

## Vesicoureteric Reflux

Clinical and Laboratory Research Including Investigation of the Role and Risks of Plastics

A Thesis for the Degree of Doctor of Philosophy in the University of Adelaide

PA DEWAN

MD MS BMedSc FRCS FRACS

### Contents

Table of Contents Acknowledgements Summary Introduction	4 8 9 11
PART I	
Studies of the Endoscopic Management of Vesicoureteric Reflux	
Introduction Other Related Research	21 22
STUDY 1	
Endoscopic Management of Primary Vesicoureteric Reflux in Irish Children	27
STUDY 2	
Endoscopic Management of Vesicoureteric Reflux in Children with Spina Bifida in Ireland	31
STUDY 3	
Endoscopic Management of Vesicoureteric Reflux into Duplex Ureters	36
STUDY 4	
Endoscopic Correction of Vesicoureteric Reflux in Infants	41
STUDY 5	
Endoscopic Management of Vesicoureteric Reflux in South Australian Children - Short-Term outcome	47
STUDY 6	
Endoscopic Management of Vesicoureteric Reflux in South Australian Children - Long-Term Follow-up	52
STUDY 7	
Correlation of the Endoscopic Appearance with Clinical Outcome of Submucosal Polytef Paste Injection in Vesicoureteric Reflux	55
Endoscopic Management of Vesicoureteric Reflux	
Discussion	60
Distribution.	

#### PART II Risks of Plastics - Laboratory and Clinical Studies 82 Introduction LABORATORY STUDY 1 Short-Term Response to Subcutaneously and Intravenously Injected Polytef and Bioplastique in a Rat Model 86 Materials and Methods 88 Results **LABORATORY STUDY 2** Long-Term Histological Response to Subcutaneously Injected Polytef and Bioplastique in a Rat Model 97 Materials and Methods Results 99 Polytef 100 Bioplastique 102 Control **LABORATORY STUDY 3** Long-Term Histological Response to intravenously Injected Polytef and Bioplastique in a Rat Model 103 Materials and Methods Results 104 Polytef 106 Bioplastique LABORATORY STUDY 4 Histological Response to Injected Polytef and Bioplastique in the Sheep Brain 107 Materials and Methods Results 108 Ten minutes 108 Six months LABORATORY STUDY 5 An In Vitro Study of Silicone Migration from Intravenous Fluid Tubing as used in Paediatric Practice 111 Materials and Methods 112 Specimen Preparation 113 Results

Skin Migration Following Periurethral PTFE Injection for Urinary

120

STUDY 6: - Case Report of Migration

Incontinence

STUDY 7: - Vascular Access Device	
A Study of Particulate Migration In Vivo from an Implanted Vascular Access Device used in Paediatric Practice	
Introduction Materials and Methods	122 122
Results Detailed Patient Specimen Infuse-a-port Results Infuse-a-port and Sample 13 Summary	129 132 139
Risks of Plastics - Laboratory and Clinical Studies	
Discussion	140
PART III	
Vesicoureteric Reflux - Clinical and Laboratory Studies	
Introduction	155
STUDY 1	
Surgical Management of VUR	
Patients and Methods Results	157 159
STUDY 2	
Progressive Antenatal Renal Deterioration Associated With High Grade Vesicoureteric Reflux	
Introduction Patients and Methods Results	165 175 175
STUDY 3	
Infant Pig Model of Vesicoureteric Reflux	
Introduction Materials and Methods Results	181 181 182
STUDY 4	
Ureteric Tunnel Incision in the Fetal Pig: A Model for Non-obstructive Pre- natal Vesicoureteric Reflux	
Introduction Materials and Methods Results	183 183 186

# Vesicoureteric Reflux - Clinical and Laboratory Studies

Discussion	189
Overview of Clinical and Laboratory Studies	229
References	231
Publications	267
Conference Paper Presentations	269
Glossary	271

#### Summary

The understanding of vesicoureteric reflux (VUR) has still only reached the level of "expanding ignorance". This state of affairs is because past workers have often drawn conclusions which, in retrospect, have been based on inadequate evidence. The Ransley and Risdon theory of the "big bang" is one of the best examples, where the renal injury was attributed to the first infection: it has now come to light, with the advent of frequent use of pre-natal ultrasound, that many of those with VUR have abnormal renal parenchyma before infection has occurred [1].

This study was undertaken to review the outcome of the application of new technology for the endoscopic management of VUR and, more importantly, to investigate how the subcutaneous tissue, lung and brain of animals respond to Teflon and silicone. The results, and the literature, indicate that injections under the ureteric orifice can cure VUR and that the tissue response to the plastics becomes quiescent. The question of malignant risk remains open, but the risk would appear low, possibly lower with the smaller Teflon particles than for the larger silicone microspheres.

The research into embolisation from solid implants from intravenous tubing and the possibility of antibody formation to implanted plastics were included, to place the use of injectable plastic in perspective with other clinical uses of plastics: the patient with migration of Teflon to the skin was included to highlight the need for caution in the use of plastic injection techniques. This subgroup of experiments indicates that particles are shed into the blood stream during routine paediatric intravenous infusions, and remain in the patient when the sheath around an implantable device remains *in situ* after removal of the implant.

The operation of open ureteric reimplant for the treatment of VUR is well established; thus there was nothing new in achieving reflux resolution for the patients thus treated

in Adelaide. However, finding improved renal growth after ureteric reimplant for high grade VUR is noteworthy, and the clarification of the debate on the issues surrounding the management of VUR is long over-due.

The next experimental step was to embark on the development of a model of fetal VUR, and the pursuit of information on pre-natal diagnosis of renal anomalies. These studies will hopefully open the door to further research which will help clarify our understanding of the pathophysiology of VUR. It would appear that kidneys do undergo progressive adverse changes *in utero*, possibly secondary to VUR.

The greatest achievement of this study may have been the *further* expansion of my ignorance! I have found more questions than answers and hope to have stimulated others to look for answers, rather than jumping to conclusions.