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Peritoneal Dialysis: A Review

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Peritoneal dialysis has become a commonly practiced technique for the treatment of both acute and chronic kidney failure and for removal of dialyzable exogenous and endogenous poisons. With the increased availability of medical services today and the further increases expected in the future, peritoneal dialysis likely will find ever widening use, particularly for elderly patients.

The amounts of sterile fluid required for peritoneal dialysis are quite large, the average procedure utilizing 40–60 l. for a single patient. Along with this fluid, special administration sets, catheters, trocars, syringes, and auxiliary drugs and services are needed which the pharmacist may be called upon to supply. Thus, the pharmacist should be knowledgeable as to the process of peritoneal dialysis and the drugs, supplies, and services it requires, and he should be prepared to assist in the selection or adjustment of fluids to fit the needs of a particular patient.

For this country to achieve the goal of extending medical services to all in need of them, it seems likely that peritoneal dialysis will have to be commonly conducted in the home by the patient himself. This situation will place a new burden on the pharmacist to supply the needs of the patients in his locality, to advise the patients on many associated problems, and to consult with the physicians on the care of the patients.

For the research pharmacist, peritoneal dialysis presents a special challenge. At present the process is relatively simple, and little has been done to develop more sophisticated agents to increase the safety of the patient, increase clearances of given toxins, or promote the dialysis of drugs and poisons now considered "nondialyzable." Thus, there exists in this field a great opportunity for the pharmaceutical scientist to apply his special knowledge and skill for the benefit of a large number of seriously ill persons.

HISTORICAL DEVELOPMENT OF PERITONEAL DIALYSIS

Wegner (1) is credited with the first experiments on peritoneal lavage. In 1877, he studied the fall in temperature produced by introducing cold saline solution into the peritoneum; in the course of this work, he noted that hypertonic dextrose or glycerin was increased in volume by body water. In 1894, Starling and Tubby (2) studied the transference of substances from solution in the peritoneal cavity to the blood and in the reverse direction. They demonstrated that transport from the peritoneum *via* the lymph must be so slow as to be negligible, and they concluded that passage must occur directly to the blood. They showed that hypertonic solutions would increase in volume when instilled into the peritoneum and that hypotonic solutions would decrease in volume. Indigo carmine and methylene blue were observed to be readily absorbed from the peritoneum. Starling and Tubby (2) found that absorption of serum from the peritoneum was extremely slow, while absorption of an isotonic crystalloid solution might be fairly rapid. In their search for an explanation, they failed to recognize the tendency of the

individual species in solution to attain independent equilibrium with the body fluids.

Cunningham (3), in 1920, examined the absorption of dextrose from a 10% solution in an effort to evaluate intraperitoneal injection as a means for administering large volumes of fluid. His studies on rats showed complete absorption of the fluid within a little more than 12 hr. He observed some changes in mesothelial cells in the diaphragm, spleen, and omentum with animals given repeated daily administrations, but these changes were rapidly reversible and no permanent or threatening effects were observed.

Putnam (4), in 1922, demonstrated the properties of the peritoneal membrane remarkably well. He injected, intraperitoneally, water and saline solutions with an added dye, trypan blue, and analyzed the peritoneal fluid at intervals of time, measuring chloride, urea, dextrose, dye, protein, and total fluid volume. He found chloride and urea to equilibrate between blood and peritoneal fluid in 2–3 hr. and the volume of fluid to decrease continuously to nearly zero in 9 hr. The relative dye concentration followed the total fluid volume quite closely. Putnam (4) also observed that several dyes (Congo red, alizarin, acid fuchsin, and trypan blue), when injected intravenously, did not appear in peritoneal fluid. This was due, most likely, to binding of the dyes to serum proteins, which was not recognized at the time. Putnam (4) also showed that a number of other organic compounds and dyes pass the peritoneal membrane, including salicylate, ferrocyanide, phenolsulfonphthalein, and iodide. He concluded that, except for the anomaly observed with dyes as previously mentioned, the peritoneal membrane behaves much like a simple colloidal membrane as used in the laboratory.

A number of other workers (5) demonstrated in similar fashion the permeability of the peritoneal membrane to crystalloids and water.

Ganter (6), in 1923, made the first evaluation of peritoneal dialysis for the treatment of uremia. He used rabbits and guinea pigs with ligated ureters and dialyzed with small volumes (50 ml.) of physiological saline. He allowed the fluid to remain in the peritoneum for 2–4 hr., at which time the nonprotein nitrogen in the dialysate was approximately equal to that of the blood. The amount of fluid recovered was low, 10–30 ml. Ganter (6) reported moderate clinical improvement in animals so treated. It is now known that the volumes of fluid used in Ganter's experiments were too small for rapid removal of endogenous poisons, and the composition of the fluid was such that fairly rapid absorption would occur, thus reducing the effectiveness of the dialysis.

Bliss *et al.* (7), in 1932, treated nephrectomized and kidney-functionless dogs with balanced salt solutions, using 750 ml. of fluid for each exchange, a 10-min. dwell time, and up to 20 exchanges of fluid. Their results were dramatic as to the removal of nonprotein nitrogen. Animals survived up to 16 days. These authors identified phosphate, creatinine, urochrome, urea, sulfates, chlorides, and traces of protein in the return fluid.

Abbott and Shea (8) gave considerable thought to the conditions for which peritoneal dialysis should be utilized, to the types of fluid most likely to be successful, to the volumes of fluid to be used, and to the method by which the fluid should be exchanged. They compared 5% dextrose, Ringer's solution, Hartmann's solution, and a Solution A (a balanced salt solution with bicarbonate, phosphate, magnesium, and dextrose). They concluded that Ringer's solution is not suitable for peritoneal lavage since it reduces blood bicarbonate, and they suggested that the use of added bicarbonate in the fluid is desirable. Furthermore, they found the intermittent dialysis procedure to be more practical than a continuous flow method.

Wear *et al.* (9) also recognized the value of Hartmann's solution for removal of nonprotein nitrogen and the need to prevent acidosis. Haam and Fine (10) observed similar removal of nonprotein nitrogen with intermittent dialysis.

Seligman *et al.* (11), in 1946, studied the treatment of nephrectomized dogs with continuous flow dialysis and found that the uremic animal could be successfully managed. They used fluids containing concentrations of electrolytes matched to normal extracellular fluid.

Grollman *et al.* (12) resolved several of the problems in treating uremia by peritoneal dialysis. They treated nephrectomized dogs and later human patients by more frequent dialysis but with fewer exchanges. They restricted the dietary intake so as to avoid excess inorganic salts and protein, and they adjusted the dialysis fluids as required for the individual. These modifications, along with careful attention to avoid infection or pyrogenic reaction and blood transfusion when severe anemia threatened, enabled them to keep dogs alive much longer than had previous workers. This research demonstrated most clearly the benefit of peritoneal dialysis in the treatment of uremia. Intermittent dialysis has since been employed successfully in many hospitals and homes (13–26).

THE PERITONEAL MEMBRANE

For a substance to pass from the blood to the fluid in the peritoneum, it must cross the peritoneal membrane. The anatomical structure of this membrane has been well described (27–30), and it would be of immense value to know the mechanism of transport across this membrane along with the factors affecting it. But knowledge of this function is quite limited. The total area of the membrane is said to be approximately 22,000 $cm.^2$ (31). Of this surface, it would appear that the mesentery must be the most effective portion, since it probably represents the largest fraction of the total area, it is richly supplied with blood vessels, and it is probably in better contact with the peritoneal fluid than other portions of the membrane. Early work of Starling and Tubby (2) showed that transport *via* lymph is negligible in most instances. Thus, it appears that passive diffusion across the peritoneal membrane remains the basic process by which substances equilibrate between peritoneal fluid and blood.

Gosselin and Berndt (32–35) measured the permeability of the isolated mesentery to radioactive rubidium

and phosphorus and were able to estimate a porosity for the membrane. They also postulated that the mesentery may function in transport as three separate layers. Knochel *et al.* (36) postulated that the mesentery may act as a classical lipid membrane and allow passage only of undissociated molecules with relatively high oil/water partition coefficients. Shenouda and Mattocks (37) measured transport in both directions and concluded that ionization appeared to have little effect on the rate of passage across the mesentery. Later, Penzotti (38) tested compounds known to accelerate peritoneal dialysis *in vivo* and found that they had no effect on dialysis across the isolated membrane. This finding led him to question the validity of results obtained with the isolated mesentery. His results might also be explained on the basis that transport across the mesentery is not the limiting factor in peritoneal dialysis, but some other step in the process, such as passage across the capillary membrane, may control the rate of passage from blood to dialysate.

McLean *et al.* (39) found that tris(hydroxymethyl)-aminomethane increased the rate of diffusion of urea into the peritoneum; since urea is nonionized in the medium, they concluded that the effect must be an alteration in membrane permeability. Henderson (40–42) noted that hypertonic solutions enhanced the transfer of urea into the peritoneum and, at first, concluded that the effect persisted even though the hypertonic fluid was replaced by isotonic medium. This led him to believe that alteration in membrane permeability had occurred. These findings indicate that methods of improving rates of transfer across the peritoneal membrane may be possible so that more effective peritoneal dialysis might be accomplished.

PERITONEAL DIALYSIS TECHNIQUES AND PROCEDURES

As a result of the experience of many workers, a relatively simple general procedure for conducting peritoneal dialysis has evolved. The intermittent method is generally preferred because of its simplicity, ease of maintaining a closed sterile system, and the lack of a need for complicated equipment. A precise detailed description of the technique was presented by Maxwell *et al.* (43). Briefly, it consists of inserting a sterile catheter into the peritoneum through a small incision in the midline of the abdomen about one-third of the way from the umbilicus to the pubic bone. The catheter is placed in such a position that it is not entangled with the omentum or mesentery, and a natural pathway is sought where little resistance is encountered. In some instances, placement of the catheter is made easier by injection of an initial volume of 1–2 l. of fluid by hypodermic syringe prior to insertion of the trocar and catheter. This procedure enables one to avoid the complications of entanglement with the membrane and aids in avoiding puncture of the intestines.

Once the catheter is inserted, care is taken to protect the skin and abdominal muscle in the region of insertion from introduction of bacteria through movement of the catheter caused by manipulation or normal movement of the abdomen in breathing. This is achieved by generous use of topical antiseptics and coverage with a sterile gauze pad. The aseptic technique must be used in connecting the solution tubing, and new sterile tubing is commonly used with each new exchange. The usual practice is to instill 2 l. of peritoneal dialysis fluid for each exchange, allowing inflow and outflow by gravity. When the fluid has remained in the peritoneum for the prescribed dwell time, usually 15–60 min., the fluid bottles are lowered below the patient level and the dialysate is collected in the original bottles without opening the system. In this procedure, it is important to keep the tubing filled with fluid so as to establish a syphoning action for draining without delay. Amounts of fluid returned approximate those introduced, except where highly hypertonic or hypotonic fluids are used. In this stage of the process, it is important to prevent contamination of the fluids in the return bottles and tubing; otherwise, bacteria may find their way back to the peritoneum to cause infection. This is achieved by use of bacterial filters through which air is vented or by use of collapsible plastic bags as fluid containers. Recycling by this procedure is continued with new supplies of sterile fluid until the desired effect is attained (urea nitrogen, creatinine, or other indicator substance reaches acceptable level). Others have also described the general methods for conducting intermittent dialysis (44, 45).

Askari *et al.* (46) described in detail a typical continuous peritoneal dialysis procedure. Two tubes or catheters are placed in the peritoneum, one on each side of the abdomen, with the inflow and outflow tips so placed as to minimize direct flow from one to the other (shortcircuiting). Fluid is introduced and drained by gravity in a continuous flow of about 2 l./hr. for an adult. This procedure has the advantage of having no loss of dialysis time required for drainage. Theoretically, it should give more rapid dialysis due to maintenance of lower concentrations of endogenous poisons in the dialysate and a higher diffusion gradient. These advantages are often not realized, however, due to direct channeling and relatively poor exposure of the fresh fluid to the mesentery.

Shinaberger *et al.* (47) combined the use of continuous dialysis with an extracorporeal dialyzer. The fluid in the peritoneum was cycled through a twin-coil dialyzer where endogenous poisons were dialyzed through the cellophane membrane into an electrolyte bath made with tap water. Efficient dialysis was reported utilizing high flow rates, with a minimum loss of protein from the patient and the need for only 4–6 l. of sterile dialysis fluid for the complete treatment. In comparing several different methods for dialysis, Miller *et al.* (48) found no significant advantage to the combined dialysis method over rapid flow with continuous dialysis. Apparently, these workers did not consider the advantage of needing much less sterile fluid, which may be especially important in home dialysis.

The efficiency of dialysis is generally expressed in terms of clearances, these being independent of blood level and thus comparable from one dialysis to another. Clearances are calculated by the well-known equation:

$$C = UV/P \qquad \text{(Eq. 1)}$$

where C is the clearance in milliliters per minute, U is the concentration of the species being followed (usually urea or creatinine) in the return fluid, V is the flow rate of dialysis fluid in milliliters per minute (total volume of fluid returned divided by total time involved in the exchange), and P is the average plasma concentration in the same units as U (usually the average of samples taken at the beginning and end of an exchange).

Several variations in procedure or technique may significantly affect the efficiency of peritoneal dialysis. Gross and McDonald (49) found that dialysis fluid warmed to 37° gave 35% better clearances than fluid introduced at 20°. Although most workers reported using fluids that were warmed to body temperature, the findings of Gross and McDonald serve to caution against laxity in controlling this factor.

Several workers examined the effect of flow rate of dialysis fluid on clearance. The volume of fluid used for each exchange was not varied greatly, presumably to avoid overdistention of the abdomen and discomfort to the patient. Thus, increases in flow rates were achieved chiefly by shortening the dwell time of the fluid in the abdomen. This makes comparison difficult, since during the period of introduction and drainage of the fluid the full volume is not within the peritoneum, and the time used for introduction and drainage may vary from one worker to the next.

Boen (50) compared urea clearances to flow rates for 268 exchanges (22 dialyses in 16 patients). His rates ranged from about 250 ml./hr. to 5 l./hr. He found an increase in clearance with flow rate up to a maximum average clearance of 28.5 ml./min. at a flow rate of 3.5 l./hr. and then a moderate decrease in clearance at higher flow rates. Boen (50) recognized this decrease as having questionable significance, since averages at the higher rates represented relatively few tests.

Gross and McDonald (49) compared clearances for flow rates from 1.1 to 8.5 l./hr. without observing a maximum. Tenckhoff *et al.* (51) also found continued increase in clearance with increased flow rates. Later, Penzotti and Mattocks (52) pointed out that the maximum reported by Boen (50) could be predicted mathematically when one considers the effect of drainage time on the flow rate.

Several mechanical devices have been developed to minimize the attendant time in peritoneal dialysis, to make home dialysis more practical, and to increase flow rates for greater efficiency.

An automatic cycling machine was developed by Boen *et al.* (53) in 1962. A pump transfers fluid from a large carboy to an elevated 2-l. bottle, and a time-controlled stopcock is opened to allow gravity flow of the fluid into the peritoneum. The bottle is then refilled for the next exchange, and a small vacuum pump creates a negative pressure on the receiving carboy. At the end of the dwell time, a stopcock is automatically opened to direct flow from the peritoneum into the receiving carboy. Thus, the whole cycle is operated by a timer which can be preset to the cycle desired. A typical setting was 5 min. input, 30 min. dwell, and 10 min. drain. Experience with a similar device was reported by Sicilia *et al.* (54). McDonald (55) used a recycling machine which contained a bacterial filter to sterilize the fluid as it was used. This enabled him to use nonsterile water for the dialysis fluid, with considerable savings in cost and effort. He recognized the possibility of failing to remove pyrogenic substances with the filter but encountered no difficulty in his tests. Tenckhoff *et al.* (56) and Lasker *et al.* (57) reported successful use of recycling machines for home dialysis.

Schwid and Vidt (58) made some inexpensive, simple, and quite useful modifications for automatically stopping the outflow at the desired volume, thus preventing the introduction of air into the peritoneum. Miller *et al.* (48) compared several methods of dialysis, including the Shinaberger method, and found the most increase in clearance with rapid intermittent exchanges but no increase with extracorporeal dialysis.

Several workers reported the use of indwelling buttons or openings and indwelling catheters which facilitate the introduction of peritoneal dialysis fluid. Boen *et al.* (53) designed a fitting which was implanted in the abdominal wall. This served as a tube through which the peritoneal catheter could be readily inserted and avoided the need for repeated puncture. A silicone rubber cannula for implantation was described in 1964 (59). It is implanted so as to act as a suspended perforated coil in the peritoneal cavity. The cannula is protected by a cap and dressing when not in use. Palmer and McDonnell (26) reported on the successful use of this cannula over several years. Tenckhoff and Curtis (60) reported on the long-term use of two types of implanted silastic catheters which proved particularly useful for home dialysis. Barry *et al.* (61) also reported on the use of an indwelling catheter with which they had several failures. Malette *et al.* (62) described the design and use of a peritoneal access button which is implanted beneath the skin and thus might reduce the incidence of infection. Although there have been problems with these devices, the implanted catheter is promising and seems to be a necessity if a large number of patients are to be treated at home by peritoneal dialysis.

The irrigating solutions used in peritoneal dialysis vary but generally contain electrolytes in concentrations approaching those of extracellular fluid: Na, 140 meq./l.; Ca, 3–3.5 meq./l.; Mg, 1.5 meq./l.; Cl, 101–104 meq./l.; and lactate, bicarbonate, or acetate, 40–45 meq./l. Potassium may be added as plasma levels fall during dialysis or it may be present in the solution at minimum level, 2.5–3.5 meq./l. Dextrose is added to increase the osmotic pressure to match or slightly exceed the osmolarity of the uremic extracellular fluid, the usual concentration being 1.5–2.0%. Much higher levels of dextrose are used when treating edema, usually 7–10%. Often the composition of the fluid is modified to suit the individual patient (63).

The use of lactate instead of bicarbonate has made the preparation of commercial solutions feasible, preventing precipitation of calcium and allowing autoclaving without loss of fixed base. More recently, acetate was used, having the advantages of being less susceptible to bacterial growth (64) and of forming less easily caramelized solutions (65).

The presence of minerals hastens the caramelization of dextrose on autoclaving, and bisulfite is often used

to retard oxidation. High concentrations of bisulfite, as have been used with 7% dextrose solutions, may constitute a toxic hazard (66, 67). Substantial caramelization not only causes undesirable discoloration but also appears to cause toxic effects (64). The caramelization problem becomes much more difficult with large containers, since heating time for sterilization is greatly increased to allow for heat conduction throughout the body of fluid. Thus, this becomes a major difficulty in supplying the large volumes of fluid for home use and the automatic cycling machines. At present, most workers use commercial solutions available in 1- and 2-l. containers.

Yutuc *et al.* (68) reported on the use of sorbitol in place of dextrose for peritoneal dialysis fluids. Sorbitol is stable to autoclaving in the fluid and would eliminate the difficulty in handling large volumes. Yutuc *et al.* (68) observed no untoward reactions in their tests and found the plasma levels of sorbitol to remain at low levels. Apparently, due to slower absorption from the peritoneum, the sorbitol enables more water to be removed than does dextrose. Sorbitol should be used with caution since it may be quite slowly metabolized and, in the absence of urinary function, its plasma level might become sufficiently high to cause dehydration of the tissues.

Gjessing (69) added amino acids to the peritoneal dialysis fluid and found that this substantially reduced the loss of serum protein and amino acids in patients who were regularly dialyzed. This procedure promises to offer a simple way to avoid one side effect commonly encountered in chronic patients.

KINETICS OF PERITONEAL DIALYSIS

Several mathematical relationships have been used to describe the process of peritoneal dialysis for the purpose of interpreting results and for predicting results for a given set of conditions. Boen (70) calculated ratios of clearances for various substances to the clearance of urea, thus obtaining relative diffusion rates across the peritoneal membrane. Such calculations on one set of data gave the following ratios (×100): potassium, 90; phosphate, 62; creatinine, 61; uric acid, 62; calcium, 51; magnesium, 47; and indican, 40. These values are useful in evaluating the efficiency of dialysis, in considering the practicality of removal of a new substance by dialysis, and in predicting the time needed for a given dialysis.

Henderson and Nolph (42) derived an equation for calculating dialysance based on principles of passive diffusion. They showed that the dialysance ratio of inulin to urea, D_i/D_u, should be essentially constant if the membrane areas for permeation of the two substances are not changed. They also noted that a change in the volume of distribution of a substance would not significantly affect the dialysance ratio. With these equations, they examined data obtained by using hypertonic solutions followed by isotonic solutions in the course of peritoneal dialysis. They found that the hypertonic solution accelerated dialysis and the effect persisted even though followed by isotonic fluids. The hypertonic solution caused a change in dialysance ratio, indicating a true effect on the membrane. These workers postulated several possible mechanisms for this effect and thought the most likely one to be a change in membrane pore structure.

Penzotti and Mattocks (71) used a two-compartment model to describe the peritoneal dialysis process for urea and found that the data fit well to the corresponding equations of Rescigno and Segre (72). The pseudo-first-order constants were then used to compare dialysis rates with different fluids. In later work, Penzotti and Mattocks (52) applied these equations and constants to intermittent dialysis, assuming a constant rate of drainage. Predicted values for clearances were generally somewhat lower than observed values, although the agreement was reasonable and relative values and trends were in good agreement.

CLINICAL APPLICATIONS OF PERITONEAL DIALYSIS

Acute Renal Failure—The first marked success with peritoneal dialysis was the treatment of acute renal failure. This was to be expected, since techniques and procedures suitable for long-term treatment evolved with experience. Boen (73) summarized the indications for dialysis as hyperkalemia, gross overhydration, severe acidosis, or marked clinical deterioration; he stated that long-term peritoneal dialysis in chronic renal failure was not yet justified. He summarized his results from patients with acute renal failure.

Hager and Merrill (74), in 1963, took the attitude that the patient should be spared the clinical manifestations of uremia and that dialysis should be started early enough to maintain the blood chemistry as nearly normal as possible. They pointed to several advantages of peritoneal dialysis over hemodialysis in such cases, including the availability of equipment, the shorter time to institute dialysis, and the applicability to a larger spectrum of patients. They felt that the slower clearance with peritoneal dialysis may be a significant advantage since it allows time for equilibrium of extracellular and intracellular fluids. In their report, they cautioned against the use of lactate-containing fluids where liver failure may be present. A summary of their procedures and experiences is included in their report.

Norman *et al.* (75) reported their experiences with patients having open-heart surgery. They recommended early use of peritoneal dialysis for these patients once definite symptoms of renal failure are observed.

Schwartz *et al.* (76), in 1966, reported on the success in treatment of acute renal failure with peritoneal dialysis over 6 years at Walter Reed Army Medical Center. They noted that successful dialysis with acute renal failure encouraged clinicians to consider peritoneal dialysis for other conditions characterized by homeostatic imbalance.

In some hypercatabolic conditions, the accumulation of tissue breakdown products is so rapid that peritoneal dialysis has been said to be too slow to lower the blood levels sufficiently (77–79), and hemodialysis is recommended. Cameron *et al.* (80), on the basis of their experience, disagreed with this conclusion. In such conditions, the use of peritoneal dialysis still is in question (81).

In 1962, Etteldorf *et al.* (82) reported on the use of peritoneal dialysis for acute renal failure in children. In one case, they repeated dialysis 85 times during a 33-day period. They found the procedure to be both practical and effective. Since then, Lloyd-Still and Atwell (83) reported on treatment of infants with acute renal failure for whom hemodialysis was difficult. Manley and Collipp (84) and Lugo *et al.* (85) later reported on treatment of neonates with peritoneal dialysis. Both groups considered peritoneal dialysis to be a potential lifesaving procedure in acute renal failure of the newborn.

Among the many other applications of peritoneal dialysis to acute renal failure, an especially interesting one is the treatment of patients who suffer renal failure as a result of falciparum malaria. Several workers reported success with this application (86, 87).

Chronic Renal Failure—Long-term treatment of chronic uremia by peritoneal dialysis has been encouraging but not completely satisfactory. Boen *et al.* (53), in 1962, had a patient who could no longer be maintained on hemodialysis due to a clotting problem at the site of cannulation. They used an implanted catheter and automatic cycling machine and reported satisfactory results with two to three treatments per week for 12 weeks.

Pateras *et al.* (88), in the same year, summarized results with 30 chronic uremia patients. Their results were encouraging, although they did not report the period of time over which the patients were maintained on peritoneal dialysis.

Stevens *et al.* (89) reported on 54 cases of chronic uremia treated by peritoneal dialysis between 1961 and 1963. All patients demonstrated biochemical improvement, and all but six showed clinical improvement. Fifteen of the patients survived longer than 3 months from the time of first dialysis, and seven survived more than 6 months. These workers suggested that those patients with a urine volume of 1 l./day prior to initial dialysis appear to have the best chance of prolonged survival on peritoneal dialysis and that this may be a criterion for selection of chronic patients for treatment.

Vertes *et al.* (90) treated 11 geriatric patients with peritoneal dialysis, noting that most or all of these patients would probably not be considered eligible for hemodialysis. Of these patients, five had an acute exacerbation of previously benign renal failure which was controlled with peritoneal dialysis for a short time; they were then discharged under dietary restrictions. Four patients had advanced chronic renal failure and were maintained satisfactorily by peritoneal dialysis to the time of the report. Two patients required dialysis for edema associated with chronic renal failure and these responded well. These workers suggested that peritoneal dialysis be tried more frequently on the geriatric uremia patient.

Palmer and McDonnell (26) reported on treatment of seven patients over 50 years of age who had end-stage chronic renal failure and who could no longer be maintained with conservative management. They used the "intramural cannula," a silicone rubber catheter, which was implanted in the abdomen. Six of the patients were maintained in a satisfactory state from 6 months to 3.5 years at the time of the report.

Abella *et al.* (91) treated six patients with terminal renal failure and found the implanted peritoneal button of Merrill *et al.* (92) to be unsatisfactory. They used repeated puncture for peritoneal dialysis. Most of their patients were later given transplants. The greatest difficulty with these patients during peritoneal dialysis was peritoneal infection.

Goldsmith *et al.* (93) found peritoneal dialysis to serve well in maintaining seven of eight patients during their wait for renal transplantation.

In 1968, Edelbaum *et al.* (94) reported on the use of peritoneal dialysis in acute episodes of chronic renal disease. They recognized the need for peritoneal dialysis when patients cannot be subjected to hemodialysis, but their experience with repeated peritoneal dialysis was poor. Problems consisted primarily of peritoneal infection, limited biochemical control, and loss of protein.

Numerous others published reports and summaries on the use of peritoneal dialysis for both acute and chronic uremia (95–129). Sufficient experience has now been gained that it is an accepted procedure and is used in practically all medical centers. One of the most interesting developments has been the use of peritoneal dialysis in the home. The work of Tenckhoff and Curtis (60) gives special encouragement to those looking forward to management of all patients who will benefit by peritoneal dialysis.

Removal of Endogenous Poisons—Peritoneal dialysis has been used not only for removal of the endogenous toxins accumulated in the uremic patient but also for other diseased conditions in which endotoxins accumulate.

A case of hyperammonaemia due to ornithine transcarbamilase deficiency in an infant was reported by Herrin and McCredie (130). Immediately before dialysis, blood ammonia was 1970 mcg. %, and hourly cycles of intermittent peritoneal dialysis were instituted. The ammonia level fell to 800 mcg. % after 4 hr. and to 640 mcg. % 12 hr. later, with regain of consciousness. Dialysis was continued for 36 hr., with reduction of blood ammonia to 330 mcg. %.

A deeply comatose, moribund patient with homologous serum hepatitis was also treated with peritoneal dialysis (131). Blood ammonia decreased from 560 to 294 mcg. % after 24 hr. of dialysis. Clinical improvement following peritoneal dialysis in another case was reported (132), blood ammonia being lowered from 800 to 100 mcg. %. Dialysate concentrations of ammonia ranged from 200 to 100 mcg. % in this case. Krebs and Flynn (133) treated a patient with acute hepatitis who developed hepatic coma. Exchange transfusion was used and, to prevent accumulation of ammonia resulting from use of 7-day-old banked blood, peritoneal dialysis was instituted concurrently. Gradual and steady clinical improvement was noted, with striking reduction of serum bilirubin, although no data were presented on ammonia levels.

The removal of both direct-reacting and indirect-reacting bilirubin *via* peritoneal dialysis was studied (134). Minimal amounts of bilirubin (0.5 mg. %), all

direct reacting, were found in the dialysate with standard dialyzing fluid. The addition of albumin to the dialysate gave a progressive increase in removal of both direct- and indirect-reacting fractions of bilirubin. Despite removal of 747 mg. of bilirubin by dialysis, the patient's serum concentration had not decreased at the end of dialysis. Hobolth and Devantier (135) dialyzed a 4-day-old jaundiced newborn using an albumin-containing dialysis fluid. Their results were in agreement with those of Grollman and Odell (134) on indirect-reacting bilirubin. In both cases, serum half-life was 57.9 hr. and the removal rate was 1.2% of the total body bilirubin per hour. In an experimental study on Gunn rats (136), the addition of 3.5% human serum albumin to the dialysis fluid resulted in removal of over half the bilirubin of circulating blood. Replacement of albumin by various concentrations of dextran, polyvinylpyrrolidone, or lipid proved ineffective in extracting bilirubin.

Hyperuricemia-complicated leukemia has been treated with peritoneal dialysis (137–140). Up to 4.5 g. of uric acid was removed in 29 hr. of dialysis (137). A peritoneal urate clearance, ranging from 4.3 to 13.0 ml./min., was reported by Barry *et al.* (138). Maher *et al.* (140) treated a leukemic patient in whom mannitol had failed to produce diuresis. They administered allopurinol to block further urate synthesis and instituted peritoneal dialysis. The urate blood level was decreased sharply.

Using dogs as experimental animals, Knochel and Mason (141) found that alkalinization of the dialysate with tris(hydroxymethyl)aminomethane or acidification of plasma by induced respiratory acidosis increased urate concentration in the peritoneal fluid. This finding suggested that the peritoneum has a preferential permeability to nonionized uric acid. Urate diffusion across the membrane was not affected by lactate or pyrazinamide, both agents being known to block renal excretion, and this was indicative that transport across the peritoneal membrane of urate is not active transport.

Oxalate has also been removed by peritoneal dialysis. Zarembski *et al.* (142) used continuous dialysis on a patient with primary hyperoxaluria and renal failure. The peritoneal clearance of oxalate was found to be 5.1–6.6 ml./min. Despite the removal of 43 mg./day, the plasma oxalate remained elevated, probably due to the rate of endogenous production exceeding the rate of dialysis.

Peritoneal dialysis was used to treat acute pancreatitis, with the rationalization that the damaged pancreas may liberate toxic proteolytic enzymes and vasoactive peptides into the peritoneal cavity and that these might be removed by peritoneal lavage to reduce the complications of shock and visceral damage (143). Rasmussen (144) used hypothermic peritoneal dialysis in treating experimental hemorrhagic pancreatitis and reported that this technique markedly decreased the amount of hemorrhage and necrosis within the pancreas as well as the rise in serum enzymes. Favorable results also were reported with peritoneal dialysis alone (145, 146) or with added proteinase inhibitor (143).

Removal of Drugs and Exogenous Poisons—A wide variety of drugs and industrial chemicals are involved in accidental poisonings and attempted suicides, and either peritoneal dialysis or hemodialysis is often used in an attempt to remove these agents. In general, hemodialysis offers more rapid removal, which is of prime importance in such cases, but often an artificial kidney is not available or the patient's condition does not allow its use. Excellent summaries of dialysis in the treatment of poisonings were published by Maher and Schreiner (147) and Schreiner (148).

Sedatives and Tranquilizers—In the broad group of sedatives and tranquilizers, the barbiturates are the most commonly met in poisonings, especially in attempted suicides. Of these, pentobarbital is the most frequent agent. In 1951, Muirhead (149) suggested the use of peritoneal dialysis for barbiturate intoxication; since then, it has been studied by several workers. Lackey *et al.* (150) used isotonic and hypertonic dialysis fluids in dogs and found that not more than 6.9% of the dose was removed in a 3-hr. period and that the hypertonic fluid was no better than isotonic. Bloomer (151) studied the removal of pentobarbital and concluded that the amount removed by peritoneal dialysis was so low, about one-fourth that removed by metabolism, that he questioned its value. Berman and Vogelsang (152) studied the effect of albumin added to the dialysis fluid and obtained clearances 2–3 times that with standard fluid. Bourne (153) also tested fluid with human serum albumin added and found that the preservative in the albumin interfered with the barbiturate assay. Later, Bourne *et al.* (154) repeated these tests, using radioactive pentobarbital, and found albumin to increase the amount removed by only 30%. This result was partially due to low returns of dialysate because of coagulation of the albumin in the peritoneum, and a full return would have yielded an increase of about 75%.

Recently, Kudla *et al.* (155) studied peritoneal dialysis of pentobarbital in rabbits and found that 0.25% of *N*-myristyl-β-aminopropionic acid added to dialysis fluid gave clearances about twice that of control fluid. A case of attempted suicide with pentobarbital was treated by Valtin (156). Peritoneal dialysis was conducted for 14 hr. The initial and final serum concentrations were 3.6 and 2.2 mg. %, respectively. Dialysis removed 182 mg. of the drug. The estimated dose taken was 3–4 g. Lash *et al.* (157) utilized peritoneal dialysis for both removal of drug and "core" rewarming. The patient was saved. Approximately 237 mg. of drug was removed, and the dose taken was 3 g. From reports to date, it is still dubious that peritoneal dialysis removes sufficient pentobarbital to have a significant effect upon the patient's condition.

With the other barbiturates, the rate of removal by peritoneal dialysis is said to be related to their rate of diffusion, degree of protein binding, and degree of ionization (158). Campion and North (158) tested the addition of albumin and tris(hydroxymethyl)aminomethane to the dialysis fluids. The albumin served to bind the barbiturates within the peritoneum, while the tris(hydroxymethyl)aminomethane caused ionization of them in the peritoneal fluid, both effects reducing the effective concentration within the dialysate and

thus increasing the concentration gradient and rate of diffusion. They obtained clearances for three barbiturates with control and 6% albumin solutions, respectively, as follows: for amobarbital, 6.2 and 10.2 ml./min.; for secobarbital, 5.7 and 9.7 ml./min.; and for phenobarbital, 4.8 and 6.3 ml./min. Knochel *et al.* (36) previously found tris(hydroxymethyl)-aminomethane to remove phenobarbital at twice the rate of control fluid; later, Knochel and Barry (159) demonstrated removal of secobarbital 10 times as fast with tris(hydroxymethyl)aminomethane as with control fluid. Berman and Vogelsang (152) found addition of albumin to remove secobarbital 1.5 times as fast as the control. Kudla *et al.* (155) found 0.25% *N*-myristyl-β-aminopropionic acid to give clearances for phenobarbital of about 1.8 times the control; for amobarbital and butabarbital, clearances were about twice those for the control.

Rosenbaum and Mandanas (160) used a recirculation technique with anion-exchange resin and tested dialysis with lipid and albumin fluids for removal of phenobarbital. They found 5% albumin to be the most effective agent. Setter *et al.* (161) obtained clearances for secobarbital of 4 ml./min. with control fluid and 6 ml./min. with 2.5% albumin. Cohen (14) used peritoneal dialysis for removal of amobarbital in a poisoning case. With an initial blood level of 1.65 mg. %, he removed 129 mg. The amount absorbed by the patient was unknown. In a patient who had ingested 1.3 g. secobarbital and 3.5 g. butabarbital, urinary clearance was poor and peritoneal dialysis cleared 5–10 times as much as did the kidneys (162). Whiting *et al.* (163) were able to remove 2.24 g. of phenobarbital by two courses of dialysis, 36 hr. each, from a patient who had probably ingested 10 g. of the drug. From the literature reports, it appears that peritoneal dialysis is an effective means for removal of phenobarbital, it is somewhat effective clinically with butabarbital and amobarbital, and its clinical value with secobarbital and pentobarbital is questionable.

Glutethimide has been involved in a number of poisonings, and overdosage is particularly difficult to manage (164). Peritoneal dialysis was used by Frey (165) in treatment of a patient who had ingested 15 g. of the drug. Thirty-two exchanges, one every 2 hr., were performed. The amount of glutethimide recovered in the dialysate was 705 mg. (4.7% of the dose) which, though small, was 5 times as much as was excreted by the kidneys. Both Frey (165) and Barbour (166) recommended peritoneal dialysis in spite of the low concentrations removed in dialysate. The rapidity with which peritoneal dialysis can be started and the fact that it can be maintained constantly led them to feel that it was advantageous. McDonald *et al.* (167), in 1963, did not recommend peritoneal dialysis as adequate treatment for glutethimide intoxication. DeMyttenaere *et al.* (168) used forced diuresis, hemodialysis, and peritoneal dialysis concurrently on a case of glutethimide poisoning and recommended that use of the three procedures together be considered. Shinaberger *et al.* (169) developed a procedure for using 15% cottonseed oil emulsion as the dialysis fluid and tested it on dogs. With the lipid emulsion, they were able to increase the extraction of glutethimide more than fivefold.

Diphenylhydantoin is one of the most widely used anticonvulsants. Although there are relatively few reported cases of severe intoxication with it, early and rapid reduction in blood and tissue concentrations of diphenylhydantoin after large overdoses is believed to be of great urgency to avoid permanent damage to the nervous system (170, 171). Tenckhoff *et al.* (170) dialyzed a child who had been in a coma for 3 days following the ingestion of about 2.8 g. of the drug. Blood levels decreased from 11.2 to 0.75 mg. % in the first 16 hr. of dialysis and to 0.35 mg. % after 24 more hr. of peritoneal dialysis. Another case of acute toxicity was successfully treated with peritoneal dialysis by Andia *et al.* (172). The dialysate attained a concentration equal to two-thirds that of the plasma in 1 hr. Effective peritoneal dialysis was reported by Blair *et al.* (171) in a case of mixed diphenylhydantoin and primidone poisoning, with significant reduction in blood levels of both drugs. In experimental studies on rabbits, Kudla *et al.* (155) found that dialysis fluid with 0.25% *N*-myristyl-β-aminopropionic acid gave twice the peritoneal clearance obtained with a control fluid.

There is evidence for the beneficial use of peritoneal dialysis in the treatment of meprobamate intoxication. Hardy *et al.* (173) reported the successful treatment of a case of attempted suicide after ingestion of 32 g. of meprobamate as well as amobarbital and secobarbital. Dyment *et al.* (174) treated a case of meprobamate poisoning by peritoneal dialysis and reported a peritoneal clearance of 3.5 ml./min. In another patient who ingested 20 g. of meprobamate, Mouton *et al.* (175) reported recovery of 1375 mg. in the dialysate and a decrease in blood level from more than 10 to 0.8 mg. %. Removal of more than 1 g. in the dialysate and 900 mg. in the urine was reported by Castelle and Sode (176). In an experimental study to evaluate the potential of peritoneal dialysis, Maddock and Bloomer (177) used Ringer's lactate solution in a dog. The peritoneal concentration of meprobamate reached about 50% of the plasma concentration or about 60% of the concentration of diffusible meprobamate in 60 min.

Treatment of ethchlorvynol poisoning has been successfully carried out with peritoneal dialysis, although there are conflicting reports on the value of added albumin in the dialysis fluid. Schultz *et al.* (178) found that the addition of albumin significantly increased the removal rate of ethchlorvynol, but Teehan *et al.* (179) were unable to confirm this finding. Exchanges containing albumin gave only slight increases in removal which they attributed to a small increase in drainage volume due to the oncotic effect of added protein. In their study the concentration of the drug was the same in dialysates with and without albumin. They reported a peritoneal clearance of 18.5 ml./min. A combination of peritoneal dialysis and exchange transfusion was used in treating a child with acute ethchlorvynol intoxication (180).

Neuromuscular blockage by gallamine was promptly reversed by peritoneal dialysis in a patient with renal failure who received the drug during a surgical operation (181). A case of methaqualone poisoning was

treated by Proudfoot *et al.* (182) by alternate peritoneal dialysis and hemodialysis. Peritoneal clearance of methaqualone was estimated to be 7.5 ml./min. Paraldehyde intoxication was treated by peritoneal dialysis (183); metabolic acidosis associated with paraldehyde poisoning was properly corrected, but blood levels and clearances of the drug were not reported. Schreiner (148), in his extensive review, stated that the phenothiazines are not dialyzable. He cited a number of publications in which neither hemodialysis nor peritoneal dialysis was successful in removing these drugs.

Analgesics—Numerous cases of salicylate toxicity are encountered because of accidental ingestion, therapeutic overdosage, and suicidal attempt. The ensuing alterations in body chemistry represent a complex and serious metabolic disturbance. The initial respiratory alkalosis, as a result of hyperventilation due to stimulation of the respiratory center, is soon followed by metabolic acidosis. The complexity of such disturbance is greatest in infants and small children (184, 185).

Salicylate is readily removed by peritoneal dialysis, and clinical improvement in intoxicated patients following dialysis is well documented (166, 186–188). Cohen (14) reported recovery of 4.1 g. of salicylate in the dialysis fluid in a case of aspirin poisoning. In another case (189), the blood salicylate level was reduced from 78 mg. % by peritoneal dialysis, with removal of 427 mg. in the dialysate.

Success in accelerating salicylate dialysis *via* substances added to the dialysis fluid has been achieved. Nahas *et al.* (190, 191) used tris(hydroxymethyl)-aminomethane and bicarbonate with the aim of maintaining a maximum concentration gradient through high dialysate pH. Their experimental work with dogs gave 1.3 and 1.6 times as much removal with tris-(hydroxymethyl)aminomethane and bicarbonate, respectively, as with control fluid. The addition of albumin to the dialysis fluid also enhanced the removal of salicylate by virtue of the high affinity of salicylate for protein, especially at low concentrations. Etteldorf *et al.* (192) used 5% albumin solutions and pooled serum on dogs to remove about 1.5 times as much salicylate as with the control. Similar results were reported by James *et al.* (193). Three times as much salicylate was removed by the combined administration of bicarbonate and peritoneal dialysis with 5% albumin as by urine alkalinization alone (194). Etchart (195) recovered 3 g. of salicylate from 12 l. of dialysate during 16 hr. of peritoneal dialysis. Favorable clinical results and removal rates were also reported with 5% albumin solutions (196, 197). Mattocks (198) could accelerate salicylate clearance in rabbits by nearly 5 times by using a solution containing 1% anthranilic acid and 0.25% *N*-myristyl-β-aminopropionic acid. It was thought that the local unbinding effect of anthranilic acid on salicylate, both in plasma and on membrane proteins, might play a role in this acceleration. With 0.25% *N*-myristyl-β-aminopropionic acid alone added to the control fluid, peritoneal clearance was more than twice that of the control fluid.

Methyl salicylate poisoning also has been treated with peritoneal dialysis (14, 199, 200). Kloss and Boeckman (201) lowered the blood salicylate level in an infant poisoned with methyl salicylate from 118 mg. % after 24 hr. of dialysis, and 176 mg. of salicylate was removed in the peritoneal fluid.

Acute poisoning after ingestion of propoxyphene is rare. Karliner (202) listed 15 cases from the literature, including a fatal case he had treated with 122 exchanges of peritoneal fluid. Initial blood level was 0.97 mcg./ml., and the dialysate concentration ranged from 0.24 to 0.03 mcg./ml.

Peritoneal dialysis was used to treat a patient with acute acetaminophen poisoning after ingestion of 24.4 g. (203). The initial blood level of the drug was 10.2 mcg./ml., and 10.2 mg. was removed in the dialysate in 6 hr.

Antidepressants—Wallace *et al.* (204) reported the successful treatment of a 9.08-kg. (20-lb.) child who had typical symptoms of amphetamine toxicity and had ingested an unknown number of tablets containing 15 mg. methamphetamine and 65 mg. phenobarbital each. Because of difficulties in hemodialyzing a small child and the promptness with which peritoneal dialysis could be started, peritoneal dialysis was chosen for treatment. After dialysis for 5 hr., the symptoms of toxicity abated. A total of 67 mg. of methamphetamine and 140 mg. of phenobarbital was removed in the dialysate. In an experimental study, Zalis *et al.* (205) administered lethal doses of amphetamine to dogs and treated the test group of 13 animals with peritoneal dialysis over 6 hr. Eighty-five percent of the animals showed no signs of toxicity, and 69% survived. The authors noted that the recovery of unchanged amphetamine in the dialysate was so low, 2.3%, that it did not reflect the value of the treatment. They concluded that peritoneal dialysis appears to be an effective form of therapy for amphetamine poisoning.

Sunshine and Yaffe (206) reported a case of amitryptyline poisoning in a 15-month-old child where peritoneal dialysis was used for 16 hr., removing only 0.15% of the ingested drug. They suggested that firm protein binding, rapid entry into and fixation to body tissues, and poor water solubility of the drug accounted for its poor removal.

Lipkin and Kushnick (207) successfully treated a child with pargyline poisoning by using peritoneal dialysis. Intermittent exchange was continued for 24 hr., at which time the patient was much improved. Amounts of drug extracted by dialysis were not measured.

Alcohols—Setter *et al.* (208) summarized results with removal of methanol by hemodialysis and peritoneal dialysis. They pointed out that with extremely high levels of methanol, hemodialysis should be used to reduce the level as rapidly as possible with the hope of avoiding visual impairment. In dogs dialyzed with 1.5 and 7% glucose fluids, average clearances were 24 and 31 ml./min., respectively, using peritoneal dialysis. Stinebaugh (209), in 1960, reported on clinical use of peritoneal dialysis in methanol intoxication. Initial blood levels of 180 and 200 mg. % in two patients were reduced to zero after 18 and 12 hr. of dialysis. A third patient, with an initial blood level of 532 mg. %, died. In the two patients who recovered, vision was left impaired. Wenzl *et al.* (210) reported the recovery of a 10-week-old infant with severe

methanol poisoning by treatment with peritoneal dialysis and intravenous bicarbonate. During an outbreak of methanol poisoning in Kentucky, Kane *et al.* (211) treated four cases with peritoneal dialysis, three of whom survived. Peritoneal clearances were 5–10 times that obtained with forced diuresis. For ethanol poisoning in a 4-year-old child, Dickerman *et al.* (212) used peritoneal dialysis and increased the removal of alcohol more than twofold over the expected rate without dialysis.

Heavy Metals—Mehbod (213) combined the use of calcium sodium edetate and peritoneal dialysis in the treatment of acute lead poisoning. He found that intravenous edetate greatly increased the amount of lead removed in the dialysate in three of four patients. Even with edetate, considerably more lead was cleared by dialysis than by the kidneys. Batson and Peterson (214) reported the use of peritoneal dialysis along with dimercaprol for mercury poisoning and recommended the combined procedure. Covey (215) used edetate along with peritoneal dialysis for the recovery of a child with ferrous sulfate poisoning. Lavender and Bell (216) found peritoneal dialysis to remove so little iron in a case of iron intoxication in an adult that its use was of doubtful value.

Miscellaneous Drugs and Poisons—Cocco and Pazourek (217) treated a 3-year-old child, who had swallowed 2304 mg. of isoniazid, with peritoneal dialysis for 72 hr., recovering 52% of the dose in the return fluid.

Gurr (218) used peritoneal dialysis after hemodialysis in the treatment of a patient with eucalyptus oil poisoning. The value of peritoneal dialysis in this case was not clear.

Yeh *et al.* (219) found that peritoneal dialysis and hemodialysis removed about the same amounts of α-methyldopa (60%) in patients using this drug.

Successful removal of boric acid in poisoning cases can be effected by peritoneal dialysis (20, 220–222). Segar (220) reported on three newborns who were severely poisoned through error by using boric acid solutions in their feeding mixture. Two survived. Marked clinical improvement was noted following 2 days of peritoneal dialysis, and dialysis removed 3.5 and 2.2 g. of boric acid in the two surviving cases Wong *et al.* (221) also reported favorable results with peritoneal dialysis for boric acid intoxication. Baliah *et al.* (222) treated an infant with boric acid poisoning, with the serum concentration dropping from 43 to 30 mg. % after 10 hr. of dialysis and to 15 mg. % after 34 hr. The amount removed in the dialysate was more than 752 mg.

The efficiency of peritoneal dialysis for the removal of quinine is controversial. Markham *et al.* (223) successfully dialyzed a patient who had ingested 3.84 g. of quinine sulfate. Over 16 hr., dialysis removed 415 mg., associated with a decline of plasma level from 9.2 to 5.25 mg./l. McKenzie *et al.* (224) also described cases of severe quinine poisoning. In one patient, dialysis for 24 hr. removed 640 mg., but blood levels were not available. In the second patient, 24 hr. of dialysis was accompanied by a decrease in plasma level from 9.2 to 5 mg./l. Other workers (87, 225–227) reported peritoneal dialysis to remove insignificant amounts of quinine in humans and in dogs. Poor peritoneal clearance was thought to be due to high protein binding, 70% (228). Quinine extraction after alkaline buffering of the dialysis fluid with tris(hydroxymethyl)aminomethane to pH 10 was one-fourth as great as with commercial fluid, pH 5.0 (225). This finding leads one to expect that the ionized form of quinine may be dialyzed more rapidly; if so, the variation in results reported may have been due to pH conditions of the individual dialysis.

Ackerman *et al.* (229) studied the dialysis of digoxin in 14 patients and reported a peritoneal clearance of 8 ml./min. and a serum half-life of 88 hr.

Graw and Clarke (230) reported a case of mixed chlorpropamide and salicylate toxicity. Peritoneal dialysis removed an insignificant amount of chlorpropamide, even with the addition of albumin.

Schmitt *et al.* (231) studied the clearance of bromide in dogs and reported a peritoneal clearance of 13.7 ml./min. as compared to 0.4 ml./min. for spontaneous urinary clearance.

A patient who took 40 g. of sodium chlorate was successfully managed by peritoneal dialysis (232). Pringle and Smith (233) also mentioned a case where the patient recovered after 14 days of dialysis.

Peritoneal dialysis was demonstrated to be effective in clearing chromium in a case of potassium dichromate toxicity, with a drop in serum level from 590 to 90 mcg. % after 84 hr. (234).

Thomas (235) treated a patient who had ingested 150 ml. of Lysol (50% cresols in soap) with peritoneal dialysis for 23 hr. The first exchange was found to contain 10 mg. free phenol. The initial total phenol serum level was 950 mcg. %.

Atkins *et al.* (236) treated cycloserine poisoning with peritoneal dialysis and obtained good reduction in plasma levels and removal of toxic symptoms after 21 hr. Measurements of amount in dialysate were felt to be inaccurate due to decomposition of the drug in the fluid and failure to account for metabolites.

Swick *et al.* (237) used peritoneal dialysis in colistin intoxication in a patient where renal failure had occurred. Dialysis effectively removed the drug and restored the kidney function.

Morton (238) treated a 15-month-old child for tetracycline intoxication and demonstrated efficient removal of the drug in the dialysate. She pointed to the value of peritoneal dialysis, particularly in the period of oliguria.

PROBLEMS OF ELECTROLYTE BALANCE

The problems and complications of electrolyte balance in peritoneal dialysis are numerous and complex. Only a few of these, which are peculiar to peritoneal dialysis, can be included in this review. In general, problems have stemmed from: (*a*) failure to take into account that each chemical species will seek equilibrium without regard to the other substances present; (*b*) failure to adjust concentrations to allow for volume changes in dialysis fluid, especially when it is hypertonic; (*c*) failure to account for changes in binding of

certain electrolytes with change in pH; and (*d*) removal of certain electrolytes from extracellular fluid so rapidly that equilibrium between intracellular and extracellular fluids cannot be maintained. These "failures" are not the result of negligence but are due to the fact that the dynamics of the substances under these conditions and their interrelationships are not fully understood. A number of these complications, as well as other hazards of peritoneal dialysis, were discussed by Maher and Schreiner (239), Ribot *et al.* (240), Matalon *et al.* (241), and Stewart *et al.* (242).

Maher and Schreiner (239) described the dialysis disequilibrium syndrome which results from overly rapid removal of urea from extracellular fluid. This creates an osmotic gradient between extracellular fluid and intracellular fluid which may result in cerebral edema. They also discussed the problem encountered with hypertonic solutions in patients with carbohydrate intolerance. Glucose is added to make the solution hypertonic so as to remove large amounts of water. Water moves into the fluid faster than glucose is absorbed, and the glucose is expected to be metabolized rapidly enough to keep the blood sugar low. The patient who cannot metabolize the glucose rapidly may attain extremely high glucose blood levels, which may lead to cellular dehydration.

In the use of hypertonic dialysis solutions, the movement of water is generally faster than that of electrolytes; rapid exchanges of such fluid may remove a disproportionate amount of water, causing concentration of the extracellular electrolytes. This was the finding of Nolph *et al.* (243) with sodium, and it explained the frequent occurrence of hypernatremia with the use of hypertonic dialysis fluids. They suggested the adjustment of sodium concentrations in hypertonic fluids by a simple factor which allows for the sieving coefficient of the ion.

Swales (244) measured sodium absorption in a number of dialyzed patients. He found that the usual dialysis fluid, with 140 meq./l. of sodium, may greatly increase the plasma sodium level of the hyponatremic patient and thus may result in pulmonary edema and heart failure. Swales (244) suggested that this be avoided either by use of low sodium fluid for the hyponatremic patient or by use of fluids sufficiently hypertonic to assure withdrawal of large volumes of fluid from the patient.

The uremic patient on digitalis therapy may have a digitalis level above normal to adjust for the depressant effect of high potassium levels. Upon dialysis with low potassium fluids, the depressant effect may be removed and the patient endangered by digitalis toxicity. Maher and Schreiner (239) encountered nine such episodes.

Hypocalcemia is a common finding in chronic uremia patients, even though calcium is included in the dialysis fluid. Garrett and Cuddihee (245) measured calcium diffusion and concluded that, on the average, 13% of instilled calcium is absorbed across the peritoneal membrane. The absorption was found to be a function of the fluid loss during dialysis. Atkinson *et al.* (246) made radiological measurements of the mineral content of bone of patients on maintenance dialysis, and their results showed a gradual loss of bone with time.

COMPLICATIONS AND HAZARDS OF PERITONEAL DIALYSIS

Peritoneal Infection—In early studies of peritoneal dialysis, infection of the peritoneum was recognized as a major hazard (247, 248); it still is a problem, especially in chronic cases (243). Frank *et al.* (248), in 1946, suggested that the chief sources of contamination were improper preparation of fluid and apparatus, introduction of bacteria *via* the skin at the site of puncture, and introduction of contaminated air into the catheter. These sources have been removed by development of present-day commercial catheters, fluids, and administration sets and by better preparation and protection of the puncture area. The addition of other substances to the dialysis fluid at the bedside undoubtedly results in some contamination, as has been the case with intravenous fluids, but the development of intravenous additive programs should improve this situation.

In spite of the improved techniques and equipment, reports in recent years still showed frequent occurrence of peritoneal infection (56, 57, 249–251). Some of the practices of handling administration sets were faulty, such as using the tubing for repeated dialysis over a period of time long enough to develop significant growths from slight contamination in the tubing, allowing the outflow tube to be in contact with collected fluid, and using nonsterile containers for collection of outflow fluid. Mowbray (252) and Cohen and Percival (25) demonstrated the reduction in infection which might be attained *via* improvements in technique.

It was found that the return fluid is commonly contaminated with bacteria; Schweinburg *et al.* (253) demonstrated that bacteria can migrate across the intestine, which may explain the frequent finding of contaminated effluent in the absence of any indication of peritonitis.

A number of workers used antibiotics prophylactically in peritoneal dialysis, often by adding them directly to the dialysis fluid (85, 93, 94, 115, 244, 250). Others felt that this was unnecessary and even irrational, since the antibiotic being used may not be effective against the organism involved (60, 254).

The present attitude with regard to antibiotics appears to be not to use them prophylactically but to institute therapy promptly should evidence of infection be found. Numerous articles have appeared regarding the effectiveness of antibiotics in peritonitis when administered therapeutically in the dialysis fluid (255–265). Although there is variation between drugs and between infections, the general attitude appears to be that antibiotics should be used intraperitoneally for local effect and intramuscularly (when appropriate) for systemic effect when septicemia is present.

Loss of Protein—Occurrence of protein in dialysate was noted early; and Boen (266) found 0.5–1.0 g./l., representing a loss of about 40 g. in a 48-hr. dialysis period. The distribution of proteins was roughly equivalent to that of serum.

Berlyne *et al.* (267) measured protein losses in 12 patients. Volumes of dialysis fluid varied from 14 to 79 l. and protein concentration in return fluid ranged from 0.68 to 4.49 g./l. Total protein losses for individual patients ranged from 10 to 207 g., which led to a mea-

surable fall in serum protein. They recommended that plasma protein levels be followed in peritoneal dialysis patients and that replacement therapy be instituted as needed.

Strauch *et al.* (268) studied the effect of variables of procedure in peritoneal dialysis upon the loss of protein. They observed that longer periods of stay of fluid in the abdomen resulted in higher protein loss, that increased osmolarity of the fluid gave higher loss, and that the loss of protein was greatest in the first exchange, dropping rapidly during the following five periods and then remaining practically constant. Their findings were interpreted as representing a constant rate of transfer from blood into dialysate, thus yielding the higher concentration in the first exchange with highest concentration gradient and highest concentration with longest dwell time. They pointed out that the loss in patients with peritonitis may reach 300 g.; in such cases, the loss cannot be made up by dietary means. They recommended recovery of proteins between dialyses and reinfusion, use of fluids with as low an osmolarity as possible, use of as short a cycle time as possible, and intravenous replacement of protein for patients in negative nitrogen balance.

In another report, Berlyne *et al.* (269) measured amino acid losses, as well as protein losses, and found a wide spectrum of amino acids present in the dialysate. Average losses of amino acids were 2.96 g. for an average of 27 l. of dialysate. The protein losses were 10–40 g., but there seemed to be no direct correlation between protein and amino acid losses. They pointed out that the loss of amino acids causes the hypoproteinemia to be more persistent. They recommended dietary or parenteral replacement of amino acids as well as proteins.

Gordon and Rubini (270) studied losses in 38 patients. The average protein loss in dialysis was about 72 g., with a wide variation of 27–248 g. lost during a 24-hr. dialysis. The wide variations could not be attributed to osmolarity of fluid, infection, plasma protein concentration, or clinical state of the patient. Protein losses tended to be consistent with the same patient in repeated dialysis. In successive exchanges, the concentration was usually higher in the first. Protein concentration increased with increased osmolarity (for a given patient). Sampling of a single exchange showed the protein to reach a concentration maximum in about 20 min.

Lindner and Tenckhoff (271) ran protein balance studies on patients who had been on peritoneal dialysis at home for 6 months or longer. They found nitrogen losses greater than intake on dialysis days, but this situation was more than compensated for during nondialysis days. The protein losses during dialysis were lower than had been previously observed when repeated puncture was used or than were usually reported in the literature; the authors suggested that the atraumatic nature of dialysis with implanted catheters, as used in this study, may explain this finding. Their data showed that long-term peritoneal dialysis can maintain the patient active and well to a degree comparable to that with hemodialysis.

An interesting observation was recorded by Gutch (272), who found that silastic catheters appeared to cause lower protein loss than those made of other materials. No mechanism for this finding is yet presented.

Pulmonary Complications—Pulmonary complications are occasionally an adverse side effect of peritoneal dialysis. Berlyne *et al.* (273) included pneumonia, atelectasis, purulent bronchitis, and pleural effusion in this category. They stated that distention of the peritoneal cavity with dialysis fluid causes elevation of the diaphragm, with reduction in vital capacity. For the uremic patient with lowered resistance, infection of the collapsed segments may occur and further infection may result from aspiration of retained bronchial secretions due to inhibition of coughing. They compared patients with a 2-hr. dialysis cycle to those with a 45-min. cycle which used a 5–7-min. drainage facilitated by vacuum. They also varied dialysis fluid volume. With the slow cycle, 2-l. dialysis, six of eight patients developed pulmonary complications. With the rapid cycle, 2-l. dialysis, three of seven patients had pulmonary problems; with the rapid cycle, 1-l. dialysis, only one of nine patients had a pulmonary complication. These workers recommended reduction of the amount of dialysis fluid for each exchange from 2 to 1 l., shorter cycles for exchange, reduction of overall dialysis time, and use of a sitting position during dialysis.

Swartz *et al.* (274) studied conditions leading to pulmonary edema during peritoneal dialysis. They found that in most patients in supine position and in all patients in sitting position, the instillation of peritoneal fluid led to an immediate fall in cardiac output. This fall was reversed by drainage of the fluid. They suggested this effect may be due to a decrease in lung volume and vascular bed due to mechanical factors or by release of pressor amines causing pulmonary vasoconstriction. They recommended that, upon recognition of pulmonary edema, the dialysis fluid be drained immediately. They further stated that dialysis can usually be restarted using smaller volumes of fluid without difficulty.

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RESEARCH ARTICLES

Molecular Interactions and Solubility of Polar Nonelectrolytes in Nonpolar Solvents

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Abstract □ An attempt was made to describe quantitatively the deviations from ideal solubility of nonelectrolytes in nonpolar solvents as a result of three contributions: (*a*) entropic, (*b*) regular solution, and (*c*) specific interactions. The relative magnitudes of these contributions were theoretically estimated. Experimentally, it was found that for the systems studied involving poorly soluble polar solutes in a series of hydrocarbon solvents, the entropic correction term appeared to account for deviation from ideal solubility behavior. Regular solution correction appeared to be unnecessary for these systems. Specific interactions were found to be the dominant factors in determining solubilities of polar solutes in solvents possessing acid–base characters. Solvate association constants between various solutes and chloroform or ether were determined by the solubility technique. The good agreement between solubility data and solvate equilibria equations for a wide variety of chemically different solutes and the two interacting solvents seems to indicate support for the stoichiometric solvate species treatment of solubility.

Keyphrases □ Solubility, nonelectrolytes, polar—in nonpolar solvents, consideration of entropic–enthalpic–specific interactions □ Nonelectrolytes, polar, solubility in nonpolar solvents—consideration of entropic, enthalpic, and specific interactions □ Solvation—polar organic solvents, stoichiometric species approach

The ability to predict thermodynamic activity coefficients of drug molecules in any given environment would be of immense value in considerations of mechanisms of drug delivery. The magnitudes of these coefficients are largely determined by the nature and extent of molecular interactions between the dissolved drug and its surrounding solvent molecules. The various types of interactions present in different environments are often reflected in the macroscopic solubility of the drug in these media. A careful analysis of the various factors and their relative contributions that determine the solubility would help toward a better understanding of molecular interactions in solution.

The solubility of nonpolar nonelectrolytes in nonpolar solvents can often be explained on the basis of cohesive energy differences between the components (1). The same regular solution treatment, however, has now been extended to systems involving polar nonelectrolytes as well as polar solvents such as dimethylacetamide, propylene glycol (2), nitrobenzene, and carbon disulfide (3). Recently, Higuchi *et al.* (4) pointed out that although straight-line correlations can sometimes be obtained for irregular systems using the solubility parameter (5), correlation with regular solution theory in these cases goes well beyond its original intentions. Instead, the data can be better explained on the basis of specific solvation (6).

In this paper, data are presented on the solubility of a variety of nonelectrolytes such as acetanilide, carbazole, picric acid, salicylic acid, and phthalic anhydride in organic solvents ranging from the completely nonpolar hydrocarbons through more polar solvents such as chloroform, diethyl ether, and acetic acid. The results are analyzed to determine quantitatively the relative contribution of "physical" *versus* "chemical" interactions toward solubility in these systems. The nature of specific solvation involving polar organic solvents is also discussed.

EXPERIMENTAL

Reagents—All reagents were of reagent grade. Cyclohexane was distilled over phosphorus pentoxide. *n*-Hexane (ACS) was used without further purification. Isooctane (2,2,4-trimethylpentane) was distilled over sodium. Dodecane was passed through a column of silica gel. *n*-Heptane, decane, and hexadecane were purified by passing the solvent through a column of silica gel and then distilling over sodium under reduced pressure. Diethyl ether, tetrahydrofuran, and *n*-propyl ether were distilled over lithium aluminum hydride. Chloroform was washed with distilled water five to six