

PAPERS AND ORIGINALS

Disappearance of vesicoureteric reflux during long-term prophylaxis of urinary tract infection in children

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Summary

Seventy-five children aged 3 weeks to 12 years and found on investigation of symptomatic urinary infection to have vesicoureteric reflux were managed conservatively with continuous low-dose prophylaxis. Serial cystographic and renal growth studies were performed during seven to 15 years' follow-up.

Reflux disappeared spontaneously in 53 children (71%) and from 79% of the affected ureters. This occurred at any age and not only in infancy or at puberty. The initial severity of reflux was the most important factor affecting the outcome. Reflux disappeared from 85% of ureters of normal calibre but from only 41% of dilated ureters. Gross reflux associated with existing severe renal scarring was least likely to disappear. Nevertheless, reflux stopped in 12 of the 19 initially scarred renal units (63%). Reflux was as likely to disappear in children who had a recurrence of urinary infection as in those who had no further infection. Renal growth appeared to be normal in 93% of kidneys and fresh or extending scarring was seen in only two children.

Management programmes for children with vesicoureteric reflux should take into account the self-limiting nature of three-quarters of the reflux found on investigating uncomplicated urinary tract infection.

Introduction

There is a close association in childhood between urinary infection, vesicoureteric reflux, and renal scarring of the

"radiological chronic pyelonephritis" type.^{1 2} An earlier interest in reflux and its possible consequences was reawakened by the observations of Hodson and Edwards³ and of Hutch *et al*,⁴ and operations were devised for correcting reflux at a time when neither its aetiology nor its possible effects upon the kidney were fully understood. Since reflux in childhood is usually found during the investigation of a urinary tract infection, the relative importance of infection and of reflux in the pathogenesis of scarring or of impaired renal growth has been particularly difficult to determine.

We therefore studied the effects of reflux in children who were maintained on long-term low-dose prophylaxis to prevent further urinary infection.

Children presenting with urinary infection in the Children's Department, University College Hospital, and found to have vesicoureteric reflux have generally been managed on a conservative regimen apart from a short period from 1961 to 1963, when ureteric reimplantation was quite often recommended. Since then surgical treatment has been advised for less than 10% of children with reflux. Nephroureterectomy was performed in children with the combination of severe unilateral scarring, hypertension, and gross ureteric dilatation. Reflux-stopping procedures were advised in infants with grossly dilated ureters, in children in whom for medical or social reasons (such as failure to attend clinics) it became impossible to prevent further infection, and in children with evidence of fresh or progressive renal scarring.

Over 250 infants and children with vesicoureteric reflux have been managed on a conservative regimen and we now report the results of seven to 15 years' follow-up of the first 75 children treated in this way. An earlier follow-up study of this group was briefly reported in 1969.⁵

Methods

The group comprised 75 children (58 girls and 17 boys) who presented with urinary infection in 1956-67 and in whom reflux was shown radiologically at least two weeks after the presenting infection had been controlled. Their ages ranged from 3 weeks to 12 years at the start and up to 24 years at the end of the study. Of the 19 infants aged under 1 year, eight were boys. Of the remaining 56 children, nine were boys. All the children had normal plasma urea and creatinine concentrations. In five girls there was a family history of reflux. Three

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children had a blood pressure greater than 140/90 mm Hg on presentation. Children with obstructive urinary tract disease, whether mechanical or neuropathic were excluded from the study.

BACTERIOLOGY

Since all the children were admitted to the study before 1967 infection was originally diagnosed by Guttman and Stokes's method,⁶ which was based on obtaining a significant pure bacterial growth from a clean fresh specimen of urine. Most children also had more than 20 white cells per μ l of uncentrifuged urine. After 1969 a surface-viable counting technique was used, and a pure growth of 100 000 or more organisms/ml fresh urine was regarded as evidence of infection.

RADIOLOGY

Children were investigated as outpatients by intravenous urography (IVU) and micturating cystourethrography (MCU). The latter was carried out at least two weeks after the presenting infection had been eradicated. Limited examinations were repeated every two years until reflux disappeared, in which case a confirmatory cystogram was carried out one year later.

IVU—For the initial investigation a four-film IVU was performed using Conray 280 (meglumine iothalamate) 2.2 ml/kg body weight to a maximum dose of 20 ml. The follow-up IVU was usually confined to a single film of the kidneys taken 15 minutes after the injection of the contrast medium. The renal length was measured and then related to that expected for the child's height.⁷ Renal growth was considered to be slow when the lag between the expected renal growth in length and that observed exceeded 1 cm over the period of follow-up. Growth was considered normal if renal length increased at or above the rate expected from the increase in the child's height.

MCU—For the MCU the bladder of the wakeful child was filled to capacity with 15-25% diodone introduced through a fine polyethylene catheter (infant feeding tube No 6-8 French gauge), which was then removed. Micturition was screened throughout with an image intensifier and the results recorded by means of "spot films." Reflux was classified as follows^{8,9}: grade I, minimal reflux; grade II, reflux extending up to the kidney only on voiding; grade III, reflux up to the kidney that occurred also during filling of the bladder; and grade IV, reflux up to the kidney accompanied by some degree of ureteric or renal pelvic dilatation, or both.

Radiological features on presentation—Coarse renal scarring (radiological chronic pyelonephritis or reflux nephropathy) characterised by reduced renal size, localised thinning of the renal substance, and associated calyceal deformity was present initially in 19 kidneys (17 children), its incidence being equally distributed among all age groups. Other morphological variants and their outcome are shown in table I. Vesicoureteric reflux was initially present in 116 ureters in the 75 children, being bilateral in 41 of them. When first demonstrated, the severity of reflux was: grade I, 18 ureters; grade II, 22 ureters; grade III, 59 ureters; and grade IV, 17 ureters. During the course of the study reflux was shown in five further ureters, which had been normal on initial examination.

TABLE I—Radiological features associated with vesicoureteric reflux

	Children	Ureters	
		Reflux initially	Reflux stopped
Renal scarring	17	19	12
Duplex kidneys	4	6	4
Ectopic kidney	1	1	1
Horseshoe kidney	1	2	2
Total	23	28	19

TREATMENT AND FOLLOW-UP

Low-dose prophylaxis was continued while reflux was present and until a second successive negative micturating cystogram was obtained. The drugs used at first were either sulphadimidine or sulphafurazole, 20-30 mg/kg/day, or nitrofurantoin, 1-2 mg/kg/day. Recently cotrimoxazole, 10 mg sulphamethoxazole and 2 mg trimethoprim/kg/day, has been preferred. The children were also encouraged to void every

two or three hours, perform double micturition at bedtime, and open their bowels regularly. A clinical and bacteriological examination was performed every three months, with more frequent visits when symptoms or proved infection returned. Follow-up intervals were extended to six or 12 months when the urinary tract had remained free from infection for two years after reflux had stopped. Hospital admission was avoided almost entirely.

Results

During the period of observation reflux disappeared in 53 children (71%) (11 boys and 42 girls). Nine of these had had established renal scarring on presentation. Reflux stopped in 95 of the 121 refluxing ureters (79%), including 12 of the 19 ureters draining scarred kidneys (63%). Fifty-three children (71%) remained free from infection and 22 had one or more infections during follow-up.

Overall renal growth was satisfactory in 70 (93%) of the children but fresh scarring appeared or extended in two kidneys.

DISAPPEARANCE OF REFLUX

Age—Reflux disappeared from the ureters of children of all ages, there being no tendency for it to stop at any particular time such as at puberty or in early childhood (fig 1). It stopped in 38 (65%) of the 58 children in whom the diagnosis was made before the age of 7 and

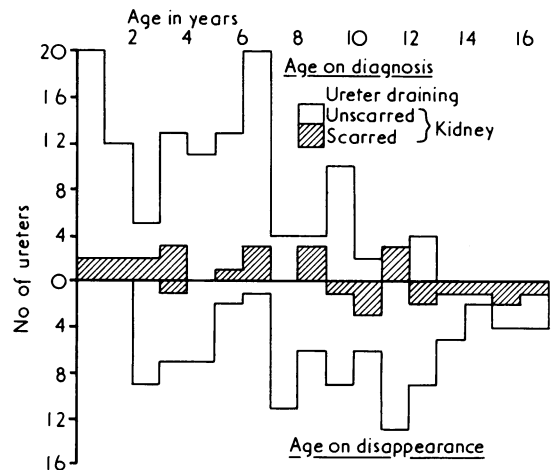


FIG 1—Age on diagnosis of reflux in 121 ureters and on its disappearance in 95 ureters. Ureters draining scarred and unscarred kidneys are indicated.

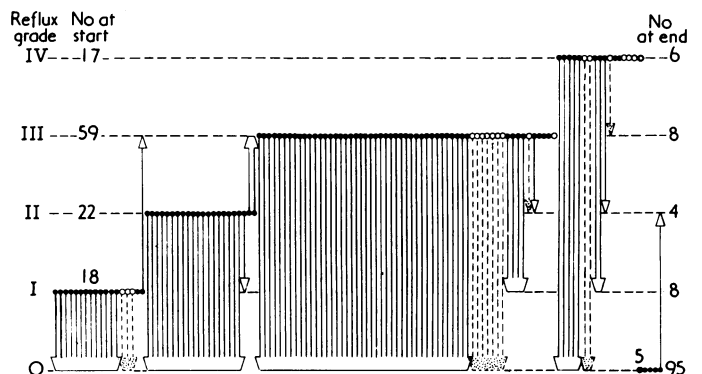


FIG 2—Progress of reflux in 121 ureters during seven to 15 years' follow-up. Each ureter is represented by a circle (solid circles represent those draining unscarred kidneys). They are grouped according to severity of reflux on first cystogram. Early in follow-up period reflux appeared in five contralateral ureters, subsequently disappearing in four. Arrows indicate change in severity of reflux during observation. Reflux disappeared in 85% of ureters with grade I, II, or III reflux on diagnosis and in 41% of those with grade IV.

in all but two of the 17 children (88%) in whom it was first diagnosed at 7 or over. It stopped in all children who had unilateral reflux draining a normal kidney and in both ureters in 62% of the children with bilateral reflux.

Severity—Reflux stopped in 89%, 86%, and 83% of the ureters with initial grades I, II, and III reflux respectively but in only 41% of those with grade IV reflux initially (fig 2). The difference between grade IV ureters and the others was highly significant ($P < 0.001$).

Duration—There was a continuing tendency for reflux to disappear even though it had been present for five years or more; reflux of any severity could disappear within two years of diagnosis or persist for up to 10 years before disappearing. The timing of disappearance of reflux is shown in fig 3. In each two-year period reflux disappeared in 20-30% of those ureters in which it was still present.

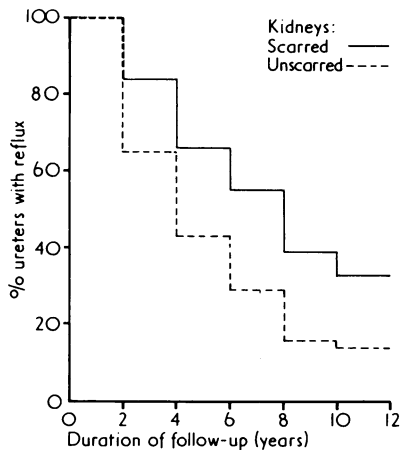


FIG 3—Percentage of ureters followed in which reflux persisted related to duration of follow up.

Infection—There was no significant correlation between the recurrence of infection and the tendency for reflux to disappear (table II). Reflux disappeared in 59% of the children who developed a further urinary infection and in 75% of those who did not. Reflux reappeared intermittently in 17 children but this was not related to infection. It subsequently disappeared on two consecutive cystograms in 15 of these children.

Sex and family history—Reflux was as likely to disappear in boys as in girls and it also disappeared in four of the five children in whom there was a family history of reflux.

Renal abnormalities—Reflux stopped in 63% of the ureters draining scarred kidneys compared with 81% of the ureters draining unscarred renal units. The progress of reflux in association with other renal abnormalities is shown in table I.

TABLE II—Relation between reflux and urinary infection

Reflux	Children			Ureters		
	Recurrence of infection	No further infection	Total	Recurrence of infection	No further infection	Total
Persisting	9	13	22	11	15	26
Disappearing	13	40	53	25	70	95
Total	22	53	75	36	85	121
χ^2	2.01*			1.20*		

*Not significant.

RENAL GROWTH

Renal growth over the period of the study was assessed in 71 of the 75 children, three children with duplex kidneys and one with a horseshoe kidney being excluded. Thus there were 113 kidneys with refluxing ureters in which renal growth data were available. The results are summarised in table III. Normal renal growth seemed to

TABLE III—Overall renal growth in 113 kidneys drained by refluxing ureters

Kidneys initially	Renal growth		Total
	Slow	Normal	
Scarred	5*	14	19
Unscarred	3*	91	94
Total	8†	105	113

*Included one fresh or extending scar.
†Included two fresh or extending scars.

have taken place in 97% of the unscarred kidneys and 74% of kidneys that were scarred initially.

A fresh scar appeared in the previously normal kidney of a boy aged 10 and appeared to extend in the already scarred kidney of another boy aged 7. In both the scarring followed an infection in the presence of grade III-IV reflux.

PERSISTENT REFLUX

Reflux persisted throughout the period of observation in 16 children (19 ureters). Surgical reimplantation was undertaken in three further children (four ureters)—the two boys with fresh scarring and a girl aged 18 whose infection recurred, with enuresis, when her prophylactic antibacterial treatment was discontinued after five years' freedom from infection. Three children (three refluxing ureters) were lost to follow-up after three and four years. In only three children was there no change in the severity of their reflux. All had evidence of ureteric dilatation on IVU and it was gross on MCU. Each related kidney showed generalised renal scarring with reduced renal size, uniform calyceal dilatation, and thinning of the renal substance.

CLINICAL PROGRESS

No significant side effects developed to the antibacterial drugs, and physical growth was normal in all the children. Hypertension was controlled with hypotensive drugs.

Discussion

This study was originally planned to differentiate the effect of sterile reflux from that of refluxed infected urine on the growth of the kidney but it soon became apparent that in many children reflux is self-limiting since it ceased in 83% of the ureters and over 70% of the children followed. This confirmed observations⁵⁻⁹⁻¹² that reflux tends to stop spontaneously with time. Furthermore, this appeared to be a continuing process and one which could take place over several years, with lessening of reflux often preceding its complete cessation. Persistence of reflux for over six to 12 months is often regarded as an indication for its surgical correction, but in this series reflux stopped within two years of diagnosis in only 28% of the children (38% of ureters) in whom it finally ceased. On the other hand, an isolated negative cystogram does not prove permanent disappearance of reflux and a minor degree of reflux returned during continuing prophylaxis in about a fifth of the ureters before finally disappearing.

The severity of reflux was the most important factor determining the disappearance or persistence of reflux. Reflux disappeared spontaneously from only 41% of the ureters with grade IV reflux compared with 85% of those with less severe grades of refluxes.

The initial cystogram was always carried out at least two weeks after a urinary infection, so that it is not possible to comment on vesical infection as a possible cause of vesicoureteric reflux. In our study, however, the likelihood that reflux would disappear did not differ significantly between the children who had further infections and those who remained free from them (table II). We have no evidence therefore that antibacterial treatment "cures" reflux.

The value of long-term prophylaxis lies in preventing reinfection of the bladder, with the accompanying risk of ascending infection of the kidney while the vesicoureteric junction remains incompetent.⁹ Both co-trimoxazole and nitrofurantoin are satisfactory prophylactic drugs^{13 14}; their action can be enhanced if overdistension of the bladder and the accumulation of residual urine are avoided by regular complete voiding and by double micturition at least once daily.

Lenaghan *et al.*¹⁵ using intermittent short courses of antibacterial drugs for treating recurrent infections in 102 children with reflux, recorded a spontaneous cessation of reflux in only 42%. Altogether 66% of ureters of normal calibre and 26% of initially dilated ureters stopped refluxing over five to 18 years' observation compared with 85% of normal-calibre ureters and 41% of dilated ureters in our series. Moreover, Lenaghan *et al.* observed fresh scarring in 21% of initially normal kidneys, while we observed this in only 1%.

In each two-year period we found that reflux disappeared from 20-30% of the refluxing ureters being followed. This was probably an effect of maturation, the obliquity of the insertion of the ureter and hence its intramural length and valvular competence increasing with age.¹⁶ King *et al.*¹⁷ also regard the length of the intramural segment as an important guide to prognosis. This is also consistent with the smaller proportion of children in whom reflux stopped in the series of MacGregor and Freeman,¹⁸ where there was a mean follow-up of five years compared with seven to 15 years in this study (mean nine years).

The finding that reflux disappeared from 12 of the 19 scarred kidneys is consistent with Vermillion and Heale's observations¹⁹ in patients aged over 12 with chronic non-obstructive pyelonephritic scarring. They showed vesicoureteric reflux in only 45 out of 97 scarred kidneys, although 86 (89%) of the ureteric orifices were found on cystoscopy to have "abnormalities of such degree that reflux is likely to have occurred in the past," suggesting that childhood reflux had stopped. In view of these findings, the cystoscopic appearances are perhaps of less importance in determining management than the observation of normal renal growth without scarring.

Social, geographical, and temperamental factors in the child and the family must be considered in planning the long-term

management of each child with urinary tract infection and vesicoureteric reflux, but any treatment programme should take into account the self-limiting nature of reflux in over three-quarters of the children affected.

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Release of copper from copper-bearing intrauterine contraceptive devices

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Summary

We measured the rate of release from copper-bearing intrauterine contraceptive devices (IUDs) with varying copper surface areas. Over 135 days of observation the release rate decreased exponentially. This decrease in the

release rate was associated with the deposition of a protein layer on the surface of the metal. The bioavailability of copper on IUDs was not related to the volume of copper remaining on the device. Consequently any increase in the copper surface area of an IUD is unlikely to affect the duration of its copper-dependent contraceptive action.

Introduction

Early published data on the rate of copper loss from copper IUDs showed a uniform rate of release after an initial high loss¹ and have been used to calculate the duration of their use based on copper loss.² More recent studies have questioned the constant release-rate of copper and the long-term effectiveness of copper-bearing IUDs after finding that the copper acquires a coating of calcareous salts in utero that reduces its availability.^{3 4} The clinical importance of this observation has been vindicated

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