Kidney International, Vol. 37 (1990), pp. 822–832

NEPHROLOGY FORUM

Assessing the adequacy of dialysis

Principal discussant: RAYMOND M. HAKIM

Vanderbilt University, Nashville, Tennessee

Case presentation

A 59-year-old black man developed end-stage renal disease secondary to hypertension. Maintenance hemodialysis was initiated 9 years ago, and 3 years ago he received a cadaveric renal transplant. He experienced three rejection episodes over the following 6 months, but renal function stabilized at an adequate level.

Two years ago, however, gradually worsening renal function was noted. Renal biopsy at that time showed moderately severe chronic rejection, and hemodialysis was reinstituted one month later. Because of moderate residual urine output (500–600 cc/day), he was dialyzed only 2 times weekly, 4 hours each time, at a blood flow of 200 ml/min and dialysate flow of 500 ml/min. Initially, the blood urea nitrogen (BUN) and serum creatinine were in the range of 62–75 mg/dl and 13–15 mg/dl, respectively; the hematocrit was stable at 25%. Over the next few months, the predialysis BUN (measured on a monthly basis) gradually rose to 90–100 mg/dl; the total CO_2 decreased to 14 mM/liter. The hematocrit was approximately 20% and he required approximately two units of packed red blood cells per month to maintain this level. Kinetic modeling was performed 9 months ago. The KT/V was 0.78 (K = dialyzer clearance at the specified blood flow, T = time on dialysis, V = volume of distribution of urea). The residual glomerular filtration rate was less than 2 ml/min, and the "time-averaged concentration" of BUN (TAC_{urea}) was 73 mg/dl. The protein catabolic rate was calculated to be 0.77 g/kg/day.

Eight months ago, he complained of shortness of breath on exertion and developed paroxysmal nocturnal dyspnea; examination disclosed bilateral rales. His estimated "dry weight" was reduced by 2 kg during hemodialysis and he felt less dyspneic. Seven months ago, however, he complained of a cough productive of sputum, and he had chills and a temperature of 101.8° F.

When first seen at Vanderbilt University Medical Center (VUMC), he had an infiltrate in the right midlung field consistent with pneumonia. A sputum culture subsequently grew *H. influenza*, which was sensitive to amoxicillin/clavulonate. A plain chest film revealed bilateral pleural effusions and signs consistent with congestive heart failure. An echocardiogram demonstrated moderate anterior and posterior pericardial fluid without evidence of tamponade. Neurologic examination showed a fluctuating mental status, with good orientation to person and place but not to time and date. Occasionally, he was confused and was unable to follow a train of thought or to follow commands. His speech was not dysarthric. He had spontaneous myoclonus of his arms and legs at rest. Cranial nerves were intact, and motor strength and reflexes were within normal limits. He had decreased vibratory, light-touch, pinprick, and proprioceptor responses distally in both legs. At the time of admission to VUMC, the BUN was 112 mg/dl; serum creatinine, 19 mg/dl; and total CO_2, 12 mM/liter. The albumin was 2.9 g/dl. Hematocrit was 17%. The administration of intravenous antibiotics was followed by a rapid defervescence. He was dialyzed daily; postdialysis estimated dry weight, which fell to 63 kg, was approximately 7 kg below his previously estimated dry weight, and approximately 28 kg less than his "ideal body weight." The signs and symptoms of fluid overload gradually improved. His mental status and myoclonus also improved gradually, and he was discharged on a regimen of thrice-weekly dialysis, at a blood flow of 350 ml/min and a dialysate flow of 500 ml/min.

Two months following discharge, he felt much better and his appetite had improved. The protein catabolic rate was 1.26 g/kg/day, and the TAC_{urea} was 47 mg/dl; the KT/V was calculated to be 1.38. His estimated dry weight increased gradually to 73 kg without any evidence of fluid overload. The hematocrit has stabilized at 25% without transfusion, and the pain and numbness in his legs have improved significantly.

Five months ago, he was seen in Day Surgery for carpal-tunnel release after he complained of numbness and tingling in the median nerve distribution of both hands, with the symptoms more acute in his left (access) arm than in his right. A radiograph of the hands showed a radiolucent lesion in the head of the left radius. Subsequent pathologic examination of the carpal-tunnel sheath demonstrated staining with Congo red, sensitive to permanganate pretreatment; the tissue also stained positively with fluorescein-conjugated anti-β_2 microglobulin.

Discussion

DR. RAYMOND M. HAKIM (*Director, Clinical Services, Division of Nephrology, and Associate Professor of Medicine, Vanderbilt Hospital, Nashville, Tennessee*): Nephrologists who care for patients undergoing chronic dialysis are often asked by patients to reduce their dialysis time or frequency. The recent availability of "high-flux" and "high-efficiency" dialyzers has made it possible to reduce the time of dialysis to considerably less than that only a decade ago. Economic issues also have contributed to the trend toward shorter dialysis. Unless enough attention is paid to criteria that determine the adequacy of

Presentation of the Forum is made possible by grants from Pfizer, Incorporated; CIBA-GEIGY Corp; Merck Sharp & Dohme; and Sandoz, Incorporated.

dialysis, however, I believe that an inappropriate reduction in dialysis time might not only increase morbidity but also the mortality rate in these patients.

This trend toward shorter dialysis time has come about at a time when technological innovations in the manufacturing of dialysis membranes have led to improvements in their biocompatibility and to a better understanding of the role that blood-membrane interactions play in the pathogenesis of the complications of dialysis therapy. Selection of the appropriate membrane thus has become an increasingly important component of the dialysis prescription. Although biocompatibility of these membranes does affect acute intradialytic events, the characteristics of the dialysis membrane also have an important impact on interdialytic patient morbidity.

The patient presented today highlights specific clinical presentations of these two important issues, that is, dialysis duration and membrane characteristics. Although on the surface these issues are not directly related, I believe that they should be considered together because they relate to the most critical dialysis issue—the adequacy of dialysis. Too short a dialysis leads to inadequate removal of small molecules (urea), whereas use of a relatively impermeable membrane can lead to inadequate removal of "middle-molecules" (for example, β_2-microglobulin). In my discussion today, I will examine each issue separately, but it is obvious that both issues can surface in the same patient, as described in this case.

Urea removal

Studies to determine optimal prescriptions for dialysis usually have compared "standard treatment" with reduced "dialysis dose." Thus, although these studies have allowed us to recognize inadequate dialysis clinically, no studies have defined the "optimal" dialysis prescription. For the purposes of this discussion, I would like to define optimal dialysis prescription as one that does not increase, but may reduce, the morbidity and mortality associated with renal failure and dialysis. Nevertheless, measures for avoiding inadequate dialysis are a first step in the process of optimizing therapy.

The National Cooperative Dialysis Study (NCDS) provided the most comprehensive look at the adequacy of dialysis. Sponsored by the National Institutes of Health, it prospectively examined the clinical outcomes of four different dialysis regimens [1, 2]. These investigations were based on elegant modeling of the dialysis procedure by Gotch [3, 4], Sargent [5], and others [6, 7]. The choice of urea as the principal "uremic toxin" in these models was based on historic considerations [8] and the fact that urea is produced stoichiometrically from net protein catabolism [9]. Urea is also an easily measurable substance of low molecular weight and rapid diffusivity, to which a single-pool kinetic model could be applied. In an attempt to define separately the potential impact of "middle molecules," which were difficult to measure and likely to be governed by diffusion across multiple compartments, dialysis time was used as the surrogate for middle molecules [1]. The underlying, and reasonable, assumption was that longer dialysis time would allow a gradual reduction of the level of these molecules.

In the NCDS study, 165 patients were randomized into 4 groups and each was treated with different dialysis regimens. Table 1 shows these groups and their control parameters. The independent variables used in the study were two primary

Table 1. Designated groups of the NCDS study

Experimental group	Dialysis time (*hours*)	BUN, *mg/dl*	
		Predialysis (*midweek*)	Time-averaged
I (long dialysis time, low BUN)	4.5 to 5.0	60 to 80	50
II (long dialysis time, high BUN)	4.5 to 5.0	110 to 130	100
III (short dialysis time, low BUN)	2.5 to 3.5	60 to 80	50
IV (short dialysis time, high BUN)	2.5 to 3.5	110 to 130	100

treatment parameters, namely, the length of dialysis treatment and TAC_{urea}, defined in a simplified mathematical formulation as:

$$TAC_{urea} = \frac{T_d\,(C_1 + C_2) + I_d\,(C_2 + C_3)}{2\,(T_d + I_d)} \qquad (1)$$

where C_1 is the concentration of BUN at the initiation of dialysis, C_2 is the concentration of BUN at the end of dialysis, C_3 is the concentration of BUN at the beginning of the next dialysis, T_d is the dialysis time, and I_d is the interdialysis time. The results of the study showed a significant difference in clinical outcome, defined by withdrawal from the study either for medical reasons or for hospitalizations other than those related to vascular access [10]. Withdrawal from the experimental phase for medical reasons was significantly greater in the high TAC_{urea} groups than in the lower TAC_{urea} groups; hospitalizations (non-access-related) also were significantly higher in the high TAC_{urea} groups. At the end of one year, the proportion of patients remaining out of the hospital was 86% for group I, 46% for group II, 69% for group III, and 31% for group IV. Dialysis time was not a statistically independent risk factor in clinical outcomes in the initial report [1]. Subsequent analysis, however, indicated that in the 2 groups with high TAC_{urea} (groups II and IV; Table 1), more patients with the shorter dialysis time were hospitalized, even when TAC_{urea} was similar [10, 11].

In the context of this discussion of the adequacy of dialysis, it is important that we review some of the reasons for withdrawal from the study and for hospitalization in the high-TAC_{urea} group. What were the specific long-term complications of inadequate dialysis? Of the patients in group IV (high TAC_{urea}, short time), 44% had at least one morbid cardiovascular event, compared with 11% of patients in the control group (I). Similarly, 17 of 23 hospitalizations and 5 of 14 dropouts in the high-TAC_{urea} groups (group II and IV) were due to cardiovascular causes. Shorter dialysis time also was associated with an increased number of hospitalizations due to cardiovascular morbidity. Of 23 hospitalizations in the short-dialysis group (groups III and IV), 17 (74%) were for cardiovascular causes, whereas only 22% of the total hospitalizations were for cardiovascular causes in the long-dialysis-time groups (groups I and II). Thus, although cardiovascular morbidity is not usually attributed to inadequate dialysis, it became clear in the NCDS study that higher TAC_{urea} and shorter dialysis time are associated with increased cardiovascular morbidity. This increase in mortality occurred despite the absence of significant changes in standard cardiovascular risk factors (such as cholesterol, triglycerides, and heart size). The systolic blood pressure did

increase in the high-TAC_{urea}, short-time group (group IV), but only by a minor degree [10].

Gastrointestinal disorders also were more common in the high-TAC_{urea} groups (groups II and IV). Whereas only one of the patients in the low-TAC_{urea} groups (groups I and III) required hospitalization (for elective gastrointestinal surgery), 14 patients in the high-TAC_{urea} groups (groups II and IV) required hospitalization for gastrointestinal disorders [12]. Gastrointestinal illnesses not requiring hospitalizations also were more prevalent in the high-TAC_{urea} groups [12]. Transfusion requirements were higher and mean hematocrit lower in the high-TAC_{urea} groups [13]; mean values for sensory and motor nerve conduction velocity progressively deteriorated in the high-BUN, short-dialysis-time group (group IV) compared with the low-TAC_{urea} groups (groups I and III) [14]. Thus, the NCDS study clearly demonstrated that, compared with standard treatment at the time of the study (4.5 hours, TAC_{urea} = 52 mg/dl), reduction of the efficiency of dialysis leads to a multiplicity of adverse symptoms, which can persist even after a return to "adequate" dialysis.

During experimental therapy (24 weeks), the mortality rate did not significantly differ among these four groups. But in the 12 months after termination of the study—when patients were returned to their conventional treatment—9 of 13 deaths (predominantly from cardiovascular and infectious causes) occurred in patients previously enrolled in the high-TAC_{urea} groups (groups II and IV). This important observation suggests that the effects of inadequate dialysis are not easily or quickly reversed, even when the intensity and efficiency of dialysis are increased.

More than a decade ago, Teschan and colleagues at Vanderbilt University conducted another important study regarding the adequacy of dialysis [15]. Using the observation that "few if any patients display even the mildest uremic symptoms" at a residual renal function of 10% of normal glomerular filtration rate, Teschan proposed a minimum dialytic clearance equal to 10 ml/min, or 100 liters/week. When this clearance was normalized to the average volume of distribution of urea (total body water), the target dialytic clearance became approximately 3000 ml/week/liter of body water. Therefore, for a regimen of 3 dialyses per week, a target of 1 liter of urea nitrogen clearance/dialysis/liter of body water, or a "dialysis index" defined as KT/V of 1 (K = dialyzer urea clearance at the specified blood flow in ml/min, T = dialysis time in minutes, and V = volume of distribution of urea in ml) was defined as "adequate" and was utilized as a reference point. During an experimental protocol lasting 6 months, in which patients were "underdialyzed" with a total dialytic clearance of 2000 ml/week/liter of body water (equivalent to a KT/V of 0.66), Teschan and colleagues studied a number of neurobehavioral variables and administered a scored clinical self-evaluation questionnaire. They identified manifestations of underdialysis from abnormalities in the electroencephalogram (EEG)-tracing-derived "discriminant score," a computer-derived composite index of abnormal EEG findings [15, 16]. In addition, these underdialyzed patients exhibited deterioration of "continuous memory" (the ability to recall whether a number has been previously displayed among 6 digits) and an increase in "choice reaction time" (the time latency between random flashing of one of three colors [red, yellow, or green light] and the selection by the patient of one of two keys labeled "red" or "not red") [15]. Although these neurobehavioral variables, and the clinical self-evaluation test scores, worsened significantly in all patients, "the patients continued to report their good health to their doctors as well as their satisfaction with their shortened dialysis time." Teschan also noted a decrease in predialysis temperature, an increase in blood pressure, and an increase in the number of transfusions during the experimental phase of this study [15].

Both the NCDS and the Vanderbilt studies pointed out the importance and the interrelationship of dietary intake, particularly protein, and the adequacy of dialysis. During the experimental phase of the Vanderbilt study, albumin concentration significantly decreased [15]. More important, Teschan noted that although urea *clearance* decreased by 33%, the urea concentration rose only by 15% and interdialytic weight gains declined; these findings suggested decreased food intake [15]. Similarly, in the NCDS study, patients in the high-TAC_{urea}, short-dialysis-time group (group IV) had the largest reduction in dietary protein intake, as determined by calculation of protein catabolic rate (PCR) [17]. In fact, a low PCR was second only to a high TAC_{urea} in predicting drop-out and hospitalization rates. In the final analysis of the NCDS study, all these parameters—the TAC_{urea}, the PCR, and dialysis time—have been combined in contour plots that determine the "probability of failure" (as defined by withdrawal for medical reasons, hospitalizations, or death) in dialysis patients [11].

Which of these two parameters of urea removal, TAC_{urea} or KT/V, is a better gauge of "optimal dialysis" for small molecules? Using some simplifying assumptions, such as absence of residual renal function, no change in weight between dialyses, and constant interdialytic interval (dialysis every other day rather than 3 times weekly), a mathematical relationship exists between these two parameters, and calculation of one can be made from measurement of the other [18]. To the extent that these assumptions are not completely valid, however, I favor the use of TAC_{urea} over KT/V. The major reason for this preference is that TAC_{urea} incorporates the measurement of interdialytic changes in urea nitrogen, from which protein catabolic rate and dietary protein intake also can be calculated [9]. As an aside, it should be emphasized that patient-recalled or patient-recorded dietary intakes are not accurate [12]. The assessment of adequacy of dialysis must include not only a low TAC_{urea}, but a low TAC_{urea} in the setting of adequate dietary intake, usually estimated by a dietary protein intake of at least 1 g/kg/day. The patient presented today is an example of a man with "acceptable" predialysis BUN levels but who was both underdialyzed and slowly starving, as documented by his considerable weight loss.

Use of the KT/V parameter is hampered by the fact that the calculation of its components (K, T, V) depends on a host of measurements, all subject to error [19]. Further, the errors most often lead the clinician to overestimate KT/V and thus reduce dialysis time. For example, K (the effective dialyzer clearance) is often taken from in-vitro data, whereas in-vivo clearances tend to be 15% to 20% lower in many dialyzers at the same blood flow. In-vitro measurements also are typically given at blood flows of 200 ml/min, whereas most dialysis is now

performed at blood flows of 300 ml/min and higher in the case of high-efficiency or high-flux dialyzers. Accurate in-vivo clearance data generally are not readily available at these higher blood flow rates [20]. Decreases in clearance toward the end of a dialysis session due to dialyzer fiber occlusion also are not usually considered. Most important, these clearances do not take into account fistula recirculation, which is often in the range of 15% to 20%, thereby resulting in a decrease in effective clearance [21]. Recirculation also can increase at the higher blood flows used today. Thus, in the patients dialyzed with high-flux or high-efficiency dialyzers at blood flows up to 400 ml/min, the effective clearance can be substantially less than one calculated from blood measurements across a dialyzer [21]. Even dialysis time (T_d) often is overestimated by nursing staff as well as by the patient. The T_d is the time of dialysis during which the effective clearance of the dialyzer is applicable. However, if the blood flow is not maximal from initiation of dialysis, then the effective clearance, or effective time, is less than calculated. Surveys of dialysis staff often indicate that the T_d is calculated from the time the patient has the needle inserted until hemostasis is obtained. However, approximately 5% to 10% of this time passes in the absence of effective dialysis. The volume of distribution of urea (V), often assumed to be a constant ratio of total body weight, may not be so in all patients. It can vary depending on body habitus and whether the weight is measured before or after dialysis. Finally, calculation of KT/V does not take into account residual renal function, which can play an important role in the adequacy of dialysis of small-molecular-weight substances. Although calculation of KT/V globally (rather than its components) can be made from the difference between pre- and post-BUN, and would reduce these potential errors, this type of calculation requires more complex mathematical manipulation.

Calculation of TAC_{urea} primarily depends on pre- and post-dialysis urea nitrogen values and is less subject to such errors. However, the BUN level immediately after dialysis can be 5% to 10% lower than that 30 minutes later, because of re-equilibration between the vascular and intracellular pools [22]. The extent of this rebound increases as dialysis efficiency (more urea clearance per unit time) increases. This is particularly applicable to high-flux and high-efficiency dialysis regimens.

What should the target TAC_{urea} be for optimal dialysis? As pointed out recently, we must move beyond the question of adequacy to questions of optimal dialysis dose [23–25]. The answer to this question clearly has two components. What is the acceptable risk or failure rate, and what is tolerable for patients who need to undergo this treatment three times weekly? The NCDS contour plots, representing the probability of failure as a function of TAC and PCR, can provide an answer [10, 18]. If a probability of failure of 10% is acceptable for "adequate" dialysis, and assuming protein intake of 1 g/kg/day and a dialysis time of 4 hours per session, a TAC_{urea} of around 50 mg/dl is the target. To achieve a failure rate of substantially less than 10%—that is, optimal dialysis by my definition—may require even lower TAC_{urea}, again, in the setting of adequate nutrition. Changes in TAC_{urea} are a function of patient-dependent and patient-independent variables (Table 2) and, once determined, can be easily achieved by changes in dialysis time, or dialytic clearance according to the following formula:

Table 2. Variables influencing dialysis prescription

Patient category	Dialysis-related category
Residual renal function	Interdialysis time
Volume of distribution	Intradialysis time
Generation rate of "uremic toxin"	Dialyzer clearance
Endogenous rate	Area times permeability of the dialyzer
Diet	Biocompatibility-related catabolic processes
Access recirculation	Flow rate
	Blood
	Dialysate
	Postdialysis urea rebound

$$\frac{K_{d(current)} \times TAC_{(current)}}{TAC_{(desired)}} = \frac{K_{d(desired,\ new\ time)} \times T_{d(desired)}}{T_{d(current)}} \quad (2)$$

This equation can be solved for either a new dialysis time [$T_{d(desired)}$] if one wishes to use the same dialyzer clearance as shown in the following equation, or for a new dialyzer clearance [$K_{d(desired)}$] if dialysis time remains constant.

$$T_{d(desired)} = \frac{K_{d(current)} \times TAC_{(current)} \times T_{d(current)}}{K_{d(desired,\ new\ time)} \times TAC_{(desired)}} \quad (3)$$

Two groups recently re-analyzed the NCDS data. On the basis of a discontinuous distribution of probability of failure and KT/V values in the NCDS study, Gotch and Sargent have advocated a threshold KT/V of greater than 0.8 at a protein catabolic rate of greater than 0.8 g/kg/day for adequate therapy [26]. More recently, re-analysis of edited data from the NCDS by Keshaviah and Collins indicated that participating patients had a continuous distribution of KT/V [27]. By extrapolating the linear relationship of KT/V with the probability of failure, they concluded that failure is negligible once KT/V reaches approximately 1.3. Although the linear dependence of failure rate to KT/V is somewhat controversial (as I just mentioned, Gotch and Sargent have advocated a KT/V greater than 0.8 as a threshold value), the evidence for a continuous relationship between higher KT/V and lower failure rate is, in my estimation, more compelling.

Does optimization of dialysis (with utilization of KT/V values of greater than 1) affect patient mortality, the ultimate complication of dialysis? Most of the evidence available to examine this question is circumstantial and depends on comparisons of mortality rates for patients in different settings. Retrospective analysis of two groups of hemodialysis patients has shown that patients dialyzed for prolonged periods do indeed have a lower mortality rate. In France, a group of 373 patients, including 63 "high-risk" patients dialyzed for 22 to 24 hours/week (at night), had an overall 10-year survival of 75%—an annual mortality of 2.5% [28]. In the U.S., a group of 362 hemodialysis patients without major systemic illnesses were reported to have a 5-year survival of 84% (annual mortality of 3.2%), and an average hospitalization rate of approximately 10 days per patient per year [29]. A retrospective analysis of the dialysis prescription in this group showed that they had a KT/V of between 1.2 and 1.4 [24].

In sharp contrast, the national annual mortality rate of the

Table 3. Annual mortality rate of ESRD patients in different countries

	Mean age (*yrs*)	% All patients >65 yrs	% New enrollees >65 yrs	Gross mortality (%)
EDTA	–	15.8	–	10.4
W. Germany	58.0	22.6	30.7	11.0
France	57.0	18.8	31.7	7.8
Sweden	59.0	21.7	37.0	14.7
New Zealand	–	–	–	14.2
Australia	–	–	–	13.6
Canada	–	–	–	16.9
Japan	–	10.1	30.0	8.7
USA	55.5	26.0	35.5	22.8

dialysis population in the United States is rising, from 20.6% in 1979 to 23.4% in 1987, despite major advances in dialytic techniques (volumetric control of ultrafiltration, bicarbonate dialysate, and safer heparinization) [30]. This mortality rate is considerably higher than the average annual mortality of 10.4% in European countries [31]. The end point of the survival calculation in the European data was either death or date of change to another treatment mode, such as peritoneal dialysis or transplantation. Thus, actual mortality is likely even lower. Neither the mean age of the dialysis patient (55.5 years in the United States, 57–59 in different European countries) nor the percentage of new patients over 65 years of age (35.5% in the U.S., 31% in West Germany, 37% in Sweden) accounts for all of this difference (Table 3). However, a marked difference in dialysis times between the U.S. and other countries does exist. Whereas in the United States the average dialysis time is 9 hours per week, in Europe the average is 12 hours per week and in Japan it is 15 hrs/week. Furthermore, missed dialyses and "signing off early" decrease the cumulative dialysis dose even further in the U.S., whereas in Europe signing off early is much less common (personal communication, Dr. Allan Hull).

Other studies have also shown that relative risk of mortality, both from cardiovascular and non-cardiovascular causes, was significantly higher for patients dialyzed twice a week compared with those dialyzed three times a week [32]. The former group also had lower body-mass index and cholesterol concentration, consistent with malnutrition. Interestingly, there was no difference in predialysis urea concentration between the groups [32]. Uncontrolled studies of long-term (>10 years) dialysis have shown that survivors have consistently been patients dialyzed for extended periods [33, 34].

A somewhat more direct confirmation of the impact of the dialysis prescription on mortality was presented at the American Society of Nephrology meeting in 1988. The data from Dumler and associates support the notion that the relative risk of mortality is significantly higher when the KT/V is less than 0.8 and when the PCR is less than 0.8 g/kg/day [35]. In another study of 650 patients, the relative risk of mortality was 2.0 when dialysis time was less than 3 hours, 30 minutes, and risk was significantly lower in units practicing kinetic modeling [36].

In conclusion, kinetic modeling provides a reasonable guidepost for measuring the adequacy of dialysis. If one believes that we should "above all, do no harm," we must aim for a KT/V of 1.2 to 1.3 or a TAC_{urea} of less than 50 mg/dl, in the setting of a dietary protein intake of approximately 1 g/kg/day. Understanding and applying these concepts is particularly important in this era of "short-time" dialysis.

β_2 microglobulin removal

The patient under discussion had a second set of problems that confront nephrologists caring for patients on long-term (>5 years) dialysis: elevated serum β_2-microglobulin (β_2m) levels, carpal tunnel compression syndrome, and, occasionally, radiologic evidence for amyloid bone disease. The clinical manifestations of inadequate removal of β_2-microglobulin, a protein with a molecular weight in the range of 11,800 daltons (therefore, a "middle molecule"), are more prevalent and recognized more often in long-term dialysis patients [37]. Deposition of amyloid fibrils that consist of intact β_2m polymers has been recognized in dialysis patients only since 1985 [38, 39], and the association of these fibrils with carpal tunnel syndrome is now well recognized [40, 41]. We now know that β_2m amyloid deposits in bone and produces a newly recognized type of osteoarthropathy characterized by progressively enlarging cystic radiolucent lesions without surrounding sclerosis [37, 42, 43]. Although the radiologic findings in some patients are unambiguous, histologic examination of biopsy material often is required for definitive diagnosis. Clinically, β_2m amyloid arthropathy can produce pain, noninflammatory swelling, and dysfunction of joints, and can result in pathologic fractures, particularly if it involves the femoral head and neck [43]. The pathogenesis of this disorder is not well understood; all dialysis patients without residual renal function have elevated serum levels of β_2m, the precursor of this novel type of amyloid bone disease [44]. Although initial reports suggested that the type of dialysis membrane has no role in the development of the disease, recent studies document that the lowest levels of β_2m occur in patients dialyzed with large-pore (high-flux) hemodialysis or hemofiltration membranes, probably because these membranes allow convective, diffusive, and possibly adsorptive clearance of β_2m [45–48]. A potential role for cuprophane membranes, associated with complement activation [49] and monocyte activation [50] in the increased generation of β_2m also has been proposed [51–53]. In patients chronically dialyzed with large-pore membranes, the incidence of amyloid bone disease is much less than in those dialyzed with cuprophane membranes. Indeed, a recent study pointed out that none of the patients dialyzed solely with the polyacrylonitrile membrane for as long as 15 years developed carpal tunnel syndrome, whereas 6 of 20 patients dialyzed with cuprophane membranes for 10 years had evidence of carpal tunnel syndrome [54]. Thus, the use of biocompatible, larger-pore membranes such as the polyacrylonitrile or polysulfone might prevent (or considerably retard) the development of carpal tunnel syndrome and β_2m amyloid bone disease by allowing a higher rate of removal, a decreased rate of synthesis, and a lower serum level of β_2m [55–57]. I believe that in the near future, adequacy of dialysis will be defined not only by efficient removal of urea, but also by the efficient removal of β_2 microglobulin [58].

A recent study has suggested that the determination of the adequacy of dialysis using KT/V (and urea as a surrogate small molecule) and protein catabolic rate as an index of nutrition might not be independent of the type of dialyzer membrane used. Dialysis by more biocompatible and larger-pore membranes (such as the polyacrylonitrile or polysulfone membrane)

that have higher clearances for middle molecules might require a lower dialysis dose than hemodialysis by cellulosic membrane [59]. This hypothesis, which needs confirmation, might provide a link between the two issues of urea and β_2m removal, an issue that has not been well explored so far.

I conclude that many of the long-term complications of hemodialysis patients are preventable, and that adequacy of dialysis must be defined by removal both of small-molecular-weight (for example, urea) and high-molecular-weight (for example, β_2m) substances. As our understanding of the pathogenesis of these complications improves, we not only can provide patients with adequate dialysis but with optimal dialysis that offers them a long, healthy survival.

Questions and answers

DR. JOHN T. HARRINGTON (*Chief of Medicine, Newton-Wellesley Hospital, Newton, Massachusetts*): You spent a great deal of time discussing the National Cooperative Dialysis Study. That study was published in 1981, so the study itself must have taken place in the late 1970s. By that time studies by Teschan [60] and studies by Kiley [61] in Albany had demonstrated that the incidence of uremic electroencephalographic abnormalities statistically was related to prevailing levels of urea nitrogen and creatinine. Given that information, what was the rationale for dialyzing patients who had BUNs of 100 to 120 mg/dl? Admittedly, I am looking at the results of the NCDS in retrospect. Trying to argue from the vantage point of 1977 to 1979—with the information available at that time—I think one might have predicted that group IV would do the worst.

DR. HAKIM: The rationale of the NCDS and its evolution from the early workshops of the Artificial Kidney-Chronic Uremia Program (AKCUP) of the National Institutes of Health was well outlined by Dr. Wineman (program director and project officer of that study) [62]. In summary, the study design and the protocol were based on several multidisciplinary conferences that started as early as 1972 [3]. The final protocol was developed in December 1974. Dr. Kiley's article, published in 1975 [61], advocated that dialysis therapy be carried out three times weekly, rather than twice weekly, and work by Teschan, Ginn, et al in 1979 did not define at that time a specific target urea [60]. It is fair to say that in 1974 neither a target urea concentration nor the timing of sampling (pre- or post-dialysis, mid-week, or early in the week, etc.) was well known, nor indeed whether urea was the target molecule to be evaluated. The most common index of dialysis at that time was based on the square meter-hour hypothesis [63] and dialysis index [7], which assumed that materials in the 1000 to 3000 dalton range (rather than urea) were what caused the neurotoxicity of uremia. It is also important to keep in mind that even for group IV, whose average TAC_{urea} during the experimental period was 93.6 mg/dl, the mid-week pre-dialysis BUN was 115 ± 9 mg/dl, a value that is still encountered in many dialysis patients; in fact, the TAC_{urea} of group IV (which can be considered as equivalent to the ambient urea level of chronic renal failure patients) was still lower than what some nephrologists, even at present, would consider as guideposts for initiation of hemodialysis.

DR. ANDREW S. LEVEY (*Division of Nephrology, New England Medical Center, Boston, Massachusetts*): Do you think the newer dialysis machines that can precisely control ultrafiltration and the rate of fluid removal, as well as those that yield higher clearances, result in better treatment both in the short term and long term?

DR. HAKIM: Unquestionably, the technologic advances in dialysis therapy helped improve the frequency and severity of intradialytic and interdialytic symptoms. The widespread use of bicarbonate instead of acetate as the base in the dialysate clearly has led to a reduction in the incidence of nausea, vomiting, and hypotension [64]. The introduction of precise ultrafiltration systems and sodium modeling also has allowed the gradual and controlled reduction of plasma water to within 0.2 kg of target and has led to a reduction in the incidence of cramps and hypotension. Finally, the use of so-called "high-flux" and "high-efficiency" large-surface-area dialyzers has allowed consideration of shorter dialysis sessions. However, it is precisely in these situations where kinetic modeling and the determination of adequacy of dialysis become even more important. The shorter the dialysis time, the less the margin of safety in the delivery of adequate dialysis. A reduction of 15 minutes in dialysis time or a reduction of 10% in the clearance of a dialyzer is relatively more important when the prescribed dialysis time is 3 hours or when the assumed clearance is 300 ml/min than when one is dealing with the usual 4-hour dialysis and 200 ml/min urea clearance. In the setting of high-flux dialyzers, higher dialytic clearances at higher blood flows can only be achieved if recirculation in the access is low [21]. Similarly, although one can achieve much higher ultrafiltration rates with these newer dialyzers, there is still limitation on the rate at which these can be tolerated, and adverse symptoms increase exponentially as rates of ultrafiltration exceed 1.2 liters/hr [65].

DR. JEROME P. KASSIRER (*Associate Physician-in-Chief, New England Medical Center*): You indicated that a correlation exists between increasing mortality rate and shortened time on dialysis. Can you elaborate on a possible causal link between the two?

DR. HAKIM: The correlation I meant to emphasize in the discussion of the case is between increasing mortality rate and inadequate or inappropriately short dialysis time. These correlations are primarily based on retrospective studies and include the studies by Laurent [28], Shapiro [29] and, more recently, by Dumler [35] and Levin [36]. The first two studies showed that prolonged survival is associated with long dialysis; the other two studies, so far in abstract form, have shown the inverse, that is, that patients who receive inadequate dialysis ($KT/V < 0.8$) have a higher mortality rate. At the time the study by Levin was undertaken, no high-flux or high-efficiency dialyzers were available, and the study clearly showed that patients dialyzed less than 3.5 hours had a higher mortality rate. During the experimental period of the NCDS study (52 weeks), there was no difference in the mortality rate of patients among the 4 groups, but within one year after returning from experimental therapy to routine dialysis, 13 of the participating patients died, 10 of whom were in the high-TAC_{urea} groups (II and IV) [17]. Specific causes of mortality in these patients included predominantly cardiovascular and infectious causes. The causal links of the pathophysiology relating inadequate dialysis to cardiovascular risk factors are speculative and include arrhythmia from hyperkalemia, congestive heart failure, and hypertension from inadequate removal of volume leading to exacerbation of

coronary artery disease. The link between infection and inadequate dialysis time probably relates to the generally deleterious effects of uremia and malnutrition that result from inadequate dialysis on neutrophil and immune functions [66].

DR. NICOLAOS E. MADIAS (*Chief, Division of Nephrology, New England Medical Center*): Were the patients in the NCDS study stratified according to intensity of dialysis prior to the initiation of the study, or according to other variables of morbidity, such as cardiovascular history and diabetes mellitus?

DR. HAKIM: Prior to randomization, more than 50 variables were analyzed to determine whether any significant baseline differences existed among the 4 experimental groups. This analysis showed that, with few exceptions, the demographic and medical profiles of the 4 groups were quite similar prior to randomization. Only 6 of 50 variables showed marginal statistical significance, and the clinical impact of these differences was judged to be minimum. In any event, all statistical analysis of the experimental phase data were adjusted for control phase values [17].

DR. DAVID B. BERNARD (*Director, Clinical Nephrology, Boston University Medical Center*): With regard to Dr. Harrington's question about the rationale of the NCDS having included a high-BUN group, I presume the reason was that the investigators were not regarding BUN as a toxin per se and were examining its reliability as a marker of uremic "toxins" in general. Theoretically, a group of dialyzed patients might have been identified who had high BUNs yet still did well because other toxins, such as "middle molecules," were being adequately removed by the various experimental modifications in the dialysis prescription.

DR. HAKIM: Yes, that is correct. As I stated earlier, the protocols of the NCDS study were finalized in 1974. The relevance of the numerous biochemical abnormalities in uremic serum, detected by increasingly sophisticated laboratory methods, to the clinical illness called "uremia" was not clear then, and even at present is not well established. I think this uncertainty was another reason for deciding on group IV.

DR. BERNARD: I have another question about the conclusions of the NCDS. All studies were done on cellulosic dialysis membranes, so how certain can we be that the findings are applicable to today's generation of largely synthetic membranes? A TAC_{urea} of 50 achieved on a polyacrylonitrile membrane, for example, might not adequately remove other potential toxins having molecular weights different than that of urea. This point has been made previously [67]. Is this of sufficient importance to justify a further study?

DR. HAKIM: I would strongly favor such a study. At the time the NCDS study was ongoing, only cuprophane or regenerated cellulosic membranes were available; neither bicarbonate dialysate nor controlled ultrafiltration devices were available. The newer synthetic membranes with larger pores and higher clearances of substances in the "middle molecule" range indeed might change the parameters of dialysis adequacy, whether KT/V, TAC_{urea}, or PCR. Indeed, in a recent article, Lindsay proposes that possibility and suggests that the use of large-pore synthetic membranes might allow the safe delivery of a lower dialysis dose [59]. My plea is that until this study is done, we should use what we know in assessing the adequacy of dialysis.

DR. BERNARD: I have a question about dialysis-associated amyloid disease. Some years ago, we studied several specimens of tissue removed at surgery for carpal tunnel syndrome and stained for amyloid. Surprisingly, relatively few—about 20%—stained positively. Does this mean that special staining techniques or specific antibodies are needed to demonstrate the presence of this form of amyloid material, or that causes of carpal tunnel syndrome other than amyloid deposition exist in these patients? Should we not assume that these cases are all amyloid related? What is your experience in this regard?

DR. HAKIM: The incidence of amyloid fibrils in the dialysis-associated carpal tunnel syndrome (CTS) is reported in the literature to range from 0% to 100% [58]. Our own experience suggests that it is present in more than 50% of the patients presenting with CTS. I suspect the major factor involved in the wide range of these reported incidences is the small series of patients and the variable length of time these patients have been on dialysis. As you know, the incidence of CTS and other manifestations of β_2m amyloid deposits increases with dialysis time. Recent evidence suggests that it is particularly prevalent in long-term dialysis patients dialyzed with cuprophane membranes, and less so in patients dialyzed with the polyacrylonitrile or similar other synthetic membranes [54, 58].

DR. BERNARD: My final question! Based on the clearance of β_2-microglobulin across the peritoneal membrane, can you predict whether patients on CAPD are prone to a similar risk of dialysis-associated amyloid disease?

DR. HAKIM: The clearance of β_2-microglobulin across the peritoneal membrane has been reported to be 0.9 ± 0.4 ml/min/1.73 m^2 and the mean loss of β_2-microglobulin was approximately 20 mg/2 liter exchange [68]. In general, the level of β_2-microglobulin in CAPD patients is 70% of that in hemodialysis patients, and there have been few reported cases of amyloid fibrils in CTS of CAPD patients [69]. However, a recent report suggests that the incidence of CTS in patients undergoing peritoneal dialysis (14%) is only slightly less than that in hemodialysis patients (18%) [70]. It is possible that other factors (frequency of peritonitis, dialysate pH, etc.) affect these reported results. In addition, dialysis-associated amyloid disease is a disease of long-term dialysis patients, and few centers have large series of patients on long-term peritoneal dialysis. Therefore it is difficult to arrive at a specific incidence in these patients. What is clear is that peritoneal dialysis is not a therapy for the complication of high β_2-microglobulin levels in dialysis patients.

DR. RONALD D. PERRONE (*Division of Nephrology, New England Medical Center*): Could you bring us up to date on other markers of the uremic state? Is there any information on more direct measurements of altered cell metabolism, such as sodium-potassium-ATPase? Has anything been done to make such measurements useful clinically?

DR. HAKIM: Several candidate molecules that accumulate in chronic renal failure have been proposed to explain the uremic state. These range from parathyroid hormones [71] to indoles, phenols, and polyamines [72]. It is fair to say that although all these putative molecules alter cellular activity in one way or another, and mimic in animal experiments some uremic symptoms, almost all of these studies have been tested in acute toxicity conditions, with little attention paid to intracellular concentrations, synergy, or tachyphylaxis [72]. Our inability to quantitate indices of the disabling "uremic illness" plays a role

in this confusion. I believe that the quantitative probes of the nervous system function proposed by the studies of Teschan [60] so far present the best assessment of the clinical illness of uremia. The task, difficult as it is, is to develop these indices and attempt to correlate them with specific biologic parameters.

DR. KASSIRER: Anemia could produce symptoms in patients with advanced renal failure. Has anemia been factored out as one of the important features that cause substantial disability? We should have some information on this issue now that synthetic erythropoietin is being made available.

DR. HAKIM: The advent of erythropoietin (EPO) in combination with biocompatible dialyzers and the other technologic advances discussed earlier indeed might force us to change our perception of what the "uremic" state is and the disabilities that may be associated with it. Reports have appeared on the biologic effects of EPO [73, 74], and there are a number of abstracts on the symptomatic changes experienced by dialysis patients with EPO; it is clear that patients' fatigue as well as their well-being and sexuality are improved with the use of EPO [75, 76]. However, its long-term effects on morbidity and mortality are not yet known. Nevertheless, I think the issue of the adequacy of dialysis will be more important with the advent of EPO because the net clearance of urea, potassium, and phosphate is likely to be reduced to a variable extent in patients on EPO, depending on the respective distribution of these substances in intracellular and extracellular spaces.

DR. HARRINGTON: I am struck by the remarkable difference in mortality between the United States, almost 25%, and Europe, roughly 10%. You mentioned the difference in dialysis time. What other factors might play a role in the difference in mortality rates? My own bias is that the difference relates to comorbid events. Are there data on specific differences in the prevalence of comorbid conditions such as diabetes or ischemic heart disease?

DR. HAKIM: Unfortunately no data on comorbid events are uniform enough to be comparable between different countries, such as the United States registry and the European registry. Each country has a different way of providing dialysis-related information. However, even in the younger age group (less than 34 years), there is a major difference in mortality. For patients less than 34 years, the annual European mortality is 6%, whereas in the United States, it is 12.7% [31]. Dr. Allan Hull, who was kind enough to share a manuscript he is preparing on this issue, suggests in that manuscript that neither differences in age nor prevalence of diabetes can account for these differences. Instead, he suggests that dialysis time, which is longer in Europe (12 hrs/week) and in Japan (15 hrs/week) than in the United States (9 hrs/week), might be a factor. One of my own biases is that this difference in mortality may be partly due to the use of non-biocompatible (predominantly cuprophane) membrane in the U.S., whereas in Europe and Japan, the use of biocompatible dialysis membranes is much more common.

DR. MADIAS: How does dialyzer reuse affect the adequacy of dialysis?

DR. HAKIM: For cuprophane dialyzers, if the residual fiber bundle volume of the dialyzer is greater than 75% of the original volume (which is the standard cut-off for reuse), the clearance and ultrafiltration characteristics are not significantly affected; therefore, cuprophane dialyzer reuse should not affect the adequacy of dialysis [77]. No such data are available for the more "open pore structure" of the high-flux membranes, and it is important to get this information.

DR. HARRINGTON: I have two questions. First, how often do you calculate TAC_{urea} nitrogen and make alterations based on the results? Second, in patients with carpal tunnel syndrome, where else in the body does the β_2-microglobulin deposit, and does it contribute to disease elsewhere?

DR. HAKIM: These are two important questions. The first addresses the practical steps in the determination of the adequacy of dialysis. We determine fistula recirculation during the initiation of dialysis on every patient or whenever we are using a new access for the first time to get a "baseline" value. We also start every patient on 4 hours of dialysis, because it is much easier to reduce dialysis time than to increase it. We do kinetic modeling using "pre-, post-, and pre-BUN," and determine endogenous residual renal function, if present, within one month of initiation of dialysis. We then calculate TAC_{urea} and KT/V and PCR from these data. Because residual renal function decreases rapidly after the first few months on hemodialysis, we use this initial kinetic modeling data as an index to make sure patients are not underdialyzed. We repeat all measurements quarterly and aim to keep KT/V at 1.2 and TAC_{urea} at 50 mg/dl. Under these conditions, PCR often rises gradually to at least 1.0 g/kg/day. If KT/V is less than 1.0, we will increase dialysis time, increase dialytic clearance (by using large-surface-area dialyzers), or, if recirculation is greater than 20%, correct the recirculation problem by revising the arteriovenous fistula.

DR. HARRINGTON: Do you know specifically whether β_2-microglobulin deposits in heart valves or in the myocardium?

DR. HAKIM: The extent of extraskeletal soft tissue involvement by β_2-microglobulin-related amyloidosis appears to be much less than its involvement with the skeletal system [58], but autopsy reports have documented the presence of β_2-microglobulin amyloid deposits in vascular tissue including the heart, although I am not sure they specifically address the issue of cardiac valves. It is important to know that there are several types of amyloidosis related to different types of paraproteins. The diagnosis of β_2-microglobulin amyloidosis should be made not only by the classic birefringence, but by the sensitivity of the tissue staining of Congo red to potassium permanganate, and more directly by its uptake of antibodies to β_2-microglobulin.

DR. KLEMENS MEYER (*Fellow in Nephrology, New England Medical Center*): As you mentioned, cardiovascular disease is a major source of comorbidity in dialysis patients. Suppose one compares well-dialyzed patients with the rest of the population. Do aggressive attempts to prevent or treat coronary disease have more effect, less effect, or comparable effects in those two groups?

DR. HAKIM: If one is comparing cardiovascular morbidity between well-dialyzed and poorly dialyzed patients, then, as the NCDS has shown, the incidence of cardiovascular morbidity is much higher in the poorly dialyzed patients [10]. Therefore, optimal dialysis will prevent or reduce the incidence of cardiovascular events. As far as whether the treatment of coronary artery disease is less or more effective in the dialyzed patients, I do not have the data, but I suspect the answer is yes, because a well-dialyzed patient is also one who can respond better to interventions.

DR. GEETHA NARAYAN (*Division of Nephrology, St. Eliza-*

beth's Hospital, Boston): You commented that TAC_{urea} might be a better way of measuring the adequacy of dialysis than is KT/V. We have made observations in some of our patients on high-flux dialysis that suggest the same. Our patients have KT/Vs in the "adequate" range by current accepted standards, along with adequate PCRs. Yet they have mid-week predialysis BUNs higher than what you would predict from the given KT/V and PCR. Could this discrepancy be due to the rapid rebound in BUN within minutes of completing dialysis that you referred to earlier? In all patients, the dialysis time is charted by the dialysis clock, not the wall clock, and inadequate dialysis due to compromised time would not be a factor.

DR. HAKIM: Recirculation might be the culprit in this situation. Using high-flux dialyzers at high blood flow rates will increase the percentage of recirculation and decrease effective dialytic clearance [21]. If one uses calculated or in-vitro clearances, a patient can have adequate KT/V but inadequate measured TAC_{urea} value and high mid-week BUN. A hint to that problem can be found if the calculated volume of distribution of urea is higher than expected (> 0.65 of body weight). The extent of rebound in urea concentration following termination of dialysis has been recently shown to be higher the greater the dialytic clearance. In the case of high-flux dialyzers, the rebound in urea concentration immediately post dialysis can be 8% to 10% [22].

DR. NARAYAN: We have been using blood flows of only 350 to 400 ml/min. We have calculated recirculation in many of these patients, and it has not been excessive. The post-BUN value that we are measuring, before rebound, might be lower than the value after rebound, so could it be that the calculated KT/V overestimates the actual dialysis delivered? Could that explain the higher mid-week BUN levels we are seeing? Perhaps we should be using a double-pool urea model instead of the single-pool model currently used.

DR. HAKIM: Both post-dialysis BUN rebound and access recirculation could account for this difference. As far as using a double-pool model for urea, it should be considered only if the dialytic clearance approaches the clearance of urea from intracellular to extracellular spaces. This is estimated to be approximately 600 ml/min, although substantial individual variations exist; urea double-pool models, which add considerably to the complexity of the calculation, do not need to be considered at currently available dialytic clearances.

DR. JEANINE CARLSON (*Chief of Medicine, St. Margaret's Hospital, Boston*): The data presented in your slides demonstrate a correlation between morbidity and TAC_{urea}. Although it will vary from patient to patient, we don't usually institute dialysis until their BUN is in the range of 100 to 200 mg/dl, which is higher than any of the TAC_{urea} levels I saw on your slides. Would you comment on when you begin dialysis? Specifically, do you think it would be beneficial to our patients if we started sooner?

DR. HAKIM: Many patients with chronic renal failure deny symptoms until their BUN is at the levels you mentioned, and patients and physicians are often reluctant to start dialysis in the absence of uremic symptoms. My own feeling is that patients are generally apprehensive of dialysis and tolerate or adjust to increasing incapacitation. Patients also spontaneously self-restrict their protein intake with advancing renal failure; therefore their BUN does not reflect the degree of renal insufficiency [78]. Dialysis therefore is initiated in many patients after loss of greater than 10% of body weight. On the other hand, work by Shemesh has clearly shown that serum creatinine is a poor reflection of true GFR [79]. Thus, what we have adopted in our clinical practice is the idea of determining true GFR by ^{125}I iothalamate. We prepare patients' access when the GFR is less than 15 ml/min, and we initiate dialysis when the GFR is less than 10 ml/min or if the patient loses more than 5% of body weight. For many patients dialysis is a lifelong commitment, so this preparation must be accompanied by a strong emphasis on compliance, because patients who do not "feel" sick prior to initiation of dialysis may be less likely to be convinced that they need dialysis three times per week.

DR. LEVEY: If the TAC_{urea} in a patient on peritoneal dialysis is 50 mg/dl, it is likely that the protein catabolic rate can't be as high as 0.8 g/kg/day. In fact, that protein intake is only 70% to 80% of the recommended dietary protein intake for such patients. Thus we are forced to the conclusion that the average BUN for patients on peritoneal dialysis ought to be about 80 mg/dl. In fact, that is the range I aim for in my practice. My patients who are doing well and eating well do have BUNs in the 80s. How does that observation square with the notion that urea is a good marker for the toxic substance that determines dialysis adequacy?

DR. HAKIM: The weekly dialytic clearance by peritoneal dialysis is generally two-thirds what hemodialysis can deliver. The reasons peritoneal dialysis patients do not have higher TAC_{urea} levels are several. In the first place, many patients initiated on peritoneal dialysis retain their residual renal function for longer periods; second, many peritoneal dialysis patients generally do not eat a lot of protein, because they have early satiety from the calories they receive from dialysate glucose. Many peritoneal dialysis patients are in fact protein malnourished, and I believe that this, along with the protein loss in the dialysate, might account for the high incidence of peritonitis and the generally low BUN that they have despite reduced dialytic clearance. As far as what target urea to aim for, I would suggest that until we have a study to monitor the adequacy of dialysis in peritoneal dialysis patients in terms of urea concentration, the emphasis should be on a PCR of greater than 0.8 g/kg/day; the frequency of exchange should be adjusted to allow as low a TAC_{urea} as practical in this setting.

DR. MICHAEL P. MADAIO (*Division of Nephrology, New England Medical Center*): Is the incidence of amyloidosis dependent on the type of membrane you use? I ask that question because it is well known that different membranes have different effects on the immune system.

DR. HAKIM: There was some confusion about this issue in the initial studies because the studies compared patients who were on one or another type of membrane for a relatively short period and because patients in different groups were not matched for residual renal function, a major determinant of β_2-microglobulin serum concentration [68]. Subsequently, other studies have shown that patients who have been on hemodialysis using synthetic membranes, such as the polyacrylonitrile (PAN) membrane, have a significantly lower level of β_2-microglobulin and a lower incidence of amyloidosis than do patients dialyzed with the cuprophane membrane [54]. The question that is being investigated at present is whether this is only due to the ability of the synthetic membrane to absorb or

clear β_2-microglobulin or whether the cuprophane membrane, which is well known to elicit a number of inflammatory responses, plays a role in the increased synthesis of β_2-microglobulin [52]. In our laboratory, preliminary work suggests that, indeed, mononuclear cells harvested from patients dialyzed with cuprophane membrane have a significantly higher rate of β_2-microglobulin release than when the cells are harvested during the time the patients are dialyzed with a biocompatible membrane. However, this remains to be confirmed. Finally, although many long-term dialysis patients have elevated β_2-microglobulin, the triggering factor(s) that lead this substance to form into amyloid deposits in skeletal sites is not known [80, 81].

Reprint requests to Dr. R. Hakim, Division of Nephrology, Vanderbilt University, Nashville, Tennessee 37232, USA

Acknowledgments

The author would like to thank Drs. William Stone, Gerald Schulman, P. Kesheviah, and Thomas Parker for valuable input and discussion; Dr. Thomas Parker for the use of Table 2 and equations (2) and (3); and Dr. Allan R. Hull for the use of Table 3.

References

1. Lowrie EG, Laird NM, Parker TF, Sargent JA: Effect of the hemodialysis prescription on patient morbidity. Report from the National Cooperative Dialysis Study. *N Engl J Med* 305:1176–1181, 1981
2. Lowrie EG, Laird NM (eds): Cooperative Dialysis Study. *Kidney Int* (suppl 13) 23:S1–S122, 1983
3. Gotch FA, Krueger KK (eds): Adequacy of dialysis. *Kidney Int* (suppl 2) 7:S1–S263, 1975
4. Gotch FA: A quantitative evaluation of small and middle molecule toxicity in therapy of uremia. *Dial Transplant* 9:183–192, 1980
5. Sargent JA: Control of dialysis by a single-pool urea model: The National Cooperative Dialysis Study. *Kidney Int* (suppl 13) 23: S19–S25, 1983
6. Frost TH, Kerr DNS: Kinetics of hemodialysis: A theoretical study of the removal of solutes in chronic renal failure compared to normal health. *Kidney Int* 12:41–50, 1977
7. Babb AL, Strand MJ, Uvelli DA, Milutinovic J, Scribner BH: Quantitative description of dialysis treatment: A dialysis index. *Kidney Int* (suppl 2) 7:S23–S29, 1975
8. Schreiner GE: The search for the uremic toxin(s). *Kidney Int* (suppl 3) 7:S270–S275, 1975
9. Borah MD, Schoenfeld PY, Gotch FA, Sargent JA, Wolfson M, Humphreys MH: Nitrogen balance during intermittent dialysis therapy of uremia. *Kidney Int* 14:491–500, 1978
10. Harter H: Review of significant findings from the National Cooperative Dialysis Study and recommendations. *Kidney Int* (suppl 13) 23:S107–S112, 1983
11. Laird NM, Berkey C, Lowrie EG: Modeling success or failure of dialysis therapy: The National Cooperative Dialysis Study. *Kidney Int* (suppl 13) 23:S101–S106, 1983
12. Schoenfeld PY, Henry RR, Laird NM, Roxe DM: Assessment of nutritional status of the NCDS population. *Kidney Int* (suppl 13) 23:S80–S88, 1983
13. Santiago G, Rao TKS, Laird NM: Effect of dialysis therapy on the hematopoietic system: The National Cooperative Dialysis Study. *Kidney Int* (suppl 13) 23:S95–S100, 1983
14. Teschan PE, Bourne JR, Reed RB, Ward JW: Electrophysiological and neurobehavioral response to therapy. The NCDS Study. *Kidney Int* (suppl 13) 23:S58–S65, 1983
15. Teschan PE, Ginn HE, Bourne JR, Ward JW: Neurobehavioral probes for adequacy of dialysis. *Trans Am Soc Artif Intern Organs* 23:556–560, 1977
16. Hughes JR: Correlations between EEG and chemical changes in uremic electroencephalopathy. *Clin Neurophysiol* 48:583–590, 1980
17. Parker TF, Laird NM, Lowrie EG: Comparison of the study groups in the National Cooperative Dialysis Study and a description of morbidity, mortality and patient withdrawal. *Kidney Int* (suppl 13) 23:S42–S49, 1983
18. Lowrie EG, Teehan BP: Principles of prescribing dialysis therapy: Implementing recommendations from the National Cooperative Dialysis Study. *Kidney Int* (suppl 13) 23:S113–S122, 1983
19. Goldstein MB, Jindal KK: Urea kinetic modelling. *Semin Dial* 1:82–85, 1988
20. Collins A, Ilstrup K, Hanson G, Berkseth R, Keshaviah P: Rapid high-efficiency hemodialysis. *Artif Organs* 10:185–188, 1986
21. Collins A, Hanson G, Berkseth R, Keshaviah P: Recirculation and effective clearances (*abstract*). *Kidney Int* 33:219, 1988
22. Pedrini LA, Zereik S, Rasmy S: Causes, kinetics and clinical implications of post hemodialysis urea rebound. *Kidney Int* 34: 817–825, 1988
23. Lundin AP: Hemodialysis: How much is enough? *Semin Dial* 1:8–10, 1988
24. Keshaviah P, Collins A: Hemodialysis: How much is enough? *Semin Dial* 1:3–4, 1988
25. Lindsay RM: Hemodialysis: How much is enough? *Semin Dial* 1:6–8, 1988
26. Gotch F, Sargent J: A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int* 28:526–534, 1985
27. Keshaviah P, Collins A: A re-appraisal of the National Cooperative Dialysis Study (*abstract*). *Kidney Int* 33:227, 1988
28. Laurent G, Calemard E, Charra B: Long dialysis: A review of fifteen years in one center, 1968–1983. *Proc Eur Dial Transplant Proc* 20:122–134, 1983
29. Shapiro FL, Umen A: Risk factors in hemodialysis patient survival. *ASAIO J* 6:176–184, 1983
30. End Stage Renal Disease Facility Survey tables. 1987. *Contemp Dial Nephrol* 10:35–37, 1989
31. Brunner FP, Broyer M, Brynger H, Challah S, Dykes SR, Fassbinder W, Oules R, Rizzoni G, Selwood NH, Wing AJ: Survival on renal replacement therapy: Data from the EDTA Registry. *Nephrol Dial Transplant* 3:109–122, 1988
32. Degoulet P, Legrain M, Reach I, Aime F, Devries C, Rojas P, Jacobs C: Mortality risk factors in patients treated by chronic hemodialysis. *Nephron* 31:103–110, 1982
33. Neff MS, Eiser AR, Slifkin RF, Baum M, Baez A, Gupta S, Amarga E: Patients surviving 10 years of dialysis. *Am J Med* 74:996–1004, 1983
34. Gutman RA: Characteristics of long-term (14 years) survivors of maintenance dialysis. *Nephron* 33:111–115, 1983
35. Dumler F, Zasuwa G, Peterson E, Levin NW: Hemodialysis survival in a single institution. A risk factor approach (*abstract*). *Kidney Int* 35:245, 1989
36. Levin NW, Held PJ, Diamond LH, Bovjerg R, Pauly MV: Mortality impacts of shorter dialysis procedures (*abstract*). *Kidney Int* 35:254, 1989
37. Fenves AZ, Emmett M, White MG, Greenway G, Michaels DB: Carpal tunnel syndrome with cystic bone lesions secondary to amyloidosis in chronic hemodialysis patients. *Am J Kidney Dis* 7:130–134, 1986
38. Gorevic PD, Casey TT, Stone WJ, DiRaimondo CR, Prelli FC, Fangione B: Beta-2 microglobulin is an amyloidogenic protein in man. *J Clin Invest* 76:2425–2429, 1985
39. Gejyo F, Yamada T, Odani S, Nakagawa Y, Arakawa M, Kunitomo T, Kataoka M, Suzuki M, Hirasawa Y, Shirahama T, Cohen AS, Schmid K: A new form of amyloid protein associated wtih chronic hemodialysis was identified as β_2-microglobulin. *Biochem Biophys Res Commun* 129:701–706, 1985
40. Laurent G, Calemard E, Charra B: Dialysis related amyloidosis. *Kidney Int* (suppl 24) 33:32–34, 1988
41. Van Ypersele de Strihou C, Honhon B, Vandenbroucke JM, Huaux JP, Noel H, Maldague B: Dialysis amyloidosis. *Adv Nephrol* 17:401–422, 1988
42. Bouteiller G, Ton That H, Goudable C: Amyloidosis in chronic hemodialysis: rheumatologic aspects. *Contrib Nephrol* 62:67–74, 1988
43. DiRaimondo CR, Casey TT, DiRaimondo CV, Stone WJ:

Pathologic fractures associated with idiopathic amyloidosis of bone in chronic hemodialysis patients. *Nephron* 43:22–27, 1986
44. CASEY TT, STONE WJ, DIRAIMONDO CR, BRANTLEY BD, DIRAIMONDO CV, GOREVIC PD, PAGE DL: Tumoral amyloidosis of beta 2-microglobulin origin in association with long-term hemodialysis. *Hum Pathol* 17:731–738, 1986
45. MAYER G, THUM J, WOLOSZCZUK W, GRAF H: Beta-2-microglobulin in hemodialysis patients. Effects of different dialyzers and different dialysis procedures. *Am J Nephrol* 8:280–284, 1988
46. ZINGRAFF J, BEYNE P, URENA P, UZAN M, MAN NK, DESCHAM ØS-LATSCHA B, DRUEKE T: Influence of haemodialysis membranes on β_2-microglobulin kinetics: in vivo and in vitro studies. *Nephrol Dial Transplant* 3:284–290, 1988
47. KAISER JP, HAGEMANN J, VON HERRATH D, SCHAEFER K: Different handling of beta 2-microglobulin during hemodialysis and hemofiltration. *Nephron* 48:132–135, 1988
48. FLOGE J, GRANOLLERAS C, BINGEL M, DESCHODT G, BRANGER B, OULES R, KOCH KM: β_2-microglobulin kinetics during haemodialysis and haemofiltration. *Nephrol Dial Transplant* 1:223–228, 1987
49. HAKIM RM, FEARON DT, LAZARUS JM: Biocompatibility of dialysis memembranes: Effects of chronic complement activation. *Kidney Int* 26:194–200, 1984
50. SZTEIN MB, VOGEL SN, SIPE JD, MURPHY PA, MIZEL SB, OPPENHEIM JJ, ROSENTREICH DL: The role of macrophages in the acute-phase response SAA inducer is closely related to lymphocyte activating factor and endogenous pyrogen. *Cell Immunol* 63:164–169, 1981
51. BOMMER J, SEELIG P, SEELIG R, GEERLINGS W, BOMMER G, RITZ E: Determinants of plasma β_2 microglobulin concentration: Possible relation to membrane bicompatibility. *Nephrol Dial Transplant* 2:22–25, 1987
52. DRUEKE T, ZINGRAFF J: Beta-2 microglobulin-related amyloidosis in long-term hemodialysis patients: possible pathogenetic mechanisms. *Contrib Nephrol* 59:99–109, 1987
53. FLOEGE J, GRANOLLERAS C, KOCH KM, SHALDON S: Which membrane? Should beta-2-microglobulin decide on the choice of today's hemodialysis membrane? *Nephron* 50:177–181, 1988
54. CHANARD J, BINDI P, MAHEUT H, DION JJ, LAVAUD P, BIREMBAULT P, LACOUR F, TOUPANCE O: Low prevalence of carpal tunnel syndrome in patients hemodialyzed with high-flux membrane (*abstract*). *Nephrol Dial Transplant* 3:551, 1988
55. BLUMBERG A, BURGI W: Behavior of β_2-microglobulin in patients with chronic renal failure undergoing hemodialysis, hemodiafiltration and continuous ambulatory peritoneal dialysis (CAPD). *Clin Nephrol* 27:245–249, 1987
56. ROCKEL A, HERTEL J, FIEGEL P, ABDELHAMID S, PANITZ N, WALB D: Permeability and secondary membrane formation of a high flux polysulfone hemofilter. *Kidney Int* 30:429–432, 1986
57. JORSTADT S, SMEBY LC, BALSTAD T, WIDEROE TE: Removal, generation and adsorption of beta-2 microglobulin during hemofiltration with five different membranes. *Blood Purif* 6:96–105, 1988
58. STONE WJ, HAKIM RM: Beta-2-microglobulin amyloidosis in long term dialysis patients. *Am J Nephrol* 9:177–183, 1989
59. LINDSAY RM, SPANNER E: A hypothesis: The protein catabolic rate is dependent upon the type and amount of treatment in dialyzed uremic patients. *Am J Kidney Dis* 13:382–389, 1989
60. TESCHAN PE, GINN HE, BOURNE JR, WARD JW, HAMEL B, NUNNALLY JC, MUSSO M, VAUGHN WK: Quantitative indices of clinical uremia. *Kidney Int* 15:676–697, 1979
61. KILEY JE, HINES O: Electroencephalographic evaluation of uremia. *Arch Intern Med* 116:67–73, 1975
62. WINEMAN RJ: Rationale of the National Cooperative Dialysis Study. *Kidney Int* (suppl 13) 23:58–510, 1983
63. BABB AL, POPOVICH RP, CHRISTOPHER TG, SCRIBNER BH: The genesis of the square meter-hour hypothesis. *Trans ASAIO* 17: 81–91, 1971
64. HAKIM RM, PONTZER MA, TILTON D, LAZARUS JM, GOTTLIEB MN: Effects of acetate and bicarbonate dialysis in stable chronic dialysis patients. *Kidney Int* 28:535–540, 1985
65. RONCO C, BRENDOLAN A, BRAGANTINI L, CHIARAMONTE S, FABRIS A, FERIANI M, DELL'AQUILA R, MILAN M, SCABARDI M, PINNA V, LAGREC G: Technical and clinical evaluation of different short, highly efficient dialysis techniques. *Contrib Nephrol* 5:61–72, 1987
66. LEVIN SL, VAN EPPS D: Neutrophil and monocyte alterations in chronic dialysis patients. *Am J Kidney Dis* 9:381–395, 1987
67. LINDSAY RM, HENDERSON LW: Adequacy of dialysis. *Kidney Int* (suppl 24) 33:S92–S99, 1988
68. DIRAIMONDO CR, MCCARLEY P, STONE WJ: Beta-2 microglobulin in peritoneal dialysis patients: serum levels and peritoneal clearances. *Perit Dial Bull* 8:43–47, 1988
69. TIELMANS, C, DRATIRA M, BERGMANN P, GOLDMAN M, FLAMION B, COLLART F, WENS R: Continuous ambulatory peritoneal dialysis vs haemodialysis: A lesser risk of amyloidosis? *Nephrol Dial Transplant* 3:291–294, 1988
70. BENZ RL, SIEGFRIED JW, TESCHAN B: Carpal tunnel syndrome in dialysis patients: Comparison between continous ambulatory peritoneal dialysis and hemodialysis populations. *Am J Kidney Dis* 11:473–476, 1988
71. MASSRY SG: Parathyroid hormone as a uremic toxin, in *Textbook of Nephrology*, edited by MASSRY SG, GLASSOCK RJ, Baltimore, Williams & Wilkins, 1989, pp 1126–1144
72. CAMPBELL RA: Other uremic toxins, in *Textbook of Nephrology*, edited by MASSRY SG, GLASSOCK RJ, Baltimore, Williams & Wilkins, 1989, pp 1144–1153
73. ESCHBACH JW, EGRIE JC, DOWNING MR, BROWNE JK, ADAMSON JW: Correction of the anemia of end-stage renal disease with recombinant human erythropoietin: results of a combined phase I and II clinical trial. *N Engl J Med* 316:73–78, 1987
74. BOMMER J, ALEXION C, MULLER-BUHL U, EIFERT J, RITZ E: Recombinant human erythropoietin therapy in haemodialysis patients—dose determination and clinical experience. *Nephrol Dial Transplant* 2:238–242, 1987
75. KEOWN PA: The effect of recombinant human erythropoietin upon quality of life and functional capacity of anemic patients or chronic hemodialysis (*abstract*). *Kidney Int* 35:195, 1989
76. GIBILARO SD, DELANO BG, QUINN R, LUNDIN AP, GALONSKY R, FREIDMAN EA: Improved quality of life while receiving recombinant erythropoietin (*abstract*). *Kidney Int* 35:247, 1989
77. OGDEN DA: Simultaneous reprocessing of hollow-fibre dialyzers and blood tubing sets for multiple use. *Dial Transplant* 13:366–375, 1984
78. HAKIM RM, LAZARUS JM: Biochemical parameters in chronic renal failure. *Am J Kidney Dis* 11:238–247, 1988
79. SHEMESH O, GOLBETZ H, KRISS JP, MYERS BD: Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int* 28:830–838, 1985
80. HAMPL H, LOBECK H, BARTEL-SCHWAZE S, STEIN S, EULITZ M, LINKE R: Clinical, morphologic, biochemical and immunohistochemical aspects of dialysis associated amyloidosis. *Trans ASAIO* 33:250–259, 1987
81. DIRAIMONDO CR, STONE WJ: A β_2m amyloidosis. *Int J Artif Organs* 10:281–283, 1987