Kidney International, Vol. 40 (1991), pp. 326–341

NEPHROLOGY FORUM

Dietary protein restriction in patients with chronic renal failure

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Case presentation

A 54-year-old woman from Texas sought a second medical opinion 6 years ago at the Brigham and Women's Hospital in Boston because of concern about her family history of renal disease. In 1978, her creatinine clearance (C_{cr}) was reported to be 56 ml/min and her blood pressure 170/100 mm Hg. She had been told by her family physician that she had hypertension and chronic renal failure and had been given a thiazide diuretic. She has an extensive family history of nephritis involving at least 4 generations (Fig. 1).

Between 1978 and 1984, her physician treated her for urinary infections and hypertension. In 1981, her C_{cr} was 42 ml/min. In 1983, she had a urinary infection with pyuria; her C_{cr} was 30 ml/min and a hearing test was "normal." In the fall of 1984, she was referred to a nephrologist who noted hypertension and edema. Measurement of glomerular filtration rate (GFR) by ^{125}I-iothalamate renal clearance disclosed a value of 20.7 ml/min; propranolol and a thiazide diuretic were prescribed. She came to me for another opinion; since then she has been followed annually, and every 4 to 8 weeks by the referring nephrologist.

In October 1984, I found the patient to be a well-nourished woman in no acute distress except for understandable concern about her prognosis for familial renal disease (Fig. 1). She had not had a renal biopsy, but renal biopsy of others in the family had shown an interstitial nephritis; none of the family members had any hearing disorder. A review of systems revealed hypertension but no hearing impairment. She had no symptoms suggesting cardiopulmonary disease except for mild fatigue on exercising, but she did complain of intermittent constipation. Urinary symptoms included bouts of frequency and urgency occurring about two times a year that had been diagnosed as urinary tract infections. She also had noted swelling of her ankles, especially after sitting for long periods.

Physical examination revealed a slender, pleasant woman who was well informed about the consequence of renal failure. She weighed 55.5 kg and her blood pressure was 200/98 mm Hg. Her pulse was 86 beats/min; respirations, 16/min; and she had no skin lesions. The physical examination was unremarkable except for 1+ pedal edema bilaterally. Serum biochemistry values were: urea nitrogen, 59 mg/dl; serum creatinine, 2.9 mg/dl; bicarbonate, 27 mEq/liter; potassium, 4.1 mEq/liter; calcium, 9 mg/dl; phosphorus, 4.8 mg/dl; uric acid, 7.4 mg/dl; alkaline phosphatase, 67 U/liter; triglycerides, 131 mg/dl; and cholesterol, 231 mg/dl. Her hematocrit was 36%, and the white count and platelet count were normal. Urinalysis showed 1+ protein and 8–10 erythrocytes/high-power field, but no leukocytes or casts.

The purpose of a restricted diet was discussed with the patient and her husband, and she decided to begin this therapy. She was evaluated by a dietician who judged her usual intake to include more than 60 g of protein/day (>1 g/kg/day); she was instructed how to calculate the protein content of foods. She was given diet plans for a 25 g/day protein (mixed-quality) and 30 kcal/kg/day diet. Her medications included Aminess, 5 tablets 3 times daily; calcium carbonate, 3.75 g/day; B-vitamin complex, 1 tablet daily; furosemide, 80 mg/day; and atenolol, 50 mg/day. Over the past 6 years, she has been in regular contact with a dietician.

During these 6 years, the patient has been treated for hypertension with several types of drugs, including an angiotensin-converting-enzyme inhibitor, different beta-blockers, and calcium-channel blockers. She has had two bouts of severe diarrhea with dehydration and was hospitalized on one occasion for administration of intravenous antibiotics. Radiologic evaluation led to a diagnosis of diverticulosis. Otherwise, she has had no symptoms attributable to renal failure. Her current weight is 56.8 kg. She walks about 1 mile daily and works as a church administrator. Serial estimates of her protein intake were calculated from 24-hour urine specimens for urea nitrogen content using the relationships described by Maroni et al [1]. Urea nitrogen excretion averaged 4.8 g N/day, with a coefficient of variation of 17% (N = 44). Renal function was analyzed by measuring serum creatinine, creatinine clearance, and ^{125}I-iothalamate clearance. Values of serum creatinine, GFR, and estimated protein intake (uncorrected for the essential amino acid supplements) during the past 6 years are shown in Fig. 2.

Discussion

DR. WILLIAM E. MITCH (*Director, Renal Division, and E. Garland Herndon Professor of Medicine, Emory University School of Medicine, Atlanta, Georgia*): Early studies revealing that patients with chronic renal failure and severe uremia improved symptomatically when dietary protein was restricted became the initial rationale for dietary therapy [2, 3]. In some as-yet-unidentified way, the accumulation of nitrogenous waste products and inorganic ions causes the clinical and metabolic disturbances characteristic of uremia. Dietary protein restriction has been used as therapy because excess dietary protein (in contrast to carbohydrate and fat) is not stored but is degraded to urea and other waste products, which accumulate in patients

Presentation of the Forum is made possible by grants from Pfizer, Incorporated; Sandoz, Incorporated; Marion Merrell Dow Incorporated; Merck Sharp & Dohme International; and Amgen Incorporated.

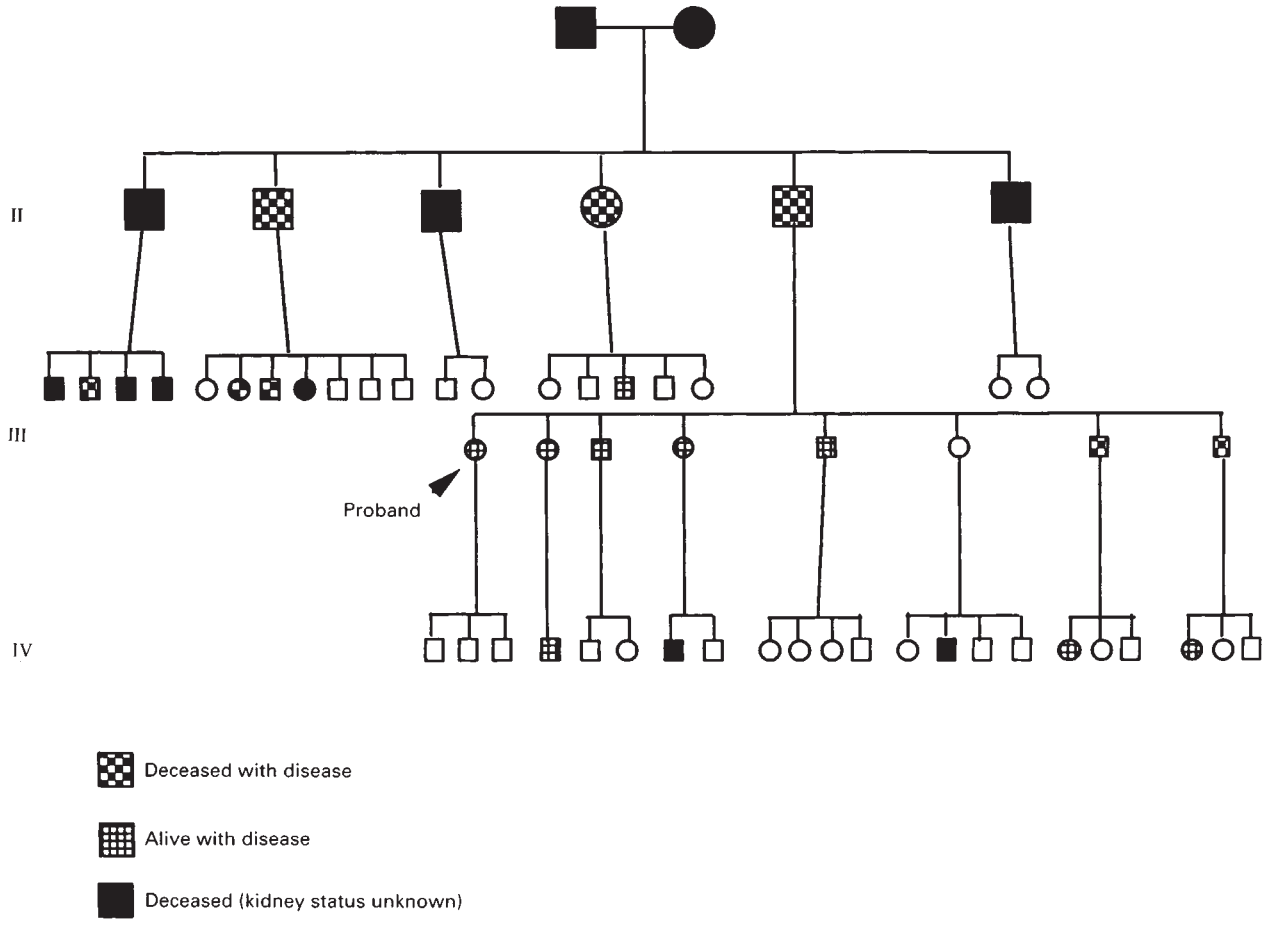

Fig. 1. *Clinical observations in 58 members (4 generations) of a family with a hereditary form of renal disease.* The disease is inherited in an autosomal dominant fashion. The patient (proband) has intermittent microscopic hematuria and chronic renal failure.

with impaired renal function. Protein restriction also helps control the accumulation of sodium, potassium, phosphates, and other ions normally excreted by the kidney because foods rich in protein contain large amounts of these ions as well. The difficulty in implementing dietary protein restriction therapy is that an inadequate protein intake results in net degradation of endogenous protein stores, which contributes to the loss of lean body mass observed in severely uremic subjects treated with excessively restricted diets [4].

As the patient discussed demonstrates, it is possible to avoid this complication; the treatment she has followed for 6 years yields a protein intake equivalent to about 38 g/day. Her weight has remained stable; she continues to work and exercise regularly. She has overcome bouts of diverticulitis on two occasions. Stabilization of her residual renal function over this same 6-year period (Fig. 2) also raises the possibility that dietary protein restriction might slow the rate of loss of renal function, even in patients with inherited forms of renal disease. Prospective trials currently are underway in Europe, Japan, and the United States to test this exciting but unproved possibility.

I will discuss the principles underlying the implementation of a low-protein diet in patients with chronic renal failure and will place special emphasis on factors affecting nutritional status. I also will address the evidence that dietary manipulation can influence the course of renal insufficiency.

Urea and protein intake

No single toxin has been identified that can account for the spectrum of abnormalities found in uremia. Urea has been the most widely studied because the BUN concentration is related to the severity of uremia. This relationship was underscored when the National Cooperative Dialysis Study reported that maintaining the average BUN close to 50 mg/dl was associated with fewer complications than was maintaining the average BUN approximately 90 mg/dl by less-intensive dialysis [5]. Johnson et al tested the toxicity of urea by adding it to the dialysis bath of otherwise "well-dialyzed" patients [6]. They found that raising the BUN to about 140 mg/dl for more than one week reproduced uremic symptoms. On the other hand, a moderately high BUN causes few symptoms when renal function is otherwise normal. Patients with defects in their ability to excrete urea who have moderate azotemia even though their GFR is normal do not have uremic symptoms [7], nor did a woman who ate enormous quantities of fishmeal protein and maintained a BUN above 65 mg/dl for at least 3 years [8].

Regardless of whether urea per se is toxic, the rate of urea

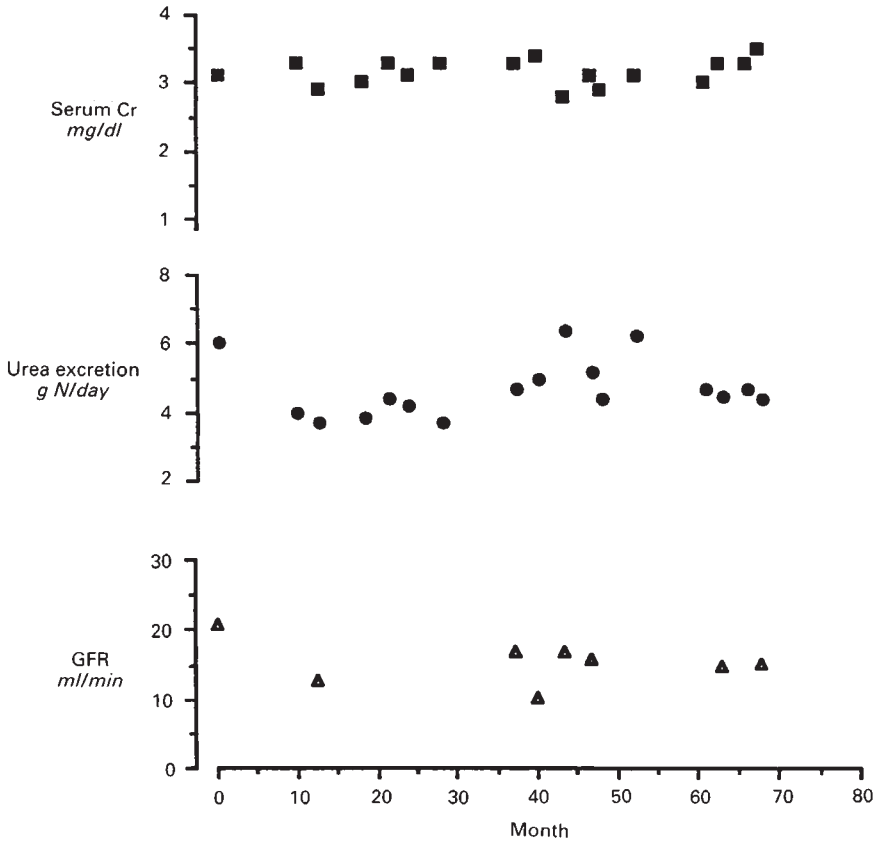

Fig. 2. *Serial values of serum creatinine, 24-hour urea excretion, and ^{125}I-iothalamate clearance (GFR) in the patient discussed here with chronic renal failure from hereditary renal disease.* The 24-hour urea excretion values were used to calculate protein intake as described by Maroni et al [1].

production is directly related to the amount of protein eaten (Fig. 3). Hence, the BUN concentration is related to protein intake, provided urea clearance is stable. This relationship arises because urea is synthesized using nitrogen derived from amino acid catabolism. The only suggestion that urea metabolism is abnormal in uremic subjects is that some patients have a mildly high arterial ammonia level [9].

Urea has three fates: it is excreted by the kidney, accumulates in body water, or is metabolized to ammonia plus carbon dioxide by gastrointestinal bacteria. In the last case, the ammonia is recycled to urea in the liver. Consequently, there is no net loss of nitrogen or urea [10]. The difference between urea produced and recycled is termed "urea nitrogen appearance" (UNA); it is the urea that "appears" in urine and body water. The UNA is physiologically important because it closely correlates with the amount of nitrogen (and therefore protein) eaten [1, 11]. Fortunately, UNA can be measured easily.

To measure UNA, the average daily urea nitrogen excretion first must be determined. Since urea excretion is not constant throughout the day, shorter collections will not suffice. The second step is calculating the average change in the urea pool. This calculation is relatively simple because the urea space is equal to body water, assumed to be 60% of body weight in nonedematous patients [1, 12]. Because urea distributes equally throughout body water, the average change in the pool can be calculated from changes in BUN and weight measured over 5 days [10]. To calculate UNA, the daily rate of change in the urea pool (either positive or negative) is added to the average rate of urea excretion measured over 3 days. Obviously, if the BUN and weight are stable (that is, the patient is in a steady state), the UNA is equal to urea nitrogen excretion. Calculation of UNA assumes that short-term variations in body weight reflect only changes in body-water content.

Calculation of UNA can be used in a least three ways to assess dietary therapy of patients with chronic renal failure. The assessments are based on the principle of conservation of mass and the following relationship: $B_N = I_N - [UNA + 0.031$ gN/kg/day]. *First*, when nitrogen intake (I_N) is known, nitrogen balance (B_N) can be estimated accurately because nonurea nitrogen (NUN) excretion does not vary substantially with protein intake (Table 1). The average value of NUN is 0.031 gN/kg/day (Fig. 4) [1]. Thus, nitrogen intake (16% of protein intake) minus the sum of UNA plus the product of 0.031 gN/kg and body weight gives an estimate of B_N (Table 1). In 19 non-dialyzed patients with chronic renal failure consuming 34 to 94 grams of protein/day, B_N estimated by this method did not differ statistically from values obtained by actual measurement of B_N [1]. *Second*, if B_N is assumed to be zero, protein intake can be estimated from UNA using the same relationship (Table 1). When the estimated and prescribed intakes differ by more than 20%, investigation for occult gastrointestinal bleeding or an unrecognized catabolic illness is indicated; or, intensive dietary counseling might be needed. *Third*, if urea clearance is known, the steady-state BUN expected for a prescribed protein intake can be calculated: if the quotient of UNA in gN/day divided by urea clearance in liters/day is multiplied by 100, the answer is the steady-state BUN in mg/dl (Table 1). Note that in the third example, the steady-state BUN is being calculated

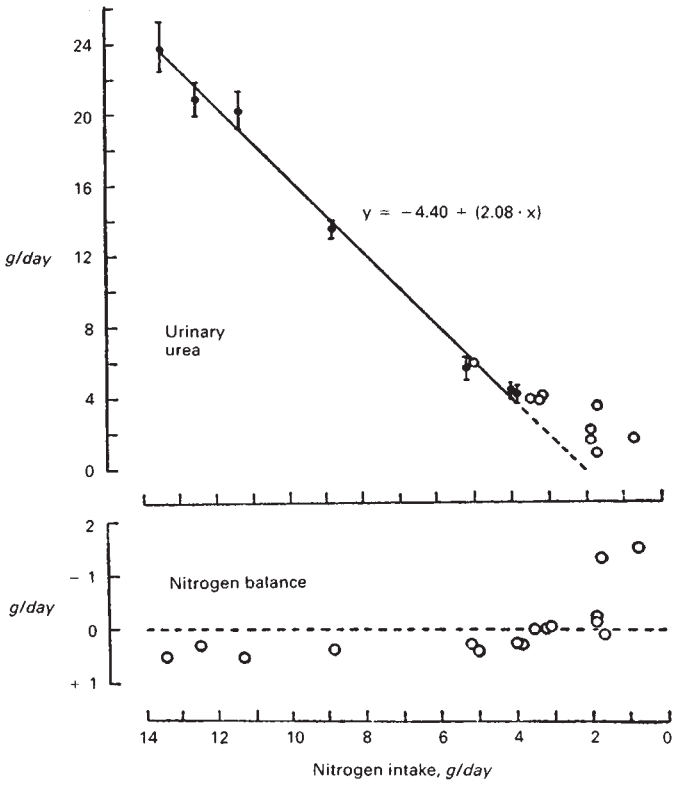

Fig. 3. *Nitrogen balance and urinary urea as a function of nitrogen intake in patients with chronic uremia fed varying quantities of dietary protein.* Subjects fed less than 4 g nitrogen/day were in neutral or negative balance. When the diet contained more than 4 g nitrogen/day, balance was slightly positive, but the increment in intake was equal to the increment in urinary urea nitrogen. (From Ref. 11).

(thus BUN and weight must be stable), so UNA is equal to urea excretion.

I emphasize these concepts because of their practical utility and because I want to clarify some confusing terminology. Similar concepts were used by Sargent et al to describe urea generation (G_u) and the protein catabolic rate (PCR) [13]. In dialysis patients as well as nondialysis patients, the nitrogen for urea synthesis is derived from amino acid degradation. In short, net urea production (or G_u) in dialysis patients is the same as UNA. Because G_u and UNA are calculated from the same variables, they both closely parallel nitrogen (and therefore protein) intake. The more confusing term, PCR, is simply the protein equivalent of the UNA plus a constant for non-urea nitrogen excretion of 1.7 gN/day. As I said, PCR closely approximates protein intake in patients who are in nearly zero nitrogen balance (B_N). Clearly, PCR does not measure protein catabolism because the daily turnover of protein in humans is far greater than protein intake (and hence, PCR). Results of isotope dilution studies place both the rate of protein synthesis and of degradation at 45–55 gN/day [14], roughly equivalent to the protein in 1.0 to 1.5 kg muscle. Although the principle of conservation of mass dictates that the difference between "whole-body" protein synthesis and degradation must equal waste nitrogen production × 6.25, the implication that PCR yields insight into, or is a measure of, whole-body protein catabolism is erroneous.

Table 1. Relationships among protein intake, nitrogen balance, and steady-state BUN[a]

If the protein intake of a 70 kg patient is 50 g/day and the steady-state urea excretion (UNA) is 10.3 gN/day, then:

$$B_N = I_N - (UNA + NUN)$$
$$B_N = 12.8 - [10.3 + (0.31 \times 70)]$$
$$B_N = 0$$

If nitrogen balance is assumed to be zero, then intake can be estimated:

$$B_N = I_N - UNA - NUN$$
$$I_N = UNA + (0.31\ gN/kg/day \times weight)$$

If a 70 kg patient has a urea clearance of 8.6 liters/day (6 ml/min), then the steady-state BUN is estimated as:

$$\text{steady-state BUN} = \frac{(I_N - 0.031\ gN/kg)}{(C_{urea})} \times 100$$

[a] Abbreviations: B_N, nitrogen balance (gN/day); I_N, nitrogen intake (gN/day); UNA, urea nitrogen appearance rate (gN/day); BUN, blood urea nitrogen concentration (mg/dl); C_{urea}, urea clearance (liters/day).

Using estimates of UNA and NUN to evaluate nitrogen metabolism has limitations. First, incomplete urine collection can limit the precision of calculations based on UNA. The only way to reduce this error is to collect urine for 3 days and obtain an average value. Second, urea clearance varies during the day. This variation could explain why several days are required for normal subjects to reach a new steady-state of urea excretion following a change in diet [14]. In patients with renal damage, urea clearance may vary less during the day, but more time will be required to achieve a new steady state with stable BUN and weight. These factors make it imperative to include an estimate of the change in accumulated urea when assessing UNA in patients with renal insufficiency; for normal subjects, estimating changes in accumulated urea is not critical because of the 7- to 8-hour half-life of urea. Even in normal subjects, changes in the size of the pool do not fully explain the delay in achieving a steady state following changes in dietary protein. Perhaps differences in protein utilization (and hence, waste nitrogen production) occur in the presence of large day-to-day changes in dietary protein.

Third, proteinuria can affect accurate measurement of nitrogen metabolism. The 0.031 gN/kg/day value for non-urea nitrogen excretion was derived from patients with urinary protein excretion less than 5 g/day (Fig. 4). If proteinuria exceeds 5 g/day, the extra nitrogen lost must be added to the NUN value. Evidence indicates that proteinuria affects protein balance. Kaysen and associates showed that in nephrotic rats, proteinuria decreased lean body mass, and raising dietary protein exacerbated proteinuria [15]. In humans, the same group of investigators showed that reducing dietary protein to 0.8 g/kg body wt/day from 1.6 g/kg/day resulted in less proteinuria without compromising albumin homeostasis [16]. Even though a protein-restricted diet can spare albumin stores, its effect on body protein stores is less clear, especially during long-term therapy.

The protein requirement, defined as the minimum amount of protein that balances obligatory nitrogen losses while maintaining energy equilibrium and permitting modest physical activity, can be divided into two components: total nitrogen and essen-

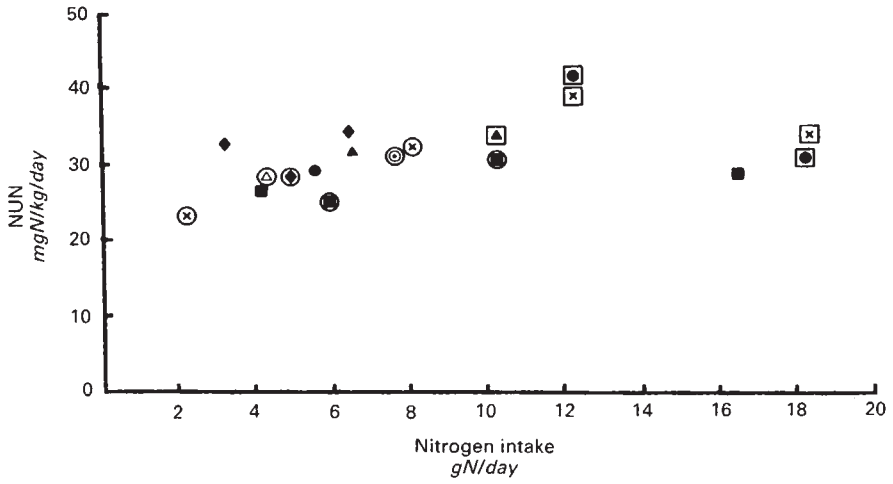

Fig. 4. *Calculated values of total non-urea nitrogen excretion (NUN) in normal subjects (▲, ●, ■), and patients with chronic renal failure being treated with nutritional therapy (◆, ⊗, ◬, ◈) by dialysis (◙, ◭), or CAPD (⊠, ◙). The average value found in the study by Maroni et al was 0.031 g nitrogen/kg/day (◎).* (From Ref. 1.)

tial amino acids (EAA). From these considerations, a prescribed diet may be deficient in protein quantity, quality (that is, the amount of EAA), or both. Despite its limitations, nitrogen balance (B_N) remains the "gold standard" for assessing dietary protein requirements [14]. To measure B_N, the difference in nitrogen in the diet and that in urine and stool plus an "allowance" (for example, 0.5 gN/day to account for minor losses from sweat, desquamated skin, or hair) is obtained. For uremic patients, the urea pool also must be taken into account.

When defining nitrogen requirements, one must specify an adequate energy intake, because for any given protein intake, B_N improves when calories are increased [17]. It is important that we understand how current protein recommendations were established: they are based on interpolation of several measurements of B_N in individuals to identify the level of dietary protein that should produce zero B_N for groups of subjects. Because the recommended intake for all subjects is based on extrapolation of data from individuals, the recommended intake doesn't always apply to groups of patients differing in age, degrees of activity, etc.; clearly the protein required by an individual could vary substantially from the minimum value. For these reasons the Food and Agriculture Organization/World Health Organization/United Nations University (FAO/WHO/UNU) "expert group" introduced the concept of a safe intake level [17]. This safe level is defined as the average requirement plus two standard deviations, a value that should meet the protein requirements of all but 2.5% of individuals.

Serum albumin and transferrin levels are used extensively to assess nutritional status [18]. Experience with other serum proteins is too limited to recommend their use. When using serum albumin, one should recognize that its concentration is determined by many factors, including the synthesis, catabolism, and excretion of albumin; changes in plasma volume; and distribution between extracellular and intravascular spaces. In malnourished nonuremic subjects, as well as in chronically uremic and nephrotic patients, both albumin synthesis and catabolism can be decreased; in addition, evidence suggests that albumin shifts into the intravascular compartment [16, 18, 19]. Clearly, the plasma albumin concentration need not accurately reflect total albumin mass under these circumstances.

Serum transferrin is another indicator of malnutrition; it has a shorter half-life than albumin (about 8 days versus 20 days for albumin). However, transferrin concentration, like albumin, varies with hydration and protein turnover but also changes in the presence of inflammation and/or changes in iron stores [18, 20].

Besides measurements of B_N and serum proteins, anthropometrics (weight, mid-arm muscle circumference, triceps skinfold thickness) are commonly used to estimate body composition and nutritional adequacy [18]. Reproducibility depends on the skill of the observer, the number of sites examined, the use of the dominant or non-dominant arm, and the degree of hydration (for example, in dialysis patients). Unfortunately, many of the values used as standards were obtained from studies in underdeveloped countries, where the health of the study population was not defined and may not represent a standard for normal values. Also, the influences of age and socioeconomic status have not been evaluated. Finally, virtually no data have examined how closely subnormal anthropometric values relate to an adverse clinical outcome. Thus, serial anthropometric measurements in the same individual are more likely to provide useful information.

The concentrations of plasma amino acids also have been used to assess nutritional status [20]. But the amino acid pattern generally reflects the disease process, recent changes in protein intake, or both, and is a less sensitive indicator of body composition than are serum proteins and anthropometrics. On the other hand, measurements of plasma amino acids have revealed abnormalities that seem to be characteristic of uremia. For example, the tyrosine level is low because uremia limits the activity of the enzyme converting phenylalanine to tyrosine [20]. Also, metabolic acidosis activates skeletal muscle branched-chain amino acid dehydrogenase, the rate-limiting enzyme regulating breakdown of these amino acids [21, 22]. In fact, the subnormal levels of branched-chain amino acids present in rats with chronic renal failure could be attributed to metabolic acidosis [21]. Recent data from Bergström and associates suggest a similar adverse effect of acidosis in humans; these authors documented a close correlation between serum bicarbonate and the concentration of valine in muscle of dialysis patients [23]. Plasma amino acid levels might provide insight into methods of improving nutrition. Alvestrand et al studied

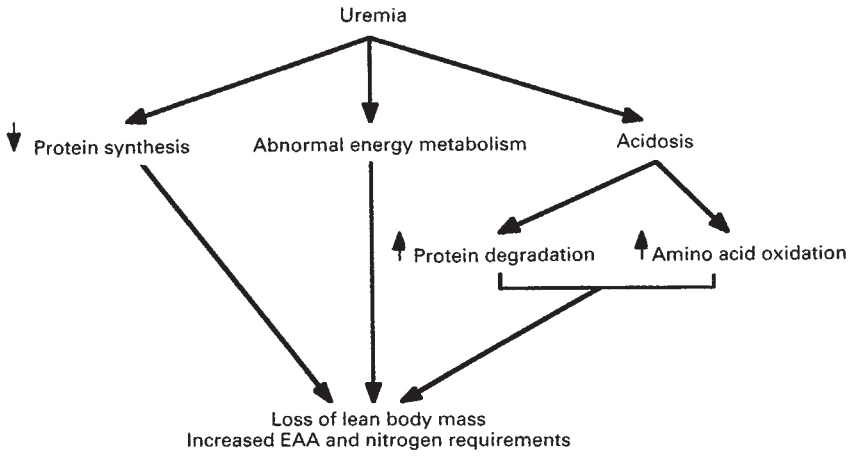

Fig. 5. *Factors causing loss of lean body mass and increased essential amino acid (EAA) and nitrogen requirements in uremia.* Results from experimental animals with renal insufficiency indicate that both abnormal energy metabolism and metabolic acidosis compromise nitrogen metabolism; there is also evidence that an unidentified factor in uremia limits the capacity for protein synthesis.

predialysis patients fed 16 to 20 g of protein plus a supplement of EAA in proportions designed to correct abnormalities in amino acid concentrations [24]. The regimen substantially corrected intracellular amino acid concentrations and improved B_N.

Protein conservation in chronic uremia

In rats with chronic renal failure, abnormalities in protein metabolism include increased protein and amino acid degradation and impaired insulin-stimulated protein synthesis in muscle (Fig. 5) [25]. The catabolic effects of uremia are accentuated by fasting [26]. To date, the only factor in uremia shown to impair protein metabolism is metabolic acidosis. Even mild metabolic acidosis (serum bicarbonate less than 21 mM) can account for accelerated catabolism of protein and branched-chain amino acids in muscle of rats with chronic renal failure. Both catabolic processes were fully corrected when sodium bicarbonate was added to the diet [20, 25]. The same adverse effects of acidosis are present in humans with chronic renal failure; sodium bicarbonate decreases urea production and improves B_N in these patients [27]. As I noted, evidence indicates that acidosis changes branched-chain amino acid metabolism in muscle of patients with chronic renal failure [23]. Together these results suggest that the metabolic acidosis of chronic renal failure increases nitrogen requirements and could counteract adaptive responses to a low-protein diet.

Energy metabolism also influences protein metabolism in chronic renal failure (Fig. 5). In rats with chronic renal failure, adiposity is subnormal and inversely correlates with body weight and muscle protein turnover [26]. Besides the evidence that insulin-mediated glucose metabolism is abnormal in uremia, muscle lactate production correlates highly with protein turnover [27].

The metabolic responses that permit adaptation to a protein-restricted diet were identified only recently. The problems of assessing "whole-body" protein synthesis and degradation and interpreting how changes in these values are expressed in specific tissues continue to perplex investigators. Moreover, there are large voids in our understanding of factors controlling protein metabolism [28].

Changes in whole-body protein metabolism have been examined by analysis of the turnover of infused amino acids. The technique requires a constant infusion of a labeled amino acid and collection of expired carbon dioxide to allow calculation of rates of protein synthesis and breakdown as well as amino acid catabolism [29]. Normal subjects primarily respond to a sharp change in dietary protein by varying amino acid oxidation. When protein intake is below the minimum requirement, however, additional responses are activated, including a decrease both in protein synthesis and degradation [30, 31]. Slowing of protein turnover blunts the adverse effects of an inadequate diet on protein stores but it does not prevent loss of body protein. The importance of understanding protein nutrition is that acidosis in uremia could increase amino acid oxidation and protein breakdown and thus limit a patient's capacity to successfully adapt to a low-protein diet.

Information about how patients with chronic renal failure adapt to a low-protein diet is limited. Goodship and colleagues used the amino acid infusion technique in patients whose average serum creatinine was 5 mg/dl and in normal subjects. Both groups were fed two levels of protein, 1.0 and 0.6 g protein/kg/day [29]. They tested the subjects' capacity to adapt to the minimum protein intake (0.6 g/kg/day) by measuring whole-body amino acid oxidation and protein synthesis and degradation; they also measured B_N. The authors reached two important conclusions: (*1*) The metabolic responses to the low-protein diet of patients with chronic renal failure and normal subjects were indistinguishable. Both groups had reduced amino acid oxidation and protein degradation; protein synthesis changed minimally with the low-protein diet. However, none of the patients was acidotic, so more severely uremic (or acidotic) patients might have different responses from normal subjects. For example, acidosis could stimulate protein breakdown and reduce the efficiency of using dietary protein by stimulating essential amino acid catabolism. (*2*) The normal subjects and the patients were in negative B_N during the first week of the low-protein diet (Fig. 6). This response could not be explained by a low energy intake or by changes in the urea pool (the latter was measured). It is interesting that the nitrogen balance occurring with a low-protein diet was distinctly different from that of the patients fed even less protein but given a supplement of ketoacids [32]. In patients fed this regimen, B_N was zero.

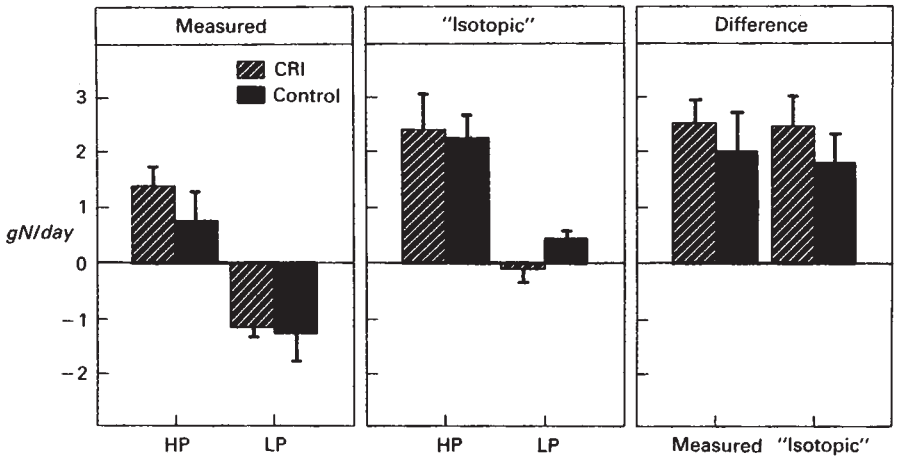

Fig. 6. *Nitrogen balances measured using classical and isotopic methods in patients with chronic renal failure (CRI) and in normal subjects fed 1 g protein/kg/day (HP) and 0.6 g protein/kg/day (LP).* Isotopic nitrogen balance was calculated from rates of protein synthesis and degradation measured during infusion of L-[1-^{13}C] leucine and extrapolated to represent rates over 24 hours. The difference is the nitrogen balance during the HP period minus that in the LP period for CRI patients and normal subjects. The difference in measured or calculated nitrogen balances was the same for both groups of subjects. (From Ref. 29.)

Dietary protein requirements in uremia

More than 25 years ago, studies suggested that patients with advanced chronic renal failure could maintain B_N while consuming very low amounts of protein (about 4 SD below the mean requirement for normal subjects) [2, 3]. Giordano postulated that nitrogen derived from urea degradation could be used to synthesize amino acids and ultimately protein [2]. Tests of this hypothesis in patients with chronic renal failure have failed to confirm that urea reutilization contributes significantly to protein nutrition. For example, only 2% to 6% of the nitrogen in albumin from patients with chronic renal failure was derived from urea degradation [33]. Furthermore, when we suppressed urea degradation by administering nonabsorbable aminoglycoside antibiotics orally, analysis of urea kinetics showed that ammonia derived from urea degradation was simply recycled to urea [10] and B_N actually improved [34]. Clearly, if ammonia arising from urea degradation is an important source of nitrogen for amino acid synthesis, B_N should have become negative when urea degradation was inhibited. We concluded that urea degradation does not contribute substantially to nutrition in patients with chronic renal failure.

The FAO/WHO/UNU expert group concluded that the average protein requirement for normal subjects is about 0.6 g protein/kg/day [17]. It is now recognized that predialysis patients require about the same amount as normal subjects. To ensure an adequate intake of EAA, approximately two-thirds of the protein should be of "high biologic value" (for example, eggs or lean meat) and calories must be sufficient to meet energy requirements [35]. These recommendations are emphasized because of reports that this level of protein is associated with negative B_N, at least during the first week of adaptation to the diet [29].

More severe protein limitation than the minimum requirement of 0.6 g protein/kg/day is ill advised because EAA intake would be insufficient to maintain B_N. An acceptable alternative is further limitation of protein (about 20 g/day) and the addition of a supplement of EAA or their nitrogen-free analogues (ketoacids). This strategy actually could increase the variety of foods and improve compliance because all protein does not have to be of the "high-quality" type. Generally, a regimen of 15 to 25 g/day of unrestricted quality protein plus EAA provided in capsules or tablets promptly corrects uremic symptoms while promoting neutral B_N and muscular strength and maintaining serum albumin and transferrin [24]. In another study, serum albumin and transferrin were maintained and lean body mass increased or remained stable as long as no intercurrent illnesses prevented an adequate caloric intake [36].

Essential amino acids usually are provided in the proportions recommended for normal subjects. It is likely, however, that these proportions are not optimal for patients with chronic renal failure, because plasma and intracellular concentrations of amino acids in uremic patients differ markedly from those in normal subjects or normal subjects eating a low-protein diet [20].

A newer EAA supplement (Aminess-Novum, KabiVitrum) contains tyrosine. Tyrosine's synthesis from phenylalanine is reduced in uremic patients, and giving them tyrosine seems to improve their nutrition [20]. Histidine is included in this new supplement because these patients given a histidine-deficient diet developed a syndrome characterized by malaise, an erythematous scaling rash, and negative B_N; supplemental histidine rapidly corrected these abnormalities [20]. The new EAA supplement also contains a higher proportion of valine. During long-term therapy, intracellular amino acid concentrations improved, as did B_N [24]. These results strongly suggest that the amino acid requirements of uremic subjects are different from those of normal individuals.

Nitrogen intake also can be reduced by taking advantage of the capacity of most tissues to convert the alpha keto analogues of seven EAA (ketoacids) to EAA. Ketoacids of the two remaining EAA, lysine and threonine, are not transaminated, and these amino acids must be provided. Proof that a mixture of ketoacids could replace their respective amino acids in the diet of patients with chronic renal failure was provided by showing that B_N was zero over periods of 5 to 7 days even when patients were eating a virtually protein-free (and hence, EAA-free) diet [37].

In early studies, ketoacids were provided to uremic patients as calcium salts [20]. Gastrointestinal distress was an occasional problem, and about 5% of patients developed hypercalcemia during long-term therapy, although the latter was rarely clinically significant. A new supplement was designed to avoid the problems associated with calcium salts while providing a more optimal proportion of ketoacids and amino acids for

uremic patients [32]. Ketoacids of the branched-chain amino acids are given as salts of basic amino acids (ornithine, lysine, and histidine). Tyrosine, small amounts of threonine, and the hydroxy analogue of methionine are added, but phenylalanine and tryptophan are omitted because the diet contains enough of these amino acids to achieve nitrogen balance [32].

A diet containing 20 to 25 g of mixed-quality protein plus this mixture of ketoacids produced a zero B_N and decreased UNA in patients with severe chronic renal failure (average GFR, 4.8 ml/min) [32]. Weight and serum albumin and transferrin levels were maintained over periods ranging from 4 to 19 months [32]. These results are particularly interesting because the supplement was "unbalanced"; that is, it lacked certain EAA or EAA analogues. It is important that neither the ketoacid nor an EAA supplement has any detectable nutritional benefit in uremic subjects eating more than 40 g/day of predominantly high-quality protein, presumably because the excess EAA or analogues are metabolized [20].

Lucas et al suggested that a ketoacid regimen can reduce lean body mass [19]. They treated 12 patients with only 0.2 g protein/kg/day (versus approximately 0.3 g/kg in other studies) and with approximately 50% of the amount of ketoacids used by others [20, 32]. Therapy was associated with a decrease in symptoms as well as a decrease in BUN, serum phosphate, parathyroid hormone, and the calcium-phosphorus product. Despite stable serum albumin and transferrin levels, the body weight, creatinine excretion, and mid-arm muscle circumference decreased significantly, suggesting loss of lean body mass. This study emphasizes the importance of providing a sufficient intake of protein and ketoacids (and possibly energy); it also points out the hazards of monitoring changes in plasma proteins as the sole index of nutritional status.

A possible anabolic effect of ketoacids is supported by studies suggesting that alpha ketoisocaproate (the ketoacid of leucine) improves protein conservation. In-vitro studies using rat muscle show that alpha ketoisocaproate reduced protein degradation [38]. Evidence also points to an anticatabolic effect in humans. Infusion of alpha ketoisocaproate into starving, obese adults with normal renal function decreased urea nitrogen production, whereas an equimolar infusion of leucine did not change B_N [39]. The clinical relevance of alpha ketoisocaproate to dietary therapy is presently unclear, and further investigation is warranted.

A ketoacid regimen also might improve clinical and biochemical evidence of secondary hyperparathyroidism. For example, ketoacid therapy treatment has been associated with decreased serum phosphate, alkaline phosphatase, and parathyroid hormone, as well as with increased serum calcium and improvement in renal osteodystrophy [20]. Serum levels of 1,25-dihydroxy-cholecalciferol increased, whereas serum concentrations of 25-hydroxy-cholecalciferol and calcitonin did not change [20]. Although the improvement in divalent ion metabolism is likely due in part to the concomitant reduction in dietary phosphorus associated with this regimen, suppression of phosphate absorption also might contribute; calcium salts of ketoacids appear to be at least as effective as calcium carbonate in binding phosphorus [20].

Improvement in metabolic acidosis is an obvious consequence of the reduction in hydrogen ion produced during metabolism of dietary phosphate and sulfur-containing amino acids. Lessening the catabolic influence of acidosis might partially explain the beneficial effect of restricted diets on protein metabolism in renal failure [21, 25, 27]. In summary, long-term treatment of patients with severe renal insufficiency with a very-low-protein diet supplemented with EAA or ketoacids maintains nutrition while reducing uremic symptoms, secondary hyperparathyroidism, and metabolic acidosis.

High-protein diets have been used for nephrotic patients but, in view of recent reports, the appropriateness of this maneuver is questionable [16]. When albumin turnover and excretion were measured in 9 nephrotic subjects fed a high- (1.6 g/kg/day) and low- (0.8 g/kg/day) protein diet containing 35 kcal/kg/day for 10 to 14 days, the more restrictive diet was associated with a significant reduction in albumin excretion (mean, −2.74 g/day; range, −0.1 to −7.4 g/day) and with a small increase in serum albumin (+0.2 g/dl). Although albumin synthesis was lower with the 0.8 g/kg/day diet, this decrease was more than compensated for by decreases in albumin catabolism and fractional excretion. Albumin synthesis did increase significantly on the high-protein diet but was offset by increased proteinuria. In spite of these encouraging results, simultaneous measurements of B_N and other nutritional indices are needed to assess body protein stores before protein-restricted diets can be recommended for all nephrotic patients. Moreover, protein-depleted subjects and children might require more dietary protein.

Energy requirements in uremia

The energy requirement is defined as the calories needed to maintain health and normal physical activity. Because inadequate calories, defective energy metabolism, or both could raise protein requirements and aggravate uremia, successful therapy requires that caloric intake be adequate. Unfortunately, little is known about factors influencing energy requirements or the complex relationship between caloric intake and maintenance of protein stores.

The FAO/WHO/UNU recommendations for energy intakes were determined from approximately 11,000 basal metabolic rates in healthy individuals of both sexes and all ages. Although these recommendations are considered the best available, it should be recognized that as much as 50% of the variability in energy requirements must be attributed to factors other than age, gender, and weight [17]. With regard to designing a diet for a uremic patient, the precision of estimating the energy requirement depends heavily on the consistency and accuracy of estimated time spent on various physical activities.

In patients with chronic renal failure, adaptation to inadequate caloric intake could involve changes in metabolism, decreased physical activity, and/or loss of lean body mass (Fig. 5). In semi-starved subjects, the basal metabolic rate decreased about 15% over 3 weeks; further adaptation reduced lean body mass [17]. Well-nourished individuals can achieve energy balance with only one-half of their usual calories if physical activity is limited, but lean body mass will diminish. Evidence suggests that the range of caloric intake compatible with successful adaptation is small [17].

Few studies have examined the caloric requirements of patients with chronic renal failure or how they adapt to a reduced caloric intake. Kopple et al varied the energy intake of 6 pre-dialysis patients between 15–45 kcal/kg/day while keeping protein intake at 0.55–0.60 g protein/kg/day. The authors con-

cluded that 35 kcal/kg/day could adequately maintain B_N [35]. The same group found that energy expenditure of predialysis and hemodialyzed patients during rest and exercise did not differ from that of control subjects [40]. Thus, calorie requirements of stable patients with chronic renal failure, like protein requirements, seem to be similar to those of normal subjects [20].

Progression of chronic renal failure

Patients with established renal failure rarely recover; they continue to lose renal function even when the disease process that initially damaged the kidneys is no longer active [20]. In the early 1970s, it was believed that the natural history of renal insufficiency was unpredictable; the outcome of renal disease usually was described as the percentage of patients surviving until end-stage renal disease occurred or until a predetermined level of serum creatinine was reached. In fact, the rate of loss of renal function over time is constant in the majority of patients, although its magnitude can vary widely among individuals with the same disease. To what degree the severity of the underlying disease process, other concomitant factors such as hypertension, or the method used to assess renal function contribute to variability in rates of progression is unknown.

Accurate assessment of the natural history of progressive renal insufficiency is useful both for prognosis and for determining whether therapy has altered the course of the underlying disease. To evaluate the efficacy of a specific therapy and/or factor(s) influencing the loss of residual renal function, two questions must be asked: (*1*) How can residual renal function be estimated; and (*2*) How can changes in renal function be measured most precisely? These questions address different tasks; the former determines renal function at one point in time, whereas the latter examines how renal function changes during the course of the illness.

The glomerular filtration rate has been estimated from serum creatinine. However, a single value of serum creatinine is only a crude estimate of the glomerular filtration rate; serum creatinine might not be elevated above the 95% confidence interval of "normal" until the GFR has declined by at least 50% [41]. As Levey discussed in a recent Nephrology Forum devoted solely to the issue of measurement of GFR, variability in creatinine production and tubular secretion results in wide confidence intervals for the relationship between serum creatinine and inulin clearance [42]. As renal failure advances, creatinine excretion decreases due to extrarenal creatinine clearance [43]. Extrarenal clearance was found to be relatively constant, averaging 0.038 liter/kg/day; this finding indicates that as renal function declines, extrarenal metabolism represents a progressively greater proportion of total creatinine elimination. Several factors influence creatinine production, so it is not surprising that questions have arisen about its use as a measure of renal function. There also is the problem of day-to-day variability in 24-hour creatinine clearances [44, 45]. These concerns limit the use of serum creatinine and creatinine clearance as a measurement of GFR and, by implication, the number of functioning nephrons. Although this topic has been reviewed, the published data comparing methods are scarce [41, 42, 44, 45].

One major problem in analyzing whether changes in diet alter the progression of renal disease is determining the predictability of repetitive measurements of renal function. The realization that the decline is predictable and that it occurs at a constant rate was first recognized in 1976, when it was reported that the decline in the reciprocal of serum creatinine (S_{cr}^{-1}) over periods averaging 71 months was linear in 31 of 34 patients [46]. Patients in this initial report had not had any dietary manipulation. At least two lines of evidence suggest that changes in the clearance of creatinine and S_{cr}^{-1} might not reflect changes in GFR as accurately as the renal clearance of radiolabeled glomerular markers. First, fractional tubular creatinine secretion was found to vary inversely with GFR in patients followed longitudinally [41]. In patients whose GFR improved by about 33%, Shemesh et al found that changes in creatinine clearance or S_{cr}^{-1} suggested only about a 13% improvement. Of 26 patients who underwent a remission (defined as an increase in GFR and a decrease in albuminuria), serum creatinine did not decline in 14, and only 13 of the 26 had an increase in creatinine clearance. On the other hand, serum creatinine increased in all but 3 of 28 patients with declining function, whereas creatinine clearance declined in 22 of 28 patients. Thus, changes in creatinine clearance and S_{cr}^{-1} seemed to be more sensitive in detecting a decline in GFR than in identifying an increase in GFR. These results emphasize that variability between GFR and serum creatinine is likely to be greatest in individuals with modest reductions in GFR.

Second, Walser and coworkers compared changes in creatinine clearance and S_{cr}^{-1} (corrected for an average value of urinary creatinine) with the renal clearance of ^{99m}technetium diethylene triaminopentaacetic acid (^{99m}Tc-DTPA) in 17 patients with moderate to severe chronic renal failure (GFR, 4 to 23 ml/min) [45]. Over an average of 15 months, the slope of creatinine clearance with time declined more rapidly and had greater variance than did the renal clearance of ^{99m}Tc-DTPA. Although the authors concluded that 9 of 22 observations revealed differing slopes between changes in creatinine and ^{99m}Tc-DTPA clearances during all or part of the observation period, the choice of periods analyzed is sensitive to observer bias. Over the entire observation period, 4 of 22 observation periods revealed different slopes for the two methods, and 3 of those 4 periods suggested progression by creatinine clearance when none was seen by ^{99m}Tc-DTPA. In the remaining case, the isotope clearance suggested improvement while creatinine clearance remained stable. Interestingly, in 2 of 4 patients whose slopes revealed stable ^{99m}Tc-DTPA clearances but progression by creatinine clearance, dialysis was required; thus, in those 2 patients, creatinine clearance was a better measure of clinical outcome than was ^{99m}Tc-DTPA clearance.

When rates of progression, as defined by changes in $1/S_{cr}$, were compared with ^{99m}Tc-DTPA clearance, the variances were similar, and the average slope for the groups did not differ; 6 of 22 slopes were statistically different between the two methods when the entire observation period was analyzed. In two instances, ^{99m}Tc-DTPA renal clearance remained stable, whereas S_{cr}^{-1} declined. In two cases, both methods showed progression (but the rate was statistically greater with the S_{cr}^{-1} method). In two instances each, S_{cr}^{-1} remained stable but ^{99m}Tc-DTPA improved or decreased respectively. Thus, in only 4 of 22 patients would an inappropriate conclusion regarding directional changes in renal function have been reached by utilizing S_{cr}^{-1}. These data support the original proposal that renal function can be monitored and is lost at a constant rate.

Regardless, decisions about the effect of the diet on progression require more than changes in serum creatinine concentration. Fortunately, the Modification of Diet in Renal Disease (MDRD) trial uses ^{125}I-iothalamate to measure GFR, and this practice will avoid the problem in that study [47].

After considering the variability in rates of progression among individuals and the standard error of the slopes of their regression lines, Walser concluded that at least four measurements of GFR would be necessary to detect progression in most patients and that little would be gained by requiring more than five measurements [44]. Only the most rapid rates are detectable with just three measurements. Consequently, estimates of progression based on two measurements (an initial and final value) cannot establish progression rates in individuals unless the fall in GFR greatly exceeds the error in GFR measurements. Interestingly, as GFR declines, so does its error; hence, progression becomes easier to detect [20].

During the last 15 years, evidence has suggested that dietary therapy can slow the progression of chronic renal failure. Many of these studies have been criticized because of study design (including the lack of randomization), retrospective analysis, compliance issues, and/or the use of changes in the serum creatinine or creatinine clearance to assess progression. Consequently, conclusions regarding the efficacy of dietary protein and/or phosphorus restriction on progression of chronic renal failure in humans must be considered tentative.

Nonetheless, three nutritional regimens have been prescribed to slow progression: (*1*) a conventional low-protein diet containing 0.6 g protein/kg body weight/day of primarily high-quality protein; (*2*) a very-low-protein diet supplemented with essential amino acids; and (*3*) a very-low-protein diet supplemented with ketoacids.

The principal evidence that the use of unsupplemented, low-protein diets can favorably influence the course of chronic renal failure is derived from three reports [48–50], two of which were randomized, prospective trials. In the earliest study, Maschio et al in Verona compared the rates of progression in three groups of patients [48]. Groups I and II were separated on the basis of initial serum creatinine value, and each received a diet containing 0.6 g/kg of predominantly high-quality protein, 40 kcal/kg energy intake, about 650 mg of phosphorus, and 1.0 to 1.5 g of calcium daily. The initial serum creatinine in Groups I (25 patients), II (20 patients), and III (30 patients) were 1.5 to 2.7 mg/dl, 2.9 to 5.4 mg/dl, and 1.6 to 4.7 mg/dl, respectively. Group III was a control population consuming an unrestricted diet with average daily intakes of protein, phosphorus, and calcium of 70 g, 900 mg, and 800 mg, respectively. Progression was assessed by changes in serum creatinine or S_{cr}^{-1}. Groups I and II had a far slower loss of renal function than did the control group; the rate of decline was significantly slower in the patients who began treatment at an earlier stage of disease.

The Verona group has periodically updated their experience. In 1989 they reported on 390 patients treated with a low-protein diet for 54 ± 28 months: 57% of the patients had a stable serum creatinine level, 11% had slower renal deterioration (defined as an increase in S_{cr} between 0.02 and 0.04 mg/dl/month and 32% had rapid renal deterioration (greater than 0.04 mg/dl/month) [51]. Individuals with milder renal disease seemed to have a more favorable course, and patients with interstitial nephritis fared better than did those with chronic glomerulonephritis or polycystic kidney disease. Initial serum creatinine, proteinuria on presentation, and systolic and diastolic blood pressures were found to be independent prognostic factors. No adverse effects of dietary therapy were noted, and indices of protein nutrition were well maintained [48]. However, after an additional 5 years of dietary restriction, the researchers noted significant loss of muscle protein and a decrease in serum albumin and serum transferrin concentrations (despite stable body weight and indices of muscle mass) in a subgroup of 8 patients; this finding suggests that nutritional status tends to worsen after 5 or more years [52]. Unfortunately, the energy intake of these 8 patients was lower than that prescribed (26–29 kcal/kg/day), so it is not clear that dietary protein restriction alone causes protein wasting.

In 1984, Rosman and coworkers reported the results of their prospective randomized trial involving 149 patients followed for at least 18 months (average of 24 months) after assignment to low-protein or control diets [49]. The prescription depended on the degree of renal insufficiency: 0.6 or 0.4 g/kg/day of protein for patients with creatinine clearances between 30–60 ml/min or 10–30 ml/min, respectively. They concluded that a low-protein diet significantly slowed the increase in serum creatinine, and that patients under 40 years of age progressed more rapidly than did older subjects. The authors noted no adverse influence of protein restriction on nutritional status. These authors subsequently reported a 4-year followup of 153 of 248 patients entering the study [53]. Although a significant benefit of dietary protein restriction still was noted, it was most apparent in the group with more advanced disease. In both the control and low-protein diet groups, males showed a more rapid loss of creatinine clearance but also seemed to respond to protein restriction; females did not seem to benefit from dietary modification. Furthermore, slowing of disease progression was evident only in patients with glomerulonephritis. Disease progression in patients with polycystic kidney disease appeared to be entirely related to blood pressure, whereas in the other diagnostic groups, variability in blood pressure did not correlate with preservation of renal function. Finally, body weight and serum proteins were stable over 36 months of dietary therapy, but prescribing less than the minimum daily requirement of protein to patients with a creatinine clearance less than 30 ml/min could be hazardous nonetheless [17].

In Australia, Ihle et al compared a diet containing 0.4 g protein/kg/day with an unrestricted protein intake in 64 subjects who were followed for 18 months in a prospective, randomized trial [50]. The groups were initially well matched for blood pressure, serum creatinine (range, 4.0 to 11.0 mg/dl), and calcium and phosphorus values. Changes in GFR were determined from the plasma disappearance of ^{51}Cr-EDTA. End-stage renal failure developed in 9 of 33 patients (27%) who followed the unrestricted diet compared with only 2 of 31 (6%) who were compliant with the protein-restricted diet ($P < 0.05$); the GFR decreased on average from about 15 ml/min to 6 ml/min in the former group, whereas it did not change significantly in the protein-restricted group (from approximately 14 ml/min to 12 ml/min). The outcome of patients who did not comply with the restricted diet was not detailed. Although serum albumin and estimates of muscle mass remained stable over the 18-month followup, weight, serum transferrin, and total lymphocyte count decreased significantly. Because the

phosphorus content of the protein-restricted diet was approximately 30% to 40% less than that of the unrestricted diet, the relative importance of dietary protein versus phosphorus restriction on progression cannot be determined. The decline in some, but not all, nutritional indices also raises concern about prescribing less than the minimum daily requirement of protein to patients with renal insufficiency. Clearly, we also need more sensitive methods for assessing the nutritional adequacy of currently recommended dietary regimens.

How did very-low-protein diets supplemented with essential amino acids affect the progression of chronic renal failure? Alvestrand and associates treated 17 patients who had well-defined rates of decline of S_{cr}^{-1} before beginning a regimen of 15–20 g of mixed-quality protein plus an EAA supplement provided as tablets (containing 1.8 to 2.8 g nitrogen). The patients were followed for an average of 355 days. Progression was apparent even though many patients had been consuming a diet restricted to 0.6 g protein/kg/day [24, 54]. Only 3 patients did not show substantial slowing of progression. Interim reports from an ongoing prospective, randomized trial by the same group have cast doubt on what influence diet exerts on these results and raises the possibility that better blood pressure control and closer followup slowed progression of renal disease [55]. Slowing of progression appeared to be related to a very small, but significant, reduction in diastolic blood pressure (2 mm Hg); loss of function was greater in patients with proteinuria. The relationship with blood pressure appears to exist at levels well within the range considered "normal," so more stringent blood pressure control than traditionally accepted might exert a favorable effect on renal function. Although 57 patients were initially enrolled in the study, only 5 subjects in the protein-restricted group and 9 in the control group satisfied the requirements of the study. The authors concluded that rates of progression before and after randomization did not differ, nor could an effect of dietary protein restriction on progression be discerned. Of note, the average intake of protein in the EAA-treated group was higher than prescribed and although significant, the difference from the intake of the unrestricted subjects (0.65 g/kg/day versus 0.86 g/kg/day) was not striking.

In summary, an EAA regimen can be effective in controlling the symptoms of chronic renal failure, but any benefit on progression of disease remains uncertain. The major advantage over a conventional low-protein diet is the greater variety of foods, which might make the regimen more acceptable. It appears to have little or no advantage in terms of improved nitrogen conservation when compared with a conventional low-protein diet.

Very-low-protein diets supplemented with ketoacids also have been assessed. Barsotti and colleagues examined progression in 31 patients treated with a diet containing 0.5 g/kg of high-quality protein and 600 mg of phosphorus/day; all showed a linear decline in creatinine clearance despite dietary protein restriction [56]. Twelve subjects were then treated for 10 to 15 months with approximately 0.2 g protein/kg/day, 300 mg/day of phosphorus, plus a ketoacid-amino acid mixture. Eleven of the 12 had a marked decrease in the loss of creatinine clearance; only one patient continued to lose renal function at the same rate. The same group reported their experience with this regimen in a larger number of patients whose renal insufficiency progressed despite therapy with a conventional low-protein unsupplemented diet. In patients compliant with the ketoacid regimen, the decline in creatinine clearance was halted (0.1 ± 0.12 ml/min). Patients who were less compliant (average UNA, 6.3 gN/day) continued to lose renal function. We evaluated a regimen containing 20 to 30 g of protein supplemented with a mixture of the basic amino acid salts of ketoacids in 25 patients [57]. Among 17 patients who demonstrated well-defined rates of disease progression, 10 (59%) exhibited a significantly slower rise in the serum creatinine level during long-term treatment (average, 20 months). Seven of these 17 patients began treatment before the serum creatinine reached 8 mg/dl; in 6, the serum creatinine remained at or below the level at the start of treatment. Thus, it appears that this regimen has a more favorable influence if initiated relatively early in the course of renal failure.

All these studies suggesting a beneficial effect of protein and/or phosphorus restriction are based on creatinine measurements, which can be unreliable estimates of progression. These results also have not adequately compared a ketoacid-based regimen with an EAA regimen or with a low-protein, unsupplemented diet. Walser and colleagues evaluated 12 patients given a regimen containing 0.3 g protein/kg/day plus EAA; all had progressive decline in creatinine clearance [58]. After the EAA were changed to a ketoacid supplement, renal failure in all 6 patients whose serum creatinine level exceeded 7.5 mg/dl continued to progress. In contrast, 6 of 7 patients whose serum creatinine level was between 6.0 and 7.4 mg/dl at crossover had stable values of GFR during the one- to two-year followup; one patient who was noncompliant had to go on dialysis.

In summary, despite many provocative observations, it is not established whether dietary protein and/or phosphorus restriction can slow the progression of chronic renal failure or whether a ketoacid-based regimen confers a therapeutic advantage. One or more of the prospective, randomized multicenter trials now in progress might answer these questions.

Let me conclude with a short comment on the progression of renal disease in diabetic patients. A substantial proportion of patients with insulin-dependent diabetes will develop renal failure. Why some, but not all, patients are at risk is not known. A genetic susceptibility to diabetic nephropathy might be important; diabetic siblings of patients with overt nephropathy are more likely to have nephropathy, and black diabetic patients have a higher incidence of end-stage renal disease when compared with white patients. Hypertension can accelerate diabetic nephropathy, and effective antihypertensive therapy reportedly slows the decline in renal function [59].

Most investigators believe that microalbuminuria indicates a high risk for the development of clinical diabetic nephropathy. This observation is of interest because short-term dietary protein restriction reduces protein losses in diabetic patients with microalbuminuria [60].

Data on the efficacy of dietary protein restriction in slowing progression of renal failure are limited. In a recent study of 19 insulin-dependent diabetic patients with persistent proteinuria, conversion from an unrestricted diet (average, 1.13 g protein/kg/day) to a diet averaging 0.67 g protein/kg/day was associated with a significant reduction in the rate of decline in GFR (from 0.61 to 0.14 ml/min/month) [61]. Slowing of progression was significant even after adjustments were made for differences in blood pressure, energy intake, and glycosylated hemoglobin

level. Albumin excretion and its fractional clearance also fell with the low-protein diet. Another recent study found a similar benefit of a low-protein diet on the progression of diabetic nephropathy [62].

In summary, dietary protein restriction has been used by many investigators to treat uremic symptoms. Our understanding of the metabolic changes required to maintain nutrition and to monitor compliance has increased rapidly. However, much work is needed to define how uremia affects protein turnover and how changes in lean body mass can be monitored most effectively. Foods designed to be low in protein and phosphorus are needed to improve compliance. Such knowledge will be especially useful if results from prospective clinical trials strengthen the results of the reports reviewed.

Questions and answers

DR. NICOLAOS E. MADIAS (*Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts*): You stated that a decrease in protein intake in the company of ketoacid supplementation can improve renal osteodystrophy on the basis of decreasing the level of PTH and increasing the concentration of 1,25 dihydroxycholecalciferol. Is there any evidence derived by direct or indirect methods that the severity of renal osteodystrophy is indeed lessened by utilization of such a dietary regimen?

DR. MITCH: Data from Germany suggest that a low-protein, low-phosphorus diet plus calcium ketoacids is associated with a reduction in the level of parathyroid hormone in the blood [63]. Maschio and colleagues showed that patients fed 0.6 g protein/kg/day had stabilization of the histology of bone on bone biopsy [64]. I don't know of a study of bone biopsy in patients given ketoacids.

DR. JOHN T. HARRINGTON (*Chief of Medicine, Newton-Wellesley Hospital, Newton, Massachusetts*): You mentioned that a decreased dietary protein intake decreases amino acid oxidation. What is the link between those two steps?

DR. MITCH: I don't think anybody knows. One possibility is that the low-protein diet reduces glucocorticoids because glucocorticoids influence the activity of the enzyme that breaks down the essential, branched-chain amino acids [65].

DR. ANDREW S. LEVEY (*Division of Nephrology, New England Medical Center*): I'd like to return to data from the study by Ihle et al [50]. These investigators demonstrated a lower rate of loss of renal function in patients with moderately severe renal insufficiency (mean GFR, 25 ml/min/1.73 m^2) treated with a low-protein diet. It was interesting to note that protein intake estimated from urinary urea excretion was 0.7–0.8 g/kg/day in the low-protein-diet group and 0.9–1.0 g/kg/day in the unrestricted-protein-diet group. Thus the dietary intervention appeared to be only a relatively small reduction in protein intake, and the level of protein intake that was achieved was a level that is customary in many parts of the world. Would you comment on the "dose-response" relationship between the level of protein intake and the proposed beneficial effect on delaying the progression of renal disease?

DR. MITCH: Interestingly, the protein intake slowing progression in diabetic patients also was approximately 0.7 g/kg/day. Perhaps a response could be achieved without marked dietary restriction, or it might be that the response is graded, or that patients with certain types of disease won't respond. The patient discussed had inherited nephropathy, yet apparently she responded. Barsotti suggested that the ketoacid regimen slows the decline in creatinine clearance experienced by patients with polycystic disease [66].

DR. MADIAS: Regarding your data in rats showing that metabolic acidosis accelerates protein catabolism, have studies in humans with chronic renal failure related protein degradation to the prevailing degree of acidemia? Have any formal studies examined this issue in adults with renal tubular acidosis?

DR. MITCH: I know of 3 studies showing that correcting the plasma bicarbonate improved nitrogen balance in patients with chronic renal failure [67–69]. Children with inherited renal tubular acidosis have improved growth when they are given sodium bicarbonate [70]. Finally, Bergström and associates recently showed that the blood bicarbonate level in dialysis patients correlates directly with the valine concentration in muscle; hence, acidosis likely stimulates valine catabolism and limits protein utilization [23].

DR. MADIAS: Has the effect of respiratory acidosis on protein metabolism been examined?

DR. MITCH: Not to my knowledge.

DR. PAUL KURTIN (*Director, Dialysis Unit, New England Medical Center*): In contrast to your studies and those of others you quoted [33, 34], growing infants can incorporate exogenous urea into non-essential amino acids. In addition, we have observed that adults in acute renal failure given parenteral essential amino acids and adequate calories can have a fall in BUN [71]. This finding suggests the incorporation of endogenous urea into non-essential amino acids and protein anabolism. Would you please comment on this? Second, would you comment on the studies by Bonomini, which suggest that the longer a patient is on a low-protein diet, the worse the results of anemia and nerve conduction studies after dialysis is started [72].

DR. MITCH: Not only in infants but also in malnourished adults can urea improve nitrogen balance [73]. On the other hand, in adult patients with chronic renal failure fed an adequate amount of calories, we find no evidence that urea nitrogren is utilized to synthesize amino acids. In patients with acute renal failure, the lower nitrogen intake occurring with feeding essential amino acids could reduce urea production and hence the BUN. Regarding the initiation of dialysis, the decision generally is based on clinical criteria, and if patients do not have uremic symptoms, dialysis is not necessary.

DR. KURTIN: I interpreted Bonomini's studies as showing that if patients are started on dialysis based on a pre-determined BUN, and if they are on a low-protein diet, it will take longer for these patients to reach the target BUN, while other components of the uremic syndrome can progress.

DR. MITCH: I suspect we need careful studies to examine whether dialysis benefits these patients.

DR. MADIAS: To what extent should the recommendations for protein restriction in chronic renal failure be changed as a function of age, that is, for children, adults, and the elderly? Also, what about patients who are on high-dose steroid treatment?

DR. MITCH: You asked two important questions. Nobody has studied requirements as a function of the age of uremic patients. Patients given high doses of glucocorticoids, and patients with the nephrotic syndrome also remain a mystery, at least regard-

ing their protein requirement. Studies of the safety of low-protein diets in severely nephrotic patients and/or patients taking glucocorticoids are needed because this is an important clinical problem.

DR. MADIAS: Should one modify the dietary recommendations during periods of stress (for example, intercurrent illness) as one does for non-uremic subjects?

DR. MITCH: That approach appears rational as long as the extra protein does not cause uremic symptoms.

DR. HARRINGTON: I remain a skeptic about the effect of a low protein intake. I would argue that the most important thing you did was control the patient's blood pressure. Both experimentally and clinically, in say accelerated hypertension and in diabetes, I believe that control of blood pressure is paramount. In the studies that have been done about the efficacy of a low protein intake, has the role of control of hypertension been taken into account? I can't imagine that any nephrologist would leave patients with blood pressures of 222/120 mm Hg merely to carry out the rigorous study that I want.

DR. MITCH: The definitive study hasn't been done because blood pressure is always treated. However, controlling blood pressure alone seems to have the most benefit in slowing progression to renal failure in patients with accelerated hypertension.

DR. LEVEY: In the study by Ihle et al, patients in the low-protein-diet group lost 2–4 kg in weight on average during the first few months of followup. In my experience, this is a common finding in patients who follow a low-protein diet. Has anyone carefully studied such patients to determine whether weight loss is the result of loss of body fat, salt, or muscle?

DR. MITCH: In the patients we treated for many months with a very-low-protein diet, we found no significant change in weight on average [32, 57]. Some patients did lose weight, but we did not examine whether there was loss of bone, fluid, or muscle and fat. Lucas et al prescribed half the amount of ketoacids and less than half the amount of protein as others use, so those results should not be extrapolated to other patients treated with ketoacids [19].

DR. MADIAS: In your view, what is the importance of changes in insulin and glucagon levels for the abnormalities in intermediary metabolism in uremia?

DR. MITCH: We found that uremia is associated with resistance to insulin in terms of protein metabolism [74]. The importance of glucagon and other hormones in impairing protein metabolism in uremia is less certain [20].

DR. HARRINGTON: What is the impact of gender on progression of renal disease? I ask because Lombet et al have reported that renal insufficiency in the ⅝ nephrectomized female rat didn't progress at the same rate as in male rats [75].

DR. MITCH: Some studies suggest that women respond to a low-protein diet, but the question has not been examined in detail [49, 53].

DR. RONALD PERRONE (*Division of Nephrology, New England Medical Center*): When you first place an ambulatory patient on a low-protein diet and measure the estimated protein intake using urea nitrogen, how do you distinguish the noncompliant patient from the patient in negative nitrogen balance? At what point are you able to rely on the urinary urea nitrogen as an indicator of compliance?

DR. MITCH: You raise critically important issues. As long as the BUN and weight are changing (weight being an index of total body water), then urea excretion cannot be used to estimate protein intake. If the BUN and weight are stable and urea nitrogen excretion is consistently higher than the amount of dietary protein nitrogen prescribed, then only two possibilities exist: (*1*) the patient is eating too much, or (*2*) the patient is catabolic or has gastrointestinal bleeding. Distinguishing between the possibilities requires careful examination and evaluation by a dietician. Finally, the test should be repeated.

DR. PERRONE: Are there any specific parameters of catabolism that you would follow up?

DR. MITCH: During long-term therapy, body weight, serum albumin, and transferrin seem to be reliable. We believe the serum bicarbonate should be kept above 22 mM.

DR. BRIAN PEREIRA (*Fellow, Division of Nephrology, New England Medical Center*): What would you consider early enough, as far as dietary intervention is concerned? My second question relates to protein restriction in acute renal failure. Has anyone studied whether intervention has any effect on the speed or completeness of recovery in acute renal failure?

DR. MITCH: These data do not prove protein restriction slows progression even though the diet will reduce symptoms. If a patient has a rising serum creatinine and a high BUN, then a low-protein diet should be considered. Regarding low-protein diets in acute renal failure, attempts to show improved survival from acute renal failure with different types of amino acids or low-protein regimens have not proved that survival improves [76]. I believe that we need a method of limiting catabolism stimulated by other illnesses or renal failure itself. We can replace renal function, but until catabolism can be controlled, it seems unlikely that survival time will improve.

DR. HARRINGTON: How much time does it take for the nutritionist to teach a new patient about a 0.6 g/kg intake, and how often do patients have to see the nutritionist? Please try to be as quantitative as possible in your answers.

DR. MITCH: That depends on the intelligence of the patient and his or her commitment plus the skill of the dietician. Dieticians in the MDRD study spend quite a bit of time educating these patients, but in our studies the dietician meets with the patient during the initial hospitalization in the clinical research center and monthly thereafter. Each visit lasts 30 to 45 minutes. After about 6 to 8 months, many patients are seen every other month, and we calculate that they are compliant based on urea excretion and body weight [1].

DR. KURTIN: In healthy individuals, as total protein intake falls, energy intake must increase to maintain nitrogen balance. Do you maintain your patients on diets of 35 kcal/kg? What caloric intake do you recommend for the very-low-protein diets?

DR. MITCH: It is difficult to maintain a low-protein diet and a high-calorie diet without using supplements of carbohydrate polymers. This supplement is not too sweet and will increase calories. However, we often do not achieve the desired 35 kcal/kg.

DR. GEETHA NARAYAN (*Nephrologist, St. Elizabeth's Hospital, Brighton, Massachusetts*): In developing countries like India, renal disease requiring dialysis seems to be just as prevalent in lower socioeconomic groups as in higher despite the fact that these people often consume diets very low in protein, even bordering on protein calorie malnutrition at times.

Hence, at least in these populations, other factors seem to override the effects of a low-protein diet. Would you comment on this, and are any data available on protein intake in these patients?

DR. MITCH: You raise an interesting point. Perhaps patients in underdeveloped countries don't see a physician until they have advanced uremia, and they can have secondary illnesses. The patient discussed today had loss of renal function each time she had a bout of diarrhea and fever. Fortunately, she recovered. We concluded that an infection along with diarrhea or fever can impair renal function acutely. If other illnesses complicate renal failure in a patient from a third world country, the patient might not receive medical care until renal failure is quite advanced.

DR. MADIAS: What might be the implications of a protein-restricted diet and the provision of adequate energy from nonprotein sources on the lipid abnormalities of uremia?

DR. MITCH: This question hasn't been examined carefully in predialysis patients. In patients we have treated, hypertriglyceridemia often is present, but an elevated total cholesterol is unusual.

DR. LEVEY: Would you speculate on the mechanism of the proposed beneficial effect of low-protein diets and essential ketoacid supplements in retarding the progression of renal disease?

DR. MITCH: If the diet works in patients with inherited renal disease and in patients with diabetes and/or other types of diseases, a common factor probably is present in all patients. Such a factor has not been identified. In the patients we treated, I have tried unsuccessfully to find a correlation between mean blood pressure, systolic or diastolic pressure, and rates of progression. Regarding ketoacids, I don't know whether there is a special effect; they might permit a lower protein intake. Barsotti and associates followed patients whose renal disease progressed while they ate 0.6 g protein/kg/day, but this progression stopped when the patients began the ketoacid regimen [56].

DR. LEVEY: I agree that the published data comparing rates of decline in GFR (measured as clearance of radioisotope-labeled filtration markers), creatinine clearance, and reciprocal serum creatinine are scarce, and that until it is determined that these latter measures correlate closely with the rate of decline in GFR, it is important that we include measurements of GFR in studies of the effect of interventions on the course of progressive renal disease. I do not agree, however, with the suggestion that an apparent linear decline in the rate of decline in renal function, measured as either GFR, creatinine clearance, or reciprocal serum creatinine, justifies using the patients as their own "controls" in such studies, rather than using a concurrent control group that does not receive the intervention. Interpretation of changes in the rate of decline in individual patients requires assessment of 4 things: (*1*) carry-over effects from the previous interval; (*2*) effects of factors other than the intervention that could influence renal function; (*3*) regression to the mean [47], and (*4*) spontaneous breakpoints [47]. In principle, it is possible to assess these effects only if a concurrent control group is studied or if the experimental group is studied on both diets in a crossover design in random order.

DR. HARRINGTON: I have a question for Dr. Levey. The MDRD Study has been going on for a few years. What is the latest information from that important study?

DR. LEVEY: Two groups of patients are being evaluated in the MDRD study; one group has GFRs of 25–55 ml/min/1.73 m^2 (Study A), and the other has GFRs of 13–24 ml/min/1.73 m^2 (Study B). The patients in Study B have renal function comparable to that in the patients studied by Ihle et al in Australia. As of the end of 1990, we have randomized 200 patients into Study B, which compares a diet containing 0.575 g/kg/day protein with a diet containing 0.28 g/kg/day protein supplemented with essential keto acids. This study should enable us to determine whether there are different effects of different low-protein diets in patients with severe impairment in renal function. In addition, in each diet group we are comparing two levels of blood pressure: a usual blood pressure goal of MAP (mean arterial pressure) $\leq$ 107 mm Hg (equivalent to $\leq$ 140/90 mm Hg) and a low blood pressure goal of MAP $\leq$ 92 mm Hg (equivalent to $\leq$ 127/75 mm Hg). Hopefully this strategy will enable us to determine whether the level of arterial blood pressure affects the progression of renal disease. In Study A, we have randomized approximately 400 patients to one of two diet groups, a usual-protein diet containing 1.3 g/kg/day versus a low-protein diet containing 0.575 g/kg/day. Patients in each group also are randomized to either the usual or low blood pressure goal. This study will test the effectiveness of a low-protein diet and lower-than-usual level of blood pressure in patients with mild to moderate impairment in renal function. After completion of enrollment, the planned duration of followup is approximately 2 years.

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Acknowledgment

This work was supported in part by National Institutes of Health grants RO1DK-40907 and RO1DK-37175.

References

1. MARONI BJ, STEINMAN T, MITCH WE: A method for estimating nitrogen intake of patients with chronic renal failure. *Kidney Int* 27:58–65, 1985
2. GIORDANO C: Use of exogenous and endogenous urea for protein synthesis in normal and uremic subjects. *J Lab Clin Med* 62:231–246, 1963
3. GIOVANNETTI S, MAGGIORE Q: A low-nitrogen diet with proteins of high biological value for severe chronic uremia. *Lancet* 1:1000–1003, 1964
4. COLES GA: Body composition in chronic renal failure. *Q J Med* 41:25–47, 1972
5. LOWRIE EG, LAIRD NM, PARKER TF, SARGENT JA: The effect of hemodialysis prescription on patient morbidity. *N Engl J Med* 305:1176–1181, 1972
6. JOHNSON WJ, HAGGE WH, WAGONER RD, DINAPOLU RP, ROSEVEAR JW: Effects of urea loading in patients with far-advanced renal failure. *Mayo Clin Proc* 47:21–29, 1972
7. CONTE G, DAL CANTON A, TERRIBILE M, CIANCIARUSO B, DI MINNO G, PANNAIN M, RUSSO D, ANDREUCCI VE: Renal handling of urea in subjects with persistent azotemia and normal renal function. *Kidney Int* 32:721–727, 1987
8. RICHARDS P, BROWN CL: Urea metabolism in an azotemic woman with normal renal function. *Lancet* 2:207–209, 1975
9. DEFERRARI G, GARIBOTTO G, ROBAUDO C, GHIGGERI GM, TIZIANELLO R: Brain metabolism of amino acids and ammonia in patients with chronic renal insufficiency. *Kidney Int* 20:505–510, 1981

10. MITCH WE, LIETMAN PS, WALSER M: Effects of oral neomycin and kanamycin in chronic renal failure: I. Urea metabolism. *Kidney Int* 11:116–122, 1977
11. COTTINI EP, GALLINA DL, DOMINGUEZ JM: Urea excretion in adult humans with varying degrees of kidney malfunction fed milk, egg or an amino acid mixture: Assessment of nitrogen balance. *J Nutr* 103:11–19, 1973
12. MITCH ME, WILCOX CS: Disorders of body fluids, sodium and potassium in chronic renal failure. *Am J Med* 72:536–550, 1982
13. SARGENT J, GOTCH F, BORAH M, PIERCY L, SPINOZZI N, SCHOENFELD P, HUMPHREYS M: Urea kinetics: a guide to nutritional management of renal failure. *Am J Clin Nutr* 31:1696–1702, 1978
14. YOUNG V: Some metabolic and nutritional considerations of dietary protein restriction, in *Contemp Issues Nephrol: The Progressive Nature of Renal Disease*, edited by MITCH ME, New York, Churchill Livingstone, 1986, pp 263–283
15. KAYSEN GA, DAVIES RW, HUTCHISON FN: Effect of dietary protein intake and angiotensin converting enzyme inhibition in Heymann nephritis. *Kidney Int* S154–S162, 1989
16. KAYSEN GA, GAMBERTOGLIO J, JIMENEZ I, JONES H, HUTCHISON FN: Effect of dietary protein intake on albumin homeostasis in nephrotic patients. *Kidney Int* 29:572–577, 1986
17. FAO/WHO/UNO: Energy and protein requirements, in *Technical Report Series* 724. Geneva, World Health Organization, 1985, pp 1–206
18. BLUMENKRANTZ MJ, KOPPLE JD, GUTMAN RA, CHAN YK, BARBOUR GL, ROBERTS C, SHEN FH, GANDHI VC, TUCKER CT, CURTIS FK, COBURN JW: Methods for assessing nutritional status of patients with renal failure. *Am J Clin Nutr* 33:1567–1585, 1980
19. LUCAS PA, MEADOWS JH, ROBERTS DE, COLES GA: The risks and benefits of a low protein-essential amino acid-keto acid diet. *Kidney Int* 29:995–1003, 1986
20. MITCH WE, WALSER M: Nutritional therapy of the uremic patient, in *The Kidney* (4th ed), edited by BRENNER BM, RECTOR FC, Philadelphia, Saunders, 1991, pp 2186–2222
21. HARA Y, MAY RC, KELLY RA, MITCH WE: Acidosis, not azotemia, stimulates branched-chain amino acid catabolism in uremic rats. *Kidney Int* 32:808–814, 1987
22. MAY RC, HARA Y, KELLY RA, BROCK KP, BUSE MG, MITCH WE: Branched-chain amino acid metabolism in rat muscle: Abnormal regulation in acidosis. *Am J Physiol* 252:E712–E718, 1987
23. BERGSTRÖM J, ALVESTRAND A, FURST P: Plasma and muscle free amino acids in maintenance hemodialysis patients without protein malnutrition. *Kidney Int* 38:108–114, 1990
24. ALVESTRAND A, AHLBERG M, FURST P, BERGSTRÖM J: Clinical results of long-term treatment with a low protein diet and a new amino acid preparation in patients with chronic uremia. *Clin Nephrol* 19:67–73, 1983
25. MAY RC, KELLY RA, MITCH WE: Mechanisms for defects in muscle protein metabolism in rats with chronic uremia: The influence of metabolic acidosis. *J Clin Invest* 79:1099–1103, 1087
26. LI JB, WASSNER SJ: Protein synthesis and degradation in skeletal muscle of chronically uremic rats. *Kidney Int* 29:1136–1143, 1986
27. MITCH WE: Uremia and the control of protein metabolism. *Nephron* 49:89–93, 1988
28. KETTLEHUT IC, WING SS, GOLDBERG AL: Endocrine regulation of protein breakdown in skeletal muscle. *Diabetes/Metabolism Revs* 4:751–772, 1988
29. GOODSHIP THJ, MITCH WE, HOERR RA, WAGNER DA, STEINMAN TI, YOUNG VR: Adaptation to low-protein diets in renal failure: Leucine turnover and nitrogen balance. *J Am Soc Nephrol* 1:66–75, 1990
30. YOUNG VR: 1987 McCollum award lecture. Kinetics of human amino acid metabolism: nutritional implications and some lessons. *Am J Clin Nutr* 46:709–725, 1987
31. MOTIL KJ, MATTHEWS DE, BIER DM, BURKE JF, MUNRO HN, YOUNG VR: Whole-body leucine and lysine metabolism: response to dietary protein intake in young men. *Am J Physiol* 240:E712–E721, 1981
32. MITCH WE, ABRAS E, WALSER M: Long-term effects of a new ketoacid-amino acid supplement in patients with chronic renal failure. *Kidney Int* 22:48–53, 1982
33. VARCOE R, HALLIDAY D, CARSON ER, RICHARDS P, TAVILL AS: Efficiency of utilization of urea nitrogen for albumin synthesis by chronically uremic and normal man. *Clin Sci Mol Med* 48:379–390, 1975
34. MITCH WE, WALSER M: Effects of oral neomycin and kanomycin in chronic uremic patients. II. Nitrogen balance. *Kidney Int* 11:123–127, 1977
35. KOPPLE JD, MONTEON FJ, SHAIB JK: Effect of energy intake on nitrogen metabolism in nondialyzed patients with chronic renal failure. *Kidney Int* 29:734–742, 1986
36. ATTMAN PO, EWALD J, ISAKSSON B: Body composition during long-term treatment of uremia with amino acid supplemented low-protein diets. *Am J Clin Nutr* 33:801–807, 1980
37. MITCH WE, WALSER M: Utilization of calcium L-phenyllactate as a substitute for phenylalanine by uremic subjects. *Metabolism* 26:1041–1044, 1977
38. MITCH WE, CLARK AS: Specificity of the effect of leucine and its metabolites on protein degradation in skeletal muscle. *Biochem J* 222:579–586, 1984
39. MITCH WE, WALSER M, SAPIR DG: Nitrogen-sparing induced by leucine compared with that induced by its keto-analogue, alpha-ketoisocaproate, in fasting obese man. *J Clin Invest* 67:553–562, 1981
40. MONTEON FJ, LAIDLAW SA, SHAIB JK, KOPPLE JD: Energy expenditure in patients with chronic renal failure. *Kidney Int* 30:741–747, 1986
41. SHEMESH O, GOLBETZ H, KRISS JP, MYERS BD: Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int* 28:830–838, 1985
42. LEVEY AS: Nephrology Forum: Measurement of renal function in chronic renal disease. *Kidney Int* 38:167–184, 1990
43. MITCH WE, COLLIER VU, WALSER M: Creatinine metabolism in chronic renal failure. *Clin Sci* 58:327–335, 1980
44. WALSER M: Progression of chronic renal failure in man. *Kidney Int* 37:1195–1210, 1990
45. WALSER M, DREW HH, LAFRANCE ND: Creatinine measurements often yield false estimates of progression in chronic renal failure. *Kidney Int* 34:412–418, 1988
46. MITCH WE, BUFFINGTON GA, LEMANN J, WALSER M: A simple method of estimating progression of chronic renal failure. *Lancet* 2:1326–1328, 1976
47. Modification of Diet in Renal Disease Study, prepared by LEVEY AS, GASSMAN JJ, HALL PM, WALKER WG: Assessing the progression of renal disease in clinical studies: Effects of duration of followup and regression to the mean. *J Am Soc Nephrol*, in press
48. MASCHIO G, OLDRIZZI L, TESSITORE N, D'ANGELO A, VALVO L, LUPO A, LOSCHIAVO C, FABRIS A, GAMMARO L, RUGIU C, PANZETTA G: Effects of dietary protein and phosphorus restriction on the progression of early renal failure. *Kidney Int* 22:371–376, 1982
49. ROSMAN JB, MEIJER S, SLUITER WJ, TER WEE PM, PIERS-BECHT TP, DONKER AJM: Prospective randomised trial of early dietary protein restriction in chronic renal failure. *Lancet* 2:1291–1295, 1984
50. IHLE BU, BECKER GJ, WHITWORTH JA, CHARLWOOD RA, KINCAID-SMITH PS: The effect of protein restriction on the progression of renal insufficiency. *N Engl J Med* 321:1773–1777, 1989
51. OLDRIZZI L, RUGIU C, MASCHIO G: The Verona experience on the effect of diet on progression of renal failure. *Kidney Int* 36:S103–S105, 1989
52. GUARNIERI GF, TOIGO G, SITULIN R, CARRARO M, TAMARO G, LUCCHESLI A, OLDRIZZI L, RUGIU C, MASCHIO G: Nutritional state in patients on long-term low-protein diet or with nephrotic syndrome. *Kidney Int* 36:S195–S200, 1989
53. ROSMAN JB, LANGER K, BRANDL M, PIERS-BECHT TPM, VAN DER HEM GK, TER WEE PM, DONKER AJM: Protein-restricted diets in chronic renal failure: A four year follow-up shows limited indications. *Kidney Int* 36:S96–S102, 1989
54. ALVESTRAND A, AHLBERG M, BERGSTRÖM J: Retardation of the progression of renal insufficiency in patients treated with low-protein diets. *Kidney Int* 24:S268–S272, 1983
55. BERGSTRÖM J, ALVESTRAND A, BUCHT H, GUTIERREZ A: Stockholm clinical study on progression of chronic renal failure—An interim report. *Kidney Int* 36:S110–S114, 1989

56. BARSOTTI G, GUIDUCCI A, CIARDELLA F, GIOVANNETTI S: Effects on renal function of a low-nitrogen diet supplemented with essential amino acids and ketoanalogues and of hemodialysis and free protein supply in patients with chronic renal failure. *Nephron* 27:113–117, 1981
57. MITCH WE, WALSER M, STEINMAN TL, HILL S, ZEGER S, TUNGSANGA K: The effect of keto acid-amino acid supplement to a restricted diet on the progression of chronic renal failure. *N Engl J Med* 311:623–629, 1984
58. WALSER M, LAFRANCE ND, WARD L, VANDUYN MA: Progression of chronic renal failure in patients given ketoacids following amino acids. *Kidney Int* 32:123–128, 1987
59. PARVING H-H, HOMMEL E, SMIDT UM: Protection of kidney function and decrease in albuminuria by captopril in insulin dependent diabetics with nephropathy. *Br Med J* 297:1086–1091, 1988
60. COHEN D, DODDS R, VIBERTI G: Effect of protein restriction in insulin dependent diabetics at risk of nephropathy. *Br Med J* 294:795–798, 1987
61. WALKER JD, DODDS RA, MURRELLS TJ, BENDING JJ, MATTOCK MB, KEEN H, VIBERTI GC: Restriction of dietary protein and progression of renal failure in diabetic nephropathy. *Lancet* 2:1411–1414, 1989
62. ZELLER KR, WHITTAKER E, SULLIVAN L, RASKIN P, JACOBSON HR: Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 324:78–83, 1991
63. SCHAEFER K, VON HERRATH D, ASMUS G, UMLAF E: The beneficial effect of ketoacids on serum phosphate and parathyroid hormone in patients with chronic uremia. *Clin Nephrol* 30:93–96, 1988
64. MASCHIO G, TESSITORE N, D'ANGELO A, BONUCCI E, LUPO A, VALVO E, LOSCHIAVO C, FABRIS A, MORACHIELLO P, PREVIATO G, FIASCHI E: Early dietary phosphorus restriction and calcium supplementation in the prevention of renal osteodystrophy. *Am J Clin Nutr* 33:1546–1554, 1980
65. BLOCK KP, RICHMOND WB, MEHARD WB, BUSE MG: Glucocorticoid-mediated activation of muscle branched-chain α-ketoacid dehydrogenase in vivo. *Am J Physiol* 252:E396–E407, 1987
66. BARSOTTI G: The role of dietary treatment on the progression of chronic renal disease, in *First Taormina Course in Nephrology*, edited by CONSOLO F, BELLINGHIERI G, SAVICA V, Editoriale Bios, Cosenza, Italy, 1990, pp 299–313
67. LYON DM, DUNLOP DM, STEWART CP: The alkaline treatment of chronic nephritis. *Lancet* 2:1009–1013, 1931
68. PAPDOYANNAKIS NJ, STEFANIDIS CJ, MCGEWOEN MG: The effect of correction of metabolic acidosis on nitrogen and potassium balance in patients with chronic renal failure. *Am J Clin Nutr* 40:623–627, 1984
69. JENKINS D, BURTON PR, BENNETT SE, BAKER F, WALLS J: The metabolic consequences of the correction of acidosis in uremia. *Nephrol Dial Transplant* 4:92–95, 1988
70. MCSHERRY E: Nephrology Forum: Renal tubular acidosis in childhood. *Kidney Int* 20:799–809, 1981
71. KURTIN PS, KOUBA J: Profound hypophosphatemia in the course of acute renal failure. *Am J Kidney Dis* 10:346–349, 1987
72. BONOMINI V, VAGELISTA A, STEFONI S: Early dialysis in renal substitutive programs. *Kidney Int* 13 (suppl 8):S112–S116, 1978
73. TRIPATHY K, KLAHR S, LOTERO H: Utilization of exogenous urea nitrogen in malnourished adults. *Metabolism* 19:253–262, 1970
74. MAY RC, CLARK AS, GOHEER A, MITCH WE: Identification of specific defects in insulin-mediated muscle metabolism in uremia. *Kidney Int* 28:490–497, 1985
75. LOMBET JR, ADLER SG, ANDERSON PS, NAST CC, OLSEN D, GLASSOCK RJ: Sex vulnerability in the subtotal nephrectomy model of glomerulosclerosis (*abstract*). *Am Soc Nephrol*, 1987, p 231A
76. MITCH WE, WILMORE DW: Nutritional considerations in the treatment of acute renal failure, in *Acute Renal Failure* (2nd ed), edited by BRENNER BM, LAZARUS JM, New York, Churchill Livingstone, 1988, pp 743–766
77. SHAH BV, LEVEY AS: Applications and limitations of reciprocal serum creatinine versus time plots (*abstract*). *Kidney Int* 35:200, 1989