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Hyponatremia in acute tubular necrosis

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HYPONATREMIA IN ACUTE TUBULAR NECROSIS

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DEFINITION, PATHOLOGY AND PATHOPHYSIOLOGY: The pathological changes in acute tubular necrosis, as described by Oliver[16], consist of two distinct tubular lesions. The type of lesion produced by a nephrotoxin consists of a uniform cellular necrosis down to but not including, the basement membrane. This lesion occurs primarly in the proximal tubule. When ischemia produces acute tubular necrosis there is a complete disruption of tubular continuity, including dissolution of the basement membrane with secondary ingrowth of connective tissue elements. This tubulorrhexis occurs at random along the entire nephron, and characteristically, many nephrons are left uninvolved. The discussion of this paper will be limited to the ischemic lesion of acute tubular necrosis.

Acute tubular necrosis may be produced by trauma with crushing of tissues, profound hemorrhage, peripheral circulatory insufficiency from any cause, transfusion reactions or other hemolytic processes, and other less common causes[15]. Any condition which leads to inadequate perfusion of the renal parenchyma may promote ischemia and necrosis of renal tubular epithelium.

Hypovolemia resulting from hemorrhage, dehydration or both, produces a compensatory vasoconstriction in certain organs in order to maintain an adequate blood flow to more sensitive areas[26]. The renal vasculature

participates in this selective vasoconstriction; therefore such hypovolemic states may significantly reduce renal blood flow. It is possible that this mechanism may maintain the blood pressure near normal levels, and thus renal ischemia may occur before there is evidence of peripheral vascular collapse.

Before making the diagnosis of acute tubular necrosis, it is imperative that certain other conditions be excluded. Such conditions include dehydration or hypovolemia, and lower urinary tract and ureteral obstruction[26].

There are various mechanisms held to be responsible for the anuria and oliguria in acute tubular necrosis. Despite the problems in obtaining precise data concerning glomerular filtration rate and renal plasma flow in acute tubular necrosis, it is almost certain that significant depression of the filtration rate occurs and is responsible in great measure for the oliguria of this disease[26]. However, there is disagreement over whether a fifty to sixty-six per cent reduction in renal blood flow maintains any significant glomerular filtration. Brun er al.[4] observed that renal blood flow and oxygen consumption were comparable in the anuric and early diuretic period, suggestive of continued filtration. Also, there are studies to suggest that early improvement

in renal function is not paralleled by improvement in renal blood flow.

Another postulated mechanism of anuria is increased interstitial pressure secondary to edema formation. This increased interstitial pressure could tend to decrease renal blood flow, collapse tubules, and impede formation and flow of urine. The increase in gross kidney weight during acute tubular necrosis and the bulging of kidney tissue through a cut capsule is evidence in favor of the presence of interstitial edema. Also, the oftentimes sudden onset of diuresis is more in favor with a decrease in interstitial pressure rather than the simultaneous healing of many nephrons. Evidence against this postulation includes the fact that interstitial edema is not consistently seen on microscopic examination. Also, Brun et al.[5], measured wedged-renal-vein pressure in patients with acute renal failure and found no difference between normal control values and anuric or diuretic periods.

Merrill[13] feels that the important factor is the relation of the interstitial pressure to intratubular pressure, and that marked increases in interstitial pressure would not necessarily be required to cause collapse of the renal tubules.

A third hypothesis is tubular back diffusion

because of disruption of tubular continuity. The data on this hypothesis is contradictory so that no definite conclusions can be drawn.

There is still some suggestion that obstruction of nephrons by casts is an important factor in the pathogenesis. Oliver and his group[16] found no correlation between the location of occluding casts and tubulorrhexic lesions. Other work points to the usefulness of administering osmotic diuretics to help prevent the formation of casts and acute tubular necrosis after burns and trauma.

NORMAL HANDLING OF SODIUM BY KIDNEY: The renal regulation of sodium is a complicated and not too well understood subject. The mechanisms responsible for the reabsorption of sodium are varied; some are related to specific changes and stimuli which occur within the kidney itself, and other influences originate at sites which are remote from the kidney. It has been demonstrated that in the proximal tubule an active transport system governs resorption of sodium, and that the bulk of the filtered sodium is resorbed in the proximal tubule. Merrill[14] points out that a marked decrease in glomerular filtration rate will result in decreased excretion of sodium if the proximal tubule continues to resorb filtered sodium at its usual rate. Similarly, a marked increase in

glomerular filtration rate may result in increased sodium excretion. However, changes in the renal tubular reabsorption of sodium contribute to variations in the urinary sodium excretion in addition to and independently of changes in the filtered load.

Welt[26] gives consideration to five factors which may modify the renal tubular reabsorption of sodium independently of changes in glomerular filtration rate.

1. Influence of Volume: By some as yet undefined mechanism, an increase in extracellular fluid volume increases, and a decrease in volume decreases the rate of sodium excretion via the effect on the renal tubular reabsorption of sodium[22]. This influence of volume has been reported by various investigators. A change from the supine to the erect posture, venesection, applying tourniquets to the limbs, have all been accompanied by a diminished rate of sodium excretion. Conversely, the infusion of a hypotonic solution[24] of salt will increase the sodium excretion. It has been postulated by various workers that these effects are mediated through volume receptors which are located in the large vessels of the thorax, the left atrium, in the intracranial area, and even in the renal circulation itself.

2. Neurogenic Influence: Data has been presented which hypothesize that an interruption of the nerve supply to the kidneys alters renal tubular activity such that the reabsorption of sodium is decreased. However, it is still uncertain as to whether the salt and water diuresis could just be on the basis of altered renal hemodynamics.

3. Influence of Adrenal Cortical Secretions: Aldosterone has been rather well established as the important sodium-retaining steroid from the adrenal cortex. The various stimuli which have been implicated in regulating the secretion of aldosterone include a decrease in extracellular volume and hyperkalemia[2].

4. Influence of the Antidiuretic Hormone: Welt[26] feels that in physiologic doses, antidiuretic hormone does not play any significant role in salt excretion, but that in larger doses antidiuretic hormone may increase salt excretion by its pressor effect on renal hemodynamics. It has been postulated that an inappropiate secretion of antidiuretic hormone may increase urinary sodium loss as a consequence of the resultant expansion of body fluid volume[21].

5. Influence of Osmotic Loads: The nature and quantity of solutes that occur in the glomerular filtrate are known to influence the rate of salt and water excretion. The

classical example of such a solute which is of low molecular weight and is poorly reabsorbed by the renal tubule is mannitol. When a solute is administered in hypertonic solutions, the effective osmolality of the extracellular fluid is increased with a resultant transfer of water from cells to the extracellular fluid. This produces a dilution of sodium and its salts in the extracellular fluid. Thus, sodium and its salts contribute a smaller amount of the total effective osmolality of the extracellular fluid, and a significant fraction of the effective osmolality is produced by mannitol. This same relationship exists in the glomerular filtrate, the end result being delivery of an increased volume of fluid to the distal tubule. Several explanations exist to explain the "osmotic diuresis" which solutions of mannitol may produce. It is suggested that a gradient exists between tubular and extracellular fluids against which the active reabsorption of sodium cannot occur. This gradient is achieved more readily in the presence of a solute such as mannitol, and so more sodium will fail to be reabsorbed[26]. Another explanation states that the delivery of a greatly increased volume of fluid to the distal tubule produces a more rapid transit through this element of the nephron[14]. This shorter time of

of contact places a limitation on the rate of sodium reabsorption. The so called "sweeping out" of water and solute produces a urine of large volume but of low concentration and specific gravity. Regardless of the decreased concentration, however, the volume increase is great enough so that an increased amount of salt is excreted.

Hyperglycemia and other solutes used as loading material may produce the same picture of "osmotic diuresis" as does mannitol. The role of urea as an osmotic diuretic is subject to controversy. Urea can produce a diuresis of water, although not as effectively as substances which remain entirely in the tubular urine because some of the filtered urea is passively diffused back through the tubule. Whether a solute load of urea can produce of sodium diuresis is open to question. Merrill[14] cites the mechanism of urea osmotic diuresis to partially explain the findings in early renal failure of a large volume of dilute urine with a tendency to sodium loss. In contrast, Welt[26] states that a solute load of urea may produce the excretion of enough water to lead to a clinical state of water deficit dehydration with hypernatremia.

In concluding a discussion of the handling of sodium by the normal kidney, reference should be made

to the countercurrent multiplier principle. This principle was reviewed by H. W. Smith[23] in 1959 based on the work of Henry Wirz and his colleagues at the University of Basle. By measuring the osmotic pressure at various levels in the rat kidney, this group found that the fluids in the cortex were isosmotic with plasma, but the medulla showed a progressive increase in osmotic pressure from the cortico-medullary junction to the tip of the papilla. At no particular level were there differences between the tubular urine, the capillary blood, and the urine in the collecting ducts. To explain these results, Wirz and his group invoked the countercurrent multiplier principle whereby the opposing streams in the descending and ascending limbs of Henle's loop play an important role. Without delving into great detail a few points of this principle will be examined. The basic principle of this system is that two streams moving in opposite directions are so placed as to promote the mutual exchange of energy or substance in one form or another. The interpretation, proposed by Gottschalk and Mylle[7], of the loop of Henle as a countercurrent osmotic multiplier is that sodium chloride reabsorption begins in the ascending limb of the loop of Henle and continues throughout the distal convolution. The hyperosmotic interstitium abstracts water from

the water-permeable descending limb with the possibility that sodium chloride diffuses into this limb. Thus the concentration of sodium in the urine delivered to the ascending limb is increased and the system acts as a countercurrent multiplier. Since an osmotically dilute urine is delivered to the distal convoluted tubule, it is felt that the ascending limb must be relatively impermeable to water. This system acts to produce an osmotic concentration gradient to the tip of the loop, and to concentrate the urine by the passive diffusion of water through the collecting ducts. The vasa recta are in free exchange with the interstitium, and serve as countercurrent exchangers, carrying away the sodium chloride reabsorbed locally and the water diffused from the urine.

The countercurrent system as relates to the fate of sodium and water in the renal tubules is still only a hypothesis and many physiologic activities of this system are still to be proven.

HYPONATREMIA IN ACUTE TUBULAR NECROSIS - ETIOLOGY: Hyponatremia is known to develop quite frequently in acute tubular necrosis. However, the exact reasons for the hyponatremia are not always clear. Several possible mechanisms will be discussed.

EXCESS ADMINISTRATION OF SODIUM FREE FLUIDS: Welt[26] states that in many instances, the hyponatremia can be explained as the result of the administration of excess quantities of water, either in absolute or relative terms. In addition, vomiting is frequently encountered, and if the volume of fluid lost by emesis is replaced with water, hyponatremia will result. Merrill[14] also shares the view that, in the absence of sodium loss, hyponatremia may be produced by the excess administration of non-sodium containing fluids. He feels that the hyponatremia is directly related to total body water[13].

The inadequacy of filtration is also implemented as producing a dilutional hyponatremia[18]. This is felt to be the mechanism in the anuric patient and at least a partial factor in patients with renal insufficiency in whom the number of functioning nephrons is reduced. In the latter group, when the filtration rate is seriously impaired, the small volume of urine that can be excreted may be insufficient to overcome dilution produced by the previous administration of sodium free intravenous fluids. Also, in a few cases, hyponatremia may develop on what would be considered a normal fluid intake, and the factor of persistent antidiuretic hormone secretion cannot be excluded in these patients.

Iseri et al.[8], in a series of five cases, also

point out the importance of the administration of excessive water but relatively small amounts of sodium in the pathogenesis of hyponatremia. They also note the effects of emesis and of gastric suction as contributing to the sodium depletion.

DILUTION BY WATER OF OXIDATION: McIntosh et al.[15] feel that the lowered serum sodium is generally a reflection of dilution due to excess body water. Such may result from iatrogenic hyperhydration in conjunction with the salt-free water of oxidation. This water of oxidation results from the catabolism of fat and protein in the presence of an inadequate caloric intake. The complete oxidation of one gram of fat liberates a little more than one milliliter of water. Any condition such as infection, endocrine dysfunction, injury, etc., will accelerate the catabolic response and increase the volume of the water of oxidation. Some anuric patients have demonstrated rates of oxidation of endogenous fat up to 600 grams a day.

Remenchik et al.[20] studied eight cases of acute renal insufficiency in which measurements of total body water and extracellular fluid volume were made. Five of eight patients demonstrated an excess amount of total body water, and all eight had an increase in

extracellular fluid volume. Two mechanisms were held responsible for the increase in water: (a) excessive fluid administration, and (b) water of oxidation and preformed water. Prior to observation, these patients daily intake equalled their twenty four hour urine output plus one liter. It was felt that the fluid intake could not account for the excess water and that the data better supported the water of oxidation mechanism.

Bluemle et al.[3] found the water of oxidation to be 303 ± 30 ml. per twenty-four hours and preformed water to be 24 ± 75 ml. per twenty-four hours. Thus, the catabolic response during oliguria could account for the excess body water and produce a dilutional hyponatremia. Some cases which show a sudden increase in the rate of cellular catabolism with the release of cellular water, are also accompanied by increasing azotemia and hyperkalemia[26].

CELLULAR UPTAKE OF SODIUM: The ionic distribution of sodium and potassium across the cell membrane is the result of conditions maintained at the expense of energy from cellular metabolism[10]. When these metabolic processes are impaired, the normal ratios of intracellular to extracellular potassium and extracellular to intracellular sodium are disturbed. Thus, hyponatremia may be seen as

an "adaptation" phenomenon, but it is not known whether this involves a shift of water out of the cell or a shift of sodium into the cell[14].

Iseri et al.[8] reported a case of acute tubular necrosis in which the patient retained a total of 2,350 ml. of water and 288 mEq. of sodium over a two day period. If the retained water and sodium had remained in the extracellular compartment, a minimal rise in plasma sodium should have occurred, but the serum sodium decreased from 112 to 110 mEq. per liter. They calculated that sixty-two per cent of the retained sodium and only forty-three per cent of the retained water were taken up by the cells.

Several investigators tend to minimize the importance of compartmental shifts of sodium in the development of hyponatremia; however much of the work has not dealt specifically with acute tubular necrosis[6,26].

IMPAIRED RENAL CONSERVATION OF SODIUM: In patients with early renal failure, the excretion of fixed cation in response to an acid load may be large and continuous, since no increase in ammonia excretion and only a minimal increase in hydrogen ion excretion can be expected. This mechanism also serves as a possible explanation for the urinary sodium loses in the polyuria phase of renal failure[14]. This mechanism is felt to

occur in the syndromes of "tubular acidosis", and probably in early renal failure of any etiology. There is also a possibility that the tubular pathology may result in failure of sodium reabsorption through mechanisms other than those operative for bicarbonate-bound base. During the polyuric stage, osmotic diuresis may also occur to increase sodium loss.

It has been shown that during the later part of the oliguric phase of acute tubular necrosis, sodium can be eliminated in the urine in concentrations up to three-fourths of that in the plasma[8]. The excretion of sodium in such high concentrations in the face of marked hyponatremia is felt to reflect renal damage. The losses via this mechanism became significant toward the end of the oliguric phase, as the urinary volume rises to between 500 and 1000 ml. daily. However, the urine remains hypotonic to plasma, and the hyponatremia may be alleviated by supplying the urinary sodium loss only.

MISCELLANEOUS - HYPONATREMIA IN RENAL DISEASE: Parrish[19] and his group studied the relation between inulin and sodium clearances in forty-four patients with renal disease including five cases of acute tubular necrosis. Their results reveal a correlation between inulin

clearance and sodium clearance. This suggests that filtered sodium is the more important element in determining sodium excretion although factors such as tubular reabsorption cannot be excluded. Their results under conditions of sodium loading gave further evidence that there are instances when a decreased tubular reabsorption of sodium appears to play a role in sodium excretion.

Olmstead and Roth[17] measured the contribution of the serum sodium to the total freezing point depression of the serum in various hyponatremic states. Their series included four cases of acute tubular necrosis, in which they found a decreased serum sodium but also the finding of hypertonicity as measured by marked depression in the freezing point of the serum. In these cases, the serum sodium did not contribute its expected percentage of the freezing point depression. The findings of hyponatremia with hypertonicity made up one of their four types of serum hyponatremia as determined by their methods.

TREATMENT OF HYPONATREMIA IN ACUTE TUBULAR NECROSIS: The treatment of hyponatremia will be discussed in reference to the oliguric and diuretic stages of acute tubular necrosis.

Because of the importance of dilution due to excess body water in the pathogenesis of hyponatremia, proper fluid replacement is of paramount importance in the prevention and treatment of hyponatremia. The first step in fluid replacement is to determine the total daily fluid loss from urine, stool, gastric secretions as vomitus or obtained by suction, sweat, and insensible loss. The two routes of expired water vapor and diffusion of water by evaporation through the skin constitute the insensible water loss. In the oliguric patient, in the absence of marked basal metabolic change, one may use the figure of 0.5 - 0.6 cc. of water /Kg. of body weight /hour as a rough guide to estimate insensible loss[14]. Others estimate that a 70 Kg. afebrile patient will lose from 800 to 1000 ml. per day by sweat and insensible means[25].

Fluid replacement is accomplished by the exogenous administration of water as well as by the endogenous water of oxidation. The water of metabolism may only be estimated. A 70 Kg. patient without obvious infection or excessive tissue destruction will produce around 500 ml. per day[15]. Merrill feels that in the average case of acute renal failure a daily intake of 400 ml. plus renal and gastrointestinal losses is sufficient to maintain water balance[13].

However, such calculations of fluid replacement are no more than approximations. Therefore, the state of hydration of the patient must be carefully evaluated before the fluid replacement is determined. The accuracy of the estimate of the volume that is used to replace the losses can be evaluated by frequent determinations of the serum sodium concentration and by daily observations of weight. In the absence of the administration or loss of sodium, a decrease or an increase in the serum sodium suggests too much or too little water respectively[26]. Because of the usual unavoidable situation of being unable to provide an adequate caloric intake, a loss of weight is to be expected. The average adult patient should lose about one-half pound or more per day[3]. Other investigators give a figure of 0.3 - 0.4 Kg. /day weight loss, depending upon the inadequacy of caloric intake[14]. Failure to lose at least some weight every day suggests expansion of the body fluids and increases the tendency to overhydrate[13]. Welt[3] states that in many cases, hyponatremia can be avoided if excessive volumes of water are not administered, and if fluid and electrolyte losses by vomiting are minimized and replaced with fluids similar in composition to the fluids lost.

The fundamental difficulty in managing problems of sodium balance in the anuric patient involves the

replacement of pre-existing deficits, and then maintenance of balance. Because of the loss of body tissue through catabolism, a relative decrease in total body fluid is required, and so small negative balances for both water and sodium may follow the pattern of the general weight loss due to inadequate caloric intake. Thus, no sodium is required when there are no obvious losses[14]. Kolff[9] feels that in acute anuria, sodium should not be given because it cannot be excreted.

There is controversy whether hyponatremia should be corrected when it develops during the oliguric phase of acute tubular necrosis. A careful analysis of the entire picture is necessary before a decision can be reached. It is important to correct any previous sodium deficits and to replace the day-to-day sodium losses. If the hyponatremia results from a loss of fluid with electrolytes and replacement with just water, the administration of sodium is clearly indicated. The development of hyponatremia which results from excess administration or ingestion of water without loss of electrolytes presents a different problem. A reduction of water intake is the proper management for these cases. Hyponatremia in association with significant hyperkalemia or with symptoms arising from the acidosis probably deserves

attempts at correction[26].

Hyponatremia without any sodium loss occurs via two general mechanisms. The first being that of dilution. The second probably involves a disorder in the mechanism by which the so called "metabolic pump" maintains a normal serum sodium. The latter mechanism may be seen as an "adaptation" phenomenon. Neither of these types benefits from the administration of sodium[14]. Water restriction is the treatment of choice for the dilutional hyponatremia, and the "adaptation" type is only improved by correction of the underlying metabolic defect, the exact nature of which are unknown.

On occasion, the therapist will be in doubt as to what role sodium losses play in the development of the hyponatremia, and a trial of sodium replacement will be attempted. Leaf[11] has emphasized that hyponatremia does not in itself further impair renal function, but that the difficulty is produced by the sodium loss and dehydration. In cases of doubt, sodium solutions should be administered with caution because of the potential threat of pulmonary edema. When hyponatremia is to be corrected, hypertonic solutions of sodium salts should be used. Three to five per cent solutions of sodium chloride are commonly used. Sodium lactate and bicarbonate are also in common usage in varying amounts

depending on the degree of depression of the concentration of bicarbonate and the degree of the hypochloremia.

When attempting to correct hyponatremia, the quantity of sodium which must be given has to be calculated on the basis of the volume of total body water rather than the volume of the extracellular fluid alone[26]. This is based on the concept of osmotic uniformity between the intracellular and extracellular compartments, and that one cannot increase the tonicity of one compartment without increasing the tonicity the same amount in the other. Thus, even though sodium salts are confined mainly in the extracellular fluid, their osmotic effects involve total body water.

Merrill[14] feels that although this therapeutic approach is theoretically sound, it is not fully applicable clinically. He has found that in conditions where sodium lack is at fault, clinical improvement often times begins before the serum sodium reaches normal levels. Therefore, he recommends that no more than thirty per cent of the calculated amount be given initially. If, after several hours observation, serum sodium rises, urine output improves, and the clinical status improves, another twenty or thirty per cent of the calculated solution may be given. Conversely, if the serum sodium does not rise, urine output does not

increase, and clinical improvement does not occur, attempts to correct the hyponatremia should be abandoned.

The diuretic phase of acute tubular necrosis is characterized by the excretion of large volumes of dilute urine often accompanied by large electrolyte losses. These losses must be replaced to prevent water and electrolyte depletion. Failure to replace these losses may result in a diminished urine volume, increased azotemia, and a general delay in recovery. It has been pointed out that many patients during the oliguric stage become overhydrated, either from excessive exogenous or endogenous sources, and these patients eliminate this excess water during the diuretic phase[14]. Therefore, total replacement of these losses will simply maintain the overhydrated state. Thus, the replacement of fluids should be determined by the state of hydration at the onset of diuresis rather than the urinary losses alone.

Determining the amount of sodium lost in the urine during the diuretic phase is helpful in deciding how much should be replaced. The sodium losses will usually be found to vary between 60 and 90 m.M. per liter of urine[26]. Kolff[9] states that in general, three grams of sodium chloride for each liter of urine excreted is sufficient replacement and a total of

five grams should be adequate for nearly all patients who are not severely hyponatremic. Observations of several cases of acute tubular necrosis indicate that as long as polyuria persists and renal homeostasis of electrolyte is impaired, it is necessary to control the proportion of electrolyte to water in the diet[12]. This is best done in accordance with plasma and urinary concentrations.

CASE MATERIAL:

Patient One: A forty-one year old white female had given birth to her third child on September 25, 1959 with a subsequent postpartum hemorrhage. She was given plasma that night and received 500 cc. of incompatible whole blood on September 26, at which time she developed chills, fever, loin pain, and shock. Oliguria developed subsequent to that time and she passed only a few cc. of urine each day. She was given more blood and intravenous fluids on the following day and still had very little urinary output. She also received fluid in large amounts up until the time of admission on September 30, Nausea, hiccoughs, and heartburn ensued on the day of admission. The physical examination revealed subcutaneous edema of the back and sacral area, and a loud second pulmonic heart sound. The impression upon admission was that the patient was in the oliguric phase of acute renal

insufficiency due to acute tubular necrosis following the incompatible blood transfusion. The initial laboratory data revealed a hemoglobin of 7.1 gram per 100 ml.; blood urea nitrogen of 140 mg. per 100 ml. and a CO_2 of 12.5 mEq. per liter.

The accompanying table presents the relevant data concerning the fluid balance and the serum and urinary sodium levels.

Clinical Course:

October 1 - A chest film was interpreted as showing some degree of cardiac dilitation.

October 2 - The subcutaneous edema was still present although decreased since the day of admission. Also, the second pulmonic sound was less accentuated.

October 5 - The first dialysis was done on this day because of a rising blood urea nitrogen and continued oliguria. The sodium concentration in the bath was 133 mEq./L. The serum sodium pre and post dialysis remained at 130 mEq./L.

October 6 - Some subcutaneous edema of the back was noted.

October 15 - Oral feedings were begun.

October 16 - The patient had an episode of hypotension.

October 17 - The second dialysis was performed

TABLE ONE

Date	Urinary Sodium mEq./L.	Serum Sodium mEq./L.	Intake cc.	Output cc.	Sodium Intake mEq./L.	Weight lbs.
9/30		142	800 18 hr.	115 18 hr.		
10/1			700	95		
10/2			900	210		134.5
10/3			800	375		134
10/4			800	180		
10/5		130	2225	82		
10/6		130	1000	92		
10/7		134	800	190		126
10/8			800	160		127
10/9			1000	275		127
10/10			600	375		
10/11			500	450		126.5
10/12		130	1100	688		
10/13			1350	870		
10/14	60.8	118	1800	1355		122
10/15			2200	1865	100	120
10/16	60	117	5225	550	183	
10/17	38.8	146	3930	640	167	
10/18		154	1665	1450		
10/19	24.4	122	1995	3025		
10/20	50.8	118	3040	3325		
10/21	50	126	2930	2300	200	
10/22	42.9	118	2365	1700		
10/25	50	130	3575	3150		
10/28	74	142	2375	2650		

with the patient having episodes of hypotension and irregular respirations. The pre dialysis serum sodium was 146 mEq./L. and the post dialysis reading was 154 mEq./L. The sodium concentration in the dialysis bath was 133 mEq./L.

October 18 - Peri orbital edema was noted.

October 19 - There was less edema. A 1500 mg. sodium diet was begun.

October 20 - A non-restrictive sodium diet was begun.

Comment: It is surprising that upon admission the serum sodium was within normal limits because the patient revealed evidence of overhydration. However, during the course of the next five days, the serum sodium subsequently fell to 130 mEq./L. During this five day period the total fluid intake was 3900 cc. with a total output of 975 cc. Arbitrarily assigning figures of 500 cc. per day for water of oxidation and 1000 cc. per day for insensible loss, a total of 2000 cc. of fluid would be required to replace this deficit over the five day period. Thus, 2000 cc. plus the 975 cc. urinary loss still leaves a 925 cc. intake greater than calculated total loss. Accordingly, this deficit, the formation of sodium-free water of oxidation, and urinary sodium loss could all contribute to the

hyponatremia. Increased amounts of fluids were given on September 5 in order to replace the fluids lost by ultrafiltration as a result of the hemodialysis. The diuretic phase began on September 11 with the serum sodium remaining low. The sudden drop in the serum sodium from 130 mEq./L. to 118 mEq./L. is difficult to fully explain; however, the urinary sodium loss was 60 mEq./L. and sodium free fluids were being administered. A prompt rise was noted when sodium was added to the intravenous fluids. The weight loss over a thirteen day period totaled 14.5 pounds. The expected weight loss would be from seven to nine pounds. This additional weight loss could represent overhydration during the oliguric phase with considerable loss of weight with the onset of diuresis. The most plausible explanation for the hyponatremia which occurred after the second dialysis is related to the inadequate replacement of urinary sodium losses, although the exact sodium intake is unknown. The patient subsequently corrected her hyponatremic state in spite of large urinary sodium losses.

CASE TWO:

A seventy year old white male was admitted to a hospital on June 1, 1960 with severe urethral hemorrhage. The patient was cystoscoped and had a

transurethral resection on June 23. The pre operative non protein nitrogen was 51.5 mg. per 100 ml. There was no demonstrable period of shock or severe hemorrhage with the surgery, and there was no apparent period of oliguria following surgery. The patient was observed to be clinically uremic on June 30, and was transferred to another hospital on July 2. He had received 2500 cc. of intravenous fluids on July 2 with an eight hour output of 425 cc. Physical examination revealed a hyperirritable, twitching, confused white male. Mild sacral edema was present. The diagnostic impression was acute tubular necrosis following the transurethral resection without any period of oliguria. The initial blood urea nitrogen was 250 mg. per 100 cc. See Table Two:

Clinical Course: Because of a rapidly rising blood urea nitrogen, increasing irritability, and moderate hyperkalemia, the patient underwent hemodialysis on July 5. The pre dialysis serum sodium was 114 mEq./L. The sodium concentration in the dialysis bath was maintained at 138 mEq./L. and the serum sodium on the day following dialysis was 120 mEq./L. Oral feedings were instituted on July 9; the exact amount of sodium in these feedings is unknown.

Comment: This patient presented with acute tubular necrosis without any recognizable period of oliguria.

TABLE TWO

Date	Urinary Sodium mEq./L.	Serum Sodium mEq./L.	Intake cc.	Output cc.	Sodium Intake mEq./L.
7/3		120	2330	1400	
7/4	39	124	3000	1400	
7/5		114	3000	800	77
7/6	31.6	120	2500	1880	77
7/7			2500	2310	
7/8	36	126	2500	3110	100
7/9		123	3240	4700	120
7/10			3120	3700	179
7/11	58	136	3490	4000	219
7/12			3760	3300	154
7/13	63	137	3250	3900	154

He was hyponatremic upon admission, but after dialysis, replacement of sodium losses, and renal repair the hyponatremic state was corrected. There are various mechanisms which could have contributed to the initial hyponatremia. Such mechanisms include the fact that he presented some evidence of overhydration upon admission, but the exact type of fluids given prior to admission are not known. Also, the water of oxidation would aid in producing a dilutional hypernatremia. The mechanism of an impaired renal conservation of sodium, although difficult to evaluate, could play a role in the pathogenesis of the hyponatremia. Also, an osmotic diuresis may have occurred to increase sodium loss.

During the charted eleven days the total intake exceeded the output by 2190 cc. Assuming that the patient lost 500 cc. per day via insensible loss, an intake deficit of 3310 cc. occurs over this eleven day period. Also, an undetermined amount of fluid was lost by ultra filtration. A certain amount of this fluid loss could represent a loss of excessive fluid accumulated earlier in the course of the disease. Unfortunately daily body weights are not available to further evaluate the patient's state of hydration.

CASE THREE:

A nineteen year old female was admitted to a hospital on April 2, 1960. She had previously been in a car accident in June, 1959 and sustained a fracture of the left femur. There was non-union of the fracture, and two operations were performed on the left femur. On March 29, 1960 the patient had a bone graft. Much bleeding occurred at the donor sites but there was no hypotension.

Her blood type was reported as A positive. She received A positive blood during the first operation, and O negative blood during the second operation. On March 29 she received two units of O negative blood because she couldn't be crossmatched. The blood was given while the patient was under anesthesia. Oliguria developed after the operation on March 29, and her urine was dark in color. She received 2000 cc. of fluids intravenously on March 30, and put out only 175 cc. of urine. She received one liter of fluids on March 31 and again on April 1. She put out 150 cc. of urine from March 31 to April 1. The initial diagnostic impression was acute tubular necrosis secondary to a blood transfusion reaction.

It was later found that she had an incompatibility to Duffy's sub-group.

Clinical Course:

April 4 - The patient was grossly overhydrated as evidenced by the findings of peripheral edema, a loud second pulmonic sound, rales in the lung bases, and radiographic evidence of pulmonary edema.

April 5 - The basilar rales were decreased.

April 6 - The patient underwent hemodialysis because of a rising blood urea nitrogen and general deterioration. Two hundred cc. of fluid were lost by ultrafiltration.

April 21 - The patient's condition became worse.

April 22 - The second hemodialysis was done. The pre dialysis serum sodium was 116 mEq./L. and the post dialysis reading was 132 mEq./L. The concentration of sodium in the dialysis bath was 138 mEq./L. A total of 1500 cc. of fluid was lost by ultrafiltration.

April 24 - The patient developed a septicemia.

April 28 - The general condition improved and the patient maintained a normal serum sodium the remainder of her hospital course.

Comment: The patient's serum sodium of 133 mEq./L. on April 4 is best explained by her overhydrated state. On this day she was clinically overhydrated with evidence of peripheral edema and pulmonary edema.

From March 30 to April 3 she received a total

of 6500 cc. of fluids with a urinary output of only 845 cc., leaving a deficit of 5655 cc.. Allowing 2500 cc. for insensible loss over this five day period, a deficit of 3155 cc. still exists. This amount of fluid could certainly produce a dilutional hyponatremia. With marked restriction of fluid intake, the serum sodium subsequently rose to normal levels. The sudden fall in the serum sodium from a level of 146 mEq./L. on April 8 to a level of 125 mEq./L. on April 11 is difficult to fully explain. The fluid intake from April 8 to April 10 only exceeded the urinary output by approximately one liter. This would hardly account for the insensible loss.

However, several other mechanisms could contribute to the hyponatremia. She was receiving sodium-free fluids to replace her losses. Also she had some emesis in which sodium was lost. In addition, the factor of dilution by the water of oxidation may have played a part in the pathogenesis of the hyponatremia. It is interesting to note that the urinary sodium loss never exceeded 33 mEq./L. which means that a serum to urinary sodium ratio of approximately four to one was maintained throughout her clinical course. With approximate replacement of urinary sodium losses, the patient gradually corrected her hyponatremic state.

TABLE THREE

Date	Urinary Sodium mEq./L.	Serum Sodium mEq./L.	Intake cc.	Output cc.	Sodium Intake mEq./L.
4/2			500	300	
4/3			2000	220	
4/4		133	335	215	
4/5		138.5	265	62	
4/6		136	500	429	
4/7			700	240	
4/8		146	750	285	
4/9			840	350	
4/10			800	700	
4/11	28	125	1315	790	
4/12	30	120	1400	1060	25
4/13	31	123	1575	1330	30
4/14	32	123	1995	1080	40
4/15	33	118	1995	1335	40
4/16	32	117.5	2275	1825	50
4/17			2715	2170	30
4/18	32	120	2560	1675	60
4/19	26		2785	1100	50
4/20	25	115	1740	1536	40
4/21	19	110	1105	1350	30
4/22	14	132	2060	465	20
4/23	2.1	127	2359	875	127
4/24	12.8		2507	1573	20
4/25	12.4	122	2365	1975	20
4/26	23.6	125	2500	2030	60
4/27	31		2590	1641	
4/28	29	137	860	635	

SUMMARY

Brief mention was made of the pathological changes and etiology of acute tubular necrosis, followed by a short discussion of the mechanisms responsible for the anuria and oliguria in acute tubular necrosis. The normal handling of sodium by the kidney was investigated including consideration of various factors which may modify the renal tubular reabsorption of sodium independently of changes in glomerular filtration rate. The counter-current multiplier principle was also discussed.

Hyponatremia is known to develop quite frequently in acute tubular necrosis, but the exact reasons are not always demonstrable. Various mechanisms have been implicated including; (1) the excess administration of sodium free fluids, (2) dilution by water of oxidation, (3) the cellular uptake of sodium, and (4) impaired renal conservation of sodium. Several studies which dealt in general with the problem of hyponatremia in renal disease were also reviewed.

The treatment of hyponatremia in acute tubular necrosis involves the replacement of pre-existing deficits, and then proper maintenance of fluid and sodium balance. Various factors including the

previous state of hydration, serum sodium levels, urinary sodium losses, daily total body weights, and others must all be carefully evaluated in the proper management of the hyponatremia. During the diuretic phase, urinary sodium losses greatly increase and therapy must be gauged accordingly.

CONCLUSION

It is now generally agreed, that any condition which produces inadequate perfusion of the renal parenchyma may promote renal ischemia and lead to necrosis of the renal tubular epithelium. Thus, numerous pathological states may produce acute tubular necrosis. No definite conclusion can be drawn as to the mechanism of oliguria and anuria, so common to acute tubular necrosis. Many workers feel that the depression of the renal plasma flow and glomerular filtration rate are responsible in great measure for the oliguria and anuria. The factor of increased interstitial pressure secondary to edema formation presents with contradictory data. The mechanisms of tubular back diffusion and obstruction of nephrons by casts also are not clearly defined.

The mechanisms responsible for the reabsorption of sodium are related to specific changes which occur in the kidney itself and other changes which occur at sites far remote from the kidney. There is rather general acceptance that an active transport system in the proximal tubule governs the renal reabsorption of sodium. The exact influence of antidiuretic hormone, extracellular fluid volume, nervous impulses, and adrenal cortical steroids is still in the postulation stage. The fact that an increased osmotic load may

result in increased renal sodium losses has been well demonstrated, but the exact explanation is still controversial.

There is good evidence that in many cases of acute tubular necrosis, the hyponatremia can at least be partially explained by the excess administration of sodium free fluids, and thus bears a relationship to the total body water. This dilutional factor also occurs when vomiting appears, and the volume of fluid lost is replaced by sodium free fluids. The inadequacy of filtration in the anuric and severely oliguric patient also contributes to the dilutional hyponatremia. The production of salt free water of oxidation also aids in the production of sodium dilution. The factor of the cellular uptake of sodium in the pathogenesis of hyponatremia is highly controversial and no definite conclusion can be reached. The impaired renal conservation of sodium probably also contributes to the hyponatremia. In the diuretic phase, an osmotic diuresis may also occur to further contribute to increase sodium loss.

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