Kidney International, Vol. 58 (2000), pp. 1987–1995

Unilateral ureteral obstruction in neonatal rats leads to renal insufficiency in adulthood

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Unilateral ureteral obstruction in neonatal rats leads to renal insufficiency in adulthood.

Background. Although unilateral ureteropelvic junction obstruction is the most common cause of congenital obstructive nephropathy in infants and children, management remains controversial, and follow-up after pyeloplasty is generally limited to the pediatric ages. We have developed a model of temporary unilateral ureteral obstruction (UUO) in the neonatal rat: One month following the relief of five-day UUO, the glomerular filtration rate (GFR) of the postobstructed kidney was normal despite a 40% reduction in the number of glomeruli and residual vascular, glomerular, tubular, and interstitial injury.

Methods. To determine whether hyperfiltration and residual injury of remaining nephrons leads to progression of renal insufficiency in later life, 31 rats were sham operated or subjected to left UUO at one day of age, with relief of UUO five days later, and were studied at one year of age. GFR was measured by inulin clearance, and the number of glomeruli, tubular atrophy, glomerular sclerosis, and interstitial fibrosis were measured by histomorphometry in sham, obstructed (UUO), and intact opposite kidneys. Intrarenal macrophages and α-smooth muscle actin were identified by immunohistochemistry.

Results. Despite relief of UUO, ultimate growth of the postobstructed kidney was impaired. The number of glomeruli was reduced by 40%, and GFR was decreased by 80%. However, despite significant compensatory growth of the opposite kidney, there was no compensatory increase in GFR, and proteinuria was increased. Moreover, glomerular sclerosis, tubular atrophy, macrophage infiltration, and interstitial fibrosis were significantly increased not only in the postobstructed kidney, but also in the opposite kidney.

Conclusions. Although GFR is initially maintained following relief of five-day UUO in the neonatal rat, there is eventual profound loss of function of the postobstructed and opposite kidneys because of progressive tubulointerstitial and glomerular damage. These findings suggest that despite normal postoperative GFR in infancy, children undergoing pyeloplasty for ureteropelvic junction obstruction should be followed into adulthood. Elucidation of the cellular response to temporary UUO may lead to improved methods to assess renal growth, injury, and functional reserve in patients with congenital obstructive nephropathy.

Key words: growth, hydronephrosis, glomerular sclerosis, interstitial fibrosis, congenital obstructive nephropathy.

Received for publication February 10, 2000
and in revised form May 11, 2000
Accepted for publication May 30, 2000

Unilateral ureteropelvic junction obstruction is the most common cause of obstructive nephropathy in infants and children. However, management of these patients remains controversial, with some advocating early surgical repair [1, 2] and others favoring prolonged observation [3, 4]. Unfortunately, in most published series of infants undergoing pyeloplasty, follow-up is limited to the pediatric ages. The long-term implications of early intervention are therefore unknown. One of the problems in the management of these patients lies in the definition of significant congenital urinary tract obstruction. While Koff proposes that obstruction constitutes a lesion that if uncorrected leads to renal functional deterioration [5], Peters emphasizes that a critical lesion will impair normal functional renal maturation [6]. In a recent report, renal histology from children with ureteropelvic junction obstruction revealed interstitial inflammation and focal glomerular sclerosis, which are suggestive of hyperfiltration injury [7]. Moreover, most of the patients had proteinuria increased in the obstructed kidney compared with the contralateral kidney [7]. The authors conclude that hyperfiltration injury should be sought in patients with ureteropelvic junction obstruction and an intact contralateral kidney. Others have shown a correlation between interstitial changes and glomerular sclerosis on the one hand and differential renal function on the other [8].

Three factors limit the clinical decision-making process: (*1*) a need for an accurate measure of the glomerular filtration rate (GFR) of each kidney, (*2*) a need for a reliable marker of renal parenchymal injury, and (*3*) adaptation by the contralateral kidney, both in growth and function, in response to the changes in the obstructed kidney.

Clinical ureteropelvic junction obstruction is generally partial, possibly with intermittent complete obstruction. Whereas a model of partial unilateral ureteral obstruction (UUO) has been created by enveloping the ureter in the psoas muscle, the result is variable and leads to a very mild nonprogressive functional impairment [9, 10]. We have developed a model of temporary complete UUO in the neonatal rat that is highly reproducible, with

the severity of renal histologic changes being directly dependent on the duration of obstruction [11]. In addition, we have demonstrated that following one month of recovery, relief of obstruction decreases (but does not normalize) renal vascular, glomerular, tubular, and interstitial changes [12]. Thus, renal tubular proliferation is suppressed. Apoptosis is increased, and tubular expression of transforming growth factor-β1, clusterin, and vimentin is increased in the postobstructed kidney [12]. Moreover, renal interstitial collagen accumulation and interstitial fibroblast expression of α-smooth muscle actin are threefold greater than normal in the postobstructed kidney [12]. Although microvascular renin distribution is increased and there is a 40% reduction in the number of glomeruli, the GFR of the postobstructed kidney is entirely normal at one month of age [12]. We tested the following hypotheses: (*1*) nephron loss and residual injury persisting following the period of early postnatal obstruction leads to progressive renal damage, and (*2*) ongoing injury to the postobstructed kidney leads to impairment of the intact opposite kidney and renal insufficiency in adulthood.

METHODS

Twenty-one male Sprague-Dawley rats were sham operated or subjected to complete UUO under isoflurane anesthesia within the first day of life, with removal of the obstruction after five days, as described previously [11]. At one year of age, rats were anesthetized with intraperitoneal sodium pentobarbital (65 mg/kg), and 0.85% sodium chloride containing ^{3}H inulin was infused in a jugular vein at 3 mL/kg/hour as described previously [12]. The mean arterial blood pressure was measured using a cannula placed in a carotid artery. Ureters were exposed through a midline incision, and the diameter was measured at the midpoint of each ureter. Ureters were cannulated with polyethylene catheters for urine collection. Following a 45-minute equilibration period, three 20-minute urine collections were obtained. The GFR was calculated from the inulin clearance, and urine sodium and potassium content were measured by flame photometry. Urine protein concentration was determined by the amidoschwartz method.

In 10 additional rats, animals were sacrificed by sodium pentobarbital injection, and kidneys were removed for histologic study. Kidneys were fixed in 4% buffered formalin, embedded in paraffin, and sectioned at 4 μm as described previously [12]. The number of glomeruli per sagittal section was determined as previously reported [12]. Relative glomerular sclerosis and interstitial fibrosis were quantitated in kidney sections stained with Masson's trichrome stain. The glomerular tuft area and number of glomeruli containing segmental sclerosis were determined in each of 10 fields under ×450 magnification.

Table 1. Characteristics of rats

	Sham	UUO-relief
Body weight *g*	655 ± 17	647 ± 10
Blood pressure *mm Hg*	118 ± 2	118 ± 4
Hematocrit %	49.6 ± 0.01	47.2 ± 0.01[a]
Left ureteral diameter *mm*	1.04 ± 0.04	1.08 ± 0.05

[a] $P < 0.05$ vs. Sham

The distribution of interstitial collagen was determined in Masson-stained sections by a point-counting method as described previously [11]. Tubular atrophy was identified by thickened tubular basement membranes in periodic acid-Schiff (PAS)-stained sections [11]. The distribution of α-smooth muscle-containing fibroblasts and of ED-1–positive macrophages was determined by immunohistochemistry as described previously [12, 13].

Data are presented as mean ± SE. Comparisons between UUO and sham groups were made by Student's *t* test for unpaired data; comparisons between left and right kidneys were made using Student's *t* test for paired data; statistical significance was defined as $P < 0.05$.

RESULTS

As shown in Table 1, body weight did not differ between groups. As shown in Figure 1A, compared with sham-operated controls, the weight of the postobstructed kidney was decreased by 41%, whereas the weight of the contralateral kidney was increased by 42%, thereby maintaining a complete balance in renal mass. A similar effect was observed for dry kidney weight (Fig. 1B). Blood pressure was not affected by prior UUO, whereas hematocrit was significantly reduced in the experimental group (Table 1). GFR was reduced by over 80% in the postobstructed kidney, but was not increased in the contralateral kidney despite the compensatory renal growth (Fig. 1). Thus, although total renal mass was preserved, total renal function was reduced by 40% as a consequence of five-day UUO in the neonatal period.

As shown in Figure 2A, urine flow was not significantly reduced in the postobstructed kidney. Since left ureteral diameter was not different between experimental and control groups (Table 1), there was no residual obstruction in animals subjected to five-day UUO. However, urine flow from the intact kidney was double that of the postobstructed or control kidney (Fig. 2A). Urine sodium excretion by either kidney was not altered by UUO (Fig. 2B), but urine potassium excretion was reduced for the postobstructed kidney and increased from the intact opposite kidney (Fig. 2C). Urine total protein excretion was increased for the intact kidney, but not the postobstructed kidney (Fig. 2D).

As shown in Figure 3A, the number of glomeruli in right kidneys was significantly greater than in left kidneys. The relative number of glomeruli was reduced by

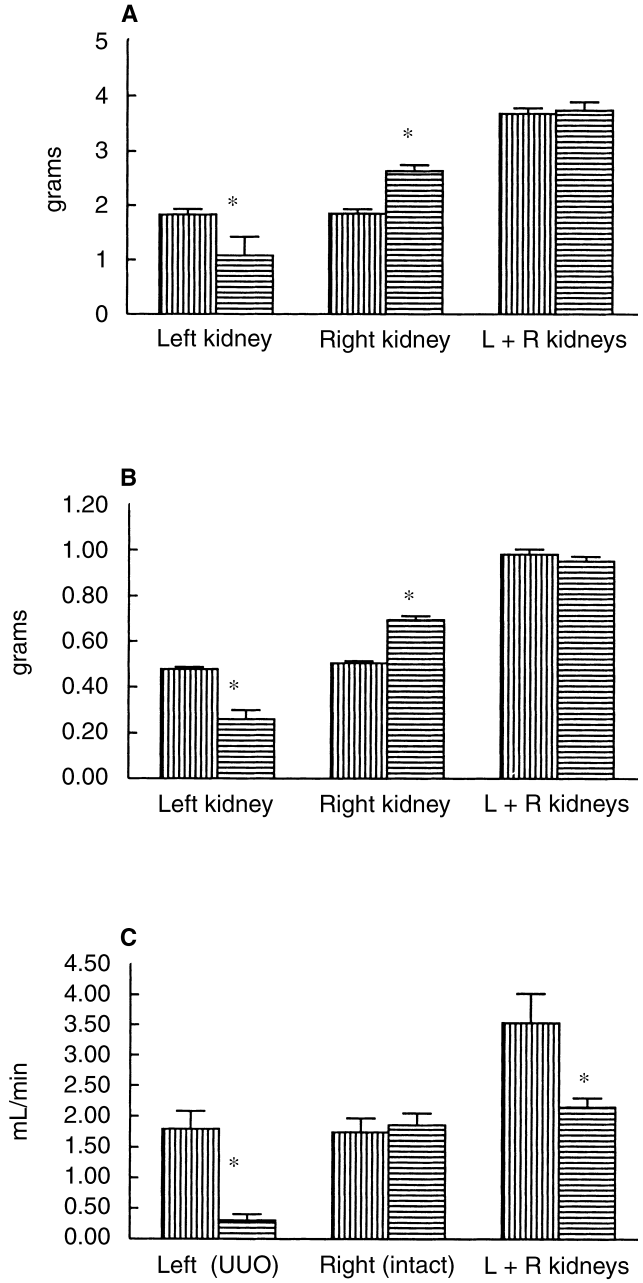

Fig. 1. Effects of neonatal unilateral ureteral obstruction (UUO) on renal mass and glomerular filtration rate (GFR). (*A*) Wet kidney weight. (*B*) Dry kidney weight. (*C*) GFR. Symbols are: (▥) sham; (▤) left UUO; *$P < 0.05$ vs. sham kidney(s).

40% in the postobstructed kidney ($P < 0.05$), while there was no effect of UUO on the number of glomeruli in the contralateral kidney (Fig. 3A). The mean glomerular diameter was not different between the two kidneys of sham-operated rats, whereas glomerular diameter was reduced by 23% in the postobstructed kidney (Fig. 3B). Focal glomerular sclerosis was present in over one third of glomeruli even in sham-operated rats, with the right kidney containing slightly more sclerotic glomeruli than the left (Fig. 3C). Glomerular sclerosis was significantly increased to over 50% in both postobstructed and contralateral kidneys (Figs. 3C and 4D–F).

Compared with sham-operated rats, tubular atrophy was increased by twofold to threefold in both postobstructed and contralateral kidneys (Figs. 4A–C and 5A). Compared with sham-operated rats, interstitial fibrosis was sixfold greater in postobstructed kidneys and twofold greater in contralateral kidneys (Figs. 4D–F and 5B). Immunoreactive interstitial α-smooth muscle actin was increased over 10-fold in the postobstructed kidney, but was not significantly increased in the contralateral kidneys (Figs. 5C and 6A–C). In contrast, interstitial macrophage infiltration, determined by ED-1–staining cells, was increased fivefold to ninefold in both postobstructed and contralateral kidneys (Figs. 5D and 6D–F).

DISCUSSION

A major finding in this study is that despite relief of UUO, the ultimate growth of the kidney subjected to only five-day obstruction in the neonatal period is impaired. Moreover, whereas we have shown previously that GFR of the postobstructed kidney is normal one month after relief of the obstruction, longer follow-up reveals a progressive reduction in function. In a preliminary report, we have found that three months following relief of five-day UUO in the neonatal rat, the GFR of the postobstructed kidney was reduced by 50% (abstract; Chevalier et al, *Pediatr Res* 47:445A, 2000). This indicates that the changes in the present study are due to the consequences of UUO rather than to aging alone. It is likely that one of the primary reasons for the deterioration in GFR is a 40% reduction in the number of nephrons that is present at the time of release of obstruction and persists after one month and one year [12].

In a previous study of rats subjected to seven days of complete UUO at three to four weeks of age, the postobstructed GFR accounted for only 25% of the total at follow-up 14 to 70 weeks later [14]. The results in this report differ from ours in that there was no progressive decrease in GFR over the follow-up interval of over a year. This may be explained by the older age of the animals at the time of obstruction, and the first interval of study after release of obstruction was three months rather than one month, as in our previous report [12, 14]. Of interest, when young rats were subjected to partial UUO by placing the ureter in a slit in the psoas muscle, there was no reduction in GFR at any of the follow-up points in all but one animal [14]. This is in agreement with reports by Josephson et al, who found little reduction in GFR in this model even during persistent obstruction [9, 10]. It would therefore appear that the degree of obstruction in this model of partial UUO is not sufficient to impair normal functional renal maturation, as defined by Peters [6]. We have previously described a model of

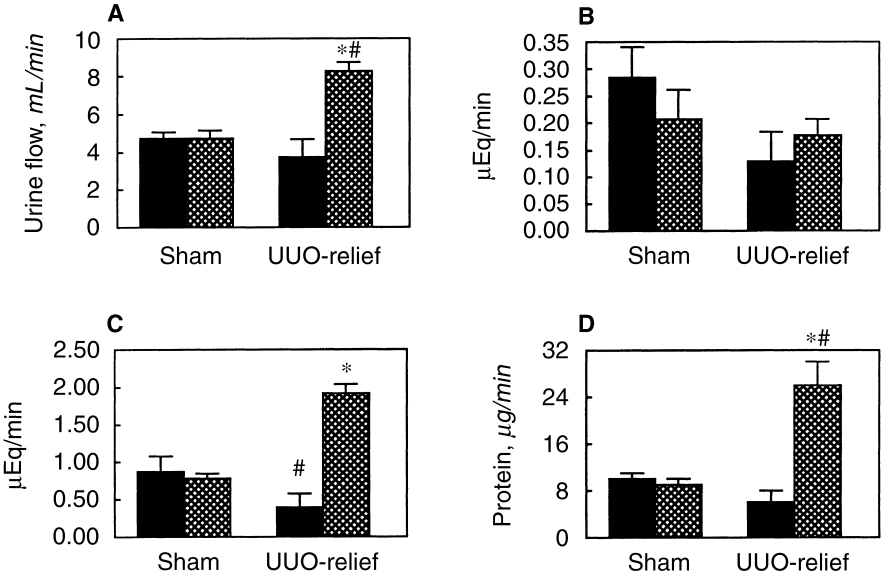

Fig. 2. Effects of neonatal UUO on renal function. (*A*) Urine flow rate. (*B*) Urine sodium excretion. (*C*) Urine potassium excretion. (*D*) Urine protein excretion. Symbols are: (■) left (UUO) kidney; (▨) right (intact kidney). $*P < 0.05$ vs. contralateral kidney; $\#P < 0.05$ vs. sham.

partial UUO in the neonatal guinea pig, a species in which nephrogenesis is complete before birth [15–17]. Similar to the results of the present study, despite relief of 10-day partial UUO in the neonatal guinea pig, renal growth and function of the postobstructed kidney are impaired eight weeks later [18]. An interesting finding in this model is a shift in angiotensin-dependent vasoconstriction from the obstructed kidney to the intact opposite kidney following the relief of obstruction [19]. The progressive injury to the intact kidney revealed in the present study may therefore be due in part to ongoing activation of the renin-angiotensin system. In this regard, chronic treatment of mice with angiotensin-converting enzyme prevents mesangial expansion resulting from normal aging [20]. A key issue in explaining the findings of the present study is the nature of the primary event leading to progression of renal insufficiency in adulthood. In this context, it is important to consider the potential contribution of glomeruli, tubules, and interstitium separately.

Effects on glomeruli

We have shown that chronic UUO in the neonatal rat results in a significant reduction in nephrons and early hyperfiltration by remaining nephrons in the postobstructed kidney [12]. Others have shown that unilateral nephrectomy in young rats leads to more severe glomerular sclerosis and proteinuria in young than adult rats [21]. Unilateral nephrectomy in the young rat has been shown to lead to decreased GFR two years later [22]. Moreover, the rate of fall in the GFR is accelerated if the animal receives a high-protein diet, which is associated also with increased proteinuria [22]. After 24 weeks, 10-day-old rats subjected to unilateral nephrectomy developed a significant increase in glomerular tuft volume and heavy proteinuria [23]. Close inspection of the glomeruli revealed changes in glomerular capillary and podocyte architecture, tuft adhesions to Bowman's capsule, and glomerular sclerosis [23]. These investigators suggest that the glomerular capillary dilations precede glomerular sclerosis [23]. In the present study, glomerular size was reduced in the postobstructed kidney, and despite a reduction in nephron number, there was no increase in glomerular size in the intact opposite kidney. We have reported previously that one month following relief of UUO, the glomerular tuft area is not changed in either postobstructed or intact opposite kidney [12]. However, if the obstruction is persistent throughout the first month of life, glomerular size is reduced in the obstructed kidney and increased in the opposite kidney [12]. These results indicate that glomerular growth is dependent not only on the total number of glomeruli in both kidneys, but also on the history of unilateral temporary obstructive nephron injury. In contrast, the development of glomerular sclerosis was similar in both kidneys of the experimental group, indicating that susceptibility to sclerosis is independent of the initial renal insult and is a late manifestation of progression.

Micropuncture measurements have shown that single-nephron GFR of superficial glomeruli of rats subjected to subtotal nephrectomy increases 240% in young animals, but only 60% in adults, while the increase in whole kidney GFR was similar in both age groups [24]. While focal glomerular sclerosis was far greater in young than adult animals, the lesions were located predominantly in juxtamedullary glomeruli, which had less hyperfiltration [24]. These results suggest that as in the present study, immature glomeruli are more susceptible to sclerosis independent of hemodynamic factors [24].

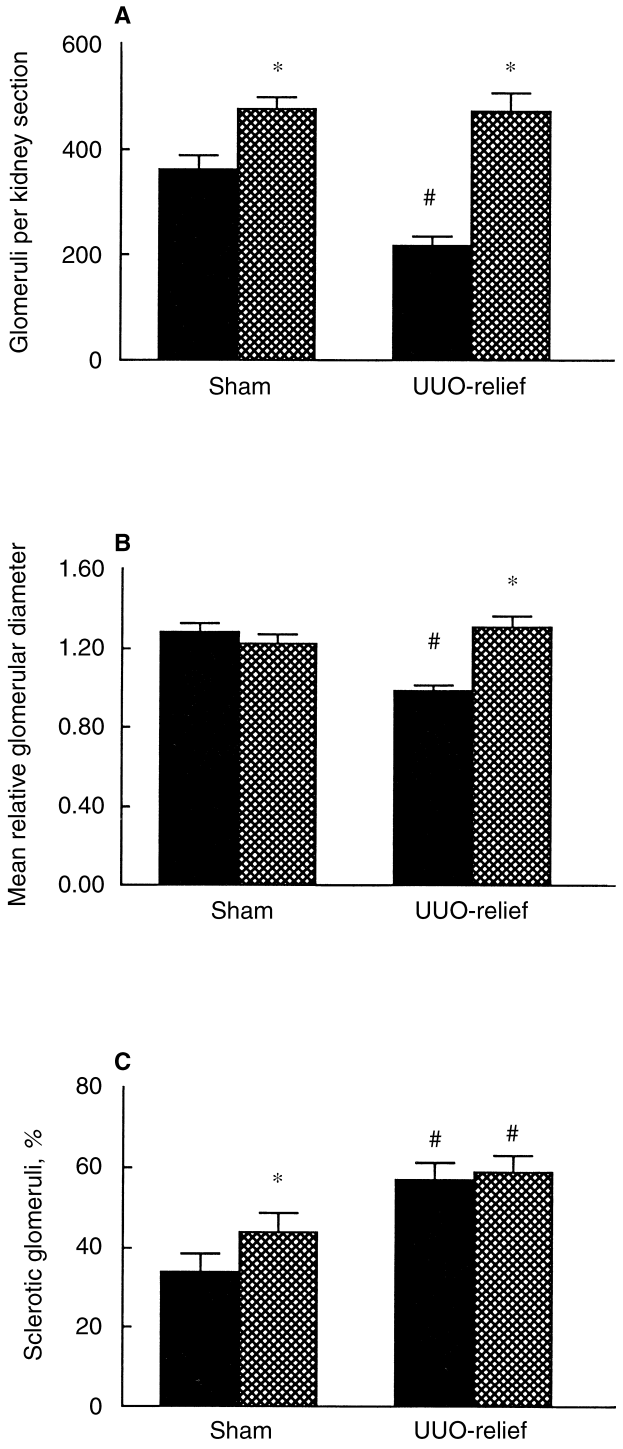

Fig. 3. Effects of neonatal UUO on glomeruli. (*A*) Relative number of glomeruli per kidney. (*B*) Relative glomerular diameter. (*C*) Fraction of glomeruli with segmental sclerosis. Symbols are: (■) left (UUO) kidney; (▨) right (intact kidney). $*P < 0.05$ vs. contralateral kidney; $\#P < 0.05$ vs. sham.

Brenner and Mackenzie have long cited the importance of nephron number as a primary determinant of the progression of renal disease, emphasizing more recently the greater impact of congenital nephron loss [25]. Although glomerular sclerosis was initially thought to be a direct result of hyperfiltration [26, 27], micropuncture studies have shown that increased proteinuria resulting from nephron loss actually comes from the hyperfiltering intact glomeruli rather than sclerotic glomeruli [28]. In the present study, urine protein excretion was increased from the intact kidney, but not from the postobstructed kidney. This is due entirely to the greater GFR of the intact kidney. The presence of proteinuria is presumably the result of glomerular injury present in both kidneys. Although we found a small but significantly greater number of glomeruli in the right compared with left kidneys of sham-operated rats, kidney weight, GFR, and protein excretion did not differ between the two kidneys. The cause of the difference in number of glomeruli in sham-operated animals is not clear and may be a characteristic of the strain of rats.

While hypertension aggravates the development of glomerular sclerosis [29], postobstructed rats in the present study were not hypertensive compared with sham-operated controls. Glomerular hyperfiltration and hypertension are not required for the development of glomerular sclerosis, and angiotensin-converting enzyme inhibition attenuates glomerular sclerosis independent of glomerular capillary pressure [30]. There is increasing appreciation of the nonhemodynamic factors mediating glomerular and interstitial fibrosis, as angiotensin II can induce fibrotic injury independent of hypertension [31], and stimulation of transforming growth factor-β1 has been implicated in the fibrogenic action of angiotensin [32]. Recent elegant molecular techniques have confirmed the role of this cytokine in the progression of renal disease [33]. As described in previous reports, progressive glomerular sclerosis is characteristic of the aging rat kidney [34, 35]. The significant additional glomerular sclerosis developing in both postobstructed and intact opposite kidneys in the present study likely relates to the unique susceptibility of immature glomeruli to loss of nephron number. The underlying mechanisms probably include altered production of growth factors and cytokines in the developing kidney. These include overexpression of renin and transforming growth factor-β1 and underexpression of epidermal growth factor [36]. In addition, maturational changes in angiotensin II receptor distribution may account for developmental changes in the renal cellular response to UUO [37, 38].

Effects on tubules

In contrast to primary glomerular injury, chronic UUO first alters tubular structure and function. We have shown that one month following relief of five-day UUO in the neonatal rat, tubular cell proliferation remains suppressed, and apoptosis persists [12]. Moreover, tubular production of epidermal growth factor remains suppressed [12], an effect that may be of primary importance

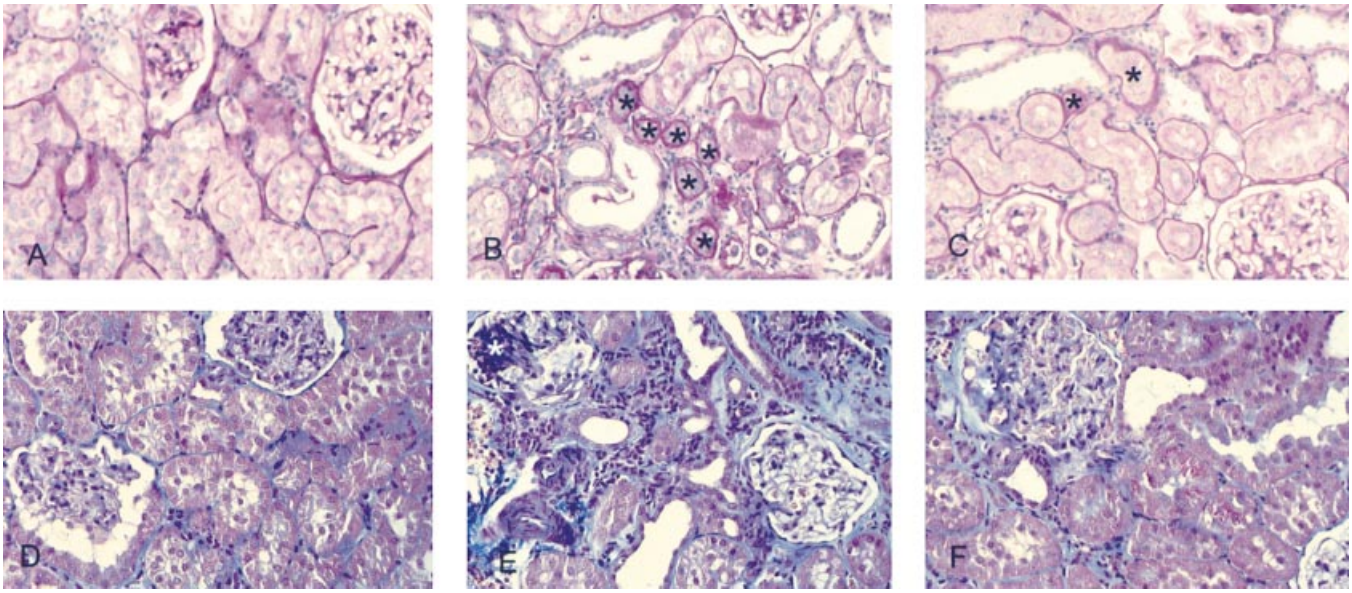

Fig. 4. Representative photomicrographs of kidneys showing periodic acid-Schiff (*A* to *C*) and Masson's trichrome staining (*D* to *F*). (*A*) Control kidney has few atrophic tubules. (*B*) Postobstructed kidney contains numerous atrophic tubules characterized by thickened tubular basement membranes (*). (*C*) Intact opposite kidney also contains atrophic tubules (*). (*D*) Control kidney showing mild interstitial collagen accumulation (blue staining). (*E*) Postobstructed kidney contains numerous glomeruli with focal glomerular sclerosis (*) as well as extensive interstitial collagen accumulation. (*F*) Intact opposite kidney also contains sclerotic glomeruli and interstitial collagen accumulation.

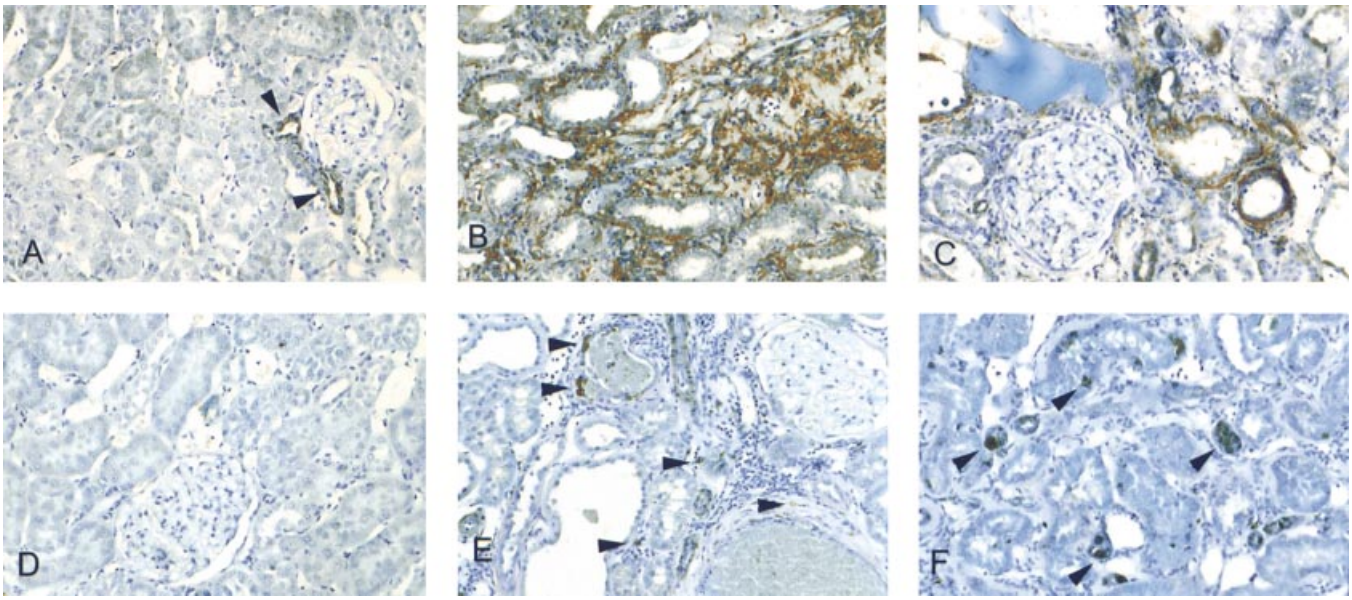

Fig. 6. Representative photomicrographs of kidneys showing immunoreactive α-smooth muscle actin (*A* to *C*) and macrophages (*D* to *F*). (*A*) Control kidney showing brown-staining immunoreactive α-smooth muscle actin afferent and efferent glomerular arterioles (arrowheads). (*B*) Postobstructed kidney showing extensive interstitial immunoreactive α-smooth muscle actin distribution. (*C*) Intact opposite kidney showing α-smooth muscle actin surrounding some of the tubules. (*D*) Control kidney showing virtually no macrophages. (*E* and *F*) Postobstructed and intact opposite kidneys contain numerous macrophages in the tubules and interstitium.

in view of our recent demonstration that exogenous administration of this growth factor can attenuate the tubular injury one month following relief of UUO [11]. In a recent study of the remnant kidney model, atubular glomeruli were found to be more prevalent than obsolescent glomeruli 25 weeks after ablation [39]. Although remnant glomeruli developed segmental sclerotic lesions with mild tubular atrophy, 20% of glomeruli were no longer connected to tubules, and these glomeruli were themselves atrophic [39]. These investigators conclude that tubular injury begins to cause loss of remnant nephron function early after ablation, when glomerular scle-

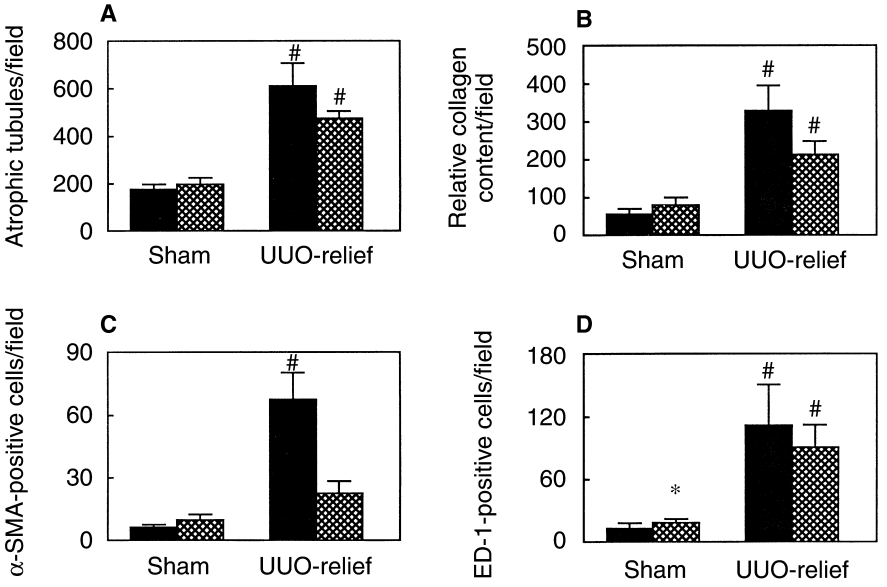

Fig. 5. Effects of neonatal UUO on renal tubules and interstitium. (*A*) Relative distribution of atrophic tubules. (*B*) Relative distribution of interstitial collagen. (*C*) Relative distribution of interstitial α-smooth muscle actin. (*D*) Relative distribution of ED-1–positive macrophages. Symbols are: (■) left (UUO) kidney; (▨) right (intact kidney). $*P < 0.05$ vs. contralateral kidney; $\#P < 0.05$ vs. sham.

rosis is only beginning [39]. Since tubular atrophy precedes glomerular sclerosis in this model, tubular injury is likely the proximate cause of the loss of function in remnant nephrons. This sequence also is likely to occur in the postobstructed kidney described in the present study. As there was no increase in the number of nephrons, the compensatory growth of the opposite kidney is a consequence of tubular growth, which can result from cellular proliferation or hypertrophy. We have found that three days following UUO in the neonatal rat, tubular cell proliferation is increased in the opposite kidney compared with the obstructed kidney [37]. As a result of deterioration of the postobstructed kidney, the contralateral kidney presumably develops progressive injury similar to the remnant kidney model.

Following 24-hour UUO, the conductances of sodium and potassium in the apical membrane and relative potassium conductance in the basolateral membrane are decreased in the obstructed and increased in the intact opposite kidney [40]. In the present study, despite the significant tubular changes in both postobstructed and intact opposite kidneys, sodium excretion was maintained by each kidney at a level not different from control animals. Moreover, potassium excretion was appropriately increased by the intact opposite kidney to compensate for the profound reduction in GFR of the postobstructed kidney.

Effects on interstitium

There is accumulating evidence that renal tubular cell injury leads to progressive injury to the surrounding interstitium, with growth factors and cytokines produced by epithelial cells stimulating fibroblasts and inflammatory cells in the interstitium [41]. In rats, interstitial fibrosis increases with advancing age, with a parallel increase in interstitial macrophages and α-smooth muscle actin-positive fibroblasts surrounding regenerating tubules [42]. Regenerating tubules may contribute to interstitial fibrosis by stimulating macrophage production of fibrogenic cytokines and by stimulating myofibroblast development through the release of growth factors [42, 43]. It is likely that the progression of interstitial changes in the postobstructed kidney follows a similar course, as evidenced by the increased infiltration of macrophages and α-smooth muscle actin-positive fibroblasts in the present study. Although interstitial collagen deposition and macrophage infiltration are similar in both kidneys of the experimental group, there is clearly an additive effect of temporary UUO on the progression of interstitial changes in the ipsilateral kidney, as interstitial α-smooth muscle actin remains elevated in the postobstructed but not in the contralateral kidney. Elucidation of this derangement in the interstitial environment one year after relief of only five-day UUO may provide insight into the pathogenesis of this disorder.

Clinical correlates

The renal histologic changes described in the present study are remarkably similar to those in patients with severe ureteropelvic junction obstruction. These include glomerular sclerosis and glomerular dropout, interstitial fibrosis with collagen deposition, interstitial cellular infiltrate, and tubular atrophy [7, 8, 44, 45]. A significant difference between the human and rodent kidney, however, is the increased glomerular sclerosis with normal aging present in the rat [34, 35]. It is likely that the deterioration in the intact opposite kidney in the present study is a consequence of prolonged hyperfiltration caused by the reduced nephron number in the postob-

structed kidney. In a preliminary study, we have found that three months following relief of five-day UUO in the neonatal rat, there is compensatory growth of the opposite kidney (abstract; Chevalier et al, *Pediatr Res* 47:445A, 2000). While the early loss of less than 50% of the total normal number of nephrons therefore leads to progressive injury to remaining nephrons in the rat, human nephrons may be less susceptible. Patients with unilateral renal agenesis can develop sclerosis of glomeruli in the single kidney and may be at increased risk of developing proteinuria and hypertension in adulthood [46, 47]. While there are no published data for humans indicating a "critical" number of nephrons necessary to prevent the development of sclerotic changes in the remaining glomeruli, based on these reports, it is likely that a reduction of less than 50% can also lead to progressive injury of remaining glomeruli in humans.

In comparing the findings of the present study with the available clinical approaches to infants with UUO, some dilemmas emerge. First, renal growth is generally followed by renal ultrasound measurements, while function is assessed by radionuclide scans. As shown earlier in the time course in our experimental model, whole kidney function can be deceptive in the context of a significant reduction in nephron number, if the remaining nephrons are hyperfiltering [12]. This phenomenon presumably explains a lack of correlation of differential renal function with histologic findings in some children with unilateral ureteropelvic junction obstruction [44]. Despite normal GFR in the postobstructed kidney after one month, the present study reveals that function declines by 80% a year later. Second, as shown in the present study, compensatory growth of the contralateral kidney may not maintain a compensatory increase in function. Thus, both ultrasonographic and radionuclide measurements performed in the patient with congenital obstructive nephropathy must be interpreted with caution. In addition, urinary tract infection may play a significant role in progression, particularly at younger ages [8]. In the future, improved markers will be developed to assess renal growth, injury, and functional capacity. While relief of UUO in the present study did not avert eventual renal structural and functional deterioration, we have reported previously that the severity of the changes at one month is directly dependent on the duration of obstruction before relief [11]. It is clear that prolonged follow-up of patients is necessary to evaluate the effects of surgical intervention: A primary benefit of early pyeloplasty is the prevention of progressive functional loss, as evidenced by the loss of function associated with a delayed diagnosis [48–50]. While the present study does not address the question of the timing of relief of obstruction on functional recovery, we have performed preliminary studies indicating that five-day UUO in the 15-day-old rat (at which time nephrogenesis is complete) results in poorer renal growth and function than relief in the immediate postnatal period (abstract; Chevalier et al, *Pediatr Res* 47:445A, 2000). This suggests that in the rat, as in the human, delayed relief of obstruction is deleterious.

In summary, we have shown that in a model of long-term recovery following relief of UUO in the neonatal rat, growth, and nephron number of the postobstructed kidney were reduced by 40%. In addition, there was an increase in interstitial α-smooth muscle actin distribution, and GFR was decreased by 80%. In the intact opposite kidney, the number of glomeruli and GFR were not increased, despite a 40% increase in growth. In both the postobstructed and contralateral kidneys, there was an increase in glomerular sclerosis, tubular atrophy, interstitial fibrosis, and macrophage infiltration. We conclude that although GFR is initially maintained following relief of UUO, eventually there is a profound loss of function of the postobstructed kidney because of progressive tubulointerstitial and glomerular damage. Adaptive growth of the contralateral kidney does not maintain compensatory function because of progressive tubulointerstitial and glomerular damage. In the future, early administration of growth factors, such as epidermal growth factor [13, 51] or insulin-like growth factor I [52], may provide a nonsurgical therapeutic alternative to enhancing ultimate renal function.

ACKNOWLEDGMENTS

This research was supported in part by National Institutes of Health (NIH) Research Center of Excellence in Pediatric Nephrology and Urology, DK44756 and DK52612; NIH O'Brien Center of Excellence in Nephrology and Urology, DK45179; and NIH Child Health Research Center, HD28810.

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