Bradley A. Warady
Franz Schaefer
Steven R. Alexander
Editors

Pediatric Dialysis

Second Edition

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ISBN 978-1-4614-0720-1 e-ISBN 978-1-4614-0721-8
DOI 10.1007/978-1-4614-0721-8
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2011941584

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

We thank our families for the support they provide us.
We thank our colleagues for the insight they share with us.
We thank our patients for the trust they have in us.

The editors

Preface

The provision of optimal dialysis therapy to children requires a thorough understanding of the multidisciplinary manner in which the pediatric patient is affected by renal insufficiency. It was based on this philosophy that the inaugural edition of *Pediatric Dialysis* was published in 2004. Since that time, advances have taken place in dialysis-related care with the creation of a wealth of new knowledge, outpacing much of the content that occupied a prominent place in the original text. In response, we believe that even in this age of the electronic transmission of information, the availability of a contemporary, comprehensive, and authoritative source of information such as *Pediatric Dialysis* cannot only help facilitate the provision of superb patient care by seasoned clinicians, but it also can help meet the demand of our young trainees for the information that they require as a foundation for the future advances that they will surely initiate.

We are, in turn, fortunate to have been able to enlist the collaboration of over 70 colleagues from North America, Europe, and Asia to thoroughly update this text, which remains the most comprehensive source of state-of-the-art information on the dialysis of infants, children, and adolescents currently available. To them, we are eternally grateful for their commitment to this project. The inclusion of a host of new authors from "both sides of the pond" with their unique and fresh perspectives, combined with many authors from the first edition and all with recognized expertise on the topic chosen for their review, has resulted in a text that is clinically relevant and that will someday hopefully duplicate the appearance of one of the initial editions, owned by a dialysis nurse and characterized as being "full of worn pages as a result of almost daily use." The addition of several new chapters, including *Conservation of Residual Renal Function in Children Reaching End-Stage Renal Disease, Intensified Hemodialysis in Children,* and *Transitioning the Adolescent Dialysis Patient to Adult Care*, should contribute to that end.

As clinicians ourselves who have spent many hours over the past three decades on hospital wards, in the intensive care unit, and in the dialysis unit applying what we have learned from the documented experience of others, we know that this text is undoubtedly the product of the hard work and ingenuity exhibited by the global pediatric nephrology community and, as such,

cannot help but to serve as a valuable tool with a singular emphasis on successfully caring for our challenging patient population. If that goal can be achieved through the publication of the second edition of *Pediatric Dialysis* and even one child benefits from our combined efforts, it will all have been worthwhile.

Kansas City, MO, USA — Bradley A. Warady
Heidelberg, Germany — Franz Schaefer
Stanford, CA, USA — Steven R. Alexander

Acknowledgment

The editors would like to acknowledge the superb administrative support of Cynthia Kiel, whose contributions to this text were exceptional. Similarly, the editors would like to thank Kevin Wright from Springer, whose project management skills and unwavering support and patience contributed greatly to the successful completion of this book.

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Part I

Essential Primers

Notes on the History of Dialysis Therapy in Children

1

Steven R. Alexander and Pierre Cochat

Key Words
Dialysis therapy • Children • History

Introduction

In his authoritative and entertaining monograph on the history of dialysis, Stewart Cameron calls attention to the important role played by the development of dialysis technology in the founding of nephrology as a medical specialty [1]. Prior to the 1950s and 1960s, the study and management of disorders of the kidney was the province of general physicians. Along with the introduction of the renal biopsy and its interpretation [2], the introduction of dialysis was "…an important motor which accelerated the emergence of nephrology as a specialty. Suddenly there was a need for specialist knowledge to apply the complex data from the increasing number of critically ill patients who survived their primary disease only to go into acute renal failure…" [1]. When long-term dialysis became possible in the 1960s, hundreds of units sprang up in North America and Europe spawning a new breed of physicians who "…trained frantically to run them…" These physicians adopted a culture that was more "active" than the traditional contemplative approach of medicine specialties, and by the 1970s, nephrology had become "…an autonomous specialty with an uneasy relationship to general internal medicine. There is no doubt that those physicians who chose to make dialysis their principal interest were to some extent a breed apart, with whom physicians in general found it difficult to relate…" [1].

In contrast, the discipline of pediatric nephrology emerged in response to different drivers. Based on the classic work of pediatric physiologists on fluid and electrolyte metabolism, regulation of intracellular and extracellular fluid, acid–base homeostasis, and parenteral fluid therapy, the first generation of pediatric nephrologists who arose in the 1950s and 1960s were rarely exposed to the care of children with acute or chronic renal failure [3, 4]. It is emblematic that the early starting point of pediatric nephrology as a specialty is traced by some to the organization of the International Study of Kidney Disease in Children (ISKDC) in the 1960s, which was a study of childhood nephrotic syndrome [1]. Early pediatric nephrologists rarely

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B.A. Warady et al. (eds.), *Pediatric Dialysis*, DOI 10.1007/978-1-4614-0721-8_1,

cared for children suffering what is now called acute kidney injury (AKI), a role more often played by pediatric surgeons. Those who cared for children with what is now known as chronic kidney disease (CKD) focused on dietary restrictions and diuretic, antibiotic, and electrolyte therapies, attempting to ease the progression to end-stage renal disease (ESRD). When ESRD was reached, older children and adolescents often had to look to adult ESRD programs for access to chronic dialysis and transplantation; infants and younger children were frequently offered only palliative care [5].

During the past five decades, the landscape has changed dramatically. Acute and chronic dialysis is now routinely available for children throughout the world, and the study of dialysis therapy and the disordered physiology of the pediatric patient with AKI or ESRD has come to occupy a prominent if not dominant place in pediatric nephrology research [4]. Pediatric nephrology training programs worldwide are expected to teach trainees how to dialyze children of all ages, and modern pediatric nephrology training program graduates come equipped with technical skills unimagined by the founders of the specialty. With increasing acceptance of universal access to dialysis therapy for children has come a concomitant growth in the demand for pediatric nephrologists, leading to a steady increase in the size of pediatric nephrology programs. Unlike adult dialysis programs, many of which long ago separated from their academic roots, pediatric dialysis programs remain firmly grounded in university medical centers and medical school-affiliated children's hospitals, a fortunate association that has promoted, sustained, and demanded a culture of scientific inquiry in what easily could have become a purely technical and derivative discipline.

In this chapter, we have attempted to briefly review selected high points in the development of dialysis therapy for children. We have left to the chapters that follow a detailed description of these innovations. Our goal is to place them in historical context, acknowledging the debt owed to those pioneering pediatric nephrologists, nurses, engineers, dieticians, and social workers and their young patients whose efforts have helped make a complex and life-sustaining therapy a part of routine medical management for children throughout the world.

Dialysis: The Founding Fathers

The term *dialysis* has both Latin and Greek roots and refers to a separation or dissolution: (from *dialyein* – to separate; *dia* – apart; *lyein* – to loose) [6]. The modern understanding of the term is the result of the work of a Scottish physical chemist, Thomas Graham (1805–1869) who redefined *dialysis* to reflect his newfound understanding of the ability of a semipermeable membrane (Graham's own concept) to separate solutions containing a crystalloid from a colloid [7]. Using sheets of vegetable parchment impregnated with starch as the membrane, Graham observed that some substances (e.g., sugars) crossed the membrane and would crystallize on drying, while larger molecules like gum arabic would remain in the original solution. Based on his own discovery of the laws governing diffusion of gasses, Graham realized that the crystalloid molecules moved by the force of diffusion across the membrane which prevented the movement of larger molecules. For this work, Graham is known as the "father of modern dialysis" [8].

Earlier work by a Frenchman, Rene' Dutrochet (1776–1847) introduced the term *osmosis* to describe the movement of water down concentration gradients of salts across membranes that retard the movement of solutes. Dutrochet's *osmotic pressure* forms the basis of osmotic-induced ultrafiltration and has earned him the sobriquet, "grandfather of dialysis" [9].

Application of these principles led scientists in the late nineteenth century to explore the use of semipermeable membranes in the laboratory to investigate the properties of many substances. Animal membranes were popular, including the peritoneal membrane (of calves), but the concept was limited to separation and purification of substances. Beginning with the animal experiments of John Jacob Abel (1857–1938) and his team in Baltimore, the early twentieth century saw much progress in the ability to perform dialysis in living animals. In 1913, Abel's team built an apparatus using hollow collodion tubes encased in a glass cylinder that foretold the design of modern hollow fiber dialyzers. They called the process

"vividiffusion" and were the first to conceive of dialysis as a means of removing "…substances from the blood whose accumulation is detrimental to life…" [10]. However, clinical application of these techniques would be delayed until mid-century when both hemodialysis (HD) and peritoneal dialysis gained traction as treatments for renal failure in humans.

Peritoneal Dialysis

The roots of the use of peritoneal dialysis (PD) in children can be traced to the use of the peritoneal cavity to treat dehydration in infants. In 1918, two Johns Hopkins pediatricians, Kenneth Blackfan and Kenneth Maxcy, first described the successful fluid resuscitation of dehydrated infants using intraperitoneal injections of saline solution [11]. At that time, dehydrated infants too small or dehydrated to permit intravenous access, were treated by injecting fluids into the subcutaneous tissues ("clysis"), a method Blackfan and Maxcy noted was often "disappointing," because "…absorption from the subcutaneous tissues is often very slow and after repeated injections is almost nil…" Injection of physiologic sodium chloride solution directly into the peritoneal cavity was "…simple…practicable and accompanied by a minimum of risk to the patient…" [11]. These same characteristic features, simplicity, practicality, and safety, have made peritoneal dialysis particularly well suited for use in children for the past 60 years.

The first reports of the use of the peritoneum to treat children with renal failure appeared in 1948 [12] and 1949 [13] at a time when worldwide reported clinical experience with PD totaled only 100 patients [14]. These first pediatric acute PD reports are of interest in part because they describe in arresting detail many of the problems that have continued to complicate the use of PD in children.

Writing in the premier issue of the journal Pediatrics, a pediatrician, Allan Bloxsum, and his urologist colleague at Houston's St. Joseph's Hospital, Norborne Powell, described the treatment of an oliguric 10-year-old boy who suffered acute glomerulonephritis complicating scarlet fever. Severely hypertensive, fluid overloaded, and becoming increasingly cyanotic, "…it appeared that the boy was going to die…" [12]. Modeling their technique on methods first described in adults in 1946 [15], Bloxsum and Powell had #30 Fr. mushroom catheters surgically placed into the right and left lower quadrants to serve as irrigating tubes. The irrigating solution was mammalian Tyrode's solution, then in common use as a surgical irrigant. It contained sodium, potassium, chloride, magnesium, phosphate, bicarbonate, and dextrose in near-physiologic concentrations, along with penicillin (only 5,000 units/L), sulfadiazine, and heparin. Fluid from 1-L autoclaved flasks was dripped continuously at 10 mL/min into one catheter while being drained by gravity from the other. Peritoneal lavage was continued for 4 days, during which the patient's azotemia worsened, but enough ultrafiltration occurred to improve blood pressure from 186/130 to 148/105. Fortunately, a spontaneous diuresis began almost immediately, and by the third day of treatment, the boy had begun to recover. During lavage, the drainage catheter often became obstructed requiring reversal of flow through the two catheters and eventual application of suction to the drainage line. By the fourth day, the system would no longer drain at all, with fluid leaking freely around both catheters. Peritoneal fluid cultures were positive for three organisms, which may have been contaminants, as the boy did not display signs of clinical peritonitis. Although Bloxsum and Powell entitled their paper: "The treatment of acute temporary dysfunction of the kidneys by peritoneal irrigation: Successful treatment of a 10-year old male child," the contribution of peritoneal irrigation to the child's successful recovery is questionable.

The 1949 experience of Henry Swan and Harry H. Gordon was more promising [13]. These pioneering Denver pediatric surgeons employed continuous peritoneal lavage to treat three acutely anuric children, 9 months, 3 years, and 8 years of age. Rigid surgical suction tips covered by metal sheaths with multiple perforations were implanted into the upper abdomen and pelvis allowing large volumes (~33 L/day) of sterile, physiologic

Tyrode's solution to flow by gravity from 20-L carboys continuously into and out of the abdomen. Ultrafiltration was controlled by adjusting the dextrose concentration between 2% and 4%, while dialysate temperature was regulated by changing the number of illuminated incandescent 60-W lightbulbs in a box placed over the inflow tubing. The two older children regained normal renal function and survived after 9 and 12 days of peritoneal lavage; the infant was sustained for 28 days, but did not regain renal function and succumbed to obscure complications. Peritonitis occurred only once and responded to intraperitoneal antibiotics. Removal of urea and maintenance of fluid balance were successful in all three children, although obviously herculean efforts were required to deliver this therapy [13]. Although impractical and technically difficult to deliver, the continuous peritoneal lavage of Swan and Gordon should be credited as the first conclusive demonstration of the lifesaving potential of PD when used to treat acute renal failure in children.

It was more than a decade before the use of PD in children was again reported. During the 1950s and early 1960s, the development of disposable nylon catheters [16] and commercially prepared dialysis solutions led to the replacement of continuous peritoneal lavage techniques with intermittent forms of PD, allowing the routine use of peritoneal dialysis as a treatment for AKI and some intoxications in adults [17]. These methods were adapted for use in children in the early 1960s by teams in Indianapolis and Memphis [18, 19] who also showed how PD could be effective in the treatment of the boric acid and salicylate intoxications commonly seen in small children at that time [20, 21]. Subsequent reports established PD as the most frequently employed renal replacement therapy (RRT) for AKI in pediatric patients [22–28]. Compared to hemodialysis (HD), PD appeared ideally suited for use in children. It was intrinsically simple, practical, safe, and easily adapted for use in patients of all ages and sizes, from premature newborn infants to fully grown adolescents. In contrast, HD at this early stage of development required large extracorporeal blood circuits and vascular access that was difficult to achieve and maintain in pediatric patients (see later in this chapter).

Although successful as a treatment for AKI, early PD techniques were poorly suited for the child with end-stage renal disease (ESRD). The need to reinsert the dialysis catheter for each treatment made prolonged use of PD in young patients problematic. In the largest published pediatric series from the disposable catheter period, Feldman, Baliah, and Drummond maintained seven children, ages 6–14 years on intermittent peritoneal dialysis (IPD) for 3.5–8 months while awaiting transplantation. Treatments were infrequent, ranging from every 7–12 days to every 4–12 weeks. Although complications were few, at the time of the report, two children had died, two had been transferred to hemodialysis, and three remained on IPD; no child had been successfully transplanted [29].

More than any other advance, it was the development of a permanent peritoneal catheter that made long-term PD an acceptable form of treatment for pediatric patients. First proposed by Palmer, Quinton, and Gray in 1964 [30] and later refined by Tenckhoff and Schechter in 1968 [31], the permanent PD catheter revolutionized chronic PD for adults and children in the same way the Scribner shunt transformed chronic hemodialysis, making long-term renal replacement therapy possible. In Seattle, the new permanent peritoneal catheters were combined with an existing automated dialysate delivery system that had been designed by Boen, Mion, Curtis, and Shilipetar for use in the home [32, 33]. In the early 1970s, this work culminated in Seattle in the establishment of the first pediatric chronic home PD program [34]. The success of the Seattle program throughout the 1970s showed that chronic IPD could be a practical option for some children with ESRD [35].

Additional limited experience with chronic IPD was reported from several other pediatric centers [36–39], but enthusiasm for the technique was limited. Chronic IPD seemed to involve many of the least desirable features of chronic HD, including substantial fluid and dietary restrictions, immobility during treatments that lasted many hours, and the need for complex machinery requiring parental or nursing supervision, without providing the one great advantage of HD: efficiency. Moreover, it became clear from efforts

to maintain adult ESRD patients on chronic IPD that long-term technique survival was not often achieved [40]. Inadequate dialysis and frequent peritonitis were cited as the most common causes of IPD failure in the 1970s, leading to widespread reliance on HD among adult dialysis programs and limited access to chronic RRT for children, especially infants. In fact, pediatric dialysis and transplant programs at the time routinely excluded infants and small children, reasoning with Hurley that "…although it is technically possible to perform hemodialysis and transplantation in these children, the myriad of well-known problems… should contraindicate such therapy …" [41], and with Reinhart: "…we may find the price the child pays for life too great…" [42]. During a period in which advances in ESRD therapy pushed the upper age limits for successful therapy well into the seventh and eighth decades, the youngest ESRD patients remained therapeutic orphans, considered by many to have severely limited chances for survival [43, 44].

The description of what became known as continuous ambulatory peritoneal dialysis (CAPD) by Robert Popovich and Jack Moncrief and associates in 1976 heralded a new era in the treatment of ESRD in children [44]. As originally described, 2 L of dialysate were infused into an adult and retained for 4–5 h, then drained and repeated a total of five times per day while the patient went about regular daily activities [45]. As early experience with CAPD in adults was analyzed by pediatric nephrologists it became clear that this new modality offered theoretical advantages to children when compared to HD and IPD that included near steady-state biochemical control, no disequilibrium syndrome, greatly reduced fluid and dietary restrictions, and freedom from repeated dialysis needle punctures. CAPD allowed children of all ages to receive dialysis at home, which offered a more normal childhood. And for the first time, CAPD made it possible to routinely provide chronic dialysis for infants and small children, which meant that this population could now be safely maintained on CAPD until they reached transplantable age and size.

The first child to receive CAPD was a 3-year-old girl in Toronto in 1978 [46, 47]. Although a number of pediatric dialysis programs in North America [48–51] and Europe [52, 53] quickly followed suit, enthusiasm in many areas was tempered by the availability of dialysis fluid only in 2,000-mL containers. In Canada, small-volume plastic dialysis fluid containers were provided by Baxter, Inc. soon after the first pediatric CAPD patients were trained there in 1978, but it would be another 2 years before small-volume containers became available in the United States and much of the rest of the world [54].

During the 1980s, the popularity of CAPD for children spread worldwide [55]. In Japan, where transplantation was less common due to religious prohibitions on organ donation, Masataka Honda and other pioneers established large CAPD programs that demonstrated the long-term capabilities of the modality in children [56]. Pediatric nephrologists in developing countries soon realized that CAPD was relatively affordable, which meant that ESRD was no longer an inexorably lethal condition for children from families with limited resources [57–59]. And throughout the world, the survival of so many more children with ESRD increased the demand for the multidisciplinary pediatric specialists required to care for them.

The next big step in the evolution of PD for children was the resurgence of automated cycling machinery. As we have seen, during the 1960s and 1970s, automated PD machinery was used to deliver chronic IPD, but treatments were infrequent, with patients often receiving three PD treatments per week, usually for 12 h overnight. Following the success of CAPD, in the early 1980s quality of life issues made a revival of interest in automated PD inevitable in those countries that could afford it. The CAPD technique required interruption of daily activities several times each day for dialysis exchanges; how much easier and less intrusive it would be to relegate dialysis to nightly exchanges performed by automated cyclers while the patient and family slept.

The first reports of an automated dialysis fluid cycling device adapted to provide "continuous" cycler PD (CCPD) were published in 1981 by groups in Charlotte, North Carolina and Houston, Texas [60, 61]. The technique maintained the principle of continuous PD by cycling dialysate exchanges through the night and leaving an exchange in place during the day. CCPD was first

shown to work in a pediatric patient by the Houston group in 1981 [61]. Soon CCPD became extremely popular among pediatric dialysis programs in developed countries worldwide [62–66].

During the late 1980s improvements in renal transplantation increased renal allograft and patient survival rates so dramatically in children that all forms of dialysis were viewed even more as a bridge to get children safely to or between kidney transplants [62]. The ready availability of potent vitamin D analogues, ESRD-friendly phosphate binders and nutritional supplements and formulas, controlled enteral nutrition via gastrostomy or nasogastric tubes, recombinant human erythropoietin, and recombinant human growth hormone (see Chaps. 22, 23, 25, and 27) gave pediatric nephrologists a powerful armamentarium with which to bring the child on chronic dialysis safely to transplantation in optimal condition – well nourished, normally grown, with minimal renal anemia and bone disease. Attention could then be turned to quality of life issues, scholastic and emotional development, and child and family psychosocial adjustment to the rigors of ESRD and chronic dialysis (see Chaps. 29, 30, and 33).

Before 1982, fewer than 100 pediatric patients had been treated with CAPD worldwide, and CCPD for children was virtually unknown. During the ensuing three decades, continuous forms of PD became available in pediatric dialysis centers throughout the world. Regional, national, and international multicenter study groups and registries developed during this period have since added much to our knowledge of peritoneal dialysis in children [63–67]. These efforts have spawned an extensive series of clinical guidelines and treatment options that will be discussed in many of the chapters that follow.

Hemodialysis

The clinical use of an "artificial kidney" was pioneered in 1944 in adult patients suffering from acute renal failure by Willem J ("Pim") Kolff [68], a Dutch physician in Nazi-occupied Holland during the Second World War. Kolff's interest in dialysis grew from his experiences caring for young patients with renal failure for whom treatment options were essentially nonexistent at that time [69]. Prior to Kolff's remarkable invention, the stage had been set for the introduction of an extracorporeal dialysis device by the availability of two key elements: heparin and cellophane.

Heparin was first purified from an extract of liver tissue in 1916 by a second year medical student at Johns Hopkins, Jay MacLean, working in the laboratory of a prominent hematologist, William H. Howell [70]. Heparin rapidly replaced hirudin, a naturally occurring, but often toxic anticoagulant extracted from the heads and gullets of leeches.

The basis for cellophane is cellulose, a substance first purified from wood in 1885. Cellophane had been available since 1910 as sheets of cellulose acetate used in the packing industry, but it had the necessary qualities of a good dialysis membrane: It could be easily sterilized without injury to the material and had a long shelf life. When cellophane tubes became widely available as sausage casings in the 1920s, studies in animals showed the casings also made excellent diffusion membranes [71]. Clinical application of cellophane and heparin in the construction of a dialysis device awaited Kolff's invention of the rotating drum kidney in 1944.

Pediatric application of the Kolff artificial kidney was first reported in 1950 by John Merrill and his colleagues in Boston who included a 3½-year-old boy with nephrotic syndrome in their initial series of 42 adult patients dialyzed using a rotating drum machine essentially the same as Kolff's original design [72]. As described by Merrill:

> Blood is led from the radial artery by means of an inlying glass cannula through a rotating coupling to the surface of a revolving metal drum. Here it passes through a length of cellophane tubing (~20 meters) wound spirally around the drum, and is carried by the motion of the drum to the distal end. During its course, the blood-filled tubing is passed through a rinsing fluid maintained at a constant temperature of 101 degrees F in a 100 liter container. Into this medium, diffusion from the blood takes place through the cellophane membrane. Distally, the blood is passed through a second rotating coupling, and pumped to inflow flasks, whence it is fed by gravity to a vein in the forearm through another inlying cannula. [72]

Merrill's pediatric patient received a single 4-h dialysis treatment and was said to have had "…modest improvement, but of short duration…" [72].

In 1955, FM Mateer, L. Greenman, and T.S. Danowski described their experience at the Children's Hospital of Pittsburgh with eight hemodialysis treatments in five severely uremic children, 7–15 years of age, all of whom were "…either stuporous or confused… overbreathing present in three of the five… (one child) had developed pulmonary edema, and convulsions had appeared in (two children)…" [73]. Their equipment was built by the Westinghouse Company based on an Alwall coil kidney design [74]. Alwall's coil kidney in effect turned Kolff's rotating drum on its end submerging the coils of cellophane tubing completely in the dialysate bath. Mateer's version of the coil kidney was more compact than the Kolff machine, consisting of ~15 m of $1\frac{1}{8}$ in. cellophane tubing wound on stainless steel screens submerged in a warmed 32 L bath of dialysate. An in-line roller pump propelled heparinized blood through the tubing from radial artery through the cellophane coils to return via the saphenous vein. Dialysate consisted of Pittsburgh tap water to which were added sodium, calcium, chloride, bicarbonate, glucose, and variable amounts of potassium; a fresh batch was mixed every 200 min, and with every bath change an antibiotic (usually oxytetracycline) was injected into the tubing leading to the artificial kidney [73].

For these severely uremic children, dialysis was clearly a heroic treatment that was surprisingly effective, if only temporarily. After treatments lasting 2–13 h, all patients became more alert, pulmonary edema and overbreathing improved, phosphorus levels fell, and blood nonprotein nitrogen levels decreased from an average of 231 to 113 mg/dL. Two of the five children survived, one recovering normal renal function after an episode of what may have been hemolytic uremic syndrome ("…previously well…bloody diarrhea…oliguria, albuminuria, profound anemia…"). Mateer concluded that, while dialysis had been successful in supporting this child's reversible ATN, "…in view of the difficulty in assessing elements of reversibility of renal failure in chronic states, more frequent use of dialysis is indicated in these situations…" [73].

In 1957, Frank H Carter and a team at the Cleveland Clinic that included Willem Kolff, who had emigrated to the United States in 1950, next described eight hemodialysis treatments in five children (2–14 years of age) using an improved disposable Alwall twin coil kidney that could be modified for children <20 kg by using only one of the two coils, thereby reducing priming volume from 750 to 400 mL [75]. The coils sat in the warmed rinsing bath with rinsing fluid circulating over the blood-filled cellophane tubing. Vascular access was via a large-bore polyvinyl catheter inserted into the inferior vena cava via a saphenous vein cutdown with return of dialyzed blood to a large vein in the arm. Roller pump speed was 200–400 mL/min. Catheters remained in place until the child died or recovered sufficient renal function to no longer need dialysis [75].

Four of the five children survived, including a 2-year-old boy with probable acute glomerulonephritis who presented anuric with a blood urea nitrogen (BUN) of 322 mg/dL. Carter noted that "…in the hands of a well-trained team, hemodialysis is not only helpful in producing a smoother course in these children, but it may also be lifesaving…" [75].

Unlike the concise and constricted prose demanded by modern journal editors, the papers by Mateer and Carter published 50 years ago are wonderfully detailed, conveying the intensity and drama that must have attended these early hemodialysis sessions. While some laboratory testing was available, management decisions relied primarily on clinical judgment. Presaging modern use of aggressive RRT in critically ill children, Mateer concluded that:

> …the relative safety of the procedure (hemodialysis) warrants an increased use in uremic patients whose prognosis has been considered hopeless, with the goal that time will thereby be provided for recovery for those who have reversible lesions… [73]

Intoxications with salicylates or barbiturates represented another potential use for hemodialysis in children [76], but while potentially lifesaving in cases of reversible AKI or intoxications, the role of periodic hemodialysis in the management of irreversible renal failure in children faced daunting technical challenges, the first of which was the absence of a reusable vascular access. This problem was first solved in 1960 by Belding Scribner and the team in Seattle with the development of a Teflon(R)-silastic shunt that still bears his name [77]. The Scribner shunt consisted of silastic-teflon cannulas inserted in the radial artery and a nearby forearm vein that were connected to each other between dialysis treatments and could be separated and connected to the arterial and venous tubing of a dialysis apparatus. Smaller versions of the Scribner shunt were soon adapted for use in children [78], and by the mid-1960s the availability of repeated vascular access via these shunts made chronic hemodialysis in children a reality.

Using a pumpless system developed for pediatric patients by Robert Hickman and Belding Scribner in Seattle in the early 1960s [79], the first large pediatric chronic hemodialysis programs were established in Seattle [80], San Francisco [81], Los Angeles [82], Minneapolis [83], London [84], and Paris [85].

The San Francisco experience is illustrative of the problems encountered and overcome by these pioneering pediatric centers during this early period so critical to the successful adaptation of chronic hemodialysis for children. In a report summarizing their initial experience from 1966 to 1969, Donald Potter and his associates at San Francisco General Hospital described the chronic hemodialysis of 14 children 2–16 years of age weighing 10–52 kg [81]. Time on dialysis ranged from 1 to 27 months, with five children receiving dialysis at home. For the first 3 years of the pediatric dialysis program, children were selected for dialysis in competition with adult patients by a committee, a stark reminder of the earliest days of chronic hemodialysis when the scarcity of this resource forced painful decisions into the hands of so-called "Life and Death Committees" [86]. By 1969, a separate pediatric unit had been created in San Francisco, and children were accepted "… on a first-come, first served basis if they were medically stable…" [81].

Using the Seattle pumpless method [79], Potter's patients were dialyzed thrice weekly primarily using the recently introduced flat plate dialyzers and an automated dialysate delivery system. The basic flat plate device, known as a Kiil kidney [87], consisted of two grooved polypropylene plates separated by a sheet of cellophane clamped tightly together. Blood flowed through the enclosed dialyzer down the grooves on one side of the cellophane membrane across from dialysate flowing in the grooves of the plate on the other side of the membrane in a counter current direction. One or more of these membrane "sandwiches" could be clamped together to construct the dialyzer. The parents of the children treated at home in the early days of the program were required to construct a Kiil dialyzer for every treatment (Donald Potter, MD, personal communication, 2011).

Vascular access was via arteriovenous shunts originating in the radial, brachial, posterior tibial, or femoral artery. Extracorporeal volume during treatment averaged 14% of estimated blood volume, and blood loss with each treatment was 20–40 mL. Transfusions were given when the hematocrit fell to 15%, leading to a mean transfusion requirement of 0.5 unit of packed red blood cells per month. The highest dialyzer clearance available was 128 mL/min, and because of this low clearance, five of the children were dialyzed 18–27 h/week. Dialysis prescriptions were adjusted according to pre-dialysis BUN, which averaged 70–86 mg/dL [81].

There were many complications, including hemodynamic decompensation due to the a-v shunt, shunt clotting and infection, anemia, hypertension, renal bone disease, congestive heart failure, uremic pericarditis, and growth delay. Despite these difficulties, there was only one death, and at the time of the 1970 report, seven children had received successful kidney transplants [81]. Looking back on his early experience, Potter recently recalled that although hemodialysis in 1970 appeared to be a potentially successful therapy for uremic children, there were many who doubted its technical problems

could be overcome sufficiently to allow its routine use in children. According to Potter, three major subsequent advances turned the tide: (1) improved vascular access with the introduction of arteriovenous fistulas and permanent double-lumen catheters, (2) the introduction of smaller more efficient dialyzers and lower-volume dialysis circuits, and (3) the development of dialysis equipment with more precise ultrafiltration monitoring and control capability (Donald Potter, personal communication, 2011).

The problem of ultrafiltration monitoring in infants, at once the most critical due to their small body size and narrow blood volume safety limits, was solved ingeniously by another pioneering pediatric hemodialysis program in Minneapolis led by Michael Mauer and Carl Kjellstrand who developed electronic weighing equipment on which the dialyzing infant lay throughout the procedure. The equipment required meticulous calibration, but was able to very accurately measure weight changes to within 3 g [88]. In a review published in 1976, Mauer and R.E. Lynch addressed these issues and others in an engaging description of the state of the art of pediatric hemodialysis in North America in the early 1970s [89].

Developments in Europe paralleled those in North America. In 1975, the second edition of the famous French textbook of pediatric nephrology was coedited by Pierre Royer, Renée Habib, Michel Broyer, and Chantal Loirat. There were six pages about hemodialysis (HD), stating as follows: "The management of end-stage renal disease in children is a recent experience, and pediatric maintenance hemodialysis had really begun in 1969–70 in Europe" [90]. According to these authors, there were three major contraindications to chronic dialysis in children: (1) systemic disease such as lupus, (2) mental retardation, and (3) young age, i.e., below 18 months. Vascular accesses included only (radial or femoral) arteriovenous shunt or fistula so that such a procedure was limited to children older than 2–3 years. There was no specific device for pediatric dialysis, and children suffered from many uncomfortable/unacceptable side effects (seizures, severe hypotension) during hemodialysis sessions. Morbidity mainly included arterial hypertension, renal osteodystrophy, anemia, undernutrition, and poor growth velocity. However, actuarial patient survival was reported to be 90% after 3 years on chronic hemodialysis [90].

By the early 1970s, it became clear among pediatric nephrologists in North America and Europe that the care of children with ESRD required separate facilities from those in which adult patients were dialyzed. The concept of specialized pediatric dialysis centers was pioneered in Europe by Broyer, Scharer, Chantler, Donkerwolke, Rizzoni, and others who stressed the importance of concentrating pediatric ESRD patients in multidisciplinary pediatric centers specially equipped by experience and expertise to care for children on dialysis and for their families [91]. These units were usually attached to University departments of pediatrics, as was the case in similar units established in North America. However, no single pediatric center in Europe or North America could hope to treat enough patients to properly develop the therapy. As a result, the concept of large national and international patient databases or registries of children receiving RRT was born.

The first of these was the work of the European Dialysis and Transplant Association (EDTA), which in 1971 published the first report devoted entirely to the care of pediatric dialysis patients [92]. The 1971 report presented data on 296 patients aged less than 15 years at the start of RRT who were receiving treatment at 122 centers, only five of which had treated three or more pediatric patients, reflecting the practice in Europe at that time of managing children on dialysis in adult units. In 1976, the components of a pediatric dialysis center were rigorously defined by the EDTA to include pediatricians, pediatric nurses, dieticians, social workers, child psychologists, school facilities, along with a separate children's ward in which therapy was provided away from adult patients [93]. Close association with a transplant program was also prescribed, reflecting early recognition of the critical importance of transplantation as the therapy of choice for children with ESRD. By 1989, nearly 80% of all children receiving dialysis in the countries of the EDTA were cared for in specialized pediatric centers [94].

The most recent report on pediatric dialysis in Europe appeared in 2010 summarizing data on 483 incident and 2,512 prevalent pediatric dialysis patients (age <15 years) from 28 countries [95]. In comparison to the last demographic report of the former EDTA registry 14 years ago, the authors found in 2007 a nearly threefold higher incidence and prevalence of RRT among children aged younger than 15 years. They speculated that the difference was likely to be due to underreporting to the previous EDTA registry, the recent achievement of RRT programs for all children in many countries, and an increasing acceptance and survival of infants and children with multiple comorbidities in pediatric RRT programs in Europe, resulting in a truly increased incidence and prevalence of RRT [95].

In North America, the success of the EDTA pediatric registry prompted over 60 pediatric ESRD programs to band together in 1987 to form what is now called the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) [96]. The NAPRTCS is a voluntary registry restricted to pediatric centers in Canada, the United States, Mexico, and Costa Rica that initially focused on transplant patients. In 1992, the NAPRTCS expanded to include dialysis patients and in 1994 expanded again to include children with chronic kidney disease (CKD). In a recent report from 2008, the NAPRTCS presented data on 6,491 children treated with dialysis in North American centers since 1992, approximately one-third of whom had received hemodialysis (http://web.emmes.com/study/peds). A complete listing of the more than 130 publications based on NAPRTCS data that have appeared since 1990 is available on the NAPRTCS web site, as are all of its most recent Annual Data Reports (http://web.emmes.com/study/peds).

Both the EDTA and the NAPRTCS registries have catalogued and promoted the steady growth and development of RRT for children that has occurred since the 1970s and 1980s. During the last three decades, HD in children has dramatically improved, with the near disappearance of many of the complications that once plagued pediatric hemodialysis: disequilibrium syndrome, need for blood transfusions, disabling bone disease and uremic dwarfism, aluminum encephalopathy, pyrogenic reactions and symptoms of bioincompatibility, malnutrition, intradialytic symptomatic hypovolemia, seizures and developmental delay, just to name a few.

Indeed the history of maintenance HD in children has been strongly modified by the introduction of more efficient and biocompatible synthetic membranes, by erythropoietin treatment, by growth hormone therapy, by the development of new therapeutic approaches to bone disease and calcium-phosphate disorders, by advances in vascular accesses (microsurgery for arteriovenous fistulas, new materials for cuffed tunneled venous catheters), by introducing pediatric data for dialysis adequacy measurement (Kt/V, urea reduction ratio), by novel dialysis strategies (high-flux dialysis, hemodiafiltration), by optimizing the use of anticoagulation (low molecular weight heparins, regional trisodium citrate), by improving dialysis water quality and bacterial safety (ultrapure dialysate), by noninvasive investigation of vascular access blood flow, by using urokinase or tPA for the management of the thrombosed hemodialysis catheter, by improving nutritional assessment and support, by using new machines with precise control of ultrafiltration by volumetric assessment and continuous blood volume monitoring during dialysis sessions, by the availability of specific small size dialyzers and tubing for infants, and by the use of sodium modeling [97–102]. In the mean time, HD practice has benefited from specific medical and staff training, including courses, fellowship programs, and congresses. Specific regulations have been established for HD practice in children, according to local health-care organization, public health, resources, and law. During this period, patient morbidity and mortality have significantly decreased. Worldwide experience has resulted in large databases and general practical guidelines [103–105]. However this only includes developed countries since the cost of HD is rather high, and such a technique is not available/accessible in many developing countries.

Among the most recent advances, some of them have brought significant improvement in HD for children:

- Daily online hemodiafiltration allows better nutrition, reduces blood pressure, improves

left ventricular size and function, improves calcium x phosphate control, better controls chronic microinflammation, and promotes catch-up growth in children [98, 106].
- The lowest age limit for starting HD in children has dropped, including neonates thanks to specific devices and improvement in general care of such patients [107].
- Various high-tech pediatric permanent HD catheters have been developed.
- There is a better worldwide knowledge and investigation of cardiovascular risk factors leading to better long-term control and prevention of cardiovascular disease [107].
- The use of several online monitoring equipment for chemical/physical signals during HD and biofeedback is growing, such as continuous noninvasive monitoring of relative blood volume changes during HD, patient-dialysate sodium gradient assessment, ionic dialysance and plasma conductivity (calculated from online inlet and outlet dialysate conductivity measurements), estimation of sodium concentration derived from conductivity, intra-HD urea kinetics and delivered dialysis dose from online urea monitors, dialysate temperature modulation according to blood temperature monitoring [108].

All these improvements have led to better quality of life, better nutritional status, better neurological development, better psychosocial outcome, and better patient survival, and all have their origins in the work of pioneering medical teams, patients, and families beginning more than 60 years ago. The following chapters will address these and other recent advances in dialysis therapy for children.

References

1. Cameron JS. A history of the treatment of renal failure by dialysis. New York: Oxford University Press Inc.; 2002. p. 179–85.
2. Cameron JS, Hicks J. The introduction of renal biopsy into nephrology from 1901 to 1961: a paradigm of the forming of nephrology by technology. Am J Nephrol. 1997;17:347–58.
3. Barnett HL, Edelmann Jr CM. Development of pediatric nephrology. Am J Kidney Dis. 1990;16:557–62.
4. Chesney RW. The development of pediatric nephrology. Pediatr Res. 2002;52:770–8.
5. Scharer K, Fine RN. The history of dialysis therapy in children. In: Warady BA, Schaefer FS, Fine RN, Alexander SR, editors. Pediatric dialysis. Dordrecht: Kluwer Academic Publishers Inc.; 2004. p. 1–11.
6. Webster's New Twentieth Century Dictionary. Collins World Publishing, 1978. p. 503.
7. Graham T. Liquid diffusion applied to analysis. Philos Trans R Soc Lond B Biol Sci. 1862;151:183–224. Cited in Reference 1, p. 27.
8. Negoi D, Nolph KD. History of peritoneal dialysis. In: Khanna R, Krediet RT, editors. Nolph and Gokal's textbook of peritoneal dialysis. 3rd ed. New York: Springer; 2009. p. 1–2.
9. Negoi D, Nolph KD. History of peritoneal dialysis. In: Khanna R, Krediet RT, editors. Nolph and Gokal's textbook of peritoneal dialysis. 3rd ed. New York: Springer; 2009. p. 2.
10. Abel JJ, Rowntree LG, Turner BB. On the removal of diffusible substances from the blood of living animals by dialysis. J Pharmacol Exp Ther. 1913–1914; 5:275–316.
11. Blackfan KD, Maxcy KF. The intraperitoneal injection of saline solution. Am J Dis Child. 1918;15: 19–28.
12. Bloxsum A, Powell N. The treatment of acute temporary dysfunction of the kidneys by peritoneal irrigation. Pediatrics. 1948;1:52–7.
13. Swan H, Gordon HH. Peritoneal lavage in the treatment of anuria in children. Pediatrics. 1949;4: 586–95.
14. Odel HM, Ferris DO, Power MH. Peritoneal lavage as an effective means of extra-renal excretion. Am J Med. 1950;9:63–77.
15. Fine J, Frank HA, Seligman AM. The treatment of acute renal failure by peritoneal irrigation. Ann Surg. 1946;124:857–75.
16. Weston RE, Roberts M. Clinical use of a stylet catheter for peritoneal dialysis. Arch Intern Med. 1965; 15:659–62.
17. Maxwell MH, Rockney RB, Kleeman CR, Twiss MR. Peritoneal dialysis: technique and applications. JAMA. 1959;170:917–24.
18. Segar WE, Gibson RK, Rhamy R. Peritoneal dialysis in infants and small children. Pediatrics. 1961;27: 603–13.
19. Etteldorf JN, Dobbins WT, Sweeney MJ, Smith JD, Whittington GL, Sheffield JA, et al. Intermittent peritoneal dialysis in the management of acute renal failure in children. J Pediatr. 1962;60:327–39.
20. Segar WE. Peritoneal dialysis in treatment of boric acid poisoning. N Engl J Med. 1960;262:708–800.
21. Ettledorf JN, Dobbins WT, Summitt RL, Rainwater WT, Fischer RL. Intermittent peritoneal dialysis using 5 per cent albumin in the treatment of salicylate intoxication in children. J Pediatr. 1961;58:226–36.
22. Lloyd-Still JD, Atwell JD. Renal failure in infancy, with special reference to the use of peritoneal dialysis. J Pediatr Surg. 1966;1:466–75.

23. Manley GL, Collipp PJ. Renal failure in the newborn: treatment with peritoneal dialysis. Am J Dis Child. 1968;115:107–10.
24. Lugo G, Ceballos R, Brown W, Polhill R, Cassady G. Acute renal failure in the neonate managed by peritoneal dialysis: preliminary report of two cases. Am J Dis Child. 1969;118:655–9.
25. Giantantonio CA, Vitacco M, Mendilaharzu J, Mendilaharzu F, Rutty A. Acute renal failure in infancy and childhood: clinical course and treatment of 41 patients. J Pediatr. 1962;61:660–78.
26. Wiggelinkhuizen J. Peritoneal dialysis in children. S Afr Med J. 1971;45:1047–54.
27. Day RE, White RHR. Peritoneal dialysis in children: review of 8 years' experience. Arch Dis Child. 1977;52:56–61.
28. Chan JCM. Peritoneal dialysis for renal failure in childhood. Clin Pediatr. 1978;17:349–54.
29. Feldman W, Baliah T, Drummond KN. Intermittent peritoneal dialysis in the management of chronic renal failure in children. Am J Dis Child. 1968;116:30–6.
30. Palmer RA, Quinton WE, Gray J-F. Prolonged peritoneal dialysis for chronic renal failure. Lancet. 1964;1:700–2.
31. Tenckhoff H, Schechter H. A bacteriologically safe peritoneal access device. ASAIO Trans. 1968;14: 181–7.
32. Boen ST, Mion CM, Curtis FK, Shilitar G. Periodic peritoneal dialysis using the repeated puncture technique and an automatic cycling machine. ASAIO Trans. 1964;10:409–14.
33. Tenckhoff H, Meston B, Shilipetar G. A simplified automatic peritoneal dialysis system. ASAIO Trans. 1972;18:436–40.
34. Counts S, Hickman R, Garbaccio A, Tenckhoff H. Chronic home peritoneal dialysis in children. ASAIO Trans. 1973;19:157–67.
35. Hickman RO. Nine years' experience with chronic peritoneal dialysis in childhood. Nephrol Dial Transplant. 1978;7:803.
36. Brouhard BH, Berger M, Cunningham RJ, Petrusik T, Allen W, Lynch RE, et al. Home peritoneal dialysis in children. ASAIO Trans. 1979;25:90–4.
37. Baluarte HJ, Grossman MB, Polinsky MS, Elzouki AY, Prebis JW, Gruskin AB. Experience with intermittent home peritoneal dialysis (IHPD) in children (Abstract). Pediatr Res. 1980;14:994.
38. Lorentz WB, Hamilton RW, Disher B. Home peritoneal dialysis during infancy. Clin Nephrol. 1981;15: 194–7.
39. Potter DE, McDaid TK, Ramirez JA. Peritoneal dialysis in children. In: Atkins RC, Thomson NM, Farrell PC, editors. Peritoneal dialysis. New York: Churchill Livingstone; 1981. p. 356–61.
40. Ahmad S, Gallagher N, Shen S. Intermittent peritoneal dialysis: status re-assessed. ASAIO Trans. 1979; 25:86–8.
41. Hurley JK. Kidney transplantation in infants (Letter). J Pediatr. 1978;93:538.
42. Reinhart JB. The doctor's dilemma: whether or not to recommend continuous renal dialysis or renal homotransplantations for the child with end-stage renal disease. J Pediatr. 1970;77:505.
43. Dialysis and transplantation in young children (Editorial). Br Med J. 1979; No 6170, London, Saturday, 21 April; 2:1033–4.
44. Popovich RP, Moncrief JW, Dechard JF. The definition of a novel portable/wearable equilibrium dialysis technique (Abstract). ASAIO Trans. 1976; 5:64.
45. Moncrief JW, Popovich RP, Nolph KD. The history and current status of continuous ambulatory peritoneal dialysis. Am J Kidney Dis. 1990;16:579–84.
46. Oreopoulos DG, Katirtzoglou A, Arbus G, Cordy P. Dialysis and transplantation in young children (Letter). Br Med J. 1979;1:1628–9.
47. Balfe JW, Irwin MA. Continuous ambulatory peritoneal dialysis in pediatrics. In: Legain M, editor. Continuous ambulatory peritoneal dialysis. Amsterdam: Excerpta Medica; 1980. p. 131–6.
48. Alexander SR, Tseng CH, Maksym KA, Talwalker YA. Clinical parameters in continuous ambulatory peritoneal dialysis for infants and young children. In: Moncrief JW, Popovich RP, editors. CAPD update. New York: Masson Publishing; 1981. p. 195–209.
49. Kohaut EC. Continuous ambulatory peritoneal dialysis: a preliminary pediatric experience. Am J Dis Child. 1981;135:270–1.
50. Potter DE, McDaid TK, McHenry K, Mar H. Continuous ambulatory peritoneal dialysis (CAPD) in children. ASAIO Trans. 1981;27:64–7.
51. Salusky IB, Lucullo L, Nelson P, Fine RN. Continuous ambulatory peritoneal dialysis in children. Pediatr Clin North Am. 1982;29:1005–12.
52. Guillot M, Clermont M-J, Gagnadoux M-F, Broyer M. Nineteen months' experience with continuous ambulatory peritoneal dialysis in children: main clinical and biological results. In: Gahl GM, Kessel M, Nolph KD, editors. Advances in peritoneal dialysis. Amsterdam: Excerpta Medica; 1981. p. 203–7.
53. Eastham EJ, Kirplani H, Francis D, Gokal R, Jackson RH. Pediatric continuous ambulatory peritoneal dialysis. Arch Dis Child. 1982;57:677–80.
54. Alexander SR. Pediatric CAPD update-1983. Perit Dial Bull. 1983;3(Suppl):S15–22.
55. Alexander SR, Honda M. Continuous ambulatory peritoneal dialysis for children: a decade of worldwide growth and development. Kidney Int. 1993;43(Suppl):S65–74.
56. Honda M, Itaka K, Kawaguchi H, et al. The Japanese data on CAPD: a ten year experience. A report of the Study Group of the Pediatric PD Conference. Perit Dial Int. 1996;16:269–75.
57. Munoz AR, Salazar GML, Gordillo PG. Adequacy of chronic peritoneal dialysis in low socioeconomic class uremic children. Int J Pediatr Nephrol. 1986;7:81–4.
58. Bakkaloglu SA, Ekim M, Sever L, et al. Chronic peritoneal dialysis in Turkish children: a multicenter study. Pediatr Nephrol. 2005;20:644–51.

59. Grunberg J, Verocay MC, Rebori A, et al. Twenty years' pediatric chronic peritoneal dialysis in Uruguay: patient and technique survival. Pediatr Nephrol. 2005;20:1315–19.
60. Diaz-Buxo JA, Farmer CD, Walker PJ, Chandler JT, Holt KL. Continuous cyclic peritoneal dialysis: a preliminary report. Artif Organs. 1981;5:157–61.
61. Price CG, Suki WN. Newer modifications of peritoneal dialysis: options in treatment of patients with renal failure. Am J Nephrol. 1981;1:97–104.
62. Seikaly M, Ho PL, Emmett L, Tejani A. The 12th annual report of the North American Pediatric Renal Transplant Cooperative Study: renal transplantation from 1987 to 1998. Pediatr Transplant. 2001;5: 215–31.
63. Warady BA, Sullivan EK, Alexander SR. Lessons from the peritoneal dialysis patient database: a report of the North American Pediatric Renal Transplant Cooperative Study. Kidney Int. 1996;49(Suppl): S68–71.
64. Edefonti A, Verrina E, Schaefer F, Fischbach M, Watson A. The European experience with CAPD/ CCPD in children. In: Fine RN, Alexander SR, Warady BA, editors. CAPD/CCPD in children. Boston: Kluwer Academic Publishers; 1998. p. 17–34.
65. Fine RN, Ho M. The role of APD in the management of pediatric patients: a report of the North American Pediatric Renal Transplant Cooperative Study. Semin Dial. 2002;15:427–9.
66. Van der Heijden BJ, van Dijk PC, Vernier-Jones K, Jager KJ, Briggs JD. Renal replacement therapy in children: data from 12 registries in Europe. Pediatr Nephrol. 2004;19:213–21.
67. Verrina E, Edefonti A, Gianglio B, et al. A multicenter experience on patient and technique survival in children on chronic dialysis. Pediatr Nephrol. 2004;19:82–90.
68. Kolff WJ, Berk HTH, Ter Welle M, van der Leg JW, van Dijk EC, van Noordwijk J. The artificial kidney: a dialyser with great area. Acta Med Scand. 1944;117: 121–34.
69. Kolff WJ. First clinical experience with the artificial kidney. Ann Intern Med. 1965;62:608–19.
70. MacLean J. The thromboplastic action of cephalin. Am J Physiol. 1916;41:250–7.
71. Andrus FC. Use of Visking sausage casing for ultrafiltration. Proc Soc Exp Biol Med. 1919;27:127–8.
72. Merrill JP, Smith III S, Callahan III EJ, Thorn GW. The use of an artificial kidney. II. Clinical experience. J Clin Invest. 1950;29:425–38.
73. Mateer FM, Greenman L, Danowski TS. Hemodialysis of the uremic child. Am J Dis Child. 1955;89:645–55.
74. Alwall N. Apparatus for dialysis of the blood in vivo. Acta Med Scand. 1947;128:317–35.
75. Carter FH, Aoyama S, Mercer RD, Kolff WJ. Hemodialysis in children: report of five cases. J Pediatr. 1957;51:125–36.
76. Kallen RJ, Zaltzman S, Coe FL, Metcoff J. Hemodialysis in children: technique, kinetic aspects related to varying body size, and application to salicylate intoxication, acute renal failure and some other disorders. Medicine. 1966;45:1–50.
77. Quinton W, Dillard D, Scribner B. Cannulation of blood vessels for prolonged hemodialysis. ASAIO Trans. 1960;6:104.
78. Morse TS. Synthetic arteriovenous shunts for hemodialysis in children. J Pediatr Surg. 1970;5:23–31.
79. Hickman RO, Scribner BH. Application of the pumpless hemodialysis system to infants and children. ASAIO Trans. 1962;8:309–14.
80. Hutchings RH, Hickman R, Scribner BH. Chronic hemodialysis in a pre-adolescent. Pediatrics. 1966; 37:68–73.
81. Potter D, Larsen D, Leumann E, Perin D, Simmons J, Piel CF, et al. Treatment of chronic uremia in childhood. II. Hemodialysis. Pediatrics. 1970;46:678–89.
82. Fine RN, DePalma JR, Lieberman E, Donnell GN, Gordon A, Maxwell MH. Extended hemodialysis in children with chronic renal failure. J Pediatr. 1968; 73:706–13.
83. Mauer SM, Shideman JR, Buselmeier TJ, Kjellstrand CM. Long-term hemodialysis in the neonatal period. Am J Dis Child. 1973;125:269–72.
84. Boulton-Jones JM, Cameron JS, Bewick M, Ogg CS, Meadow SR, Ellis FG. Treatment of terminal renal failure in children by home dialysis and transplantation. Arch Dis Child. 1971;46:457–64.
85. Broyer M, Loirat C, Kleinknecht C. Technical aspects and results of regular hemodialysis in children. Acta Paediatr Scand. 1972;61:677–84.
86. Obituary. Belding Scribner: inventor of shunt dialysis. BMJ. 2003;327(7407):167.
87. Cole JJ, Pollard TL, Murray JS. Studies on the modified polypropylene Kiil dialyser. ASAIO Trans. 1963;9:67–72.
88. Kjellstrand CM, Mauer SM, Shideman JR, Buselmeier TJ. Accurate weight monitoring during pediatric hemodialysis. Nephron. 1973;10:302–5.
89. Mauer SM, Lynch RE. Hemodialysis techniques for infants and children. Pediatr Clin North Am. 1976;23:843–56.
90. Broyer M. Dialyse et transplantation rénale. In: Royer P, Habib R, Broyer M, Loirat C, editors. Néphrologie Pédiatrique. Paris: Flammarion Médecin-Sciences; 1975. p. 302–13.
91. Broyer M, Chantler C, Donckerwolke R, Rizzoni G. Renal replacement therapy in children. In: Mahaer JF, editor. Replacement of renal function by dialysis. 3rd ed. Boston: Kluwer Academic Publisher; 1989. p. 720–49.
92. Scharer K, Brunner FP, Gurland HJ, Harlen H, Parsons FM. Combined report on regular dialysis and renal transplantation of children in Europe, 1971. Proc EDTA. 1972;9:191–200.
93. Chantler C, Donckerwolke RA, Brunner FP, Gurland H, Hathway RA, Jacobs C, et al. Combined report on