Fine & Gruskin

End Stage Renal Disease in Children

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Dedicated to

our wives—Peachie and Shawney
our children—Glenn, Jeffrey, Joanne, Karen, Michael, and Robin

whose patience, tolerance, and support have given us the privilege and time to pursue end stage renal disease in children

and our colleagues, patients, and families who have helped us learn so that it might be easier for those who follow.

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Preface

The outlook for children afflicted with end stage renal disease (ESRD) has changed dramatically during the past quarter century. From utter despair the dual modalities of dialysis and transplantation now permit cautious optimism. Not only have the lives of many children been prolonged, but in the process of caring for these children intense investigative efforts have been stimulated to understand the consequences of uremia. Much has been learned about ESRD in children and it is now appropriate to bring together our collective knowledge.

Although many of the clinical problems confronting medical personnel caring for the child with ESRD are similar to those encountered in adult patients, unique differences primarily related to factors related to growth and development do exist. Optimal care requires that these characteristics be considered when rendering care to children with ESRD. It is these differences which have led to the development of this text.

Quality care for the child with ESRD is complex, extending across many of the classical boundaries involved in health care, and is best accomplished by a team approach. The care of the child with ESRD requires participation of professional personnel from many disciplines in order to adequately address the total needs of the child and members of his or her family. Such care also requires knowledge and experience ranging from the experimental to the practical and applied. This book contains information pertaining to all aspects of care required for the child with ESRD. Such a comprehensive approach is evident from the varied backgrounds of the individuals who have contributed.

The editors are exceedingly grateful to the contributors who have taken the time and effort to summarize available data as well as to relate their current experiences and thoughts in a rapidly changing medical specialty. Many have been pioneers in the development of ESRD care in children. We believe that all who share in the care of the child with ESRD will find the information helpful in caring for their patients.

Delivery of medical care to children is founded on helping individuals. The Talmud says that the act of saving one life is tantamount to saving the world. The information contained in this text will certainly not solve the multitude of problems that currently confronts this troubled world. But if one child suffers less and his or her life is made less onerous by the information in this text, then the effort expended by all those involved will have been justified.

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Historical Perspective of the Treatment of ESRD in Children

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A historical perspective of the treatment of children afflicted with end stage renal disease (ESRD) encompasses not only the evolution of the therapeutic modalities of peritoneal dialysis, hemodialysis, and renal transplantation but also an analysis of the philosophical considerations prevalent during the past two decades regarding the desirability of prolonging life by extraordinary means in an otherwise fatal disease.

In 1964 Conrad M. Riley, M.D., in an editorial comment in the Journal of Pediatrics[1] thoughtfully reviewed the dilemma of utilizing the emerging treatment modality of renal transplantation for children with ESRD. Dr. Riley's insight was obtained primarily from the pioneering program initiated by Dr. Thomas Starzl at the University of Colorado.

Riley felt that the decision to offer such treatment should be "balanced" by two major judgments: "The length of prolongation of life" and "the expected totality of discomfort factors as seen through the eyes of the child." In regard to the latter, he emphasized the potential for continued growth retardation following successful transplantation, resulting in the kidney's being housed in a "healthy dwarf." At that time the life expectancy of pediatric allograft recipients could only be anticipated and the discomfort factors only estimated.

Six years later, John B. Reinhart, M.D., commented in the same journal on the initial reports from pediatric dialysis and transplant centers.[2] He "seriously questioned the value of chronic dialysis or renal transplantation" in children because of the "cost to the child in terms of physical and emotional discomfort." In addition, he felt that "progress of dialysis and renal transplantation for children should be carefully evaluated in terms, not of gross survival, but in parameters of meaningful growth and development—living."

These disquieting comments stimulated those involved in caring for children with ESRD to carefully evaluate the psychosocial and rehabilitative effects of such therapeutic intervention on the patients and their families. Reports from individual pediatric centers in the United States[3,4] as well as cooperative studies in Europe[5] addressed the issue regarding the virtue of employing these new therapeutic modalities in children. The fact that children appeared to resume their premorbid level of functioning after one year of a successful transplant indicated that renal transplantation was the optimal therapeutic modality for the child with ESRD.[7] Therefore, although all the questions raised by Riley and Reinhart have not been definitively answered, there is currently general acceptance of the virtue of treating children and adolescents with ESRD by means of dialysis and transplantation in affluent countries.

PERITONEAL DIALYSIS (PD)

In 1922, Putnam defined the peritoneum as a dialyzing membrane and extended previous studies initiated in the nineteenth century.[8] These studies established that solutes

and water could be added to or removed from the body by placing solutions of appropriate composition in the peritoneal cavity. The peritoneal membrane was characterized as semipermeable and inert.

The first reported use of the peritoneal membrane to remove uremic substances in man was by Ganter in 1923.[9] He envisaged PD as a replacement for kidney function in individuals with chronic renal failure. During the subsequent three decades, minimal advances occurred because of inadequate peritoneal access devices, morbidity and mortality from peritonitis, and the limited availability of acceptable dialysis solutions. The widespread clinical use of PD was initiated by Maxwell et al. in 1959.[10] The authors described the use of commercially available dialysate solutions and disposable tubing sets. These technical advances facilitated the use of PD in acutely ill patients. The technique required opening the system to potential bacterial contamination during each dialysis pass, which obviated the use of PD for prolonged periods of time. In 1964, Boen et al. described a closed system which minimized the potential for bacterial contamination during repeated procedures.[11] This concept led to the development of automated PD machines. Such equipment utilized ordinary tap water and a concentrated dialysate solution to deliver large volumes of sterile dialysate. The automated equipment was a significant technical advance which facilitated repetitive PD by minimizing the incidence of peritonitis and by reducing the volume and therefore the cost of commercially sterilized dialysate. In conjunction with the permanently implantable peritoneal access catheter described by Tenckhoff and Schechter in 1968,[12] the automated equipment permitted the use of intermittent PD as a realistic alternative for patients with ESRD.

The actual use of intermittent peritoneal dialysis (IPD) as a primary treatment modality was minimal, however. Reduced efficiency of solute and water removal was a major disadvantage, compared to hemodialysis (HD). To achieve comparable results, the weekly dialysis time for IPD was almost three times that of HD. Consequently, IPD was impractical in the hospital setting primarily because of significantly increased personnel costs. It followed that, from a practical standpoint, family involvement was required in order to initiate IPD in the home. In addition, peritonitis remained an impediment. These factors, along with the increased availability of HD, curtailed interest in IPD as a primary treatment modality. Nevertheless, certain centers for adults fostered the use of home IPD for selected patients. Meanwhile, experience with IPD in pediatric patients was limited, until the difficulties encountered with long-term hemodialysis in children stimulated renewed interest.[13–15]

In 1976 Popovich et al. described a "novel portable/wearable equilibrium, peritoneal dialysis technique."[16] This technique utilized instillation of dialysate in the peritoneal cavity four or five times daily for periods of four to eight hours and was labeled continuous ambulatory peritoneal dialysis (CAPD). The procedure alleviated the clinical consequences of uremia and led to a biochemical steady state. Excessive fluid removal was accomplished by increasing the osmolality of the dialysate solution. Conceptually, CAPD had a significant impact; however, the use of bottles containing dialysate solution necessitated "breaking" the system twice during each pass, or eight to ten times daily, leading to unacceptable high rates of peritonitis. In 1978 Oreopoulos et al. introduced the use of plastic bags filled with dialysate.[17] Following instillation of the dialysate solution, the bag could be attached to the body rather easily and utilized for efflux of dialysate four to eight hours later. The number of disconnections was reduced and the incidence of peritonitis decreased markedly to one episode every 10.5 patient-months. In July, 1980, the Food and Drug Administration approved the sale of 500 and 1000 ml of dialysate in plastic bags in the United States, and this permitted the potential widespread use of CAPD in pediatric patients. Preliminary reports from Canada,[18] the United States,[19] and Europe[20] indicate that CAPD is gaining acceptance as a primary treatment modality for children with ESRD, especially young children weighing less than 20 kg.

HEMODIALYSIS

Although the modern use of an artificial kidney was introduced by Kolff and Berk in 1944,[21] successful hemodialysis in a child was not reported until 1955.[22] In 1958 Holliday reviewed the use of the artificial kidney in children.[23] Published experience at that time consisted of 10 patients described in two reports.[22,24] Serious technical difficulties re-

lated to the size of pediatric patients and lack of experienced personnel were considered primary factors contributing to the meager use of hemodialysis in pediatric patients. Between 1958 and 1966 numerous reports appeared describing various modifications designed to overcome serious technical difficulties, thereby facilitating successful hemodialysis in children.[25–37] These reports dealt mainly with problems of vascular access and modifications of existing dialysis equipment to accommodate the smaller blood volume of younger patients who required acute hemodialysis. A majority of children received only one or two dialyses for acute renal insufficiency or accidental poisoning.

Kallen et al. in 1966 reviewed the subject of hemodialysis in children and was able to find reports of 62 patients in the pediatric age group treated with short-term hemodialysis for renal insufficiency.[37] These authors added 22 children from their experience. In addition, 27 children with accidental poisoning had been treated with hemodialysis by 1966.[38] Thus, the feasibility of utilizing an artificial kidney to treat children with acute disorders was established. However, at that time less than a dozen children with chronic renal insufficiency had undergone extended hemodialysis.[37, 39–42]

A disquieting note in the applicability of hemodialysis in treating children with chronic renal insufficiency was raised by a group at the University of Washington.[42] They related their experience with extended dialysis in a preadolescent girl over a period of 23 months. In addition to encountering cannula difficulties and a myriad of psychological problems, they were unable to demonstrate growth in this patient despite multiple manipulations of the dialysis regimen. Because of their unrewarding experience, especially the child's failure to grow, they proposed a concept that extended hemodialysis was not applicable to the pediatric age group.

Despite these reservations two pediatric programs were initiated in California in 1967 to treat children with ESRD. These centers, in addition to providing clinical care, demonstrated the feasibility of extended hemodialysis in children.[3, 4] Subsequent programs evolved in other parts of the United States,[43] Canada,[44] and Western Europe[44] to extend hemodialysis to children with ESRD.

In the United States, federal legislation was enacted in 1973 which entitled every citizen, regardless of age, to obtain Medicare reimbursement for dialysis and transplantation; this was a major impetus in extending care to all children with ESRD. However, financial constraints remain an impediment to the use of hemodialysis in children with ESRD in many areas of the world.

TRANSPLANTATION

The concept of organ transplantation can be found in Greek mythology; however, one of the first bona fide considerations of organ transplantation was by Gaspare Tagliacozzi in 1597.[46] He was requested by a nobleman with a destroyed syphilitic nose to replace the nose with one from a slave. Tagliacozzi discarded the idea with the statement that "the singular character of the individual entirely dissuades us from attempting this work on another person."

Almost 400 years have passed since Tagliacozzi made the above statement, yet the singular character of the individual—i.e., the ability of the body to recognize foreign substances and call forth an immunologic reaction to eliminate them—remains the omnipresent impediment to successful organ transplantation today.

The first attempt at kidney transplantation in man was by Emmerich Ullmann in Vienna in 1902.[47] A pig kidney was unsuccessfully transplanted to the elbow of a uremic woman.

In 1906 Paul Ehrlich transplanted a mouse tumor into a rat.[48] He noted that the tumor would grow for approximately eight days and then regressed. Conceptually, Ehrlich proposed that each species synthesized a substance that was vital for survival and growth, and that the mouse tumor regressed because the rat could not provide the species-specific "vital substance." In actuality, the rat, in all probability, rejected the mouse tumor. The "immunity theory" of transplant rejection was initially proposed by James B. Murphy in 1912.[49] He advanced the concept that the small lymphocyte was primarily involved in tissue rejection. Seventy years hence the search for the specific small lymphocyte continues.

Marked advances in our understanding of the immunity theory were made by Medawar in 1943[50] and Billingham, Brent, and Medawar in 1953.[51] Medawar demonstrated that accelerated rejection or *second set reaction* occurred with repeated grafting from the same

donor. The concept of *immunologic tolerance* was first demonstrated experimentally by Billingham, Brent, and Medawar. Inoculation of fetal mice or chick embryos with donor tissue resulted in permanent acceptance of such donor tissue following grafting after birth or hatching. Grafts from third-party donors were rejected. During the past 20 years, attempts to unlock the mechanism of immunologic tolerance in order to apply it to clinical organ transplantation as a means of specific immunosuppression have not come to fruition. Consequently, nonspecific immunosuppression remains the sole treatment modality currently utilized.

Slightly more than a quarter of a century ago, in 1954, the first successful clinical renal transplants in man were reported by Murray and colleagues from the Peter Bent Brigham Hospital in Boston.[52] These transplants were between identical twins and therefore obviated the immunologic phenomenon of rejection.

Subsequently, attention was directed toward methods of nonspecific immunosuppression in order to facilitate clinical renal transplantation using more immunologically disparate donors, living as well as cadaver.

In 1959 Hamburger et al. reported the use of whole body irradiation as a method of nonspecific immunosuppression.[53] The degree of bone marrow suppression and subsequent infection rate minimized enthusiasm for this method. Calne et al. in 1961 reported the successful prolongation of survival of canine renal allografts with an experimental drug which was subsequently named azathioprine (Imuran).[54] These studies led to the use of azathioprine in clinical renal transplantation. In 1962 Goodwin et al. demonstrated the efficiency of corticosteroids in reversing clinical rejection episodes.[55] For the past two decades azathioprine and corticosteroids have remained the primary immunosuppressive drugs used in clinical renal transplantation.

Because azathioprine and corticosteroids were not totally effective in suppressing rejection, alternative approaches were sought. In 1967 Starzl et al. introduced antilymphocyte serum as an immunosuppressive agent.[56] For about 15 years this agent in various forms has been used with equivocal results. Controlled studies in adults have both confirmed[57] and refuted its efficacy.[58] A recent controlled study utilizing antithymocyte globulin in pediatric recipients has not confirmed improvement in cadaver allograft survival rates.[59] Therefore, although antithymocyte globulin is now available commercially for the treatment of rejection episodes, its prophylactic use in clinical renal transplantation to prevent rejection and increase allograft survival rates remains equivocal.

More recently, Borel et al. demonstrated potent immunosuppressive effects from an antifungal agent, cyclosporin A.[60] Initial enthusiastic reports are available utilizing cyclosporin A in adult[61] and pediatric allograft recipients[62]; however, the results of additional controlled studies are awaited before this new drug can be added with confidence to the immunosuppressive regimen for clinical renal transplantation.[63, 64]

In the early 1960's when clinical renal transplantation was just beginning to be utilized for patients with ESRD, a few children received allografts at major transplant centers.[65] Subsequently, in the late 1960's and early 1970's, numerous reports indicated the general acceptance of renal transplantation for children with ESRD. In fact, most pediatric nephrologists involved in the care of children with ESRD have concluded that a successful renal transplant is the optimal treatment modality.

The major impediment to successful renal transplantation in children remains immunologic. In addition, optimization of growth, as will be discussed in a subsequent chapter, is a major concern for those caring for pediatric recipients. The success of the procedure must be measured in the pediatric patient not only in terms of providing sufficient function to avoid the need for dialysis but also in terms of growth and development. In this regard, only an allograft which provides a glomerular filtrate rate in excess of 60 ml/min/1.73 m^2 should be considered a success.[66]

During the past quarter of a century, the lives of many children with ESRD have been prolonged. Many children and adolescents have reached adulthood and are engaged in productive lives. However, the disquieting comments of Riley and Reinhart regarding the virtue of treating children with ESRD need to be considered carefully each time we embark upon a treatment program for such a child.

REFERENCES

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