Abstract Congenital obstructive nephropathy remains one of the most-important causes of renal insufficiency in children. This review focuses on the unique interactions that result from urinary tract obstruction during the period of renal development in the neonatal rodent. Following unilateral ureteral obstruction (UUO), growth of the obstructed kidney is impaired and compensatory growth by the intact opposite kidney is related directly to the duration of obstruction. Development of the renal vasculature is delayed by UUO, and the activity of the intrarenal renin-angiotensin system is enhanced throughout the period of obstruction. Glomerular maturation is also delayed by UUO, and nephrogenesis is permanently impaired. The effects of UUO on the developing tubule are also profound, with a suppression of proliferation, stimulation of apoptosis, and the maintenance of an immature phenotype by tubular epithelial cells. Expression of tubular epidermal growth factor is suppressed and transforming growth factor-β1 and clusterin are increased. Maturation of interstitial fibroblasts is delayed, with progression of tubular atrophy and interstitial fibrosis resulting in part from continued activation of the renin-angiotensin system and oxygen radicals. The mechanisms underlying the embryological development of obstruction remain to be elucidated, and are not the subject of this review. In some cases of congenital obstructive nephropathy, renal maldevelopment (such as renal dysplasia) may be modulated by factors other than the primary obstruction to urine flow.

A variety of animal models have been created to investigate the pathophysiology of congenital obstructive nephropathy. The timing of renal development in the fetal sheep is similar to that in the human (nephrogenesis is completed before birth), and the size of the animal allows fetal manipulation. The guinea pig also completes nephrogenesis before birth, but its small size makes fetal manipulation difficult, necessitating neonatal studies. The opossum has been investigated, because fetal development in marsupials is largely extraterine, thereby allowing more-convenient access for surgical intervention. In the rat and mouse, most nephrons are formed postnatally, such that experimental urinary tract obstruction in the neonatal period is analogous to that arising in the human in midtrimester. While no one model is ideal, the present review will focus on studies performed in neonatal rodents, which have allowed elucidation of a number of the renal molecular and cellular consequences of urinary tract obstruction in early development. The experimental surgical obstruction of a single ureter (UUO) most closely parallels human ureteropelvic junction obstruction, which is characterized by hydrone-
phrrotic rather than dysplastic alterations in the renal parenchyma.

**Renal growth and counterbalance**

It has been over 50 years since Hinman [4] described compensatory growth of the intact opposite kidney following UUO in the rat. Chronic UUO in the fetal sheep impairs growth of the obstructed kidney and stimulates compensatory growth of the opposite kidney [5]. A similar response is noted in the guinea pig, in which the impairment of growth of the obstructed kidney and compensatory growth of the opposite kidney are inversely proportional to the age of the animal at the time of obstruction [6]. It would therefore appear that while the developing kidney is more susceptible to the effects of ipsilateral UUO, adaptive growth by the opposite kidney is also enhanced. We have shown recently in the neonatal rat that UUO impairs growth of the obstructed kidney and stimulates growth of the opposite kidney in direct proportion to the duration of obstruction [7]. Chronic UUO in the neonatal rat reduces DNA content of the obstructed kidney, and increases that of the intact opposite kidney [2]. Fetal compensatory renal growth has been demonstrated also in humans [8], and adaptive growth of the opposite kidney has been proposed as a sensitive index of the severity of obstruction in infants with ureteropelvic junction obstruction [9].

There are fundamental differences between normal and compensatory renal growth. SILber and Malvin [10] demonstrated that compensatory growth is reversible, whereas normal growth is not. However, we showed that contralateral nephrectomy in the neonatal guinea pig with partial UUO preserves renal growth (but less than a normal kidney remaining after contralateral nephrectomy) [11]. It is likely that growth of the single partially obstructed kidney in this case represents the net effects of slowed growth due to ipsilateral UUO and enhanced growth due to contralateral nephrectomy.

Recent studies indicate that whereas angiotensin acts as a growth factor in normal renal development [12], it is not necessary for compensatory renal growth in the neonatal mouse [13]. Compensatory renal growth in the neonate is primarily hyperplastic, whereas that in the adult is hypertrophic [14]. It is likely that insulin-like growth factor-1 plays a role in neonatal (but not adult) compensatory renal growth [15].

**Vascular development**

Fetal development of the renal vasculature is characterized by a diffuse distribution of renin along the length of the afferent arterioles and the interlobular arteries, with gradual localization to the juxtaglomerular region only in the early neonatal period [16]. Renal nerve activity is increased in early development [17], and is responsible at least in part for increased renal renin activity [18]. Interference with the activity of the renin-angiotensin system (RAS) during this critical period results in abnormal development of the renal vasculature [19, 20]. The RAS is normally highly active during early development, which contributes to a high renal vascular resistance in the fetus and neonate [21].

Chronic UUO in the neonatal rat results in a rapid and sustained increase in renal renin gene expression [2], and persistence of the fetal pattern of renin distribution [22]. In addition to increased immunolocalization of renin along the microvasculature, chronic UUO in the neonatal rat also increases the number of renin-secreting cells [23]. This is modulated by renal nerve activity [24]. Relief of obstruction reduces the extent of renin distribution along afferent arterioles of the neonatal rat (R.L. Chevalier, unpublished observations) and normalizes the renin content of the postobstructed neonatal guinea pig kidney [25]. Activation of the intrarenal RAS is therefore dynamically modulated by tubular fluid flow, intratubular pressure, or mechanical distention of the tubule.

Chronic UUO in the neonatal rat or guinea pig results in a marked increase in renal vascular resistance of the obstructed kidney and vasodilatation of the intact opposite kidney [11, 26]. Chronic UUO in the guinea pig increases angiotensin-dependent renal vasoconstriction in the obstructed kidney independent of renal nerves [27]. Vasodilatation of the opposite kidney may be mediated by renal nerves or contralateral renal renin suppression [2, 26]. Chronic inhibition of angiotensin converting enzyme in the neonatal guinea pig with chronic partial UUO prevents the reduction in blood flow to the obstructed kidney, indicating that angiotensin plays a major role in vasoconstriction [28]. However, renal blood flow is not normalized 10 days after relief of temporary UUO in the neonatal guinea pig, and enalapril has no salutary effect, suggesting that additional vasoconstrictors are involved in the postobstructed kidney [25]. However, angiotensin converting enzyme inhibition reduces vascular resistance of the intact opposite kidney, which may be the result of an increased sensitivity of angiotensin II receptors in response to relief of obstruction [25]. Thromboxanes have been shown to act as additional modulators of renal vascular resistance following ipsilateral [29, 30] or in rats with congenital spontaneous hydronephrosis [31]. Interestingly, vasodilator prostaglandins appear to contribute to vasodilatation of the intact opposite kidney [32].

The role of nitric oxide, a potent vasodilator, in modulation of renal vascular tone depends on whether ureteral obstruction is unilateral or bilateral. Following release of bilateral ureteral obstruction, renal nitric oxide synthase activity is decreased [33], whereas following UUO, nitric oxide synthase activity is increased, thereby counteracting the vasoconstrictor responses described above [34]. It appears that one of the salutary effects of enalapril on the obstructed kidney is a consequence of increased nitric oxide generation [35]. Following 24 h of UUO, glomerular soluble guanylate cyclase activity is increased (through angiotensin II stimulation), while