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哈里森

肾脏病学

HARRISON'S Nephrology and Acid–Base Disorders

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出版说明

《哈里森内科学》（Harrison's Principles of Internal Medicine）是一部内科学经典名著，也是美国及多个国家医学院校的首选内科学教科书。该书 1945 年由美国权威内科学家哈里森（Tinsley R. Harrison）首先提议并组织编写，第 1 版于 1950 年问世，并立即引起广泛的赞誉与好评。自此，随着医学科学的发展以及在市场的热销，该书每 4 年修订一次，历时半个多世纪，已出版至第 17 版，成为内科学发展的基石和风向标，享有"内科学著作之父"的美誉。

为了读者阅读和携带方便，更专注于内科学各亚科领域，《哈里森内科学》分册系列书问世了。该分册系列以《哈里森内科学》（第 17 版）中相关领域的内容为蓝本，并参考了《哈里森内科学》（第 17 版）出版以来的最新文献，强调基础与临床的整合，汇集了本领域内最新的进展，是内科学各亚科领域的权威教科书。

在医学领域，英文原版经典专著经过几十年甚至上百年的发展，在知识点的架构上形成了科学而完备的体系，不但语言规范、地道，而且更新及时，具有权威性和先进性。无论是临床医生、教师还是医学生，有这样一本经典专著放在案头，经常翻阅，不但可以获取医学知识，对提高专业外语水平也大有裨益。

本次引进出版：

- 哈里森心血管病学
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- 哈里森临床神经病学
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PREFACE

The Editors of *Harrison's Principles of Internal Medicine* refer to it as the "Mother Book," a description that confers respect but also acknowledges its size and its ancestral status among the growing list of Harrison's products, which now include *Harrison's Manual of Medicine, Harrison's Online,* and *Harrison's Practice,* an online, highly structured reference for point-of-care use and continuing education. This book, *Harrison's Nephrology and Acid-Base Disorders,* is a compilation of chapters related to kidney function.

Our readers consistently note the sophistication of the material in the specialty sections of *Harrison's.* Our goal was to bring this information to our audience in a more compact and usable form. Because the topic is more focused, it is possible to enhance the presentation of the material by enlarging the text and the tables. We have also included a Review and Self-Assessment section that includes questions and answers to provoke reflection and to provide additional teaching points.

Renal dysfunction, electrolyte, and acid-base disorders are among the most common problems faced by the clinician. Indeed, hyponatremia is consistently the most frequently searched term for readers of *Harrison's Online.* Unlike some specialties, there is no specific renal exam. Instead, the specialty relies heavily on laboratory tests, urinalyses, and characteristics of urinary sediments. Evaluation and management of renal disease also requires a broad knowledge of physiology and pathology since the kidney is involved in many systemic disorders. Thus, this book considers a broad spectrum of topics including acid-base and electrolyte disorders, vascular injury to the kidney, as well as specific diseases of the kidney.

Kidney disorders, such as glomerulonephritis, can be a primary cause for clinical presentation. More commonly, however, the kidney is affected secondary to other medical problems such as diabetes, shock, or complications from dye administration or medications. As such, renal dysfunction may be manifest by azotemia, hypertension, proteinuria, or an abnormal urinary sediment, and it may herald the presence of an underlying medical disorder. Renal insufficiency may also appear late in the course of chronic conditions such as diabetes, lupus, or scleroderma and significantly alter a patient's quality of life. Fortunately, intervention can often reverse or delay renal insufficiency. And, when this is not possible, dialysis and renal transplant provide life-saving therapies.

Understanding normal and abnormal renal function provides a strong foundation for diagnosis and clinical management. Therefore, topics such as acidosis and alkalosis, fluid and electrolyte disorders, and hypercalcemia are covered here. These basic topics are useful in all fields of medicine and represent a frequent source of renal consultation.

The first section of the book, "Introduction to the Renal System," provides a systems overview, beginning with renal development, function, and physiology, as well as providing an overview of how the kidney responds to injury. The integration of pathophysiology with clinical management is a hallmark of *Harrison's,* and can be found throughout each of the subsequent disease-oriented chapters. The book is divided into seven main sections that reflect the scope of nephrology: (I) Introduction to the Renal System; (II) Alterations of Renal Function and Electrolytes; (III) Acute and Chronic Renal Failure; (IV) Glomerular and Tubular Disorders; (V) Renal Vascular Disease; (VI) Urinary Tract Infections and Obstruction; and (VII) Cancer of the Kidney and Urinary Tract.

While *Harrison's Nephrology and Acid-Base Disorders* is classic in its organization, readers will sense the impact of the scientific advances as they explore the individual chapters in each section. Genetics and molecular biology are transforming the field of nephrology, whether illuminating the genetic basis of a tubular disorder or explaining the regenerative capacity of the kidney. Recent clinical studies involving common diseases like chronic kidney disease, hypertensive vascular disease, and urinary tract infections provide powerful evidence for medical decision making and treatment. These rapid changes in nephrology are exciting for new students of medicine and underscore the need for practicing physicians to continuously update their knowledge base and clinical skills.

Our access to information through web-based journals and databases is remarkably efficient. While these sources of information are invaluable, the daunting body of data creates an even greater need for synthesis and for highlighting important facts. Thus, the preparation of these chapters is a special craft that requires the ability to distill core information from the ever-expanding knowledge base. The editors are therefore indebted to our authors, a group of internationally recognized authorities who are masters at providing a comprehensive overview while being able to distill a topic into a concise and interesting chapter. We are grateful to Emily Cowan for assisting with research and preparation of this book. Our colleagues at McGraw-Hill continue to innovate in healthcare publishing. This new product was championed by Jim Shanahan and impeccably produced by Kim Davis.

We hope you find this book useful in your effort to achieve continuous learning on behalf of your patients.

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NOTICE

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

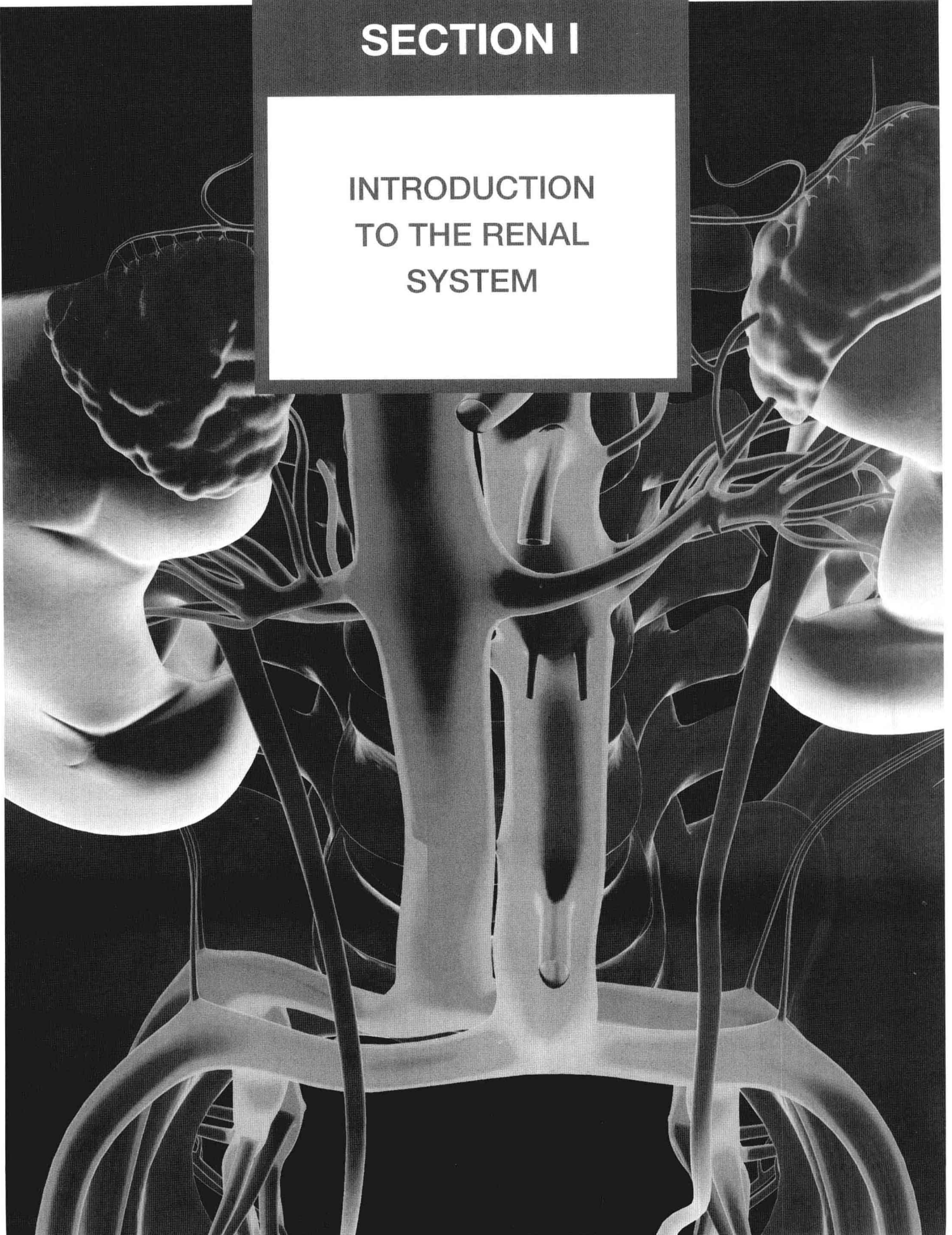The global icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.

The genetic icons identify a clinical issue with an explicit genetic relationship.

SECTION I

INTRODUCTION TO THE RENAL SYSTEM

CHAPTER 1

BASIC BIOLOGY OF THE KIDNEY

Alfred L. George, Jr. ■ Eric G. Neilson

The kidney is one of the most highly differentiated organs in the body. Nearly 30 different cell types can be found in the renal interstitium or along segmented nephrons, blood vessels, and filtering capillaries at the conclusion of embryological development. This panoply of cells modulates a variety of complex physiologic processes. Endocrine functions, the regulation of blood pressure and intraglomerular hemodynamics, solute and water transport, acid–base balance, and removal of fuel or drug metabolites are all accomplished by intricate mechanisms of renal response. This breadth of physiology hinges on the clever ingenuity of nephron architecture that evolved as complex organisms came out of water to live on land.

EMBRYOLOGICAL DEVELOPMENT

The kidney develops from within the intermediate mesoderm under the timed or sequential control of a growing number of genes, described in Fig. 1-1. The transcription of these genes is guided by morphogenic cues that invite ureteric buds to penetrate the metanephric blastema, where they induce primary mesenchymal cells to form early nephrons. This induction involves a number of complex signaling pathways mediated by c-Met, fibroblast growth factor, transforming growth factor β, glial cell–derived neurotrophic factor, hepatocyte growth factor, epithelial growth factor, and the Wnt family of proteins. The ureteric buds derive from the posterior nephric ducts and mature into collecting ducts that eventually funnel to a renal pelvis and ureter. Induced mesenchyme undergoes mesenchymal-epithelial transitions to form comma-shaped bodies at the proximal end of each ureteric bud. These lead to the formation of S-shaped nephrons that cleft and enjoin with penetrating endothelial cells derived from sprouting angioblasts. Under the influence of vascular endothelial growth factor A, these penetrating cells form capillaries with surrounding mesangial cells that differentiate into a glomerular filter for plasma water and solute. The ureteric buds branch, and each branch produces a new set of nephrons. The number of branching events ultimately determines the total number of nephrons in each kidney. There are approximately 900,000 glomeruli in each kidney in normal-birth-weight adults and as few as 225,000 in low-birth-weight adults. In the latter case, a failure to complete the last one or two rounds of branching leads to smaller kidneys and increased risk for hypertension and cardiovascular disease later in life.

Glomeruli evolved as complex capillary filters with fenestrated endothelia. Outlining each capillary is a basement membrane covered by epithelial podocytes. Podocytes attach by special foot processes and share a slit-pore membrane with their neighbor. The slit-pore membrane is formed by the interaction of nephrin, annexin-4, CD2AP, FAT, ZO-1, P-cadherin, podocin, and neph 1–3 proteins. These glomerular capillaries seat
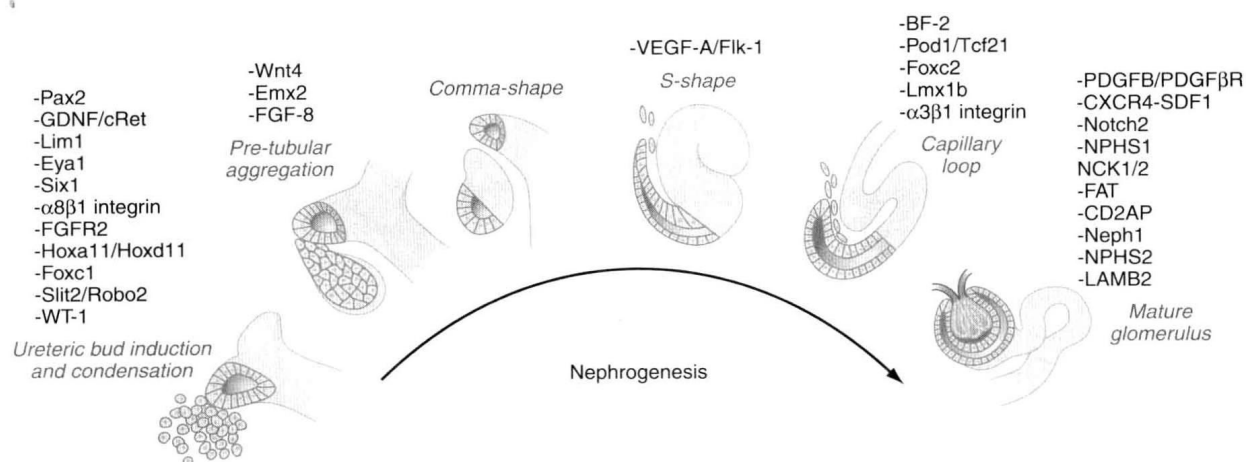
FIGURE 1-1
Genes controlling renal nephrogenesis. A growing number of genes have been identified at various stages of glomerulotubular development in mammalian kidney. The genes listed have been tested in various genetically modified mice, and their location corresponds to the classical stages of kidney development postulated by Saxen in 1987. GDNF, giant cell line–derived neutrophilic factor; FGFR2, fibroblast growth factor receptor 2; WT-1, Wilms tumor gene 1; FGF-8, fibroblast growth factor 8; VEGF-A/ Flk-1, vascular endothelial growth factor–A/fetal liver kinase-1; PDGFB, platelet-derived growth factor B; PDGFβR, PDGFβ receptor; SDF-1, stromal-derived factor 1; NPHS1, nephrin; NCK1/2, NCK-adaptor protein; CD2AP, CD2-associated protein; NPHS2, podocin; LAMB2, laminin beta-2.

in a mesangial matrix shrouded by parietal and proximal tubular epithelia forming Bowman's capsule. Mesangial cells have an embryonic lineage consistent with arteriolar or juxtaglomerular cells and contain contractile actin-myosin fibers. These cells make contact with glomerular capillary loops, and their matrix holds them in condensed arrangement. Between nephrons lies the renal interstitium. This region forms the functional space surrounding glomeruli and their downstream tubules, which are home to resident and trafficking cells, such as fibroblasts, dendritic cells, occasional lymphocytes, and lipid-laden macrophages. The cortical and medullary capillaries, which siphon off solute and water following tubular reclamation of glomerular filtrate, are also part of the interstitial fabric as well as a web of connective tissue that supports the kidney's emblematic architecture of folding tubules. The relational precision of these structures determines the unique physiology of the kidney.

Each nephron segments during embryological development into a proximal tubule, descending and ascending limbs of the loop of Henle, distal tubule, and the collecting duct. These classic tubular segments have subsegments recognized by highly unique epithelia serving regional physiology. All nephrons have the same structural components, but there are two types whose structure depends on their location within the kidney. The majority of nephrons are cortical, with glomeruli located in the mid- to outer cortex. Fewer nephrons are juxtamedullary, with glomeruli at the boundary of the cortex and outer medulla. Cortical nephrons have short loops of Henle, whereas juxtamedullary nephrons have long loops of Henle. There are critical differences in blood supply as well. The peritubular capillaries surrounding cortical nephrons are shared among adjacent nephrons. By contrast, juxtamedullary nephrons use separate capillaries called *vasa recta*. Cortical nephrons perform most of the glomerular filtration because there are more of them and because their afferent arterioles are larger than their respective efferent arterioles. The juxtamedullary nephrons, with longer loops of Henle, create a hyperosmolar gradient that allows for the production of concentrated urine. How developmental instructions specify the differentiation of all these unique epithelia among various tubular segments is still unknown.

DETERMINANTS AND REGULATION OF GLOMERULAR FILTRATION

Renal blood flow drains approximately 20% of the cardiac output, or 1000 mL/min. Blood reaches each nephron through the afferent arteriole leading into a glomerular capillary where large amounts of fluid and solutes are filtered as tubular fluid. The distal ends of the glomerular capillaries coalesce to form an efferent arteriole leading to the first segment of a second capillary network (peritubular capillaries) surrounding the cortical tubules (Fig. 1-2A). Thus, the cortical nephron has two capillary beds arranged in series separated by the efferent arteriole that regulates the hydrostatic pressure in both capillary beds. The peritubular capillaries empty

4 into small venous branches, which coalesce into larger veins to eventually form the renal vein.

The hydrostatic pressure gradient across the glomerular capillary wall is the primary driving force for glomerular filtration. Oncotic pressure within the capillary lumen, determined by the concentration of unfiltered plasma proteins, partially offsets the hydrostatic pressure gradient and opposes filtration. As the oncotic pressure rises along the length of the glomerular capillary, the driving force for filtration falls to zero before reaching the efferent arteriole. Approximately 20% of the renal plasma flow is filtered into Bowman's space, and the ratio of glomerular filtration rate (GFR) to renal plasma flow determines the filtration fraction. Several factors, mostly hemodynamic, contribute to the regulation of filtration under physiologic conditions.

Although glomerular filtration is affected by renal artery pressure, this relationship is not linear across the range of physiologic blood pressures. Autoregulation of glomerular filtration is the result of three major factors that modulate either afferent or efferent arteriolar tone: these include an autonomous vasoreactive (myogenic) reflex in the afferent arteriole, *tubuloglomerular feedback*, and angiotensin II–mediated vasoconstriction of the efferent arteriole. The myogenic reflex is a first line of defense against fluctuations in renal blood flow. Acute changes in renal perfusion pressure evoke reflex constriction or dilatation of the afferent arteriole in response to increased or decreased pressure, respectively. This phenomenon helps protect the glomerular capillary from sudden elevations in systolic pressure.

Tubuloglomerular feedback changes the rate of filtration and tubular flow by reflex vasoconstriction or dilatation of the afferent arteriole. Tubuloglomerular feedback is mediated by specialized cells in the thick ascending limb of the loop of Henle called the *macula densa* that act as sensors of solute concentration and flow of tubular fluid. With high tubular flow rates, a proxy for an inappropriately high filtration rate, there is increased solute delivery to the macula densa (**Fig. 1-2B**), which evokes vasoconstriction of the afferent arteriole causing the GFR to return to normal. One component of the soluble signal from the macula densa is adenosine triphosphate (ATP), which is released by the cells during increased NaCl reabsorption. ATP is metabolized in the extracellular space by ecto-59-nucleotidase to generate adenosine, a potent vasoconstrictor of the afferent arteriole. Direct release of adenosine by macula densa cells also occurs. During conditions associated with a fall in filtration rate, reduced solute delivery to the macula densa attenuates the tubuloglomerular response, allowing afferent arteriolar dilatation and restoring glomerular filtration to normal levels. Loop diuretics block tubuloglomerular feedback by interfering with NaCl reabsorption by macula densa cells. Angiotensin II and reactive oxygen

A

B

C
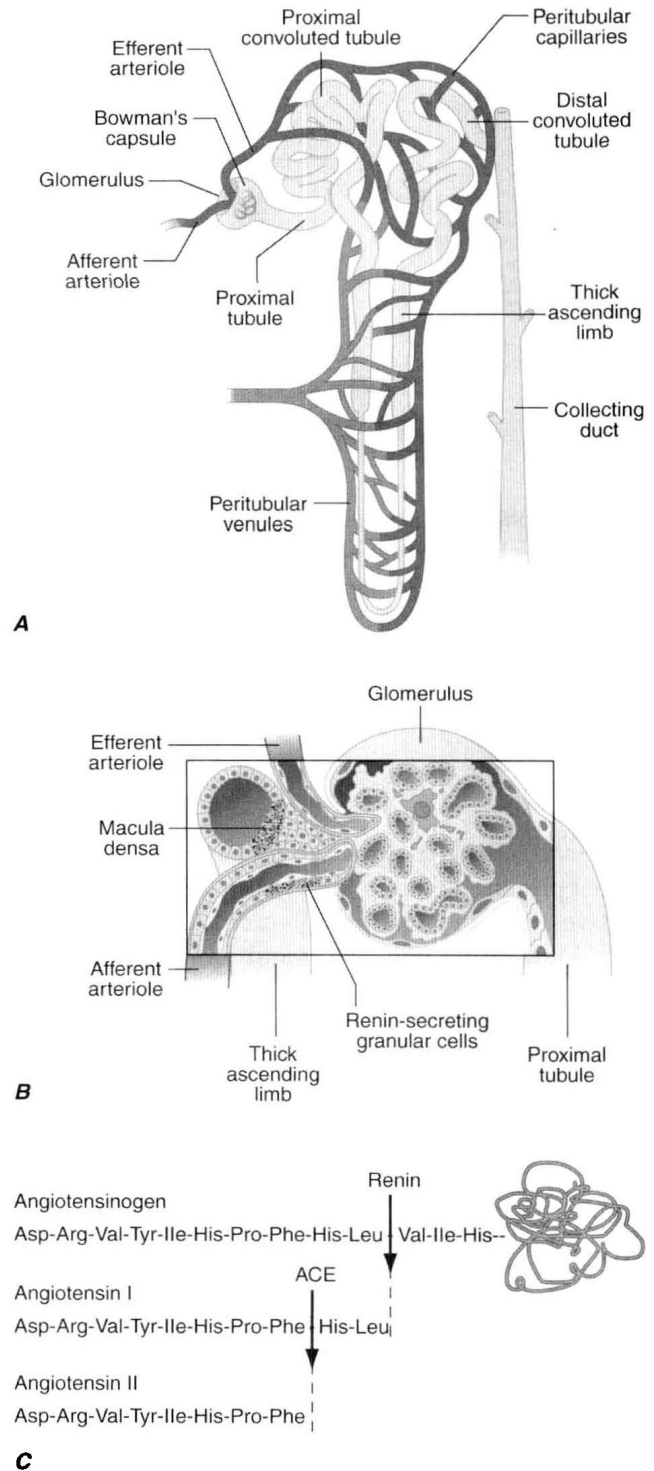
FIGURE 1-2

Renal microcirculation and the renin-angiotensin system. **A.** Diagram illustrating relationships of the nephron with glomerular and peritubular capillaries. **B.** Expanded view of the glomerulus with its juxtaglomerular apparatus including the macula densa and adjacent afferent arteriole. **C.** Proteolytic processing steps in the generation of angiotensin II.

species enhance, while nitric oxide blunts tubuloglomerular feedback.

The third component underlying autoregulation of filtration rate involves angiotensin II. During states of reduced renal blood flow, renin is released from granular

cells within the wall of the afferent arteriole near the macula densa in a region called the juxtaglomerular apparatus (Fig. 1-2B). Renin, a proteolytic enzyme, catalyzes the conversion of angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II by angiotensin-converting enzyme (ACE) (Fig. 1-2C). Angiotensin II evokes vasoconstriction of the efferent arteriole, and the resulting increased glomerular hydrostatic pressure elevates filtration to normal levels.

MECHANISMS OF RENAL TUBULAR TRANSPORT

The renal tubules are composed of highly differentiated epithelia that vary dramatically in morphology and function along the nephron (Fig. 1-3). The cells lining the various tubular segments form monolayers connected to one another by a specialized region of the adjacent lateral membranes called the *tight junction*. Tight junctions form an occlusive barrier that separates the lumen of the tubule from the interstitial spaces surrounding the tubule. These specialized junctions also divide the cell membrane into discrete domains: the apical membrane faces the tubular lumen, and the basolateral membrane faces the interstitium. This physical separation of membranes allows cells to allocate membrane proteins and lipids asymmetrically to different regions of the membrane. Owing to this feature, renal epithelial cells are said to be *polarized*. The asymmetrical assignment of membrane proteins, especially proteins mediating transport processes, provides the structural machinery for directional movement of fluid and solutes by the nephron.

FIGURE 1-3

Transport activities of the major nephron segments. Representative cells from five major tubular segments are illustrated with the lumen side (apical membrane) facing left and interstitial side (basolateral membrane) facing right. **A.** Proximal tubular cells. **B.** Typical cell in the thick ascending limb of the loop of Henle. **C.** Distal convoluted tubular cell. **D.** Overview of entire nephron. **E.** Cortical collecting duct cells. **F.** Typical cell in the inner medullary collecting duct. The major membrane transporters, channels, and pumps are drawn with arrows indicating the direction of solute or water movement. For some events, the stoichiometry of transport is indicated by numerals preceding the solute. Targets for major diuretic agents are labeled. The actions of hormones are illustrated by arrows with plus signs for stimulatory effects and lines with perpendicular ends for inhibitory events. Dotted lines indicate free diffusion across cell membranes. The dashed line indicates water impermeability of cell membranes in the thick ascending limb and distal convoluted tubule.

6 EPITHELIAL SOLUTE TRANSPORT

There are two types of epithelial transport. The movement of fluid and solutes sequentially across the apical and basolateral cell membranes (or vice versa) mediated by transporters, channels, or pumps is called *cellular transport*. By contrast, movement of fluid and solutes through the narrow passageway between adjacent cells is called *paracellular transport*. Paracellular transport occurs through tight junctions, indicating that they are not completely "tight." Indeed, some epithelial cell layers allow rather robust paracellular transport to occur (*leaky epithelia*), whereas other epithelia have more effective tight junctions (*tight epithelia*). In addition, because the ability of ions to flow through the paracellular pathway determines the electrical resistance across the epithelial monolayer, leaky and tight epithelia are also referred to as low- and high-resistance epithelia, respectively. The proximal tubule contains leaky epithelia, whereas distal nephron segments, such as the collecting duct, contain tight epithelia. Leaky epithelia are best suited for bulk fluid reabsorption, whereas tight epithelia allow for more refined control and regulation of transport.

MEMBRANE TRANSPORT

Cell membranes are composed of hydrophobic lipids that repel water and aqueous solutes. The movement of solutes and water across cell membranes is made possible by discrete classes of integral membrane proteins, including channels, pumps, and transporters. These different components mediate specific types of transport activities, including *active transport* (pumps), *passive transport* (channels), *facilitated diffusion* (transporters), and *secondary active transport* (co-transporters). Different cell types in the mammalian nephron are endowed with distinct combinations of proteins that serve specific transport functions. Active transport requires metabolic energy generated by the hydrolysis of ATP. The classes of protein that mediate active transport ("pumps") are ion-translocating ATPases, including the ubiquitous Na$^+$/K$^+$-ATPase, the H$^+$-ATPases, and Ca^{2+}-ATPases. Active transport can create asymmetrical ion concentrations across a cell membrane and can move ions against a chemical gradient. The potential energy stored in a concentration gradient of an ion such as Na$^+$ can be utilized to drive transport through other mechanisms (secondary active transport). Pumps are often *electrogenic*, meaning they can create an asymmetrical distribution of electrostatic charges across the membrane and establish a voltage or membrane potential. The movement of solutes through a membrane protein by simple diffusion is called passive transport. This activity is mediated by channels created by selectively permeable membrane proteins, and it allows solute or water to move across a

membrane driven by favorable *concentration gradients* or *electrochemical potential*. Examples in the kidney include water channels (aquaporins), K$^+$ channels, epithelial Na$^+$ channels, and Cl$^-$ channels. Facilitated diffusion is a specialized type of passive transport mediated by simple transporters called *carriers* or *uniporters*. For example, a family of hexose transporters (GLUTs 1–13) mediates glucose uptake by cells. These transporters are driven by the concentration gradient for glucose, which is highest in extracellular fluids and lowest in the cytoplasm due to rapid metabolism. Many transporters operate by translocating two or more ions/solutes in concert either in the same direction (*symporters* or *co-transporters*) or in opposite directions (*antiporters* or *exchangers*) across the cell membrane. The movement of two or more ions/solutes may produce no net change in the balance of electrostatic charges across the membrane (*electroneutral*), or a transport event may alter the balance of charges (*electrogenic*). Several inherited disorders of renal tubular solute and water transport occur as a consequence of mutations in genes encoding a variety of channels, transporter proteins, and their regulators (Table 1-1)

SEGMENTAL NEPHRON FUNCTIONS

Each anatomic segment of the nephron has unique characteristics and specialized functions that enable selective transport of solutes and water (Fig. 1-3). Through sequential events of reabsorption and secretion along the nephron, tubular fluid is progressively conditioned into final urine for excretion. Knowledge of the major tubular mechanisms responsible for solute and water transport is critical for understanding hormonal regulation of kidney function and the pharmacologic manipulation of renal excretion.

PROXIMAL TUBULE

The proximal tubule is responsible for reabsorbing ~60% of filtered NaCl and water, as well as ~90% of filtered bicarbonate and most critical nutrients such as glucose and amino acids. The proximal tubule utilizes both cellular and paracellular transport mechanisms. The apical membrane of proximal tubular cells has an expanded surface area available for reabsorptive work created by a dense array of microvilli called the *brush border*, and comparatively leaky tight junctions further enable high-capacity fluid reabsorption.

Solute and water pass through these tight junctions to enter the lateral intercellular space where absorption by the peritubular capillaries occurs. Bulk fluid reabsorption by the proximal tubule is driven by high oncotic pressure and low hydrostatic pressure within the peritubular capillaries. Physiologic adjustments in GFR made by changing efferent arteriolar tone cause proportional changes in reabsorption, a phenomenon known as

TABLE 1-1

INHERITED DISORDERS AFFECTING RENAL TUBULAR ION AND SOLUTE TRANSPORT		
DISEASE OR SYNDROME	**GENE**	**OMIMA[a]**
Disorders Involving the Proximal Tubule		
Proximal renal tubular acidosis	Sodium bicarbonate co-transporter (*SLC4A4*, 4q21)	604278
Faconi-Bickel syndrome	Glucose transporter-2 (*SLC2A2* 3q26.1-q26.3)	227810
Isolated renal glycosuria	Sodium glucose co-transporter (*SLC5A2*,16p11.2)	233100
Cystinuria, type I	Cystine, dibasic and neutral amino acid transporter (*SLC3A1*, 2p16.3)	220100
Cystinuria, non-type I	Amino acid transporter, light subunit (*SLC7A9*, 19q13.1)	600918
Lysinuric protein intolerance	Amino acid transporter (*SLC7A7*, 4q11.2)	222700
Hereditary hypophosphatemic rickets with hypercalcemia	Sodium phosphate co-transporter (*SLC34A3*, 9q34)	241530
Renal hypouricemia	Urate-anion exchanger (*SLC22A12*, 11q13)	220150
Dent's disease	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)	300009
X-linked recessive nephrolithiasis with renal failure	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)	310468
X-linked recessive hypophosphatemic rickets	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)	307800
Disorders Involving the Loop of Henle		
Bartter's syndrome, type 1	Sodium potassium-chloride co-transporter (*SLC12A1*,15q15-q21)	241200
Bartter's syndrome, type 2	Potassium channel, ROMK (*KCNJ1*, 11q24)	601678
Bartter's syndrome, type 3	Chloride channel, ClC-Kb (*CLCNKB*, 1p36)	602023
Bartter's syndrome with sensorineural deafness	Chloride channel accessory subunit, barttin (*BSND*, 1p31)	602522
Autosomal dominant hypocalcemia with Bartter-like syndrome	Calcium-sensing receptor (*CASR*, 3q13.3-q21)	601199
Familial hypocalciuric hypercalcemia	Calcium-sensing receptor (*CASR*, 3q13.3-q21)	145980
Primary hypomagnesemia	Claudin-16 or paracellin-1 (*CLDN16* or *PCLN1*, 3q27)	248250
Isolated renal magnesium loss	Sodium potassium ATPase, γ_1-subunit (*ATP1G1*, 11q23)	154020
Primary hypomagnesemia with secondary hypocalcemia	Melastatin-related transient receptor potential cation channel 6 (*TRPM6*, 9q22)	602014
Disorders Involving the Distal Tubule and Collecting Duct		
Gitelman's syndrome	Sodium-chloride co-transporter (*SLC12A3*, 16q13)	263800
Pseudoaldosteronism (Liddle's syndrome)	Epithelial sodium channel β and γ subunits (*SCNN1B, SCNN1G*, 16p13-p12)	177200
Recessive pseudohypoaldosteronism type 1	Epithelial sodium channel, α, β, and γ subunits (*SCNN1A*, 12p13; *SCNN1B, SCNN1G*, 16p13-p12)	264350
Pseudohypoaldosteronism type 2 (Gordon's hyperkalemia-hypertension syndrome)	Kinases WNK-1, WNK-4 (*WNK1*, 12p13; *WNK4*, 17q21-q22)	145260

(Continued)

TABLE 1-1 (CONTINUED)

INHERITED DISORDERS AFFECTING RENAL TUBULAR ION AND SOLUTE TRANSPORT

DISEASE OR SYNDROME	GENE	OMIM^a
Disorders Involving the Distal Tubule and Collecting Duct		
X-linked nephrogenic diabetes insipidus	Vasopressin V$_2$ receptor (AVPR2, Xq28)	304800
Nephrogenic diabetes insipidus (autosomal)	Water channel, aquaporin-2 (AQP2, 12q13)	125800
Distal renal tubular acidosis, autosomal dominant	Anion exchanger-1 (SLC4A1, 17q21-q22)	179800
Distal renal tubular acidosis, autosomal recessive	Anion exchanger-1 (SLC4A1, 17q21-q22)	602722
Distal renal tubular acidosis with neural deafness	Proton ATPase, β1 subunit (ATP6B1, 2cen-q13)	192132
Distal renal tubular acidosis with normal hearing	Proton ATPase, 116-kD subunit (ATP6N1B, 7q33-q34)	602722

^{a}Online Mendelian Inheritance in Man database (http://www.ncbi.nlm.nih.gov/Omim).

glomerulotubular balance. For example, vasoconstriction of the efferent arteriole by angiotensin II will increase glomerular capillary hydrostatic pressure but lower pressure in the peritubular capillaries. At the same time, increased GFR and filtration fraction cause a rise in oncotic pressure near the end of the glomerular capillary. These changes, a lowered hydrostatic and increased oncotic pressure, increase the driving force for fluid absorption by the peritubular capillaries.

Cellular transport of most solutes by the proximal tubule is coupled to the Na$^+$ concentration gradient established by the activity of a basolateral Na$^+$/K$^+$-ATPase (Fig. 1-3A). This active transport mechanism maintains a steep Na$^+$ gradient by keeping intracellular Na$^+$ concentrations low. Solute reabsorption is coupled to the Na$^+$ gradient by Na$^+$-dependent co-transporters such as Na$^+$-glucose and the Na$^+$-phosphate. In addition to the paracellular route, water reabsorption also occurs through the cellular pathway enabled by constitutively active water channels (aquaporin-1) present on both apical and basolateral membranes. In addition, small, local *osmotic gradients* close to plasma membranes generated by cellular Na$^+$ reabsorption are likely responsible for driving directional water movement across proximal tubule cells.

Proximal tubular cells reclaim bicarbonate by a mechanism dependent on carbonic anhydrases. Filtered bicarbonate is first titrated by protons delivered to the lumen by Na$^+$/H$^+$ exchange. The resulting carbonic acid is metabolized by brush border carbonic anhydrase to water and carbon dioxide. Dissolved carbon dioxide then diffuses into the cell, where it is enzymatically hydrated by cytoplasmic carbonic anhydrase to reform carbonic acid. Finally, intracellular carbonic acid dissociates into free protons and bicarbonate anions, and bicarbonate exits

the cell through a basolateral Na$^+$/HCO$_3^-$ co-transporter. This process is saturable, resulting in renal bicarbonate excretion when plasma levels exceed the physiologically normal range (24–26 meq/L). Carbonic anhydrase inhibitors such as acetazolamide, a class of weak diuretic agents, block proximal tubule reabsorption of bicarbonate and are useful for alkalinizing the urine.

Chloride is poorly reabsorbed throughout the first segment of the proximal tubule, and a rise in Cl$^-$ concentration counterbalances the removal of bicarbonate anion from tubular fluid. In later proximal tubular segments, cellular Cl$^-$ reabsorption is initiated by apical exchange of cellular formate for higher luminal concentrations of Cl$^-$. Once in the lumen, formate anions are titrated by H$^+$ (provided by Na$^+$/H$^+$ exchange) to generate neutral formic acid, which can diffuse passively across the apical membrane back into the cell where it dissociates a proton and is recycled. Basolateral Cl$^-$ exit is mediated by a K$^+$/Cl$^-$ co-transporter.

Reabsorption of glucose is nearly complete by the end of the proximal tubule. Cellular transport of glucose is mediated by apical Na$^+$-glucose co-transport coupled with basolateral, facilitated diffusion by a glucose transporter. This process is also saturable, leading to glycosuria when plasma levels exceed 180–200 mg/dL, as seen in untreated diabetes mellitus.

The proximal tubule possesses specific transporters capable of secreting a variety of organic acids (carboxylate anions) and bases (mostly primary amine cations). Organic anions transported by these systems include urate, ketoacid anions, and several protein-bound drugs not filtered at the glomerulus (penicillins, cephalosporins, and salicylates). Probenecid inhibits renal organic anion secretion and can be clinically useful for raising plasma

concentrations of certain drugs like penicillin and oseltamivir. Organic cations secreted by the proximal tubule include various biogenic amine neurotransmitters (dopamine, acetylcholine, epinephrine, norepinephrine, and histamine) and creatinine. Certain drugs like cimetidine and trimethoprim compete with endogenous compounds for transport by the organic cation pathways. These drugs elevate levels of serum creatinine, but this change does not reflect changes in the GFR.

The proximal tubule, through distinct classes of Na$^+$-dependent and Na$^+$-independent transport systems, reabsorbs amino acids efficiently. These transporters are specific for different groups of amino acids. For example, cystine, lysine, arginine, and ornithine are transported by a system comprising two proteins encoded by the SLC3A1 and SLC7A9 genes. Mutations in either SLC3A1 or SLC7A9 impair reabsorption of these amino acids and cause the disease cystinuria. Peptide hormones, such as insulin and growth hormone, β$_2$-microglobulin, and other small proteins, are taken up by the proximal tubule through a process of absorptive endocytosis and are degraded in acidified endocytic vesicles or lysosomes. Acidification of these vesicles depends on a "proton pump" (vacuolar H$^+$-ATPase) and a Cl$^-$ channel. Impaired acidification of endocytic vesicles because of mutations in a Cl$^-$ channel gene (CLCN5) causes low-molecular-weight proteinuria in Dent's disease. Renal ammoniagenesis from glutamine in the proximal tubule provides a major tubular fluid buffer to ensure excretion of secreted H$^+$ ion as NH$_4^+$ by the collecting duct. Cellular K$^+$ levels inversely modulate ammoniagenesis, and in the setting of high serum K$^+$ from hypoaldosteronism, reduced ammoniagenesis facilitates the appearance of type IV renal tubular acidosis.

LOOP OF HENLE

The loop of Henle consists of three major segments: descending thin limb, ascending thin limb, and ascending thick limb. These divisions are based on cellular morphology and anatomic location, but also correlate well with specialization of function. Approximately 15–25% of filtered NaCl is reabsorbed in the loop of Henle, mainly by the thick ascending limb. The loop of Henle has a critically important role in urinary concentrating ability by contributing to the generation of a hypertonic medullary interstitium in a process called countercurrent multiplication. The loop of Henle is the site of action for the most potent class of diuretic agents (loop diuretics) and contributes to reabsorption of calcium and magnesium ions.

The descending thin limb is highly water permeable owing to dense expression of constitutively active aquaporin-1 water channels. By contrast, water permeability is negligible in the ascending limb. In the thick ascending limb, there is a high level of secondary active salt transport

enabled by the Na$^+$/K$^+$/2Cl$^-$ co-transporter on the apical membrane in series with basolateral Cl$^-$ channels and Na$^+$/K$^+$-ATPase (Fig. 1-3B). The Na$^+$/K$^+$/2Cl$^-$ co-transporter is the primary target for loop diuretics. Tubular fluid K$^+$ is the limiting substrate for this co-transporter (tubular concentration of K$^+$ is similar to plasma, about 4 meq/L), but it is maintained by K$^+$ recycling through an apical potassium channel. An inherited disorder of the thick ascending limb, Bartter's syndrome, results in a salt-wasting renal disease associated with hypokalemia and metabolic alkalosis. Loss-of-function mutations in one of four distinct genes encoding components of the Na$^+$/K$^+$/2Cl$^-$ co-transporter (NKCC2), apical K$^+$ channel (KCNJ1), or basolateral Cl$^-$ channel (CLCNKB, BSND) can cause the syndrome.

Potassium recycling also contributes to a positive electrostatic charge in the lumen relative to the interstitium, which promotes divalent cation (Mg^{2+} and Ca^{2+}) reabsorption through the paracellular pathway. A Ca^{2+}-sensing, G-protein coupled receptor (CaSR) on basolateral membranes regulates NaCl reabsorption in the thick ascending limb through dual signaling mechanisms utilizing either cyclic adenosine monophosphate (AMP) or eicosanoids. This receptor enables a steep relationship between plasma Ca^{2+} levels and renal Ca^{2+} excretion. Loss-of-function mutations in CaSR cause familial hypercalcemic hypocalciuria because of a blunted response of the thick ascending limb to exocellular Ca^{2+}. Mutations in CLDN16 encoding paracellin-1, a transmembrane protein located within the tight junction complex, leads to familial hypomagnesemia with hypercalcuria and nephrocalcinosis, suggesting that the ion conductance of the paracellular pathway in the thick limb is regulated. Mutations in TRPM6 encoding an Mg^{2+} permeable ion channel also cause familial hypomagnesemia with hypocalcemia. A molecular complex of TRPM6 and TRPM7 proteins is critical for Mg^{2+} reabsorption in the thick ascending limb of Henle.

The loop of Henle contributes to urine concentrating ability by establishing a hypertonic medullary interstitium, which promotes water reabsorption by a more distal nephron segment, the inner medullary collecting duct. Countercurrent multiplication produces a hypertonic medullary interstitium using two countercurrent systems: the loop of Henle (opposing descending and ascending limbs) and the vasa recta (medullary peritubular capillaries enveloping the loop). The countercurrent flow in these two systems helps maintain the hypertonic environment of the inner medulla, but NaCl reabsorption by the thick ascending limb is the primary initiating event. Reabsorption of NaCl without water dilutes the tubular fluid and adds new osmoles to the interstitial fluid surrounding the thick ascending limb. Because the descending thin limb is highly water permeable, osmotic equilibrium occurs between the descending-limb tubular fluid and the interstitial space, leading to progressive