CURRENT NEPHROLOGY

VOLUME 9

Edited by
Harvey C. Gonick, M.D.

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Preface

The modern ideal finds its prototype in art and its method in science. . . . At the stage which civilization has reached, the exact is a necessary element in what is splendid, and artistic feeling is not only served but completed by the scientific approach. . . .

Victor Hugo, *Les Miserables*

This timeless quotation from Victor Hugo seems especially appropriate to medicine in general, and to nephrology in particular. Some view medicine as an art; others as a science of increasing exactitude. In truth, the art and the science are complimentary. The ideal for the practicing nephrologist is to apply the hard-won knowledge from clinical and basic experimentation to improve the well-being of those unfortunate enough to suffer from kidney and related disorders.

Volume 9 of *Current Nephrology* continues our now well-established format of providing an annual update of the scientific advances in each of the acknowledged disciplines within nephrology, with one important exception. A decision was made to omit the chapter on Clinical Transplantation from this year's edition. In Volume 8, the chapter on this subject included an extensive review of cyclosporine. It was obvious that we had at hand an unusually potent but potentially nephrotoxic immunosuppressive drug, whose role in clinical transplantation had yet to be defined precisely. The current year has not provided indisputable new evidence as to just how this agent will mesh with our previous observations on tissue typing, blood transfusions, and existing drugs. These and other issues in transplantation will be provided in next year's volume.

Returning readers will recall that we have in the past occasionally included "mini-reviews" on topics of special interest. In this year's volume, Dr. Michael Simenhoff reviews the role of the bowel in uremia, a topic that has been largely neglected, but, we think you will agree, is of import in the care of chronic renal

failure. Dr. Simenhoff is uniquely qualified to write this chapter as he is one of very few investigators who have addressed this question in their research. Similarly, Dr. Michael Weiner, a pioneer in the application of nuclear magnetic resonance to the study of metabolic changes within the kidney, has provided us with a mini-review of the current usage of this exciting new technique in clinical nephrology.

The authors and I wish you a pleasant voyage on the sea of learning.

HARVEY C. GONICK

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CHAPTER 1

Peritoneal Dialysis

Karl D. Nolph

FROM SEPTEMBER 1983 to September 1984, there were more than 400 publications dealing with peritoneal dialysis. This does not include the complete *Proceedings of the Fourth National Conference on CAPD* in Kansas City in February 1984 nor the *Proceedings of the Third International Symposium on Peritoneal Dialysis* in Washington in June 1984. These *Proceedings* are in press at the time of preparation of this chapter and will be reviewed next year.

At the Third International Peritoneal Dialysis Symposium, the International Society for Peritoneal Dialysis was formed. The *Peritoneal Dialysis Bulletin* will become the official journal of the new society.

The above comments reflect the growing interest in peritoneal dialysis therapy. Publications during the past year will be reviewed by categories as indicated.

PERITONEAL SOLUTE AND WATER TRANSPORT[1–57]

Studies of Solute Transport Kinetics

Several reports dealt with the complex nature of the peritoneal membrane (as reviewed in previous editions of this chapter) and mathematical models for assessing peritoneal mass transfer.[2, 6, 9, 12] In an anephric dog model using 2-L exchanges in 20- to 25-kg dogs, ultrafiltration with 4.25% dextrose exchanges at four hours and eight hours were 587 and 610 ml, respectively. Since these values are only slightly below average values reported in adult humans, the results sug-

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gest that dogs have a larger ratio of peritoneal surface area to body weight.[2] A simple kinetic model for assessing peritoneal mass transfer was described.[6] The model requires blood and dialysate sampling and can be readily solved without resort to involved computation. The model has been recommended for the routine monitoring of mass transfer capability in patients undergoing continuous ambulatory peritoneal dialysis (CAPD).

Peritoneal transfer kinetics were studied for multiple solutes of differing molecular size in anuric adult rabbits with ligated ureters. These studies confirmed that the peritoneal transport kinetics of creatinine, inulin, and protein are qualitatively similar to those in humans.[22] The authors of this study found no effect of vasoactive drugs on the efficiency of peritoneal transport. We have reviewed rabbit studies in previous editions of this chapter that are in contrast to these findings.

In clinical studies, the effects of vasoactive additives in IPD were documented.[23] Studies with vasoactive substances in clinical settings have also been reviewed in earlier chapters.

The permeability of the mesothelium to rubidium and albumin was evaluated in vitro.[27] Approximately 0.03% of the mesothelial surface area appeared available for free diffusion of rubidium. Albumin transport appeared to involve more than simple diffusion. The results of this study suggested that the mesothelium was ten times less permeable than that described in earlier reports. Although the authors favored intercellular transport, they did not exclude the possibility of a transcellular route. Pinocytosis was suggested as important for albumin transport. In my opinion, these studies in isolated tissues are often associated with membrane injury and artifacts related to the handling of the tissue.

Studies in rats suggested that activation of the alternate pathway of complement may cause changes in protein loss during peritoneal dialysis.[28] In these studies, rats received intra-arterial injections of a fluorescent dye conjugated to rat serum albumin and underwent a 3.5-hour series of 15-minute peritoneal dialysis exchanges. After control exchanges, rats received either intra-arterial zymosine-activated rat serum, saline, unactivated rat serum, or endotoxin. Zymosine-activated rat serum and endotoxin injections (both intraperitoneal and intra-arterial), each of which may activate the alternate pathway of complement, produced a dramatic increase in dialysate protein concentrations.

A review of solute exchange in capillary beds emphasized problems in calculating capillary exchange kinetics from venous outflow concentrations in various tissues.[10] Assumptions and calculations are suggested which might have a future role in studies of peritoneal capillary exchange.

More experiences were reported with 3-L exchanges in humans.[19, 35, 52] Clearances of small solutes during CAPD with 3-L exchanges are increased as a function of increased dialysate flow per unit time. Large solute clearances are minimally affected. These findings suggest that fluid membrane contact is not increased substantially going from 2- to 3-L exchanges in average-sized adults.

A method to eliminate protein losses was described.[21] An Amicon hemofilter was connected to a Tenckhoff catheter. All proteins leaving the abdomen in the

dialysate fluid were trapped in the filter and returned to the patient's abdomen with the next infusion of dialysate. Although the protein losses were all returned, the protein concentration in the dialysate fluid at the end of a series of exchanges was far less than expected. Based on usual protein losses, the authors calculated an expected dialysate concentration after a series of exchanges. Even if this concentration had occurred, it should not have significantly affected the concentration difference and net diffusion between serum and dialysate. Thus, the mechanism for the decrease in protein movement into the peritoneal cavity during this procedure is not readily understood.

Pharmacokinetic Studies

Table 1 summarizes pharmacokinetic studies of specific solutes. A few of these will be highlighted.

Iron dextran, an electron dense tracer, was given intravenously to rabbits to monitor its movement from plasma to the peritoneal cavity during peritoneal dialysis.[3] Following peritoneal dialysis, the peritoneum was fixed in vitro at various times after the injection of iron dextran. Large amounts of the tracer were detected in effluent from the peritoneal cavity. Electron microscopic studies revealed particles of iron dextran in the endothelial cells, the interstitium, and the mesothelial cells adjacent to vessels. Tracer was not demonstrated in intercellular spaces. In mesothelial cells, particles were found exclusively in vesicles, while in endothelial

TABLE 1.—PHARMACOKINETICS OF SPECIFIC SOLUTES

SOLUTE	COMMENTS	REFERENCES
Iron dextran	Transport via vesicles	3
Carnitine	Significant losses, normal plasma levels	25
Oxalate	Low clearances	32
Parathormone	Low clearance, increased with nitroprusside	29
Prednisolone	Low clearance	48
Procainamide	Low clearances of drug and metabolite	49
Theophylline	Low clearance	41
Iron with deferoxamine	Weekly clearance on CAPD > HD	43
Uric acid	Low clearance	44
Mexiletine	Low clearance	45
Cimetidine	Low clearance	46
Propranolol	Low clearance	47, 50
Phenytoin	Low clearance	42
Aluminum in CAPD	Phosphate binders increase serum Al	37

cells they were both in vesicles and free in cytoplasm. In previous editions, we have reviewed studies with smaller tracers (30,000 daltons) moving primarily through intercellular spaces. Iron dextran is much larger (200,000 daltons). Thus, the differences in transport routes may have to do with size.

Despite high carnitine losses into the dialysate of CAPD patients, no significant difference in mean plasma carnitine concentration as compared to the value in normal subjects was found.[25]

The mean mass transfer coefficient (MTC) for parathormone (PTH, 5,500 to 6,000 daltons) in 29 patients undergoing CAPD was assessed.[29] Mean MTC values for inulin (5,200 daltons) and parathormone were 2.8 and 1.0, respectively. MTC values for PTH and inulin were significantly correlated ($r = 0.5$; $P < .01$). No correlation was found for MTC values and the duration of CAPD therapy or the number of episodes of peritonitis. Both acute peritonitis and intraperitoneal nitroprusside increased PTH MTC.

The peritoneal dialysis clearance of procainamide in adults undergoing CAPD with five 2-L exchanges per day was 6.5 ml/min.[49] N-acetylprocainamide clearance by peritoneal dialysis was 5.3 ml/min. These clearances are much lower than those reported for hemodialysis, and thus procainamide therapy should be initiated with reduced dosages.

In a patient with iron overload, iron removal was evaluated on CAPD during administration of IV deferoxamine (1.5 gm three times weekly) and during intraperitoneal deferoxamine administration (250 mg/L).[43] No iron was detectable in baseline dialysate. Peritoneal clearances of creatinine were unchanged by deferoxamine usage. On the average, the peritoneal dialysate outflow contained 45% of deferoxamine instilled by intraperitoneal administration. Intravenous deferoxamine during CAPD removed 78 mg of iron per week. Intraperitoneal administration removed 99.4 mg/wk adding deferoxamine to each of five exchanges per day for seven consecutive days. In the same patient while undergoing hemodialysis, IV deferoxamine during treatments resulted in a weekly removal of 49.6 mg. Thus, CAPD seems capable of removing large amounts of iron using deferoxamine by the intraperitoneal route. Long-term studies are needed to determine toxic effects, if any, of deferoxamine on the peritoneal membrane. None were apparent in this patient over a period of three months.

In 22 patients undergoing CAPD, the evolution of serum aluminum levels during a two-year period and peritoneal transfer of aluminum were studied.[37] Patients used dialysate with an aluminum concentration of 0.25 to 0.30 μmoles/L. In patients who had never received aluminum-containing phosphate binders, mean serum aluminum levels stabilized at 0.60 μmoles/L. In patients using phosphate binders, aluminum serum concentration increased (despite the increase of aluminum excretion through the peritoneal route) to a mean value near 2 μmoles/L. In patients previously treated by hemodialysis, mean values decreased from nearly 4 to nearly 2 μmoles/L. These patients were also receiving phosphate binders. Mean values for aluminum removal (μmoles/24 hr) related to serum concentrations and ranged from 0.50 to 5.46 in the three groups mentioned above.

Membrane Alterations

Oreopoulos[1] classified suspected causes of acute and chronic peritoneal injury. This classification is shown in Table 2. In this same review, the peritoneal reactions to injury were summarized as acute (presumably in part reversible) and chronic (most likely irreversible). Acute reactions include inflammation with predominantly a neutrophil or eosinophilic response, increased fibrinogen in dialysate with increased fibrin formation, the release of inflammatory mediators, and associated changes in passive transport properties of the membrane. These reactions are often associated with pain. Mesothelial denudation, thinning of mesothelial microvilli, interstitial thinning, and microcirculatory vasodilatory changes may be present with these acute reactions. Chronic injuries may show effects of chronic inflammation, particularly submesothelial fibrosis. Some thickening and submesothelial fibrosis is not uncommon in patients undergoing chronic peritoneal dialysis, but seems to be of little functional consequence. Many patients have undergone long-term peritoneal dialysis for over five years and some for as long as ten years.[33] Severe thickening with encapsulation of the bowel in a fibrous bag is termed *encapsulating peritoneal sclerosis* and will be discussed below. This review also focused on whether acetate may be involved in acute injury or the development of encapsulating peritoneal sclerosis. This issue will also be addressed.

An excellent summary of what is known about the anatomy of the peritoneum was published.[4] Studies supporting the vesicular and intercellular routes for solute transport were reviewed in detail. I am in full agreement with the conclusion of this review—namely, that although "we have gained a significant insight on the ultrastructure of the normal peritoneum, further research is required to elucidate the mechanisms of transport across the peritoneum and the changes that may occur after long-term peritoneal dialysis."[4]

TABLE 2.—CLASSIFICATION OF PERITONEAL INSULTS*

Acute
Infection
pH
Osmolality
Chemicals
Chlorhexidine, iodine, Na hypochlorite, formaldehyde, endotoxin, plasticizers, acetate, and certain antibiotics
Temperature
Chronic
pH
Osmotic agents
Chemicals as above and their breakdown products
Internal chemicals (practolol)
Heparin
Others

*Modified from Oreopoulos.[1]

An anatomic study in rabbits reported that indomethacin added to peritoneal dialysis solution (2.5 to 5.0 mg/kg) caused an increase in the size of pinocytotic vesicles of the endothelial cells and an almost complete disappearance of the endothelial intercellular spaces.[5] The authors suggested that indomethacin inhibited local synthesis of prostaglandins and/or acted directly on cellular metabolism uncoupling the mechanism of oxidative phosphorylation.

To assess the effects of diabetic microangiopathy on peritoneal clearances, peritoneal dialysis was performed in normal rats, in rats with gentamicin-induced acute renal failure, and in rats with mild and severe alloxan-induced diabetes mellitus.[13] Peritoneal clearances of urea, inulin, and albumin were significantly increased in the severely diabetic rats compared with other groups. The structural abnormalities included unusually small adipose cells in the capillary basement membrane layering and neovascularization in the peritoneums of the severely diabetic rats. Just as diabetic nephropathy may present with increased glomerular permeability, peritoneal permeability may increase in this animal model of diabetes mellitus. Previous editions of this chapter have mentioned reduced peritoneal clearances with far advanced diabetes mellitus in patients undergoing peritoneal dialysis. Perhaps these differences reflect the duration of the disease and the extent of the vascular alterations.

Peritoneal sclerosis has received extensive attention.[40, 51, 54, 55] One report describes six patients in whom peritoneal sclerosis developed after discontinuing peritoneal dialysis.[40] The patients had been maintained on peritoneal dialysis for 1.5 to 5.4 years. All of the patients had been maintained on CAPD; four also used acetate with this form of therapy. Three developed a loss of ultrafiltration resulting in transfer to hemodialysis or hemofiltration. All patients experienced nausea and vomiting, abdominal pain, and weight loss early in their course, and all manifested eventual small-bowel obstruction. Two cases had never had peritoneal infection; one patient had had as many as five episodes. Two patients used β-blockers. Four patients had been exposed to formaldehyde with a reverse osmosis (RO) machine.'

Another report described encapsulating peritoneal sclerosis in nine patients treated by CAPD for seven to 42 months. The buffer of dialysis solution was exclusively acetate in seven cases and lactate and acetate in two others. Peritonitis averaged one episode every 5.7 patient months. Major symptoms included an early decrease in ultrafiltration rate in six patients, and anorexia, nausea, and vomiting in seven. The diagnosis was established during surgery for obstruction in five cases and during an attempt to implant a new catheter in four others. The entire peritoneal surface was opaque, markedly thickened, and sclerotic, and numerous adhesions were encountered. One patient died while receiving CAPD treatment, four died nine to 15 months after transfer, of malnutrition and recurrent obstructive episodes.

Although these reports suggest that acetate might be a common factor, cases in Scotland have been described where lactate was the only solution buffer.[55] One editorial suggested that the incidence could be reduced by rapidly controlling

peritonitis and by eliminating the irritant properties of catheters, dialysate, and other materials used in performing peritoneal dialysis.[51] It is certainly not clear that any of these factors are causative, however. It is also of interest that, so far, the problem is almost nonexistent in North America and Australia.

Studies of Ultrafiltration

Table 3 summarizes the numerous studies related to ultrafiltration during peritoneal dialysis.

Numerous polyanions have been studied as possible osmotic agents for peritoneal dialysis.[7, 16] Although these are effective as osmotic agents in vitro and across the peritoneum, those studied to date cause toxic injury to the peritoneum of rats.

It is well known that ultrafiltration enhances solute-removal rates by convection. Several papers quantitatively assessed the magnitude of convective transport for different solutes.[8, 30] One study supported previous findings suggesting that ultrafiltrate derives primarily from extracellular fluid.[30] Mesothelial cells appear to resist solute and water flux in response to an immediately adjacent osmotic gradient.

Polyglucose[24] and glycerol[26, 31] were assessed as osmotic agents for peritoneal dialysis. Both can generate ultrafiltration. However, at the concentrations used to generate usual clinical amounts of ultrafiltration, caloric absorption and total carbon absorption are similar to caloric and carbon absorption with glucose. This is because small molecular weight glycerol is so rapidly absorbed and because the relatively high molecular weight of polyglucose requires increased concentrations to generate adequate osmotic pressure.

There continues to be interest in amino acids as osmotic agents.[53] These yield ultrafiltration and absorption of the amino acids contributes to the body nitrogen stores. Although results are very promising, expense is a major drawback.

Loss of ultrafiltration has received extensive attention, particularly in Europe.

TABLE 3.—ULTRAFILTRATION STUDIES

STUDY	COMMENTS	REFERENCES
Polyanions as osmotic agents	Effective, peritoneal injury with most	7, 16
Convective transport	Does not mobilize ICF potassium	8, 30
Polyglucose	Carbon absorption/ml UF similar to glucose	24
Glycerol	Rapid absorption, need high concentrations	26, 31
Loss of ultrafiltration	Rapid glucose absorption with certain solutions	1, 11, 34, 38–39, 56–57
Aminoacids	Source of N, effective osmotically, expensive	53