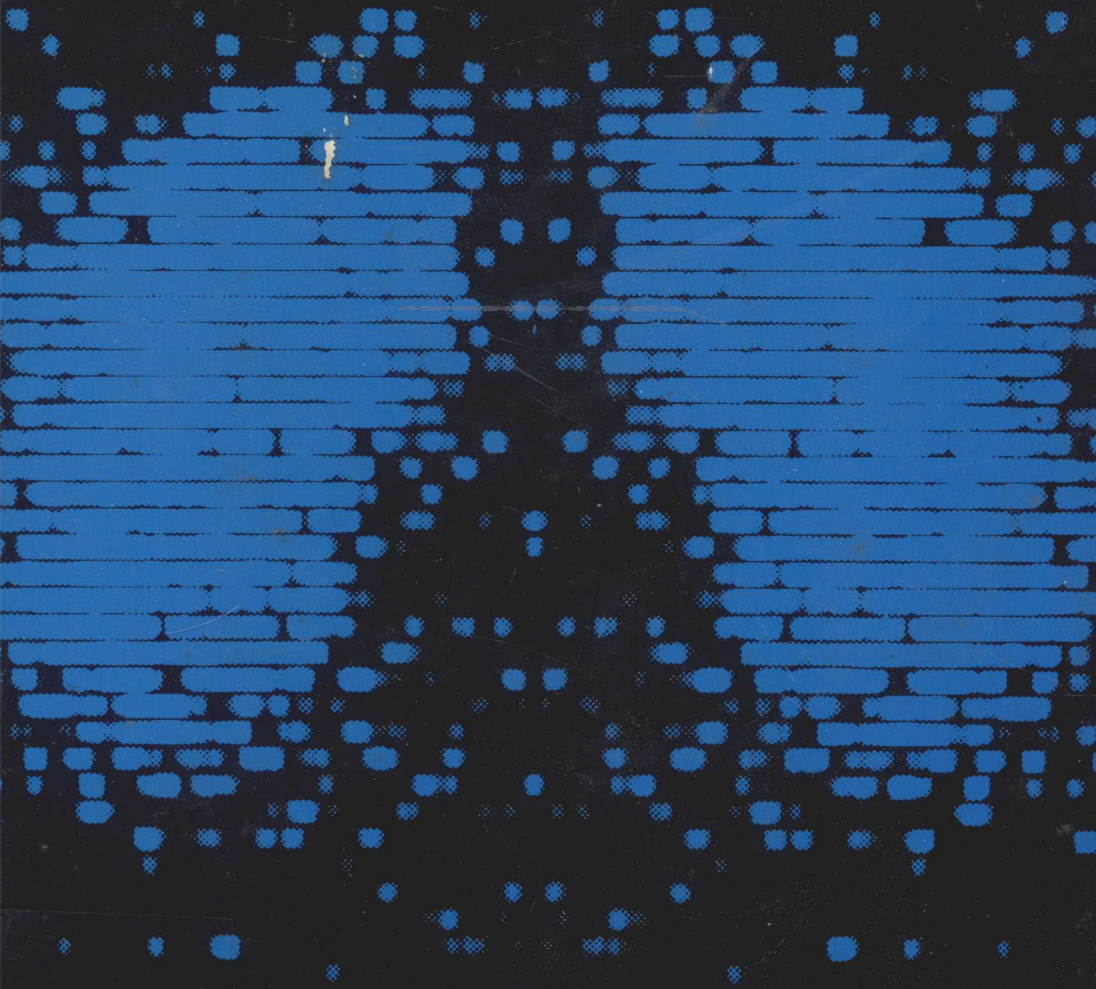
Second Edition

Renal and Electrolyte Disorders

Edited by
Robert W. Schrier, M.D.



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Robert W. Schrier, M.D.

Professor and Chairman, Department of Medicine,
University of Colorado School of Medicine,
Denver, Colorado

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Renal and Electrolyte Disorders

To Barbara
and
David, Debbie,
Doug, Derek, and
Denise

Contributing Authors

Allen C. Alfrey, M.D.
Professor of Medicine, and Co-Head, Division of Renal Diseases, University of Colorado School of Medicine; Chief, Renal Services, Veterans Administration Hospital, Denver

Robert J. Anderson, M.D.
Associate Professor of Medicine, University of Colorado School of Medicine, Denver

Tomas Berl, M.D.
Associate Professor of Medicine, University of Colorado School of Medicine; Director, Home Dialysis Training Unit, University Hospital, Denver

John D. Conger, M.D.
Associate Professor of Medicine, University of Colorado School of Medicine; Director, Hemodialysis Unit, Veterans Administration Hospital, Denver

Patricia A. Gabow, M.D.
Associate Professor of Medicine, University of Colorado School of Medicine; Chief, Nephrology Section, Denver General Hospital, Denver

Richard J. Glassock, M.D.
Professor of Medicine, UCLA School of Medicine, Los Angeles; Chief, Division of Nephrology and Hypertension, Los Angeles County Harbor-UCLA Medical Center, Torrance, California

Stephen J. Guggenheim, M.D.
Associate Professor of Pathology and Medicine, University of Colorado School of Medicine; Assistant Chief, Laboratory Service, Veterans Administration Hospital, Denver

Martin P. Hutt, M.D.
Professor of Medicine, University of Colorado School of Medicine; Chief, Renal Clinic, Colorado General Hospital, Denver

William D. Kaehny, M.D.
Associate Professor of Medicine, University of Colorado School of Medicine; Director, Home Dialysis Unit, Veterans Administration Hospital, Denver

James P. Knochel, M.D.
Professor and Vice Chairman; Department of Internal Medicine, The University of Texas Southwestern Medical School at Dallas; Chief, Medical Service, and Chief, Renal Section, Department of Internal Medicine, Dallas Veterans Administration Medical Center

Stuart L. Linas, M.D.
Assistant Professor of Medicine, University of Colorado School of Medicine; Attending Physician, Denver General Hospital, Denver

Keith M. McDonald, M.D.
Clinical Professor of Medicine, University of Colorado School of Medicine, Denver

Rawle M. McIntosh, M.D. (deceased)
Professor of Pediatrics and Medicine, University of Colorado School of Medicine, Denver

Thomas R. Miller, M.D.
Assistant Clinical Professor of Internal Medicine, The University of Tennessee Center for the Health Sciences, College of Medicine, Knoxville, Tennessee

Linda N. Peterson, Ph.D.
Assistant Professor of Physiology and Medicine, University of Colorado School of Medicine, Denver

Mordecai M. Popovtzer, M.D.
Professor of Medicine, Hebrew University–Hadassah Medical School, Jerusalem; Head of Nephrology Services, Hadassah University Hospital, Kiryat Hadassah, Jerusalem, Israel.

Robert W. Schrier, M.D.
Professor and Chairman, Department of Medicine, University of Colorado School of Medicine, Denver

Preface

The second edition of *Renal and Electrolyte Disorders* is the result of the enthusiastic acceptance of the first edition by medical students, house staff, trainees in nephrology, and practitioners. We are very appreciative of this acceptance and have made every effort to update and improve the contents of the second edition. The central theme of *Renal and Electrolyte Disorders,* however, remains the pathophysiological understanding of disease. It is our belief that a knowledge of pathophysiology is necessary to approach diagnosis and treatment of disease states in a systematic, logical, and effective manner.

As in the first edition, the majority of authors are members of the Division of Renal Diseases of the Department of Medicine at the University of Colorado School of Medicine. We hope that this approach has enabled us to maintain continuity and coordination of style and content. Dr. Richard Glassock, Professor of Medicine at the UCLA School of Medicine and Chief of Nephrology at Los Angeles County Harbor-UCLA Medical Center, however, was invited to co-author the chapters on proteinuria and nephrotic syndromes (Chapter 14) and clinical and immunopathological aspects of glomerulopathies (Chapter 15) in this second edition. The material on immunological models and mechanisms in renal disease (Chapter 15) and clinical aspects of glomerulopathies (Chapter 16) in the first edition have been combined in Chapter 15 of the second edition. Dr. James Knochel, Professor of Internal Medicine at the University of Texas Southwestern Medical School and Chief of Nephrology at the Dallas Veterans Administration Hospital, has co-authored Chapter 6 in the second edition and has included much important new information in the area of phosphorus depletion. These contributions of Drs. Glassock and Knochel have clearly strengthened the presentation of material in Chapters 6, 14, and 15 in the second edition. Other new contributions are by individuals who have joined the Division of Renal Diseases at the University of Colorado School of Medicine since the appearance of the first edition. Included are Drs. Robert Anderson, Linda Peterson, and Stuart Linas. They have made important contributions to the topics of sodium metabolism (Chapter 2), potassium metabolism (Chapter 3), and the renin-angiotensin-aldosterone system (Chapter 8). All other chapters also have been extensively rewritten and updated.

We wish to acknowledge and thank several individuals who reviewed various portions of the second edition, including Drs. Mortimer Levy, Fred Wright, Richard Tannen, Stuart S. Howard, Saulo Klahr, Jerome Kassirer, Adrian Katz, and Marshall Lindheimer. Linda Benson provided excellent secretarial support for the second edition.

R. W. S.

Renal and Electrolyte Disorders

Contents

1 Disorders of Water Metabolism

Robert W. Schrier
Tomas Berl

HISTORICAL AND EVOLUTIONARY ASPECTS OF RENAL CONCENTRATING AND DILUTING PROCESSES

In *From Fish to Philosopher,* Homer Smith [194] suggested that the concentrating capacity of the mammalian kidney may have played an important role in the evolution of various biological species, including *Homo sapiens.* An abbreviated schema of the evolutionary development of the nephron that he proposed is shown in Figure 1-1. He suggested that the earliest protovertebrates resided in a saltwater environment that had a composition similar to their own extracellular fluid (ECF). These species could therefore ingest freely from the surrounding sea without greatly disturbing the composition of their own *milieu interieur.* The elimination of wastes also was a simple process of propelling their own ECF, which contained the dissolved waste products, through conduits in their skin into the external saltwater environment. However, when these early vertebrates migrated into freshwater streams, the evolution of a relatively water-impermeable integument was mandatory to avoid fatal dilution from their hyposmotic, freshwater environment. Thus a vascular tuft, which we now call the glomerulus, developed, enabling the fish to filter the excess fluid from their blood.

Since salt preservation was extremely important in this freshwater environment, the proximal tubule, with its capacity for avid reabsorption of salt, evolved. Since this proximal tubule was also permeable to water, fluid was reabsorbed in an isosmotic manner. The proximal tubule thus answered the need for salt conservation but did not allow the excretion of hypotonic urine, which is mandatory for organisms ingesting hypotonic fluid from their freshwater environment. The need for such excretion was met by the development of the distal tubule, which could dilute urine. In this portion of the nephron, salt was reabsorbed without water, since the distal tubular epithelium was relatively impermeable to water. The fish could then excrete the excess solute-free water they had obtained from their freshwater environment without concomitantly losing their body salts.

Several million years later, after the problem of excreting large amounts of water without salt was solved by the evolution of a nephron with a glomerulus and a proximal and distal tubule, vertebrates began to reside on dry land. In this terrestrial environment the problem of salt conservation persisted, but the excretion of large volumes of fluid was no longer necessary; paradoxically, conservation of fluid was of primary importance in the new arid environment. The kidneys of reptiles, birds, and mammals, however, had glomeruli, which filtered

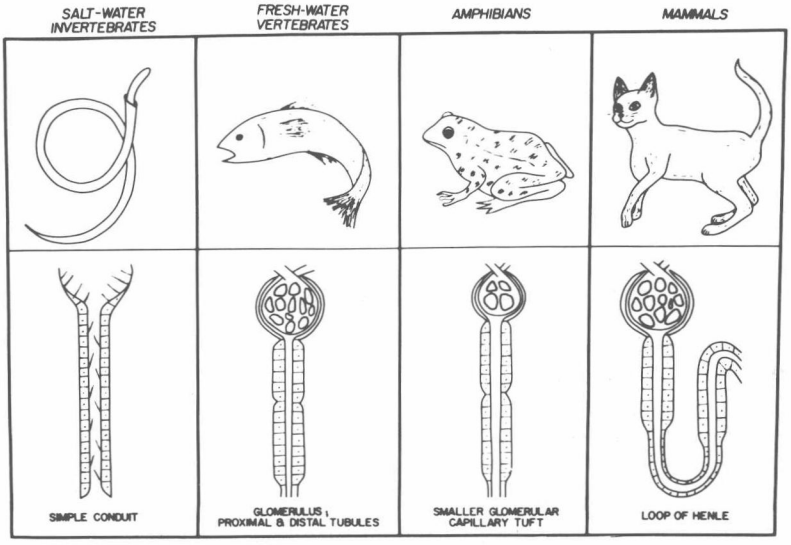

Figure 1-1. Evolutionary development of mammalian nephron. (Adapted from H. W. Smith, *From Fish to Philosopher: The Story of Our Internal Environment.* Boston: Little Brown, 1953. Reprinted by permission.)

large amounts of fluid and salt, even though excretion of only minute amounts of these substances was needed to maintain daily balance. In reptiles and birds the kidneys responded to this challenge by a decrease in the number of capillary loops in their glomerular tufts. In some fish, such as the sea horse and pipefish, which may have been the first vertebrates to return to the sea, aglomerular kidneys actually evolved. Tubular secretory systems also evolved in the nephron to allow elimination of nitrogenous wastes without the need for extremely large filtered volumes of fluid. Lastly, a relatively insoluble nitrogenous end product, uric acid, was produced, which could be excreted in supersaturated solutions with a minimal amount of water loss.

In mammals, however, the high pressure glomerular filters were maintained, but a system developed for concentrating their urine, namely, the countercurrent mechanism. Mammals, along with birds, are unique among vertebrates in possessing loops of Henle and in their ability to compensate for water deficits by elaborating a urine more concentrated than blood. As early as 1909 Peter [154] recognized the anatomical relationship between the ability to concentrate urine and the length of the loops of Henle in the kidney.

COUNTERCURRENT CONCENTRATING MECHANISM

In 1942 the functional significance of the loops of Henle was proposed when Drs. Kuhn and Ryffel of the physical chemistry department at the University

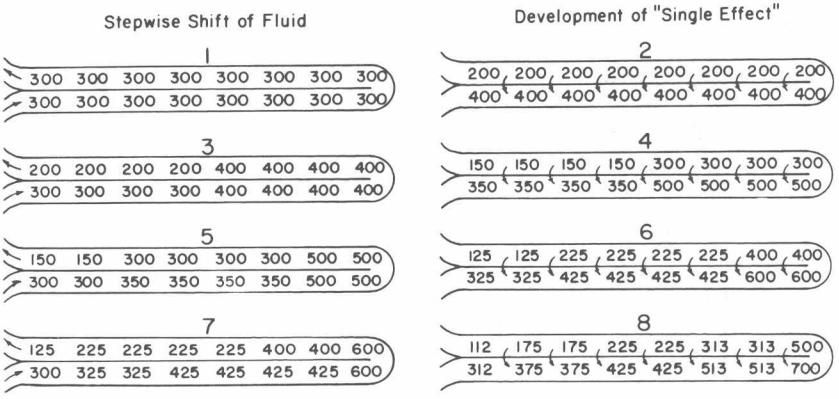

Figure 1-2. Countercurrent multiplier system. Active chloride and passive sodium transport without water in the ascending limb of Henle's loop establish the 200 mOsm/kg H_2O gradient between the hairpin loops, i.e., *single effect.* As new tubular fluid enters the descending limb from the cortical proximal tubule and tubular fluid leaves the medulla to enter the cortical portion of the distal nephron, the 200 mOsm/kg gradient is maintained (right) along the loops of Henle. This schema depicts the hairpin loops of Henle in juxtaposition, whereas in the mammalian kidney the medullary vasa recta and medullary interstitium are involved in the multiplication process. For clarity the movement of fluid through the hairpin loop (left) and the single effect (right) are depicted separately, although obviously they occur simultaneously in vivo. The net result of this countercurrent multiplication system is to amplify a 200 mOsm/kg H_2O gradient to 400 mOsm/kg H_2O, i.e., fluid enters at 300 mOsm/kg H_2O (step 7) yet reaches an osmolality of 700 mOsm/kg H_2O at the hairpin turn (step 8). The capacity of the countercurrent system to multiply the single effect is limited primarily by the relative length of the medullary loops of Henle. In man the countercurrent multiplier system increases a 200 mOsm/kg H_2O gradient to a 900 mOsm/kg H_2O gradient; specifically, fluid enters the medulla at 300 mOsm/kg H_2O and reaches 1200 mOsm/kg H_2O at the hairpin turn in the loop of Henle. Furthermore, in the presence of ADH the medullary collecting duct becomes water-permeable. This allows osmotic water equilibration to occur between collecting duct fluid and the medullary osmotic gradient, so that man can maximally concentrate urine to 1200 mOsm/kg H_2O. (From R. F. Pitts, *Physiology of the Kidney and Body Fluids* [3rd ed.]. Chicago: Year Book, 1974.)

of Basel, Switzerland, originated the concept of the countercurrent multiplier system for urine concentration [118]. The hypothesis states that a small difference in osmotic concentration (single effect, or *einzeln Effekt*) at any point between fluid flowing in opposite directions in two parallel tubes connected in hairpin manner can be multiplied many times along the length of the tubes. This is illustrated in Figure 1-2 for a 200 mOsm gradient. In the kidney such a gradient would result in a high osmolar concentration difference between the corticomedullary junction and the hairpin loop at the tip of the papilla (Fig. 1-3).

When the countercurrent multiplier system was proposed for the kidney by

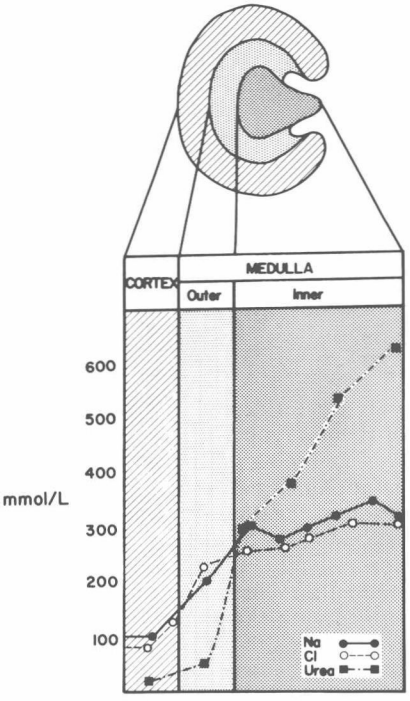

Figure 1-3. Corticomedullary concentration gradients for sodium chloride and urea (Adapted from K. J. Ullrich, K. Kramer, and J. W. Boylon, Present knowledge of the counter-current system in the mammalian kidney. *Prog. Cardiovasc. Dis.* 3:395–431, 1961. By permission of Grune & Stratton.)

Kuhn and Ryffel [118], the basic principle of a countercurrent exchange system was not new to biological systems. In contrast to countercurrent multiplication, countercurrent exchange is not initiated by an energy-requiring single effect. An example of a countercurrent exchange system in nature occurs in some arctic birds that walk around in snow or wade in ice water. If the temperature of their feet were maintained near core body temperature, the rate of heat loss would be considerable. The actual heat loss is negligible, however, since the feet of arctic birds have a temperature close to that of the snow or ice water. This is because the arteries and veins that emerge from the bird's thigh are intricately intertwined into a rete mirabile, and this juxtaposition of blood vessels facilitates the exchange of heat from arterial to venous blood (Fig. 1-4). The arterial blood therefore is cooled and carries little heat to the bird's feet, while the venous blood is warmed, thus preventing the cold peripheral blood from lowering core body temperature. In this manner these arctic birds can maintain their core body temperature with only a slight loss of calories and at the same time keep their feet refrigerated. Numerous other thermal countercurrent exchange systems are present in the limbs of other mammals, such as arctic dogs, porcupines, reindeer, whales, and seals.

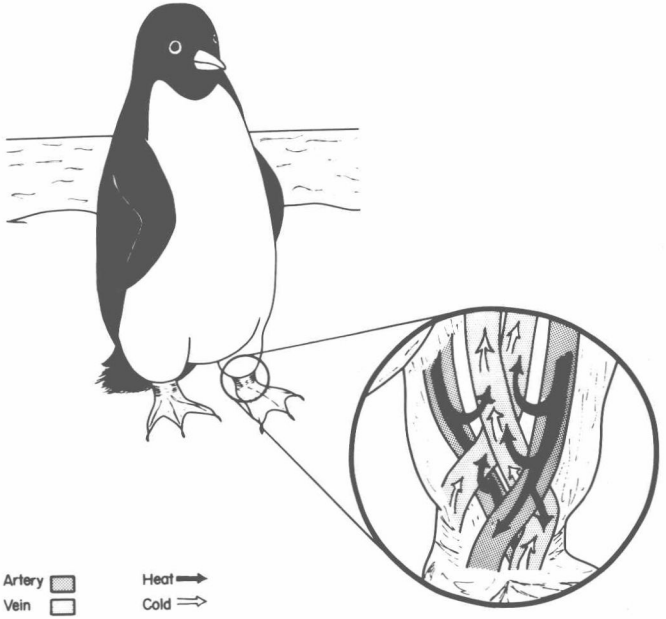

Figure 1-4. Countercurrent exchange mechanism for heat preservation in arctic bird.

Basic Determinants of the Concentrating and Diluting Process in the Kidney

With this background in mind we shall briefly discuss some of the factors that affect the concentrating and diluting processes in the mammalian kidney [89, 156, 210] before we proceed to the clinical disorders of water metabolism. Several aspects of the countercurrent mechanism are depicted in Figure 1-5. It is important to emphasize that many of these events are the same whether the final excreted urine is hypotonic or hypertonic to plasma.

Glomerular Filtration Rate and Proximal Tubular Reabsorption

The rates of glomerular filtration and proximal tubular reabsorption are important primarily in determining the rate of sodium and water delivery to the more distal portions of the nephron, where the renal concentrating and diluting mechanisms are operative. Since fluid reabsorption in the proximal tubule is isosmotic, owing to the water permeability of tubular epithelium, tubular fluid is neither concentrated nor diluted in the proximal portion of the nephron. Rather, after approximately 70 percent of glomerular filtrate is reabsorbed in the proximal tubules, the remaining 30 percent of fluid entering the loop of Henle is still isotonic to plasma. A decrease in glomerular filtration rate (GFR) or an increase in proximal tubular

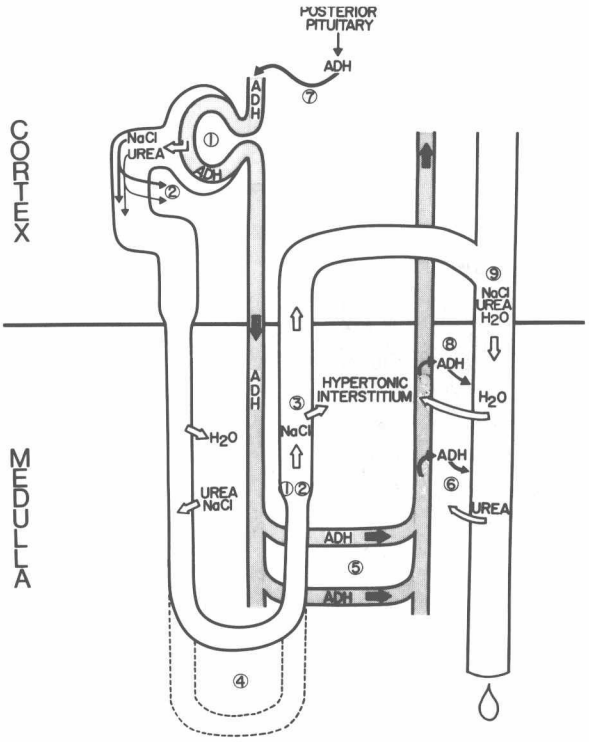

Figure 1-5. Potential determinants of the renal concentrating mechanism. (1) GFR as a determinant of fluid and solute delivery to ascending limb of loop of Henle. (2) Proximal tubular reabsorption as a determinant of fluid and solute delivery to ascending limb of loop of Henle. (3) Sodium chloride transport in water-impermeable ascending limb. (4) Length and integrity of long loops of Henle in inner medulla and papilla. (5) Rate of medullary blood flow in vasa recta. (6) Urea availability. (7) Presence of ADH. (8) Response of cortical and medullary collecting duct to ADH. (9) Rate of solute and water delivery as a determinant of completeness of osmotic equilibration with interstitium.

reabsorption, or both, may diminish the amount of fluid delivered to the distal nephron and thus limit the renal capacity to excrete water. Similarly a diminished GFR and increased proximal tubular reabsorption may limit the delivery of sodium chloride to the ascending limb, where the tubular transport of these ions without water initiates the formation of the hypertonic medullary interstitium. With diminished delivery of sodium chloride to the ascending limb, the resultant lowering of medullary hypertonicity will impair maximal renal concentrating capacity by limiting the osmotic gradient for water movement from the collecting duct.