

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

L. PAUL ROY
MB BS BSc (Med) FRACP

Thesis submitted in fulfilment of the requirements
for the Degree of Doctor of Medicine,
University of Sydney

Department of Paediatrics & Child Health, University of Sydney;
Department of Nephrology,
Royal Alexandra Hospital for Children, Westmead, Sydney

February 2005

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

THEME OF THESIS

PUBLICATIONS

SECTION 1 : Histology, immunochemistry and electron microscopy of renal tissue.

1. Roy LP Percutaneous Renal Biopsy in Childhood.
Australian Paediatric Journal 1969; 5:8-12
2. Roy LP Vernier RC/ Michael AF/ Effect of Protein Load Proteinuria on
Glomerular Polyanion.
Proceedings of The Society of Experimental and Biological Medicine 1972;
141:870-/874
3. Roy LP Fish AJ/ Vernier RL/ Michael AF/
Recurrent Macroscopic Hematuria/ Focal Nephritis and Mesangial
Deposition of Immunoglobulin and Complement.
Journal of Pediatrics 1973; 82:767-/772
4. Roy LP Westburg GN/ Michael AF/
Nephrotic Syndrome: No evidence of a role for IgE.
Clinical and Experimental Immunology 1973; 13:553-/559
5. Roy LP Focal Sclerosing Glomerulopathy and the Nephrotic Syndrome.
Australian Paediatric Journal 1974; 10:235
6. Roy LP Properdin and Recurrent Macroscopic Haematuria.
Australian 7 N.Z. Journal of Medicine 1975; 5:191-/194
7. Roy LP Webster/ H.L. Alpha-/1-/anti-/trypsin
and Membranoproliferative Glomerulonephritis.
Pediatrics 1977; 60:784 (letter)
8. McDonald DT/ Roy LP Microangiopathic Haemolysis/ Thrombocytopenia
and Nephrotic Syndrome associated with Membranous Nephropathy in a
Vietnamese Boy.
Australian Paediatric Journal 1988; 24:311-/313

SECTION 2 : Complement studies

9. Roy LP, Worsdall, PA, Haemolytic assay of the alternate (properdin) pathway.
Australian Paediatric Journal, 1976; 12:233-234

10. **Roy LP, Worsdall PA, Acute post-streptococcal glomerulonephritis - complement studies.
Australian.Paediatric.Journal, 1978; 14:289**
11. **Roy LP, Worsdall PA, Transplacental transfer of C3 Nephritic factor(C3Nef)
Australian Paediatric Journal, 1980; 16:210**

SECTION 3 : Urinary tract infection and the role of vesicoureteric reflux in renal injury.

12. **Roy LP, Sulphamethoxazole-Trimethoprim in Infancy.
Medical Journal of Australia, 1971; 1:148**
13. **Roy LP, Acidifying effect of Ascorbic Acid.
New England Journal of Medicine, 1977; 297:1350 (letter)**
14. **Howman-Giles, R. Uren, Roy LP, Filmer RB
Volume Expansion Diuretic Renal Scan in Urinary Tract.
Journal of Nuclear Medicine, 1987; 28:824-828**
15. **Craig JC, Knight JF, Sureshkumar P, Mantz E, Roy LP, Effect of Circumcision on Incidence of urinary tract infection in preschool boys
Journal of Pediatrics, 1996; 128:23-27**
16. **Craig JC, Knight JF, Sureshkumar P, Lam A, Onikul E, Roy L.P,
Vesicoureteric
Reflux and timing of micturating cystourethrography after urinary tract infection.
Archives of Diseases of Childhood, 1997; 76:275-277**
17. **Craig J C, Irwig LM, Christie J, Lam A, Onikul E, Knight J F, Sureshkumar P, Roy L P, Variation in the diagnosis of vesicoureteric reflux using micturating cystourethrography.
Pediatric Nephrology, 1997; 11:455-459**
18. **Craig JC, Irwig LM, Knight JF, Roy LP, Trends in the health burden due to urinary tract infection in children in Australia.
Journal of Paediatrics and Child Health, 1997; 33:434-438**
19. **Craig JC, Irwig LM, Knight JK, Sureshkumar P, Roy LP, Symptomatic urinary tract infection in preschool children.
Journal of Paediatrics & Child Health, 1998; 34:154-159**
20. **Craig JC, Irwig LM, Howman-Giles RB. Uren RF, Bernard EJ, Knight JF, Sureshkumar P, Roy LP, Variability in the interpretation of dimercaptosuccinic acid scintigraphy after urinary tract infection in children.
Journal of Nuclear Medicine.1998; 39:1428-32**

21. Panaretto KS, Craig JC, Knight JF, Howman-Giles R, Sureshkumar P, Roy LP, Risk factors for recurrent urinary tract infection in preschool children. *Journal of Paediatrics & Child Health*, 1999; 35:454-459
22. Craig JC, Irwig LM, Knight JF, Roy LP, Does treatment of vesicoureteric childhood prevent end-stage renal disease attributable to reflux nephropathy? *Pediatrics*, 2000; 105:1236-41
23. Roy LP/ Irwig L/ Craig JC/ Knight JF/ Hodson EM/ Henderson-/Smart D/ Jones C/ Burke J. A multicentre double-/blind controlled trial of chemoprophylaxis in children with isolated vesicoureteric reflux. Proceedings of Pediatric Nephrology Seminar XXIX Miami/ Florida/ USA (University of Miami School of Medicine/ 2002: 109-/112

SECTION 4 : Treatment of renal failure, acute and chronic.

24. Brown J/ Dorman D/ Roy LP/ Acute Renal Failure due to overdosage of Colistin. *Medical Journal of Australia*/ 1970: 2: 923-/924
25. Roy LP/ Management of chronic renal failure in children *Australian Paediatric Journal*/ 1980: 16:137
26. Hodson EM/ Shaw PF/ Evans RA/ Dunstan CR/ Hills EE/ Wong SYP/ Rosenberg AR/ Roy LP/ Growth retardation and Renal Osteodystrophy in Children with Chronic Renal Failure. *Journal of Paediatrics*/1983: 103:735-/740
27. Hodson EM/ Evans RA/ Dunstan CR/ Hills EE/ Wong SYP/ Rosenberg AR/ Roy LP/ Treatment of childhood renal osteodystrophy with calcitriol or ergocalciferol. *Clinical Nephrology*/ 1985: 24:192-/200
28. Hall BM/ Tiller DJ/ Horvath JS/ Duggin GG/ Johnson JR/ Roy LP/ Hurley B/ Harris JP/ Rogers JR/ Stephen MS/ Boulas J/ Thompson JF/ May J.Sheil A.G Treatment of renal transplantation rejection. *Medical Journal of Australia*/ 1985: 142:179-/185
29. Knight JF/ Roy LP/ Sheil AGR/ Catch-/up growth in children with successful renal transplants immunosuppressed with cyclosporin alone. *Lancet*/ 1985: 1:159-/160
30. Hodson EM/ Knight JF/ Sheil AGR/ Roy LP/ Cyclosporin A as Sole Immunosuppressive Agent in Renal Transplantation in Children: Effect on Catch-/up Growth. *Transplant Proceedings*/ 1989: 21:1687-/1692

31. Hodson EM/ Brown AS/ Roy LP/ Rosenberg AR/ Insulin like growth factor-1/ growth hormone dependent insulin-/like growth factor binding protein and growth in children with chronic renal failure.
Pediatric Nephrology/ 1992; 6:433-438
32. Reed EE/ Roy LP/ Gaskin KJ/ Knight JF/ Nutritional intervention and growth in children with chronic renal failure.
Journal of Renal Nutrition/ 1998; 8:122-126
33. Baur LA/ Knight JF/ Crawford BA/ Reed E/ Roy LP/ Allen BJ/ Gaskin KJ/ Total body Nitrogen in children with Chronic Renal Failure and Short Stature.
European Journal of Clinical Nutrition/ 1994; 48:433-441
34. Liounis B/ Roy LP/ Thompson JF/ May J/ Sheil AGR/ The Living Related Kidney Donor: A Follow-up Study.
Medical Journal of Australia/ 1988; 148:436-444
35. Hodson EM/ Knight JF/ Sheil AGR/ Roy LP/ Harris JP/ Rogers JR/ Stephen M/ Boulas J/ Thompson JF/ May J/ End Stage Renal Failure in Children: 16 years Experience in one Centre.
Medical Journal of Australia/ 1990; 152:245-250

SECTION 5 : Blood pressure in children

36. Roy LP/ Tiller DJ/ Jones DL/ The Range of Blood Pressure in Australian Children.
Medical Journal of Australia/ 1984; 141:9-12

SECTION 6 : Nephrotic syndrome and proteinuria

37. Alfiler CA, Roy LP, Doran T, Sheldon A, Bashir H, HLA-DRw7 and steroid-responsive nephrotic syndrome of childhood.
Clinical Nephrology, 1981;14:71-74

SECTION 7 : Inherited metabolic diseases: cystinosis, syndrome of apparent mineralocorticoid excess

38. Roy LP, Pollard AC, Cysteamine therapy for cystinosis.
Lancet, 1978; 2:729-730
39. Roy LP, Zhang GY, Diagnosis of cystinosis and the heterozygote from polymorphonuclear leukocyte cystine content
Kidney International, 1993;45:1269
40. Roy LP, Normal growth in nephropathic cystinosis treated with Cysteamine.

Pediatric Nephrology, 1987; 1:C40

41. **Funder JW/ Pearce PT/ Myles K/ Roy LP Apparent Mineralocorticoid excess/ Pseudohypoaldosteronism/ and Urinary Electrolyte Excretion: Toward a redefinition of mineralocorticoid action.
FASEB Journal/ 1990; 4:3234-/3238**

SECTION 8 : Haemolytic uraemic syndrome

42. **Roy LP, Alfiler CA, Haemolytic Uraemic Syndrome: Follow-up of 32 patients.
Australian College of Paediatrics, 24th Annual Meeting .
Australian Paediatric Journal, 1978; 15:209**
43. **Crawford B, Roy LP, Knight JF, Hyperglycemia in Hemolytic Uremic Syndrome.
Journal of Paediatrics & Child Health, 1990; 26:225-226**
44. **Bergin M, Menser MA, Procopis PG, Roy LP, Shaw PJ, Stevens M.
Central Nervous system toxoplasmosis and haemolytic uraemic syndrome.
New England Journal of Medicine, 1987; 314:1540-1541**

SECTION 9 : Illustrative case studies

45. **Howman-/Giles RH/ Roy LP/ Extreme hypernatraemia in a child receiving gastrostomy feeding.
Australian Paediatric Journal/ 1976; 12:167**
46. **Mansour A/ Reye RDK/ Roy LP/ Oligomeganephronia with covered anus in Twins.
Australian Paediatric Journal/ 1977; 13:187-/192**
47. **Barrera M/ Roy LP/ Stevens M/ Long Term Follow-/up after Unilateral Nephrectomy for Wilm's Tumour.
Pediatric Nephrology/1989; 3:430-/432**
48. **Stalens J-/P/ Falk M/ Howman-/Giles R/ Knight JF/ Roy LP/ "Milky" urine -/
A Child with Chyluria.
European Journal of Pediatrics/ 1992; 151:61-/62**
49. **Suthers G.K/ Roy LP/ Stevens M/ Control of Nephroblastoma : Associated hypertension and polydipsia by Captopril.
Australian Paediatric Journal/ 1987; 23: 245-/246**

DERIVATIVE REFERENCES

50. Roy LP Fish AJ/ Michael AF/ Vernier RL/ Etiologic Agents of Immune Deposit Disease. In Progress. in Clinical Immunology/ Vol 1/ Ed Robert Schwartz/ Grune and Stratten/ N.Y. 1972
51. Roy LP Recurrent Haematuria -/ Editorial comment Medical Journal of Australia 1973; 142:1127-/1128 Kidney International/ 1973; 3: 105-/115
52. Michael AF/ McLean RH/ Roy LP Westburg/ NG/ Hoyer JR/ Fish AJ/ Vernier R.L/ Immunologic aspects of the Nephrotic Syndrome. Kidney International/ 1973;3:105-/115
53. Roy LP Fish AJ/ Michael AF/ Renal Disorders. In Immunologic Disorders in infants and children. Second edition. Ed. Stiehm ER/ Fulginiti VA/ WB Saunders/ Philadelphia. 1980
54. Roy LP Glomerulonephritis and related diseases. Hypertension. In Practical Paediatrics. Ed. Robinson/ M.J. Churchill Livingstone. 1986
55. Knight JF/ Falk MC/ Ng G/ Fanning GC/ Artlett/ CM/ Roy LP IgA Nephropathy: Immunogenic Studies of Australian Patients. Contributions to Nephrology/ 1995; 111:18-/23
56. Roy LP Nephritic Syndromes/ Acute and Chronic Renal Failure/ Dialysis and Transplantation. In Textbook of Paediatric Practice. Ed. Thong/ Y.H. Butterworths/ 1989
57. Roy LP, Kamath KR, Serum complement in coeliac disease. Australian Paediatric Journal, 1976; 12:210-211
58. Charlesworth JA/ Pussell BA/ Roy LP Lawrence S/ Robertson MR/ The Complement System and Infectious Mononucleosis. Australian and N.Z. Journal of Medicine/ 1977; 7: 23-/26
59. Charlesworth JA/ Lawrence S/ Worsdall PA/ Roy LP Boughton CR/ Acute Hepatitis: Significance of changes in complement components Clinical and Exp. Immunology/ 1977; 28: 496-/501
60. Charlesworth JA, Pussell BA, Roy LP, Robertson MR, Beveridge J, Measles infection: Involvement of the complement system. Clinical & Experimental Immunology, 1976; 24:401-406
61. Vernon J/ Kemp AS/ Van Asperen PP/ Worsdall PA/ Roy LP Yeast Opsonisation and Phagocytosis studied by a Visual Assay and Measurement of Neutrophil Chemiluminescence. Journal of Clinical & Laboratory Immunology/ 1984; 14:93-/97
62. Roy LP, The Diagnosis and Management Urinary Tract Infections in Children.

Bulletin of the Postgraduate Committee in Medicine University of Sydney. 1970; 25:174-177

63. **Roy LP, Localisation of the site of urinary tract infection. Australian Paediatric Journal, 1978; 14:141-142**
64. **Roy L. P. Childhood urinary infections. Australian Prescriber, 1999; 22:40-43**
65. **Wheeler D, Vimalachandra D, Hodson EM, Roy LP, Smith G, Craig JC. Antibiotics and surgery for vesico-ureteric reflux: a meta-analysis of randomised controlled trials. Archives of Diseases of Childhood., 2003; 88:688-694**
66. **Roy LP Acute renal failure in children Bulletin of the Post-/Graduate Committee in Medicine/ University of Sydney. 1974; 30:109-/112**
67. **Roy LP Paediatric dialysis in Australia In : Peritoneal Dialysis. Eds Atkins RC/ Thomson NM and Farrell PC/ Publishers. Churchill Livingstone 1981**
68. **Roy LP Treatment of children with end stage renal failure. Australian Paediatric Journal/1983; 19: 207 (editorial).**
69. **Roy LP Renal Failure (Dialysis) in Physical Disabilities: A Reference for Schools. Department of School Education/ NSW Government. 1994**
70. **Roy LP. Blood Pressure Levels in Children. Medical Journal of Australia/ 1988; 149: 117 (editorial)**
71. **Roy LP (1988). Drug Therapy in Childhood Hypertension. Indian Journal of Paediatrics/1988; 55:359-/371**
72. **Roy LP., High blood pressure in the young-what should be done. National Heart Foundation of Australia - Managing blood pressure, 1990**
73. **Roy L P, Measurement of Blood Pressure in Children. Editorial Comment Journal of Paediatrics & Child Health/ 1997; 33:477-/478**
74. **Roy LP, Investigating the child with unexpected proteinuria Medicine Today July 2000 Republished in Modern Medicine(Middle East Edition) 2001:18:48-50**
75. **Roy LP Hereditary and Tubular Renal Disorders. Medicine International/1986; 2: 1329-/1336**

76. **Roy LP, Paediatric Nephrology
In Textbook of Renal Disease Eds Judith A. Whitworth, J.R. Lawrence AO. 2nd
Edition 1994 page 411-428**

REFERENCES TO WORK OF OTHER SCIENTISTS

77. Farquhar MG, Vernier RL, Good RA, An electron microscope study of the glomerular in nephrosis, glomerulonephritis and lupus erythematosis
Journal of experimental Medicine 1957; 106:649
78. Vernier RL, Papermaster BW, Oliver K, Benet E, Good RA, Morphologic studies of the mechanism of proteinuria
American Journal of Diseases of Childhood, 1960; 100:476
79. Michael AF, Blau E, Vernier RL, Glomerular polyanion. Alteration in aminonucleoside nephrosis.
Laboratory Investigation ,1970; 23:649-657
80. Gerber MA, Paronetto F, IgE in glomerular of patients with nephrotic syndrome
Lancet, 1971; 1:1097
81. Moroz SP, Cutz E, Balfe JW, Sars-Korlsak, Membranoproliferative glomerulonephritis in childhood cirrhosis associated with alpha-1 antitrypsin deficiency.
Pediatrics, 1976; 57:232-238
82. Judson CF, Nicholson P, Blood pressure in normal children
American Journal of Disease of Childhood, 1914; 8:251-268
83. Korotkoff HC, Transactions of the Imperial Academy of Medicine St Petersburg
1905; 11:365
84. Report of the Task Force on Blood Pressure in Children
Pediatrics, 1977; 59 (Suppl):797-820
85. Thoene JG, Oshima RG, Crawhall JC, Olson DL, Schneider JA, Intracellular cystine depletion by aminothiols in vitro and in vivo.
Journal of Clinical Investigation, 1976; 58:180-188

ACKNOWLEDGEMENTS

The work in this thesis has been made possible by the encouragement, support and collaboration of a number of paediatricians and investigators over a period of 30 years, initially at Royal Prince Alfred Hospital (RPAH) and the Royal Alexandra Hospital for Children (RAHC) Camperdown, Sydney, and then for 2 years at the University of Minnesota, Minneapolis, USA. The studies then continued in Sydney at RAHC and RPAH. The studies were funded by the Postgraduate Foundation in Medicine, University of Sydney, the National Kidney Foundation, USA, Kidney Health Australia, (previously The Australian Kidney Foundation), The Children's Medical Research Foundation, Sydney, The National Health and Medical Research Foundation, and Manildra Holdings.

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.

In succeeding years I was joined by Fellows who took part in a variety of studies. Dr Elisabeth Hodson now Head of Nephrology at RAHC, Dr Carmelo (Mike) Alfiler, Dr Mohammed Hanif, Dr John Knight, Dr Fiona Mackie, Dr Michael Falk, Dr Magaly Barrera and Professor Jonathan Craig. I was fortunate to have ongoing support and collaboration from members of the staff of RAHC including Dr Dennis Arnold, Professor Louise Baur, Dr John Boulas, Dr Chris Cowell, Professor Kevin Gaskin, Dr Robert Howman-Giles, Professor Craig Mellis, Professor Kim Oates, Professor John Overton, Professor Martin Silink, and Dr Michael Stevens. Ms Margaret English and Ms Jill Farquhar played a critical role in the nursing care of the children and helped immensely in creating an environment in which critical questioning of methods of investigation and treatment were the norm.

The staff of the Centre for Kidney Research, RAHC provided valuable support to this work and special thanks are due to Premala Sureshkumar, Scientific Officer, for her contributions

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