Excretory and Endocrine functions of the kidney

The kidneys are the main excretory organs which eliminate in the urine, most metabolites primarily those containing nitrogen such as ammonia, urea and creatinine.

The production and excretion of urine is termed **diuresis**. Therefore the major function of the kidney involves the elimination of degradable by products, toxic substance, excess water, salt and some drugs from the body.

The kidney also maintains homeostasis by participating in the water-salt metabolism (eliminates excess salt & water) and also through osmoregulation. Hence, together with other mechanisms the kidney maintains the acid base balance of the body by modifying the rate of secretion of acid or alkaline phosphate when the blood becomes acidic or alkaline.

The kidney also mediates the synthesis of a number of compounds and also eliminates these compound e.g. Hippuric acid which is a product of glycocol and benzoic acid and ammonia which is a product of deamination of amino acid.

The kidney also functions in the secretion of the organic acids and bases including K^+ and H^+. They are also involved in lipid – protein, carbohydrate metabolism such as arginine metabolism, gluconeogenesis and peptide hydrolysis.

The kidneys are also a source of hormones e.g. Angiotensin II, D – hormones, prostaglandins and Erythropoietin. Erythropoietin, synthesized in the kidney, stimulates the production of red blood cells in the bone marrow and thus, regulates the oxygen carrying capacity of the blood.

Therefore the kidney maintains relative homeostasis by regulating the osmotic pressure, acid – base balance, synthesis, secretion and excretion of metabolic by products.

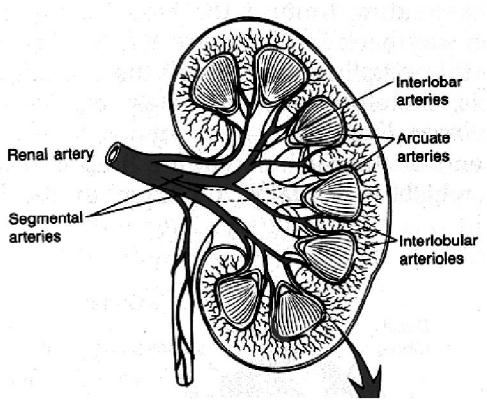


Diagram of the inner portions of the kidney

Summary of the functions of the kidney

- Conservation of water, fixed cations, glucose and amino acids. This implies the return to the body fluids of the amount of the substances required by the body's needs, with the excesses being excreted in the urine.
- Elimination of nitrogenous end products of protein metabolism, primarily urea (uric acid in birds), creatinine and ammonia.
- Elimination of excess H^+ and the maintenance of physiological pH of body fluids.
- Elimination of complex organic compound both endogenous and exogenous.
- Secretion of endocrine substances e.g. erythropoietin which assumes a role in normal hematopoiesis, renin which is involved in the regulation of aldosterone secretion by the adrenal cortex.

C.N.S. contribution to Renal Iintegration

Maximum urine concentration requires the secretion of antidiuretic hormone (ADH) or vasopressin by the hypothalamo – neurohypophyseal complex.

Reflexes from peripheral receptors (e.g. the postulated volume receptors) may influence renal functions by central nervous integration through hypothalamus and autonomic nervous system.

Hypothalamic mediation of the adenohypophyseal secretion represents another pathway through which the CNS may alter the output of hormones that modify renal functions.

Thyroid hormones and adenohypophyseal growth hormone exerts tropic effect on the kidney. The hormones that assume major importance in kidney function regulation are steroid secretions of the adrenal cortex and the hormones of the parathyroid gland e.g. the permissive action of the cortisol-type steroids is essential for maximal rates of H_20 excretion, while aldosterone regulates transport of K^+ into urine and the retention of Na^+ within body fluids.

The hormone of the parathyroid gland influences the rate of Calcium and Phosphate excretion into the urine.

The normal kidney demonstrates considerable functional autonomy and is adequately perfused with blood. Just a smalll percentage decrease in any given process can be produced by removing a specific neuro-humoral or endocrine mediator. Volumes of fluids passing through the kidney each day are of such magnitude that small percentage decreases in any given function usually represents a major crisis in terms of maintaining the physiological integrity of the body fluid compartments.

AnAtomy of the kidney

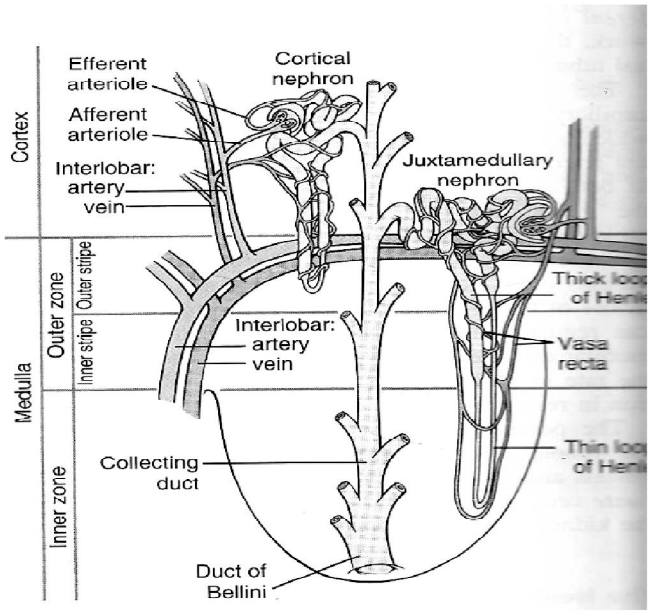
Nephrons, which are the functional units of kidney are of 2 types in mammals and are distinguished by:

- Locus of the origin i.e. the area of the cortex in which the glomeruli are found.
- The extent to which the loops of Henle penetrates the medulla.

Types of Nephron

(1) Cortical / corticomedullary nephrons: They arise from glomeruli located in the *peripheral* and *central area* of the kidney cortex with their loops of Henle extending into the corticomedullary junctional area and to variable levels of the outer medulla.

(2) Juxtamedullary nephrons: They originate from glomeruli situated in the deeper portion of the cortex adjacent to the corticomedullary junctional area with their loop of Henle, particularly the thin segments extending into medullary substance. Many of the longer looped nephrons penetrate to the medullary crest or renal papilla.



Schematic representation of cortical and juxtamedullary nephrons

PrinciPal mechanism of nePhron functions

A. Nephron filters a large portion of plasma ($^1/_5$) from glomeruli blood throughout the glomerular membrane into the tubular system.

B. As filtered fluids pass through the tubular systems, unwanted substances are allowed to pass out into urine, while wanted substances are reabsorbed back into the plasma through the peritubular capillary network

Functions oF the renal tubules

Filtration: An average of 21% of the blood pumped by the heart each minute flows through the kidneys. Of the total volume of blood plasma that flow through the glomerular capillaries, about 19% passes through the filtration membrane into the Bowman's capsule to become filtrate. In all of the nephrons of both kidneys, about 180lt of filtrate are produed each day but only about 1% or less of the filtate becomes urine.

Filtration is the passage of plasma, aqueous, ionic and crystalloid components of blood across the filtrates membrane of the renal corpuscles (Bowman's capsule and glomerulus) into the Bowman's space. Erythrocytes and most of the plasma proteins {albumin, a blood protein with a diameter slightly less than the openings in the filtration barriers enters the filtrate in trace (small) amount} do not filter through the glomerular membrane. In other respects, the glomerular filtrate prior to its entrance into the proximal convolutions is almost identical in composition and osmolality to plasma.

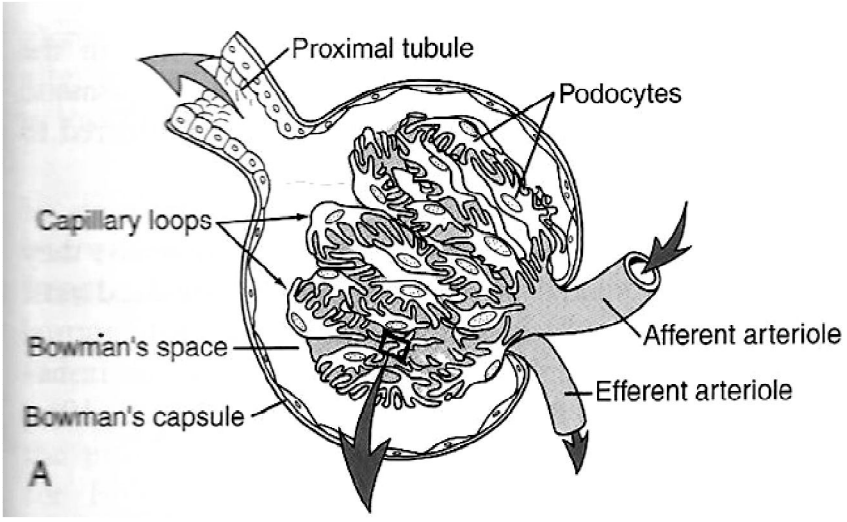


Diagram of the glomerulus and bowman's capsule

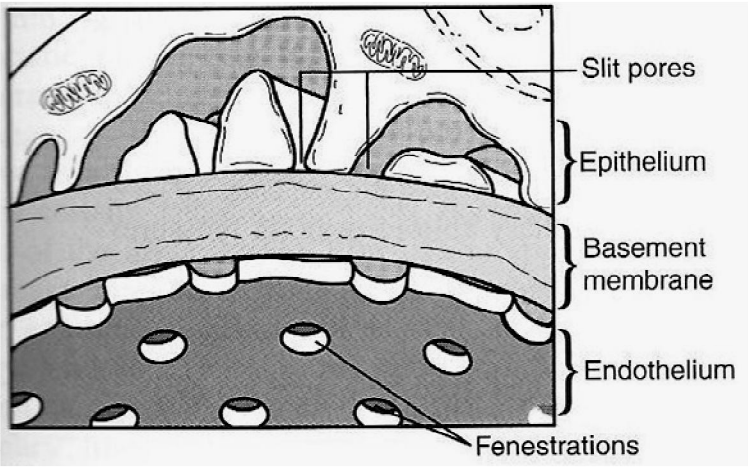


Diagram of the filtration membrane of the glomerulus and bowman's capsule

Re-absorption: About 99% of the filtrate volume is reabsorbed and enters the peritubular capillaries. Reabsorption as used here means that a substances moves from the tubular lumen to the peritubular capillary and it is not allowed to get into the collecting duct. The reabsorbed filtrate flows through the renal vein to enter the general circulation. Excess ions and metabolic waste e.g. urea, uric acid and creatinine are not readily reabsorbed. Therefore the small volume of urine produced contains a high concentration of metabolic waste products. Tubular reabsorption may result from either passive back diffusion or active cellular transport.

Secretion: Tubular secretion is similar to reabsorption except that substances enter the renal the renal tubules instead of leaving it. Tubular secretion can either be active or passive. e.g. NH_3 diffuses into the lumen of the nephron whereas H^+, K^+, creatinine, histamine & penicillin are actively transported into the nephrons.

SPECIFIC FUNCTIONS OF NEPHRON

The glomeruli and the proximal convoluted tubules: The glomeruli function primarily as filters**. The glomeruli membrane is composed of the endothelium of the glomeruli capillaries, a basement membrane and the invaginations of the Bowman's capsule.**

The membrane is of differential permeability that permits the passage of aqueous, ionic and crystalloid components of blood into the Bowman's space.

Erythrocytes and most of the plasma proteins do not filter through the membrane.

Proximal convoluted tubule is the primary site for reabsorbing solute and water. Tubular fluid near the end of the PCT is devoid of glucose and amino acids and most of the filtered proteins and has a fluid- plasma osmolal ratio of 1.

Quantitative estimates indicate that only 20% of the original glomerular filtrate remains after its passage through the PCT. In summary, the primary function of the PCT is to return 70% of the glomerular filtrate into the peritubular blood and hence into the systemic circulation.

When plasma glucose concentrations are normal, all of the filtered glucose is transported from the tubular fluid of the PCT into the plasma.

Amino acids are almost entirely removed (reabsorbed) from the proximal tubular fluid. The major determinants of PCT reabsorption apparently are:

1. Active transport of Na against an electrochemical gradient, from the tubular fluid into the peritubular interstitial fluid and capillary blood.
2. H^+ -Na^+ exchange processes
3. Reabsorptions of glucose

Chloride either diffuses along with Na^+ to maintain electrical neutrality or may also be transported by some carrier system.

Other substances that are actively transported from the PCT includes proteins, Na^+, K^+, Ca^{2+}, HCO_3^-, CL^-. The PCT is permeable to water. As solute molecules are transported from the PCT to the peritubular capillaries, water moves by osmosis in the same direction.

N.B: Difference between osmolality & osmolarity, active and passive transport.

Consequently, 65% of the glomerular filtrate volume is reabsorbed from the PCT. Creatinine and urea which are other nitrogenous components of glomerular filtrate are differentially affected by events in the PCT. Creatinine which is not reabsorbed by the nephrons becomes more concentrated as reabsorption proceeds while urea on the other hand diffuses readily across most biological membranes. Approximately 30-40% of filtered urea is reabsorbed in the PCT. H^+ is actively secreted in the PCT.

How? The epithelial cells secrete large quantities of H^+ across the wall of the nephrone into the filtrate.

Loop of Henle: Tubular fluids in Henle's loops become increasingly hypertonic as it passes through the medulla. The descending limb of Henle's loop (DLH) is apparently permeable to the

passage of ions & crystalloids. Both NaCl and urea are added by passive diffusion to the tubular fluid in this segment from the medullary interstitium. Fluids from the tip of Henle's loop are almost equal in composition and the osmolality to the medullary interstitial fluid. The initial segment of the ascending limb of Henle's loop (ALH) may be less permeable than the descending, but some equilibration occur between tubular fluids and medullar interstitium. **LH, therefore functions as a counter current diffusion system in concert/association with the vasa recta**, as NaCl and urea diffuse circuitously from the ascending segment into the medullary interstitium and into the descending segment.

The medullary segment of the thick ascending LH is relatively impermeable to water and it is the site of active transport system that translocates chloride (accompanied by sodium) against the significant concentration from the tubular fluid into the interstitial fluid into the interstitial fluid of the of the inner medulla. Since NaCl is reabsorbed at this site into the interstitial fluid, the tubular fluid becomes increasingly dilute.

N.B.: Water excretion (elimination of dilute urine) is not a passive process solely related to the absence of ADH. The active transport of chloride (accompanied by sodium) from the relatively water– impermeable ascending LH represents an essential energy dependent process in the formation of dilute urine.

Active chloride transport from the thick ascending loop of Henle could supply NaCl to be carried into and sequestered within the **counter current multiplier**. NaCl and particularly urea apparently can be concentrated solely by passive diffusion within the counter current multiplier system of the thin portion of the LH and side by side the apposed descending and ascending vasa recta. The maintenance of the gradient is enhanced by the progressive decrease in medullary blood flow from the inner medulla to the medullary crest or papilla.

N. B. the daily production of primary urine (glomerular filtrate) is about 150 – 180 liters, but due to tubular reabsorption of H_20 and numerous substances from the primary urine, only 1-1.5 liters of the secondary urine is excreted daily.

concentrating mechanism of the kidney

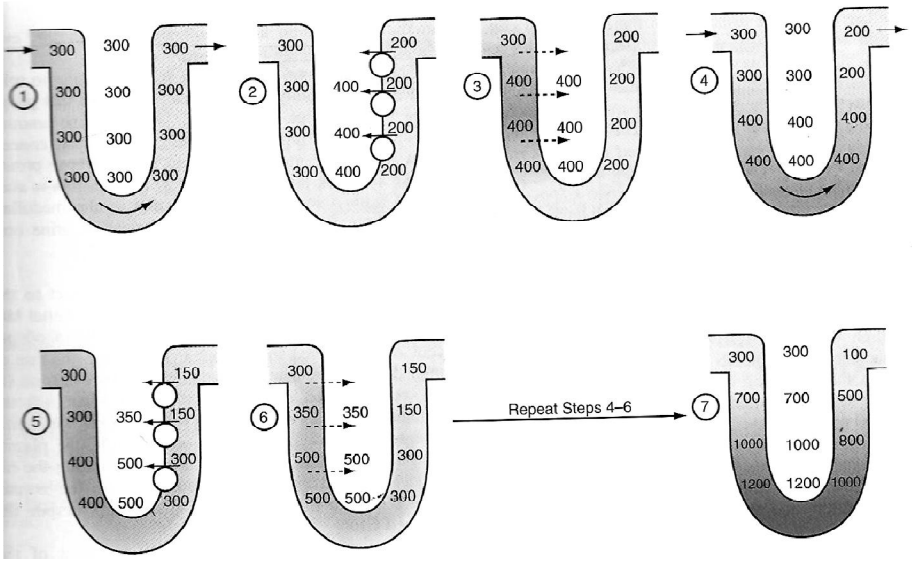
By the time the tubular fluid leaves the PCT, its volume has been considerably reduced and certain chemicals have been reabsorbed or excreted, but the osmotic concentration of the urine is still essentially the same as blood. Some additional reabsorption and excretion occurs in the

distal convoluted tubule (DCT) and in the collecting duct (CD), but concentration of urine primarily involves movements of CL^-, Na^+ and water. A major function of the LH is to establish differences in osmotic concentration of NaCl in the fluid surrounding the collecting duct from the upper cortex down to the inner medulla of the kidney.

Tubular fluid that enters the descending limb of the LH has an osmotic concentration similar to blood and the membrane of the descending LH is permeable to H_20 but not to NaCl. The membrane of the ascending limb of LH actively transports chloride from tubular fluid to interstitial fluid bathing the nephron. Sodium passively moves from tubular fluid to interstitial fluid but the membrane of the ascending LH is not permeable to H_20. As a result, NaCl accumulates in fluid surrounding the nephron in increasing concentration from the cortex down through the medulla. The descending LH serves to provide NaCl to be transported out the ascending limb.

N.B.: Water is withdrawn from the tubular fluid in the descending limb.

The LH is called a **counter current multiplier**.



Counter current multiplier system in the loop of Henle for producing a hyperosmotic renal medulla

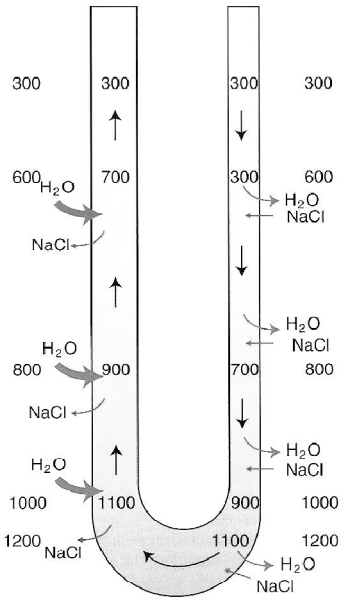
Why? Fluid flow in the ascending limb of LH is counter current to the flow of the descending limb and the collecting duct. In addition energy is expended to produce concentration gradient along the loop and collecting duct. Each small section of membrane on the ascending limb transports a certain amount of NaCl against a particular difference in concentration. This

addition of small sections of membrane along the entire length of the ascending limb produces a multiplicative effect because multiplication is a series of successive addition of the same amount. When tubular fluid reaches the top of the ascending limb, it may be slightly less concentrated than blood plasma resulting in some H_20 movement by osmosis to blood and further reduction of urine volume. As fluid passes back down through the CD, water will move by osmosis out of urine if the CD membranes are permeable to water (i.e. in the presence of ADH).

Because the concentration of fluids surrounding the collecting duct increases along their length, more and more water can be withdrawn by osmosis as the fluid move down the CD.

The H_20 that moves from the descending limb of LH and the collecting duct must be removed from the fluid surrounding the nephron tubules; otherwise the gradient of NaCl concentration will be dilute. Water removal occurs with blood flow in the capillary loops called vasa recta.

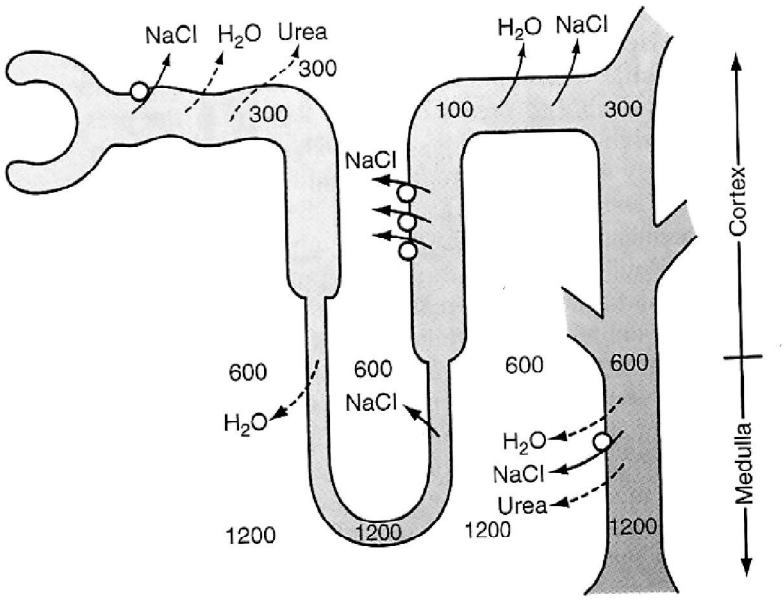
Counter current exchanger: Venous blood leaving the glomerulus gains NaCl by diffusion and looses water by osmosis on the descending limb of the vasa recta, but by looping back, the blood loses sodium by diffusion and gains water by osmosis on the ascending limb.



Counter current exchanger system in the loop of Henle and Vasa recta for producing a hyperosmotic renal medulla

Urea diffuses across all of the membranes in the nephron tubules and in the vasa recta. Urea is transported passively and becomes more concentrated in tubular fluid in CD as a consequence of

the movement of water out of the ducts and into blood. The permeability of the CD to water and urea is variable, depending upon the presence of ADH.



Distal convoluted tubule and collecting duct: The distal CT receives a hypotonic fluid from the medullary region. Isoosmotic equilibration occurs in the 1^{st} $^1/_3{}^{rd}$ of the DCT (assuming that the kidney is elaborating a concentrated urine) as water leaves the tubular fluids in the direction of its concentration gradient. Further isoosmotic reabsorption occurs in the remaining portions of the DCT secondary to Na transport from tubular fluid into plasma. The osmolality of the fluid at the end of DCT is equal to the osmolality of plasma but quantitatively now represents approximately 5% of the original glomerular filtrate.

N.B.: Isoosmotic equilibration of tublar fluid does not occur in the DCT of dog nephrons. Rather the tubular fluid at the end of DCT is still hypotonic to plasma. Some portions of the ascending LH in the dog kidney appear to be involved in the processes that regulate urine concentration and dilution. Fluid entering the DCT shows a fluid – plasma osmolal ratio of 0.5 – 0.6 when the dog is elaborating a concentrated urine. Under conditions of water diuresis, i.e. when the kidney excretes a hypotonic urine, the osmolal ratio may be as low as 0.2.

Final concentration of urine takes place in the collecting duct as these terminal segments of the nephron system carry the urine through the medulla to the renal pelvis. The permeability of the collecting duct to water and urea is variable depending upon the presence of ADH. When the kidney is excreting concentrated urine i.e. in the presence of ADH, the collecting duct becomes

increasingly permeable to water and urea. Water, free of solute, then passes in the direction of its concentration, from the lumen of the collecting duct into the hypertonic medullary interstitium. As the fluid in the collecting duct becomes concentrated, urea concentration in the collecting duct fluid increases until it exceeds the urea concentration in the medulla. Urea then diffuses from the collecting duct fluid into the medullary interstitium, thus, obligating the reabsorption of H_20 from the collecting duct fluid.

The collecting duct appears to be relatively impermeable to non-urea solute e.g. Na, K salts of chloride, sulphate, bi-carbonate and to creatinine, and these solutes becomes increasingly concentrated. The net result of these processes is the excretion of urine that may be 5-7 times the concentration of plasma.

Dilute urine is excreted when the release of ADH is inhibited. The primary target organs of ADH are the collecting duct, but the DCT and ALH in the dog at least, share to some extent as sites of action of this hormone. In the absence of ADH, the DCT, CD and the ALH in the dog becomes relatively impermeable to water and urea. Na reabsorption still takes place from the fluid in DCT, but water movement is decreased; concurrently, water reabsorption in the CD is markedly inhibited. Therefore, the absence of ADH, results in water diuresis i.e. the excretion of large volume of urine hypotonc to plasma.

The specialized morphology and metabolism of the medulla permits the mammalian kidney to concentrate urine and thereby conserve water. However, there is evidence that the hyperosmosity / hyperosmolatity may also be detrimental. It has been shown that chronic infectious diseases of the kidney may also be closely associated with the maintenance of the cortico-medullary osmotic gradient.

Reasons are:

- The hyperosmotic environment of the medulla apparently inhibits the migration of leucocytes to the sites of infection, thus depriving the area of one of the primary defense mechanisms against bacteria.
- The relatively small medullary blood flow, will limit the amount of antimicrobial drugs that could be carried into the medulla.

These 2 factors complicate the therapeutic management of renal infection.

The urine concentrating process functions most effectively when protein intake is sufficient to maintain positive nitrogen balance. Protein deficient diet results in impairment in the capacity of the kidney to conserve water.

There may be subtle changes in the permeability characteristics as protein turnover in the kidney responds to unfavorable nitrogen equilibrium. Enzyme synthesis in the kidney may be similarly affected. Urea, however, assumes an important role in the renal responses to changes in protein intake. The urea component of the cortico-medullary osmotic gradient is virtually eliminated by protein deficiency and urea excretion falls to low levels. As urine is concentrated in the CD, there is a minimal reabsorption of urea and the amount of water reabsorption obligated by urea diffusion is greatly reduced.

A decrease in the cortico-medullary osmotic gradient also occurs since the quantity of urea is decreased. Water conservation, therefore, depends to a large extent upon reabsorption and is decreased as the result of the decrease in the osmolality of the medullary interstitium.