Reflux Nephropathy

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Introduction

The frequent association between chronic atrophic pyelonephritis and vesicoureteral reflux (VUR) was noted just over 25 years ago, and the term reflux nephropathy (RN) was quickly substituted for other words used previously to describe the localized injury and scarring from suppurative inflammation in the renal parenchyma [8]. In the pre-antibiotic era, chronic atrophic pyelonephritis was recognized as a common cause of hypertension and chronic renal insufficiency. In fact, up to 20% of patients at autopsy were found to have pyelonephritis and, when data were available, 45% of them were known to be hypertensive before death [43].

In 1929, an unusual but consistent pathologic finding was observed in kidneys of several patients with severe hypertension [6]. An aglomerular, fibrous band of tissue overlying a calyx gave the appearance of a circumferential groove in the renal parenchyma. These peculiar lesions were considered congenital and, subsequently, were referred to as the Ask-Upmark kidney [33]. Whether the lesions were associated with VUR is unknown because the observations were made before the introduction of radiocontrast cystography. Similar renal lesions in hypertensive children, some of whom were studied for VUR, were often, but not always, associated with VUR and urinary tract infection (UTI). For nearly two decades, these aglomerular lesions were referred to as segmental renal hypoplasia, which implied a localized failure of normal metanephric development. Finally, a series of patients whose kidneys had segmental renal lesions similar to Ask-Upmark kidneys and to segmental renal hypoplasia were observed in serial radiographic and pathologic studies; most of these patients had VUR as well as documented UTI [4]. Careful dissection in some of these kidneys revealed parenchymal lesions in various stages of development – acute inflammatory lesions only days old adjacent to completed aglomerular scars with no evidence of inflammation. It became quite evident that the aglomerular grooves or hypoplastic segments, described previously, were actually atrophic parenchymal scars resulting from localized pyelonephritis in previously normal renal tissue that had contained glomeruli and tubular structures. These lesions could now be referred to, more correctly, as *segmental renal atrophy* [11].

The proposed mechanism for pyelonephritis in humans has been that bacteria, multiplying rapidly in bladder urine, cross an incompetent ureterovesical junction as intravesical pressure increases during micturition. The inoculum reaches the renal pelvis and calyces, enters the papillary collecting tubules in one or more renal pyramids through the ducts of Bellini – intrarenal reflux (IRR) – and causes suppurative inflammation. The resulting injury may heal by scarring, and even a single scar may be associated with severe hyperten-

sion later in life. When scarring is more extensive and both kidneys are damaged, not only hypertension, but also chronic renal insufficiency or end-stage renal disease (ESRD) may develop. Although characteristic radiographic findings and histopathologic features of RN may be observed in kidneys never known to be infected or subjected to VUR, such cases have been considered unusual.

Once the relationship of renal injury to VUR was established, it was reasonable to think that eliminating VUR by surgery could prevent subsequent episodes of pyelonephritis and its clinical consequences. Clinical efforts over more than 30 years produced about 3,000 published reports on VUR and UTI [20]. Most so-called studies were focused on surgical techniques for restoring competence to the ureterovesical junction. When appropriate clinical trials were finally completed, just in the past decade, surgical correction was found to offer no advantage over conservative medical management in preventing renal scarring [13, 37]. Further understanding of the mechanisms whereby VUR injures the kidney acutely and initiates progressive injury without further infection, therefore, must come from future studies, not of the ureterovesical junction, but rather of the human kidney's responses to sterile injury as well as suppurative inflammation both before and after birth.

Incidence

The true incidence of RN is unknown. Perhaps the best evidence for RN being a distinct and, therefore, significant clinical problem is that it accounts for 15 – 25% of patients treated for ESRD in Europe and Australia/New Zealand [19]. There is no reason to think that the prevalence is less among patients with chronic renal insufficiency in North America, where RN has been shown to be a major cause of hypertension and ESRD in children and adolescents (Table 1).

Primary VUR includes only those patients in whom no other anatomic or functional abnormality can be identified and has been demonstrated in < 1% of humans with no prior history of UTI [2]. However, primary VUR will be found in 20 – 50% of children investigated following the first UTI (the highest incidence in the first year of life), 20% at 12 years of age, and only 5% in adults. A long-held notion has been that the incidence of VUR is higher when the voiding cystourethrogram (VCUG) is performed soon after an acute UTI, so the recommendation has been to wait for 4 to 6 weeks after the UTI to order the diagnostic study. Although no report has been made of the incidence of VUR between early and late studies within a single center, the incidence of VUR among children of various ages has not varied when studies at different centers were done either within the first week or more than 3 weeks following UTI [2]. There seems to be no merit in the practice of delaying a diagnostic VCUG once the urine has been rendered sterile, only to "minimize" the number of children with VUR. There may have been a time in the past when the diagnosis of VUR of any grade resulted in an attempt at surgical correction, but this is no longer the case. Today, children with UTI managed conservatively tend to get better clinical supervision, more education about the consequences of UTI and longer periods of follow-up when VUR is identified.

There is no gender difference in the incidence of primary VUR with UTI. The absolute number of girls with VUR is actually greater than the number of boys, but this is related more to the higher incidence of UTI in girls than boys after the first year of life. This

Table 1. Causes of ESRD in Pediatric Patients (Birth – 18 years old). UT Southwestern Medical Center at Dallas 1980 – 1989.

	n
Primary Uropathies	
Primary vesicoureteral reflux	19
Renal hypoplasia/dysplasia	14
Obstructive uropathy	14
Prune-belly syndrome	3
Neurogenic bladder	2
	52%
Glomerulopathies	
Focal segmental glomerulosclerosis	15
Rapidly progressive glomerulonephritis	3
Unclassified chronic glomerulonephritis	3
Membranoproliferative glomerulonephritis	3
Anaphylactoid purpura	2
Systemic lupus erythematosus	2
Hemolytic-uremic syndrome	2
Goodpasture syndrome	1
Congenital nephrotic syndrome	1
	32%
Miscellaneous	
Nephronophthisis	5
Autosomal recessive polycystic kidney disease	5
Neonatal cortical or medullary necrosis	3
Oligomeganephonia	1
Cystinosis	1
Hyperoxaluria	1
	16%
Total number of patients	100

incidence of VUR is similar among white, Hispanic and Asian children with UTI, but VUR is identified less often in black children. Moreover, RN is an unusual cause of hypertension or chronic renal insufficiency among black adolescents and young adults.

Primary VUR will be identified in 27 – 45% of asymptomatic siblings of children with VUR [36]. If one child in a family has renal scarring at the time primary VUR is found, the incidence of VUR in siblings may be even higher. As more genetic studies of families with VUR have been conducted, it would appear that primary VUR, with or without RN, does occur in multiple generations implying vertical transmission suggestive of a pattern of autosomal dominance with variable penetrance. A specific gene locus has not yet been identified. Scarred kidneys may also be associated with secondary VUR from anatomical obstruction as in posterior urethral valves, prune-belly syndrome, ureteropelvic

junction obstruction and urolithiasis, as well as from functional obstruction in a neurogenic bladder or with dysfunctional micturition – none of which are inherited problems.

One of the most common serious bacterial infection in infants and young children presenting with fever is UTI. Some general idea of the prevalence of RN in the general population can be learned from the frequency of a first UTI being, on average, 2.8% in children under five years of age. In the 1990 census there were 18,264,096 of these infants and young children in the United States. Therefore, approximately 511,394 children will have a first UTI by their fifth birthdays, and 30 – 50% or between 150,000 and 250,000 will, if examined, have VUR. The estimates of any degree of renal scarring from VUR and pyelonephritis – one simple scar, perhaps, or multiple scars involving one or both kidneys – have been reported between 12 – 50%, depending upon length of follow-up and methods used to assess renal scarring. The longer the follow-up and the more experienced the investigator, the more often renal scarring will be detected. Also, carefully performed intravenous pyelograms (IVP) and technetium-99m-dimercaptosuccinic acid (DMSA) renal scans found more scars than renal ultrasonography or poorly-done IVP. In a recent study of very young infants with acute pyelonephritis, for example, up to 40% of infants with VUR studied by DMSA scans six months after a UTI had some degree of renal scarring, but not all had VUR [24]. It will be important to follow these patients long-term to record the clinical significance of renal scars detected at this very young age.

If, for example, only 30% of infants and young children under 5 years of age with VUR and UTI develop renal scarring, there should be around 61,367 of them with RN. Assuming no renal scarring ever occurred after 5 years of age and no deaths among children and adolescents with renal scarring, approximately 368,204 people (3.3:1000) currently under 30 years of age in the United States alone should have RN. Only half of children recognized to have acute pyelonephritis, however, will have VUR demonstrated. One study found renal scarring following an episode of acute pyelonephritis in 37% of children without VUR [40]. Until recently, those children with UTI but without VUR have not been subjected routinely to follow-up renal imaging studies. Just how many of them will develop hypertension or renal insufficiency later in life is yet to be determined, but these patients will add to the overall incidence of RN in the general population.

More than half of children with a first UTI, with or without VUR, will experience another UTI within 6 months [31]. With each subsequent infection, the risk of renal injury is increased from 9% after the first UTI to 58% after the fourth [28]. A delay in effective therapy, which is not unusual in an infant or child whose complaints do not suggest UTI, can double the rate of scarring, and, therefore, increase the incidence of RN.

Despite opinions to the contrary, acute renal injury from pyelonephritis definitely causes scarring in children over 5 years of age – even in the absence of detectable VUR [10]. As children grow, VUR tends to resolve gradually in most infants and young children [20], while the incidence of UTI increases to 6 – 8% of school-age girls. Moreover, the rate of VUR resolution in these older children is slower. The consequences of secondary VUR, particularly in decompensated urinary bladders with recurrent UTI, as well as pyelonephritis complicating urolithiasis, only add to the total number of individuals suffering from RN. Perhaps the only reliable statement that could be made about RN to date is that its incidence has been underestimated – especially in the United States.

Etiology

RN has been attributed to pyelonephritis associated with VUR – more specifically IRR – in infants and young children (Figure 1). Few, if any, would argue that suppurative pyelonephritis can cause significant and permanent renal injury. The pathogenesis of renal scarring from VUR-associated pyelonephritis has been produced experimentally in animals either by injecting bacteria into the renal parenchyma or inoculating the bladder with fecal flora after VUR had been created. Shortly thereafter, one or more focal lesions of suppurative inflammation could be demonstrated in the renal parenchyma and, if effective antibiotic therapy was not provided within 5 days, renal scarring developed even though further bacterial growth was eradicated [38]. When treatment was delayed in children with UTI, the incidence of renal scarring was increased 4-fold over those treated promptly [49]. It seems that an inflammatory cascade is initiated by the bacteria within the renal parenchyma, much like that described for endotoxemia, which permits the inflammatory response to continue long after effective antibiotic therapy is introduced [39]. The evolution of the acute inflammatory lesions either to complete resolution or permanent scarring has been demonstrated by serial DMSA renal scintigraphy. Pyelonephritis caused by *P-fimbriated E. coli* seems related more frequently to renal scarring than some other common pathogens. The unique ability of this organism to attach itself to uroepithelium may allow it to cross the ureterovesical junction when VUR is not present and, perhaps, persist in the urinary tract longer than other bacteria.

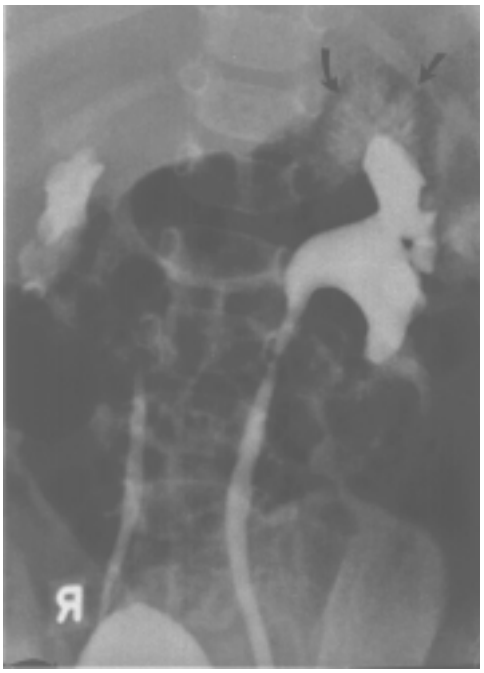

Figure 1. Intrarenal reflux (arrows) into the collecting ducts which extends into the outer cortex of the upper pole of a young girl's left kidney during voiding cystourethrography. There is no evidence of cortical thinning or scarring.

Whether sterile VUR can cause similar renal injury, however, is still actively debated. There is no doubt that typical atrophic renal scarring can be induced when sterile VUR is produced experimentally in animals, but the intravesical pressure required for scarring exceeds 60 cm water – higher than normal voiding pressures measured in children. Some will argue, therefore, that in the absence of bladder outlet obstruction or a decompensated, noncompliant bladder generating high intravesical pressures, renal injury is never associated with sterile VUR. The greatest argument favoring a role for sterile reflux, however, is the scarring associated with VUR in the fetal urinary tract where the urine is always sterile. The developing kidney of the fetus and young infant appears more easily damaged from VUR than does the kidney of an adult and probably older children as well. As more fetuses with dilated urinary tracts have been identified as having renal scarring associated

with VUR – not obstruction – at birth, it is hard to deny sterile VUR causes renal injury with scarring which is different from dysplasia. Segmental scars have been described in dysplastic kidneys subjected to primary VUR as well as obstructed urinary tracts [4]. When studied postnatally, a kidney with dysplasia will have the same ultrasonographic and, perhaps, DMSA scintigraphic appearance as the scarred kidney; however, an IVP will demonstrate segmental scars and calyceal deformities characteristic of RN even in abnormally small kidneys (Figure 2). Kidneys that are small from dysplasia alone will not excrete the radiographic contrast material, so the kidney will not be visualized by IVP. This limitation to more modern diagnostic imaging studies, now favored widely over IVP, is often overlooked as a means of establishing the diagnosis of RN in small kidneys.

Just what kind of intravesical pressure is "normal" for human infants and children? Before toilet training, intravesical pressures generated in normal bladders during micturition rarely exceed 35 cm water. On the other hand, during or after toilet training, when young children are rewarded for postponing micturition or, on their own, delay bladder emptying to continue playing or engage in other activities, intravesical pressures can easily exceed 35 cm water. Add to this any increase in intra-abdominal pressure that will increase intravesical pressure further, as would occur when the child jumps down steps, lands prone in a fall or coughs vigorously with a respiratory illness, and intravesical may exceed 100 cm water. Moreover, there is little dampening of pressure transmitted from the bladder to the renal pelvis across a refluxing ureterovesical junction. A distinct group of young children, for reasons yet unexplained, suffer from dysfunctional micturition, where there is poor coordination of sphincter relaxation during bladder contraction. Higher than normal intravesical pressures may reach 200 cm water in some children both during and between attempts at micturition. Recurrent UTI, which is typical in children with dysfunctional micturition, adds to the incidence and severity of renal injury. Other symptoms of dysfunctional micturition include infrequent micturition, dysuria in the absence of UTI, diurnal incontinence, nocturnal enuresis and constipation. This condition is complicated by VUR, but when unrecognized and inadequately treated,

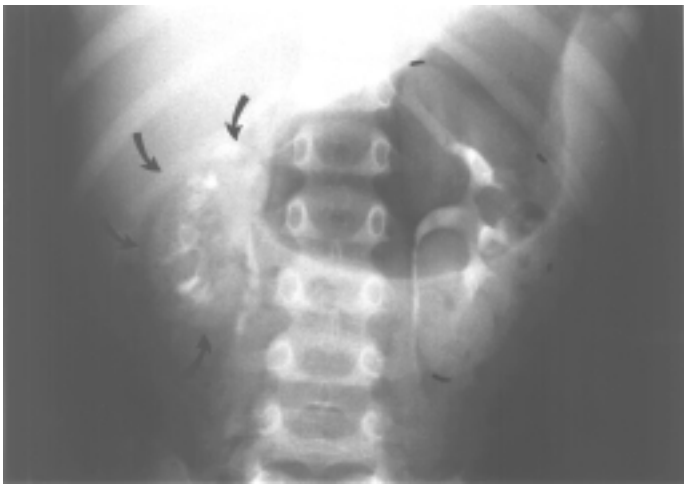

Figure 2. Intravenous pyelogram in 3 yo male discovered to have right Grade II vesicoureteral reflux following a first recognized urinary tract infection. There is generalized cortical atrophy (arrows) in the abnormally small right kidney with deformed calyces. Note how well the small kidney excreted the contrast agent that is typical of chronic atrophic pyelonephritis or reflux nephropathy. The left kidney is unusually large because of compensatory hypertrophy, but is otherwise normal.

VUR fails to resolve spontaneously as it does in other children, and anti-reflux surgery often fails.

Statements have been made that only IRR can cause renal injury. When the renal pelvis of either the human or animal kidney was filled with contrast material under pressure, the contrast solution was found not only to enter the papillary collecting ducts but also to traverse the length of the entire nephron reaching Bowman's space. Because IRR is rarely identified or, perhaps, recognized when a voiding study is done, the conclusion stated in many references is that the actual incidence of IRR is low. Again, this problem is relative only to the detection of IRR which, when seen, is a transient phenomenon at peak voiding pressure (Figure 1). The frequency of IRR being identified is directly related to the interest and skill of the observer performing the VCUG. If renal scarring were possible only with IRR, but IRR is never identified – even in repeated studies – then an entirely new, alternate mechanism for the development of segmental renal lesions must be tendered.

Renal scarring is most evident on diagnostic imaging studies in either upper or lower poles. The porcine model of the refluxing kidney was favored by some investigators because, like the human kidney, the pig kidney has compound papillae draining polar pyramids. The assumption was that IRR occurred more easily in these compound papillae; however, scarring occurs frequently in association with simple papillae as well and in the mid-region of kidneys where small scars seem more difficult to detect by IVP or ultrasonography. Another popular hypothesis advanced 20 years ago was the *"Big-Bang theory"* which meant that the kidney was scarred, sometimes irreversibly, after a single episode of infected IRR. For example, one month following a first UTI, the right kidney of a 3-year-old child with mild (Grade I) VUR was normal (Figure

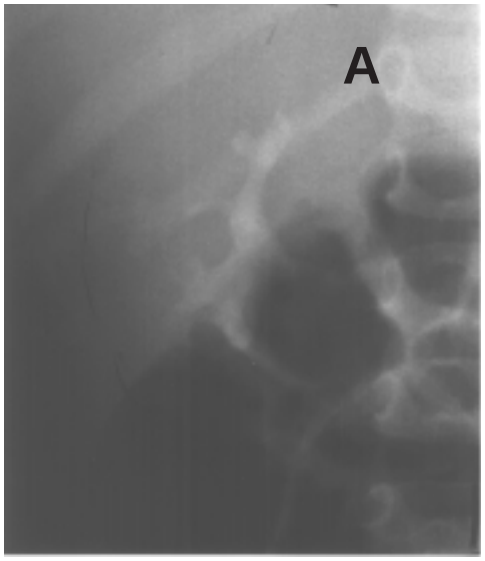

Figure 3a.

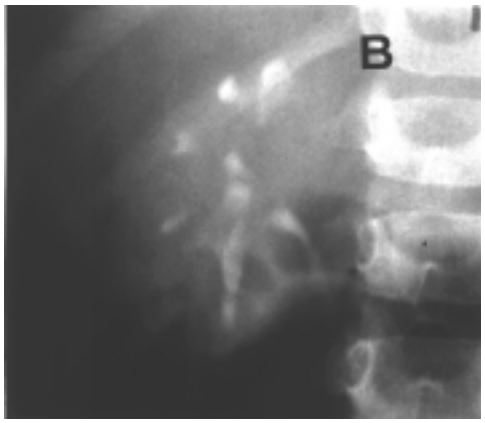

Figure 3b.

Figure 3. The appearance of the right kidney (A) was normal following the first urinary tract infection in a 3 yo female who had right Grade I vesicoureteral reflux. One year later, during which the urine was documented to have remained sterile and the reflux had not worsened, the same kidney (B) is reduced in overall size from 4.5 to 3.0 vertebral bodies due to cortical atrophy. The calyces in all regions exhibit the swallowtail deformity of chronic atrophic pyelonephritis or reflux nephropathy.

3a). One year later, VUR remained mild, compliance with conservative management including antibiotic prophylaxis was good and the urine had been confirmed sterile by culture at regular intervals. The kidney, however, was reduced to approximately half its previous size and exhibited generalized renal scarring with calyceal abnormalities (Figure 3b). On the other hand, new and progressive scarring over several or many years have been reported often in patients subjected to serial IVP during follow-up for VUR [37]. The histopathologic identification of lesions in various stages of development supports the idea that multiple scars may result as well from a *"series of little bangs"* [12]. This latter hypothesis appears to have support from the increase in the incidence of renal scarring with recurrent pyelonephritis [28].

It is widely accepted that the prevalence of renal scarring among all patients with VUR is related directly to the grade of VUR observed during voiding cystourethrography. When VUR is associated with a dilated collecting system (International Grades III – V), renal scarring will be noted in 28 – 50% of kidneys. The number of scarred kidneys associated only with non-dilating VUR (Grades I – II) is usually overlooked because the incidence of scarring is only about 10%. Many seem willing to attribute the renal injury in children with lesser grades of VUR to an earlier time when "VUR must have been more severe" because VUR tends to resolve in most, if not all children, with time and continued growth. When infants and young children with radiographically normal kidneys were followed in serial studies for 5 years after their first recognized UTI, 28% of kidneys subjected to grade III VUR were scarred while only 10% of kidneys with grades 0, I and II VUR had scars [3]. The importance of these observations is not that the incidence of renal scarring was less with mild and moderate VUR, but rather that the total number of scarred kidneys is greater because more patients have mild and moderate VUR than severe VUR. The consequences of renal scarring from any grade of VUR should not be ignored.

Case Presentation

Following her first recognized UTI, a 3-year-old white female was found to have Grade I VUR on the right. Both kidneys were normal by renal ultrasonography. There was no additional UTI, but 5 years later, the patient presented to an emergency department with heart failure. Her blood pressure was 210/160 mm Hg. Once her hypertension was controlled, the heart failure abated. Evaluation revealed Grade I VUR still on the right – no change in 5 years. However, the IVP revealed a single scar in the upper pole of the right kidney.

There has been a long running debate over whether renal scarring from UTI and VUR ever occurs after 5 years of age. In fact, some would argue that all renal injury is initiated by VUR *in utero* and detected only when diagnostic imaging is performed postnatally following the first UTI. Others have claimed that renal scarring never results from VUR and UTI and that so-called scars are actually areas of renal dysplasia. Certainly, most patients with recognized RN have a history of UTI in early childhood. A recent retrospective study could identify few scars by DMSA scintigraphy to develop in children with VUR after 4 years of age [48]. One prospective study in children of all ages found no renal scar to develop beyond 2 years after the last episode of pyelonephritis [13]. On the other hand, 2 other prospective studies noted new scars not only later than 2 years from the last febrile UTI but also to occur in subjects older than 5

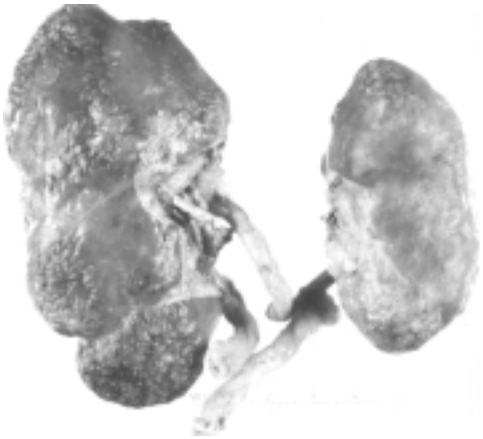

Figure 4. Both kidneys were removed from this 14 yo female before transplantation. Grade III vesicoureteral reflux was demonstrated into both ureters of the duplicated but unobstructed right collecting system as well as the single left ureter. This girl presented at the age of 9 years with hypertensive encephalopathy and had only one recognized prior urinary tract infection. In spite of satisfactory control of her hypertension without ACE inhibition, surgical repair of her reflux, and sterile urine, progressive deterioration in renal function was observed over the next 5 years (see Figure 11, upper panel, square symbols labeled SR).

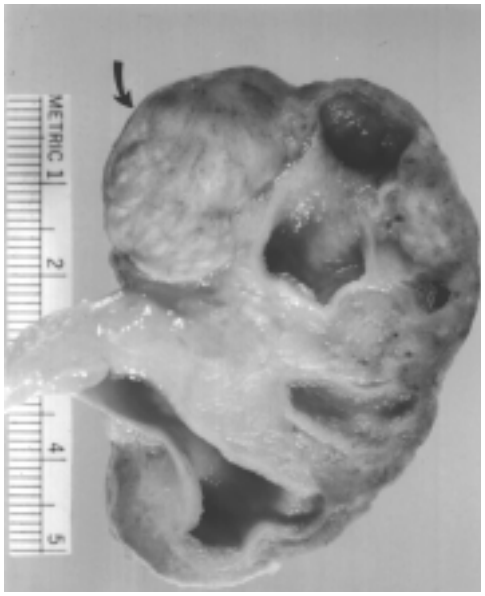

Figure 5. The left kidney from a 13 yo female who presented with ESRD and no evidence of prior hypertension or urinary tract infection. A thin rim of aglomerular parenchyma was present over each calyx. In the upper pole an unscarred pyramid (arrow) had evidence for compensatory hypertrophy and what was responsible for most of her residual renal function. There was no histopathologic evidence of renal dysplasia.

years of age [3, 37]. Recently, adolescent patients with febrile UTI – a group rarely subjected to diagnostic imaging – were studied by DMSA scintigraphy. The rate of renal scarring was compared in infants (43%) and found actually to be higher in young children (84%) and adolescents (80%) [10].

Pathology

The gross morphologic appearance of kidneys scarred by pyelonephritis associated with VUR is illustrated in Figure 4. The kidney is usually reduced in weight as well as overall dimension if scarring is extensive. When there is only one or, perhaps, 2 segmental scars, however, the kidney may otherwise appear normal. Any irregular contour of the uncut kidney's surface is due to areas of segmental atrophy separated by unscarred parenchyma that has undergone compensatory hypertrophy. When the scarring is mainly in polar regions, the mid-portion of the kidney may have a nearly round appearance because of the compensatory growth in unscarred pyramids. When the kidney is bisected longitudinally through the pelvocalyceal system (Figure 5), scarred areas can be seen to overlie a dilated or deformed calyx. Pelvocalyceal dilatation is not a constant finding in RN. The histopathologic features of RN will be missed if the pathologist, hoping to find renal tissue

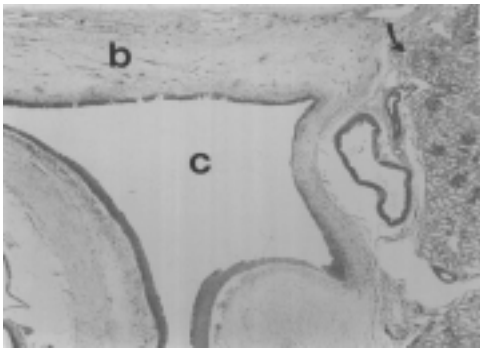

Figure 6. Microscopic examination of the aglomerular fibrous band of tissue (b) overlying a calyx (c). The segment is well demarcated from the normal renal cortex with glomeruli and tubular structures to the right of the calyx (arrow). (PAS stain; 18x magnification).

not yet completely destroyed, examines only sections from the most normal looking areas. To make the diagnosis of RN, a section for microscopic examination should be taken across a scar to include both the adjacent, more normal appearing parenchyma, as well as the underlying calyx.

Microscopically, a completely atrophic scar will be seen as an aglomerular band of tissue overlying a calyx (Figure 6). This band represents once normal renal cortex and medulla injured when IRR, with or without infection, disrupted the collecting duct epithelium and caused local inflammation. The inflammatory response irreversibly damaged either the medullary or papillary collecting ducts associated with those nephrons, the post-glomerular medullary vessels, or both. In time, the segmental injury causes loss of normal histology with the lesions variably containing atrophic tubules, tubular microcysts, sclerotic glomeruli and arcuate vessels separating the atrophic cortex from the atrophic medulla [4, 11]. Depending on the timing of the histologic examination after the injury was initiated, the various phases of acute tubular disruption with mild to marked inflammation – even pus – may be found in proximity to a much older, completely atrophic lesion, especially in a kidney which has been or continues to be injured repeatedly over a period of years. The lesions of RN have been identified even in patients whose VUR was surgically corrected years before the kidney was removed [12]. Other histopathologic features of RN may include renal dysplasia in kidneys subjected to intrauterine VUR or obstruction during metanephric development, but kidneys injured only after birth should not contain dysplasia [4]. When one kidney is scarred in RN, the contralateral kidney, if never subjected to VUR or infection, may exhibit focal glomerulosclerosis [29]. This finding suggests a humoral mechanism by which injury to one kidney can cause changes in the opposite kidney. Based on studies of remnant kidneys focal glomerulosclerosis in RN may be explained better as evidence of glomerular hyperfiltration. A very good candidate for the circulating factor may be angiotensin II (Ang II) produced either after renin is released in increased amounts from the scarred kidney or to increased efferent arteriolar resistance and glomerular filtration by the normal kidney.

Diagnosis

Confirming the clinical diagnosis of RN in any given patient requires a high index of suspicion. Firstly, one must believe that the renal lesions associated with VUR represent a distinct pathologic entity. Distinguishing the problem from other clinical entities, in which a kidney may also be small, requires a certain familiarity with the specific features of RN. A

history of UTI or VUR in a sibling should alert the clinician to the possibility of RN. The medical history of a patient with RN is important, but the physical examination is usually unhelpful unless the patient already has developed complications of renal scarring, particularly hypertension and its clinical consequences. Not all patients presenting with RN will have had a UTI recognized in the past and, if so, will not have had radiographic investigation to document the presence of VUR. This was the case of the 13-year-old white female who presented with ESRD and normal blood pressure; one of her kidneys is pictured in Figure 5. The absence of VUR, particularly in older children with UTI and renal scarring, does not guarantee that VUR was never present because the natural tendency is for VUR to resolve with age [3, 20].

One or more febrile UTIs in infants and young children, with or without VUR, place them at risk of renal injury with subsequent parenchymal scarring. A longer interval between the clinical onset of pyelonephritis to the first dose of an effective antibiotic will increase the chance for renal scarring [49]. With recurrent UTI, the incidence of renal scarring increases from 9% after the first UTI to 58% after the fourth [28]. When VUR is detected, renal scarring can be expected to be present or develop in 50% of children with severe VUR (Grades IV and V), 28% with moderate VUR (Grade III) and in 10% of mild VUR (Grades I and II) [3, 44]. Symptoms of dysfunctional micturition such as diurnal incontinence, infrequent and incomplete micturition and constipation, mostly in females, imply higher intravesical pressures, persistent dilating VUR, recurrent UTI and a greater likelihood of renal scarring.

Voiding Cystourethrography (VCUG)

Clinical recommendations have been made consistently in general pediatrics, pediatric nephrology and urology literature for more than 50 years that each infant or child with a first febrile UTI undergo radiologic investigation to detect an anatomic or functional abnormality which may cause further damage to the urinary tract [34]. In addition, boys at any age and girls under 3 years of age should be studied following the first UTIs whether it is symptomatic or not. More recently, the recommendation has been made to investigate asymptomatic siblings of children with VUR – at least those < 5 years of age – in the hope of detecting VUR before the first UTI can occur [36]. These directions have been followed reluctantly by some and inconsistently by others. The principles of treating cystitis in sexually active women often prevail in managing UTI in children, particularly when the physician is not a pediatrician. There seems to be an aversion by many parents to subject their child to the perceived emotional and physical trauma of bladder catheterization. Substituting renal ultrasonography for the cystogram may identify an upper tract abnormality, like a dilated calyx or advanced cortical atrophy, but will not eliminate the possibility of VUR [14]. When the child's physician is not convinced of its value, the workup is often not pursued.

Until recently, contrast VCUGs were done initially and as frequently as every 6 months during follow-up of a patient with VUR. In the past, when VUR worsened or a renal scar was noted, surgical correction of the VUR was recommended. Upon learning from prospective clinical trials that all grades of VUR either resolved spontaneously or the renal outcome could not be altered appreciably by surgical intervention, whether or not the kidney was

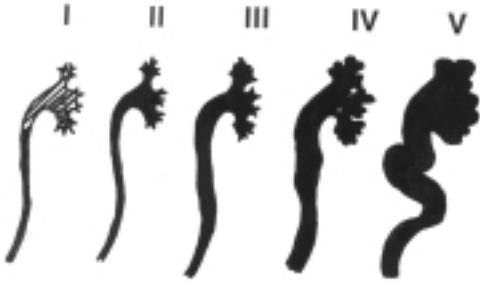

Figure 7. Grading of vesicoureteral reflux according to the classification of the International Reflux Study in Children. The black areas of the collecting system represents contrast material from the bladder, which flows retrograde across the ureterovesical junction during micturition. If the contrast material enters the ureter but does not reach the renal pelvis, Grade I is assigned. When the contrast material fills but does not distend either the ureter, pelvis or calyces, Grade II is assigned. If either the pelvocalyceal system or ureter is distended, reflux is considered Grade III. In Grades IV and V, the ureter becomes progressively more tortuous, the pelvis is more dilated and the calyces are more blunted, losing their papillary impressions.

already scarred, follow-up radiographic studies were ordered less often. A more sensitive test to detect VUR is the radionuclide cystogram, which is recommended for all females, for sibling screening and for follow-up studies. Grading VUR as being more than dilating or non-dilating is not possible with radionuclide cystography, but this does not diminish its clinical value. The contrast VCUG is still recommended for the first study of the male bladder to detect posterior urethral valves. Either type of cystographic study should include observations after the catheter is removed and during micturition when intravesical pressure is highest and the possibility for VUR being detected and graded in a standardized fashion is more likely.

Through the years, there have been 3 or more different grading classifications of VUR. The classification used by the International Reflux Study in Children has now replaced all others and facilitates comparison of data from one study to another (Figure 7). The grading of VUR should be done under standardized conditions. The bladder is gradually filled, but not overdistended, at 70 cm water pressure. If VUR is observed before the bladder is filled with radiocontrast or radionuclide material, the reflux is said to occur when intravesical pressure is low. When VUR is noted only during micturition, the reflux is considered to occur at high intravesical pressure only. The grading of VUR depends on whether the contrast or radionuclide reaches the renal pelvis; if it does not, the VUR is grade I. If the reflux fills but does not distend the ureter or renal pelvis, it is grade II. Grades III, IV and V depend on the extent to which the collecting system is distended by VUR and how tortuous the ureter has become – an effect of dilating VUR and time. An acute distention of the collecting system by an overly aggressive filling of the bladder can cause mild VUR to be assigned a higher grade. A renal ultrasound examination or IVP done before or sometime after the VCUG will, in this case, not show the collecting system to be dilated. When studied subsequently, the VUR may have "improved" or even have resolved if the intravesical pressure remains normal during the procedure. Patients whose collecting systems by IVP or renal ultrasonography are dilated and who exhibit grades III, IV or V VUR usually have long-standing reflux that may have been originally under high pressure. Once the collecting system is damaged, however, the benefit of elastic fibers and smooth muscle layers do not permit its return to its former caliber, and VUR will occur even at low intravesical pressure. The grade of VUR in these ureters is much less likely to improve even after many years of observation.

While great importance has been paid and much time spent on the grading of VUR, it is probably enough to know whether the VUR

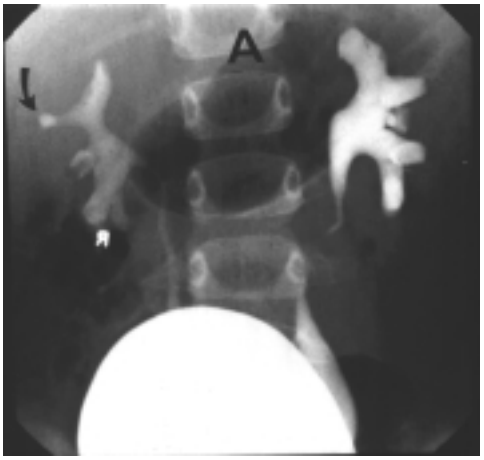

Figure 8a.

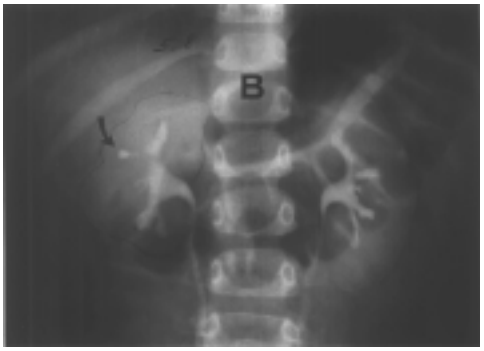

Figure 8b.

Figure 8. Bilateral vesicoureteral reflux, Grade III on the right and Grade IV on the left, noted during a VCUG (A) in a 2 yo female following her second recognized urinary tract infection. The renal ultrasound examination was reported as normal. Because the calyces were deformed on the voiding study, an IVP (B) was performed and revealed cortical atrophy on the right with the very same calyceal deformity (arrows).

caused dilatation of the collecting system or not – a reflection of the intravesical pressure and, perhaps, the pressure exerted at the ducts of Bellini to cause IRR. When VUR causes the entire collecting system to be filled completely (Grade II or higher), the calyceal abnormality associated with scarring is often identified and, if the renal outline is seen well, parenchymal thickness over the calyx can be assessed. These findings, when present, are important and should never be overlooked – the VCUG is not just a VUR detecting study. In Figure 8, the same calyceal deformities and parenchymal thickness over the calyx can be appreciated on both the VCUG (Figure 8a) as well as the IVP (Figure 8b).

Intravenous Pyelography (IVP)

The standard IVP was the diagnostic study done most often in the initial, and usually annual, evaluation of patients with VUR to detect scarring. While imaging studies introduced more recently may be more convenient, as with renal ultrasonography, or more sensitive in detecting renal injury earlier, as claimed for DMSA scintigraphy, IVP remains the best and, sometimes, only test available which depicts the anatomy of the calyces, renal pelvis and ureters. The history of allergic reactions to the contrast material used before the availability in most centers of non-ionic preparations, now used in most centers, has been another excuse used to forego the IVP. The sensitivity of identifying significant renal injury among the various studies depends more on the experience of the technician/observer than on the inherent superiority of the study itself [45]. Although many radiologists have abandoned the practice of bowel preparation before an IVP is done, it is still essential to empty the colon of feces to assure good visualization, especially of the renal parenchyma, but also to see the collecting systems well. Feces in either flexure of the colon may obscure a renal cortical defect or abnormal calyx. To further improve the quality of the imaging, the patient should be hydropenic

(thirsted until the urine specific gravity is > 1.025, or 8 – 12 hours, except in infants), and the volume of contrast material should be injected in age-related doses to get a good nephrogram on a film at 1 – 3 minutes after injection. Subsequent films should be obtained to visualize the contrast-filled pelvocalyceal systems and ureters. The characteristic renal lesion of RN will be thinning of the renal cortex overlying a calyx that may or may not be abnormal. As originally described, the calyx associated with the scar was referred to as a swallowtail deformity [25] (Figure 8). Basically, this calyx has no papillary impression and, when filled by the excreted radiographic contrast material, no longer has its normal appearance, which resembles a white china teacup.

The radiologic diagnosis of a renal scar should be suspected when a calyx is clearly abnormal or deformed either on IVP or VCUG (if VUR is present), when the renal length or parenchymal surface area is > 2 standard deviations (SD) below the recognized mean size for age or height, or when there is a discrepancy between the lengths of the right and left kidneys of > 0.5 cm. A scar may be present when the renal cortex is thin in one area (> 2SD below the mean normal value), usually overlying a calyx which may or may not be deformed [37]. The two-dimensional measurement or planimetric surface area (PSA) of the kidney will give important information for determining whether there has been any reduction of functioning renal parenchyma compared to normal, especially when renal injury has resulted more in poor renal growth rather than discrete segmental scarring [16]. Changes in the combined PSA of both kidneys have been correlated well to changes in glomerular filtration rate (GFR) [1]. There may be little difference between the apparent thickness of the scarred segment and the adjacent normal renal tissue especially in infants whose cortical height may be ≤ 10 mm. When the normal renal parenchyma on either side of the scar grows or undergoes compensatory hypertrophy, the scarred segment – which does not grow – may be noted on the next IVP [42]. Even when done carefully and interpreted by an experienced observer, the IVP may not show convincing evidence of renal scarring for 6 months to 6 years after the diagnosis of VUR was made, especially in infants and young children [4]. Suggestive evidence of renal scarring, which may precede the detection of a definite renal scar, is a discrepancy in size between kidneys. The kidney with scarring may be smaller than normal, while the contralateral kidney, if truly unaffected, will be larger than normal because of compensatory hypertrophy (Figure 2). If the PSA of the two kidneys were combined, the total PSA (scarred + normal large kidneys) may actually be normal, as will overall renal function.

Renal Ultrasonography

The factors of convenience and safety provide the basis for recommending that renal ultrasonography is preferable for diagnostic screening of at least the kidney and upper urinary tract of children with UTI. In fact, the suggestion that the ultrasound exam be the only diagnostic study for a child with febrile UTI has been made, but is not yet widely accepted. The basis for this recommendation has been that when kidneys appear normal following a UTI and the collecting systems are not dilated, then it matters little whether the patient has VUR because management will be directed at preventing further UTI, rather than deciding for or against surgical repair of VUR. There is some merit to this proposal. However, ultrasonography is rela-

tive insensitive at detecting all but severe renal scarring and does not identify VUR unless the collecting system is dilated – even then one study reported the sensitivity to be no more than 25% [14]. Dilated calyces are often mistaken for simple renal cysts (Figure 10a). For those who have relied on knowing whether VUR is present, not knowing about the status of the VUR presents a clinical dilemma.

Case Presentation

A white female had 2 recognized UTIs with fever and several other episodes of unexplained fever treated with antibiotics before her first radiologic investigation at 4 years of age. The renal ultrasound was reported to be normal, and no VUR was detected on a radionuclide VCUG. The patient was treated with antibiotic prophylaxis for one year without breakthrough UTI. Once the treatment was discontinued – the patient had no VUR and the ultrasound was normal – a febrile UTI occurred within 2 months. After appropriate antibiotic treatment for the acute pyelonephritis, prophylaxis was prescribed again for 6 months, and the patient remained free of UTI. After stopping daily antibiotic therapy, the patient had another febrile UTI one month later. Re-evaluation of the patient at 6 years of age revealed both kidneys to be "normal" by ultrasound (Figure 9a) except that the length of the left kidney (6.4 cm), which at 4 years of age had been at the lower limit of normal, had not changed during the 2 years between the studies and was 6.6 cm (> 2SD below the mean normal value for age). The right kidney measured 8.1 cm and had grown normally. A DMSA renal scan was performed to investigate the small left kidney (Figure 9b). Extensive parenchymal scarring of the upper and lower poles of the left kidney was identified. Careful re-evaluation of both renal ultrasound studies revealed no evidence of renal scarring other than the small size of left kidney. Had the variable of renal size been overlooked, which is all too often the case, this patient would have been considered normal and appropriate follow-up for a child with a scarred kidney would not have been planned.

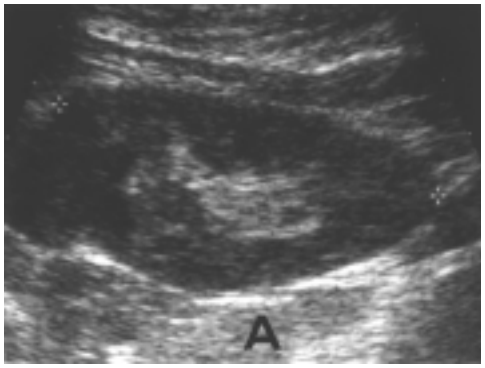

Figure 9a.

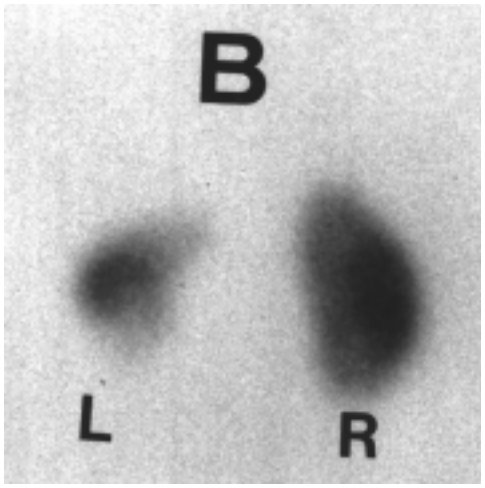

Figure 9b.

Figure 9. Renal ultrasound examination of the left kidney in a 6 yo female with a history of recurrent urinary tract infection. The overall appearance of the image (A) is normal but the length (+) was 6.4 cm (> 2 SD below normal mean length for age). A DMSA renal scan (B) revealed extensive scarring of both upper and lower poles of the left kidney.

Technetium-99m-Dimercaptosuccinic Acid (DMSA) Scintigraphy

The DMSA scan offers less radiation than conventional urography, is much more convenient for the patient, requires no bowel preparation or fluid restriction and has little or no risk of an allergic reaction. The shortcomings of the DMSA renal scan include an inability to estimate renal size or function or to assess calyceal morphology. Moreover, the DMSA scan takes a minimum of 3 hours, is expensive – about twice that of the IVP or renal ultrasound examination – and has what is probably too much interobserver variability. Individual observers may be consistent with their interpretations of DMSA renal scans only about 85% of the time, but the interobserver variability may be even greater. Some clinicians have recommended a DMSA renal scan be performed during an acute episode of UTI to confirm the diagnosis of pyelonephritis. Then, a follow-up DMSA scan at least 3 months later, after acute inflammatory changes have resolved, will confirm the presence of any renal scarring in the areas of inflammation noted on the original study. Managing the costs of such recommendations may prove problematic in the future. Moreover, knowing renal parenchymal inflammation is present in a febrile child with significant bacteriuria will have no impact on clinical decision for treatment. Recently, 40% of infants [24] and 80% of children and adolescents [10] with febrile UTI were found to have renal scarring by DMSA studies done 2 – 6 months later. There are no long-term data on the outcome of scarred kidneys identified so soon after acute injury.

There are now just about as many opinions for how UTI in children should be evaluated as there are physicians treating them. While clinicians more experienced with the management of UTI and VUR in children may have held on for too long to outdated ideas, inexperienced observers – especially non-clinicians who perform meta-analyses on other people's incomplete data – are recommending radical departures from conventional approaches. One such meta-analysis [17] concluded that there was no correlation between diagnostic imaging and clinical outcome in patients with UTI – an obvious notion, just as there would be no expected relationship between bone marrow aspiration and the outcome of patients with leukemia. Because there has been little progress to date in preventing renal scarring associated with UTI and VUR, several reports have recommended little or no investigation be done to detect VUR or renal scarring – just treat the UTI when it occurs. After a careful and extensive review of the medical literature for the past 30 years, the American Urological Association published a report to give clinical guidelines, especially for urologists but for other physicians as well, to standardize the diagnostic approach and clinical management of children found to have VUR following a first UTI [20].

Clinical Outcome

The natural history of acute pyelonephritis can be characterized from clinical descriptions in the pre-antibiotic era as fever and flank pain lasting 4 – 7 days. Subsequently, the patient either died from urosepsis or became entirely asymptomatic. Many of those who apparently recovered from acute pyelonephritis exhibited recurrent bouts of "suppurative nephritis" and died years later, sometimes of heart failure or stroke. When

indirect measurements of arterial blood pressure came to be measured more routinely about 60 years ago, there was a clinical debate over what the upper limits of normal systolic blood pressure should be – 120 or 140 mmHg. The higher limit was accepted. Nevertheless, it became possible in autopsy series to correlate antemortem hypertension with its cardiorenal complications. A direct relationship between pyelonephritis and hypertension was established more clearly when nephrectomy in unilateral renal scarring was followed by an abrupt return of the blood pressure to normal. Of particular interest was the frequent finding of pyelonephritis in patients who had succumbed to cardiovascular disease that likely was secondary to unrecognized or untreated hypertension. Effective pharmacologic control of hypertension and, therefore, prevention of its cardiorenal consequences became possible only in the past 30 years. Recently, the upper limit of normal blood pressure which appears to afford some cardiorenal advantage – 125 mmHg – seems to be closer to the recommendation of the losers in the original debate.

Hypertension

The cause of sustained hypertension in 26% of adolescents at one U.S. center [5] and in 35% of children referred to a single center in the U.K. [18] was renal scarring or RN. Hypertension has been detected in up to 50% of adults with RN [30], depending, again, on how long patients with renal scarring were seen for follow-up evaluations. In one series, hypertension was detected, on average, 8 years after the diagnosis of VUR was made and 2 years after the first renal scar was detected on serial IVP [42]. Another study found hypertension 27 years after the diagnosis of VUR was made [26]. The most common presentation of RN-associated hypertension in women is encephalopathy or heart failure which usually occurs around puberty, when taking birth control pills or during pregnancy: all periods associated with increased estrogen. Estrogen is thought to increase the production of angiotensinogen, at least during pregnancy. Many women are unaware of their RN before their hypertension is identified. For reasons yet unexplained, hypertension from RN is less common in adolescent males. The mechanism for hypertension in older adults with renal scarring, mainly from pyelonephritis associated with urinary tract obstruction or urolithiasis, may be multifactorial and requires a slightly different kind of clinical evaluation and management.

Hypertension in RN is angiotensin mediated and easily controlled in most cases with an ACE inhibitor or AT_1 receptor blocker given once daily. Plasma renin activity (PRA) in the segmental venous drainage of a renal scar has been demonstrated, whereas the PRA from blood sampled only from the main renal vein may be normal, owing to its dilution with blood draining normal areas of the kidney [27]. The resulting increase in angiotensin production raises vascular resistance and pressure in both the systemic and renal circulations. The hypertension may not produce recognizable symptoms often until there is headache, a disturbance in visual acuity, seizure activity, heart failure, or stroke. Retinopathy consisting of arteriolar changes, hemorrhages, cotton wool spots and papilledema will be noted on physical examination in many patients. Moreover, concentric hypertrophy of the left ventricle will be detected by echocardiography. The duration of sustained hypertension required to produce these changes before severe symptoms necessitate a precipitous evaluation is not known, but it is thought to be at least 2 months and

maybe longer. Before the availability of reliable treatment, not every case of severe hypertension in adults was associated with retinopathy for as long as 2 years of more. Unsuspected and uncontrolled hypertension may itself damage the scarred kidney further and accelerate deterioration of renal function as recognized for many years in patients with malignant nephrosclerosis.

Case Presentation

A typical presentation in which the diagnosis of RN was missed initially is illustrated by the following case. A 15-year-old white female was treated by a gynecologist for severe menorrhagia and anemia with blood transfusion and an oral contraceptive agent. The patient's blood pressure was 100/68 mmHg at the outset of treatment. Within a month, the patient began to complain of blurred vision that worsened over several months before she presented to the emergency department with encephalopathy, retinopathy including papilledema and a blood pressure of 260/140 mmHg. A CT scan of the head was reported to be normal. The only biochemical abnormality detected was a serum creatinine concentration of 2.0 mg/dL, which represented an estimated reduction in overall kidney function to < 50% of normal. In an adult critical care setting, the patient's blood pressure was lowered, but not well controlled, first by nitroprusside then by nitroglycerin with the addition of labetalol and clonidine. Nevertheless, the encephalopathy improved. Further evaluation included renal ultrasonography which was interpreted as normal except for a small "cyst" in the outer renal cortex (Figure 10a) No observer appreciated that the length of each kidney (8.3 cm and 8.8 cm) was > 2 SD below the normal mean length for age [22]. Selective renal arteriography revealed no vascular abnormality and was considered normal, except for what appeared to be fetal lobulations bilaterally, (Figure 10b). Because no renal arterial lesion was identified, delayed films were omitted, so the pelvocalyceal systems were never visualized.

Upon discharge from the hospital, the parents consulted yet another physician because the blood pressure was poorly controlled on increasing doses of clonidine and labetalol. The patient's school performance had deteriorated, and she was sleepy during the day despite adequate sleep at night. After reviewing the patient's prior records, the physician noted the small size of both kidneys and ordered an IVP to "complete" the angiographic study and demonstrated conclusively that the "fetal lobulations", which do not have such an exaggerated appearance in the mature kidney, really represented bilateral renal scarring. The segmentations in the renal cortex of both kidneys were immediately above abnormal calyces and the "cyst" noted on the ultrasound examination was, in fact, a dilated calyx (Figure 10c).

The estrogen-containing oral contraceptive agent was discontinued, and an ACE inhibitor was prescribed as monotherapy for severe hypertension. The patient's blood pressure has remained at 110/65 mmHg with enalapril 10 mg daily as the only medication. Within a month, the patient's school performance had returned to its previous superior level. Six months later, the concentric left ventricular hypertrophy had resolved. However, the serum creatinine concentration remained elevated at 1.6 mg/dL, meaning the patient is at high risk to experience further deterioration of renal function.

While all 3 studies either suggested or confirmed the correct diagnosis of RN, neither the internist who admitted the patient for hypertensive encephalopathy nor the various radi-

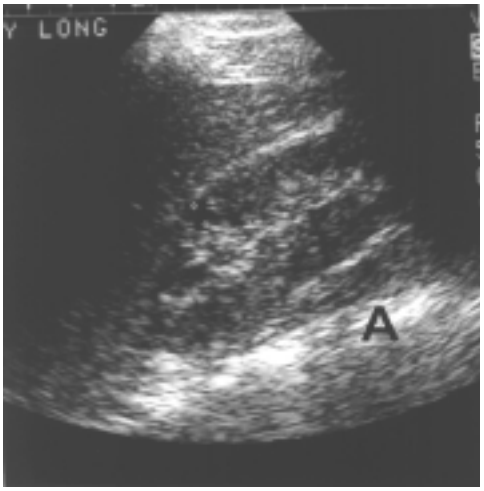

Figure 10a.

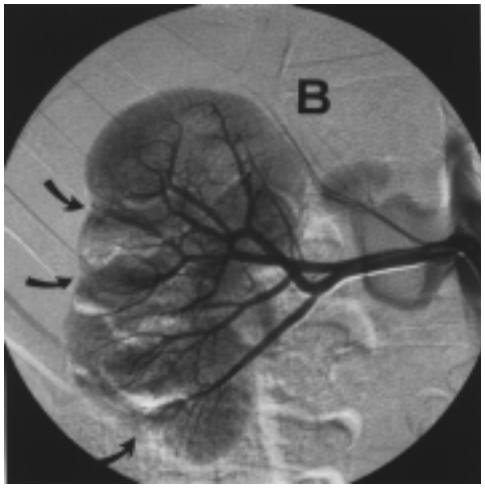

Figure 10b.

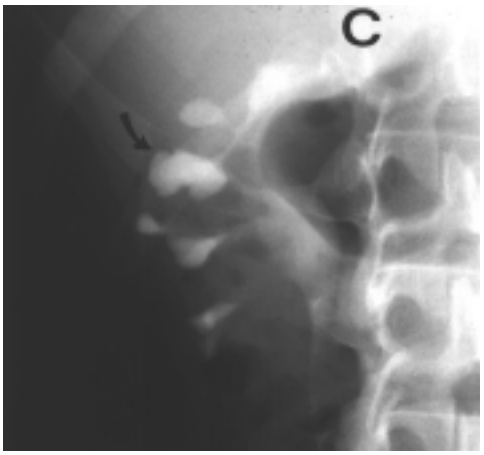

Figure 10c.

Figure 10. A 15 yo female presented with hypertensive encephalopathy. The renal ultrasound examination (A) was read as normal except for a "small cyst" (limits demarcated) in the upper pole of the right kidney. Selective renal angiography (B) was interpreted as normal with bilateral "fetal lobulations" (arrows; right kidney), but the study is characteristic of angiographic findings in reflux nephropathy. An IVP (C) demonstrated segmental cortical atrophy with deformed calyces – reflux nephropathy. The "cyst" noted on the sonogram (arrow) is actually a dilated calyx.

ologists performing the imaging studies appeared to be familiar with the typical presentation and diagnostic features of RN. Unfortunately, this clinical scenario is not uncommon. The absence of a prior history of UTI or recurrent febrile illnesses in the first years of life is not so unusual in patients with RN. Acute UTI at this age is not recalled by the patient and the parents may not recall the past medical history of the child or may not be available to provide such a history in adult patients. However, there is almost no other cause of hypertension with such a dramatic onset of symptoms in adolescent females soon after puberty, after estrogen-containing oral contraceptive agent is prescribed or with pregnancy.

Chronic Renal Insufficiency

Chronic renal insufficiency develops only in patients with RN who have bilateral, severe

renal scarring and may be recognized only when patients are examined for other problems, such as hypertension. The approximately 1% of patients born with a single kidney and those who lose a kidney after birth are at risk of a reduction in GFR with only unilateral renal injury from VUR or UTI. Undetected hypertension may, in fact, cause further injury to a scarred kidney and, itself, account for the development of chronic renal insufficiency – even ESRD. This deterioration in renal function might have been prevented had the hypertension been detected soon after its onset and treated appropriately. It is not unusual for scarred kidneys to exhibit deterioration of overall renal function > 20 years after the last episode of pyelonephritis [26] and after VUR has resolved or corrected surgically. Therefore, RN may be the cause of the large number of adult patients with small kidneys presenting with ESRD without a clinical diagnosis.

The overall prevalence of chronic renal insufficiency in RN is difficult even to estimate, but 24% of adolescents and 17% of adults under 40 years of age presenting for end-stage care in Australia/New Zealand have RN listed as their primary diagnosis [19]. In the United States, there has been less interest in establishing a specific diagnosis of RN in ESRD patients. When patients – hypertensive or not – are found to have small kidneys by renal ultrasound, further efforts at making a diagnosis are usually abandoned. Most native kidneys are no longer removed for hypertension or in preparation for transplantation. Even if they are, the diseased kidneys are usually not examined carefully – just given an arbitrary diagnosis of end-stage kidney. A North American registry of more than 4000 children and adolescents with ESRD listed the prevalence of RN among these patients at only 4 – 5% [24]. However, the diagnosis submitted for these patients was only a clinical impression because, in most of them, no histopathologic confirmation of the diagnosis was required. In this registry, there was a large group of patients with conditions associated with secondary VUR (obstructive uropathy) and hypoplasia/dysplasia, i.e. small kidneys, some of which may indeed have been injured by VUR or UTI. By comparison, in the first 100 patients < 18 years of age who were transplanted in a single center where histopathologic diagnosis was established in every patient (Table 1), the most common cause for ESRD was RN in 38%; 19% had primary VUR with or without UTI and another 19% had secondary VUR. Similar numbers were reported for ESRD in children from France, Germany and New Zealand [2].

Pregnancy

The incidence of UTI, especially pyelonephritis, during pregnancy was greater in women with renal scarring following UTI in childhood [35]. Moreover, blood pressures were higher in pregnant women with renal scarring than in those with unscarred kidneys. An inverse relationship between maternal blood pressure from any cause and fetal weight has been reported [15]. RN is the basis for pregnancy-induced hypertension in many women, but the correct diagnosis, for one reason or another, is not made very often. It is possible that the blood pressure in most women with RN returns to normal following delivery and after estrogen production has diminished, just as it does in toxemia. Some women with RN will remain hypertensive but asymptomatic post-partum, while others will become markedly hypertensive either with estrogen therapy as part of contraception or during a subsequent pregnancy. A most dramatic deterioration of renal function has been

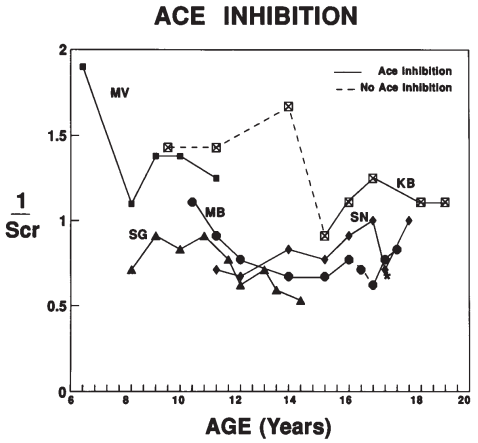

Figure 11. The reciprocal of the serum creatinine concentration (1/Scr) compared to the age of 5 females with bilateral renal scarring, chronic renal insufficiency and hypertension. The broken line (labeled KB) connecting the crossed square symbols represents the treatment period before an ACE inhibitor was available and hypertension was controlled with other drugs. No significant deterioration of renal function over 5 years or more of follow-up observation when hypertension was controlled satisfactorily with an ACE inhibitor.

reported in pregnant women with RN more than 20 years after a febrile UTI [26]. Not only do some of these women become dialysis-dependent during pregnancy, but not all recover following delivery of the fetus and require renal replacement therapy.

Case Presentation

A 16-year-old white female had the diagnosis of RN made when she presented at the age of 11 years with hypertensive encephalopathy (Figure 11, diamond-shaped symbols labeled SN). Renal scarring assessed by IVP was severe bilaterally, and serum creatinine concentration was elevated for age at 1.4 mg/dL (1/serum creatinine = 0.7). The hypertension was managed easily with enalapril 10 mg daily. Over the next 5 years, blood pressure, monitored regularly at home and quarterly by her physician, remained below 110/70 mmHg with no treatment other than enalapril. Renal function improved as evidenced by a gradual decrease in serum creatinine to 1.0 mg/dL even though the patient had increased her lean body mass, completed pubertal development and achieved a normal final adult height by 16 years of age. Despite warnings of the consequences of pregnancy with RN, of hypertension being more difficult to manage when estrogen-containing oral contraceptive agents were taken, and of fetal injury from ACE inhibition therapy, the patient engaged in unprotected sex. After having stable renal function and normal blood pressure for 5 years on the same dose of enalapril, the patient developed a sudden increase in blood pressure to 160/110 mmHg and an increase in serum creatinine to 1.4 mg/dL (decrease in 1/serum creatinine to 0.7). The patient had always been compliant with therapy and even an increase in the enalapril to 20 mg twice daily did not lower the blood pressure. Although denying the possibility of pregnancy, the patient had a positive pregnancy test. By dates and ultrasonography, the pregnancy was estimated at 6 – 8 weeks gestation. The patient chose to abort the fetus and, within 24 hours, her blood pressure was normal. The enalapril dose was reduced again to 10 mg daily and good blood pressure control continued over the next year. Importantly, GFR returned to its antepartum level estimated by a serum creatinine of 1.0 mg/dL. Progesterone-only contraceptive agents were prescribed for the patient without noticeable changes in her blood pressure. The patient was advised that if ever in the future she chose to risk another pregnancy, ACE inhibition therapy must first be discontinued and other antihypertensive agents used to control blood pressure.

ACE inhibitors now carry the warning about their use for treating hypertension, renal disease or heart failure in women of childbearing age. ACE fetopathy has been described as a severe failure of the fetus to develop normally, especially the kidneys, owing, perhaps, to angiotensin being an important growth factor that influences angiogenesis and tissue remodeling. Moreover, the unique hemodynamic changes in the pregnant female, particularly the gradual reduction of blood pressure when PRA and plasma angiotensin levels, indicators of potent vasoconstrictor activity, are increased above normal. When an ACE inhibitor was given during the second and third trimesters of pregnancy, unresponsive hypotension and irreversible renal failure in the newborn infant have been described. Because hypertension in RN is angiotensin-mediated, other antihypertensive agents cannot be expected to give as predictable control of blood pressure as an ACE inhibitor or AT_1 receptor antagonist. Because of the risk of worsened hypertension, ACE fetopathy, and deterioration of GFR – even ESRD – during pregnancy, consideration of a woman with RN becoming pregnant must be a part of the patient's education, but only at the appropriate time when emotional development permits rational decision making.

Progression

There has been no satisfactory explanation to date that characterizes how a kidney, damaged in the past by VUR or pyelonephritis, continues over many years to exhibit parenchymal changes. Newly-identified scars or worsening of established scars usually would suggest further renal injury but not in the absence of VUR, after anatomic or functional obstruction was relieved and when the urine has remained sterile. It is unreasonable to think the progression of renal lesions in RN is due to a prolonged scarring process that takes years to complete – scarring should be completed in months, not years. Acute inflammatory changes in the renal medulla, identical to those associated with IRR and infection, have been identified in scarred kidneys in which VUR had been repaired surgically more than a year before, and the urine was documented to be sterile by frequent cultures for 2 months before nephrectomy [12]. The only difference noted in the lesions found was the paucity of inflammatory cells compared to the ones associated with infection.

One possible explanation for continued scarring in those treated surgically could be that the antireflux procedure itself disturbed ureteral peristalsis. In experimental studies of the canine ureter, re-implantation was associated with reverse peristalsis so that urine flowed retrograde towards the renal pelvis which, instead of VUR, there would be ureteropelvic reflux and, perhaps, IRR. This same phenomenon may occur more proximally when urine from the renal pelvis re-enters the ducts of Bellini, referred to as pyelorenal backflow and observed in micropuncture studies of the rat papilla during progressive saline diuresis. Although most attention to date has been given to the surgical techniques used to correct VUR, no study has been reported on the effect the various procedures have, if any, on normal ureteral physiology.

For lack of a better explanation, and because sterile inflammation has been observed in these kidneys, a immunological mechanism has been proposed as a cause of progressive renal injury. This notion has persisted in spite of the lack of evidence to support it. Perhaps, it is easier to accept at face value because the kidney is injured by so many other immune-mediated diseases. Even a reaction

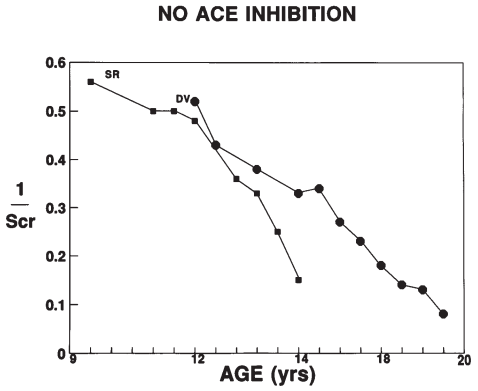

Figure 12. The reciprocal of the serum creatinine concentration (1/Scr) compared to the age of 2 females with bilateral renal scarring, chronic renal insufficiency and hypertension. Progressive deterioration of renal function over 5 – 8 years after VUR corrected, urine remained sterile, and hypertension was controlled satisfactorily with drugs other than an ACE inhibitor.

to Tamm-Horsfall protein has been proposed, but most of these lesions do not contain unusual amounts of PAS positive material.

Consistent blood pressure control at a mean arterial pressure ≤ 100 mmHg, or 125/75 mmHg, is considered essential to slowing the progressive deterioration of renal function in diabetic nephropathy and in primary renal diseases like pyelonephritis. Because many patients with RN are identified because of hypertension, one might argue that the progressive nature of these lesions represent the renal damage caused by uncontrolled hypertension or malignant nephrosclerosis. Media hypertrophy and endothelial proliferation has been identified regularly in the renal vasculature. However, progression has been observed in kidneys never exposed to systemic hypertension as well as those where hypertension has been well-controlled by medication other than ACE inhibitors soon after its onset (Figure 12).

Two findings in kidneys that exhibit deterioration of structure and function may provide evidence for a mechanism to explain the progressive nature of this renal lesion. One finding is compensatory hypertrophy. In RN, the remaining normal parenchyma undergoes marked compensatory changes that may be associated with an actual increase in overall renal dimensions. When this is seen in a child, further normal renal growth may be naively assumed. Compensatory changes allow GFR to remain stable for awhile. By the time GFR has been reduced to 50% of normal, 90% of the functioning renal mass has been destroyed. The other finding is the histopathologic feature of focal glomerulosclerosis – even in unscarred contralateral kidneys – causing some, but not all, to consider this lesion specific for RN. Moderate and heavy proteinuria has been identified in many patients with RN, and is an almost certain sign of eventual ESRD [30]. Most children and adolescents with RN have nothing more than mild proteinuria. Patients with bilateral RN may have increased urinary excretion of microalbumin, retinol-binding protein or N-acetyl-beta-D-glucosaminidase excretion before clinical proteinuria being detected by urinalysis [47]. Whether there is a role for proteinuria to damage renal tubules or cause interstitial inflammation in RN has been mentioned. The glomerular findings described for RN, therefore, appear similar, if not identical, to lesions in remnant kidneys, which may be consequent to hyperfiltration rather than a continuum of injury initiated by IRR in the past. In any event, proteinuria appears to be the hallmark of progressive deterioration of renal function.

ACE inhibition therapy, which does not eliminate intrarenal angiotensin production much more than by half [7], has been shown to reduce proteinuria and to slow the progressive deterioration of renal function in kidneys scarred by pyelonephritis [9]. ACE inhibition

affords a benefit in RN not seen when hypertension is treated successfully with other antihypertensive drugs [23]. Progressive changes in renal function in young hypertensive females with RN are depicted in Figure 12 by serial ratio of 1/serum creatinine over 5 years or longer. Those 2 patients whose blood pressure was controlled effectively with drugs available before the introduction of ACE inhibitors (propranalol and hydralazine) exhibited progressive deterioration of GFR; both were treated first by dialysis, then received a renal allograft. By comparison, the girls treated first with captopril and later with enalapril had their blood pressures controlled as well, but exhibited little change in GFR. The criticism of using 1/serum creatinine in children is acknowledged, but these girls were of similar ages when the diagnosis of RN with hypertension was made. Moreover, all had severe scarring of both kidneys with similar elevations of systolic pressure to > 180 mm Hg and of diastolic pressure to > 120 mm Hg before treatment. This benefit of ACE inhibition may extend as well to normotensive patients with RN and other progressive renal diseases.

The protection afforded the damaged kidney by ACE inhibition is not mediated solely through control of blood pressure [23]. The production of angiotensin in the intrarenal circulation and tubules has been shown to be approximately 1000 fold greater than in the systemic circulation [41]. Similarly, the renal metabolism of angiotensin was demonstrated to be as efficient as its synthesis. A disturbance either in the production of angiotensin or its metabolism could cause localized renal ischemia, perhaps, by intense vasoconstriction of glomerular or post-glomerular blood vessels. angiotensin is also known as a growth factor important in angiogenesis, tissue remodeling after injury and hypertrophy of smooth muscle. Moreover, it may promote fibroblastic activity not only to facilitate the repair of injured tissue but also to cause scarring – even progressive fibrosis. Therefore, many of the consequences attributed once to IRR or infection may, in fact, be explained better by a localized increased production of angiotensin in the repair of damaged tissue. Once initiated, either the further production of angiotensin or a failure of its intrarenal metabolism may promote compensatory responses at first, then cause hyperfiltration and ischemic injury resulting in progressive reduction in renal size – simulating progressive scarring, with gradual deterioration in overall renal function. Perhaps even more aggressive efforts to control angiotensin, say with higher doses of ACE inhibitors and angiotensin receptor blockade, or both may afford even better control of remnant kidneys, not only in RN, but also other renal diseases characterized by progressive deterioration of structure and function.

Dietary protein intake has been shown in renal ablation models and in various renal diseases, both diabetic and non-diabetic, to have an adverse effect on kidney function. While conclusive evidence for any clinical benefit of a protein-restricted diet in retarding or preventing progression altogether of renal disease in humans has not been demonstrated to date, there is enough information to suggest a role for reducing protein intake in most patients with chronic renal disease, even when renal functional impairment is mild or moderate. When combined with other measures such as control of hypertension and inhibition of angiotensin, the ADA recommended normal protein intake each day for adolescents and young adults of 1 g/kg body weight is considerably less than the usual protein intake for most people living in North America, and may be beneficial in overall efforts to preserve renal function.

Strategies for Prevention

RN is one of very few kidney diseases with the immediate potential of not just being modified, but actually prevented. Although there is a potential risk for renal injury from acute pyelonephritis at any age, most scarring which leads to chronic renal insufficiency seems to originate in infancy and early childhood when the kidney appears more vulnerable to insult, when symptoms of UTI may be overlooked or mistaken, and when appropriate treatment may not be instituted promptly. Whether a patient has pyelonephritis or only cystitis at the time of an acute illness is an academic discussion for a later time. Also, the debate about whether to treat asymptomatic bacteriuria should not enter into any decision of a febrile child, especially if the child is known to have VUR.

Firstly, the clinical suspicion of acute pyelonephritis at any age must be confirmed by urine culture; urinalysis never serves more than a screening role either in diagnosis of the first UTI or during follow-up of children with a prior UTI. Even the most experienced clinician – using reagent strips for leukocyte esterase and nitrite, semi-quantitative urine white blood cells estimates, Gram stains of uncentrifuged urine, C-reactive protein measurements or erythrocyte sedimentation rates (ESR) – cannot be relied upon to discern the clinical differences. The urine culture is the gold standard for establishing the diagnosis of UTI regardless of the patient's age. All the other laboratory tests may improve clinical suspicion of UTI before the preliminary results of the urine culture are known, but, in reality, only increase the cost of making the diagnosis. Acute renal inflammatory lesions by DMSA renal scans have been described in some patients thought at first to have only cystitis.

Therapeutic intervention, however, does not have to be delayed for a urine culture report. Antibiotic treatment should be instituted immediately after the clinical diagnosis is suspected and the urine culture obtained. Where patient or parent non-compliance may be anticipated, parenteral antibiotic therapy should be considered. No antibiotic will be effective against every urinary pathogen, therefore the drug initially prescribed may need to be changed when the sensitivities of the organism are known or the urine obtained for culture after 48 hours of treatment is not yet sterile. The duration of treatment is somewhat arbitrary. In the uncomplicated urinary tract, 1 – 3 days of oral or parenteral treatment with an appropriate antibiotic has been shown to be sufficient. Failure of an abbreviated course of antibiotic therapy has been associated with a high incidence of urinary tract abnormality. Seven to 10 days of antibiotic treatment is more conventional, even though there are no studies to confirm any additional benefit. The treatment should continue, at least in a prophylactic regimen, until the decision is made for instrumenting the bladder for VCUG in those children who have not previously undergone radiologic investigation. More importantly, the urine should still be sterile a week after discontinuing treatment of any duration. The goal of the clinical follow-up is to assure, as best one can, that the urine remains sterile. Even under the most compliant circumstances, breakthrough UTI can be expected in a third of patients who have VUR. The best clinical outcomes have been reported in an uncontrolled trial with long-term daily antibiotic prophylaxis where new scars in patients with VUR were detected in only about 2% of patients – these were considered non-compliant with therapy [46]. By comparison, new scars were observed in up to 21% of patients with VUR treated acutely as each new UTI was recognized [32].

There is a clinical notion that has gained popularity in recent years that renal scarring in patients with VUR cannot be prevented. In other words, because most patients with renal scarring already have it when first evaluated for UTI and most of these patients are identified in the first 5 years of life, this pessimistic viewpoint holds that preventing renal damage is not possible. Evidence to the contrary includes new scars observed to develop in older children, adolescents and adults with previously normal kidneys or in locations within the kidney of acute lesions of pyelonephritis identified by DMSA technology that progress to scarring. Finally, in Sweden, where the management of UTI in children has been a priority in a socialized system with good access to medical care and follow-up, the incidence of renal scarring in patients with VUR has been reduced significantly – compared to results reported 25 years ago – to what is probably the lowest reported incidence in the world today, about 10%. This clinical evidence supports experimental observations in which renal scarring in animals was avoided when appropriate antibiotic therapy was initiated within 5 days of pyelonephritis being induced.

Patients at risk of renal scarring must be identified early and, if possible, before the first UTI ever develops. Screening programs are not recommended because the yield of pathology in asymptomatic children is < 0.5%. There are 2 situations in which screening patients at risk of renal scarring has merit. The first is the newborn infant whose dilated urinary tract was noted by fetal ultrasound examination. While the kidney may have sustained injury before birth, it would be secondary to VUR alone because fetal urine is sterile. Most of these infants will develop UTI within the first week of postnatal life, which permits pyelonephritis to develop in kidneys already damaged, perhaps, by VUR or obstruction. Any protection afforded these infants by prophylactic antibiotic treatment from birth seems warranted at least until the urinary tract can be investigated. The other group of children at risk of renal injury from UTI associated with VUR are siblings of patients with VUR. It is generally agreed, at present, that all siblings < 5 years of age should have a screening VCUG performed. This age limit has been set arbitrarily. The incidence of VUR in asymptomatic siblings decreases with age – just as it does in those with UTI – but may still be identified in children older than 5 years. VUR-associated renal injury which is manifested in successive generations may be enough reason to ignore the factor of age to assure each family member at risk is identified and protected as early as possible. Each newborn sibling of patients with VUR should be placed on antibiotic prophylaxis until the VCUG can be scheduled. While this practice may seem overly aggressive to some, it is a very conservative attitude for those who have observed a normal kidney damaged irreversibly by a single episode of pyelonephritis (Figure 3).

There will be no progress in reducing the incidence of RN without education. Clinicians who treat children must understand their unique problems associated with UTI and provide consistent treatment, evaluation and surveillance of patients with UTI through young adult life. Then, treating or consulting physicians must educate the patient or parents as to the importance of being compliant with treatment and the consequences that may be expected to follow even a single episode of UTI in a child. Finally, society, in general, needs to become aware of the morbidity associated with UTI. Because cystitis is common among sexually-active women – who often are mothers, the almost casual approach by physicians to the diagnosis and treatment of their bladder infections, conveys the message

that UTI in their children, their nieces and nephews and their neighbors' children can be treated casually as well.

Conclusion

Even as late as 1950, the only antibacterial agents available to treat acute pyelonephritis were sulfa compounds and streptomycin. Moreover, the treatment of usually severe, sometimes malignant hypertension associated with chronic atrophic pyelonephritis was limited to barbiturates and reserpine as recently as 1965. Therefore, a cardiorenal complication of pyelonephritis proved fatal for many individuals in the past and will continue to do so even today.

Unfortunately, the pendulum may be swinging away from a more aggressive pursuit of UTI, at least in children. The greatest clinical discouragement comes from very little progress being made over the past 30 years in our understanding of the pathophysiologic mechanisms in RN. The bulk of the medical literature to date represents, with few exceptions, case reports and experience with various surgical techniques rather than well designed, controlled clinical trials. The clinician treating the first UTI in a child does not always appreciate the potential risk of the infection, and is not the one who will provide the medical care later in life when the patient develops hypertension, heart disease, stroke or chronic renal insufficiency. In the absence of a much more consistent clinical care path, including long-term outcome measures, renal injury from pyelonephritis is unlikely to be eliminated entirely.

If pyelonephritis can be detected early in its course, treated effectively and further episodes of UTI prevented, the incidence of renal scarring may be reduced significantly. Moreover, if the patient with renal scarring is monitored closely to detect hypertension that is then treated effectively with an effective inhibitor of angiotensin, the complications attributable to systemic hypertension itself can be avoided. Once chronic renal insufficiency has developed, further deterioration of renal function in RN may be modified by dietary protein restriction and by inhibiting angiotensin – even in normotensive patients. Preliminary clinical data provide hope that development of ESRD in patients with RN can be delayed – if not avoided altogether. It is not yet time to accept defeat in our pursuit of understanding the mechanisms of renal injury from VUR-associated pyelonephritis. Too many patients are still at risk.

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