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**Past, Present and Future of
End-Stage Renal Disease Therapy
in the United States**

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Abstract

Dialysis was first described and used in 1854 to separate substances in aqueous solution based on different rates of diffusion through a semipermeable membrane. *In vivo* hemodialysis was performed in animals early in the twentieth century. Hemodialysis was first carried out in patients with acute renal failure in The Netherlands during the Second World War and in the United States in 1948. Repetitive hemodialysis for the treatment of chronic renal failure due to end-stage renal disease had to await the development of an acceptable long-lasting vascular access in 1960. The subsequent successful development of a technique to create an adequate arteriovenous fistula in 1972 permitted the rapid growth of dialysis programs, when the cost of this therapy was largely paid for by Medicare. Equipment has been developed to foster home-care hemodialysis and chronic ambulatory peritoneal dialysis.

Enhancements in renal replacement therapy included the availability of recombinant human erythropoietin, calcitriol, and effective antihypertensive drugs. Technical advances in hemodialysis followed the use of bicarbonate dialysate, more biocompatible membranes, membranes of higher porosity, and ultrafiltration. Questions remain regarding the evaluation of the adequacy of dialysis which is to be achieved or prescribed.

Careful attention to the management of the patient with progressive chronic renal insufficiency is crucial in dealing with the inevitable onset of uremia and the initiation of dialysis and/or renal transplantation. The cost of renal replacement therefore represents a great societal burden. A better understanding of how to prevent onset and progression of specific nephropathies along with the availability of new and more effective equipment for renal replacement therapy has a high priority.

- Editor

Introduction

The essence of this presentation can be summarized as follows: Before 1960, end-stage renal disease (ESRD) meant unavoidable death; in 1997, there were about 250,000 patients with ESRD being kept alive in this country with a variety of renal replacement therapies. The dramatic change which took place over the course of four decades represents a story of fantastic medical success which I will now review.

Historical Perspective

The term dialysis was coined in 1854 by the Scottish chemist Thomas Graham to refer to the separation of substances from solution based on their different diffusion through a semipermeable membrane. Graham performed a variety of *in vitro* experiments of the movements of various solutes through dialysis membranes (1). The English scientist D.W. Richardson made the first *in vitro* dialysis of human blood in 1889. He coined the term "crystalloid" to refer to solutes of the blood which readily passed through the membrane and "colloid" for those which did not (1). Abel, Rowntree and Turner, working at Johns Hopkins University, performed the first *in vivo* dialysis, but only in animals (1). Hass in Germany is credited with performing the first dialysis in humans (1). In 1944, Kolff and Berk designed the rotating-drum artificial kidney, the first truly functional hemodialysis apparatus (2). At the end of the Second World War, Kolff sent some of his artificial kidneys as a gift to several countries; one of these kidneys came to The Mount Sinai Hospital, where in 1948 it was first utilized to perform hemodialysis in a patient with bichloride of mercury poisoning (3).

While the technical capacity to perform dialysis was already available to treat patients with acute renal failure before 1960, the lack of an acceptable long-term vascular access limited the use of dialysis for the prolonged treatment of chronic renal failure. Frequent cannulation of peripheral veins led to inadequate flow, inflammation, thrombosis and eventual loss of these veins. In reality, after a few months, the patient would no longer have any accessible veins with which to continue dialysis. Thus, the single most important contribution to the establishment of chronic hemodialysis was the creation of the Quinton-Scribner shunt in 1960 (4). Unfortunately, this external arteriovenous shunt was plagued by infection and thrombosis. A major advance in the vascular access problem took place in 1966 with the creation of an arteriovenous fistula in the forearm by Brescia et al. (5). The endogenous arteriovenous fistula immediately became, and still remains, the gold standard of vascular access for chronic hemodialysis.

The advent of the Brescia-Cimino arteriovenous fistula initiated the era of chronic hemodialysis, but the new technique was expensive and only a limited number of patients could be admitted to the few chronic dialysis programs then established throughout the country. In 1972, the federal government expanded Medicare to include payment of 80% of the cost of renal replacement therapy (6). The growth of ESRD therapy in this country thereafter was dramatic. At the present time, approximately a quarter of a million people are being maintained with renal replacement therapy.

Recent Advances in the Treatment of ESRD

There have been 3 main recent advances which have had a great influence in the treatment of patients with chronic renal insufficiency:

- C Availability of recombinant human erythropoietin, which has allowed the virtual elimination of severe anemia in ESRD patients. Data from the United States Renal Data System (USRDS) show that the average hematocrit of dialysis patients in the United States has increased from 27% in 1989, the year when erythropoietin was introduced, to about 32% in 1995 (7). Medicare recently approved an increment in the allowable level of hematocrit, which most likely will produce further increases in the value on a national basis.

- C Availability of calcitriol [1,25(OH)₂-vitamin D], the active form of vitamin D, which together with dietary phosphate restrictions and the use of intestinal phosphate binders should minimize the consequences of renal osteodystrophy and severe secondary hyperparathyroidism in patients with ESRD (8).

- C A large armamentarium of medications to control blood pressure in most patients with chronic renal insufficiency.

The availability of exogenous erythropoietin and calcitriol permits pharmacological replacement of most of these endocrine functions of the kidney. However, we still cannot replace the excretory function of the kidney, except through dialysis or transplantation. Sufficient amounts of sodium and water can be eliminated via the gastrointestinal tract, particularly if a poorly absorbed sugar such as sorbitol is administered to induce enough diarrhea. The oral administration of cation-exchange polystyrene (Kayexalate⁷) resins can enhance the fecal loss of potassium and thereby offset the daily dietary intake of potassium. The obvious disadvantage of this approach is the diarrhea, but many patients would be ready to accept 1B3 loose bowel movements per day rather than dialysis. Unfortunately, none of these possible maneuvers correct the uremic syndrome and prolong survival (9, 10).

Main Advances in Dialytic Therapy

The main technical advances in hemodialysis have been (11, 12):

- C Introduction of bicarbonate dialysate which allows the elimination of acetate as the alkali source with a significant improvement of symptoms during dialysis.

- C Development of more biocompatible membranes for dialyzers. Biocompatibility is defined in terms of the extent to which membranes activate the complement cascade after being exposed to blood. A completely biocompatible membrane does not activate complement.

- C Introduction of membranes of higher porosity which may be able to increase the removal of middle molecules.

C

C Development of dialysis machines with the capability of programming the concentrations

C of sodium and bicarbonate in the dialysate.

C Development of dialysis machines which can be scheduled to ensure accurate removal of fluid by ultrafiltration during the treatment.

C High-efficiency hemodialysis allowing for less real time on dialysis without sacrificing the amount of small molecular solutes removed.

C A somewhat better understanding of what adequacy of dialysis means through more widespread use of the concept of Kt/V , a numerical index of dialysis adequacy. Kt/V is a dimensionless parameter which is calculated from the dialyzer urea clearance (K), duration of dialysis (t) and volume of distribution of urea in the body (V).

At present, a typical hemodialysis prescription includes 3 treatments per week of 3B4 hours, each with a reusable dialyzer of surface area of more than 1 M². An extracorporeal blood flow rate of 300B500 mL/min is targeted, while the dialysate flow rate is maintained at 500B800 mL/min. The aim of each hemodialysis session is to achieve a Kt/V in excess of 1.2/session.

The main advances in peritoneal dialysis have been (13, 14):

C The establishment and development of chronic peritoneal dialysis as an alternative modality of renal treatment for ESRD patients during the past 3 decades.

C Development in the techniques of connecting peritoneal catheters to dialysate bags, which significantly diminish the incidence of peritonitis to a current average of about one episode of peritonitis/patient/1.5 years.

C Development of new, compact, almost noiseless programmable machines capable of automatically cycling peritoneal dialysis fluid in and out at night while the patient sleeps.

C A somewhat better understanding of what adequacy of dialysis means through the general use of the Kt/V , already defined above.

There are 2 main forms of chronic peritoneal dialysis: Continuous Ambulatory Peritoneal Dialysis (CAPD) and Automatic Peritoneal Dialysis (APD). The typical prescription in CAPD is 4B5 exchanges per day of 2B3 liters each. For APD, most of the exchanges take place at night with a dwell time that may vary from one to several hours. Many patients may need to add a manual exchange during the daytime.

Approach to the Patient in the Pre-ESRD Phase

The most important parameters of medical care for patients with chronic renal insufficiency include:

- C Attempts at slowing down the progression to ESRD with maneuvers such as dietary protein restriction, tight blood pressure control and the use of ACE inhibitors.
- C Normalization of the blood pressure.
- C Normalization of serum calcium and serum phosphorus.
- C Normalization of hematocrit.
- C Avoidance of nephrotoxic drugs.
- C Treatment of urinary tract infection.

The patient with chronic renal disease who is experiencing progressive loss of renal function should be aware of, and not surprised about, the possible need for dialysis or transplantation. Formulating a life plan is an important element in the strategy to deal with the inevitable onset of uremia (15). This planning includes the projection of a probable course to ESRD, assessment of possible renal transplantation and the choice of dialysis modality. Once the patient and physician decide on hemodialysis, planning for early creation of vascular access is essential.

Determining when to initiate dialysis in the course of the progressive worsening in renal function is controversial (16). No single factor provides guidelines for every patient. For example, an asymptomatic 40-year-old man with a serum creatinine of 10 mg/dL as the result of slow progression of polycystic kidney disease may still get by on conservative therapy, while a 40-year-old woman with a serum creatinine of 5 mg/dL secondary to progression of diabetic nephropathy and concomitant congestive heart failure may benefit from initiation of dialysis. One extreme is the work of Bonomini et al. (17) in Bologna, who advocate initiation of dialysis at residual creatinine clearances between 15-20 mL/min. These authors have reported much better survival rates in patients who are started early on dialysis.

Modality of Therapy Choice

The ideal therapy for ESRD should be the implantation of an immunologically inert allogeneic or xenogeneic kidney graft or the implantation of an artificial organ capable of replacing deficient excretory function. Obviously, we are not at this stage yet, and because of the scarcity of organs available for kidney transplantation, most patients reaching ESRD will have to choose a modality of dialysis therapy.

No prospective, controlled, randomized studies have examined the effect of modality of therapy on morbidity and mortality. The prevalent sensitivity to patient preference and to patient

rights precludes such a trial. As a result, lacking experimental data, the physician must rely on uncontrolled trials, personal experience and intuition ("clinical judgment") to determine the best modality of dialysis (15).

Tables 1 and 2 summarize the advantages and disadvantages of both peritoneal dialysis and

TABLE 1

Advantages and Disadvantages of Chronic Peritoneal Dialysis

Advantages

continuous process maintains steady-state blood chemistry values
slow removal of fluid is gentle on the cardiovascular system
almost perfect control of blood pressure
more freedom in food and fluid intake
patients have full control on the treatment
survival seems to be comparable to hemodialysis

Disadvantages

low clearance forces for continuous or semicontinuous treatment and limits the maximal Kt/V delivered in anuric patients
significant daily glucose load
high incidence of abdominal hernias
risk of peritonitis

TABLE 2

Advantages and Disadvantages of Chronic Hemodialysis

Advantages

high clearances allow for intermittent therapy, i.e., 3 times weekly
survival seems to be comparable to peritoneal dialysis, although it is theoretically possible that higher current levels of Kt/V might produce better outcome than PD
no glucose load
no predisposition to abdominal hernias

Disadvantages

intermittent process gives unsteady chemistry values
rather fast removal of fluid is sometimes stressful to the cardiovascular system
variation in fluid status makes continuous blood pressure control almost impossible
less freedom in food and fluid intake
patients have less control on their treatment
risk of vascular access infection and thrombosis

hemodialysis. All of the enumerated disadvantages of in-center hemodialysis can be eliminated with daily nocturnal home hemodialysis (DNHH) (18): (a) daily removal of fluid eliminates the need for

wide swings in the volume and body chemistry status; (b) a lower rate of blood flow allows the utilization of a transcutaneous double lumen catheter for vascular access if a fistula is not available; and (c) one can initiate treatment with about 2 hours of daily treatment at a blood flow rate of about 200 mL/min.

Unfortunately, DNHH requires the availability of a dialysis machine which is capable of both automatically cleaning and testing the dialyzer for reuse as well as regenerating dialysate fluid locally. The second important requirement for this modality of therapy is the presence of a second person at home to assist with the vascular access and possible troubleshooting during treatment. However, once these dialysis machines become commercially available, DNHH may become an important alternative modality of dialysis therapy.

How to Evaluate Adequacy of Dialysis

The National Cooperative Dialysis Study (NCDS) in the 1980s was the first to establish some guidelines for hemodialysis prescriptions. This study randomized 160 patients into four treatment options: low vs high BUN and short vs long treatment time (19). The study showed that patients with higher BUN had greater morbidity and mortality than those with lower BUN concentrations. Later analysis of the data by Gotch and Sargent (20) emphasized the concept of Kt/V as an index of dialysis adequacy. For the non-nephrologist, it should suffice to know that Kt/V is a value directly calculated from the BUN values obtained pre- and post-dialysis. The greater the numerical value of Kt/V, the greater is the dose of dialysis delivered.

Several other studies have helped to confirm the notion that there is a direct relationship between dialysis dose and outcome. I will review the most representative of these studies. Owen et al. (21), in a retrospective analysis of data during a single dialysis treatment in 13,473 patients, showed that the urea reduction rate (ratio between the intradialytic decrement in BUN concentration and the pre-dialysis BUN concentration expressed as a percentage) was inversely correlated with the risk of death; a decrease in urea reduction ratio from greater than 70% to less than 45% was associated with an increased odds ratio for death from 1.04 to 1.84. Parker et al. (22) showed that an increase in the average Kt/V from 1.18 in 1989 to 1.46 in 1992 was associated with a decrease in the crude annual mortality rate from 23% to 17%. Hakim et al. (23) showed that an increase in Kt/V from 0.82 in 1988 to 1.18 in 1991 was associated with a decrease in the gross rate of mortality from 22.8% to 9.1%.

Despite all of the above information, there were no official standards for hemodialysis dosing until the NIH convened a panel of invited experts in 1993 to develop a consensus regarding the minimal dose of dialysis to be achieved. Although a safe level of Kt/V of 1.0 for each of 3 weekly hemodialyses had been recommended before, based on data derived from the NCDS, this panel now recommended an increase to 1.2 (24). Several factors played a role in changing the level of Kt/V recommended. These included the fact that patients in the NCDS had been highly selected and were in relatively good health. Patient follow-up was short. Existence of more recent data suggested that patients with comorbid conditions required more dialysis, particularly since the target value of 1.0 for Kt/V almost guaranteed that a percentage of patients would be underdialyzed. Finally, it was

shown that more dialysis could be delivered safely despite variations in equipment and measurements in different dialysis units. More recently, the results of the USRDS Case Mix Adequacy Study (25), also supported the target Kt/V value of 1.2 set by the NIH Consensus.

The definition of adequacy of peritoneal dialysis has also changed over time, but the effect of varying dialysis doses on an outcome was not clearly established until the results of the CANUSA Study became available (26). The CANUSA Study, a multicenter study of CAPD patients from Canada and the United States, concluded that a weekly Kt/V in CAPD of 2.1 or a Ccr of 70L/wk/1.73M² is associated with a better outcome (26).

How Are We Doing?

The crude annual mortality rate of dialysis patients has remained at about 20% in the United States (7). An analysis of the causes of death shows that cardiovascular disease is responsible for approximately 50% of this mortality while infection causes about 15% (7). The usual risk factors for coronary artery disease are present and include hypertension, smoking, and hypercholesterolemia. However, there are some risk factors more specifically associated with renal disease, such as anemia, hyperphosphatemia, hyperparathyroidism and hyperhomocysteinemia (27).

An emphasis on the prevention of these risk factors should be a strong clinical consideration in the medical approach to these patients. Unfortunately, this situation is complicated by the increasing age of the population as well as numbers of patients with diabetes mellitus being dialyzed.

International Comparisons

The mortality rate for ESRD patients in the United States, about 20% per year, is higher than in most other industrialized nations (28). This fact has generated a great deal of controversy in the dialysis community. Friedman (29) has offered several reasons why American mortality rates are higher: (a) European countries ration ESRD treatment by age, sex and comorbidity; (b) European countries seem to underreport deaths; and (c) low kidney transplant rates in Japan may improve dialysis outcomes by increasing the proportion of younger and relatively healthier patients on hemodialysis. However, a number of studies have suggested that a major cause of the high mortality in the United States is underdialysis (30, 31). The recent trend toward increasing the delivered Kt/V in the United States may help physicians decide whether this increase in dialysis dose is associated with a better outcome (7). Unfortunately, the simultaneous trend toward an increase in the mean age of ESRD patients may cast some doubt on any conclusions (7).

Cost of Treatment

When the Social Security Administration assumed responsibility for payment of 80% of the costs of treating ESRD, it was anticipated that as much as half a billion healthcare dollars might be expended annually. The current yearly cost is as much as \$13 billions (7). Thus, the cost of treating ESRD is beyond the budget of underdeveloped and developing nations (32).

Future Perspectives

The current decade has seen a fantastic development of techniques of molecular medicine

that offer the promise of dramatic advances not only in the prevention of ESRD but also in the area of renal replacement therapy (33). This whole field is open to every kind of speculation. It may be useful to consider new and perhaps even radical proposals. I will summarize just a few of the areas where advances can make real changes.

- C Advances in the area of renal transplantation: better immunosuppressive regimens for allotransplants and/or xenotransplants (34).
- C Development of an implantable, fully-bionic artificial kidney (35).
- C Development of dialysis machines for daily nightly home hemodialysis. This may enable a good number of patients to move from a center to home dialysis. The question of whether indigent, undereducated patients are suitable for home hemodialysis, has been answered affirmatively (6).
- C Design of an on-line system to create solutions for individual patients.
- C Development of bioengineered bacterial flora to recycle urea and other nitrogenous compounds back into amino acids and protein in the gastrointestinal tract (36). The assumption here is that uremia is mostly the result of nitrogenous compounds.
- C Ability to genetically transfer all the required metabolic machinery to the mesothelial cells of the peritoneal cavity so that they can recycle nonprotein nitrogen into amino acids and proteins (37).
- C A charged macromolecular polymer to be affixed to peritoneal mesothelial cells. This polymer will provide the osmotic force to draw water into the peritoneal space. This fluid could then be eliminated via the bladder coupled to a valved one-way pump (38).
- C Rapid progress in the prevention of specific nephropathies: for example, successful implantation of pancreatic β cells might reduce the number of patients progressing to ESRD from diabetic nephropathy in the coming decade (39).

It may be argued that due to advances in transplantation there will be no need for dialysis in the near future, but the overall lack of transplantable kidneys, the aging of the population and personal preference most likely will keep at least a proportion of ESRD patients on dialysis through the 21st century.

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