior to the initiation of therapy, since K^+ administration can exacerbate both the hyperkalemic and normokalemic forms (see Chap. 28).[48,59] Furthermore, excess potassium administration during an acute episode may lead to posttreatment hyperkale potassium moves back out of the cells.[52,54]

Prevention of hypokalemic episodes consists of the restoration of euthyroic thyrotoxic patients and the administration of a β -adrenergic blocker in eith or thyrotoxic periodic paralysis. β -blockers can minimize the number and s attacks and, in most cases, limit the fall in the plasma potassium concentra[52] A nonselective β -blocker (such as propranolol) should be given, since these agents are less likely to inhibit the β_2 -receptor-mediated hypokalemic effect of epinephr and may therefore be less likely to prevent paralytic episodes.[47]

Other modalities that may be effective for prevention include K^+ supplementation, K^+-sparing diuretics, a low-carbohydrate diet, and the carbonic anhydrase i acetazolamide.[48,52,53,54,55,56,57,58,59,60,61] and[62]

Treatment of anemia or neutropenia

An acute increase in hematopoietic cell production by the bone marrow is a with K^+ uptake by the new cells, which may be of sufficient magnitude to ind hypokalemia. As an example, the administration

of folic acid or vitamin B_{12} to patients with megaloblastic anemia frequently lead a reduction in the plasma K^+ concentration to 3.0 meq/L or below, with the possi development of cardiac arrhythmias; this response is most pronounced with first 48 h, when red cell and platelet production are at their peak.[63] In comparison, a significant fall in the plasma K^+ concentration is unusual with other anemias (suc that due to iron deficiency), since treatment of these disorders results in a slower rate of new cell production.

Marked hypokalemia can also be induced by the administration of granulocy macrophage colony-stimulating factor (GM–CSF) to correct neutropenia. Th patients who have a marked increase in white cell production may have a p

concentration that falls below 2 meq/L.[64]

The plasma K^+ concentration may also fall below 3.0 meq/L following multiple transfusions with frozen, washed red cells.[65] These cells, but not those stored in acid-citrate-dextran, lose up to 50 percent of their K^+ during storage. In the recipient, K^+ rapidly moves into the cells to repair the deficit.

Pseudohypokalemia

Metabolically active cells can take up K^+ after blood has been drawn. In this settir which has been described in cases of acute myeloid leukemia associated w high white cell count, the patient may have a relatively normal plasma K^+ concentration, but the measured value may be below 1.0 meq/L (without any symptoms) if the blood is first allowed to stand for a prolonged period at ro temperature.[66] This problem can be avoided if the plasma or serum is rapidly separated from the cells or if the blood is stored at 4°C.

Hypothermia

Accidental or induced hypothermia can lower the plasma K^+ concentration to below 3.0 meq/L, apparently as a result of K^+ entry into the cells.[67,68] This effect is readily reversible during rewarming and may be associated with "overshoot *hyper*kalemia, particularly if K^+ has been given during the period of hypothermia.[67] Furthermore, patients who are essentially dead following accidental hypoth present with a plasma K^+ concentration above 10 to 20 meq/L as a result of irreversible tissue necrosis.[68]

Chloroquine intoxication

Hypokalemia, with the plasma potassium concentration falling below 2.0 me severe cases, is a common finding in acute chloroquine intoxication.[69] This effect is presumably mediated by potassium movement into the cells and can be exac by the administration of epinephrine to help treat the intoxication.

Increased Gastrointestinal Losses

In normal subjects, approximately 3 to 6 liters of gastric, pancreatic, biliary intestinal secretions is released into the gastrointestinal lumen each day. A these fluids are then reabsorbed, as only 100 to 200 mL of water and 5 to 1 K^+ are lost in the stool. Since each of these secretions contains K^+, the loss of any of them (because of decreased absorption or increased secretion) can lead

depletion. This can be seen with vomiting (although urinary losses are gen more important in this setting; see below), diarrhea, intestinal fistulas or tu drainage, or the loss of colonic secretions from a villous adenoma or from c laxative abuse.[70,71,72,73,74,75 and 76]

Hypokalemia is most common when the losses occur over a prolonged perio

with a villous adenoma, or are acute and massive[77]. In cholera, for example, daily stool losses may average 8 liters of water, 1000 meq of Na^+, and 100 meq of K^+[71]. Similarly, daily fluid losses in excess of 6 liters and K^+ losses in excess of 300 meq have been reported in patients with the VIPoma syndrome (severe, watery d and histamine-fast achlorhydria, usually but not always due to a vasoactive peptide–producing non-β -cell islet cell tumor)[72,73] and[74].

In many cases, however, increased fecal losses cannot explain all of the po deficit. Normal subjects ingest an average of about 80 meq of potassium pe Urinary potassium excretion should fall below 15 to 25 meq/day in the pres potassium deficit[1,2]. Thus, fecal losses (normally about 10 meq/day) must exce to 65 meq/day to directly induce hypokalemia. Many patients who become hypokalemic have a lower level of fecal potassium excretion, indicating tha factors (such as decreased intake and perhaps hyperaldosteronism-induced potassium excretion) must also play a contributory role[77].

Increased Urinary Losses

Urinary K^+ excretion is primarily determined by K^+ secretion in the distal nephron, particularly the cortical collecting tubule (see Chapter 12). Inappropriate urinary K^+ loss leading to hypokalemia is most often due to conditions associated with mineralocorticoid excess and/or increased urinary flow of water to the distal Na secretory site (Table 27-1).

Loop and thiazide-type diuretics

Hypokalemia is a relatively common problem with the loop and thiazide-type diuretics. When hydrochlorothiazide is used to treat essential hypertension example, the incidence of hypokalemia is dose-related, with the fall in the p potassium concentration averaging about 0.5 meq/L with 50 mg per day[78,79]. Chlorthalidone, which is longer-acting, has a greater kaliuretic effect, lowe plasma potassium concentration by 0.8 to 0.9 meq/L at a 50-mg/day dose[78].

Two factors appear to be responsible for the increased K^+ excretion with these agents[1]: increased flow to the distal secretory site, as a result of inhibition and water reabsorption in the loop of Henle or distal tubule, and[2] secretion of aldosterone, as a result of both the underlying disease (heart cirrhosis) and the induction of volume depletion[80,81]. In addition, diuretic-induced hypomagnesemia (see below) and, with loop diuretics, decreased K^+ reabsorption by the Na^+-K^+-$2Cl^-$ carrier in the loop of Henle (see Figure 4-2) also may promote K^+ loss in the urine.

The degree of K^+ loss is dose-dependent. This is an important issue in many patients with mild to moderate essential hypertension, in whom diuretic-ind

hypokalemia has become a less frequent problem since the demonstration t

dose thiazide therapy (e.g. 12.5 mg of hydrochlorothiazide or its equivalent frequently produces an antihypertensive effect similar to that of higher dos only a minimal reduction in the plasma K^+ concentration (Fig. 27-2).[82,83]

If the diuretic dose and dietary intake are relatively constant, the bulk of th will occur during the first 2 weeks of therapy (see Fig. 45-8).[84] At this time, *a new steady state is reached in which K^+ intake and output are again equal*. Although the diuretic continues to promote K^+ wasting, this effect is counteracted by the combination of a decrease in distal flow (induced by the associated hypovo and the direct K^+-sparing effect of hypokalemia (see "Symptoms," below).[1,2]

Treatment

Diuretic-induced hypokalemia has been associated with an increased incide arrhythmias,[85] and diuretic therapy in both hypertension and heart failure has associated with an increased incidence of arrhythmic death that can be pre a K^+-sparing diuretic (such as spironolactone) and may therefore be due to depletion.[86,87,88] and[89] For these reasons, even mild diuretic-induced hypokalemia is usually treated, and some physicians try to maintain the pla concentration above 4 meq/L in patients with heart failure. This can be ach either with KCl supplements (usually requiring 40 meq/day to raise the plas concentration by about 0.5 meq/L)[79] with a K^+-sparing diuretic, which can also partially correct diuretic-induced magnesium depletion by diminishing magn excretion.[79]

Correction of hypokalemia may have an additional advantage in hypertensiv patients, further lowering the blood pressure by 5 to 10 mmHg in some case[90,91] How this occurs is not well understood, but increased Na^+ excretion may contribute.

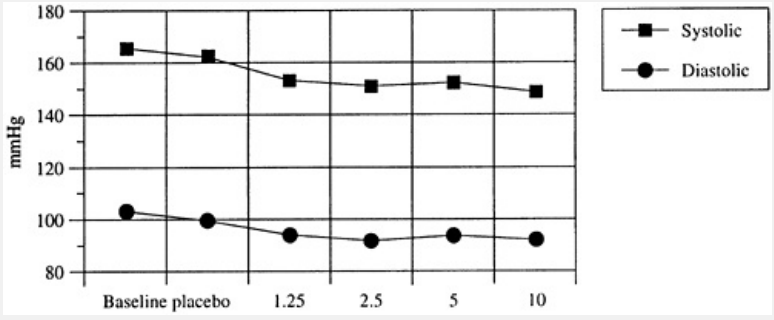

Figure 27-2 Antihypertensive response to bendrofluazide in relation to dose (multiply to 10 to get equivalent doses of hydrochlorothiazide). The initia of 1.25 mg lowers the blood pressure in comparison to placebo; however, doses produced little further antihypertensive response. Each treatment g contained approximately 52 patients. (*Data from Carlsen JE, Kober L, Torp-Pedersen C, Johannsen P: BMJ 300:975, 1990, with permission.*)

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Mineralocorticoid excess

Aldosterone, the primary endogenous mineralocorticoid, stimulates the reab of Na^+ and the secretion of K^+ and H^+ (see Chap. 6). Consequently, the excessive secretion of aldosterone (or any other mineralocorticoid) an lead to hypoka metabolic alkalosis.[92,93,94] and[95] Edema, however, does not usually occur in otherwise normal subjects, since the initial Na^+ retention is followed by a spontaneous natriuresis, a phenomenon referred to as *aldosterone escape*. Both the ensuing rise in systemic blood pressure and enhanced secretion of atrial na peptide contribute to this increase in Na^+ excretion (see page 185).

For hypokalemia to occur, there must be adequate delivery of Na^+ and water to the distal nephron. When distal flow is reduced because of effective circulating depletion, K^+ secretion may be relatively unchanged despite the presence of hyperaldosteronism.[96] Thus, patients with uncomplicated heart failure or cirrho typically have a normal plasma K^+ concentration. However, hypokalemia may rapi ensue if distal delivery is enhanced by the administration of diuretics.

Primary mineralocorticoid excess occurs in a variety of uncommon condition (see Table 27-2).[92,93,94] and[95] In addition to hypokalemia and metabolic alkalosis, thes disorders are also associated with hypertension and mild hypernatremia. Vo expansion initiates the elevation in blood pressure[97] and also accounts for the rise in the plasma Na^+ concentration (to about 145 meq/L) by causing an upward resetting of the osmostat (see page 75).[98]

Primary hyperaldosteronism

The autonomous hypersecretion of aldosterone may result from a unilateral adenoma or carcinoma or from bilateral hyperplasia.[92,93,94] and[95] An adenoma is responsible for about 65 percent of cases, with

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hyperplasia accounting for most of the remaining patients. Because of the r hypervolemia, the plasma renin activity is typically (but not always) reduce disorders.[92] Hyperplasia is generally a milder disease, with less hypersecret aldosterone and less hypokalemia.

Table 27-2 Causes of primary mineralocorticoid excess

Primary hyperaldosteronism
A. Adenoma

B. Hyperplasia
C. Carcinoma

Cushing's disease (some cases)
Chronic ingestion of exogenous mineralocorticoid

A. Fludrocortisone

Hyperreninism

A. Renal artery stenosis
B. Renin-secreting tumor

Glucocorticoid-remediable hyperaldosteronism
Hypersecretion of deoxycorticosterone or other mineralocorticoid

A. CYP17 (17α-hydroxylase) deficiency
B. CYP11B1 (11β-hydroxylase) deficiency
C. Normal levels of cortisol with chronic licorice ingestion or the syndr
of apparent mineralocorticoid excess

The factors responsible for adrenal hyperplasia are not well understood[94]. Increased sensitivity of the adrenal zona glomerulosa to angiotensin II may be a contr factor. This relationship could explain the characteristic rise in the plasma aldosterone concentration between an 8 A.M. supin sample and a noon upri sample, since assumption of the upright posture leads to pooling of blood i lower extremities, mild effective volume depletion, and activation of the ren angiotensin system. In comparison, there is usually no change or a slight d aldosterone levels during the day in patients with an adrenal adenoma, a d that has been used to distinguish between these conditions.

In another rare form of adrenal hyperplasia with autosomal dominant inherit hypersecretion of aldosterone is reversed by the administration of a glucoc such as dexamethasone[99,100]. Normal subjects synthesize aldosterone in the zo glomerulosa, but not in the adrenocorticotropic hormone (ACTH)–sensitive fasciculata, which lacks the enzymes required to add the necessary aldehyd corticosterone at the 18-carbon position (Fig. 27-3).

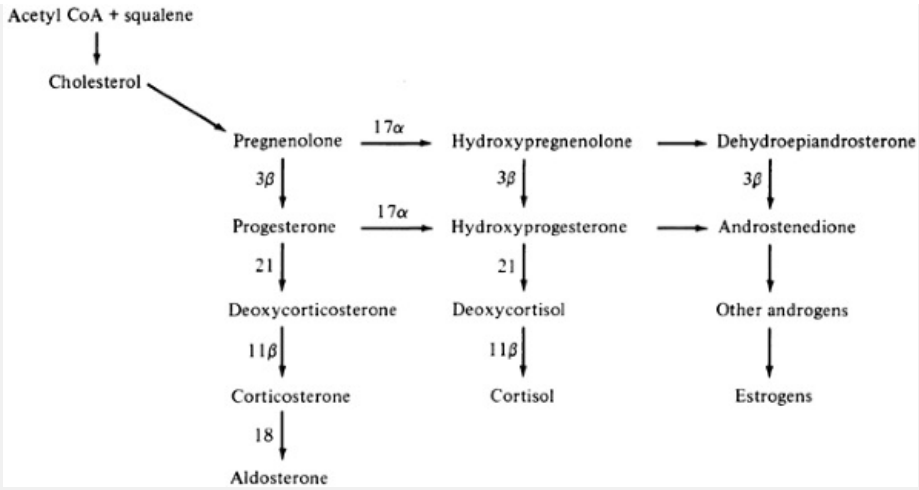

Figure 27-Schematic pathways of adrenal steroid biosynthesis. The numb at the arrows refer to specific enzymes: 17α equals 17α-hydroxylase; 3β e 3β-hydroxysteroid dehydrogenase; 21 equals 21-hydroxylase; 11β equals hydroxylase; 18 refers to a two-step process resulting in the addition of a aldehyde at the 18-carbon position. The last reactions occur only in the z glomerulosa, which is the site of aldosterone secretion. A deficiency in ar these enzymes can lead to abnormal mineralocorticoid (as well as glucocc and androgen) production.

Glucocorticoid-suppressible hyperaldosteronism appears to result from a *chimeric gene* on chromosome 8 containing the regulatory subunit of 11β-hydroxylase enzyme that converts deoxycortisol into cortisol) and the coding sequences aldosterone synthase (the enzyme responsible for the addition at an 18-ald[99] The presence of the 11β-hydroxylase portion both locates the ensuing enzy zona fasciculata and makes it ACTH-responsive. Thus, the normal levels of required for cortisol secretion lead to hypersecretion of aldosterone; this p can be corrected by the exogenous administration of glucocorticoid, which diminish ACTH release.

There is a second form of autosomal dominant familial hyperaldosteronism reversed by glucocorticoid therapy. The pathogenesis of this disorder is no understood.[101]

Cushing's syndrome (glucocorticoid excess)

Cortisol, the most active glucocorticoid, is synthesized in the zona fascicul the influence of ACTH. Cortisol binds as avidly as aldosterone to the mineralocorticoid receptor; nevertheless, cortisol normally has weak mineralocorticoid activity because it is inactivated to cortisone at the aldos sensitive cells in the collecting tubules (see "Licorice and the Syndrome of Apparen Mineralocorticoid Excess" below).[102,103] However, some patients with Cushing's syndrome develop hypokalemia and metabolic alkalosis. This is most likely in patients with ectopic ACTH production who markedly oversecrete cortiso

setting, the rate of delivery of cortisol may exceed its rate of inactivation, allowing it to act as a mineralocorticoid.[104] In addition, increased secretion of other ACTH-dependent mineralocorticoids (such as deoxycorticosterone and corticosterone) may play a contributory role.[105,106]

Hypercortisolism can result from hypersecretion of ACTH (due to a pituitary or a nonendocrine ACTH-producing tumor), from primary adrenal diseases (adenoma or carcinoma), or from exogenous glucocorticoid therapy.[107,108] The degree of hypokalemia is directly related to the level of cortisol secretion, being most severe in those states with the highest hormone production, namely, adrenal carcinoma and nonendocrine tumors.[106] Although Cushing's syndrome can also be seen with chronic therapy with oral prednisone or dexamethasone, these compounds have little mineralocorticoid activity and are less likely to produce hypokalemia or hypertension.

In contrast to primary hyperaldosteronism, the hypertension in Cushing's syndrome is not directly related to Na^+ retention and volume expansion.[97,109] As a result, the plasma renin activity is generally normal or increased, not reduced as with primary aldosterone excess.[93,109] Why the blood pressure rises in this disorder is not well understood.[109,110]

The complete approach to the diagnosis and therapy of Cushing's syndrome is beyond the scope of this discussion.[108,111,112] Reviewed briefly, patients generally have the classic cushingoid features, particularly central obesity, ecchymoses, muscle weakness. There are three stages in the diagnostic evaluation of patients suspected to have Cushing's syndrome.

- Determining whether hypercortisolism is present, usually by measuring urinary cortisol excretion or the plasma cortisol concentration after the administration of low-dose dexamethasone.[111]
- Determining whether the hypercortisolism is ACTH-independent or ACTH-dependent; i.e., does the patient have primary adrenal disease or an ACTH-secreting tumor? This can usually be determined by measurement of plasma ACTH.[112]
- Determining the source of the excess ACTH in ACTH-dependent hypercortisolism; i.e., does the patient have an ACTH-secreting pituitary adenoma (Cushing's disease) or an ACTH-secreting nonpituitary tumor (ectopic ACTH syndrome)? The high-dose dexamethasone suppression test is usually the first test performed.[112]

Treatment generally consists of removal of a unilateral adrenal lesion or transsphenoidal microsurgery for pituitary disease.[113,114]

Congenital adrenal hyperplasia

Deoxycorticosterone (DOC) and corticosterone are synthesized in the adrenal

and possess significant mineralocorticoid activity. The secretion of these h is regulated by ACTH, not angiotensin II and the plasma K^+ concentration, which are the primary determinants of aldosterone release (see Chap. 26). When cortisol production is reduced because of an adrenal enzyme deficiency, the secreti ACTH and therefore of DOC and corticosterone will be persistently elevate the affected enzyme is required for their synthesis. This sequence can be s two forms of congenital adrenal hyperplasia, CYP11B1 (11β-hydroxylase) ar (17α-hydroxylase) deficiency (Fig. 27-3).[115] The latter is nonvirilizing, since androgen production is also dependent upon 17-hydroxylation.

Glucocorticoid and K^+ balance can be restored in these disorders by the administration of cortisol, which lowers ACTH, DOC, and corticosterone sec normal. There is, however, a risk of inducing *hypo*natremia and *hyper*kalemia with this regimen, since the enzyme deficiencies also impair the synthesis of alc (Fig. 27-3).[115] As a result, mineralocorticoid replacement with fludrocortisone also be required.

A syndrome similar to that seen with CYP11B1 deficiency—hypersecretion o DOC, corticosterone, and adrenal androgens—can also occur in the rare di known as familial glucocorticoid resistance.[116] This condition appears to result fro an inherited abnormality in the glucocorticoid receptor, preventing it from b cortisol.[117] The net effect is adrenal stimulation due to high ACTH levels eve though the plasma cortisol concentration is elevated.

Licorice and the syndrome of apparent mineralocorticoi excess

Subjects who chronically ingest large amounts of licorice (or licorice-conta chewing tobacco or gum) can develop a reversible syndrome that is clinical to primary hyperaldosteronism.[118,119] A steroid in licorice, glycyrrhetinic acid, ha slight mineralocorticoid activity; more importantly, this compound also impa

the action of the enzyme 11β-hydroxysteroid dehydrogenase, which convert to cortisone in aldosterone target tissues such as the collecting tubules in kidney.[102,121]

As noted above, cortisol binds to the mineralocorticoid receptor with an avi to that of aldosterone and circulates in a much higher concentration; thus, would inappropriately function as the primary mineralocorticoid were it not locally by 11β-hydroxysteroid dehydrogenase and other *in vivo* enzymes to metabolites such as cortisone.[102,103] This conversion is impaired with licorice-induced inhibition of 11β-hydroxysteroid dehydrogenase, thereby allowing c activate the mineralocorticoid receptors and produce a clinical picture of pr hyperaldosteronism.[103,119] One major difference is that endogenous aldosteron secretion is appropriately suppressed in this setting.[102,103]

A similar pathophysiology occurs in the *syndrome of apparent mineralocorticoid excess*. This disorder is characterized by mutations in the 11β-hydroxysteroi

dehydrogenase gene that once again allow cortisol to act as the major endo mineralocorticoid.[122,123] Therapy usually includes spironolactone (which comp for the mineralocorticoid receptor), potassium supplements, and a low-salt theory, the administration of dexamethasone (which has little activity at the mineralocorticoid receptor) should reverse the hypokalemia by diminishing secretion of ACTH and therefore cortisol. However, preliminary clinical obs suggest that dexamethasone is only occasionally effective.[124]

Hyperreninism

Primary hypersecretion of renin can result in a syndrome that mimics the cl findings of primary hyperaldosteronism, except that the *plasma renin activity* is elevated. This may occur with rare, renin-secreting tumors of the juxtaglomeru apparatus[125,126] and[127] or, more commonly, with renovascular hypertension (artery stenosis, malignant hypertension, vasculitis, scleroderma), in which ischemia induces nonsuppressible renin release.

Renal arteriography usually establishes the correct diagnosis, although sm secreting tumors may be missed.[126] Selective venography or renal vein renin sampling may be necessary in this setting, in which the findings of hyperte hypokalemia, *increased* plasma renin activity, and normal renal arteries are suggestive of a renin-secreting tumor or possibly surreptitious diuretic use patient with underlying essential hypertension.

Other mineralocorticoids

On rare occasions, the hypersecretion of other mineralocorticoids can lead hypokalemia and hypertension. Included in this group are patients with DOC producing adenomas[93,128] and, as described above, congenital adrenal hyperp due to CYP11B1 or CYP17 deficiency. Nonaldosterone mineralocorticoid exc also be induced by the administration of fludrocortisone, a synthetic mineralocorticoid used in the treatment of hypoaldosteronism and also pres some nasal sprays.[129]

Liddle's syndrome

A clinical picture similar to that of primary hyperaldosteronism, although in of mineralocorticoids, is seen in Liddle's syndrome.

This is a rare autosomal dominant condition characterized by a mutation in collecting tubule Na^+ channel, producing a *gain of function* with enhanced Na^+ reabsorption.[130,131] It is distinguished from true primary hyperaldosteroni the combination of low renin and low aldosterone levels.

Therapy consists of the administration of amiloride or triamterene, K^+-sparing diuretics that directly close the sodium channel.[132] The mineralocorticoid antagonist spironolactone is ineffective, since the increase in Na^+ reabsorption is not mediated by aldosterone.

Bartter's and Gitelman's syndromes

Bartter's and Gitelman's syndromes are rare disorders that present with hyp and metabolic alkalosis but, in contrast to primary hyperaldosteronism, no hypertension.[133,134] and[135] The pathogenesis of these disorders is similar to seen with loop and thiazide-type diuretics, since there is a primary reductio transport in the loop of Henle and the distal tubule, respectively.

The genetic defect in Bartter's syndrome involves the transporters in the th ascending limb of the loop of Henle. The process of active sodium chloride in this segment is mediated at the luminal membrane by the loop diuretic–s Na^+-K^+-$2Cl^-$ cotransporter, which results in sodium chloride entry into the tul cells, and by potassium channels, which permit reabsorbed potassium to lea into the lumen for continued K^+-$2Cl^-$ cotransport (see Fig. 4-2).[136] At the basolateral membrane, chloride channels permit the chloride that has enter cell to exit and be returned to the systemic circulation. Bartter's syndrome from a defect in the gene for any one of these three transporters, illustratir requirement for their integrated function in loop transport.[137,138] and[139]

The genetic defect in Gitelman's syndrome is a mutation in the gene coding thiazide-sensitive Na-Cl cotransporter in the distal tubule.[140] A defect in this transporter can account for both the magnesium wasting and the often mark decrease in calcium excretion (the opposite of the hypercalciuria seen in B syndrome).[140] Gitelman's syndrome is often inherited, and both autosomal re and dominant forms have been described.[141]

Bartter's syndrome generally presents early in life (before the age of 6). Th tendency to sodium wasting leads to hyperreninemia, hyperaldosteronism, a hypokalemic alkalosis.[133,142] Increased secretion of vasodilator prostaglandins (prostaglandin E and prostacyclin) is also present in this condition and may explain why the blood pressure remains normal.[142]

Other common findings are growth and mental retardation, polyuria, polydip decreased concentrating ability, hypercalciuria,[143] and a plasma magnesium concentration that is normal or only mildly reduced. These urinary findings compatible with the defect in the medullary portion of the thick ascending l segment plays a central role in creating the counter-current gradient requir urinary concentration, and both calcium and magnesium are passively reabs this site down gradients created by sodium chloride transport (see Chapt. 3 and 4).

Gitelman's syndrome is a more benign condition than Bartter's syndrome. It diagnosed incidentally in late childhood or even adulthood.[134,143] Affected patients may present with tetany or are discovered incidentally when they are found hypokalemia, metabolic alkalosis, and hypomagnesemia.[144] Other typical findings are hyperaldosteronism, hyperreninemia, and hypo-calciuria;[143] concentrating ability is maintained, indicating intact function in the medullary thick limb.

The diagnosis of Bartter's or Gitelman's syndrome is basically one of exclusion.[133,134] Surreptitious diuretic use (which can usually be detected by urine assay for diuretics) or vomiting can replicate most of the biochemical hormonal findings,[145,146] and[147] although the urine Cl^- concentration should be low in the latter condition.[147]

Since the tubular defect cannot be corrected, treatment in these disorders at minimizing the effects of the secondary increases in aldosterone and prostaglandin secretion. The combination of a nonsteroidal anti-inflammato (NSAID) and a potassium-sparing diuretic (such as spironolactone or amilor in higher than usual doses of up to 300 and 40 mg/day, respectively, to mor completely block distal potassium secretion) can raise the plasma potassiu concentration toward normal, largely reverse the metabolic alkalosis, and p correct the hypomagnesemia.[137,148,149] and[150]

A similar response can be induced by the use of an angiotensin converting inhibitor, which diminishes the production of angiotensin II and aldosterone.[151,152] The acute reduction in angiotensin II levels in this setting can lead to symp hypotension in some cases. This problem is often transient (lasting only 3 and can be minimized by the initial use of low doses.

Most patients also require oral potassium and magnesium supplementation, drug therapy is usually incompletely effective. However, the restoration of magnesium and potassium balance is often difficult to achieve. Diarrhea fre limits the dose of magnesium given, and the magnesium that is absorbed te excreted in the urine. Persistent hypomagnesemia can contribute to urinary potassium loss, making correction of the hypokalemia more difficult.

Increased flow to the distal nephron

Increased flow of water and Na^+ to the collecting tubules and possibly K^+ wasting occurs in those states in which proximal, loop, or distal tubule NaCl reabso decreased (Table 27-1). As described above with diuretics and Bartter's and Gitelman's syndromes, the initial Na^+ wasting leads to a secondary rise in aldosterone release, further contributing to the tendency to hypokalemia.

Salt-wasting nephropathies

In a variety of renal diseases, particularly tubulointerstitial disorders such interstitial nephritis (as with Sjögren's syndrome or lupus) or urinary tract obstruction, Na^+ and water reabsorption are impaired, leading to increased Na^+ delivery to the K^+ secretory site and secondary

hyperaldosteronism. As a result, increased K^+ secretion and hypokalemia can occur in a manner similar to that induced by diuretics or Bartter's syndrome.[153,154,155] and[156]

This mechanism may also account for the development of hypokalemia in

hypercalcemic states, since calcium-induced tubular damage may impair Na^+ reabsorption.[159] Similarly, lysozyme-induced tubular injury may be at least in responsible for the renal K^+ wasting and relatively marked hypokalemia that may be associated with leukemia, particularly acute monocytic or myelomonocytic leukemia.[160,161] and[162] K^+ entry into the metabolically active leukemic cells may also contribute to the fall in the plasma K^+ concentration in this disorder.[161]

Sodium reabsorption with a nonreabsorbable anion

The ability of increased distal delivery to enhance K^+ secretion is augmented if Na^+ is presented to the distal secretory site with a nonreabsorbable anion other than Cl^-. In this setting, the lumen-negative electrical gradient created by Na^+ reabsorption is increased, since it cannot be dissipated by Cl^- reabsorption. The net effect is enhanced secretion of K^+ and H^+.

Examples in which the distal delivery of relatively large quantities of a nonreabsorbable anion can induce hypokalemia include vomiting or type 2 renal tubular acidosis (see below), β-hydroxybutyrate in diabetic ketoacidosis, hippurate following toluene use (glue-sniffing), or a penicillin derivative in patients receiving high-dose penicillin therapy.[163,164] and[165] As an example, the plasma potassium concentration has been reported to be below 2 meq/L in approximately one-fourth of patients with toluene-induced metabolic acidosis.[165]

The effect of nonreabsorbable anions is likely to be most prominent when there is concurrent volume depletion. In this setting, the decreased delivery of Cl^- and the enhanced secretion of aldosterone both promote K^+ secretion.[164] There is also evidence that anions differ in their ability to enhance K^+ secretion. In humans, for example, HCO_3^- (following the administration of a carbonic anhydrase inhibitor to diminish proximal HCO_3^- reabsorption) has a greater effect than sulfate (induced by the ingestion of sulfur-containing amino acids),[164] although why this might occur is not known.

Vomiting or nasogastric suction

Hypokalemia is a common finding with persistent loss of gastric secretions. Although some K^+ is present in this fluid (about 5 to 10 meq/L), most of the deficit is initially due to urinary losses.[70] The mechanism by which this occurs is as follows: Gastric juice contains a high concentration of HCl. Thus, its removal leads to elevations in the plasma HCO_3^- concentration and the filtered HCO_3^- load [glomerular filtration rate (GFR) times plasma HCO_3^- concentration], as well as hypovolemia and secondary hyperaldosteronism. The excess filtered HCO_3^- load exceeds reabsorptive capacity, which cannot increase acutely. As a result, HCO_3^- and water delivery to the distal nephron are

enhanced; the ensuing reabsorption of some of this Na^+ in the cortical collecting tubule is accompanied by increased K^+ secretion, since HCO_3^- acts as a nonreabsorbable anion.

This K^+-wasting state is generally transient. Within 48 to 72 h, proximal Na^+ and HCO_3^- reabsorption rise in response to the hypovolemia; less HCO_3^- is delivered distally, and K^+ excretion falls (see page 566).[170] Further K^+ loss at this time is primarily due to continued removal of gastric secretions.

Metabolic acidosis

Increased urinary K^+ loss also occurs in several forms of metabolic acidosis, generally by mechanisms similar to that in vomiting.[166] In diabetic ketoacidosis, for example, increased quantities of Na^+ and water (due to the glucose osmotic diuresis) are presented to the distal nephron with β -hydroxybutyrate and acetoacetate.[29] In type 2 (proximal) renal tubular acidosis, on the other hand, K^+ is delivered with HCO_3^- because of a primary reduction in proximal HCO_3^- transport.[167] This effect is most prominent after the institution of alkali therapy, which raises the filtered HCO_3^- load far above proximal reabsorptive capacity (see Fig. 19-7).

A somewhat different mechanism is operative in type 1 (distal) renal tubular acidosis. In this condition, distal H^+ secretion is reduced. As a result, Na^+ reabsorption must occur in exchange for K^+ if Na^+ balance is to be maintained (see page 616).[167] Severe K^+ depletion with a plasma K^+ concentration below 2.0 meq/L may occur in this disorder. Although renal tubular acidosis is a rare condition, one of the more common causes in adults is Sjögren's syndrome.[168] In some patients with this disorder, the renal manifestations can precede the characteristic extrarenal findings by several years or more.[168]

In addition to these factors, distal flow may be directly increased in metabolic acidosis. Approximately one-third of proximal Na^+ reabsorption is passive, occuring down gradients created primarily by HCO_3^- reabsorption (see Chap. 3). In metabolic acidosis, less HCO_3^- is reabsorbed proximally (since less is filtered), thereby decreasing passive NaCl and water transport and augmenting distal delivery.[169]

Amphotericin B

Hypokalemia due to increased urinary losses occurs in up to half of patients with amphotericin B.[170,171] Increased membrane permeability due to an interaction of amphotericin with membrane sterols probably plays an important role in this complication.[172] This defect can promote distal K^+ secretion both by increasing the K^+ permeability of the luminal membrane and, via the mechanism described

by the concurrent type 1 renal tubular acidosis that is often present.[170] The latter problem is probably related to increased membrane permeability to the H_2CO_3, thereby allowing secreted acid to back-diffuse out of the tubular lu

Hypomagnesemia

Hypomagnesemia is a relatively common finding in hypokalemic patients, be in up to 40 percent of cases.[173,174] In some patients, the underlying abnormality such as cisplatin toxicity or primary hyperaldosteronism, impairs both K^+ and magnesium reabsorption by the kidney.[175,176]

In addition, hypomagnesemia from any cause can lead to K^+ depletion (due to both urinary and fecal losses) and hypokalemia.[173,177] The mechanism responsible for the inappropriate kaliuresis is not well understood, although decreased rea in the loop of Henle and perhaps the cortical collecting tubule may be responsible.[178,179]

Hypocalcemia, due to both diminished secretion of parathyroid hormone and resistance to its effect, is also commonly present in hypomagnesemic patients.[180,181,182] and[183] If otherwise unexplained, this combination of hypokalemia and hypocalcemia is highly suggestive of underlying magnesiu depletion.[177]

Correction of the hypokalemia generally requires the restoration of magnes balance.[173,174,177] Simply giving K^+ alone is usually ineffective, as the exogenc K^+ is excreted in the urine rather than being taken up by the cells.[169,170] Magnesium repletion should preferably begin with oral magnesium chloride magnesium lactate in patients who are markedly K^+ depleted. Magnesium sulfate should initially be avoided, since it can initially increase losses as the sulfate acts as a nonreabsorbable anion.[184]

Poluria

A marked increase in urine volume can induce K^+ loss by an unusual mechanism. Normal subjects can lower the urine K^+ concentration to a minimum of 5 to 15 meq in the presence of K^+ depletion.[1] Although this generally leads to adequate K^+ conservation, the obligatory K^+ loss can exceed 50 to 150 meq/day if the urine output is 10 L/day or more. This degree of K^+ loss is most likely to occur with primary polydipsia.[185] Although a similar degree of polyuria can occur in centra diabetes insipidus, these patients usually seek medical care soon after the has begun.

L-Dopa

Increased urinary loss and mild hypokalemia can be induced by the adminis

L-dopa.[186] The mechanism by which this occurs is uncertain, although local dopamine formation may be important.

Increased Sweat Losses

Only small amounts of K^+ are normally lost in the sweat each day, since the vol is low and the K^+ concentration is only 5 to 10 meq/L. However, substantial K^+ losses can occur when sweat production is chronically increased. For exam L/day or more may be produced in subjects exercising in a hot climate.[187] Unless K^+ intake is appropriately increased, K^+ depletion may occur, a change that can predispose to the development of rhabdomyolysis (see below). Urinary loss contribute to this problem, since aldosterone secretion is enhanced by both (via catecholamine-induced renin secretion) and volume

loss and is not immediately suppressed when Na^+ is ingested to restore normovolemia.[187,188]

Dialysis

Patients on chronic dialysis are typically dialyzed against a low-K^+ solution to remove dietary K^+. Patients on chronic peritoneal dialysis, for example, may lo meq of K^+ per day. This loss is generally well tolerated, but it can lead to K^+ depletion if intake is reduced or there are concurrent gastrointestinal losse[189] Approximately 10 to 35 percent of patients on continuous peritoneal dialysi potassium supplements.[190]

A somewhat different mechanism may be operative in patients with underlyi depletion in whom severe acidemia results in the movement of K^+ out of the cells and therefore a relatively normal baseline plasma K^+ concentration. In this setting, acute hemodialysis can rapidly correct the acidemia, resulting in K^+ entering cells and a potentially large fall in the plasma K^+ concentration even though little or no has been lost by dialysis.[191]

Potassium Depletion without Hypokalemia

In most conditions, the plasma K^+ concentration varies directly with body K^+ stores. Thus, hypokalemia is generally associated with K^+ depletion, as a 200- to 400-meq K^+ deficit is required to lower the plasma K^+ concentration from 4 to 3 meq/L.[192] However, this relationship is disturbed in disorders that affect the distribut between the cells and the extracellular fluid. As noted above, an elevation pH, increased availability of insulin, and periodic paralysis are all associat movement into the cells and hypokalemia without K^+ depletion. Conversely, acidemia can mask underlying K^+ depletion by maintaining a normal plasma K^+ concentration.[13,191]

Another example of this dissociation occurs in a variety of chronic diseases heart failure, renal failure, cirrhosis, and malnutrition. Patients with these may have a normal plasma K^+ concentration despite a 10 to 15 percent fall in bo K^+ stores.[193,194] and[195] The preferential loss of K^+ from the cells is associated with an increase in the cell Na^+ concentration and a reduction in the magnitude o the resting membrane potential, suggesting impaired function of the Na^+-K^+-ATPase pump in the cell membrane.[195,196] and[197]

The clinical significance of these changes, which cannot be detected by rou laboratory tests, is not well understood. These patients do not have the sy signs of hypokalemia, since the plasma K^+ concentration is normal (the K^+ had been in the cells being excreted in the urine). Normalization of balance will only with reversal of the underlying disease.[193] K^+ supplements alone are ineffective, as they are excreted in the urine, not taken up by the cells.[193,194]

SYMPTOMS

A variety of abnormalities may be associated with hypoK^+emia (Table 27-3) Although the severity of these changes is generally related to the degree o hypokalemia, there is substantial individual variability. Marked symptoms ar unless the plasma K^+ concentration is below 2.5 to 3.0 meq/L, but in susceptib patients even mild reductions in the plasma K^+ concentration can predispose to potential fatal arrhythmias.

Muscle Weakness

Hypokalemia can induce muscle weakness and paralysis. The mechanism by this occurs is complex. Initially, hypokalemia increases the ratio of the K^+ concentration in the cell to that in the extracellular fluid, thereby hyperpola cell membrane (i.e., making the resting potential more cell-interior negative according to the following equation:

$$E_m = -61 \log \frac{r[K^+]_c + 0.01[Na^+]_c}{r[K^+]_e + 0.01[Na^+]_e} \qquad (27\text{-}1)$$

where E_m is the resting membrane potential, r is the 3 : 2 active transport ra Na^+-K^+-ATPase pump, 0.01 is the relative membrane permeability of K^+ to Na^+, and the subscripts c and e refer to the cellular and extracellular concentrations respectively.[195]

As a result of these relationships, membrane excitability should be reduced the resting potential is now further away from the threshold that must be re before an action potential can be generated. However, the initial hyperpola (greater electronegativity) of the cell membrane removes the normal state o inactivation of sodium channels; the ensuing increase in Na^+ permeability *enhances neuromuscular excitability*; less of an exciting stimulus is now required to

generate an action potential.[198] These changes may be manifested clinically by muscle weakness and cardiac arrhythmias.

Table 27-3 Abnormalities induced by hypokalemia

Muscle weakness or paralysis (including intestinal ileus
Cardiac arrhythmias, especially with digitalis, coronary ischemia, or per
left ventricular hypertrophy
Rhabdomyolysis
Renal dysfunction
A. Impaired concentrating ability, leading to polyuria and polydipsia
B. Increased ammonia production (can induce hepatic coma in cirrhosis
C. Impaired urinary acidification
D. Increased bicarbonate reabsorption
E. Renal insufficiency
F. Abnormal NaCl reabsorption
Hyperglycemia

P.858

Muscle weakness usually does not begin until the plasma K^+ concentration is less than 2.5 meq/L. There is, however, variability in this relationship because of effects of the plasma Ca^{2+} concentration, the extracellular pH, and the rapidity and manner in which hypokalemia develops (see page 825). As an example, patients with chronic K^+ loss may be relatively asymptomatic because part of the K^+ lost from the extracellular fluid is replaced by movement out of the cells.[192] The deficit in both compartments *minimizes the change in the ratio of the* K^+ *concentrations* and, therefore, in the resting potential and membrane excitability. In contrast, acute entry into cells (as occurs in periodic paralysis) can lead to marked weakness or paralysis,[48] in part because the cell K^+ concentration has increased, resulting in a much larger change in the concentration ratio.

The pattern of muscle weakness is relatively characteristic.[199] The lower extremities are most commonly involved first, particularly the quadriceps. In more severe cases the muscles of the trunk, of the upper extremities, and eventually of respiration become affected, and death may ensue from respiratory failure. The cranial muscles, in comparison, are rarely involved.

Cramps, paresthesias, tetany, muscle tenderness, and atrophy also may occur.[195] In addition, involvement of smooth muscles in the gastrointestinal tract can produce paralytic ileus and the symptoms of abdominal distention, anorexia, nausea, vomiting, and constipation.

Cardiac Arrhythmias

A variety of cardiac arrhythmias can be induced by hypokalemia. These incl premature atrial and ventricular beats, sinus bradycardia, paroxysmal atrial junctional tachycardia, atrioventricular block, and even ventricular tachyca fibrillation.[200,201,202] and [203]

The mechanism by which arrhythmias occur in this setting is incompletely understood.[200,201] Hypokalemia directly *enhances automaticity* (perhaps via the increase in excitability noted above) and also *delays ventricular repolarization*. The primary event during the latter process is movement of K^+ out of the cells; this occurs passively down the favorable electrochemical gradient (cell interior now po that is created during depolarization (see p. 82).[200] The rate of repolarization is therefore in part dependent upon the K^+ permeability of the cell membrane, which appears to vary directly with the plasma K^+ concentration.[200,201,204] Thus, hypokalemia reduces K^+ permeability and consequently slows the rate of repolarization.

This delay in ventricular repolarization is important clinically, because it pr duration of the relative refractory period. This change predisposes to *reentrant arrhythmias*, since the ensuing impulse is blocked from going down the norma conductive pathway.[200] As a result, the impulse travels down adjacent, slower pathways, eventually leading to depolarization of the blocked area in a retr manner and the establishment of a reentrant pathway.

As described above, diuretic therapy in both hypertension (particularly if th ventricular hypertrophy) and heart failure has been associated with an incr incidence of arrhythmic death that can be prevented by using K^+-sparing diuretic (such as spironolactone) and may therefore be due to hypokalemia.[86,87,88] and [89,205] A possible contributing factor in some patients is stress-induced release of epinephrine, which can further lower the plasma K^+ concentration (Fig. 27-1).

Other risk factors are coronary ischemia[203] and digitalis therapy.[206,207] and [208] Digitalis-induced arrhythmias typically occur with toxic plasma levels of K^+, but can be seen with normal drug levels when hypokalemia is present.[208] Diuretic-induced hypokalemia and hypomagnesemia should be particularly a patients who are also treated with drugs that prolong the QT interval, since combination can predispose to polymorphic ventricular tachycardia and tors pointes.[88]

Electrocardiographic changes

The electrocardiogram is a reflection of the electrical events in the heart. T wave represents atrial depolarization, the QRS complex represents ventricu depolarization, and the ST segment and T and U waves represent ventricul Purkinje fiber repolarization, respectively.[198,200,209] The atrial repolarization wave

is lost in the QRS complex.

In addition to arrhythmias, hypokalemia produces characteristic changes in electrocardiogram that are primarily due to *delayed ventricular repolarization*.[201] There is depression of the ST segment, a decrease in the amplitude of the and an increase in the amplitude of U waves, which occur at the end of the and are often seen in the lateral precordial leads (V_4 to V_6) (Fig. 27-4). With more severe K^+ depletion, increased amplitude and width of the P wave, prolongat the PR interval, and widening of the QRS complex may occur.[201] These changes begin to be seen when the plasma K^+ concentration is less than 3.0 meq/L and ar present in approximately 90 percent of patients with a plasma K^+ concentration under 2.7 meq/L.[201,210] They are rapidly reversible with K^+ repletion.

Rhabdomyolysis

Muscle cramps, rhabdomyolysis, and myoglobinuria, possibly leading to ren may be seen in patients with severe K^+ depletion (plasma K^+ concentration

less than 2.5 meq/L).[167,211,212] and [213] The role of K^+ in the regulation of skeletal muscle blood flow appears to play an important role in the develop this problem.[214] During exercise, there is normally an appropriate increase in muscle perfusion to meet enhanced energy demands. This hyperemic respo mediated in part by the release of K^+ from skeletal muscle cells. The ensuing loca elevation in the K^+ concentration causes vasodilation, which enhances blood f However, the cellular release of K^+ is impaired by K^+ depletion. As a result, there is a lesser increase in blood flow, possibly resulting in cramps, ischemic necr rhabdomyolysis.[214] In addition to hypoperfusion, hypokalemia-induced impairm muscle metabolism may contribute to the muscle dysfunction.[211]

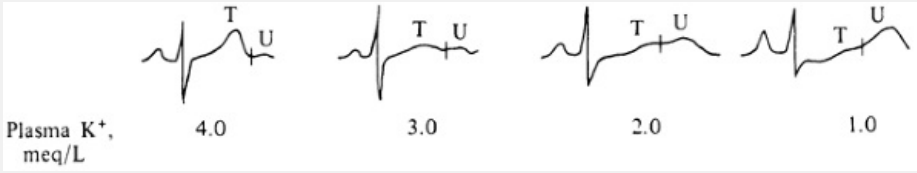

Figure 27-4 Electrocardiogram in hypokalemia. As the plasma K^+ concentration falls, the initial changes are ST-segment depression, decreased amplitude T wave, and increased height of the U wave. With more severe hypokalem P-wave amplitude is increased, as is the duration of the QRS complex. Th approximate relationship between these changes and the plasma K^+

concentration is indicated, although there is substantial interpatient varia
(*Adapted from Surawicz, AB: Heart 73:814, 1967, with permission*)

Renal Dysfunction

K^+ depletion can interfere with a variety of renal functions (see Table 27-3).[199,215,216] Each of these changes is usually reversible with K^+ repletion. One important function that is maintained, however, is the ability to conserve K^+ as an adaptive response mediated both by decreased secretion and by enhanced reabsorption (via a H^+-K^+-ATPase) in the collecting tubules (see page 393).[3,4,5,6] and[7] The increase in active reabsorption and reversible resistance to the k action of aldosterone permit appropriate K^+ conservation even though aldosterone secretion may be enhanced due to concurrent hypovolemia (for example, as of gastrointestinal losses or diuretic therapy).[217]

Thus, patients with *extrarenal causes of K^+ depletion should excrete less than 25 meq of K^+ per day* in the urine.[1,2] This response may be important in the differential diagnosis of K^+ depletion of uncertain etiology (see "Diagnosis" below).

Impaired urinary concentration

Polyuria and polydipsia are not uncommon in patients with chronic hypokale[218] These symptoms may be due both to a primary stimulation of thirst and to d urinary concentrating ability.[219] The latter change is associated with diminished collecting tubule responsiveness to ADH. How this occurs is incompletely understood, but decreased expression of aquaporin-2, the ADH-sensitive wa channel, may play at least a contributory role.[220] Hypokalemia may also impair countercurrent function by interfering with NaCl transport in the thick asce limb.[221,222]

In general, the maximum urine osmolality (which in normal subjects is 900 t mosmol/kg) remains above 300 mosmol/kg with K^+ depletion (Fig. 27-5). This is in contrast to values that may be below 150 mosmol/kg in patients with centra insipidus or congenital nephrogenic diabetes insipidus (see Chaps. 23 and 24). Consequently, the degree of polyuria is typically mild with hypokalemia, as output usually remains below 3 L/day.

The concentrating defect is both dose- and time-related.[218] The maximum urine osmolality begins to fall when the K^+ deficit exceeds 200 meq and reaches its minimum at a deficit of 400 meq, a level at which the plasma K^+ concentration

should be below 3.0 meq/L. The fall in the urine osmolality occurs slowly o weeks, presumably reflecting the gradual impairment in cell function (Fig. 27-5).

Ammonia production and urinary acidification

Hypokalemia results in an increase in NH_3 and NH_4^+ production by the renal tubular cells.[223] These compounds then enter both the tubular lumen and the peritul capillary, resulting in increases in urinary NH_4^+ excretion and in the NH_3 concentration in the renal vein.[223,224] and[225]

This effect may be related in part to a transcellular cation exchange. K^+ moves out of the cells with hypokalemia in an attempt to replete the diminish extracellular stores.[192] Electroneutrality is maintained in this setting in part by entry into the cells.[16,17] The ensuing *intracellular acidosis*[21] can then stimulate NH_4^+ production and H^+ secretion,[226] a mechanism similar to that thought to be responsible for the appropriate increase in NH_4^+ excretion seen with metabolic acidosis (see chap. 11).

These changes in renal function may be clinically important in patients with hepatic disease, in whom hypokalemia can precipitate hepatic coma.[225,227] In addition to the increase in NH_3 production, the commonly associated metabolic alkalosis may also contribute to this problem by driving the reaction

$$NH_3 + H^+ \leftrightarrow NH_4^+ \qquad (27\text{-}2)$$

to the left. The relative increase in the concentration of nonpolar and there soluble NH_3 promotes the entry of NH_3 (and possibly other toxic amines) into the brain. Correction of these electrolyte disturbances with KCl may reverse th encephalopathy without any other therapy.[225,227]

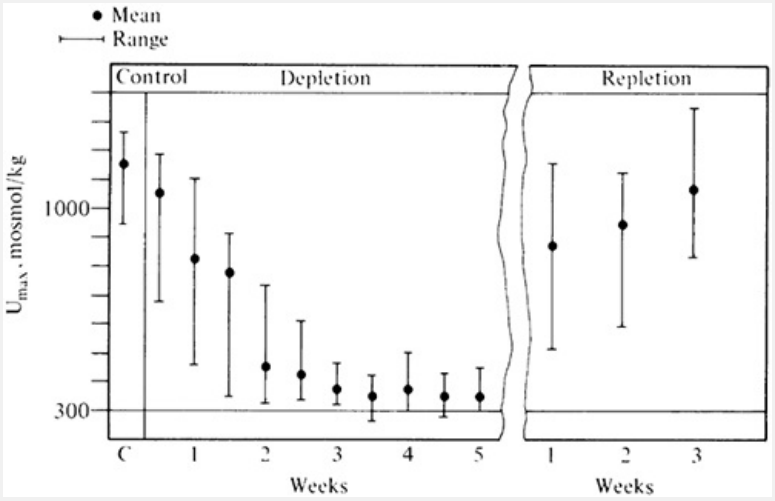

Figure 27-5 Impaired ability to maximally concentrate the urine (U_{max}) in patients with progressive potassium depletion. The average K^+ deficit was 350 meq, or about 10 percent of the total body K^+. (*From K Rubin, J Clin Invest 40:2215, 1961, by copyright permission of the American Society for Clini Investigation.*)

The hypokalemia-induced increase in NH_3 excretion also *raises the urine pH* by driving Eq. 27-2 to the right. In patients with concurrent metabolic acidosis du diarrhea or laxative abuse, the relatively alkaline urine falsely suggests the of renal tubular acidosis. These possibilities can be distinguished by meas of the *urine anion gap*, which is negative with hypokalemia alone, since NH_4^+ excretion is appropriately increased, but positive in renal tubular acidosis (589).

Bicarbonate reabsorption

The increases in the cell H^+ concentration and H^+ secretion induced by hypokalemia also promote HCO_3^- reabsorption (see Fig. 11-16).[19,20,228] This effect can contribute to the perpetuation of a concurrent metabolic alkalosis, since it delays excretion of the excess HCO_3^- in the urine (see Chap. 18).[18]

Nephropathy of potassium depletion

In humans, K^+ depletion produces a characteristic vacuolar lesion in the epith cells of the proximal tubule and occasionally the distal tubules.[215,216] This lesion occurs primarily with chronic K^+ depletion and generally requires at least 1 mont develop. Interstitial fibrosis, tubular atrophy, and cyst formation, particular renal medulla, also may be seen.[229,230]

The pathogenesis of the tubulointerstitial lesions is not well understood. An intriguing hypothesis that has been documented in experimental animals is hypokalemia-induced elevation in NH_3 production (via the fall in intracellular pH) results in local NH_3 accumulation in the interstitium.[231] This NH_3 can directly activate the complement system, which may then produce tubular injury. It h been proposed that the intracellular acidosis or perhaps the increase in am formation may be a stimulus to the cellular proliferation that is required for formation.[232]

Regardless of the mechanism, the vacuolar changes are reversed within we months after K^+ repletion. However, the secondary changes of interstitial fi and tubular dilatation may be irreversible. Although the glomerular filtration be reduced when the patient is hypokalemic, it usually improves after the re of normal K^+ balance.[215] However, persistent renal insufficiency following chro K^+ depletion can occur, primarily in patients with advanced tubulointerstitia disease.[233]

NaCl reabsorption

Hypokalemia has a dual effect on Na^+ excretion, impairing both the ability to excr a Na^+ load and the ability to conserve Na^+ maximally. As an example, a low K^+ can increase tubular Na^+ reabsorption, apparently via an effect in the proximal

tubule or loop of Henle.[223,234] This effect can, in patients on a high-K^+ diet, lead to Na^+ retention and a small rise in systemic blood pressure.[90,235] It is unclear, however, whether the volume expansion is directly responsible for the hype response. K^+ supplementation can lower the blood pressure by an average of mmHg in patients with essential hypertension.[91,236] This hypotensive effective of K^+ is not seen in subjects who are

on a low-Na^+ diet, suggesting that the hemodynamic effects of K^+ are at least in part related to changes in Na^+ balance.[237]

On the other hand, the ability to lower the urine concentration of NaCl to b meq/L in the presence of volume depletion may also be impaired by modera severe hypokalemia.[216,238] Diminished Cl^- reabsorption in the loop of Henle and collecting tubules has been demonstrated in this setting, although the mech which it occurs is unclear.[221,239,240]

DIAGNOSIS

The cause of hypokalemia can usually be determined from the history, whic reveal complaints of vomiting or diarrhea, the use of diuretics, or recurrent episodes of muscle weakness in periodic paralysis. When the diagnosis is n apparent, the most likely diagnoses are *surreptitious* vomiting, diarrhea, or diuretic use or one of the causes of primary mineralocorticoid excess. In this settin measurement of *urinary K^+ excretion* and assessment of *acid-base status* may be helpful.

Urinary Potassium Excretion

As described above, hypokalemic patients with extrarenal losses (or diureti after the drug effect has worn off) should excrete less than 25 meq/day of K^+ in the urine;[1,2] values above this level suggest at least a contribution from urinary K^+ wasting (see Fig. 27-5). The efficiency of K^+ conservation (minimum concentration to 15 meq/L) is less than that for Na^+ (minimum concentration less than 5 meq/L).[1,2] This phenomenon may be related to leakage (down a favorable concentratio gradient) of cellular K^+ into the lumen through a relatively nonselective cation channel in the luminal membrane of the inner medullary collecting duct.[241]

Random measurement of the urine K^+ concentration is simpler to perform, but may be less accurate than a 24-h collection. It is likely that extrarenal losses ar if the random urine K^+ concentration is below 15 meq/L (unless the patient is markedly polyuric).[185] Somewhat higher values, however, do not necessarily in K^+ wasting. For example, a patient appropriately excreting 20 meq/day will seemingly high urine K^+ concentration of 50 meq/L if the daily urine volume is 400 mL. This is most likely to occur with volume depletion; although secon hyperaldosteronism is commonly present, its effect is counteracted by the a

reduction in distal flow.[96]

Hypovolemia (as evidenced by urine Na^+ concentration below 25 meq/L) can also diminish the degree of kaliuresis in patients with primary mineralocorticoid excess. In this setting, the response to volume repletion may be exceptional. K^+ excretion will not change significantly in patients with extrarenal losses, because the ensuing reduction in distal flow will be balanced by a reduction in aldosterone

release; in contrast, K^+ excretion may rise markedly in primary hyperaldosteronism, where aldosterone secretion is nonsuppressible.[242]

Table 27-4 Acid-base disorders in hypokalemia

Metabolic acidosis may be seen	Metabolic alkalosis may be seen
Loss of lower intestinal secretions (diarrhea, laxative abuse)	Diuretic therapy
Ketoacidosis	Vomiting or nasogastric suction
Renal tubular acidosis	Mineralocorticoid excess
Salt-wasting nephropathies	Penicillin derivatives

Acid-Base Status

Some hypokalemic states are associated with acid-base disturbances that may aid in establishing the correct diagnosis (Table 27-4). In a patient with *metabolic acidosis and urinary K^+ wasting*, for example, diabetic ketoacidosis, renal tubular acidosis (in which the urine pH is generally above 5.3; see Chapter 19), and salt-wasting nephropathy (in which renal insufficiency is typically present and accounts for the acidemia) should be excluded. If these disorders are not present and urinary K^+ excretion is low, then surreptitious diarrhea, perhaps due to laxative abuse, is likely to be present.[76]

In contrast, the combination of *hypokalemia and metabolic alkalosis* is usually due to diuretic use, vomiting (both of which may be surreptitious), or, less often, one of the causes of mineralocorticoid excess or one of the rare genetic disorders (Gitelman's, Bartter's, or Gitelman's syndrome). The first two conditions are often associated with volume depletion. Thus, the findings of decreased skin turgor, flat neck veins, and postural hypotension are suggestive of one of these problems, since primary mineralocorticoid excess leads to mild volume expansion.

The urine Cl^- concentration also may be helpful, since a value below 25 meq/L is strongly suggestive of vomiting or diuretic therapy (after the drug effect has dissipated). If, on the other hand, the urine Cl^- concentration exceeds 40 meq/L, a urinary assay for diuretics should be obtained. If this is negative and the patient is *normotensive*, then Bartter's or Gitelman's syndrome may be present. If, however, the patient is *hypertensive*, the evaluation outlined in Fig. 27-6 should be initiated (see "Primary Hyperaldosteronism," below).

Clinical Examples

The following case histories illustrate how this approach can be utilized in patients in whom the cause of the hypokalemia is uncertain.

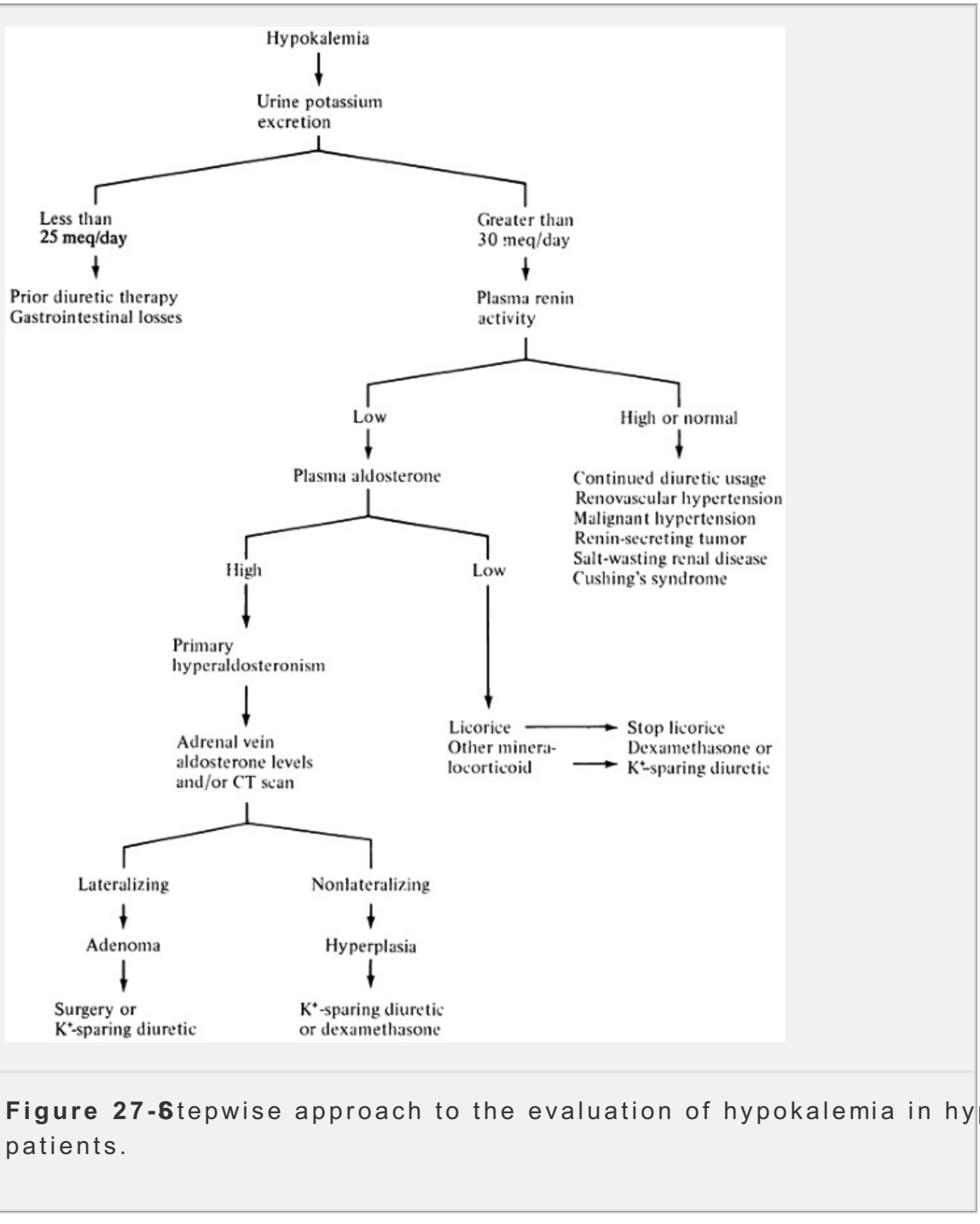

Figure 27-6 Stepwise approach to the evaluation of hypokalemia in hypertensive patients.

Case History 27-1

A 36-year-old woman is started on diuretics twice weekly for mild pedal ede
During a routine follow-up, she is noted to be hypertensive (duration unkno
noted are an estimated jugular venous pressure below the clavicle and moderate
decrease in skin turgor. The following laboratory tests are obtained:

Plasma $[Na^+]$	=	136 meq/L	Arterial pH	=	7.47
$[K^+]$	=	3.0 meq/L	Urine $[Na^+]$	=	60 meq/L
$[Cl^-]$	=	98 meq/L	$[K^+]$	=	45 meq/L
$[HCO_3^-]$	=	29 meq/L	$[Cl^-]$	=	48 meqL

The patient is initially given 2 liters of isotonic saline over 12 h; the Na^+ repea
concentration is now 20 meq/L.

Comment

The combination of hypertension, hypokalemia, hyperkaliuria, and metaboli
alkalosis suggests the possible diagnosis of primary hyperaldosteronism du
example, to an adrenal adenoma. Diuretic therapy can produce a similar pic
patient with essential hypertension, but drug intake seemed to be too infre
this case. However, the physical findings and the slight degree of hyponatr
to the presence of volume depletion. Furthermore, the fall in Na^+ the urine
concentration after saline administration is best explained by attenuation o
diuretic effect, thereby unmasking persistent hypovolemia. In comparison, a
load in primary hyperaldosteronism should produce a marked and appropria
Na^+ excretion.

Case History 27-2

A 22-year-old woman complains of persistent weakness, but denies all othe
symptoms. The physical examination is unremarkable, with the blood pressu
normal. The following laboratory data are obtained:

Plasma $[Na^+]$	=	136 meq/L	Arterial pH	=	7.30
$[K^+]$	=	2.7 meq/L	Urine $[Na^+]$	=	7 meq/L
$[Cl^-]$	=	108 meq/L	$[K^+]$	=	12 meq/L
$[HCO_3^-]$	=	17 meq/L			

Comment

The low urine K^+ concentration suggests extrarenal losses. Although the patie
denies vomiting or diarrhea, the low urine Na^+ concentration indicates that she is
volume-depleted and must have some unadmitted source of fluid loss. The p
of metabolic acidosis points toward diarrhea, perhaps induced by laxative a

Primary Hyperaldosteronism

Primary mineralocorticoid excess should be suspected in any patient with
hypertension and unexplained hypokalemia, although renovascular hyperter

diuretic therapy are more common causes of this problem.[93,243] Normokalemic hyperaldosteronism does occur and may be more common than currently sus In one study, for example, more than 50 percent of recently diagnosed case not hypokalemic at presentation.[244] Similar findings have been found in

the glucocorticoid-remediable hyperaldosteronism.[100] Aldosterone release in the latter disorder is primarily under the influence of ACTH. With the normal ci rhythm of ACTH release, aldosterone secretion should be above normal for of the day, which may explain the lesser tendency to hypokalemia.

Despite these observations, it is not at present feasible to screen every hy patient for the presence of primary hyperaldosteronism. However, at the lea screening should be performed in all patients with otherwise unexplained hypokalemia and in those with severe or resistant hypertension.[131] It has been suggested that use of the random plasma aldosterone-to-renin ratio describ may permit screening of many if not most hypertensive patients.

Even more rare are those patients with primary hyperaldosteronism who are hypokalemic but normotensive.[245] In this setting, the unexplained persistent reduction in the plasma K^+ concentration warrants evaluation for mineralocortic excess.

The following approach is recommended for the evaluation of the hypertens patient with unexplained hypokalemia and metabolic alkalosis (Fig. 27-6).[94]

- *24-h urine collection.* A 24-h urine collection for K^+ will differentiate inappropriate urinary losses (greater than 25 to 30 meq/day) from extra previous urinary losses. Diuretics, which can directly increase K^+ excretion, must be discontinued prior to the collection. It is also important that the not be volume-depleted (as evidenced by a urine Na^+ concentration below 25 meq/L), since the associated decrease in distal delivery can reduce K^+ even in patients with hyperaldosteronism.

  On the other hand, the degree of K^+ wasting, and therefore the diagnostic accuracy, can be increased by a high-Na^+ diet, as the combination of augmented distal flow and hypersecretion of aldosterone enhances K^+ secretion.[242,246] A high-Na^+ diet can also be given to patients with a borderline plasma K^+ concentration, since *Na^+-induced hypokalemia is strongly indicative of nonsuppressible hyperaldosteronism.*[92,242] In comparison, increased K^+ loss and hypokalemia are not induced in normal subjects by Na^+ loading, because the ensuing volume expansion inhibits the secretion o and therefore of aldosterone.[242,246]
- *Plasma renin activity.* The plasma renin activity should be measured in tho patients with persistent hypokalemia and an inappropriately high rate o

excretion.[92,93] and[94] An elevated value is most often due to renovascular malignant hypertension, diuretic usage, or a rare renin-secreting tumor. value is highly suggestive of some form of mineralocorticoid excess (or syndrome in which there is a primary increase in collecting tubule Na^+ function);[131,247] the mild volume expansion in these disorders suppresses renin release. The plasma renin activity is typically normal in Cushing's syndrome, which is usually accompanied by a cushingoid appearance.[109]

- *Aldosterone secretion*—The triad of hypokalemia, urinary potassium wasting and a low plasma renin activity is highly suggestive of mineralocorticoid

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excess. The disorders that can cause this problem can be differentiated one another by measuring the plasma aldosterone concentration or the excretion of aldosterone metabolites.[92,93,94] and[95] A low plasma level indicates the overproduction of a nonaldosterone mineralocorticoid.[93] Examples described above include severe Cushing's syndrome, some forms of con adrenal hyperplasia, DOC-producing tumors [which usually can be detec computed tomography (CT) scanning or magnetic resonance imaging], th ingestion of licorice or the syndrome of apparent mineralocorticoid exce use of the synthetic mineralocorticoid fludrocortisone, and Liddle's syn

On the other hand, a clearly high plasma aldosterone concentration (gre than 30 ng/dL or 24-h urinary aldosterone excretion (above 15 μug/day) toward one of the causes of hyperaldosteronism.[243] The diagnostic accuracy of this measurement can be increased by attempting to *suppress endogenous aldosterone production* via the administration of 2 liters of isotonic saline intravenously over 4 h (while recumbent).[92,94,248] The plasma aldosterone concentration in normal subjects should fall to 6 ng/dL or below, where above 10 ng/dL are consistent with primary hyperaldosteronism.[248] Levels between 6 and 10 ng/dL are nondiagnostic; in this setting, a more prolo suppression test (in which the plasma aldosterone concentration should less than 6 ng/dL) should be performed using a diet high in Na^+ and 0.6 to 1.2 mg/day of fludrocortisone (a synthetic mineralocorticoid) for 3 days.[92,248] Potentially confounding variables should be eliminated to prevent possi misinterpretation of these tests. Thus, the plasma aldosterone concentr should be measured with the patient recumbent, off K^+ supplements (both standing and K^+ loading can increase aldosterone secretion), and relative normokalemic (since hypokalemia can reduce aldosterone release).[249]

- *Plasma aldosterone to renin ratio*—The presence of high plasma aldosterone levels (PA) and low plasma renin activity (PRA) in primary hyperaldoste has led to the suggestion that the PA/PRA ratio can be used as an effec screening test for primary hyperaldosteronism.[244,250] The mean value for the ratio in normal subjects and patients with essential hypertension is 4 to versus more than 30 to 50 in most patients with primary

hyperaldosteronism.[250,251]

Optimal performance of this test requires eliminating other factors that renin and aldosterone. These include correction of hypokalemia with po chloride and the cessation of therapy with diuretics, calcium channel bl and high-dose beta-blockers.

In one study, for example, blood was drawn at 8 A.M. after 2 h of ambul The combination of a plasma aldosterone concentration above 20 ng/dL PA/PRA ratio above 30 (with the PRA expressed in units of ng/mL/h) hac sensitivity and specificity of 90 percent for the diagnosis of primary hyperaldosteronism.[250] In a selected population in which the incidence

of primary hyperaldosteronism was 20 percent, the positive and negativ predictive values for these findings were 70 and 98 percent. The mean the PA/PRA ratio in normotensive controls and patients with essential hypertension is 4 to 5.

It has also been suggested that the PA/PRA ratio can be used to screen normokalemic patients who otherwise would not be detected.[244] The cost-effectiveness of screening all hypertensive patients for primary hyperaldosteronism is uncertain, but screening is probably indicated in with severe or resistant hypertension.[244] Unfortunately, it is more difficult to discontinue antihypertensive medications in these cases. Another, less limitation is that the ratio will not detect patients in whom excess mineralocorticoid activity is not due to aldosterone.

- *Adenoma versus hyperplasia*—Since the diagnosis of primary nonsuppressibl hyperaldosteronism has been established, a *unilateral adenoma or carcinoma must be distinguished from bilateral hyperplasia* because of the differing therapies required: surgery with a unilateral tumor and medical therapy bilateral hyperplasia (see below).[92,93,94] and [95,251] In general, hyperplasia is a less severe disease, with a lower rate of aldosterone secretion and a degree of hypokalemia. There is, however, substantial overlap.

  A variety of indirect tests have been utilized to make this distinction, bu correct diagnosis can be most accurately made by CT scanning or magn resonance imaging, or, if necessary, by measurement of adrenal vein aldosterone concentrations (a test that should be performed only by a r experienced with this procedure).[44,244,252,253] and [254] The radiologic tests may identify a unilateral adrenal mass, which is indicative of an adenon rarely a carcinoma, with a sensitivity of 67 to 85 percent. However, the of a mass is not diagnostic of hyperplasia, since small tumors (less tha in diameter) can be missed in 15 to 25 percent of cases.[252,253] Furthermore, the finding of bilateral nodules may reflect a unilateral aldosteronoma p contralateral nonfunctioning nodule rather than adrenal hyperplasia.[253]

  The net effect is that CT scanning alone may be inaccurate; in one stuc patients with a unilateral adenoma, for example, five were incorrectly d

as having bilateral disease.[253] Thus, the presence of bilateral lesions on CT scan should be followed by measurement of adrenal vein aldosterone le iodocholesterol scanning to determine whether the hypersecretion of aldosterone is coming from one or both adrenal glands.[253,254] Although not widely available, scintillation scanning with ^{131}I-iodocholesterol (a precursor of aldsoterone) may be even more accurate than CT scanning in detecting unilateral lesion.[93,255]

The rationale for measuring adrenal vein aldosterone concentrations is unilateral adenoma is associated with a marked (usually greater than te increase in adrenal vein aldosterone concentration on the side of the tu whereas there is little difference between the two sides with bilateral hyperplasia.[256,257] and[258] The test is best performed before and 15 min

after the administration of ACTH, which acutely stimulates aldosterone and increases the difference between the two sides when an adrenal ad is present.[256] To be certain that the samples are from the adrenal veins, should also be measured in the same samples; the serum cortisol conce should be roughly the same in both adrenal veins, but much higher than peripheral vein sample.

Adrenal vein sampling may be most useful when there is no adrenal abn on CT, or when both adrenal glands are abnormal but asymmetric. In on six of fifteen patients with normal or minimal adrenal thickening and fou with bilateral adrenal masses on CT had a unilateral source of aldoster adrenal venous sampling.[248]

TREATMENT

The initial step in the treatment of hypokalemia must be the assessment of physiologic effects of the K^+ deficit. As described above, there is a wide variatic the degree to which a given reduction in the plasma K^+ concentration will produce symptoms. Thus, monitoring of the electrocardiogram and muscle strength, *reflect the functional consequences of* K^+ *depletion*, is an essential part of the management of patients with severe hypokalemia.

As with other electrolyte disorders, the first aim of therapy is to get the pat danger, not to immediately correct the entire K^+ deficit. The potential risk of the overly rapid administration of K^+ is illustrated in Fig. 27-7. In this patient,

who had hypokalemia and flaccid paralysis, the intravenous infusion of 80 K^+ over 15 min resulted in a change in the electrocardiogram from one typical hypokalemia to one characteristic of severe hyperkalemia.

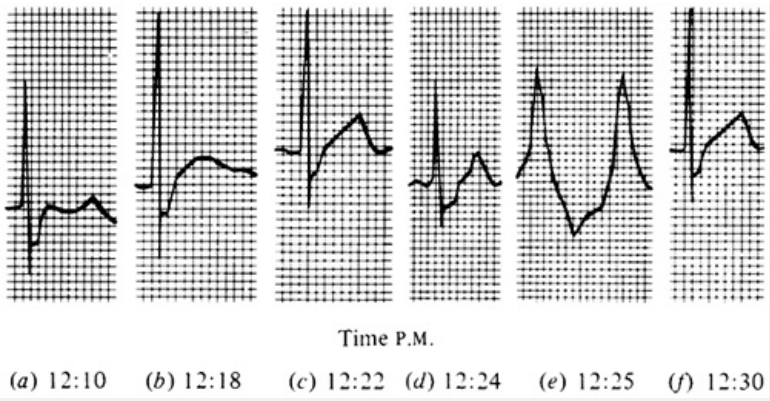

Figure 27-2 Electrocardio-gram (ECG) during the intravenous administration of 80 meq of K^+ over 15 min. (a) Initial ECG shows the typical changes of hypokalemia, with flat T wave and prominent U wave. (b) After 45 meq, the T wave is returning. (c) After 65 meq, the T wave is normal. (d and e) After 80 meq, signs of hyperkalemia appear: peaked T wave and widening of the QRS complex. (f) Slowing of the K^+ infusion is associated with return of the tracing to normal. *(From Seftel HC, Kew MC: Diabetes 15:694, 1966, with permission.)*

Potassium Deficit

The potassium deficit can only be approximated, since there is no definite correlation between the plasma K^+ concentration and body K^+ stores. In general, a reduction in the plasma K^+ concentration from 4.0 to 3.0 meq/L requires the loss of 200 to 300 meq of K^+.[192,259] An additional 200- to 400-meq deficit will lower the plasma K^+ concentration to 2.0 meq/L. However, continued loss of K^+ may not produce much more hypokalemia, as the release of K^+ from the cells is usually able to maintain the plasma K^+ concentration near 2.0 meq/L.[259]

These estimates of the K^+ deficit assume that there is a normal distribution of K^+ between the cells and the extracellular fluid. In patients with periodic paralysis, for example, body K^+ stores are normal, since the hypokalemia is due entirely to movement of K^+ into the cells. In this setting, giving K^+ is needed to normalize the plasma K^+ concentration, not to repair a deficit of K^+.

The effects of the extracellular pH and the plasma osmolality are also important in evaluating the potassium status of the patient. In particular, acidemia (in renal failure or renal tubular acidosis) or hyperosmolality (in diabetic ketoacidosis) frequently raises the plasma K^+ concentration and masks the severity of the K^+ depletion. This has important therapeutic implications, because correction of the acidemia or hyperglycemia can lead to marked hypokalemia.[29,191]

Use of Potassium Chloride

A variety of potassium preparations are available for oral and intravenous use

including the Cl^-, HCO_3^-, †† phosphate, and gluconate salts. There are two majo advantages to the use of KCl in depleted patients. First, metabolic alkalosis is commonly associated with hypokalemia. These patients tend to be both K^+ depleted and Cl^- depleted as well (due, for example, to diuretics or vomiting), and the *administration of Cl is essential for correction of both the alkalosis and the K^+ deficit*. Other K^+ salts are less effective in inducing positive K^+ balance and may increase the severity of the alkalemia (since the anions are nonreabsorbable and therefore can promote K^+ loss; see page 568).[260,261]

Second, the $[K^+]_i/[K^+]_e$ ratio (the main determinant of the resting membrane potential) is affected primarily by changes in $[K^+]_e$ since the extracellular K^+ concentration is so much lower than that in the cells. Consequently, the aim therapy is to rapidly increase the plasma (and extracellular) K^+ concentration in a severely hypokalemic patient with muscle weakness, arrhythmias, or advanc electrocardiographic changes. If equal doses of KCl and $KHCO_3$ are given,

there will be a significantly greater increase in the plasma K^+ concentration with KCl than with $KHCO_3$ (Fig. 27-8). This difference is probably related to the ability of HCO_3^- to enter the cells in comparison to that of Cl^-, which is mostly limited to the extracellular fluid.[262] As a result, K^+ follows HCO_3^- into the cells to maintain electroneutrality, producing a lesser increase in the plasma K^+ concentration. Although $KHCO_3$ is not as effective as KCl in metabolic alkalosis or severe hypokalemia, it may be the preferred K^+ salt in certain patients with mild degrees of hypokalemia and metabolic acidosis. For example, patients with renal tubular acidosis tend to waste K^+ in the urine and become K^+ depleted (see chap. 19). In this setting, chronic therapy with $KHCO_3$ (or K^+ citrate, which is more palatable) tends to correct both the K^+ depletion and the acidemia.

Oral

KCl can be given orally in crystalline form (salt substitutes), as a liquid, or release tablet or capsule. Slow-release preparations are generally better to than the poorly palatable KCl solutions. However, these tablets or capsules rare cases lead to ulcerative or stenotic lesions in the gastrointestinal trac result of the local accumulation of high concentrations of K^+.[263,264] Salt substitute (which contains between 50 and 65 meq per level teaspoon) may be the ide oral therapy, being safe, well tolerated, and much cheaper than the other preparations.[265]

In comparison, the traditional therapy of treating chronic hypokalemia (mos due to diuretics) with K^+-rich foods such as orange juice or bananas is less desirable. These foods contain phosphate and citrate rather than chloride a

therefore less likely to correct the hypokalemia and metabolic alkalosis. 260266

addition, fruit ingestion involves an increase in caloric intake in excess of kcal/day. This is a particular disadvantage with obese patients with hyperte whom weight reduction may lower the systemic blood pressure. 267

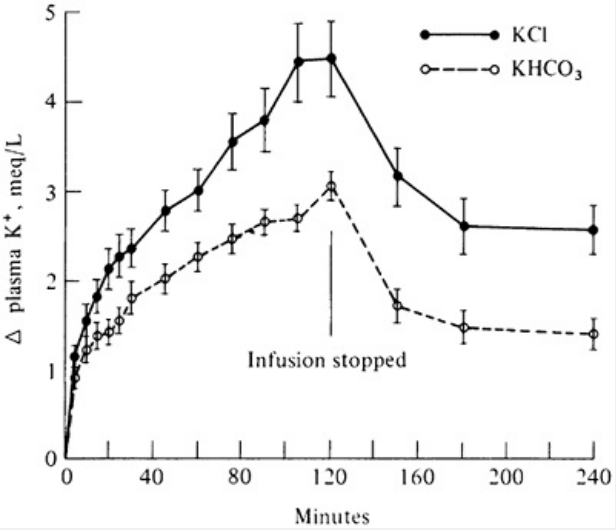

Figure 27-6 Changes in plasma K^+ concentration of potassium-depleted dogs during infusion with KCl and $KHCO_3$. (*From Villamil MF, DeLand EC, Henney P, Maloney JV Jr:* Am J Physiol *229:161, 1975, with permission.*)

Intravenous

In patients who are unable to eat, K^+ must be given intravenously. The standard intravenous KCl solution contains 2 meq each of K^+ and Cl^- per milliliter. In most circumstances, 20 to 40 meq of K^+ (10 to 20 mL) is added to each liter of dextros saline solution. However, the addition of this quantity of K^+ to 1 liter of a dextrose solution may lead to a transient *reduction in the plasma K^+ concentration of 0.2 to 1.4 meq/L*, particularly when only 20 meq/L is added.[30] This effect is presumably due to enhanced insulin secretion stimulated by the infusion of glucose.

Although normal subjects can tolerate this decrease in the plasma K^+ concentration, arrhythmias may be precipitated in patients who are hypokalemic or taking digitalis.[30] Consequently, K^+ supplementation should be given in a non-dextrose containing solution, usually in a concentration of 40 meq/L. In general, no m 60 meq/L should be given through a peripheral vein, since higher concentra K^+ are very irritating, resulting in pain and sclerosis of the vein.

Rate of Potassium Repletion

The majority of patients have mild to moderate hypokalemia, with the plasm K^+

concentration ranging between 3.0 and 3.5 meq/L. This degree of K^+ depletion is usually well tolerated in the absence of digitalis therapy[206,207] and[208] or severe hepatic disease.[225,227] Treatment is not urgent in this setting and must be dir toward both repair of the K^+ deficit and prevention of further K^+ loss by correcting the underlying disorder (such as diarrhea). These patients can usually be t with oral KCl at an initial dose of 60 to 80 meq/day. However, larger amoun required if there is continued K^+ loss. In primary hyperaldosteronism, for example oral K^+ therapy is of minor benefit, and a K^+-sparing diuretic is required to maintai a normal plasma K^+ concentration.[268,269] and[270]

In the occasional patient with severe symptoms or marked hypokalemia, K^+ must be given more rapidly. This is more easily done orally, as the plasma K^+ concentration will acutely rise by as much as 1.0 to 1.5 meq/L after 40 to 60 meq and by 2 meq/L after 135 to 160 meq.[271,272] These maximum effects, however, are *transient*, since most of the administered K^+ will enter the cells to repair the cell deficit.[273] As a result, the plasma K^+ concentration must be carefully monitored and given K^+ as necessary. A patient with a plasma K^+ concentration of 2.0 meq/L, for example, may have a total K^+ deficit of as much as 400 to 800 meq.[192]

Large doses of K^+ are much more difficult to give intravenously, since the limi meq/L means that a large volume of fluid also must be given. This tendency overload is enhanced by the preferential use of saline-containing solutions one-quarter-isotonic saline) because of the desire to avoid dextrose

administration.[30] Despite these obstacles, some patients must be treated intravenously.

In general, intravenous K^+ is administered at a *maximum rate of 10 to 20 meq/h*, although as much as 40 to 100 meq/h has been given to patients with paral life-threatening arrhythmias.[274,275] and[276] In the latter setting, solutions containing as much as 200 meq of K^+ per liter (as with 20 meq in 100 mL of isotor saline) have been used.[277,278] These solutions are best tolerated if given into large vein (such as the femoral vein); infusions through a central venous li probably be avoided (although they have been safely used),[278] since the local increase in the K^+ concentration might, in some cases, have deleterious effect cardiac conduction.

The necessity for such aggressive therapy has been reported primarily in p with diabetic ketoacidosis who are hypokalemic at presentation (see Chapter 25).[275,276] In this setting, the administration of insulin and the ensuing redu the plasma glucose concentration will drive K^+ into the cells, further reducing the plasma K^+ concentration if KCl is withheld. Since the average fluid deficit in patients is 3 to 6 liters, rapid K^+ replacement can be achieved by adding 60 meq

K^+ to each liter of fluid. This example again illustrates that the factors that the internal distribution of K^+ (plasma osmolality, availability of insulin) must be taken into account when evaluating the hypokalemic patient.

It must be emphasized that the rapid administration of K^+ is potentially dangerous *even in severely K^+-depleted patients* and should be used only in life-threatening situations. A rate in excess of 80 meq/h can result in the electrocardiographic changes of hyperkalemia (Fig. 27-7) or complete heart block.[279] Thus, continuous monitoring of the electrocardiogram is essential in this setting. In addition, concentrated solutions should contain only a limited amount of K^+ per container (as with 20 meq in 100 mL of isotonic saline) to avoid the accidental administration of very large quantities of K^+.[278]

Primary Hyperaldosteronism

The mode of therapy in primary hyperaldosteronism varies with the underlying disease. Surgery is the preferred treatment in patients with an adenoma or carcinoma, since unilateral adrenalectomy, which can be performed laparoscopically,[280] results in a fall in blood pressure, a marked reduction in aldosterone secretion, and correction of the hypokalemia in virtually all patients.[281,282,283 and 284] However, a lesser degree of hypertension persists in as many as 40 percent of cases.[282,283 and 284]

Surgery (subtotal adrenalectomy) is much less successful with adrenal hyperplasia as only a minority of patients have a clinically important hypotensive response.[93,94,281] The reasons for the failure of surgery to control the blood pressure are incompletely understood. In some patients, the development of secondary nephrosclerosis after many years of uncontrolled hypertension may be a contributory role.[282,283] An alternative explanation is that adrenal hyperplasia may be

a *variant of essential hypertension* in which increased sensitivity of the adrenal cortex to angiotensin II leads to the elevation in aldosterone release and hypokalemia, which is typically milder than in patients with an adenoma.[92]

As a result of these observations, *surgery should be considered only in patients with a unilateral tumor*, as determined by measurement of adrenal vein aldosterone concentrations or CT scanning. In patients who are not surgical candidates because they have hyperplasia, a K^+-sparing diuretic (spironolactone, triamterene, or amiloride) can lower the blood pressure and correct the hypokalemia.[268,269,270,285] These responses can be sustained over the long term.[285]

Amiloride (10 to 40 mg/day) may be the best tolerated, since it can be given once daily and avoids the gastrointestinal and endocrine side effects (menstrual irregularities, gynecomastia, and hypogonadism) associated with spironolactone.[268] If the hypertension persists in patients with bilateral hyperplasia

administration of an angiotensin converting enzyme inhibitor may be benefi perhaps reflecting the role of angiotensin II as an aldosterone secretagogu disorder.

A K^+-sparing diuretic is also indicated in the syndrome of apparent mineralc excess (in which cortisol is the major endogenous mineralocorticoid) and in syndrome. In the latter disorder, either amiloride or triamterene should be g close the Na^+ channels in the collecting tubule; spironolactone is relatively ineffective, since the increase in Na^+ channel activity is not mediated by aldosterone.[132]

In comparison, dexamethasone or another glucocorticoid is the treatment of those patients with bilateral hyperplasia in whom aldosterone secretion app be mediated by ACTH (e.g., CYP11B1- or CYP17-deficient forms of congeni adrenal hyperplasia or glucocorticoid-remediable hyperaldosteronism). The disorder should be suspected when children with a positive family history o hypertension (often in young adults) are affected.[100] The dexamethasone dose should be the lowest required to correct the hypokalemia and hypertension. symptoms of glucocorticoid excess should not occur.

PROBLEMS

27-1A 22-year-old woman complains of easy fatigability and weakness. has no other complaints. The physical examination is unremarkable, ir a normal blood pressure. The following laboratory data are obtained:

$$\begin{aligned}\text{Plasma } [Na^+] &= 141 \text{ meq/L}\\ [K^+] &= 2.1 \text{ meq/L}\\ [Cl^-] &= 85 \text{ meq/L}\\ [HCO_3^-] &= 45 \text{ meq/L}\\ \text{Urine } [Na+] &= 80 \text{ meq/day}\\ [K^+] &= 170 \text{ meq/day}\end{aligned}$$

a. **What is the differential diagnosis?**

b. **What test would you order next?**

27-2A patient is noted to have a plasma K^+ concentration of 2.7 meq/L. Match the other laboratory changes that are present with the likely diagnosis

a.

(*a*)	Plasma $[HCO_3^-]$	= 27 meq/L	1. Renal tubular acidosis
	Arterial pH	= 7.43	
	Urine $[K^+]$	= 10 meq/L	
	U_{osm}	= 102 mosmol/kg	2. Hypomagnesemia

b.

(*b*)	Plasma $[HCO_3^-]$	= 27 meq/L	
	$[Ca^{2+}]$	= 7.3 mg/dL	
	[Albumin]	= 4.1 g/dL	3. Primary polydipsia
	Arterial pH	= 7.46	
	Urine $[K^+]$	= 45 meq/day	

c.

(*c*)	Plasma $[HCO_3^-]$	=	14 meq/L	4. Laxative abuse
	Arterial pH	=	7.28	
	Urine $[K^+]$	=	52 meq/day	
	Urine pH	=	6.0	
	Urine anion gap	=	+25	5. Primary hyperaldosteronism

d.

(*d*)	Plasma $[HCO_3^-]$	=	14 meq/L	
	Arterial pH	=	7.28	
	Urine $[K^+]$	=	18 meq/day	6. Vomiting
	Urine pH	=	4.9	
	Urine anion gap	=	−27	

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Footnotes

* The effect of clay on K^+ balance varies with the type of clay ingested. Red cla
example, contains a relatively large amount of K^+, and its ingestion can lead to
hyperkalemia in patients with advanced renal failure.[11]

† Most of these provocative factors, such as a carbohydrate meal or stress
lower the plasma K^+ concentration in normal subjects, but the effect is much le
pronounced and symptoms do not occur.

‡ Na^+-wasting states can also lead to *hyper*kalemia if they are associated with
hypoaldosteronism (see Chap. 28) or reduced renal perfusion due to lack of
replacement of urinary Na^+ losses.[157,158]

¶ Despite the K^+ depletion, the plasma K^+ concentration may be normal or even
elevated because acidemia promotes movement of K^+ out of the cells (see page
379).[13]

** The urine Cl^- concentration is often a more accurate indicator of volume sta
than the urine Na^+ concentration in patients with metabolic alkalosis (see page 565).
The need to excrete the excess HCO_3^- in this disorder can lead to the loss of
$NaHCO_3$ and a relatively high urine Na^+ concentration, despite the presence of
volume depletion. The urine Cl^- concentration, in comparison, will be appropriate
reduced.

†† Acetate and citrate salts are also available. These organic anions are ra
metabolized into HCO_3^- in the body.

‡‡ Rather than HCO_3^- entering into the cells, intracellular H^+ ions may be released
into the extracellular fluid to buffer the excess HCO_3^-. In either case, K^+
tend to move into the cells to maintain electroneutrality.

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Chapter Twenty-Eight
Hyperkalemia

The introduction to disorders of K^+ balance presented in Chap. 26 should be read before proceeding with this discussion.

DEFENSE AGAINST HYPERKALEMIA

Hyperkalemia is a rare occurrence in normal subjects, because the body is effective in preventing excessive K^+ accumulation in the extracellular fluid. For example, a 40-meq K^+ load could acutely raise the plasma K^+ concentration by 2.4 meq/L or more if it were distributed only through the normal extracellular vo 15 to 17 L. However, the increment in the plasma K^+ concentration is often less than 1.0 meq/L in this setting,[1] because of an adaptive response consisting of two st (see Chap. 12):

- Initial uptake of most of the excess K^+ by the cells, mediated primarily by insulin, the β_2-adrenergic receptors (both of which increase the activity of Na^+-K^+-ATPase pump), and K^+ itself.[2,3,4] and[5]

- The subsequent urinary excretion of most of the excess K^+ over the next 6 to 8 h.[6,7] The small elevation in the plasma K^+ concentration is responsible for this appropriate increase in K^+ excretion, both directly and by increasing the rel of aldosterone.[8,9,10,11] and[12]

  In addition to these acute changes, the ability to tolerate a K^+ load is increased by the chronic ingestion of a high-K^+ diet. As a result, normal subjects can maintain K^+ balance as intake *slowly* increased from the normal level of abo 80 meq/day up to 400 meq/day or more.[13,14] This ability to handle what might be a lethal K^+ load if given acutely is called *adaptation*. This phenomenon is due primarily to more rapid K^+ excretion in the urine (Fig. 12-13).[15] Two other factors, both of which are stimulated by aldosterone, also may pla contributory role: a possible increase in K^+ entry into the cells[16,17] and enhanced gastrointestinal losses due to colonic secretion of K^+.[18]

The facilitated kaliuresis during adaptation is due to *enhanced K^+ secretion throughout the late distal nephron*, including the short connecting segment an the principal cells in the cortical and outer medullary collecting tubules [19,20] and [21] Both increased secretion of aldosterone and a small elevation in plasma K^+ concentration are required for the complete expression of this response.[20,21] They act in part by enhancing Na^+-K^+-ATPase activity in these segments,[22,23] either directly or by increasing the entry of luminal K^+ into the cell.[11,12] The elevation in pump activity, which is associated with a mark increase in the area of the basolateral membrane (the site at which the K^+-ATPase pumps are inserted),[15] augments K^+ movement from the peritubular capillary into the tubular cells, thereby increasing the size of the K^+ transport pool and promoting passive K^+ secretion into the tubular lumen.

Potassium adaptation begins after a single high-K^+ meal[24] and then increases in efficiency with continued K^+ intake. The efficacy of adaptation in humans can be illustrated by the response to chronic oral K^+ loading (400 meq/day) in normal subjects.[14] The plasma K^+ concentration rose from 3.8 to 4.8 meq/L and the plasma aldosterone levels increased 2.5-fold in the first 2–3 days (Fig. 28-1). By 20 days, however, both the plasma K^+ concentration (4.2 meq/L) and the plasma aldosterone concentration had partially returned toward baseline even though urinary K^+ excretion remained very high.

The increased efficiency of K^+ secretion at this time may have been related to the hyperkalemia-induced rise in Na^+-K^+-ATPase activity in the K^+-secreting cells.[22,23] Indirect evidence in support of this hypothesis in the above study of K^+ loading was the observation that discontinuing the high-K^+ intake led to transient Na^+ retention that could have reflected the time required for Na^+-K^+-ATPase activity to fall back to normal.[14]

The major clinical example of adaptation is *chronic renal failure*. In this disorder, the combination of a constant K^+ intake and fewer functioning nephrons requires an increase in K^+ excretion per nephron.[25,26] This response allows relative normokalemia to be maintained even in advanced renal f long as intake is not excessive, the urine output and therefore distal flo are adequate, and aldosterone secretion can be appropriately enhanced[27,28]

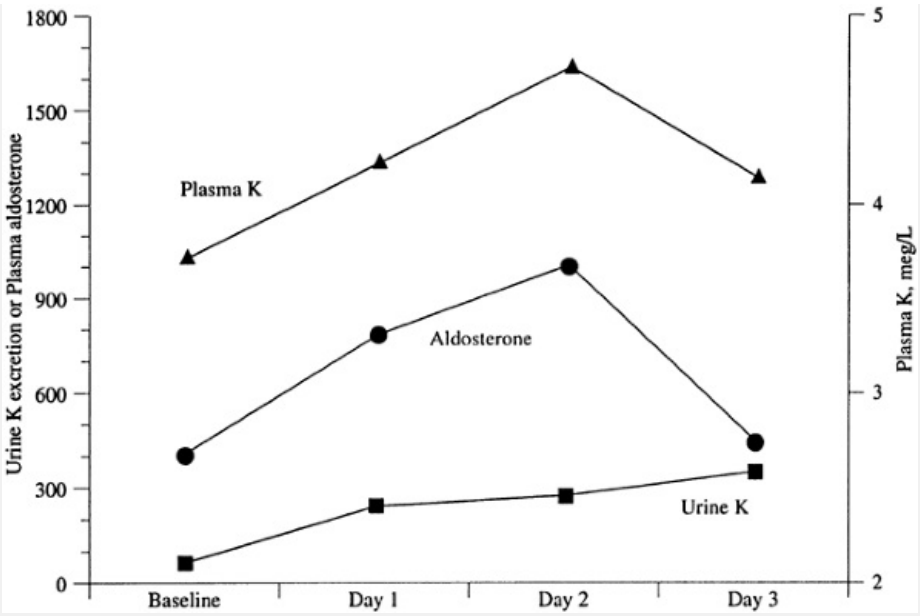

Figure 28-8 Response to increasing K^+ intake to 400 meq/day in normal subjects. Urinary K^+ excretion rises to this level within 2 days and is then maintained. This response is initially driven by elevations in the plasma K^+ and aldosterone concentrations. By day 20, the efficiency of K^+ secretion has increased, resulting in a lesser elevation in the plasma K^+ concentration (to 4.2 meq/L) and normalization of the plasma aldosterone concentration. (*Adapted from Rabelink TJ, Koomans HA, Hené RJ, Dorhout Mees EJ, Boer P: Kidney Int 38:942, 1990. Reprinted by permission of Kidney International.*)

Studies in experimental animals with renal failure have shown that Na-K^+-ATPase activity in the distal nephron is elevated, an expected correlate of enhanced K^+ secretion per nephron.[29] However, this elevation in pump activity is seen only when K^+ intake is normal, not when intake is restricted *in proportion to the fall in GFR*, a situation in which increased K^+ secretion per nephron is not required.[29] This finding suggests that the rise in Na-K^+-ATPase activity is appropriate and specific, not incidentally induced by insufficiency.

K^+ adaptation in renal failure is also associated with aldosterone-induced increases in Na-K^+-ATPase activity and K^+ secretion in the colon.[30] This response becomes physiologically important in patients with end-stage renal failure on chronic dialysis, in whom enhanced fecal losses may account for excretion of as much as 30 to 50 percent of dietary K^+ intake.[31]

ETIOLOGY

Potassium enters the body by oral intake or intravenous infusion, is stored cells, and is then excreted primarily in the urine. Thus, an abnormality in a

or more of these processes can lead to hyperkalemia (Table 28-1). It should be noted, however, that *chronic hyperkalemia is always associated with an impair in urinary K^+ excretion* (due primarily to hypoaldosteronism or diminished dista flow), since the elevation in the plasma K^+ concentration would not persist if excretory capacity were normal (Fig. 28-1).

This section will review the major causes of hyperkalemia, some of which a related,[32,33] as well as the diagnosis and treatment of specific disorders. Th general principles involved in the approach to the hyperkalemic patient will considered separately later in the chapter.

Increased Intake

In normal subjects, an acute K^+ load produces a dose-dependent elevation in the plasma K^+ concentration.[1] For example, 135 to 160 meq of oral K^+ can transiently raise the plasma K^+ concentration by 2.5 to 3.5 meq/L, a change that generally well tolerated.[7] Ingesting more than 160 meq, however, can produce a potenti fatal increase in the plasma K^+ concentration to above 8.0 meq/L, even in patien with normal renal function.[34]

Table 28-1 Etiology of hyperkalemia

Increased intake[2]

A. Oral
B. Intravenous

Movement from cells into extracellular fluid

A. Pseudohyperkalemia[2]
B. Metabolic acidosis
C. Insulin deficiency and hyperosmolality in uncontrolled diabetes melli[2] also acute hyperosmolality due to hypernatremia or the administratio hypertonic mannitol
D. Tissue catabolism[2]
E. β-Adrenergic blockade
F. Severe exercise
G. Digitalis overdose
H. Periodic paralysis—hyperkalemic form
I. Cardiac surgery
J. Succinylcholine
K. Arginine

Decreased urinary excretion

A. Renal failure[a]
B. Effective circulating volume depletion[a]
C. Hypoaldosteronism[a] (see Table 28-2)
D. Type 1 renal tubular acidosis—hyperkalemic form
E. Selective potassium secretory defect

[a] Most common causes

Severe hyperkalemia is more likely to occur with a rapid intravenous infusio infants because of their small size. Severe hyperkalemia and even cardiac have been reported in infants after the administration of potassium penicill intravenous bolus,[35] the accidental ingestion of a KCl-containing salt substitut[36] or the use of stored blood for exchange transfusions.[37] K^+ is gradually released from the red cells of stored blood, resulting in an extracellular K^+ concentration that by 21 days can reach 30 meq/L in whole blood and 90 meq/L in packed cells[38,39] The risk of K^+ overload can be minimized by selecting only blood collected le 5 days prior to transfusion and by washing any unit of blood immediately be infusion to remove extracellular potassium.

Hyperkalemia is more common when K^+ is given to patients with any of the causes of impaired K^+ excretion listed in Table 28-1. In this setting, a K^+ load that would normally be well tolerated can lead to substantial elevations in the plasma K^+ concentration. In addition to dietary intake, other sources of K^+ include K^+ supplements, salt substitutes,[40,41] low Na^+ soups,[42] and red clay (clay ingestion is relatively frequent in certain rural areas in the southeastern United States)[43]

Movement from Cells into Extracellular Fluid

A transcellular shift of K^+ out of the cells is a relatively common cause of acute hyperkalemia (Table 28-1). In these disorders, the rise in the plasma K^+ concentration is too rapid to be corrected by excretion of the excess K^+ in the urine.

Pseudohyperkalemia

Pseudohyperkalemia refers to those conditions in which the elevation in the measured K^+ concentration is due to K^+ movement out of the cells *during or after* the drawing of the blood specimen. The major cause of this problem is mec trauma during venipuncture, resulting in the release of K^+ from red cells. Since hemoglobin is also released in this setting, the serum will have a character tint. Repeated clenching and unclenching of the fist after the tourniquet ha

applied (in an attempt to make the veins more apparent) may play a contrib artifactually raising the plasma K^+ concentration by as much as 1 to 2 meq/L as tl exercise causes K^+ to be released from the cells (see "Severe Exercise," below).[44]

Another cause of pseudohyperkalemia results from measurement of the seru extracellular fluid separated from the red cells (if clotting has occurred) rather than the plasma K^+ concentration. In normal subjects, a small amount of K^+ moves out of white cells and platelets during coagulation. Consequently, the meas serum K^+ concentration exceeds the true level in the plasma by 0.1 to as mu 0.5 meq/L, a difference that is clinically unimportant.[45,46] However, much more K^+ may be released in patients with marked leukocytosis or thrombocytosis (wl platelet count greater than 100,000/mm^3 or 400,000/mm^3, respectively). In these conditions, there may be a spurious elevation in the serum K^+ concentration to as high as 9 meq/L.[46,47,48] and[49] With thrombocytosis, for example, the serum K^+ concentration rises by approximately 0.15 meq/L for every 100,000/mm^3 elevation in the platelet count.[46]

A rare familial condition has also been described in which in vitro loss of K^+ occurs because of abnormally permeable red cells.[50,51] True hyperkalemia does not occur in vivo, since the excess K^+ is excreted in the urine. Familial pseudohyperkalemia maps to the gene locus as hereditary xerocytosis, a genetic disorder characterized by t presence in the peripheral smear of erythrocytes that are hyperchromic bec marked cellular dehydration; the gene product has not been identified.[52]

The presence of pseudohyperkalemia should be suspected when there is nc apparent cause for the elevation in the plasma K^+ concentration and when there are no changes in muscle strength or the electrocardiogram, since the true K^+ concentration is normal. Careful venipuncture to avoid hemolysis and meas of the plasma (not the serum) K^+ concentration usually establish the correct diagnosis. In the familial disorder, in vitro loss of K^+ can be prevented by rapid centrifugation to separate the red cells from the plasma.

Metabolic acidosis

Metabolic acidosis (other than organic acidoses such as lactic acidosis or ketoacidosis) results in movement of K^+ out of the cells (see page 379); this transcellular shift is obligated by the need to maintain electroneutrality, as the excess H^+ ions are buffered intracellularly.[53] The rise in the plasma K^+ concentration is variable, ranging from 0.2 to 1.7 meq/L for every 0.1-unit r in the arterial pH.[53]

The net effect depends upon both the severity of the acidemia and the stat balance. Patients with marked acidemia and relatively normal K^+ stores may become

hyperkalemic. In comparison, the plasma K^+ concentration may be normal or reduce if there is concurrent K^+ depletion due, for example, to diarrhea or renal tubula acidosis.[54,55] It should be appreciated, however, that the plasma K^+ concentration in this setting is *higher than it should be* (in relation to body K^+ stores) and that correction of the acidemia will lead to hypokalemia unless K^+ supplements are also administered.

Insulin deficiency and hyperglycemia

Hyperkalemia due to K^+ movement out of the cells is a common finding in patien with diabetic ketoacidosis or nonketotic hyperglycemia, even though total b K^+ stores are almost invariably depleted (see Chapter 25).[56,57] Insulin deficiency (but probably not acidemia[53]) may contribute to this response, since insulin normall promotes K^+ entry into the cells.[58] However, the associated hyperglycemia and hyperosmolality appear to play a more important role.[1,59,60] This can be illustrated by the response to glucose administration (Fig. 28-2). In normal subjects, the ensuing release of insulin minimizes the rise in the plasma glucose concent and produces a mild degree of *hypo*kalemia. In comparison, there is no increase i insulin secretion in insulin-dependent diabetics, resulting in both hyperglyc hyperkalemia.

The elevation in the plasma osmolality in this setting pulls water and the K^+ out of the cells.[61,62] Two factors contribute to this response. First, the loss of water ra K^+ concentration in the cells, thereby creating a favorable gradient for pass exit through *potassium channels* in the cell membrane. Second, the

frictional forces between the solvent (water) and the solute can result in K^+ being carried along with water through *water channels* in the cell membrane. This phenomenon of solvent drag is independent of the electrochemical gradient for K^+ diffusion. (A similar translocation of K^+ out of the cells can occur when acute hyperosmolality is induced by hypernatremia or the administration of hypert mannitol.[62,63])

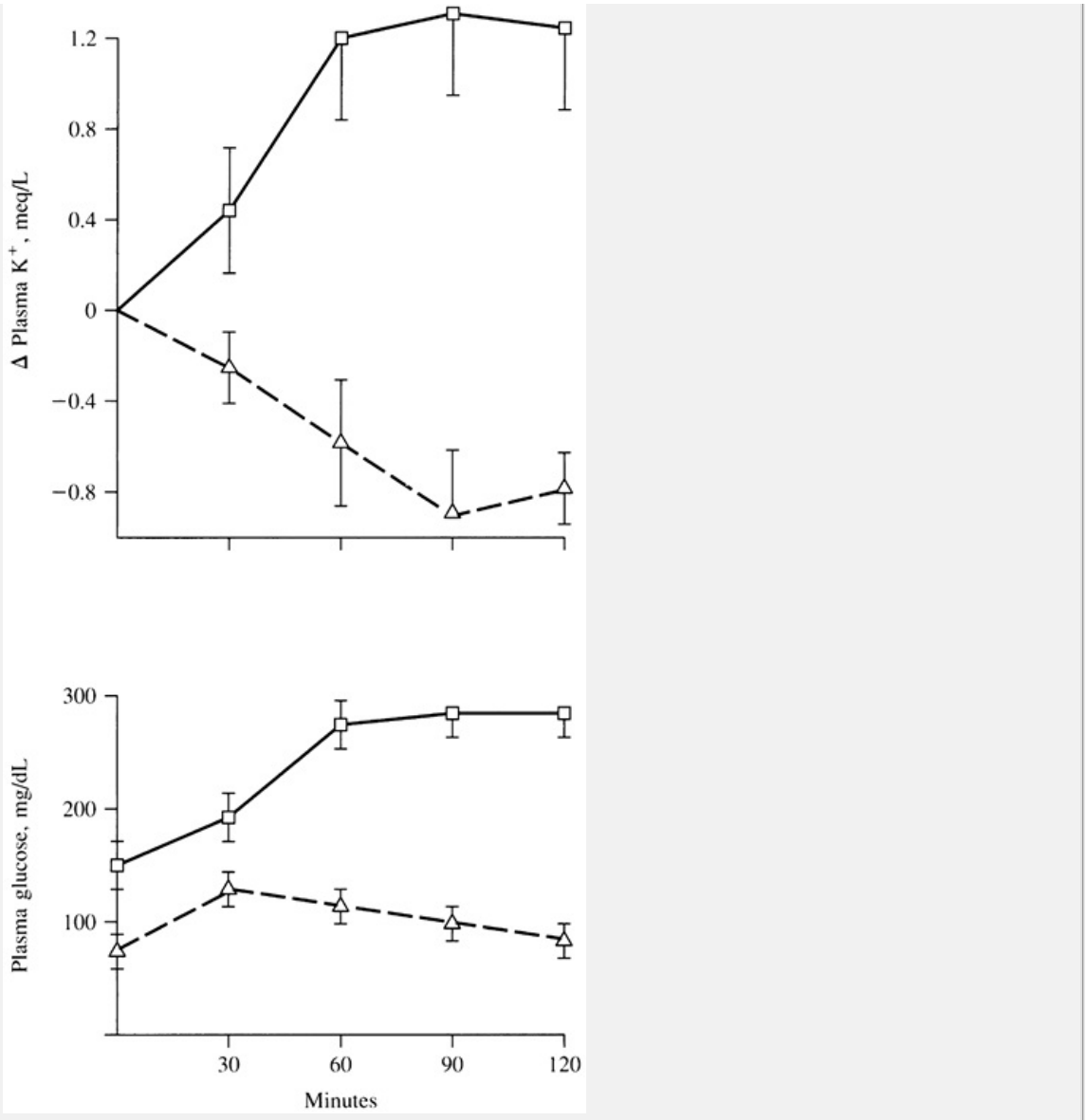

Figure 28-2 Effect of glucose infusion on the plasma K^+ and glucose concentrations in normal subjects (triangles) and in diabetics (squares). The plasma K^+ concentration falls in normals due to the release of insulin but rises in diabetics because of the development of hyper-glycemia and hyperosmolality. (*From Nicolis GL, Kahn T, Sanchez A, Gabrielli L, Arch Intern Med 141:49, 1981. Copyright, 1981, American Medical Association.*)

Although hyperkalemia at presentation is common in uncontrolled diabetes, the severity of this problem is limited by the concurrent renal and gastrointestinal K^+ losses.[56,57] In comparison, fatal hyperkalemia (with the plasma K^+ concentration exceeding 8 to 9 meq/L) can be induced by hyperglycemia in dialysis patients who are less likely to become depleted of K^+ because they do not have a glucose osmotic diuresis.[64]

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Several other factors also may promote the development of hyperkalemia in

patients, even if they are relatively well controlled. These include renal fai diabetic nephropathy, hyporeninemic hypoaldosteronism (see below), and d sympathetic activity due either to diabetic autonomic neuropathy or to the u adrenergic blockers to treat hypertension.

Insulin deficiency also may contribute to the rise in the plasma K^+ concentration following the administration of somatostatin, which is available for clinical intravenous infusion. The elevation in the plasma K^+ concentration averages 0.6 meq/L in normal subjects[58] but can reach 1.5 meq/L in patients with end-stage r disease who may already be hyperkalemic prior to the infusion.[65] In this setting, potentially serious hyperkalemia can ensue.

Tissue catabolism

When the rate of tissue breakdown is increased, large amounts of K^+ may be released into the extracellular fluid; hyperkalemia can occur, particularly if failure is present. Clinical examples of hypercatabolism include the trauma,[66] administration of cytotoxic agents to patients with malignant lymphomas, le and occasionally solid tumors (called the tumor lysis syndrome),[67,68] massive hemolysis,[69] or the condition found in patients who are essentially dead follo severe accidental hypothermia.[70] In the last setting, marked irreversible tissue necrosis can result in a plasma K^+ concentration above 10 to 20 meq/L. Since proteins (metabolized in part into urea), phosphates, and nucleic acids (me into uric acid) are also released from the cells in catabolic states, increase blood urea nitrogen (BUN) and plasma phosphate and uric acid concentrati also typically found.

β-Adrenergic blockade

β -Adrenergic blockers interfere with the β_2-adrenergic facilitation of K^+ entry into cells (see Fig. 12-2),[71,72] and[73] In most cases, this effect is associated with or minor elevation in the plasma K^+ concentration of less than 0.5 meq/L, since the excess extracellular K^+ can be excreted in the urine. True hyperkalemia is rare[74] unless it is associated with a superimposed problem, such as a load of K^+, severe exercise, hypoaldosteronism, end-stage renal failure, or cardiac sur below).[73,75,76,77] and[78] A relatively β_1-selective adrenergic blocker (such as atenolol) is safer in these settings.[79]

Severe exercise

Potassium is normally released from muscle cells during exercise. This resp in part reflect a delay between K^+ exit during depolarization and subsequent reuptake by the Na^+-K^+-ATPase pump.[2,4] With severe exercise, however, an additional factor may become important. Muscle cells have ATP-dependent K^+ channels that are inhibited by ATP. Thus, a reduction in ATP levels with ma

exercise can open up more channels, thereby promoting K^+ release.[80] from the cells.

The movement of K^+ out of the cells during exercise has a physiologic functio
local elevation in the plasma K^+ concentration has a vasodilatory effect that
contributes to the enhanced blood flow (and therefore energy delivery) to t

exercising muscle.[80,81]

The elevation in *systemic* plasma K^+ concentration is less pronounced than th
local rise and is directly related to the degree of exercise: 0.3 to 0.4 meq/L
walking,[82] 0.7 to 1.2 meq/L with moderate exertion (including prolonged aero
exercise, as with marathon running),[73,75,83,84] and as much as 2.0 meq/L with
possible electrocardiographic alterations following severe exercise to exha
which is often accompanied by lactic acidosis.[76,85,86] These changes are reversed
after several minutes of rest and may be associated with a mild rebound hy
of 0.4 to 0.5 meq/L below the baseline level.[83,86]

Exercise-induced hyperkalemia is attenuated by prior physical conditioning.[87]
Conditioning enhances cellular Na^+-K^+-ATPase activity, an adaptation that may be
responsible for the lesser release of K^+ during acute exercise.[4,87]

Although the rise in the plasma K^+ concentration is generally well tolerated,
hyperkalemia may be in part responsible for some of the cases of sudden d
occur during exercise.[88] This may be more likely to occur if there is an additior
abnormality in K^+ handling, such as rhabdomyolysis during a marathon race.[89] The
plasma K^+ concentration can also approach 8.0 meq/L with severe exercise i
patients taking a β -adrenergic blocker.[76] In addition to the effect of hyperkalemia
the postexercise mild hypokalemia may be arrhythmogenic, particularly in p
with underlying coronary heart disease.[85]

Digitalis overdose

The Na^+-K^+-ATPase pump in the cell membrane is inhibited in a dose-depend
manner by digitalis.[90] Thus, the administration of digitalis tends to increase th
plasma K^+ concentration as a result of the release of K^+ from the cells. When
digitalis is used in therapeutic doses, this effect is relatively small, althou
may be some impairment in the ability to handle a load of K^+.[91] However, severe
hyperkalemia (plasma K^+ concentration up to 13 meq/L) has resulted from the
ingestion of massive amounts of digitalis following a suicide attempt.[92,93]

Hyperkalemic periodic paralysis

The hyperkalemic form of periodic paralysis is a familial disorder with auto
dominant inheritance that is characterized by recurrent attacks of muscle w
or paralysis.[94,95] and[96] Most patients with this disorder also have myotonic

symptoms, particularly in the cold. Episodes are precipitated by rest after e the ingestion of K^+; they are associated with an elevation in the plasma K^+ concentration that is due either to a release from the cells or to an inability of ingested K^+ to enter the cells.[94,95,96] and[97] The degree of hyperkalemia is frequently mild (less than 5.5 meq/L), although the plasma K^+ concentration can exceed 7 meq/L in some patients.[95] Attacks are also associated with a fall in the plasma Na^+ concentration and a rise in the plasma protein concentration; the findings suggest that Na^+ and water enter the cell as K^+ leaves.[97]

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The primary abnormality in this condition in at least some families appears point mutation in the skeletal muscle Na^+ channel gene.[96,98,99] This is associated with sustained Na^+ currents,[100] and the activity of this channel may be further increased by a slight elevation in the plasma K^+ concentration.[99] The ensuing entry of Na^+ into the cell will depolarize the cell membrane, thereby fa K^+ diffusion out of the cells (since the concentration in the cell is so much than that in the extracellular fluid) and the development of hypokalemia.

The diagnosis of periodic paralysis should be suspected from the personal family history of *recurrent* episodes of muscle weakness and the elevated plasm concentration during an attack. In contrast to hypokalemic periodic paralys which the muscle weakness may be profound and last for up to 48 h, episod usually mild in the hyperkalemic form, with a duration of less than[94] and 1 to 2 h. diagnosis can be confirmed by the induction of muscle weakness and hyper after a relatively small oral K^+ load (0.5 to 1.0 meq/kg).[94,95,96] and[97]

Treatment is aimed at correcting the hyperkalemia and then attempting to p further episodes. Albuterol, a β -adrenergic agonist used to treat bronchoc may be particularly effective in reversing the acute symptoms by driving K^+ into cells.[101] Modalities used chronically include limiting exercise (if this precipi attacks), ingestion of a low-K^+, high-carbohydrate diet (carbohydrates promote K^+ entry into cells via increased insulin secretion), and including enough K^+ with a thiazide diuretic or a mineralocorticoid (such as fludrocortisone).[94] The addition of the carbonic anhydrase inhibitor acetazolamide may also be beneficial, per increasing urinary K^+ excretion (see[94,102] Chap. 15).

Cardiac surgery

Patients on cardiac bypass may develop a mild elevation in the plasma K^+ concentration

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as normal circulation is restored,[103] particularly if they have been taking a β-adrenergic blocker.[78] Two factors may contribute to this problem: (1) washout of ischemic areas that were underperfused during bypass and (2) previously

surgery is performed under hypothermic conditions). The induction of hypot
causes K^+ to move into the cells by an unknown mechanism.[104,105] Reversal of this
effect with rewarming may be associated with "overshoot" hyperkalemia, pa
if K^+ has been given during the period of hypothermia.[104]

Succinylcholine

Succinylcholine is a muscle relaxant used in general anesthesia. It acts by
depolarizing the cell membrane, i.e., it reduces the magnitude of the restin
membrane potential. Since the cell interior becomes less electronegative, t
the movement of positively charged ions (mainly K^+) out of the cells into the extracellular
fluid. In normal subjects, the result is a small rise in the plasma K^+ concentration of
0.5 meq/L or less.[106] However, in patients with burns, extensive trauma, tetanu
neuromuscular diseases, succinylcholine can induce an increase in the plas
concentration of as much as 6 meq/L, leading to cardiac arrhythmias and ev
cardiac arrest.[106,107] Although it is unclear why these patients are at such hig
risk, the increase in the plasma K^+ concentration (which usually occurs within 5 n
can be minimized by the prior administration of tubocurarine.[106]

Arginine

Arginine hydrochloride is metabolized in part to hydrochloric acid and has b
in the treatment of refractory metabolic alkalosis. Marked hyperkalemia is a
complication with this drug and is presumably due to the movement of K^+ out of cells
as cationic arginine enters the cells.[108,109] This effect may be more pronounced i
HIV-infected patients.[110]

Decreased Urinary Excretion

Potassium excretion is normally so efficient that even a massive chronic inc
K^+ intake will not produce hyperkalemia in normal subjects (Fig. 28-11).[14] Thus, for
hyperkalemia to persist, urinary K^+ excretory capacity must be reduced. There ar
three major causes of this problem: renal failure, effective circulating volur
depletion, and hypoaldosteronism.

Renal failure

As described above, K^+ balance is maintained in renal failure by increased exc
per functioning nephron.[25,26] and[27,111] This adaptation, which is mediated in pa
by aldosterone and enhanced Na^+-K^+-ATPase activity,[28,29] is effective as long as
the urine output remains adequate. However, the ability to excrete K^+ falls once
oliguria develops, primarily as a result of the decrease in flow to the distal
site.[27,112] In this setting, some of the K^+ derived from dietary intake is likely to b
retained, resulting in a persistent elevation in the plasma K^+ concentration.[113]

When hyperkalemia develop in a nonoliguric patient, some other factor is u

superimposed, such as enhanced tissue breakdown, hypoaldosteronism (se
or increased K^+ intake. As an example, patients with renal failure who are in b
on a regular diet may have an exaggerated rise in the plasma K^+ concentration
following a K^+ load.[7,26,27,114] Despite a low absolute rate of K^+ excretion in this
setting, the rate divided by the GFR (an index of K^+ excretion per functioning
nephron) is similar to that in normal subjects given a K^+ load.[26] This finding
suggests that the retention of K^+ in renal failure is due to *few nephrons, not to a
specific defect in K^+ secretion*.[27,114]

In addition to the diminished kaliuresis, K^+ entry into the cells is also impaired in
renal failure.[113,115] This is manifested by a low cell K^+ concentration in the basal
state (despite a normal or elevated plasma level)[116] and diminished cellular uptake
of K^+ after a K^+ load (Fig. 28-3).[117,118,119] Decreased Na^+,K^+-ATPase activity
(presumably due to retained uremic toxins that impair the transcription of m
the α_1 isoform of the Na^+,K^+-ATPase pump in skeletal muscle[120]) and possibly
metabolic acidosis[53,54] are primarily responsible for the altered distribution of K^+ in
this setting.

Although insulin resistance is also present in renal failure, this defect is li
hypoglycemic response. The ability of insulin to promote K^+ entry into the cells
appears to be preserved and therefore does not contribute to the tendency
hyperkalemia.[121,122]

There is, however, an abnormality in the relationship between carbohydrate
potassium metabolism in advanced renal failure, since fasting can lead to a
elevation in the plasma K^+ concentration (averaging 1 meq/L after 36 h) in patie
requiring maintenance dialysis.[123,124] Decreased insulin release induced by fasti
appears to be of primary importance, since the hyperkalemia can be preven
reversed by the administration of insulin plus glucose or, to a lesser degre
administration of glucose alone.[119,124] On the other hand, the degree of
hyperkalemia following a dietary K^+ load is minimized by concurrent glucose intak
which stimulates endogenous insulin secretion.[119]

Effective circulating volume depletion

Effective circulating volume depletion can be produced by fluid loss from th
sequestration into a noncirculating space, or diminished tissue perfusion in
failure or cirrhosis (Chap. 8). K^+ depletion is often present in these disorders
a result of the loss of K^+-containing fluids, either as a primary event or seconda
the use of diuretics in heart failure.

However, the ability to handle a K^+ load is impaired by hypovolemia, an effect tha
can lead to an elevation in the plasma K^+ concentration in some patients.

Reductions in urinary excretion and perhaps K^+ entry into cells contribute to this problem.[125,126] Volume depletion may be associated with both a low glomerular filtration rate and enhanced proximal Na^+ and water reabsorption. The net effect is an often marked decrease in distal fluid delivery, thereby diminishing K^+ secretion despite the hypovolemia-induced secondary hyperaldosteronism. Why cell entry of the excess K^+ is impaired in this setting is not understood.[17]

A clinical example of the effect of volume depletion may be seen in renal failure. One of the changes that can occur in this disorder is an inability to maximally conserve Na^+.[127,128] In most patients, the obligatory loss of Na^+ is relatively small and not clinically important on a regular diet.[128] If, however, intake is decreased or extrarenal losses are enhanced, volume depletion will ensue. The resultant decrease in renal perfusion can then lead to reduced K^+ excretion and hyperkalemia.[129]

The same sequence may be seen in severe congestive heart failure, which is usually associated with a reduction in renal perfusion. Life-threatening hyperkalemia may be seen in this setting, particularly in patients also taking KCl supplements.[130] The routine administration of angiotensin converting enzyme inhibitors in these patients also contributes to the tendency to hyperkalemia by impairing the synthesis of angiotensin II and therefore the release of aldosterone.[131]

A similar problem can occasionally occur in patients with relatively normal renal function, as illustrated by the following case history.

Case History 28-1

A 63-year-old woman complains of a diarrheal illness lasting for 4 to 5 days. At this time, her weight has dropped 3 kg, she

has noted a marked reduction in urine output, and her intake has been limited primarily to fluids (particularly orange juice) and fruits. The physical examination reveals postural hypotension and decreased skin turgor. The laboratory data are the following:

Plasma $[Na^+]$	=	130 meq/L	BUN	=	31 mg/dL
$[K^+]$	=	6.7 meq/L	[Creatinine]	=	1.2 mg/dL
$[Cl^-]$	=	98 meq/L	Urine $[Na^+]$	=	12 meq/L
$[HCO_3^-]$	=	21 meq/L	$[K^+]$	=	62 meq/L

Comment

The history, physical findings, and low urine Na^+ concentration are indicative of volume depletion. Although the urine K^+ concentration appears to be appropriately elevated, it is likely that the urine volume is below 500 mL/day and therefore the daily K^+ excretion is less than 30 meq. The combination of decreased urinary K^+ excretion and the relatively high K^+ intake (orange juice and fruits) is responsible for the hyperkalemia.

Hypoaldosteronism

Hypoaldosteronism can be induced by a variety of conditions that interfere either the production or the effect of aldosterone (Table 28-2). The most common causes are hyporeninemic hypoaldosteronism and K^+-sparing diuretics in adults, and adrenal enzyme deficiencies (particularly 21-hydroxylase deficiency) in children. Adrenal insufficiency, perhaps due to cytomegalovirus,

Mycobacterium avium-intracellulare, or HIV itself, is also a recognized finding in patients with AIDS,[132,133] although the administration of high-dose trimethoprim to treat *Pneumocystis carinii* pneumonia also may contribute to the rise in the plasma K^+ concentration in these patients (see below).

Table 28-2 Causes of hypoaldosteronism

Associated with decreased activity of the renin-angiotensin system

A. Hyporeninemic hypoaldosteronism with mild to moderate renal insufficiency
B. Nonsteroidal anti-inflammatory drugs, with the possible exception of sulindac
C. Converting enzyme inhibitors
D. Cyclosporine
E. Acquired immune deficiency syndrome
F. Hypervolemia in chronic dialysis patients

Primary decrease in adrenal synthesis

A. Low cortisol levels
    1. Primary adrenal insufficiency
    2. Congenital adrenal hyperplasia—primarily 21-hydroxylase deficie
B. Normal cortisol levels
    1. Heparin
    2. Isolated hypoaldosteronism
    3. Post–removal of adrenal adenoma

Aldosterone resistance

A. Potassium-sparing diuretics (including high-dose trimethoprim in AID
B. Cyclosporine
C. Pseudohypoaldosteronism

In addition to hyperkalemia, varying degrees of Na^+ wasting and metabolic acidosis are present in hypoaldosteronism, since aldosterone normally promotes Na^+

reabsorption and as well as secretion (see chap. 6).[134,135] and[136] The metabolic acidosis (called type 4 renal tubular acidosis; see Chap. 19) is also due in part to the hyperkalemia, as evidenced by correction of the acidemia when plasma concentration is normalized.[137,138] This effect of hyperkalemia may be in part due to a transcellular action exchange; as some of the excess enters the cells (through channels in the cell membrane), electroneutrality is maintained part by movement into the cells (perhaps via exchange).[139,140] The ensuing *intracellular alkalosis* might then reduce both reabsorption (see Fig. 11-14) and secretion by the renal tubular cells.[138,139,141] As a result, there would be a reduction in net acid excretion, thereby leading to retention of the daily acid load and the subsequent development of metabolic acidosis.

Most production occurs in the proximal tubule. Thus, a hyperkalemia-induced reduction in excretion should be a proximal event if diminished production were the primary problem. In one experiment, however, hyperkalemia diminished excretion but not its delivery out of the proximal tubule, suggesting that distal segments must be involved.[142] One possibility is that the increased concentration in the luminal fluid competitively inhibits entry into the site on the -- carrier in the thick ascending limb of the loop of Henle (see Fig. 4-2), as a result, loop reabsorption and subsequent medullary recycling would be impaired, thereby reducing the efficiency of accumulation in the medullary interstitium and its subsequent secretion into the medullary collecting tubule (see page 341).[142,143]

Hyporeninemic hypoaldosteronism

In the absence of an obvious cause (oliguric renal failure, salt substitutes, potassium-sparing diuretics, angiotensin converting enzyme inhibitors), the syndrome of hyporeninemic hypoaldosteronism appears to account for 50 to 75 percent of initially unexplained hyperkalemia in adults.[134,144,145] This disorder has the following characteristics[134,145]:

- Most patients have mild to moderate renal insufficiency with a creatinine clearance of 20 to 75 mL/min.
- Approximately 50 percent have diabetes mellitus, with chronic interstitial nephritis accounting for most of the remaining cases.
- Roughly 85 percent have a reduced plasma renin activity.
- Patients typically present with asymptomatic hyperkalemia.

The hypoaldosteronism in this setting appears to be multifactorial.[134,145] The low renin levels can clearly contribute, since angiotensin II is a major

physiologic stimulus to aldosterone secretion. On the other hand, several

observations suggest that there may also be an *intra-adrenal* defect. These include a normal plasma renin activity in some patients,[134,146] an inability of infused angiotensin II to stimulate aldosterone secretion,[147,148] and the demonstration that nephrectomized patients (who have no renin) still have normal aldosterone production that is directly stimulated by the associated rise in the plasma K^+ concentration.[149]

Studies in diabetic animals have demonstrated an impaired zona glomerulosa response to angiotensin II that is due to a postreceptor defect.[150] How this might occur is not known, but it appears to be relatively specific, since the increase in aldosterone release following ACTH is not diminished.

The presence of *renal insufficiency* is also an important determinant of the propensity to hyperkalemia. Although decreased aldosterone release can impair urinary K^+ excretion, patients with normal renal function can compensate because a small rise in the plasma K^+ concentration directly enhances distal K^+ secretion (see Fig. 12-10).[9] In diabetes mellitus, for example, hypoaldosteronism may occur relatively early, but hyperkalemia is not seen until the additional insult of renal insufficiency is superimposed.[148,151,152]

How these renal and adrenal changes might occur is incompletely understood. One possibility is that a *defect in prostaglandin production* might be involved,[153] since prostaglandins promote renin secretion (see Chapter 22) and appear to facilitate aldosterone release by angiotensin II.[154] Furthermore, nonsteroidal anti-inflammatory drugs (NSAID, which inhibit prostaglandin synthesis) can induce hyporeninemic hypoaldosteronism.[155,156] The rise in the plasma K^+ concentration is variable, averaging only 0.2 meq/L in patients with normal renal function, occasionally exceeding 1 meq/L when renal insufficiency is superimposed.[157]

Another hypothesis suggests that hypervolemia associated with renal disease may be the primary event. Volume expansion *leads to increased release of atrial natriuretic peptide*, a hormone that can then directly suppress the renal release of renin and potassium-induced adrenal release of aldosterone (see Chapter 6).[158] Hyporeninemia, hypoaldosteronism, and high levels of atrial natriuretic peptide are, for example, common in patients with acute glomerulonephritis (such as postinfectious glomerulonephritis) and chronic renal disease, and prior to dialysis in patients with end-stage renal failure.[159,160] These changes can lead to hyperkalemia in selected patients with glomerulonephritis.[160] Removal of the excess fluid or recovery from the glomerular injury reverses these hormonal changes, resulting in the normalization of K^+ balance.

Volume expansion may also explain in part the propensity of diabetics to develop this disorder. This increased filtered load of glucose imposed by hyperglycemia enhances proximal tubule Na^+ reabsorption by the Na^+-glucose cotransporter in the luminal

membrane (see page 90). In addition, a defect in the conversion of the precurs prorenin (or inactive renin) into active renin has been demonstrated both ir diabetics[161,162] and in other patients with renal disease and hypoaldosteronism.[163] How this abnormality might occur is unclear, although d damage to the renin-producing juxtaglomerular cells may be involved.

Diabetes also may directly impair adrenal function, as evidenced by decrea release of aldosterone in response to angiotensin II.[148] This defect may be related to atrophy of the zona glomerulosa, possibly as a result of removal of the n trophic effect of insulin on these cells.[164]

A syndrome similar to hyporeninemic hypoaldosteronism may be also seen i other settings. These include the use of angiotensin converting enzyme inh (which impair the conversion of angiotensin I into angiotensin II),[165,166] acquired immune deficiency syndrome,[167] and the administration of cyclosporine.[168,169] Renal transplant recipients treated with cyclosporine, for example, have higher plasma K^+ concentrations than those treated with predniso and azathioprine. In addition to decreased aldosterone release, there is als evidence that cyclosporine impairs tubular K^+ secretion.[169,170]

How these renal and extrarenal effects occur is not well understood. In vitr suggest that cyclosporine can diminish Na^+-K^+-ATPase activity in the K^+ secretory cells in the cortical and outer medullary collecting tubules but not in most o nephron segments.[170] Such a defect would diminish K^+ accumulation in the tubular cells and therefore the size of the K^+ secretory pool. There is also evidence that cyclosporine directly impairs the secretory process by inhibiting the lumina channels through which K^+ is secreted.[171] The applicability of these findings to th development of hyperkalemia in humans is uncertain.

The decrease in aldosterone release with angiotensin converting enzyme (A inhibitors may be due to two factors: a reduced concentration of circulating angiotensin II and diminished *intra-adrenal* angiotensin II, which may mediate part o most of the stimulatory effect of hyperkalemia.[172,173] As with other causes of hypoaldosteronism, the rise in the plasma K^+ concentration after ACE inhibition is generally less than 0.5 meq/L if renal function is normal.[165] However, potentially dangerous hyperkalemia can occur in patients who have renal insufficiency high normal or elevated baseline plasma K^+ concentration or in patients who are also taking a K^+-sparing diuretic or K^+ supplements.[165,166] This interaction has become a more important concern, since both angiotensin converting enzym inhibitors and the K^+-sparing diuretic spironolactone are given to many patient heart failure because they improve survival.[174]

The hyperkalemia observed with HIV-infected patients is often multifactoria[175]

addition to adrenal insufficiency, which may be infectious in origin,[132,133] other factors include drugs (trimethoprim, pentamidine; see below) and a diminish response to aldosterone.[176]

Primary adrenal insufficiency

Patients with primary adrenal insufficiency (or bilateral adrenalectomy) hav diminished glucocorticoid as well as mineralocorticoid secretion. Autoimmun destruction of the steroid-producing cells in the adrenal cortex and AIDS ar common causes of this problem in adults.[175,177] One major antigen against which the autoantibodies are directed in

autoimmune disease in adults appears to be the enzyme CYP21A2 (21-hydroxylase).[178,179] This enzyme converts progesterone into deoxycorticoster in the zona glumerulosa and 17-hydroxyprogesterone into deoxycortisol in t fasciculata. Other antibody targets CYP11A1 (side-chain cleavage enzyme) CYP17 (17α-hydroxylase).[179]

The hormonal and electrolyte findings are different in patients with pituitar who have secondary hypoadrenalism. In this setting, aldosterone secretion relatively normal, since adrenocorticotropic hormone (ACTH) does not have role in the regulation of aldosterone release (see page 182).[180,181] As a result, these patients do not become hyperkalemic.

Adrenal enzyme deficiencies

The pathways involved in adrenal steroid synthesis are illustrated in Fig. 28-3, addition to aldosterone, deoxycorticosterone (DOC) and corticosterone also mineralocorticoid activity. Their secretion, however, is determined primarily —not, as with aldosterone, by angiotensin II or the plasma K^+ concentration.[180,181] and[182] Signs of mineralocorticoid deficiency may be seen with reduced acti enzymes involved in steps *prior to the formation of DOC* (3β-hydroxysteroid dehydrogenase and CYP21A2) or in the *conversion of corticosterone to aldosterone*.[182] ¶ The two steps involved in the latter conversion are mediated single multifunctional cytochrome P450 enzyme called CYP11B2 (aldosteron synthase or corticosterone methyl oxidase).[183,184] The activity of this enzyme is normally suppressed in the zona fasciculata[185,186] preventing aldosterone secretion from being inappropriately regulated by ACTH.

Deficiencies in the enzymes prior to DOC formation may be associated with concurrent abnormalities in cortisol and androgen production.[182,183,188] On the other hand, children with a defect in aldosterone synthase have isolated hypoaldosteronism.[186,189] Congenital isolated hypoaldosteronism is a rare inh disorder that is transmitted as an autosomal recessive trait. Affected infant recurrent dehydration, salt wasting, and failure to thrive.[183,188]

Treatment varies with the type of enzyme deficiency. Mineralocorticoid repl

is sufficient in patients with isolated hypoaldosteronism, whereas those wit common CYP21A2 deficiency require replacement of both glucocorticoid an mineralocorticoid.[190]

The response to glucocorticoid replacement (usually with hydrocortisone or dexamethasone) should be assessed by measuring serum 17-hydroxyproges (which accumulates in untreated patients), androstenedione or testosterone and prepubertal boys to assess for virilization), growth velocity, and the ra skeletal maturation. The goal is to use the lowest effective dose to prevent glucocorticoid excess.

Mineralocorticoid is usually given as fludrocortisone, in a dose sufficient t normal serum sodium and potassium concentrations and to lower the

plasma renin activity to normal; excessive dosing can induce hypertension, hypokalemia, and possibly impaired growth.

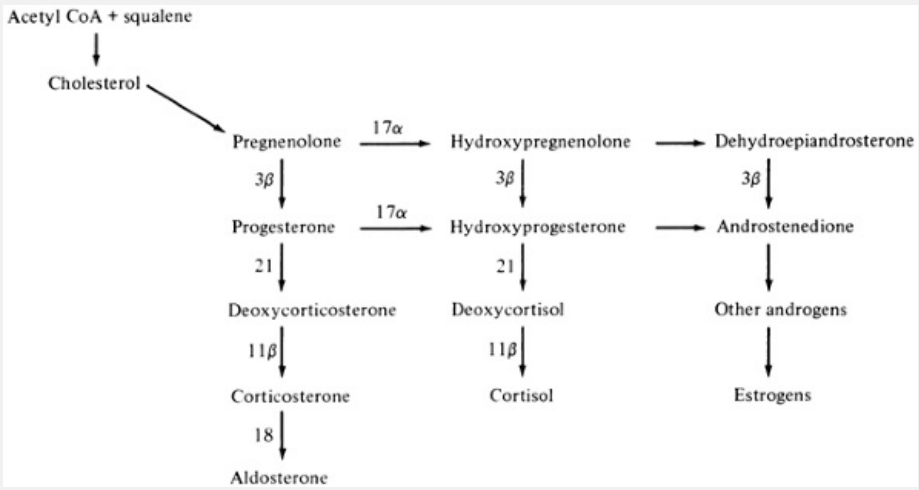

Figure 28-3 Schematic pathways of adrenal steroid biosynthesis. The numb at the arrows refer to specific enzymes: 17α equals 17α-hydroxylase; 3β e 3β-hydroxysteroid dehydrogenase; 21 equals 21-hydroxylase; 11β equals hydroxylase; 18 refers to a two-step process resulting in the addition of a aldehyde at the 18-carbon position. The last reactions occur only in the z glomerulosa, which is the site of aldosterone secretion. A deficiency in ar these enzymes can lead to abnormal mineralocorticoid (as well as glucocc and androgen) production.

Heparin

Heparin therapy reduces aldosterone secretion by a direct action on the ad gland.[191,192] It is not clear, however, whether this represents an effect of he itself or of its preservative chlorbutol.[193] Regardless of the mechanism, even low- dose heparin can lead to a 75 percent reduction in plasma aldosterone leve 4 to 7 days.[194] Hyperkalemia, however, is seen only if some superimposed pr

is present, such as renal insufficiency.[191,195] The aldosterone deficiency in this setting is readily reversible with discontinuation of the drug.

Post-removal of adrenal adenoma

In patients with primary *hyper*aldosteronism due to an adrenal adenoma, the chro overproduction of aldosterone suppresses the normal tissue in the zona glo As a result, surgical removal of the tumor leads to a transient period of hypoaldosteronism that can last up to 6 months or more.[196,197]

Potassium-sparing diuretics

The K^+-sparing diuretics impair distal K^+ secretion—spironolactone by antagonizin the effect of aldosterone, and amiloride and triamterene by directly closing K^+ channel in the luminal membrane of the collecting tubular cells (Chapter 15). As a result, the use of any of these

drugs can produce hyperkalemia, particularly in patients who have renal ins or who are taking K^+ supplements, an angiotensin converting enzyme inhibitor, NSAID.[41,198]

Two antibiotics—trimethoprim (usually given as trimethoprim-sulfamethoxaz pentamidine—can also cause hyperkalemia by closing the sodium channels.[199,200,201,202,203] and[204] Trimethoprim-induced hyperkalemia is dos dependent, being primarily seen at the very high doses used in patients wit AIDS.[199,200] and[201] However, trimethoprim can raise the plasma potassium concentration even when used in conventional doses, particularly in the elderly.[202,203,205] One study performed a prospective chart review of 80 pati who did not have renal insufficiency or another cause of altered potassium homeostasis who were treated for at least 5 days with conventional doses o trimethoprim-sulfamethoxazole.[202] There was a mean rise in the plasma potassiu concentration of 1.2 meq/L, from 3.9 to 5.1 meq/L; 21 percent of patients h plasma potassium concentration ≥5.5 meq/L. The peak effect was at 4 to 5 Patients with mild renal insufficiency may be at risk for more severe hyperkalemia.[203]

Pseudohypoaldosteronism

Reduced aldosterone effect can be induced by either genetic or acquired e resistance (called pseudohypoaldosteronism). This disorder is associated v volume depletion, Na^+ wasting, hyperkalemia, and markedly elevated levels of and aldosterone, findings similar to those with aldosterone resistance induced by K^+-sparing diuretics.[206,207]

The acquired form of pseudohypoaldosteronism is limited to the kidney and primarily with tubulointerstitial diseases such as urinary tract obstruction, pyelonephritis, acute interstitial nephritis, and amyloidosis.[208,209,210] and[211] It is

presumed that tubular injury is responsible for the diminished response to aldosterone in these disorders.

There are two rare genetic forms of pseudohypoaldosteronism: type 1 and t

Type 1 pseudohypoaldosteronism consists of two different disorders with differer modes of inheritance, clinical manifestations, course, and pathogenesis[212,213]

- Autosomal recessive, in which the defect is permanent and all aldosterc organs are involved (including the kidney, colon, and salivary glands)
- Autosomal dominant or sporadic, in which the defect may improve with a in some cases, involves only the kidney

The autosomal recessive form is due to a defect in the collecting tubule so channel, making it relatively unresponsive to aldosterone,[213,214] while the defect in the autosomal dominant or sporadic form often involves the gene for the mineralocorticoid receptor.[215]

The clinical presentation of type 1 pseudohypoaldosteronism in children is that with the more common CYP21A2 deficiency. However, the normal serum concentrations of 17-hydroxyprogesterone and cortisol and the elevated

serum concentration of aldosterone usually allow the diagnosis of pseudohypoaldosteronism to be established.

Initial therapy of type 1 pseudohypoaldosteronism consists of a high-salt di prevents volume depletion and, by enhancing sodium delivery to the potass secretory site in the collecting tubules, increases potassium excretion and plasma potassium concentration. High-dose fludrocortisone [1 to 2 mg/day (0.05 to 0.1 mg/day in adrenal insufficiency)] or carbenoxolone may be bene high salt intake is ineffective or not well tolerated.[216] Carbenoxolone prevents the inactivation of cortisol to cortisone, thereby allowing cortisol (which circula much higher concentrations than aldosterone) to act as a mineralocorticoid should be followed carefully, since the aldosterone resistance often resolve the first few years.[217]

Patients with *type 2 pseudohypoaldosteronism* (Gordon's syndrome) present with hyperkalemia but no other signs of hypoaldosteronism. Rather than being v depleted due to salt wasting, these patients present with hypertension, nor function, and low or low normal plasma renin activity and aldosterone concentrations.[218,219] and[220] The defect, which is probably transmitted as an autosomal dominant trait, may be in a gene located on chromosome 1, 12, a 17.[221,221a]

Although the abnormal gene product has not been identified, the primary de this disorder may be enhanced distal chloride reabsorption.[218–220] As a result, sodium is reabsorbed distally with chloride, not in exchange for potassium hydrogen. The net effect is hyperkalemia, volume expansion, and hypertens which secondarily suppress renin secretion. Many of these abnormalities ca

corrected by a thiazide diuretic, suggesting that the primary defect in this d may be increased activity of the thiazide-sensitive sodium-chloride cotrans the luminal membrane of the cells in the distal tubule and adjacent connect segment.[220]

Type 1 renal tubular acidosis—hyperkalemic form

Type 1 (distal) renal tubular acidosis (RTA) is an uncommon disorder chara by impaired distal H^+ secretion, resulting in metabolic acidosis with an inappropriately high urine pH above 5.3 (see p. 419). *Hyp*okalemia frequently occurs in this disorder, in part because the decreased distal H^+ secretion requires that Na^+ reabsorption occur in exchange for K^+.[55] However, hyperkalemia may be seen when the underlying mechanism is a primary decrease in distal Na^+ reabsorption.[222] The relative inability to reabsorb cations impairs the generation of the lumen-negative potential difference that promotes both K^+ and H^+ secretion.[222]

Hyperkalemic RTA most often occurs in patients with obstructive uropathy (decreased Na^+K^+-ATPase activity may account for the reductions in Na^+ reabsorption and K^+ secretion),[223,224] and[225] and sickle cell disease.[6,226] These disorders, however, may also be associated with hyporeninemic hypoaldosteronism,[223,226] a condition that is treated differently from RTA.

The distinction between RTA and hypoaldosteronism can be established by measuring the plasma aldosterone concentration, which is normal in RTA, a

urine pH, which in the presence of metabolic acidosis is appropriately belo most patients with aldosterone deficiency.[226,227] However, the separation between these disorders is not necessarily so clear. Some patients appear to have t different defects: an impairment in H^+-ATPase pump, which is responsible for t RTA, and hypoaldosteronism or aldosterone resistance induced by tubular i which is responsible for the hyperkalemia.[228]

Treatment of hyperkalemia in type 1 RTA consists of alkali therapy (often g Na^+ citrate, which is better tolerated than $NaHCO_3$), a low-K^+ diet, and, if necessary, a diuretic to increase flow to the K^+ secretory site.

Selective potassium secretory defect

In some patients, hyperkalemia occurs with inappropriately low urinary K^+ excretion, normal renin and aldosterone levels, and vascular Na^+ wasting. This rare syndrome of an apparently selective defect in K^+ secretion that does not respond to exogenous mineralocorticoid has been described with sickle cell anemia, renal transpl rejection, and lupus nephritis.[6,229,230] The lack of Na^+ wasting and a normal antinatriuretic response to exogenous mineralocorticoid indicate that the ur abnormality in these patients is not simple aldosterone resistance.

The pathogenesis of this defect is not understood, but a process similar to

hyperkalemic RTA may be involved. About one-half of patients have a metab acidosis that, in at least in some cases, is associated with an elevated urin pH.[229,230] Alternatively, selective impairment of K^+ secretion may be the sole abnormality, since hyperkalemia can induce metabolic acidosis by, as descr above, reducing NH_4^+ and therefore net acid excretion.[138,139,140] and [141]

The diagnosis of a selective K^+ secretory defect is made by exclusion. This diso can be differentiated from one of the causes of hypoaldosteronism by demo that aldosterone levels are normal and that the administration of fludrocort leads to a reduction in Na^+ excretion without affecting that of K^+.[6,230] This distinction is important therapeutically, since therapy consists of low-K^+, high-Na diet plus a diuretic, not mineralocorticoid replacement. Thiazides may be m effective than a loop diuretic in this setting;[230] why this might occur is uncertain, unless there is specific inhibition of increased distal NaCl reabsorption.

SYMPTOMS

The changes induced by hyperkalemia are essentially limited to muscle wea and abnormal cardiac conduction, which can lead to potentially fatal arrhyt However, patients may also complain of symptoms related to the underlying such as polyuria and polydipsia in uncontrolled diabetes

mellitus or salt wasting, weight loss, and failure to thrive in infants with hypoaldosteronism.

Muscle Weakness

The muscle weakness associated with hyperkalemia appears to result from in neuromuscular conduction. The increase in the plasma K^+ concentration reduces the ratio of the intracellular K^+ concentration to that in the extracellular fluid, resulting in a decrease in the magnitude of the resting membrane potential Chap. 26). Although this should increase membrane excitability (since less o depolarizing stimulus is required to generate an action potential), the effec patients is different. Persistent depolarization *inactivates sodium channels* in the cell membrane, thereby producing a *decrease* in membrane excitability[232] that may be manifested clinically by muscle weakness or paralysis and/or impaired c conduction.

Muscle weakness typically does not develop until the plasma K^+ concentration exceeds 8 meq/L.[233,234] and [235] However, patients with periodic paralysis may become symptomatic at a plasma K^+ concentration below 5.5 meq/L,[95] probably because abnormal membrane function is the primary defect in this disorder.

Muscle weakness most often begins in the lower extremities and ascends to and upper extremities.[233] The respiratory muscles and those supplied by the cr nerves are usually spared.

Cardiac Arrhythmias

Disturbances in cardiac conduction, which can lead to ventricular fibrillatio standstill, pose the greatest danger to the patient with hyperkalemia.[233,236] Consequently, monitoring of the electrocardiogram (ECG) is an essential pa management of this disorder. As the plasma K^+ concentration rises, there is a characteristic sequence of changes in the ECG that is due to the effects of hyperkalemia on atrial and ventricular depolarization (represented by the P QRS complex, respectively) and repolarization (represented by the T wave ventricular repolarization, with the atrial repolarization wave being lost in t complex).[236,237,238 and 239]

The earliest changes are peaked, narrow T waves and a shortened QT inte which reflect abnormally *rapid repolarization* (Fig. 28-4).[236] On occasion, this may be confused with the tall T waves seen with myocardial ischemia. However, the interval is usually normal or prolonged during ischemic episodes.[236]

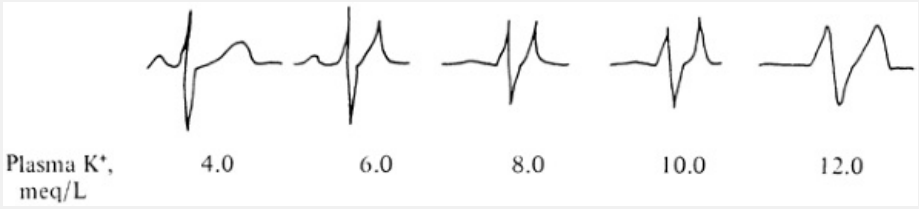

Figure 28-4 Electrocardiogram in hyperkalemia. The initial change is peaki and narrowing of the T wave with a short QT interval. With more severe hyperkalemia, widening of the QRS complex, decreased amplitude and eve loss of the P wave, and a sine-wave pattern as the QRS complex merges v the T wave may be seen. The approximate relationship between these cha and the plasma K^+ concentration is indicated, although there is a large interpatient variability. (*Adapted from Surawicz B: Am Heart J 73:814, 1967, with permission.*)

The alteration in T-wave configuration typically becomes prominent when th K^+ concentration exceeds 6 meq/L. At a plasma K^+ concentration above 7 to 8 meq/L, further changes in the electrocardiogram occur that are primarily du *delayed depolarization*.[236] The result is prolongation of the PR interval, wide of the QRS complex with no change in configuration (the electrocardiograph manifestation of slowed ventricular depolarization), and decreased amplitud widening, and eventual loss of the P wave (Fig. 28-5). The final change is wave pattern as the widened QRS complex merges with the T wave, followe

ventricular fibrillation or standstill.

The tendency to severe arrhythmias also may be related in part to heteroge changes in myocardial conduction, as the epicardium is more prominently a than the endocardium.[239] Despite these changes in conduction, the contractilit cardiac muscle seems to be unaffected by hyperkalemia.[242]

The approximate relationship between the degree of hyperkalemia and the l changes is depicted in Fig. 28-4. This relationship, however, is variable; in rare cases, the ECG may be normal or near normal despite a marked elevation i plasma K^+ concentration to above 9 meq/L, a level that is usually life-threatening.[243]

The lack of predictability of the electrocardiographic changes in hyperkaler largely due to the influence of other factors that can affect cardiac conduct examples, the cardiac toxicity of hyperkalemia is enhanced by hypocalcemia[244] hyponatremia,[245] acidemia,[246] and a rapid elevation in the plasma K^+ concentration (see "Treatment," below).[237,247] Thus, patients with renal failure may be particularly sensitive to hyperkalemia, since hypocalcemia (due to phospha retention and vitamin D deficiency), metabolic acidosis (due to reduced NH_4^+ excretion), and hyponatremia (due to water retention) all may be present (s Chapters 6, 19, and 23). On the other hand, hypernatremia and hypercalcemia

counteract the membrane changes of hyperkalemia, thereby minimizing the risk.[243]

DIAGNOSIS

The initial evaluation of the hyperkalemic patient should include: a complet (including questions about dietary intake and a history of kidney disease, d mellitus, the use of K^+-sparing diuretics, or recurrent episodes of muscle weak physical examination (looking for muscle weakness or the signs of volume d or edema), an electrocardiogram, and measurement of arterial pH and the b nitrogen (BUN), plasma creatinine, glucose, and Na^+, K^+, and Ca^{2+} concentrations.

With this information, the approach to diagnosis can be simplified by consi separately the three groups of conditions associated with hyperkalemia: inc intake, K^+ release from the cells, and reduced urinary K^+ excretion. As described above, increased intake is the sole cause of hyperkalemia only when a mas has been given acutely; it may, however, play an important contributory rol patients with underlying renal disease or hypoaldosteronism. Thus, a caref history should be obtained, looking for the intake of K^+-rich foods and for the possible use of salt substitutes or K^+ supplements.

The diagnosis of one of the disorders associated with K^+ release from the cells (Table 28-1) can usually be made from the history or laboratory data, as, for example, with marked hyperglycemia. *Pseudohyperkalemia* should be suspected if

there is no apparent cause for the elevation in the plasma K^+ concentration or if there are no electrocardiographic changes at a plasma K^+ concentration greater than 6.5 to 7.0 meq/L. Once hemolysis during venipuncture has been excluded (b drawing blood without a tourniquet or clenching of the fist), the diagnosis o the other forms of pseudohyperkalemia can be confirmed by the findings of plasma (not serum) K^+ concentration and a marked elevation in either the white blood cell or platelet count.

If none of these disorders is present or if the patient has persistent hyperk then decreased urinary K^+ excretion must be contributing to the rise in the plas K^+ concentration. The kidney is so efficient in excreting K^+ that normal excretory function will prevent the persistence of hyperkalemia (see Fig. 28-14). Measuring the urine K^+ concentration is generally *not helpful*, since the value must be *inappropriately low to permit perpetuation of the hyperkalemia*, however; calculation of the transtubular K^+ gradient permits estimation of the degree of aldosterone effect (see below).

Severe renal failure is a common cause of hyperkalemia. It is characterized marked elevations in the BUN and plasma creatinine concentration or, in pa with acute renal failure, a progressive increase in these parameters. Hyper more likely to occur if there is also an increased K^+ load. As an example, approximately 50 percent of patients with posttraumatic renal failure, in wh

tissue catabolism is enhanced, develop a plasma K^+ concentration above 7 meq/L unless early therapy is instituted.[66]

Effective volume depletion as a cause of hyperkalemia can usually be exclu the history (possibly including vomiting, diarrhea, heart failure) and physic examination. True volume depletion may be associated with decreased skin an estimated jugular venous pressure below 0.5 cm H_2O, tachycardia, and a postural fall in blood pressure (see p. 14). In contrast, heart failure is typically associ with peripheral and/or pulmonary edema, and cirrhosis with prominent ascit underlying renal function is normal, the urine Na^+ concentration should be less than 25 meq/L in these disorders, as Na^+ reabsorption is enhanced in an attempt to restore normovolemia.

Hypoaldosteronism

If renal function is normal or only moderately impaired and no other etiolog chronic hyperkalemia is apparent, the patient should be evaluated for one o causes of hypoaldosteronism.

The age of the patient is an important determinant of the cause of hypoaldosteronism. In adults, hyporeninemic hypoaldosteronism and primar insufficiency are most common. The latter diagnosis should be suspected c signs of cortisol deficiency are present, such as salt craving, fasting hypog or hyperpigmentation of the skin and mucous membranes (due to the hypers

of ACTH). In comparison, enzyme deficiencies and type 1 pseudohypoaldost begin in infancy or childhood.

Na^+ wasting may be relatively severe in children with hypoaldosteronism, w typically present with volume depletion, hyperkalemia, hyponatremia, metab acidosis, and an elevated urine Na^+ concentration. In comparison, adults with this disorder typically have less severe aldosterone deficiency and tend to pres asymptomatic hyperkalemia.[134] Sodium wasting and volume depletion are not typically seen in the absence of concurrent hypocortisolism due to primary insufficiency.[134] Other factors, such as angiotensin II, norepinephrine, and a reduction in blood pressure, can combine to maintain relatively normal Na^+ balance in this setting, despite the reduced levels of aldosterone (see Chapter 8). What is generally lost, however, is the ability to conserve Na^+ maximally. A urine Na^+ concentration below 10 to 15 meq/L is unusual, because this gradient is att the aldosterone-sensitive sites in the cortical and inner medullary collectin

The evaluation for hypoaldosteronism should begin with discontinuation of potential offending drug, such as a NSAID, angiotensin converting enzyme i K^+-sparing diuretic, or heparin. If these agents are not being used, measur the *morning* plasma renin activity and aldosterone and cortisol concentration establish the correct diagnosis (Table 28-3).[134] To minimize the incidence of confusing borderline values, the patient should be given 20 to 40 mg of furosemide at and 6 A.M. before the blood specimen is obtained. This

regimen enhances aldosterone secretion (via stimulation of renin) in norma but not in patients with hypoaldosteronism.[134]

Table 28-3 Plasma renin activity, aldosterone and cortisol levels, and response to mineralocorticoi therapy in major causes of idiopathic hypoaldosteronism

Disorder	Plasma renin activity	Plasma aldosterone	Plasma cortisol	Response to aldosterone
Hyporeninism	↓–nl	↓	nl	nl
Primary adrenal insufficiency	↑	↓	↓	nl
Enzyme deficiencies				
Congenital adrenal	↑	↓	↓	nl

hyperplasia				
Isolated hypoaldosteronism	↑	↓	nl	nl
Pseudohypoaldosteronism	↑	↑	nl	0–↓

An indirect way to estimate the effect of aldosterone would be to measure t fluid K^+ concentration at the end of the cortical collecting tubule, after most secretion has occurred. This can be estimated clinically if the following ass are correct: The urine osmolality at this site is similar to that of the plasma equilibration with the isosmotic interstitium will occur in the presence of AD Chap. 4), and little or no K^+ secretion or reabsorption takes place in the medulla collecting tubule. In this setting, the K^+ concentration will rise in the medulla because of the loss of water; this can be accounted for by dividing the urin concentration by the osmolality (U_{osm}/P_{osm}). Thus the *transtubular K^+ gradient* (TTKG) is equal to[248]

$$TTKG = \frac{[U_{K^+} \div U_{osm}/P_{osm}]}{P_{K^+}}$$

This estimation is relatively accurate as long as the urine is not dilute and Na^+ concentration is above 25 meq/L, so that urinary Na^+ delivery is not limiting.[248]

The TTKG in normal subjects on a regular diet is 8 to 9 and rises to above K^+ load, indicating increased K^+ secretion.[249] Thus, a value below 7 and particularly below 5 in a hyperkalemic patient is highly suggestive of hypoaldosteronism. If, for example, the K^+ is 30 meq/L, the P_{K^+} is 6.5 meq/L, and the U_{osm} and P_{osm} are 560 mosmol/kg and 280 mosmol/kg, respectively, then

$$TTKG = \frac{30 \div 560/280}{6.5}$$

$$= 2.3$$

This low value is consistent with hypoaldosteronism.

TREATMENT

The treatment of hyperkalemia varies with the severity of the electrolyte disturbance.[68,250] As described above, severe symptoms usually do not occur

the plasma K^+ concentration is above 7.5 meq/L.[233,234] There is, however, substantial interpatient variability, since factors such as the plasma Ca^{2+} concentration and acid-base balance can modify the toxicity of hyperkalemi[244,246] As a result, it is essential to monitor the ECG and muscle strength, which a *functional consequences* of hyperkalemia, as well as the plasma K^+ concentration.

A plasma K^+ concentration above 8 meq/L, severe muscle weakness, or marke

electrocardiographic changes (Fig. 28-5) are potentially life-threatening an *immediate* treatment with almost all of the modalities listed in Table 28-4. In comparison, an asymptomatic elevation in the plasma K^+ concentration of 6.5 meq/L can be treated *solely with a cation exchange*, since rapid therapy is not necessary.

Reversing the effects of hyperkalemia can be achieved by direct antagonisr membrane actions and by lowering the plasma K^+ concentration, either by driving K^+ into the cells (which will increase the $[K^+]_i/[K^+]_e$ ratio toward normal) or by removin K^+ from the body (Table 28-4).[115] In addition, further K^+ intake should be limited. Commonly ignored sources of K^+ are K^+ salt substitutes, stored blood, and K penicillin, which contains 1.6 meq of K^+ per million units of penicillin.

Calcium

The severe symptoms of hyperkalemia are due to decreased membrane exci resulting from inactivation of membrane Na^+ channels.[232] Via a mechanism that is not well understood, calcium antagonizes this effect of K^+, restoring membrane excitability toward normal.[251] Conversely, a decrease in the plasma Ca^{2+} concentration enhances the toxicity of hyperkalemia.[244]

Table 28-4 Treatment of hyperkalemia

Antagonism of membrane actions

A. Calcium
B. Hypertonic Na^+ solution (if hyponatremic)

Increased K^+ entry into the cells

A. Glucose and insulin
B. $NaHCO_3$
C. β_2-Adrenergic agonists
D. Hypertonic Na^+ solution (if hyponatremic)

Removal of the excess K^+

A. Diuretics
B. Cation-exchange resin (Kayexalate)
C. Hemodialysis or peritoneal dialysis

The protective effect of Ca^{2+} administration begins within minutes but is relative short-lived. Thus, Ca^{2+} is used only in patients with severe K^+ intoxication, who cannot wait the 30 to 60 min before glucose and insulin begin to act.

The usual dose is 10 mL (1 ampul) of a 10% calcium gluconate solution infu slowly over 2 to 3 min under electrocardiographic monitoring.* This dose ca repeated after 5 min if the electrocardiographic changes persist. Ca^{2+} should be used only when absolutely necessary (as with loss of P waves or widening QRS complex) in patients taking digitalis, because hypercalcemia, like hypo can precipitate digitalis toxicity.

Insulin and Glucose

Increasing the availability of insulin lowers the plasma K^+ concentration by driving K^+ into cells.[58,124,252] This effect is mediated by increased activity of the Na^+-K^+ ATPase pump, particularly the α (2+) isoform in skeletal muscle.[253,254] and[255]

Plasma insulin levels can be increased by administering insulin (10 units of insulin with 30 to 50 g of glucose to prevent hypoglycemia) or by enhancing endogenous insulin release by infusing glucose alone (50 mL of a 50 perce glucose solution given intravenously). This regimen usually lowers the plasma K^+ concentration by 0.5 to 1.5 meq/L, an effect that begins within 1 h and may many hours.[115] Plasma insulin levels are higher and the reduction in the plasma K^+ concentration more pronounced with the insulin-glucose combination.[124] However, insulin-glucose can cause symptomatic hypoglycemia unless an adequate a glucose is given both initially and as an ongoing dextrose infusion to preve reduction in the plasma glucose concentration.[115,256]

Insulin alone may be sufficient in diabetic patients who are already hypergl while insulin-glucose can be given if the plasma glucose concentration is n normal. Care must be taken to avoid an elevation in the plasma glucose concentration, since the ensuing elevation in the plasma osmolality can exa the hyperkalemia (see Fig. 28-2).

At least in end-stage renal failure, insulin and glucose more predictably lov plasma K^+ concentration than either $NaHCO_3$ or a β-adrenergic agonist.[115,124,257] Although renal failure is associated with resistance to the hypoglycemic effect of insulin, the ability of insulin to increase Na^+-K^+-ATPase activity and therefore to promote K^+ entry into the cells is preserved.[121,122]

Sodium Bicarbonate

Whereas metabolic acidosis can result in the release of K^+ from cells, raising the pH with $NaHCO_3$ drives K^+ into the cells.[53] In addition to the pH change, the elevation in the plasma HCO_3^- concentration appears to directly contribute to th

effect (by an unknown mechanism[258]); consequently, the infusion of $NaHCO_3$ will lower the plasma K^+ concentration and alleviate the signs of hyperkalemia, particularly in a patient with metabolic acidosis.[258,259] This effect begins within 30 to 60 min and may persist for many hours.

There is, however, a limitation to the administration of sodium bicarbonate. patients with severe hyperkalemia have advanced renal failure, which preve excretion of the excess potassium. When used as monotherapy in this settir sodium bicarbonate generally produces *little acute reduction* in the plasma potassium concentration.[113,257,260,261] The plasma K^+ concentration generally falls by no more than 0.5 meq/L in the first 6 h, half of which is due to dilut the administered fluid. However, most of the patients in these studies had l metabolic acidosis; a potassium-lowering effect would be expected in patie moderate to severe acidemia.

The usual dose is 44 to 50 meq of $NaHCO_3$ infused slowly over 5 min; this dose ca be repeated within 30 min, if necessary. Alternatively, an ampule of $NaHCO_3$ can be added to a glucose and saline solution.

Administration of a hypertonic bicarbonate solution may have an additional advantage in hyponatremic patients, since raising the plasma Na^+ concentration can reverse the electrocardiographic effects of hyperkalemia.[245,262] Both an increase in the rate of membrane depolarization and a fall in the plasma potassium con by dilution may contribute to this effect.[262]

β_2-Adrenergic Agonists

Like insulin, the β_2-adrenergic receptors drive K^+ into the cells[71,72] and[73] by increasing Na^+-K^+-ATPase activity.[4] One consequence of this relationship is that epinephrine released during a stress response can cause transient hypokal variety of clinical settings (see Chap. 27). There is less information on the use of β_2-agonists to treat hyperkalemia, but preliminary results suggest that albuter 20 mg by nebulizer in 4 mL of saline over 10 min or 0.5 mg intravenously) c the plasma K^+ concentration by 0.5 to 1.5 meq/L.[113,263,264] The peak effect is seen within 30 min with intravenous infusion, but is delayed for 90 min with inhalation.[264] Tachycardia and precipitation of angina pectoris are potential s effects; as a result, these agents should be avoided in patients with active disease.

As with sodium bicarbonate, there is a limitation to the use of epinephrine i advanced renal failure, since there is a blunted hypokalemic response in th setting.[124,265] This relative resistance appears to reflect an increased sensi the α-adrenergic actions of epinephrine; the α-receptors act to drive K^+ out of the cells (see page 375), thereby counteracting the reverse effect of β_2-stimulation.[265] β -adrenergic responsiveness is generally preserved, although four of ten p one study had less than a 0.5-meq/L fall in the plasma potassium concentra

the administration of albuterol.[266]

Thus, albuterol is the adrenergic agent of choice for severe hyperkalemia i stage renal disease. It should be given in combination with insulin plus glu maximize the reduction in the plasma potassium concentration.[266]

The effects of insulin, $NaHCO_3$, and β_2 agonists are transient, as the K^+ is driven into the cells reenters the extracellular fluid after several hours. Th measures are usually followed by diuretics, cation-exchange resins, or dial remove the excess K^+ from the body. In addition, a cation-exchange resin alone be sufficient in a patient with mild, asymptomatic hyperkalemia.

Diuretics

Loop or thiazide-type diuretics increase urinary K^+ excretion primarily by enhancing the flow rate to the K^+ secretory site in the distal nephron (see Chap. 15). These agents are not widely used in the treatment of acute hyperkalemia, since pa with this problem often have impaired renal function and are unlikely to res diuretic therapy with a significant rise in K^+ excretion. Diuretics are, however, usef in chronic hyperkalemia due to hypoaldosteronism,[267] heart failure (where they will also treat the fluid overload), or a selective K^+ secretory defect.[230]

Cation-Exchange Resin

The major cation-exchange resin available is sodium polystyrene sulfonate (Kayexalate), prepared in the sodium phase. In the gut, this resin takes up K^+ (and, to lesser degrees, Ca^{2+} and Mg^{2+}) and releases Na^+. Each gram of resin may bind as much as 1 meq of K^+ and release 1 to 2 meq of Na^+.[268,269]

When administered orally, 20 g of resin should be given with 100 mL of a 20 sorbitol solution to prevent constipation. This can be repeated every 4 to 6 necessary. Lower doses (5 g, two or three times a day) are generally well t and can be used to treat chronic hyperkalemia that cannot be controlled by means.

In patients who cannot take oral fluids, the resin can be given as a retentic In this situation, 50 g of resin is mixed with 50 mL of 70% sorbitol plus 100 of tap water and kept in the colon for at least 30 to 60 min and preferably 2 The colon should then be irrigated with a non-sodium-containing solution to possible colonic mucosal injury.[270] Each enema can lower the plasma K^+ concentration by as much as 0.5 to 1.0 meq/L. The enemas can be repeated to 4 h if necessary.

The major side effects of sodium polystyrene sulfonate are nausea, constip hypokalemia (due to excessive use), and retention of the Na^+ that has been exchanged for K^+. In patients with oliguric renal failure or those with cardiac disease, for example, enough Na^+ may be retained to precipitate pulmonary

edema.[268]

Intestinal necrosis is a potential complication, leading to severe abdominal a usual requirement for surgery. The risk appears to be greatest, approach percent of cases, when the resin is given with sorbitol within the first week surgery.[271,272] and[273] At least two factors are thought to increase the susceptibility to intestinal necrosis in this setting:

1. Decreased colonic motility, due to postoperative ileus and/or the admini of opiates, increases the duration of drug contact with the intestinal mu
2. Hypertonic sorbitol may directly damage the intestinal mucosa.

It has been suggested that cleansing enemas given before and after resin e may be protective by preventing drug retention in the intestinal lumen.[272]

Dialysis

In almost all patients, the conservative measures described above will reve hyperkalemia. However, when these measures are ineffective or severe hyp is present, either hemodialysis or peritoneal dialysis can be used. Hemodia preferred, because the rate of K^+ removal is many times faster than with peritone dialysis.[274] Dialysis is particularly important in patients with acute renal fail are hypercatabolic, as cell breakdown can result in the release of large qua K^+ into the extracellular fluid.[66]

Summary

One report found the following mean changes in the plasma K^+ concentration at 1 h after the institution of each particular therapy in hyperkalemic patients with stage renal disease:[257]

- No change with sodium bicarbonate in patients with little or no metaboli acidosis; thus, the main indication for bicarbonate therapy is the preser moderate to severe acidemia.
- A 0.3-meq/L reduction with epinephrine; a greater response, similar to t insulin and glucose, is typically seen with albuterol, which has no α-adr activity.
- A 0.85-meq/L reduction with insulin and glucose.
- A 1.3-meq/L reduction with hemodialysis.

Hyporeninemic Hypoaldosteronism

The proper therapy of hyporeninemic hypoaldosteronism, the most common unexplained hyperkalemia in adults, varies with the underlying etiology. If i induced, the offending agent should be discontinued, if possible.

Fludrocortisone, a synthetic mineralocorticoid, is in theory the mainstay of hyporeninemic hypoaldosteronism, since it corrects the mineralocorticoid d As much as 0.2 to 1.0 mg/day may be required (in comparison to 0.05 to 0.1 in primary adrenal insufficiency).[134,137] This supraphysiologic dose probably reflects aldosterone resistance induced by the underlying renal disease.

Although it can restore balance, fludrocortisone is rarely used in most patients because it can exacerbate preexistent hypertension or edema induced by th underlying renal insufficiency. Control of the hyperkalemia can usually be a by the combination of a low-K^+ diet plus a loop of thiazide-type diuretic to increa urinary K^+ losses.[134,267]

PROBLEMS

28-1A 62-year-old man with mild chronic renal failure (plasma creatini concentration equals 2.1 mg/dL) and normokalemia is started on a low diet for hypertension. Two weeks later, he notices that he is unable to himself out of a chair. On physical examination, slightly decreased sk and marked proximal muscle weakness are found. The ECG reveals pe waves and some widening of the P wave and QRS complex. The follow blood test results are obtained:

Plasma $[Na^+] = 130$ meq/L
$[K^+] = 9.8$ meq/L
$[Cl^-] = 98$ meq/L
$[HCO_3^-] = 17$ meq/L
[Creatinine] = 2.7 mg/dL
Arterial pH = 7.32

a. **What are the most likely factors responsible for the elevation in th plasma K^+ concentration?**
b. **How do you know this is not pseudohyperkalemia?**
c. **How would you treat the hyperkalemia?**
d. **If the plasma K^+ concentration were only 6.4 meq/L and there were n changes in muscle strength or the ECG, how would you lower the p K^+ concentration?**

28-2A 54-year-old man with no prior medical history complains of chro fatigue. The positive physical findings include a blood pressure of 10 increased skin pigmentation. The skin turgor is relatively normal. The laboratory data are as follows:

Plasma $[Na^+]$	=	130 meq/L	BUN	=	28 mg/dL
$[K^+]$	=	6.8 meq/L	[Creatinine]	=	1.2 mg/dL
$[Cl^-]$	=	100 meq/L	Urine $[Na^+]$	=	50 meq/L
$[HCO_3^-]$	=	20 meq/L	$[K^+]$	=	34 meq/L
[Glucose]	=	90 mg/dL	U_{osm}	=	550 mosmol/kg

The electrocardiogram shows mild peaking of the T waves in the prec

leads. An infusion of glucose and insulin in appropriate proportions re an episode of hypoglycemia.

a. **Is the urine K^+ concentration of 34 meq/L helpful in determining the correct diagnosis?**

b. **What is the most likely diagnosis?**

c. **How would you treat this patient?**

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Footnotes

* A similar effect can be caused by repeated fist clenching during blood dra[44] This is an artifact of blood drawing, however, since it is limited to that fore

† One exception to the generalized reduction in Na^+-K^+-ATPase activity in uremia occurs in the renal cortical collecting tubule, where Na^+-K^+-ATPase activity is increased and enhanced in these cells because of the need to increase K^+ secretion per nephron.[29]

‡ The plasma renin activity is typically increased, not reduced, with these since angiotensin II normally decreases renin release by feedback inhibitio

¶ Although CYP11B1 (11β-hydroxylase) deficiency also decreases aldostero production by impairing the conversion of DOC to corticosterone, there is a of DOC, leading to signs of mineralocorticoid excess (hypertension and hypokalemia), not mineralocorticoid deficiency.[180187]

** Most hyperkalemic patients with lupus nephritis have either hyporeninem hypoaldosteronism or advanced renal failure, not an isolated defect in K^+ excretion.[231]

†† The primary event during repolarization is movement of K^+ out into the cells; this occur passively down the favorable electrochemical gradient (cell interior now po that is created during depolarization (see page 823). The rate of repolarization is therefore in part dependent upon the permeability of the cell membrane, which appears to vary directly with the plasma K^+ concentration.[236238] Thus, hyperkalemia increases K^+ permeability and consequently augments the rate of repolarization.

‡‡ Depolarization is mostly due to a marked elevation in the permeability of the cell membrane, resulting in the rapid entry of Na^+ into the cell.[232240241] As described above, the fall in resting potential induced by hyperkalemia inact membrane Na^+ channels, thereby slowing the rate of depolarization.

¶¶ Ca^{2+} should not be given in HCO_3^--containing solutions, since this combinatio can result in the precipitation of the insoluble salt $CaCO_3$.

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Chapter Twenty-Nine
Answers to the problems

CHAPTER 1

1-1 Excretion equals filtration minus net reabsorption. This simple relations often overlooked clinically. Acute renal failure, for example, is characterize glomerular filtration rate. An increase in urine output in this setting is usua assumed to represent an elevation in filtration and therefore improved rena However, a decrease in reabsorption with no change in filtration also can a the increase in output. These possibilities can be distinguished by followin plasma creatinine concentration, an indirect reflection of the glomerular filt (see Chap. 2). If filtration has risen to an important degree, more creatinine v filtered and excreted, resulting in a reduction in the plasma creatinine conc toward baseline. In contrast, this parameter will remain stable or continue t there has only been less reabsorption.

CHAPTER 2

2-1 The glomerular filtration rate cannot be estimated from the plasma creat concentration in this setting, since the patient is not in a steady state.

2-2

The administration of dopamine will

a. Increase renal blood flow by diminishing renal vascular resistance.
b. Produce no change or a lesser increase in glomerular filtration rate, sir dilatation of the efferent arteriole will tend to lower the intraglomerular thereby counteracting the effects of afferent dilatation and enhanced fl

c. Reduce the filtration fraction, because less of the plasma delivered to t glomeruli is now filtered.
d. Lower the albumin concentration in the peritubular capillary, since a lov filtration results in less hemoconcentration of the fluid leaving the glom This response may in part explain the ability of dopamine to decrease p Na^+ reabsorption (see page 208).

2.3

a. By preferentially dilating the efferent arteriole, an angiotensin converti enzyme inhibitor will tend to lower the intraglomerular pressure. In com dilatation of the afferent arteriole by other antihypertensive agents allo of the systemic pressure to be transmitted to the glomeruli, thereby mai the intraglomerular pressure despite the reduction in systemic pressure

b. Intraglomerular "hypertension" has been thought to be an important mec secondary glomerular injury in a variety of slowly progressive renal dis including diabetic nephropathy. Thus, the reduction in intraglomerular p with a converting enzyme inhibitor might be beneficial in the long term.[1]

2-4

a. The creatinine clearance can be estimated from

$$C_{cr}, mL/min = \frac{U_{cr} \times V}{P_{cr}}$$
$$= \frac{125\,mg/dL}{3.5\,mg/dL} \times \frac{800\,mL/day}{1440\,min/day}$$
$$= 20\,mL/min$$

b. The total creatinine excretion is 1000 mg or 12.5 mg/kg/day. This proba represents an incomplete collection (and therefore an underestimate of creatinine clearance), since a normal man should excrete 20 to 25 mg/k On the other hand, the creatinine clearance itself (even when performe optimal conditions) overestimates the true glomerular filtration rate in p with renal disease, as a result of increased creatinine secretion by the cation secretory pump in the proximal tubule.

CHAPTER 3

3-1 Because of the phenomenon of glomerulotubular balance, an increase ir glomerular filtration rate without change in volume will

a. Have no effect on fractional Na^+ reabsorption.

b. Increase absolute Na^+ reabsorption, since a constant fraction of a larger lo being reabsorbed.

3-2 Because of diminished activity of the Na^+-H^+ antiporter, parathyroid hormone should

a. Decrease proximal HCO_3^- reabsorption, which is largely mediated by the Na H^+ exchanger (see Chap. 10).

b. Reduce both the passive and active transport of Cl^-. In most clinical subjects, the former process results from the favorable concentration gradient genera

the preferential reabsorption of HCO_3^- in the early proximal tubule, and the latter process is mediated in part by a Cl^--formate exchanger that operates in parallel with the Na^+-NH_4^+ antiporter.

c. Diminish proximal water reabsorption, which passively follows the osmo gradient established by NaCl and $NaHCO_3$ transport.

3-3

a. Volume depletion leads to enhanced proximal Na^+ and water reabsorption. The increased removal of water raises the tubular fluid urea concentration, in enhanced passive urea reabsorption, a fall in urea excretion, and a r BUN.

b. The glomerular filtration rate is probably normal or near normal, since t plasma creatinine concentration is unchanged.

c. Both increased urate reabsorption (promoted by enhanced Na^+ reabsorption) and reduced secretion (due to competition from the ketoacid anions) lea fall in urate excretion and hyperuricemia.

3-4

a. The decrease in the plasma HCO_3^- concentration leads to reductions in the filtered HCO_3^- load and therefore proximal HCO_3^- reabsorption. This will be associated with a fall in proximal NaCl reabsorption, since HCO_3^- reabsorption by Na^+-H^+ exchange promotes both passive and active transport (the latter in part via the Cl^--formate exchanger that operates in parallel with the Na^+-H^+ antiporter).

b. Proximal citrate reabsorption will be increased; the fall in pH associate metabolic acidosis appears to act in part by converting filtered $citrate^{3-}$ into more easily reabsorbed $citrate^{2-}$.

c. Stone formation is increased in distal renal tubular acidosis (see page 510). Several factors contribute to this complication, including the high urine (which promotes calcium phosphate precipitation) and the reduction in c excretion (since citrate is normally a potent inhibitor of calcium stone f by forming a nondissociable but solute complex with calcium). Bone buf the excess acid also may play a role by increasing calcium release from and subsequent urinary calcium excretion.

CHAPTER 4

4-1 NaCl reabsorption without water in the medullary ascending limb and ur movement from the medullary collecting tubule into the interstitium are the factors in the generation of the medullary osmotic gradient. The vasa recta

capillaries also play an important role by minimizing the removal of the exc

4-2 NaCl reabsorption without water in the medullary ascending limb has tw
1 the medullary interstitium becomes hyperosmotic, and 2 the tubular

fluid becomes dilute. Thus, this step plays a central role in both concentrat
dilution.

NaCl reabsorption without water in the cortical ascending limb and distal tu
further lowers the urine osmolality and contributes to urinary dilution. Sinc
blood flow is so high, however, the cortical interstitium does not become
hyperosmotic and urinary concentration is not directly affected.

4-3

a. Concentrating ability will be increased as a result of the enhanced accu
of interstitial solute.
b. Reabsorption throughout the thick ascending limb is flow-dependent, be
limited by the maximum tubular fluid-to-plasma concentration gradient fo
Na^+
that can be achieved. It may be, for example, that the minimum tubular
Na^+
concentration that can be achieved by the end of the cortical thick asce
limb is about 75 meq/L. Thus, increased NaCl reabsorption in the medul
aspect will lead to decreased reabsorption in the cortical aspect, since
limiting gradient cannot be exceeded. The net effect is that ADH has
redistributed some NaCl transport from the cortex in the medulla; thus,
concentrating ability is increased with no change in total NaCl reabsorption.
Na^+

4-4 From the answers to Prob. 4-2, a diuretic that inhibits both concentratio
dilution acts in the medullary thick ascending limb. In comparison, a diureti
impairs dilution but does not affect concentration probably acts in the corti
ascending limb or the distal tubule. Thus, the effects of diuretics on concer
and dilution are one of the methods that have been used to determine their
action within the nephron (see Chap. 15).

4-5 The tubular fluid leaving the proximal tubule is isosmotic to plasma. In t
descending limb, osmotic equilibration with the concentrated interstitium le
water reabsorption. Thus, any factor that decreases medullary tonicity will
reduce descending limb water transport. This occurs with an osmotic diures
because the associated increase in medullary blood flow washes out some
medullary solute. A similar effect should occur in central diabetes insipidus
absence of ADH will diminish interstitial urea accumulation (see Figs. 4-10 and 4-11).

4-6 Urea generation and subsequent excretion are diminished on a low-prot
Thus, less urea will accumulate in the interstitium, resulting in a mild decre
concentrating ability.
2

CHAPTER 6

6-1 Renin secretion is reduced by an autonomous adrenal adenoma, probabl

because of the volume expansion induced by the initial Na^+ and water retention. In comparison, renin release is enhanced by volume depletion, and the increa formation of angiotensin II is responsible for the secondary hyperaldosteron

6-2 The secretion of ADH is stimulated by a rise in the effective P_{osm}. Since urea is an ineffective osmole, an elevation in the BUN does not increase the effect P_{osm} or ADH release.

6-3 The loss of water in the urine will initially raise the P_{osm}, resulting in a potent stimulus to thirst. As a result, patients who lack ADH remain in near-normal balance despite urinary losses that can exceed 10 L/day.

6-4 The major stimuli to renal calcitriol synthesis are parathyroid hormone a hypophosphatemia. Thus, ingestion of a high-phosphate diet and hypoparat (either primary or induced by a high-calcium diet) will lower calcitriol produ Phosphate retention is also largely responsible for the initial fall in calcitri patients with renal insufficiency. This can be reversed, however, if phospha is restricted, thereby diminishing phosphate levels and allowing calcitriol s increase toward normal.

6-5

a. A Na^+ load without water will cause both volume expansion and an eleva the plasma Na^+ concentration and P_{osm}. As a result, ANP and ADH levels will rise and aldosterone secretion will fall (see page 278 for a review of the differences between volume regulation and osmoregulation).
b. A water load will be rapidly excreted, since the ensuing fall in P_{osm} will diminish ADH release, resulting in the excretion of a dilute urine. This process i efficient that ANP and aldosterone secretion will not change.
c. Isotonic saline will expand volume without affecting osmolality. Thus, Al rise, aldosterone will fall, and ADH will be unaffected.
d. Isosmotic volume loss will enhance the secretion of aldosterone and AD latter via the aortic and cardiac volume receptors) and diminish the rele ANP.

6-6 Hypercalciuria may transiently lower the plasma Ca^{2+} concentration. However, this will stimulate the secretion of PTH, which then restores normocalcemia increasing both bone resorption and, via enhanced calcitriol synthesis, inte Ca^{2+} absorption. In the new steady state, the increment in Ca^{2+} excretion will be balanced by more efficient Ca^{2+} absorption.

6-7 Aldosterone does not raise the plasma Na^+ concentration because there will be equivalent retention of water in the collecting tubules if ADH is present. If A absent, the ensuing small elevation in the plasma Na^+ concentration will stimulate both ADH release and thirst, also leading to water retention.

6-8 Renal prostaglandins play an important role in maintaining renal perfusi conditions in which there are high levels of the vasoconstrictors angiotensi norepinephrine. This can occur with a low-salt diet, heart failure, or volume due to severe vomiting (*a*, *d*, and *e*). In these settings, a nonsteroidal anti-inflammatory drug can induce renal ischemia and a fall in the glomerular fil rate.

CHAPTER 7

7-1 The plasma Na^+ concentration is the primary determinant of the P_{osm} since Na^+ salts are the major extracellular osmoles. There is, however, no predic relationship between the plasma Na^+ concentration and the extracellular volume: The latter is determined by the total amount of Na^+ and of water present, whereas the former is determined by the ratio between the amounts of solute ($Na^+ + K^+$) and water that are present.

7-2 The addition of glucose to the extracellular fluid, as in uncontrolled dia mellitus, will (a) raise the P_{osm} and (b) cause water to move out of the cells, the increasing the extracellular volume, reducing the intracellular volume, and the plasma Na^+ concentration (by dilution).

7-3 The P_{osm} can be calculated from

$$P_{osm} \cong 2 \times \text{plasma } [Na^+] + \frac{BUN}{2.8} + \frac{[glucose]}{18}$$

$$290 \cong 250 + \frac{28}{2.8} + \frac{[glucose]}{18}$$

$$[Glucose] \cong 540\ mg/dL$$

7.4

a. An increase in arterial blood pressure will have little direct effect on th volume, because of autoregulation of the capillary hydraulic pressure b precapillary sphincter.

b. A decrease in venous pressure will reduce capillary hydraulic pressure, promoting the movement of interstitial fluid into the capillary and plasm expansion.

c. A mild reduction in the plasma albumin concentration should have little the plasma volume. The transcapillary oncotic pressure gradient will re relatively stable in this setting as a result of a parallel decline in the ir oncotic pressure. Both washout of interstitial proteins by increased lym flow and diminished albumin movement across the capillary wall (due to hypoalbuminemia) will contribute to this response.

CHAPTER 8

8-1

a. An acute myocardial infarction will initially diminish the effective circula volume (because of the fall in cardiac output) and therefore urinary Na^+ excretion, without affecting either the plasma volume or total extracellu volume.

b. A high-Na^+ diet will expand the plasma, extracellular, and effective circul volumes and increase urinary Na^+ excretion.

c. The retention of ingested water will also expand the plasma, extracellul effective circulating volumes and increase urinary Na^+ excretion.

8-2 Diuretic-induced hypovolemia enhances the release of renin. The ensuir increase in the formation of angiotensin II will tend to raise the blood press thereby minimizing the hypotensive effect of the diuretic.

8-3 (d) The rate of urinary Na^+ excretion is generally the best estimate of the effective circulating volume, since it reflects the physiologic assessment of kidney's systemic hemodynamics. A low rate of Na^+ excretion (urine Na^+ concentration below 25 meq/L in the absence of marked polyuria) is genera diagnostic of volume depletion unless there is selective renal ischemia due bilateral renal artery stenosis or acute glomerular disease. The cardiac out plasma volume, and systemic blood pressure are less accurate. For exampl blood pressure may be prevented by the compensatory rise in sympathetic t the other hand, the cardiac output may be misleadingly elevated if there ar arteriovenous fistulas or vasodilatation, as occurs in hepatic cirrhosis.

8-4 In the steady state, Na^+ intake and excretion are equal even in a patient on diuretic therapy. In this setting, the natriuretic effect of the diuretic is cour by enhanced Na^+ reabsorption, which may be induced by the compensatory increases in angiotensin II, aldosterone, and norepinephrine production. Th steady state is generally attained within 2 weeks, as long as diuretic dose dietary Na^+ intake remain relatively constant (see page 453).

8-5

a. Isotonic saline will expand volume without affecting osmolality. Thus, Al rise, aldosterone will fall, and ADH will be unaffected. The net effect is excess Na^+ will appropriately be excreted in a relatively isosmotic urine.

b. A water load will be rapidly excreted, as the ensuing fall in P_{osm} will diminish ADH release. This will lead to a fall in U_{osm} with little change in the rate of Na^+ excretion (although the urine Na^+ concentration will fall by dilution).

c. A Na^+ load without water will cause both volume expansion and an eleva the plasma Na^+ concentration and P_{osm}, thereby activating both the volume regulatory and osmoregulatory systems. As a result, ANP and ADH level

rise and aldosterone secretion will fall. In this setting, both the urine Na^+ concentration and U_{osm} will be elevated, allowing the excretion of the excess Na^+ with little water loss.

d. Half-isotonic saline will cause volume expansion and hypoosmolality. The ANP and Na^+ excretion will rise, while aldosterone, ADH, and the U_{osm} will fall. The net effect is that the excess Na^+ will appropriately be excreted in a dilute urine.

CHAPTER 9

9-1 The loss of isosmotic diarrheal fluid will (*a*) reduce the effective circulating volume, (*b*) diminish urinary Na^+ excretion, (*c*) and (*d*) have no direct effect on the P_{osm} or the plasma Na^+ concentration, and (*e*) and (*f*) increase ADH release and therefore the U_{osm}. The ingestion of water in this setting will result in water retention (because of the high ADH levels) and hyponatremia.

9-2 The $Na^+ + K^+$ concentration in the fluid that is lost is less than that in the in this example. As a result, water is being lost in excess of effective solute the plasma Na^+ concentration is generally determined by

$$\text{Plasma } [Na^+] \cong \frac{Na_e^+ + K_e^+}{TBW}$$

the plasma Na^+ concentration will rise.

9-3 There is no predictable relationship between the plasma Na^+ concentration (which is regulated by the osmoregulatory pathway) and urinary Na^+ excretion (which is determined by changes in the effective circulating volume).

9-4 Two factors contribute to the inability to excrete water normally in volume depletion: increased release of ADH and reduced fluid delivery to the diluting segment in the ascending limb of the loop of Henle because of enhanced proximal Na^+ and water reabsorption.

9-5 The minimum U_{osm} is unaffected by beer drinking. However, this is also dependent upon the rate of solute excretion. Since K^+, Na^+, and urea excretion are low in a subject ingesting only beer, solute excretion will also be low. Suppose, for example, that the U_{osm} can be lowered to 75 mosmol/kg and that the P_{osm} is 300 mosmol/kg. The maximum urine output in this setting will be 10 liters in a normal subject excreting 750 mosmol of solute per day, but only 3 liters in a beer drinker excreting 225 mosmol of solute. The respective CH_2O will be as follows:

$$C_{H_2O} = V\left(1 - \frac{U_{osm}}{P_{osm}}\right)$$
$$= 10\left(1 - \frac{75}{300}\right)$$
$$= 7.5 \text{ liters in a normal subject}$$
$$C_{H_2O} = 3\left(1 - \frac{U_{osm}}{P_{osm}}\right)$$
$$= 2.25 \text{ liters in a beer drinker}$$

9.6

a. Although the U_{osm} is the same in both examples, there are important differ in the rate of electrolyte-free water reabsorption:

$$T^e_{C_{H_2O}} = V\left[\left(\frac{U_{Na^+} + K^+}{P_{Na^+}}\right) - 1\right]$$

In the patient with the syndrome of inappropriate ADH secretion,

$$T^e_{C_{H_2O}} = 1\left[\left(\frac{130}{130}\right) - 1\right]$$
$$= 0$$

Thus, there is no electrolyte free water reabsorption in this setting. In comparison, in the patient with heart failure,

$$T^e_{C_{H_2O}} = 1\left[\left(\frac{60}{130}\right) - 1\right]$$
$$= -540\,\text{mL}$$

b. At similar levels of water intake, the patient with heart failure will be le to retain water and become hyponatremic because the kidney is excretir mL of free water each day (a minus value for free water reabsorption re free water excretion).

CHAPTER 10

10-1 Buffers minimize changes in the free H^+ concentration by appropriately taking up ($H^+ + Buf \rightarrow HBuf$) or releasing ($HBuf \rightarrow H^+ + Buf$) H^+ ions. The efficacy of a buffer is determined by the quantity of buffer present and the relation of the pK_a of the buffer to the pH of the solution. In addition, the ability to increase CO_2 the effectiveness of the H_2CO_3–CO_2 buffer system.

10-2 The fall in the plasma HCO_3^- concentration is due to the different rates with which the administered HCO_3^- enters the different fluid compartments. The adde HCO_3^- is initially limited to the vascular space, resulting in a large increase plasma HCO_3^- concentration. The HCO_3^- then equilibrates throughout the total extracellular fluid (within 15 min) and subsequently with the cell buffers (a that reaches completion within 2 to 4 h). Both of these processes reduce th

HCO_3^- concentration toward the baseline level. As discussed in Chap. 11, acid-base balance is restored in this setting by the excretion of the excess HCO_3^-.

This time-related effect of exogenous HCO_3^- becomes clinically important when HCO_3^- is given to treat metabolic acidosis (see Chap. 19). The increment in the plasma HCO_3^- concentration and therefore in the extracellular pH will be grea measured within 15 min than after equilibration with the cell buffers has oc 2 to 4 h. Thus, it should not be assumed that early measurements (which w overestimate the true elevation in the plasma HCO_3^- concentration) represent the steady-state condition.

10-3 The quantity of available extracellular and intracellular buffers will det how much of a reduction in pH will occur. Buffering capacity is best estimat the initial plasma HCO_3^- concentration. Patients with a low baseline level due t preexisting metabolic acidosis are more prone to a major reduction in pH fo acid load.

CHAPTER 11

11-1 The primary adaptive response of the kidney to an acid load is increas H^+ production and excretion. As a result, reduced titratable acid excretion will effect on acid-base balance, since enhanced NH_4^+ excretion can compensate for this defect. In comparison, the ability to augment titratable acid excretion i Thus, a marked decline in NH_4^+ excretion (as occurs in advanced renal failure) v lead to H^+ retention and metabolic acidosis.

11-2 The buffering of HCl and H_2SO_4 by $NaHCO_3$ results in the respective generation of NaCl and Na_2SO_4. When the NaCl is presented to the distal nephr the reabsorption of Na^+ will be followed by that of Cl^-. In comparison, SO_4^{2-} is a nonreabsorbable anion; thus, the distal reabsorption of Na^+ creates a greater lumen-negative potential difference that promotes the luminal accumulation of H^+. The relatively low luminal Cl^- concentration in this setting also may contribute by generating a more favorable gradient for Cl^- to be cosecreted with H^+. The net effect is increased acid excretion and therefore a lesser degree of metabolic acid H_2SO_4 is given.

11-3

a. Net acid excretion is equal to the following:

$$\text{Net acid excretion} = NH_4^+ + \text{titratable acidity} - HCO_3^-$$

$$= 80 \text{ meq/day in the normal subject}$$

$$= 215 \text{ meq/day in the patient with metabolic acido}$$

b. In comparison, total H^+ excretion is equal to

$$\begin{aligned}\text{Total acid excretion} &= HCO_3^- \text{ reabsorption} + NH_4^+ + \text{titratable acidity}\\ &= 4320\ (180 \times 24) + 50 + 30\\ &= 4400 \text{ meq/day in the normal subject}\\ &= 1080\ (180 \times 6) + 140 + 75\\ &= 1295 \text{ meq/day in the patient with metabolic acidosis}\end{aligned}$$

Note that net acid excretion is appropriately increased in metabolic acidosi though total H^+ secretion is actually reduced as a result of the marked reduct the filtered HCO_3^- load.

11-4 At a urine pH of 5.80 with 60 mmol of phosphate,

$$5.80 = 6.80 + \log\frac{x}{60 - x}$$

$$[HPO_4^{2-}] = x = 5.45 \text{ mmol}$$

$$[H_2PO_4^-] = 60 - x = 54.55 \text{ mmol}$$

In the filtrate, however, the initial pH was 7.40, similar to that in the plasm

$$7.40 = 6.80 + \log\frac{x}{60 - x}$$

$$[HPO_4^{2-}] = 48 \text{ mmol}$$

$$[H_2PO_4^-] = 12 \text{ mmol}$$

Thus, 42.55 mmol of HPO_4^{2-} (48-5.45) has been converted to $H_2PO_4^-$ by buffering; this is the quantity of titratable acidity excreted as $H_2PO_4^-$.

Titratable acidity is measured by the number of milliequivalents of NaOH th be added to an acid urine to return the pH to 7.40. NH_4^+ excretion is not included in this titration, since the pK_a of the NH_3-NH_4^+ system is 9.0. Thus, raising the urine pH from 5.80 to 7.40 will have little effect on the NH_4^+/NH_3 ratio.

11-5 The metabolic alkalosis persists in this setting because both volume ar depletion enhance HCO_3^- reabsorption, thereby preventing the excretion of the excess HCO_3^- (see Chap. 18).

CHAPTER 12

12-1 Aldosterone deficiency initially decreases urinary K^+ excretion. The ensuing rise in the plasma K^+ concentration, however, is a direct stimulus to distal K^+ secretion, eventually leading to a new steady state in which intake and out again equal (see Fig. 12-10).

12-2 Increasing Na^+ intake will enhance distal flow, resulting in augmented K^+ secretion and hypokalemia in patients with primary hyperaldosteronism. K^+ wasting does not occur in normal subjects, because the high Na^+ intake suppresses the

release of aldosterone.[5]

12-3 Urinary K^+ excretion should be helpful in this setting, being less than 25 meq/day with extrarenal losses (or with a diuretic when the drug effect has worn off) but above this level with renal K^+ wasting.

12-4 Spontaneous K^+ wasting and hypokalemia do not occur with effective volume depletion, because the decline in distal flow counteracts the stimulatory effect of secondary hyperaldosteronism. If, however, distal flow is augmented with a thiazide-type diuretic, then urinary K^+ losses will increase and the plasma K^+ concentration may fall.

12-5 (*a*, *c*, and possibly *b*). A converting enzyme inhibitor diminishes the release of aldosterone; a β -adrenergic blocker impairs the entry of K^+ into cells after a K^+ load; and glucose can, in diabetics, raise the plasma K^+ concentration by elevating both the plasma glucose concentration and plasma osmolality (see Fig. 12-3).

12-6 There will be little direct effect on K^+ excretion, since the stimulatory effect of the high distal flow is counteracted by removal of ADH, which normally

promotes K^+ secretion. In some patients, however, renal K^+ wasting can occur because the urine K^+ concentration cannot be reduced below 5 to 10 meq/L. Thus, a urine output of 10 L/day can lead to obligatory K^+ losses of 50 to 100 meq/day.[6]

CHAPTER 14

14-1

a. The shock state is probably due to the sequestration of fluid in the infarcted bowel.

b. Fluid replacement should proceed with isotonic saline. Blood is not necessary initially, since the hematocrit of 53 percent suggests hemoconcentration rather than loss of fluid from the vascular space.

c. The high urine Na^+ concentration indicates that this is diuresis, not a water diuresis as in diabetes insipidus (see Chap. 24 for a discussion of the approach to the polyuric patient). In this patient with a positive balance of 7 liters prior to surgery, it is likely that the diuresis represents an appropriate attempt to excrete the excess salt. Nevertheless, Na^+ wasting of this degree is extremely rare.

d. The correct therapy is to administer replacement fluids (such as half-isotonic saline at 50 to 100 mL/h), while allowing the patient to develop negative balance. If the diuresis is appropriate, it will cease spontaneously without the patient developing any of the signs of volume depletion, such as diminished turgor or hypotension.

14-2 For each liter of water lost, about 60 percent comes from the cells and

percent from the extracellular fluid. Although the water is initially lost from extracellular fluid, the ensuing rise in the P_{osm} causes a proportionate volume of wate out of the cells. In comparison, each liter of isotonic saline loses entirely from the extracellular fluid, producing a greater reduction in the extracellular vo possibly also in the arterial blood pressure.

14-3 There is no role for the use of pure dextrose solutions in the treatment hypovolemic shock, since only 40 percent of the fluid will remain in the extr space. In addition, the retention of free water can lead to symptomatic hypo Isotonic saline is the solution of choice; this applies even to patients who a hypernatremic, since isotonic saline will still be hypoosmotic to plasma, the tending to lower the plasma Na^+ concentration toward normal.

14-4

a. Volume repletion is responsible for the increase in Na^+ excretion and urine output.

b. The central venous pressure alone is not an adequate determinant of vo status, since the normal range is 1 to 8 cm H_2O. Thus, 3 cm H_2O is normal in some subjects and low in others.

c. The elevation in BUN on admission represents urea accumulation over 1 as a result of reduced urea excretion. Although normovolemia was resto 18 h, a longer period is required for the renal excretion of the excess u

P.943

14.5

a. The patient is depleted of both Na^+ and water (physical findings) and K^+. In addition, the hypernatremia indicates that water has been lost in excess of solute the replacement fluid should be hypotonic and contain Na^+ and K^+. For example, quarter-isotonic saline to which 20 to 40 meq/liter of KCl has been added. This solution can be safely given at an initial rate of 100 mL/h. (The fo calculating the rate of correction of hypernatremia is derived on page 7

14-6

a. Any definition of hypotension must be made in relation to the patient's b blood pressure. Although 110/70 appears normal, it is probably low in th patient with a past history of hypertension.

b. Volume depletion from unreplaced insensible losses must be accompani rise in the plasma Na^+ concentration, since relatively solute-free water has lost. The normal plasma Na^+ concentration in this patient indicates that both Na^+ and water have been lost in proportion and therefore that a solute loss of Na^+ be present. In this case, the history of hypertension and the concurrent hypokalemia and metabolic alkalosis suggest that diuretic therapy is the

cause.

CHAPTER 15

15-1 1. (c) The thiazides are the treatment of choice for hypercalciuric ston disease, since they lower calcium excretion both by increasing distal Ca^{2+} reabsorption and, via volume depletion, by increasing proximal Na^{+} and secondary Ca^{2+} reabsorption.

2. (d) Spironolactone is preferred in cirrhosis, occasionally being more effe a loop diuretic (since it does not require secretion into the tubular lumen) a protecting against the development of hypokalemic alkalosis, which can pre hepatic coma in some cases.

3.(a) Acetazolamide will cause preferential loss of $NaHCO_3$, thereby correcting both the metabolic alkalosis and fluid overload.

4. (b) Loop diuretics directly increase Ca^{2+} excretion by diminishing passive Ca^{2+} reabsorption in the loop of Henle.

5. (b) A loop diuretic is also helpful in hyponatremic patients, who tend to h ADH levels and therefore inappropriate water retention. By interfering with reabsorption, the medullary accumulation of solute and therefore concentra ability and the degree of water retention are diminished.

15-2

a. Hypoalbuminemia limits the degree of protein-binding, resulting in a wic extravascular distribution of the diuretic and therefore a slower rate of to the kidney.

b. Both angiotensin II and aldosterone enhance Na^{+} reabsorption (in the proximal and collecting tubules, respectively), directly impairing the natriuretic r to the diuretic.

c. Hypotension, via the pressure natriuresis phenomenon, increases Na^{+} reabsorption, thereby counteracting the effect of the diuretic.

CHAPTER 16

16-1 (*a* and *d*) Tissue perfusion may fall after the appropriate use of diuretics heart failure and cirrhosis. With mild hypoalbuminemia or renal failure, on t hand, there is primary renal Na^{+} retention, and removal of the excess fluid will lo the effective circulating volume from a high level down toward normal.

(b) A reduction in the effective circulating volume will lead sequentially to i proximal Na^{+} and water reabsorption, enhanced passive proximal urea reabso and a rise in the BUN. The urine Na^{+} concentration is already low (in the absence diuretics) in most patients with heart failure and cirrhosis, and a small furth

reduction is hard to detect.

16-2

a. The oliguria and azotemia are due to effective volume depletion resultir either overdiuresis or a primary fall in cardiac output following the myo infarction.

b. No. Patients with diastolic dysfunction have a normal ejection fraction b output due to impaired diastolic filling. Furthermore, a moderately reduc ejection fraction does not necessarily mean that cardiac output is reduc cardiac dilatation may allow a normal stroke volume to be maintained de impaired contractility.

c. No. Primary left ventricular damage may be associated with normal righ ventricular function. Remember that a low jugular venous pressure may normal (normal range equals 1 to 8 cm H_2O).

d. The extracellular volume in this previously healthy man was normal on a and then must have declined after fluid removal with the diuretic.

e. Therapy should be aimed at increasing the effective circulating volume normal. If there is no evidence of pulmonary congestion, overdiuresis m the primary problem, and cautious liberalization of Na^+ intake may restore normal tissue perfusion. If this is ineffective or if pulmonary congestion present, then treatment must be aimed at increasing cardiac function ar therefore renal perfusion with vasodilators or digitalis.

CHAPTER 17

17-1

a. 26 nanoeq/L (40× 0.8× 0.8)

b. The H^+ concentration is 63 nanoeq/L at a pH of 7.20 (40× 1.25× 1.25) ar nanoeq/L at a pH of 7.10 (63× 1.25). Thus, the H^+ concentration at a pH of 7.15 is 72 nanoeq/L [63+0.5× (80-63)].

c. The H^+ concentration at a pH of 7.30 is 50 nanoeq/L (40× 1.25). Thus, a of 7.24, the H^+ concentration is 59 nanoeq/L [50+0.6× (63-50)].

17-2

a. Metabolic acidosis—low pH, low HCO_3^- concentration, compensatory reductior in P_{CO_2}.

b. Chronic respiratory alkalosis—high pH, low P_{CO_2}, compensatory reduction in HCO_3^- concentration. Note that a low HCO_3^- concentration does not necessaril reflect a metabolic acidosis.

c. Combined respiratory and metabolic acidosis—low pH, high P_{CO_2}, low HCO_3^- concentration.

d. Metabolic alkalosis—high pH, high HCO_3^- concentration, compensatory elevation in P_{CO_2}.

17-3

a. This patient has a pure metabolic acidosis.

b. If the P_{CO_2} remains constant, the plasma HCO_3^- concentration must be raised to 5 meq/L to increase the pH to 7.20 (hydrogen ion concentration equals 63 nanoeq/L):

$$63 = 24 \times \frac{13}{[HCO_3^-]}$$

$$[HCO_3^-] = 5\,\text{meq/L}$$

c. At a P_{CO_2} of 18 mmHg,

$$63 = 24 \times \frac{13}{[HCO_3^-]}$$

$$[HCO_3^-] = 6.9\,\text{meq/L}$$

These examples illustrate that in patients who are able to hyperventilate in response to metabolic acidosis, only a small elevation in the plasma HCO_3^- concentration is initially required to get the patient out of danger.

CHAPTER 18

18-1

a. The acute metabolic alkalosis is due to the citrate load from the multipl transfusions.

b. The urine Na^+ should be less than 15 meq/L and the urine pH acid (due to maximum $NaHCO_3$ reabsorption), since effective volume depletion persists possible, however, that the HCO_3^- reabsorptive capacity may not be sufficiently increased to reabsorb all of the marked increment in the filtered HCO_3^- load. In this setting, the urine Na^+ concentration and pH may be elevated because of obligatory $NaHCO_3$ excretion. A low urine Cl^- concentration will still be present because the patient remains hypovolemic.

c. Acetazolamide is the preferred therapy, both to remove the excess fluid and cause a preferential $NaHCO_3$ diuresis. Saline loading is not indicated, since it will result in a marked increase in ascites formation.

18-2

a. This patient is both volume- and K^+-depleted. Thus, treatment should consist half-isotonic saline to which 40 meq/L (as KCl) should be added.

b. Correction of volume and K^+ depletion will allow the excess HCO_3^- to be excreted. Thus, the anion gap between the high Na^+ and K^+ concentration

and low urine Cl^- concentration is due primarily to HCO_3^-. If, for example, the urine pH is 7.8 (H^+ concentration equals 16 nanoeq/L) and the urine P_{CO_2} is 46 mmHg (similar to the renal venous P_{CO_2}), then

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]}$$

$$16 = 24 \times \frac{46}{[HCO_3^-]}$$

$$[HCO_3^-] = 69\ \text{meq/L}$$

Note that the urine Cl^- concentration is still low in this patient, indicating the need for further fluid and Cl^- replacement; the urine Na^+ concentration is not an accurate estimate of volume status in this setting because the excretion of HCO_3^- obligates Na^+ loss.

18-3

a. The differential diagnosis of unexplained hypokalemia, urinary K^+, and metabolic alkalosis includes surreptitious diuretic use or vomiting (during the phase of HCO_3^- excretion in which both Na^+ and K^+ excretion are increased; see page 565) or some form of primary hyperaldosteronism. The normal blood pressure in this patient excludes all of the causes of the last condition other than Bartter's syndrome.

b. The urine Cl^- concentration should be measured next. A value below 25 meq/L is highly suggestive of vomiting (which was present in this case), whereas a high value is consistent with diuretic use or Bartter's syndrome. The last two conditions can usually be distinguished by a urinary assay for diuretics.

CHAPTER 19

19-1

a. No. The extracellular pH has not been measured, so the patient may have a chronic respiratory alkalosis with an appropriate compensatory reduction in plasma HCO_3^- concentration.

b. Yes. Although the pH is relatively well maintained, this occurs only by marked hyperventilation (P_{CO_2} equals 14 mmHg) that is probably symptomatic. The administration of $NaHCO_3$ will partially correct the acidemia and therefore the

stimulus to ventilation.

19-2

a. This patient has a combined respiratory and high anion gap metabolic a most likely due to seizure-induced lactic acidosis.

b. No. Cessation of the seizure will allow the excess lactate to be metabol to HCO_3^-.

c. There is likely to be no change, since neither lactic acidosis nor its cor seems to affect the internal distribution of K^+.

19-3

a. 3. Type 1 RTA in adults is associated with a progressive but slow declir plasma HCO_3^- concentration as some of the dietary H^+ load is retained each day.

b. 2. Type 1 RTA in infants is associated with a more rapid fall in the plas HCO_3^- concentration because the higher urine pH also obligates a fixed of HCO_3^- loss.

c. 1. The plasma HCO_3^- concentration falls rapidly in type 2 RTA and then stabilizes once the reduced level of reabsorptive capacity has been reached.

At a near-normal plasma HCO_3^- concentration following HCO_3^- administration, these disorders can be distinguished by calculating the fractional excre HCO_3^-: less than 3 percent in type 1 RTA in adults, 5 to 10 percent in in type 1 RTA, and greater than 15 percent in type 2 RTA (see FRTA 19-6).

19-4

a. 2. Hypoaldosteronism is associated with hyperkalemia, an acid urine pH positive urine anion gap, since hyperkalemia impairs NH_4^+ production and excretion.

b. 1. Diarrhea can lead to hypokalemia, which raises proximal NH_3 production and excretion, thereby elevating the urine pH. This disorder can be distingu from RTA since NH_4^+ excretion is appropriately increased, as evidenced by negative urine anion gap.

c. 3. The high urine pH and positive urine anion gap are suggestive of typ The degree of metabolic acidosis is more severe than is typically seen 2 RTA, which can induce all of the other findings in this example.

19-5

a. This patient has a mixed metabolic and respiratory acidosis since a P_{CO_2} of 40 mmHg is inappropriately high in a patient with a plasma HCO_3^- concentration of 9 meq/L. The expected value is about 22 mmHg, since normally P_{CO_2} falls by about 1.2 mmHg for every 1 meq/L reduction in the plasma HCO_3^- concentration.

b. The H^+ concentration at a pH of 7.20 is 63 meq/L. Thus,

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]}$$

$$63 = 24 \times \frac{40}{[HCO_3^-]}$$

$$[HCO_3^-] = 15\ \text{meq/L}$$

c. At this degree of acidemia, the initial distribution of the excess acid is percent of lean body weight. Thus,

$$HCO_3^-\ \text{deficit} = 0.6 \times 80 \times (15 - 9)$$

$$= 288\ \text{meq}$$

d. The above formula is dependent upon the presence of a steady state. S patient is losing 1 liter of diarrheal fluid per hour, there is continuous HCO_3^- loss that is not being replaced.

e. Body K^+ stores are probably markedly reduced. This is masked as the ma acidemia promotes K^+ movement out of the cells, thereby accounting for th initially normal plasma K^+ concentration.

19-6

a. The metabolic acidosis in renal failure is primarily due to reduced NH_4^+ excretion, which prevents the urinary excretion of all of dietary acid loa

b. The second arterial pH was measured only 30 min after the administrati $NaHCO_3$, before equilibration with the intracellular buffers had occurred the later reductions in the plasma HCO_3^- concentration and pH probably reflected the effect of intracellular buffering; in addition, continued aci also may have played a contributory role.

CHAPTER 20

20-1 It is easiest to answer this problem by first determining the acid-base d represented by the three sets of blood values:

a. The low pH and high P_{CO_2} indicate a respiratory acidosis. This is P_{CO_2} 25 mmHg above normal; in chronic respiratory acidosis, this should be ass with a plasma HCO_3^- concentration of approximately 33 meq/L (3.5 meq/L increase in the plasma HCO_3^- concentration for each 10 mmHg elevation in t P_{CO_2}). Thus, the HCO_3^- concentration of 37 meq/L represents a superimpo metabolic alkalosis.

b. At a P_{CO_2} of 60 mmHg, the plasma HCO_3^- concentration should be roughly 26 meq/L in acute respiratory acidosis (1 meq/L increase per 10 mmHg elev the P_{CO_2}) and 31 meq/L in chronic respiratory acidosis. Therefore, the measured HCO_3^- concentration of 26 meq/L can reflect either uncomplicat acute respiratory acidosis *or* chronic respiratory acidosis with a superimpose metabolic acidosis (which lowers the HCO_3^- concentration from 31 to 26 meq/L)

c. Uncomplicated chronic respiratory acidosis *or* acute respiratory acidosis with a superimposed metabolic alkalosis (raising the HCO_3^- concentration from 26 to 32 meq/L).

The correct diagnosis can be made only by correlating the history with the values:

1. Chronic bronchitis plus diarrhea suggests chronic respiratory acidosis v superimposed metabolic acidosis, or (b).
2. Marked obesity suggest chronic hypercapnia, or (c).
3. Severe acute asthma suggests acute respiratory acidosis, or (b).
4. Chronic bronchitis plus diuretic therapy suggests chronic respiratory ac with superimposed metabolic alkalosis, or (a).

20-2

a. From the history and laboratory values, the probable diagnosis is acute superimposed upon chronic respiratory acidosis (see Fig. 20-6

b. Patients with chronic hypercapnia rely on the hypoxemic drive to ventila This is removed by the administration of oxygen, resulting in further hypoventilation and a rise in the P_{CO_2}.

c. The patient cannot tolerate the administration of oxygen, nor can he tol P_{O_2} on 30 mmHg of room air. Thus, some form of mechanical ventilation probably endotracheal intubation are required.

d. Rapid normalization of the P_{CO_2} will lead to a posthypercapnic alkalosis, sin the elevated plasma HCO_3^- concentration will persist.

e. Correction of the posthypercapnic alkalosis requires the urinary excreti excess HCO_3^- as $NaHCO_3$. In the presence of volume depletion (low Na^+ urine N concentration), however, HCO_3^- excretion will not occur until normovolemia i restored.

20-3

a. Metabolic alkalosis, with the elevated P_{CO_2} reflecting the appropriate respiratory compensation.

b. The (A–a) O_2 gradient is 13 mmHg, making underlying lung disease and c hypercapnia unlikely.

$$\begin{aligned}(\text{A-a})\ O_2\ \text{gradient} &= P_{I_{O_2}} - 1.25Pa_{CO_2} - Pa_{O_2}\\ &= 150 - 64 - 73\\ &= 13\ \text{mmHg}\end{aligned}$$

CHAPTER 22

22-1

a. The P_{osm} can be calculated from

$$\begin{aligned}\text{Calculated } P_{osm} &= 2 \times \text{plasma } [Na^+] + \frac{\text{BUN}}{2.8} + \frac{[\text{glucose}]}{18}\\ &= 250 + 50 + 6\\ &= 306\ \text{mosmol/kg}\end{aligned}$$

b. No. The effective P_{osm} is actually reduced at 256 mosmol/kg, since the contribution of the ineffective osmole urea must be excluded.

22-1

a. The administration of isotonic fluids to a patient who can excrete only a isosmotic urine will lead to hyperosmolality and a rise in the plasma Na^+ concentration, since no free water is given to replace insensible losses skin and respiratory tract.

b. Half-isotonic saline plus 77 meq/L of KCl is also an isosmotic fluid and will have the same osmotic effect as isotonic saline. At first glance, it m that the addition to the extracellular fluid of a solution with a Na^+ con less than that of the plasma (and extracellular fluid) should lower the p Na^+ concentration. However, not all of this fluid remains in the extracell space. This can be appreciated if each liter of the added fluid is viewed

having two components: 500 mL of isotonic NaCl, which stays in the extracellular fluid, and 500 mL of isotonic KCl, which must either enter or be excreted in the urine to prevent fatal hyperkalemia.

Thus, the osmotic effect of this solution is similar to that of isotonic saline comparison, the administration of half-isotonic saline alone will lower the P_{osm} the plasma Na^+ concentration, since it is a hypotonic fluid. These concepts a clinically important, since the osmotic contribution of Na^+ in intravenous fluids is frequently ignored.

CHAPTER 23

23-1 All of these factors contributed to the hyponatremia. Hydrochlorothiazi induced volume depletion (physical findings plus low urine Na^+ concentration), which enhanced ADH release (high U_{osm} of 540 mosmol/kg), resulting in water retentio and hyponatremia. The loss of K^+ also played a contributory role via a transcellu K^+-Na^+ exchange.

Therapy should include the administration of Na^+ and K^+ in a hypertonic solution, such as 40 meq of KCl added to each liter of isotonic saline. There is little justification for water restriction, since the patient is volume-depleted. In v metabolic alkalosis, KCl, not potassium citrate, is indicated (since citrate i metabolized into HCO_3^-). Half-isotonic saline should also be avoided, because hypotonic solution that will further lower the plasma Na^+ concentration.

23-2 The hyponatremia in this patient is due to volume depletion, probably i by diuretic therapy for hypertension. The physical findings suggestive of hypovolemia, hypokalemia, and high plasma HCO_3^- concentration are all compatible with this diagnosis.

Pseudohyponatremia due to mannitol is not present, since the measured P_{osm} is low and is similar to the calculated value [Calculated $P_{osm} = 2 \times [120 + (125/18)] + (15/2.8)$ = 252 mosmol/kg]. SIADH due to the stroke also cannot account for the hyponatremia; the hyponatremia must have *preceded* the stroke, since the patient subsequently received only 100 mL of water, a quantity that is insufficient t the plasma Na^+ concentration.

23-3 1. (b) This edematous patient is both water- and sodium-overloaded, a should be treated with both water and sodium restriction.

2. (f) The combination of marked hyponatremia and a very concentrated uri be treated with hypertonic saline plus a loop diuretic (such as furosemide) the U_{osm}

3. (d) True volume depletion with mild hyponatremia is best treated with isc saline.

4. (c) No therapy is required for pseudohyponatremia (normal P_{osm})

5. (b) This edematous patient, like the one with renal failure, is both water sodium-overloaded.

6. (*a* or *e*) Either water restriction alone or the use of hypertonic saline is re

in this patient with presumed SIADH and asymptomatic hyponatremia. A loop is not necessary, since the U_{osm} is only 290 mosmol/kg.

23-4

a. The most likely diagnosis is SIADH due to the oat cell carcinoma.

b. Hypertonic saline should be given initially in view of the marked hyponatremia and neurologic symptoms. The approximate deficit of Na^+ that must be corrected to raise the plasma Na^+ concentration to a safe value of 120 meq/L can be estimated from

$$Na^+ \text{ deficit} = 0.6 \times 70 \times (120 - 105)$$
$$= 630 \text{ meq}$$

This requires approximately 1200 mL of 3% saline, which should be given at a rate of 40 mL/h over 30 h to raise the plasma Na^+ concentration by 0.5 meq/L/h. Furosemide will enhance the efficacy of this regimen by lowering U_{osm} thereby increasing free-water excretion.

23-5 Volume depletion increases the proximal reabsorption of Na^+ and secondarily that of uric acid (see page 90). The result is an increase in the plasma uric acid concentration. In comparison, SIADH is associated with initial volume expansion, thereby increasing Na^+ and uric acid excretion. Thus, the plasma uric acid concentration is typically below 4 mg/dL in this disorder.

CHAPTER 24

24-1

a. Polydipsia and polyuria with a dilute urine is due either to primary polydipsia or to central or nephrogenic diabetes insipidus. Sarcoidosis can produce either of these conditions: the first two by hypothalamic infiltration and nephrogenic diabetes insipidus by hypercalcemia. The only clue to the correct diagnosis is the low plasma Na^+ concentration and U_{osm} suggesting water overload due to primary polydipsia.

b. The diagnosis can be established by the water-restriction test followed by administration of dDAVP or aqueous vasopressin after the maximum U_{osm} has been achieved or the P_{osm} reaches 295 mosmol/kg.

24-2 (*b* and *e*) Insensible water losses that were not replaced as a result of decreased thirst were the major factors responsible for the hypernatremia in this patient. The diarrhea also may have made a contribution, if it was an osmotic diarrhea in which the Na^+ ($+K^+$) concentration in the diarrheal fluid was less than that in the plasma (see page 293). In this setting, water would be lost in excess of effective solute (thereby promoting the development of hypernatremia), even if the diarrheal fluid was isosmotic to plasma.

The low urine Na^+ concentration in this patient is indicative of volume depleti
There is no predictable relationship between the plasma Na^+ concentration

(a measure of osmolality) and the urine Na^+ concentration (which varies with the effective circulating volume).

(d) The water deficit can be approximated from

$$\text{Water deficit} = 0.4 \times 50 \times \left(\frac{174}{140} - 1\right)$$

$$= 5 \text{ liters}$$

This deficit should be repaired gradually over 68 h (34 meq/L reduction in t Na^+ concentration at a rate of 0.5 meq/L per h); thus, fluid should be given approximate rate of 75 mL/h. Continuing insensible losses of 40 mL/h must replaced, leading to a total of 115 mL/h of free water. In addition, this patie Na^+-depleted from diuretic therapy and diarrhea. Thus, initial fluid therapy probably be given as quarter-isotonic saline. This fluid, however, is only th quarters free water. Therefore, 150 mL/h [(4/3)× 115] must be given to prov necessary free water.

24-3

a. The diagnosis of central diabetes insipidus can be confirmed by the administration of dDAVP or aqueous vasopressin, which should raise the U_{osm} and lower the urine volume. There is no need to do the water-restrictio since the P_{osm} is already 350 mosmol/kg.

b. The water deficit can be estimated from

$$\text{Water deficit} = 0.5 \times 70 \times \left(\frac{168}{140} - 1\right)$$

$$= 7 \text{ liters}$$

c. This deficit should be replaced gradually over 56 h at the rate of 125 m Another 50 mL/h should be added to replace continuing insensible losse 175 mL/h can be given as dextrose in water. There is no history of Na^+ loss and therefore no requirement for saline administration.

d. The late development of hyponatremia is probably due to SIADH. The administration of vasopressin tannate in oil results in nonsuppressible ADH levels, which can lead to water retention if too much water is take

CHAPTER 25

25-1

a. The patient has both diabetic ketoacidosis and a superimposed metabol alkalosis due to vomiting. Notice that the anion gap is 28 meq/L (16 me above normal), which should be associated with a reduction in the plas HCO_3^- concentration to about 10 meq/L. The substantially high value in

case is indicative of the underlying metabolic alkalosis.

b. Dehydration undoubtedly is responsible for much of the decline in renal In addition, acetoacetate is measured as creatinine in the standard ass resulting in a further apparent elevation in the plasma creatinine conce

c. The major electrolyte problems in this patient are hypokalemia and volu depletion. The hyperglycemia and metabolic acidosis are relatively mild immediate correction of these disturbances with insulin is not necessary may be deleterious by driving K^+ into the cells, possibly inducing arrhythmias Thus, the initial therapy should consist of isotonic or half-isotonic salir which 40 meq/L of KCl is added. This regimen will correct the hypokalen volume depletion and will slowly ameliorate the hyperglycemia, both by and by improving renal function, thereby enhancing glucose excretion.

The patient should also be started on antimicorbial therapy for presumed a pyelonephritis. This infection was probably responsible for the loss of diab control.

25-2

a. The acidemia is due to retention of H^+ ions from the ketoacids; the associated anions (β -hydroxybutyrate and acetoacetate) were presumably excretec urine, resulting in only a minor elevation in the anion gap.

b. The patient should be given insulin with glucose. This will correct the ketoacidosis without the risk of hypoglycemia.

CHAPTER 26

26-1

a. Correction of the acidemia will drive K^+ into the cells, further reducing the plasma K^+ concentration. In this setting, in which the acidemia is not sev alkali therapy should be withheld until K^+ supplements have partially corrected the hypokalemia.

b. Hypocalcemia *protects* against the effects of hypokalemia via an uncertain mechanism. Thus, treatment of the hypokalemia should precede correcti the hypocalcemia.

It should be noted that, for the same reasons, hypokalemia protects agains neuromuscular effects of hypocalcemia. Thus, increasing the plasma K^+ concentration in this setting may precipitate hypocalcemic tetany. However, this risk is generally less serious than the potentially fatal cardiac arrhythmias that induced by severe hypokalemia.

CHAPTER 27

27-1

a. The differential diagnosis of unexplained hypokalemia, urinary K^+, and metabolic alkalosis includes surreptitious diuretic use or vomiting (duri phase of HCO_3^- excretion in which both Na^+ and K^+ excretion are increased; seepage 566) or some form of primary hyperaldosteronism. The normal bl pressure in this patient excludes all of the causes of the last condition than Bartter's syndrome.

b. These disorders can be distinguished by viewing this as a diagnostic pr metabolic alkalosis and measuring the urine Cl^- concentration (see Chap. 18). A value below 25 meq/L is highly suggestive of vomiting (which was

present in this case), whereas a higher value is consistent with diuretic Bartter's syndrome. The last two conditions can usually be distinguishe urinary assay for diuretics.

27-2

a. 3. The low U_{osm} is consistent with primary water overload, which shuts of secretion. Although the urine K^+ concentration is appropriately reduced, the urine volume is probably very high, resulting in an inappropriately high level of K^+ excretion.

b. 2. The major clue suggesting hypomagnesemia is the presence of hypoc

c. 1. Metabolic acidosis with a high urine pH and positive urine anion gap Chap. 19) is diagnostic of renal tubular acidosis.

d. 4. Metabolic acidosis with a normally acid urine pH, an appropriately ne urine anion gap (reflecting the adaptive increase in NH_4^+ excretion), and a low urine K^+ concentration is compatible with extrarenal loss of K^+ and HCO_3^-, as occurs with laxative abuse.

CHAPTER 28

28-1

a. The underlying renal insufficiency, superimposed volume depletion (due wasting after the acute institution of a low-Na^+ diet), and metabolic acidosis all may play a contributory role. However, many patients have these proble without life-threatening hyperkalemia. Therefore, the patient should be questioned about increased K^+ intake; this patient gave a history of using la quantities of KCl-containing salt substitute.

b. By definition, pseudohyperkalemia produces no symptoms or signs of K^+ intoxication.

c. The patient has both severe muscle weakness and electrocardiographic changes. Therefore, therapy should be initiated with calcium gluconate, by glucose, insulin, and $NaHCO_3$ temporarily drive K^+ into the cells. For example 500 mL of 10% dextrose in saline plus 10 units of regular insul 45 meq of $NaHCO_3$ infused over 30 min will lower the plasma K^+ concentration, raise the plasma Na^+ concentration, and produce volume expansion. Sodiur polystyrene sulfonate should be given orally and repeated as necessary remove the excess K^+. Dialysis should not be required, since the patient do not have severe renal failure.

d. Mild asymptomatic hyperkalemia can be treated solely with sodium poly sulfonate.

28-2

a. By definition, patients with chronic hyperkalemic have a defect in renal excretion, since normal subjects would rapidly excrete the excess K^+ in urine. Thus, the urine K^+ concentration of 34 meq/L is inappropriately low. T transtubular K^+ gradient (TTKG) can be calculated in this patient to asses degree of aldosterone effect:

$$\begin{aligned} \text{TTKG} &= \left[U_{K^+} \div \frac{U_{osm}}{P_{osm}} \right] \div P_{K^+} \\ &= \left[34 \div \frac{550}{275} \right] \div 6.8 \\ &= 2.5 \end{aligned}$$

where 275 represents the calculated P_{osm}. The TTKG is low in this patient, a finding that is consistent with some form of mineralocorticoid deficiency resistance.

b. The findings of low blood pressure, increased skin pigmentation, a low and hypoglycemia after the administration of glucose and insulin all poi probable diagnosis of primary adrenal insufficiency.

c. Acutely, sodium polystyrene sulfonate can be given to lower the plasma K^+ concentration. Chronically, both glucocorticoid and mineralocorticoid replacement will be required because of the persistent adrenal dysfunct

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Chapter Thirty

Summary of equations and formulas

UNITS OF MEASUREMENT

$$\text{mmol/L} = \frac{\text{mg/dL} \times 10}{\text{molecular weight}}$$

$$\text{meq/L} = \text{mmol/L} \times \text{valence}$$

$$\text{mosmol/kg} = \text{n} \times \text{mmol/L}$$

where n=number of dissociable particles per molecules.

TUBULAR FUNCTION

Variations in tubular reabsorption are the major way in which the kidneys a and water excretion. There are, however, *no absolute normal values* for the urine Na^+ or K^+ concentration, osmolality, or pH, since these parameters vary with For example, the urine Na^+ concentration should be less than 10 to 15 meq/L wi volume depletion but may exceed 100 meq/L after a Na^+ load. Similarly, the U_{osm} may fall below 100 mosmol/kg after a large water load but should exceed 8(mosmol/kg after water restriction has led to a rise in the plasma Na^+ concentration above 145 meq/L. Thus, a U_{osm} of 300 mosmol/kg is *inappropriately low* in the latter setting, suggesting either lack of or resistance to antidiuretic hormor

P.957

ACID-BASE

$$\text{pH} = 6.10 + \log \frac{[HCO_3^-]}{0.03P_{CO_2}}$$

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]}$$

$$\text{Plasma anion gap} = [Na^+] = ([Cl^-] + [HCO_3^-])$$

$$\text{Urine anion gap} = ([Na^+] + [K^+]) - [Cl^-]$$

Conversion of pH into Hydrogen Concentration

$$\text{pH of } 7.40 = [H^+] \text{ of } 40 \text{ nanoeq/L}$$

For each 0.1-unit increase in pH, multiple $[H^+]$ by 0.8:

$$\text{pH of } 7.60 = 40 \times 0.8 \times 0.8$$

$$[H^+] = 26 \text{ nanoeq/L}$$

For each 0.1 unit fall in pH, multiply $[H^+]$ by 1.25:

$$\text{pH of } 7.30 = 40 \times 1.25$$

$$[H^+] = 50 \text{ nanoeq/L}$$

For each 0.1-unit increase in pH, multiply $[H^+]$ by 0.8:

pH of 7.60 = 40× 0.8×0.8

$[H^+]$ = 26 nanoeq/L

For each 0.1 unit fall in pH, multiply $[H^+]$ by 1.25:

pH of 7.30 =40×1.25

$[H^+]$ = 50 nanoeq/L

Renal and Respiratory Compensations in Acid-Base Disorders

Metabolic acidosis:

1.2-mmHg fall in PCO_2 per 1-meq/L decrease in plasma $[HCO_3^-]$

Metabolic alkalosis:

0.6-mmHg rise in PCO_2 per 1-meq/L elevation in plasma $[HCO_3^-]$

Respiratory acidosis:

Acute: 1-meq/L increase in plasma $[HCO_3^-]$ per 10-mmHg rise in PCO_2

Chronic: 3.5-meq/L elevation in plasma $[HCO_3^-]$ per 10-mmHg increase in PCO_2

Respiratory alkalosis:

Acute: 2-meq/L fall in plasma $[HCO_3^-]$ per 10-mmHg decrease in PCO_2

Chronic: 4-meq/L reduction in plasma $[HCO_3^-]$ per 10-mmHg fall in PCO_2

Estimation of Bicarbonate Deficit and Excess

In severe metabolic acidosis with a plasma HCO_3^- concentration below 10 meq/L:

HCO_3^- deficit (meq) [congruent] 0.7×lean body weight (kg)× (10-plasma $[HCO_3^-]$)

This formula applies only when the plasma HCO_3^- concentration is very low and the cell and bone buffers are responsible for almost all buffering of excess H^+

Once the plasma HCO_3^- concentration is above 10 meq/L, however, there is mo extracellular buffering and the apparent space of distribution of the HCO_3^- fall times the lean body weight.

In metabolic alkalosis

$$HCO_3^- \text{ excess (meq)} \cong 0.5 \times \text{lean body weight} \times (\text{plasma } [HCO_3^-] - 24)$$

OSMOLALITY AND THE PLASMA SODIUM CONCENTRATION

$$P_{osm} \cong 2 \times \text{plasma } [Na^+] + \frac{[\text{glucose}]}{18} + \frac{\text{BUN}}{2.8}$$

$$\text{Effective } P_{osm} \cong 2 \times \text{plasma } [Na^+] + \frac{[\text{glucose}]}{18}$$

$$\text{Plasma } [Na^+] \cong \frac{Na_e^+ + K_e^+}{\text{total body water}}$$

Plasma Sodium Concentration in Hyperglycemia

For each 62-mg/dL increment in the plasma glucose concentration, there wi reciprocal 1-meq/L reduction in the plasma Na^+ concentration because of the osmotic movement of water from the cells into the extracellular fluid. Thus, hyperglycemia results in a dissociation between the P_{osm} (which is increased) and the plasma Na^+ concentration (which may be reduced).

Hyponatremia

$$Na^+ \text{ deficit (meq)} \cong 0.6^* \times \text{lean body weight (kg)} \times (140 - \text{plasma } [Na^+])$$

This formula estimates the amount of Na^+ required to raise the plasma Na^+ concentration back up to 140 meq/L. It may not represent the total Na^+ deficit, however, since there may be an additional *isosmotic* Na^+ and water loss (due, for example, to diuretics or diarrhea).

Hypernatremia

$$\text{Water deficit (liters)} \cong 0.5 \times \text{lean body weight (kg)} \times \left(\frac{\text{plasma } [Na^+]}{140} - 1\right)$$

MISCELLANEOUS

Alveolar-Arterial Oxygen Gradient

$$(A - a)\ O_2 \text{ gradient} = P_{I_{O_2}} (150 \text{ mmHg on room air}) - 1.25 \times Pa_{CO_2} - Pa_{O_2}$$

Plasma Calcium Concentration and Hypoalbuminemi

For every 1-g/dL fall in the plasma albumin concentration, there will be less Ca^{2+} leading to an 0.8 mg/dL reduction in the plasma Ca^{2+} concentration. This does not represent true hypocalcemia, however, since there is no change in the physiologically important free (or ionized) Ca^{2+} concentration.

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