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SPECIAL ARTICLE

A History of Pediatric Specialties

The following is the first article in this series. It describes the development of the specialty of Pediatric Nephrology. Dr. Chesney reviews its history, emphasizing the remarkable advances in the understanding and treatment of renal disease in childhood. We learn also of how the specialty evolved with the establishment, internationally, of societies, meetings, and journals. Finally, Dr. Chesney looks to the future and describes current research into the many fields of renal disease and development.

Alvin Zipursky
Editor-in-Chief

The Development of Pediatric Nephrology

RUSSELL W. CHESNEY

Department of Pediatrics, University of Tennessee College of Medicine, LeBonheur Children's Medical Center, Memphis, Tennessee 38103

ABSTRACT

Pediatric nephrology, as a discipline, arose from descriptive studies of childhood glomerulonephritis in Europe and the field of pediatric metabolism in the United States. While pediatric scientists before 1950 were concerned with fluid and electrolyte metabolism, regulation of intracellular and extracellular fluid, acid-base homeostasis, and parenteral fluid therapy, the defined field of nephrology developed after the Second World War around six major advances: ACTH and glucocorticoid therapy for nephrotic syndrome; renal biopsy to diagnose glomerular disease; the role of immunologic factors in glomerular injury; the use of dialysis as renal replacement therapy; renal transplantation as the optimal form of therapy in children with end stage renal failure; and recognition of renal disease in the etiology of 80% of cases of childhood hypertension. These discoveries led to focused research, the definition of specific training in nephrology, establishment of an American, European, and an International Society of Pediatric Nephrology, as well as an American Sub-Board of Pediatric Nephrology, and the inception of a journal, *Pediatric Nephrology*, now in its 15th year. Major research themes have included developmental nephrology, transplantation immunology, and concerns about growth in children with renal disease. Many clinical entities have been described in detail, some of which are almost confined to children. The scientific basis of pediatric nephrology, ongoing patient care needs, and its technical aspects – renal biopsy, dialysis and transplantation – assure its continuing future as a major pediatric discipline on all continents. **(*Pediatr Res* 52: 770–778, 2002)**

I. THE ORIGINS OF INTEREST IN CHILDHOOD RENAL DISEASES: 1820–1950

The development of the discipline of pediatric nephrology arose from clinical research conducted in the 130-year period from 1820 to 1950. It was during this period that pediatric scientists became interested in the definition of glomerular disorders and in fluid and electrolyte metabolism, the maintenance of normal volume and tonicity and acid-base status, as well as the pathophysiology of such disorders as rickets and diarrhea (1–5) (Table 1).

Pediatric kidney disease was initially considered from a descriptive rather than quantitative perspective. Early treatises on kidney diseases in children were remarkably accurate in terms of their clinical descriptions of various renal disorders, particularly glomerular conditions. In the 11th edition of Eduard Henoch's classic text *Kinderkrankheiten* (6), he describes

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Correspondence: Russell W. Chesney, M.D., Department of Pediatrics, University of Tennessee College of Medicine, LeBonheur Children's Medical Center, Room 306, 50 N. Dunlap Street, Memphis, TN 38103; e-mail: rchesney@utmem.edu

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Table 1. *Dates of historic significance in Pediatric Nephrology*

1880s–present	German and Viennese interest in urinary flow rates, and excretion in neonates; studies in glomerular nephritis—Langstein and Henoch
1906	Studies of acidosis—Howland and Holt
1910–1940	Studies of rickets—Park and Hess
1930–1950	Insight into fluid and electrolyte balance; acid-base physiology; potassium divalent minerals—Gamble, Darrow, Cooke, Harrison
1948	Annual Conference on Nephrotic Syndrome (precursor of NKF, ASN, ASPN)
1950s	Renal biopsy comes into use—Minnesota, Cincinnati, Cornell, Northwestern, Chicago, Paris, London, Heidelberg
1961	Reports of peritoneal dialysis in infants—Segar, Etteldorf
1966	European Society of Pediatric Nephrology founded
1968–1972	Hemodialysis begins in children—Metcoff, Fine, Potter, Mauer, Schärer (Heidelberg), Broyer (Paris)
1969	American Society of Pediatric Nephrology begins—Heymann first president
1969	Use of alkylating agents in treatment of glomerular disease not responsive to steroids—Good, Drummond, Michael, Grupe, West, Etteldorf
1968–1972	Transplantation in children—San Francisco, Cincinnati, Los Angeles, Colorado, Heidelberg, London, Hannover, Paris
1971	International Society of Pediatric Nephrology begins—Arneil (Glasgow)
1972	Federal legislation to support end stage renal care—Greifer
1973	Synthesis of $1,25(OH)_2$ vitamin D and use in children—DeLuca, Norman, Chan, Chesney
1973–1976	First textbooks of pediatric nephrology—Royer, Rubin, Barrett, Lieberman, James
1974	Sub-Board of Pediatric Nephrology—McCrory, Chair
1977	Workshop on Growth in Renal Failure, Carmel, CA—Holliday
1978	CAPD described and used in children—Fine, Salusky
1979	Aluminum recognized as neurotoxin
1980	First Workshop on Developmental Renal Physiology, New York—Spitzer
1983	Beginning of lobbying efforts on behalf of pediatric nephrology research agenda—ASPN council and members
1986	AIDS nephropathy described (Strauss)
1987	Workforce group report—ASPN appointees
1987	The journal *Pediatric Nephrology* initiated—Chantler, Robson (eds)
1987	Erythropoietin used in treatment of anemia of chronic renal failure
1990	National Kidney and Urology Diseases advisory board identifies need for more federal pediatric nephrology support
1992 on	Ion channel mutations responsible for many renal tubular syndromes, polycystic renal diseases, and nephrogenic diabetes insipidus
1990s	Renal transplantation results improve with new therapeutic approaches
1997	Quality goals in dialysis established
2000	Proteomics defines defects in congenital nephrotic syndrome, renal hypomagnesemia, and variants of Alport syndrome

the full syndrome of purpura, severe abdominal pain, melena, "rheumatoid-like" pain and nephritis. This form of IgA nephropathy now bears the name of Henoch and his teacher Johann Lukas Schönlein. An early textbook of urology includes a section on Bright disease of infancy and childhood (7), which contained many features of the untreated uremic child, including uremic frost and brawny skin, seldom encountered today. Most textbooks of the late 19th and early 20th century had extensive descriptions of renal tuberculosis, post-scarlet fever renal disease, Bright's disease, and albuminuria (6–10). Otto Heubner, who succeeded Henoch in the professorship at Berlin, fully described orthostatic proteinuria and its generally benign prognosis (6, 8). Renal disease in this era in Europe was clearly the purview of urologists and pathologists in addition to pediatricians and other physicians. German and Viennese pediatrics dominated this phase of nephrology and the nosology of disease (Table 1).

A term prevalent in the first half of the 20th century to denote a pale, enlarged, and puffy kidney from hypoproteinemia was *nephrosis.* As popularized by F. Volhard and T. Fahr, and C. Munck, nephrosis was largely replaced by the more descriptive term *nephrotic syndrome*, which indicates the features of hypoproteinemia, edema, and hypercholesterolemia (11). Thomas Addis (12), a Scotsman who taught at Stanford, was highly critical of the term nephrosis as being "at best a nominal interim diagnosis, a convenience for the moment." Although the term nephrosis persisted into the 1950s and 1960s in individual papers (14), by 1960 it was largely gone (15, 16). Another common term was Bright's disease (7, 9, 10), which denoted chronic renal failure, proteinuria, edema, hypertension, and a fatal prognosis (7, 12, 13). This term, too, has vanished.

In the late 19th and early 20th centuries, other investigators, particularly in Germany and the United States, evaluated normal and pathophysiologic renal-related processes in neonates, including the composition of urine, urine volume excretion, and a disorder termed urate nephropathy (8–10). The field of study of the founding scholars, such as John Howland, Daniel Darrow, James L. Gamble, Alan Butler, W. Emmett Holt, McKim Marriott, A. Ritter von Reuss (Vienna), William Wallace, and others, has been termed *metabolism* (1, 2, 4, 5). The field of metabolism encompassed classical studies of rickets, the acidosis of diarrheal dehydration, nephrosis, and factors regulating growth. The development of this field was dependent on the elucidation of laboratory methods used to monitor renal and metabolic disorders. Of the 51 winners of the American Pediatric Society's (APS) highest award, the Howland Award, 10 scholars—Edwards Park, Gamble, Darrow, Holt, Butler, Harold and Helen Harrison, Henry Barnett, Robert E. Cooke, and Gilbert Forbes, as well as Howland himself and his student Marriott—gained their fame for studies in metabolism and their laboratory-based approach. Charles Janeway and Robert Good, two other Howland recipients, are viewed as key figures in the development of pediatric immunology, but had interest in and made key observations about childhood renal disease. These individuals can be perceived as some of the

immediate American founders of nephrology, particularly in their belief in hypothesis-based quantitative science (1–5, 8–10). From this broad discipline of metabolism emerged nephrology, endocrinology, nutrition, biochemical genetics, and other fields. Other articles will discuss the evolution of those other fields; this treatise will emphasize nephrology.

Among the Puritans on the legendary voyage of the *Mayflower* in the autumn of 1620 was young John Howland of Fenstanton, East Anglia. During the passage to New England, Howland fell overboard and, remarkably, was fished out and saved.1 Nearly 300 years later, in 1912, his descendant, bearing the same name, founded the first full-time department of pediatrics at a medical school. As chair at Johns Hopkins, Howland championed the concept of pediatric clinical research emphasizing the collection of quantitative data, physiologic principles, and biochemical techniques (4). Thus, the miraculous rescue at sea of a young Puritan had an impact on the development of academic pediatrics in the United States, as well as the field of pediatric nephrology. Howland was proud of his ancestor and disputed the family legend that the fall overboard was related to inebriation.

An influential textbook of adult and pediatric kidney disease in children was the 1950 publication Addis' *Glomerular Nephritis* (12). This book contained precise descriptions of childhood renal syndromes including acute and chronic glomerulonephritis. The book also gave a full description of the Addis count; the 24-hour excretion of erythrocytes, with both normal and abnormal values. Addis' text also described his nephritis outpatient clinic at Stanford, including patient histories, his methods for diagnosis, and how to prepare a low protein diet, as well as ways to reduce dietary sodium intake (12). He also described extensive and well-designed experimental studies in rats involving nephrectomy followed by measurement of urinary protein excretion and other dietary manipulations. Finally, his extensively complete, long-term follow-up studies are of interest in terms of the natural history of childhood renal disease, particularly chronic glomerulonephritis.

Henoch, Heubner, Langstein, and Addis all made extensive observations concerning the nephritis associated with scarlatina and diphtheria, and following congenital syphilis (6–10, 12). Another early monograph by Karel de Leeuw described the prognosis of various forms of nephritis, which was far less optimistic than today (13).

Where these early scholars of glomerulonephritis could be criticized was in their tendency to lump nearly all forms of nephritis into limited forms (6–10, 12). Their views of glomerular disease arose largely from kidney tissue derived at autopsy and from the fact that some children recovered having been treated with bed rest and various diets. Their schemes for disease progression were sometimes accurate and sometimes not (7, 12, 13). What was required was a means of precisely defining renal disease, its various forms, and safe and effective therapeutic approaches. Those requirements became possible in the 1950s because of scientific advances including the development of the technique of percutaneous renal biopsy.

II. EMERGENCE OF PEDIATRIC NEPHROLOGY AS A DISTINCT DISCIPLINE: 1950–1970

A history of the discipline would be incomplete without a discussion of the name of the subspecialty, which could have been of Greek (Nephros) or Latin (Ren) origin. The term *pediatric nephrology* derives from both Greek and late Latin etymology, now viewed as part of the International Scientific Vocabulary, and first appeared in an important book entitled *Current Problems in Childhood Nephrology* written in 1963 by a group of nephrologists, (Pierre Royer, Rene Habib, and Henri Mathiew), at Hôpital des Enfants-Malades in Paris. Their experience was further expanded in a 1973 book termed *Néphrologie Pédiatrique*, which was translated into English in a 1974 edition published in the United States (14). This edition also was by the three authors mentioned above and Michel Broyer. Had this book not appeared, the field might well have been termed childhood kidney disease, renal disease, or possibly even renology, despite the current acceptance of *nephrology* by the world's scientific community. Mitchell Rubin, a major pioneer in the discipline, also chose the title *Pediatric Nephrology* for his textbook of 1975 (15) as well as Ellen Lieberman in her textbook of 1976 named *Clinical Pediatric Nephrology* (16). Nephrology has remained the term for the discipline.

As is frequently the case in the evolution of any new field, the period from 1948 to the founding of the American Society of Pediatric Nephrology in 1969 and the European Society of Pediatric Nephrology in 1966 was marked by six fundamental scientific and/or technologic discoveries regarding the kidney, its function, and disorders. These advances were so pivotal that pediatric nephrology subsequently could never be considered as part of any other discipline (Table 2). In order of discovery, these events were: *1*) that ACTH or glucocorticoids could induce remission in the common form of childhood nephrotic syndrome; *2*) that a percutaneous renal biopsy in a child with urinary abnormalities could help define the clinicopathologic features of the underlying renal disorder and could distinguish histologic variants of the nephrotic syndrome; *3*) newly emerging immunologic techniques could be used to help define the

Table 2. *The six critical discoveries that underlie pediatric nephrology as a discipline*

1. The use of ACTH and glucocorticoids in the treatment of childhood idiopathic nephrotic syndrome
2. Percutaneous renal biopsies in children permit classification of glomerular disease
3. Immunologic factors are essential in many renal diseases, especially those involving the glomerulus
4. End stage renal disease can be treated with dialysis as renal replacement therapy
5. Children can receive renal allografts from living or cadaveric donors
6. Hypertension in children is largely the consequence of renal disease (80% of cases)

[1]This remarkable story of John Howland on the voyage of the Mayflower was recounted on the BBC/PBS television series *The Story of English* and can be read in the companion book also titled *The Story of English* and authored by Robert McCrum, William Cran, and Robert MacNeil, Penguin Books, New York, 1992. See also the chapter on John F. Howland by W.C. Davidson in *Pediatric Profiles*, Borden Veeder (ed), Mosby, St. Louis 1957, pp. 161–174, and T. E. Cone Jr.'s *History of American Pediatrics*, Little Brown, Boston, 1979.

nature and mechanism of glomerular injury; *4*) children could be treated with hemo- or peritoneal dialysis for chronic renal failure to prolong life; *5*) children could have renal function restored by renal transplantation; *6*) and hypertension in childhood was largely (80%) the result of renal disease (17–23). Of these six discoveries, the fact that ACTH or glucocorticoids could induce remission in children with nephrotic syndrome and prevent death due to infection and malnutrition was clearly the seminal event. The nephrotic syndrome of childhood had a mortality rate of 40 to 50%, which was halved by the use of antibiotics to treat life-threatening infections, particularly peritonitis (15). Shortly after the discovery of ACTH and cortisol in the 1940s, ACTH was used in a series of clinical trials in nephrotic children in relapse. Farnsworth (24), Barnett *et al.* (25), Riley (26), Rappaport (27) *et al.*, and Metcoff *et al.* (28) showed in trials in Michigan, New York, and Philadelphia that many of their more than 130 childhood subjects underwent a diuresis, demonstrated improved renal function (increased GFR and renal plasma flow), had a decline in urine protein, and a fall in serum cholesterol. This capacity to induce remission by oral glucocorticoid therapy led students of nephrology to seek explanations for why some children responded rapidly, and why treatment failures still persisted. In this instance, in the late 1950s and early 1960s an examination of renal tissue obtained by renal biopsy provided the tool to answer some of these questions, particularly when the renal tissue specimen was examined by the full array of light, immunofluorescent, and electron microscopy.

Beginning in 1948, a precursor of the National Kidney Foundation sponsored the Annual Conference on the Nephrotic Syndrome, which was later changed to The Annual Conference on the Kidney. These meetings, which also emphasized renal physiology and kidney diseases, were organized by one of Gamble's students, Jack Metcoff, from Boston Children's Hospital, and later from the Michael Reese Hospital. Major input came from Mitchell Rubin, Milton Rappaport, Walter Heymann, Henry Barnett, and Philip Calcagno. Meetings were selective with an attendance of seldom more than 40 people. These meetings dealt with the use of ACTH or glucocorticoids in the therapy of idiopathic nephrotic syndrome in terms of proper dosage and length of therapy. Papers presented here began to define the clinical features of various forms of this syndrome in terms of therapeutic response and biopsy appearance. Basic science and work in progress was emphasized as well as renal pathology.

Out of the kidney conferences arose the International Study of Kidney Disease in Children (ISKDC), which initiated important renal biopsy studies of children with renal disease in many European centers, Canada, Mexico, and the United States. The ISKDC was organized in the United States by Henry Barnett, Chester Edelmann, Jr., and Ira Greifer, all from New York and included an international working group consisting of Gavin Arneil (Glasgow), Niilo Hallman (Helsinki), Harmen Tiddens (Netherlands), Habib (Paris), Richard White (Birmingham, UK), Jay Bernstein (Einstein in NY), Jacob Churg (Mt. Sinai in New York), Gustavo Gordillo (Mexico City), Luther Travis (Galveston), and Teruo Kitagawa (Tokyo) (Fig. 1). This group designed prospective studies to elucidate the clinical features and prognosis of important glomerular syndromes including minimal lesion nephrotic syndrome, pediatric IgA nephropathy, focal sclerosing glomerulonephritis, membranous nephropathy, and mesangioproliferative glomerulonephritis (18, 29, 30). This network linked investigators in the United States and Europe and conducted remarkably informative studies of the value of renal biopsy as a tool and the correlation of biopsy findings with treatment and prognosis (18, 29, 30). The use of light microscopy, immunofluorescence, and electron microscopy techniques by the ISKDC and other groups permitted the clinicopathologic identification of several important renal disorders including membranoproliferative glomerulonephritis (31, 32), IgA nephropathy (Berger disease) (33), and membranous nephropathy (34).

While students of metabolism were focused on fluid and electrolyte metabolism and were fully capable of treating nephrotic children with glucocorticoids and antibiotics, the discipline of nephrology was moving into the realm of the treatment of childhood renal disease by focusing upon the structure and function of the kidney, upon renal biopsy, and after the late 1960s upon dialysis and transplantation as being essential components of the discipline. By 1970, the uremic child, *per se*, was becoming a focus for study and clinical care. All trainees from the 1970s onward would need these skills and new training programs emerged to train future nephrologists. Moreover, the focus of the discipline was upon the kidney and urinary tract and its several tissue components—glomerulus, vascular system, proximal tubule, loop of Henle, distal tubule, and collecting duct, as well as the ureters, bladder, and urethra, rather than on fluid balance and homeostasis.

American pediatric nephrologists were instrumental in the development of two societies focused in internal medicine (90% of members of both societies are nephrologist internists). As noted, the Metcoff Annual Conference on the Nephrotic Syndrome was the precursor of the National Kidney Foundation (NKF). In 1966, Henry Barnett, Robert Good, and Robert Vernier were among the founders of the American Society of Nephrology (ASN). Robert Vernier and Alfred Michael have also served as Presidents of the ASN; the only Pediatric Nephrologists to be chosen.

The American Society for Pediatric Nephrology (ASPN) was formed in Atlantic City in 1969 by Henry Barnett, Walter Heymann, Clark West, Chester Edelmann, and others. This latter group has since held annual meetings at the time of the American Pediatric Society-Society for Pediatric Research (APS-SPR) meetings. The ASPN has been of major importance in formulating the agenda for pediatric nephrology in its roles as an educational society, in terms of public policy and in fostering the research agenda of the discipline. It has also been instrumental in recruiting trainees into the discipline (Table 3). From the international cooperation engendered among pediatric nephrologists at the Annual Conference on the Kidney and the ASPN, there arose the formation of the International Pediatric Nephrology Association (IPNA) in 1971, which formally held meetings in Mexico, France, and Washington, DC, in 1968, 1971, and 1973, respectively. These two organizations have been important in the growth of the discipline relating to

Figure 1. The first meeting of members of the International Study of Kidney Disease, which convened in 1966. This group ultimately led to the formation of the International Pediatric Nephrology Association (IPNA) in 1971. The individuals shown are: *Kneeling in front—left to right*: C. William Daeschner, James R. Kimmey; *Standing — left to right:* Harmen A.W.M. Tiddens, Andreas Fanconi, Geoffrey Rose, Walter Holland, Gustavo Gordillo, Mineo Kanasawa, J.S. Cameron, Mark Abramowicz, Osamu Kobayashi, Ira Greifer, Richard H.R. White, Jussi Vilska, Rénee Habib, Niilo Hallman, David Long, Chester Edelmann, Luther Travis, Gavin Arneil, Ralph Hendrickse, Wallace McCrory. (Used by permission. Chester M. Edelmann, Jr., M.D., Albert Einstein College of Medicine of Yeshiva University, Bronx, New York.)

promotion of research agendas, symposia on clinical advances, and continuing education for pediatric nephrologists.

The European Society of Pediatric Nephrology (ESPN) founded in Glasgow by Gavin Arneil in 1966 has been remarkably important to the development of the field of pediatric nephrology (Table 4). Members come from each European nation and the meeting site rotates from country to country. The ESPN has been important in setting the standards for dialysis and transplantation in Europe as well as in developing transnational consortia of the study of numerous disorders. The ESPN frequently invites speakers from the United States and Canada and also plays an important role in the operations of IPNA. The close cooperation between the ASPN and the ESPN in the operation of IPNA has permitted interactions among American and European pediatric nephrologists and the rapid dissemination of new knowledge. The result has been several cross Atlantic textbooks and numerous transnational studies.

III. DEVELOPMENT OF TRAINING PROGRAMS: 1970–1980

In the mid-1970s the scientific direction of pediatric nephrology diverged into two major schools of thought: renal immunology and renal physiology. Three major sites of fellowship training in the immunologic school were the University of Minnesota, Cincinnati Children's Hospital, and Case Western Reserve. Later, Boston Children's Hospital became another important training site. These centers, respectively, focused on animal models of glomerular disease, extremely well-conducted clinicopathologic studies in children, and a fundamental immunologic approach to understanding glomerulonephritis including the role of complement pathway consumption and T cell and B cell function (17, 32, 35). The physiologic approach, first espoused by Homer Smith, was the mode of operation at Albert Einstein, Buffalo, Georgetown, University of California — San Francisco, and University of Texas-Galveston. Important areas of focus were developmental renal physiology, including studies of GFR, acid-base physiology, and handling of drugs (36–39), as well as fluid overload in glomerulonephritis (40, 41). While Metcoff was instrumental in encouraging the study of glomerular disease and the nephrotic syndrome through his National Kidney Foundation Conferences, his own interest was in edema formation in children and nutrition in uremia (42). Vernier was involved in highly original studies in renal development and the origin of the glomerulus using the electron microscopic to follow early renal structural events (43). Several strong adult medicine groups, including Yale, the National Institutes of Health, Cornell, and Dallas, focused upon the physiologic approach also trained pediatric nephrologists. Each of these groups had trainees from the United States and Canada, Europe, Japan, and Australia that resulted in the expansion of the field worldwide. In addition, both McGill (Keith Drummond) and Toronto (Philip Rance) developed strong programs that have trained many Canadian nephrologists as well as Europeans and Australians.

Table 3. *American Founders of Pediatric Nephrology and their Area of Discovery*

1. Henry Barnett—(Albert Einstein) Developmental nephrology and clearance measurements in infants.
2. Jay Bernstein (Albert Einstein) Renal pathologist who defined developmental defects and cystic diseases.
3. Philip Calcagno (Georgetown) Developmental nephrology and drug handling by immature kidney.
4. Daniel Darrow (Yale) Metabolism expert and fluid and electrolyte therapy, especially the role of potassium.
5. Chester Edelmann, Jr. (Albert Einstein) Classification of renal tubular acidoses and renal function of the immature.
6. James Gamble (Harvard) Metabolism and fluid and electrolyte therapy, parenteral fluid therapy.
7. Robert Good, Jr. (Minnesota) Immunologic mechanisms of renal disease and transplantation biology.
8. Ira Greifer (Albert Einstein) Treatment of nephrotic syndrome and organization of pediatric nephrology on national and global scale.
9. Walter Heyman (Case Western) Model of nephrotic syndrome which resembles membraneous nephropathy.
10. Malcolm Holliday (University of California, San Francisco) Renal nutrition and growth of uremic children.
11. Charles Janeway (Harvard) Studies on immune defects in children with nephrotic syndrome.
12. Wallace McCrory (Cornell) Developmental nephrology and pathophysiology of glomerulonephritis. Chair of first Sub-Board of Pediatric Nephrology.
13. Alfred Michael (Minnesota) Pathogenesis and therapy of glomerular diseases.
14. Jack Metcoff (Harvard, Michael Reese) Pathogenesis and therapy of nephrotic syndrome. Conferences on the kidney.
15. Mitchell Rubin (Buffalo) Developmental nephrology. Editor of first textbook *Pediatric Nephrology*.
16. Adrian Spitzer (Albert Einstein) Developmental nephrology and renal handling of phosphate. Organized workshops on development.
17. Luther Travis (Galveston) Diabetic nephropathy and fluid therapy for burns.
18. Robert Vernier (Minnesota) Mechanisms of glomerular disease and development of the glomerulus by use of electron microscope.
19. Clark West (Cincinnati) Immunologic mechanisms of glomerular disease and immunopathology.

Good and Janeway will also be considered in the History of Immunology
Darrow and Gamble will also be considered in the History of Fluid and Electrolytes.

Table 4. *European Founders of Pediatric Nephrology and Their Areas of Discovery*

1. Anita Aperia (Stockholm)—Renal handling of sodium by the preterm and term neonate kidney
2. Gavin Arneil (Glasgow)—Treatment of nephrotic syndrome and founder of ESPN and IPNA
3. T. Martin Barratt (London)—Pathogenesis of nephrotic syndrome. Editor of *Pediatric Nephrology* textbook
4. Horst Bickel (Heidelberg)—Supports large nephrology unit formation and discoveries in cystinosis
5. Johannes Brödehl (Hannover)—Develops large dialysis and transplant efforts; metabolic renal disease and renal phosphate handling
6. Michel Broyer (Paris)—Renal transplantation and dialysis; cystinosis; directs large Paris unit
7. Cyril Chantler (London)—Role of nutrition in renal disease; develops large dialysis and transplant unit, first co-editor of *Pediatric Nephrology*
8. Rosanna Coppo (Genoa)—Studies in IgA nephropathy and other glomerular diseases
9. Louis Callis (Barcelona)—Studies on calcium disorders
10. Fabio Sereni (Milan)—Development of Italian *Pediatric Nephrology*—End-stage renal disease care. Developmental Nephrology
11. Guido Fanconi (Zurich)—Described many pediatric nephrologic syndromes
12. Antonio Gasser (Vienna)—Described and named the hemolytic-uremic syndrome
13. Marie-Claire Gubler (Paris)—Pathophysiology of glomerulonephropathies with pathologic correlates
14. Jean-Pierre Guignard (Lausanne)—Studies of neonatal renal function
15. Rénee Habib (Paris)—Preeminent renal pathologist whose classification of glomerular diseases is widely accepted
16. Niino Hallman (Helsinki)—Descriptions of congenital nephrotic syndrome of Finnish type
17. Edouard Henoch (Berlin)—Described Henoch-Schoenlein purpura
18. Ernst Leumann (Zurich)—Studies of childhood renal diseases including disorders of calcium metabolism
19. Otto Mehls (Heidelberg)—Studies on renal osteodystrophy and growth hormone use in childhood renal disease
20. Leo Monnens (Groningen)—Metabolic and genetic studies in renal disease
21. H Ritter von Reuss (Vienna; Berlin)—Neonatal urinary excretion patterns
22. Juan Rodriquez-Soriano (Bilbao)—Studies of renal tubular acidosis
23. Pierre Royer (Paris)—Author of first textbook on pediatric nephrology, organizer of Paris School of Pediatric Nephrology; described many renal syndromes
24. Karl Schärer (Heidelberg)—Organizer of largest German unit and studies in hypertension, dialysis, transplantation and body composition
25. Harmen Tiddens (Utrecht)—A founder of Dutch pediatric nephrology involved in international pediatric nephrology trials and founding of ESPN
26. Richard White (Birmingham)—Clinicopathologic studies of glomerular disease
27. D Innes Williams (London)—Important figure in development of pediatric urology
28. Jan Winberg (Stockholm)—Studies of urinary tract infections

At the same time large pediatric nephrology units were being developed in Western Europe. These units were comprehensive in that they included clinical nephrology, renal biopsy, renal pathology, dialysis, and transplantation as well as active renal research. The larger units have been and are located at Karolinska University in Stockholm, Sweden (Anita Aperia, Jan Winberg); Hannover University, Germany (Johannes Brödehl); Heidelberg University, Germany (Horst Bickel, Karl Schärer); University of Paris (Royer, Broyer, Habib); Guy's Hospital, London (Sir Cyril Chantler), and Great Ormond Street (John Soothill and Martin Barrett). Guido Fanconi at Zurich had previously developed a major site for training, and two Swiss nephrology units emerged, one in Zurich (Ernst Leumann) and one in Lausanne (Jean-Pierre Guignard). Each of these units was also responsible for training pediatric nephrologists across Europe and in the remainder of the world. European investigators were particularly prominent in the study of urinary tract infections, obstructive uropathy, and reflux nephropathy, as well as glomerulonephritis.

In terms of clinical pediatric nephrology, all modern programs in the United States, Canada, and Europe became involved in the use of renal biopsy techniques, dialysis, and the beginnings of transplantation. Nephrologists became interested in clinical research studies in uremic children who demonstrated growth failure, bone disease, acidosis, malnutrition, and hypertension. Recognition of the impact of chronic renal failure on growth had been first recognized by Lucas in 1883 (11) and has emerged as an important theme in the field since the

early 1970s. Numerous groups in the United States, Canada, Europe, and Asia have all made important contributions to studies of growth (Table 1).

In 1972, a remarkable and important U.S. Federal Act, Public Law 92–603, which affected clinical care, provided that Medicare would cover the cost and medical care for both dialysis and transplantation for individuals, including children, with end stage renal disease. This act expanded adult dialysis services and led to the development of chronic pediatric dialysis services and strong interest in pediatric transplantation (21, 22, 43–46). The importance of Public Law 92–603 is that it provides renal replacement care for "that stage of renal impairment that cannot be favorably influenced by conservative management alone and requires dialysis and/or kidney transplantation to maintain life or health" (47). The noteworthy feature of this act was that children with young parents could receive an expensive form of therapy—hemodialysis and renal transplantation—without consuming all of the assets of the family. The principal pediatric nephrologist working with adult nephrologists, the NKF, the ASN, and transplant surgeons in developing support for this bill was Greifer at Einstein in New York. He effectively lobbied with adult-oriented colleagues to move this agenda forward in the world of Washington, DC politics.

Because of universal health care coverage in Western Europe, the organization of pediatric dialysis and transplant centers occurred as part of each nation's health system.

IV. RESEARCH THEMES SINCE 1970

By the late 1970s research developed in the discipline of pediatric nephrology around several key themes: *1*) renal micropuncture and microperfusion; *2*) the anatomy, physiology, biochemistry, and cell biology of renal development; *3*) growth failure and impaired nutritional status in children with renal disease; *4*) inherited acid-base disorders in children; *5*) glomerulonephritis and mechanisms of glomerular injury; *6*) the effect of vesicoureteral reflux and factors important in reflux nephropathy; *7*) clinical features and immunology of the nephrotic syndrome; *8*) the causes, pathogenesis, and therapy of the hemolytic uremic syndrome; *9*) the epidemiology, clinical features, and pathogenesis of acute post streptococcal-glomerulonephritis (and other post-infectious causes); *10*) inherited renal tubular disorders; *11*) renal osteodystrophy; *12*) the biology, immunology, and clinical features of renal transplantation; and *13*) dialysis techniques and kinetics (48) (Table 3). Several renal diseases are mostly found in children and were the subject of inquiry: the hemolytic uremic syndrome (HUS), Henoch-Schönlein purpura, cystinosis, Lowe syndrome; minimal lesion nephrotic syndrome, congenital nephrotic syndrome, acute post-infectious glomerulonephritis, and posterior urethral valves. Other major areas of research focus have included pediatric hypertension, childhood renal osteodystrophy, cystic diseases of kidneys, renal dysplasia, hypoplasia, agenesis, and renal vein thrombosis in neonates (49). These disorders have received extensive attention by pediatric nephrologists, and important advances in the pathophysiology, physiology, genetics, and etiology of these conditions has occurred. For example, the role of Shigella-like toxins produced by *Escherichia coli* 1057:H7 and other *E. coli* strains in the etiology and pathogenesis of HUS is now recognized (50). The role of renal parenchymal atrophy in the failure of the synthesis of $1,25(OH)_2$ vitamin D has also been established (51).

The discipline of pediatric nephrology has been and continues to be engaged in research studies on infections of the lower urinary tract, of the renal parenchyma and of their relation to obstruction and reflux. Studies in these areas have been strongest in the United Kingdom, Europe, and Japan, particularly the studies of Jean Smille (UK), Jan Winberg (Sweden), D. Innes Williams (UK), and Hans Olbing (Essen). However, several U.S. Centers have placed emphasis on these areas especially University of Virginia (Robert Chevalier), University of Missouri-Kansas City (Stanley Hellerstein), and University of Texas Southwestern (Billy S. Arant). Another effective means of collaboration to pursue these research topics occurred between pediatric urologists and nephrologists.

By the late 1960s The American Board of Internal Medicine had developed a Sub-Board in Nephrology. Because adult nephrologists were becoming involved in renal replacement therapy, it was deemed necessary to certify pediatricians who could care for uremic children. As well, because there existed a scientific basis for the discipline in pediatrics, a Sub-Board was appropriate. The initial Sub-Board members were Wallace McCrory (Chair), Keith Drummond, M.A. Holliday, C. William Daeshner, Chester Edelmann, Alfred Michael, and Luther Travis. The first certification examination was given in 1974 and every 3 years since. While no European Board of Pediatric Nephrology has been established, this may occur as the European Union further develops.

The American Academy of Pediatrics developed an active section in pediatric nephrology, which chooses senior pediatric nephrologists who have made major contributions to the field as recipients of an annual Henry Barnett award.

Since the early 1980s, pediatric nephrology research has moved from descriptive studies to a more mechanistic approach with the use of biochemical, molecular biologic, and cell biologic approaches (52, 53). As mentioned, a dominant theme in pediatric nephrology has remained growth and the best means to optimize the growth of children with chronic renal disease (54, 55). The use of hormones, reversal of acidosis, improvement in nutritional intake, intensified dialysis, and predialytic transplantation have all been advocated to reverse growth failure (56).

Fundamental research in pediatric nephrology has received considerable national recognition. Since 1939, 13 recipients of the E. Mead Johnson Award in Pediatric Research have been active in renal-related research. Four pediatric nephrologists—Henry Barnett, Renee Habib, Robert Vernier and Clark West—have won the John P. Peters Award of the ASN, and one, Alan Krensky, has won the Young Investigator Award from the same society for his studies in transplantation immunology.

In 1976, shortly after the description of chronic ambulatory peritoneal dialysis, it was recognized that this form of therapy would be of particular value in children (57). It has been widely used in children since 1980. Because of the small size

of blood vessels required for vascular access, peritoneal dialysis was an appealing option in smaller children. In larger children this form of therapy would permit more consistent school attendance. At present this technique and modifications made to improve this method are more widely used in children than in adults. Aside from bacterial peritonitis from catheter and tunnel contamination as a side effect, this method offers the child and family greater freedom. This technique has led to numerous clinical research studies.

Because National Institutes of Health study sections have little pediatric expertise, it became necessary for the ASPN to lobby for more pediatric nephrology representation and to emphasize areas of important research focus. This public policy function of the ASPN has expanded over the past 20 years. An increasing number of requests for proposals have covered topics relevant to pediatric nephrology and have resulted in substantial extramural support for these areas. Among other aspects, it demonstrates the spirit of cooperation prevalent in the discipline as well as the need to vigorously campaign for extramural funding to examine the relevant questions in the field. This same spirit has permitted the development of several multicenter networks aimed at enhancing research activities and improving the quality of patient care through prospective studies. Among these are the Southwestern Pediatric Nephrology Study Group, the New York–New Jersey Pediatric Nephrology Group, regional groups such as the North American Pediatric Renal Transplantation Cooperative Study (NAPRTCS), and others (58). These groups have published extensively and involve far more patients in clinical and medication trials than possible from single center studies.

After meetings in 1985, a publications sub-committee of IPNA determined that a new pediatric nephrology journal should be established to serve the pediatric nephrologists of the world. This journal would become the official publication of IPNA as well as the American Society of Pediatric Nephrology (ASPN), the European Society of Pediatric Nephrology, the Japanese Pediatric Nephrology Society, the Asian Pediatric Nephrology Society, and the Association of Latin American Nephrology in Pediatrics. With Sir Cyril Chantler (London) and Alan Robson (New Orleans) as its founding editors, it is now in its 15th year and receives more than 300 manuscripts annually. This journal publishes peer reviewed original articles and brief reports in clinical pediatric nephrology and basic science, as well as invited reviews on a variety of topics, and several other features, including rapid publications, clinical quizzes, letters to the editors. The Journal has an American and European Editor and manuscripts are always reviewed on both continents.

V. THE FUTURE OF PEDIATRIC NEPHROLOGY: 1990 ONWARD

As the field of pediatric nephrology enters the new century, the research portfolio of the discipline is richer. Numerous groups are investigating the development of the renal vascular system, the ontogeny of the renin-angiotensin and aldosterone system, the mechanisms of cell recovery from hypoxic injury, transcription factors important in apoptosis and renal cell differentiation, and the elucidation of gene abnormalities in a variety of hereditary renal disorders including Bartter syndrome, Liddle syndrome, cystinosis, pseudohypoaldosteronism, polycystic renal disease, and other conditions (59). A large European multination consortium has been particularly successful in discovering mutant genes in hereditary renal disease. The role of molecular mechanisms is being examined as a basis for glomerular injury (60). Newer modalities of anti-rejection therapy permit a 1-year renal allograft graft survival rate of more than 95% (61). The field of pediatric nephrology continues to use contemporary molecular biologic tools (62), to more clearly define familial and genetic factors important in renal disease (63), to explore new technologies to enhance therapy of renal failure (64), to reexamine old "truths" in the light of new information (65), and to reassess clinical issues in the light of current imaging techniques (66).

The field of pediatric nephrology has come a long distance from its status 50 years ago, of which Robert E. Cooke stated "the abysmal ignorance that exists in the field of clinical renal disease is illustrated by the deficiencies that exist, such as the inability to determine whether we are dealing with such obvious clinical conditions as glomerulonephritis or pyelonephritis, conditions that, as medical students, we are taught were clear-cut entities; likewise that nephrosis was a definite disease" (67). Methods such as organ culture, cell signaling, *in situ* hybridization, transgenic and knockout mouse models, positional cloning, and elucidation of the human genome have begun to close this abyss. The knowledge base of pediatric nephrology continues to expand and to support strong improvements in patient care. However, equally as important, the world's pediatric nephrologists are bound together through the IPNA and its broad-ranging programs of support in education and publication. The discipline enthusiastically celebrated its 53rd anniversary of ACTH therapy in nephrotic syndrome, and 30th international anniversary at the IPNA Congress in Seattle in September 2001.

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