Regular review**Vesicoureteric reflux and renal scarring**

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The urinary tract is often the site of bacterial infection during childhood. Population screening studies show a slight prevalence of boys during the neonatal period, followed by transition during infancy to a greater prevalence of girls, which progressively increases during the preschool years. Underlying structural abnormalities of the urinary tract are found in 30-50% of girls and in a somewhat higher proportion of boys with bacteriologically confirmed infection. Some of the abnormalities shown by routine radiological investigation after urinary tract infection—for example, partial duplication—are coincidental. Those abnormalities that play an aetiological role have in common distension and stasis as the underlying functional defect, and consist of (a) organic obstruction, (b) neuropathic bladder with functional obstruction, and (c) vesicoureteric reflux (VUR). The latter is by far the commonest abnormality and is the subject of this review.

During cystourethrography it is observed that VUR may occur during filling but is more likely to do so during voiding. Reflux occurring during filling is more likely when the ureter is grossly dilated and the vesicoureteric orifice is permanently open. It is possible, however, that it also occurs with a less severely incompetent vesicoureteric orifice if the patient also suffers from an unstable bladder, as detrusor contractions against a closed sphincter can generate appreciably higher intravesical pressures than those associated with voiding.¹ In a dilated system, a large volume of urine may be refluxed and will subsequently return to the bladder when the detrusor muscle relaxes after voiding, so that a residue is present continuously. It is this residue that almost certainly encourages bacterial colonisation of the bladder. Lesser degrees of VUR, in which radio-opaque contrast fluid is seen to enter an undilated ureter transiently, have correspondingly less clinical importance.

In both clinical practice and research it is necessary to evaluate the severity of VUR; several grading systems have been evolved,²⁻⁵ differing

essentially in their definitions of severe reflux. In Birmingham we have used a simple system⁴ based on that of Rolleston *et al*²:

Grade 1—Reflux of contrast medium on filling or micturition which fails to reach the renal pelvis.

Grade 2—Reflux reaching the pelvis and calyces but without calyceal distension.

Grade 3—Reflux with distension of calyces.

While to include grotesquely dilated and tortuous ureters, often draining dysplastic kidneys, in grade 3 may be an oversimplification, the system elaborated by the International Reflux Study in Children goes to the opposite extreme of splitting severe VUR into grades 3-5 and further subdividing each of five grades into A, B, and C—a total of 15 subdivisions.⁵ Such a complex system is more vulnerable to small errors of interpretation, and underlines the reality that reflux exhibits a continuous range of severity.

Reflux associated renal scarring

Although the possible role of VUR as a cause of urinary tract infection was first recognised 85 years ago,⁶ it was the demonstration in 1960 by Hodson and Edwards of an association with renal scarring which renewed interest in the problem and generated the multidirectional research which is still gathering momentum more than quarter of a century later.⁷ Since then the relationship between VUR and renal scarring has been extensively documented, particularly by Smellie *et al*,^{3,8} and it is now a decade since we showed a significant correlation between the severity of VUR and the prevalence of renal scarring.⁴ Because of this association, Bailey proposed the term *reflux nephropathy* which has now superseded the older term 'chronic pyelonephritis'.⁹

RADIOLOGICAL APPEARANCES

The radiological appearances of so called 'chronic atrophic pyelonephritis' were described in detail by

Hodson.¹⁰ In health the renal parenchyma, as measured from the tip of each outermost papilla to the overlying renal outline, is thicker in the polar regions than in the middle third of the kidney; moreover the four polar measurements are approximately equal. The earliest sign of a focal scar is a reduction of cortical thickness. As the scar becomes more obvious, from contraction of fibrous tissue, the renal outline becomes indented while the underlying calyx becomes flattened ('blunted') and finally clubbed, from destruction of the papilla. It requires a very high standard of radiological preparation to detect small, early scars and, indeed, to exclude the presence of scarring. Focal scarring occurs more often in the upper than the lower poles, while bipolar and generalised scarring are both commoner than that which is confined to the middle zone; these observations are of relevance to the pathogenesis of reflux nephropathy (see below).

PATHOLOGY

Reflux nephropathy is primarily a tubulointerstitial disease. The histological changes were described in a now classical study of 100 necropsy cases of 'chronic pyelonephritis' by Weiss and Parker, who drew attention to the frequent origin of the condition during childhood.¹¹ The changes have been further elaborated by Heptinstall.¹² The interstitial tissue is infiltrated by chronic inflammatory cells, including lymphocytes and plasma cells, but in contracted scars these are less prominent and are replaced by collagen. The tubules show basement membrane thickening, epithelial cell atrophy, and collapse of the lumen, and eventually disappear. An additional and very characteristic change is dilatation of other tubules, with thin, atrophic epithelium and the inclusion of homogeneous eosinophilic casts—an appearance similar to normal thyroid tissue. Arteries and arterioles invariably show medial and intimal thickening when hypertension is present but may also do so in its absence. The glomerular changes are entirely secondary and are of two main kinds: (a) periglomerular fibrosis which is probably related to chronic interstitial inflammation; and (b) collapse or hyalinisation of the glomerular tuft, with or without concentric rings of collagen formed within the Bowman's capsule. The changes occurring in adjacent, unscarred renal tissue are essentially those of compensatory hypertrophy affecting both tubules and glomeruli, the latter often increasing in diameter by one third.¹³ Other glomeruli may undergo segmental sclerosis, however, an aspect that will be considered later.

PATHOGENESIS

The two contrasting observations that 47% of all

children with reflux, and even 21% of those with severe VUR, did not show reflux nephropathy, while a rare child with radiologically typical renal scarring did not have VUR,⁴ suggest that the relationship between reflux and the nephropathy is not a simple one. The finding of scarring without VUR, usually in an older child, is easy to explain with the knowledge that reflux has a tendency to resolve spontaneously, given time.³

The demonstration of intrarenal reflux was a landmark in the understanding of VUR. Rolleston *et al* observed that renal scarring developed in precisely the same anatomical segment of the kidney as that in which intrarenal reflux had been shown radiologically.¹⁴ Hodson *et al* confirmed these findings experimentally in pigs.¹⁵ Ransley and Risdon showed that in human necropsy preparations from infants and young children some papillae were fused together to form compound structures in which papillary ducts opened perpendicularly on to a flat or concave surface, rather than tangentially on to the sides of conical structures.¹⁶ Such compound papillae were found more often in the polar than mid-zone regions of the kidney—a distribution which coincides precisely with that of radiologically observed scars.¹⁰ Here then was a mechanism whereby infected urine from the bladder could gain access to the renal parenchyma. Hodson *et al* succeeded in causing parenchymal scarring in refluxing pigs with sterile urine, but their model was one of chronic bladder neck obstruction.¹⁵ Ransley and Risdon, however, were unable to reproduce their results and concluded that non-obstructive reflux nephropathy only developed in the presence of urinary tract infection.¹⁷ In practice this is what we observe in humans.

In Hodson's experimental model high intravesical pressures were sustained through progressive compression of the urethra by a ring that was designed not to expand as the piglet grew.¹⁵ This raised the question whether raised pressure could play a part in the aetiology of reflux nephropathy. In primary VUR there is no evidence of obstruction and high intravesical pressures are only likely in the presence of detrusor instability associated with dyssynergia. Taylor *et al* found that although a high proportion of both girls and boys with VUR also had detrusor instability, its presence or absence did not correlate with either the prevalence of reflux nephropathy¹ or the rate of resolution of reflux.¹⁸

It is of considerable interest that most reflux associated renal scars detected are already present when the patient is first investigated. In a retrospective survey involving 23 paediatric departments in the United Kingdom, Smellie *et al* were able to document only 87 new scars over a 22 year period.¹⁹

These developed at any age from infancy to 9 years but were rare after the seventh birthday. In a prospective therapeutic trial the Birmingham Reflux Study Group detected only 10 new scars among 161 children, the oldest being 7 years old.²⁰ This is relevant to the observation that intrarenal reflux has not been shown after the fifth birthday¹⁴ and indicates that it is the youngest children who are most vulnerable to the consequences of VUR. In our prospective study we noted that 57% of infants with severe VUR already had reflux nephropathy at initial investigation.²⁰

It has to be accepted that diffusely scarred, shrunken kidneys found in infants with hugely dilated, refluxing ureters probably represent dysplasia, although the precise aetiological role of sterile, intrauterine VUR is still unsettled.²¹ Hereditary factors may also play a part in the anatomical malformations affecting the ureterovesical junction that permit reflux to occur.²²

CLINICAL SIGNIFICANCE

In epidemiological surveys of schoolgirls aged 5–11 years, one third of those with covert bacteriuria were found to have VUR and one fifth reflux nephropathy.^{23–25} Similarly, in a retrospective analysis of outpatients with urinary tract infection (from whom we excluded children with neuropathic bladder, obstructive uropathy, and congenital renal anomalies) we found that 52% of 104 children had VUR and that 23% of their kidneys were scarred.⁴ It is noteworthy that all but one of the infants in this series had severe reflux, and that there were more boys than girls in this age group. From a total of more than 50 000 schoolgirls screened Hodson estimated the prevalence of reflux nephropathy to be one in 250 individuals.²⁶

There is an increased risk of hypertension due to both unilateral and bilateral reflux nephropathy,²⁷ and of progression to chronic renal failure in the case of extensive bilateral disease. While there are as yet no reliable figures for the incidence of chronic renal failure based on prospective studies, preliminary figures suggest that this is around 5–6%.²⁰ Nevertheless, 'chronic pyelonephritis' accounted for 27% of children²⁸ and 21% of adults²⁹ entering renal replacement programmes in Europe, and reflux nephropathy was found to be the commonest single cause of chronic renal failure in a large childhood series.³⁰ Thus any effective method of preventing the development or extension of renal scarring might be expected to have an appreciable impact on the escalating costs of dialysis and transplantation.

Management of VUR

From the foregoing discussion we may conclude that

human reflux nephropathy is a largely acquired lesion, dependent upon the coexistence of VUR, intrarenal reflux, and urinary tract infection. In our present state of knowledge intrarenal reflux is unalterable, and we are left with reflux and infection to treat. The main aims of treatment are firstly the relief of symptoms, which are mainly due to urinary tract infection and detrusor instability, and secondly the prevention or limitation of renal parenchymal damage.

SYMPTOMATIC TREATMENT

Symptomatic management has been fully discussed elsewhere and will merely be summarised here.^{31 32} A notable finding in our prospective therapeutic trial was that children exposed to breakthrough urinary tract infection during the first two years' observation showed no higher incidence of progressive renal scarring or new scar formation than those unexposed.^{33 34} Moreover, 82% of scars that progressed, and all 10 new ones that developed, were observed to do so during the first two years' treatment.²⁰ As the radiologically witnessed renal scar is the late result of parenchymal fibrous contraction³⁵ it is probable that all these changes were initiated before entry into the study. Although there is no doubt that carefully monitored chemoprophylaxis can reduce the incidence of bacteriuria,³⁶ these recent findings bring into question its long term value as a means of preventing progressive scarring. Compliance with treatment can never, in practice, be monitored with perfection, and in our study we showed breakthrough urinary tract infection in a quarter of the children who were nominally receiving chemoprophylaxis.²⁰ Hitherto many would have regarded the withholding of treatment in the presence of VUR and renal scarring as unethical, but these recent observations suggest the need for a controlled study in which chemotherapy is given only for symptomatic urinary tract infection. In the meantime our practice is to maintain chemoprophylaxis for a period of two years in children who are less than 5 years old at diagnosis, and in whom grade 2–3 VUR is present. The two most effective drugs are nitrofurantoin and trimethoprim, because the emergence of bacterial resistance against them is fortunately rare. Nitrofurantoin suspension is apt to cause nausea and sometimes vomiting, but older children can usually swallow 50 mg capsules of the drug. Either drug should be given as a single evening dose of 1–2 mg/kg/day.

Other aspects of medical management include the encouragement of a liberal fluid intake to create a bladder washout effect, and in girls with detrusor instability of sufficient intensity to cause diurnal incontinence a programme of voiding every two

hours can be used.^{31 32} Double voiding, particularly at bedtime, can be employed to reduce the residual bladder urine volume that results from grossly dilated ureters and tends to encourage urinary tract infection. An important but poorly recognised feature of recurrent urinary tract infection and VUR is constipation.³² The poor perineal muscular relaxation that accompanies detrusor instability impedes both bladder and rectal emptying, and careful abdominal palpation almost invariably shows a distended descending colon. Thus an essential component of management is the introduction of a high fibre diet which, by increasing faecal bulk and softness, facilitates muscular relaxation and thereby helps to reduce residual urine.

Operative correction of VUR has a high technical success rate in experienced hands,²⁰ and this would seem to be a logical way of preventing infected urine from reaching the renal parenchyma. Claims of improved renal growth after ureteric reimplantation, however, were not supported by parallel observations in control patients treated medically.³⁷ Moreover, the possible benefits of reimplantation must be balanced against the tendency for reflux to resolve spontaneously over a long period.^{3 38}

In 1975 the Birmingham Reflux Study Group set up a prospective trial of operative compared with non-operative treatment of severe VUR. Children with grade 3 VUR were randomly allocated within three age groups (<1, 1–5, 6–14 years old at entry) and reinvestigated, functionally and radiologically, at intervals of two and five years from operation or from allocation to non-operative treatment. Altogether 161 children have been observed for two years and 104 of them for five years. The five year results²⁰ confirmed and extended those obtained after two years' observation.^{33 34} No significant differences were observed between treatment modes in the incidence of breakthrough urinary tract infection, renal excretory function and concentrating ability, renal growth, the progression of existing scars, or the development of new ones. The technical success rate of reimplantation was 98% whereas 51% of ureters treated non-operatively still showed grade 3 VUR after five years' chemoprophylaxis. When reflux was bilateral there was an increased tendency for it to persist. The long term effects of VUR persisting into adulthood remain to be evaluated; nevertheless its persistence did not adversely affect renal growth or increase the risks of scar progression.

Thus we have failed to show superiority for either mode of treatment; indeed the extremely poor growth of scarred kidneys in children aged more than 5 years at entry to the study questions whether any form of intervention is likely to be effective in

older patients. In contrast, younger children showed evidence of catch up renal growth after two years' chemoprophylaxis, and are the ones who are more likely to benefit from treatment. Ransley and Risdon showed in refluxing piglets that irreversible renal scarring could develop within one week of introducing *Escherichia coli* into the bladder.³⁹ The high prevalence of scarring already present in our patients at entry to the study,²⁰ even in infants, suggests that this is also true of humans, and underlines the need for more prompt diagnosis and vigorous treatment of the first urinary tract infection. Although severe VUR may now be suspected antenatally from the ultrasonic appearance of the urinary tract,⁴⁰ cystourethrography is necessary postnatally to confirm the diagnosis. What is needed, and yet still eludes us, is a reliable and non-invasive method of diagnosing reflux in neonates.

Meanwhile the choice of treatment of VUR remains arbitrary and will depend on social factors that may influence compliance with prolonged chemotherapy, the availability of surgical skill, and perhaps parental preference. The endoscopic injection of Teflon under the bladder mucosa immediately below the affected ureteric orifice sounds a promising alternative to the conventional but more invasive surgical reimplantation procedure,⁴¹ but has not yet been assessed prospectively in a controlled manner.

Prognosis

What does the future hold for patients with persistent reflux and those who have sustained renal damage? Little is known about the effects of persistent VUR in subjects with undamaged kidneys, although preliminary evidence suggests that their renal function is secure.⁴² It can be speculated that those individuals who have not developed reflux nephropathy during childhood will never do so because their kidneys do not possess refluxing papillae. Patients with reflux nephropathy are at increased risk of hypertension,²⁷ although in our experience this is a rare complication of unilateral scarring. Patients with bilateral nephropathy may or may not show impaired renal function, depending upon the extent of the scarring.

Until recently we have argued that the future health of individuals in whom the scarring is confined to one kidney is secure, based on glomerular filtration measurements carried out during childhood.³¹ There is increasing evidence, however, that a proportion of these patients sustain secondary changes of a progressive nature in the contralateral kidney. Persistent, heavy proteinuria is recognised

as a sinister development in patients with reflux nephropathy,⁴³ and it is invariably present in those who progress to end stage renal failure.⁴⁴ Kincaid-Smith showed focal and segmental glomerulosclerosis in a high proportion of renal biopsy and nephrectomy specimens obtained from adult patients with reflux nephropathy and proteinuria, including some with normal or near normal renal function.⁴⁵ That they were present in the unscarred contralateral kidney in four patients with unilateral reflux nephropathy was a highly significant finding. In women with proteinuria, focal and segmental glomerulosclerosis, and raised plasma creatinine concentrations, the advent of either pregnancy or accelerated hypertension may lead to rapid deterioration of renal function.⁴⁶

Ongoing research

Little is known about the early evolution of proteinuria in reflux nephropathy. Most of the patients investigated were adults, although similar glomerular lesions have been reported in a few children.^{47 48} The introduction of more sensitive methods of determining protein concentration, however, has made observations on 'microproteinuria' possible. Bell *et al* recently showed significantly increased excretion rates of albumin and retinol binding protein in children with severe VUR and renal scarring, compared with those whose kidneys were unscarred.⁴⁹ Using the Coomassie blue dye binding method of measuring total protein concentration, which is both simple and cheap yet more sensitive than the biuret method at low concentrations, we first determined the normal range of protein:creatinine ratios in early morning urine samples obtained from 377 healthy subjects aged 3–19 years.⁵⁰ We then assessed proteinuria in children with VUR, finding no correlation with the degree of reflux but a trend towards increasing microproteinuria with increasingly severe renal scarring, and an inverse correlation with glomerular filtration rate as determined by slope clearance of ⁵¹chromium edetic acid.⁵¹

These findings have prompted in depth studies of microproteinuria in reflux nephropathy in children. Our preliminary renal biopsy studies have confirmed that focal and segmental glomerulosclerosis accompanies proteinuria even of short duration and at below nephrotic levels. The lesion appears to originate in the parahilar region of the glomerulus. Additionally we have observed thickening and hyaline droplet infiltration of the hilar arterioles in unscarred glomeruli (M Morita, RHR White, F Raafat, unpublished observations). These changes are compatible with Brenner's finding that rats

develop proteinuria and glomerular sclerosis after extensive renal ablation, if maintained on normal or high dietary protein intakes, and with his hypothesis that the changes are haemodynamically mediated.⁵² Moreover, we have shown that experimental restriction of dietary protein intake in children with reflux nephropathy and proteinuria consistently leads to reduction of the urinary protein excretion rate (CM Taylor, JS Elises, E Buchanan, DJ Worthington, RHR White, MH Winterborn, unpublished observations). While it would be premature to conclude that dietary protein restriction is an effective form of preventive management, these early results have nevertheless encouraged us to pursue these investigations further.

The past quarter century has witnessed a wealth of significant contributions to the understanding of VUR and reflux nephropathy, in which the late Professor John Hodson had a prominent place from the start,⁵³ and yet it is apparent that there remains ahead of us a lifetime of research in this fascinating and important field of medicine.

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References

- 1 Taylor CM, Corkery JJ, White RHR. Micturition symptoms and unstable bladder activity in girls with primary vesicoureteric reflux. *Br J Urol* 1982;**54**:494–8.
- 2 Rolleston GL, Shannon FT, Utley WLF. Relationship of infantile vesicoureteric reflux to renal damage. *Br Med J* 1970;**i**:460–3.
- 3 Smellie JM, Edwards D, Hunter N, Normand ICS, Prescod N. Vesicoureteric reflux and renal scarring. *Kidney Int* 1975;**8**(suppl 4):S65–72.
- 4 Shah KJ, Robins DG, White RHR. Renal scarring and vesicoureteric reflux. *Arch Dis Child* 1978;**53**:210–7.
- 5 Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Möbius TE. International system of radiographic grading of vesicoureteric reflux. *Pediatr Radiol* 1985;**15**:105–9.
- 6 Sampson JA. Ascending renal infection with special reference to the reflux of urine from the bladder into the ureters as an aetiological factor in its causation and maintenance. *Bulletin of the Johns Hopkins Hospital* 1903;**14**:334–50.
- 7 Hodson CJ, Edwards D. Chronic pyelonephritis and vesicoureteric reflux. *Clin Radiol* 1960;**11**:219–31.
- 8 Smellie JM, Hodson CJ, Edwards D, Normand ICS. Clinical and radiological features of urinary tract infection in childhood. *Br Med J* 1964;**ii**:1222–6.
- 9 Bailey RR. The relationship of vesico-ureteric reflux to urinary tract infection and chronic pyelonephritis—reflux nephropathy. *Clin Nephrol* 1973;**1**:132–41.
- 10 Hodson CJ. The radiological contribution toward the diagnosis of chronic pyelonephritis. *Radiology* 1967;**88**:857–71.
- 11 Weiss S, Parker F. Pyelonephritis: its relation to vascular lesions and to arterial hypertension. *Medicine (Baltimore)* 1939;**18**:221–315.
- 12 Heptinstall RH. Pyelonephritis. II. Pathological features. *Pathology of the kidney*. Boston: Little, Brown, 1966:421–54.

- ¹³ El-Khatib MT, Becker GJ, Kincaid-Smith P. Morphometric aspects of reflux nephropathy. *Kidney Int* 1987;**32**:261-6.
- ¹⁴ Rolleston GL, Maling TMJ, Hodson CJ. Intrarenal reflux and the scarred kidney. *Arch Dis Child* 1974;**49**:531-9.
- ¹⁵ Hodson CJ, Maling TMJ, McManamon PJ, Lewis MG. The pathogenesis of reflux nephropathy (chronic atrophic pyelonephritis). *Br J Radiol* 1975;**suppl 13**:1-26.
- ¹⁶ Ransley PG, Risdon RA. Renal papillary morphology in infants and young children. *Urol Res* 1975;**3**:111-3.
- ¹⁷ Ransley PG, Risdon RA. Reflux and renal scarring. *Br J Radiol* 1978;**suppl 14**:1-35.
- ¹⁸ Taylor CM. Unstable bladder activity and the rate of resolution of vesico-ureteric reflux. In Hodson CJ, Heptinstall RH, eds. *Contributions to nephrology: reflux nephropathy update*. Basel: Karger, 1984:238-46.
- ¹⁹ Smellie JM, Ransley PG, Normand ICS, Prescod N, Edwards D. Development of new renal scars: a collaborative study. *Br Med J* 1985;**290**:1957-60.
- ²⁰ Birmingham Reflux Study Group. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: five years' observation. *Br Med J* 1987;**295**:237-41.
- ²¹ Risdon RA. The small scarred kidney of childhood: a congenital or an acquired lesion. *Pediatr Nephrol* 1987;**1**:632-7.
- ²² De Vargas A, Evans K, Ransley P, et al. A family study of vesicoureteric reflux. *J Med Genet* 1978;**15**:85-96.
- ²³ Savage DCL, Wilson MI, McHardy M, Dewar DAE, Fee WM. Covert bacteriuria of childhood: a clinical and epidemiological study. *Arch Dis Child* 1973;**48**:8-20.
- ²⁴ McLachlan MSF, Meller ST, Verrier Jones ER, et al. Urinary tract in schoolgirls with covert bacteriuria. *Arch Dis Child* 1975;**50**:253-8.
- ²⁵ Edwards B, White RHR, Maxted H, Deverill I, White PA. Screening methods for covert bacteriuria in schoolgirls. *Br Med J* 1975;**iii**:463-7.
- ²⁶ Hodson J. Reflux nephropathy. *Med Clin North Am* 1978;**62**:1201-21.
- ²⁷ Wallace DMA, Rothwell DL, Williams DI. The long-term follow-up of surgically treated vesicoureteric reflux. *Br J Urol* 1978;**50**:479-84.
- ²⁸ Donckerwolcke RA, Chantler C, Brunner FP, et al. Combined report on regular dialysis and transplantation of children in Europe, 1977. In Robinson BHB, Hawkins JB, eds. *Proceedings of the European Dialysis and Transplant Association*. London: Pitman, 1978;**15**:77-114.
- ²⁹ Wing AJ, Brunner FP, Brynger HAO, et al. Combined report on regular dialysis and transplantation in Europe, 1977. In Robinson BHB, Hawkins JB, eds. *Proceedings of the European Dialysis and Transplant Association*. London: Pitman, 1978;**15**:2-76.
- ³⁰ Chantler C. Progressive loss of renal function. In Holliday MA, Barratt TM, Vernier RL, eds. *Pediatric nephrology*. 2nd ed. Baltimore: Williams and Wilkins, 1987:773-98.
- ³¹ White RHR, Taylor CM. The non-operative management of primary vesicoureteric reflux. In Johnston JH, ed. *Management of vesicoureteric reflux*. Baltimore: Williams and Wilkins, 1984:117-36.
- ³² White RHR. Management of urinary tract infection. *Arch Dis Child* 1987;**62**:421-7.
- ³³ Birmingham Reflux Study Group. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux: two years' observation in 96 children. *Br Med J* 1983;**287**:171-4.
- ³⁴ Birmingham Reflux Study Group. A prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux: two years' observation in 96 children. In Hodson CJ, Heptinstall RH, eds. *Contributions to nephrology: reflux nephropathy update*. Basel: Karger, 1984:169-85.
- ³⁵ Scott JES. The role of surgery in the management of vesicoureteric reflux. *Kidney Int* 1975;**8(suppl 4)**:S73-80.
- ³⁶ Smellie JM, Gruneberg RN, Bantock HM, Prescod N. Prophylactic co-trimoxazole and trimethoprim in the management of urinary tract infection in children. *Pediatr Nephrol* 1988;**2**:12-7.
- ³⁷ McRae CU, Shannon FT, Utley WLF. Effect on renal growth of reimplantation of refluxing ureters. *Lancet* 1974;**ii**:1310-2.
- ³⁸ Edwards D, Normand ICS, Prescod N, Smellie JM. Disappearance of vesicoureteric reflux during long-term prophylaxis of urinary tract infection. *Br Med J* 1977;**iii**:285-8.
- ³⁹ Ransley PG, Risdon RA. Reflux nephropathy: effects of antimicrobial therapy on the evolution of the early pyelonephritic scar. *Kidney Int* 1981;**20**:733-42.
- ⁴⁰ Watson AR, Readett D, Nelson CS, Kapila L, Mayell MJ. Dilemmas associated with antenatally detected urinary tract abnormalities. *Arch Dis Child* 1988;**63**:719-22.
- ⁴¹ O'Donnell B, Puri P. Endoscopic correction of primary vesicoureteric reflux. *Br J Urol* 1986;**58**:601-4.
- ⁴² Verrier Jones K, Asscher AW, Verrier Jones ER, Mattholie K, Leach K, Thomson GM. Glomerular filtration rate in schoolgirls with covert bacteriuria. *Br Med J* 1982;**285**:1307-10.
- ⁴³ Kincaid-Smith P, Becker G. Reflux nephropathy and chronic atrophic pyelonephritis: a review. *J Infect Dis* 1978;**138**:774-80.
- ⁴⁴ Bailey RR. End-stage reflux nephropathy. *Nephron* 1981;**27**:302-6.
- ⁴⁵ Kincaid-Smith P. Glomerular lesions in atrophic pyelonephritis and reflux nephropathy. *Kidney Int* 1975;**8(suppl 4)**:S81-83.
- ⁴⁶ Becker GJ, Ihle BU, Fairley KF, Bastos M, Kincaid-Smith P. Effect of pregnancy on moderate renal failure in reflux nephropathy. *Br Med J* 1986;**292**:796-8.
- ⁴⁷ Aladjem M, Schoeneman MJ, Bennett B, Levitt S, Spitzer A, Greifer I. Focal glomerulosclerosis with proteinuria and chronic interstitial nephritis. *NY State J Med* 1978;**78**:579-81.
- ⁴⁸ Bhathena DB, Weiss JM, Holland NH, et al. Focal and segmental glomerular sclerosis in reflux nephropathy. *Am J Med* 1980;**68**:886-92.
- ⁴⁹ Bell FG, Wilkin TJ, Atwell JD. Microproteinuria in children with vesicoureteric reflux. *Br J Urol* 1986;**58**:605-9.
- ⁵⁰ Elises JS, Griffiths PD, Hocking MD, Taylor CM, White RHR. Simplified quantification of urinary protein excretion in children. *Clin Nephrol* 1988;**30**:225-9.
- ⁵¹ White RHR, Taylor CM, Elises JS, Griffiths PD. Proteinuria and reflux nephropathy. In: Walker RG, Kincaid-Smith P, eds. *Proceedings of the First CJ Hodson Symposium on Reflux Nephropathy*. Melbourne: Broughton Printing, 1987:15-20.
- ⁵² Brenner BM. Nephrology forum. Hemodynamically mediated glomerular injury and the progressive nature of kidney disease. *Kidney Int* 1983;**23**:647-55.
- ⁵³ Smellie JM. John Hodson: an appreciation of his achievement and contributions to paediatric nephrology. *Pediatr Nephrol* 1987;**1**:563-5.

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