The optimization of continuous ambulatory peritoneal dialysis

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CASE PRESENTATION

A 55-year-old Greek Canadian, a restaurant owner, developed end-stage renal disease secondary to proliferative glomerulonephritis of 3 years’ duration. Because he was fatigued, had a poor appetite with occasional morning nausea, and could not sleep well, he began continuous ambulatory peritoneal dialysis (CAPD) 5 years ago through a surgically implanted Toronto Western peritoneal catheter. At that time his weight was 71 kg and body surface area 1.76 m². He had substantial residual renal function, with a 24-hour creatinine clearance of 9.0 ml/min, a urea clearance of 4.3 ml/min, and a urine volume of 1100 ml/day. Initial biochemical investigations showed a serum albumin of 3.5 g/dl (Bromuresol green method); hemoglobin, 10.1 g/dl; and hematocrit, 33%. He was started on a “standard” CAPD regimen of 2-liter exchanges four times daily. At the end of the second week, clearance measurements with the Adequest® program were as follows: D/P creatinine, 0.85; KT/V (urea), 2.57 (1.07 renal and 1.5 peritoneal); weekly creatinine clearance (WCC) corrected for 1.73 m² BSA, 113 liters (65 liters renal and 48 liters peritoneal); and normalized equivalent of protein nitrogen appearance (NPNA), 0.8 g/kg/day. The blood urea was 20 mm/liter; serum creatinine, 416 μM/liter (4.7 mg/dl); and blood pressure, 150/80 mm Hg.

For the next two years he did well on CAPD. He felt well and continued working in his restaurant. His appetite was good, he slept well, and he had an active sexual life. For the first year, his blood pressure was normal without antihypertensive medication, but he required medication thereafter. He had no episodes of peritonitis and gained 5 kg. However, his urine output gradually declined despite large doses of furosemide. At the beginning of the third year, despite an increasing dose and number of antihypertensive medications, he complained of progressive fatigue, anorexia, and ankle swelling. He was hypertensive (blood pressure, 180/100 mm Hg), and his urine output was negligible. His serum albumin had decreased to 3.0 g/dl, the blood urea had decreased to 12 mm/liter, and the serum creatinine was 1100 μM/liter (12.5 mg/dl). On repeat assessment, his clearances were KT/V, 1.55 (1.45 peritoneal and 0.1 renal), and WCC, 48 liters (42 liters peritoneal and 6 liters renal). His NPNA had decreased to 0.65 g/kg/day. His weight had increased by 3 kg and he was edematous.

His CAPD prescription was increased to 2.5 liters 4 times daily, after which his KT/V increased to 1.75 (1.65 peritoneal and 0.1 renal) and his weekly creatinine clearance to 58 liters (52 liters peritoneal and 6 liters renal). After 3 months, his NPNA remained low at 0.60 g/kg/day. His uremic symptoms and hypertension became worse, and he could not achieve his target weight despite three hypertonic exchanges per day. Average ultrafiltration with 2.5% glucose at four hours was 25 ml, and with 4.25% glucose was 180 ml. Dialysate protein losses were 12 g/day and his serum albumin fell to 2.8 g/dl. Because his condition was getting worse, he was transferred to automated peritoneal dialysis (APD) with 4 × 2.8 liter exchange over nine hours each night and a three-hour 2.5 liter exchange each evening.

On this regimen, his KT/V was 2.1 and creatinine clearance 60 liters/week. Furthermore, his net ultrafiltration increased, he attained his target weight and, after six months, his NPNA had increased to 0.8 g/kg/day, but his serum albumin remained low at 3.1 g/l. Clinically he felt better. He was able to sleep well and he resumed working part-time work in his restaurant. Three months later he received a successful transplant with a cadaveric kidney.

DISCUSSION

DR. DIMITRIOS G. OREOPOULOS (Director, Peritoneal Dialysis Program, The Toronto Hospital—Western Division, and Professor of Medicine, University of Toronto, Toronto, Ontario, Canada): A Nephrology Forum given in 1983 by Dr. Stephen Vas [1] was devoted to the diagnosis and treatment of peritonitis—at that time, the main complication of CAPD. Since then, the introduction of several disconnect systems has decreased the rate of peritonitis substantially. Although it is still a serious complication, peritonitis is no longer the main reason resulting

Presentation of this Forum is made possible by grants from Merck & Company, Incorporated; Astra Pharmaceuticals; Hoechst Marion Roussel, Incorporated; Dialysis Clinic, Incorporated; and R & D Laboratories, Incorporated.

Key words: chronic renal failure, peritoneal dialysis, nutrition, adequacy.

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in discontinuation of CAPD and transfer to hemodialysis (HD). Instead, the main cause for failure of CAPD in Canada currently is inadequate dialysis; 12% of CAPD patients fail for this reason versus 8.6% because of peritonitis [2]. Underdialysis is now common among CAPD patients because an increasing number have been treated with this technique for more than three years, an interval over which residual renal function usually declines to zero.

Today’s patient, a 55-year-old man with high peritoneal permeability (defined by D/P creatinine > 0.80) was started relatively early on dialysis. That is, his endogenous creatinine clearance (Cкр) was 9.0 ml/min. The low serum albumin (3.5 g/dl) at the start of dialysis might have been due to a combination of factors such as proteinuria, about which we have no information, and an inadequate protein intake. His clinical symptoms improved and his elevated blood pressure was controlled by CAPD. In addition, his appetite improved and he gained weight. By the end of the second year, however, he again became uremic and hypertension returned; a further decrease in his serum albumin and a decrease in blood urea indicated low protein intake and confirmed the low NPNA of 0.65 g/kg/day. These changes primarily reflect the decline in his residual renal function with the resulting inadequate clearance of urea and creatinine. An increase in the dialysis solution volume to 10 liters/day did not improve his symptoms or correct his significant ultrafiltration failure secondary to his high transport state (that is, fast glucose absorption causing dissipation of the osmotic gradient responsible for ultrafiltration).

His clinical condition improved, however, after his dialysis technique was converted to APD, an enhanced type of dialysis with short night exchanges of large volumes, and one relatively long (3-hour) exchange during the daytime. His urea and creatinine clearances improved, and his fluid status was better controlled. After six months, his NPNA increased but his serum albumin level remained low. This man’s history demonstrates all the points about adequacy of peritoneal dialysis that I will discuss during this Forum, specifically, the clearance of small molecules (KT/V urea, WCC), the importance of residual renal function, the central role of malnutrition, the phenomenon of high peritoneal permeability and, finally, the importance of fluid/volume overload and its control.

When physicians devise regimens for patients with chronic renal failure, the treatment is optimal if it eliminates all signs and symptoms of the disease and ensures the same life expectancy as they would have in the absence of the disease. With few exceptions, however [3], the life expectancy of dialysis patients is much shorter than that of an aged-matched population, and the term “adequate dialysis” is a compromise that implies an “acceptable outcome,” which one hopes will be close to optimal [4].

In the 1960s and 1970s, clinicians based their definitions of adequacy of dialysis on their clinical acumen and a review of classic biochemical parameters such as blood urea, creatinine level, and hematocrit. These parameters remain valid, albeit insufficient, criteria for determining the adequacy of dialysis. Symptoms and signs of underdialysis such as nausea, vomiting, fatigue, weakness, insomnia, and restless legs also should be rigorously sought in assessing the adequacy of dialysis. These latter criteria can be due to other causes, however, and it is difficult to quantitate them. For these reasons, these symptoms and signs are not sufficient for defining adequacy and predicting outcome. Furthermore, one might not recognize underdialysis early if one bases the diagnosis only on clinical and biochemical parameters, and it might not be possible to “catch up” if the dose of dialysis is not increased soon after underdialysis begins. We therefore need now objective, quantifiable parameters by which we can assess adequacy of dialysis and detect underdialysis before clinical symptoms and signs appear.

In this presentation I will discuss only three major dialysis-related factors that can predict outcome, and I will discuss the relationship among them: small-solute clearances, nutrition, and fluid/volume control. These three factors probably are interrelated, and achieving adequate dialysis requires that we address all three together. Optimization of all three clearly will improve outcomes for all our CAPD patients. I will not examine the effect of cardiovascular disease, lipid abnormalities and their control on dialysis outcome, or issues concerning quality of life, not because they are not important, but because I believe their impact on patient survival deserves a separate discussion.

### Small-solute clearances

The National Cooperative Dialysis Study (NCDS), the first attempt at providing objective parameters of adequacy [5], showed that parameters derived from urea kinetic modeling (UKM) best describe the adequacy of hemodialysis. According to that study, indicators of a low morbidity are an NPNA > 1 g/kg/day, and a time-averaged concentration of BUN ~50 mg/dl. Based on the results of the NCDS study, Gotch and Sargent developed the concept of KT/V that integrated efficiency of solute clearance (K), treatment time (T), and patient size (V) [6]. This dimensionless measure of fractional clearance of body water for urea has been accepted and validated as an index of adequacy for hemodialysis. After establishing that KT/V was a reliable predictor of outcome in hemodialysis, it was reasonable to extrapolate these same concepts to the prediction of outcome in patients on peritoneal dialysis. In hemodialysis, the rate of solute removal changes during dialysis because the concentration of blood urea decreases during dialysis. In CAPD, because the blood urea concentration is rela-
tively constant, clearance and solute removal stay about the same and are related in a linear fashion. In most CAPD patients, the urea in dialysate and plasma achieve virtual equilibrium. Thus, given the stable blood urea concentration, the drain volume is equivalent to urea removal (KT) [4]. This constant relationship between blood levels and removal rate allows continuous treatments like CAPD to remove the same volume of solute per week as does thrice-weekly hemodialysis sessions, even though the clearance rates are substantially lower: 5 to 10 ml/min for CAPD versus 200 to 300 ml/min for HD [7, 8].

Measuring KT/V in PD patients. After repeated measurements of KTrp/V, which includes both the contribution of the renal (KTr/V) and the peritoneal clearance (KTP/V), the coefficient of variation is 8% [10]. The greatest variability is seen with KTr/V (35%); only moderate variability is seen for KTP/V (7%) [10]. The renal component varies even more widely when the amount of urine excreted in 24 hours is very low (1–2 voidings/day), in which case calculations of clearance should be based on a 48-hour urine collection.

The peritoneal component (KTP/V) of KTrp/V varies chiefly because of variations in the calculation of V, that is, the volume of distribution of urea. For practical purposes, this is considered equal to the total-body water, although studies using isotopes of urea found that urea distribution space can be smaller than total-body water space by approximately 12% to 14% [11]. Total body water (V) can be estimated as a fixed fraction of body weight (60% of BW for men and 55% of BW for women) or an average of 58% for any individual, or by anthropometric formulas such as the Watson formula, which most investigators now consider the method of choice [12].

Because no agreement has been reached concerning the weight to be used in estimating V, different results of KT/V have been reported. In general, estimates of V based on actual weight should be most accurate when actual and desired (ideal) weight do not differ greatly [12]. In obese patients (wt > 20% of ideal BW), V should be calculated using ideal BW [12]. Otherwise, the V will be overestimated and KT/V underestimated. In wasted patients, KT/V will be misleadingly high if one uses actual body weight for the calculation of V; instead, to derive a KT/V indicative of a dialysis dose related to a healthier weight, one should use standard body weight, which can be obtained after calculating V with the Watson formula and dividing it by 0.58 [9]. The recommendation of the Dialysis Outcome Quality Initiative (DOQI) work group for the malnourished patient, in whom no other cause of malnutrition is discovered, is to increase the dose of dialysis by multiplying the target KT/V by the ratio V desired/V actual [13].

Comparing KT/V targets in PD and HD: A paradox. Although it is logical to attempt to extrapolate UKM data from patients treated with HD to those treated with PD, it is paradoxical that the typical KT/V delivered to CAPD patients is between 1.2 and 2.4 per week [14]. By HD standards, this figure is well below the accepted level of 3.0 to 3.6/week; however, numerous comparisons of the two modalities have shown no difference in morbidity and mortality. Keshaviah and colleagues have tried to resolve this paradox by invoking the peak concentration hypothesis [15], which asserts that the success of CAPD is related to its continuous, steady-state nature. If uremic toxicity is associated with the peak concentration of BUN rather than its time-average value, then in hemodialysis patients, for approximately one-half of the week the BUN will exceed the time-average urea concentration (TAC). Therefore, for hemodialysis the KT/V would have to be higher than that of CAPD to keep the peak BUN at the same level and achieve equivalent control of uremia [16]. On the basis of this hypothesis, Keshaviah calculated that, for a hemodialysis KT/V of 1.3 per treatment, the corresponding weekly CAPD KT/V is 2.0. (Fig. 1) [15]. Other possible reasons why CAPD patients appear to need less urea clearance compared to those on hemodialysis include the lack of changes in hydration and blood pH, the high clearance of large or middle molecules, a less catabolic environment, and better preservation of residual renal function (RRF).

The rate of decline in residual renal function appears slower in PD than in HD [17, 18]. Possible reasons for this difference are: (1) stable high BUN levels in CAPD; (2) absence of marked fluid shifts permitting hemodynamic stability and avoidance of glomerular ischemia; (3) reduced dietary protein intake combined with increased protein losses in dialysate; (4) absence of cytokine-medi-
ated responses to extracorporeal exposure to dialysis membrane; and (5) the continuous volume-expanded state that often is associated with CAPD [17, 18]. I will return to the importance of residual renal function in small solute clearance and nutrition in a few moments.

**What level of KT/V (urea) gives an acceptable outcome?** Churchill recently reviewed all studies that attempted to determine adequate targets of weekly KT/V urea [19]. He divided the studies into three groups: those that base KT/V targets on theoretical constructs, prospective studies using univariate analysis, and prospective studies using multivariate analysis. Table 1 summarizes the results of the theoretical constructs and those based on cohort studies with univariate analysis. With a few exceptions, most studies seem to indicate that a weekly KT/V ≥ 1.9 provides better survival and a better clinical outcome.

Four prospective controlled studies have used multivariate analysis to assess the relationship between KT/V and outcome and to define other independent variables that predict increased risk of death [20–23]. Techan et al, who studied 51 patients over a period of five years, found that decreased serum albumin, older age, longer time on CAPD, and decreased KT/V were associated with decreased survival [20]. Genestier and colleagues found that older age, cardiovascular disease, diabetes, worse comorbidity score, and lower initial KT/V and WCC were associated with a worse survival in their study of 201 patients [21]. Maiorca and coworkers, who studied 68 prevalent patients over three years, determined that older age, peripheral vascular disease, dyslipidemia, arrhythmia, initial serum albumin < 3.5 g/dl, and weekly KT/V < 1.7 were detrimental factors [22]. The presence of residual renal function and a KT/V > 1.98 were associated with significantly better survival.

Although not a randomized controlled trial, the CAN-USA study provides the best support for a correlation between small-solute clearance and patient outcome [23]. This study followed for a minimum of two years 680 patients who started CAPD in 14 centers in Canada and the US. Analysis of survival showed that, during these two years, both dialysis dose and non-dialysis-related factors were related to the likelihood of death. When the Cox proportional hazards model was used with dialysis dose and nutritional status as time-dependent covariants, the relative risk of death increased with increasing age, insulin-dependent diabetes mellitus (IDDM), cardiovascular disease, decreasing serum albumin, poor nutritional status, and being dialyzed in the US. Higher clearance, inclusive of residual renal function, was associated with better patient survival, ability to continue treatment with CAPD, and less frequent hospitalization. The expected two-year patient survival based on sustained KT/V and creatinine clearance steadily increased over the range of values studied; no plateau effect was seen at the highest doses of KT/V (2.3) or creatinine clearance (95/liter/week/1.73 m² BSA); hence no minimum target could be set. The higher the weekly KT/V urea and creatinine clearance, the better the survival.

One should be cautious when interpreting the CAN-USA results; these data are inferences from a statistical model and are not derived from a prospective controlled study. Although the study showed a clear association between dose and outcome, it does not ensure causality. Furthermore, the CANUSA and other studies that suggest that targets of dialysis adequacy correlate with patient outcome base their conclusions on adequacy values that include both dialysis and residual renal clearance [20, 23]. However, in all of them the decline of the renal component of KT/V (KTr/V) over time is responsible for most of the variation in total clearance because the peritoneal clearance remains relatively stable [20, 23–25]. Recent analysis of the CANUSA results indicated that changes in residual renal function, but not those in peritoneal clearance, were significantly correlated with outcome [26]; in other words, the CANUSA and similar studies show that, as residual renal function declined, mortality increased. Today we have no study that indicates whether one can improve outcome by increasing peritoneal clearance to compensate for declining renal function. Recently, however, we retrospectively reviewed 115 anuric CAPD patients in our program and correlated peritoneal KT/V with outcome (Fig. 2; unpublished data). Those who had a KTp/V of < 1.75 had a significantly higher mortality rate than did patients whose KTp/V exceeded 1.75 (Fig. 2). In other words, there is a minimum peritoneal urea clearance (KTp/V of 1.75) below which mortality is increased.

Not all studies have confirmed the correlation between KT/V and patient outcome [24, 27]. This variability in the published results is due partially to differences in

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<th>Table 1. Summary of studies investigating KT/V targets for CAPD</th>
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<td><strong>Targets based on theoretical constructs</strong></td>
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<td>Popovich et al</td>
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<td>Techan</td>
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<td>Keshaviah</td>
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<td>Prospective cohort studies/ univariate analysis</td>
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<td>Blake</td>
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*From Ref. 19*
mended in the late 1970s a weekly creatinine clearance of 100 liters for hemodialysis and 50 liters for peritoneal dialysis [29]. Subsequently, Twardowski and colleagues recommended 40 to 50 liters/1.73 m² BSA based on their clinical experience [30]. Arkouche and coworkers found these levels inadequate and proposed higher levels, 60 liters/week/1.73 m² BSA [31]. Maiorca et al concluded that, for a KT/V of 1.96, above which survival was excellent, the equivalent WCC was 58 liters [22]. According to the CANUSA study, the higher the creatinine clearance (sum of renal and peritoneal), the better the outcome, and a clearance of 70 liter/1.73 m² was associated with a 78% survival at 2 years, the same as a KT/V of >2.1 [23]. The targets recommended by DOQI for continuous treatments such as CAPD and CCPD (WCC of 60 liters/1.73 m²) are slightly lower than the target of WCC > 70 liters, which one would deduce from the CANUSA study. Selgas et al found that WCC was a much weaker predictor of outcome than urea clearance [32]. Similarly, Blake et al noted no relationship between total WCC and mortality except for WCC values > 48 liters/1.73 m² [33]. No consensus exists as to whether urea or creatinine clearance is a better marker of adequacy. In fact, in about 20% of patients, one finds a distinct dissociation between these two markers [34].

Discrepancy between KT/V and weekly creatinine clearance can be due to (1) the different levels of residual renal function, (2) the difference in the rate of equilibration for urea and creatinine between plasma and the dialysis solution, and (3) the utilization of different normalizing constant (that is, V for urea and body surface area for creatinine). Thus in a group of CAPD patients with some residual renal function, renal KTr/V urea contributed on average only 17% to the total KTrp/V, whereas the renal creatinine clearance contributed 35% to the overall creatinine clearance [35]. This difference was due to the reabsorption of urea and the secretion of creatinine in the renal tubules; therefore, early in CAPD, when patients have some residual renal function, it is easier to achieve creatinine clearance targets than KT/V urea targets. On the contrary, when patients become anuric, it is easier to achieve KT/V urea targets because of the slower equilibration of creatinine compared to urea. For the same reason, during APD at night, when exchanges dwell in the peritoneal cavity over short periods, urea clearance targets are easier to achieve than creatinine targets [36]. The use of a different normalizing constant (that is, V for urea and body surface area for creatinine) is an additional reason for the discrepancy between KT/V and WCC. Thus for an obese patient, an overestimation of V can result in a low KT/V. Body weight changes have less effect on BSA and therefore on normalized WCC [37].

[Diagram: Fig. 2. Comparison of anuric CAPD patients with KT/V values above (■) or below (○) 1.75. (P < 0.05.)]
Table 2. Formulas calculating dietary protein intake from urea levels in CAPD patients

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<th>Author</th>
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<tr>
<td>Randerson [43]</td>
<td>PNA (g/day) = 8.0 + 0.15 UA (mM/day)</td>
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<tr>
<td>Bergström [44]</td>
<td>PNA (g/day) = 19 + 0.2134 UA (mM/day)</td>
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<tr>
<td>Kopple [46]</td>
<td>PNA (g/day) = 6.8 + 0.97 UNA (g/day)</td>
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* PNA, protein equivalent of nitrogen appearance; UA, urea in dialysate and urine.

** Formula cited here is Dr. Bergström’s revision [45] of the original version [44].

† UNA, urea nitrogen appearance.

Nutrition

The observation that the dose of dialysis is related to the NPNA (an index of the patient’s protein intake and appetite) led Lindsay and Spanner to suggest that in hemodialysis, good nutritional status, as indicated by a protein equivalent of nitrogen appearance (PNA) > 1 g/day, is the major determinant of low morbidity [38]; however, good nutrition cannot be obtained without adequate dialysis, as indicated by a KT/V > 1.0 per hemodialysis session. One can assess nutrition by clinical evaluation, dietary history, anthropometric measurements, and various biophysical and biochemical methods. Among the anthropometric indices, one of the simplest and most useful is subjective global assessment, which includes four items: weight loss in the previous six months, anorexia, loss of subcutaneous fat, and assessment of muscle wasting. According to this method, patients are characterized as well nourished, mildly malnourished, or severely malnourished. This method has been validated in CAPD patients [39].

The PNA. In addition to providing the KT/V, urea kinetic modeling can be used to calculate daily protein intake based on the amount of urea excreted (urea appearance), assuming that the patient is in neutral balance. The protein intake, thus calculated, used to be called the protein catabolic rate. However, since the actual catabolic rate is 5 to 6 times that of daily protein intake [40], and we do not know whether the patient is catabolic, a better term is “protein equivalent of nitrogen appearance.” Some investigators have found a high correlation between actual dietary protein intake, estimated by food records, and the PNA [41]; others have noticed a marked discrepancy between the two [42].

Table 2 shows the various formulas proposed for the calculation of protein intake for urea appearance. The Randerson equation, derived from hemodialysis patients, has been validated in CAPD patients [43]; to this result, one should add the value of estimated protein losses. Bergström’s formula, based on nitrogen balance data among CAPD patients, takes into account the greater non-urea nitrogen losses in peritoneal dialysis [44] and therefore yields significantly higher values than the Randerson formula. The formula presented here [45] differs from that in the original publication, which contained a small error (corrected by Dr. J. Bergström, personal communication). Kopple’s formula, which also is founded on balance studies, gives values between those obtained with the Randerson and Bergström formulas [46]. Although the Randerson formula has been the preferred method to date, I agree with the conclusion of Mandolfo et al [47] that the Bergström formula, which is based on balance studies, should become the standard method.

Because larger patients should have a higher protein intake than smaller patients, it has been a common practice to adjust the PNA to the patient’s body weight to create a normalized PNA (NPNA) that can be used for comparison and correlation purposes. However, this normalization process creates significant problems because clinicians have not agreed what weight to use for this calculation. None of the various proposals, or for that matter the normalization concept itself, has been clinically validated [5, 48]. Thus, if the present, actual body weight is used, normalization creates a mathematical bias in obese patients, in whom the NPNA is underestimated, and in the wasted individual in whom NPNA is overestimated. Alternatives that have been suggested are: (1) using standard body weight (= V/0.58), where V is calculated by the Watson formula, which takes into account age, gender, height, and weight and (2) desirable body weight, which is the midpoint of the range associated with greatest longevity for normal individuals of the same age range, gender, and skeletal frame as the patient. These weights are published in the actuarial tables of the Metropolitan Life Insurance Company. Although normalization using these techniques provides higher values of NPNA for the obese and lower for the wasted, none of these alternatives has been validated in any published studies; hence we should test their usefulness in prospective studies. Canaud et al recently proposed normalizing the PNA to the lean body mass, because muscle mass constitutes the major reserve of endogenous proteins and nitrogen fuel within the body, thus establishing a link between PNA and lean body mass [49].

The NPNA is an important reflection of protein intake but, measured by various formulas, the correlation coefficient between dietary protein intake and NPNA is about 0.6, which is less than impressive [43, 50]. In CAPD, in contrast to hemodialysis, in which NPNA is an important predictor of outcome [14], NPNA frequently correlates with technique failure but not with other outcomes [20–24, 48, 50, 51]. The PNA is inversely related to age, being lower in older patients [52] and in diabetics. In Selgas’ study, patients with NPNA > 1 g/kg/day had a lower rate of hospitalization compared to those with a value < 1.0 g/kg/day [32]. Harty et al have questioned the validity of adjusting PNA [48] in light of the failure of NPNA to reflect conventional parameters of nutrition in cross-sectional analyses of hemodialysis [52] and CAPD pa-
patients [24]. Their study of 147 CAPD patients showed no correlation between NPNA and measures of nutrition or measures of body composition and disclosed no significant differences between well-nourished and malnourished patients. Until a proven method for normalizing PNA is developed and validated, the clinician should be aware of the risks of normalization as currently applied with regard to obese and wasted patients.

**Dialysis dose and nutrition.** The precise relationship between adequacy of dialysis and nutritional status has remained elusive and is a continuing subject of debate [53]. Uremia commonly leads to anorexia, which generally is thought to be due to the accumulation of toxic compounds that inhibit appetite [44, 54]. In elegant experiments in rats, Bergström and colleagues demonstrated that uremic toxins with a molecular weight between 1.0 and 1.5 kD (extracted from both uremic serum and normal urine) suppress appetite [55]; when these molecules were injected intraperitoneally into normal rats, their food intake decreased in a dose-related fashion. The CANUSA study recently confirmed that anorectic uremic patients who reach end-stage disease commonly regain their appetite after initiation of dialysis [53]. This observation suggests that uremic toxins that cause anorexia are removed by dialysis. It also is common clinical experience that inadequately dialyzed patients have a poor appetite and occasionally a special aversion to meat, and that sometimes their appetite improves when the dialysis prescription is appropriately modified [56]. On the other hand, well-dialized patients feel good and eat well. For years now, but especially for the last 5 to 10 years, investigators have attempted to validate these clinical impressions by establishing a relationship between dialysis dose and the amount of dietary protein intake [57]. Establishing such a relationship would be of particular importance because it would unify two factors, dialysis dose and nutritional status, both of which are strong predictors of outcome. Such a relationship would give nutrition a central role and thus would have important therapeutic implications, because one could improve nutrition by increasing dialysis dose.

In 1989 Lindsay and Spanner established the relationship between KT/V and NPNA for hemodialysis and CAPD patients. They observed that the slope of the relationship was lower among CAPD than hemodialysis patients. Among hemodialysis patients dialyzed with a cellulosic membrane, the mean slope was 0.61, whereas among those dialyzed with polyacrylonitrile membranes, the slope was higher (1.08) [38]. Subsequently Lysaght et al [17] and other investigators [20, 58] confirmed the positive relationship between NPNA and KT/V in CAPD patients. Contrary to the findings of Lindsay and Spanner [38], other investigators found that the slope between KT/V and NPNA is higher (1.5 to 2.0 ×) in CAPD patients than in hemodialysis patients [17, 58]. This observation suggests that increasing the dialysis dose has a more salutary effect in CAPD. Bergström et al, who analyzed pooled data of balanced studies—their own and those of Blumenkrantz et al [59]—found a good correlation between NPNA and KT/V in both hemodialysis and CAPD but a steeper slope in CAPD [44].

The finding of a steeper slope for CAPD than hemodialysis supports the peak concentration hypothesis [15], and the role of middle molecules as a uremic toxin. Bergström and Lindholm also suggested that the release of catabolic cytokines, the development of acidosis between dialysis sessions, and the loss of amino acids during hemodialysis has an even greater impact on catabolism than do protein losses in CAPD patients [60]. Furthermore, glucose absorption can have a protein-sparing effect [35, 60], although Bergström and Lindholm could find no relationship between the amount of glucose absorbed and the protein or energy intake, nor any difference in protein/energy intakes, whether the abdomen was empty or filled with dialysis solution.

Harty and colleagues challenged the validity of this relationship [35, 48]. First they reported that, although they observed a correlation between KT/V and NPNA, this relationship did not exist between unadjusted PNA and KT/V. Instead they found only a weak correlation between unadjusted PNA and unadjusted urea clearance (KT). Paradoxically, malnourished patients had the highest values for normalized urea clearances (KT/V), producing a significant but inverse correlation between KT/V and lean body mass [35]. This paradox could be partially resolved when, instead of normalizing to actual weight, the clearance was normalized to ideal body weight obtained from the National Health and Nutrition Examination Survey (NHANES) tables; then a weakly positive correlation emerged between KT/V and some nutritional parameters. Interestingly, in the latter case, the contribution of residual renal function, not the level of peritoneal clearance, was responsible for the positive correlation.

These observations led Harty and colleagues to argue forcefully and convincingly that this relationship is conceptually and mathematically flawed [35]. They pointed out that, because KT/V and NPNA share three components (Table 3), any relationship between the two must be due, in part, to mathematical coupling. They supported this contention further when they showed that randomly

<table>
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<tr>
<th>Table 3. Shared components are responsible for the correlation between KT/V and NPNA (mathematical coupling)*</th>
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<tr>
<td><strong>KT/V</strong></td>
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<tr>
<td>Dialysate urea × dialysate vol.</td>
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<tr>
<td>Plasma urea</td>
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<td>V (Const × wt)</td>
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</table>

* From Ref. 35
protein intake was measured. (4) A dissociation in the relationship occurs when PNA is increased or decreased by changes in protein intake [66]. (5) KT/V and NPNA are more closely related in diabetics than in non-diabetics [67]. More than any other evidence, however, longitudinal studies support a physiologic basis for the relationship between NPNA and KT/V. Such studies are not affected by a spurious correlation, because an increase in urea generation due to an increase in KT/V would provide unequivocal evidence of increased production and removal of urea nitrogen. Under these circumstances, an increase in NPNA in the absence of weight loss or acute stress could result only from an increase in protein intake [68]. Of course the strongest support for the influence of dialysis dose on nutritional status would be a correlation between changes in dialysis dose and changes in various nutritional estimates, such as subjective global assessment (SGA) and lean body mass (or serum albumin).

Table 4 provides a summary of several prospective longitudinal studies on the effect of KT/V on NPNA and other nutritional parameters. Lindsay et al, who increased KT/V from 0.59 to 0.9 among eight CAPD patients for three months, observed an improvement in NPNA by 0.282 g/kg/day [69]. Haimburger and colleagues increased weekly KT/V from 1.53 to 1.89 in 19 CAPD patients over three months and observed an increase in NPNA and an increase in serum albumin from 2.91 ± 0.41 to 3.05 ± 0.43 g/dl, which was not statistically significant [70]. After an increase in weekly KT/V in 17 CAPD patients from 1.44 to 1.78 for one month, Burkart et al observed an increase in NPNA from 0.616 to 0.695 g/kg/day (P < 0.05) and in serum albumin from 3.5 (mean of 3 monthly albumin values prior to change) to 3.69 g/dl (3 monthly albumin values after change) (P < 0.035) [71]. Uribarri and coworkers increased weekly KT/V from 1.85 to 2.3 in 23 patients for 6 months and observed an increase in serum albumin from 3.55 to 3.83 g/dl, but not of NPNA (0.98 to 1.0 g/kg/day) [72]. By increasing KT/V by 25% in 40 malnourished CAPD patients, Davies et al halted or partially reversed their nutritional decline (improvement in lean body mass), but it took at least 6 months to see the benefit of intervention [73]. Lynn et al increased KT/V among 10 patients from the previously accepted targets of >1.6 to a new KT/V of 2.81 [74]. They demonstrated significant increases in NPNA levels of >1.0 g/kg/day in 9 of 10 patients [74]. These patients reverted to baseline NPNA levels four weeks after returning to their original dialysis prescription. Williams et al prospectively studied 10 patients after change of KT/V from 1.37 to 1.68 for three months. Neither NPNA nor serum albumin changed significantly [75]. Harty et al increased weekly KT/V from 1.5 to 1.8 in 33 patients for 3 months but could show no increase in NPNA [76]. Prospectively, Malhotra et al increased the KT/V from
Table 4. Summary of prospective longitudinal studies of the effect of changes in KT/V on NPNA, serum albumin, or other nutritional parameters

<table>
<thead>
<tr>
<th>Study</th>
<th>KT/V initial/terminal</th>
<th>Duration</th>
<th>N</th>
<th>Changes in NPNA or ΔNPNP g/kg/day</th>
<th>Change in mean serum albumin before/after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindsay et al [69]</td>
<td>0.59/0.9</td>
<td>3</td>
<td>8</td>
<td>0.282</td>
<td>2.91/3.05 g/dl</td>
</tr>
<tr>
<td>Heimburger et al [70]</td>
<td>1.53/1.89</td>
<td>3</td>
<td>19</td>
<td>0.81/0.87</td>
<td></td>
</tr>
<tr>
<td>Burkart et al [71]</td>
<td>1.44/1.78</td>
<td>1</td>
<td>17</td>
<td>0.616/0.695</td>
<td>3.5/3.7 g/dl</td>
</tr>
<tr>
<td>Uribarri et al [72]</td>
<td>1.85/2.3</td>
<td>6</td>
<td>23</td>
<td>0.98/1.0</td>
<td></td>
</tr>
<tr>
<td>Davies et al [73]</td>
<td>Δ125%</td>
<td>&gt;6</td>
<td>40</td>
<td>0.86/0.91</td>
<td>Improvement in LBM⁻</td>
</tr>
<tr>
<td>Lynn [74]</td>
<td>&gt;1.6/2.81</td>
<td></td>
<td></td>
<td>Sign. incr. in PNA in 9/10 patients&gt;1.0 g/kg/day</td>
<td></td>
</tr>
<tr>
<td>Williams [75]</td>
<td>1.37/1.68</td>
<td>3</td>
<td>10</td>
<td>0.88/0.89</td>
<td></td>
</tr>
<tr>
<td>Harty et al [76]</td>
<td>1.5/1.8</td>
<td>3</td>
<td>33</td>
<td>No changes</td>
<td></td>
</tr>
<tr>
<td>Malhotra et al [77]</td>
<td>1.4/2.1</td>
<td>8 ± 5</td>
<td>37</td>
<td>0.74/0.96⁷</td>
<td>No changes in mean serum albumin 3.4/3.3 (decreased in 18, increased in 15, unchanged in 4)</td>
</tr>
</tbody>
</table>

¹ P < 0.05  
² LBM, lean body mass; PNA, protein equivalent of nitrogen appearance

1.4 to 2.1 in 37 patients [77]. Appetite improved and NPNA increased from 0.74 to 0.96 g/kg/day, but the mean serum albumin of the group did not change. In individual patients, however, the serum albumin decreased in 18 and increased in 15; those in whom serum albumin increased were younger and had a higher dietary protein intake and BUN after the increase in dialysis dose.

Obviously these results are inconclusive. Analysis of the CANUSA results provides the best evidence of the effect of urea clearance on nutritional parameters [53]. Thus, after initiation of dialysis, weekly total KT/V increased by 1.5 and weekly total CCr by 35.6 liters/1.73 m². During the first six months, there was improvement in the mean subjective global assessment, lean body mass, and percentage of lean body mass. The subjective global assessment increased by 0.72 U (P < 0.001), the lean body mass by 1.6 kg (P < 0.001), and the percentage of lean body mass by 1.4% (P = 0.01). However, no statistically significant changes were noted in serum albumin, PCR, or normalized PCR. This improvement in several unrelated markers of nutritional status during the first six months of CAPD supports the contention that improved toxin clearance contributes to improved nutritional status [53]. However, the correlations were weak, so non-dialysis factors such as comorbidity likely have an important influence on nutritional status. Serum albumin levels, although not influenced by dialysis dose, remained a strong predictor of outcome. This observation suggests that serum albumin level is influenced more strongly by non-nutritional factors, such as comorbidity and peritoneal albumin losses.

Malnutrition. Malnutrition has a complex pathogenesis and does not depend only on adequacy of dialysis. Hence two major types (or causes) of malnutrition frequently occur together in dialysis patients (Fig. 4). The first, uremic malnutrition, is related to the uremic disorder per se [50]. Another contributing factor in the malnutrition of dialysis patients is metabolic acidosis which, even when slight, can increase the catabolism of branch-chain amino acids (valine, leucine, and isoleucine) and lead to valine depletion that limits protein synthesis. A portion of this uremic malnutrition would respond to increases in small-solute clearance and correction of acidosis, but a further portion might be related more to defective protein anabolism, secondary to dysfunction of the growth hormone/IGF-1 endocrine axis. This latter portion might respond better to the administration of agents such as rHGH or even anabolic steroids than to increases in dialytic dose [78].

The second major type of malnutrition, which might be termed comorbid malnutrition, that is, secondary to diabetes, heart failure, chronic inflammation, malignancy, etc., would not respond to alterations in dialytic dose or even protein intake. Infections are important stimulants of protein catabolism; these, combined with increased protein losses, which vary between 5 and 15 g/day and increase significantly with peritonitis, can lead to malnutrition and hypoalbuminemia in CAPD patients [60]. Malnutrition in individual patients can be of one type or the other or even a mix of these [50].

Fluid/volume control

Low urea clearance and malnutrition/hypoalbuminemia increase the risk of death, while cardiovascular deaths are the main cause of mortality in CAPD patients. Therefore, it is logical for us to speculate that low KT/V and malnutrition increase the risk of death from cardiovascular causes. How might low KT/V values and malnutrition modify cardiovascular risk? Harty et al suggest that insufficient clearance returns the patient to the pre-dialysis uremic milieu and thus increases the likelihood of cardiac dysfunction [25]. However, another possible relationship ties dialysis adequacy targets and cardiovascular mortality: the relationship between fluid overload...
Various pathogenetic mechanisms of malnutrition in CAPD patients. (From Ref. 50.)

and hypertension, which leads to atherosclerosis and left-ventricular hypertrophy [79]. Thus, volume overload can directly affect cardiovascular mortality through the development of hypertension and left-ventricular hypertrophy [80], which in turn identify the dialysis patients who are at risk of sudden death, stroke, and congestive heart failure [81, 82]. Fluid volume control becomes more difficult when anuria supervenes two to four years after the initiation of CAPD. By that time, peritoneal ultrafiltration has declined in as many as 30% of CAPD patients, who then develop fluid retention [83, 84]. Most CAPD patients suffer from fluid overload, as indicated by central wedge pressure measurements and measurements of plasma cGMP levels—a marker of the hydration state [18, 85, 86]. Charra et al have achieved success in managing hypertension through control of extracellular fluid volume [3]; they believe this approach is superior to pharmacologic control. Also, they have noted that even small increases in fluid volume increase the patient's resistance to antihypertensive medication.

Patients have been classified into four groups on the basis of peritoneal transport: low (L), low average (LA), high average (HA), and high transporters (HI) [87]. The high transporters (D/Pcreat > 0.80) need special attention from the nephrologist. These patients have significantly lower serum albumin levels and NPNA, and lower body mass than do the other groups [88]. The low albumin level probably is the result of increased protein losses across the peritoneum. Also, these patients have a low NPNA, disproportionate to the level of KT/V, which might be due to increased use of high-glucose solutions that, in turn, decrease appetite.

In the CANUSA study, the two-year patient survival probabilities were 91%, 80%, 72%, and 68% for L, LA, HA, and HI, respectively [89]. All groups have low serum albumin and low lean body mass, but we do not know whether (in these patients) these indices have the same predictive value as if they were the result of malnutrition. Harty et al found no evidence of excess malnutrition [assessed by anthropometric and serum protein values and subjective global assessment (SGA) categorization, composite nutritional index] in high transporters [35], whereas Nolph and colleagues did [88]. Nolph et al recommended that high transporters may warrant increased clearance and protein intake targets. An alternative explanation for the increased mortality rate among high transporters is the low ultrafiltration that leads to fluid overload, which (when chronic) can lead to left-ventricular hypertrophy and cardiovascular disease [80, 90]. We do not know the best treatment for high transporters, but volume control likely is important. High transporters thus are candidates for nocturnal intermittent PD with short exchanges. This technique leads to better ultrafiltration, slightly reduced protein losses, lower glucose absorption, and better protein intake [88]. Whether conversion to NIPD will lead to higher survival rates is not known. In an outstanding recent review, Bergström and Lindholm described a hypothesis integrating malnutrition, cardiac disease, and mortality [91].

Improving KT/V in underdialyzed patients

The need for an increase in KT/V becomes critical when the patient becomes anuric; special attention must be paid to those of large body size, especially patients who (with respect to peritoneal permeability) are low transporters. Before one institutes a change in the dialysis prescription, one must ensure that the patient is compliant with the dialysis instructions. Blake et al noted that patients ignore 20% to 30% of all prescribed changes in their dialysis treatment plan, and usually the staff
cannot detect this [92]. Furthermore, some patients run
the risk of reducing the effective exchange volume when
they flush larger volumes (than they have been in-
structed) during the flush of the lines, either because of
ignorance or because they are in a hurry to finish the
exchange. Noncompliance that can lead to inadequate
dialysis appears to be more frequent in the US than in
Canada, and this factor might account, at least in part,
for the observed difference in the mortality rate between
the two countries [92].

Of the various ways of enhancing peritoneal dialysis,
increasing the exchange volume is the most critical, least
expensive, and least intrusive into the patient’s life [93].
Schoenfeld et al found that clearance of small molecules
increases linearly with intraperitoneal volumes [94]. Ke-
shaviah et al confirmed this observation and found that
the fill volumes needed to achieve peak clearance in-
creased with increasing body surface area: approximately
2.5 liters for a person of average size and 3.0 to 3.5
liters for an average BSA of 2 m² [95]. The net ultrafiltration is increased in response to higher volumes
because of better maintenance of the dialysate-to-plasma
glucose concentration gradient. Concerns about the use
of increased volumes include risk of hernia, increased
-glucose absorption from the larger intraperitoneal vol-
ume, increased costs, and diminished quality of life be-
cause of the extra time required for dialysis, which leads
to decreased patient acceptance of the procedure [28].
Finally, urea and creatinine clearances were significantly
higher (up to 1.7×) in the supine than the upright posi-
tion [94, 96].

In the majority of anuric CAPD patients, the “stan-
dard” CAPD protocol of four two-liter exchanges per
day is not adequate to achieve the recommended small-
solute targets. Accordingly, the physician should modify
the protocol, taking into account the patient’s size and
peritoneal permeability. Anuric patients who want to
remain on CAPD require a fifth exchange that can be
accomplished in the night with the “night exchanger”
Quantum® (Baxter). In most cases, however, the patient’s
dialysis treatment will have to be converted to automated
peritoneal dialysis, that is, either continuous cyclic peri-
toneal dialysis (CCPD), with two liters left in the perito-
neal cavity during the daytime or with one or two ex-
changes during the daytime (enhanced CCPD).

Certain principles should govern the prescription of
automated peritoneal dialysis. (1) The target for KT/V
on intermittent treatments should be higher than that
for patients on CAPD. The recent DOQI group recom-
mended a KT/V of 2.2 and creatinine clearance of 66
liters/week/1.73 m². (2) If the creatinine clearance target
is maintained when one is switching from CAPD to NIPD,
urea clearance targets automatically will be achieved.
(3) The same quantity of the total dialysate delivered
in larger volumes of fewer exchanges produces better
clearances. (4) The longer a patient stays on automated
peritoneal dialysis at night, the better the clearance. (5)
Increasing the number of exchanges over a given period
does not always increase clearances and, in patients with
low peritoneal transport, can even decrease clearances.
(6) Many large patients require two daytime exchanges.
(7) Tidal PD, in which the peritoneal cavity is not drained
completely but a volume of 1.0 to 1.5 liters is left in
the peritoneal cavity between exchanges, theoretically
is better but has been somewhat disappointing in practice
[97]. In trying to optimize dialysis, we should not forget
that whatever measures we recommend should be com-
patible with costs and the patient’s time availability and
quality of life. As Nolph said, our goal must be to offer
dialysis so that our patients will live comfortably rather
than merely live so they can do dialysis [98].

Although the topic of my discussion has been adequacy
of CAPD, let me briefly comment on the utility of this
concept in patients with severe, chronic renal failure. If
maintaining targets of small-solute clearance and good
-nutritional status is critical for the patient on dialysis, it is
reasonable to assume that these same targets, especially
those established for a continuous therapy like CAPD,
are also critical for the patient with declining renal func-
tion. In this case dialysis should start when residual renal
function falls below the targets. This view is supported
by the observation that initial KT/V is inversely related
to hospital admission rates, number of hospitalization
days [99], and patient survival [53, 100]. Similarly, nutri-
tional status at the start of dialysis is predictive of long-
term outcome [23]. The DOQI group recommends that
patients be advised to initiate some form of dialysis when
the weekly renal KT/V urea falls below 2.0 unless the
patient’s edema-free weight is stable, NPNA is above
0.8 kg/day, and the patient has no clinical symptoms.
One has to balance the benefits of this approach against
the patient’s desire to postpone dialysis as long as pos-
bile, and the increased costs and potential risks of dialysis.
Prospective, controlled studies should establish the poten-
tial benefits of the early start before it is widely ac-
cepted and practiced.

Before I conclude, let me make a comment on the stan-
ardization of guidelines. There is no doubt that the
practice of peritoneal dialysis varies among centers
within a country and also among various countries. In a
recent survey, Ganz et al revealed a significant variation
in dialysis practice and, most important, in various labo-
atory parameters (that is, hemoglobin, albumin, PTH)
among various centers in British Columbia [101]. The
DOQI guidelines on adequacy of peritoneal dialysis re-
present the first attempt to develop an approach to de-
crease discordance among centers and improve patient
outcome. I consider this important effort only the begin-
ning, and I envision regular revisions based on new evi-
dence in the years to come.
QUESTION AND ANSWERS

DR. NICOLAOS E. MADIAS (Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts): You addressed the paradox that patients maintained on peritoneal dialysis have a life expectancy similar to those maintained on hemodialysis despite markedly lower KT/V values, and you accounted for this paradox by invoking the peak concentration hypothesis. Although attractive, this is merely a hypothesis and, after all, there are ample differences between these two modalities. Could you please offer other potential explanations for this phenomenon?

DR. OREOPoulos: Other possible explanations include the stable hydration and blood chemistry in CAPD patients, the high clearance of large molecules, a better preservation of residual renal function, and a less catabolic environment. The weight of hemodialysis patients often fluctuates by 3 to 6 kg between dialyses, while that of CAPD patients remains constant. Their biochemical values increase to a maximum before hemodialysis and decrease dramatically at its end. On the contrary, the weight and blood chemistry of CAPD patients do not fluctuate. The CAPD patients definitely have less acidosis than do the hemodialysis patients; serum bicarbonate levels in the former group range from about 24 to 28 mm/liter. In hemodialysis, the interaction between blood and the dialysis membrane produces various cytokines that can be nephrotoxic. Finally, in CAPD, residual renal function reportedly declines at a much slower rate than it does in patients treated by hemodialysis. All these differences taken together might explain the similar mortality rate between the two treatment modalities, despite lower clearances of small molecules with CAPD.

DR. MADIAS: Why does residual renal function decline at a slower rate in CAPD than does in hemodialysis?

DR. OREOPoulos: There are various potential reasons. In addition to the release of cytokines during the hemodialysis procedure, CAPD patients have a lower protein intake than do hemodialysis patients. This difference in protein intake is accentuated further by peritoneal losses of protein during CAPD. Furthermore, CAPD patients are in a continuous state of fluid expansion when compared with hemodialysis patients [85, 86]. Finally, CAPD patients do not experience the decreases in blood pressure that are so frequent during hemodialysis. These factors taken together might contribute to the better maintenance of residual renal function in CAPD patients.

DR. MADIAS: You did not say much about hypoalbuminemia in peritoneal dialysis patients. Is it as ominous a predictor of mortality in peritoneal dialysis as it is in hemodialysis? Is it related to underdialysis?

DR. OREOPoulos: I spoke chiefly about other nutritional indices of malnutrition and did not discuss albumin levels because many factors other than malnutrition affect serum albumin levels. There is no doubt that, in large series, CAPD patients have lower mean serum albumin levels than do hemodialysis patients. However, low serum albumin does not always reflect nutritional status. In an excellent study, Kaysen and Schoenfeld showed that CAPD patients have reduced catabolism and increased anabolism and therefore their total albumin mass does not differ from that in controls [102]. According to these authors, the main reason for hypoalbuminemia in CAPD is an increase in the volume of distribution of the albumin mass. It is almost universally accepted that, both in hemodialysis and peritoneal dialysis, hypoalbuminemia is a strong predictor of mortality [20, 33, 40]. However, it seems that the level of albumin does not have the same effect on outcome in peritoneal dialysis as in hemodialysis. Thus, whereas in hemodialysis the relative risk (RR) of death was significantly increased when serum albumin was 3.0 to 3.5 g/dl, in CAPD such an increase in mortality appeared when the albumin concentration was less than 3.0 g/dl [103]. The strongest single predictor of low serum albumin is high peritoneal permeability that leads to low albumin levels either through the increased protein (albumin) losses or through overhydration and hemodilution of serum albumin [104]. Recently Han et al [105] and Yeun and Kaysen [106] showed that serum albumin is strongly influenced by its role as an inverse acute-phase reactant; both groups hypothesized that the same patterns of cytokine activation associated with acute-phase reaction also could increase vascular and thus peritoneal permeability. Additional factors that can lead to hypoalbuminemia are diabetes and cardiovascular disease, which by themselves lead to increased mortality rates. In patients with these disorders, hypoalbuminemia is an index of the severity of the disease and not necessarily of malnutrition. Finally, I would like to stress that the method of measuring albumin can affect serum albumin levels; the most frequently used method—the colorimetric test using Brom cresol green—markedly overestimates albumin levels, whereas the Brom cresol purple method gives values that slightly underestimate the true level compared with the “gold standard,” which is the nephelometry measurement [40]. Because albumin is affected by so many factors, it is not as good an index of nutrition as are other nutritional parameters.

DR. MADIAS: Would you please comment on the effect of intraperitoneal amino acids on the level of malnutrition in general, and on serum albumin in particular?

DR. OREOPoulos: Very early in the history of CAPD, circa 1978, when we recognized that malnutrition was an early complication of CAPD, we suggested replacing glucose as an osmotic agent with amino acids [107]. In this way we could dialyze the patients with amino acid solutions and simultaneously replace protein losses. Although this was a great idea, it took the industry 15 years...
to come up with commercial amino-acid-containing solutions. Such solutions are not yet available in the US but have been used for the last 4 to 5 years in Europe (Nutrineal® with 1.1% amino acids, Baxter). Dialysis with one or two daily exchanges of Nutrineal for as long as four weeks produces a positive nitrogen balance [108]. However, serum albumin increased only minimally. Subsequently, in a large study 71 patients received one to two exchanges with Nutrineal for three months and were compared with 63 patients who were dialyzed with standard solutions [109]. Even though the differences between the two groups were not great, a subgroup of malnourished patients treated with amino acids showed an increase in serum albumin and improvement in other nutritional parameters. Thus I believe that the use of amino-acid-containing solutions has a place in severely malnourished patients on CAPD.

**Dr. John T. Harrington** (Dean, Tufts University School of Medicine, Boston, Massachusetts): Dimitrios, thank you for a wonderful review. In your comments about Peter Blake’s study, did you say that patients with a KT/V less than 1.5 had a good outcome? That finding is at variance with other observations. Could you tell us more about your interpretation of Blake’s study?

**Dr. Oreopoulos**: No, I did not say that, John. Indeed, I might not have been clear about that point. Blake found that mortality increases after the KT/V falls below 1.5. He could not find a difference in mortality with high levels, however. Actually, what he found makes sense; if you keep decreasing dialysis dose, eventually the patients will suffer increased morbidity and mortality due to uremia. However, Blake’s cut-off point was lower than that in other studies. All other studies showed increased mortality if KT/V falls below 1.8 to 2.0. In Blake’s series, the cut-off point was below 1.5. The difference between his and other studies might be due to the fact that he did not measure KT/V but merely calculated it; yet, when he re-analyzed the data using the measured KT/V, his original findings remained unchanged. The most likely explanation is that the number of patients followed was too small for Blake to detect the benefits of higher clearances on mortality.

**Dr. Ronald D. Perrone** (Division of Nephrology, New England Medical Center): You spoke of the mathematical relationship between KT/V and NPNA because of the shared variables. Have any good studies looked at the relationship between weekly creatinine clearance, an independent measure of adequacy, and NPNA?

**Dr. Oreopoulos**: The only study I can quote is the CANUSA study [23]. During the first six months, because of the initiation of dialysis, total weekly creatinine clearances rose by approximately 30 to 40 liters (provided by dialysis), and there was an increase in the subjective global assessment and in lean body mass but not in serum albumin or NPNA. During the subsequent 12 months, when total weekly creatinine clearance did not change, the nutritional parameters did not change either.

**Dr. Madias**: Mathematical bias notwithstanding, you indicated that in two different populations the relationship between KT/V and NPNA was steeper in CAPD than in hemodialysis. What might be the basis for this difference?

**Dr. Oreopoulos**: This observation supports the peak concentration hypothesis in that the CAPD patients have constant biochemical values. An intermittent therapy requires a higher weekly KT/V to maintain the BUN peaks at or below the steady BUN of CAPD, assuming a similar protein intake and urea excretion rates. Thus, if elevated BUN peaks are associated with appetite suppression (directly or indirectly), a higher weekly KT/V would be required with an intermittent therapy to yield a given NPNA. The observation also emphasizes the importance of toxic substances of middle or large molecular weight that can be removed more effectively by peritoneal dialysis than by hemodialysis.

**Dr. Geetha Narayan** (Division of Nephrology, St. Elizabeth’s Medical Center, Brighton, Massachusetts): I believe that you said that both the well-nourished and the malnourished groups had the same NPNA when adjusted for standardized weight. Could you explain that?

**Dr. Oreopoulos**: Harty et al compared a group of patients who were well nourished and another group of malnourished patients (who had lost weight) and found, as you would expect, that the calculated daily PNA—that is, an expression of the daily protein intake expressed in grams per day—was higher in the well-nourished group than in the malnourished group [48]. However, when they normalized the PNA with the patients’ present weight (NPNA, that is, g/kg/day), they found the reverse; that is, the NPNA was higher in the malnourished patients, who had lost body weight, than in the well-nourished ones. This is a misleading paradox.

**Dr. Ajay K. Singh** (Director of Clinical Nephrology, Brigham & Women’s Hospital, Boston, Massachusetts): A consensus appears to be emerging in the management of ESRD patients that hemodialysis rather than peritoneal dialysis is the preferable dialytic option for larger patients. In a recent study by your group addressing this issue [110], I believe you compared patients weighing 80 kg or more with a group whose body weight was 60 to 80 kg. Could you elaborate on the findings in that study and tell us whether you agree with this emerging consensus?

**Dr. Oreopoulos**: In that study, we compared the survival of CAPD patients whose weight was over 80 kg with those whose weight was less than 60 kg and found no difference in mortality rate between the two groups [110]. Unfortunately, we did not have data on their KT/V, but you would expect, would you not, that because the daily dialysis volumes were similar in the two groups,
there probably were differences in their KT/Vs. These findings are similar to those of Kopple et al, who found that overweight hemodialysis patients, despite lower percent urea reduction rates, had better survival rates [111]. Heavier patients might have an advantage in that they are better nourished to begin with, and this might compensate for the fact that they receive relatively less dialysis. Interestingly, in our study, we found a significantly higher mortality rate in both groups among those patients who had lost weight. This brings us back to the central role of nutrition. Another explanation for our findings would be that the patients with the higher body weights might have had better residual renal function. I believe that if there is some residual renal function, as during the first year or two of renal replacement therapy, you can treat with CAPD almost any individual irrespective of his or her weight. All problems start when the patient becomes anuric. In our experience, however, the required KT/V targets need not necessarily be as high in the anuric patient; we found that, after you provide a KT/V over 1.75, the survival rate is excellent: 80% the first 2 years. Is it possible that the anuric patient does not need a clearance as high as that in the patient with residual renal function? Confirmation of our observation with prospective studies is required.

Dr. Singh: There appears to be a striking correlation between membrane permeability characteristics and mortality. This relationship would suggest that peritoneal equilibration test (PET) studies should become an integral and early part of the evaluation and management of virtually every PD patient. Can you tell us about your practice?

Dr. Oreopoulos: I will tell you what we are doing in our unit and what are the DOQI recommendations. We do an Adequest®, which provides measurement of PET, KT/V, weekly creatinine clearance (WCC), and NPNA in each of our new patients; we do not do it during the first two to three weeks of CAPD, because a PET performed within the first week after initiation of peritoneal dialysis can yield a higher transport result than would a PET performed a few weeks later [112]. The DOQI recommends that we obtain baseline measurements of KT/V and creatinine clearance two or three times during the first six months, and then obtain a solid baseline value, and then measure these parameters every 6 to 12 months thereafter. However, all one needs to measure in the followup is the creatinine and urea in peritoneal effluent and urine. Repeating the PET is unnecessary because usually it does not change. You should perform a formal equilibration test only if there is an unexpected change in either peritoneal creatinine equilibration or ultrafiltration. In our unit, we ask the patients to bring a 24-hour urine specimen every second visit, and we analyze this for creatinine and urea clearances because we know that patients who have adequate residual renal function have adequate KT/V and weekly creatinine clearance. After all, 1 ml of GFR provides 10 liters of weekly creatinine clearance and 0.25 of weekly KT/V. When the creatinine clearance falls below 1 ml/min or if the 24-hour urine volume drops below 100 ml/day on at least two successive occasions, we adjust the dialysis dose and repeat the adequacy test. I want to emphasize again the importance of following up the residual renal function.

Dr. Singh: Peter Blake presented some attractive data on compliance with the peritoneal dialysis prescription when he visited Boston about a year ago. In light of the disturbing data on mortality of peritoneal dialysis patients in the United States, it seems crucial to ensure compliance. Blake used questionnaires in his study, but in the individual patient, how do you assess compliance other than, of course, the “look-them-in-the-eye” test?

Dr. Oreopoulos: You should suspect non-compliance every time you find an unexplained increase in serum creatinine in the presence of the same residual creatinine clearance. In cases like that, you can measure creatinine in the effluent; if it is 15% greater than the effluent creatinine value established in the baseline period, you should suspect non-compliance. It would be likely that the patient had been skipping dialysis for some time prior to collection and that on the day of the collection was washing out the accumulated creatinine. I believe that the “look-them-in-the-eye” test is a good and reliable measure. The question, “Do you do all dialysis exchanges?” emphasizes the importance of complying with the prescription. Even if patients lie, at least they get the message. It is interesting that Blake relied on an anonymous questionnaire [92]. He assumed that the patients would tell the truth anonymously, but that assumption is open to criticism. Interestingly, he found a greater degree of non-compliance in the US than in Canada; this difference might explain some of the observed difference in mortality rates between the two populations [113, 114]. In this area, Bernardini and Piraino and colleagues provided the gold standard [115]. They went to their patients’ houses and measured the dialysate inventory. They compared the actual number of bags with the number that the patient should have on hand if the patient is compliant with the dialysis regimen. They also found that a large percentage of their patients were noncompliant. I believe that the companies that deliver the dialysis solutions might be able to help us in this respect by doing a monthly inventory.

Dr. Suphamai Bunnapradist (Renal Fellow, Division of Nephrology, New England Medical Center): Would you please comment on target KT/V in nocturnal intermittent peritoneal dialysis? Is it different from the target in CAPD?

Dr. Oreopoulos: If control of the peak urea nitrogen concentration is critical in preventing uremic toxicity, as
suggested by the peak concentration hypothesis, then any intermittent form of peritoneal dialysis requires a higher “dose” to maintain the peak concentration below the steady state [14, 15]. The DOQI recommendation for NIPD is 2.2 for weekly KT/V and 66 liters/week/1.73 m² for weekly creatinine clearance.

**Dr. Madias:** What do you recommend when you encounter discordance between the two indices—KT/V and creatinine clearance?

**Dr. Oreopoulos:** In responding to this difficult question, I will tell you what the DOQI recommends and what I am doing in my unit. The DOQI recommends that you try to achieve both targets. If you achieve only one of the two, continue with treatment but watch the patient carefully. In anuric patients and those on short exchanges with APD, it is easier to achieve KT/V targets than creatinine clearance targets. On the contrary, in those with some residual renal function, you can achieve creatinine clearance easier than KT/V. The hemodialysis community always works with urea targets, so I tend to be satisfied that I am doing a good job if my patients have an adequate KT/V, and I do not worry too much about the creatinine clearance targets.

**Dr. Madias:** You mentioned that the survival of CAPD patients is similar to that of hemodialysis patients. But analysis of the USRDS data showed that the mortality rate was higher among CAPD patients. Also, undergoing CAPD in the US was a risk factor for mortality in the CANUSA study. Could you please comment on these issues?

**Dr. Oreopoulos:** Nick is referring to the article by Bloembergen et al [113]. These authors studied a cohort of CAPD patients during the period of 1987 to 1989 and indeed found a higher mortality rate among the CAPD patients than in hemodialysis patients, especially among elderly diabetics. This study had a rather unusual methodology in that it treated each patient as a new patient each year and defined their therapeutic modality as the one in place on January 1st of that year. In other words, it was a mixture of incident and prevalent patients, some of whom must have been anuric. Also, the authors did not compare the relative incidence of co-morbidity. On the contrary, Fenton from the Canadian Registry studied all new patients on CAPD and on hemodialysis and found that all groups of patients—diabetics, non-diabetics, young and old—had a higher mortality rate with hemodialysis than with CAPD for at least the first three years of dialysis [114]. I believe that any method of analysis that omits, as the Bloembergen study did, the first year of treatment for many patients will tend to show hemodialysis in a better light than peritoneal dialysis.

Many other reasons account for the difference between the US and Canadian reports. Canadian patients seem to be more compliant with their treatment than are patients in the US [92]. Another big difference is that in Canada approximately 100 new patients per million population begin dialysis every year; in the United States, more than 250 new patients per million start dialysis every year. This difference suggests that the case mix of the American patients varies from that in Canada. I believe, however, that a very important reason for the higher mortality rate among CAPD patients in the US is that during the years 1987 to 1989, very few nephrologists were concerned about dialysis dose. All patients had the “standard” scheme of 4 × 2-liter exchanges per day, irrespective of their residual renal function and peritoneal permeability. The concepts about dialysis dose started to enter our regular practice only in the early nineties. Indeed, when Vonesh and Moran looked at the USRDS results in subsequent years, they found an improvement in the results [116]. They also noted that, at least for male patients, mortality rates for CAPD during recent years were similar to hemodialysis.

**Dr. Harrington:** You used the phrase, as does everyone in the field, “adequacy” of CAPD. Rather than aiming for “adequate” CAPD therapy, what alterations would you envision in CAPD solutions, connections, etc., if we were aiming to optimize CAPD?

**Dr. Oreopoulos:** Even though we should continue to work hard to achieve adequate clearances for our patients, we need better dialysis solutions, and a tremendous effort has been made in the last few years to develop them. We have great difficulty in maintaining our peritoneal dialysis patients over long periods. We all have patients who have been on CAPD for four to five years. However, only a few patients have been on CAPD for more than 10 years. Only one of my patients has been on CAPD for almost 20 years. In any event, these long-term survivors are an exception. I believe this is because the peritoneal membrane undergoes deleterious alterations when it is exposed to the solutions currently used over long periods. These changes lead on the one hand to poor ultrafiltration and on the other to impairment of the defense mechanisms of the peritoneal cavity, probably because of severe damage to the mesothelial cells. As a result, peritonitis in patients who have been on CAPD for five or six years or more is much more severe than the peritonitis early in CAPD. I dread the threat of peritonitis in a long-term patient of mine. I am convinced that the long-term exposure of the peritoneal membrane to unphysiologic, that is, bioincompatible, solutions makes an important contribution to these chronic changes. The present solutions are acidic (pH 5.5) and hyperosmotic. The dialysis industry is under tremendous pressure to come up with new, more “peritoneal friendly” solutions, and I believe that within the next few years we are going to see new peritoneal solutions. In Europe they have developed and use solutions that contain, instead of glucose as the osmotic agent, a large glucose polymer (Icodextrin), which achieves ultrafiltra-
tion by an increased oncotic pressure instead of the increased osmotic pressure caused by dextrose [117]. Over the long term, such solutions probably will produce ultrafiltration without causing significant peritoneal damage. Another possible benefit of such solutions is a lower caloric load and a lower generation of advanced glycosylation end products. Also, new solutions will have a neutral pH and will have bicarbonate or a mixture of bicarbonate and lactate instead of lactate as a buffer. Overall, I believe that the new solutions will probably enable us to maintain the peritoneal membrane for longer periods, but this can only be demonstrated in long-term studies.

Dr. Harrington: Peritoneal dialysis still is used much less frequently in the United States than is hemodialysis. What factors do you believe account for its relative neglect by the US nephrology community?

Dr. Oreopoulos: Alan Nissenson has reviewed the factors that contribute to the wide variation in the application of CAPD worldwide and found that reimbursement policies are critical [118]. However, I understand that in the US, the compensation is similar for the two modalities. There must be other reasons. I believe that peritoneal dialysis, especially now that CAPD is no longer a simple procedure, poses a challenge to the inexperienced nephrologist, who has to work much harder to provide exemplary care to the CAPD patient. Complications such as serious peritonitis, fluid control, and malnutrition call for greater commitment to the management of these patients. Distance from the center is also important. In Canada, where some patients live hundreds of miles away from the treatment centers, it becomes much easier to use CAPD in the patient’s own home. The patient’s attitude also is critical, and CAPD provides a good alternative for those who want to be independent and do not want to come to the hemodialysis facility three times each week. Undoubtedly, CAPD is easier than hemodialysis for children, especially the very young. Other groups who may benefit from CAPD are the elderly, especially those living at home with an assistant or those living in a nursing home. Also, younger diabetics may do better on CAPD. In conclusion, many factors are responsible for the different levels of utilization of CAPD in different centers and in different nations. But I want to emphasize that if a center has only a few patients on CAPD, the nephrologist and the nursing staff will never gain enough experience to give the patient the best possible care. Under these circumstances, the more complications and failures physicians encounter, the less enthusiastic they become in promoting the advantages of CAPD to new patients. You need a critical fraction, which I would set at around 20% to 30% of the total ESRD population of a given center, to achieve and maintain the required expertise. I believe that peritoneal dialysis is complementary to hemodialysis and transplantation in our efforts to provide our ESRD patients with the best possible renal replacement treatment.

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