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One major development in the field of kidney diseases in the 21st century will be in prevention of end-stage renal disease (ESRD). Basic research has made inroads into the understanding of the mechanisms of progression of chronic renal failure, including the understanding of the functions of genes activated by renal damage. All this may well result in a major reduction in the incidence of ESRD. The second important development will be in transplantation, which will constitute the mainstay of ESRD treatment in the next century. The clinical introduction of xenotransplantation and the cloning of one’s own organs via one’s stem cells may well represent the major areas of replacement therapy. This will reduce dialysis as a method to support the main treatments. These predictions will take some time to come to fruition. The first few decades in this century will face an increase, rather than a decrease, in the number of ESRD patients needing dialysis. Peritoneal dialysis (PD) will feature strongly in meeting this need in at least the first two decades of this century.

PD has come a long way since the introduction of continuous ambulatory PD (CAPD) as a form of renal replacement therapy (RRT) over the quarter of a century it has been in existence. There have been some dramatic improvements in outcomes in patients treated by PD, such that it is now accepted as an equivalent therapy to hemodialysis (HD). In the last 5 yr, CAPD has proven to be as effective a treatment as HD, and in some instances may offer advantages over HD. As we move into the new millennium, it is clear that PD will feature strongly in the care and management of patients in ESRD as advances in the understanding of the pathophysiologic mechanisms and means to combat the adverse effects of PD are put into practice. Currently, there are more than 130,000 patients on PD worldwide, representing approximately 15% of the total world population requiring dialysis. It is anticipated that this number will increase during the next decade, especially in developing countries.

Current Outcomes

Several analyses have been undertaken in comparing the outcomes on PD and HD. Nolph (1) analyzed the relative risk of death on PD as compared with HD and by and large found that mortality risk was equal for HD and PD in the various studies reported. After this analysis was the report of Bloembergen et al. (2), which was based on the US Renal Data Systems (USRDS) data on prevalent patients (1987, 1988, and 1989). This showed that PD subjects had a 19% higher risk of mortality as compared with patients who used HD. This was met with considerable consternation in the United States and probably did the therapy a major disservice. Analysis from the Canadian Organ Replacement Registry on patients starting RRT between 1990 and 1994 showed that for incident patients, the survival with PD was better in the first 2 yr of treatment compared with HD with subsequently no difference up to 4 yr (3). In addition, it showed that there was a significantly lower risk of death in PD patients across all ages, regardless of whether or not the patient had diabetes; for ages 0 to 64 yr, the relative risk of death was 0.54 for PD patients without diabetes (for HD, the relative risk was 1) and 0.73 for patients with diabetes. A further comparative analysis from 11 Canadian centers showed that the apparent survival advantage of PD patients was due to lower comorbidity and a lower burden of acute onset end-stage disease at the inception of dialysis; survival was otherwise equal (4).

More recent analysis of the USRDS data shows similar results: 5-yr survival of the 1993 cohort of dialysis patients is identical for PD and HD patients (5). The analysis on Medicare patients in the United States by Collins et al. (6) on the cohort of patients 1994 to 1997 concluded that in the first 2 yr of therapy, short-term PD is associated with superior outcomes compared with HD at all ages except in elderly women with diabetes. A further analysis of 17,000 PD patients from the Canadian Organ Replacement Registry database (1981 to 1997) has shown significant decrease in mortality rates during this period (7). Long-term survival from single center analysis shows no difference at 15 yr between PD and HD patients (8).

A reasonable conclusion from all this information is that mortality is the same for HD and PD when comparing identical types of patients, at least for the first 3 to 4 yr of RRT. Patient survival statistics from long-term studies in PD patients during the 1990s show a 50 to 70% 5-yr survival (5,8). It is likely that the results will continue to improve as the various developments outlined below are incorporated into routine practice.

PD to date has proven its utility and has become established in certain areas of care of patients with ESRD. These aspects, which have to be maintained or even further improved in the future, are outlined in Table 1.
Table 1. Positive points about peritoneal dialysis therapy that have been established beyond doubt

<table>
<thead>
<tr>
<th>Reason for Therapy</th>
<th>Percentage</th>
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<tr>
<td>Lower cost than HD, especially in the Western world.</td>
<td>5%</td>
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<tr>
<td>Similar survival to HD, and somewhat superior survival in the first 2 to 3 yr (see text).</td>
<td>20%</td>
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<tr>
<td>Treatment of choice for infants and younger children, especially automated PD.</td>
<td>14%</td>
</tr>
<tr>
<td>Considerable reduction in peritonitis (disconnect systems) and catheter-related infections (exit site treated with mupirocin).</td>
<td>25%</td>
</tr>
<tr>
<td>Adequate solute clearance in all but the largest anuric patients.</td>
<td>5%</td>
</tr>
<tr>
<td>Optimal treatment before transplantation.</td>
<td>5%</td>
</tr>
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* HD, hemodialysis; PD, peritoneal dialysis.

Current Problems Requiring Improvement

Technique Failure and Long-Term PD

If PD is going to achieve wider acceptance, then several outstanding problems that currently detract from greater acceptance need to be overcome. Two major issues are the higher technique failure in PD compared with HD (still related in a third of dropouts to HD to peritoneal infections) and the low rate of achieving long-term PD. The latter is to a large extent related to long-term changes in peritoneal membrane structure and function. In the analysis by Davies et al. (9), technique survival in the seven studies in the 1990s was 30 to 50% at 5 yr. The major causes of dropout derived from these analyses are shown in Figure 1. The nonachievement of long-term PD is to a large extent related to long-term changes in peritoneal membrane structure and function. Long-term (more than 10 yr) PD is limited to a small percentage of those who start PD (10), and single-center analysis shows that survival for those who use PD is 20% at 10 yr (8). The major cause of failure in long-term studies is ultrafiltration failure, inadequate solute clearance, and peritonitis (11). In data from Japan (12) long-term survival from a cohort of 242 patients was for a median of 5.8 yr, with patients’ failure to respond to this technique related to membrane problems.

Peritoneal Infections

Peritonitis remains a problem and a major source of transfer to HD (13,14), even though rates have improved dramatically with the advent of technologic improvements related to the disconnect systems (15). The problem lies in persistent unresolved peritonitis due to *Pseudomonas*, fungal, and to a lesser extent *Staphylococcus aureus* infection (16,17). At present, there appears no obvious means to prevent gram-negative and fungal infections, and the only option is to develop better therapeutic regimes to improve the outcome of these infections.

For *S. aureus* infection, there is greater reason for optimism. Several studies have shown nasal carriage of *S. aureus* is related to increased exit site infection and peritonitis (18,19). Prophylaxis with intranasal mupirocin, exit-site mupirocin, or cyclical rifampicin can dramatically reduce not only *S. aureus* exit-site infection and peritonitis, but also infections from other organisms (20,21). Mupirocin routinely administered to exit sites is now advocated in published guidelines (22) and is likely to favorably affect infection rates and survival.

Patient dropout after persistent peritonitis remains a problem, and those who require catheter removal for cure do not return to PD. More research needs to be done into techniques for safer catheter removal and reimplantation in the presence of persistent peritonitis to avoid interruption of PD. Prevention of adhesions, which are extensive in some patients with persistent peritonitis, is also important.

Peritoneal Access

Transfer of patients to HD for peritoneal access failure is now reduced to approximately 5 to 10% (Figure 1). Access-related dropout is low, and the improvement in catheter-related infections from mupirocin prophylaxis augur well for the continuing improvement in peritoneal infection. The type of catheter and method of implantation are probably less important than the meticulous care taken during implantation and subsequent care with immobilization and exit-site care; these aspects are reviewed in the catheter guidelines of the International Society of Peritoneal Dialysis (23).

Adequacy of Solute Removal

In spite of the original description by Popovich et al. (24) and the theoretical work of Teehan et al. (25) suggesting prescription formulations, CAPD has remained standardized to daily 4 × 2-L regimen with little, if any, individualization (26). This is disconcerting, because such a standard prescription simply cannot be applied to patients of varying size, residual renal function, and peritoneal permeability. It is now clear that a prescription needs to take these three factors into account. Adequate dialysis regimens need to be arrived at by variation in the number, volume, and strength of exchanges and the dwell time of each exchange.

Guidelines on targets for solute clearance have now emerged, the most prominent of which has been the National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF-DOQI) guidelines (27). The NKF-DOQI targets are a weekly Kt/V_{urea} of 2.0 and a creatinine clearance of 60 L per
week per 1.73 m² for CAPD and slightly higher targets on automated PD (APD) regimens. These have been modified to lower the targets for creatinine clearance in low transporters to 50 L per week, in line with the Canadian guidelines; high transporters have a poorer outcome (28). These have been based predominantly on the Canada-USA study (29), which showed that the greater the solute clearance at start of dialysis, if maintained over the duration of the CAPD, the better the outcome. Although there is still considerable debate surrounding the evidence for such targets (30), it is generally accepted that higher target values are desirable and should be achieved if at all feasible (31). A Kt/V_{area} of 1.7 and a creatinine clearance of 50 L/wk are absolute minimal targets, and all patients should be above these.

In developing countries, financial constraints have not yet allowed liberalization of prescriptions to meet these targets. However, results from Hong Kong suggest that lesser total daily exchange volumes can produce good outcomes (32). The new millennium will see more studies and data from these countries to verify the needs of their patients in terms of adequacy and prescription-setting.

Automated PD

One way of achieving increased dialysis is by the use of APD. Use of APD is increasing rapidly—indeed, it is the fastest-growing mode of dialysis. APD is a major advantage in patients with a hyperpermeable peritoneal membrane (high transporters) because these patients are unable to ultrafilter adequately on long-dwell regimens and experience fluid over-load on standard CAPD. The short-dwell exchanges on APD can overcome the loss of ultrafiltration. Clearly, achieving targets of solute and fluid clearance is likely to favorably affect outcomes.

APD has also major advantages for the patient from the psychosocial point of view, and this is partly the reason for its popularity. In the West, there is a growing trend toward higher targets. These trends reflect the increasing emphasis on adequacy, and the practice of PD is bound to change with this increased emphasis on prescription setting to meet targets of adequacy; variations in the various regimens available to achieve these will considerably facilitate achievement of solute clearance targets. It would be interesting to see how these increased prescriptions are going to affect outcomes.

Questions where controversies exit and where prospective controlled studies are required include the following: (1) renal versus peritoneal clearances and the equivalence; (2) small solute clearance measured via creatinine clearance and Kt/ V_{area}—which is better?; and (3) solute clearance targets—are they the same or different for special patient groups, such as patients with diabetes, children, the elderly, and underweight and obese subjects?

Peritoneal Physiology and Changes with Long-Term PD

In the last 25 yr, enormous strides have been made in the understanding of peritoneal morphology and its related physiology in terms of solute and fluid transport. This understanding has led to the development of newer PD solutions and paved the way for better treatment of patients undergoing PD with improved outcomes and longevity.

The peritoneal membrane, consisting of the mesothelium and the underlying connective tissue, is a highly developed organ that provides structural support, regulates transperitoneal transport, and mediates peritoneal defense and repair. The mesothelium acts as a highly dynamic surface; it is involved in the production of peritoneal lubricants; in solute and fluid transport; in coagulation and fibrinolysis; and in the production and remodeling of the extracellular matrix and host defense (33).

Solute passing from the blood in the peritoneal capillaries to the dialysate-filled peritoneal cavity have to pass at least three structures that can offer resistance: the capillary wall (probably the most important), the interstitial tissue, and mesothelial cell layer. Diffusion and transcapillary ultrafiltration occur in two directions across these resistances. It is now recognized that there are effectively three pores that explain the capillary transport (34). This three-pore theory recognizes ultrasmall pores, small pores, and large pores. First, ultrasmall pores (3 to 5 Å; aquaporin-1) allow the transport of water but not solutes. These have been identified in the mesothelium and the capillary endothelium (35). Glucose is effective as a crysalloid osmotic agent in spite of its small size of 2 to 3 Å, as it predominantly acts at this level. Approximately 50% of transcapillary ultrafiltration occurs through these pores. Second, colloid osmosis occurs at the level of small pores (40 to 50 Å). Interoendothelial clefts have been considered the equivalent of the small pores. Third, large pores (>150 Å; probably less than 0.1% of total pore count) are involved in macromolecular transport. In addition, there is lymphatic absorption from the peritoneal cavity (36).

Diffusion and convection are the mechanisms for solute transport, which is also bidirectional. Because of the complex structure of the various barriers to the peritoneal transport of solutes and fluid, it is simpler to regard this system as one membrane. In practical terms, the transport of low molecular weight substances across this membrane under defined conditions gives rise to dialysate/plasma ratios over the 4-h standardized dwell (peritoneal equilibration test). This defines the transporter status of the patient from high (hyperpermeability) to low (hypopermeability) and has distinct and important implications for setting the prescription (37). The permeability, combined with the surface area, gives rise to the mass transfer area coefficient, which is a measure of the diffusive permeability of the peritoneum, taking into account the surface area and the concentration gradient.

Glucose is well recognized to have several deficiencies that makes it an unsuitable agent for standard, long-dwell PD for reasons of ultrafiltration, metabolic side effects, and effect on the integrity of peritoneal membrane, especially in long-term PD use. With PD, morphologic changes do take place: functional derangement is the result. These morphologic-functional relationships are therefore vitally important. The use of unphysiologic PD solutions and episodes of infection and inflammation (38–40) lead to changes in the mesothelial layer, disorganization of the interstitium (collagen fiber disruption
and “fibrosis”), and duplication of the basement membrane both in the capillary endothelium and the mesothelial basement membrane (41). This tendency to fibrosis has been reported in long-term dialysis patients (42,43) and this is partly related to advanced glycation end products in the peritoneum (44) from glucose-protein reactions in the peritoneum. The end results of the changes are sclerosing-encapsulating peritonitis, which is infrequent (45). The Australian data reported 1.9 to 4.2% of patients with this syndrome (46), whereas the Japanese study reports a smaller incidence of 0.9 to 1.7% (47).

Loss of ultrafiltration is the most common peritoneal transport abnormality in long-term PD (48–50). The major causes of ultrafiltration failure are the presence of large vascular peritoneal surface area and decrease in osmotic conductance to glucose related to decreased aquaporin function or decrease in the ultrafiltration coefficient of the peritoneum (changes in the interstitial tissues) (51,52). Long-term PD thus produces a large vascular surface area, and the fibrosis may well affect aquaporin function.

Apart from the metabolic side effects (obesity, glucose intolerance, hyperinsulinemia, and reduced peripheral sensitivity to insulin, hyperlipidemia [53,54]), there are major issues related to the bioincompatibility. There are several pathogenic factors responsible for changes in the peritoneal membrane. These appear to be the following: (1) continuous exposure to bioincompatible dialysis fluids (shown to be toxic in vitro [55–58])—the factors that are important are a combination of low pH and lactate and glucose itself, through its metabolism via the polyol pathway (59), and molecular mechanisms such as cytokines, growth factors, and nitric oxide synthase activity (60); (2) glucose exposure leading to vascular changes of neovascularization and deposition of type IV collagen in the interstitium (61); (3) formation of advanced glycation end products in peritoneal tissue (44,62,63); and (4) the presence of glucose degradation products (GDP) generated during steam sterilization, which induces direct cytotoxicity and also accelerates the process of the formation of advanced glycation end products (55,62–64).

Glucose exposure is now regarded as a significant pathogenic factor in peritoneal membrane alteration. The goal for the clinician is to identify how to reduce patient exposure to glucose, minimize the total amount of glucose absorbed, and avoid the hyperosmolar stress and high glucose and GDP exposure to the peritoneum. Fortunately, nonglucose-based PD solutions as well as lower GDP containing solutions are now becoming available in Europe and offer a positive step forward.

There is also a need to develop sensitive means for early diagnosis of membrane damage. Further research needs to be done to assess the role of CA125 (a measure of mesothelial mass), parameters of ultrafiltration changes (peritoneal equilibration test, standard permeability analysis), and serial peritoneal biopsies in assessing membrane damage and to establish whether new solutions containing additives may prevent fibrosis. Potential research in this area includes the study of addition of hyaluronic acid to the dialysate, use of glucose-free solutions (glycerol, amino acid, icodextrin), use of dialysis solutions with neutral pH and low carbonyl stress, prevention of angiogenesis in the peritoneal membrane by use of intraperitoneal or systemic medications against formation, and deposition of advanced glycation end products. Other areas of research include the study of free radical scavengers administered by mouth or intraperitoneally.

Other Problem Areas

Only a small percentage of patients remain on CAPD-APD for more than 8 yr (10). Furthermore, as in HD, these patients show an increased cardiovascular mortality and can develop malnutrition. These are important reasons for failing to achieve long-term PD. Patient fatigue is a significant area of concern in the long-term management on PD. Mairoca et al. (65) found that patient fatigue and psychosocial factors accounted for about half the total number that changed to HD in long-term PD patients. This may in part be related to the acceptance of elderly high-risk patients, whose comorbidity and infirmity is likely to increase with time on dialysis and will enhance the difficulties of performing the dialysis procedures on a daily basis.

There is a need to develop methods to identify patients prone to fatigue. The liberal use of home care in selected patient groups, such as the elderly, and the use of PD in nursing homes could reduce the incidence of patient fatigue. Currently, some of these patients are managed in a nursing home environment (66,67); an estimated 2000 to 3000 patients with ESRD are admitted to nursing homes annually in the United States, with 13 to 15% managed on PD (68). The use of APD may be advantageous in some of these patients when relatives are involved in their dialysis. The development of respite services once or twice a year may well prevent burnout of relatives. The development of cyclers that are much simpler to operate than the current models could be of great importance in preventing burnout.

It is well recognized that cardiovascular mortality is increased severalfold in these patients. The reasons are multifactorial. There are the traditional factors increasing the risk (e.g., atherogenic lipid profile, left ventricular hypertrophy, congestive cardiac failure, smoking) and several factors related to the dialysis therapy itself. For PD, the established risk relates to the development of a hyperpermeable membrane (29). Less clear is the role of an inflammatory milieu giving rise to malnutrition and atherosclerosis (MIA syndrome) (69,70) and disordered calcium-phosphate metabolism and vascular calcification (71). The serum of PD patients is more atherogenic than the serum of HD patients (72). Relevant research should include prospective, controlled studies on the effects of statins, aspirin, folic acid, antioxidants, and strict control of serum calcium and phosphorus in the prevention of cardiovascular mortality. Also needed are studies on the effects of glucose-free dialysis solutions and the role and prevention of chronic inflammation in the production of atherosclerosis and malnutrition. The identification of elevated levels of adhesion molecules expressed on the surface of vascular endothelial cells in response to proinflammatory cytokines have already been found in malnour-
ished predialysis patients, and these are independent predictors of mortality (73).

Severe malnutrition is present in 8 to 10% of the PD patients, and another 30% have mild malnutrition (74). The goal should be to prevent this complication, which is a strong predictor of poor outcome. Future research will need to concentrate on the relationship between malnutrition and small solute clearances and the role of chronic inflammation on the development of malnutrition. There is some evidence that malnutrition is associated with chronic inflammation and high peritoneal solute transport (75), but this has not found to be so by others (76). Further research is needed to clarify the association between chronic inflammation, high transport, and malnutrition, as is the reported suggestion of an association between hypoalbuminemia and atherosclerosis (77).

PD patients are more prone to low-turnover bone disease (adynamic bone), which is associated with hypercalcemia and metastatic calcification from its inability to handle calcium load (78,79). A high calcium-phosphate product has been linked to increased mortality (80) and coronary vessel calcification, which is progressive in young HD patients studied with the new electron-beam computed tomography (81). These are exciting new findings, and there is a need to establish this in PD patients and assess the link between the higher prevalence of adynamic lesion on PD and cardiovascular outcomes.

New Trends and Future Developments

Early Start with Incremental Dialysis

Even though targets have been set for solute clearance on dialysis, patients with chronic renal failure are allowed to dwindle to clearances far below these targets before dialysis is initiated (82–84). It does not seem logical to allow patients to fall below minimal targets of adequacy and then have to increase dialysis to meet these accepted levels. In addition, this practice has major drawbacks: progressive renal failure leads to nutritional decline (85,86); in addition, the worse the small solute clearance (87,88), the worse the nutritional status at the time of initiation of dialysis, which leads to a poor outcome (89,90). Keshaviah et al. (91) addressed the issue of timely initiation of dialysis and predicted that CAPD in a hypothetical average-sized patient with high average peritoneal transport could be maintained for approximately 8 mo with a single 2.5-L exchange and from 8 to 17 mo with 2 nocturnal exchanges of 2.5 L each.

The NKF-DQOI guidelines advocated starting dialytic therapy when the residual Kt/V urea reaches 2.0; use of incremental dialysis will achieve solute clearance targets by compensating for the declining residual renal function as occurs with time. This incremental approach is possible (92,93) by performing PD only during the night or by using an exchange of icodextrin, which has prolonged ultrafiltration characteristics.

Anecdotal experience of early start (sometimes called “healthy start”) has been reported (94–96) and reviewed in an editorial (97). The reports show that it is possible to start early with incremental dialysis, but the experiences do not allow any firm conclusions to be drawn, and the case for early start with incremental dialysis needs to be substantiated with a large, randomized, prospective study. I suspect that as is the case with solute clearance targets, the practice will evolve to start patients earlier and earlier than is the current practice, in the hope that better outcomes will result. If this becomes the de facto practice, then better patient education and involvement in decision-making will be crucial for success of early initiation, as will the need for earlier referral.

Use of PD as an Initial Therapy in an Integrated RRT Program

The survival results on PD are better than on HD in the initial years of therapy (3), and technique survival on long-term PD is improving (9). It is appealing, therefore, to advocate PD as an initial therapy (98,99). If PD therapy fails for whatever reason (usually peritonitis, inadequate dialysis, or patient-related factors), then a switch from PD to HD should be considered. This approach is cost-effective and has shown better outcome results. In a Belgian study (100), this approach resulted in better survival in patients starting with PD than HD; it showed that patient outcome is not jeopardized by starting patients on PD, provided patients are transferred in a timely manner when PD-related problems arise. There are several advantages to commencing PD as an initial therapy (Table 2) pertaining to better residual renal function preservation (101), decreased incidence of hepatitis C compared with HD (102), preservation of vascular access sites (98), better initial BP control and less cardiac dysfunction (103), and better results after transplantation (104,105). The discontinuation of PD and transfer to HD at an appropriate time optimizes outcome; the failure to do so can lead to poorer outcome (9,106).

There are considerable obstacles to this approach that are almost entirely nonmedical (physician biases, funding and reimbursement policies) (107). The nephrology community needs to be better informed on the current outcomes and advances in PD. Other factors also affect modality selection. Time of referral is another important determinant. Patients that are referred late are more likely to go on to HD and remain on it (108,109). It is important, therefore, that there is early

<table>
<thead>
<tr>
<th>Table 2. Factors favoring peritoneal dialysis as the initial dialytic therapy for patients with end-stage renal disease*</th>
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<tbody>
<tr>
<td>Better survival than HD in the first 2 to 3 yr of therapy.</td>
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<tr>
<td>Better BP and fluid control in first few years of dialysis.</td>
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<tr>
<td>Better preservation of residual renal function versus HD.</td>
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<tr>
<td>Higher hemoglobin levels, less use of rHuEPO.</td>
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<td>Better outcomes after transplant.</td>
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<td>Less risk of acquiring a blood-borne virus (hepatitis C).</td>
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<td>Patient benefits, including more flexible holidays and travel</td>
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<td>and higher employment rates.</td>
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<td>Ability to expand patient numbers in a dialysis center with</td>
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<td>limited need for resources and major capital investments.</td>
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<tr>
<td>Lower staff-to-patient ratio than center HD.</td>
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<td>Less costly than center HD.</td>
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* HD, hemodialysis; rHuEPO, recombinant human erythropoietin.
referral of patient with chronic renal failure to a renal center, where the patient will undergo an unbiased education program. Experience in the United States indicates that when patients were appraised of all treatment options, the percentage starting PD was higher than the national average. The USRDS in 1997 reviewed the patient-reported process of modality choice (110). Of 1174 HD patients assessed, 17% chose this dialysis modality when the decision was patient led (35% of 1049 PD patients), 53% when it was medical team led (16% for PD), and 30% when it was joint patient–medical team decision (49% for PD). In a scenario where full patient choice is available with a scheme that provides for unbiased patient education, PD would appear to be the first option if medically suitable (99) (Figure 2). This may well turn out to be an ever-increasing trend in the new millennium.

Recent and Future Innovations in PD Solutions

As described in more detail above, there is now a greater appreciation of the deleterious effect of current solutions, especially glucose, in damaging the peritoneal membrane (111). Approaches to minimizing glucose exposure should benefit the patient. This has been shown in anecdotal studies; in patients with ultrafiltration failure, total avoidance of glucose (use of glycerol and icodextrin) has shown a return of ultrafiltration (112). This forms only one strategy in improving outcomes in PD and forms the basis for a rational approach to using the various solutions available (Table 3).

Icodextrin

The development with the greatest potential for impacting on PD therapy is the introduction of icodextrin. This glucose polymer is able to maintain a colloid osmotic gradient for longer periods of time, giving rise to prolonged ultrafiltration of at least 12 h (113,114). It is also isosmotic to uremic plasma and shows considerably less glycation and calorie absorption (115). Its use in patients with a hyperpermeable membrane and loss of ultrafiltration has extended the time on PD by a mean of 22 mo in patients who would otherwise have switched to HD (116). These are also the patients who would benefit by transferring to APD; increasingly, patients need a daytime exchange or exchanges to meet solute clearance targets. Icodextrin is ideally suited for this prolonged dwell of 10 to 14 h (117).

There is early evidence that BP control may be improved with icodextrin (118), and there may be less hyperlipidemia (119). Future areas of clinical research with icodextrin include substantiating some of the above, use of icodextrin as part of early start dialysis prescription (97), use in specialist patient groups (people with diabetes, cardiovascular instability, high transporters), its use in combination with other osmotic agents, long-dwell (14 to 16 h) use (120), and 2 exchanges per day in combination with short exchanges. The only substantial side effect from its use is skin reactions, which are severe enough (exfoliative dermatitis) for discontinuation of icodextrin in less than 1% of patients (121).

Bicarbonate as Buffer

Newer solutions have been recently introduced to minimize the affect of the peritoneal membrane. One such solution is bicarbonate based, replacing lactate as the buffer. Low pH and lactate are regarded to be deleterious to the peritoneum (57). The introduction of bicarbonate solutions into clinical practice was based on in vitro studies (58). Advances in sterilization methods and delivery systems have enhanced the feasibility of producing a bicarbonate-based solution. Several studies have reported clinical experiences with these solutions, either as bicarbonate alone or as a combination of bicarbonate and lactate (122–124).

Evidence is not yet available that bicarbonate solutions impart benefit to patients in terms of peritoneal transport and preserving peritoneal membrane integrity. However, patients who experience pain at infusion of PD fluid related to pH and lactate have been shown, in a randomized trial, to improve dramatically on bicarbonate and bicarbonate/lactate solutions (125). The solutions currently available are entirely bicarbonate or a lactate/bicarbonate mixture.

Amino Acids

Although amino acids have been studied for more than 20 yr as an osmotic agent, the current interest is largely due to the identification of significant malnutrition in the PD population; amino acids may be used to alleviate this problem. In addition, because it will replace one to two glucose exchanges per day, the glucose sparing advantage should not be dismissed.

The effects of amino acid solutions on nutritional state have been investigated by a number of groups. Most show a benefit when used in malnourished patients (126–128), but this has not been found in other studies (129,130). Use of amino acid solutions is accompanied by a rise in serum urea nitrogen and a mild degree of metabolic acidosis, which is enhanced with
the use of two exchanges per day (126); amino acid solutions can only be used in one to two exchanges per day.

Current emphasis on amino acid use in PD, other than the above indications, appears to be in providing a protein source in people whose ingestion is limited, in catabolic situations such as peritonitis, and in minimizing glucose exposure. There is no evidence that its use prevents the development of malnutrition.

Other Modifications

Another modification has been to bring about a reduction in the content of GDP, which is produced during heat sterilization and which is cytotoxic (131). Nonglucose-based PD solutions most effectively address all aspects of both systemic and local glucotoxicity. However, because glucose-based solutions cannot be used for all exchanges in CAPD or APD therapy, they are still required for at least part of the dialysis regimen. The recent development of two-chamber bags permits separation of glucose from other solution components, thereby allowing glucose to be sterilized at a lower pH than is possible in single-chamber bags. Mixing of the two compartments results in a raising of the pH, which in the case of bicarbonate-containing formulations can attain a neutral pH. The resulting solution has a pH of 6.3 and is less cytotoxic (131,132).

In a pilot study, PD transport characteristics were similar to glucose, but daily CA125 (a marker of mesothelial mass) was significantly increased (133), suggesting that mesothelial toxicity ascribed to glucose may be related to GDP. For bicarbonate/lactate-buffered two-chamber systems, sterilization of glucose at lower pH than currently performed today causes a reduction in most of the identified GDP, including acetaldehyde, 3-deoxyglucosone, and methylglyoxal. Some appear to be unchanged (e.g., glyoxal), whereas others are increased (e.g., 5-hydroxymethyl furfural, which appears to be innocuous in cytotoxicity assays). In vitro cytotoxicity and formation of advanced glycation end products are also significantly reduced in such formulations (57,134).

Because no solution is ideal, combinations of osmotic agents will allow for better efficacy and less side effects in the future. Glucose and amino acids, amino acids and glycerol, icodextrin and amino acids, and icodextrin and glycerol have all been tested in vitro or in patients in a limited way (135). In combination with bicarbonate, these would approach an ideal. One can imagine a daily regimen for CAPD consisting of an exchange of amino acids, two exchanges of bicarbonate/glucose, and an overnight exchange of icodextrin. This combination is possible now, but clinical trials are needed to assess its efficacy.

Future Strategies

Existing PD solutions were formulated for the maintenance of fluid and electrolyte balance, removal of metabolic waste, and correction of acidosis. Recent emphasis has been on improving the biocompatibility to enhance peritoneal membrane integrity and improve long-term outcomes; in addition, strategies for reduction in glucose use are available (136). Future solutions will address major clinical needs related to the maintenance of adequate nutrition, improvement in cardiovascular comorbidity, preservation of peritoneal membrane function, and achievement of adequacy of dialysis. Additives (pro cysteine, sulodexide) may help maintain various peritoneal functions and enhance adequacy (hyaluroan, atrial natriuretic peptide) (137). Increasing automation will reach its peak with dialysate regeneration (138) and the design of on-line systems to compound PD solutions that have been prescribed to provide not only toxin and fluid removal, but also nutritional and other clinical support.

Henderson’s “Perpetual Hamburger:” Recycling Waste

Henderson (139,140) believes that machine-based options may in the future gradually give way to gene therapy that uses the mesothelial cells as a site for the placement of nitrogen-fixing metabolic architecture that is now resident in both prokaryotic and eukaryotic microorganisms (141,142). Presumably urea, uric acid, creatinine, and other organic sources of nitrogen, as well as inorganic toxins such as sulfate, phosphate,
and hydrogen, will be consumed to synthesize amino acids, polypeptides, or proteins with energy derived from carbohydrate metabolism. These anabolites will be swept to the bloodstream by the subdiaphragmatic lacunae that provide entrance to the lymphatic system for macromolecular structures such as albumin and globulin. The peritoneal catheter in this instance might logically be used to introduce energy-containing bathing solutions for use by the mesothelial cell layer. One may then imagine a “perpetual hamburger” that after initial ingestion would in its molecular components be infinitely recycled. In addition, it may be possible that the technologies of HD and automated PD will coalesce in such a way that a single machine will serve to accomplish either therapy with sterile pyrogen-free dialysis fluid that is compounded on line in response to closed-loop sensors that use tap water and salt concentrates.

### Gene Therapy

Henderson (139) first postulated that machine-based options for automated PD would gradually give way to gene therapy that uses mesothelial cells. New approaches to preserving the peritoneal integrity have been investigated (38). These include molecular genetic approaches by which the use of genetically modified mesothelium is used to deliver potentially therapeutic recombinant proteins that might serve to preserve or improve the performance of the peritoneal membrane in long-term PD. *In vitro* studies on the methodologies have evolved and include expression of a cytoplasmic reporter gene in rat mesothelial cells, delivery of a secreted recombinant protein, regulation of mesothelial cell-mediated transgene delivery, and delivery of a membrane-bound recombinant protein.

The ability to genetically modify the peritoneal mesothelium by *ex vivo* and *in vivo* strategies demonstrates that the peritoneum is a modifiable membrane. This could then be used to preserve or enhance the performance and integrity of the membrane for long-term use. It could also be used to compensate for loss of residual renal function, to correct hormonal imbalance, to neutralize acidosis, to improve host defense, to prevent development of peritoneal fibrosis, and to control BP.

### Conclusion

There have been considerable advances in the delivery of PD resulting in a cost-effective therapy, which now has equivalent—if not better—outcomes as compared with HD. Technologic advances (APD, solutions), the ability to deliver adequate dialysis (both solute and fluid removal), and the minimization of damage to the peritoneal membrane (biocompatible solutions, less peritonitis) is bound to improve the outcome of patients. Preservation of the peritoneal membrane integrity is going to be a key aim, and the above measures will help. However, the mesothelial cell–mediated gene therapy potentially offers the most exciting prospects to improve the long-term performance of the peritoneal membrane.

Nonmedical factors are the most important determinants of choice of PD, and it is anticipated that these factors will continue to influence the use of PD (107). Financial reimbursement and biases of doctors continue to prejudice the use of PD. National funding policies also determine the PD penetration and use. Privately funded health care uses the smallest percentage of PD; publicly funded countries have the highest PD penetration; and mixed economies are intermediate (143). This is in spite of consistent data from many Western countries that show that PD is certainly cheaper than is center-based HD (144,145). Now that the outcomes have shown to be equivalent to those of HD in terms of survival and quality of life (146,147), it is surprising to see that PD, in some countries, has limited use (148). In the future, funding bodies, both private and public, would need to recognize this, and such recognition could be a stimulus to the further use of PD—a phenomenon that is already happening in developing countries.

There is no question that the next decade will see an enormous growth in the worldwide dialysis population; in particular, older and sicker patients will be accepted onto dialysis. It is likely, therefore, that worldwide pressures related to cost containment will dictate the use of a cost-effective therapy, which PD is proving to be. PD will continue to increase in use, but only if its efficacy continues to improve without eroding its economic benefits over HD (149). The challenge for the millennium and beyond is to develop PD therapy so that it optimizes patient medical and psychosocial outcomes and minimizes costs; this, I believe, is the future, and we need to strive to deliver this promise. Currently, only 15% of the world population that requires dialysis is managed by PD. This may well increase as therapy improves. Growth will be fastest in developing countries, and the escalating costs of dialysis treatments will push those who foot the bill to opt for more cost-effective treatment options.

### References


