A family study of vesicoureteric reflux

AIDA DE VARGAS, KATHLEEN EVANS, P. RANSLEY, A. R. ROSENBERG,
D. ROTHWELL, T. SHERWOOD, D. I. WILLIAMS, T. M. BARRATT, AND
C. O. CARTER

From the MRC Clinical Genetics Unit and Department of Immunology, Institute of Child Health; Department of Urology, The Hospital for Sick Children; Department of Urology and Radiology, Institute of Urology, London

SUMMARY Vesicoureteric reflux is now considered to be due essentially to congenital malformation of the vesicoureteric junction. It is also considered to be a major cause of renal failure in early adult life. The condition is associated with recurrent urinary tract infection and in some instances with renal scarring. When reflux is detected clinically, in the investigation of patients with recurrent urinary tract infection, renal scarring is often already present. The reflux tends to disappear in later childhood.

A family study has been made based on 186 index patients with established primary reflux, with special attention to a history of genitourinary symptoms in the sibs and parents of these patients. There were 39 sibs under the age of 4 years. For these the parents were offered investigation by micturating cystogram. The parents of 20 accepted. Reflux was shown in 3, and in 2 of these there was already renal scarring. The proportion of all infants and young children who have reflux is not accurately known, but the few published surveys of screening of normal infants and young children by micturating cystogram suggest that the prevalence is of the order of 1%. The prevalence in sibs is, then, about 10 times higher. There was a main group of 214 sibs over the age of 4 years. For these the parents were offered investigation by intravenous pyelogram only for those sibs who had a history of recurrent urinary tract infection. If renal scarring was found then a micturating cystogram was done. Of 110 sisters, 12 were 'symptomatic', renal scarring was found in 5 of these (1 was on haemodialysis), and reflux was still present in 3. Of 104 brothers 7 were 'symptomatic', renal scarring was found in 2 and reflux was present in both. For comparison, the published reports of several surveys of schoolgirls indicate that about 2 in 100 have recurrent urinary tract infection, and in about a quarter of these (0.5%) reflux was present and in about one-eighth (0.25%) renal scarring was present. The prevalence in sibs is, then, 10 to 20 times higher. Similarly in the parents: of 183 mothers 7 (1 was on haemodialysis) and of 181 fathers 2 had renal scarring.

The family findings are consistent with multifactorial inheritance, as with other common malformations.

Routine investigation, in infancy, of younger sibs of patients with vesicoureteric reflux would identify patients in whom the reflux was recognised very early. These would be valuable for the study of the natural history and management of the disorder, and the degree to which it was possible to prevent the development of renal scarring.

Vesicoureteric reflux (VUR) with its related nephropathy is a major cause of renal failure in early adult life (Hodson and Edwards, 1960; Scott and Stansfeld, 1968; Smellie and Normand, 1968; Bailey, 1973). The anomaly which underlies VUR is probably congenital, consisting of an inadequate development of muscle at the ureterovesical junction, a shortening of the intravesical segment of the ureter, and widening of the

ureteric opening into the bladder (Stephens and Lenaghan, 1962; Tanagho *et al.*, 1969). This permits reflux of urine from the bladder up the ureters to the kidneys in infancy and early childhood. However, VUR tends to disappear and in most patients has ceased by the early teens (Smellie *et al.*, 1975).

Many single families have been reported with more than one member affected by VUR (Lewy and Belman, 1975). Several surveys have indicated an

increased prevalence of VUR among close relatives of patients with the condition (Baker *et al.*, 1965; Mulcahy *et al.*, 1970; Burger and Smith, 1971; Amar, 1972; Bois *et al.*, 1975; Atwell *et al.*, 1977). Dwoskin (1976) studied the sibs of 125 patients with VUR and found that 54 of their 204 sibs also had VUR. This series was selected as only the families where parents permitted micturating cystograms on their children were included. Such studies, nevertheless, suggest that relatives of patients might provide a high risk group where routine screening might be appropriate. However, none of the surveys reported hitherto provides an accurate estimate of the proportion affected of sibs of index patients with VUR. The present study was planned to provide such an estimate.

The tendency of VUR to disappear in later childhood presents certain problems in the determination of the prevalence of the disorder in relatives. Micturating cystogram (MCU) will underestimate the frequency of the disorder in the older children and adults. The demonstration of renal scarring on intravenous urography (IVU) suggests the previous existence of VUR, though scarring is only found in 30 to 60% of children with VUR (Smellie *et al.*, 1975; Scott, 1977), and it may be difficult to distinguish radiologically between features of renal dysplasia and the scarring of reflux nephropathy.

As a compromise, therefore, in this study we elected to screen, wherever parents gave informed consent, the sibs of index patients in the following way: where the sibs were under the age of 4 years screening was by MCU for VUR followed by IVU if reflux was found to be present; where they were older by IVU for renal scarring if there was a history of urinary tract infection (UTI), followed by MCU if scarring was found. It was, however, also decided at the start of the study to offer the parents of the first 29 index patients routine IVU for renal scarring in all sibs over the age of 4 years.

Subjects

The family study was based on a main group (I) comprising 198 consecutive index patients (84 boys and 114 girls) with VUR (without other malformation) and renal scarring admitted to The Hospital for Sick Children and the Shaftesbury Hospital for ureteric reimplantation between 1964 and 1976 inclusive, and a subsidiary group (II) of 8 patients (2 boys and 6 girls) attending the clinic in 1976 in whom there was VUR but no scarring. Of the main group of 198 families, 20 were not available for study because of migration (3), adoption (1), not traced (7), parental unwillingness to take part (6), family doctor advised

against the study (3)—leaving 178 in group I and 186 in all (81 boys and 105 girls).

Methods

FAMILY HISTORY

The parents and sibs of the index patients were seen (by AV and KE) either in their own homes or on attending either hospital, with the exception of 2 living far away who were interviewed by telephone. At interview a family history was taken, paying special attention to a history of hospital admissions for urinary tract infection (UTI) and especially VUR in sibs and parents.

CLINICAL EXAMINATION

The blood pressure of parents and sibs was recorded and the height and weight of the sibs. Mid-stream specimens of urine (MSU) were collected from the first 126 of the parents and 103 of the sibs interviewed, but were then discontinued as confirmed positive cultures were obtained in only 2 of the parents and in none of the sibs. Relatives were further investigated if they had a documented history of recurrent UTI, and raised blood pressure, or had previously had urological investigations (these are henceforward called 'symptomatic').

RADIOLOGICAL INVESTIGATION

The results of investigations were classified simply as showing (a) the presence or absence of VUR on MCU and (b) the presence or absence of renal scarring on IVU. Those relatives with scarring, but with no demonstrable VUR, were classified as probably affected if they had had proven UTI in childhood, and as possibly affected if they had no such history in childhood.

Results

The families are listed in Appendix I, which shows, for index patients, degrees of reflux (grading as in Smellie, 1967, and Rolleston *et al.*, 1975) and of renal damage (basically as classified by Smellie *et al.*, 1975; Rolleston *et al.*, 1970). It also gives information about those sibs and parents selected for routine investigation; those selected for investigation because they were 'symptomatic'; the investigation performed; whether VUR was demonstrated; and whether scarring was found. Appendix II gives details of the condition in each affected relative.

TWINS

Two index patients, 1 of each sex (Nos. 104 and 185) were members of a monozygotic twin pair. The male co-twin had bilateral VUR with left scarring; the female co-twin was found unaffected on investigation by MCU.

Table 1 Sibs aged less than 4 years in all 186 families; results of MCU

Index Patient	Brothers			Sisters			All sibs		
	Number	MCU performed	VUR	Number	MCU performed	VUR	Total sibs	MCU performed	VUR
Male	8	5	1	9	6	2	17	11	3
Female	14	6	0	8	3	0	22	9	0
Total	22	11	1	17	9	2	39	20	3

Four index patients, 2 of each sex, were members of dizygotic pairs. One male index patient (No. 33) had a girl co-twin who had ureteric dilatation on IVU, probably caused by earlier VUR, but was not investigated by MCU: the other male index patient (No. 41) had a twin brother who was 'asymptomatic' and his parents did not wish for investigation. One female index patient (No. 127) had a girl co-twin who was normal on investigation, the other (No. 167) had a girl co-twin who was 'asymptomatic' but whose parents did not wish for investigation.

In summary, 1 of 2 monozygotic co-twins was affected with reflux and scarring, 1 of 4 dizygotic co-twins had dilatation of the upper urinary tract probably resulting from VUR, but 2 of the remaining 3 were not investigated radiologically.

SIBS

(a) Sibs under 4 years in total 186 families (Table 1)

There were 39 sibs in this group and the parents agreed to an MCU being performed in 20 of them (11 boys and 9 girls).

One brother of a boy patient (No. 36) was found to have bilateral VUR and scarring of the left kidney, 1 sister of a boy patient (No. 40) was found to have left reflux with scarring, and 1 sister (No. 179) was found to have right VUR without scarring. These 3 children were 'asymptomatic'. In addition 1 brother of a girl patient (No. 84) had left megaureter without VUR.

In sum, of 11 brothers routinely tested (out of a total of 22), 1 was found to have VUR, and of 9 sisters tested (out of a total of 17), 2 were found to have VUR. There was also 1 sister with symptoms of UTI who was not investigated by MCU.

(b) Sibs aged over 4 years in first 29 families (Table 2) Again, there were 39 sibs in the group and IVUs were performed on 26 of them (13 boys and 13 girls).

In none of these was scarring found on IVU. However, 2 'asymptomatic' sisters of male index patients (Nos. 110 and 181) aged 4 and 5 years were examined by MCU (contrary to the procedure of the investigation) and found in the first case to have right VUR (no IVU was done) and in the second to have bilateral VUR without scarring.

In sum, none of 13 brothers examined (out of a total of 20) was found to have reflux, but 2 of 15 sisters examined by MCU (out of a total of 19) had reflux.

(c) Sibs aged over 4 years in remaining 157 families (Table 3)

There were 214 sibs in the group. Two teenage sisters of girl patients were already known to have had symptoms in childhood and been investigated radiographically. One (No. 180) had right VUR with a scarred duplex right kidney; 1 (No. 125) had bilateral scarring with renal failure (she was on regular haemodialysis) but had not been shown to have VUR. A further 7 brothers and 10 sisters were 'symptomatic' and parents agreed to IVP in all 7 brothers and 8 of the sisters. Of these, 2 brothers of girl patients (Nos. 115 and 172) were found to have bilateral VUR with bilateral scarring and bilateral VUR with left scarring, respectively; 3 sisters of girl patients (Nos. 122, 162, and 135) had, respectively, right VUR, right VUR, and right scarring without demonstrable VUR. Another 2 sisters (Nos. 41 and 173) had a history of repeated UTI with bacteriuria, but their parents did not wish for investigation.

In sum, 2 of 7 brothers with symptoms (out of a total of 104 brothers) and 3 of 12 sisters with

Table 2 Sibs aged more than 4 years in first 29 families; results of IVU and MCU*

Index patients	Brothers			Sisters					All sibs				
	Number	IVU performed	Renal Scars	Number	IVU performed	Renal Scars	MCU performed	VUR	Number	IVU performed	Renal Scars	MCU performed	VUR
Male	7	5	0	10	7	0	2	2	17	12	0	2	2
Female	13	8	0	9	6	0	0	0	22	14	0	0	0
Total	20	13	0	19	13	0	2	2	39	26	0	2	2

*MCU performed contrary to procedure.

Table 3 *Sibs aged more than 4 years in remaining 157 families; results of IVU and MCU* in symptomatic cases*

Index patient	Brothers					Sisters					All sibs				
	Number	Symptomatic	IVU performed	Renal scars		Number	Symptomatic	IVU performed	Renal scars		Total	Symptomatic	IVU performed	Renal scars	
				VUR+	VUR-				VUR+	VUR-				VUR+	VUR-
Male	38	2	2	0	0	42	3	2	0	0	80	5	4	0	0
Female	66	5	5	2	0	68	9	8	3	2	134	14	13	5	2
Total	104	7	7	2	0	110	12	10	3	2	214	19	17	5	2

*MCU was only done if IVU showed renal scarring.

symptoms (out of a total of 110 sisters) had reflux; 2 further sisters among these 12 had scarring probably associated with earlier reflux, of whom 1 was on haemodialysis.

PARENTS

Only 2 parents (father of 116 and mother of 161) were identified as having renal scarring as a result of the survey, but several had had symptoms and had already been investigated radiologically.

One father of a boy patient (No. 99) had a history of chronic UTI in childhood, had been found at the age of 12 to have bilateral dilatation of the ureters and hydronephrosis, and at 19 had had an operation to relieve 'bladder neck obstruction'; 1 father of a girl patient (No. 126) with symptoms from childhood had had reimplantation of the left ureter at age 19 for dilatation of the left ureter with renal scarring; 1 father of a girl (No. 116) in the course of the survey was found to have hypertension and UTI and to have right renal scarring; 2 fathers investigated because of symptoms were found unaffected. One mother of a boy patient (No. 179) was known to have a right duplex kidney and ureter with VUR and scarring; 1 mother of a girl patient (No. 70) was known to have bilateral renal scarring and was on regular haemodialysis; 1 mother of a girl (No. 161) was found in the course of the survey to have hypertension, UTI, right-sided dilatation of the ureter, and renal scarring; 1 mother of a girl (No. 180) was known to have had bilateral VUR and renal scarring and had had reimplantation of both ureters at the age of 19 years; 1 mother of a girl (No. 184) was known to have had bilateral VUR and scarring and had had reimplan-

tation of both ureters at age 8; 1 mother of a girl (No. 144) was known to have had dilatation of the right upper urinary tract with scarring but without symptoms in childhood; 1 mother of a girl (No. 165) was known to have left renal scarring, found on investigation at age 18, but without childhood symptoms.

In sum, 3 fathers of the 181 on whom information was available had scarring, in 2 probably and in 1 possibly secondary to VUR; of 183 mothers on whom information was available 3 had demonstrated VUR and scarring, 1 scarring probably secondary to VUR, and 3 scarring possibly secondary to VUR.

OTHER RELATIVES

Aunts and uncles

The patients had 279 fathers' brothers and 216 fathers' sisters, and 233 mothers' brothers and 246 mothers' sisters. No investigations on these were carried out, but on taking the family history, and obtaining confirmation from hospital records, it was found that: 1 mother's brother (No. 2) with Down's syndrome died aged 22 months of bilateral pyelonephritis, and 1 mother's sister (No. 24) had dilatation of the upper urinary tract probably caused by VUR; 1 mothers' sister (No. 89) had scarring with proven VUR and 1 mother's sister (No. 146) had dilatation of both ureters and right scarring.

Cousins

The patients' cousins included: 207 fathers' brothers' sons and 186 daughters; 206 fathers' sisters' sons and 192 daughters; 166 mothers' brothers' sons and 192

Table 4 *Parents: results of IVU (mostly performed before the survey) in those symptomatic*

Index patients	Fathers				Mothers				All parents				
	Number available	Symptomatic	IVU performed	Renal scars	Number available	Symptomatic	IVU performed	Renal scars	Total available	Symptomatic	IVU performed	Renal scars	
												VUR +	VUR -
Male	78	3	1	1	79	19	15	1	157	22	16	0	2
Female	103	4	4	2	104	19	15	6	207	23	19	3	5
Total	181*	7	5	3	183*	38	30	7	364	45	35	3	7

*5 fathers and 3 mothers were not available for study.

daughters; 224 mothers' sisters' sons and 240 daughters. Again on taking the family history and obtaining confirmation from hospital records it was found that 1 father's brother's daughter (No. 76) had confirmed bilateral VUR with left scarring; 1 father's sister's daughter (No. 156) had bilateral VUR with bilateral scarring; 1 mother's brother's daughter (No. 83) had right VUR with bilateral bifid renal pelvis; and 1 mother's sister's son (No. 146) had bilateral VUR with no scarring.

Discussion

The two groups, those with, and a small group of 8 without, renal damage, may be considered together since the family findings do not differ, and they have been grouped together in the Tables. The 8 families are, however, shown separately in the Appendix.

The significance of findings in relatives depends on the frequency with which individuals similarly affected would be found in the general population. A number of small scale studies have been carried out in which routine micturating cystograms were performed on a series of children without evidence of urinary tract infection. These have shown a fairly low prevalence of VUR. For example Peters *et al.* (1967) found no VUR in 66 premature infants, Lich *et al.* (1964) found no cases in 24 children in the neonatal period, Jones and Headstream (1958) found 1 case (in a 4-month-old boy) in 70 boys and 30 girls aged 14 days to 14 years (mean age 3.5 years) in children who had a 'non-urolological admission with a negative urinalysis'. These small series indicate that perhaps about 1% of a randomly selected group of young children would be found to have VUR on MCU.

In contrast in the sibs under 4 in this series, offered routine MCU, the observed proportion with VUR lay between 1 in 11 brothers and 2 in 9 sisters (if it is assumed that those tested were representative of the whole group) and 1 in 22 for brothers and 2 in 17 for sisters (assuming none of the 15 sibs not tested have reflux).

None of the 26 sibs (out of a total of 39) over the age of 4 years in the 29 families where the parents were offered routine investigation by IVU was found to have had scarring. It is noteworthy, however, that the two symptomless sisters, who contrary to procedure had a direct MCU, were found to have reflux.

A less direct approach to the prevalence of reflux in children is given by studies of series of children for significant bacteriuria followed by micturating cystograms of those found positive. A number of such studies on schoolgirls suggest (Meadow *et al.*, 1969; Asscher *et al.*, 1973; Savage *et al.*, 1973; Parson *et al.*, 1974) that some 2% of girls between the ages of 5 and 10 have significant bacteriuria and that where

these are examined by micturating cystogram about a quarter of them have reflux. By this method the prevalence of reflux in schoolgirls is about 0.5%. However, these studies will miss those with reflux without infection and reflux which was present in early childhood but has ceased.

Unfortunately there is no routine series, in which after a full medical history, children and adults who have had repeated urinary tract infection have been investigated, with which to compare directly the findings in sibs over 4 years of age, and in the parents. However, if one assumes that about 1% of young children have reflux, that in about half the girls and less than half of the boys this leads to recurrent urinary tract infection, and that in half again this leads to renal scarring, one might expect about 0.25% of girls and somewhat fewer boys, perhaps 0.15%, to have renal scarring in association with reflux and recurrent urinary tract infection.

In contrast in the main group of families (Table 3) where the parents were not offered routine investigation of sibs over 4 years of age, 2 brothers out of 104 were shown to have reflux, 3 sisters out of 110 to have reflux, and 2 further sisters had scarring probably secondary to reflux (one of them was on regular haemodialysis). This again suggests that the proportion of brothers and sisters affected is more than 10 times that in the general population. Similarly it is noteworthy (see Table 4) that of 181 fathers, 2 were found to have scarring *probably* caused by reflux and 1 had scarring *possibly* caused by reflux, while of 183 mothers 3 had reflux, 1 had scarring *probably* secondary to reflux (and was on renal haemodialysis), and 3 had scarring *possibly* secondary to reflux. This again is some 10 times the expected proportion for men and women, respectively.

The ascertainment of affected aunts and uncles will inevitably be incomplete. For example, the index patient's mother may not know details of the health of her husband's brothers' children. It is also often difficult to get confirmation from hospital records of such more distant relatives. In view of these limitations the finding of 1 in 502 uncles and 3 in 462 aunts, 1 of 390 male and 3 of 393 female cousins affected probably represents a real though small increase over the expected values.

GENETIC MECHANISMS

The genetic interpretation of the familial concentrations found in this survey must be cautious, particularly in view of the approximate estimate of the incidence of reflux in the general population. The findings, however, are in general similar to those for other common congenital malformations such as cleft lip ($\pm$ cleft palate), pyloric stenosis, talipes equinovarus, and pyloric stenosis (Carter, 1976). They

are most economically interpreted as reflecting a multifactorial aetiology of the malformation, with the genetic predisposition depending on variation at several gene loci. This type of inheritance has already been suggested by Burger and Smith (1971). A birth frequency of the malformation of 1%, and a heritability of the malformation of 90%, would give on the multifactorial model 10%, 3%, and 2% affected, respectively, of first, second, and third degree relatives. The findings in this survey are compatible with these figures, but these do not exclude other mechanisms such as modified dominant inheritance.

The relatively high risk to the younger sibs of index patients suggests that these could be an appropriate group in whom to assess the value of early diagnosis and prophylactic treatment in the prevention of reflux nephropathy.

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Requests for reprints to Professor C. O. Carter, MRC Clinical Genetics Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

No.	Serial Degree		No. reflux	Degree renal damage	Half-sibs		Parents		Other relatives with renal tract anomaly (see Appendix 2)
	Sibship				D.O.B.				
	Paternal	Maternal			Father	Mother			
GROUP I									
1	R	L	R	L	One child families				
2					Male:				
3	1	II	III	—	3	M*	—/44	8/46S	Mo. bro.
4	2	—	III	—	3	M*	9/36	2/37	
5	3	II	—	3	M*	2/65	3/25S	5/37SI	
6	4	II	II	2	2	M*	—/40	6/49SI	
7	5	III	III	2	1	M*	4/39	3/39	
8	6	—	II	3	2	M*	10/50	—/53	
9	7	III	II	2	—	M*	3/46	7/49SI	
10	8	II	III	2	2	M*	10/49	11/51	
11	9	III	III	3	3	M*	6/44	10/44SI	
12	10	—	III	2	2	M*	3/51	9/53	
13	11	III	III	2	2	M*	—/53	5/57 SI	
14	12	III	II	2	1	M*	7/47	4/49	
15	13	III	II	3	2	M*	9/50	—	
16	14	III	III	3	3	M*	5/47	7/50	
Female:									
17	15	—	III	—	3	F*	—/53	5/32	
18	16	II	II	2	2	F*	11/59	2/39	
19	17	III	III	3	2	F*	M	11/61	
20	18	II	II	—	2	F*	M	11/60	
21	19	III	II	3	2	F*	5/16	6/26	
22	20	—	III	—	2	F*	8/38	2/33	
23	21	II	II	—	2	F*	1/36	1/46	
24	22	III	III	—	2	F*	1/43	6/39	
25	23	III	II	2	2	F*	6/40	3/44	
26	24	III	II	2	2	F*	9/43	9/46	
27	25	III	II	2	2	F*	12/52	9/51	
Two child families									
28					Male:				
29	24	III	II	3	—	F	6/34	3/39	Mo. si.
30	25	II	II	2	3	M*	6/39	7/40	
31	26	II	II	3	—	M*	5/45	9/47	
32	27	III	III	2	2	M*	8/33	9/40	
33	28	III	II	2	2	F	12/32	9/36S	
34	29	II	III	2	2	M	3/36	10/42	
35	30	III	III	3	—	F	7/40	6/37	
36	31	I	III	—	2	F	10/40	4/39SI	
37	32	III	III	3	—	M*	9/42	10/40	
38	33	III	III	2	2	F	6/32	9/34	
39	34	III	III	2	—	M*	8/42	5/40	
40	35	III	II	3	2	F	5/42	4/39	
41	36	III	III	2	—	M*	2/48	3/49SI	

Appendix 1 (continued)

Serial No.	Degree of reflux	Degree of renal damage	Sibship	Half-sibs		Parents		Other relatives with renal tract anomaly (see Appendix 2)
				Paternal	Maternal	Father	Mother	
37	—	III	—	3	M	2/73R	M*	4/70
38	II	II	3	2	F	12/68	M*	4/70
39	III	II	3	—	M	3/63	M*	7/71
40	III	II	2	—	M*	7/71	F	12/75RM+
41	III	III	2	2	F	3/68S	M*	1/72R
42	III	III	3	3	F	3/63	M*	4/72
43	II	III	—	3	F	8/69RI	M*	7/72
44	III	I	3	2	M*	1/73	M	9/74R
45	III	III	—	1	F	7/70	M*	5/73
46	III	I	3	—	M*	7/73	M	5/75
47	III	III	3	2	M	8/72	M*	d. 18 days
48	II	II	—	3	M	8/71	M*	11/73
49	III	I	3	—	F	12/71RS	M*	1/74
50	II	III	2	2	F	2/72RM	M*	4/74
51	III	III	—	3	F	12/69	M*	8/74
52	III	III	2	3	F	6/73RS	M*	3/75
Female:								
53	—	I	—	2	F	2/59	F*	1/64
54	III	II	2	—	M	8/60	F*	1/64
55	III	I	—	1	F	2/63	F*	3/64
56	III	I	3	—	F	10/61	F*	3/64
57	II	II	—	2	F*	5/64	F	10/67
58	III	III	2	3	M	9/55	F*	5/64
59	III	III	3	—	M	1/63	F*	3/65
60	III	III	—	2	F*	3/65	M	11/66RI
61	—	III	—	2	M	5/63	F*	4/65
62	—	III	—	2	F	5/61	F*	6/65
63	II	—	2	—	M	10/62	F*	7/65
64	III	III	2	2	F	1/64	F*	10/65
65	III	III	2	2	M	5/63	F*	3/66
66	III	III	2	—	F	8/60	F*	4/66
67	III	—	2	—	F	1/64	F*	5/66
68	III	II	3	—	M	2/63RI	F*	6/66
69	III	II	—	3	M	6/64	F*	8/66
70	III	III	3	2	F*	1/67	F	3/75R
71	III	II	2	—	F	8/64	F*	2/67
72	—	III	—	2	F*	2/67	M	8/65
73	III	III	2	2	M	3/64	F*	4/67
74	I	I	—	1	F	4/65	F*	5/67
75	III	III	2	2	M	9/60	F*	5/67
76	III	III	2	2	F*	12/67	M	9/70RI
77	II	II	3	—	F	9/65SI	F*	1/68
78	III	II	—	2	M	6/64RI	F*	2/68
79	II	III	2	3	M	8/64	F*	3/68
Fa. si.								
Fa. bro. dau.								

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80	II	II	3	2	E*	4/68	M	1/70		7/41	2/44	
81	—	III	—	2	F*	4/68	M	6/70		3/40	2/44S	
82	III	II	3	—	F*	9/68	M	8/71		9/39	5/47	
83	I	III	—	2	F	2/65	F*	10/68		1/31	12/31	Mo. bro. dau.
84	II	II	2	—	F*	8/69	M	3/73RM(ORT)		6/42	7/44	
85	II	II	2	—	F*	11/69	F	1/72		1/41	10/46	
86	III	I	2	—	F	8/69	F*	8/71		8/41	7/42SI	
87	I	—	2	2	F*	9/71	F	12/74R		12/44	10/45	
88	III	I	1	—	F*	9/71	F	11/73R		11/46	2/41	
89	I	III	I	3	E*	12/71	M	1/74RM		12/41	5/47	Mo. si. + +
90	III	III	3	3	F*	11/73	M	5/75R	Fsb	4/46	8/50	
Three child/families												
Male:												
91	I	II	—	1	M*	3/64	M	3/66	F	12/69		
92	—	II	—	3	M	9/58	M	9/62	M*	7/64	4/36SI	
93	III	III	1	1	F	5/63	M*	2/65	Msb	12/66	3/38	
94	III	III	—	3	M	9/60	F	3/62	M*	7/65	5/41	
95	II	2	2	2	F	12/63RI	M*	8/65	F	7/66RI	1/37	
96	III	III	3	1	M*	7/66	F	12/68	M	8/71	7/42	
97	III	—	3	—	M	9/63	F	7/65	M*	3/67	3/35	
d. 7 days												
98	III	III	2	2	M*	7/67	M	9/69RI	F	10-73RM	5/42	
99	III	I	—	1	M	7/64	M*	3/68	M	9/71	7/40SI	
100	III	I	3	—	M	1/63	F	3/64	M*	4/68	10/40	
101	III	—	2	—	M	5/67SI	M*	9/68	F	7/75R	6/38	
102	II	II	2	2	M	5/64	M	1/66	M*	2/69	6/45	
103	II	—	2	—	F	3/59	F	5/62	M*	5/69	1/39	
104	III	III	2	—	[M]	6/69+	M*	6/69]	F	6/70	4/36	
105	III	III	I	—	M	9/66	M*	6/69	F	3/72	9/43SI	
106	III	I	2	—	F	12/66	Msb	10/68	M*	6/70	3/39	Fa. si. son
107	III	III	3	2	F	6/66	M	7/69	M*	9/70	8/43ORT	
d. 1 day												
108	III	—	3	—	M	8/69RI	M*	11/71	M	9/72RM	9/45	
109	II	II	2	2	F	9/69RI	F	10/70RI	M*	1/72	11/50	
110	—	III	1	—	E	3/71M	M*	5/72	M	7/74RM	11/46	
111	II	II	2	2	M	3/71	M*	8/72	M	4/76R	7/47	
112	III	III	2	2	M	1/69R	M	7/71R	M*	11/72	3/51	
113	III	III	3	1	M*	7/73	M	10/74RM	F	1/76R	5/54	
Female:												
114	II	II	3	—	F	9/61	F*	1/63	M	6/67	8/34	11/38SI
115	II	II	—	2	F	11/60	F*	2/64	M	6/69SI++	11/26	7/33
116	II	III	—	3	F	1/61	F*	3/64	M	5/66	10/41SI+	4/42
117	I	II	2	—	M	5/60	Fsb	—/62	F*	3/64	4/30	—/37
118	II	III	—	2	M	2/57RI	F*	4/64	F	1/66RI	—	1/34
119	—	III	—	2	M	8/58R	M	7/62RI	F*	9/64	2/31	—/36
120	III	III	2	2	M	6/62	F	5/63	F*	9/64	3/36	5/40
d. 2 wks.												
121	III	III	3	—	M	6/55	F	2/60	F*	2/65	8/28SI	6/35
122	II	II	2	2	F*	5/65	F	5/67	F	12/69SI	2/34	9/37
d. 14 days												
123	—	III	—	3	F	7/62	F	8/64	F*	8/65	8/42	1/44SI
124	II	II	I	I	F	7/58	F	5/61SI	F*	8/65	3/35	10/35

Appendix 1 (continued)

Serial Degree			Sibling		Half-sibs		Parents		Other relatives with renal tract anomaly (see Appendix 2)									
No.	reflux	renal damage	Degree	Sibship	Paternal	Maternal	Father	Mother	D.O.B.									
125	I	1	2	—	F	9/60+ +	M	12/61	F*	10/65	F*	6/66	5/29	11/28ORT				
126	III	—	2	—	F*	3/66	M	2/68RI	M	6/60RI	F	3/70RI	2/39+	12/38				
127	—	III	—	2	M	7/54	M	6/66	F	1/71	F*	6/66	9/26	9/27				
128	III	3	1	M	4/64	F*	6/66	F	2/64	F*	6/66	6/66	11/24	6/33				
129	III	III	—	3	F	12/60	F	4/62	F*	7/66	F*	7/66	1/36	10/34				
130	III	III	1	1	M	12/60	F	9/62RI	F*	7/66	F*	7/66	8/31	5/32				
131	III	III	3	—	M	d. 8 mths	F	7/66	F	7/70	F*	7/70	10/34	7/26				
132	III	III	—	2	F	3/63	F*	1/65	F*	9/66	F*	9/66	1/38	6/41				
133	II	2	—	M	12/61	M	12/67RI	F	8/69RI(ORT)	F	11/73RM	6/38	—/35	6/38				
134	III	—	2	—	F*	10/66	M	11/66	F*	12/66	F	12/34	8/30	12/37SI				
135	—	III	—	3	F	2/64SI+	F*	3/67	M	3/68	F	5/43	3/42	1/44SI				
136	—	III	—	2	M	12/59	F	6/68	F*	6/67	F	10/46	12/34	7/39				
137	—	III	—	3	F	1/65	F*	6/68	F	6/67	F	7/47	5/43	11/45				
138	III	III	2	2	F*	3/67	M	12/61	F*	11/67	F	10/38	5/32	2/38				
139	—	III	—	3	F	9/62	F	6/64	F*	6/67	F	5/47	10/38	6/43				
140	III	III	2	2	M	8/58	F	1/68	F*	7/70	F	7/44	5/32	2/38				
141	—	III	2	3	M	1/66	F*	7/70	F	7/73R	M	7/41	5/47	10/47				
142	III	2	2	2	F*	9/68	F	1/72RI	M	5/73R	M	7/40	7/44	1/48				
143	III	III	2	2	F*	10/68	F	3/69	M	7/71	M	2/40	7/41	7/41				
144	II	1	2	1	M	d. 6 wks	F*	4/70	M	12/72R	M	7/40	11/42+	11/42+				
145	II	1	1	1	F	2/69	F*	6/72RI	M	12/72R	M	12/40	4/43	4/43				
146	III	1	2	2	F*	9/70	F	3/72	F	11/75R	M	12/45	2/46SI	2/46SI				
147	II	1	2	—	F*	10/70	F	3/72	M	11/75R	M	8/46	4/35	4/35				
Four child families																		
Male:																		
148	III	—	3	—	M	3/61SI	M*	3/64	[F	8/68	F	8/68SI]	4/38	9/38				
149	II	—	3	1	M*	10/64	M	2/67	M	12/69	F	8/72RM	9/41	5/44				
150	III	1	3	2	Fsb	9/63	M*	11/64	M	4/66	M	12/68	3/39	12/38SI				
151	—	III	1	2	F	5/64	M*	7/65	M	3/67	F	6/68	2/36	1/39				
152	III	III	1	3	M	7/55	F	5/62	M*	2/66	M*	2/66	4/36	9/35				
153	III	III	2	2	M	1/58RI	M	12/58RI	F	5/63RI	M	8/66	12/30	8/34				
154	III	III	1	2	F	3/55	F	5/57	M*	2/67	M	1/69	5/31	4/35SI				
155	III	III	2	3	F	6/54	M	11/64	M*	7/67	M	12/30	12/30	11/31				
156	III	III	3	3	F	7/65SI	M	11/66	M*	4/68	F	5/73RM	9/38	9/43				
157	III	III	2	2	M*	9/68	M	7/69	F	4/71	F	3/72	5/40	5/46				

Female

Fa. si. dau. + +

Four child families

Male:

162	III	—	2	—	F*	4/66	M	8/67	M	11/68SI	F	7/70SI			1/47	11/49
163	II	—	—	—	F	4/52	F	2/58	F*	9/66	M	9/67			6/22	7/28
164	III	III	1	1	M	10/65	F*	1/67	F	4/68	M	3/74R			4/32	3/41
165	—	II	—	2	F*	10/67	F	1/69SI	M	8/70	M	7/73RM			10/44	11/48+
166	III	III	2	3	M	11/57	M	6/59	F	7/64	F*	3/68			10/26	3/34
167	I	III	—	2	F	12/64R	F	9/66R	F	9/72R	[F	7/74R	F*	7/74]	6/44	6/47
Five and more child families																
Male:																
168	II	II	—	2	M	6/47	F	6/48	F	6/53	F	4/57	F	7/61	4/14	10/28
169	III	II	2	1	F	1/63	M	6/64	M	6/66	F	10/68	M*	9/70	4/34	6/32
170	—	III	—	3	Fsb	3/64	F	3/65	F	6/66	F	10/67	M*	1/70	12/43	6/46
d. 9 mths																
Female:																
171	III	III	3	2	M	5/60R	M	10/61R	M	9/62R	M	10/63R(S)	F*	3/65	12/27	6/39
172	—	III	2	2	M	10/64	F*	10/65	M	4/67SI+	F	12/68	F	9/73RM	7/41	6/38
173	II	II	3	2	F	10/49S	M	6/53	M	4/55	M	11/57	F*	6/65	7/31	9/32
174	II	II	—	2	F	3/58	M	5/59	F	3/61	F	5/63	F*	1/66	11/33	11/36
175	III	—	3	—	M	10/54	M	12/56	[M	4/61	M	4/61]	F*	6/68	7/31	9/32
d. 8 mths																
176	II	III	—	1	M	2/54	F	7/55	F	11/59	M	9/61	M	11/62	8/32	8/36
177	III	III	2	3	F	10/60	F	12/66	M	11/67	F*	3/69	F	1/71	1/33	2/42
178	II	III	1	2	F	12/68	[M	1/69SI	M	1/69]	M	8/70SI	F*	8/71	1/42	7/40
d. 4 mths																
M —/63																
F 6/75RM																
M 6/67																
d. 4 mths																
F 12/64																
F* 12/68																
M 9/73R																
M 12/72RM																
GROUP II																
Two child families																
Male:																
179	III	III			M*	9/72	F	1/75RM							7/43	3/48+
Female:																
180	II	II			F	5/65+	F*	7/69							4/41	10/42++
Three child families																
Male:																
181	III	III			F	12/70RI	M*	4/72	M	5/74RM					1/48	1/54
Female:																
182	II	II			F*	10/68	M	10/71	F	1/73R					8/37	1/44
183	II	II			F	—/66	M	—/67	F*	3/68					10/48	8/48
184	II	II			M	3/66	M	3/69	M	1/76R					1/37	3/45++
185	II	II			F	6/68	[F	4/70RM	F*	4/70]	M	5/73R			2/45	9/38
Four child family																
Female:																
186	II	II			F	9/62	F*	12/68	M	6/67	M	10/71			8/39	7/43

Appendix 2 Affected relatives including those with other renal tract anomaly (ORT)

<i>Sibs</i>		
<i>of male patients:</i>		
33	Co-twin, sister	2/69 Asymptomatic—IVU—dilatation of right upper urinary tract
36	Brother	9/72 Asymptomatic—IVU, MCU—bilateral reflux with left renal scarring, small left kidney
40	Sister	12/75 Asymptomatic—IVU, MCU—left-sided reflux up to kidney outlining normal calyceal pattern
104	Co-twin, brother	6/69 Asymptomatic—IVU, MCU—bilateral reflux and moderate left scarring
110	Sister	3/71 Asymptomatic—IVU, MCU—right reflux, no renal scarring
179	Sister	1/75 Asymptomatic—IVU, MCU—right reflux, no renal scarring
181	Sister	12/70 Asymptomatic—bilateral reflux, more marked on left side
<i>of female patients:</i>		
84	Brother	3/73 ORT Asymptomatic—IVU—left obstructive congenital megaureter without reflux
115	Brother	6/69 Proved urinary tract infections, IVU, MCU—gross bilateral vesicoureteral reflux with scarring of upper pole of left kidney
122	Sister	12/69 IVU, MCU—right reflux, small right kidney, no evidence of scarring
125	Sister	9/60 Already known to have bilateral renal damage with chronic renal failure—on renal dialysis
134	Sister	8/69 ORT Asymptomatic—IVU—small right kidney—8 cm compared with left which is 11 cm; no evidence of scarring, existence of right renal hypoplasia
135	Sister	2/64 IVU, MCU—symptoms—marked scarring upper pole right kidney without reflux
162	Sister	7/70 IVU, MCU—symptoms—right-sided reflux, no scarring
172	Brother	4/67 MCU—bilateral reflux to pelvic brim during filling and also on left, scarring
180	Sister	5/65 Already known to have right reflux, duplex right kidney and scarring
<i>Parents</i>		
<i>of male patients:</i>		
99	Father	4/37 Known to have bilateral dilatation of ureters and hydronephrosis with bladder neck obstruction
179	Mother	3/48 Known to have duplex right kidney with double ureter with reflux and scarring
<i>of female patients:</i>		
70	Mother	12/42 Known to have bilateral renal scarring on renal dialysis
106	Mother	8/43 ORT Known to have duplex pelvic calyceal system
116	Father	10/41 Symptoms—hypertension—IVU—small right kidney with right scarring
125	Mother	11/28 ORT Known to have absent right kidney with compensatory hypertrophy
126	Father	2/39 Childhood symptoms—chronic left scarring dilatation lower portion left ureter
144	Mother	11/42 Adult symptoms—dilatation right upper renal tract and right scarring
161	Mother	10/39 Symptomatic—IVU—right-sided dilatation and renal scarring
165	Mother	11/48 Symptoms as adult—IVU—left renal scarring
180	Mother	10/42 Known to have bilateral reflux and bilateral scarring
184	Mother	3/45 Known to have bilateral reflux and bilateral scarring
<i>Uncles and Aunts</i>		
<i>of male patients:</i>		
2	Mother's brother	Down's syndrome. bilateral pyelonephritis, died subacute retention urine at 2 2/12
<i>of female patients:</i>		
24	Mother's sister	Right-sided hydronephrosis, no scarring
66	Father's sister	ORT Known right renal dysplasia, ectopic ureteric orifice, right nephrectomy
89	Mother's sister	Known to have scarring and proven reflux
119	Father's sister	ORT Known right renal dysplasia
146	Mother's sister	IVU—known to have dilatation of both ureters and right scarring
<i>Cousins</i>		
<i>of male patients:</i>		
105	Father's sister's son	ORT Known stricture lower end left ureter and left hydronephrosis, left nephrectomy aged 6/12
156	Father's sister's daughter	Known severe bilateral reflux, bilateral scarring
<i>of female patients:</i>		
76	Father's brother's daughter	Known to have severe bilateral reflux and left scarring
83	Mother's brother's daughter	Known to have recurrent UTI at 15/12, bilateral bifid renal pelvis, right reflux
146	Mother's sister's son	Known to have bilateral reflux, no scarring