Chapter 1
History of Peritoneal Dialysis

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Peritoneal dialysis (PD) is a home-based dialysis modality for patients with end-stage kidney disease (ESKD). For the past several decades, PD has provided flexibility in performing dialysis treatments helping ESKD patients maintain their everyday activities, work, and travel [1]. This flexibility also provides patients with the option to dialyze during sleeping or waking hours and effectively eliminates the need for frequent trips to outpatient dialysis centers. The concept of PD steadily evolved over the centuries through the creativity, dedication, and diligence of several key innovators. By learning about the evolution and history of PD, the reader will gain a more comprehensive understanding of the overall importance of PD and will develop an appreciation for the amount of research, innovation, and perseverance that lead to the current status of PD. This chapter will outline the history of PD and review a number of major scientific breakthroughs that have collectively shaped how PD is currently practiced.

Peritoneal dialysis has its origins in early civilization when the presence of the peritoneum was first discovered. Observations of the peritoneal cavity date back to ancient Egyptian records of animal dissection and are described in the Ebers Papyrus, written in 1552 B.C., as a definitely outlined cavity in which the viscera are somehow suspended [2, 3]. Despite these ancient discoveries, the knowledge and understanding of the explicit structure and functions of the peritoneal membrane remained very limited until the late nineteenth century, when the effect of the discovery of cells began feverishly reverberating throughout medicine and physiology [2]. In early Greek descriptions, physicians like Galen recognized the

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peritoneum in the abdomen of injured gladiators. The word peritoneum is derived from the Greek word *peritonaion*, in which *peri* means "around" and *ton* means "to stretch" [4].

The very first perception of peritoneal dialysis is thought to have occurred in the 1740s from an early surgeon by the name of Christopher Warrick in England who attempted to perform a novel treatment. At that time, Warrick was treating a 50-year-old woman with severe ascites by installing claret wine and Bristol water into her peritoneum with a leather pipe. After the patient recovered successfully, Reverend Stephen Hales wrote about the treatment and proposed that two trochars could be used to allow for in and out lavage of the ascitic fluid [4]. In 1862, Friedrich Daniel von Recklinghausen published information on the peritoneal membrane's cellular components and anatomy for the first time [5]. Later in 1877, a German investigator by the name of G. Wegner explained the idea of peritoneal ultrafiltration. Wegner used animal models to permeate hypertonic solutions made of glycerin and salts to demonstrate increased concentration of the drained peritoneal fluid. Building upon this, he also explained how changing the sugar solution could alter the peritoneal membrane [6].

In 1884, two Englishman, Ernest Henry Starling and Alfred Herbert Tubby, discovered that the peritoneal fluid can be bidirectional and that the removal of fluid from the peritoneum was affected by the quantity of membranal blood vessels. In 1918, Desider Engel, working in Prague, demonstrated that proteins can transport through the peritoneal cavity. A year later, in 1919, M. Rosenberg discovered that the concentration of urea in the blood was equal to that in the peritoneum. This, he concluded, proved that urea could be removed from the body using peritoneal dialysis. Then in 1923, Dr. Tracy J. Putnam used dog models to demonstrate that the peritoneum was a natural "dialyzing membrane" [7].

Simultaneously in 1923, a researcher at the University of Wurzburg named George Ganter was trying to determine how the peritoneum could be effectively utilized to dialyze actual patients in a clinical setting. To implement his idea, Ganter first conducted animal experiments and began by ligating the ureters of guinea pigs. He would inject a saline solution into their peritoneal cavity, where it would dwell for several hours before it was drained. He applied the same technique to treat his first patient, a young woman who presented with ureteral obstruction and uterine cancer. Ganter instilled varying volumes of a saline solution in the patient's peritoneum (1 to 3 liters per fill) until her blood chemistry levels normalized, and she was discharged home [4]. However, the patient subsequently died. Ganter concluded that PD therapy needed to be continued consistently for the patient to survive. Through his comprehensive research efforts, Ganter introduced several impactful concepts and techniques related to the treatment of patients on PD that are still being used today such as the need for sterile solutions, the modification of ultrafiltration by changing the glucose concentration, and the requirements of peritoneal access. In addition, he elaborated that the risk of infection would hinder the procedure and the time and volume of the dwell would determine solute removal. Ganter's research underpinned a foundation of understanding for the future of PD [4].

Despite these early advances, access to the peritoneal cavity remained challenging. In the early 1920s, Stephen Rosenak and P. Sewon created a metal catheter for

the infusion of solution into the peritoneal cavity that helped alleviate some of the existing difficulties maintaining adequate outflow due to the improper position of the previous simple hollow needle being utilized by Ganter. One of the milestones in the history of PD occurred at the Wisconsin General Hospital in 1936. A group of physicians headed by J.B. Wear, I.R. Sisk, and A.J. Tinkle performed PD on a patient who had presented to them with urinary obstruction. For the first time ever documented, consistently performed PD successfully used to treat kidney failure secondary to urinary obstruction. This trial demonstrated that patients can safely and successfully be treated with peritoneal dialysis. After World War I, PD was being used to treat acute kidney failure by German investigators [4].

In the mid-1940s, Dr. P.S.M. Kop, who was an associate of Willem Kolff in Holland working with hemodialysis at the time, quickly turned his attention to the exciting new dialysis modality of PD. Kop built a PD system that integrated gravity, allowing for the dialysis solution to infuse into the peritoneal cavity more easily. There were many different pieces of equipment used for this device, including large glass catheters to infuse the dialysate solution into the peritoneal cavity, latex rubber tubing to transport the dialysate solution to the patient, and large porcelain containers to store the dialysate solution. Kop and his group successfully treated 21 patients using this new integrated system, most of whom survived [4]. During World War II, the battlefield quickly became a lucrative opportunity for advancing dialysis research by treating injured or sick soldiers through PD. This research opportunity first presented itself to two physicians at Beth Israel Hospital in Boston, Massachusetts, in 1945, when Dr. Howard Frank and Dr. Arnold Seligman turned to PD as a potential strategy for treating acute kidney failure on the battlefield. The system that they utilized was like that of Kop and addressed many previously encountered technical issues, such as modifying the solution to best fit each individual patient's clinical needs and optimal flow rates. In addition, they utilized two catheters to reduce the likelihood of obstruction during the outflow portion of the procedure and used large sterile bottles to minimize the chances of contamination and related infections [Figs. 1.1 and 1.2]. That same year, they were able to successfully treat a patient with acute kidney injury caused by an overdose of sulfa drugs using this modified system [8]. This became one of the main turning points in the advancement of peritoneal dialysis.

Even with these improved systems, access to the peritoneal cavity still remained a barrier to achieve optimal outcomes, with the most common approach employing metal trochars left in place for hours at a time. These trochars, though effective, often contributed to intra-abdominal infections, and it was evident that further improvements in peritoneal access were required. In 1952, Arthur Grollman from the Southwestern Medical School in Dallas, Texas, described a new approach that he had researched. This new approach utilized 1-liter containers attached to a plastic tube; this plastic tube was then connected to a polyethylene catheter. The polyethylene catheter was groundbreaking for two main reasons: first, the tube was more flexible and could safely be left in place for longer periods of time, and second, Grollman had installed tiny holes at the intraperitoneal portion of the catheter, which kept the patient's body tissue from hindering the drainage. Overall, this

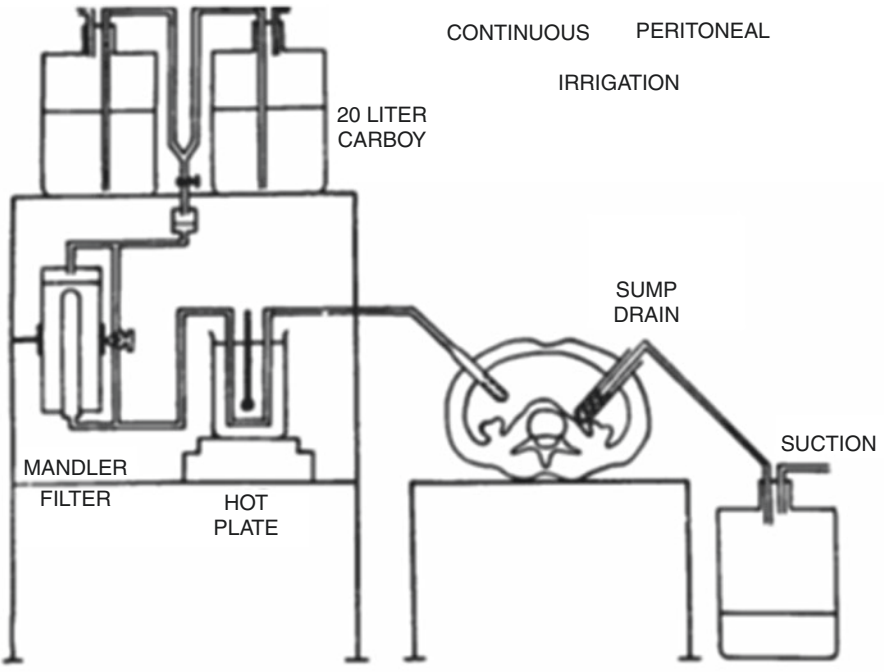

Fig. 1.1 Continuous open peritoneal irrigation by Frank, Seligman and Fine

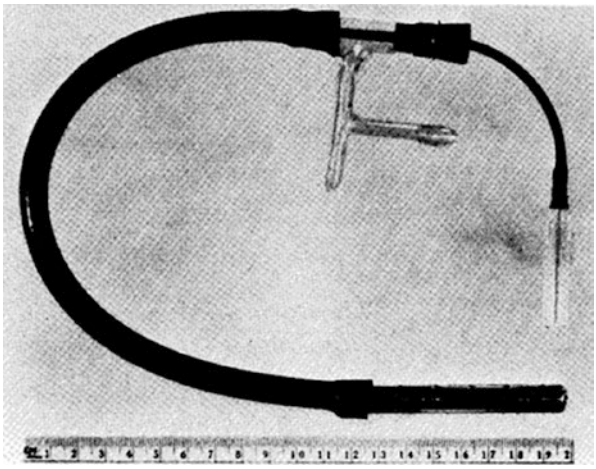

Fig. 1.2 The flexible sump-drain of Frank, Seligman and Fine, composed of ordinary rubber glass and stainless steel

allowed for better inflow and outflow of the fluid throughout the abdomen and peritoneum [9]. Furthermore, Grollman proposed that the fluid should remain in the abdomen for 30 minutes and then be drained into the sterile storage container [4].

In 1959 at the Naval Hospital in San Francisco, California, a research team led by Paul Doolan was also looking into PD under battlefield conditions. Doolan and

his group created a modified version of Grollman's groundbreaking polyethylene catheter. This new catheter allowed for long-term usage while maintaining its flexibility. In addition, it had several side holes and grooves that provided improved drainage and further minimized drain hole blockage. Around this same time, Richard Ruben, who also worked at the Naval Hospital and was finishing his tour of duty, was asked to treat a woman with kidney failure. Ruben decided to initiate this patient on PD with Doolan's new and improved catheter. After the patient received dialysis, her condition dramatically improved, but once it was stopped, she would begin to deteriorate again. After examining this pattern, Ruben suggested that the patient could go home for the week but should return to the center on weekends to receive dialysis. They continued this pattern of treatment for 7 months and only had to replace the catheter once during this period [10].

In 1959, Dr. Morton Maxwell at the Wadsworth VA Hospital in Los Angeles, California, analyzed the research already conducted on PD by Frank, Seligman, and Grollman and wanted to build a more simplistic system for treating acute kidney failure. He wanted to create a system that was easy to connect, utilize, and disconnect by medical professionals. Also, with the goal of minimizing infection risk, he used fewer tubing connections [11]. Maxwell reached out to a local intravenous solution manufacturer and commissioned them to design a customized glass container that would hold the PD dialysate and would be attached to a plastic tubing and a polyethylene catheter. This new system consisted of instilling 2 liters of peritoneal solution into the peritoneal cavity, leaving the solution to dwell for 30 minutes and then draining the peritoneal solution back into the original container, repeating these exchanges as necessary [4]. These exchanges were done continuously until the patient's blood chemistry levels were normalized. Using his method, Maxwell was able to successfully treat many patients. His work was published in the "Peritoneal Dialysis: 1. Technique and Applications" article in 1959, demonstrating the medical importance and simplicity of his procedure, which became known as the "Maxwell technique." This was a tremendous accomplishment in the field of PD, as dialysis was no longer limited to specific hospitals that already had the necessary, specialized equipment in place. PD could now be done in any hospital which had the required basic supplies [4].

In late 1959, Fred S.T. Boen published a thesis on PD in Holland. In his thesis, he discussed the advantages of PD, highlighting the simplicity of the procedure and emphasizing that the PD minimized the likelihood of sudden blood volume changes, allowed for altering the procedure by adjusting the dialysate for better management of volume and electrolytes, and had the potential to be safely utilized as a long-term dialysis modality. He described the influence of glucose concentration on the ultrafiltration [4]. Boen was invited by Dr. Belding Scribner to continue his research at the Northwest Kidney Centers in Seattle, Washington. Accepting the offer, Boen relocated to Seattle in 1962, where he developed an automatic peritoneal dialysis system that operated overnight without requiring the supervision of a physician [12]. His system included 20- to 40-liter bottles for the dialysate, a capped latex catheter, sump drainage that held more fluid, larger infusion bottles for repeated infusions, and a drainage monitor to measure the amount of fluid being pulled out

from the patient. Even with these new developments, Boen still had serious concerns about peritonitis. The new catheter he created was an open system that could significantly increase the patient's risk of infection, so he abandoned this technique and went back to the earlier system of removing the catheter at the end of each procedure. Boen is considered as one of the founding fathers in the field of PD [4].

In 1963, Dr. Henry Tenckhoff working at the University of Washington joined Boen's group and expressed his concerns about the difficulty of transporting 40-liter dialysate bottles to the patient's home for treatments [4]. He was able to eliminate this arduous requirement by installing a water still inside the patient's home to get sterile water. The sterile water was then mixed with the dialysate concentrate, which was cycled in and out of the peritoneum by a controller unit. Although this simplified the procedure, the catheter still needed further modifications. Tenckhoff improved his design by customizing the catheter that was previously designed by Wayne Quinton and Dr. Russell Palmer. He shortened their siliconized catheter and suggested that there can be a straight and curled design to it. Additionally, he added Dacron felt cuffs to assist in sealing the openings through the peritoneum. Lastly, he designed and added a metal trochar to help place and position the catheter more easily [13]. Following these modifications, Tenckhoff's new system was complete and ready to be used for performing PD on patients.

Norman Lasker, the acting director of the Renal Division at the Seton Hall College of Medicine in New Jersey, had visited the Seattle group to gain better insight of the new automated systems that had been created by Tenckhoff. After seeing his system, Lasker was concerned about the difficulty of managing a system like this at his own group. To address this, he started working to create a simpler system that utilized 2-liter sterile glass bottles, a device to warm the dialysate solutions, a device to measure the volume of infused dialysate, and a drainage bag. He soon began treating patients in their homes with his new automated cycler device with great success [4]. Shortly after Lasker had created and tested his new automated cycler, Dimitrios Oreopoulos, who had recently been tasked with running a four-bed intermittent PD program at the Toronto Western Hospital, ordered several "Lasker's cyclers" for his home patients, as he had been very impressed with Lasker's design. Oreopoulos's program quickly became very successful, thanks to these cyclers, and his program expanded to more than 70 patients on intermittent dialysis, making it one of the largest PD programs in the world at that time [4].

In 1975, Dr. Jack Moncrief established an in-center hemodialysis program in Austin, Texas, where a patient by the name of Peter Pilcher was admitted to begin his hemodialysis treatments. After Peter's fistula would not function, it became clear that he was not a viable candidate for hemodialysis. Moncrief suggested that the patient move to Dallas, where he could transition to PD. When the patient refused, Moncrief decided to join forces with Robert Popovich, a biomedical engineer, to develop a PD system to save the patient's life. Their system included a 2-liter bottle with tubing and a Tenckhoff catheter attached. In addition, Popovich recommended that five 2-liter exchanges should be performed to normalize the patient's blood chemistry levels. Therefore, the fluid would need to remain in the peritoneum for a total of 4 hours and then be drained. This process, hypothesized

and tested by Moncrief, Popovich, and another researcher named K. D. Nolph, became known as "continuous ambulatory peritoneal dialysis" (CAPD) [14]. Eventually, Dr. Oreopoulos adopted this new technique and started a CAPD program at his practice in Toronto as well, with a few minor modifications. He changed the sterile glass dialysate bottle to a sterile plastic polyvinyl chloride (PVC) bag for easy transport, which resulted in an overall decrease in infections, and was met with positive feedback from patients [15]. Furthermore, Oreopoulos collaborated with Baxter to design a PVC bag with a spike at the end for a more sterile, secure, and easier way to attach the bag to the tubing [4].

Continuing to improve upon their original design, Moncrief and Popovich created an ultraviolet exposure system located at the spike of the bag to help decrease the chances of infection even further. In Italy, Dr. Umberto Buoncristiani created the flush-before-fill mechanism, known as the "Y-system." This system allowed for bacteria to be rinsed away before the new dialysate was instilled into the patient, significantly reducing the chances of peritonitis [16]. This "Y-system" was eventually changed to a double-bag system for the purpose of requiring only one connection. In 1978, the Food and Drug Administration (FDA) approved the CAPD procedure, and in the following year, Baxter brought to the market the CAPD system, which included an antiseptic solution for the maintenance of the bag and spike, a Luer lock made out of titanium for catheter connection, tubing with a one-sided spike at the end, and solution bags [4]. In 1981, Dr. Jose Diaz-Buxo and Dr. D. Nakayama developed a hybrid system called "continuous cyclic peritoneal dialysis" (CCPD). This system utilized a cycler device that instilled and drained dialysate on a continuous basis at night with a 1- to 2-liter dwell during the day. It allowed for the peritoneum to be in continuous contact with dialysate fluid for 24 hours [4].

In 1983, Medicare legislation permitted PD to be reimbursed at a rate indistinguishable from that of in-center hemodialysis. As news of this legislation spread, PD symposiums began to be held worldwide, giving clinicians and researchers opportunities to present PD clinical research, to share and discuss physician and patient experiences with PD, and the benefits of PD [4]. At the end of the 1980s, PD cyclers continued to expand and improve in their hardware components and layout, making them less bulky, quieter, and most importantly safer. Cyclers such as PCS 2000 produced by Fresenius, Pac-X and Pac-XTRA by Baxter, and PD T by Gambro all incorporated these changes [17]. The machines allowed for utilization of disposable materials and personalization of dwell time and volume to fit the patient's needs.

Patients could dialyze with a wide range of treatment schedules such as intermittent PD (IPD), nightly intermittent PD (NIPD), CCPD, and tidal volume prescription (TPD). Then in 1994, HomeChoice was produced by Baxter. This machine was portable and weighed 12 kg, which was lighter than the previous machines. Also, its new volumetric pumps allowed for accurate exchanges [17]. The next edition, HomeChoice Pro, allowed for a 60-day treatment recording and storage on a 2 Mb data card. This helped healthcare providers better manage patients' therapy, by utilizing the card to retrieve historical data on patients' treatments and assess the adherence to therapy. As other companies witnessed the success of these features, they started to adopt similar features on machines such as Serena, Sleep Safe, PD

100 T, PD 101, and PD 200. The latest edition of these machines incorporated a 60- to 180-day treatment recording period and the opportunity to prescribe exchange fill volume, total dialysate volume, and tidal time [17].

Machines like Serena and Sleep Safe allowed for decision-making on the number of cycles and dwell time. In addition, Sleep Safe had the ability to detect the usage of wrong solution bags and displayed the percentage of glucose per cycle. They had different ways of moving and measuring volume. Serena utilized pressure chambers which had a gravity-based system and allowed for prescription in breakpoint modality, preventing spending a large amount of time at the end of the exchange and its enhanced drainage [17]. Sleep Safe and HomeChoice Pro utilized hydraulic and pneumatic pumps and used a volumetric system. All machines that were being produced came with a built-in battery that allowed for treatment suspension and data storage in case of a power outage. With the enhancement of software technology, cyclers were beginning to get programmed based on patient's treatment and personal data [17].

Recent cyclers such as HomeChoice Claria, Amia, Kaguya, and Sleep Safe consist of bidirectional communication properties and new treatment schedules. The great transformation of PD happened with the bidirectional communication between the patient's cycler at home and the medical care team at a given facility. This feature can be utilized with the HomeChoice Claria cycler [17]. It has the Sharesource portal, in which medical professionals can adjust dialysis prescriptions, obtain treatment data, and resolve problems by simply logging into the portal. Lastly, Sharesource provides opportunities for remote patient management (RPM), which enhances the quality of treatment, reduces in-center patient visits and costs, and decreases technique failure and patient dropout rates [17].

The demand for pursuing and utilizing PD as a dialysis modality continues to grow rapidly, and PD is now universally recognized as a very safe and cost-efficient dialysis modality. As PD continues to advance and flourish, it is important to understand the history of PD and to appreciate all the innovations, trials, and tribulations that took place in order for PD to progress to the current status. Thanks to the dedication, perseverance, and creativity of many individuals throughout history, PD has become a mainstay of modern home dialysis therapy and has given ESKD patients a safe, convenient, and effective way to receive life-saving dialysis treatments in the comfort of their own home.

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