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Introduction:
Adequacy of Dialysis: Problems and Challenges

> *"When you can measure what you are speaking about and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind."*
>
> Lord Kelvin (1824–1907)

Hemodialysis, which began as an exploratory attempt to sustain the lives of selected patients in the 1950s, now provides life-saving therapy to millions of individuals with kidney failure worldwide. After the introduction of maintenance hemodialysis, the availability of other forms of therapy for kidney failure led to the adoption of the more inclusive term of *renal replacement therapy* to encompass hemodialysis and peritoneal dialysis, as well as kidney transplantation. The present issue of *Seminars in Nephrology* addresses only the adequacy of hemodialysis. The use of the word *dialysis* in the title of this issue, its articles, and the text that follows refer only to that of hemodialysis and its adequacy.

Unfortunately, despite major advances in the technology of hemodialysis and in the management of its complications, the morbidity and mortality of patients on dialysis remain high, at a time that the incidence and prevalence of kidney failure persistently are increasing. Hence, the early and continued concern with the adequacy of dialysis and of the elusive quest for optimal dialysis.

Because the ultimate intent of any renal replacement therapy is to provide optimal treatment, it is only fair to admit from the outset that no matter how sophisticated dialysis may become, it would be impossible for it to replace the homeostatic role of the kidneys. The normal functions of the kidney are just too complex and its continuous response to variable bodily needs is integrated too finely to duplicate or even attempt to replicate with any artificial form of therapy, even if it were to be delivered daily or continuously. Hence, the importance of providing at least adequate dialysis. Regrettably, although the adequacy of dialysis has been a lofty goal, there still is no consensus of what constitutes adequate dialysis. Its principal limitation stems from the admonition of Lord Kelvin quoted earlier. We just do not have a measure of it and cannot express it in numbers.

Soon after the introduction of hemodialysis, it became evident that the features of uremia, another vague and nonquantified term, respond slowly and actually progress on dialysis, and that more dialysis was necessary for good health than that needed to sustain life. The initial response throughout the 1970s was to increase the size of the dialyzer, blood or dialysate flow rates, and time or frequency of dialysis; all of which yielded positive results but were empiric responses, as has been the case with most of what we wishfully would like to term the *science of dialysis*. To cite the example of just one issue that finally is being questioned, why is dialysis delivered 3 times per week?

The only exception to this handicap has been that of the dose of dialysis. In the early 1980s, the National Cooperative Dialysis Study for the first time established urea kinetics as a quantifiable measure of dialysis dose. What began as TAC_{urea}, soon was reworked and improved to that of single-pool Kt/V, and by the 1990s to that of equilibrated Kt/V. The use of urea, a relatively small molecule, as a surrogate marker of dialysis dose has been criticized from the outset. On the other hand, none of the early and concerted efforts to identify a dialyzable uremic toxin have yielded an identifiable factor that could be used as a preferred measure. One remnant of these initial concerns still in vogue is that of the middle molecules, a notion that remains vague, nonquantified, and, at best, an elusive hypothesis that awaits clarification. That molecules other than urea are removed during dialysis at variable rates is a fact of the physics of dialysis. To assume that there is a single identifiable molecule that is a uremic toxin is simplistic. There just are too many metabolic abnormalities that are corrected at varying rates during dialysis to assume that the removal of 1 or more molecule, be it urea, a middle molecule, or a larger molecule, would provide an answer to the benefits of dialysis or a better measure of the adequate dose of dialysis to deliver.

In the clinical application of Kt/V it is essential to note that it is merely a measure of the dose of dialysis, whether one uses the clearance of urea or that of any other molecule to

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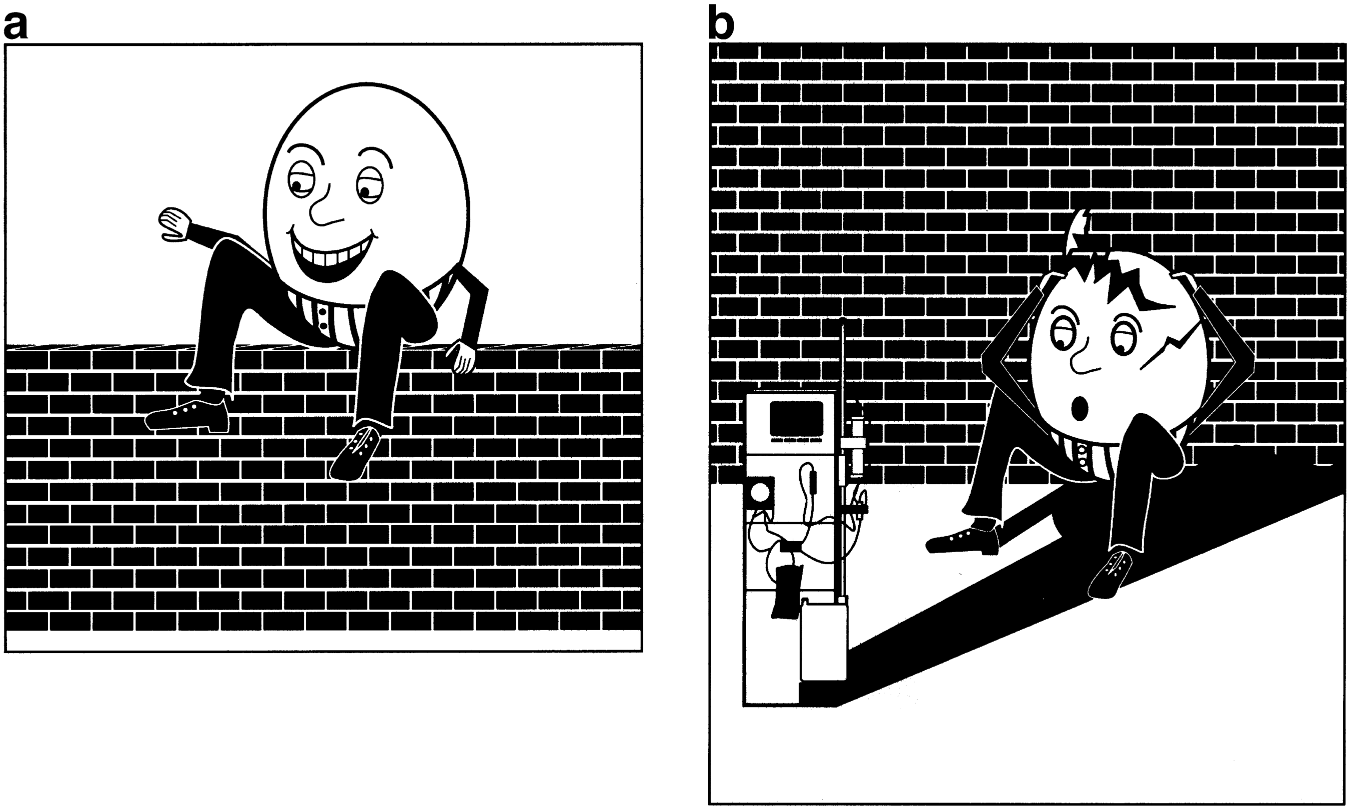

Figure 1 A metaphor of Humpty Dumpty to the patient with fragile kidney failure presenting to dialysis.

measure it. It is not a measure of adequacy. In addition, it confounds variables such as time, and manipulates others, such as blood and dialysate flow, to achieve a selected dose. Its confounders (time) and manipulated variables (blood and dialysate flow) have not been subjected to analysis. They continue to be used by the old rule of "more is better" as long as the desired dose is achieved. But, is more blood flow good or safe for everybody? Or, should the time on dialysis be the same for everyone as is often the case in current practice?

These limitations and caveats notwithstanding, the fact is that a clear link between the dose of dialysis, as measured by various formulae based on urea kinetics, and clinical outcomes of morbidity and mortality has been established. As such, Kt/V is the only available value that fulfills some of the concerns of Lord Kelvin, and therein may be a lesson of what more needs to be accomplished. The fact remains that physical determinants of adequacy other than the dose of dialysis have not been quantified or subjected to mathematic analysis. Is it not time to heed the admonition of Lord Kelvin in better examining the adequacy of dialysis by beginning the quantification of other physical parameters that affect adequacy? The number of dialyzer re-use and membrane pore size would be some examples of this. It should be possible to establish a standard dose-response curve for each of the physical variables of dialysis. In doing so, the y (response) axis could be a hard measure of outcome (mortality or morbidity), and the x (dose) axis could be the variable being examined. As with any such dose-response study, the result would be an S-shaped curve, with a narrow identifiable range for x in which the major incremental responses in y occur, subsequent to which the response is modest and ultimately becomes flat. Such a curve would provide not only a quantifiable measure of the adequate range for the variable in question, but also would define the range beyond which added supplies or staff demands and cost to achieve further modest improvements become a limiting factor. As each of the variables is quantified, it may even become possible to integrate them into a single generalizable formula for the physical determinants of the adequacy of dialysis. It is only then that the physics of clinical dialysis would begin its evolution from an empiric to a scientific discipline, expressed in numbers to show that we know something about it.

However, even then the problem of adequacy still would be unresolved because in addition to physical factors, patient-related factors, components of the care team, and, economic considerations determine the adequacy of dialysis. The present issue of *Seminars in Nephrology* addresses only selected aspects of the first 2 (physical and patient related) of these determinants. The equally important care team components and economic considerations are beyond the scope set by the page limits of this issue.

Concerning patient-related factors, it is clear from the available information that, independent of any measure of adequacy, some patients do better than others on dialysis. Unfortunately, there is a dearth of information on this issue, which often is dismissed as one of compliance or adherence. The article by Newmann and Litchfield, whose combined experience of living with end-stage renal disease is 71 years, covers some of these issues.

Finally, mention should be made of one of the most important components of patient-related factors not covered in this issue. Patients now initiated on dialysis have an average of 2 to 3 serious comorbid conditions and an Index of Co-Existing Disease score of greater than 2. No matter how sophisticated the adequacy of dialysis may become or how close to an optimal level it may be possible to deliver dialysis, it would be simplistic to assume that established comorbidities and complications would reverse on dialysis. An analogy of this can be made to the nursery rhyme of Humpty Dumpty. Taking the metaphor of the fragile kidney failure patient now presenting to dialysis to Humpty Dumpty (Fig 1), the rhyme then may be paraphrased to:

Humpty Dumpty sat on a wall
Humpty Dumpty had a great fall
All the bestest dialysis machines in the world
And all the bestest kidney doctors on earth
Could not put Humpty Dumpty back together again

In brief, we cannot expect to improve outcomes of patients on maintenance dialysis by merely concentrating on adequacy of dialysis. The care of these patients must begin early, at the start of kidney disease, not only to slow the progressive loss of kidney function, but also to prevent its complications, so that patients whose disease progresses to kidney failure and who begin dialysis are in the best condition of health possible. It is only then that the adequacy of dialysis will yield its best outcomes. This finally has begun to receive the attention it deserves. Several initiatives, such as the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation, are beginning to focus on this problem. Coupled with initiatives to quantify and improve the adequacy of dialysis, the future is promising.

Garabed Eknoyan, MD
Guest Editor