Annotation

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Bacteriuria, reflux, and renal scarring

Much of the confusion in the discussion of these topics reflects differences of nomenclature not of fact, and a failure to relate the wide variation in severity both of reflux and of renal damage to their long-term implications.

In this article, significant *bacteriuria* denotes the presence of actively multiplying organisms in the urinary tract and is indicated in girls by a pure growth of at least 10^5 organisms/ml on culturing two consecutive clean, fresh specimens of urine. Lesser counts may be significant in boys, as is any growth on culture of bladder urine obtained by suprapubic aspiration. *Reflux* is the backflow of urine from bladder to ureter. It is considered to be abnormal and varies in aetiology, severity, and prognosis. The 'renal damage' discussed is the scarring of *chronic pyelonephritis*, which is recognizable morphologically and radiologically by the irregular distribution of coarse scars with deformity or frank clubbing of a calyx directly associated with thinning of the overlying renal tissue. There is usually a reduction in renal size (Hodson, 1965). (Some authors have classified as chronic pyelonephritis kidneys which fail to show all three of these features and this has made the comparison of different studies more difficult.) The regular association of these findings with reflux has led to the introduction of the term 'reflux nephropathy' (Bailey, 1973), but until the precise mechanical role of reflux is more firmly established the use of the term 'chronic pyelonephritis' is perhaps preferable. Chronic pyelonephritis varies in degree from the unilateral single polar scar to more extensive scarring (which if bilateral may lead to impaired renal function), and to the small shrunken kidney usually found to have severe associated reflux and often hypertension.

The association of bacteriuria with renal scarring is well known. Up to 25% of such children investigated, whether seen in hospital or discovered during screening programmes, are found to have some degree of renal scarring though this is likely to be of serious significance in no more than 10%. 20% of the University College Hospital series of children with chronic pyelonephritis had raised blood pressure and 10% had some degree of renal failure (Smellie *et al.*, 1975). Similarly, children with coarsely scarred kidneys almost invariably have reflux. In a few, established chronic pyelonephritis has been reported in the absence of reflux, but in these the possibility that previously existing reflux had already disappeared cannot be excluded. The occasional persistence of paraureteric saccules or the finding of patulous ureteric orifices on cystoscopy in such children support this view.

However, vascular, mechanical, or immunological factors as well as infection may contribute to the formation and progression of renal scars; and hypertension, obstruction, or areas of renal dysplasia as well as reflux may be important in individual children.

Reflux

The effect of reflux in the pathogenesis of renal scarring is to encourage infection of the bladder urine, to provide access from bladder to kidney, and possibly to exert a damaging mechanical effect upon the renal tissues. Reflux may be expected to predispose to recurrent infection by forming a residue on the return of refluxed urine to the bladder. Residual urine may also linger in the dilated renal pelvis in children with severe reflux, particularly when urine flow is reduced by thirsting. Though recurrences may be seen as often in infected children without reflux as with it, this is not surprising since reflux is only one of many factors interfering with bladder defences. Children without reflux will have some other transient or permanent defect of bladder emptying or of the bladder mucosa which renders them, like those with reflux, liable to urinary infection. The ease with which organisms multiplying in bladder urine can reach the kidney through an incompetent vesicoureteral valve is apparent, and there is evidence that bacteria may facilitate this retrograde movement by impairing or reversing ureteric peristalsis.

The mechanical role of reflux has been the focus of much recent attention, particularly in the study of pyelotubular backflow (the flow of dye or urine

from renal pelvis to renal substance) which provides a means whereby organisms refluxed from the bladder can reach the renal tissue. This has been recognized for some time during retrograde pyelography (Braasch and Emmett, 1951). Rolleston, Maling, and Hodson (1974) noted intrarenal reflux, usually polar in distribution, in some infants and young children investigated by micturating cystourethrography for urinary tract infection and found to have severe reflux. The subsequent appearance in some of these children of scarring in the areas of intrarenal reflux is a convincing demonstration of the susceptibility of the infant kidney to this form of insult. The rapid growth at this age of the surrounding normal renal tissue further accentuates the appearance of the contracting scar which may take as long as 2 years to develop fully.

Similarly, Hodson and his colleagues (1975) using as a model the multipapillary kidney of the pig, have shown the development of renal scars, apparently identical morphologically to human chronic pyelonephritis, in areas where intrarenal reflux had been induced. Partial urethral obstruction was required to produce the critical pressure necessary for intrarenal reflux to occur. Furthermore, if infection was introduced to this system, bacterial invasion was confined to areas of intrarenal reflux and this combination of these two nearly always resulted in severe and rapid scar formation.

Recently Ransley and Risdon (1974) have demonstrated in the pig the anatomical basis for intrarenal reflux by showing that the circular openings of the collecting ducts in the upper and lower polar papillae are unlikely to be occluded by rising intracalyceal pressure, in contrast to the slit-like duct orifices in the mid-zone papillae. The reversal of flow in the papillary duct, however, will only occur when the pressure gradient from calyx to collecting system is reversed.

So far there has been little convincing evidence in children of renal scarring developing in the unobstructed and uninfected renal tract, though in the young infant it is possible that the pressure effects of severe reflux may impair renal growth. The mechanics both of micturition and of reflux merit further study (Williams, 1970).

Bacteriuria is more common in male than female newborn infants. It is also in male infants that the more severe degrees of reflux are to be found, and in some instances this is associated with impairment of urinary flow either at urethral or vesicoureteric junction level. Renal changes found with sterile reflux have been reported by Hutch and Smith (1969). They were mainly of 'back pressure' type and were almost entirely in boys or young men. No progression of the changes was reported and it could be postulated that the damage dated back to early infancy when the mechanics of micturition were disturbed, or silent infection occurred. Stephens (1972) has observed sterile reflux persisting for over 10 years without deterioration of the renal status.

Developing scars

One of the striking features in clinical studies of chronic pyelonephritis is how often scarring is already established when the child is first investigated and how seldom scarring is seen to develop in a kidney previously known to be normal. There are several possible explanations for this. (a) That the renal damage is present from birth or early infancy, or is superimposed on renal dysplasia and is only discovered during investigation of a later urinary infection. (b) That urinary infection and accompanying renal damage continue unrecognized during the early years, perhaps temporarily interrupted by antibiotic therapy given for some other infection. (c) That either the first infection is not fully investigated, or if the pyelogram is normal later films are considered unnecessary, even if there are repeated infections.

However, it is in the study of developing scars that the important aetiological factors are likely to emerge. Where prospective studies have been made and new scarring observed, it has almost invariably developed in a kidney drained by a refluxing ureter and in a urinary tract which has been infected. (In some children in whom infection has seemed an uncertain factor in scar formation, urine cultures have been omitted or infrequent.) The most vulnerable are the kidneys of young children with severe reflux (Penn and Breidahl, 1967; Rolleston *et al.*, 1974; Filly *et al.*, 1974; Smellie *et al.*, 1975). Scars can appear throughout childhood but tend to be less extensive in older children when earlier recognition of infection is more likely.

In Winberg *et al.*'s study (1974) of children with symptomatic urinary infection, fresh or extending scarring was seen in 4% but there was no differentiation between those with and without reflux.

Antibody studies have shown rising titres against the infecting organism when renal tissue is involved. These have been found during symptomatic infections in children with urethral obstruction and also in those with reflux with or without chronic pyelonephritis. There was less if any rise in antibody titre when further infections occurred in children with reflux receiving prophylactic antibio-

tic treatment (Smellie *et al.*, 1973). On the other hand, localizing studies have indicated that where there is neither obstruction nor reflux, 85% of infections are confined to the lower urinary tract. Bacteriuria in this group, even if recurrent, has a benign prognosis (Smellie and Normand, 1968; MacGregor and Freeman, 1968; Fair *et al.*, 1974).

Treatment

The effectiveness of treatment must be assessed not only on the elimination of urinary infection but also on renal growth, the prevention of scarring, and the physical well-being of the child including his renal function and blood pressure.

Antibacterial treatment. The problem in treating urinary tract infection is less that of eradicating the initial infection than of preventing further infections. Approximately 90% of recurrences in the absence of obstruction are reinfections with a fresh organism, and not relapses of an inadequately treated infection (Bergström *et al.*, 1967; Grüneberg, Smellie and Leakey, 1973). The fresh infection originates from the bowel flora, the identity and antibacterial sensitivity of which in turn depend largely upon the preceding antibacterial treatment.

Treatment has been approached in two ways. The first is to use short courses of antibiotics in therapeutic doses repeated for each fresh infection. With this method Kunin (1971), Fair *et al.* (1974), and Verrier Jones *et al.* (1975) have found that after each successive course of treatment approximately 20% of infected children have no further infections. A small number, however, will continue to have repeated infections. If these occur in girls with no obstruction or reflux the renal prognosis is good and the purpose of treatment is to relieve their symptoms.

The second approach is to use long-term low-dosage prophylaxis the object of which is to prevent multiplication in the bladder of further ascending bacterial invaders. For this purpose, the lowest effective dose should be used of a drug which ideally is absorbed high in the gut, excreted in high concentration in the urine, and does not affect bacterial flora of the lower bowel. This drug is given so long as the bladder defence remains impaired. This impairment may simply require attention to voiding and bowel habits or time to allow the bladder mucosal inflammation to subside. On the other hand, continued treatment may be necessary as long as reflux, or whatever else renders the patient susceptible to infection, persists. 2 months' continued treatment makes little or no difference to recurrence rates in girls (Bergström *et al.*, 1968), but while children have been receiving longer periods of prophylaxis, the reinfection rate has been markedly reduced (Normand and Smellie, 1965; Grüneberg *et al.*, 1973).

Effective prophylactic drugs include nitrofurantoin (1–2 mg/kg per d) and cotrimoxazole (5–10 mg sulphamethoxazole and 1–2 mg trimethoprim/kg per d), as would be expected on theoretical grounds. Sulphafurazole and sulphadimidine (20–40 mg/kg per d) are also useful, provided full-dosage sulphonamide has not been used in treating the initial infection as this frequently induces resistance in the lower bowel flora. They have the advantage of being less expensive. No significant side effects have been observed using the dosage schedules above for any of these drugs over long periods, though nitrofurantoin may occasionally produce nausea. Recurrence of infection during the course of long-term prophylaxis (assuming that obstructive lesions have been excluded) may occur either because of bowel organism resistance to the current prophylactic drug, or because the child has not been taking treatment, or the prophylactic dosage is too low. The drug-resistance of the organism infecting the urine and further questioning of the child and her parents will help to differentiate these causes and indicate appropriate treatment. The resistant organism requires a change to a short, full-dosage course of an effective antibacterial, followed by a return to prophylactic dosage of the original or another drug.

Further infections during prophylaxis tend to be symptomless, which underlines the importance of regular bacteriological monitoring of the urine. When repeated infections occur in the presence of reflux, established scars may extend, as had been seen in children receiving intermittent treatment for individual episodes of infection (Fair *et al.*, 1974). When using a regimen of long-term low-dosage antibacterial therapy for children with reflux, excluding those with obstruction or gross upper tract dilatation, normal renal growth without scarring has been observed in 90% (Smellie, 1970; MacGregor and Freeman, 1975).

Surgical treatment of reflux. Surgical intervention is necessary in all reflux which complicates obstructive lesions, such as urethral valves, ureterocoele, etc. Each child must be considered individually, but there appears to be little indication for ureteric reimplantation for any but the most severe reflux without a preliminary period of conservative management. There is a considerable tendency for reflux to stop naturally, and in most instances permanently. The advantages of opera-

tion must be weighed against the possible complications, particularly of early or delayed vesicoureteric obstruction. Extension of scarring was observed after successful ureteric reimplantation in children in whom urinary infection immediately preceded operation (Filly *et al.*, 1974). Transient postoperative vesicoureteric obstruction due to oedema and inflammation may have contributed to this. There is a great need for further long-term studies of renal growth after surgical correction of reflux. However, it is in children with severe reflux, particularly if this is associated with renal scarring, that reflux is least likely to stop spontaneously and renal growth may be slower than normal in this same group of children (Smellie, 1970; MacGregor and Freeman, 1975). These children, together with those in whom infection cannot be controlled medically (for any reason including social problems), should be considered for surgical correction. Fewer than 10% of the children with reflux (including those with other urinary tract malformations) seen at University College Hospital Children's Department since 1964 have satisfied these criteria. They represent only a small minority of children suffering from urinary tract infection.

Screening

Screening for bacteriuria has been undertaken as an epidemiological study to establish its prevalence in women and girls of all ages and in the newborn. Screening has also been employed to see if children at particular risk of renal damage could be identified. A number of important features have emerged.

(1) Many of the children discovered do have some symptoms, but these have not been sufficiently severe to merit a visit to the doctor. Similarly, 40–60% of children comprising hospital series have no specific urinary symptoms.
(2) Some children discovered on screening had a past history of treated symptomatic infection, but they had not been investigated or followed up. In Dundee, for example, 5 of the original 20 infected schoolchildren found on screening at the age of 5 had a previous history, and 3 of these had reflux and established renal scarring when they were investigated (Savage *et al.*, 1969).
(3) Reflux and renal scarring were found with similar frequency among infected children identified on screening and those presenting at hospital.
(4) 'Symptomless' bacteriuria can be intermittent, or disappear spontaneously (Abbott, 1972; Verrier Jones *et al.*, 1975), or be preceded or followed by symptomatic infection (Kunin, 1971).
(5) Since, on repeated screening, a further group of bacteriuric girls is found, screening, to be fully comprehensive, would require serial examinations throughout childhood.
(6) Though boys suffer fewer infections and these are more often symptomatic, they should not be overlooked. 2 of the 3 infected boys found on screening 1600 boys in Newcastle had serious renal lesions (Newcastle Asymptomatic Bacteriuria Research Group, 1975).

The economic justification for population screening for bacteriuria remains in doubt, though costs can be reduced by the use of dip slides (Arneil, McAllister, and Kay, 1973; Asscher *et al.*, 1973). This technique also facilitates preschool screening and the earlier recognition of bacteriuria by health visitor and family doctor in a young sick child. The familial incidence of reflux and chronic pyelonephritis, which has been increasingly noted (Frye, Patel, and Parsons, 1974), may also provide a rewarding line of search for infants and children at risk.

Conclusion

An extensive literature continues to accumulate on these topics, but from it a fairly uniform message can be discerned. In general, children with recurrent urinary infection who have neither reflux nor obstruction have an excellent renal prognosis, though they may be troubled by tiresome symptoms. Renal scars can, however, develop and progress during childhood. This is most likely in infants and young children with marked reflux and who develop repeated or persistent urinary tract infection. A small proportion of these children, usually among those in whom renal damage is well established when they are first investigated, will progress to renal failure and hypertension.

The prognosis of children in whom scarring develops in later childhood is not yet known. It has been regarded as benign, perhaps because infections in older children are usually recognized, investigated, and treated. The optimal methods of treatment both for young infants with reflux and for bacteriuric schoolgirls are currently the subject of therapeutic trials, the results of which will be of great interest.

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