THE ROLE OF THE RENAL CONCENTRATING MECHANISMS IN THE REGULATION OF SERUM SODIUM CONCENTRATION

Internal Medicine Grand Rounds
Parkland Memorial Hospital
April 29, 1976

Juha P. Kokko, M.D., Ph.D.

The total body water content is, in large part, determined by the total amount of salt in the body, while the salt and water concentration is ultimately controlled by the kidney. In spite of wide fluctuations in the intake of salt and water, the renal mechanisms maintain the serum sodium chloride concentration within a very narrow range: sodium chloride concentrations above 148 mEq/L are abnormal and, therefore, are referred to as hypernatremic states while sodium chloride concentrations below 135 mEq/L represent hyponatremic conditions. The kidney is able to subserve this critically important regulatory role by virtue of being the target organ of various stimuli regulating salt and water homeostasis. Significant recent technological advances have greatly enhanced our understanding concerning the mechanisms by which the kidney is able to generate both dilute and concentrated urine. The necessary consequence of increased formation of dilute urine, or in physiological terms, increased renal free water excretion, would be the concentration of serum salt concentration, while increased renal free water reabsorption would lead to dilution of serum salt concentration. The kidney is able to form both dilute and concentrated urine through the operation of the countercurrent multiplication system. The purpose of this communication is to review the recent development in the countercurrent multiplication area and to discuss how this information relates to the clinical states with deranged metabolism of salt and water.

The general architecture of the renal countercurrent multiplication system was initially developed by Wirtz, Hargitay and Kuhn in 1951 (1). Since this time a number of alternate models of countercurrent multiplication system have been proposed. In general, all of the models have shared the common feature that the energy source, or "single effect", has been localized within one of the medullary structures. However, most of these models have been advanced by theoretical arguments without experimental basis. Previously it was not possible to obtain the necessary experimental data because of the inaccessibility of the nephron segments to conventional micropuncture techniques.

In the latter part of the 1960's, the technique where isolated segment of tubules are perfused in vitro was applied for the first time to the loops of Henle (2). This technique has a twofold methodological advantage over the previous micropuncture technique in that the characteristics of all segments of nephron can be directly examined and that both the intraluminal and peritubular environment can be exactly controlled. Using the experimental results obtained from the thin descending limb (2,3) and the thin ascending limb of Henle (4), Kokko and Rector (5) proposed a completely new modification of the original model of countercurrent multiplication system. The fundamental difference between this and the previous model is that the new model removed the necessity of postulating active transport processes in the thin ascending limb. This model thus was consistent with the experimental results, and also satisfied the mathematical formulations which were simultaneously developed by Stephenson (6).

The salient features of this model are summarized in the Appendix (page 5). Its efficient operation requires some unique nephron segmental membrane properties and specific and complex anatomic relationships between the various medullary structures. The reader is referred to other works (5,6) for more detailed consideration of the countercurrent multiplication system.

In this model the major energy source resides only in the thick ascending limb of Henle. This segment separates salt from water by an active electrogenic chloride pump (7,8). As the chloride is actively added to the interstitium, sodium follows it passively down a potential gradient generated by the chloride pump. The net result of these events in a segment impermeant to water (7,8), is to create a dilute fluid with a relatively low concentration of salt and a relatively high concentration of urea. The fluid then courses through the distal convoluted tubule which is impermeant to urea (9) and to water both in the presence and absence of antidiuretic hormone (10). In the presence of ADH the urea concentration in cortical and outer medullary collecting ducts is then raised by virtue of water abstraction and secondary osmotic equilibration. Since the cortical and outer medullary segments of the collecting duct are impermeant to urea (11-13), the urea is unable to diffuse down its concentration gradient. In contrast, the papillary collecting duct, has a finite permeability to urea (13,14). As the fluid with a high concentration of urea enters the terminal segment of the collecting duct, the urea gradient is partly dissipated by diffusion of urea into the papillary interstitium. Additional urea may enter the papillary interstitium by back-diffusing from the pelvic urine which normally bathes the papilla (15,16). In turn, the high interstitial concentration of urea and salt would act to abstract water from the thin descending limb of Henle. This segment is quite permeable to water (2) but relatively impermeable to both urea (3) and NaCl (2). Osmotic equilibration by water abstraction from the descending limb of Henle would result in an intraluminal NaCl concentration greater than that of the surrounding interstitium. The mechanism by which this occurs is illustrated in the Appendix (page 6). The fluid then enters the thin ascending limb of Henle where the membrane characteristics are drastically different from the descending limb of Henle. The thin ascending limb of Henle is impermeable to water while being highly permeable to both sodium and chloride (4) and moderately permeable to urea. The in vitro (4) and in vivo (17-20) studies have not disclosed any convincing evidence that the thin ascending limb is capable of active transport. However, due to the favorable diffusion gradient of salt, NaCl would diffuse down its concentration gradient while a lesser quantity of urea would enter the thin ascending limb of Henle. The net effect would be addition of solute to the papillary interstitium.

Though this model of countercurrent multiplication system was developed on experimental data from rabbits, there is reason to believe that the same general principles are applicable to the human kidney. Recently studies have been conducted perfusing isolated thick ascending limbs of Henle (21) and collecting ducts (22) obtained from the human kidney which indicate that these segments share the same properties as their rabbit counter segments.

It is important to recognize that urea occupies a pivotal role in the countercurrent multiplication system depicted in the Appendix (page 5). If urea did not exist in the system, the NaCl concentration gradient could not be developed in the descending limb of Henle, and accordingly, the thin ascending limb of Henle could not add salt to the papillary interstitium. Under these circumstances the urine concentration would not be maximal, but rather, reflect only the work capacity of the chloride pump existing in the thick ascending limb of Henle. It is clear, from the principles outlined above, that the kidney can form either dilute urine (increased free water excretion) or concentrated urine (increased free water reabsorption).

Table I (Appendix, page 7) lists those clinical states which impair the renal concentrating capacity. Various mechanisms are operative in disrupting the ability to generate maximally concentrated urine. A low papillary urea concentration is responsible in part for the failure to form a concentrated urine in chronic renal failure, starvation and psychogenic water drinking. Osmotic diuresis plays a role in the failure to form a concentrated urine in post obstructive diuresis, post renal transplantation and in chronic renal failure. A collecting duct poorly responsive to antidiuretic hormone is responsible for the concentrating defect in patients with hypokalemia, hypercalcemia and congenital nephrogenic diabetes insipidus. Many diuretics inhibit NaCl transport in the thick ascending limb of Henle, and therefore, decrease the salt concentration in the medullary interstitium. It is not completely clear why patients with sickle cell disease or trait are unable to form concentrated urine. The most probable reason is disruption of the normal complex flow dynamics existing between tubular reabsorption and vascular outflow of reabsorbate.

Table II (Appendix, page 13) summarizes clinical states which impair free water formation and/or excretion. Common to all these clinical states is a tendency to hyponatremia. In patients on rigid sodium restriction with effective hypovolemia, adequate quantities of free water cannot be generated because of decreased delivery of filtrate to the diluting segment. The decreased delivery of filtrate may be on the basis of a decreased glomerular filtration rate and/or an increased proximal fluid reabsorption. It is not clear why patients with adrenal insufficiency are not able to form maximal amounts of free water. In clinical states associated with inappropriate secretion of ADH, increased back diffusion of free water results in decreased free water excretion.

Treatment of the various clinical states with deranged salt and water homeostasis must be individualized and designed to correct the underlying pathogenesis responsible for the physiologic abnormalities.

In summary, the present editorial has presented a model of the countercurrent multiplication system in which both the thin descending and thin ascending limb of Henle operate as purely passive equilibrating segments. This passive model is theoretically feasible and consistent with the available experimental data. The model stresses the importance of urea recirculation and allows for understanding of the pathophysiology behind many of the clinical states associated with deranged balance of sodium and water.

References:

1. Wirtz H, Hargitay B, Kuhn W: Localization des Konzentrierungsprozesses in der Niere durch direlete Kryoskopie. Helv Pharmacol Acta 9:196, 1951.

2. Kokko JP: Sodium and water transport in the descending limb of Henle. J Clin Invest 49:1838, 1970.

3. Kokko JP: Urea transport in the proximal tubule and the descending limb of Henle. J Clin Invest 51:1999, 1972.

4. Imai M, Kokko JP: NaCl, urea and H_2O transport in the thin ascending limb of Henle: Generation of osmotic gradients by passive diffusion of solutes. J Clin Invest 53:393, 1974.

5. Kokko JP, Rector FC Jr: Countercurrent multiplication system without active transport in inner medulla - new model. Kidney Int 2:214, 1972.

6. Stephenson J: Concentration of urine in central core model of the renal counterflow system. Kidney Int 2:85, 1972.

7. Rocha AS, Kokko JP: Sodium chloride and water transport in the medullary thick ascending limb of Henle. J Clin Invest 52:612, 1973.

8. Burg MB, Green N: Function of the thick ascending limb of Henle's loop. Am J Physiol 224:659, 1973.

9. Capek K, Fuchs G, Rumrich G, Ullrich KJ: Harnstoffpermeabilitat der corticalen Tubulusabschnitte von Ratten in Andidiurese und Wasserdiurese. Pflugers Arch ges Physiol 290:237, 1966.

10. Gross JB, Imai M, Kokko JP: A functional comparison of the cortical collecting tubule and the distal convoluted tubule. J Clin Invest 55:1284, 1975.

11. Burg M, Helman S, Grantham J, Orloff J: Effect of vasopressin on the permeability of isolated rabbit cortical collecting tubules to urea, acetamide and thiourea. Urea and kidney. Excerpta Med Intern Congr Ser No 195, p. 193, 1968.

12. Schafer JA, Andreoli TE: The effect of antidiuretic hormone on solute flows in mammalian collecting tubules. J Clin Invest 51:1279, 1972.

13. Rocha AS, Kokko JP: Permeability of the medullary nephron segments to urea and water: Effect of vasopressin. Kidney Int 6:379, 1974.

14. Morgan T, Sakai F, Berliner RW: In vitro permeabiity of medullary collecting ducts to water and urea. Am J Physiol 214:574, 1968.

15. Gertz KH, Schmidet-Nielsen B, Pagel D: Exchange of water, urea and salt between the mammalian renal papilla and the surrounding urine. Fed Proc 25:327, 1966 (abstract).

16. Schutz W, Schnerman J: Pelvic urine composition as a determinant of inner medullary solute concentration and urine osmolality. Pflugers Arch 334:154, 1972.

17. Gottschalk CW: Osmotic concentration and dilution of the urine. Am J Med 36:670, 1964.

18. Marsh DJ, Soloman S: Analysis of electrolyte movement in thin Henle's loops of hamster papilla. Am J Physiol 208:1119, 1965.

19. Marsh DJ: Solute and water flows in thin limb of Henle's loop in the hamster kidney. Am J Phsyiol 218, 824, 1970.

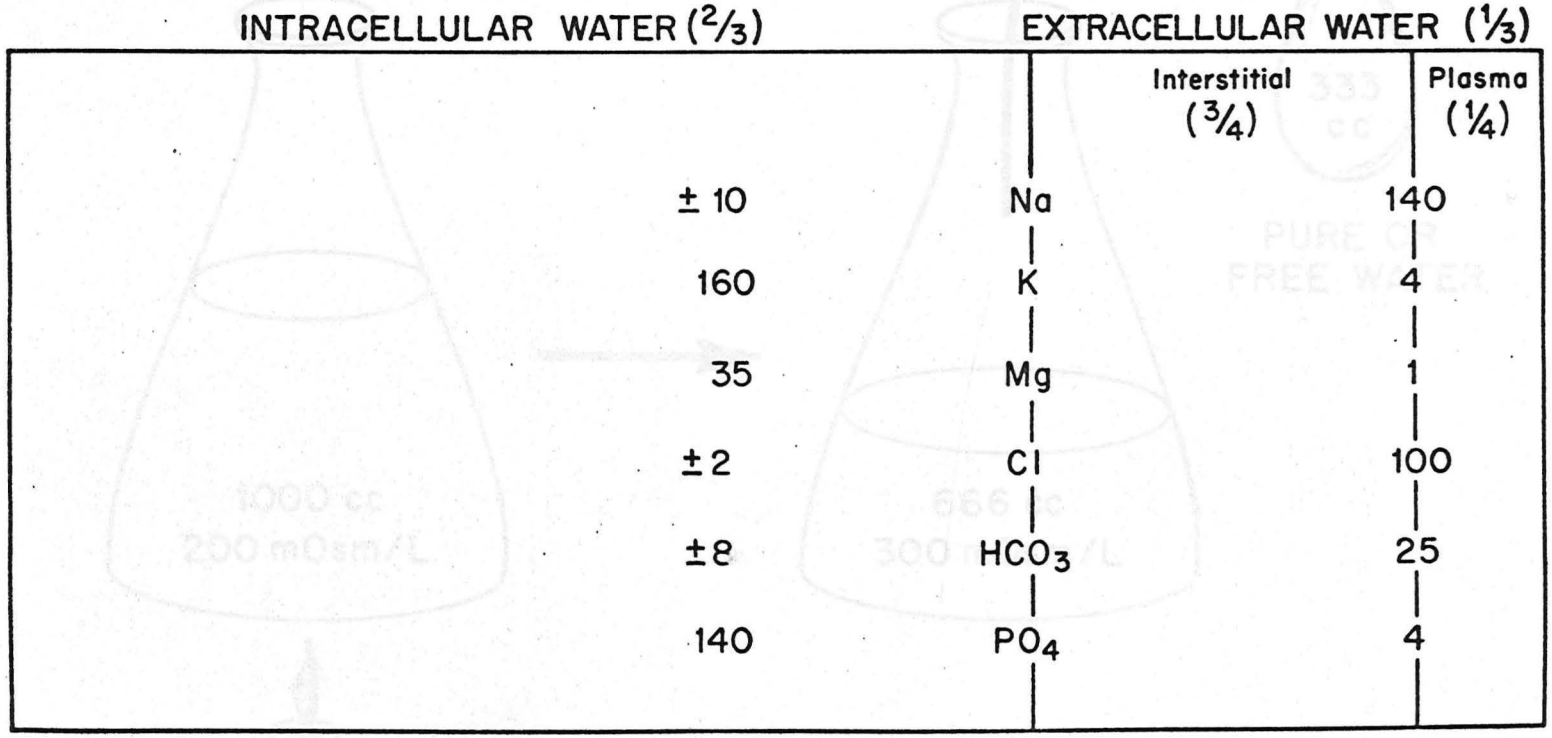
20. Morgan T, Berliner RW: Permeability of the loop of Henle, vasa recta, and collecting ducts to water and urea. Am J Physiol 215:108, 1968.

21. Jacobson HR, Kawamura S, Gross JB, Kokko JP: Electrophysiological study of isolated human thick ascending limbs of Henle. Clin Res 24:468A, 1976 (abstract).

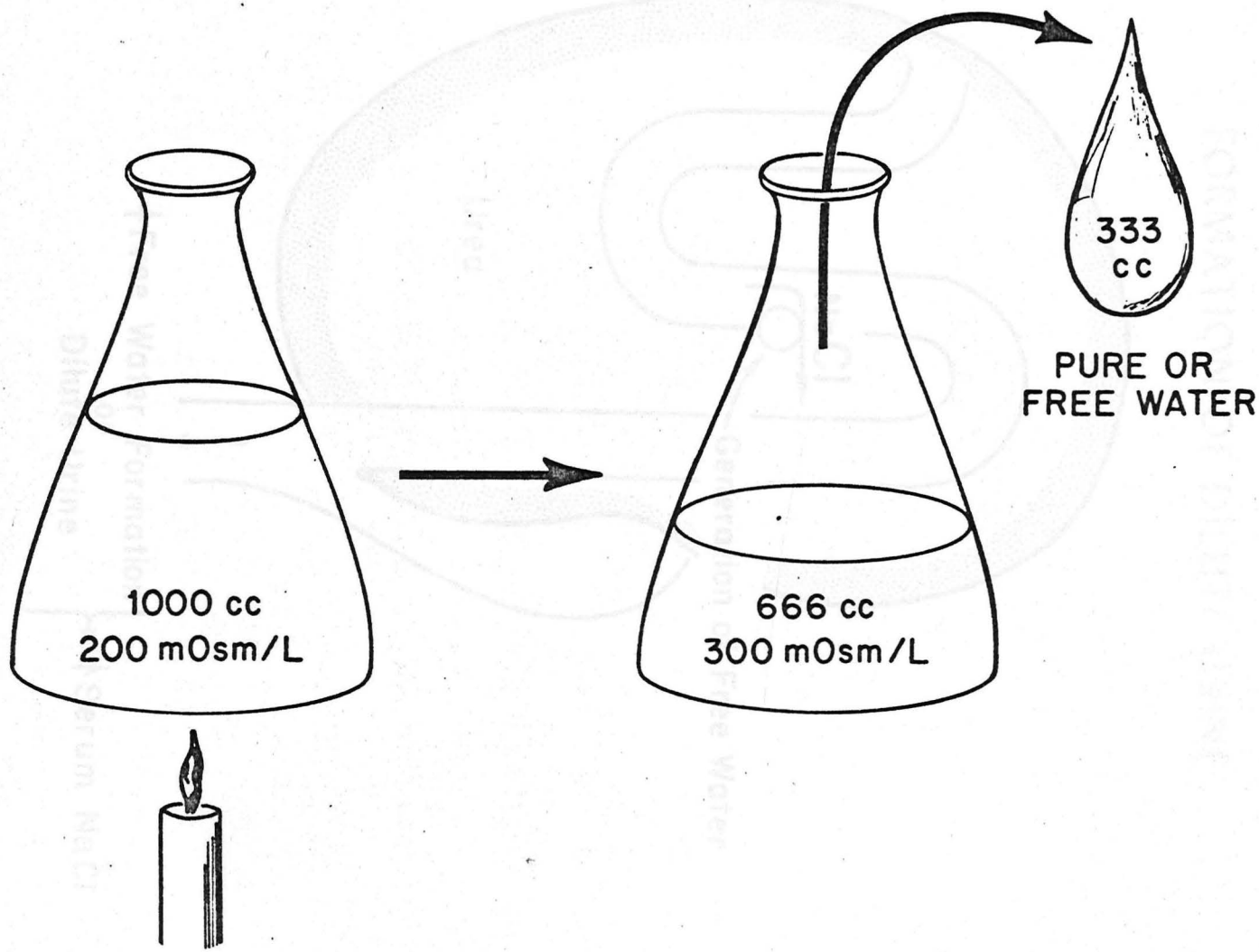
22. Jacobson HR, Gross JB, Kawamura S, Kokko JP: Evidence for active chloride reabsorption in the human collecting duct. Am Soc Neph 8:84, 1975 (abstract).

APPENDIX

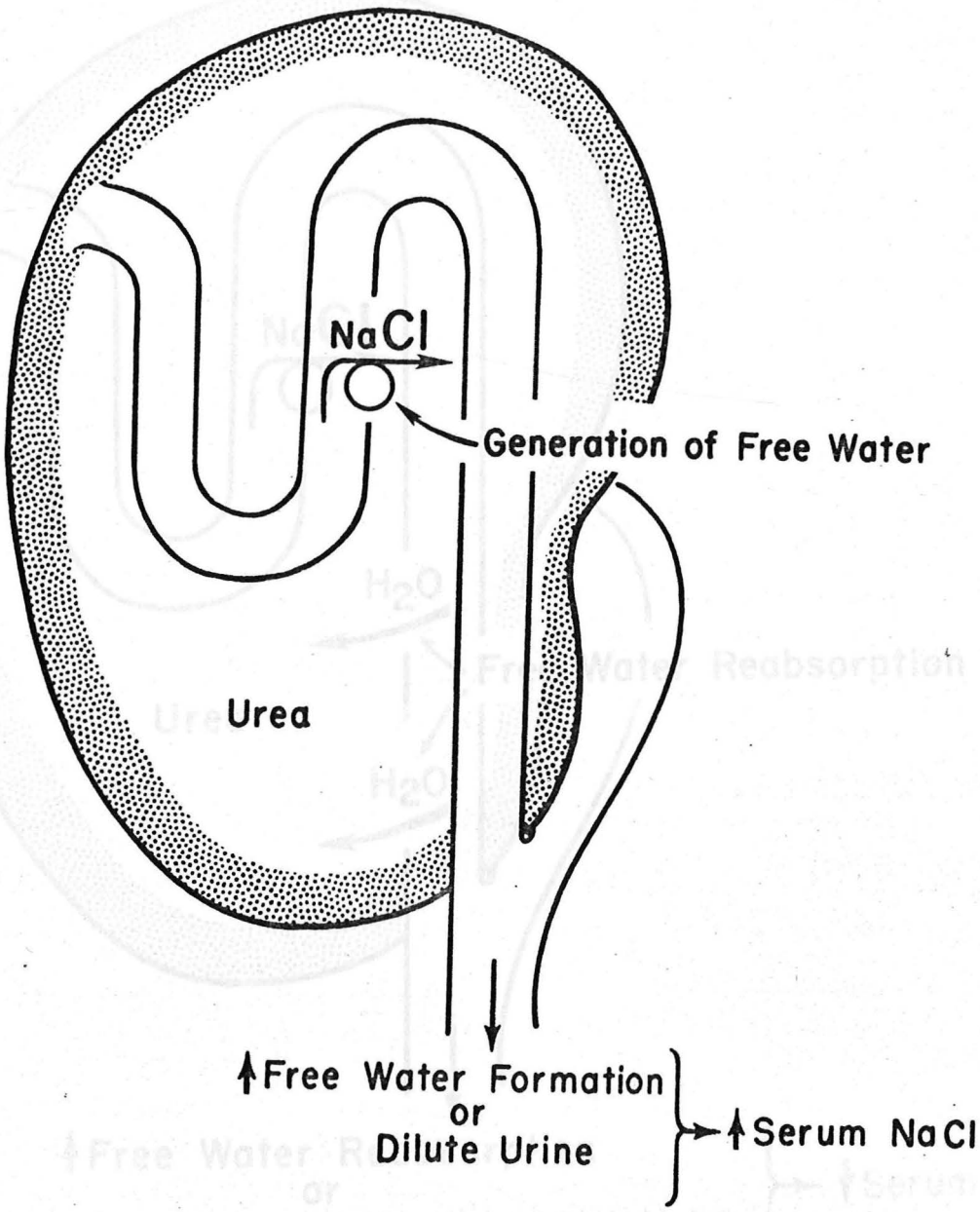
TOTAL BODY WATER
(50 - 70% of Body Weight)



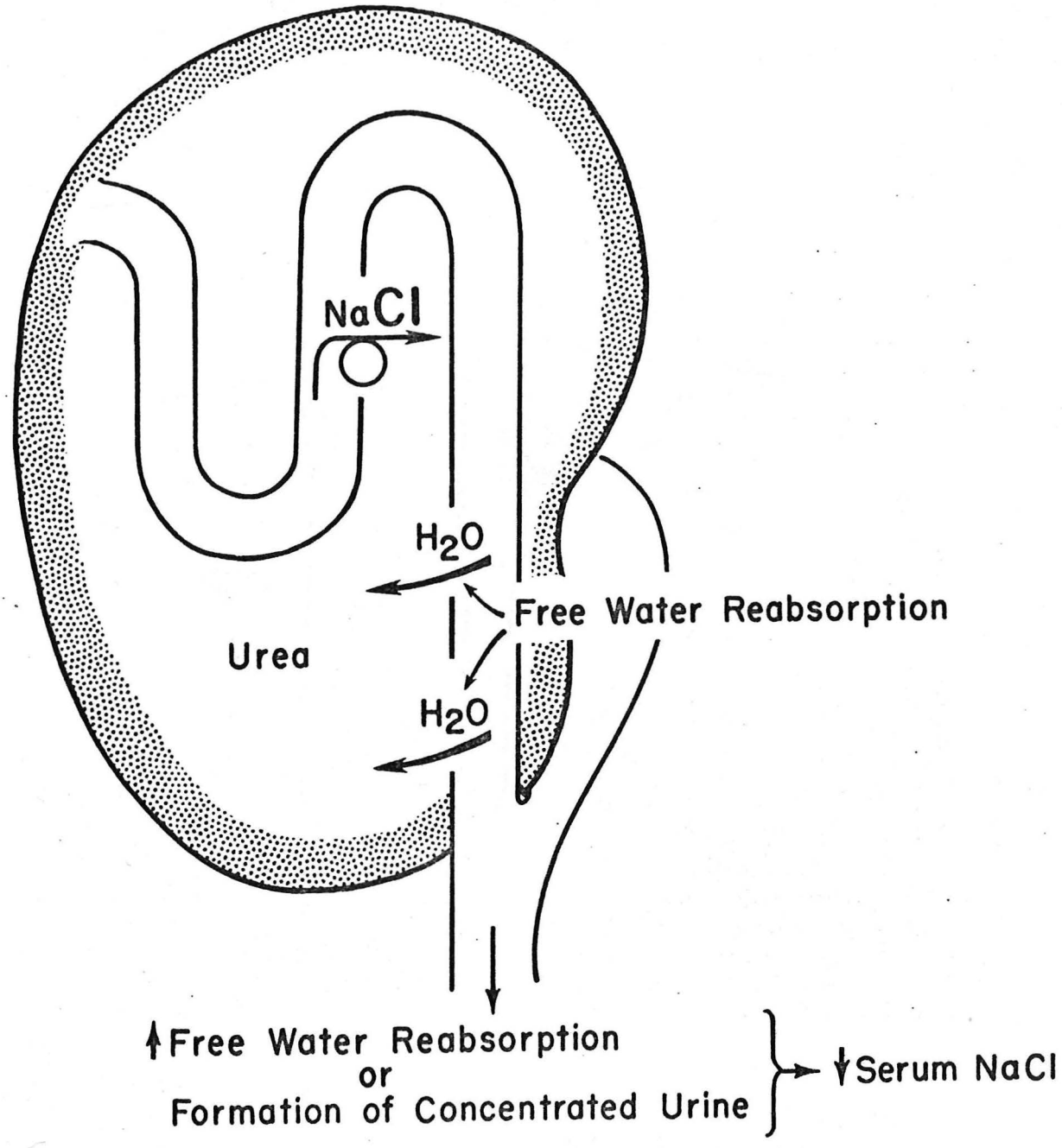
DEFINITION OF "FREE WATER"



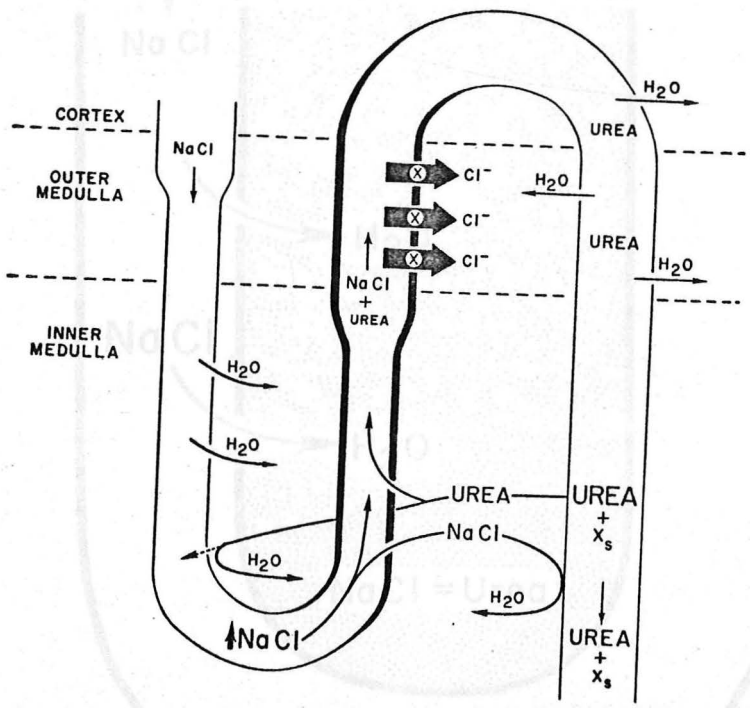
FORMATION OF DILUTE URINE



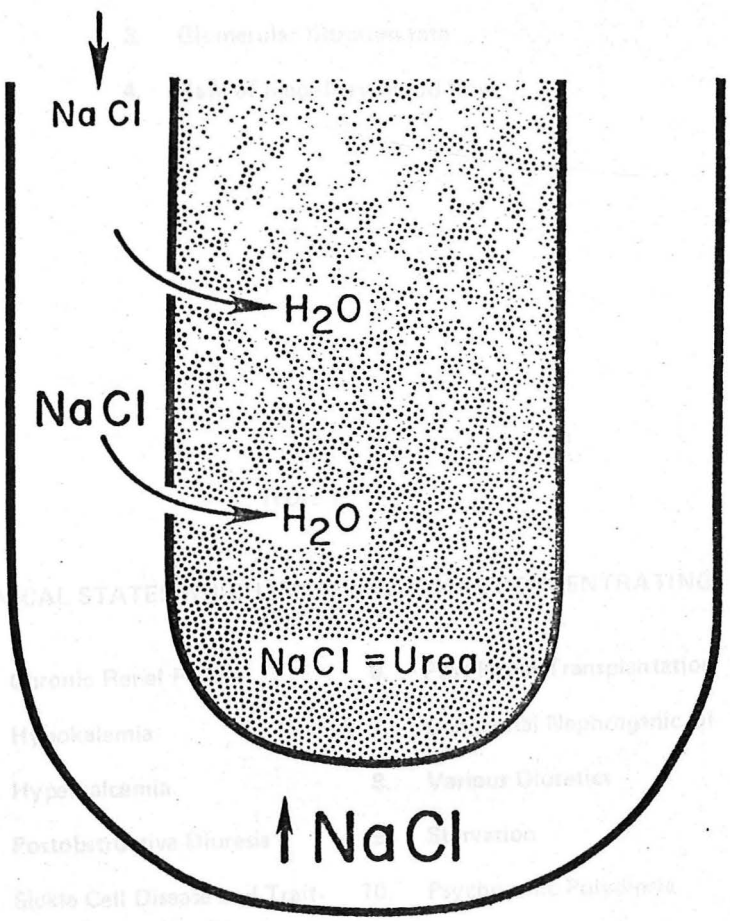
FORMATION OF CONCENTRATED URINE



PASSIVE EQUILIBRATION MODEL OF COUNTERCURRENT MULTIPLICATION SYSTEM



SCHEMATICS TO DEMONSTRATE THE GENERATION
OF NaCl GRADIENT BY THE
THIN DESCENDING LIMB OF HENLE



RENAL FACTORS INFLUENCING MAXIMAL CONCENTRATING CAPACITY IN THE PRESENCE OF ADH

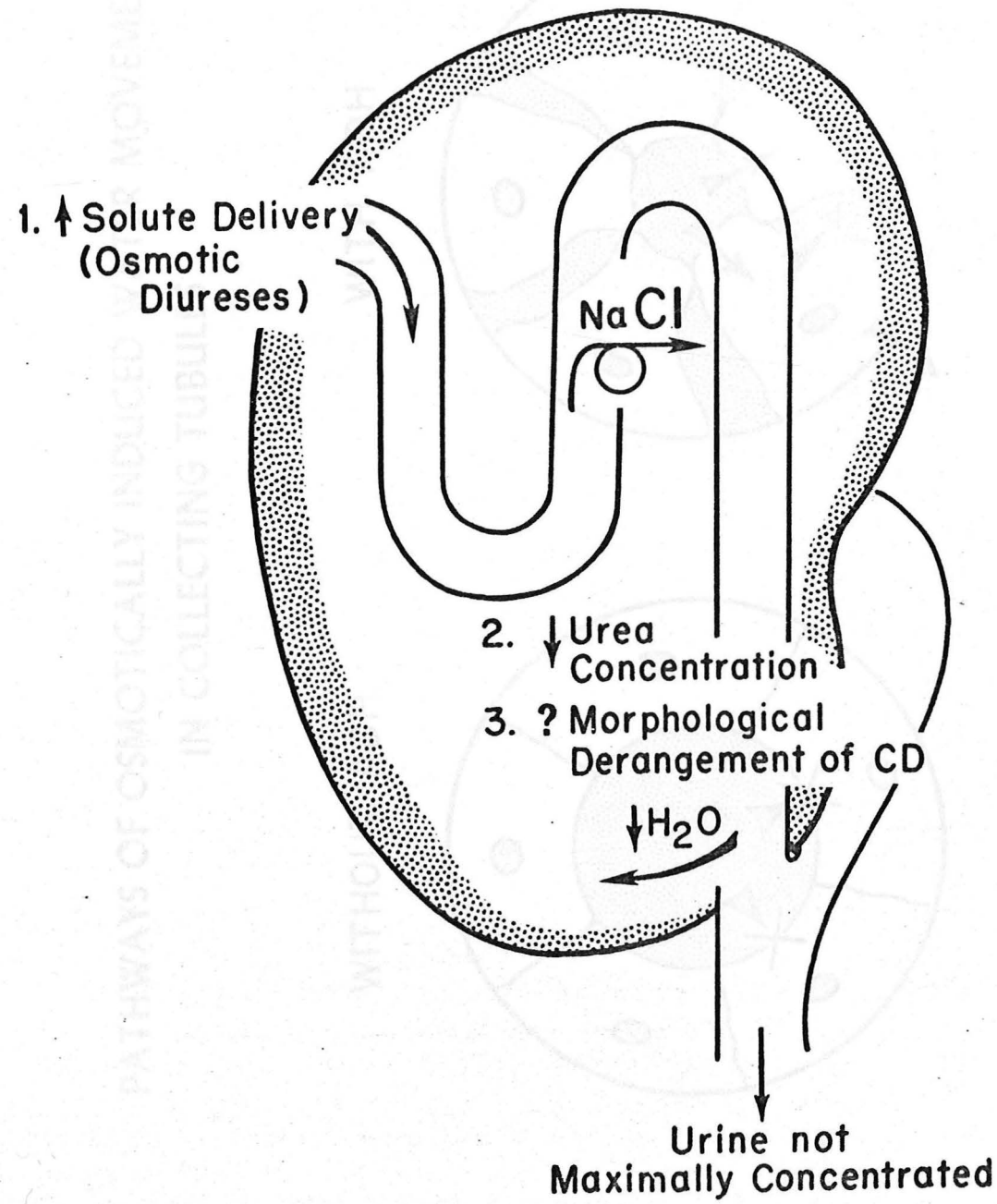
1. Papillary urea concentration
2. Rate of solute excretion
3. Glomerular filtration rate
4. Rate of medullary blood flow

Table I

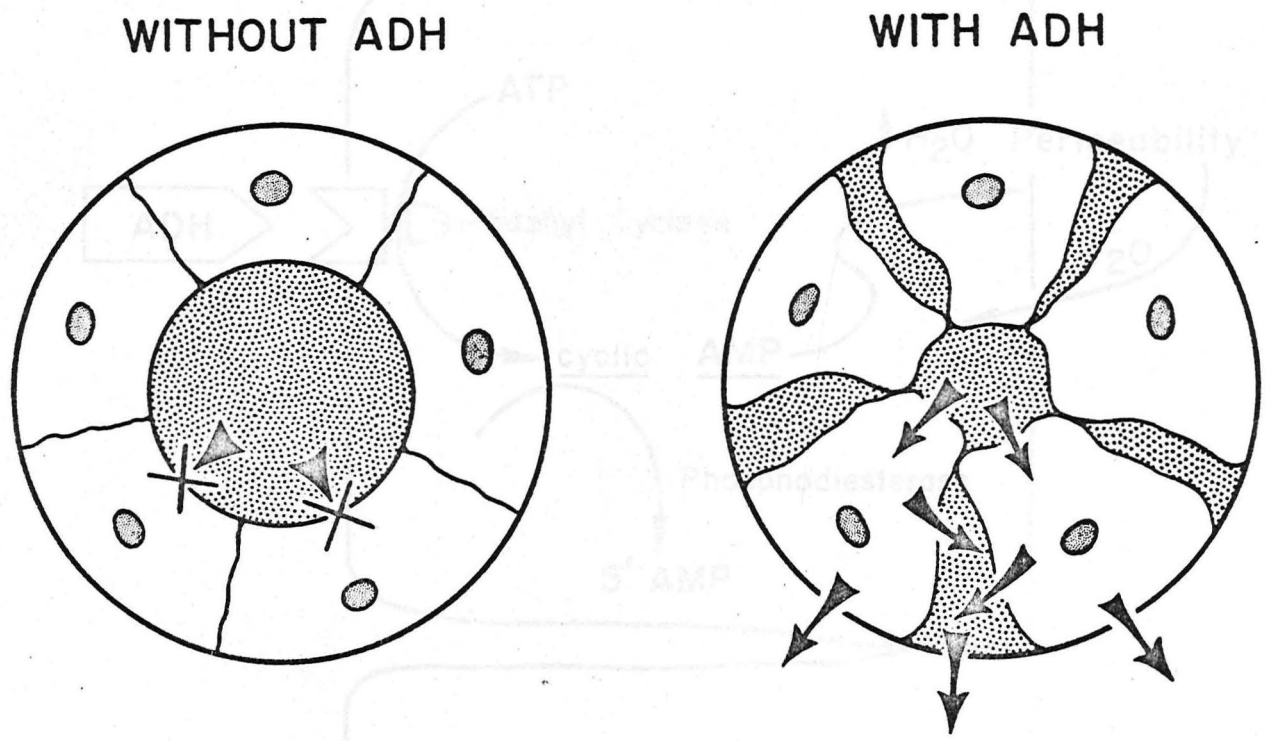
CLINICAL STATES WHICH IMPAIR MAXIMAL CONCENTRATING CAPACITY

1. Chronic Renal Failure
2. Hypokalemia
3. Hypercalcemia
4. Postobstructive Diuresis
5. Sickle Cell Disease and Trait
6. Post Renal Transplantation
7. Congenital Nephrogenic DI
8. Various Diuretics
9. Starvation
10. Psychogenic Polydipsia

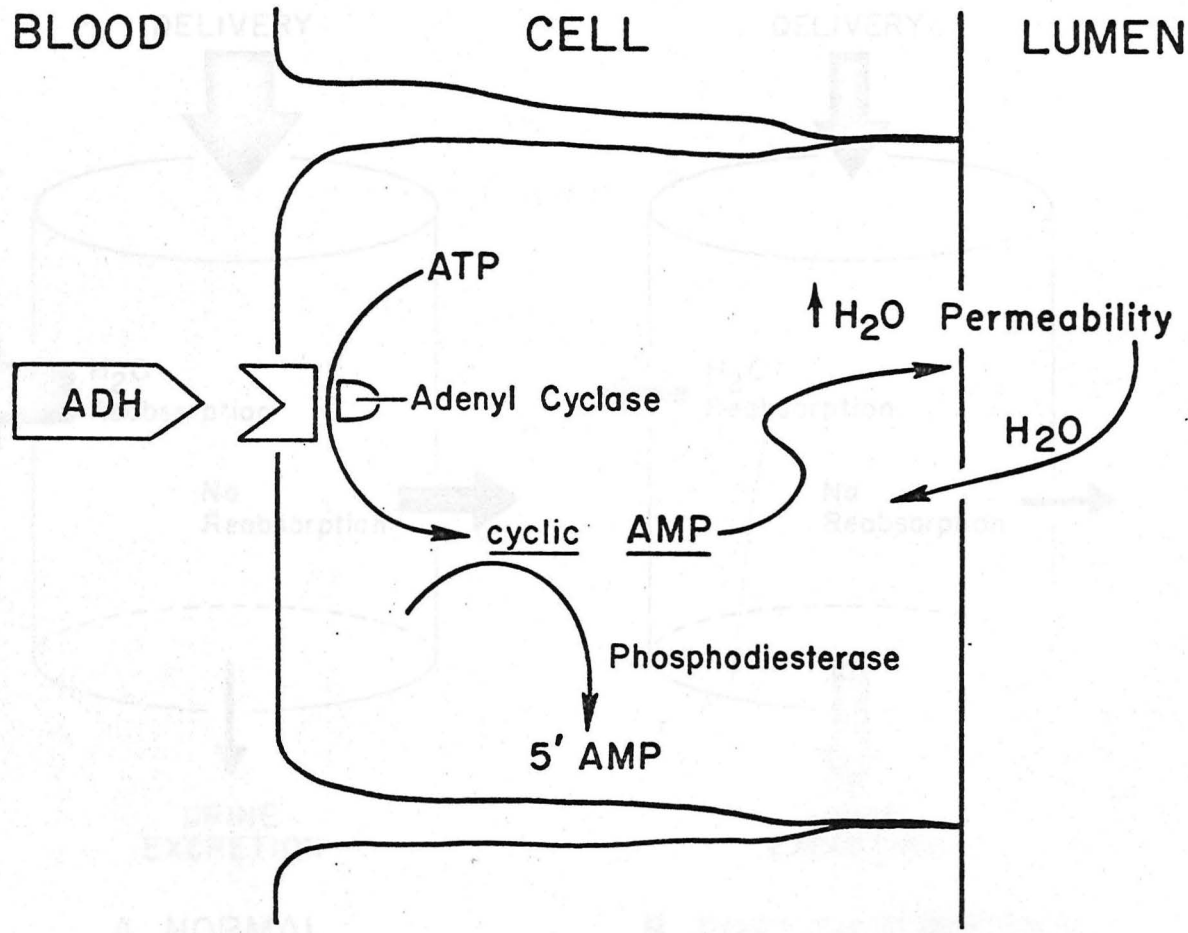
FAILURE TO FORM MAXIMALLY CONCENTRATED URINE IN CHRONIC RENAL FAILURE



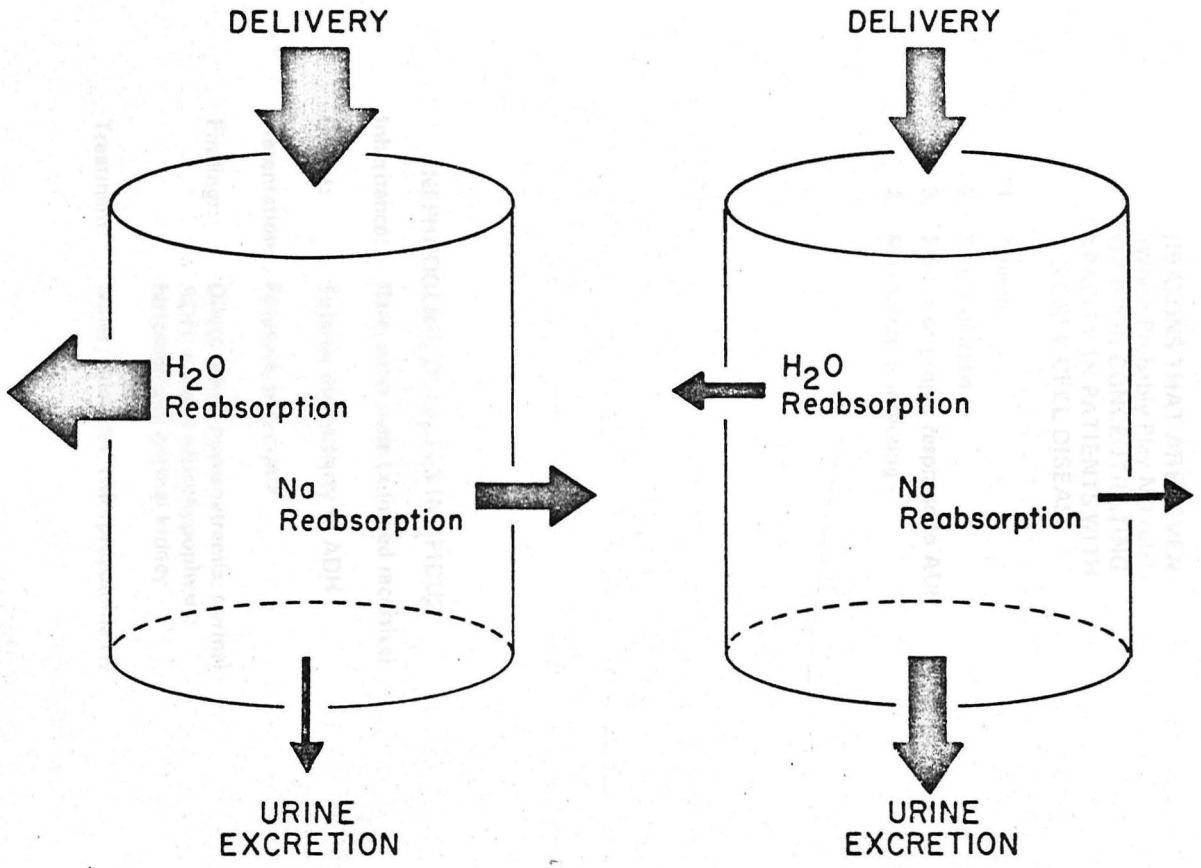
PATHWAYS OF OSMOTICALLY INDUCED WATER MOVEMENT IN COLLECTING TUBULES



CELLULAR MECHANISM OF VASOPRESSIN ACTION



CRITICAL ROLE OF THE COLLECTING DUCT IN POST-OBSTRUCTIVE DIURESIS



REASONS THAT ARE GIVEN (Which Probably Play NO role) FOR POOR CONCENTRATING CAPACITY IN PATIENTS WITH SICKLE CELL DISEASE

1. Anemia
2. Solute diuresis
3. Failure of proper response to ADH
4. Microinfarcts in young

NEPHROGENIC DIABETES INSIPIDUS

Inheritance:	Rare, most male (x-linked recessive)
Defect:	Tubular insensitivity to ADH
Presentation:	Polyuria; polydipsia
Findings:	Dilute urine; hypernatremia; normal ADH; normal neurohypophysis; histologically normal kidney
Treatment:	Water; thiazides; chlorpropamide (?)

DIFFERENTIAL WORK-UP

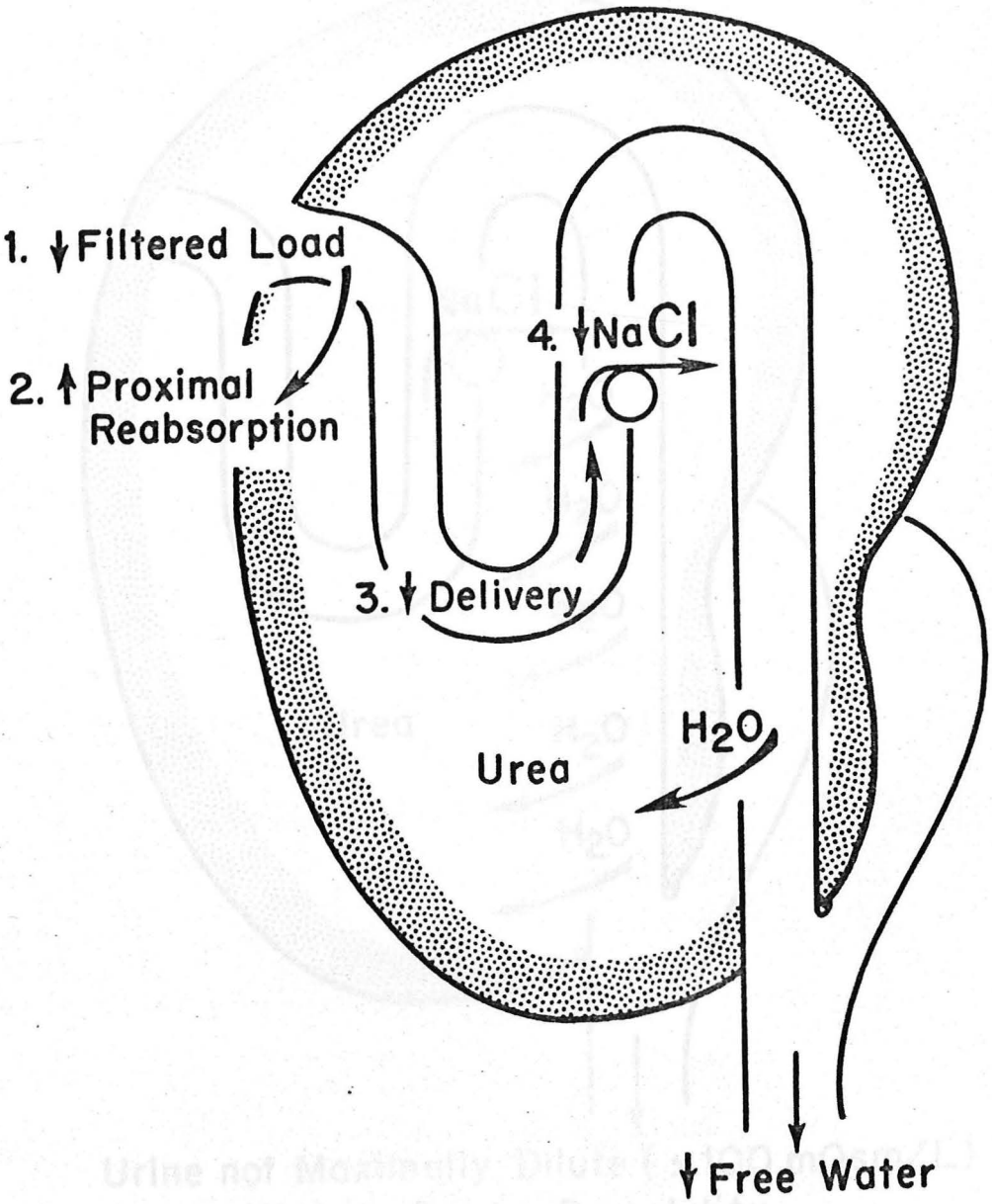
1. Dehydration (stop at 3% body weight loss)
2. Hickey-Hare (300 cc 5% NaCl IV)
3. Vasopressin (5 units IV)
4. Radio-immunoassay for ADH

Table II

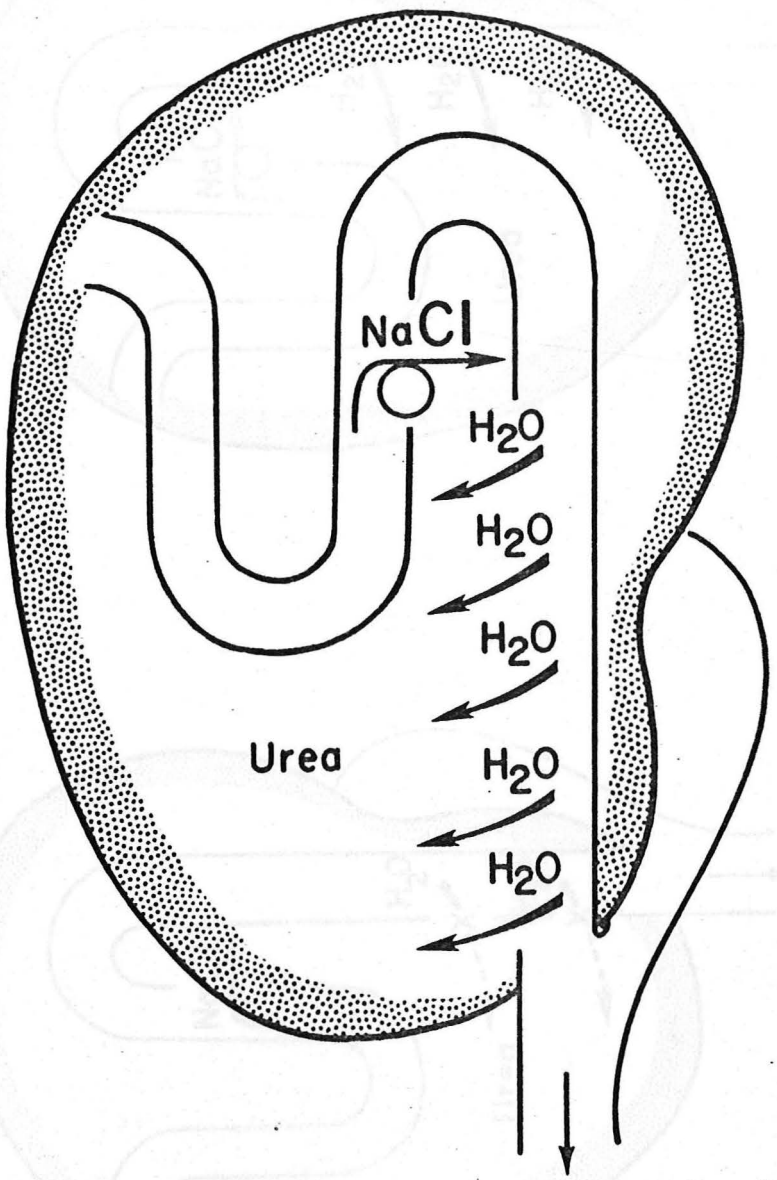
CLINICAL STATES WHICH IMPAIR MAXIMAL FREE WATER FORMATION AND/OR EXCRETION

1. Rigid sodium restriction
2. True hypovolemia
3. Effective hypovolemia
   a. chronic CHF
   b. cirrhosis
   c. nephrotic syndrome
4. Adrenal insufficiency
5. Inappropriate ADH secretion
6. Diuretics

DECREASED FREE WATER FORMATION WITH SODIUM RESTRICTION

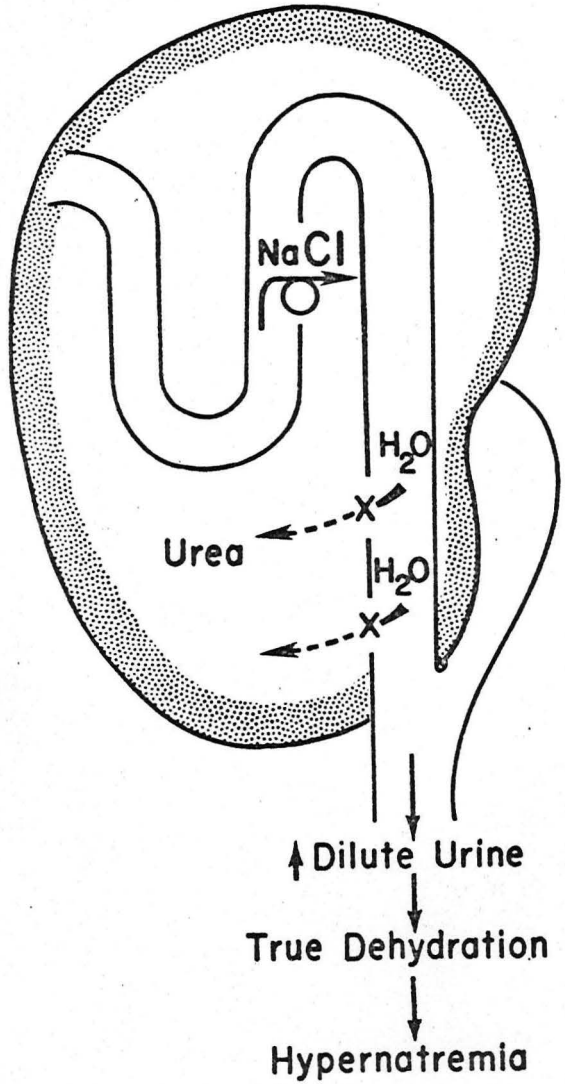


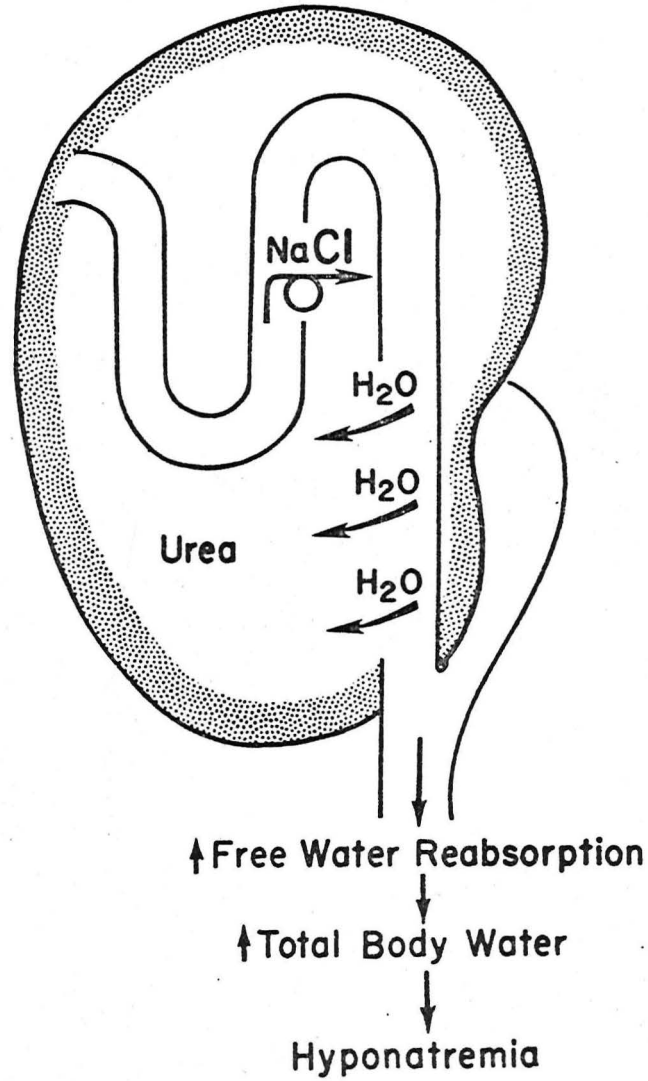
INCREASED FREE WATER REABSORPTION WITH INAPPROPRIATELY INCREASED ADH



Urine not Maximally Dilute (>100 mOsm/L)
with Low Serum Osmolality

SUMMARY


NaCl
H_2O
Urea
H_2O
Dilute Urine
True Dehydration
Hypernatremia


NaCl
H_2O
H_2O
Urea
H_2O
Free Water Reabsorption
Total Body Water
Hyponatremia