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Five-year study of medical or surgical treatment in children with severe reflux: radiological renal findings

The International Reflux Study in Children

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Abstract. The renal findings on intravenous urography (IVU) are reported in 306 children (73 boys, 233 girls) from eight European centres entered into an international study comparing medical and surgical management of children with urinary tract infection and severe vesico-ureteric reflux followed for 5 years. One hundred and fifty-five children were randomly allocated to medical and 151 to surgical treatment. Protocol and investigative techniques were standardised and randomisation, data collection and analysis were performed centrally in Essen, Germany. At entry 149 (49%) has established renal scarring (79 medical, 70 surgical). Children with normal kidneys (105), areas of thinned parenchyma (52) and grade of reflux were also evenly distributed. IVU was repeated at 6, 18 and 54 months and serial urine culture, ^{99m}technetium-dimercaptosuccinic acid scans and plasma creatinine estimations were performed. Two hundred and seventy-two children (89%) completed this follow-up. In 174 children (57%), (90 medical, 84 surgical) there was renal growth without morphological change. New renal scars developed in 19 children treated medically and 20 surgically; 12 (5 medical, 7 surgical) developed in previously normal kidneys. Six followed post-operative obstruction. No significant difference in outcome was found between medical or surgical management in terms of the development of new renal lesions or the progression of established renal scars.

Key words: Vesico-ureteric reflux – Renal scarring – Urinary tract infection – Thinning of renal parenchyma – Intravenous urography

Introduction

A prospective multicentre study of the management of children with severe vesico-ureteric reflux (VUR) (grades III and IV, International grading) [1, 2] into one or both ureters was undertaken in Europe and in the United States

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Table 1. Main features at entry of 306 children managed according to protocol, 155 treated medically and 151 treated surgically. The more severe abnormality in each child is recorded[a]

		Medical ($n = 155$)	Surgical ($n = 151$)	Total ($n = 306$)
Sex	Male	37	36	73
	Female	118	115	233
Age (years)	0 – 1.9	50	47	97
	2 – 4.9	56	66	122
	5 – 10.5	49	38	87
Renal morphology	Normal	54	51	105
	Thin areas	22 (2)	30 (3)	52 (5)
	Scarring	79 (27)	70 (19)	149 (46)
Parenchymal area	Normal	97	98	195
	Reduced	58 (10)	53 (4)	111 (14)
Maximum VUR	Grade III	31 (23)	25 (19)	56 (42)
	Grade IV	124 (96)	126 (99)	250 (195)
	Total	155 (119)	151 (118)	306 (237)

VUR, Vesico-ureteric reflux

[a] Two hundred and thirty-seven children had bilateral VUR and 51 had bilateral parenchymal abnormalities at entry and these are shown in parentheses

with a main data collection and co-ordinating centre in Essen, Germany [International Reflux Study in children (IRSC)]. The objective was to compare the results of medical and surgical treatment in terms of renal growth and function, the development of new scars and recurrence of infections. The success of surgery and change in reflux grade were observed and a clinical assessment was made of somatic growth and blood pressure.

Recruitment was started in 1980 and completed in 1985 when 401 children aged 6 days to 11 years had been recruited from eight centres in Europe and 132 from 16 American centres. It had been estimated statistically that 400 patients would be needed to detect a difference of 10% in the outcome between the two treatment groups. This paper reports the results of the radiological renal assessment on intravenous urography (IVU) of the children entered and followed in Europe.

Patients and methods

The protocol, methods, terminology and exclusion criteria have already been described [3].

Patients

Four hundred and one children (89 males, 312 females) with grade III or IV reflux [4] (only grade IV under the age of 1 year) were recruited into the European limb of the study. They were aged 6 days to 11 years (median age 3.5 years), and started on a medical regimen of continuous low-dose prophylaxis with attention to fluid intake, bowel function and regular micturition. All had a past history of urinary tract infection (UTI), half of them within the 6 months before entry. Children with renal malformations, such as a complete duplex system, outflow obstruction, neurogenic bladder or clinically overt bladder dysfunction, or a history of previous urinary tract surgery were excluded.

IVU and a voiding cysto-urethrogram (VCU) were carried out before recruitment. The VCU was repeated 2 – 6 months after recruitment and 1 – 23 (median 3.8) months after the previous VCU, to confirm appropriate severity of VUR for acceptance into the study, and then annually, usually by isotope cystography, until VUR ceased. The data of the second VCU was used as the date of entry to the study.

Eighty (20%) of the original children recruited were ineligible for randomisation because of improvement or disappearance of their VUR by the time of the second VCU. These children continued on a medical regimen and were followed regularly in a sideline group. They will be reported separately. The remaining 321 were entered into the study and were randomised to medical and surgical management with stratification according to age, sex, grade of VUR, presence of renal scarring, interval since the last infection and the local treatment centre [3]. After randomisation, 15 children (3 medical, 12 surgical) did not follow the treatment allocated, mainly because of parental preference. Thus, 306 children were treated according to their random allocation, 155 children medically and 151 surgically (Table 1).

Methods

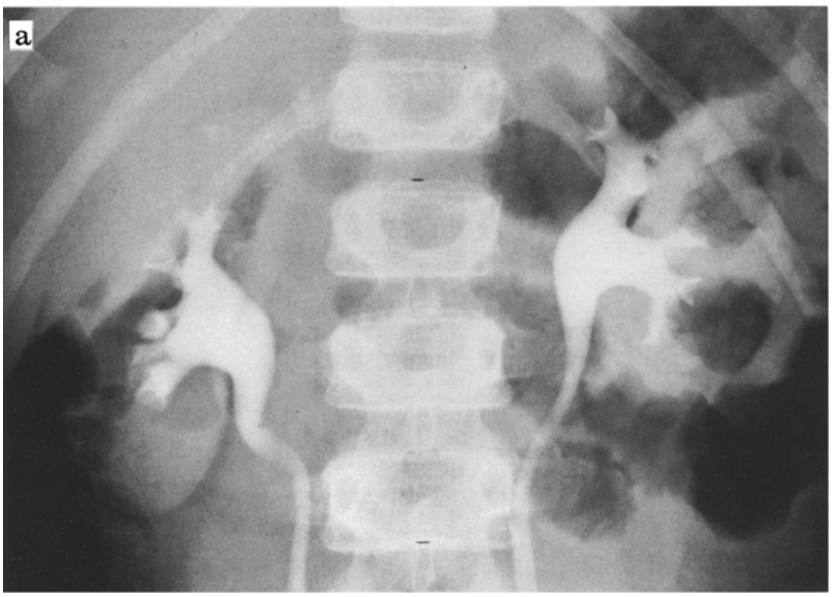
Intravenous urography

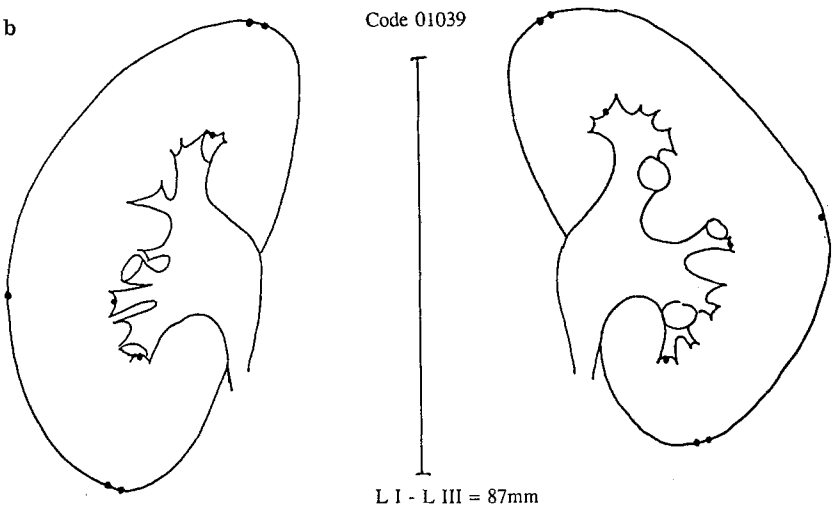
Follow-up IVU was planned at 6, 18 and 54 months after entry or surgery. An additional IVU was performed at entry in those in whom the recruitment IVU was inadequate or performed more than 6 months previously. In 4 children there was no radiological follow-up, 6 had their last IVU at 6 months, 15 after 18 months and 9 had their last IVU (not according to protocol) at 30 and 42 months.

All the IVU films were assessed qualitatively and quantitatively by at least three experienced observers, and those considered abnormal were further reviewed by a panel of five (I. C., K-D. E., T. T.-M., J. M. S. and I. W.). Two renal tracings were made independently and agreed upon. Measurements of renal length, parenchymal thickness of upper and lower poles and lateral zone, and the projected planimetric area (PPA) of each kidney tracing were made and compared with a nomogram, giving a standard deviation score (SDS) for each measurement related to the measurement of L1-3 which was also made [5, 6].

The renal morphological appearance of the series of IVUs in each child in conjunction with renal measurements expressed in absolute numbers and SDS were then reviewed by the full panel without knowledge of treatment or of the presence or severity of VUR or UTI history.

A parallel ^{99m}technetium-dimercaptosuccinic acid (DMSA) scan was carried out at the same intervals as the IVU with an additional scan at 2.5 years. The results of these will be reported separately.





	Right kidney mm	SD	Right/left ratio SD	Left kidney mm	SD	Normal mm
Length	102	-1.4	0.75	94	-2.5	110
Upper pole	25	-1.3	0.25	24	-1.6	29
Lateral aspect	22	+0.5	0.32	20	-0.3	21
Lower pole	28	0.0	**3.85**	**19**	**-3.2**	28
PPA (area)	3420 (mm^2)	-1.8	0.33	3250 (mm^2)	-2.2	4150 (mm^2)

Fig. 1. a Intravenous urograph of a 10-year-old girl with parenchymal thinning of the left lower pole, which remained unchanged over 5 years, no scars. Right kidney normal. **b** Kidney tracing with parenchymal measurements. *PPA*, Projected planimetric area; *SD*, standard deviation

Terminology

Renal scarring. Hodson's radiological definition was used of a reduction in parenchymal thickness overlying a deformed calyx, irregularly distributed in the kidney and usually with an overall reduction in renal size [7]. Scars were typed in each kidney according to Smellie et al. [8] as follows:

Type A. Mild: one or two parenchymal scars only.
Type B. Severe: more extensive, irregular scarring with some areas of normal tissue.
Type C. "Back pressure": fairly uniform parenchymal thinning and generalised calyceal deformity.
Type D. "End-stage": shrunken kidneys. Those in which the planimetric parenchymal area was less than –5 SDS were included.

Thinning of renal parenchyma. This descriptive term was used where there was localised or generalised reduction of parenchymal thickness by at least –2.5 SDS with normal underlying calyces (Fig. 1).

New renal scars. These were observed on IVU and developed either in a previously normal or thinned area of parenchyma. New scars were seen in kidneys which at entry were normal or scarred or had thin areas.

Table 2. Intravenous urography (IVU) findings during the study in 306 children randomised to medical or surgical treatment[a, b]

	Medical	Surgical	Total
Change in renal parenchyma			
New renal scars	19	20	39
New areas of thinning	11	15	26
Progression of existing scars	33	30	63
General	17	17	34
Local	16	13	29
Thinning no longer seen	4	5	9
No change in renal parenchyma			
Normal	47	37	84
Thin areas only	10	16	26
Scarring	29	26	55
Missing data	2	2	4
Total	155	151	306

[a] Three hundred and two children were followed for at least 6 months
[b] The maximum change per child is recorded

Table 3. Details of 39 children who developed new renal scars on IVU during the study

		No. of children with new scars	
		Medical	Surgical[a]
Sex	Boys	7	6 (3)
	Girls	12	14 (3)
Age (years) when new scars observed	0–1.9	11	10 (4)
	2–4.9	3	6 (2)
	>5	5	4
Renal morphology at entry	Normal	5	7 (2)
	Thin areas	7	5 (1)
	Scarred	7	8 (3)
Maximum VUR grade at entry	III	2	3
	IV	17	17 (6)

[a] New scars developing after post-operative obstruction are shown in parentheses

Progression. In some kidneys the structural appearance remained unaltered over 5 years, the only change being growth. Local progression of scars occurred when the calyceal deformity increased and overlying parenchyma became thinner without a reduction in SDS for renal size. Progression of scarring was *general* when several scarred areas of the kidney were involved and there was an overall reduction in kidney planimetric area of more than 1 SDS (i.e. slow growth).

Renal size was based on renal length, parenchymal measurements and PPA. Reduced renal size was defined as a reduction of at least 2 SDS in PPA.

Acute pyelonephritis. A clinical diagnosis of acute pyelonephritis was made when significant bacteriuria was accompanied by fever of 38.5° C or higher and other symptoms. A sedimentation rate >25 mm/h and C-reactive protein >30 mg/l were additional findings [9].

Presentation of results

The radiological outcome of the treatment is presented for each child, referring to the kidney with the more severe renal change and the more severe reflux grade. Details of progress in individual kidneys and of VUR in separate ureters will be published later.

Statistical methods

Randomisation to medical or surgical management was performed using a computer programme, stratifying according to age, sex, VUR grade, renal scars, interval since last UTI and hospital, using methods described by Zehlen [10]. It was calculated that 200 patients would need to be recruited into each group to obtain an 80% power of detecting a difference of at least 10% in the acquisition of new scars, with a 5% risk of a Type I error.

Comparison of frequencies and tests of homogeneity of contingency tables on rank-ordered scales were performed by simple chi-squared tests according to Brandt/Snedecor or the chi-squared trend test of Cochran [11]. It was not necessary to take any covariable into account because stratified randomisation was completed successfully. A life-table analysis and generalised rank test of Gehan-Wilcoxon was performed to compare the groups in the primary outcome of development or progression of renal scars.

Results

The main features at entry of the 306 children in whom the study protocol was followed are summarised in Table 1. Seventy-nine (51%) of the 155 in the medical group and 70 (46%) of the 151 in the surgical group, already had estab-

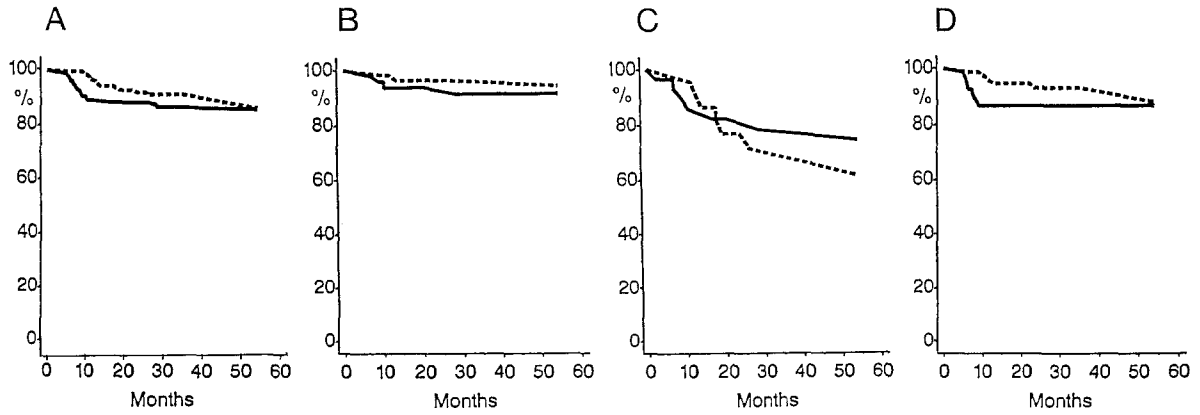


Fig. 2. Life-table analysis of new renal scars developing in 39 children during a 5-year follow-up of 155 children managed medically (– – – –) and 151 children managed surgically (———). **A** All children (306, surgical $n = 151$, medical $n = 155$), no significant difference in treatment groups; **B** 105 children with normal kidneys at entry (surgical $n = 51$, medical $n = 54$) (NS); **C** 52 children with only thinning of parenchyma at entry (surgical $n = 30$, medical $n = 22$) (NS); **D** 149 children with scarred kidney(s) at entry (surgical $n = 70$, medical $n = 79$) (NS)

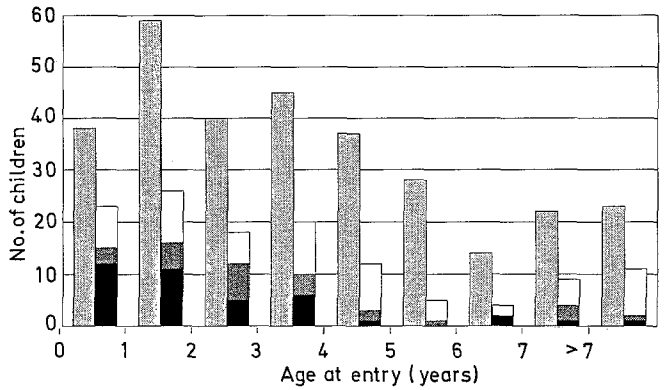


Fig. 3. Age at entry and renal parenchymal change in all 306 randomly allocated children during 5 years' study. The left column of each pair represents all children entering the study in that age bracket. The right column shows parenchymal changes subsequently developing for each age group at entry. ▨, All; ■, new scars; ▤, new thinning; □, progression

lished renal scarring at entry. There was no difference in the type and extent of scarring between the two groups.

Overall results

Of the 306 children entering the study, 272 (89%) completed the 5-year radiological follow-up, 136 from each group. Four children had no further IVU after entry, so that 153 (medical) and 149 (surgical) children had at least 6 months radiological follow-up, and 152 (medical) and 144 (surgical) had at least 18 months follow-up. During this follow-up period, the numbers of children with renal scarring remained similar in the two treatment groups. The development of new scars, new areas of parenchymal thinning and progression of established scars were also evenly distributed between children treated medically and surgically (Tables 2, 3).

No parenchymal change. There was renal growth and no change, or an improvement, in renal morphology in 174 children, more than half of those entered, 90 managed medically and 84 surgically. This number includes 165 children with no morphological change and 9 children in whom areas of thinned parenchyma were no longer seen.

Table 4. Summary of data in 26 children developing new thin areas

		No. of children with new thin areas	
		Medical	Surgical[a]
Sex	Boys	5	4
	Girls	6	11 (2)
Age (years) when new thin areas observed	0–1.9	1	2 (1)
	2–4.9	4	3 (1)
	>5	6	10
Renal morphology at entry	Normal	3	9 (2)
	Thin areas	3	4
	Scarred	5	2
Maximum VUR grade at entry	III	2	4
	IV	9	11 (2)

[a] New thin areas after post-operative obstruction are shown in parentheses

Table 5. Renal outcome on IVU in 52 children with kidneys which showed only areas of thinned parenchyma at entry

	Medical	Surgical	Total
New scars	7	5	12
Additional thinning	3	4	7
No change	10	16[a]	26
No longer seen	1	4	5
Missing data	1	1	2
Total	22	30	52

[a] In 2 children treated surgically a new scar developed in the contralateral normal kidney recorded here as "no change"

Parenchymal change. A change of renal parenchyma was observed during the study in 128 children, 63 treated medically and 65 surgically, with similar numbers developing new renal scars, new areas of parenchymal thinning and progression of established scars (Table 2).

New renal scars. These developed in 39 children, 19 managed medically and 20 surgically (Table 2). In 5 of these, new scarring was bilateral, 4 in the medical and 1 in the surgical treatment group. A total of 24 children, evenly distributed between the groups, developed scars in kidneys without definite scarring at entry, 12 with normal kidneys at entry and 12 children with thin areas (Table 3). Among these, type A scars developed in 6 of the medical and 7 of the surgical group, type B scars in 4 and 2, and type C scars in 2 and 3 children, respectively. Thus, there was no significant difference in the extent of new scarring. Seven children in the medical and 8 in the surgical group developed further scars in normal areas of kidneys which were already scarred at entry.

The proportion of children developing new scars during the study is shown in a life table in Fig. 2. There was no statistical difference between the two treatment groups at 5 years, but new scars were observed earlier in the surgical group, with all but 2 being apparent on IVU performed about 6 months after surgery.

New areas of parenchymal thinning or progression of established scars (Table 2). No significant difference was seen between the two treatment groups. Some of the new thinned areas were seen in normal, some in scarred kidneys and some in kidneys with another thin area at entry (Table 4). There was thus no significant difference between the children in the two treatment groups in the acquisition of new scars, new areas of parenchymal thinning or progression of established scars.

Other results

Age and sex of children with renal parenchymal changes during the study. Figure 3 shows the age at entry of children and the numbers subsequently developing new scars, new thin areas and progression of established scars. Twenty-three (24%) of the 97 infants and children who entered under the age of 2 years, developed new scars, compared with 12 (10%) of the 122 children recruited between 2 and 5 years, and 5% thereafter. Among the 12 children developing new scars in previously normal kidneys, 5 (4 medical, 1 surgical) entered the study under the age of 2 years, 5 between the age of 2 and 5 years (1 medical, 4 surgical) and 2 (both surgical) aged 5 years or over. Six of these new scars were first observed between 2 and 5 years, 4 in children aged 5 and over, and 2 under 2 years. The median age of entry of the 5 children managed medically was 1.0 years and of the 7 treated surgically 4.0 years.

Altogether, 13 (18%) boys and 26 (11%) girls developed new scars ($P < 0.1$). There was a similar frequency pattern in the first 2 years of life, although a higher proportion of the 73 boys than of the 233 girls presented under the age of 2 years.

Reflux status and renal parenchymal appearance. One hundred and forty-nine children (79 medical, 70 surgical) had established renal scarring at entry. In each instance the scarred kidney was drained at entry by a ureter with grade III or IV reflux. VUR was also present at entry in all the renal units developing new renal scars or new areas of parenchymal thinning during the study. This was grade IV in 34 children of the 39 developing new scars (17 medical, 17 surgical). In 1 of these, the new scar developed after post-operative obstruction of an ureter showing grade II reflux at entry, not in the more severely refluxing unit. Children with lesser grades of VUR were not studied, but no new scars developed in a non-refluxing renal unit among the 69 children with unilateral VUR.

UTI and renal scarring. UTI occurred in every child before entry into the study, and a recurrence of bacteriuria was reported in 10 of the 19 children in the medical group in whom a new scar was subsequently observed, and in 9 of the 20 surgically treated children. Bacteriuria during the study was accompanied by fever and acute pyelonephritic symptoms in 9 of the medical and 7 of the surgical patients developing new scars.

Twenty-two medically and 23 surgically treated children had a symptomatic UTI within 4 weeks of the entry IVU. Half of the children in each group showed new lesions or progression of existing ones during the study.

Surgical complications. Ten children (5 boys, 5 girls) developed post-operative vesico-ureteric junction (VUJ) obstruction, 7 requiring further surgery. Of these, 6 (3 boys all aged 1 year and 3 girls aged 2, 3 and 4 years at entry) developed new renal scars. These occurred in children with normal kidneys (2), thin areas (1) and scarred kidneys (3). New thin areas and progression of scarring were seen in the other 4 (Tables 3, 4).

Children with parenchymal thinning. Fifty-two children had thinned areas as the only parenchymal variant at entry. This was present unilaterally in 47 and bilaterally in 5, 22 of them in the medical and 30 in the surgical group. The outcome in these children is shown in Table 5. Among the 105 children with normal kidneys at entry, 12 (3 medical, 9 surgical) appeared to develop new areas of thinning. New thin areas were also seen in 7 children (3 medical, 4 surgi-

cal) with thin areas at entry, and in 7 children with scarred kidneys (Table 4).

Treatment changes. Among the 15 children not treated according to randomisation, 3 changed from medical to surgical and 12 from surgical to medical treatment, and follow-up was continued. A change in parenchyma was seen during follow-up in 4 children, 1 treated surgically and 3 medically. One of these, a girl with normal kidneys randomised to medical treatment, had two febrile attacks of UTI (clinical acute pyelonephritis) between the first and the second VCU before entry and was changed to surgical treatment. Both ureters were reimplanted, one becoming obstructed. She developed a new scar in that kidney and after the second reimplantation she refluxed freely once more into the scarred renal unit. These 15 children, with treatment changes immediately after randomisation, were not included in the analysis.

A change of treatment from medical to surgical was also made in 2 children at the request of the parents at 14 and 18 months after entry. Three others underwent ureteric reimplantation at 22, 23 and 26 months after entry because of recurrent "acute pyelonephritis". All 5 children with late changes of treatment are included in the overall results and have been analysed according to the randomisation at entry.

Discussion

This paper reports the outcome in the European limb of an international, multicentre, randomised treatment trial of children with severe reflux and a history of UTI, comparing the radiological renal findings on IVU in children managed medically and surgically. All the IVUs were assessed by experienced observers but occasional problems in interpretation were encountered; for example where there were multiple scars or soon after an acute symptomatic infection or where VUR was severe with pelvicalyceal dilatation. In these, a panel agreement was reached without knowledge of treatment, and this applied to both treatment groups equally.

At the end of 5 years of serial observations, there was no numerical difference between the children treated medically or surgically in terms of development of new renal scars, new areas of parenchymal thinning, progression of existing scars (Table 3) or renal growth (to be published). Although 90 children treated medically and 84 treated surgically showed either improvement or no morphological renal change during the study, 19 treated medically and 20 treated surgically developed new scars in normal or previously scarred kidneys. This result confirms the findings of the earlier Birmingham study that neither treatment can fully protect the kidneys from further damage [12, 13]. In the Birmingham study, however, all the new scars were present by the 2-year follow-up IVU whereas in the IRSC, new scars were first seen both earlier and later than 2 years after entry. New scars were recognised earlier in the study in the surgical group than in the medical group (Fig. 2). Perhaps most scars had already been initiated at entry (which was considered to be likely in the Birmingham study) and the scarring process might have been accelerated by surgical intervention. Alternatively it might be suggested that with continuing VUR in the medical group the kidney remained at risk of exposure to urinary infection or high pressure and therefore of fresh scarring. Reflux persisted continuously or intermittently in 80% of the medical patients, although mainly of a lesser severity, without impairment of growth or the development of new renal lesions in the great majority. Among the 12 children who developed new scars in previously normal kidneys, the 5 children treated medically were younger at entry than the 7 managed surgically. Recurrences of urinary infection and their relationship to renal scarring will be published separately [14].

Only children with grade III or IV reflux into at least one ureter were entered. This was bilateral in 57%; in others a lesser grade (20%) or no reflux (23%) was seen in the opposite ureter. These severe grades of reflux carry a high risk of associated renal damage, and almost half the children had scarred kidneys at entry. New damage or progression of existing scarring during this study was confined to renal units with severe reflux at entry (except in 1 child post-operatively). No conclusions can be drawn, however, about children with lesser grades of reflux.

In 6 children, new scars developed following post-operative VUJ obstruction. This complication was most common under the age of 3 years but also occurred in 1 girl of 5 years. Age was also a prominent factor in the prognosis, as Winberg et al. [15] and Berg and Johansson [16] have noted. The highest risk of new scar development during this study was in children entering under the age of 3 years, although a lesser risk still remained in the older child.

The significance of areas of thinned parenchyma is being explored. They have previously been regarded as normal morphological variants, or as "arrested" scars, or as local growth failure or as pyelonephritic scars where the relevant calyx has remained unfilled by contrast medium [17–20]. Twelve (23%) of the children in the IRSC with only thin areas at entry, developed new scars in that area, indicating that such children should be kept under continued observation. In over half, the appearance remained unchanged. In 7, new thin areas appeared and a few thin areas were no longer visible on follow-up. This might be attributed either to the effect of treatment or to the thin area being a normal variant.

No morphological change occurred during the study in 55 children with established scarring on entry (29 medical, 26 surgical), but in 33 children treated medically and 30 treated surgically, scarring progressed with further parenchymal thinning, or increased calyceal deformity or both. Where there were only one or two scarred areas (type A), there was growth of sufficient normal parenchyma to compensate for the change. With more extensive type B scarring, the SDS for the planimetric area was usually progressively reduced when focal scars developed fully. Progression was considered to be part of the natural history of the scarring process. Nevertheless, some renal scars, either new or already established, remained unchanged throughout the study and some progressed to fully developed scars, with no difference between the treatment groups. A detailed evaluation in individual kidneys of new

scars, areas of parenchymal thinning and progression of parenchymal lesions is being made in relation to infection, reflux grade and findings on DMSA scans. The results will be reported separately.

Of some interest in this study was the variation in results between individual centres. In several centres where 50–90 patients were recruited, they were managed in specialist clinics for UTI with continuity of experienced care. The recurrence rate for infection and the incidence of new scar development, or of scar progression, was lower in both medical and surgical groups in these centres than in those recruiting smaller numbers. This supports the view already established in other conditions that the prognosis is generally improved when children are managed together under interested specialist care.

Only 5% of children entering the study with normal kidneys developed new scars, and over half of these were over 2 years of age at entry. Vigilance in detection and management of UTI cannot be relaxed after infancy, and the diagnosis, careful management and follow-up of children with severe reflux is essential at any age in childhood. This study has not shown superiority of either medical or surgical management and a clinical assessment will influence the choice. Renal scarring is a permanent change and whenever possible its development should be anticipated and prevented [2].

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