Dialysis at a Crossroads: Reverse Engineering Renal Replacement Therapy

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E ngineering is the profession that is responsible for designing, constructing, and manufacturing products, systems, and structures. Csete and Doyle (1) noted that the theory and practice of complex engineering systems has progressed to the point that they often embody Arthur C. Clarke’s dictum, “Any sufficiently advanced technology is indistinguishable from magic.” In the 20th century, the development and implementation of dialysis as a life-sustaining therapy for kidney failure constituted a “magical” medical advance.

The expansion of hemodialysis into a chronic renal replacement therapy also created a new field of medical science, sometimes termed the physiology of the artificial kidney. When the National Cooperative Dialysis Study (NCDS), the first landmark randomized trial in dialysis, demonstrated that a higher dose of delivered dialysis (measured as the time-averaged plasma concentration of urea) was associated with a lower risk for subsequent hospitalization (2), a science of dialysis had emerged (3). Gotch and Sargent (4) used NCDS data to develop the concept of Kt/V\textsubscript{urea}, a dimensionless construct that relates the clearance of urea to its volume of distribution, as a measure of dialysis dose. Nephrologists became familiar with concepts of diffusive and convective clearance, volume of distribution, and solute modeling. Quantifying the dialysis prescription became part of the parlance of clinical nephrology, thereby objectifying the “magical” early results with dialysis therapy.

Urea is an attractive molecule for kinetic modeling. It is readily and accurately measurable, its volume of distribution generally reflects total body water, and it is neither lipophilic nor highly protein bound. Furthermore, urea kinetic modeling is an attractive paradigm for the physiology of the artificial kidney because urea removal is concentration dependent and high urea concentration discriminates a uremic and a nonuremic state. Therefore, as long as data clearly supported the concept that the amount of urea removal closely associated with clinical outcomes in dialysis patients, the paradigm of hemodialysis therapy as renal replacement therapy was on a sound conceptual footing.

The limitations of dialysis as treatment of uremia now are becoming more apparent, bringing dialysis therapy to a crossroads. Over the past decade, there has been minimal improvement in the risk for hospitalization or mortality, even adjusting for changing demographics and comorbidities in dialysis patients and despite steady improvement in achieving identified dialysis clinical performance measures, including Kt/V\textsubscript{urea} (Figure 1A) (5). Perhaps even more alarming, recent US Renal Data System data indicate that risk-adjusted mortality of long-term dialysis patients (vintage > 5 yr) has been increasing rather than decreasing over time (Figure 1B). This suggests that cumulative toxicity from uremia is unabated and perhaps even exacerbated by recent changes in dialysis care. In comparison, transplantation, the current therapy of choice for ESRD, has made strides in improving patient and graft survival.

Data from three recently published randomized, clinical trials are particularly challenging. The HEMO Study used a 2 × 2 factorial design to examine whether a high dose of dialysis (as measured by Kt/V\textsubscript{urea}) or use of high-flux dialysis membranes could improve morbidity and mortality for hemodialysis patients. The results supported the null hypothesis in both treatment arms (Figure 1C) (6). The ADEMEX Trial, another well-conducted clinical trial, similarly did not demonstrate a relationship between peritoneal dialysis dose and patient outcomes (Figure 1D) (7). These studies suggest that there may be a threshold dialysis dose above which there is a significant plateauing of augmented benefit. Recently, an eagerly awaited study did not support the hypothesis that the use of statins would significantly lower the rate of cardiovascular complications in dialysis patients with diabetes (8). Given the lack of recent progress, a reexamination of the engineering principles that are at the root of dialysis therapy, and a comparison with kidney physiology is timely.

A Pioneering Era

In the beginning of dialysis was a generation of pioneers exemplified by Dr. Willem J. Kolff. Working in Groningen and then Kampen around World War II, Kolff accomplished the first lifesaving dialysis treatment. Kolff, as with other dialysis pioneers, was motivated by his helplessness as a physician who cared for young patients who were dying of uremia. His physiologic approach to renal replacement therapy was relatively simple and direct: “I decided that if I could remove from this patient just as much urea as he formed every day, that he could live” (9). The practicality of his approach also was reflected in his use of cellophane tubing from artificial sausage skin as the...
first dialyzer membrane: “When I took a piece of cellophane tubing—artificial sausage skin—and put it in a water bath and put 400 mg% of urea in the blood inside that cellophane tubing and shook it up and down, to my surprise saw that in a period of one minute, most of the urea had been removed” (9). Kolff treated his first patient in 1943. This young woman with ESRD was dialyzed 12 times successfully but ultimately died because of a lack of vascular access. In 1945, Kolff treated with dialysis a young woman (ironically jailed for being a Nazi sympathizer) who had developed acute renal failure. This woman ultimately recovered renal function and lived for a number of years, thus becoming the first long-term survivor after dialysis therapy.

Other early pioneers of dialysis, such as Belding Scribner, also were motivated and even haunted by the stark clinical realities faced in the care of young patients who are dying of uremia. Scribner has recounted the moment of inspiration that would lead to successful chronic dialysis therapy (10):

“Mr. Saunders had not passed any urine in a week, a fact that made the original diagnosis suspect. A biopsy of his kidney revealed the tragic answer. The original diagnosis was wrong. Mr. Saunders had a disease which had totally and irreversibly destroyed his kidneys. They would never function again.

“What to do? . . . we did the only thing we could do. We had an agonizing conversation with Mrs. Saunders and told her to take her husband back home to Spokane where he could die.

“Then one morning about 4:00 a.m., I woke up and grooped for a piece of paper and pencil to jot down the basic idea for the shunted cannulas which would make it possible to treat people like Joe Saunders again and again with the artificial kidney without destroying two blood vessels each time.”

As noted by Peitzman (3,11), the development of the Kolff rotating drum kidney and the Scribner shunt involved solving engineering problems (e.g., problems of biomaterials and spatial organization) rather than applying science to the recapitulation of kidney function. The stories of the seminal discoveries by these two leading clinical investigators, in which clinical tragedy became the mother of invention, have achieved near-mythic proportion. In 2002, Kolff and Scribner received the prestigious Albert Lasker Award for Clinical and Medical Research “for the development of renal hemodialysis, which changed kidney failure from a fatal to a treatable disease, prolonging the useful lives of millions of patients” (12).

**Reverse Engineering**

Kolff’s great and marvelously empiric contribution, closer in spirit to tinkering than modern engineering, was to use every-
day materials in the construct of a practical and functional dialysis machine. Modern engineering is a complex process that encompasses forward and reverse engineering. Forward engineering is the traditional process of moving from a high level of abstraction to the physical implementation of a design. Reverse engineering is the inverse process, in which one attempts to understand an already functioning system so as to make appropriate changes (Figure 2). The term “reverse engineering” originated in the analysis of computer hardware and software, where the practice of deciphering designs from finished products is commonplace. The purpose of reverse engineering is to investigate a system so as to increase overall comprehension for both maintenance and new developmental purposes. Reverse engineering elucidates the structure of a system by reasoning backward from observations of its behavior. The process involves identifying modules and subsystems, defining the interfaces between subsystems, and creating an architecture of system structure. When successful, reverse engineering can provide a high-level blueprint for understanding how a product works. Among the key objectives of reverse engineering (originally described by Chikofsky and Cross) are the ability to cope with complexity, to generate alternate views, to detect side effects, to facilitate reuse of a system, to synthesize a higher level of abstraction, and to facilitate re-engineering of a system (13). All these concepts are applicable to a contemporary analysis of the physiology of the normal and artificial kidney.

Reverse Engineering of Natural Kidney Physiology

Concepts that are derived from complex engineering also increasingly are being applied to biology (14). Dennett (15) and others have argued that one definition of biology is the reverse engineering of natural systems. Robustness, modularity, and recurrent circuits are engineering concepts that are applicable to understanding complex biologic networks (1). In complex living organisms, the organ system that is most responsible for finely regulating environmental homeostasis is the kidney. Homer Smith, the brilliant 20th-century evolutionary kidney physiologist, emphasized maintenance of the milieu intérieur as the most critical aspect of kidney function (16). In his landmark treatise From Fish to Philosopher, Smith (17) accounted for the development of renal tubules and glomeruli as an evolutionary response to the movement of organisms from a seawater to a freshwater environment. In Smith’s construct, primordial organisms that lived in a seawater environment did not need to conserve water or salt but did need to eliminate toxic solutes that were unable to be cleared by simple diffusion. Therefore, even in aglomerular early life forms, organic anions, cations, and other toxins could be excreted against concentration gradients via simple tubular structures. Grantham and Wallace (18) also have emphasized the secretory role of the mammalian kidney tubule (Figure 3).

Evolution, including the evolution of kidney function, is a process that is analogous to forward engineering, whereby iterative designs are based on trial and error. Jacob (19) viewed evolution as tinkering rather than engineering. However, others have noted that evolutionary change often has much in common with good engineering design (20). Alon (20) stated, “Evolution, by constant tinkering, appears to converge again and again on the same circuit patterns in different nonhomologous systems.” An examination of Smith’s writing indicates that he clearly viewed evolution as a tinkering process. Smith accounted for the subsequent addition of the glomerulus to the detoxifying tubular apparatus as a process that is designed to conserve salt and excrete free water in a freshwater environment. The resulting terrestrial mammalian kidney is enormously inefficient and energy-consuming, illustrating the tinkering premise. Smith (17) famously stated, “What engineer, wishing to regulate the composition of the internal environment of the body on which the function of every bone, gland, muscle, and nerve depends, would devise a scheme that operated by throwing the whole thing out 16 times a day and rely on grabbing from it, as it fell to earth, only those precious elements which he wanted to keep?”

Smith also noted, “The filtration-reabsorption system is now so firmly established that there is no easy way to overhaul it and to convert it to a purely tubular kidney as the marine fishes have done.” In reasoning backward from change in function to change in structure, Smith’s contribution can be viewed as the
glomerular filtration varies depending on the environment.

phy or elimination of glomeruli. Therefore, the dominance of fresh water or terrestrial environment. Return to the sea diminishes the importance of glomerular filtration, leading to atrophy or elimination of glomeruli. Therefore, the dominance of glomerular filtration varies depending on the environment. Reprinted from reference (18), with permission.

first effort to reverse engineer an understanding of normal kidney physiology.

Reverse Engineering of Artificial Kidney Physiology

I believe that there are lessons that we can learn from the legacy of Smith that are applicable to dialysis. Kolff and nearly all subsequent dialysis investigators have used a forward engineering approach in moving from a high-level abstraction (need to replace kidney function) to the physical implementation of a renal replacement therapy system (dialysis). Modifications to dialysis made over time to improve the engineering (e.g., the development of hollow fiber dialyzers, volumetric-controlled ultrafiltration, and variable dialysate composition) are the result of an ongoing forward engineering process (Table 1). Furthermore, the prevailing approach has been focused on recapitulating glomerular function. Improvements in dialysis membrane design consistently have focused on replicating the permselectivity of the glomerular filtration barrier. Even current practice guidelines for the classification of chronic kidney disease rely exclusively on estimation of GFR and virtually ignore tubular function (21). The tubule, in Smith's view the major component of the nephron that is responsible for toxic solute removal, has been underemphasized in the classification and treatment of kidney disease.

Whereas the renal excretion of toxic solutes involves both glomerular filtration and tubular secretion, many toxic organic compounds are taken up at the basolateral membrane followed by excretion at the brush border of apical membranes. For example, the renal secretion of organic anions across the proximal tubular epithelium is achieved by coordination of uptake and efflux transporters (22–24). Members of the organic anion transport family mediate uptake of uremic toxins such as indoxyl sulfate and 3-carboxy-4-methyl-5-propyl-2-furanpropionate (25). Organic cations similarly are taken up and ultimately excreted via renal tubular secretory processes. Recently, the human transporter protein that mediates the final excretion step for toxic organic cations at the apical membrane was identified (26). A number of low molecular weight proteins that accumulate in uremia, such as β-2 microglobulin, parathyroid hormone, and advanced glycation end product peptides, are excreted by the kidney after binding to megalin, a multiligand endocytic receptor located in proximal tubule epithelia (27,28). Other studies indicate that proximal tubules serve a redox function by discriminating between cysteine and cystine at the apical surface of the proximal tubule and by intracellular reduction of cystine to cysteine during reabsorption (29). Thus, considerable evidence demonstrates the importance at a molecular level of the renal tubular epithelia in modulating uremic toxicity.

It is clear that the largest roadblock to improving dialysis outcomes is a phenomenally high rate of cardiovascular morbidity and mortality in the dialysis population (30). Uremic cardiovascular disease is characterized by accelerated atherogenesis, aggressive intimal hyperplasia development, and vascular calcification. Altered left ventricular geometry and associated cardiomyopathy also are present in the majority of dialysis patients. Data from Parfrey and associates (31,32) suggest that underlying cardiomyopathy may be even more important than coronary perfusion disorders as an adverse prognostic indicator in dialysis patients. Metabolic derangements that include oxidative stress, acute-phase inflammation, and endothelial dysfunction contribute to uremic cardiovascular disease (33,34). Dialysis therapy in comparison with successful kidney transplantation has not proved as effective in significantly altering the proinflammatory, pro-oxidative milieu interieur (35). Contemporary uremia research aims to identify specific molecules (including homocysteine, cysteine, byproducts of oxidation and glycoxidation, nitric oxide inhibitors such as asymmetric dimethylarginine, and proinflammatory cytokines such as IL-6) that accumulate excessively in uremia and cause vascular injury (36). Many of these toxic compounds do not display concentration-dependency toxicity and are not well removed by dialysis. These toxins often are excreted by healthy mammalian kidneys via tubular processing (secretion and metabolism), rather than primarily through glomerular filtration. One potential higher level of abstraction (or blueprint) that is derivable from reverse engineering is the suggestion that replicating renal tubular function must be incorporated somehow.

Table 1. Forward engineering in hemodialysis

| From high level abstraction to detailed implementation Initial development (Kolff) Design modifications | ’off the shelf’ dialyzers hollow fiber dialyzers volumetric controlled ultrafiltration variable dialysate composition urea kinetic modeling |

Evolution of Renal Tubules and Glomeruli

Figure 3. Schematic view of the relationship of renal tubule and glomerular function over the course of evolution. The glomerular apparatus is added to facilitate free water clearance in a freshwater or terrestrial environment. Return to the sea diminished the importance of glomerular filtration, leading to atrophy or elimination of glomeruli. Therefore, the dominance of glomerular filtration varies depending on the environment. Reprinted from reference (18), with permission.
into dialysis therapy for more effective treatment of uremic toxicity, as is the case with kidney transplantation (Figure 4).

Although the essential components of dialysis as renal replacement therapy are largely unchanged dating back half of a century, we are entering a new era in biomedicine that emphasizes interdisciplinary and translational research (37). Applications of hybrid therapies involving advances in molecular cell biology, developmental biology, and computational biology will support new types of device development and therapeutics. Therefore, the prospects for development of novel renal replacement therapies are bright. Innovative therapies that are currently being considered include development of wearable artificial kidneys (38), hybrid renal-assist devices that combine cellular therapy with plasma separation (39), and genetic engineering to increase cellular detoxification potential (41). Nanotechnology may be applicable to dialytic therapies (42). New concepts such as frequent (quidi-} 


dian) dialysis or slow (nocturnal) dialysis are even being applied to conventional dialysis therapies. The development of novel renal replacement therapies will allow hypotheses that are based on reverse engineering concepts to be testable in the future.

Although it is difficult to forecast fully how novel and innovative therapies may improve the outcomes of renal replacement therapy, a number of hypotheses can be generated. Cell-based therapies and hybrid renal-assist devices have considerable potential to replicate more fully normal tubular function and solute processing. Wearable artificial kidneys, in addition to minimizing plasma solute concentration variability over time, may have different clearance properties as a result of the use of sorbents with capacity for solute adsorption. Genetic engineering approaches may more robustly remove specific toxins. For example, implantation of bioengineered megalin-expressing cells would be expected to enhance greatly the clearance of low molecular weight proteins, and the engineering of organic anion and cation transporter would be expected to modulate clearance of these toxic solutes (41).

Even with the development of new technologies, the role of the kidney in maintaining the milieu intérieur is likely to be too complex and integrated into a continued response to variable changes in the body’s chemistry to ever be fully replicated. Perhaps even the most successful, novel renal replacement therapy devices, although improving outcomes, still may exhibit a threshold plateau benefit (albeit a higher level than conventional dialysis) that will not fully replicate normal kidney function (Figure 5). Finally, it also must be recognized that many patients initiate renal replacement therapy with an existing heavy burden of comorbid disease. This also may contribute to a plateauing effect even with novel renal replacement therapies.

A Moment in Dialysis History

In a fascinating moment in the history of nephrology, Willem Kolff (the dialysis pioneer) and Homer Smith (the pioneering kidney physiologist), two Lasker awardees for kidney disease research, met on at least one occasion. Kolff had been invited by Professor Isador Snapper to visit Mt. Sinai Hospital in New York. Indeed, Kolff left a rotating drum artificial kidney at Mt. Sinai, where Alfred P. Fishman, a leading American physiologist, became one of the early American experimenters with the artificial kidney (43). Unfortunately, Kolff, the pragmatic, goal-
directed, tinkerer, and engineer, and Smith, the curiosity-driven experimentalist examining how evolution tinkers with kidney function, did not recognize common ground (Figure 6). In the ensuing half-century, it has frequently remained true that students of dialysis and students of kidney physiology have remained intellectually separated, often even when working in the same academic department. One can only hope that moving forward, as science increasingly becomes interdisciplinary, boundaries and barriers of this type finally will disappear. As Alon stated, “The similarity between the creations of tinkerer and engineer also raises a fundamental scientific challenge: Understanding the laws of nature that unite evolved and designed systems” (20).

References


