CONSERVATIVE MANAGEMENT OF CHRONIC RENAL FAILURE

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"It is a long time since we have not seen Dr. Lwoff."

Anton Chekov
Uncle Vanya

INTRODUCTION

Chronic renal disease annually results in the need for renal replacement therapy (dialysis or transplantation) in approximately 50 to 60 persons per million. The annual Federal budget for such therapy may soon reach $3 billion. Though this direct dollar cost may appear enormous, it may be dwarfed by the cost of lost productivity and the individual and family stress imposed by debilitating chronic disease. The cost, morbidity and mortality associated with renal transplantation and chronic dialysis dictate that the practicing physician attempt to maintain renal function in patients with chronic renal failure for as long as possible, and, if possible, to prevent the progression of the underlying renal disease.

Chronic renal failure is defined as a disease with pathological renal damage and persistently reduced glomerular filtration rate (GFR). Established chronic renal failure frequently progresses to end stage even when the primary disease process is inactive. There is no question that such chronic processes as diabetes mellitus, polycystic kidney disease, and a variety of immune-mediated nephritic syndromes contribute principally to the long-term loss of renal function. However, relentless progression to end stage also occurs in patients who sustain renal injury as a result of bilateral cortical necrosis (1), post-infectious glomerulonephritis (2), vesico-ureteral reflux (3), and unilateral renal agenesis (4). Infection, hypertension or the use of nephrotoxic drugs may contribute to the progressive loss of renal function in some cases, but cannot account for all such instances (5). Even in patients with severe hypertension and renal insufficiency, aggressive blood pressure control may not prevent the eventual decline of renal function (6).

The following discussion will focus on conservative measures which may forestall the need for dialysis or improve the general condition of those who require dialysis support.

THE UREMIC TOXIN

Uremia means "urine in the blood" and implies that substances normally excreted in the urine are retained and thereby cause toxicity. Because uremia, in many respects, resembles systemic intoxication, considerable research has been directed toward identifying the retained substance(s) responsible. The list of putative toxins is long and grows yearly. A discussion of the evidence which implicates these substances is beyond the scope of this presentation, but a list of some of the more frequently mentioned candidates is shown below (7).

Compounds Implicated in Uremic Toxicity

A. Organic Metabolites

Urea	Aromatic Amines
Creatinine	Uric Acid
Guanidine Compounds	Oxalic Acid
Aliphatic Amines	Myoinositol
Phenols	2,3-butylene glycol

B. Peptides and Protein Degradation Products
Middle Molecules (m.w. = 300-1500)

Amino Acids	$Beta_2$-microglobulin

C. Enzymes

Renin	Lysozyme
Ribonuclease	

D. Hormones

Parathyroid Hormone	Calcitonin
Glucagon	"Natriuretic Hormone"
Growth Hormone	

The uremic syndrome is the clinical manifestation of end stage renal disease and affects virtually every organ system.

The Uremic Syndrome

Organ System	Clinical Manifestations
1) Cardiovascular	Volume Overload Hypertension Accelerated Atherosclerosis Pericarditis
2) Hematopoietic	Anemia
3) Neurologic	Encephalopathy Peripheral Neuropathy
4) Gastrointestinal	Gastroenteritis Colitis Pancreatitis Peptic Ulcers
5) Pulmonary	Pneumonitis Pleuritis
6) Endocrine	Hyperparathyroidism Carbohydrate Intolerance Infertility
7) Integument	Pruritus Hyperpigmentation
8) Musculoskeletal	Osteodystrophy Metastatic Calcification Myopathy
9) Immunologic	Impaired delayed hypersensitivity

Because uremia adversely affects such a variety of tissues and because active infection, immune mechanisms and hypertension fail to account for the decline in renal function in many patients, it may not be unreasonable to assume that retained uremic substances promote the progressive loss of renal function.

DIETARY PROTEIN AND CHRONIC RENAL FAILURE

The hepatic generation of urea and hence the plasma urea concentration are, in large part, directly related to the dietary protein intake. It is well known that dietary nitrogen restriction (and subsequent reduction in the circulating concentration of urea) often decrease uremic symptoms. The notion that dietary factors may influence the progression of disease is not a new concept. In 1917, Rowntree, a contributing author to Musser and Kelly's Handbook of Practical Treatment (8), recommended a low nitrogen diet for patients with chronic nephritis. The physiological basis of this recommendation is somewhat unclear, however, as the same volume also recommends a low nitrogen diet for gastric ulcer, myocardial insufficiency and glaucoma. Thirty years later, Addis (9) suggested that protein intake be restricted in cases of early renal insufficiency. He proposed that reduction in the nitrogen waste load would reduce renal work and preserve renal function. In a series of experiments with rats, he demonstrated a relative preservation of renal weight (10) and glomerular filtration rate (11) by decreasing the proportion of dietary nitrogen fed to animals with surgically induced renal insufficiency. Addis argued that the excretion of nitrogenous waste, chiefly urea, required thermodynamic work, and likened the nephron to cardiac muscle in valular heart disease. He proposed that the increase in workload would lead to hypertrophy, strain and finally to organ failure. Somewhat later, Farr and Smadel (12) showed that dietary protein restriction preserved renal function in rats after either surgical ablation or the administration of nephrotoxic serum. The test animals were divided into three groups of 15 each and fed an isocaloric diet containing 5%, 18% or 40% crude protein. Renal insufficiency was produced by either surgical ablation or by the administration of heterologous anti-rat kidney serum. Eleven of those fed the low protein diet recovered near normal renal function and none died. However, seven of those fed the 18% (normal protein) diet and thirteen of those fed the high protein diet died, presumably from renal failure. These authors concluded that dietary protein was harmful due to an increase in acid load.

By the late 1950s it was found that renal work was most closely related to sodium reabsorption, and thus the ideas of Addis and his contemporaries fell from favor. Because a normal protein diet seemingly had little adverse effect on the renal function of humans, the advent of hemodialysis and a fear of protein-calorie malnutrition, clinical interest in protein-restricted diets virtually disappeared. Until recently, only a few have continued to publically recommend protein restriction in the routine management of chronic renal insufficiency (13).

NEPHRON HYPERTROPHY AND DIETARY PROTEIN

When significant portions of the normal renal mass are surgically removed, the remaining (remnant) renal tissue characteristically undergoes histological and functional hypertrophy. Following unilateral nephrectomy, glomerular filtration may approach presurgical levels within six months. Such increases in remnant nephron filtration have been classically regarded as adaptive. However, at least two groups of investigators (14,24), using animal models, have shown that drastic reduction in the renal mass (usually >75%) leads to failure in remaining nephrons. Further, the

rate of decline in the remnant nephrons increased in direct proportion to renal mass ablated.

Three decades ago Chanutin and Ferris (14) reported that 5/6 nephrectomy leads to a progressive rise in blood pressure, proteinuria and histological glomerular damage in the rat. The same authors reported that increasing dietary protein in a stepwise fashion resulted in incremental increases in proteinuria, hypertension and mortality (15,16). These investigators varied the type of dietary protein, but could not identify any particularly nephrotoxic group.

Recently Hostetter and his associates (17) have demonstrated an increase in single nephron glomerular capillary plasma flow and pressure at seven days following a subtotal nephrectomy in the rat. However, when dietary protein was reduced from 40% to 6% of the total, these changes were abolished. A similar effect can be observed in animals with immune-mediated CRF. As previously cited, Farr and Smadel (12) observed a more rapid decline in GFR and increased proteinuria following treatment with nephrotoxic serum in rats on a 40% protein diet as compared to similarly treated animals fed a 5% protein diet. Further, Friend and associates have shown that the "lupus-like" nephropathy of NZB x NZW rats could be influenced by diet. They found that lowering either dietary protein or total calorie content reduced the number of immune complex deposits in the glomerular basement membrane. These studies present striking evidence that dietary factors may influence the progression of chronic renal disease. Though protein is most frequently implicated, the exact identity of the offending agent is still unclear.

DIETARY PROTEIN AND STRUCTURAL RENAL DAMAGE

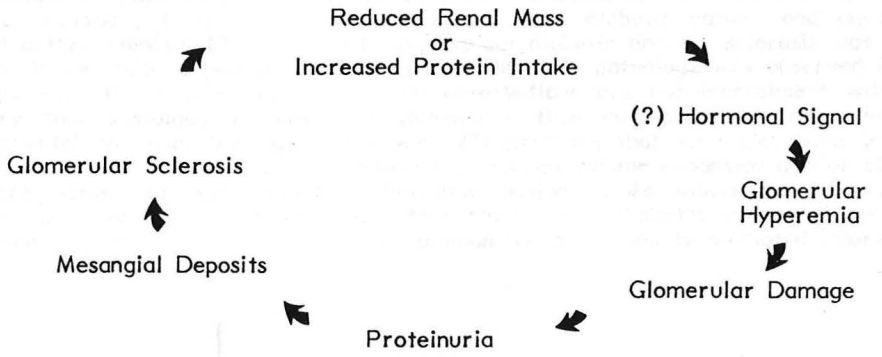
Age-related glomerular sclerosis is an established observation in both humans (18,19) and laboratory animals (20,21). By two years of age, most male rats fed standard laboratory diets (20-25% crude protein) exhibit progressive sclerosis of the majority of glomeruli. On the other hand, female rats, which eat less and have lower body weights, have significantly fewer lesions at the same age (23). Both sexes can be protected by restriction of dietary protein, most strikingly if dietary nitrogen is reduced enough to limit growth. Conversely, glomerular sclerosis can be accelerated in both sexes by increasing the dietary protein content.

Following unilateral nephrectomy in the rat, the increase in glomerular capillary flow, pressure and filtration rate (previously presumed to be adaptive) are associated with an increase in the rate of glomerular sclerosis (25,26). Following 90% renal ablation, a diet containing 6% protein has been shown to blunt the increase in glomerular pressure and flow and decrease the proteinuria and glomerular sclerosis observed in similar animals fed a standard (20-25% protein) laboratory diet (17). It has therefore been proposed that the so-called adaptive hyperfiltration in remnant nephrons is in fact maladaptive and hastens the progression of renal failure.

Expanding the above hypothesis, Brenner and his associates (27-30) have proposed that glomerular sclerosis is (a) protein induced (or at least accelerated) and (b) the final common pathway of many seemingly unrelated renal diseases in both man and animals. The theory is elegant in its simplicity and is summarized as follows: An increase in dietary protein relative to the functioning renal mass causes renal vasodilatation and hyperperfusion of the glomeruli, at the expense of increased capillary pressures. The signal for the renal vasodilatation is not known, but appears to be mediated by a somatostatin-inhibitable mechanism (28). This

hyperemic renal response can be duplicated by feeding certain amino acids, but not urea. Further, this response can be duplicated by infusion of growth hormone or glucagon. If the stimulus to hyperfiltration is removed (dietary protein restriction), glomerular filtration returns to previous levels. If, however, the stimulus continues, the elevated transcapillary flux disrupts the glomerular capillary basement membrane and macromolecular filtration (proteinuria) ensues. Progression of this injury increases proteinuria and the mesangial accumulation of protein deposits. Such deposits eventually result in glomerular sclerosis. As sclerosis proceeds and the functioning renal mass contracts, the remaining nephrons experience an even greater filtration load and a vicious cycle is established.

Hyperfiltration-Glomerular Sclerosis Model

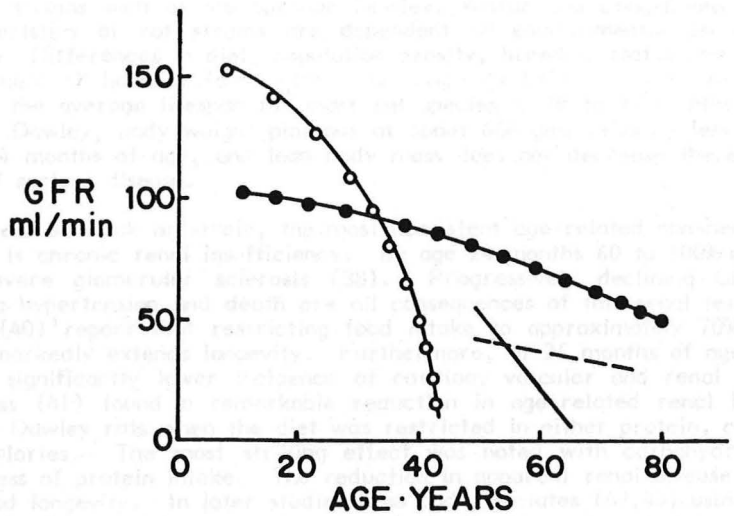


MECHANISM OF HEMODYNAMIC GLOMERULAR INJURY

The increase in mean glomerular transcapillary pressure may injure the capillary membrane in a manner analogous to the effects of systemic hypertension on arterioles. However, systemic hypertension per se does not account for the glomerular sclerosis observed in the renal ablation model. Purkerson et al. (31) reported that rats subjected to partial infarction of one kidney develop significant systemic hypertension, but glomerular morphologic changes do not occur. In yet another group of experiments, extensive renal ablation followed by control of systemic blood pressure failed to prevent progressive sclerosis of the remnant renal mass. These authors thus suggest that some critical reduction in renal mass was necessary for the development of the progressive glomerular lesions. Furthermore, intrarenal hemodynamics differ sharply between hypertensive rats with intact kidneys and those with extensive reduction of renal mass. Those hypertensive animals with intact kidneys show no increase in glomerular pressures and glomerular plasma flow tends to be decreased, due primarily to an increase in intrarenal vascular resistance (32,33). It would thus appear that the intrarenal hyperemia which occurs as a result of extensive renal loss occurs independently of systemic hypertension and is essentially a failure of glomerular capillary autoregulation. As previously pointed out, drastic dietary protein restriction reduces this intrarenal hyperperfusion and prevents the associated glomerular morphologic changes.

HYPERFILTRATION AND HUMAN RENAL DISEASE

Pathological studies of kidneys from humans with diffuse renal disease reveal hypertrophic changes in nephrons not affected by the primary process. These changes are presumably the result of a reduction in functional renal mass (23). As most physicians know too well, most patients with glomerular filtration rates of 25 ml/min or less will eventually require hemodialysis or transplantation, even though the original disease may be inactive. Progressive glomerular sclerosis mediated by hyperfiltration may offer one explanation for this observation. Hostetter and Brenner (30) have now extended this theory to include diabetic nephropathy. They propose that the hyperfiltration that occurs in the first decade of juvenile diabetes not only contributes to the progression of nephropathy, but may also initiate the glomerular injury. Studies of experimental diabetes in rats demonstrate that changes in intrarenal hemodynamics can influence the progression of the diabetic renal lesions (34). Further, there is at least one report of a diabetic patient and unilateral renal artery stenosis (35). At autopsy, typical diabetic nodular sclerosis was found in the kidney with a patent renal artery, while little pathology was observed in the kidney with the stenotic artery. Such observations are not inconsistent with the theory that sustained increases in glomerular flow and pressure are ultimately detrimental to renal function. Brenner (29) proposes that such elevations in flow and pressure may result from hyperglycemia induced volume expansion and/or altered glucoregulatory or vasoregulatory hormone action. As illustrated below, the progressive loss of renal function due to normal aging, diabetes and extensive renal ablation may in each case represent a common hemodynamically mediated injury.



(FROM MEYER, ET AL: REF. 23)
o JUVENILE DIABETES
● NORMAL AGING
– EXTENSIVE RENAL ABLATION
-- RENAL ABLATION + DIET RESTRICTION

HUMAN RENAL DISEASE: MODELS AND QUESTIONS

The protein-induced hyperfiltration/glomerular sclerosis theory of progressive chronic renal failure is simple and the data seem to argue strongly in its favor. Should this theory prove applicable to humans, the implications are far reaching in terms of both human morbidity and dollars. Ogden (36) has recently voiced concern regarding the fate of living kidney transplant donors. He fears that if the age-related decline in renal function is indeed due to a lifetime of dietary protein excess, such donors would obviously be at increased risk for serious renal insufficiency. Goldszer and his associates (37) have recently reported the current status of 25 adults (mean age = 60 years) who had donated a kidney at least ten years previously. Though they found no incidence of significant renal insufficiency, seven of the 19 who had donated ten to 14 years previously had diastolic blood pressures greater than 90 mm Hg. This group had daily urine protein excretions of 130 $\pm$ 19 SEM mg/day. At the time of donation none were hypertensive or had a daily urinary protein content greater than 50 mg. Of six who had donated a kidney more than 15 years before, three were hypertensive and excreted an average of 366 $\pm$ 127 mg protein/day. Such data are certainly not compelling, but speak clearly for a need for multicenter study of this situation.

Though the available data support a role for dietary protein in the progression of renal insufficiency in rats, relatively little data is available for humans. Furthermore, any animal model for disease must be viewed in the context of the physiology of that species. Rats are the most studied species in modern medical research. This is largely the result of convenient size, ease of handling and moderate maintenance costs as compared to other animals. Most commonly used are outbred strains such as the Sprague Dawley, Wistar and Long-Evans. The survival characteristics of rat strains are dependent on environmental as well as genetic factors. Differences in diet, population density, breeding status and microbiological environment all have profound effects on longevity (38). With minor variations due to sex, the average lifespan for most rat species is 24 to 27 months (27). In the Sprague Dawley, body weight plateaus at about 600 gms (slightly less in females) at 18 to 24 months of age, and lean body mass does not decrease thereafter until the onset of serious disease.

Regardless of stock or strain, the most consistent age-related non-neoplastic disease of rats is chronic renal insufficiency. By age 24 months 60 to 100% of such animals have severe glomerular sclerosis (38). Progressively declining GFR, azotemia, systemic hypertension and death are all consequences of this renal lesion. Berg and Simms (40) report that restricting food intake to approximately 70% of ad libitum intake markedly extends longevity. Furthermore, at 26 months of age these animals have a significantly lower incidence of cardiac, vascular and renal disease. Bras and Ross (41) found a remarkable reduction in age-related renal lesions in male Sprague Dawley rats when the diet was restricted in either protein, carbohydrate or total calories. The most striking effect was noted with carbohydrate restriction regardless of protein intake. The reduction in apparent renal disease coincided with increased longevity. In later studies Ross and associates (42,43) using a freedom of choice feeding model, concluded that both the amount and type of diet a rat consumes before midlife was the best predictor of longevity. Early in life a high protein diet extended lifespan, while after midlife the opposite was true. In summary, the rat is a short-lived animal with a high rate of age-related renal disease whose longevity and health are remarkably sensitive to dietary manipulation. Such observations raise questions regarding the appropriateness of the rat as a physiological model for chronic human renal disease.

Recent editorials (43) have raised even further questions regarding the protein-induced hyperfiltration model of chronic renal failure. The model indicates that proteinuria results in mesangial protein deposition, a forerunner to glomerular sclerosis. This hypothesis may or may not be easily reconciled with the observation of stable renal function in patients with orthostatic proteinuria for as long as 20 years (44). Others (45,46) have observed that patients with the nephrotic syndrome whose proteinuria could be maintained between 150 mg and 2.0 gm/day may maintain a normal GFR for as long as 15 years. Such observations might be construed as detracting from the hypothesis or may merely indicate that some critical level of proteinuria (presumably greater than 2.0 gm/day) is necessary to produce significant glomerular sclerosis.

There is also some uncertainty as to whether protein, per se, or some other dietary element is the agent which promotes renal failure. Ibels (47) and later Tomford (48) have shown that dietary phosphorus restriction in rats with remnant kidneys prevents deterioration of the GFR. Similar results have been reported in cats (49). It should be noted, however, that the renal insufficiency associated with phosphorus feeding is characterized by renal mineralization, inflammation and fibrosis rather than glomerular sclerosis.

Attempts to separate the effect of dietary protein and phorphorus in remnant kidney models have frequently yielded confusing results. Kikuchi and his associates (50) have reported prolonged survival of rats with surgically induced renal insufficiency by feeding a diet low in both protein (6%) and phosphorus (0.12%). However, the survival of animals fed either a low protein or low phosphorus diet produced intermediate survival rates, when compared to rats on an unrestricted diet, but were not different from each other. Interestingly, no effect on the decline in renal function was observed with any of these diets. Similar results have been reported by others (51).

While human studies are limited, some have yielded encouraging results. Barsotti and associates (52) have studied the effect of a low protein (0.5 gm/kg body weight), low phosphorus (0.7 mg/kg) on 20 patients with chronic renal insufficiency (mean creatinine clearance = 25-30 ml/min). Over an 11-month study period, these patients' creatinine clearance decreased by 0.1 $\pm$ 0.4 ml/min. while the clearance of 19 similar patients who consumed a relatively unrestricted diet declined by an average of 0.6 $\pm$ 0.7 ml/min. Such studies suggest that some form of dietary modulation may be important in retarding the progression of renal insufficiency. However, the identity of the offending dietary element (protein?, phosphorus?, total calories?, others?) remains rather obscure. The answer to this question will probably require the long-term use of chemically defined diets in large numbers of patients.

Whether dietary manipulation can actually halt or significantly retard the progression of renal insufficiency will obviously require considerably more investigation. Large numbers of patients, carefully defined diets and long study periods will be required in order to settle these issues.

PROTEIN RESTRICTION AND UREMIC SYMPTOMATOLOGY

Whether the restriction of dietary protein can actually slow the progression of renal insufficiency may still be open to question. Nevertheless, reduction in azotemia can clearly forestall the need for dialysis and/or reduce uremic symptoms. Evidence has

been cited that alternately supports (53) and refutes (54) the role that urea plays in the clinical manifestations of uremia. Bergstrom and Furst (55) have suggested that any substance considered a uremic toxin should fulfill four criteria as listed:

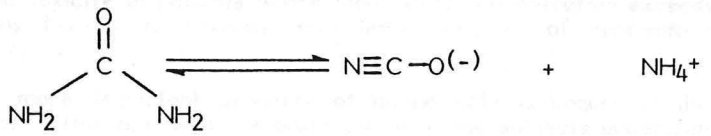
1. The compound should be chemically defined and measurable in biological fluid.

2. The plasma or tissue concentrations of the compound should be higher in uremic than in nonuremic patients.

3. High concentrations should be related to uremic symptoms.

4. Toxic effects should be obtained in experimental models at concentrations comparable to those found in the body fluids or uremic patients.

With the possible exception of some hormones, urea is the only organic compound that clearly fulfills all the aforementioned criteria. The effects of sustained high plasma urea concentrations have been examined in patients on chronic hemodialysis (56). Dialysate urea concentrations of 300 mg/dl were associated with malaise, vomiting, bleeding and headache. Hypothermia, a frequent finding in uremia, can be induced in normal animals by infusions of urea (57). This observation has been ascribed to impaired energy production, which appears to underlie many conditions in which metabolic hypothermia occurs. In this regard it is interesting that urea in solution spontaneously undergoes partial decompensation to ammonia and cyanate.



Urea Cyanate Ammonium

Cyanate ions react irreversibly with the N-terminal groups of many proteins (carbamylation) and, when present in high concentration, may inhibit the action of some enzymes. Since the action of cyanate on proteins is irreversible, it is conceivable that total intracellular fluid, and thus toxicity, may be manifest long after measurable extracellular concentrations have disappeared. The ability of cyanate to produce hypothermia, hyperglycemia and central nervous system depression might explain at least some of the toxic effects of azotemia. Diets rich in protein nitrogen not only increase the blood urea concentration but also contribute to the accumulation of organic acids, amines, phosphates and sulfates, all of which may contribute to uremic toxicity. The most effective nutritional program for the treatment of chronic renal failure in the predialysis phase would be one that maintains protein-calorie nutrition while minimizing the intake of compounds which contribute to uremic toxicity.

Protein-free diets, in which essential amino acids are supplied as crystalline supplements, have been tried but are not readily accepted by patients. Bergstrom and Furst (58) have shown that a diet containing 20 to 30 gm/day of mixed quality protein is reasonably acceptable to most patients. Unfortunately, such a diet is deficient in essential amino acids. Crystalline amino acid supplements of valine,

isoleucine, leucine, methionine, tryptophan, phenylalanine, lysine, threonine and histidine can be used in combination with 25 gm/day protein diets to meet essential amino acid requirements (59). Despite improvement in nitrogen balance and clinical status (increased plasma protein concentration, decreased urea production and maintenance of lean body mass), the optimal proportion and dose of essential amino acids are not known.

Nitrogen-free ketoanalogues of essential amino acids have been shown to be adequate substitutes for several essential amino acids (60).

Amino Acid	Keto-Analogue
$R\text{-}CH(NH_3)\text{-}COOH$	$R\text{-}C(=O)\text{-}COOH$

(where R is any organic group)

Mitch and Walser have been instrumental in demonstrating the effectiveness of both keto-analogues and other amino acid substitutes such as hydroxy-analogues of methionine (61) and phenylalanine (62) in the maintenance of nitrogen balance in uremic patients. The obvious advantage of such analogues is to decrease the daily nitrogen intake by 1.5 to 2.0 gm/day. Such a reduction in dietary nitrogen can diminish urea accumulation by about one-third. This could be of clear benefit in reducing urea toxicity in patients whose blood urea concentration exceeds 100 mg/dl. However, any benefit to patients with lesser degrees of azotemia may be less apparent (63).

Perhaps the more important property of amino acid analogues is their nitrogen-sparing effect. This has been demonstrated in obese subjects undergoing near total fasting (60). In these and other studies, keto-analogues of essential amino acids, branched chain amino acids, or keto-leucine alone, significantly reduced urinary nitrogen. Experience is now substantial with 20 to 30 gm (mixed quality) protein diets supplemented with nitrogen-free amino acid analogues, primarily as calcium salts (64). In almost all cases improvement was noted in nutritional status, nitrogen balance, BUN and plasma phosphorus concentrations. However, no benefit is noted if the daily nitrogen intake exceeds 7 to 9 gm/day (roughly equivalent to 50 to 60 gm protein) (65,66). Despite relatively encouraging results, problems exist with the clinical use of amino acid analogues. Calcium salts are distasteful and must be given as coated tablets. Sodium salts of analogues have been developed but would likely result in intolerable sodium loads in many patients. Furthermore, most diets supplemented with analogues do not alter the abnormal pattern of circulating amino acids observed in uremic patients. Walser and his associates (60) have shown that normalization of plasma amino acids not only improves the nutritional status of pre-uremic patients, but may also slow the progression of renal insufficiency. The optimal amount and type of amino acid (or analogue) supplement necessary is apparently a matter of considerable individual variation.

PRACTICAL APPROACHES TO CHRONIC RENAL FAILURE

Assessing the Progression of Renal Insufficiency

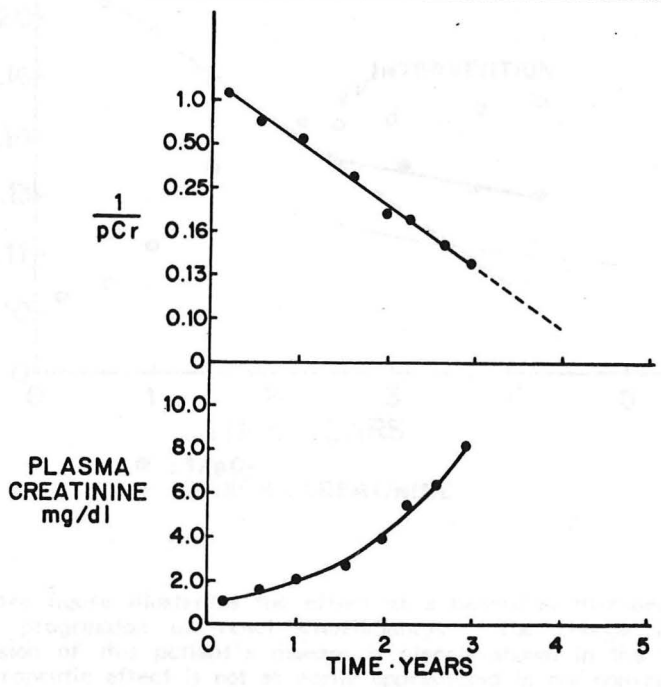
Key to the assessment of any potential therapy is the ability to predict the natural history of the condition in question. The rate of progression of chronic renal failure

has traditionally been calculated as statistical means determined from large groups of patients. In one large study, Ahlmen (67) determined that the average time for the serum creatinine to increase from 5.0 mg/dl to terminal uremia was 10.8 months. However, in this mixed group of patients the range was from one month to more than two years. Obviously, this type of analysis is of little benefit to the clinician or investigator dealing with small numbers of patients. Repeated measurements of GFR by inulin or ^{131}I-iothalamate (Glofil®) clearance are expensive and cumbersome. The clearance of endogenous creatinine has thus become the clinical standard for estimating renal function. Creatinine is the anhydride of creatine, which is present in muscle, brain and blood in its free form and in its phosphorylated form as phosphocreatine. The amount of creatinine produced daily is proportinal to the total pool of creatine and phosphocreatine. Because more than 90% of creatine is contained in muscle, the pool size estimates the total muscle mass. Creatine is produced by endogenous synthesis from amino acids and is ingested preformed in the diet. One gram of red meat contains approximately 4.2 mg of creatine (68). Dietary and synthesized creatine is present in the extracellular space, but can be taken up by muscle against a 200 to 1 gradient (69). The extracellular pool is thus small, and most creatine is contained in muscle. Crim and his colleagues (70), using isotopic dilution methods found that the daily conversion of creatine to creatinine was about 1.7% of the total creatine pool. Using this concept, Mitch and Walser (68) have calculated the half-time to a new steady state creatinine excretion following significant dietary changes to be 41 days. This would seem to indicate that the daily excretion of creatinine is relatively stable, and in fact this assumption has promoted the reliance on creatinine clearances as a stable index of renal function. However, daily creatinine excretion may not be as uniform as such calculations would predict. At least two groups (71,72) have shown that daily creatinine excretion may vary as much as 16% per day in normal subjects. Such large variations may be explained by the dietary content of creatinine. Cooking red meat may increase its creatinine content (conversion of creatine to creatinine) by a factor of 8 to 9. The ingestion of as little as 10 oz. of cooked meat might theoretically increase the creatinine excretion by as much as 900 mg/day.

Yet another factor which confounds the day-to-day use of creatinine excretion as an indicator of renal function is the observation that creatinine accumulates in the blood of uremic patients at a slower rate than would be predicted by its rate of formation (73). This so-called "creatinine deficit" is not completely understood, but such factors as metabolism by bowel microflora (74,75) and even in vivo recycling of creatinine to creatine (75) may be involved.

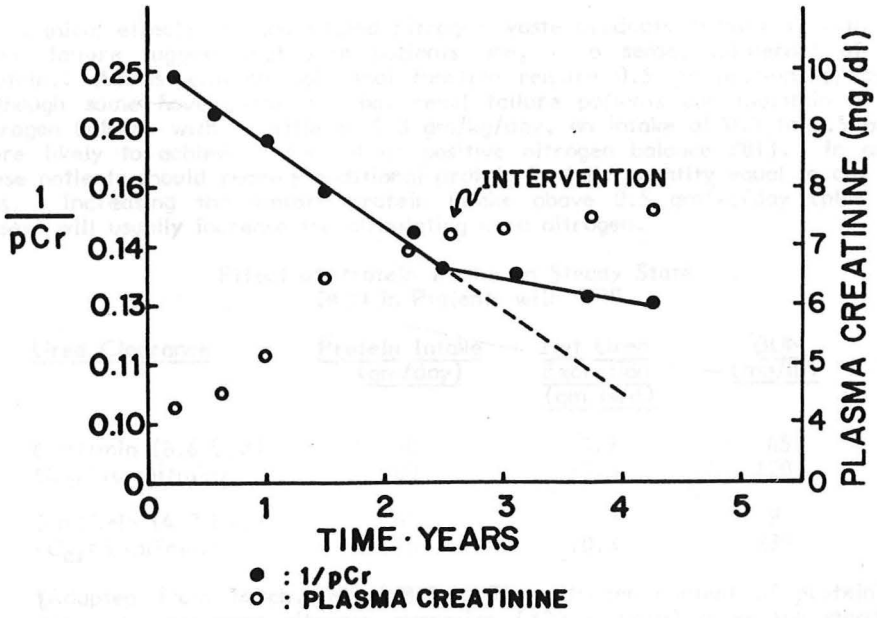
In 1976 Mitch and associates (76) introduced a relatively simple method to gauge the rate of progression of chronic renal failure in individual patients using the reciprocal of the plasma creatinine concentration vs. time. They initially showed that this relationship (1/pCr vs. time) declined in a linear fashion in 31 of 34 patients studied. Since that time numerous groups have employed this relationship to estimate the rate of disease progression in a variety of renal diseases (68,77,78). In some instances the reciprocal relation is not linear, and Rutherford (79) has proposed that the logarithm of the plasma creatinine vs. time will restore linearity. A linear reciprocal relation implies that renal function is lost at a constant rate. When the logarithmatic function is linear, a constant fraction of residual renal function is lost with time. Though most published reports appear to support the use of the reciprocal function, there apparently are cases in which the log function is more appropriate. The disease or patient characteristics which determine which

function will be linear are not known. Nevertheless, if one can establish that the loss of renal function can be translated into a function which is linear with respect to time, linear regression analysis will allow one to determine the effect of therapeutic interventions on the disease process.



The above figure represents the course of a patient with chronic glomerulonephritis. The dashed portion of the reciprocal plot is an extrapolation of the plot and indicates that this patient will reach clearance of less than 10 ml/minute (roughly equal to a serum creatinine of 10 mg/dl) at about three years ten months.

Plasma creatinine could theoretically be affected by changes in diet or lean body mass. However, after any such change has occurred, the plasma creatinine should reach a new steady state (half time = 41 days) and further changes should reflect changes in renal clearance. Therefore, one should likely not ascribe any change in the time vs. reciprocal creatinine relationship to a real change in the progression of disease until it has persisted for at least four months.



The above figure illustrates the effect of a beneficial therapeutic intervention on the progression of renal insufficiency. The change in the rate of progression of this patient's disease is clearly shown in the reciprocal plot. The therapeutic effect is not so easily appreciated in the non-reciprocal plot.

DIETARY STRATEGIES IN CLINICAL PRACTICE

Whether dietary restrictions can slow or halt the progression of renal failure is yet unproven. However, there is little question that proper dietary management can prevent certain uremic complications, decrease azotemia and improve the patient's general health and sense of well being. The following discussion will focus on patients who are at or very near end stage renal function. The principles outlined may or may not be appropriate for those patients undergoing dialysis therapy.

The objectives of conservative dietary management in patients with chronic renal failure are:

1. To delay the need for dialysis.
2. To improve patient comfort.
3. To prolong life until dialysis or transplantation can be undertaken.
4. To prevent volume overload, cardiac failure and hypertension.

5. To prevent electrolyte disturbances.

The clinical effects of accumulated nitrogen waste products in patients with chronic renal failure suggest that such patients are, in a sense, intolerant of dietary protein. Adults with normal renal function require 0.5 gm protein/kg/day (80). Although some have suggested that renal failure patients can maintain a positive nitrogen balance with as little as 0.3 gm/kg/day, an intake of 0.4 to 0.5 gm/kg is more likely to achieve a neutral or positive nitrogen balance (81). In addition, these patients should receive additional protein in daily quantity equal to any urinary loss. Increasing the dietary protein intake above 0.5 gm/kg/day (plus urinary losses) will usually increase the circulating urea nitrogen.

Effect of Protein Intake on Steady State BUN in Patients with CRF

Urea Clearance	Protein Intake (gm/day)	Net Urea Excretion (gm N/d)	BUN (mg/dl)
6 ml/min (8.6 L/d)	40	3.9	45
(C_{cr}=10 ml/min)	80	10.3	120
3 ml/min (4.3 L/d)	40	3.9	91
(C_{cr}=5 ml/min)	80	10.3	239

[Adapted from Mitch, WE (68)]. The nitrogen content of protein (=16%) minus the non-urea nitrogen excretion ($\bar{X}$=2.5 gm/d) gives the steady state quantity of urea which must be excreted daily. Rearrangement of the basic clearance formula (C = uv/p) permits calculation of BUN. C_{cr} = creatinine clearance.

On the other hand, when daily protein intake is reduced to 0.3 gm/kg or less, negative nitrogen balance is likely, even though azotemia and symptoms may improve. A sample of 50 gm high quality protein diet (sufficient for a 70 kg adult) is shown below.

50 gm Protein Diet: Sample Menu

Breakfast	Lunch	Dinner
Pineapple juice (½ c)	Cranberry juice (½ c)	Apple juice (½ c)
Buttered grits (½ c)	SF broiled fowl (1 oz)	SF roast beef (2 oz)
Scrambled egg (1)	SF rice (2/3 c)	Noodles (1/3 c)
Toast (1 slice)	Glazed carrots (½ c)	Mixed greens (½ c)
SF margarine (2 tsp)	Fresh apple (1)	Congealed fruit (½ c)
Jelly (1 tsp)	Cookie (2)	Angelfood cake (1 slice)
Whole milk (½ c)	Iced tea	Blueberries (½ c)
Creamer (1 Tbsp)	Sugar (2 tsp)	Iced tea
Sugar (2 tsp)		Sugar (2 tsp)

SF = salt free

Approximate calories:	2200
protein:	50 gm
sodium:	85 mEq
potassium:	60 mEq

(Adapted from Clinical Nutrition Manual, Charlotte, NC, 1984)

Although such diets shoud be planned to meet the National Research Council's recommended daily allowances, renal disease may alter the absorption and utilization of vitamins, especially those that are water-soluble. For this reason a B-complex/vitamin C supplement is usually indicated. The requirements for fat soluble vitamins are less well established and should be individualized (especially vitamin D).

In principle, dietary protein may be restricted to less than 0.5 gm/kg/day and the difference replaced by essential amino acid supplements, such as Amin-Aid©, a product of American McGaw. This powdered supplement is prepared in 8 oz. of water and contains 6.6 gm/package of essential amino acids, 124 gm carbohydrate, 15.7 gm fat and less than 5 mEq sodium. Though pleasantly flavored and reasonably well tolerated over a few days, this product and others like it are expensive and are likely not acceptable for long-term use due principally to dietary monotony. In practical terms, intolerance for 0.5 gm protein/kg/day usually signals the need for dialysis.

Sodium, water and potassium are always of concern in patients in moderate to severe renal insufficiency, and together or individually account for considerable morbidity among these patients. Even a brief overview of these topics is far beyond the scope of this presentation and the reader is referred to the standard reference sources. However, it should be mentioned that patient tolerance of fluid and electrolytes is an individual matter with considerable variation. The single most important factor governing fluid and electrolyte tolerance is daily urine volume. Though the likelihood is good that a patient capable of producing one to two liters of urine per day will not require strict water or potassium restriction, the individual who cannot produce one liter per day is at increased risk for volume and/or potassium-related problems. It is fortunate that diets which restrict protein also contain relatively little potassium. The decision to impose fluid, sodium and additional potassium restriction is a matter of clinical judgment. Frequent assessments of clinical volume status, blood pressure and plasma electrolytes are critical in this regard.

Calcium and phosphous metabolism is a matter of considerable importance in patients with chronic renal insufficiency which deserves considerably more attention than can be given in this discussion. Nevertheless, a few generalizations are possible. Phosphorus retention may begin when the GFR declines to 50 ml/min. However, clinically detectable hyperphosphatemia may not be evident until considerably later. Because phosphorus retention results in secondary hyperparathyroidism which may ultimately lead to disabling osteodystrophy, control of phosphorus absorption is vital. Although foods rich in phosphorus such as meats and dairy products may be restricted, the phosphorus intake by most patients is still excessive and phosphate binding antacids are required. Aluminium hydroxide gels or tablets are usually given three to four times per day in amounts sufficient to maintain the plasma phosphorus in the normal range. Because calcium absorption and the biosynthesis of vitamin D is usually deranged in these patients, supplementation of one or both may be required. However, the administration of calcium salts and especially vitamin D must be undertaken with great caution. Hyperphosphotemia usually contraindicates either vitamin D or calcium adminstration.

THE BOWEL: EXPANDING ROLES IN UREMIA

Early in this century several investigators (82-84) proposed that the gastrointestinal tract might be employed to remove uremic waste products. Initial work showed that significant quantities of urea could be removed via the intestine and interest increased until the introduction of the artificial kidney. In the past 20 years interest has been renewed in the use of the bowel for adjuvant, if not primary, therapy in uremic patients. This work has yet to produce a readily acceptable alternative to dialysis or transplantation, but it has yielded information and techniques which may eventually allow the reduction of dialysis intensity and improve the overall management of uremic patients.

The large surface area, resistance to infection and permeability characteristics make the intestine an attractive internal artificial kidney. Manipulation of the GI tract for the purpose of solute and water removal has taken essentially three forms:

1. Perfusion of varying GI tract segments with various "dialysate" solutions.

2. Oral administration of raw sorbent materials.

3. Oral administration of artificial membrane enclosed sorbents and enzymes.

The earliest and most widely investigated technique is bowel perfusion. Through the use of a variety of models the basic physical transport characteristics of the small intestine have been established.

Urea Removal by Small Bowel Perfusion

No. Patients	Segment	Length (cm)	Perf. Rate (ml/hr)	Blood Urea (mg/dl)	Urea Removed (mg/hr)	Adjusted Urea Clearance (ml/min)
23	Jejunum	187± 23	922± 191	204± 17	850± 178	34±4.9
12	Ileum	146± 24	1386± 350	215± 28	863± 402	23±4.5

[Condensed and adapted from Sparks, 1979 (85)].

The adjusted urea clearance is obtained by normalization of the measured clearance to a 630 cm length and 200 ml/hr perfusion rate. The relationship is as follows:

$$C_{adj} = C_{cal}\ 630/L\ (2000/F)^{K}\ ,\ \text{where } K = 0.369$$

These data indicate that if the entire small bowel could be used with a suitable sorbent and if the blood to bowel concentration gradient could be maintained, the resultant urea clearance would approach 30 ml/min. Over a 24-hour period, with a blood urea concentration of 150 mg/dl (BUN = 68 mg/dl), over 70 gm of urea would pass into the intestinal lumen. In practical terms, however, it is unlikely that perfusate could be kept in the small bowel continuously, and the blood to perfusate gradient might decrease with time although it is unlikely to be of signficant magnitude to influence urea movement.

Similar data has been obtained for the small intestinal clearance of creatinine, uric acid and phosphorus. The combined jejunal and ileal clearances are shown below.

Small Bowel Clearances
(Combined ileojejunal perfusion)

	Average Clearance (ml/min)
Creatinine	14.1 ± 10.1
Uric Acid	18.3 ± 10.4
Phosphorus	3.9 ± 2.7

(Reference 80)

Since the early work by Kolff et al. (85,86), there have been few attempts to measure urea removal by stomach or colon perfusion. The results have been highly variable and are not encouraging.

In recent years Young, Lee and Tang (87) in Taiwan have employed oral saline as the sole therapy for end stage renal disease. The patients drink 7 liters of a saline/mannitol solution over a period of three hours. Profuse diarrhea develops within 45 minutes after the start of drinking and subsides within 25 minutes after drinking ends. The procedure is carried out three times weekly. These authors

have treated 17 uremic patients for periods of three to 16 months ($\bar{x}$ = 6.8 months). Measured intestinal clearances of creatinine and urea were 6.4 ± 0.9 and 29.0 ± 2.6 ml/min, respectively, and remained constant throughout the study period. The authors report that there were no serious complications and that the treatment was readily acceptable to the involved patients. Though it is currently unlikely that such treatment will replace more conventional techniques, it effectively demonstrates that the GI tract may serve as a useful adjuvant.

Sorbents such as activated charcoal and oxidized starch have been orally administered to uremic patients with variable but interesting results. Though activated charcoal is able to bind significant quantities of urea in vitro, its effect on the BUN of uremic patients has proved disappointing. Friedman et al. (88) were unable to show any beneficial effect on BUN or the plasma creatinine of 35 gm/day of orally administered charcoal. They did, however, observe a significant reduction in plasma cholesterol and triglycerides. Similar results have been obtained in animal models (84).

Giordano (89) and Man (90) have fed oxystarch (oxidized starch) to uremic patients in order to increase fecal nitrogen excretion by binding intestinal ammonia derived from urealysis.

Effect of Oxystarch on Fecal Nitrogen

	Fecal Mass (gm/day)	Fecal Nitrogen (gm/day)
Control period	95 ± 35	1.08 ± 0.42
Oxystarch (30 gm/day)	233 ± 89 $p<0.01$	2.09 ± 0.63 $p<0.01$

That the observed increase in fecal nitrogen is not merely a consequence of increased fecal mass was demonstrated by the administration of methyl cellulose which similarly increased fecal mass but had no effect on nitrogen. A combination of oxystarch and activated charcoal has been evaluated by Friedman (91), again without measurable effect on plasma urea or creatinine. Unfortunately, fecal nitrogen content was not measured. Plasma cholesterol, however, decreased by an average of 34 mg/dl. Such results may reflect the short-term nature of the trials or altered binding characteristics of sorbents when in the GI tract. Sparks (92) has shown that the adsorptive capacity of charcoal for creatinine is 25-fold lower in the presence of GI tract fluid than in buffer solutions. Bile acids and higher molecular weight (C_{16}-C_{18}) fatty acids may also account for some of this inhibition.

Given that a variety of potentially toxic solutes are able to cross the intestinal mucosa, attention has recently turned to sorbent systems which are acceptable to patients, inexpensive and which exert some degree of specificity for varying solutes. To this end, Asher and his associates (93-95) have developed liquid membrane capsules (LMC). LMC are drops of a continuous oil emulsion which contain an aqueous internal phase and are suspended in a suitable aqueous external solution. The active (internal) phase can be a reagent which will trap toxins diffusing across the oil membrane, or an enzyme which can be released from the LMC into the intestinal lumen. The specific oil phase can be formulated for the specific function of the LMC. For trapping the oil phase must be indigestable, i.e. mineral oil.

Asher and his colleagues (95), using dogs with acute renal failure, have perfused the proximal jejunum with LMCs containing saline (control) or citric acid in a urease solution. Urease hydrolyzes urea to ammonia and CO_2, while citric acid traps ammonia as NH_4^+. The urease/LMC suspension was administered in 50 ml doses each half hour for nine hours. Though the BUN rose during the test period in both groups, the observed increase in the experimental group was 13.7 mg/dl while that of the control animals was 34.2 mg/dl. These experiments yield a urea clearance of 2.90 ml/min. The rate limiting factor for GI urea removal appears to be the transfer of urea from the blood to the bowel lumen. In fact, the in vitro urea adsorptive capacity of LMCs is approximately ten times the in vivo clearance of urea. Given that mucosal transport is the rate limiting step, then the urea clearances reported by several groups (85,86,96) using either bowel profusion or diarrhea therapy might be feasible using high rate sorbents such as LMCs. If GI urea clearances approaching 25 to 30 ml/min were achievable in humans during all waking hours, all urea generated could be removed using LMCs.

The removal of urea alone would be a useful adjuvant to other methods of managing chronic uremia. Further, the technology could be expanded to other toxins. A wide range of molecular species might be removed using LMC encapsulated charcoal. The ion excluding nature of LMCs should prevent the permeation and adsorption of bile and fatty acids which have previously limited the usefulness of charcoal. Finally, miniaturization of hemodialysis apparatus sufficient to allow complete portability has been described (97). The clinical introduction of such equipment is hindered by the size of the dialysate tank. The primary function of this volume of dialysate is to dilute urea. If most of the generated urea load could be removed via the gastrointestinal tract, tank size could be drastically reduced and truly portable, perhaps even ambulatory equipment would be possible.

CONCLUSION

The cost of end stage renal disease in terms of lives and dollars is rivaled only by heart disease and cancer. Until recently, most forms of progressive renal insufficiency were considered untreatable and such patients received relatively nonspecific therapy in anticipation of impending dialysis or renal transplantation. There is now evidence, primarily in animals, that the restriction of dietary protein may preserve renal function or at least slow the progression of advancing renal failure. The models are imperfect and the mechanism is somewhat unclear. Nonetheless, such a simple and potentially beneficial therapy deserves exhaustive investigation. Even if dietary manipulation should prove ineffective in preventing end stage renal disease, its usefulness in controlling uremic symptoms and delaying the need for dialysis can hardly be denied. With careful attention to detail and patient compliance many of the more serious complications of uremia can be avoided with the appropriate diet.

A variety of sorbent materials are currently under investigation which may ultimately enable the clinician to employ the GI tract as an adjuvant to other methods of therapy for the renal failure patient.

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