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Nitrogen balance during intermittent dialysis therapy of uremia

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Nitrogen balance during intermittent dialysis therapy of uremia. Daily measurements of nitrogen balance were made at two levels of protein intake in five patients undergoing chronic intermittent dialysis therapy. During ingestion of high (1.4 g/kg of body wt) protein intake, nitrogen balance was positive on nondialysis days and negative on dialysis days, so that cumulative balance for the week of study was not different from zero. During ingestion of low (0.5 g/kg) protein intake, nitrogen balance was approximately zero on nondialysis days but was again negative on dialysis days, so that cumulative balance for this period was negative. The negative nitrogen balance observed on dialysis days was associated with a higher rate of urea nitrogen generation (G_u, g/24 hr, determined by a kinetic model of urea nitrogen in dialysis patients) that was most evident in the hours immediately following dialysis. Net protein catabolic rate (PCR, g/24 hr), derived from total nitrogen mass balance equations, correlated very closely with G_u: $G_u = 0.154\ PCR - 1.7$, $r = 0.96$. This relationship agreed well with previous observations made in nondialyzed uremic patients under more steady-state conditions. These studies demonstrate that nitrogen balance is negative on dialysis days regardless of protein intake, and that G_u is higher on dialysis days. The negative nitrogen balance could result from amino acid loss in dialysate and from increased protein catabolism stimulated by loss of glucose into dialysate.

Bilan d'azote au cours du traitement de l'urémie par dialyse intermittente. Des évaluations quotidiennes du bilan d'azote ont été réalisées à deux niveaux d'apports protéiques chez 5 malades soumis à la dialyse itérative. Au cours de l'ingestion d'un apport élevé (1,4 g/kg poids corporel) de protéines le bilan d'azote est positif les jours sans dialyse et négatif les jours avec dialyse de telle sorte que le bilan cumulatif d'une semaine est nul. Au cours de l'ingestion d'un apport faible (0,5 mg/kg poids corporel) de protéines le bilan d'azote est approximativement nul les jours sans dialyse mais négatif les jours avec dialyse de telle sorte que le bilan cumulatif est négatif. Le bilan négatif observé les jours avec dialyse est associé à un débit plus élevé de génération d'urée (G_u, mg/24 hr, déterminé par un modèle cinétique de l'azote uréique chez les malades dialysés) qui est le plus net dans les heures immédiatement consécutives à la dialyse. Le débit net de catabolisme protéique (PCR, g/24 hr) dérivé des équations du bilan de la masse totale d'azote est très correlé avec G_u: $G_u = 0{,}154\ PCR - 1{,}7$; r, 0,96. Cette relation est en accord avec des observations faites antérieurement chez des malades urémiques non dialysés dans de meilleures conditions d'état stationnaire. Ces études démontrent que le bilan d'azote est négatif le jour de la dialyse quel que soit l'apport protéique et que Gû est plus élevé ces jours-là. Le bilan d'azote négatif peut être la conséquence de la perte d'acides aminés dans le dialysat et de l'augmentation du catabolisme protéique induite par la perte de glucose dans le dialysat.

Determination of optimal intake of dietary constituents is an important goal in the management of the patient with chronic renal failure. Suboptimal dietary intake caused by uremic gastrointestinal symptoms or prescription of low protein diets may result in protein and calorie depletion; unrestricted protein intake may increase urea production and exacerbate uremic symptoms [1]. Dietary protein intake of 0.25 to 0.5 g/kg of body wt is necessary to maintain nitrogen balance in normal patients [2]. In patients with advanced chronic renal failure, nitrogen balance can be maintained despite marked protein restriction, provided that the ingested protein is of high biological value and that the total calories ingested remain greater than a certain minimum, 35 kcal/kg [3]. By contrast, a larger dietary protein intake has been recommended for patients undergoing intermittent dialysis treatment (IDT). Observations in patients dialyzed twice weekly with Kiil dialyzers indicate that protein intake of 0.75 to 1.0 g/kg is necessary to maintain nitrogen balance [4, 5]. The reasons for this increased protein requirement compared to that of patients not on chronic dialysis remain to be elucidated. The purpose of the present study was to determine the influence of dialysis on nitrogen metabolism and external nitrogen balance

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at low and high levels of dietary protein intake. Net nitrogen balance was corrected for changes in the body content of the major nitrogen catabolites (nitrogen in urea, creatinine, and uric acid), thereby permitting the conclusion that negative and positive balances reflect tissue catabolism and anabolism, respectively.

Methods

Patients. Five patients (three men and two women) with end-stage renal disease were studied in the Clinical Research Center at San Francisco General Hospital (Table 1). They had received chronic hemodialysis therapy for 3 months to 7 years; patients C and E were anephric. They were in general good health without recent intercurrent illness or other complications; none had diabetes mellitus or other systemic disease. All patients met the following criteria: stable clinical course and nutritional state, small interdialytic weight gain (≤1 kg), minimal residual renal function (urea clearance <2 cc/min), and ability to comply with the conditions of a metabolic balance study and to compile accurate prestudy diet records. The purpose of the studies and the potential risks involved were fully explained to each patient, and written consent was obtained. The experimental protocol and the consent form received the approval of the University of California Committee on Human Research and the San Francisco General Hospital Clinical Research Center.

Diets and experimental periods. All patients were studied at two levels of dietary protein intake, 1.4 and 0.5 g/kg (Table 1). The higher level was chosen to reflect a usual protein intake in healthy individuals, and the lower level was a previously suggested maintenance protein intake in patients with chronic renal failure [6]. The high protein diet averaged 77% high biologic value protein, and the low protein diet contained 37% high biological value protein. The diets were designed to conform to the tastes of the individual patients and to reflect their usual diets at home. Total energy intake ranged from 20.5 to 30.9 kcal/kg/day throughout the study periods; estimated caloric intake was constant for each patient during each dietary period, and was tailored to match usual caloric intake (Table 1). To maintain a more normal diet pattern at the same energy intake during the low protein period without resorting to the use of formulas or other caloric supplements, ingested protein was of lower biologic value than it was during the high protein period. Four patients began the study on the high protein intake, and one patient initially received the low protein diet. The choice of initial diet was made on the basis of that diet which agreed most closely with the patient's usual protein intake as estimated from diet records kept for the 2 weeks prior to study. All patients received meals at 8 A.M., 12 noon, and 5 P.M., as well as an evening snack at 10 P.M. On dialysis days, breakfast was eaten shortly after the start of dialysis, and lunch was eaten following completion of dialysis. The study diets were well-tolerated by all patients with the exception of one patient (B) who could not eat all the food during the high protein period. All patients received a daily multivitamin preparation (Sigtabs®), mineral supplements (calcium carbonate), and phosphate binders as needed. One patient (E) received an anabolic steroid (fluoxymesterone, 20 mg daily) for treatment of anemia, as well as maintenance steroid replacement (dexamethasone, 1.0 mg/day) for adrenal insufficiency.

Sample collections and analyses. Daily urine and stool collections were made throughout each experimental period. Serum was obtained daily for mea-

Table 1. Diet characteristics in five chronically hemodialyzed patients undergoing nitrogen balance measurements

Patient	Sex	Age *yr*	Wt *kg*	Period[a]	Protein			Calories	
					Total *g*	Per kg body wt *g*	%HBV[b]	Total	Per kg body wt *kcal*
A	M	65	82.5	I	115.6	1.40	83	2,047	24.8
				II	43.1	.52	42	2,050	24.8
B	F	62	54.7	I	—	—	—	—	—
				II	25.5	.47	38	1,122	20.5
C	M	62	69.0	I	98.2	1.42	77	1,960	28.4
				II	30.8	.45	31	1,931	27.9
D	F	49	70.1	I	84.7	1.21	81	1,752	25.0
				II	34.7	.49	54	1,743	24.9
E	M	35	55.5	I	81.9	1.47	68	1,714	30.9
				II	28.5	.51	20	1,705	30.7

[a] Period I: High protein diet; Period II: low protein diet
[b] %HBV: percent of dietary protein that was of high biologic value (animal or dairy protein)

surement of urea nitrogen (SUN), creatinine, and uric acid; in addition, postdialysis samples were collected on treatment days. A duplicate diet for each period was homogenized and an aliquot taken for analysis. Urine, when available, and stool samples were pooled into 7-day periods and analyzed for total nitrogen by the micro-Kjeldahl method of Block et al, with 1-g aliquots [7]. Aliquots of total dialysate collections from each dialysis, and of diet from each diet period (with the exception of patient B's diet during the high protein period), were also analyzed for total nitrogen by the same method. All solid samples were assayed in triplicate and liquid samples in duplicate. Recovery of added nitrogen averaged 95 ± 5%. Creatinine, urea nitrogen, and uric acid in serum, urine, and dialysate were measured using standard methods for the autoanalyzer [8–10].

The experimental diet was administered on day 0, and balance measurements were made on days 1 through 6. The diet was then changed on day 7, and balance measurements were repeated on days 7 through 13. The period of high protein ingestion is called period I, and consisted of 4 nondialysis days and 2 days in which hemodialysis took place according to the patient's usual treatment regimen. The period of low protein ingestion is called period II, and consisted of 4 nondialysis and 3 dialysis days. As stated above, period II followed period I in four of the five patients.

Calculations: Nitrogen mass balance. To determine the quantitative relationship between urea nitrogen production and protein catabolism, it is necessary to make independent measurements of both net protein catabolic rate (PCR) and urea nitrogen appearance or generation rate (G_u). PCR was calculated from nitrogen mass balance measurements as follows. Body nitrogen (N) accumulation (or loss) over a time period Δt from t_1 to t_2 is determined by the balance between N intake (N_I) and N loss (N_O):

$$[\text{Body N accumulation}]_{\Delta t} = [\text{body N content}]_{t_2} - [\text{body N content}]_{t_1} = [N_I]_{\Delta t} - [N_O]_{\Delta t} \quad (1)$$

Body N content can be considered to exist in two major compartments, a relatively stable amount of N in tissue proteins (N_T), and a more labile pool of nonprotein N from protein catabolism (N_{Cat}). For the purposes of these studies, N_{Cat} is taken to be the amount of N contained in urea, creatinine, and uric acid dissolved in body fluids, and mention of these solutes refers to their N contents. Substitution of these terms into Equation 1 leads to

$$[N_T + N_{Cat}]_{t_2} - [N_T + N_{Cat}]_{t_1} = [N_I]_{\Delta t} - [N_O]_{\Delta t} \quad (2)$$

which, for the interval Δt can be rewritten as

$$\Delta N_T = N_T - N_O - \Delta N_{Cat} \quad (3)$$

where ΔN_T is tissue nitrogen balance, referred to subsequently as TNB. In these studies, the sole source of N_I was dietary protein intake (DPI), and it was measured as total N in aliquots of homogenized diet as described above. N loss occurred through urinary (N_U) and fecal (N_F) N excretion, and through loss of N in dialysate (N_D) occurring on dialysis days:

$$N_O = N_U + N_F + N_D \quad (4)$$

N loss via these routes was measured from total N determinations of collected samples as described; N losses from skin, sweat, and breath were ignored in these studies. The change in the body pool of N_{Cat} during the balance interval was determined from the changes in concentration (C) of urea (u), creatinine (cr), and uric acid (ua) in plasma from the beginning to the end of the interval multiplied by each solute's volume of distribution (V):

$$\Delta N_{Cat} = \Delta C_u V_u + \Delta C_{cr} V_{cr} + \Delta C_{ua} V_{ua} \quad (5)$$

V for these solutes was calculated using a computer-assisted single-pool model of solute kinetics in patients undergoing IDT [11, 12]; verification of the model predictions for V_u with that measured directly by urea infusion will be the subject of a separate report.[1]

Thus, all unknown terms on the right side of Equation 3 could be calculated from easily measured variables, thereby permitting solution for TNB. Since biologic protein on average consists of 16% N, all N terms can be expressed as protein equivalents by multiplying by 6.25. Net PCR is defined as the sum of the N_O and N_{Cat} terms of Equation 3, expressed as protein equivalents:

$$PCR = 6.25\ (N_O + \Delta N_{Cat}) \quad (6)$$

[1] Numerous studies [13–16] have suggested that the urea space is a single compartment closely equated to total body water, and that distribution volume for creatinine closely resembles that for urea [17, 18], but that uric acid is distributed in a volume about half the total body water [19]. Although kinetics of creatinine and uric acid in dialysis patients are more accurately described using multipool models [20–22], errors introduced by estimating distribution volumes from single-pool kinetics will be small, particularly since over 90% of ΔN_{Cat} was accounted for by urea N in these studies.

Urea nitrogen generation. An independent measure of urea nitrogen appearance or generation (G_u) was obtained by means of a kinetic model describing urea accumulation between dialyses and removal during dialysis [11]. This model assumes single-pool distribution of urea in the body. Agreement between the predictions of the kinetic model and direct calculation of G_u from urea nitrogen mass balance is excellent and will be presented in a separate report. This measurement of G_u represents an estimate of net urea nitrogen generation, and it may be considered to be similar to the urea appearance rate as defined by Walser et al [23].

All data are presented as mean ± 1 SD; statistical significance of differences between groups was assessed with Student's *t* test for paired or unpaired data.

Results

Nitrogen balance on high and low protein intakes. Observations on nitrogen balance were available for a total of 24 days in four patients ingesting the high protein diet (period I) and for 33 days in five patients during the low protein period (period II). The results of these determinations are shown in Table 2. During period I, cumulative TNB was positive in two patients, about even in a third, and negative in the other; mean cumulative TNB for the whole group was +5.7 ± (SD) 7.8 g of N per patient for the 6 days of study or +0.95 ± 2.6 g of N per patient per day; these values are not significantly different from zero. During period II, cumulative TNB was negative in each of the five patients. The mean value was −12.1 ± 8.8 g of N per patient for the study period, a value significantly less than zero ($P < 0.05$). This is equivalent to 11.5 g of negative protein balance per patient per day, or 75.6 g of tissue protein lost per patient for the entire period. Stool nitrogen loss did not differ significantly between the two periods ($P > 0.10$).

Table 2 and Fig. 1 show the data on daily TNB for the patients during the two study periods. During period I, daily TNB was negative on 6 of 8 dialysis days and was only slightly positive (<0.8 g of N) on the other 2 days. During period II, TNB was negative on 12 of 13 dialysis days (Table 2). Overall, TNB on dialysis days during both periods averaged −2.5 ± 2.4 g of N per patient per day, a value significantly less than that of +0.5 ± 2.4 g of N per patient per day observed on nondialysis days ($P < 0.001$). This same difference is observed if the data within either period I or period II alone are considered. During period I, TNB was −1.4 ± 2.2 g of N per patient per day on dialysis days and +2.1 ± 1.9 g of N per patient per day on nondialysis days ($P < 0.001$); during period II the corresponding figures were −3.1 ± 2.3 and −1.0 ± 1.8 g of N per patient per day, respectively ($P < 0.05$). Although TNB was more negative on dialysis days in period II than it was in period I, this difference did not reach statistical significance ($P > 0.10$). On the other hand, TNB on nondialysis days during period I was significantly greater (more positive) than was the corresponding value observed during period II ($P < 0.001$).

In view of this negative TNB on dialysis days, it

Table 2. Daily tissue nitrogen balance in five patients receiving intermittent dialysis therapy[a]

Day	Patient A	B	C	D	E	Mean daily nitrogen balance
Period I: High protein intake						
1	+ 5.88	—	+ 3.95	+ 3.70	0.00	+ 3.38
2	+ 4.31	—	+ 2.93	+ 0.94	0.00	+ 2.05
3[b]	+ 0.72	—	− 5.42	− 0.28	− 1.50	− 1.62
4	+ 2.56	—	− 0.05	+ 1.43	− 1.30	+ 0.66
5[b]	− 0.40	—	− 3.98	+ 0.77	− 1.30	− 1.23
6	+ 2.35	—	+ 2.72	+ 2.02	+ 2.80	+ 2.47
Weekly total	+15.42		+ 0.15	+ 8.58	− 1.30	+ 5.71
Period II: Low protein intake						
7[b]	—	—	− 5.88	− 4.69	− 1.89	− 4.15
8	− 1.43	−0.86	− 1.25	− 0.32	− 3.30	− 1.43
9	+ 1.09	−0.26	− 0.97	+ 0.13	− 1.41	− 0.38
10[b]	− 0.66	−3.03	− 7.69	− 1.46	− 2.80	− 3.12
11	+ 0.39	−0.57	− 0.75	− 0.64	− 2.41	− 0.79
12[b]	− 1.60	−2.02	− 5.56	− 3.79	+ 0.15	− 2.56
13	+ 1.26	−0.61	− 0.76	+ 0.27	− 7.31	− 1.43
Weekly total	− .95	−7.35	−22.86	−10.50	−18.97	−13.86

[a] Values are in grams of nitrogen per day.
[b] Days on which hemodialysis was carried out.

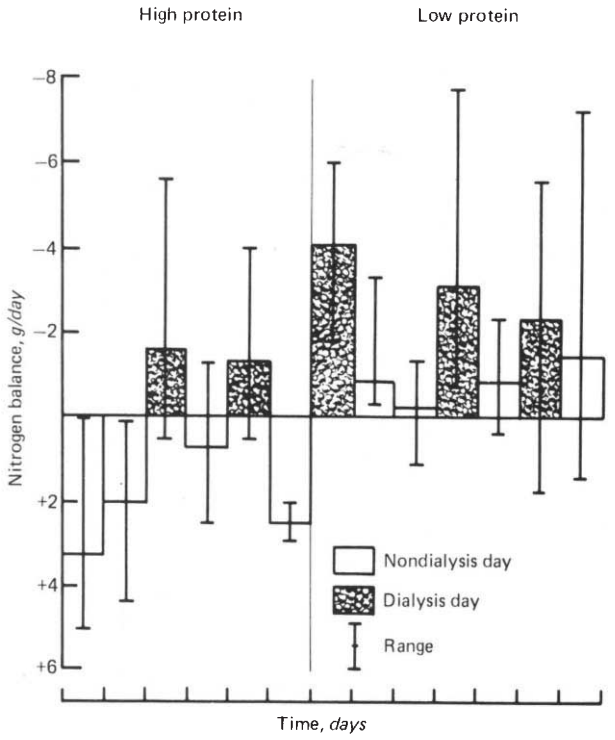

Fig. 1. *Daily tissue nitrogen balance in five patients receiving intermittent dialysis therapy during ingestion of high (1.4 g/kg) and low (0.5 g/kg) protein intakes.*

is possible that the greater number of dialyses included in period II could contribute to the cumulative negative TNB observed in this period. That this is not entirely so, however, is shown by determining average daily TNB for days 8 through 13 alone and comparing this to the value for days 1 to 6 (period I), each period consisting of 2 dialysis and 4 nondialysis days. Daily TNB for days 8 to 13 averaged -1.6 ± 1.0 g of N per patient per day, still significantly less than the corresponding value for period I ($P < 0.005$).

This catabolic effect of dialysis is shown in another form in Fig. 2. Here, PCR has been calculated according to Equation 6 and compared to daily protein intake. PCR exceeds DPI on most dialysis days, suggesting breakdown of endogenous protein, but PCR is less than DPI on nondialysis days.

The daily variations in TNB, and its individual components, are shown for a representative patient-study in Fig. 3. Nitrogen balance in grams per day is plotted on the ordinate for each day of study. Nitrogen intake is shown as the lowest (most positive) solid line, and all nitrogen output is plotted as a vertical column above this line. On nondialysis days, this consists of stool nitrogen, urine nitrogen, and adjustment for the increase in catabolite nitrogen in body fluids. Nitrogen balance for the day is then given by the uppermost solid line. On dialysis days, nitrogen output consists of dialysate (hatched area) as well as stool and urine nitrogen. The decrease in catabolite nitrogen in body fluids on dial-

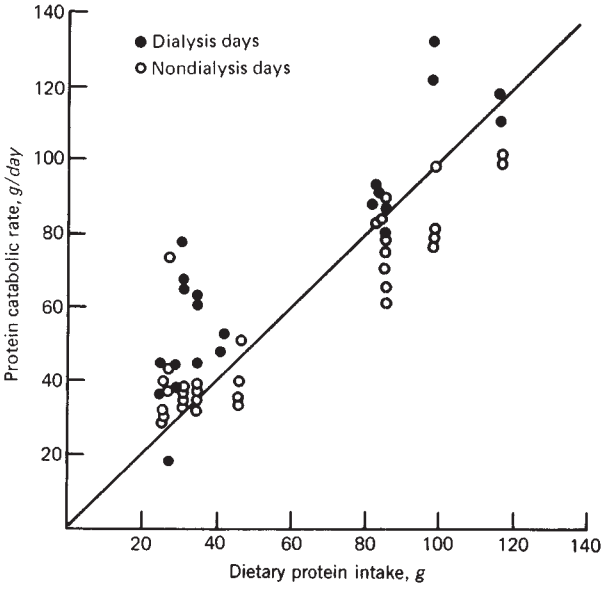

Fig. 2. *Relationship of protein catabolic rate (PCR) to dietary protein intake (DPI) in five patients undergoing chronic hemodialysis treatment.* On dialysis days (*closed circles*), PCR generally exceeds DPI, as shown by the majority of these points clustering above the line of identity. PCR on nondialysis days (*open circles*) is above the line of identity at lower DPI, and below the line at higher DPI. PCR in dialysis days, however, is higher than on nondialysis days regardless of DPI.

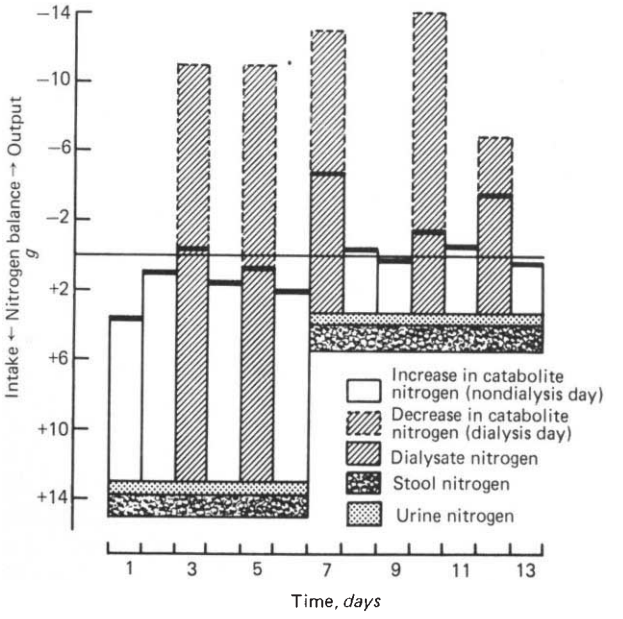

Fig. 3. *Detailed nitrogen balance measurements in patient D during high (days 1 to 6) and low (days 7 to 13) DPI.* Nondialysis days are shown by *clear bars*, dialysis days by *shaded bars*. For details, see text.

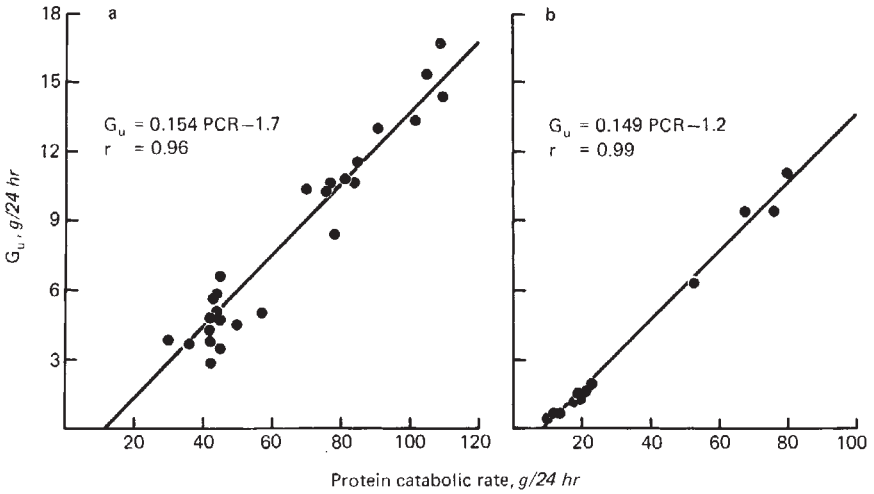

Fig. 4. *Relationship between urea nitrogen generation rate (G_u) and protein catabolic rate at different levels of protein intake.* G_u and PCR were calculated as described in Methods. *Panel a* shows the relationship in five patients receiving IDT (this study). *Panel b* shows the relationship as derived from data presented by Cottini et al [24] in patients with chronic renal insufficiency not receiving IDT.

ysis days is subtracted from dialysate nitrogen; the magnitude of this correction is indicated by the area in broken lines. Tissue nitrogen balance is then shown again by the uppermost solid line. It can be seen that during period I TNB on nondialysis days was always positive, and averaged +2.0 g of N per day for these 4 days of the study period. During period II, TNB on nondialysis days was close to zero. By contrast, TNB was negative on 4 of the 5 dialysis days, the sole exception occurring on 1 dialysis day during period I.

Relationship between urea generation rate and protein catabolic rate. Daily G_u was calculated according to the kinetic model (see Methods), and the results were compared with the simultaneously determined PCR (Equation 6). The results are shown in Fig. 4a, where G_u is plotted against PCR, each in grams per 24 hours. Over the range of PCR observed in these studies (30 to 110 g/24 hr), the expected strong correlation between these two variables was observed (G_u = 0.154 PCR − 1.7, r = 0.96). On average, each 100 g of protein catabolized gave rise to 15.4 g of urea nitrogen, a figure close to the 16 g expected if urea were the sole end-product for nitrogen from protein catabolism. That this relationship is not simply a consequence of the nonsteady-state conditions of IDT is suggested by the plot shown in Fig. 4b. Here, G_u and PCR have been derived from data in nondialyzed patients with stable chronic renal insufficiency presented by Cottini and associates [24]. Essentially the same relationship between G_u and PCR exists in the stable uremic patient as exists in the patient undergoing IDT. The negative intercepts of these lines confirm that some N excretion occurs through nonurea routes, chiefly as N in creatinine, uric acid, and stool. This accounts for a residual PCR of 11 g/24 hr in our patients when G_u is zero. This value was constant over the range of PCR observed, as shown in Fig. 5. The value of this obligatory nonurea nitrogen excretion averaged 2.2 ± 0.6 g/24 hr in these five patients, and it is close to the value of −1.7 g/24 hr obtained for the Y intercept of the relationship in Fig. 4a.[2]

Effect of hemodialysis on urea generation rate. The relationship between G_u and PCR (Fig. 4), and the observation that net PCR was higher on days on which hemodialysis occurred (Fig. 2), led to the prediction that G_u would also be higher on dialysis than nondialysis days. This was in fact the case. During period I, G_u on nondialysis days averaged 9.9 ± 3.2 g/24 hr, significantly less than the value of 12.7 ± 3.1 g/24 hr calculated for dialysis days ($P < 0.005$). During period II, the figures were 4.0 ± 1.0 g/24 hr on nondialysis days vs. 5.6 ± 1.7 g/24 hr on dialysis days ($P < 0.05$). To examine further this increased G_u on dialysis days, SUN was measured at frequent intervals following the completion of a dialysis during each period for each patient, and the rate of urea production was determined for the interval from the end of dialysis to the time of the

[2] It is likely that the magnitude of this nonurea nitrogen excretion will vary according to body size.

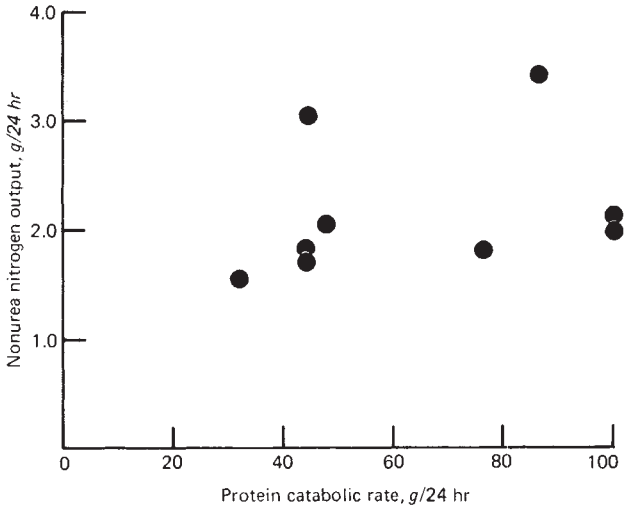

Fig. 5. *Relationship of average daily nonurea nitrogen appearance (the sum of creatinine, uric acid, and stool nitrogen) to protein catabolic rate in five patients receiving IDT.* Each patient was studied on a low protein (0.5 g/kg) diet, and four patients were studied on a high protein (1.4 g/kg) diet. Overall, no relationship could be shown between nonurea nitrogen appearance and simultaneous PCR.

blood sample. The results of these calculations are shown in Table 3; for comparison, G_u for the 24 hours preceding the dialysis is also shown. Following dialysis, urea generation abruptly increased in all patients compared to the previous day's value. This increase was observed chiefly during the first 8 hours following completion of dialysis, and occurred regardless of the level of protein intake.

Discussion

Initial observations of dietary requirements in IDT patients suggested that a protein intake of at least 0.75 g/kg was necessary to support nitrogen balance [4, 5]. Some of these studies, however, were carried out in patients just beginning IDT [4, 5], whose nutritional requirements may have been greater than those of the more stable, chronically dialyzed patient, and conclusions were based in other studies on observations made in patients studied as outpatients rather than on the metabolic ward [4]. These early investigations were also carried out with older dialysis equipment and less frequent dialysis schedules [4, 5].

Table 3. Kinetically measured urea generation rate (G_u) at increasing intervals following completion of dialysis

Patient	Period	Preceding day G_u *mg/min*	Postdialysis G_u *mg/min* At 1.5 hr	At 3 hr	At 5 hr	At 8 hr	At 20 hr
A	I	9.6	14.9	14.9	20.4	16.7	11.6
	II	4.0	9.9	9.9	11.2	6.5	4.1
B	I	3.4	18.2	15.6	12.6	10.2	4.4
	II	2.1	2.6	2.6	3.9	2.9	2.6
C	I	7.5	16.0	18.0	14.4	14.3	10.1
	II	2.5	8.0	—	4.8	3.8	3.2
D	I	6.7	14.4	9.6	10.3	8.1	7.0
	II	2.3	6.2	6.2	4.6	4.6	2.4
E	I	8.0	14.6	11.5	11.3	11.4	7.7
	II	2.6	4.2	6.3	6.3	5.5	4.6

The present studies demonstrate that ingestion of 0.5 g of protein per kg of body wt per day results in negative nitrogen balance, and thereby support the conclusions of the earlier investigations. Since our patients were stable IDT patients undergoing dialysis three times per week with more efficient dialyzers, these conclusions therefore apply to contemporary standards of dialytic treatment. Several factors in our studies, however, must be considered in reaching this conclusion. The period of study on the low protein intake was only a week long, a period perhaps too short to allow full adjustment to this level of intake to occur. Observations in nondialyzed patients with chronic renal failure have demonstrated that nitrogen balance on a low protein intake is achieved only after a prolonged period of equilibration [6]. If this applied to our patients, then a 1-week period would clearly have been insufficient to assess the consequences of the low protein diet. The earlier studies of nitrogen balance in IDT patients avoided this problem by carrying out balance measurements over several weeks' time [4, 5]. In addition, one must question whether IDT patients, with their large, cyclical oscillations in blood solute concentrations and urea pool size, ever achieve equilibration in the same sense as do nondialyzed uremic patients. Another factor which could have influenced these results was the low fraction of total ingested protein that was of high biologic value during period II. Utilization of dietary protein in uremia depends in part on the biologic value of the protein [3], and the low value protein during period II could have contributed to the negative nitrogen balance during this period. The diets used in these studies were selected in an attempt to maintain constant caloric intake without having to resort to caloric supplements; the consequence of this was a reduction in the quality of the ingested protein. Such a pattern, however, is typical of patients given protein-restricted diets as outpatients [4].

A third factor which could have influenced these results relates to the caloric intake of our patients. In nondialyzed uremics, nitrogen utilization is facil-

itated by a calorie intake of at least 35 kcal/kg [3, 25], and this figure is also recommended for dialysis patients [26]. Thus, the lower caloric intakes of our patients during period II could have been involved in the negative nitrogen balance that was observed. This nitrogen-sparing effect of calories in uremic patients is usually demonstrated in circumstances of extreme protein restriction (0.25 to 0.3 g/kg), however, and may not be as pertinent for less severe degrees of protein restriction. The caloric intakes of our patients were selected on the basis of their usual dietary patterns, and were achieved without resorting to caloric supplements. Hence, these results may be a more accurate reflection of the usual dietary patterns of IDT patients.

The cumulative negative nitrogen balance observed in these studies during period II occurred because of the predominant effect of negative nitrogen balance on dialysis days compared to the approximately neutral balance on nondialysis days. This effect of dialysis was also observed during period I, the high-protein period, where cumulative nitrogen balance was about even because positive nitrogen balance on nondialysis days was able to offset the negative balance which occurred on dialysis days. The precise factor(s) about dialysis responsible for this negative TNB on dialysis days are not clear from this study. Dialysis results in marked fluctuations not only of blood solute concentrations, but also in levels of metabolic hormones and fuels [27, 28]. In particular, amino acids are lost into dialysate in large quantities; this can amount to 1 to 3 g of amino acid N for each dialysis [1, 29–31]. The average overall negative nitrogen balance on dialysis days in these studies was −2.4 g of N per patient per day, an amount conceivably accounted for by amino acid N loss in dialysate. Although measurement of α-amino N in dialysate was not made in these experiments, an estimate of N lost in this form can be made. In dialysate, N contained in urea, creatinine, and uric acid amounted on average to 94% of total N measured by the Kjeldahl method. If the remaining 6% were all in the form of amino acid N, then an average of 1.4 g of N would be lost in this form per dialysis. These estimates thus indicate that 60% of dialysis-related negative nitrogen balance could result from loss of amino acid N in dialysate.

Data from this and other studies, however, suggest that other factors may occur to help explain the dialysis-induced negative TNB. Losses of amino acids into dialysate result in only a modest decrease in blood concentration of some amino acids, no change in others, and an actual increase in still others [28–30]. This observation suggests that the losses in dialysate are occurring in large part from an intracellular amino acid pool. Bergstrom et al measured intracellular amino acid concentrations in muscle biopsy specimens from uremic patients after peritoneal dialysis, and they found few differences from the predialysis values [32]. This suggested to them that catabolism of intracellular proteins occurred in response to dialysis to maintain intracellular amino acid pools despite the loss of amino acids in dialysate [32]. Ganda et al speculated that the normal or elevated blood concentrations of some amino acids following dialysis could reflect the accelerated release of these compounds from tissues such as muscle or liver [28]. If this occurred without marked change in intracellular amino acid concentrations [32], then ongoing catabolism of cell protein would be necessary to replace the amino acids released into the blood. Loss of glucose from blood into glucose-free dialysate, as used in these studies, causes a reduction of plasma glucose [28, 33], and stimulates gluconeogenesis [33]. Since alanine from skeletal muscle is a major amino acid substrate for hepatic gluconeogenesis [34], it is possible that glucose loss during dialysis could serve as a stimulus to protein catabolism by its effect to increase hepatic gluconeogenesis. Alanine release from skeletal muscle is increased in uremic patients, but dialysis did not appear to have an added effect (GARBER AJ: personal communication). Interestingly, Kopple and associates found that addition of glucose to the dialysate reduced by half the amount of amino acids lost during dialysis [31].

The data on postdialysis urea nitrogen generation (Table 3) are consistent with the view that protein catabolism is stimulated by dialysis. This possibility had been suggested earlier by Rubini et al on the basis of their observation of a slower rate of rise of SUN as the interval between dialyses became more lengthy [35]. In the present studies, G_u on the average more than doubled in the period immediately following dialysis, when compared to the value for the preceding 24 hours (Table 3). This enhanced urea appearance was calculated from the change in SUN concentration multiplied by the distribution volume for urea. Consequently, more marked rises in SUN immediately following dialysis could reflect a "rebound" phenomenon caused by entry of urea from a poorly cleared second pool, and not be due to an actual increase in the rate of urea generation. This, however, does not seem likely. Studies of urea kinetics using multicompartmental models have shown that any equilibration between com-

partments which occurs after dialysis does so extremely rapidly, less than 1 hour [20, 36], and that any error introduced by using a single- rather than double-pool model amounts only to about 2% [22]. The increase in G_u after dialysis was much greater than that consistent with any error of this magnitude, and could be observed for at least 8 hours, far longer than any equilibration between compartments should take. In agreement with this, we have found that infused urea in these same patients resulted in stable elevations of SUN as soon as 1 hour after infusion (BORAH MF et al: unpublished observations). These considerations suggest that the accelerated rate of rise in SUN in the postdialytic period is therefore a reflection of stimulated G_u resulting from increased PCR on dialysis days. This may help to account for the negative TNB observed on these days.

The fundamental relationship between net protein breakdown and urea nitrogen generation (Fig. 4) was preserved in patients undergoing IDT, and was not appreciably different from that seen in nondialyzed uremic patients reported by Cottini, Gallina, and Dominguez [24]. This relationship may be useful in the nutritional management of patients receiving IDT. In the stable patient, calculation of G_u by kinetic or other methods will yield an estimate of PCR according to the relationship shown in Fig. 4a. As can be seen from Equations 3 and 6, PCR will be exactly equal to DPI when TNB is zero, i.e., when the patient is in the steady state and is neither gaining nor losing tissue protein. Thus, an accurate estimate of DPI can be obtained without resorting to tedious dietary history taking. Indeed, we have found that DPI estimated in this fashion in stable patients is more accurate than are routine diet surveys conducted by an experienced dietitian [37, 38]. Using this estimate of DPI, we can then counsel the patient to increase protein intake if PCR is low, or decrease it if PCR is high. From the observations of this and other studies [4, 5], an appropriate target value for DPI (and PCR) would appear to be about 1.0 to 1.1 g/kg/24 hours. Intake of this magnitude should be sufficient to afford maximal support of TNB without resorting to excessive protein catabolism and the attendant risk of exacerbating uremic symptoms.

Of even greater potential importance is the nutritional information which this kinetic approach may provide in cases where nitrogen balance is not in the steady state (dialysis of acute renal failure; dialysis of the pediatric patient). Comparison of protein intake to kinetically determined PCR in such patients should give an accurate estimate of the extent of nonzero nitrogen balance and thereby direct attention to possible changes in nutritional therapy [38].

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