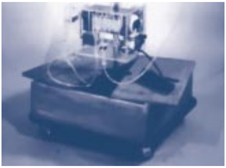
DIALYSIS COMPACT

The history and development of peritoneal dialysis


Fresenius Medical Care

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Peritoneal dialysis – from the beginning to the present

When symptoms of uremia first appear in the body, it is a sign that the kidneys are not functioning properly or have stopped filtering toxins from the blood. The Greek origin of the word "uremia" shows that the awareness of this disease goes back much further than our ability to effectively treat people this life-threatening illness. Only within the last hundred years medical research has been able to lay the fundament for replacing the kidneys' functions through dialysis.

Essentially, there are two types of dialysis: hemodialysis, which is the preferred treatment for 90% of all dialysis patients, and peritoneal dialysis. Last year we reported in detail about hemodialysis, a procedure where toxins are filtered from the blood of patients with kidney failure in an extracorporeal procedure, or a procedure outside the body. This year the DIALYSIS COMPACT supplement covers the field of peritoneal dialysis. This home dialysis treatment method uses the peritoneum as a dialysis membrane.

The first progress with this treatment type was made during the 1920s, but it would take a number of subsequent discoveries in the following decades to make peritoneal dialysis accessible for a larger number of patients with kidney disease. These advances were achieved by dedicated doctors and scientists whose efforts and discoveries led to ever-improving treatment possibilities.

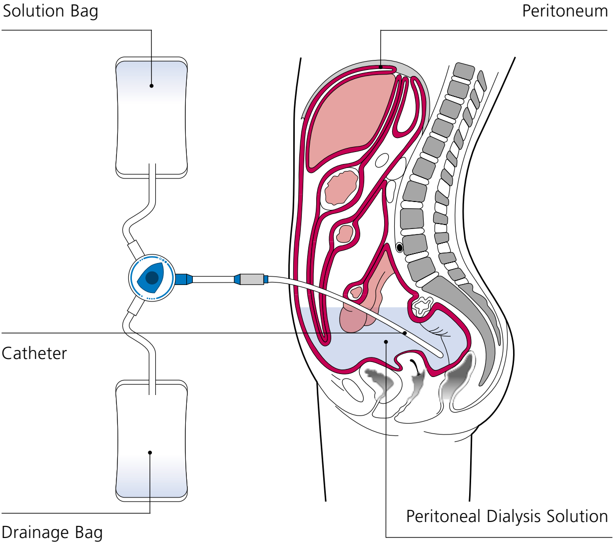
On the following pages, we offer an introduction to the fascinating history of peritoneal dialysis and the discoveries which, to this day, help to ensure a longer and better life for more than 160,000 peritoneal dialysis patients worldwide.

The fundamentals of peritoneal dialysis

As described in the introduction, peritoneal dialysis is one of the two established methods to remove toxins and excess water from the human body. The lining of the abdomen (peritoneum) is a thin, shiny membrane that has a surface of as much as two square meters and covers the entire abdominal cavity. Since the peritoneum has good blood circulation, it is an excellent natural filter membrane.

Peritoneal dialysis exploits this unique trait. First, a special fluid – the dialysis solution – is introduced at regular intervals to the abdominal cavity through a catheter. This fluid surrounds the peritoneum and allows metabolites to move from the tiny blood vessels into the dialysis fluid. Among the metabolites are the most well-known, such as urea and creatinine, as well as a number of other substances which gather in the blood of dialysis patients but are normally removed by healthy kidneys. The dialysis solution carrying these substances is then removed several hours later through the catheter and replaced by fresh solution.

In addition to the metabolites, excess water must also be removed from the patient's body. Therefore, sugar is added to the dialysis solution in a concentration far higher than it is in the blood. This offers just one option of balancing the concentration: water flows from the blood through the membrane and into the solution with the high sugar content. This process is known as osmosis.



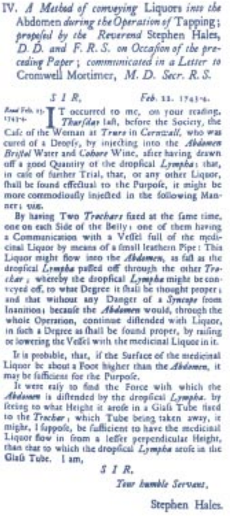
The principles of peritoneal dialysis

The first steps toward peritoneal dialysis

The term

The word "peritoneum" refers to the Greek "peritonaion" and means "to stretch". Morticians in ancient Egypt were probably the first people to get a look at the peritoneum as they prepared the organs of influential Egyptians. The famous Greek physician Galen and other medical scholars of ancient Greece studied the open abdomens of injured gladiators. Early anatomists and surgeons described the size and features of the peritoneal membrane but failed to discover its detailed structure or function. These studies were followed by Friedrich Daniel von Recklinghausen in 1862, who gave the first scientific description of the peritoneum's cellular composition.

Removing water from the abdomen in the 17th century



IV. *A Method of conveying* Liquors *into the* Abdomen *during the Operation of* Tapping; *proposed by the Reverend* Stephen Hales, *D. D. and F. R. S. on Occasion of the preceding Paper; communicated in a Letter to* Cromwell Mortimer, *M. D. Secr. R. S.*

S I R, *Feb.* 11. 1743-4.

Read Feb. 13. 1743-4.

IT occurred to me, on your reading, *Thursday* last, before the Society, the Case of the Woman at *Truro* in *Cornwall*, who was cured of a Dropsy, by injecting into the *Abdomen Bristol* Water and *Cohore* Wine, after having drawn off a good Quantity of the dropsical *Lympha*; that, in case of farther Trial, that, or any other Liquor, shall be found effectual to the Purpose, it might be more commodiously injected in the following Manner; viz.

By having Two *Trochars* fixed at the same time, one on each Side of the Belly; one of them having a Communication with a Vessel full of the medicinal Liquor by means of a small leathern Pipe: This Liquor might flow into the *Abdomen*, as fast as the dropsical *Lympha* passed off through the other *Trochar*; whereby the dropsical *Lympha* might be conveyed off, to what Degree it shall be thought proper; and that without any Danger of a *Syncope* from Inanition; because the *Abdomen* would, through the whole Operation, continue distended with Liquor, in such a Degree as shall be found proper, by raising or lowering the Vessel with the medicinal Liquor in it.

It is probable, that, if the Surface of the medicinal Liquor be about a Foot higher than the *Abdomen*, it may be sufficient for the Purpose.

It were easy to find the Force with which the *Abdomen* is distended by the dropsical *Lympha*, by seeing to what Height it arose in a Glass Tube fixed to the *Trochar*, which Tube being taken away, it might, I suppose, be sufficient to have the medicinal Liquor flow in from a lesser perpendicular Height, than that to which the dropsical *Lympha* arose in the Glass Tube. I am,

S I R,

Your humble Servant,

Stephen Hales.

Stephen Hales described an irrigation of the abdomen with red wine (1744)

Georg Ganter was the first to use peritoneal dialysis to treat a patient with kidney disease (1923)

The metabolic transport processes

In 1877, the German G. Wegner performed the first animal experiments to observe the metabolic transport processes occurring through the peritoneum. For example, he injected solutions of various contents and temperatures into rabbits and discovered that a concentrated sugar solution would lead to an increased amount of fluid in the abdominal cavity. This is how G. Wegner discovered the basis for using the peritoneum for fluid removal, or peritoneal ultrafiltration. In 1894, two Englishmen, Ernest Henry Starling and Alfred Herbert Tubby, discovered that fluid removal through the peritoneum was effected by blood vessels in the membrane.

First treatments of human beings

Stephen Hales and Christopher Warrick, an English surgeon, laid the cornerstone for peritoneal dialysis in humans in 1744: they attempted to treat a 50-year-old patient with ascites by first removing the excess abdominal fluid from the woman before using a leather tube to infuse a solution consisting of 50% water and 50% wine into her abdomen. However, the first peritoneal dialysis for uremic patients was performed quite some time later at the University of Würzburg by Georg Ganter. In 1923, after having experimented on animals, he infused one and a half liters of a physiological solution – one with the same salt concentration as the human blood's – into the abdomen of a woman who suffered from a blocked ureter. Although the treatment alleviated the symptoms temporarily, the patient died a short time later.

Between 1924 and 1938, a number of medical teams in the U.S. and Germany performed the first regularly repeated – or intermittent – peritoneal dialysis treatments and proved that the procedure can be a short-term replacement for the kidneys' natural function.

In the following years, the careful selection of materials such as porcelain, metal, latex and glass, which could be sterilized, made it possible to ensure reasonable hygienic conditions during peritoneal dialysis. Still, the procedure found only limited use, predominantly due to the lack of a safe method of accessing the patient's abdomen.

Peritoneal dialysis catheter

This safe access to the abdomen for peritoneal dialysis is provided by a catheter. Originally, metal cannulae were used to gain access to the abdominal cavity, but were replaced by stomach and oxygen tubes later on. In 1952, Arthur Grollman from Southwestern Medical School in Dallas developed a catheter that would make peritoneal dialysis treatments accessible for patients with chronic kidney failure. Grollman used a one liter container with a cap to which a plastic tube was attached. His revolutionary idea was to use a flexible catheter rather than a stiff tube, as had been the case in the past. In addition, the tip of the catheter remaining in the abdominal cavity had several small holes to allow an optimal inflow and outflow of dialysis solution.

Against the backdrop of the Korean War, the American Paul Doolan developed a catheter for long-term use in 1959. It was made of polyethylene and had a unique geometry of the holes to prevent clogging, while maximizing the flow rate. Richard Ruben, another American, performed the first peritoneal dialysis over a period of seven months, using the Doolan catheter as well as a permanent catheter that could remain in the abdominal cavity. This shows that researchers were not just intending to treat patients with acute illnesses but also patients with chronic kidney failure.

In 1968, the American Henry Tenckhoff developed the catheter named after him. Up until then, the widely used stylet catheter had already made it possible to treat patients with chronic kidney failure using peritoneal disease. However, the "repeated puncture technique" meant placing a new catheter in the abdominal cavity for each treatment. This time-consuming procedure bothered both medical personnel and patients. Tenckhoff himself had the thankless job of setting catheters in patients on weekends. So his permanent catheter not only provided him with more spare time, but also proved to be instrumental in the wide acceptance of peritoneal dialysis. The Tenckhoff catheter is still in use today. Made from silicone, it has one or two cuffs which help the catheter to grow into the peritoneum as well as into deeper layers of connective tissue.

Bags and tubes

In addition to the catheter, the development of bags and tubes also plays a decisive role in the long-term success of peritoneal dialysis. As the most common complication, peritonitis limited the spread of continuous ambulatory peritoneal dialysis (CAPD).

Sterilization of peritoneal dialysis solution in large glass bottles

Until the fall of 1978, peritoneal dialysis solution (PD solution) was only available in glass containers, connected to the permanent catheter with plastic tubes. Patients had to attach the tubes to the catheter every time they added or removed solution. Because of the high number of connections and disconnections, the danger of peritoneal infection was always imminent. Dimitrios Oreopoulos from Toronto finally made CAPD practical by introducing disposable plastic bags, which lowered the peritonitis rate considerably. Once the dialysis solution was introduced into the abdominal cavity, the plastic bag could be rolled up and remained connected to the patient's body for the duration of the treatment. To remove the solution, the bag was unrolled, and gravity pulled the used dialysis solution into the bag. At the end of the procedure, the bag was removed from the catheter and a fresh bag attached. This new technology offered patients more comfort and relative freedom.

Several Italian research teams also made a valuable contribution to the prevention of peritonitis, most notably Umberto Buoncristiani from Perugia, who invented the Y-System. This system includes an empty bag and connected tubes shaped like a “Y” dictating the flow of dialysis solution. Additionally, a bag filled with PD solution is connected to this system. First of all, the used dialysis solution is drained into the empty bag, carrying possible bacteria from the catheter connector. Then fresh dialysis solution is flushed through the tubes and into the bag for about three seconds. The connection to the abdominal cavity remains closed during this procedure. When the tubes have been flushed, the patient’s catheter connector is opened and fresh PD solution is introduced into the cavity (flush-before-fill principle). Depending on the system, the flow of PD solution (drainage, flush, filling) is controlled with clamps or a disc. This technology plays an essential part in lowering the peritonitis rate. Another advantage: patients do not have to carry a bag attached to their bodies.

The double-bag system is an improvement of the Y-system. This innovation not only provides an empty bag already attached to the Y-shaped tube system but also a bag with fresh dialysis solution. This eliminates yet another connection and further decreases the risk of infection. The double bag is the current successful conclusion of the pioneering efforts to lower the peritonitis rate in peritoneal dialysis.

Standard bag

Y-system with empty bag

Y-system with double bag

The age of continuous ambulant peritoneal dialysis (CAPD)

CAPD originated in Austin, Texas, in 1975, when Robert Popovich and Jack Moncrief discussed ways to dialyze a patient who was unable to undergo hemodialysis. These discussions led Dr. Popovich to develop comprehensive calculations based on the amount and dwell time of the dialysis solution, determining the effective removal of uremic toxins. The researchers concluded that a two-liter bag should be changed five times a day and that a PD solution should constantly remain in the patient’s body. Paradoxically, the initial announcements of their clinical findings were not taken seriously. But

THE DEFINITION OF A NOVEL PORTABLE/WEARABLE EQUILIBRIUM PERITONEAL DIALYSIS TECHNIQUE. Robert P. Popovich, Jack W. Moncrief, Jonathan F. Decherd, John B. Bomar* and W. Keith Pyle.* Depts. Chem. Engr. and Biomed Engr., The Univ. of Texas and Austin Diag. Clin., Austin, Texas.

An analysis will be presented which predicts that acceptable blood metabolite levels will result if 10 liters of dialysate per day are allowed to continuously equilibrate with body fluids. Accordingly, a portable/wearable dialysis procedure based upon equilibrium-intermittent peritoneal dialysis has been defined. Two liters of standard hypertonic dialysate fluid are infused peritoneally via a Tenckhoff catheter and allowed to equilibrate 5 hours while the patient conducts his normal activities. The dialysate is then drained and replaced with the procedure being repeated five times per day.

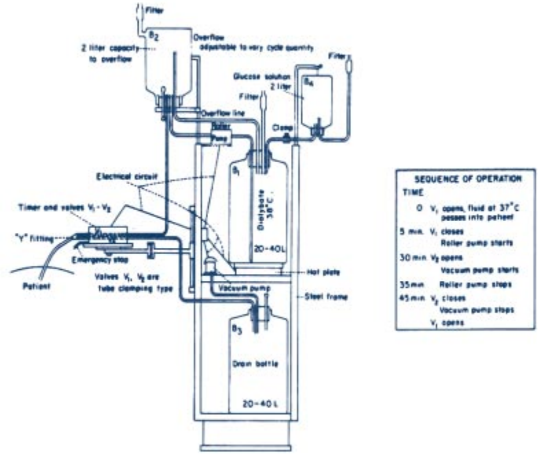
In a preliminary clinical study metabolite equilibration between blood and dialysate was achieved for BUN and creatinine but not for vitamin B-12. Steady state metabolite levels for BUN and creatinine were 40 and 9.5 mg% respectively. The patient was maintained 5 months with the new procedure with excellent clinical results followed by a successful transplant.

It is concluded that a new portable/wearable dialysis procedure has been defined. The technique does not require blood access and results in steady, low blood metabolite levels: middle molecule removal greatly exceeds that of conventional techniques.

Robert Popovich and Jack Moncrief were the first to describe CAPD (1976)

when Popovich and Moncrief presented further clinical successes in 1978, the medical community was convinced. Compared to intermittent procedures, the methods they developed made it possible to remove fluids and filter the blood more steadily and continuously (see page 8).

Automated peritoneal dialysis (APD)



Schematic structure of the first automated peritoneal dialysis machine by Fred Boen, original drawing in English (1962)

In addition to lowering the rate of infection, costs for medical staff and materials had to be decreased. Machines for automated peritoneal dialysis (APD) were developed for this purpose. APD uses a programmable machine, or cycler, that controls the volume, filling, dwell time and drainage of the solution. Thanks to automated dialysis, patients can now be dialyzed while asleep at home.

Automated peritoneal dialysis was introduced in 1962 by Fred Boen from Washington University. The machine he developed required a

40-liter container of PD solution. The invention significantly cut the amount of time needed to open and close the tubing system and connect or disconnect bags, as required by manual CAPD. Full containers were delivered to the patients' homes and retrieved when empty. Intermittent peritoneal dialysis was performed once a week.

It was again Tenckhoff who further simplified automated peritoneal dialysis. To eliminate the difficult task of maneuvering the 40-liter container, he suggested to install water preparation equipment that could provide sterile water at the patients' homes. A concentrate would then be added to the sterile water to produce dialysis solution.

Between 1961 and 1970, the American Norman Lasker combined the developments of Boen, Tenckhoff and Russel Palmer into a single advancement. "His" cycler used two-liter bottles, taking advantage of gravity to pump the PD solution, which was warmed first. In 1970, the first patients received home dialysis with this cycler.

Precursors of the current peritoneal dialysis machine by Henry Tenckhoff and Norman Lasker

The new generation of cyclers developed by Fresenius Medical Care

In 1981, José Diaz-Buxo proposed the continuous cyclic peritoneal dialysis (CCPD), which is now the most commonly used APD method. Here, excess water and toxins are removed from patients overnight using 10 to 15 liters of dialysis solution. During the day, one and a half to two liters of dialysis solution remain in the abdominal cavity.

New, biocompatible peritoneal dialysis solutions

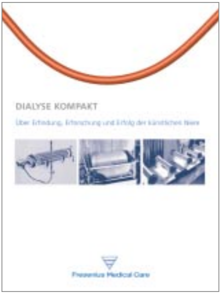
PD solutions play an increasingly important role in current peritoneal dialysis research and development. In the 1920s, Ganter used a physiological saline solution, to which glucose was added later. In 1938, Jonathan Rhoads began adding lactate to the solution to correct metabolic acidosis, which can develop if the kidneys are unable to eliminate acidic metabolic products. More than 60 years later, lactate remains the most commonly used buffer in PD solution. However, today there are also solutions containing pure bicarbonate or a mixture of the two substances, bicarbonate and lactate, to balance the acid-base status. As a substitute for glucose, dialysis solutions can also contain amino acids or glucose polymers.

New biocompatible peritoneal dialysis solution in a double bag

In the early 1980s, a widely recognized article by Axel Duwe was published, discussing the effects of individual components of PD solution on peritoneal efficiency on bacterial killing for the first time. A few years later the term "bio(in)compatibility" appeared to indicate the body's (in)tolerance of dialysis solutions. At the time, studies showed that conventional PD solutions could inhibit the activities of key cells in the peritoneum and cause long-term damage to the membrane. These complications lad to a gradual weakening of the peritoneal membrane and make it unsuitable for further use as a dialyzer. Conventional dialysis solutions have a non-physiological pH below that of the peritoneum and a high concentration of glucose degradation products. Both contribute significantly to the bioincompatibility of solutions. Now, PD solutions are offered in multi-chamber bags that have a neutral to physiological pH and a significantly lower amount of glucose degradation products.

The introduction of this new generation of PD solutions is a promising start for the development of better, more biocompatible solutions. The results of recent studies inspire confidence that new PD solutions can extend the dialyzer function of the peritoneum. Actually, a clinical study showed that a new, more biocompatible PD solution can extend a patient's survival.

This brief look at the history of peritoneal dialysis illustrates the fascinating interaction between the ideas, resourcefulness and determination of many pioneers and dedicated scientists. The success of their efforts is reflected in modern peritoneal dialysis which has attained a solid position in today's kidney replacement therapy.



This publication is the third in a series on dialysis. The first part, "Dialysis Compact – The function, diseases and treatments for the human kidney", offered information about the functions of the kidneys, the reasons for chronic kidney failure, treatment choices and the mechanics of dialysis. The second supplement, "Dialysis Compact – The invention, development and success of the artificial kidney" summarized the history of hemodialysis and the artificial kidney or dialyzer.

Both publications are available through Fresenius Medical Care's Investor Relations.

Fresenius Medical Care is the world's largest provider of products and services for individuals undergoing dialysis because of chronic kidney failure, a condition that affects more than 1.4 million people worldwide. Through our network of dialysis clinics in the U.S., Europe, Latin America, Asia and Africa, we provided kidney-replacement therapy to approximately 131,450 patients by the end of 2005. Fresenius Medical Care is also the world's leading provider of dialysis products such as hemodialysis machines, dialyzers and related disposable products.

For more information on our Company and the history of dialysis, please visit **www.fmc-ag.com**.

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