Kirk-Othmer Encyclopedia of Chemical Technology.

DIALYSIS

Dialysis is a membrane separation process in which one or more dissolved species flow across a selective barrier in response to a difference in concentration. It is the earliest molecularly separative membrane process to be identified and described (1). The mode of transport is diffusion, and separation occurs because small molecules diffuse more rapidly than larger ones, and also because the degree to which membranes restrict solute transport usually increases with permeant size. The basic principles are illustrated in Figure 1. Solute c is present at concentrations c' and c'' on opposite sides of a membrane. In the absence of differences in pressure, temperature, or electrical potential, Fick's phenomenological first-order description of diffusion, published in 1855 (2), states that solute will move from region of greater to lesser concentration and at a rate proportional to the difference. In equation 1, ϕ = unit solute flux in $g/cm^{26}{\cdot}s$; D = diffusion coefficient, cm^2/s; c = concentration in g/cm^3; x = distance in cm; and the minus sign accounts for the convention that flux is considered positive in the direction of decreasing concentration.

$$\phi = -D\frac{\partial c}{\partial x} \qquad (1)$$

Diffusion coefficients decrease roughly in proportion to the square root of molecular weight, are widely tabulated for aqueous solutions, or may be estimated from the Stokes Einstein equation (3). Ignoring boundary layer effects for the moment, and by assuming that diffusion within the membrane is analogous to that in free solution, equation 1 can be integrated across a homogeneous membrane of thickness d to yield the following equation, where S represents the dimensionless solute partition coefficient, ie, the ratio of solute concentration in external solution to that at the membrane surface, and D_M represents solute diffusion within the membrane and is assumed independent of solute concentration.

$$\phi = \frac{SD_M\Delta c}{d} \qquad (2)$$

The product SD_{M} is often termed *permeability*; if two or more solutes are dialysing at the same time, the degree of separation or enrichment is proportional to the ratio of their permeabilities. The closer the permeability of a membrane is to that of an equivalent thickness of free solution, the more rapid is the resultant dialytic transport. Considerable effort has been devoted to understanding how the physical and chemical properties of a membrane determine its permeability. The simplest approaches are geometric and consider the membrane to comprise a series of parallel pores that provide a topographic obstacle to hard noninteracting permeant molecules (4); far more complex analyses are also available (5, 6). As a general rule, permeability for a particular species increases with porosity (solute content) of the membrane and with the diameter of its pores. Equation 2 also states that the mass flow rate of solute is inversely proportional to membrane thickness, but the degree of separation (selectivity) is independent of thickness. For this reason, membranes are always made as thin as possible consistent with the requirements of mechanical strength and reliability. Equation 2 is often further simplified to the following expression for flux per unit of membrane area, where thickness is incorporated into

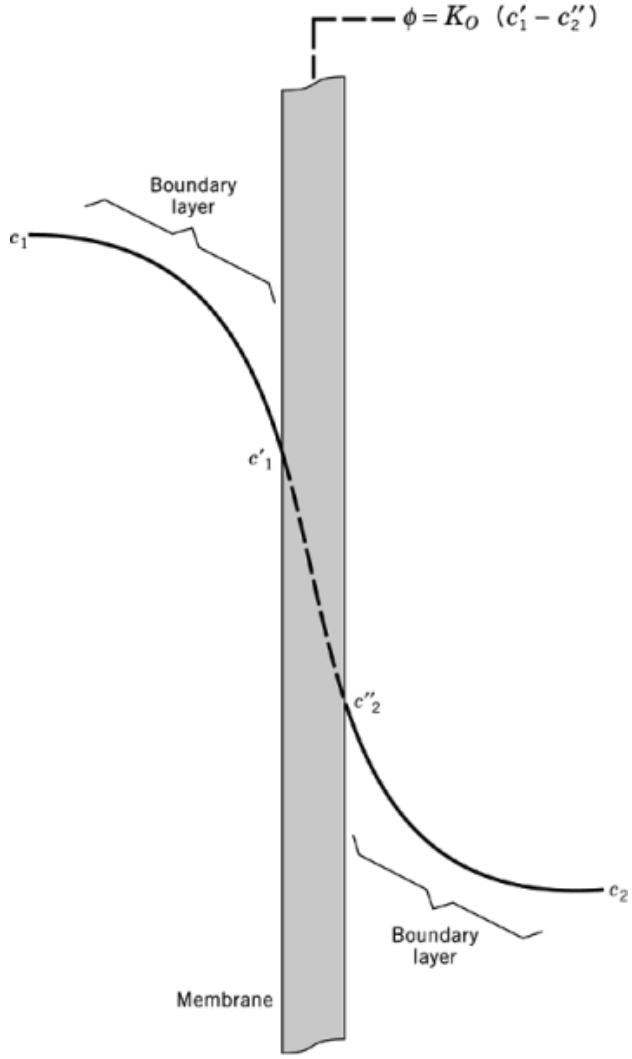

Fig. 1. General dialysis is a process by which dissolved solutes move through a membrane in response to a difference in concentration and in the absence of differences in pressure, temperature, and electrical potential. The rate of mass transport or solute flux, φ, is directly proportional to the difference in concentration at the membrane surfaces (eq. 1). Boundary layer effects, the difference between local and wall concentrations, are important in most practical applications.

an overall membrane mass-transfer coefficient, K_M, with units of cm/s.

$$\phi = K_M \Delta_C \qquad (3)$$

Dialysis transport relations need not start with Fickian diffusion; they may also be derived by integration of the basic transport equation (7) or from the phenomenological relationships of irreversible thermodynamics (8, 9).

Solutions adjacent to the membranes are rarely well mixed, and the resistance to transport resides not just in the membrane but also in the fluid regions, termed boundary layers, on both the dialysate and feed

side. Boundary layer effects typically account for from 25 to 75% of overall resistance. They are minimized by rapid convective flow tangential to the surface of the dialysing membrane. When fluid pathways are thin, juxtamembrane flow is laminar, and boundary layer resistance decreases with increasing wall shear rate. Where geometry permits higher Reynolds numbers, flow becomes turbulent and resistance varies with net tangential velocity. Geometric turbulence promoters are often employed. All tactics to reduce boundary layer result in higher energy utilization. Quantitatively, the membrane resistance becomes part of an overall coefficient K_O which, for conceptual purposes, is broken down into three independent and reciprocally additive components:

$$\frac{1}{K_O} = \frac{1}{K_B} + \frac{1}{K_M} + \frac{1}{K_D} \qquad (4)$$

$$R_O = R_B + R_M + R_D \qquad (5)$$

where K is device-averaged mass-transfer coefficient (or permeability) in cm/s, R is device-averaged resistance in s/cm, and the subscripts B, M, and D respectively denote the feedstream membrane, and dialysate. Note that K_M in equation 4 is identical to that in equation 3. K_B can be estimated for many relevant conditions of geometry and flow using mass transport analysis based on wall Sherwood Numbers (10). K_M is best obtained by measurements employing special test fixtures in which boundary layer resistances are negligible or known (11, 12). K_D is more problematic, and is usually obtained by extrapolations based on Wilson plots (13). Boundary layer theory, as well as techniques for correlation, estimation, and prediction of the constituent mass-transfer coefficients have been reviewed in two particularly lucid monographs (14, 15). Overall solute transport is obtained from local flux by mass balance and integration; for the most common case of counter-current flow:

$$\phi = \left(c_i' - c_i\right) \frac{Q_B}{A} \frac{\exp\left[\frac{K_O A}{Q_B}\left(1 - \frac{Q_B}{Q_D}\right)\right] - 1}{\exp\left[\frac{K_O A}{Q_B}\left(1 - \frac{Q_B}{Q_D}\right)\right] - \frac{Q_B}{Q_D}} \qquad (6)$$

where c'_i and c''_i represent inlet concentrations in the feed and dialysate streams in g/cm^3, A represents membrane surface area in cm^2, Q_B and Q_D are feed and dialysate flow rates in cm^3/min, and φ and K_O are as defined in equations 3 and 4. Derivations of this relationship and similar expressions for cocurrent or cross-flow geometries can be found in the literature (14, 16, 17).

Dialysis is a highly constrained process. Molecular diffusion is slow in the context of industrial dimensions. The driving force is set by the system itself, decreases in the course of purification, and is not amenable to extrinsic augmentation. The permeant species is not recovered in pure form, and is necessarily more dilute in the dialysate than in the starting stream. Low energy utilization is offset by high capital costs. For these reasons, dialysis has been largely limited to laboratory separations or specialized *in vivo* pharmacological investigations, and has enjoyed very limited success as a broad-based commercial unit operation. But the slow and gentle nature of dialysis has a special appeal for biologic applications, particularly when partial purification of the feed stream, rather than recovery of a product, is intended. Commercially significant examples include the adjustment of alcohol content of beverages and the removal of salts from solutions of proteins or other biologic macromolecules. However, the most successful and widespread application of dialysis—or for that matter of any membrane process—is the support of patients with kidney failure by repeated intermittent blood cleansing. In 1992 nearly half a million patients were maintained on dialysis, and the worldwide commercial aspects of this enterprise exceeded 15 billion U.S. dollars. Dialysis is closely related to membrane gas separation, pervaporation, ultrafiltration, and controlled release of pharmaceuticals discussed in separate sections of this *Encyclopedia* (see Controlled release technology, pharmaceuticals). Particularly common is diafiltration, combined simultaneous dialysis, and ultrafiltration (qv) (see Membrane technology).

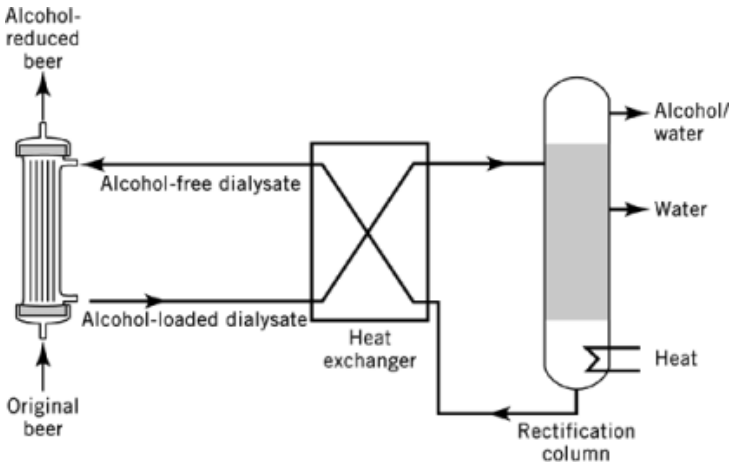

Fig. 2. Schematic of alcohol reduction in beverages. Countercurrent dialysis is combined with distillation. The separation process is isothermal, and high boiling ingredients, present in the dialysate, are preserved. In this fashion, alcohol removal is accomplished with minimal perturbation in flavor.

1. Industrial Dialysis

The recovery of caustic from hemicellulose (qv) in the rayon process was well established in the 1930s (18), and is still used in modern times (19) (see Pulp). Very few new industrial applications of dialysis emerged during the 1940–1980 period. More recently, interest has reawakened in isobaric dialysis as a unit operation for the removal of alcohol from beverages (20, 21) and in the production of products derived from biotechnology (22, 23).

Although to many an oxymoron, alcohol-free beer has grown in popularity over the past decade in response to changing life-styles and legislative restraints on alcohol consumption; markets are also developing for alcohol-free wine. By the end of 1992, 40 key beer breweries worldwide had installed dialysis plants with an annual capacity of more than 189,000 m^3 (5×10^7 gal) of beer (qv). The process is illustrated in Figure 2. Alcohol is removed from beer by dialysis, the dialysate is distilled to remove alcohol, and the raffinate is recycled as a dialysate stream. The combination of dialysis and distillation preserves the flavor of the product (24); dialysis is isothermal so the beer need not be heated. Higher boiling alcohols, esters, and carbohydrates that impart the special flavor to the beverage are already present in the dialysate and thus are not removed from the feed stream. A typical commercial installation is shown in Figure 3.

Dialysis plays an important role in the expanding biotechnology industry, but rarely as a stand-alone unit operation. It is applicable to the removal of salts from heat-sensitive or mechanically labile compounds such as vaccines, hormones, enzymes, and other bioactive cell secretions. In these instances, process efficiency is almost always increased by combining dialysis with ultrafiltration in the process known as diafiltration. Dialysis provides a simple means to control media and extracellular environment in bioreactors. Dialyzers can also offer the basis for a novel bioreactor design: the extraluminal region of a hollow fiber dialyzer provides an excellent growth environment for mammalian cells when the lumen is perfused with oxygen and nutrients (25). In the production of monoclonal antibodies, for example, a small benchtop bioreactor can readily equal the antibody production of several thousand mice. This technology is still in its early stages and considerable evolution can be anticipated in the future (see Fermentation; Reactor technology).

Fig. 3. A commercial dialysis facility showing the dialysis section of a German brewery where alcohol is removed from beer. Technical dialysis modules contain up to 50,000 capillaries and around 23 m^2 (250 ft^2) of membrane surface area. Typical plants might contain between 50 and 100 modules.(Courtesy of Holstein and Kappert Processtechnik GmBH, Dortmund, Germany.)

2. Laboratory Dialysis

Until the early 1960s, laboratory investigators relied on dialysis for the separation, concentration, and purification of a wide variety of biologic fluids. Examples include removal of a buffer from a protein solution or concentrating a polypeptide with hyperosmotic dialysate. Specialized fixtures were sometimes employed; alternatively, dialysis tubes, ie, cylinders of membrane about the size of a test tube and sealed at both ends, were simply suspended in a dialysate bath. In recent years, dialysis as a laboratory operation has been replaced largely by *ultrafiltration* and *diafiltration*.

Microdialysis is a highly specialized application of the technique (26–28). In its simplest form, a U-shaped dialysis capillary is surgically implanted into the tissue of a living animal. Isotonic dialysate is pumped through the tubing at a flow rate low enough to allow equilibration with small solutes in the host's extracellular fluid. Concentration of solutes in the exiting fluid thus approaches those in the extracellular portion of the tissue. This technique is extremely useful because it permits uninterrupted sampling of the chemistry of individual tissues or body compartments without drawing blood. Once the implant is established, a microdialysis probe is capable of sampling continuously for days or even weeks. The procedure is most widely used in rodent studies, and is most popular for direct implantation into the brain by standard animal neurosurgical techniques. Microprobe designs range from straightforward U tubes to complex concentric capillaries. Perfusate flow rate is extremely low, around 10^{-6} mL/min. Microdialysis is performed on anesthetized animals usually under microprocessor control with online analysis of the eluate. Between 500 and 1000 articles have appeared in the literature describing microdialysis experiments in animals. The technique is likely to increase in popularity in the future, though therapeutic application seems a remote possibility.

3. Hemodialysis

Serious kidney disease is surprisingly uncommon in relation to the complexity of the organ, striking between 1 in 5,000 and 1 in 10,000 of the population per year. The origin of kidney disease may be genetic, traumatic, metabolic, vascular, or immunologic, and the response of the kidney, although essentially sclerotic, may be reversible or permanent, local or systemic, rapid or slow, or any combination thereof (29, 30). Kidney failure, as distinct from kidney disease, occurs when renal function has declined to the point that the kidney can no longer satisfactorily perform its homeostatic and excretory functions. Since nature has provided kidneys with an abundance of overcapacity, patients become overtly symptomatic and identifiably diseased only after about 90% of function has been lost. When kidneys decline further and loss of capacity exceeds about 95%, some form of renal replacement therapy is required. Current alternatives include kidney transplantation and dialysis.

Despite widespread consensus that a successful transplant is the most satisfactory form of therapy for end stage renal disease, a chronic shortage of donor organs limits the number of patients receiving transplantation to about 18,000 per year (31, 32). The remainder of renal failure patients require maintenance dialysis. About 12% elect *continuous ambulatory peritoneal dialysis* (*CAPD*), the remaining 88% *hemodialysis*. In CAPD, approximately 2 liters of a sterile, nonpyrogenic and hypertonic solution of glucose and electrolyte are instilled via gravity flow into the peritoneal cavity through an indwelling catheter four times per day. Intraperitoneal fluid partially equilibrates with solutes in the plasma, and plasma water is ultrafiltered due to osmotic gradients. After 4–5 h, except at night when the exchange is lengthened to 9–11 h to accommodate sleep, the peritoneal fluid is drained, and the process repeated. Patients perform the exchanges themselves in 20–30 min, at home or in the work environment, after a training cycle which lasts only 1–2 weeks. The literature on CAPD is abundant, but is well summarized in reference texts (33, 34) and review articles (35, 36).

The remaining 88% of untransplanted patients with kidney failure receive hemodialysis. This is an intermittent therapy with patients typically having thrice-weekly treatments of from 2.5 to 4 hours. Although most hemodialysis is performed in free-standing treatment centers, it may also be provided in a hospital or performed by the patient at home. The hemodialysis circuit consists of two fluid pathways. The blood side is entirely disposable, though many centers re-use some or all circuit components in order to reduce costs. It comprises a 16-gauge needle for access to the circulation (usually through a fistula created in the patient's forearm), lengths of dioctyl phthalate plasticized poly(vinyl chloride) tubing including a special tubing segment adapted to fit into a peristaltic blood pump, the hemodialyzer itself, a venous bubble trap and an open mesh screen filter, various ports for samples and gauge connections, and a return cannula. Components of the blood-side circuit are supplied in sterile and nonpyrogenic condition; ethylene oxide is the most common sterilant, although both radiation and steam sterilization are rapidly gaining favor. The dialysate side is essentially a machine capable of proportioning out glucose and electrolyte concentrates with water to provide dialysate of appropriate composition, pumping dialysate past a restrictor valve and through the hemodialyzer at subatmospheric pressure, and monitoring temperature, circuit pressures, and flow rates. During treatment the patient's blood is anticoagulated with heparin. Typical blood flow rates are 200–350 mL/min; dialysate flow rates are usually 500 mL/min. Straightforward techniques have been developed to prime the blood side with sterile saline prior to use and to rinse back nearly all the formed elements after treatment. Although most mass transport occurs by diffusion, circuits are operated with pressure on the blood side controlled to 13.3 to 66.7 kPa (100 to 500 mm Hg) higher than on the dialysate side. This provides an opportunity to remove 2 to 4 liters of fluid along with the solute; higher rates of fluid removal are technically possible but physiologically unacceptable. Hemodialyzers must be designed with high enough hydraulic permeabilities to provide adequate fluid removal at the upper pressure range, but not so high that excessive dewatering will occur at the lower pressure ranges.

Figure 4 is a schematic of a typical hemodialyzer. Although other geometries are still employed, the preferred format is a hollow fiber hemodialyzer about 25 cm in length and 5 cm in diameter. Devices typically contain 6,000 to 10,000 capillaries, each with an inner diameter of 200 μm and a wall thickness of around 10

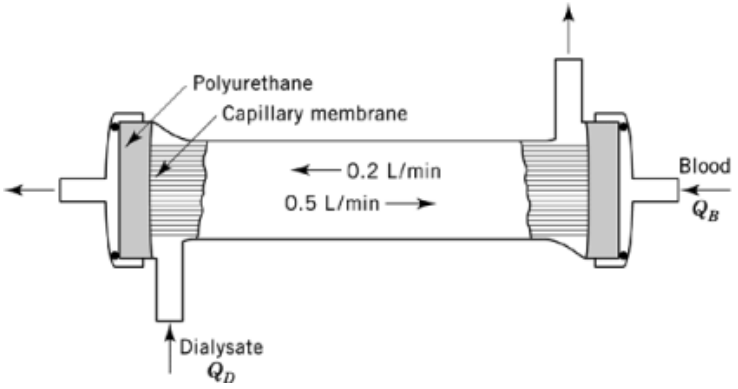

Fig. 4. Schematic of a hemodialyzer. The design of a dialyzer is close to that of a shell and tube heat exchanger. Blood enters through an inlet manifold, is distributed to a parallel bundle of fibers, and exits into a collection manifold. Dialysate flows countercurrent in an external chamber; the blood and dialysate are separated from the fibers by a polyurethane potting material. Housings are typically prepared from acrylate or polycarbonate. Production volume is greater than 50 million units per year and cost is very low, around $10 U.S. in 1992.

μm. Mean total membrane surface area is 1.1 ± 0.4 m^2. Well over 60 million hemodialyzers were produced in 1992. Because of economies of scale, unit price was on the order of $10 per unit, much lower than would be anticipated from the complexity of the device or by comparison with other membrane products. Interestingly, the hemodialyzer rarely represents more than 10% of the cost of a treatment session. This therapy is extensively described in the literature; by mid-1992, Med Line contained over 29,000 citations on hemodialysis. Several excellent reference texts provide concise and comprehensive coverage of all aspects of hemodialysis (37–40).

3.1. Engineering Aspects of Hemodialysis

Engineering interest in hemodialysis is concentrated on the optimization of the hemodialysis membrane (4, 41), the dependency of solute removal on membrane and device characteristics (14, 15), and quantitation of hemodialysis therapy through urea pharmacokinetics (42–44).

Hemodialysis membranes vary from one another in chemical composition, transport properties, and in their biocompatibility, defined here as the capacity of a material to avoid recognition and response by various host defense mechanisms (Table 1). Table 2 divides hemodialysis membranes into three classes: cellulosics, modified cellulosics, and synthetics. Cellulosics are prepared from regenerated cellulose by the cupramonium process; these extremely hydrophilic structures sorb water, bind it tightly, and form true hydrogels as is illustrated in the left hand panels of Figure 5. Their principle advantage is low unit cost; this is complemented by the strength of the highly crystalline cellulose which allows membranes to be made very thin and thus provides effective small-solute transport in relatively small hemodialyzers. The vulnerabilities of regenerated cellulose are its limited permeability to larger molecules, and the presence of labile nucleophilic groups that trigger complement activation and transient leukopenia during the first hour of a hemodialysis session. The advantages appear to outweigh the disadvantages: over 70% of current hemodialyzers are prepared from cellulosics, most of which are supplied by Akzo Faser AG under the trade name Cuprophan. At the opposite end of the spectrum are membranes prepared from synthetic, engineering thermoplastics, such as polysulfone and polyamide. These materials form anisotropic membranes with foamlike or trebacular cross sections (see the right hand panel in Fig. 5). They appear less active to the complement cascade and other physiologic identifiable defense mechanisms. In addition to this improved biocompatibility, these membranes are the least restrictive in transport to larger molecules. Drawbacks are increased cost and sufficiently high hydraulic permeability to

Table 1. Contemporary Hemodialysis Membrane Characteristics

Hydraulic permeability[a]	Solute clearance: mol wt 250	Solute clearance: mol wt >1000	Market share[b]	Absolute growth
low-flux				
KUFR = 2 – 6	high	low	70%	steady
middle-flux				
KUFR = 5 – 12	high	medium	20%	growing
high-flux/high-performance				
KUFR = 10 – 200	high	high	10%	growing

[a] KUFR = ultrafiltration coefficient in $\mathrm{mL/h \cdot m^2 \cdot mm\ Hg}$.
[b] Estimated 1992.

require specialty control mechanisms and to raise concerns over the biologic quality of dialysate fluid. Roughly 10% of hemodialyzers are produced from such hydrophobic membranes. A middle group, also accounting for 10–15% of total hemodialyzer production, comprises both derivatized cellulosics, eg, cellulose diacetate, and synthetic hydrophilic polymers. Because of regulatory vigilence, all hemodialysis membranes in use are both safe and effective; there is no sound epidemiologic evidence that selection of one membrane over another will alter a patient's morbidity, mortality, or quality of life.

The clinical performance of a hemodialyzer is usually described in terms of clearance, a term having its roots in renal physiology, which is defined as the rate of solute removal divided by the inlet flow concentration as shown in equation 7, where Cl is clearance in mL/min and all other terms are as defined previously except that, in deference to convention, flow rates are now expressed in minutes rather than seconds and feed side (c') is now synonymous with blood flow on the luminal side.

$$Cl = \frac{\phi A}{c'_i} = \frac{Q_B\left(c'_i - c'_o\right)}{c'_i} \qquad (7)$$

Note that the numerator in each of the ratios in equation 7 represents the rate of solute removal from the patient. By mass balance, clearance is related to mass-transfer coefficient K_O as defined earlier in equations 3, 4, and 5, and where each of the three expressions equal rate of mass removal in g/s.

$$K_O A \Delta c = \phi A = Clc'_i \qquad (8)$$

For consistency, clearance here is expressed in $\mathrm{cm^3/s}$ although the more common clinical units, and those used later in this chapter, are mL/min. Combination and rearrangement of equations 6–8 allows clearance to be estimated from mass-transfer coefficient and vice versa; the conditions of countercurrent flow with no dialysate recycling are shown below.

$$Cl = Q_B \frac{\exp\left[\frac{K_O A}{Q_B}\left(1 - \frac{Q_B}{Q_D}\right)\right] - 1}{\exp\left[\frac{K_O A}{Q_B}\left(1 - \frac{Q_B}{Q_D}\right)\right] - \frac{Q_B}{Q_D}} \qquad (9)$$

$$K_O = \frac{Q_B}{A\left(1 - \frac{Q_B}{Q_D}\right)} \ln\left[\frac{1 - \frac{Cl}{Q_D}}{1 - \frac{Cl}{Q_B}}\right] \qquad (10)$$

Similar expressions for other conditions of geometry and flow are found in References 14 and 15.

Table 2. Polymeric Materials for Dialysis Membranes

Material	Manufacturer
Regenerated cellulosics	
Cuprophan	Akzo
cuprammonium cellulose	Asahi
	Terumo
SCE[a]	Teijn
	Althin
Synthetically modified cellulose	
Hemophan	Akzo
cellulose acetate	Akzo
	Toyobo
	Althin
	Teijin
cellulose triacetate	Toyobo
SMC[b]	Akzo
Synthetics	
polysulfone	Akzo
	Fresenius
	NMC
	Kurary
	Kawasumi
polycarbonate	Gambro
polyamide	Gambro
polyacrylonitrile	Hospal
	Asahi
SPAN[c]	Akzo
EVAL[d]	Kawasumi/Kuraray
PMMA[e]	Torray

[a] SCE = saponified cellulose ester.
[b] SMC = specially modified cellulose.
[c] SPAN = sulfonated polyacrylonitrile.
[d] EVAL is a poly(vinyl alcohol), a copolymer of ethylene and vinyl alcohol.
[e] PMMA = poly(methyl methacrylate).

Clearance decreases with increasing permeant molecular weight and depends in complex fashion upon blood and dialysate flow rate and upon device geometry. Detailed engineering analyses are available in References (14–17). As a general rule in most contemporary dialyzers, the clearance of small solutes such as urea (mol wt = 58), creatinine (mol wt = 113) has either approached a maximum (clearance can never exceed blood flow rate) or is limited by boundary layers adjacent to the membrane; for these solutes changes in membrane permeability or membrane surface area will not significantly affect clearance whereas increases in blood flow will lead to increased clearance. In contrast, larger solutes such as inulin (mol wt $\sim$ 5200 daltons) or beta-2-microglobulin (mol wt = 11, 118 daltons), are membrane limited. Their clearance will increase, often linearly, with increasing membrane surface area, but will be largely unaffected by changes in blood or dialysate flow rate. These relationships are illustrated in Figure 6 and summarized in Table 3.

3.2. Urea Pharmacokinetics

Pharmacokinetics summarizes the relationships between solute generation, solute removal, and concentration in a patient's blood stream. In the context of hemodialysis, this analysis is most readily applied to urea, which has, as a consequence, become a surrogate for other uremic toxins in the quantitation of therapy and in attempts

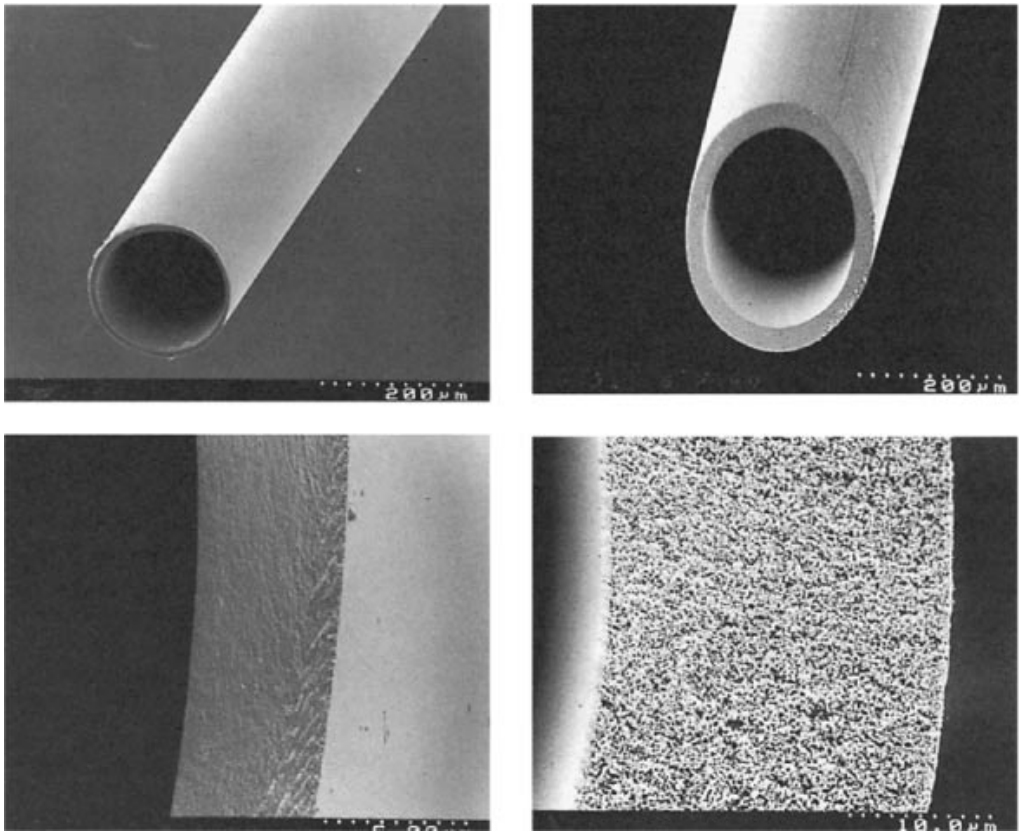

Fig. 5. Scanning electron micrographs of hollow fiber dialysis membranes. Membranes in left panels are prepared from regenerated cellulose (Cuprophan) and those on the right from a copolymer of polyacrylonitrile. The cellulosic materials are hydrogels and the synthetic thermoplastic forms a microreticulated open cell foam with a tight skin on the inner wall. Pictures at top are membrane cross sections; those below are of the wall region. Dimensions as indicated.

Table 3. Effects of Changes in Conditions of Geometry and Flow on Hemodialyser Clearance

	Effect on clearance of	
Parameter increased	Low mol wt solutes[a]	High mol wt solutes[b]
blood flow rate	increases	little or no effect
dialysate flow rate	little effect	little or no effect
membrane surface area	little effect	almost linear increase
membrane permeability	little effect	almost linear increase

[a] Mol wts of <200 daltons, eg, urea (60), creatinine (113), or uric acid (158).
[b] Mol wts of >1000 daltons, vitamin B_{12} (1355) or inulin (~ 5200).

to describe its adequacy. In the simplest case, a patient is assumed to have no residual renal function. Urea is generated from the breakdown of dietary protein, accumulates in a single pool equivalent to the patient's fluid volume, and is removed uniformly from that pool during hemodialysis. A mass balance around the patient yields the following differential equation:

$$\frac{d(cV)}{dt} = G - Clc \qquad (11)$$

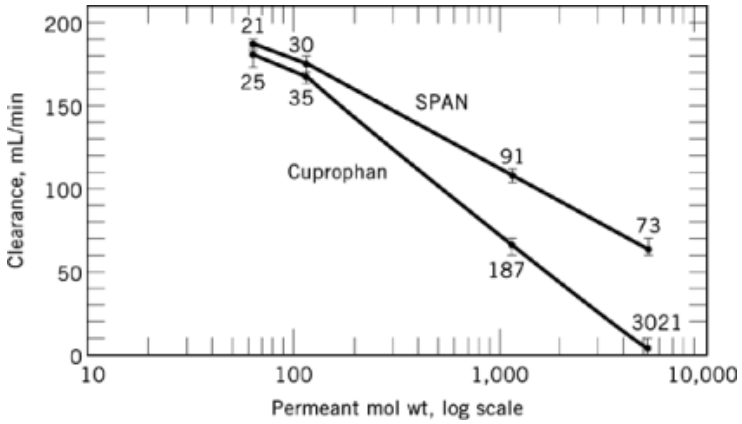

Fig. 6. Solute transport in hemodialysis. Clearance vs solute mol wt for dialyzers prepared from the two different membranes illustrated in Figure 5. Numbers next to points represent R_O in min/cm calculated from equations 10 and 5. Data is *in vitro* at 37°C with saline as the perfusion fluid. Lumen flow, dialysate flow, and transmembrane pressure were 200 mL/min, 500 mL/min, and 13.3 kPa (100 mm Hg); area=1.6 m^2. Inulin clearance of the SPAN fiber was elevated by inulin transported by the filtering fluid.

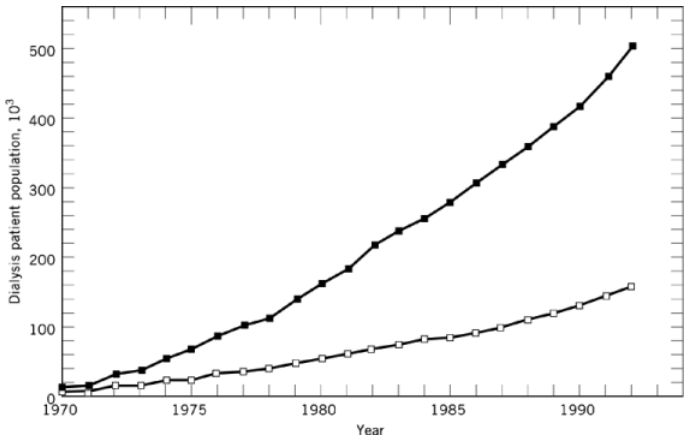

Fig. 7. Estimate of the total number of patients receiving maintenance dialysis over the past 20 years. Totals include both hemodialysis and peritoneal dialysis, but exclude transplant recipients. The fraction of patients receiving peritoneal dialysis has grown steadily from 0% in 1978 to about 12% in 1992. These data were combined from various regional registries and industry sources; demographic estimates of this ilk are accurate to within 5% (46). □, United States; ■, worldwide.

where c = whole blood urea concentration normally expressed as mg % (mg/100 mL), V = urea distribution volume in the patient in mL, G = urea generation rate in mg/min, t = time from onset of hemodialysis in minutes, and Cl = urea clearance in mL/min.

Urea concentration in the United States medical literature is often reported as BUN (blood urea nitrogen), which is urea concentration, usually in mg/dL, multiplied by a factor of 0.47. V, in equation 11, can be measured by dilution studies, but is often estimated in kinetic modeling studies as 58% of patient weight. Generation is calculated from a knowledge or an estimate of patient protein intake (each gram of protein consumed produces about 250 mg of urea; see References 43 and 44 for more exact correlations based on metabolic studies of

uremic patients). Thus a 70 kg patient, consuming a typical 1.0 g of protein per kg of body weight per day, would produce 28 g of urea distributed over a fluid volume of 40.6 L and, in the absence of any clearance, urea concentration would increase by 70 mg % (mg/100 mL) every 24 hours. The reduction of urea concentration during hemodialysis is readily obtained from equation 11 by neglecting intradialytic generation and changes in volume where c^o and c^t represent the urea concentrations in blood at the beginning and during the course of treatment.

$$c^t = c^o \exp\left(-\frac{Clt}{V}\right) \qquad (12)$$

A 3.5 h treatment of a 70 kg patient (V = 40.6 liters) with a urea clearance of 200 mL/min should result in a 64% reduction in urea concentration or a value of 0.36 for the ratio c^t/c^o; this parameter almost always falls between 0.30 and 0.45. The increase in urea concentration between hemodialysis treatments is obtained from equation 13, again assuming a constant V, where c^o is the urea concentration in the patient's blood at the end of the hemodialysis, and c^t the concentration at time t during the intradialytic interval.

$$c^t = c^o + \frac{G}{V}t \qquad (13)$$

Urea concentration typically increases by about 50 to 100 mg/100 mL/24 h. Even a small residual clearance will prove numerically significant and, for oliguric patients, the slightly more complex formulas given in References 43 and 44 should be employed. The exponential decay constant in equation 12, $Cl\ t/V$, is the net normalized quantity of hemodialysis therapy. It is calculated simply by multiplying the urea clearance in mL/min by the duration of hemodialysis, also in minutes, and dividing by the distribution volume in mL, which, in the absence of a better estimate, is taken as 0.58 $\times$ the patient weight. This parameter provides an index of the adequacy of hemodialysis (45) and based on retrospective analysis of various therapy formats, a value of 1.0 or greater for urea proposedly provides an adequate amount of hemodialysis for most patients. Although not without its critics, this approach has found nearly universal clinical acceptance, and represents the current prescriptive norm to hemodialysis therapy.

Maintenance hemodialysis has grown and expanded beyond the expectations of even the most enthusiastic of its earliest proponents. Figure 7 is a plot of the overall estimated dialysis population by year since 1970. The population at the end of 1992 exceeded 475,000; another 500,000 patients or so have received therapy at one time but have since died or had transplants. Maintenance dialysis is now available to some extent in all but the poorest nations; in economically advanced countries, excepting the United Kingdom, it is rendered as a virtual entitlement. The current worldwide mean cost of a single dialysis patient is about $30,000 per year (47); the aggregate economic magnitude of the medical application of hemodialysis thus approaches $15 billion.

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MICHAEL J. LYSAGHT
CytoTherapeutics, Inc.
ULRICH BAURMEISTER
Akzo Faser AG

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