U R E M I A*

LOUIS LEITER, M. D.
Clinical Professor of Medicine, Montefiore Hospital, New York

ORIGINALLY uremia signified the end stage of organic renal disease when urea was demonstrable in the serum. This was Bright's concept[1] based on the chemical analyses of Christison. Although it was later shown that the blood normally contained urea and that excessive urea concentration could not by itself reproduce the complex manifestations of uremia, the term "uremia" nevertheless became permanently rooted in medical texts and no one would think seriously of displacing it. Probably one of the chief reasons for this was the complete failure throughout the last hundred years to demonstrate any single metabolite or toxin the retention of which could be responsible for uremia. Each of the normally present urinary constituents has been shown to be capable of producing one or more of the major symptoms of the uremic state. But none has met the rigid scientific tests of (1) reproduction of the general state of uremia, (2) effectiveness in causing important symptoms at or near the concentration of the substance in the blood in natural uremia (Table 1).

For example, **ammonium** salts were implicated early in the etiology of uremia.[2] Intravenous injection of ammonium salts produces hyperpnea, convulsions, coma and death. The urine in the end stages of renal disease contains little ammonia, if bacterial infection or contamination is excluded, suggesting that ammonia is retained in the blood. Yet it took another 70 years before Nash and Benedict[3] showed that there is practically no ammonia in normal blood and no increase in uremic blood. In fact, the ammonia normally excreted in the urine is manufactured by the kidney itself — and the failure to produce it during renal insufficiency is a major factor in the **acidosis** of uremia.

Table 1

THEORIES OF UREMIA

1. Retention of urinary solutes
    a) Organic — urea, guanidines, phenols
    b) Inorganic — ammonium, potassium, phosphate,
        sulfate, chloride, water
2. Toxic effects of renal autolysis
3. Metabolic disorganization
4. Lack of normal renal products

What about **urea?** It rises to enormous levels in the blood and all body fluids in uremia; it produces nausea, vomiting, headache, dizziness, diarrhea, twitchings, stupor and coma on intravenous injection into normal animals. Many investigators, including the writer,[4] some 30 years ago, were seriously impressed by the analogy to natural uremia and attributed differences between the artificial and natural variety to the time element or the rate of accumulation. However, it was not realized at that time that the intravenous injection of any strongly hypertonic solution—whether of urea, sodium chloride or other electrolytes, sucrose, even glucose and alcohol – would by its excretion and resultant severe dehydrating action produce all of the symptoms described. If urea were administered more carefully, high blood levels could be achieved with practically no uremic symptoms. Furthermore, patients with high blood urea levels as a result of renal impairment often show few if any signs of clinical uremia; on the contrary, uremic symptoms may persist long after the blood urea level has been lowered into the normal range by vigorous therapy. However, we have learned, incidentally, from the experiments with urea and other hypertonic solutions that **dehydration,** if acutely produced, can cause symptoms that closely simulate some of the major manifestations of full-blown uremia, including elevations of blood urea.

How about **potassium?** No one would seriously blame uremia on potassium retention nowadays but it might well be the immediate cardiac cause of death, especially in anuric individuals with acute nephritis or toxic nephrosis, in untreated or poorly treated Addison's disease, in crisis, and in the traumatic crush syndrome. Addis and Lew,[5] Bergman and Drury[6] neatly established potassium as the lethal factor in high meat diets when fed to nephrectomized or acutely renal-insufficient rats. Potassium may be increased to dangerous concentrations in uremia; on the other hand, in some few cases it may be reduced by vomiting, diarrhea or diuresis to critically low levels in the serum. The conclusion is that, in addition to acidosis and dehydration, **specific eletrolyte disturbances** play a role in uremia (Table 2).

In uremia, the serum **calcium** level is reduced often due to retention of inorganic phosphate. Tetany may occur but ordinarily is counteracted by the increased ionization of calcium, secondary to acidosis, and the depression of the neuromuscular system by other factors in uremia. The muscular twitchings so common in advanced uremia are apparently not related to serum calcium. Convulsions in uremia are rarely to be attributed to low serum calcium ions. One must also consider the opposite situation – hypercalcemia which may result from parathyroid or bone disease of various types, from vitamin D overdosage, rarely from excessive ingestion of milk and alkalis in the management of peptic ulcer. In all of these conditions, a state closely resembling uremia may supervene even in persons with previously normal kidneys.

The story of **chloride** in uremia is also one of ups and downs, so that one may speak of hypochloremic azotemia or hyperchloremic uremia. There

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Table 2

DIAGNOSIS	BLOOD	SERUM							BLOOD
	Urea N.	Na	Cl	CO$_2$	K	Ca	P	Creatinine
	mg.%	meq/1	meq/1	meq/1	meq/1	mg.%	mg.%	mg.%
Chronic Nephritis	75	145	115	15	5	8	8	6
Pyelo-nephritis	75	130	85	25	4	8	8	8
Peptic Ulcer	75	135	75	45	3	10	5	3
Adrenal Failure	75	120	85	20	7	10	4	4
Anuric Nephrosis	75	135	85	20	7	7	12	9
Ca of Breast + Testosterone	75	135	95	25	5	16	7	4
Gastro-enteritis	75	180	145	15	3	12	7	6
Enlarged Prostate	75	150	120	15	5	9	6	3
Normal	15	145	105	30	5	10	4	1

The variability of electrolyte levels in different types of uremia. For the sake of simplicity, the figures for Na, Cl and CO$_2$ are given to the nearest 5 meq.

are many reasons why the serum chloride concentration may be reduced greatly in uremia – vomiting, diarrhea, loss in dilute urine, shift from extracellular to intracellular fluids, dilution of available chloride by excess water intake and edema formation, low intake, displacement of chloride ion by retained sulfate ion, ketone acids, lactic acid and other organic anions. The serious symptoms associated with hypochloremia are due largely to the coexistent complex metabolic disturbances. Hyperchloremia in uremic states usually results from over-treatment of acute anurias with saline solutions. Sodium chloride, with its ion ratio of chloride to sodium of 1:1, contains excess chloride, since in extracellular fluids the ratio of chloride to sodium is only 2:3. The normal kidney easily takes care of this discrepancy, but in severe renal impairment this is not the case and chloride retention with hyperchloremic acidosis results. Temporary hyperchloremic acidosis has often been produced unwittingly by physicians during vigorous saline infu-

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sion treatment of diabetic ketosis, postoperative states and other conditions of dehydration or shock during periods of relative renal insufficiency.

The role of electrolytes in the syndrome of uremia has been recently strikingly demonstrated by Grollman and his associates.[7] They prolonged life in nephrectomized dogs by diets exceedingly low in sodium chloride, potassium, phosphate and sulfate but containing protein, fat and carbohydrate and water in balanced proportions.

Granting that the syndrome of uremia is to a large extent compounded of dehydration, acidosis and electrolyte disturbances, is there a **toxic organic metabolite** responsible for the resistant anemia, the central nervous symptoms, intractable nausea and pruritus? Many investigators have blamed guanidine or its derivatives and free phenolic compounds.[8] Some of these substances, like guanidine, increase neuromuscular irritability, others are potent depressants and could cause the apathy, stupor and final coma of uremia. No one can evaluate the true role of these substances chiefly because of the lack of specific analytic methods. There are also the autolytic products of slowly degenerating or acutely ischemic or anoxic kidney tissue. To the absorption of these many of the lesions and symptoms of malignant hypertensive uremia have been attributed, originally by Ascoli[9] and more recently by Winternitz et al.,[10] Leiter and Eichelberger[11] and Masson et al.,[12] in experiments with various renal or endocrine extracts. As yet too little progress has been made in the understanding of these products.

Much of the preceding discussion applies equally to organic renal uremia and to the vast group of prerenal or extrarenal azotemias (Table 3). Is there any basic difference between **renal uremia and prerenal uremia?** If nothing is known of the patient's previous history and condition and he is examined as of the moment, one would have great difficulty in distinguishing between the two kinds of uremia. The blood chemical changes may be comparable in the two groups. The urinary chemical changes may also be the same in the two although the urinary sediment may furnish differential diagnostic clues as to the underlying condition. The reason for these similarities is not surprising in view of the common electrolyte and fluid disturbances of prerenal azotemia and renal uremia. Furthermore, if prerenal disturbances last more than a few days, severe renal hypoxia and actual tubular degeneration combine to convert the original secondary renal dysfunction into an irreversible functional disorganization. In the acute uremias of prerenal origin there is always hope for restoration of function in a previously good kidney given an adequate blood supply and a decent fluid environment. The more damaged the kidneys have been by previous infection, inflammation or vascular disease, the more dangerous does prerenal azotemia become for the individual. Since treatment for prerenal azotemia can be quite successful if begun early enough, it pays to act on the principle that all uremias are related basically.

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Table 3

TYPES OF UREMIA

ORGANIC Renal Disease
  a) acute — oliguric, anuric
  b) chronic — polyuric, oliguric

FUNCTIONAL Renal Derangement
  a) Dehydration — water, electrolytes
      (hypo-osmotic, hyperosmotic)
  b) Hemodynamic — hemorrhage, shock, heart failure
  c) Hypercalcemia — bone disease, vitamin D, hormones
  d) Obstruction — post-renal
  e) Neurogenic (Trueta shunt)

In 1937 Harrison and Mason,[13] following Volhard, Fishberg and others, excluded prerenal azotemia and defined uremia as "only that symptom complex which occurs in conjunction with and as a result of the retention in the blood of urinary waste-products." In 1945, Bradley[14] defined uremia as that "clinical state associated with nitrogen retention and disturbances of body water due to renal insufficiency, regardless of etiology." This obviously includes the renal insufficiency initiated by prerenal disturbances and is, therefore, a satisfactory definition. The emphasis on the term "clinical state" in Bradley's definition is important because one should not jump to a diagnostic conclusion on any one laboratory finding. Uremia may be indicated whenever a patient has one or more of the following symptoms: anorexia, nausea, vomiting, diarrhea, weakness, pallor, apathy, itching, irritability, confusion, stupor, twitchings, hyperpnea, dehydration or edema.

The **management of uremia** follows more or less logically, more or less empirically, from the preceding discussion of pathogenesis and mechanism, provided the individual differences in etiology and types of physiological disturbances are taken into account, otherwise the treatment of uremia will become standardized, routine, thoughtless, and, on occasion, foolish or positively harmful. Thus, uremia following upon excessive vomiting and dehydration, will require the use of large quantities of parenteral fluid and the appropriate electrolytes. Most of the initially prerenal uremias fall in this category but with one major exception – the group originated by circulatory collapse. Here the immediate indication is not to pour in large amounts of diffusible fluid but to restore blood pressure, circulating blood volume and cardiac efficiency before irreversible renal and cerebral changes occur. The problem is relatively simple in massive hemorrhage in a person with a previously good heart. It is tantalizing in the case of acute myocardial infarction with prolonged circulatory collapse and oliguria. One must run the risk of cardiac failure and pulmonary edema in order to prevent prerenal uremia. Sufficient experience in this field for safe treatment is still lacking.

Ideally, **preventive** treatment of uremia based on anticipation of its occurrence is the best therapy (Table 4). This principle has been applied brilliantly to all conditions of the gastrointestinal tract associated with

vomiting, severe diarrhea or suction drainage of one type or another. Only accurate appraisal of the daily balance of fluid and electrolytes, and frequent blood chemical analyses, will furnish the proper guide to prophylactic treatment of prerenal uremia. Many lives have been saved by this simple bookkeeping.

Table 4

PREVENTION OF UREMIA

1. Observe; measure; consider; act.
2. Record and replace extrarenal loss.
3. Watch urine and serum electrolytes.
4. Maintain open urine-way.
5. Control use of renal-acting drugs.
6. Treatment of heart failure.
7. Fluid intake in chronic nephritis.
8. Diet in acute nephritis.
9. Parenteral fluid in hypercalcemia.
10. Use of BAL in Hg poisoning.

In severe acute nephritis, as well as in other oligurias, prevention of uremia consists of sharp restriction of salt and fluid intake and of protein, depending on carbohydrate and fat to furnish basal calories. Prompt recognition and treatment of early left ventricular failure are important in preventing circulatory renal impairment. The use of BAL early in mercury or arsenic poisoning may be of decisive prophylactic value. Checking of serum calcium values in patients under treatment with vitamin D, or large doses of testosterone for metastases from carcinoma of the breast, will indicate danger zones and suggest the need for vigorous measures to maintain renal function.

In patients with hypertensive disease or severe congestive heart failure, regardless of cause, over use of the low sodium regimen and of mercurials not infrequently leads to electrolyte depletion and serious metabolic disturbances ending in uremia. Serum electrolyte analyses during such diuretic treatment will save both the patient and the physician a great deal of distress and point to the type of restorative solution, preferably hypertonic.

In chronic renal disease with renal insufficiency at the pre-uremic level, the prevention of uremia consists in maintaining a large enough urine volume – at least 1500 to 2000 cc. – to offset accumulation of nitrogenous products, checking acidosis, and avoiding edema or excessive loss of salt. Careful appraisal of the patient's renal behavior in these various directions will individualize treatment. In general, a low protein diet – 30 to 50 Gm. – is indicated, with a relatively high caloric value to spare body protein. If there is edema, salt will be restricted; if there is a tendency to acidosis a few grams of sodium citrate or bicarbonate may be given daily. It should be remembered, as Addis and others have observed, that the kidney must do as much work to dilute the urine as to concentrate it in relation to the serum filtrate. Therefore, it pays to give enough salt to permit the kidney to

excrete urine with a specific gravity of 1.012 to 1.016. Patients with chronic renal disease are in danger of uremia should they develop anorexia and diminish their intake of fluid. The uncontrolled use of either acid-forming or alkaline compounds during renal failure is fraught with hazard for obvious reasons. Finally, uremia can be precipitated by the circulatory depression caused by excessive sedation.

During periods of necessary parenteral feeding, one must compromise with reality and not attempt to do the impossible either as to nutrition or as to maintenance of large urine volumes. One should rarely exceed 3 liters of fluid per day by the intravenous route in patients with uremia due to chronic renal disease. When serum sodium and chloride are both low, restoration is best carried out by infusing a solution of sodium chloride and sodium lactate or bicarbonate in the equimolar proportion of 3:1 or 2:1, to dilute the excess chloride in ordinary saline and furnish extra bicarbonate to correct present or potential acidosis. In the presence of hyperchloremia and low serum bicarbonate, the solution administered should be sodium bicarbonate or lactate in appropriate amount. Calcium may have to be given in some instances; potassium practically never in organic uremia and certainly never without chemical evidence of low serum values. Whatever solution is used, it must be borne in mind that renal function is inadequate to make the normal clear-cut selection between electrolytes; therefore, injection should be made slowly and frequent chemical analyses done to control the effects of the treatment. Careful records must be kept of intake and output, including gastrointestinal losses.

The question of parenteral injection of protein hydrolysates or plasma protein must be considered whenever oral intake of food is impractical for more than a few days. The amount of amino acids or, better, salt-poor serum albumin, need not be more than 20 to 25 Gm. of the former or 10 to 15 Gm. of the latter daily. Unpleasant reactions toward hydrolysates must be guarded against by slow infusion and trial of various brands until one is found for the particular patient.

When using antibiotics or other chemotherapy for infections, the dosage must be adjusted downward sharply to allow for severely impaired renal excretion of these compounds. This will prevent waste of more or less expensive drugs, and what is more important, may obviate the danger of serious sensitization or toxic reactions.

In uremia caused by acute toxic or other type of nephrosis, it is generally agreed that intake of fluids and electrolytes must be restricted to daily loss during the oliguric or anuric phase. However, once diuresis sets in, there is an imminent danger of electrolyte depletion because of poor tubular reabsorption. This situation resembles the salt-losing type of chronic nephritis and must be treated in the same manner by the oral or parenteral administration of mixtures, usually 2:1, of sodium chloride and sodium bicarbonate, (5 to 15 Gm. daily), with daily analyses of urinary sodium or chloride and frequent estimations of serum sodium, chloride and bicarbonate. It may be

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necessary to follow this regimen for a few weeks. Any patient with severe renal insufficiency who is not edematous and is excreting large urine volumes is in danger of excessive electrolyte loss and should be carefully checked. In these days of widespread use of low sodium diets, it cannot be overemphasized that severe renal impairment is a contraindication to such a diet unless the physician can control his patient biochemically.

One of the most pressing questions in the treatment of uremia is whether one should resort to some type of irrigation or dialysis. This problem arises chiefly in the management of acute, reversible uremia but it also applies to some extent to chronic, irreversible uremia in the hope of tiding the patient over from a critical and premoribund to a little less precarious state. Snapper[15] and others have recently reviewed the indications for, and results of, the various procedures for the artificial dialysis of uremic patients and animals, and have arrived at the general conclusion that no one of these methods has been shown to improve the mortality statistics even in the supposedly reversible forms of uremia, as in lower nephron nephrosis. The reasons for these disappointing conclusions are the complexity of the procedure, the danger of peritonitis and ileus, the hemolytic reactions when blood is perfused through an apparatus, the difficulty in controlling hydration and electrolyte balance because of the type of solution used in the bathing fluid, or the diet taken by the patient or experimental animal. Yet there is still room for a simple, nontraumatic, nonhemolytic dialyzing machine and along with it a set of bedside chemical technics for the rapid clinical estimation of serum electrolytes, plasma volume and other essential data. With the present widespread interest in this field, rapid progress may be expected.

Summary

1. In view of the interrelationship of electrolyte and circulatory disturbances, the distinction between prerenal, or functional renal azotemia and true, or organic renal, uremia becomes superfluous even though differences in treatment and prognosis remain.

2. While the majority of the clinical manifestations of uremia are attributable to electrolyte and fluid imbalances, all potentially correctable, some specific toxemia related to protein catabolism may be an additional factor.

3. Principles of management of uremia are presented which accord with the pathogenetic mechanisms, in the hope that the individual patient's therapeutic cloth will be cut to fit the diagnostic and physiologic measurements of each case accurately, rather than by routine standards.

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