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Childhood reflux and urinary infection: a follow-up of 10–41 years in 226 adults

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Abstract. To ascertain the outcome of childhood vesico-ureteric reflux (VUR), 226 adults (37 males), mean age 27 years, were studied after 10–35 years, extended to 41 years by postal questionnaire in 161. At presentation (mean age 5 years) all had VUR (grade III–V in 68) and urinary tract infection (UTI); there was renal scarring in 85 (acquired before referral in 11 and during follow-up in 1), hypertension in 6 and impaired renal function in 5. They were managed and followed prospectively by one paediatrician; 63% of these children remained free from UTI; VUR persisted in 63 and had resolved in 69% of 193 children managed medically. At follow-up, 61% of adults had remained free from infection; 17 adults had hypertension and/or raised plasma creatinine, 16 with scarred kidneys. Their deterioration was predictable because of scar type, blood pressure or plasma creatinine levels in childhood. No new scars developed after puberty. Renal growth rates were unaffected by initial severity or persistence of VUR. On the later questionnaire, 9 further adults, mean age 38 years, had moderate hypertension. The adults with complications were those with extensive renal scarring and/or at least borderline hypertension in childhood. Those with VUR, but no scarring, and managed carefully in childhood, did not suffer serious consequences as adults. There is a need for early recognition and treatment of children with VUR and UTI to limit scar development.

Key words: Vesico-ureteric reflux – Urinary tract infection – Renal scarring, renal function, renal growth – Hypertension – Pregnancy – Follow-up

Introduction

Vesico-ureteric reflux (VUR) is usually discovered in childhood during the investigation of urinary tract infection (UTI). It can also be identified in the uninfected siblings or offspring of index patients. More recently, it has been possible to identify patients with reflux in infancy after urinary tract dilatation has been observed by antenatal ultrasonography. There has been much speculation about the long-term consequences of childhood VUR associated with UTI. Although there have been some long-term studies on children with symptomatic UTI [1], and with bacteriuria discovered on screening [2, 3], as well as children with renal scarring followed prospectively [4–7], or retrospective studies of adults [8, 9], many of the publications exploring the outcome of VUR have been short term [10]. In order to focus specifically on the outcome of children with VUR, a study was undertaken of a group of 226 adults who in childhood had UTI and VUR and who were seen, managed and followed prospectively by a single paediatrician in a London teaching hospital. The results of this follow-up spanning 10–41 years are presented.

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Subjects and methods

Subjects

Of all the children who had presented at the Paediatric Department, University College Hospital (UCH), London, between 1955 and 1980 with symptomatic urinary infection associated with VUR but without outflow obstruction, there were 236 who were aged 18 years or over in 1988. In 1988 and 1989 these adults were sought, either directly, with the help of their family doctor or through the Office of Population Census and Surveys (OPCS) [now the Office of National Statistics (ONS)] and the Family Health Practitioner Services. All but 10 were located and 3 others had died as adults. The remaining 223 were contacted and invited to attend a special follow-up clinic and to complete a questionnaire which also included a section for their general practitioner. The response of the 226 adults traced is shown in Table 1. Another postal questionnaire was conducted some 8 years later in 1995/1996 when further data from a cohort of 161 of the original adults were collected.

These 226 adults (37 males, 189 females) had presented with symptomatic UTI aged 5 days to 12 years (mean 5 years) and the majority had a history of presumed or proved recurrent UTI be-

Table 1. Study population: 226 adults (37 males, 189 females) who had vesico-ureteric reflux (VUR) and urinary tract infection (UTI) in childhood[a]

	Childhood renal status		Total
	Scarred[a]	Unscarred	
Attended clinic	58 (8)	90 (11)	148 (19)
Questionnaire	18 (6)	40 (5)	58 (11)
Information from hospital or family doctor	6 (3)	11 (3)	17 (6)
Died	3 (1)	–	3 (1)
Total	85[b] (18)	141 (19)	226 (37)

[a] Males in parentheses
[b] Scarring unilateral in 54, bilateral in 31

fore referral. They were seen in a designated clinic for children with UTI and all had VUR demonstrated by contrast micturating cysto-urethrography (MCU). VUR was bilateral in 116 children (51%) and severe in 68 (30%). When first seen, 84 (37%) had radiologically scarred kidneys and 1 developed a scar later. Of the 226, 14 (6%) (9 males, 5 females) presented under the age of 1 year; 5, all boys, with scarred kidneys; 30 (13%) (2 males, 28 females) presented aged 1 or 2 years, 10, all girls, with scarred kidneys.

In childhood, the majority were treated as out-patients; 193 patients were managed according to a strict medical protocol previously described [11–17], consisting of uninterrupted low-dose antibacterial prophylaxis until two consecutive negative cystograms were obtained and continued until after puberty if there was renal scarring. This was combined with a regimen designed to achieve complete bladder emptying by regular drinks and voiding, double micturition at bedtime and correction of constipation. The remaining 33 were treated surgically, 26 by ureteric reimplantation alone, 3 by ureteric reimplantation and contralateral nephro-ureterectomy and 4 others had a nephro-ureterectomy or a heminephrectomy. As in the medically treated patients, those with scarred kidneys were given prophylaxis.

Each patient had been seen and followed every 3 months in the Children's Urinary Infection Clinic, when height, weight and blood pressure were measured and urine was cultured. Those with hypertension were under shared care; regular contact was maintained with 2 others treated surgically and followed elsewhere. Urine culture was repeated if symptoms developed between visits. Plasma urea or creatinine was estimated annually in children with scarred kidneys. A single 12-min standard intravenous urogram (IVU) film of the renal areas was taken every 2–3 years to assess renal morphology, and renal length/growth in relation to body height [17]. Cystography was used to monitor reflux at 2-year intervals early in their management [11, 16], and later was delayed until there was no residual urine on double micturition. Follow-up was continued until 2 years after cessation of reflux or annually through adolescence if the kidneys were scarred.

Methods

The parameters studied in these adults included general health, history of recurrence of UTI and of further hospital treatment, development of hypertension or renal insufficiency, renal growth and morphology and details of pregnancy and offspring.

The 148 adults who attended had their height, weight, blood pressure and plasma creatinine measured and urine was cultured and analysed for microproteins. They were invited to undergo a one-film IVU of the renal areas and also a dimercaptosuccinic acid (DMSA) study if there had been radiological renal scarring in childhood or recent or recurrent UTI. No adult follow-up cystograms were performed. Any new abnormalities identified were discussed and the patients were referred back to the family doctor.

In those 58 patients who only responded to the questionnaire, the family doctor provided information on blood pressure, urine culture, treatment and pregnancy. Postal samples of urine for microprotein assays were obtained from some of these patients. In the remaining 17 patients, information was obtained directly from the hospital consultant or general practitioner. All 3 patients who had died had been seen after the age of 20 years.

For this study, reflux severity, originally based on a four-grade system [11, 12], was retrospectively regraded to correspond with the International Grading System, where grade I is minimal, grade II extends up to the kidney without dilatation and grades III–V include all reflux associated with dilatation of the ureter and renal pelvis [18].

The adult kidneys were assessed on IVU as before and compared with the last childhood findings. Renal length and growth in both children and adults were expressed as standard deviation scores (SD scores) in relation to the expected renal length for height, as used by Hodson et al. [19, 20] and by Klare et al. [21].

Renal scars were typed according to IVU appearances, with type A indicating one or two scars, type B more extensive scarring, type C irregularly thinned rim of parenchyma surrounding deformed renal papillae and calyces and type D a small shrunken kidney [11].

Standard adult ranges for plasma creatinine (53–97 μmol/l in females and 80–115 μmol/l in males) were used. Urinary albumin, retinol binding protein (RBP) and *N*-acetyl-β-D-glucosaminadase (NAG) were measured and expressed as the ratio to urinary creatinine [22].

The data were analysed using SPSS and Stata packages. Chi-squared and analysis of variance tests were used as appropriate. The study had the approval of the UCH Ethical Committee and the OPCS and ONS approved the release of information to enable tracing of patients.

Results

The results are presented as the findings, followed by their associations with reflux, in these 226 patients: (1) in childhood and (2) when the patients were aged 18–44 years (mean 27 years). Thus, in 1988/1989 the follow-up period was 10–35 years (mean 20.4 years). In addition, 161 of these patients responded to a postal questionnaire sent out in 1995/1996, 8 years later, extending their follow-up to 41 years.

Children

Vesico-ureteric reflux. All the children had reflux on contrast MCU when first seen and the maximum reflux grade per child is shown in Table 2. In 7 (5 males, 2 females) of the 68 children with severe reflux (grade III–V) in one or both ureters, VUR was equivalent to grade V. On the most recent childhood MCU, performed between the ages of 8 and 14 years, VUR was still present in 63 children, including 4 with ureteric reimplantations, 32 with scarred and 31 with unscarred kidneys. It remained bilateral but was less severe in 17 of the 116 children who originally had bilateral reflux. VUR had been corrected in 29 of 33 children treated surgically and had resolved spontaneously in 134 (69%) of those managed medically.

Table 2. Severity of reflux on presentation in 226 children, 85 with renal scarring[a]

VUR					
Maximum grade per child		Unilateral	Bilateral	Total	
I	minimal	27 (7)	7 (0)	34	(7)
II	↑ kidney	59 (16)	65 (15)	124	(31)
III–V	dilatation	24 (18)	44 (29)	68	(47)
	Total	110 (41)	116 (44)	226	(85)

[a] Children with renal scarring in parentheses

Urinary tract infection. All 226 children presented with UTI, recurrent in over 60%. Their further history of UTI is shown in Table 3. When last seen in childhood, all had been free from infection for 18 months to 13 years (mean 7.4 years).

Radiological renal scarring. This was demonstrated on presentation in 84 children, and was unilateral in 53 and bilateral in 31. Of these 84, 11 were known to have had structurally normal kidneys on IVU earlier in childhood, before referral to our clinic. During follow-up, 2 boys, 1 with normal and 1 with type A scarred kidneys, each developed a single new scar at the ages of 7 and 9 years. Both had VUR into the corresponding ureter and each scar followed a symptomatic infection [12, 23]. Thus a total of 85 children had radiological scarring by the age of 10 years. The scarring in the 116 affected kidneys was classified as type A in 33, type B in 49, type C in 18 and type D in 16. Apart from the boy who developed a scar in a previously unscarred kidney, there was no change in scar type during childhood.

Hypertension and renal function. Six girls had hypertension (>97th percentile for height and age) requiring treatment on presentation at 7–12 years; 4 of them had accelerated hypertension ranging from 155/110 to 225/150 mmHg. In addition, 10 children (4 males, 6 females) had borderline hypertension (systolic ≥140 mmHg or diastolic ≥90 mmHg) and 4 (1 male, 3 females) had labile (unsustained) hypertension not requiring specific treatment. All these 20 children had scarred kidneys.

Six children, 3 of them hypertensive, had a raised plasma creatinine (>80 µmol/l) or urea (>6.6 mmol/l), and in 5 others the level was at the upper limit of normal. All 11 had renal scarring which was bilateral in 10.

Renal length and growth. Satisfactory renal growth had occurred during childhood in over 90% of refluxing units and in all those without recurrence of infection [17, 24].

Somatic height. This was normally distributed with no significant difference between those with and without renal scarring, and growth remained within normal limits (P=0.25) [25].

Table 3. Recurrences of UTI in 226 children after referral, in relation to: (a) maximum reflux recorded per child and (b) renal status. There was no significant difference between those with mild or severe reflux nor between those with or without renal scarring; 63% had no recurrence during 943 patient-years' follow-up on prophylactic treatment. There were non-febrile recurrences in 83 children during 632 patient-years' observation

		No. of UTI recurrences			
		0 (n=143)	1–2 (n=57)	3+ (n=26)	Total (n=226)
(a)	Maximum VUR grade per child				
	I	21	7	6	34
	II	84	26	14	124
	III–V	38	24	6	68
(b)	Renal status				
	Unscarred	90	34	17	141
	Scarred	53	23	9	85

Associations with VUR in children. There was no significant difference in recurrences of UTI between children with grade III–V and those with grades I–II reflux (χ^2=2.70, P=0.26) or between those with or without renal scarring χ^2=0.93, P=0.34) (Table 3). Similarly there was no difference between those with persistent or no reflux at the end of childhood (39.2% and 37%).

Renal scarring was seen in 85 (38%) of the 226 children, but was significantly more prevalent in those with grades III–V VUR, 47 of 68 (69%), than in those with grades I and II VUR, 38 of 158 (24%) (χ^2=41.37, P=<0.0001, 2 df) (Table 2).

All 6 girls who presented with severe hypertension were over 7 years of age and had a past history of UTI. VUR was bilateral in 4 and grade III–V in 1. All had scarred kidneys, bilateral in 5, and 5 of the 6 had a severely scarred (type D) kidney. The 10 children who developed borderline hypertension and 4 with labile hypertension all had renal scarring; VUR had been severe in 4, but had ceased in 10 during childhood.

The 6 children with raised plasma creatinine (>2 SD) or urea levels and the 5 with borderline levels all had bilateral VUR and bilateral renal scarring (4 with one or both type C scarring and 6 with one type D). Three were on treatment for hypertension, 2 had borderline hypertension and in 2 it was labile.

Impaired renal growth in childhood was only seen in 5% of renal units, among children with small, scarred kidneys, persistent reflux and recurrence of UTI [24].

Adults

Of the 226 adults, there was an abnormality of either renal function or blood pressure in 17 (7.5%), 16 of whom had renal scarring. Of these 17, 1 had died and 2 had received renal transplants at the ages of 25–26 years. Only 13 (5.8%) of the whole group of adults had been attending hospital regularly for renal causes.

Table 4. Sixty-eight patients who had VUR grades III–V into one or both ureters in childhood showing maximum reflux per patient on the last micturating cysto-urethrogram (MCU) and the outcome in relation to management and renal scarring. The 8 adults with raised blood pressure or plasma creatinine all had renal scarring, but only 1 had persistent severe reflux[a]

Maximum VUR grade per patient on last MCU	Medical management		Surgical management		Total
	Scarred	Unscarred	Scarred	Unscarred	
No VUR	8 (1)	14	17 (3)	1	40 (4)
VUR I–II	15 (2)	6	2 (1)	–	23 (3)
VUR III–V	3 (1)	–	2	–	5 (1)
Total	26 (4)	20	21 (4)	1	68 (8)

[a] Figures in parentheses represent those adults with hypertension and/or raised plasma creatinine

Table 5. Type of recurrence of UTI in 221 adults in relation to renal status and persistence or absence of reflux on the last MCU (excluding 3 deaths and 2 transplants)

Renal status	No VUR (*n*=168) UTI			Persistent VUR (*n*=53) UTI			Total (*n*=221) UTI		
	None	Non-febrile	Acute febrile	None	Non-febrile	Acute febrile	None	Non-febrile	Acute febrile
Unscarred (*n*=141)	76	38	2	15	7	3	91	45	5
Scarred (*n*=80)	26	20	6	18	4	6	44	24	12
Total	102	58	8	33	11	9	135	69	17

Vesico-ureteric reflux. No cystograms were carried out at follow-up, but had been repeated during adolescence in a few patients. Reflux had resolved in a further 5 patients and been corrected surgically in 4 (and 1 had died). Thus on their most recent cystogram, VUR remained in 53 patients, bilateral in 8. Maximum reflux was grade I in 22 patients, grade II in 26 and grade III–IV in 5 (1 of whom had not been reinvestigated since the age of 8 years). Of the 68 with childhood grade III–V reflux (Table 4), none of the 21 patients with unscarred kidneys had developed hypertension or impaired renal function.

Urinary tract infection. No recurrence of UTI was reported in 135 (61%) of the 221 adults. Symptoms reported as "cystitis", not always confirmed microbiologically, occurred in 69 women; 12 of these women, only 3 of whom had persistent reflux, reported more than two episodes. Only 2 had a history of frequent childhood recurrences and 2 others had been treated surgically. Only 1 of 36 men reported a single recurrence. Acute febrile infections had occurred in 17 women, 9 with and 8 without persistent VUR (4 of whom had been treated surgically). Of these 17, 5 (3.5%) had unscarred and 12 (15%) had scarred kidneys (Table 5).

Radiological renal scarring. Limited follow-up IVU was performed in 135 adults (19 males, 116 females), 73 of whom had unscarred and 62 (11 males) had scarred kidneys in childhood (unilateral in 42 and bilateral in 20). This radiological follow-up, using a standardised technique throughout from the time of the IVU on referral, spanned 8–35 years (mean 19 years). The adult findings were compared with those on the last childhood IVU performed in these 135 adults between 8 and 14 years of age, after intervals of 4–24 years (median 12.6 years).

No new radiological renal scars had developed among these 135 adults between the last childhood and the adult X-ray. In 13 of the scarred kidneys the scar had become less obvious due to adjacent renal growth, though the calyx remained deformed. In 9 adults who had a large polar scar in childhood there had been progressive thinning of the parenchyma overlying a large deformed calyx, but there had also been growth of the remaining normal tissue. The only change in scar type was from B to C in 1 woman following post-operative vesico-ureteric junction obstruction.

^{99m}Technetium DMSA studies were performed in 76 adults. The renal morphology on IVU and the DMSA images corresponded well in the majority of the 56 adults with radiological renal scarring. Furthermore, in the 20 adults *without* radiological scarring, neither abnormal DMSA images nor asymmetry of function were observed, although 8 of these 20 had a history of "cystitis" and 5 others had reported an acute febrile infection.

Hypertension. Among the whole group of 226 adults, there was sustained hypertension (>140/90 mmHg) in 15

Table 6. Blood pressure recorded in 28 children and the adult outcome. The remaining 198 were normotensive in childhood and on follow-up

Children			Adults			
			Normal	Labile	Borderline	Hypertension
Hypertension	6	→	–	–	–	6[a]
Borderline	10	→	3	–	1	6
Labile	4	→	1	2	1	–
Normal	8[b]	→	–	2	3	3[b]
Total	28[b]	→	4	4	5	15[a,b]

[a] 3 transplants or death
[b] 1 male with no scarring

Table 7. Abnormal plasma creatinine levels in children and in adults. All 11 children continued to have abnormal results and are represented in the 19 adults with raised or borderline levels, 18 of whom had scarred kidneys

	Children (*n*=226)		Adults (*n*=162)	
	Raised	Borderline	Raised	Borderline
Male	2	2	3	5
Female	4	3	6	5
Total	6	5	9	10

(5 males/10 females) (Table 6). Fourteen of these had renal scarring (bilateral in 11), of whom 12 had established or borderline hypertension in childhood. Among patients who were normotensive in childhood, 8 adults had labile, borderline or sustained hypertension. However, none of the 4 children with labile hypertension had sustained hypertension as adults. At the time of the follow-up study, 1 of the hypertensive girls had died and 2 had received renal transplants, leaving a total of 12 adults who were hypertensive, 6 of whom were receiving treatment for their hypertension. A further 9 had borderline or labile hypertension. Although a higher proportion of men had hypertension (5 of 37, 13.5%) than women (10 of 189, 5.3%), these differences were not significant.

Renal function. Plasma creatinine levels were obtained in all the children and in 162 of the 226 adults, 72 with scarred and 90 with unscarred kidneys; 43 had reflux on their last MCU, 25 of them with renal scarring. The abnormal findings in 226 children and these 162 adults are shown in Table 7. All 11 children and 18 of the 19 adults with borderline or raised plasma creatinine levels had renal scarring. The 9 adults with abnormal levels included 3 women who had received renal transplants or died during follow-up, each with impaired renal function in childhood. Three other women had levels at follow-up of >97 µmol/l; 1 aged 39 years, with a level of 139 µmol/l, had presented aged 11 years with accelerated hypertension, bilateral type B scarring and grades I and II VUR which stopped spontaneously. Three men had levels over 115 µmol/l; 2 with levels over 140 µmol/l had presented under the age of 2 years with severe bilateral VUR treated surgically and bilateral type C scarring. In addition, 5 women and 5 men had levels at or near the upper limit of normal (94–96 µmol/l and 103–111 µmol/l, respectively), including 2 women with hypertension.

Uninfected urine samples from 170 adults (25 males, 145 females) (62 with renal scarring) were analysed for microproteins. Microproteinuria was found in 13 patients, 8 with scarred kidneys. The RBP excretion was increased in 11 patients, NAG in 4 patients (3 of whom were pregnant), and albumin excretion was significantly raised (>30 mg/mmol urinary creatinine/l) in only 2 women, both with bilateral renal scarring. No evidence of renal tubular damage was found where kidneys were unscarred, even among 14 who had severe (grade III–V) VUR in childhood. Of 39 who had persistent VUR on their last MCU, 3, 2 with scarred kidneys, had raised RBP excretion.

Renal length and growth. The scarred kidneys in both child and adult IVU were smaller than those without scarring. Normal renal tissue had continued to grow in the great majority. In scarred kidneys particularly, continued growth of unscarred tissue was observed beyond the age of 20 years. Renal growth was least good in severely scarred kidneys, and 4 had decreased in size.

When renal lengths in relation to height were expressed as SD scores, there was a significant difference in renal length between scarred and unscarred kidneys in both children and adults (analysis of variance $P<0.001$) (Table 8). The SD scores of the 146 kidneys in 73 adults in whom both kidneys were unscarred were normally distributed about the mean. In 42 patients with unilateral scarring, the SD scores of the adult unscarred kidney were significantly greater than those of the above 146 kidneys ($P= <0.001$). However, although the SD scores of the scarred kidneys in these 42 patients were less than those of the 40 kidneys in 20 patients with bilateral scarring, this difference was not significant ($P=0.06$). SD scores in the bilaterally scarred kidneys were widely distributed, with a range of −6.3 to +4.6 SD scores (Table 8).

Renal growth between child and adult IVU was within or above 1 SD of that expected in both kidneys in 71 (142 kidneys) of the 73 patients with unscarred kidneys. No significant difference in mean growth was seen between unscarred and scarred kidneys ($P=0.708$) (Fig. 1), or between unilaterally scarred and bilaterally scarred kidneys ($P=0.25$), indicating that the size and structure of these kidneys had been established in childhood. In the absence of renal scarring, renal growth was unaffected by persistence of VUR.

Somatic height. Adult heights were of normal distribution, with no significant difference between those with and those without scarring ($P=0.34$) or with or without persistent VUR.

Table 8. Mean renal lengths and renal growth of 270 kidneys in 135 children and adults. Renal lengths are expressed as standard deviation (SD) scores in relation to expected renal length for height

Kidneys	Mean renal length in SD scores		Mean renal growth in SD scores
	Child	Adult	
Unscarred (*n*=146)	+0.11 (+2.7 to –1.9)	+0.36 (+4.6 to –2.0)	+0.26 (+2.3 to –1.2)
Unilateral scarring			
unscarred (*n*=42)	+0.79 (+2.6 to –0.6)	+1.09 (+3.4 to –0.5)	+0.30 (+2.0 to –1.3)
scarred (*n*=42)	–1.28 (+1.2 to –4.2)	–1.53 (+1.2 to –5.0)	–0.25 (+0.7 to –1.7)
Bilateral scarring (*n*=40)	–0.77 (+3.3 to –5.3)	–0.75 (+4.6 to –6.3)	+0.02 (+2.3 to –4.9)

Associations in adults. There was no significant difference in the recurrence rate of UTI between the adults with or without persistent reflux on their last MCU (40% and 39%, respectively) or between those with scarred or unscarred kidneys (χ^2=1.9, *P*=0.10, df 1) (Table 5). However, there was a highly significant difference among the 17 women reporting acute febrile infections, between those with and without renal scarring (χ^2 with Yates' correction=7.89, *P*=0.005, df 1), but not in relation to persistent reflux. Of the 17, 9 had reflux on their last MCU while 8 did not. Of the total 15 adults with hypertension and all those with borderline and labile hypertension, 14 had renal scarring; 2 had type C and 5 type D scarring in one or both kidneys. Scarring was unilateral in 4 hypertensive adults and in 7 of those with labile or borderline hypertension. Six had grade III–V VUR in childhood and less-severe VUR persisted in 2 of them. Of the 3 hypertensive adults who had been normotensive in childhood, 2 had type C or D scars. The third, a man aged 24 years with morphologically normal kidneys, had a sustained blood pressure of 150/110 mmHg and a raised plasma creatinine. This has been investigated and treated elsewhere. His childhood reflux had stopped spontaneously at 6 years of age.

Of the 9 adults with impaired renal function, 8 had bilateral renal scarring (types C or D in 6) and 4 had grade III–V VUR in childhood (in 1 of whom VUR persisted on the last MCU); 7 were hypertensive and 2 were normotensive. Among 10 with plasma creatinine levels at the upper limit of normal, all had scarred kidneys, 3 were hypertensive, 1 had borderline hypertension and, in childhood, 7 had grade III–V VUR. Among the 53 patients with VUR on their last MCU, plasma creatinine was raised in only 1, but was near the upper limit of normal in a further 5, all with renal scarring.

Of the 17 adults with hypertension or impaired renal function, 8 had grade III–V VUR as children, and VUR was seen on their last MCU in 3. They had presented at a median age of 6.0 years: 3.0 years (3 weeks to 5.8 years) in the 5 boys and 6.75 years (3.6–12 years) in the 12 girls. This difference is significant (*P*=0.001, Mann Whitney).

Slow renal growth was only seen where kidneys were severely scarred. Persistence of reflux had no independent effect on renal growth. The initial severity of reflux had an indirect effect through its association with a higher proportion of patients with scarred kidneys. In childhood there was a close association between VUR, UTI and renal scarring but in adulthood, persistence of VUR on the last MCU did not significantly affect either recurrence of UTI, development of hypertension, impairment of renal function or renal growth.

Pregnancy. At the time of the study, 52 women had undergone 91 pregnancies; 24 of these women had scarred kidneys and 10 still had reflux on their last cystogram. Of these 52, 26 women had 43 completely normal pregnancies while the other 26 women, in addition to 11 normal pregnancies, had 37 with one or more complications (UTI, pregnancy-related hypertension or infants of low birthweight) (Table 9). A higher proportion of each of these complications occurred in women with scarred kidneys (Table 10). Of the 16 women who had hypertension during pregnancy, 10 had renal scarring and of these, 4 had undergone ureteric reimplantation, whilst 2 others had VUR on their last cystogram. Only 1 woman, with renal scarring and persistent VUR, needed hospital admission for infection.

Ten women had VUR on their last cystogram. Five of them had renal scarring, 3 of whom had abnormal preg-

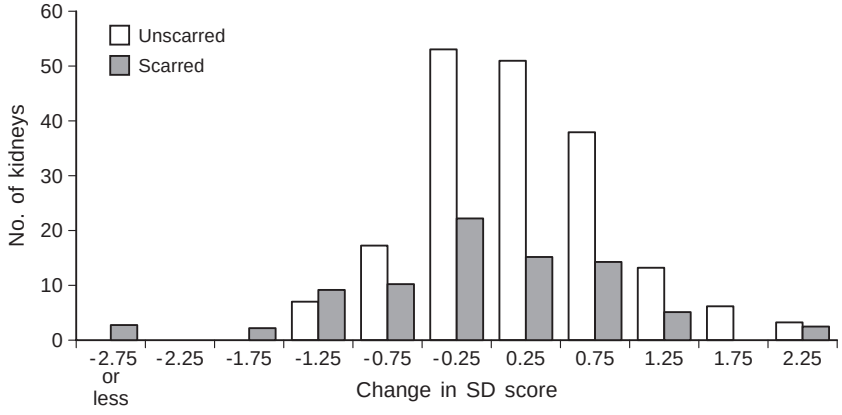

Fig. 1. Radiological growth (length) expressed as change in standard deviation (*SD*) scores of 270 kidneys in 135 patients measured over 8–35 years; 188 of the kidneys were unscarred and 82 were scarred

Table 9. Ninety-one pregnancies in 52 women who had VUR and UTI in childhood. There was persistent reflux in 5 of the 24 women with scarred and 6 of the 26 women with unscarred kidneys[a]

Renal status	Women (*n*=52)		Pregnancies (*n*=91)		
	All pregnancies normal	1 or more pregnancies abnormal	Normal	Abnormal	Total
Scarred (*n*=24)	9 (12)	15 (3)	15	24	39
Unscarred (*n*=28)	17 (31)	11 (8)	39	13	52
Total (*n*=52)	26 (43)	26 (11)	54	37	91

[a] Normal pregnancies in parentheses

Table 10. Complications occurring in 37 pregnancies among 26 women with a past history of VUR and UTI; 3 of the 15 women with scarred kidneys had VUR on their last MCU and 1 of the 11 with unscarred kidneys. More than one problem affected some pregnancies[a]

Renal status	Pregnancy complications (26 women)		
	UTI	Raised blood pressure	Infant birthweight <2,500 g
Scarred (*n*=15)	10 (14)	10 (14)	6 (8)
Unscarred (*n*=11)	5 (5)	6 (8)	1 (1)
Total	15 (19)	16 (22)	7 (9)

[a] Pregnancies in parentheses

nancies (1 mother needing an emergency cesarean section for pre-eclamptic toxaemia). In the 5 with unscarred kidneys, only 1 of 11 pregnancies was complicated (by a UTI).

Ten women had earlier undergone ureteric reimplantation. In 7 with scarred kidneys, 4 developed pregnancy-related hypertension and 4 developed UTI. The 3 with unscarred kidneys did not develop hypertension during 8 pregnancies, but 2 were complicated by an infection. Thus the 15 women who suffered a UTI during pregnancy included 6 of the 10 who had undergone ureteric reimplanatation (4 with scarred kidneys) and 9 of the 42 who had not been treated surgically. This difference is not significant (χ^2 Yates=2.044, P=0.154).

Of the 9 infants weighing 2,500 g or less, 8 were born to 6 mothers with renal scarring, 2 with persistent VUR. The only neonatal death followed delivery at 27 weeks' in a woman without VUR and with normal kidneys, after surgery for an incompetent os. Among 20 infants known to have been investigated postnatally, 6 had VUR, 2 born to mothers with unscarred kidneys. The other 4 include 1 of 2 female infants born to a woman with a renal transplant, not included in the analysis of pregnancies. Ten spontaneous miscarriages were reported in 6 women and 12 terminations had been performed for various reasons, but not for hypertension.

There was no difference in the mean plasma creatinine levels of women with scarred kidneys who had and had not undergone pregnancy (83.9 mmol/l and 81.5 mmol/l) or between those with unscarred kidneys who had or had not undergone pregnancy (68.3 mmol/l and 73.6 mmol/l).

A significant relationship was found between the presence of scarring and abnormal pregnancies using a statistical model that took into account the extra bionomial variation due to patients having multiple pregnancies (χ^2=12.50, P<0.001, estimated log odds ratio=1.569, SE=0.495). The model shows that those with scarred kidneys are more likely to have abnormal pregnancies.

Deaths. One girl with a single upper pole renal scar without persistent reflux died aged 23 years in status asthmaticus. A second death occurred in a man aged 37 years as a result of an accidental fall at work. He had undergone a left nephro-ureterectomy aged 12 years and had persistent mild VUR into a scarred right kidney, but had remained normotensive with normal renal function. The third died aged 25 years from a cerebral haemorrhage associated with uncontrolled hypertension. After presentation at 7 years with accelerated hypertension, bilateral severe renal scarring and bilateral severe reflux, she underwent a nephro-ureterectomy and contralateral ureteric reimplantation. Her renal function was impaired but her blood pressure had been fairly well controlled at her local hospital until her last few months.

Results of postal questionnaire

A further study of this group of adults was carried out in 1995/1996, when details of UTI, blood pressure, pregnancy and any other complications were sought from both patients and their doctors. Responses were received from 161 patients, 24 males, 137 females (72%). These included 79 of the 82 surviving patients with renal scarring (2 had emigrated and 1 was untraced) and 51 of the 53 who had persistent reflux on their last cystogram (including all 28 who also had renal scarring). The mean duration of follow-up of these 161 patients was 28.8 years with a range of 18–41 years. Their ages ranged from 26 to 52 years, median age 35.2 years. A recurrence of UTI was reported in 21 (27%) of those with renal scarring and in 19 (23%) of those with unscarred

kidneys, including 1 acute febrile infection in a woman without VUR or scarring.

A blood pressure of 140/90 mmHg or higher (maximum 150/100 mmHg in 1 patient) was reported in a further 9 patients, 7 of whom had renal scarring (unilateral in 5). Their ages ranged from 34 to 42 years (mean 38 years). Two had bilateral grade II VUR on their last childhood MCU: none was on hypotensive treatment. Five of them, all with scarred kidneys, had borderline or labile hypertension 8 years earlier. A further 7 women aged 31–47 years (mean 37 years) were reported to have borderline hypertension; 2 of these 7 had minimal VUR on their last MCU, none had renal scarring and 4 had a family history of hypertension. The plasma creatinine level had risen further in 2, aged 37 and 47 years, of those in whom it was already abnormal, but no patient had entered an end-stage programme and almost all continued to lead normal lives. One woman aged 44 years had received a live donor renal transplant aged 24 years and was alive and well, normotensive without hypotensive drugs. In the other "transplanted" woman aged 51 years, a second cadaver transplant had failed soon after the 1989 study and she was on a programme of dialysis and hypotensive treatment.

There had been 64 more pregnancies in a total of 46 women, 27 with and 19 without renal scarring, but complications had been reported in only 8. Two of the new infants were found to have VUR.

Discussion

The study reported here differs from most other long-term studies in being prospective and involving continuous and regular observation by a single paediatrician, through childhood and adolescence, of a group of children with VUR and UTI. They were managed on a regimen designed to prevent infection from reaching the kidney. On follow-up aged 18–37 years, over 90% were clinically well and normotensive, although in childhood 85 of the 226 patients studied (38%) had renal scarring and 68 (30%) had severe reflux with dilatation (grade III–V).

Fifteen adults had hypertension and 9 had impaired renal function, including 2 who had received renal transplants and 1 who had died from a renal-associated cause, all 3 in their 3rd decade. Because of the overlap between these conditions, there were in all only 17 adults (7.5%) with impaired renal function or hypertension, all but 1 of whom already had scarred kidneys on presentation in childhood, type C or D in 8 of them. Deterioration of renal function or blood pressure could have been predicted in 8 of these 17 adults, because they had raised blood pressure or creatinine levels in childhood, and in a further 7 where these were at the upper limit of normal.

On a further follow-up by postal questionnaire 8 years later, an additional 9 adults had developed mild to moderate hypertension, 7 of them with renal scarring and 2 with persistent mild VUR in childhood. Thus at the end of the study, hypertension meriting treatment was present in 17 (7.5%) of the total group of 226 adults with VUR in childhood, 15 of whom had renal scarring. These 15 represent 17.6% of the original 85 with scarred kidneys. In a similar group of 30 adults with scarred kidneys, Jacobson et al. [8] reported hypertension in 7 (23%). In the light of these findings continued monitoring of the blood pressure in patients with renal scarring is indicated.

We also found that as well as hypertension and impaired renal function, acute febrile UTI and complications of pregnancy were significantly related to renal scarring. In contrast, neither initial grade III–V VUR nor persistent VUR on the last childhood MCU appeared to have any significant effect on these parameters, independent of renal scarring. Raised urinary RBP, a mark of renal tubular damage, was also found almost exclusively in adults with renal scarring.

After referral and during careful childhood management at UCH, no significant renal deterioration occurred and only 2 children had developed new scars. No new radiological scars developed after puberty. It should also be emphasised that in subjects with normal IVU as adults who subsequently underwent nuclear imaging, no abnormal DMSA images or asymmetry of function were seen. Thus the radiological renal patterns were already established in childhood. There was a significance difference in mean renal size between scarred and unscarred kidneys in both the last childhood and in the adult IVU, but there was no significant difference in the overall renal growth between the two groups (although some of the very small scarred kidneys did not grow). These observations indicate that in this whole group of patients, carefully managed in childhood as described, outcome was determined almost entirely by renal status at the time of presentation to our clinic.

Nevertheless, in childhood, reflux has a role of considerable importance because of its association with renal abnormalities, both congenital and those acquired following UTI [23, 26–28]. In the patients reported here, all with childhood reflux, a high proportion had renal scars, which in 13 of the children were known to have been acquired (e.g. [12]). The possibility that VUR, particularly if severe, in childhood might cause lasting hydronephrotic damage has not, in the absence of obstruction, been substantiated.

In the earlier published childhood studies from which most of the adults in this paper were drawn, there was a tendency for boys to present early with gross reflux and often bilateral type C scarring, while girls tended to present later with a history of recurrent UTI and less-severe reflux [12]. This pattern was reflected in the 17 adults in this study with hypertension and/or impaired renal function. The women with hypertension presented over the age of 7 years with a history of recurrent UTI and with scarred kidneys and moderate reflux, while the men who had impaired renal function at the age of 31–37 years were first seen at or below the age of 2 years and had severe bilateral VUR and type C scarring. A similar pattern was seen more recently in a different group of 496 children with UTI investigated by DMSA study. Severe bilateral abnormalities of DMSA uptake were seen in infant and young boys, all with severe bilateral VUR, and in older girls with a history of recurrent

UTI, also with VUR [29]. These data illustrate the spectrum of reflux-associated renal scarring from hypo-dysplasia to post-natal acquired scars.

Martinell et al. [30], studying 65 pregnancies in 41 women with a history of UTI in childhood, noted a higher incidence of UTI and acute febrile infection in those with renal scarring and with persistent reflux than in controls. This is in keeping with our findings that both UTI and raised blood pressure occurred more frequently in women with renal scarring. The only episode of UTI requiring hospital admission occurred in a young pregnant woman with renal scarring and persistent reflux. Clearly, special consideration should be accorded to pregnant women with renal scarring. An incidental finding was a higher incidence of UTI among pregnant women whose VUR had been corrected surgically than in those not managed surgically, supporting the observations of Mansfield et al. [31].

The response to a questionnaire after a further 8 years provided information about the outcome of over 70% of the adults who were first seen as children at UCH up to 41 years earlier, including almost all the patients who had renal scarring, persistent VUR on the last MCU or severe childhood VUR. There had been little change in their status between 1989 and 1996, no further patients had entered an end-stage programme and only 2, 1 with and 1 without renal scarring, had developed hypertension requiring treatment.

This study does not describe the natural outcome of childhood VUR and, because a controlled study would have been ethically unacceptable, the contribution of careful medical management cannot be absolutely verified. It is well recognised however that compliance in a therapeutic regimen is improved by continuity of care. No radiological deterioration was seen in the present study, such as was reported by Jacobson et al. [9], although no information is available regarding management in the intervening years or the timing of renal deterioration in their study. When a comparison was made between the outcome of two similar groups of children with VUR and UTI [32] managed with either intermittent short courses of antibiotics in 102 children or with continuous long-term low-dose prophylaxis in 75 children, 21% of the former developed new radiological scars compared with 1% of the latter [16, 33]. New scars can be acquired throughout childhood [23, 34]. For example, at least 22 of the 148 children with scarred kidneys participating in the European limb of the International Reflux Study in Children with severe VUR and UTI were known to have had radiologically normal kidneys when investigated for earlier UTIs [35, 36].

Since renal scarring is permanent and irreversible, clinical management should be directed towards preventing new scar development or limiting the extension of existing scars. Delay in diagnosis and treatment has been shown to contribute to the development of renal scars [23, 37], as was found in a study of the antecedents of bilateral scarring in 52 children with reflux [38]. There is good experimental evidence to indicate that early antibacterial treatment can prevent or limit the scarring process [39, 40]. The adults reported here originally presented between 1955 and 1980 at the rather late mean age of 5 years, a similar age to those studied by Jacobson et al. [8, 9]. Of the adults in our follow-up study, only 6% presented under the age of 1 year compared with 78% of those in a recent Gothenburg study; the long-term outcome for these children will be of considerable importance [41]. They also report a good outcome, even in those with renal scarring, of a group of 111 women followed for a mean of 15 years from their first UTI in childhood [42].

The study reported here indicates that the adult outcome for children with VUR carefully managed in childhood was very good in the great majority, even when VUR persisted at the end of childhood. Deterioration of renal function or blood pressure occurred almost exclusively in those with renal scarring and was usually predictable in childhood. It is to be hoped that detection, effective treatment and investigation can be advanced to an earlier age, which might produce a lower incidence of renal scarring and renal compliations.

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