# **Early History of Home Parenteral Nutrition:** From Hospital to Home

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### Abstract



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Technologic advances in the past century have led to the ability to safely deliver parenteral nutrition (PN) to hospitalized patients. Key breakthroughs included the development of saline and glucose infusions, infusion pumps, macronutrients (lipids, dextrose, and amino acids), and central venous catheters. In the 1960s, centrally delivered PN was performed in short-term hospitalized patients by Lincoln James Lawson (North Staffordshire Royal Infirmatory, United Kingdom) and long-term patients by Stanley Dudrick (University of Pennsylvania, United States). These early studies showed that a system was needed that would allow patients with intestinal failure to be discharged from the hospital and receive home PN (HPN). In the late 1960s and early 1970s, Belding Scribner, Maurice Shils, Khursheed Jeejeebhoy, Marvin Ament, Dudrick, and their teams discharged patients from the hospital who then self-administered HPN. Shortly after these early cases of HPN, multidisciplinary centers were established first in North America, and later in Europe, to manage these complex cases. The current article describes the patients treated by these early HPN pioneers, in addition to subsequent case series reported by them and others. (Nutr Clin Pract. 2018;00:1-16)

### Keywords

central venous catheters; history; home care services; home parenteral nutrition; nutrition support; parenteral nutrition; parenteral nutrition solutions

## Introduction

The ability to provide total intravenous (IV) nutrition to a patient with an alimentary tract that cannot absorb nutrients has existed for approximately 50 years. Although the capability to deliver IV hydration or individual macronutrients (lipids, glucose, and amino acids) has existed longer, total parenteral nutrition (PN) administration by using central venous catheters was developed in the 1960s.<sup>1-3</sup> Several medical advances in the late 1800s and early 1900s ultimately overcame long-standing hindrances to safely delivering total PN. These barriers included no safe central venous access for delivery, the lack of available nutrient substrates for safe PN infusion (macronutrients, micronutrients, and vitamins), and the lack of facilities that could develop, store, and modify PN solutions.<sup>4</sup> Although World War II interrupted some of the basic scientific advances in PN, such as the development of protein hydrolysates and crystalline amino acids, important breakthroughs in areas such as venous access and infusion systems occurred during this time.

The development of reliable central venous catheters in the 1960s allowed the safe delivery of PN to hospitalized patients with close supervision of physicians, nurses, and other allied health clinicians.<sup>1-3,5</sup> However, this level of supervision could not be provided at home, which made it difficult to support patients who needed long-term or lifelong PN. One of the first cases of long-term central PN involved an infant with small bowel atresia and failure to thrive.<sup>2,3</sup> She received PN for months in the hospital until it became clear that she would be dependent on PN for the rest of her life. With no mechanism to provide this lifesaving therapy at home, PN was eventually stopped. On the basis of this case, a system for home PN (HPN) clearly needed to be developed. A few papers describe the history of HPN or PN but mainly from the treatment center's perspective.<sup>4,6-9</sup> This review of the literature describes pivotal moments in the development of PN which led to the ability to discharge patients from the hospital to self-administer HPN. In addition, this review describes the first published cases of HPN, the early experiences of the centers, and the experiences of

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Table 1. Key Published Historic Events in Home	PN	•
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Year(s)	Event	Primary Investigators
1915	Infusion pump developed that intravenously delivered glucose solutions at a constant rate.	Woodyatt
1920s	First IV lipid emulsion (ILE) made from castor oil administered to humans.	Yamakawa & Nomura
1924	Continuous IV saline and glucose drips used to treat trauma and surgical patients.	Matas
1939–1947	Protein hydrolysates developed for IV use.	Elman
1947–1948	The essential amino acids required in the human diet were described.	Rose
1952	Subclavian puncture used to resuscitate wounded soldiers.	Aubaniac
1961	Intralipid, a 100% soy-based ILE, introduced in Sweden.	Wretlind & Schuberth
1964	Crystalline amino acid solutions introduced in Germany.	Bansi
	Lipomul, a cottonseed oil-based ILE, removed from the U.S. market.	
1965	The supraclavicular approach for subclavian cannulation performed using a catheter.	Yoffa
	14 surgical patients postoperatively provided with 2600 kcal/d total PN for 8–36 days; 8 central venous catheters were used, and 1 catheter was used for 35 days.	Lawson
1966–1967	8-week-old beagles received PN as complete source of nutrition for 256 days using a central yenous catheter and showed normal growth.	Dudrick
1967-1968	First 30 patients administered long-term central PN for as long as 200 days.	Dudrick
	An infant with small bowel atresia was administered central PN for 22 months and had normal growth and development.	Dudrick
1968	An adult patient was discharged and received PN for 6 months, which was administered with assistance from local healthcare providers.	Dudrick
1969–1970	Artificial gut system developed to deliver HPN to 7 patients, either at night or during the day, using a portable infusion vest.	Scribner
	An artificial gut HPN system used to treat a 37-year-old with intestinal failure, and the full case report was published.	Shils
1970	A novel artificial gut system that used compressed air to nocturnally deliver PN was described; the first discharged patient lived for >20 years while receiving HPN using this system.	Jeejeebhoy
	Tunneled central venous catheter was first described, which eventually becomes known as the Broviac catheter.	Scribner & Broviac
1970–1975	Clinical outcomes reported for 54 patients who used the first artificial gut system.	Scribner & Shils
1971	A unique, artificial, and portable HPN system, which used a surgically implanted central venous catheter, developed in France.	Solassol & Joyeux
1973	An early case of HPN administered to a patient with short bowel syndrome reported in Europe.	Jarnum
1975–1978	Case series of pediatric patients who received HPN, including the first neonate, was reported.	Ament
1983	The Oley Foundation, a patient advocacy group, was formed.	Howard & Oldenburg (patient)

HPN, home parenteral nutrition; IV, intravenous; PN, parenteral nutrition.

the clinicians who were mentored by the initial pioneers in PN.

# Early Research on PN

Development of the essential components required for safe PN delivery has been covered elsewhere and is briefly reviewed here (Table 1).<sup>4,10,11</sup> A venous delivery system and safe nutrient substrates were the 2 pivotal breakthroughs that led to the widespread use of PN. William Harvey's landmark description of the circulatory system, first published in 1628, led to numerous attempts to inject fluids and nutrients

into the bloodstream. During the British cholera epidemic (1831–1832), William O'Shaughnessy observed that cholera decreased salt and blood volume levels. O'Shaughnessy hypothesized that replenishing the venous system with fluids could treat cholera.<sup>12</sup> Two months after the publication of O'Shaughnessy's work, another British physician, Thomas A. Latta, reported the IV delivery of a sodium chloride solution (which contained one-third the sodium of modern normal saline) by using a small silver tube attached to a syringe.<sup>12</sup> However, the mortality rate of the treated patients was >80% because these infusions were administered only after all other cholera treatments had been attempted, which

led to doubts about this therapy.<sup>12</sup> In 1964, research showed that IV saline could replace electrolyte and volume losses in patients with cholera, which supported the earlier work of Latta and O'Shaughnessy.<sup>13</sup>

In addition to fluid and electrolyte delivery, development of safe infusible macronutrients was essential to PN administration. In the early 20th century, glucose was successfully administered to humans, and in 1915 Rollin Woodyatt developed an infusion pump that delivered a glucose solution at a constant rate.<sup>14</sup> This early infusion pump consisted of a glass cylinder and metal IV needle connected to a piston driven by an electric motor. Fluid could be delivered at a rate of 10-5000 mL/h. Using this early infusion pump, Woodyatt et al demonstrated that as much as 0.85 g/kg/h glucose could be infused during 6-12 hours to healthy adults without causing glucosuria.<sup>14</sup> In 1924, Rudolph Matas introduced the concept of continuous IV infusion (ie, "drip") and demonstrated that saline and glucose infusions could be safely and effectively administered to surgical and trauma patients.<sup>15</sup> After these early observations, solutions with as much as 10% glucose were routinely infused. Phlebitis and thrombosis were observed in the peripheral veins when higher concentrations were administered (>10%glucose).7

The biochemist William Rose discovered threonine (1935), which was the last of the 20 amino acids transcribed by the genetic code to be described. He later described the essential amino acids required in the human diet.<sup>16-18</sup> This work was followed by that of Robert Elman, who administered IV protein hydrolysates (from the enzymatic hydrolysis of purified casein) to postoperative patients.<sup>19-22</sup> Interestingly, in a 1939 article on IV alimentation, Elman and Weiner reported that an average of 325 L of IV or subcutaneous glucose or IV saline solution was administered daily at Barnes and City Hospital in St. Louis, Missouri.<sup>22</sup> This shows that earlier developments in PN were commonly applied in clinical practice. In addition to being the first to administer protein hydrolysates to humans, Elman demonstrated the importance of the role of amino acids in critically ill surgical patients.<sup>11</sup> A few years later, Arvid Wretlind developed a similar protein hydrolysate using casein hydrolyzed by pancreatic enzymes, which reduced the amount of polypeptides.<sup>11</sup> These protein hydrolysates were eventually replaced with the crystalline amino acids that were first introduced in Europe in the early 1960s and in the United States in the 1970s. In 1964, Hans Bansi in Germany introduced crystalline amino acids in solution. Compared with protein hydrolysates, crystalline amino acids have the benefits of optimal nitrogen utilization and potentially fewer contaminants such as aluminum.<sup>8,23</sup>

When Woodyatt and Matas were developing IV glucose techniques and Elman and Rose were studying protein physiology, other investigators were researching IV lipid infusion.<sup>24</sup> Lipids are perhaps the most challenging of the

3 macronutrients to deliver intravenously, and early trials were largely unsuccessful. The first administration of IV lipid emulsions (ILE) to humans was reported in Japan by Yamakawa and Nomura, who used emulsions made from castor oil.<sup>25</sup> The ILE studied in early human trials were made from various sources including corn, lard, coconut, and cottonseed.<sup>25</sup> A cottonseed oil-based lipid was approved for use in the United States (Lipomul) but removed from the market in 1964 because of adverse reactions including fever, jaundice, and liver damage.<sup>25</sup> A soybean oil-based ILE (Intralipid<sup>®</sup>, Fresenius Kabi, Bad Homburg, Germany) was first developed in Sweden by Arvid Wretlind and Oscar Schuberth.<sup>8</sup> Intralipid<sup>©</sup> was a pivotal discovery and ultimately allowed all 3 macronutrients to be safely delivered to patients receiving PN. Intralipid<sup>®</sup> has been available in Europe since the early 1960s but was not approved for clinical use in the United States until 1977.<sup>8</sup> It is important to remember that, outside of research studies, the PN formula administered to patients in the hospital and the HPN formula available in the United States lacked ILE before 1977.

All macronutrient components were available for IV use by the 1960s, and clinicians identified the potential nutrition benefits of PN infusion. Early clinical administration of macronutrients to surgical patients was performed in the United Kingdom.<sup>1,26</sup> The general observation of postoperative catabolism after major gastrointestinal surgery led to the early experimental use of short-term peripheral PN (PPN). In a study of patients who underwent partial gastrectomy (n = 20), 10 patients received postoperative PPN for 5 days, which consisted of 15% cottonseed oil-based ILE (800 kcal/d), protein hydrolysate, and 4% glucose solution (which was added to make the solution isotonic). These patients were compared with a similar cohort of 10 patients who did not receive PPN.<sup>26</sup> PPN led to weight gain in 4 of 10 patients (40%) compared with weight loss in those who did not receive PPN. An additional group of patients received the same ILE-based PPN after esophageal resection (to treat carcinoma) and had lower rates of anastomotic failure than patients who did not receive PPN.<sup>26</sup> This early study of PPN set the stage for short-term and long-term central PN, but central venous catheters had to be developed first.

## Development of Central Venous Access for PN

Until the 1960s, PN consisted of individual macronutrients or electrolytes that were delivered with a catheter inserted into the peripheral veins. Unfortunately, the amount of macronutrients had to be limited in peripherally delivered PN because if it contained all the macronutrients and electrolytes sufficient to sustain life for the long term, it was too hyperosmotic. The French physician Robert Aubaniac is credited with being the first clinician to use subclavian puncture to resuscitate wounded soldiers.<sup>27,28</sup> Subsequent experiments on cadavers showed that subclavian vein cannulation could be performed in >90% of cases and within 60 seconds.<sup>29</sup> A 1963 case series by Davidson et al<sup>30</sup> evaluated 100 attempts at using subclavian venipuncture to administer IV therapy (n = 83) or to obtain blood for diagnostic tests (n = 17). They successfully performed subclavian venipuncture in 94 of 100 cases and reported 1 case of

pneumothorax and 3 neck hematomas.<sup>30</sup> At the time, however, some clinicians were not convinced that using a subclavian instead of a peripheral vein catheter would provide sufficient benefit to justify the increased risk. These early subclavian venous approaches were infraclavicular, and a subsequent case series conducted in Australia by David Yoffa<sup>31</sup> in 1965 evaluated using the supraclavicular approach on 130 patients. Only 5 failed cannulations were reported, with no reported cases of pneumothorax or hematoma. Yoffa stated that the advantages of the supraclavicular approach included that the needle is pointed away from the lung, a definite landmark is available, the distance between the skin and subclavian vein is short, and the pectoralis muscle does not need to be traversed.<sup>31</sup> At the time, the safety of these new central venous access techniques was debated and viewed skeptically compared with peripheral catheters. In an editorial published in the same issue of The Lancet as the case series by Davidson et al,<sup>32</sup> concerns were raised about the risks of the new subclavian approach versus (vs) the peripheral approach for obtaining venous access. The editorial commented that acquiring the skill needed to perform the procedure may prove difficult and that, even if this difficulty were overcome, the "clinical benefit may prove no more than marginal."<sup>32</sup>

## Short-Term Central PN

In the 1960s, patients were receiving IV fluids, individual macronutrients, and PPN containing all macronutrients through the peripheral veins for short periods.<sup>26</sup> Administering nutrients, electrolytes, and fluids to patients for more than a few days or weeks was not possible. Lincoln James Lawson (1930-2016) was a surgeon who trained in the Department of Surgery, at the University of Birmingham and Queen Elizabeth Hospital and was later a faculty member at the North Staffordshire Royal Infirmary, all in the United Kingdom.<sup>1,33</sup> In 1965, Lawson made the observation that acute loss of >30% body weight was associated with high mortality in the post operative period following major gastrointestinal surgery.<sup>1</sup> In an attempt to prevent weight loss and potentially decrease mortality, Lawson delivered a PN solution consisting of 1 L ILE (20% cottonseed oil), 1 L amino acids (10% Aminosol), and 1 L fructose (20% solution) to provide approximately 2600 kcal/d to patients (n = 14) who underwent gastrointestinal surgery and had major postoperative complications. These complications included biliary peritonitis (n = 4), esophagogastric anastomotic leakage (n = 3), polytrauma with renal failure (n = 2), jejunal fistula (n = 3), and aortic aneurysmectomy with renal failure (n = 2). Less weight loss occurred in these 14 PN patients than 8 similarly ill patients who did not receive PN and who subsequently died. The duration of PN use ranged from 8–36 days, and 5 of 14 patients (35.7%) survived.<sup>1</sup> A total of 8 central venous catheters were used because of peripheral vein failure or infusion convenience, and 1 catheter was used for 35 days.

In addition, 2 patients in this novel study underwent postoperative liver biopsy at 30 and 36 days, respectively, and had signs of diffuse lipid deposition in Kupffer cells despite normal findings on serum liver function tests. Furthermore, nitrogen balance improved when the PN components were infused together.<sup>1</sup> In a follow-up study performed in 1967, Lawson reported that 4 patients who underwent head or neck resection and received a similar 2600-calorie PN solution (but 20% Intralipid<sup>®</sup> replaced cottonseed oil) had improved postoperative nitrogen balance and minimal weight loss.<sup>33</sup> By 1965, total central PN had been administered in short-term postoperative situations, which showed its potential for long-term use in the hospital.

# Beagle Studies and Administering Long-Term Central PN to Patients

In the 1960s, the University of Pennsylvania had expertise in advancing the techniques of central venous access, thereby fostering the ideal conditions for the development of longterm PN delivery. The University of Pennsylvania group included internationally recognized and established investigators Harry Vars and Jonathan Rhoads, as well as young surgeons Stanley Dudrick, Douglas Wilmore, and Ezra Steiger, all of whom would provide major contributions to the field of nutrition.

During his intern year in 1961, Dudrick lost 3 critically ill, malnourished patients who were admitted to Rhoads' surgical service. A pivotal moment in Dudrick's career was when he received encouragement and support from Rhoads to develop a long-term PN delivery system that would support normal growth and overcome malnutrition in patients who could not be nourished enterally.<sup>34</sup> During the next few years, using experiments on beagles, Dudrick developed or modified several techniques that would become essential for hospital-delivered, long-term PN and HPN. The techniques of inserting a polyvinyl tube into the jugular or subclavian vein and threading it into the superior vena cava led to the development of the tunneled catheters now commonly used in long-term PN and HPN.34 Until that time, the medicalgrade tubing used could elicit a subcutaneous inflammatory response and thrombogenic reactions.<sup>34</sup> The University of Pennsylvania group partnered with industry to develop products such as an infusible, fat-soluble vitamin preparation. They used a 0.22-micrometer micropore filter and an air-filtering hood in the hospital pharmacy to sterilize PN solutions.

A landmark long-term study published in 1968 by the University of Pennsylvania group described how 8-weekold male beagles received a normal oral diet or total PN using the team's refined methods and techniques for up to 256 days.<sup>2</sup> The researchers inserted a polyvinyl catheter into the external jugular vein, passed it into the superior vena cava, and subcutaneously tunneled it between the scapulae.<sup>2</sup> The PN solution contained all macronutrients (except the last 2 experimental animals who did not receive lipids), micronutrients, and vitamins needed for long-term nourishment. The beagles in the PN group (n = 6) had increased weight gain and similar lean body mass at 256 days compared with the control beagles, which were fed normal dog food.<sup>2</sup>

In addition to reporting the results of the beagle studies, this article described the first 30 patients who exclusively received PN for 10-200 days.<sup>2</sup> The PN solution consisted of 20% glucose, 5% fibrin protein hydrolysate, electrolytes, trace elements, and vitamins (ILEs were absent due to removal of Lipomul from the market).<sup>2</sup> The polyvinyl catheter was percutaneously placed in the external jugular or subclavian vein and passed into the superior vena cava. Every 3 days, the exit site was cleaned with an iodine solution and antibiotic ointment and a sterile dressing was applied.<sup>2</sup> Six of these adult patients underwent long-term metabolic examinations, and the results showed long-term positive nitrogen balance. In addition, 11 of 14 enterocutaneous fistulae closed during PN administration.<sup>2</sup> The first patient to receive PN was a 52-year-old man with regional enteritis and multiple enterocutaneous fistulae. He had lost more than half of his body weight in the preceding year and weighed 80 pounds. Although initially lethargic, the patient was subsequently obtunded with depressed respirations.<sup>34</sup> The patient's serum phosphorus level, which was within the reference range before PN, quickly decreased to nearly zero. This decrease in phosphorus and his clinical symptoms were likely the result of refeeding syndrome, which would be described years later.<sup>35,36</sup> Long-term central PN could now be used to improve patient outcomes, but potential associated complications such as refeeding syndrome could also occur.

These studies were followed by the description of an infant with small bowel atresia. The patient had failure to thrive (lethargy and weight loss) despite receiving a PPN solution consisting of 10% glucose and protein hydrolysates. As the patient's condition deteriorated, the managing team consulted Dudrick.<sup>3,34</sup> The ethical and medical issues were debated by an ad hoc committee, and all clinicians agreed that PN should be administered via a central venous catheter.<sup>11</sup> Dudrick inserted a polyvinyl catheter into the jugular vein and passed it to the superior vena cava (Figure 1). Because no central venous catheters were approved for



**Figure 1.** Early system used to administer central parenteral nutrition. The infant was born with small bowel atresia and subsequently had failure to thrive. V, vein. (Adapted from Wilmore and Dudrick<sup>3</sup> and reproduced with permission.)

infant use, the team used a modified catheter from the beagle study.<sup>34</sup> A PN solution consisting of 25% glucose, 5% fibrin protein hydrolysate, vitamins, trace elements, and electrolytes was infused for 24 hours by using a peristaltic pump with variable speed control, and an inline 0.22-micrometer filter (Figure 1).<sup>3</sup> After receiving centrally delivered PN for 24 hours, the infant became responsive and active.

The infant improved in the first few months and began to gain weight. However, the team was concerned about potential complications. The first concern was metabolic bone disease, and eventually the infant showed signs of rickets.<sup>34</sup> The team determined that the amount of calcium in the PN was adequate but doubled the vitamin D level, and rickets quickly resolved. The second concern, the possibility of essential fatty acid deficiency (EFAD), was immediately considered because there was no approved lipid source for PN and the infant had not ingested lipids for a month. The team applied safflower oil to the skin after skin changes consistent with EFAD occurred (which was later biochemically confirmed). The team created their own ILE to add to the PN formula by collecting the parents' blood after a fatty meal and centrifuging the plasma (the parents and infant had type O blood). Each day they added 30-60 mL of the lipid-rich plasma to the PN solution, and EFAD resolved. The infant continued to develop and grow, and her progress was documented in journal articles for >400 days. She received PN for 22 months in the hospital and needed numerous venous catheterizations, including catheterizations of the jugular (n = 6), subclavian (n = 8), saphenous (n = 1), and cephalic veins (n = 1).<sup>11</sup> Due to the lack of technology to discharge her and administer PN at home, lack of vascular access, and the ethical issues of her

continuing to live in the hospital, PN was ultimately stopped and the patient died. The lifesaving potential of PN and the technologic advances made by Lawson and Dudrick to treat these early patients using hospital-delivered central PN cannot be understated. The inability to discharge a patient and administer PN at home remained a significant barrier to long-term PN.

## The Concept of the Artificial Gut

Although hundreds of patients were exclusively fed by PN in the hospital setting between 1965 and 1968 in the United Kingdom and United States, no patients had received HPN. As documented by the University of Pennsylvania group and by Lawson, several technologic, medical, psychologic, and financial barriers needed to be overcome before a patient could be discharged from the hospital to home where they would receive PN. Other investigators built on the groundbreaking work of the University Pennsylvania group and Lawson by devising a system to deliver PN in the home setting.<sup>37-40</sup> In the mid-1960s, at the same time that Lawson and Dudrick were working on central PN for hospitalized patients, Belding H. Scribner (1921–2003), who spent the majority of his career at the University of Washington School of Medicine in Seattle, Washington, was one of the first nephrologists to describe and study home hemodialysis (HD).<sup>41-43</sup> In addition, Scribner started one of the first outpatient HD centers and helped design an arteriovenous (AV) shunt made from Teflon<sup>©</sup> (DuPont, Wilmington, Delaware) and silicone that enabled successful long-term treatment of end-stage kidney disease.44,45

This experience with home HD and the artificial kidney gave Scribner unique insight into the barriers to HPN delivery. In addition to his major contributions to the field of nephrology, Scribner established one of the first HPN programs and described an artificial gut system for HPN that was similar to his home HD program.<sup>37,38</sup> One of his early observations was that a successful HPN system must be simple enough that a patient could self-deliver PN independent of trained healthcare providers. Scribner initially proposed using an AV shunt with a permanent segment of silicone and rubber tubing (ie, side arm) that would be inserted into the external loop of the shunt, thus allowing continuous infusion. Like Rhoads before him, Scribner had reservations about using long-term central venous catheters because of the high rate of thrombosis, especially in patients with cancer.<sup>46</sup> He demonstrated that a PN solution consisting of 50 g protein hydrolysate and 50% dextrose solution could be safely infused long term to patients with an AV shunt.<sup>37</sup>

This early artificial gut used a portable system to infuse PN either at night or during the day. As with home HD, Scribner recognized that freedom from constantly being connected to a machine would likely increase quality of life for future patients. His nocturnal artificial gut system allowed PN to be infused for 8-10 hours while the patient was sleeping (Figure 2). As with home HD, patients were taught the skills needed to safely self-administer HPN without the need of trained medical staff. When not in use during the day, the silicone and rubber side arm of the AV shunt was filled with a heparin sodium solution (1000 U/mL) and capped. Scribner developed a portable HPN infusion-vest system that consisted of a small infusion pump, battery pack, and 500-mL plastic infusion bag attached to the AV shunt (Figure 2). Valuable technical and safety lessons were learned when treating the first 3 patients who used this system (who were likely the earliest, if not the first, HPN patients), including the importance of 1) the physician setting a maximum infusion rate that could not be adjusted by the patient, 2) using completely sterile PN infusion components, 3) ensuring the absence of air emboli in the delivery tubing, 4) ensuring easy patient operation, and 5) knowing that the sudden cessation of PN infusion may lead to hypoglycemia.<sup>37</sup>

# First Case Reports of HPN

In addition to Scribner's first patients to receive HPN, early attempts at discharging patients home occurred in the late 1960s and early 1970s.<sup>37,47</sup> The University of Pennsylvania group briefly described their first patient who was discharged and received HPN in 1968.<sup>34,47</sup> The patient was a 36-year-old woman with metastatic ovarian cancer who had PN initiated in the hospital, but she wanted to be discharged to spend time with her family for the remainder of her life.<sup>34</sup> She was discharged and, with the assistance of physicians in her hometown and the pharmacist from the University of Pennsylvania, was able to manage HPN for the last 6 months of her life at home.<sup>34</sup>

The first published case report of a patient who received most of her daily nutrition from HPN was reported by Maurice Shils (1914-2015), who spent the majority of his career practicing nutrition at Memorial Sloan Kettering Cancer Center and Cornell University Medical School, New York, New York.<sup>7,8</sup> He later established a registry of patients receiving HPN in the United States and Canada.8 Scribner (as acknowledged by Shils) gave Shils an advance copy of his artificial gut manuscript and advice about using the Thomas AV shunt (which is inserted into the femoral artery and left saphenous vein) for PN infusion. In addition, Scribner provided the essential silicone and rubber side arm, which was inserted into the external loop of the AV shunt to allow continuous PN infusion; without this side arm, administering HPN to this patient would not have been possible.<sup>40</sup> A 37-year-old woman with recurrent desmoid tumors involving the small bowel mesentery received this new artificial gut.<sup>40</sup> Due to the involvement of the superior mesenteric artery, on July 9, 1969, the patient had the



**Figure 2.** Two early home nutrition patients. A, One of the first patients to self-administer home parenteral nutrition at night (10–12 hours) photographed in her home using the novel artificial gut system, devised by Belding Scribner and the University of Washington group. B, Ambulatory system with an infusion pump was designed for patients who required >10–12 hours of infusion. (Adapted from Scribner et al<sup>37</sup> and reproduced with permission.)

majority of her small bowel and a portion of her colon resected (leaving the duodenum to the distal ascending colon). During the next few months, enteral feeding with a gastrostomy tube and PN with venous indwelling catheters were attempted in the hospital (it is unclear whether central venous catheters were used).<sup>40</sup> Her stool output was large while receiving EN despite using formulas with mediumchain triglycerides and protein hydrolysates. PN, which was likely delivered peripherally, caused phlebitis and ongoing fever.

The decision was made to provide the patient with PN by using Scribner's recently proposed artificial gut system. The Thomas AV shunt was placed on October 28, 1969, and feeding began 2 weeks later.<sup>40</sup> The Thomas AV shunt was accessed using the side arm provided by Scribner, which was attached to a microfilter and VenoValve to prevent backflow (Figure 3). Extra tubing (24 feet) allowed patient mobility and was attached to one of the first available infusion pumps (IVAC 400) made by IVAC Corporation (San Diego, California). PN was contained in a plastic bag connected to the infusion pump, and a pinch photocell stopped delivery (within 10 seconds) to the drip chamber when the bag was empty (Figure 3).40 The PN solution consisted of fibrin protein hydrolysates, 50% dextrose for calories (without ILE), 0.9% sodium chloride, magnesium sulfate, potassium chloride, sodium potassium phosphate, trace elements, and multivitamins (4 commercial sources were combined). HPN was initially infused at night for 10.5-11.5 hours but was subsequently reduced to 9 hours. Urinary glucose excretion levels were <0.05%. The side arm was filled with heparin sodium solution (1000 U/mL) and capped when not being infused.<sup>40</sup> Although it is unclear how long the patient was



**Figure 3.** The home parenteral nutrition system developed by the University of Washington's artificial gut program and modified by Dr. Shils. A patient with short bowel syndrome and mesenteric ischemia due to recurrent desmoid tumors was discharged by Shils and received home parenteral nutrition using this system. The patient received nocturnal home parenteral nutrition for a few months but eventually died after a failed transplant. A-V, arteriovenous; IVAC, 400, IVAC Corporation, San Diego, California. (Adapted from Shils et al<sup>40</sup> and reproduced with permission.)

**Figure 4.** Artificial gut system developed by Jeejeebhoy at the University of Toronto. A, The system used compressed air, instead of an infusion pump, to infuse HPN. (Adapted from Jeejeebhoy et  $al^{51}$  and used with permission.) B, A central venous catheter was inserted into the facial vein and passed to the superior vena cava. (Adapted from Langer et  $al^{50}$  and used with permission.)

at home, her condition improved and she gained weight (5 kg) while receiving HPN.<sup>40</sup> She was able to selfadminister HPN with few complications. On April 27, 1970, the shunt had to be removed because of thrombosis and infection, and 4 days later another shunt was inserted to continue HPN administration. In the end, the patient underwent an intestinal transplant (approximately 2 years before the discovery of cyclosporine) and died of postoperative complications.<sup>48</sup>

At the same time Scribner and Shils reported their HPN cases and experiences, Khursheed Jeejeebhoy and his team were developing a novel artificial gut system for HPN. Jeejeebhoy is a gastroenterologist who has spent the majority of his career at the University of Toronto in Toronto, Canada.49 This early system differed from the one used by Scribner and Shils in that it used compressed air connected to a pressure-regulating gauge to infuse HPN (Figure 4). This compressed air tank was connected to 3 1-liter plastic bags containing the PN solution, which then passed through 2 microfilters before infusion (Figure 4). The PN solution had all 3 macronutrients (Intralipid<sup>®</sup> was available in Canada) combined with electrolytes, vitamins, and trace elements.<sup>50,51</sup> Unlike Scribner and Shils, Jeejeebhoy used a silicone and rubber tube that was tunneled and inserted into the common facial vein and then passed into the internal jugular vein and advanced to the superior vena cava (Figure 4).<sup>50,51</sup> Another advantage of the system designed by Jeejeebhoy was that an infusion vest was not necessary. This allowed daytime mobility and is still common practice in modern HPN delivery.<sup>51</sup>

The University of Toronto group's first patient to use this HPN system was a 36-year-old woman with right-sided abdominal pain, which subsequently manifested as ischemic bowel due to mesenteric venous thrombosis.<sup>50,51</sup> Her duodenum anastomosed to the descending colon, which later dehisced, and peritonitis occurred. In addition, the patient had intestinal fistulae that resulted in a prolonged hospital course.<sup>50,51</sup> She underwent closure of the duodenum and remaining colon, and a gastrostomy tube was placed to drain the contents of the stomach and duodenum. After a subclavian artery-placed central venous catheter failed, a tunneled catheter was placed into the facial vein, jugular vein, and vena cava on November 25, 1970 (Figure 4). After a prolonged hospital course, the patient was trained to use Jeejeebhoy's artificial gut system and self-deliver nutritionally complete central PN for 12 hours at night.<sup>50,51</sup> On July 11, 1971, the patient was discharged home to receive HPN that in many ways resembles the long-term HPN used today. These similarities include nutritionally complete PN (including ILE) that was nocturnally delivered for 12 hours using a tunneled central venous catheter.

This first patient of the University of Toronto's program underwent detailed metabolic tests for the first few years after discharge. Her amino acids levels were low, especially those of the essential amino acids.<sup>51</sup> This improved after changing the amino acid source. In addition, she had the signs and symptoms of EFAD when ILE was administered weekly, but EFAD resolved when ILE was administered daily. The catheter functioned well with no infections for the first 38 months but had to be replaced because of catheter tip thrombosis.<sup>52</sup> The patient was a mother of 3 children and was active at home and socially. She received HPN for >20 years (7403 days), but she died of an infection that originated from her gastrostomy tube's stoma.<sup>9</sup> Shils' and Jeejeebhoy's first patients had similar initial clinical courses with massive intestinal ischemia leading



to dependence on PN, but these patients had very different long-term results. One patient died after an attempted transplant and the other patient lived for 2 decades while receiving HPN, thereby setting up the debate that persists to this day about the role of intestinal transplant in these cases.<sup>53</sup>

## Case Series From Early HPN Centers

Unsurprisingly, the clinicians who discharged the first patients from the hospital to receive HPN also established the first multidisciplinary HPN centers. Building on his first cases of HPN, Scribner and the University of Washington group recognized in 1970, even before Shils' first case report was published, that using an AV shunt for long-term HPN delivery was problematic.<sup>38</sup> These problems included difficult placement into the malnourished vasculature, the high rate of clotting when shunts were used daily to infuse highly osmotic HPN solutions (vs using the shunt for 3 d/wk in HD), and the need to administer PN before the AV shunt matured weeks after placement.<sup>38,54</sup> Like Lawson and Dudrick, the University of Washington group used central venous catheters that were advanced to the superior vena cava. They designed a tunneled central venous catheter for the long-term administration of HPN made from Teflon<sup>©</sup> and silicone that was tunneled to and inserted into the subclavian vein and advanced to the superior vena cava.<sup>54</sup> The catheter's exit site was low in the chest wall and provided easier site maintenance by the patient.<sup>54</sup> They used a Dacron cuff that anchored the catheter in place by fibroblastic growth and created a barrier against infection. Additionally, in the second 1970 article, the University of Washington group recognized the importance of placing the catheter tip at the junction of the superior vena cava and right atrium.<sup>38</sup>

This early tunneled catheter was developed by Scribner's laboratory at the University of Washington and ultimately improved by Robert Atkins and John W. Broviac, who also worked in the Scribner laboratory. Broviac was an internal medicine resident and nephrology fellow, and he was responsible for placing new catheters in patients.<sup>5,54</sup> For many years, these catheters were referred to as the Broviac/Scribner catheter but are now more commonly referred to as simply Broviac catheters. Another member of the Scribner laboratory, James R. Sisley, a biomedical engineer, went on to form Evermed which manufactured these catheters.<sup>5</sup> This company was eventually purchased by BARD (New Providence, New Jersey), which manufactures the Broviac catheter today. Another Scribner laboratory member, Robert O. Hickman, a pediatric nephrology fellow (who later became the Chair of Pediatric Nephrology at Seattle Children's Hospital, Seattle, Washington), was asked to provide a catheter that could be used by bone marrowtransplant nurses. Hickman and Sisley designed a larger bore catheter (9.6 Fr vs the 6.5 Fr Broviac catheter) that would later be called a Hickman catheter and, like the original Broviac catheter, be manufactured by BARD.<sup>5,55</sup> Another key observation made by the University of Washington group was that these catheters could be repaired.<sup>56</sup> As with patients receiving HD, maintaining vascular access in HPN-dependent patients often meant life or death.

In addition to designing the central venous catheter in the early 1970s, Scribner and the University of Washington group published the first large case series of patients who received HPN. The first 2 published case series reported their first 5 years of experience administering HPN and training 43 patients (mean [range] age, 40.7 [4-72] years; 20 female, 23 male).<sup>56,57</sup> The mean duration of HPN was 12.4 months (range, 1–52 months).<sup>56</sup> A total of 78 central venous catheters were placed in these 43 patients, and 52 catheters were removed for various reasons, including catheter tip thrombosis (n = 15; 28.8%), leakage or malposition (n = 13; 25%), death of the patient (n = 9; 17.3%), completion of HPN (n = 5; 9.6%), and infection (n = 10; 19.2%).<sup>56</sup> Four cases of exit-site infection occurred, and all cultures were positive for Staphylococcus epidermidis; 2 of these catheters had to be removed because the infection could not be cleared. Eight cases of catheter-related sepsis, defined as bacteremia without a detectable focus, were identified, which corresponds to 1 case of sepsis per 5.5 patient-years of HPN. All catheters were removed, and the patients were treated with antibiotics when the cultures were positive for S aureus (n = 7) or antifungals when positive for Candida albicans (n = 1).<sup>56</sup> On the basis of the findings of this first report published in 1976, exit-site and catheter-related bloodstream infection (CRBSI) became standard long-term clinical outcomes evaluated by HPN programs. 58-60

In December 1975, Shils and the Memorial Sloan Kettering Cancer Center group reported their first 5 years of experience using HPN.<sup>39</sup> Although they did not provide detailed data on clinical outcomes, such as infection or catheter removal, numerous interesting observations were reported. Of the 11 patients trained to receive HPN in the first 5 years, 3 of 4 deaths (gastric hemorrhage, failed intestinal transplant, and recurrent cancer) were not directly related to HPN. After initially recommending AV shunts for long-term PN, they began using central venous catheters as the first-line option from 1972–1975.<sup>39,61</sup> Initially, a 12-inch polyvinyl chloride catheter was inserted and maintained for 1-2 months, which was replaced with an 8-inch Silastic catheter over a guidewire. HPN was typically administered for 8-9 hours at night, and the rate was lowered during the final hour of infusion to prevent hypoglycemia.<sup>39</sup> Shils also observed modest increases in alkaline phosphatase and transaminases levels with varying amounts of steatosis in the livers of patients who received excessive glucose from HPN.<sup>39</sup> One of the most valuable aspects of this case series was the inclusion of suitability criteria for HPN administration, which included a relatively stable clinical

state, expectation that the patient would be at home for at least several months, a suitable home environment with supportive family members, availability of a trained home infusion nurse for occasional visits, and cooperation with local physicians.<sup>39</sup>

Building on early experience using their artificial gut system, the University of Toronto group trained 73 patients to use HPN and observed them from 1970-1982.52,62,63 Like other early HPN centers, the number of patients with Crohn's disease who were trained to receive HPN increased to 34% by the end of the 1970s. The average catheter was used for 28 months and the CRBSI rates were low, especially in the 20 patients who required only 1 catheter (1 catheter was used to administer HPN for 428 months).<sup>63</sup> An interesting contribution by the University of Toronto program was a cost-utility analysis of HPN compared with periodic hospitalizations and intermittent artificial nutrition support. They retrospectively interviewed 37 of their first 73 patients (50.7%) and concluded that HPN resulted in a net savings of \$19,232 Canadian dollars (\$45,514 in 2017, adjusted for inflation) and an overall increase in survival (adjusted for quality of life) that was 4 times greater in patients who received HPN than in those who received alternative treatment.<sup>62</sup> Patients who were chronically malnourished before receiving HPN had significant improvements in quality of life during and after receiving HPN.<sup>62</sup> Under the leadership of Jeejeebhoy, the University of Toronto program published numerous articles on HPN and was involved in the creation of the Canadian Home Total Parenteral Nutrition Patient Registry, which actively tracks demographic and clinical outcomes useful to shaping HPN practice.64,65

In 1972, Dudrick was recruited to be the first Chair of the Department of Surgery at the University of Texas Medical School in Houston, Texas. In 1974, an HPN program was established at the school's university hospital, and in 1979 they reported their first 5 years of experience treating 25 patients.<sup>6,47</sup> Patient age ranged from 23 months-66 years. A total of 12 patients received HPN for less than a few months, but 14 patients received long-term HPN to treat diagnoses such as short bowel syndrome (SBS).47 Patients who received short-term HPN had subclavian central venous catheters placed, but the tunneled Broviac catheter was used to administer long-term HPN. In total, 19 Broviac catheters were used for a mean duration of 279 days, and the longest catheter was in place for almost 3 years (990 days). Five catheters were removed because of mechanical problems or thrombosis, but no cases of CRBSI were reported.47 The 1979 article also has an interesting description of the ambulatory infusion vest used by children and adults at home.

Five years later, the University of Texas Medical School (Houston, Texas) group reported details of their cohort of 133 HPN patients (age range, 6 months-78 years; treatment period, 1974–1983). The 2 most common indications for HPN were SBS (n = 32) and Crohn's disease (n = 30).<sup>6</sup> The University of Texas Medical School group placed the Broviac catheter in patients who received long-term HPN from 1974-1978 but later changed to the larger Hickman catheter.<sup>6</sup> One of these central venous catheters lasted 8.5 years, which demonstrates its durability. They reported 33 cases of CRBSI in patients with tunneled catheters (1 infection per 946 catheter-days). Of these 33 cases of CRBSI, 24 occurred in multiple episodes in only 4 patients who were receiving HPN. Similar to the earlier study of HPN patients, they reported improvements in the patient infusion vest (Figure 5).<sup>6</sup> The article also has an interesting case report of a 13-year-old boy who had received PN since he was 2 years old because of complications due to vasoactive intestinal polypeptide syndrome.<sup>6</sup> The patient gained 79 pounds while



**Figure 5.** Portable infusion systems designed by the University of Texas Medical School (Houston, Texas) group to administer home parenteral nutrition. The vest had a portable infusion pump and multiple parenteral nutrition bags. (Adapted from Dudrick et al<sup>6</sup> and used with permission.)



**Figure 6.** A, Scribner's Silastic/Teflon<sup>®</sup> original tunneled catheter with a Dacron cuff from 1970. Scribner and his fellows, including Drs. Broviac, Hickman, and Ament, would make further improvements to this original catheter. (Adapted from Atkins et al<sup>38</sup> and reproduced with permission.) **B**, Dr. Ament designed the smaller-diameter infant catheter (c), and Dr. Hickman the larger-diameter catheter that bears his name today (a). These catheters are compared with the improved Broviac/Scribner (b) catheter. (Adapted from Pollack et al<sup>72</sup> and reproduced with permission.)

receiving HPN and had normal social and developmental growth for a 13-year-old.<sup>6</sup> This patient was first reported in a 1979 article when he was 6 years old.<sup>47</sup>

Many early centers trained adults and children to receive HPN, but most patients were adults. Marvin Ament has spent the majority of his career at the University of California, Los Angeles (UCLA) and founded an HPN program in 1973 for both adults and children. Ament was trained as a pediatrician at the University of Minnesota, Minneapolis, Minnesota, completed a gastroenterology fellowship at the University of Washington, Seattle, Washington (1968–1973), and is credited with developing pediatric gastroenterology as a subspecialty.<sup>66</sup> During his time at the University of Washington, he was mentored by Scribner and Broviac and developed an interest in the pediatric HPN population while taking care of a 2-year-old with intractable diarrhea and an 8-year-old with systemic mast cell disease.<sup>66</sup>

In 1977, the UCLA group led by Ament reported their first case series of 6 children (age range, 2–17 years) who were discharged and received HPN for 1–11 months.<sup>67</sup> The 6 children had several diagnoses including chronic idiopathic intestinal pseudo-obstruction syndrome (n = 2), Crohn's disease (n = 2), SBS and fistula (n = 1), and unclassified sprue (n = 1).<sup>67</sup> The patients without chronic idiopathic intestinal pseudo-obstruction syndrome were successfully weaned off HPN. Two patients with CRBSI were treated with antibiotics but without removal of the Broviac catheters. One of the major findings of the study was the ability to discharge patients safely from the hospital with positive weight gain and decreased cost. In addition, the UCLA group described a laboratory monitoring schedule that is similar to those currently used in HPN programs.

The UCLA group quickly followed this initial study with a case series (1975–1978) that reported the clinical outcomes and complications of 34 pediatric patients (age range, 1.5 months-20.5 years) and the first neonate to receive HPN.<sup>68</sup> The duration of HPN therapy ranged from 23-786 days, and 2 patients received therapy for >500 days. Like other adult cohorts at the time, the number of patients with Crohn's disease (n = 17) was greater than earlier case series.<sup>69-71</sup> The new infant model of the Broviac catheter (which Ament developed while working with Scribner and Broviac at the University of Washington) had a smaller diameter compared to the original Scribner/Broviac (Figure 6a) and was available on a limited basis at the time of the study (Figure 6b).<sup>66,72</sup> Synthetic amino acids and Intralipid<sup>©</sup> were administered but, like many HPN components used today, macronutrients were often in short supply.<sup>68</sup> Overall, most patients demonstrated developmental growth and gained weight, including a 13-year-old patient with cystic fibrosis. In the year before HPN initiation, this patient gained only 1 kg while hospitalized 5 times for a total of 112 days. Her condition improved while receiving HPN, and she gained weight and did not require subsequent hospitalizations. All patients, except the 6 youngest patients (age range, 2 months-2.5 years), were taught to self-administer HPN, and few complications occurred. A total of 48 catheters were used in these 34 patients, and 22 catheters were removed because of complications including dislodgement, thrombosis, exit-site infection, and sepsis. The CRBSI rate was only 1 infection per 5.5 catheteryears, and C parapsilosis (n = 2) and S aureus (n = 2)were positively identified. The UCLA group continued to publish cohort and case series after these early experiences administering HPN to a pediatric population.<sup>59,73-76</sup>

HPN used by the UCLA group was compounded by the hospital pharmacy, and it was not standard in most early centers.<sup>67</sup> A surprising aspect of early HPN is that patients were taught to compound their own PN from stock solutions at home instead of procuring PN from the hospital or infusion pharmacy (as routinely done now)



**Figure 7.** Most early patients compounded their home parenteral nutrition from base stock solutions at home. A, Home-compounding station used by patients treated at Cleveland Clinic. B, Patient is shown mixing home parenteral solution from base solutions. (Pictures provided from the personal collection of Dr. Ezra Steiger.)

(Figure 7).<sup>37,39,57,61</sup> Accordingly, many early centers devised HPN formulas that were as basic and uncomplicated as possible but still delivered the essential nutrition. The UCLA group recognized that using fewer individual stock solutions and additives not only reduced the potential for contamination but also decreased costs.<sup>39,57</sup> When the HPN registry was queried in 1981 for HPN-related hospital admissions, equal numbers of patients compounded their PN formula at home (268 patients; 100 readmissions) or received compounded PN from the pharmacy (275 patients; 109 readmissions). This home-compounding system has since been replaced by premixed formulas or individualized compounded PN prepared by hospital pharmacies or home infusion companies.

Although most early discoveries related to HPN were made in North America, Europe also provided early contributions.77,78 Furthermore, most HPN administered in present-day Europe (like Canada) originates from large academic centers, and many centers have active research programs; in contrast, in the United States, most HPN is prescribed by providers who care for only a few patients.<sup>79</sup> In 1973, Stig Jarnum of Rigshospitalet in Copenhagen, Denmark, reported an early European case of HPN administered to a patient with SBS due to mesenteric infarction.<sup>77</sup> Like Shils, Scribner, and Jeejeebhoy, Jarnum studied the physiologic aspects of PN as well as disease states, such as protein-losing enteropathy, in the 1960s.<sup>80</sup> In 1978, Jarnum's group reported their first case series of 19 patients who received long-term PN, with most patients having SBS (n = 13).<sup>81</sup> Thirteen of these patients received HPN, and the patient who received HPN for the longest time (63 months) had SBS and only 25 cm of small bowel remaining.<sup>81</sup> A total of 98 catheters were used, and venous access for HPN was mostly achieved by using direct subclavian (n = 48)or Broviac catheters (n = 14). Nineteen cases of CRBSI occurred in 11 patients, and notably 16 cases (84.2%) occurred in the first 6 months of HPN administration. Jarnum's group published several studies on HPN in the fields of body composition, SBS, metabolic bone disease, and CRBSI.<sup>82-85</sup>

As Scribner and Jeejeebhoy were working on their systems, the PN research group at the University of Montpellier, Montpellier, France, which was led by Claude Solassol and Henri Joyeux, developed an artificial gut system in 1971.78,86,87 This system differed from those used in North America in that central venous access was surgically implanted in the deep venous trunk of the superior or inferior vena cava and tunneled to an exit site in the chest or abdominal region (Figure 8). The catheter consisted of Teflon<sup>©</sup> and silicone (Scurasil), and the delivery system consisted of portable, reusable U-shaped (1 L) or rectangleshaped (2 L) silicone bags (which were worn by the patient) attached to an infusion pump (Figure 9). From June 1971 to December 1972, 75 patients were admitted and used the portable PN system. It appears that 74 patients received nutrition at hospital facilities, but 1 patient reportedly received 1.5 months of HPN.78 Other European countries followed the lead of the Copenhagen and University of Montpellier groups by sending patients home with HPN, including England in 1978.77,88

The next generation of clinicians and centers to specialize in HPN followed closely on the footsteps of Dudrick, Scribner, Shils, Jeejeebhoy, Ament, Jarnum, Solassol, and Joyeux. These new centers tended to be at large academic medical centers. These centers began training, discharging, and reporting their first patients who received HPN in the 1970s and included UCLA (1973), Albany Medical College, Albany, New York (1973), Johns Hopkins, Baltimore, Maryland (1974), University of Texas Medical School, Houston, Texas (1974), Mayo Clinic, Rochester, Minnesota (1975), Cleveland Clinic, Cleveland, Ohio (1976), and Harvard University, Cambridge,



**Figure 8.** Artificial gut system for venous access. This system was designed by Solassol and Joyeux at the University of Montpellier in the early 1970s. The Teflon<sup>®</sup> and silicone (Scurasil) catheter was tunneled and eventually attached to the vena cava trunk. (Adapted from Solassol et al<sup>87</sup> and reproduced with permission.)



**Figure 9.** Two portable infusion systems used to deliver different amounts of parenteral nutrition. These systems were designed by the group at the University of Montpellier. (Adapted from Solassol et al<sup>78</sup> and reproduced with permission.)

Massachusetts (1977).<sup>47,59,69,89-93</sup> Many of the founders of these new centers were influenced by the early pioneers of HPN and include, but are not limited to, Ezra Steiger (Cleveland Clinic) who was mentored by Dudrick and Rhoads, Richard Fleming (Mayo Clinic) who was mentored by Scribner, and Lyn Howard (Albany Medical College) who was mentored by Jeejeebhoy. These individuals are internationally recognized leaders who advanced the field of HPN in numerous ways and cared for thousands of patients while mentoring the next generation of HPN clinicians. For example, in addition to training her first patient to use HPN at Albany Medical Center in 1973, Howard formed the patient advocacy group, The Oley Foundation, with her patient, Clarence "Oley" Oldenburg, in 1983. This nonprofit advocacy group for patients receiving HPN or home EN and their caregivers has grown to over 12,000 members in the past 30 years.<sup>94</sup> At some centers HPN research was initiated by internationally recognized nutrition clinicians and scientists, for example, Bruce Bistrian and George Blackburn at Harvard University who reported a recurrent case of shunt nephritis in a patient receiving HPN and later described their experiences administering HPN.93,95 In addition to his work at the University of Toronto, Jeejeebhoy mentored several Canadian HPN providers, which led to the creation of new programs in Calgary, Edmonton, Quebec, Vancouver, and Hamilton in the late 1970s as well 6 other programs in the 1980s and 1990s.9 Finally, we acknowledge that there were early cases of HPN that were not reported in the literature and thus not included in the current review, but were as important in advancing the field. One such case is a patient of Richard C. Bozian who was the Director of Nutrition at the University of Cincinnati in the 1960's and 1970's. The patient has now been on PN since 1968 the majority of this time has been at home. Her story is a true testament to advances that have been made with HPN over the past 50 years.96

# Conclusions

In the 1960s, several technologic advances in nutrition by Lawson, Dudrick, and the University of Pennsylvania led to the delivery of central PN to hospitalized patients. One of the key advances mastered by the University of Pennsylvania group was to effectively use a central venous catheter to administer long-term PN, which was later improved by Scribner, Broviac and Hickman. The first HPN delivery system was designed by Scribner, who considered many of the lessons he learned when administering home HD in the 1960s. The first full case of HPN administered using the Scribner system was described by Shils. Jeejeebhoy first delivered total PN (including ILE) to a patient at home using a central venous catheter. The subsequent development of the Broviac and Hickman catheters by Scribner's laboratory helped make long-term HPN more practical and safe. In 1981, it was estimated that since 1969 approximately 2,000 patients had been discharged and received HPN.<sup>48</sup> More than 30 years later, approximately 25,000 patients are receiving HPN in the United States.<sup>79</sup> HPN continues to be an important lifesaving therapy for patients with intestinal failure, and this will continue into the foreseeable future.

### Statement of Authorship

R. Hurt and E. Steiger contributed to conception/design of the manuscript; R. Hurt and E. Steiger contributed to

acquisition, analysis, or interpretation of the data; R. Hurt drafted the manuscript; R. Hurt and E. Steiger critically revised the manuscript; and R. Hurt and E. Steiger agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

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