

**“STUDIES RELATED TO DISEASES AFFECTING
THE KIDNEY AND URINARY TRACT IN CHILDREN
AND THEIR MANAGEMENT ”**

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My role in the introduction of paediatric nephrology to RAHC in 1966 would not have been possible without the support of Sir Norman Gregg, President, Board of Management, RAHC, Professor Thomas Stapleton, Director, Institute of Child Health, RAHC, Dr Phillip McReady General Superintendent, RAHC,, Dr JD Harley Director, Children's Medical Research Foundation (CMRF), Dr RDK Reye, Director, Dept of Pathology and Dr SEJ (Sandy) Robertson, Paediatrician. From 1970 to 1972 I studied as a Fellow in Pediatric Nephrology at The University of Minnesota supervised by Dr Alfred Michael and Dr Robert Vernier, two of the pioneers of paediatric nephrology. In Minnesota I worked closely with Dr Michael Mauer and Dr Gunnar Westberg who were also Fellows and was greatly assisted by Ms Sue Sisson in preparation of tissue for electron microscopy and the use of the electron microscope. In 1972 I returned to Sydney and was appointed Staff Physician in Nephrology. With the assistance of Dr David Tiller at RPAH I set up a combined dialysis and transplant service for children with end stage renal failure. I was fortunate to collaborate in clinical studies related to renal failure with Professor Ross Sheil, Professor John Horvath, Professor Geoff Duggin and Professor James May.

I was provided with laboratory space in the CMRF and joined by Pamela Worsdall, Biochemist, who provided support in development of laboratory studies. Dr Geoffrey Zhang, biochemist, joined us later and assisted in the studies of children with cystinosis. I am indebted to Dr Jerry Schneider, University of California, San Diego, USA in whose laboratories Dr Zhang learnt the technique of estimation of white blood cystine used to monitor therapy in children with cystinosis. Dr Tony Pollard, Biochemist at the Women's and Children's Hospital, Adelaide, collaborated in the early studies of cystinosis.

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to studies related to urinary tract infection in childhood.

I am also grateful to Ms June Fletcher, a trained nurse who, in 1980, devoted a year travelling in New South Wales, measuring the blood pressure of nearly 10,000 normal children providing normative data which is still used

The preparation of this thesis would not have been possible without the editorial assistance of my daughter Jane and the secretarial assistance of my wife Joyce

STATEMENT

I hereby certify that the work presented in this thesis is the result of original research that I have undertaken. Under “Acknowledgements” and within the “Theme” I have acknowledged the contribution of supervisors, colleagues and collaborators. The work has not been submitted for a higher degree to any other university or institution.

Leslie Paul Roy

Date _____

DEDICATION

I dedicate this thesis to my wife, Joyce, to our son Simon, his wife Catherine (nee Szentkuti) and their sons Nicholas, Max and Liam, and to our daughter Jane and her husband Thomas Hikade.

THEME FOR DOCTOR OF MEDICINE THESIS ENTITLED:

“STUDIES RELATED TO DISEASES AFFECTING THE KIDNEY AND URINARY TRACT IN CHILDREN AND THEIR MANAGEMENT”

Publications 1-49 represent studies that I have undertaken myself or conjointly over a 34 year period to investigate a variety of issues relating to diseases of the kidney and urinary tract in children. The studies were carried out at the Royal Alexandra Hospital for Children, Camperdown when I was Clinical Superintendent from 1968 - 1970; The Department of Paediatrics, University of Minnesota, Minneapolis, USA when I was Overseas Research Fellow of the Post Graduate Foundation in Medicine, University of Sydney, 1970 - 1972, then as Staff Physician in Nephrology at the Royal Alexandra Hospital for Children, Camperdown, 1972 - 1977, and then Head of that Department at the Hospital until 1995 and then as an Honorary Staff Specialist at that hospital. Some of the studies were done conjointly with members of the Renal Unit of Royal Prince Alfred Hospital where I hold an Honorary appointment and others conjointly with members of the Renal Unit of Prince Henry Hospital, Little Bay. I was appointed Clinical Associate Professor to the Department of Paediatrics and Child Health, University of Sydney in 1993.

In 1966 paediatric nephrology was in the early phase of development as a medical subspecialty. There was no definitive textbook, the first was published in 1975 (Pediatric Nephrology, Ed. Mitchell I. Rubin. Williams and Wilkins.). In the preface to the 2nd edition of Renal Disease (Blackwell) in 1967 the editor D.A.K. Black noted that he had included a chapter on paediatric aspects which had been planned for the 1st edition in 1962 but "it could not be arranged". In the chapter on Renal Disease in Children the author, D. Macaulay, comments that the mortality rate of acute renal failure in children was 50%.

When I joined the resident staff of the Royal Alexandra Hospital for Children in 1966, children with renal disease were managed by general paediatricians. There was no active program for the treatment of children with acute or chronic renal failure. A small number of kidney biopsies had been performed by Dr Trefor Morgan who, together with Dr Denis Wade, had taught me the technique while I was a resident medical officer at the Royal Prince Alfred Hospital in the preceding year. With the guidance and support of Dr S.E.J. Robertson and Dr C. Lee, Honorary Medical Officers, and Dr R.D.K. Reye, Head of the Department of Pathology, I began performing kidney biopsies on children at the request of the paediatrician in charge. In the same year, encouraged again by Doctors Robertson and Lee, and by J.C.M. Friend and J. Brown, I introduced peritoneal dialysis for the treatment of children with acute renal failure, a technique which I had also been taught by Dr Trefor Morgan whilst I was a resident at Royal Prince Alfred Hospital.

Dr Robertson encouraged me to present my experience in percutaneous renal biopsy in children at the Annual Meeting of the Australian Paediatric Association in 1968 and this study became the first paper I published in relation to disease of the urinary tract in children (1). In 1970 I was granted an Overseas Research Fellowship by the Post Graduate Foundation in Medicine, University of Sydney, to enable me to undertake a fellowship in the Department of Paediatrics at the University of Minnesota. I had the great fortune in

undertaking studies in the new discipline of paediatric nephrology and related research under the guidance of Dr A. F. Michael, Dr R.L.Vernier and Dr A. Fish. I acquired the techniques of immunopathology and electron microscopy.

On my return to Australia I established a Department of Nephrology at the Royal Alexandra Hospital for Children. I introduced immunofluorescent and electron microscopic studies for the kidney biopsies that I continued to perform and, with the support of Dr R.D.K. Reye, I provided the official reports of these studies until 1990. As a result these studies became part of the histopathologic service provided by the hospital. I continue to be consulted concerning the interpretation of some electron microscopic findings in renal tissue. With the assistance of Dr J.D. Harley I set up a laboratory in the Children's Medical Research Foundation to continue and expand the studies I had commenced during my Fellowship.

Establishing a dialysis and transplant program for children with end stage renal disease (ESRD) was extremely time consuming. At that time most children with ESRD died. The program was initially established jointly with the Renal Unit at Royal Prince Alfred Hospital in 1972 and eventually dialysis facilities were established at the Children's Hospital using predominantly peritoneal dialysis. By 1978 the existence of the Unit was well known in the general community and articles appeared in the press. One prompted the late Sir Lorimer Dods, the first Professor of Paediatrics in Australia to write to me congratulating me on what I had achieved. He remarked "I have just read with special interest Shaun's review in the SMH of some of your recent achievements in the field of renal failure in infancy and childhood and want to offer you my personal congratulations on all that you have achieved and are achieving in this area of paediatrics which, in my little world of yesterday, meant nothing more than progressive and unrelenting fatal illness".

Taking part in the development of a relatively new discipline led me to study a number of areas. I encouraged trainees to write reports concerning clinical observations and eventually I was joined by Fellows whom I encouraged and supported to study a number of different areas to ensure that children were being cared for in an environment of strong and open enquiry. This led to studies on investigations of chronic renal failure which Dr Elisabeth Hodson pursued and studies on urinary tract infection in small children for which Dr Jonathon Craig was awarded a PhD. As I had been a contributor and co-author in a number of these studies they have been included in my list of publications. As a result of this diversity I have listed the publications in 9 sections. The overall theme is to study diseases of the renal tract in children and treatments used to understand the processes and ensure the most effective treatment.

Some published abstracts of papers presented at scientific meetings have been included to clarify invitations I received to prepare reviews and chapters on various subjects and my involvement in some conjoint studies. I was author or coauthor of several book chapters, reviews, editorials and certain published studies to which I was invited to contribute as a result of my primary studies and these I have included as "Derivative References" numbered 50-76.

SECTION 1:

HISTOLOGY, IMMUNOCHEMISTRY AND ELECTRON MICROSCOPY OF RENAL TISSUE

The first formal studies of the use of kidney biopsy to study kidney disease in childhood were published in 1957. I was fortunate to study with Dr Robert Vernier who was the co author of one of the papers (77), along with Dr Robert Good and Dr Marilyn Farquhar. In the succeeding 12 years most of the reports dealt with specific applications of kidney biopsy or associated complications. Paper 1 describes my application of the technique for a variety of indications rather than to study a particular disease. The analysis demonstrated the relative safety of the technique and was the first step in the process which has led to a refinement of the indications of the procedure. This was the first published study of renal biopsy of children in Australia. Although Dr R.D.K. Rye reported the histology and reviewed the microscopy with me he felt his contribution did not require him to be a co-author. Papers 2-4 relate to studies I undertook at the University of Minnesota during my Fellowship.

Dr Vernier had shown that protein load proteinuria in experimental animals resulted in effacement of the foot processes of glomerular epithelial cells (78) and Dr Alfred Michael and his group had shown the disappearance of the sialic acid containing polyanion on the surface of epithelial cells in aminonucleoside nephrosis (79). Paper 2 describes a study in which I demonstrated that protein load proteinuria in the experimental animal also leads to diminution of the glomerular polyanion thus suggesting, as has been reported, that these changes are a secondary process. I confirmed effacement of epithelial foot processes by electron microscopy. The mechanism of proteinuria in nephrotic syndrome with minimal glomerular pathology remains uncertain.

I had commenced my studies of glomerular disease reported in Papers 3 and 4 when Dr Michael was asked to prepare a review of etiologic agents in immune deposit disease. He asked me to undertake the review which he co-authored with Dr Fish and Dr Vernier. This provided immunopathologic, electron microscopic and infectious data related to various forms of glomerulonephritis (50).

A syndrome of recurrent macroscopic haematuria in children which seemed relatively benign had been known for some time. Deposition of IgA in patients with haematuria had been recently described and I studied the findings of 16 children who had the syndrome of recurrent macroscopic haematuria and who had had a kidney biopsy. This illustrated that not all children with this syndrome have IgA deposition and a small proportion have no evidence of deposition of immunoglobulin or complement in the glomeruli. The study also indicated that the presence of proteinuria and/or hypertension were the principle adverse prognostic indicators which has been repeatedly confirmed since. This paper was cited many times in the ensuing 25 years including in the chapter on IgA nephropathy in *Pediatric Nephrology* Holliday, Barratt & Avner, 3rd Ed. Williams & Wilkins, 1994.

The association between atopic phenomena and the nephrotic syndrome had been known for some time. While I was studying in Minnesota, a study by Gerber and Paronetto (80), suggested IgE was deposited in the glomerulus of children with this condition. This seemed inconsistent with the mechanism of action of IgE and I studied kidney biopsies of 9 children with this condition as well as 12 children with other forms of proteinuria and found no

evidence of the deposition of IgE (4). I had used rabbit anti human IgE whereas Drs Gerber and Paronetto had used goat anti human IgE. Dr Gerber kindly provided me with a sample of his antiserum which I was able to show caused some atypical staining of glomeruli after absorption with human IgE suggesting some type of non-specific cross reactivity. My involvement in this program of the study of immunologic basis of renal disease led Dr Alfred Michael to invite me to be a co-author of a review of immunologic aspects of nephrotic syndrome published in *Kidney International* (52). My study of recurrent haematuria also led to an invitation to me from the *Medical Journal of Australia* to prepare an editorial comment on the condition (51).

On return to Australia I continued these studies. In Paper 5 I illustrated the variability of focal sclerosing glomerulopathy, both the clinical manifestations and response to treatment. The role of specific therapies in this condition continues to be debated. In my studies of immunologic mechanisms of renal disease I had become interested in the alternate pathway of complement activation and the role of properdin. Paper 6 illustrated that in the Syndrome of Recurrent Macroscopic haematuria the alternate pathway of complement activation appeared to be involved although a systemic disturbance of complement could not be demonstrated. Paper 7 is a brief letter pointing out that an association between alpha-1 anti trypsin deficiency and membranoproliferative glomerulonephritis reported by Moroz et al (81), was almost certainly a chance association. My continued studies in the area of immunologic renal diseases led Dr A.F. Michael to ask me to prepare a chapter on this area for a book on immunologic disorders in infants and children (53). It also led to Dr M. J. Robinson, chief physician in the Professorial Medical Unit, University of Melbourne, to ask me to write a chapter on glomerulonephritis and related diseases including hypertension for a textbook that he was preparing on Practical Paediatrics (54).

Microangiopathic haemolytic anaemia and thrombocytopenia in children usually suggest the diagnosis of haemolytic uraemic syndrome. The recurrence of the phenomenon in a child with membranous nephropathy, an unusual condition in childhood, led me to encourage the registrar who was working with me at the time, to prepare a case report describing the observation (8).

Dr J. F. Knight studied with me as a Fellow and subsequently trained overseas in paediatric nephrology extending the interest in IgA nephropathy that he had gained in my department. His paper which I assisted him to prepare, (55), was presented at an International Symposium on the condition.

At this time I was approached by Professor Y. H. Thong, Department of Child Health, University of Queensland, to prepare chapters on Nephritic Syndromes, Acute and Chronic Renal Failure and Dialysis and Transplantation for a textbook on paediatric practice that he was editing (56).

SECTION 2:

COMPLEMENT STUDIES

Involvement of the complement pathways in the inflammatory process in glomerulonephritis remained an interest after I returned from the United States. In the laboratory I set up a variety of assays including assays for the alternate pathway of complement activation (9), and

C3 nephritic factor and alternate pathway components (10). Assays of the blood of a newborn baby whose mother had hypocomplementaemic mesangiocapillary glomerulonephritis showed the transient presence of C3 nephritic factor and reduction of complement component C3 (11). The baby remained well.

As a result of establishing these methods and assessing use I was invited to take part in the evaluation of the pathogenesis of a variety of conditions. Dr Kamath (57) invited me to study coeliac disease and I showed evidence of activation of serum complement by gluten challenge. Dr Charlesworth (58), (59), (60), invited me to be involved in studies of infectious mononucleosis, acute hepatitis and measles and I was able to show both complement pathways appeared to be involved in infectious mononucleosis but the classical pathway was predominantly involved in resolution of acute hepatitis and measles. Dr Andrew Kemp invited me to be involved in the study of yeast opsonisation and phagocytosis as this was thought to be a common defect in atopic individuals but this concept was not supported although I demonstrated that two of the 17 children with atopic dermatitis had defective alternate pathway activity (61).

SECTION 3:

URINARY TRACT INFECTION AND THE ROLE OF VESICoureTERIC REFLUX IN RENAL INJURY

Although urinary tract infection had long been recognised as a common problem, in 1970 there had been few local studies. As a result, and on the basis of my interest in renal disease in children, I was invited by the Post Graduate Committee in Medicine, University of Sydney, in 1969 to give a lecture on diagnosis and management of urinary tract infection in children. This was published (62) in the *Bulletin of the Postgraduate Committee of Medicine, University of Sydney*. In the section on treatment I included the suggestion that the combination of sulphonamide and trimethoprim, which is now widely used for the treatment and prophylaxis of urinary tract infections, would possibly prove to be the therapy of choice in the future. There was considerable concern about the the potential toxicity of the combination of sulphamethoxazole and trimethoprim and the following year I had the opportunity to observe and report the use of the combination for two infants with severe gram negative infections, one urinary tract infection and the other meningitis (12). The first infant received treatment with conventional dosage but unfortunately had a complex course, was submitted to surgery, developed septicaemia and pancytopenia and died. The second infant had meningitis due to E.coli and was failing to respond to conventional treatment. The child was given double the usually recommended dose of sulphamethoxazole and trimethoprim and, apart from what was considered marginal neutropenia after 5 weeks of therapy, made a complete recovery. This was the first time the combination had been used successfully in this way. Although not a controlled study such observations can be useful in the initial phases of the introduction of a therapy. Debate continues concerning the use of prophylaxis following urinary tract infection in children. Methenamine releases formaldehyde in an acid medium which is believed to be the mechanism by which it acts as a urinary antiseptic. It has been widely used for urinary prophylaxis. It was a general recommendation that during its use that ascorbic acid be administered in order to safely decrease the urine Ph and facilitate the action of the drug. Monitoring children I was disappointed that this had failed to produce urinary acidification. I then determined that the Vitamin C that was currently marketed was in the form of sodium ascorbate which would not be expected to acidify the urine and I reported a personal

experience that demonstrated urinary acidification could be achieved as long as ascorbic acid, which is distasteful to children, was used (13). This observation has been cited in the pharmacologic literature.

In 1978 I was invited by the editor of the *Australian Paediatric Journal* to write an editorial comment on an article discussing the localisation of Gram negative urinary infection in children and infants (63). The study had involved a relatively invasive process and showed that that method had relatively low sensitivity for reflux nephropathy. As a result I suggested that the need remained for a non-invasive screening test for reflux nephropathy. This issue continues to be discussed as will be mentioned subsequently.

Urinary tract obstruction is frequently associated with adverse outcomes when urinary tract infection occurs and is suspected when upper tract dilatation is present. Dr Robert Howman-Giles and I developed the concept of volume expansion diuretic renal scan using radionuclides to accurately determine the presence of obstruction (14). The procedure developed has become a standard procedure and the paper is frequently cited in the medical and veterinary literature. The report was included in Dr Howman-Giles's thesis in fulfilment of the requirements for the degree of Doctor of Medicine, University of Sydney.

Papers 15 to 21 were based on the study of urinary tract infection which Dr Jonathon Craig undertook under my supervision and for which he was awarded a PhD, University of Sydney. The studies confirmed the positive effect of circumcision on reducing the incidence of urinary tract infection on boys in the first year of life, demonstrated that micturating cystourethrography need not be deferred for a period after a urinary tract infection and illustrated the variability in reporting degree of reflux, illustrated the health burden of urinary tract infection in children and offered a clear epidemiologic description of symptomatic urine infection in preschool children in Australia. The studies also showed that DMSA scintigraphy after urinary tract infection is a reliable investigation to demonstrate renal parenchymal defects with little inter-observer variation. The studies also demonstrated that children under 6 months of age with urinary tract infection and high degrees of reflux are at increased risk of recurrence.

In 1999 I was invited by the *Australian Prescriber* to submit an article on childhood urinary infections (64). This paper reviewed the current literature including publications that occurred as a result of Dr Craig's PhD study and pointed out that changes were occurring in the approach to the investigation of children with urinary tract infections as a result of the availability of new investigations and concerns about the significance of vesicoureteric reflux. This concern was emphasised in a review of data collected by the Australian and New Zealand Dialysis and Transplant Registry from 1971 to 1998 which showed no reduction in the incidence of end stage renal disease diagnosed as reflux nephropathy in spite of this being a period of increasing intervention by antibiotic prophylaxis and surgery (22). These concerns were further emphasised in a meta-analysis (65) of randomised controlled trials of antibiotic and surgical treatment of vesicoureteric reflux. The conclusion was that it was uncertain whether identification and treatment of children with vesicoureteric reflux confers clinically important benefit.

The introduction of antenatal ultrasound resulted necessarily in the identification of any dilatation of the urinary tract that was present in the foetus. The immediate response was to assume that these children may have vesicoureteric reflux and, in early infancy, subject them to micturating cystourethrography and prescribe prophylactic antibiotic therapy if that

phenomenon was observed. I designed a randomised double blind placebo controlled trial of antibiotic prophylaxis funded by the National Health and Medical Research Council (NHMRC). We conducted a randomised double blind placebo controlled trial of prophylaxis in infants who have been found to have vesico ureteric reflux because of antenatal ultrasound observations or because of a family history. These children had never had a urinary tract infection. This study was funded by the NHMRC. In the 3 year follow- up period no difference was noted between the two groups (23). I examined these children at the follow up visits.

On the basis of these studies we are now conducting an NHMRC funded randomised double blind placebo controlled trial of antibiotic prophylaxis for children after first urinary tract infection, stratified according to whether or not they have vesicoureteric reflux. I am the senior investigator of this study. It is a multi-centre study involving the Royal Alexandra Hospital for Children at Westmead, the Department of Paediatrics and Child Health at the Canberra Hospital and the Royal Children's Hospital, Melbourne.

SECTION 4:

TREATMENT OF RENAL FAILURE, ACUTE AND CHRONIC

Dr John Brown and Dr Allen Oldfield are reported to have used peritoneal dialysis at the Royal Alexandra Hospital for Children in the late 1960s as treatment for barbiturate and salicylate poisoning. I introduced peritoneal dialysis as a conventional treatment for acute renal failure in 1966. An early observation (24) illustrates the need to consider the nature of a toxin causing acute renal failure which may not be amenable to removal by dialysis. Following my return to Australia after training in paediatric nephrology at the University of Minnesota, I was invited by the Postgraduate Committee in Medicine, University of Sydney, to give a presentation on acute renal failure in children at a weekend course in paediatrics. This was subsequently published (66).

In relation to the treatment of children with renal failure, I established formal procedures for their treatment and in 1980 I reported the outcome of the treatment of the first 35 children with end stage renal failure at the Royal Alexandra Hospital for Children. The outcome for very young children was positive and it was possible to emphasise that, contrary to certain attitudes in Australia at the time, treatment of children with end stage renal failure under the age of 5 years of age was appropriate and effective (25).

In 1980 I was invited to give a presentation at a Pan Pacific Symposium on peritoneal dialysis in Melbourne to be held under the auspices of Australasian Society of Nephrology, The Australian Kidney Foundation and Prince Henry's Hospital, Melbourne, on Paediatric Dialysis in Australia. I was able to describe the experience with 10 children in end stage renal failure being treated with intermittent peritoneal dialysis of whom only one had required transfer to haemodialysis and of whom four were attending school full time. A presentation was made at the meeting by Dr S.T. Boen who is credited with having introduced the concept of intermittent peritoneal dialysis and in their preface the editors state that the papers presented at the symposium were "written by leading investigators from around the world". My paper is published as part of the Proceedings of the Symposium (67).

In 1983 I was invited by the Australian Paediatric Journal to provide an editorial comment on an article describing the use of extended therapy for children with end stage renal failure in

Queensland. I was able to provide positive comment on the continued introduction of integrated treatment for children with end stage renal failure in Australia (68).

Dr Elisabeth Hodson, who is now the Head of the Department of Nephrology at Westmead Children's Hospital, joined me as a Fellow in 1980. She had an interest in growth retardation and renal osteodystrophy in children with chronic renal failure. I encouraged her to pursue this area and she spent time working with Dr Richard Evans at the Repatriation General Hospital, Concord. Subsequently two articles were published in this area (26),(27), which importantly demonstrated that while renal osteodystrophy could play a role in growth failure in children with chronic renal disease it may not be the major contributor. My role consisted in assisting in design of the study, appropriate management of the patients and review of manuscripts.

Growth failure was, and continues to be, a major concern for paediatricians caring for children with end stage renal failure. As the result of our involvement in a trial of immunosuppressive therapy in patients with end stage renal failure which involved an arm where patients were treated with cyclosporine alone without corticosteroids (28) we were able to observe catch up growth occurring in children in the non steroid arm of the trial (29,30). I had been responsible for the management of the children and recording their clinical findings and I reviewed the draft manuscripts. I supported and took part in the analysis of further data on factors affecting growth of children with chronic renal failure (31,32,33). The data for the article concerning the estimation of total body nitrogen (33) was reported by Professor Louise Baur in her thesis for PhD, University of Sydney.

All those involved in living related donation of non regenerative organs for transplantation have concerns for the potential physical, emotional and material adverse events which may occur. In 1986 Betty Liounis, a medical student, joined our Unit for an elective term. She illustrated considerable interest in psycho-social aspects of families of children who had had renal failure and I encouraged her to undertake a follow-up study of living related kidney donors. Typical at the time, this study included principally family donors, but there was one emotionally related donor. The study illustrated that donors are able to make a major contribution to the life and well-being of the child and that there did not appear to be any serious long term complications of the renal donation. Most donors commented that they had not been adequately warned of the pain that they may experience from the surgical procedure (34). The student conducted all the semistructured interviews and carried out the limited physical examinations. I supervised all phases of the study and was directly involved in data analysis and preparation of the report. This was the first study of this issue and has been widely quoted. The favourable outcomes in relation to the donors renal function and blood pressure is similar to the findings reported in a study described in Section 9 paper 47. Stimulated by this survey, Dr Hodson prepared a study, The Outcome of Treatment of Renal Failure, over the first 16 years in our Unit. As the result of the analysis it was clear that although both dialysis and transplantation are acceptable therapies for children with end stage renal failure, successful transplantation provided the best opportunity for satisfactory growth and development (35).

As a result of my long term involvement in the treatment of children with end stage renal disease and the analyses of outcomes I was invited to prepare an information document (69) as a reference for schools with information concerning renal failure and the dialysis treatment of renal failure as increasing numbers of children who were being treated with peritoneal and

haemodialysis were now attending school full time.

SECTION 5

BLOOD PRESSURE IN CHILDREN

The first study of blood pressure in normal children using auscultatory sphygmomanometry was published only nine years after Korotkoff reported his observations of the sounds now bearing his name in 1905 (82), (83). Various studies of blood pressure in children were subsequently published. In 1977 a formal report of blood pressure levels in a large group of normal children in the United States was published (84). It was important to establish normal ranges in other groups of children and in 1979 the Australian Kidney Foundation agreed to fund a survey of blood pressure levels of children in New South Wales. The study was supported by Professor David Tiller, Director of the Renal Unit of Royal Prince Alfred Hospital at the time, and statistically studies were undertaken by David L. Jones a medical statistician at the New South Wales Department of Health. Centile values were established for children aged from 5-13 years. Children's height and weight were also measured and this gave data which strongly suggested that blood pressure was related to size rather than age and that obesity also seemed to have an individual effect. The data provided by this study continues to be used in standard charts in hospitals. It has been cited on 14 occasions. The publication was accompanied by a positive editorial written by Professor Colin I. Johnston from Monash University. As a result of the study and subsequent studies I was invited to prepare an editorial comment for the *Medical Journal of Australia* (70) and to prepare an article for the *Indian Journal of Paediatrics* (71) on drug therapy in childhood hypertension. I was also invited by the National Heart Foundation to provide recommendations for the management of high blood pressure in the young in a brochure that the Foundation was preparing concerning the management of blood pressure (72). My interest and contribution in the area further led to the *Journal of Paediatrics and Child Health* to invite me to submit an editorial comment on the measurement of blood pressure in children in 1997 (73).

SECTION 6

NEPHROTIC SYNDROME AND PROTEINURIA

The majority of my studies in relation to nephrotic syndrome blend into studies reported in Section 1. However, in 1977, Dr Carmelo Alfiler from the Philippines joined my Unit as a Fellow and demonstrated interest in a number of areas including the possibility that there may be genetic markers for the risk of steroid responsive nephrotic syndrome. I encouraged him to undertake a study conjointly with the tissue typing laboratory, the Red Cross Blood Transfusion Service in Sydney, which resulted in the first observation of an association between an HLA-DR antigen (HLA-DRw7) and nephrotic syndrome in spite of the fact that no relationship existed between this antigen and atopy (37). My role was to ensure valid case selection and to review the draft manuscript. This article has been cited on 45 occasions from 1981 to 2002 including Chapter 38 on Nephrotic Syndrome Pediatric Nephrology Ed Holliday, Barratt & Avner; 3rd Ed, Williams and Wilkins 1994.

As a result of my demonstrated interest in this area, Dr C. S. Pokorny, the Honorary Secretary of the Board of Continuing Education of the Royal Australasian College of Physicians, who

was series editor of *Medicine Today*, invited me to submit an article on the investigation of the child with unexpected proteinuria (74). This article was subsequently republished by permission in the Middle East Edition of *Modern Medicine*.

SECTION 7

INHERITED METABOLIC DISEASES: (A)CYSTINOSIS,(B) SYNDROME OF APPARENT MINERALOCORTICOID EXCESS

7A Cystinosis

Cystinosis is a rare disease which causes multisystem problems and in particular, end stage renal failure. It is due to intracellular accumulation of cystine crystal formation recently demonstrated to be due to a defect in membrane transport of cystine. In 1976 Thoene et al reported that a variety of aminothiols would reduce the cystine content of cultured fibroblasts (85). One of these aminothiols, cysteamine, had been used for other medical purposes and was trialled as oral medication in a child with the disease. The trial demonstrated that on the use of the compound intracellular cystine content was reduced to normal. Unfortunately the child suffered a seizure after one month of treatment and the compound was withdrawn. Prompted by this study and the apparent safety when used to treat other conditions I obtained a supply of cysteamine hydrochloride and administered it regularly to a child with cystinosis (38). This study was done in conjunction with Dr A.C. Pollard from the Department of Chemical Pathology at the Adelaide Children's Hospital who measured intracellular cystine concentrations in neutrophil samples I arranged for him to receive. We demonstrated that the compound reduced intracellular cystine content to normal and during that period no complications occurred and the child volunteered that her photophobia (caused by cystine deposition in the cornea) had improved. Over the initial period of nine months no adverse affects were noted. In spite of the initial problems with intolerance to a distasteful compound, I vigorously followed a program in attempting to have children with cystinosis regularly receive cysteamine orally. Large trials were commenced shortly after this study was published which verified safety and benefits although it is now clear that the apparent improvement in photophobia was not related directly to the therapy.

The paper has been cited on 15 occasions. I subsequently arranged the establishment of an assay for polymorphonuclear leucocyte cystine content in the laboratories for the Centre of Kidney Research at the Royal Alexandra Hospital for Children at Westmead (39). The service is used nationally to monitor the intracellular content of cystine in children with cystinosis being treated with cysteamine. A family I was caring for whose child had cystinosis had a second child affected. This child was commenced on cysteamine in early infancy and demonstrated normal growth (40). The child did eventually develop end stage renal failure but significantly later than usually occurs and without other systemic manifestations of cystinosis. There were many problems involved with the introduction of cysteamine treatment for children with cystinosis and I was involved in a number of processes involved in maintaining availability. In 2002 I was invited to visit the Department of Paediatrics, Indiana University USA, as the William C. and Ruth P. Griffith Visiting Professor and provide a presentation on cystinosis. In 1986 I was invited to prepare a summary concerning hereditary and tubular renal disorders for *Medicine International*(75).

7B Syndrome of Apparent Mineralocorticoid Excess

In 1989 I was invited by Professor John Funder from the Medical Research Centre, Prince Henry Hospital, Melbourne, to take part in a study of the rare disorder Pseudohypoaldosteronism (PHA). I was responsible for the care of a family affected by this rare syndrome. The study tested a hypothesis relating to inappropriate binding of mineralocorticoid and glucocorticoid receptors in PHA and in the Syndrome of Apparent Mineralocorticoid Excess. Four children in the family I was caring for were given carbenoxolone to inhibit 11 β -hydroxysteroid dehydrogenase. I was responsible for prescribing the compound, arranging the collection and analysis of blood and urine samples and monitoring the care of the children. The result was marked mineralocorticoid effects with antinatriuresis and elevated plasma bicarbonate. This study has demonstrated that the phenomena of the syndrome are the result of binding of mineralocorticoid receptors by the intrarenal glucocorticoid excess (41). This study had a major impact on the understanding of this condition and prompted many further studies. It has been cited 100 times.

SECTION 8

HAEMOLYTIC URAEMIC SYNDROME

This syndrome occurs sporadically and in epidemics and in most children is related to gastrointestinal infection of a Shiga toxin producing *E. coli*. It causes acute renal failure which may lead to permanent renal damage. I encouraged my Fellow, Dr Alfiler, from the Philippines, to review our experience with this condition in 1965 to 1977 and I ultimately presented this information to the Australian College of Paediatrics (42). The principal finding of the review was that the outcome of the condition could be predicted with reasonable accuracy on the basis of the presentation and course of the acute illness. Extra renal complications are described in the condition particularly involving the central nervous system but in 1989 a child was admitted under our care who had hypoglycemia complicating the haemolytic uraemic syndrome (43). The child had diarrhoea associated disease and recovered with some impairment of renal function. The child had a marginally elevated serum amylase and responded to insulin which suggested that the complication may have been due to microvascular disease involving the pancreas. I encouraged Dr Bronwyn Crawford who was the Registrar to the unit at that time, to prepare the case report and I supervised the preparation of the report. A variety of conditions may be associated with microangiopathic haemolytic anaemia and thrombocytopenia. A child was treated in whom the syndrome appeared to complicate toxoplasmosis following bone marrow transplantation (44). I was responsible for the renal care of the child and assisted in preparation of the report.

SECTION 9

ILLUSTRATIVE CASE STUDIES

Over the years I have encouraged medical trainees to analyse unusual clinical incidences. The four papers in this section illustrate the outcome of this activity. I directly supervised data collection and analysis and preparation of the reports. Dr Howman-Giles, when a Registrar in my Unit, noted that a child developed extreme hypernatraemia while receiving hyperosmolar feeds given by gastrostomy. The child had developed appropriate thirst but this was met by a sham oral water intake as he had an oesophagostomy (45). This illustrated the need to carefully assess not only intake and output but the significance of biological responses such as thirst.

In 1976 dizygotic twins were seen who had rectal atresia then known as covered anus. Dr Albert Mansour was a medical registrar in the Unit at the time and I encouraged him to report our findings in the management of these children. He found there had been a previous report of the condition occurring in twins who were monozygotic and in that instance only one child was reported to be affected. In the children seen in our unit, kidney biopsies (reported by Dr R.D.K. Reye) showed that one of the twins had bilateral renal hypoplasia and oligomeganephronia whereas the other had normal kidneys (46).

Wilm's tumour is widely regarded as a malignancy of childhood which usually responds very satisfactorily to treatment. Dr Barrera joined my department as a visiting paediatrician in 1988 and undertook a long term follow-up study of patients who had had unilateral nephrectomy and radiotherapy for Wilm's tumour. She was able to show that the outcome was good for the majority but several patients were hypertensive and two patients had reduced renal function. It was suggested that consideration be given to reducing the dose of radiation given to children with Stage 1 tumour (47). This study has been cited 21 times in a variety of studies related to modifications and outcome of the treatment of Wilm's tumor and studies of the effect of unilateral nephrectomy in man and in experimental animals

Dr Stalens was a medical registrar in my department, and Dr Falk a Fellow, when a child was admitted with milky urine. Dr Stalens prepared a report describing the diagnosis of Chyluria in this child and the use of lymphoscintigraphy to be a satisfactory and less invasive investigation than lymphography to demonstrate the site of the fistula. Dr Howman-Giles performed the radioisotopes studies (48).

In 1987 I was asked to assist in the care of a child with hypertension associated with a nephroblastoma. He also had polydipsia. At that time control of hypertension in children under these circumstances was difficult and perioperative morbidity was high. As the mechanism of the hypertension was ischaemia there was a relative contraindication to treatment with angiotensin converting enzyme inhibitors. However, I made a clinical decision to use captopril which was effective and the child underwent an uncomplicated nephrectomy and subsequent therapy. His polydipsia abruptly ceased when captopril was started. Dr Graeme Suthers, who was registrar to the renal unit at the time, noted evidence that angiotensin had a direct effect on the "thirst centre" and I encouraged him to prepare the case report (49).

In 1985 Professor Judith Whitworth and Professor James Lawrence determined to prepare a

textbook of renal disease and invited me to prepare a chapter on paediatric nephrology (76). The first edition of the book was published in 1987 and the second edition in 1994. The chapter I submitted encompasses a broad area of paediatric nephrology commencing with the antenatal diagnosis of urinary abnormalities and is illustrated clinically and histologically. It concludes with a discussion of urinary incontinence disorders in children.

I was a foundation member of the International Pediatric Nephrology Association. This year the Association honoured me with the award of Honorary Membership “In recognition of distinguished contributions to Pediatric Nephrology”. The award was presented at the opening session of the 13th Congress of the Association in Adelaide.

