HEMODIALYSIS

1. Introduction

1.1. Normal Kidney Function. As summarized in a recent review article (1), the kidneys are two fist-sized organs whose primary function is to generate urine for excretion of water and metabolic waste products. The kidneys not only remove accumulated nitrogen products (urea, creatinine, uric acid and others), but also maintain homeostasis of water and electrolytes (sodium, potassium, chloride, calcium, phosphate, magnesium) and regulate acid–base balance. In addition, human kidneys perform a few endocrine and metabolic functions, such as production of the hormone erythropoietin (a hormone which stimulates blood cell production) and conversion of vitamin D to its active form. Because of the tremendous overcapacity of normal kidney function, a person can live with only a fraction of normal kidney capacity, and the 0.1% of the population who are born with a single kidney often are not even aware of the missing kidney.

1.2. Kidney Failure. Acute renal failure (ARF) occurs when the kidneys fail due to an event such as trauma, poisoning, or surgery. Patients who recover from ARF typically do so within 10 to 14 days. Chronic kidney disease (CKD) is a degenerative process most often caused by diabetes or high blood pressure, and less frequently as a result of genetic diseases. CKD patients whose kidneys function at less than 10% of normal capacity require regular dialysis treatment and are classified as "CKD Stage V" or "End Stage Renal Disease" (ESRD) patients. In the United States, as of December 31, 2003, there were over 310,000 patients whose lives are sustained by dialysis (2). While most patients are treated by hemodialysis, which is the focus of this article, about 10% receive peritoneal dialysis, in which mass transport of water and toxins occurs across the patient's peritoneal membrane (into a periodically-refreshed infused solution) rather than via an extracorporeal blood circuit. Each year, fewer than 15,000 Americans receive a transplant each year, although over 50,000 are listed on transplant waiting lists (3).

It should be mentioned that while historically dialyzers have been called "artificial kidneys," hemodialysis does not replace the kidneys' endocrine or metabolic functions. As a result, dialysis patients are given erythropoietin and intravenous vitamin D analogues to address their anemia and bone disease. Here the focus is only on the excretory functions carried out by hemodialysis.

2. Hemodialysis System and Process

Figure 1 is a photograph of a modern hemodialysis system in use. The dialyzer is seen at the right of the photo, with red blood lines leading to and from the patient at the left, and the whitish dialysate lines seen at the right.

A hemodialysis system consists of three main components: the machine hardware, the disposable blood circuit including the dialyzer, and the dialysate solution. The primary function of the hemodialysis machine is to move fluids: (*1*) to mix dialysate from its component solutions; (*2*) to pump blood and dialysate to the dialyzer; (*3*) to control fluid removal from the patient; and (*4*) to deliver heparin.

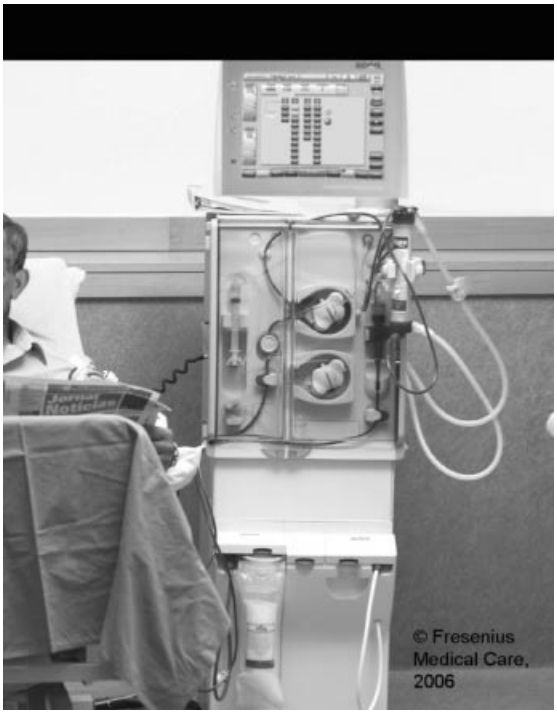


Fig. 1. Modern hemodialysis machine in use. Copyright Fresenius Medical Care (2006). Reproduced with permission.

Dialysate is prepared by mixing three fluid streams together—acid concentrate, bicarbonate concentrate, and dialysate water. Dialysate water is generated by a separate water purification system typically consisting of depth filtration, water softener, carbon tank, reverse osmosis, and deionization. The proportioning of those streams is used to achieve prescribed concentrations of two components—sodium and bicarbonate. The acid concentrate formulation is selected based on a patient's potassium and calcium levels.

Before the dialyzer is exposed to blood, it is primed with saline solution, and typically the patient is given a bolus of anticoagulant (usually heparin). Additional anticoagulant may be delivered continuously to the dialyzer or by periodic bolus injection, typically hourly.

The hemodialysis machine performs a number of monitoring functions including: conductivity monitoring (dialysate composition); pressure monitoring; air bubble detection; detection of hemolysis; detection of kinked lines; detection of disconnected lines; on-line clearance measurement (optional); access flow measurement (optional); blood volume monitoring (optional); and blood temperature monitoring (optional).

Blood is pumped out of the body to the dialyzer through one of three types of vascular accesses—a fistula (natural vessel used to create a short-circuit between an artery and vein, usually in the arm or leg), a graft [polytetrafluoroethylene (PTFE) or other artificial vessel surgically implanted between an artery and

vein] or a vascular catheter such as a central venous catheter. The blood flow rate to the dialyzer is often limited by quality of the vascular access rather than the pump setting. Pre-pump arterial pressure measurement is typically employed for monitoring the capacity of the vascular access, with a high negative pressure indicating that the vascular access is unable to supply the blood flow rate demanded by the pump, and that the actual blood flow rate is lower than the pump setting.

Figure 2 is drawing showing the essentials of the hemodialysis process. Blood is drawn from the patient using a roller pump, mixed with anticoagulant (depending on the patient's prescription), and delivered to the bottom header of the dialyzer, which distributes the blood flow among the thousands of hollow fibers.

Dialysate is generated from concentrate and water, heated, and delivered to one end of the shell space surrounding the hollow fibers. The dialysate flows among the fibers, collecting toxins, and exits to the drain. A proportioning chamber ensures that the desired amount of excess fluid is removed from the patient, ie, that the dialysate flow rate to the drain is slightly greater than the inlet dialysate flow rate.

Figure 3 shows a polysulfone hollow-fiber dialyzer (4). The hollow fibers appear white. Blood flows in through the port in the center of the blue end cap, and is distributed among the hollow fibers in the "header" region. Dialysate flows through the clear side ports. The flows of blood and dialysate within a hollow fiber dialyzer are shown in diagram in Figure 4. The flow patterns are

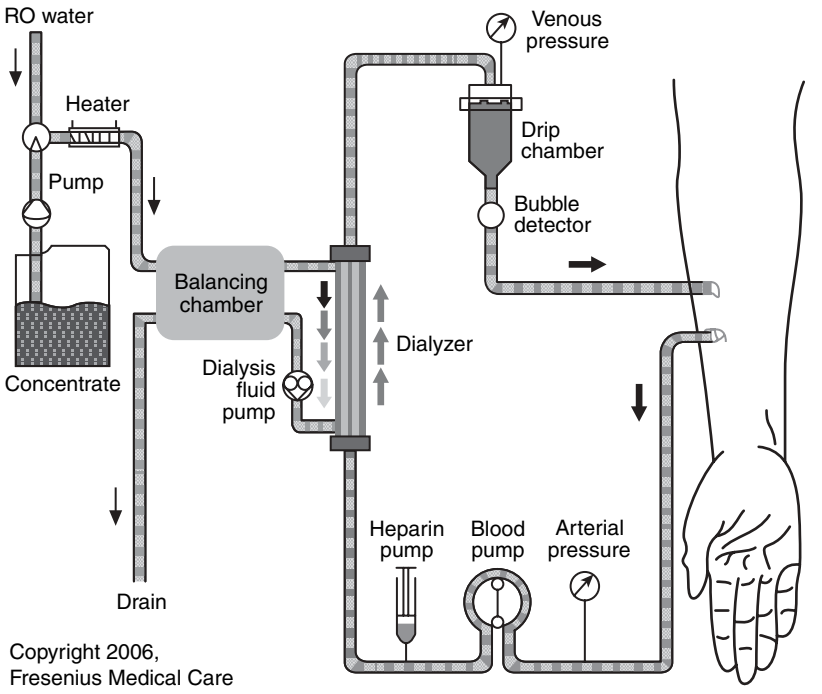


Fig. 2. Hemodialysis process, Copyright Fresenius Medical Care (2006). Reproduced with permission.

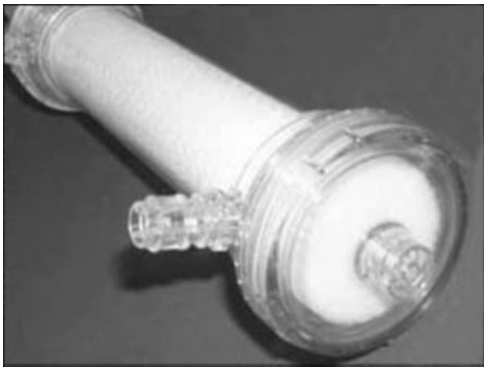


Fig. 3. Photograph of hollow fiber dialyzer. Sightech Vision Systems. Reproduced with permission.

similar to those seen in a shell-and-tube heat exchanger. Figure 5 shows an end view of a dialyzer without its end cap. The ends of the hollow fibers are embedded in polyurethane potting material. Manufacturing processes are designed to ensure a uniform distribution of hollow fibers within the potting material.

The dialyzer provides a membrane barrier that permits the passage of metabolic waste products like urea, creatinine, uric acid, and inorganic phosphate to move from the bloodstream of the patient to the dialysate, while at the same time preventing the elimination of important blood proteins like albumin and immunoglobulin.

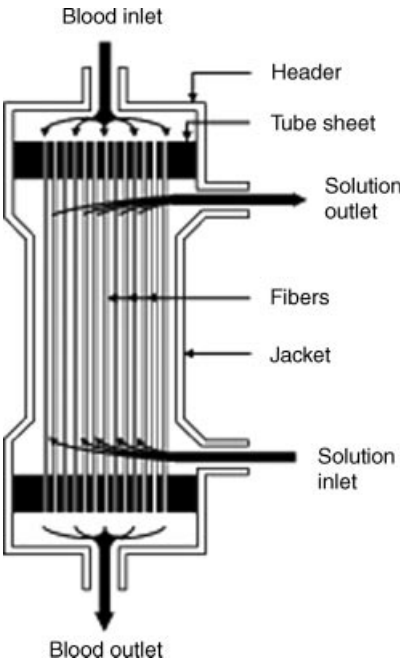


Fig. 4. Diagram of hollow fiber dialyzer.

Fig. 5. Photograph of dialyzer without end cap at Fresenius plant in St. Wendel, Germany. Copyright Fresenius Medical Care (2006). Reproduced with permission.

2.1. Hemodialysis Prescription. The dialysis prescription written by a physician specifies the dialyzer model, the dialysate composition, and the operating parameters.

Dialyzer Model. By specifying a particular dialyzer model, the membrane material, surface area, and permeability to water and solutes are fixed.

Dialysate Composition. The second element of the hemodialysis prescription is the dialysate composition. Because hemodialysis machines made by different manufacturers use different proportioning ratios of concentrate to water, the dialysate composition must be selected from among the varieties offered by the given manufacturer. Physicians can specify a potassium concentration of 0, 1, 2, 3, or 4 mEq/L and a calcium concentration of 0, 2.0, 2.25, 2.5, 3.0, or 3.5 mEq/L. The standard dialysate employed today is 2.0 K and 2.5 Ca. Years ago, higher dialysate calcium concentrations (3.5 mEq/L) were used to increase a patient's serum calcium as a method to suppress PTH hormone production. However, with the advent of calcium-based oral phosphate binders, widespread use of IV vitamin D to suppress PTH, and the increasing awareness of the problem of vascular calcification in dialysis patients, the standard dialysate calcium was lowered to the physiologically normal level of 2.5 mEq/L.

Dialysis Operating Conditions. The third element of the hemodialysis prescription is the operating conditions including flow rates and treatment time. The blood flow rate and dialysate flow rate are critical to the solute removal performance of the dialyzer. The treatment time must not only be sufficient to achieve the desired solute removal, given the blood flow rate attainable in a given patient, but also be sufficient to allow removal of the required water from a patient without exceeding the maximum ultrafiltration rate tolerated by the patient. Since the actual amount of water gained by a patient varies from treatment to treatment, the dialysis prescription includes the estimated dry weight, which is the physician's best guess at what the patient's weight would be if his kidneys were functioning properly. For patients who adhere to the prescribed dialysis frequency (ie, do not skip treatments), treatment time, and dietary fluid restrictions, the target post-treatment weight is equal to the

estimated dry weight. From treatment to treatment, typically the ultrafiltration rate is varied to achieve the target post-treatment weight.

Hemodialysis patients generally receive treatment three times per week. Over the past 30 years, with the development of more permeable membranes, average treatment times have dropped from 4 or 5 h to around 3.5 h. Typical blood flow rates in the U. S. have risen from 300 mL/min to over 400 mL/min (2). In the 1970s and 1980s, the standard dialysate flow rate was 500 mL/min. In the 1990s, dialysate flow rates of 800 mL/min became commonplace. To reduce unnecessary usage of dialysate solution at low blood flow rates, some dialysis machine manufacturers have added the option of setting the dialysate flow rate at a fixed ratio of 1.5 or 2.0 times the blood flow rate. Beyond such ratios, increasing the dialysate flow rate produces little to no improvement in solute removal rates.

3. Dialyzer Mass Transport Requirements

The terminology for characterizing dialysis membranes is somewhat unique to the dialysis field. Instead of being characterized in terms of hydraulic permeability, diffusive membrane permeabilities, and solute rejection coefficients, dialyzers are generally characterized in terms of an ultrafiltration coefficient (Kuf), solute clearances, and the product of the mass transfer coefficient times the surface area (KoA) (1).

3.1. Hydraulic Permeability/Ultrafiltration Coefficient. As with all membranes, the hydraulic permeability of a dialysis membrane varies with thickness, pore size distribution, and pore density. Because exposure to blood affects the hydraulic permeability of a dialyzer, the intrinsic water permeability of a dialysis membrane is rarely reported. Instead, the ultrafiltration coefficient (Kuf) of a dialyzer is reported as the volumetric filtration rate (mL/h) per mm Hg transmembrane pressure (TMP) across the membrane when filtering blood. The Kuf of a dialyzer is usually derived from *in-vitro* experiments using bovine blood, in which the filtration rate is measured as a function of varying TMP. The filtration rate is linear with TMP at low TMP, and reaches a plateau at high TMP (5). The slope of the linear portion of the curve is defined as the Kuf of the dialyzer. Note that because the ultrafiltration coefficient is not normalized with respect to surface area, it is the property of a dialyzer, not a property of a membrane. Thus, a dialyzer containing membranes with relatively small pores can have a high Kuf if the surface area is large.

The FDA classifies dialyzers as high flux if Kuf >8 mL/h/mm Hg (6). This classification dates back to a period when dialyzers were operated in free filtrate mode, with the filtration rate controlled by varying the transmembrane pressure (TMP). At that time, there was a concern that a small error in setting the TMP could result in excessive fluid loss from a patient. High flux dialyzers can only be used with HD machines that have volumetric control to prevent excessive fluid loss. With the possible exception of developing markets, all dialysis machines sold today employ ultrafiltration control. In the U.S. market, over 92% of patients are treated with high flux dialyzers (2). The Association for the Advancement of Medical Instrumentation (AAMI) Standards limit allowable

lot-to-lot variability in ultrafiltration by requiring that dialyzer ultrafiltration coefficients be within 20% of the value reported on the package instructions.

3.2. Solute Clearance. The clearance rate of a solute, or solute clearance, is defined as the mass removal rate divided by the concentration of the solute in the blood, and is expressed in units of mL/min. Thus, the clearance represents the equivalent volume of blood fully cleared of the solute each min, and cannot exceed the blood flow rate to the dialyzer. The term clearance was originally used as a measure of the performance of the natural kidneys, which operate continuously and rely primarily on convection for solute removal. Since dialyzers are rarely used in pure convective mode, and diffusion is the predominant mechanism of mass transport (7), a more appropriate measure of permeability would be a dialysance, which is defined as the mass removal rate divided by the concentration gradient across the membrane. Nevertheless, since physicians and nurses are the users of dialyzers, medical terminology had prevailed over engineering terminology in the characterization of dialyzers.

The Association for the Advancement of Medical Instrumentation (AAMI) Standards limit allowable lot-to-lot variability in clearance by requiring that reported clearances be within 10% of the value reported on the package instructions.

Another term used to characterize the transport properties of dialysis membranes is the so-called "mass transfer area coefficient" (MTAC), which is the product of the mass transfer coefficient (Ko) times the membrane surface area (A), or "KoA." Usually the terms MTAC and KoA reported are those for urea. While Ko should equal the maximum clearance obtained at high blood and dialysate flow rates, reports in the dialysis literature (8) discuss the variation of KoA with dialysate flow rate. Such reports reflect the manufacturers' or others' inappropriate extrapolation of KoA from data obtained at typically clinically relevant flow rates, which are not high enough to minimize boundary layer resistance. While the measurement of *in vivo* rather than *in vitro* characteristics of dialyzers is meant to provide more accurate or realistic information, it can be misleading in this context.

An equation relating the dialyzer clearance K_d to K_o, A, the blood flow rate Q_b and the dialysate flow rate Q_d can be derived from boundary layer theory (9):

$$K_d = \frac{1 - e^{[KoA/Qb^*(1-Qb/Qd)]}}{Q_b/Q_d - \exp^{[KoA/Qb^*(1-Qb/Qd)]}}$$

Figure 6 is a graph showing the calculated dependence of urea clearance on blood and dialysate flow rates. For a given blood flow rate, the clearance approaches an asymptote as the dialysate flow rate is increased. Raising the blood flow rate raises the asymptotic value. Under typical conditions, a 10 mL/min increase in blood flow rate will have a greater effect on clearance than a 10 mL/min increase in dialysate flow rate.

Since mass transport rates depend on solute size and other characteristics, evaluation of dialyzer performance requires identification of solutes to be removed. While urea (MW = 60 Da) has served as a marker solute for about 40 years, the full spectrum of solutes has yet to be identified.

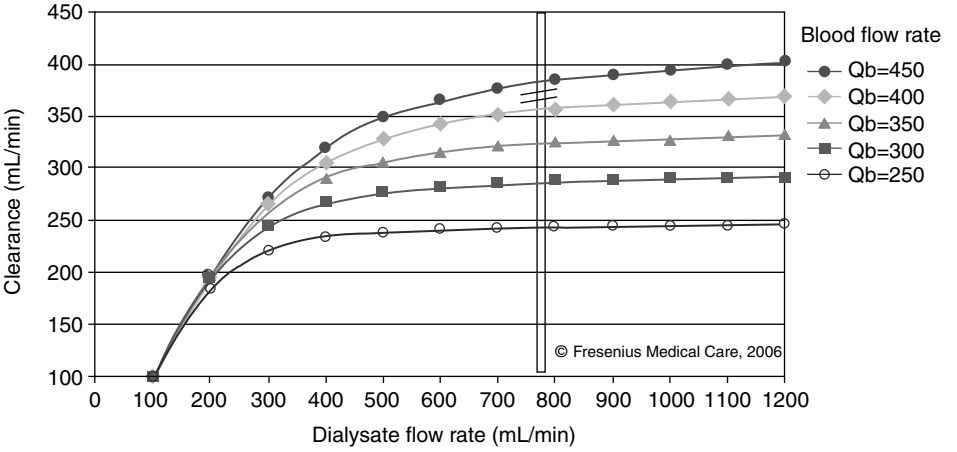


Fig. 6. Calculated solute clearance as a function of blood and dialysate flow rates. Copyright Fresenius Medical Care (2006). Reproduced with permission.

The European Uremic Toxin Work Group (EUTox) is analyzing the uremic toxins, including each toxin's normal concentration, highest mean uremic concentration, highest single ever-reported uremic concentration, molecular weight and the chemical class of each uremic retention compound (1,10). The uremic syndrome is characterized by accumulation of uremic toxins due to inadequate kidney function and new solutes are added to the list of uremic toxins every year (10). Uremic retention products differ in water solubility, protein binding and molecular weight. Under normal kidney function, the glomerular membrane in the kidney allows passage of solutes with molecular weights up to approximately 35,000 Da (11). Tubular secretion, readsorption and metabolic breakdown are all altered when the renal function is reduced. While all substances that accumulate in renal failure can be considered uremic toxins, it is not yet understood which of these toxins and how much of them should be removed, nor the relationship between retention of a particular solute and a specific toxicity. Furthermore, the removal of these solutes is dependent on a variety of different factors such as compartmental distribution, intracellular concentration, rates of transport across cell membranes, protein binding, electrostatic charge, steric configuration and molecular weight. For the purposes of discussion here, uremic toxins will be classified into three major categories based on their physiochemical properties that influence their dialytic removal (*1*) small water-soluble compounds (MW $<$ 500 Da) (*2*) so-called middle molecules (500 Da $<$ MW $<\sim$15000 Da) and (*3*) protein-bound molecules (both small and middle molecules).

Small Water-Soluble Molecules. The water-soluble toxins generally include compounds with molecular weights less than 500 Da, such as urea and creatinine. The clearances of these molecules are primarily driven by diffusion (7), but other factors such as inter-compartmental partition coefficients, inter-compartmental mass transport rates, and protein binding can also play a role. For example, while urea is in local equilibrium between plasma and red cell

water within the hemodialyzer, other solutes such as creatinine and uric acid remain partially trapped within red cells during passage through the hemodialyzer. Inorganic phosphate is a small molecular weight toxin that is removed relatively rapidly from the blood during the initial phase of the dialysis session, after which the transfer from the intracellular compartment(s) becomes rate limiting. Spalding and co-workers (12) have considered four pools of phosphate, namely, the extracellular space, intracellular space, bone and finally as glycophosphates found in the intracellular space. For solutes with such compartmentalization effects, more frequent dialysis or longer treatment times offer greater promise than more permeable dialysis membranes. NIH-sponsored studies of short daily dialysis and nocturnal dialysis are currently underway.

Middle Molecular Solutes. Several retrospective studies have provided suggestive evidence that middle molecule removal influences the outcomes in hemodialysis patients (8,13–15). Some of the examples of potential uremic toxins are B2-microglobulin, advanced glycation end products, leptin, complement proteins, proinflammatory cytokines, factor D, and granulocyte-inhibiting protein (10). Middle molecules are distributed in multiple compartments and their clearance by diffusion decreases as the molecular weight increases. Beta-2 microglobulin was the first so-called middle molecule to be linked to a specific clinical syndrome (dialysis-associated amyloidosis) occurring exclusively in hemodialysis patients. With a molecular weight of approximately 11,800 Da, beta-2 microglobulin is largely removed by convection (7), but its sieving coefficient is >0 only with high-flux membranes. Because net ultrafiltration volumes removed during dialysis are typically small (1–3 L/treatment), the quantity of solutes removed by convection is limited. Recent studies have demonstrated that increasing the "internal filtration" or "Starling's flow" (ie, positive filtrate flux near the blood inlet and negative filtrate flux near the blood outlet) by increasing the length (16) or reducing the fiber diameter (17), or increasing the dialysate-side pressure drop (18) resulted in improved clearances of middle molecules.

Protein Bound Uremic Toxins. The removal of protein-bound molecules (both small and middle molecules) is highly solute-specific, and cannot be manipulated by a simple change in hemodialysis prescription. A review of protein-bound toxins is included elsewhere (1), and is not repeated here.

Retention of Plasma Proteins. An important constraint on the maximum pore size of dialysis membranes is the need to retain plasma proteins such as albumin (MW = 66,000). Since patients are often malnourished, loss of significant plasma proteins is not clinically acceptable. Furthermore, the presence of even relatively small quantities of protein in dialysate waste streams creates a practical problem of foam being generated in drain lines and rising through floor drains.

Figure 7 shows sieving coefficient profiles for two high flux dialyzers. The sieving coefficient for small molecular weight solutes is approximately one (ie, 100% passage), while the sieving coefficient of plasma proteins is approximately zero (ie, 100% retention).

Requirements for Adequate Dialysis. The quantitative assessment of efficacy of dialysis therapy and renal function is based on the small solutes, even though the molecular weights range over three orders of magnitude. Urea and creatinine are considered to be representative or surrogates for the

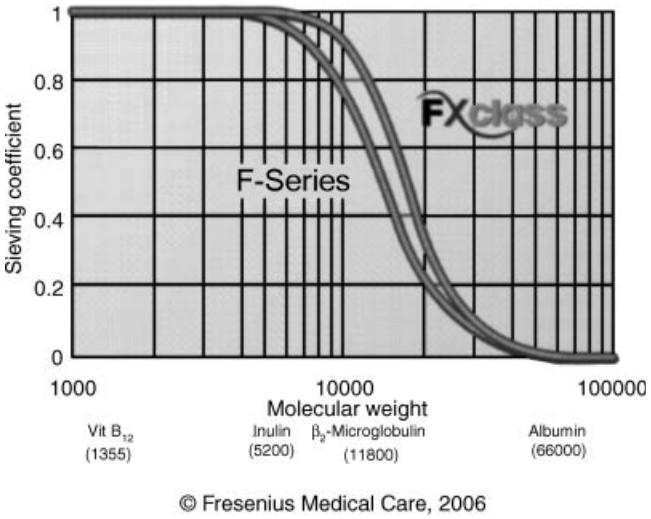


Fig. 7. Sieving coefficient profiles of two dialyzers. Sieving coefficient vs. molecular weight. Copyright Fresenius Medical Care (2005). Reproduced with permission.

small molecules and easily measured. Three different methods of accessing urea removal rates are currently used.

Urea Reduction Ratio, URR. URR is defined in terms of pre and post blood urea nitrogen (BUN) values as (19):

$$\text{URR}\ (\%) = 100 \times (\text{Pre BUN} - \text{Post BUN})/\text{Pre BUN}$$

For three times a week dialysis, the government CPM report considers a URR of 65% to be indicative of adequate dialysis (2), but recent reports suggest a target of 70% (20).

Kt/V. *Kt*/V is defined as $K =$ urea clearance, $t =$ treatment time, and $V =$ urea distribution volume. Using a simple mass balance, a single pool *Kt*/V can be calculated as:

$$Kt/V = \ln(Pre\,BUN/Post\,BUN)$$

To account for rebound due to intercompartmental gradients, the following so-called "Daugirdas II calculation" is often employed (21):

$$\frac{Kt}{V} = \ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times 0.55\frac{U_F}{W}$$

where:

$R =$ Pre BUN/Post BUN
$W =$ Post dialysis body mass of patient (kg)
$V =$ Body water (L)

U_F = Ultrafiltration volume per dialysis (L)
t = Dialysis treatment time (h)

The K/DOQI (Kidney Disease Outcome Quality Initiative) national guidelines recommend a delivered Kt/V of at least 1.2 for a thrice-weekly hemodialysis (22).

Formal Urea Kinetic Modeling (UKM). UKM, with iterative solution of the differential equations, can be used to calculate an equilibrated Kt/V, which takes into account post-dialysis solute rebound as urea moves from into the blood compartment from other spaces. Equilibrated Kt/Vs are typically about 0.2 units smaller than single pool Kt/Vs calculated from the same BUN results.

A recently developed on-line clearance monitor (23) has been demonstrated to be effective at predicting future mortality (24), indicating that it is a valid tool for assessing dialysis adequacy.

4. Other Dialysis Membrane Requirements

4.1. Membrane Biocompatibility. While transport properties play an important role in the selection of a dialyzer membrane, an equally important consideration in the evolution of the dialyzer technology has been biocompatibility, or the compatibility of the dialyzer with blood. Three aspects of biocompatibility which are important in dialysis are clotting, activation of the complement cascade, and cytokine generation.

Clotting. Clotting is generally managed through the use of systemic heparinization, although a small percentage (<5%) of dialysis treatments are performed heparin-free due to allergic reactions to heparin. A recent report suggests that as many as 50% of dialysis procedures performed in the intensive care unit are performed heparin free to avoid bleeding complications (25). While heparin-coated membrane oxygenators and hemofilters were commercialized several years, heparin-coated dialyzers have only recently been introduced (26).

Complement Activation. Complement proteins are so-named because they complement antibody activity to eliminate pathogens. The "alternate pathway" of the complement cascade is normally activated by bacterial surface molecules. Complement activation during dialysis was first identified by the rapid drop in white blood cell counts (neutropenia) during the first 30 minutes of dialysis. Regenerated cellulose membranes activate complement through the alternate pathway (27). Modified cellulose membranes approach the biocompatibility profile of synthetic materials in terms of neutropenia and complement activation.

Adsorption of Endotoxins and Cytokines. Whereas membrane materials used in downstream processing of biological products may be selected for their resistance to protein fouling, early dialysis membranes were found to be more blood compatible after adsorption of blood proteins. Endotoxins are bacterial products released from gram-negative bacteria upon death. Because endotoxins cause fever, they are also called pyrogens. Because endotoxin fragments fall in the middle molecule range, they may be inadvertently transported from dialysate to blood during high-flux dialysis, leading to cytokine generation.

Adsorption (membrane binding) is one mechanism by which hydrophobic compounds like endotoxins, cytokines, peptides, growth factors, and proteins may be removed during HD. Although adsorption during HD is a relatively poorly understood phenomenon, certain membrane characteristics play an important role. The binding characteristics, distribution of hydrophobic and hydrophilic domains, charge distribution on the surface and in the pores are important factors that govern the membrane biocompatibility. Renaux and coworkers (28) proposed classification based on the zeta potential. Adsorption primarily occurs within the pore structure of the membrane rather than only at the luminal surface which contacts the blood. Therefore, the open pore structure of high-flux membranes affords more adsorptive potential than do low-flux counterparts. Second, synthetic membranes, many of which are fundamentally hydrophobic, generally are much more adsorptive than hydrophilic cellulosic membranes (29).

While adsorption of endotoxins and cytokines is clearly desirable, one could argue that adsorptive properties of a dialyzer are not important for removal of solutes such as beta-2 microglobulin, because it does not matter to the patient whether a toxin goes down the drain or is adsorbed within the membrane wall.

Medication Interactions. Potential adverse interactions between membranes and medications are difficult to predict. In 1990, reports of life-threatening anaphylactoid reactions with polyacrylonitrile membrane dialyzers and ACE inhibitor blood pressure medications surfaced (30). These reactions were subsequently shown to be a result of bradykinin accumulation due to the combination of increased synthesis stimulated by interaction of blood with the negatively charged membrane, and reduced catabolism of bradykinin with ACE inhibitors (31,32).

Other concerns with medications have arisen related to correct dosing of potentially dialyzable drugs such as vancomycin (33).

4.2. Sterilizability. Since dialyzed blood is returned to patients, dialyzers and associated tubing must be sterilized. Historically, the most common form of sterilization used ethylene oxide. With the recognition that some patients develop allergic reactions to ethylene oxide-altered human serum albumin, ETO-HSA (34), other sterilizations methods such as gamma irradiation, steam sterilization, and e-beam sterilization have been developed. Care must be taken to characterize dialyzers after sterilization, and to ensure that any variability in sterilization regimen does not significantly alter dialyzer properties.

4.3. Dialyzer Reuse. In the 1980s and 1990s, the practice of dialyzer reuse became commonplace in the United States. At first, this was driven by both the medical benefit of improved biocompatibility and the financial benefit of reducing the cost per treatment of the use of more expensive dialyzer membranes. With the use of more biocompatible polysulfone membranes, a recent retrospective study found a 5–10% mortality benefit was associated with single use dialyzers was observed (35).

Vertical integration of dialyzer manufacturers with dialysis provider chains has enabled one major company (Fresenius) to offer single-use dialyzers to all patients. In 2003, this company reached a 50 MM dialyzer/year production milestone.

5. Membrane Materials, Spinning Technology, and Structure

Dialyzer membrane performance depends on the biomaterial used, its thickness, and the hydraulic permeability, pore size and density, biocompatibility and the hydrophilic/hydrophobic properties. Some of these properties are discussed below.

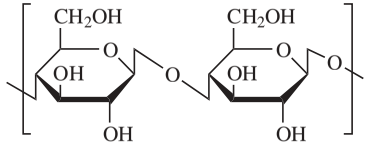
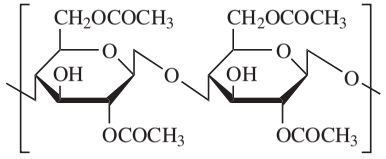
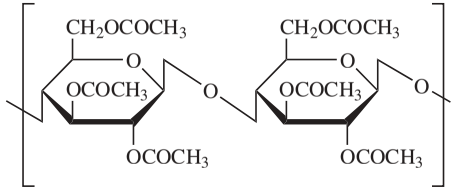
5.1. Membrane Materials. Current dialyzer membranes can be classified based on their chemical compositions as cellulosic, modified cellulosic, and synthetic. Each of these membrane types will be discussed in detail.

Cellulosic Membranes. Cellulosic membranes were exclusively used in the 1940s through 1960s. Regenerated cellulose membranes were produced using the cuprammonium process and were commonly known by the trade name "Cuprophan®" or the term "cuprammonium rayon." These are polysaccharide membranes derived from cotton linters, the short fibers left on cottonseed after long fibers have been removed. This natural cellulose is of high quality with minimal variation in its molecular chain length. Regenerated cellulose membranes can be manufactured to have very low wall thickness (6–15 μm), high pore density and low cost. Cellulosic membranes are very effective in removing low molecular weight toxins, but their very low mean pore size results in poor middle molecule removal. The membrane has a high density of hydroxyl groups on their glucosan rings, which activates the complement cascade via the alternate pathway. Activation of the complement cascade makes these membranes bio-incompatible (20). Despite being considered the least biocompatible dialyzer material, these membranes are still used in some parts of the world primarily due to their lower cost.

Modified Cellulosic Membranes. Modified cellulosic membranes are made more biocompatible by the substitution of the hydroxyl groups with other moieties or by coating the membrane with a biocompatible coating. Cellulose diacetate and cellulose triacetate differ in the degree of substitution of the hydroxyl groups with acetate groups. Other groups such as diethylaminoethyl (DEAE) and benzyl groups were added to make the membranes more biocompatible. These substituted membranes are more hydrophobic and also have a larger mean pore size, which results in higher water permeability and middle molecule clearances compared to unmodified cellulosics. This chemical modification influences membrane properties such as protein absorption, wettability, biocompatibility and clearance of both small and middle molecules. Cellulose acetate membranes have been produced by melt spinning as well as solution-diffusion processes. Table 1 lists cellulose and modified cellulose dialyzer membranes used in hemodialyzers today.

Non-cellulosic "Synthetic" Membranes. In the dialysis field, the term "synthetic membrane" is used to denote all polymeric membranes that are not cellulose-based. Table 2 lists the various synthetic membranes that are commercially available. Polymers like polyacrylonitrile (PAN), poly(methyl methacrylate) (PMMA) and ethylene vinyl alcohol (EVAL) copolymer were adapted from the textile industry, while polymers like polysulfone, polycarbonate and polyurethane were developed as engineering plastics. Synthetic membranes with high water permeability were developed in the 1960s primarily for hemofiltration. These membranes are now manufactured with a range of permeabilities. These

Table 1. **Cellulose and Modified Cellulose Membrane Materials in Hemodialyzers Today**

Membrane	Substitution of OH groups	Chemical structure
regenerated cellulose	not applicable	
cellulose acetate	acetate, nominal degree of substitution = 2.0	
cellulose triacetate	acetate, nominal degree of substitution = 3.0	

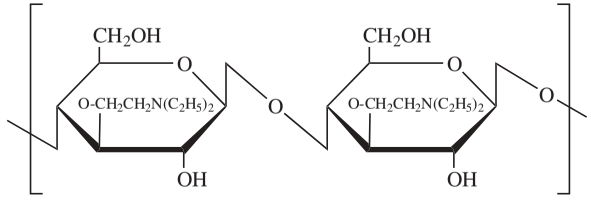
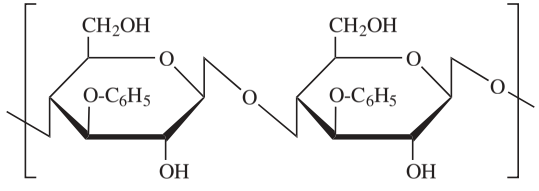
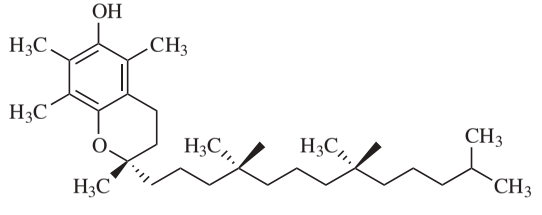
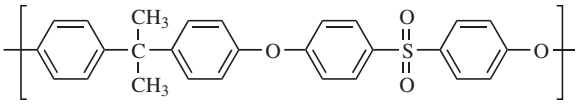
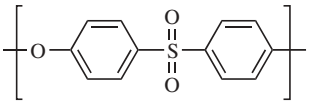
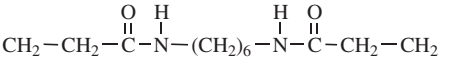
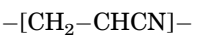
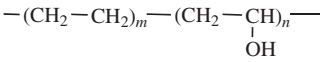
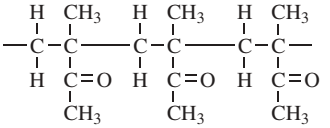
DEAE-modified cellulose	Diethylaminoethyl group	
benzyl-modified cellulose	Benzyl group	
PEG-coated cellulose	not applicable	coating: $-(CH_2-CH_2-O)_n-$
vitamin-E coated cellulose	not applicable	coating: 

Table 2. **Base Polymers for Synthetic Membranes Used in Hemodialyzers Today**

Membrane polymer	Chemical structure
polysulfone (PSu)	
polyethersulfone/polyarylethersulfone (PES)	
polyamide (PA)	
polyacrylonitrile (PAN)	
ethylene vinyl alcohol (EVAL)	
poly (methyl methacrylate) (PMMA)	

membranes have thicker walls (>20 μm) and are either symmetric or asymmetric. An asymmetric membrane consists of a skin layer, which is 1 μm thick, and a support layer, which comprises the rest of the wall thickness (36). The skin layer is in contact with the blood and controls the solute removal. The pore structure of the support layer is much more open and varies among the various synthetic membranes and this layer dictates the thermal and mechanical properties of the membranes. The average pore size in the skin layer for low flux membranes is around 10A and for the high flux membranes is around 30–50A. The pore size in the support layer is greater than 100A. The synthetic membranes that were produced early on were hydrophobic and resulted in excessive protein losses (37).

5.2. Hollow Fiber Spinning Technology. Selected polymers are dissolved with solvents and spun through tube-in-orifice nozzles to form hollow fiber structures in either dry-wet or dry spinning mode. Because the inner surface of the hollow fiber plays an important role for separation, the hollow fiber is usually spun with an inner liquid to control the pore structure of the lumen surface. Then, the fibers are introduced into coagulation bath, where pores are formed by micro-phase separation, induced by thermal and/or solvent concentration differences. Finally, the porous hollow fiber is formed with the desired inner

Fig. 8. Video of dialyzer manufacturing process at Fresenius plant in Ogden, Utah. Copyright Fresenius Medical Care (2005). Reproduced with permission.

and outer diameters, for example, ID = 200, OD = 230 μm. Membrane porosities up to around 75% may be employed, while the pore diameters are controlled in the nanometer range. The hollow fibers are wound on a spool or a reel, with the number of fibers in the bundle set by the number of revolutions of the spool.

Figure 8 is a video of dialyzer mass production at a highly automated Fresenius plant in Ogden, Utah. The movie shows fiber spinning, fiber bundles being cut from take-up spools, as well as many automated tasks in dialyzer assembly.

Spinning hollow fiber membranes is very similar regular fiber spinning, but requires substantially greater quality control to ensure product safety. For example, dimensional uniformity, micro-phase separation, and material purities must be strictly controlled to ensure consistent transport performance.

Figure 9 is a video of an automated dialyzer inspection process used at the Fresenius plant in Utah (4). Such processes help ensure the high quality of dialyzers produced worldwide.

5.3. Pore Size, Distribution, and Density. As described recently by Ronco and co-workers (38) the nature of the pore size distribution may significantly influence a membrane's sieving properties. Desirable features for a high-flux membrane include a large number of relatively large pores (radius as large as 45 Å) having a narrow distribution of sizes. This type of distribution leads ideally to a solute-sieving coefficient *vs.* molecular weight profile with a sharp cut-off at a molecular weight just below that of albumin, similar to that of the native kidney. In actual practice, all highly permeable membranes have measurable albumin sieving coefficient values, such that the design of this type of membrane involves striking a balance between optimized large molecular weight toxin removal and minimal albumin losses.

5.4. Hollow Fiber Geometry. *Inner Diameter.* The inner diameters of the current hollow fibers vary from about 180 to 220 μm. Recently dialyzers have been produced with a decreased inner fiber diameter (17). This preliminary study suggested that small changes of the inner diameter of the fiber could result in

Fig. 9. Dialyzer inspection video at Fresenius manufacturing plant in Ogden, UT. Copyright unknown. Sightech Vision Systems. Reproduced with permission. (AWAITING FORM).

dramatic changes in removal of both urea and middle molecules. High shear rates were also obtained by lowering the inner diameter of the fiber at a given blood flow rate. This leads to a reduction of the protein boundary layer and improve the membrane permeability (39). Decreasing hollow fiber inner diameter improves diffusive mass transfer by shortening path length and attenuating boundary layer effects through higher shear rates (40). However, one factors constraining possible decreases in hollow fiber inner diameter becomes evident with calculation of the axial pressure drop from Hagen-Poiseuille equation (41), which can be rearranged to

$$\Delta P = 8\,\mu L\,Q_B/ND^4$$

where, ΔP is axial pressure drop, μ is the viscosity, L is the length, Q_B is blood flow rate, N is the number of fibers and D is the hollow fiber inner diameter. Because of the exponent on D, a small decrease in hollow fiber inner diameter causes a large increase in axial pressure drop (at constant blood flow rate). Therefore, hollow fiber lumen dimensions represent a compromise that reflects both mass transfer and hydrodynamic considerations.

Wall Thickness. As mentioned previously, wall thicknesses of cellulosic fibers range from 6–15 μm. Noncellulosic membrane thicknesses are greater than 20 μm.

Axial Undulations. Since wavy hollow fibers provide better dialysate flow distribution, hollow fibers are often axially undulated in a post-spinning process. Figure 10 shows two wave patterns found in commercially available polysulfone dialyzers today. Other techniques for improving performance include radial variations in wall thickness, spacer yarns, and knitting of hollow fibers. All of these methods are designed to achieve uniform dialysate flow around all hollow fibers.

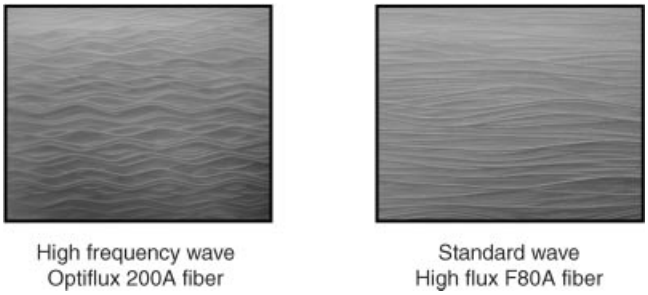


Fig. 10. Comparison of fiber undulations in two polysulfone dialyzer membranes. Copyright 2006 Fresenius Medical Care. Reproduced with permission.

6. Dialyzer Design and Performance

Dialyzer performance depends not only on the membrane properties but also on device properties.

6.1. Typical Dialyzer Dimensions. Device properties such as the fiber length, membrane surface area, number of fibers, hollow fiber packing density, and header design all affect solute clearances. Figure 3 shows a typical hemodialyzer.

Dialyzer lengths are typically 20–24 cm, and represent a trade-off between being long enough to allow virtual equilibration of dialysate and blood urea concentrations, and short enough to have acceptable axial pressure drops. Recent reports have suggested increasing dialyzer lengths to improve middle molecule clearances via internal filtration (16). Dialyzers used for adult patients typically have $1-2\,m^2$ of membrane area (measured at the lumen surface) distributed among 8,000 to 16,000 hollow fibers. Fiber packing densities are optimized to provide uniform dialysate distribution. Typical dialyzers employ packing densities of roughly 50% to 75%.

6.2. Solute Clearances. The effectiveness of dialysis as a replacement for kidney function depends on the mass transfer characteristics of the membranes as well as device parameters. Reference 1 contains a table that compares the characteristics of several dialyzers available today.

6.3. Sieving Coefficients. Sieving coefficients of marker solutes such as vitamin B-12 (MW = 1355 Da), inulin (MW = 5200 Da), and myoglobin (MW = 17,200 Da) are reported more often than sieving coefficients of known uremic toxins. Nevertheless, they serve as a useful tool in comparing potential middle molecule removal.

7. Current Market Trends

In 2004, more than one hundred million dialyzers were produced worldwide. The breakdown is approximately as follows:

- polysulfone > 65 MM/yr (60%)
- cellulose acetate/triacetate > 25 MM/yr (20–25%)
- other polymers < 20 MM/yr (15–20%)

With the recent consolidation of the top four U.S. dialysis providers into two vertically integrated companies, the field of available dialyzers is likely to narrow. Meanwhile, the decrease in dialyzer reuse will continue to drive increased production. Given that the Center for Medicare and Medicaid Services (CMS), formerly known as the Healthcare Financing Administration (HCFA), will continue its downward pressure on costs, and possibly institute a capitated payment system (ie, a fixed monthly payment to cover all patient costs including hospitalization), only incremental improvements in commercially available dialyzer membranes are expected in the next five years.

8. Future Directions

8.1. Middle Molecule Removal. While current therapy is believed to be effective in the clearance of small solutes like urea, improved removal of middle molecules and protein-bound solutes is desirable. Henderson and co-workers point to the importance of quantifying the removal of larger toxic solutes in the light of increasing evidence that shows a positive correlation between survival and middle molecule clearance in hemodialysis patients (42). A number of studies are underway to enhance the removal of middle molecules. These studies include: (*1*) variations in modes of dialysis; (*2*) changes in dialyzer design to improve internal filtration; (*3*) targeted removal of specific molecules; and (*4*) increased frequency of dialysis.

Alternative Modes of Dialysis. The standard mode of dialysis in most countries today is high-flux dialysis, in which high ultrafiltration rates are counter-balanced by back-filtration. To prevent excessive fluid loss, net ultrafiltration is controlled volumetrically. In this mode, clearances are improved over conventional hemodialysis, where low-flux membranes lead to low ultrafiltration rates and minimal convection.

Several convective therapies have been considered as alternatives to the high-flux dialysis commonly employed today.

Hemofiltration is a purely convective filtration process in which large volumes of water are removed from the patient and discarded, and sterile, pyrogen-free replacement fluid is administered. Hemofiltration is often used for acute renal failure, where large quantities of fluid (up to 20 L) must be removed in a short time (1–2 days). One form of hemofiltration, continuous arteriovenous hemofiltration (CAVH) is particularly suited for use in the intensive care unit due to the simplicity of the process and slow/"gentle" nature of the therapy. In CAVH, blood flow is driven by the arterio-venous pressure difference, rather than by a pump, the filtrate waste stream is generated by a simple gravity drain, and no dialysate is employed. Continuous veno-venous hemofiltration (CVVH) and continuous veno-venous hemodiafiltration (CVVHD) employ a blood-side pump, with and without a dialysate stream, respectively.

Conventional hemodiafiltration (HDF) utilizes large convective transport with ultrafiltration rates above 70 mL/min. Since such ultrafiltration rates result in total ultrafiltration volumes that exceed the desired weight losses in patients, sterile replacement fluid must be administered. Total replacement fluid required varies between 12 and 22 L per session. Because of the prohibitive cost of

prepackaged replacement fluid, on-line generation of sterile fluid has been employed. In this method, the plasma beta 2-microglobulin levels were reduced when compared to high flux HD (43). Furthermore, an improvement in survival (35%) has recently been reported using high efficiency (>15–25 L/session) HDF (44,45). The major drawbacks of this treatment are the complexity of the system and the increased cost of the therapy over conventional hemodialysis. New dialysis machines with on-line generation of sterile replacement fluid hold promise for overcoming these drawbacks.

Changes in Dialyzer Design to Improve Convection. One approach for increasing middle molecule removal has been to modify the dialyzer design to improve internal filtration, thereby increasing convective solute removal. Ronco and co-workers (45) have used a fixed O-ring on the dialysate side to alter the pressure profile in the dialysate compartment within the dialyzer. This results in an increased rate of filtration and back filtration without affecting the net ultrafiltration rates. Because the filtered fluid is diluted before being back-filtered, it offers improved clearance of middle molecules without the need for replacement fluid. Using a similar philosophy of increasing internal filtration, Mineshima studied the impact of fiber length and inner diameter on convective solute removal (46).

Adsorption for Toxin Removal. Immunoadsorption is another way to remove middle molecules, either specifically or nonspecifically. Adsorptive processes can be carried out either by chemically modifying a hemodialysis membrane to create adsorption sites or by the use of an add-on device (eg, affinity column) during hemodialysis. It should be mentioned that the 1–2 square meter membrane surface area on the hollow-fiber lumen is much smaller than the surface area within the porous membrane structure, and may be insufficient to provide significant toxin removal. However, one could argue that adsorptive sites within the membrane wall offer little benefit unless significant backfiltration of a toxin is taking place, because it makes no difference to the patient whether a toxin is adsorbed within the membrane walls or flushed away with the spent dialysate.

Dialysis Treatment Time and Frequency. Dialysis treatment time and frequency are important in the removal of middle molecules and other molecules which transport slowly within the human body. For small solutes such as urea, the transport gradient dissipates within the first few hours, and little is gained by extending treatment times beyond the standard 3.5–4.0 hours. Carrying out dialysis more frequently than the usual three times per week schedule results in lower peak concentrations of such small solutes, but may not result in substantially greater overall removal each week. Larger-sized solutes are more slowly transported, so equilibrium between blood and dialysate is not generally reached with a typical treatment regimen. Thus, middle molecule removal can be increased by extending the treatment time with nocturnal dialysis, especially if it is performed daily. Short daily dialysis may provide some additional middle molecule removal if "short" is not as short as half the usual treatment time in three times per week dialysis.

Removal of relatively small solutes with substantial compartmental effects, such as inorganic phosphate, may benefit the most from short daily dialysis. In the United States, nocturnal dialysis and short daily dialysis are under

investigation in studies funded by the National Institutes of Health, but are not generally available because Medicare only pays for standard treatment.

9. Conclusions

Hemodialysis sustains the lives of approximately one million patients worldwide today (2006). In the last 35 years, hemodialysis membranes have become increasingly efficient, and hemodialysis machines have become increasing sophisticated. Nevertheless, unmet clinical needs continue to drive research along a number of fronts.

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NORMA J. OFSTHUN
Corporate Research, Fresenius Medical Care