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# Pathophysiological changes in rat kidneys with partial ureteral obstruction since infancy

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**Pathophysiological changes in rat kidneys with partial ureteral obstruction since infancy.** A partial ureteral obstruction (PUO) was created in 5-day-old rats by implanting the left ureter in the psoas muscle. The surgical technique was modified to produce mild or severe hydronephrosis [Hn (m) and Hn (s)]. The rats were studied at ages between 45 and 65 days with regard to kidney weight, number of functioning glomeruli, mean arterial blood pressure (MAP), total glomerular filtration rate (GFR), nephron filtration rate (SNGFR), tubular free-flow pressure ($P_T$, and stop-flow pressure (SFP). Total GFR was determined after the release of obstruction. The other studies were performed in the obstructed state. Reference values were obtained from sham-operated and untouched control rats. The number of functioning nephrons was depressed 38% in Hn (m) and 73% in Hn (s). Total GFR was preserved in Hn (m) and depressed 54% in Hn (s). SNGFR in the remaining nephrons was significantly elevated in Hn (m) and normal in Hn (s). SFP was significantly elevated in Hn (s). The Hn (s) rats were hypertensive. The glomerular density was lower in the hydronephrotic than in the contralateral kidneys. This suggests a compensatory growth of the remaining nephrons in the Hn kidneys. We conclude that PUO present since infancy will either destroy the nephrons or elicit an adaptive response that will tend to preserve GFR.

**Modifications physiopathologiques des reins de rats avec obstruction urétérale partielle depuis l'enfance.** Une obstruction urétérale partielle (PUO) a été créée chez des rats de 5 jours en implantant l'uretère gauche dans le psoas. La technique chirurgicale a été modifiée pour produire une hydronéphrose modérée ou sévère [Hn(m) et Hn(s)]. Les rats ont été étudiés entre 45 et 65 jours d'âge en ce qui concerne le poids du rein, le nombre de glomérules fonctionnels, la pression artérielle moyenne (MAP), la filtration glomérulaire totale (GFR), la filtration néphronique (SNGFR), la pression tubulaire en flux libre ($P_T$), et la pression de stop-flow (SFP). GFR totale a été déterminée après arrêt de l'obstruction. Les autres études ont été effectuées pendant l'obstruction. Ces valeurs de référence ont été obtenues chez des rats ayant subi un simulacre d'intervention et chez des rats contrôles intacts. Le nombre de néphrons fonctionnels était diminué de 38% lors de Hn(m) et de 73% lors de Hn(s). GFR totale était préservée lors de Hn(m) et diminuée de 54% au cours de Hn(s). SNGFR des néphrons restants était significativement augmentée lors de Hn(m) et normale dans Hn(s). SFP était significativement élevée au cours de Hn(s). Les rats Hn(s) étaient hypertendus. La densité glomérulaire était moindre dans les reins hydronéphrotiques que dans les reins controlatéraux. Cela suggère une croissance compensatrice des néphrons restants dans les reins Hn. Nous concluons qu'une PUO présente depuis l'enfance soit détruira les néphrons, soit induira une réponse adaptative tendant à préserver GFR.

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The pathophysiology of obstructive hydronephrosis is usually studied with an experimental model [1–5] of kidneys that have acute or chronic complete ureteral obstruction (CUO). Although presently there are more unanswered clinical questions with regard to partial ureteral obstruction (PUO) than to CUO [6, 7], few experimental studies have been performed on kidneys with PUO [8–13].

It is generally agreed that CUO must be relieved as soon as possible, but opinions about surgery vary with regard to PUO, mainly because of uncertainty as to whether it causes significant and/or progressive renal damage.

PUO, unlike CUO, is generally congenital and the presumed renal damage in PUO has therefore been initiated during development of the kidney. With a few exceptions [14–16] ureteral obstruction has previously been created only in animals with mature kidneys.

The primary purpose of this study was to develop a suitable experimental model that simulates the commonest clinical types of PUO. This was accomplished by implanting one of the ureters into the psoas muscle in 5-day-old rats. The resulting renal damage was then evaluated by studying the rats between 45 and 65 days of age with regard to the number of remaining nephrons and the renal function, including the total GFR, nephron filtration rate, and tubular pressures.

## Methods

*Animals.* Sprague-Dawley (SD) rats (Eklund, Sweden) used in the experiments were operated on at 5 days of age, weaned at 18 days, and were thereafter kept under ordinary laboratory conditions and given a standard diet (R 3 Ewos, Sweden)-and water ad libitum. They were studied between 45 and 65 days of age with regard to the number of nephrons and renal function.

We used both untouched and sham-operated rats of the same breed and sex as the operated rats as control animals.

At the age of 45 days, the body weight of Eklund Sprague-Dawley rats averaged 188 ± 6 g; at the age of 65 days the body weight averaged 273 ± 22 g. The body weight averaged 227 ± 12 g in the severely hydronephrotic group, 238 ± 10 g in the moderately hydronephrotic group, 204 ± 8 g in the sham-operated group, and 250 ± 10 g in the control group. The relationship between body weight and age did not differ in the hydronephrotic and control groups. We have therefore chosen to relate kidney weight and values for filtration rate to body weight.

Spontaneous hydronephrosis was seldom seen in the rats used, but when it was, the rat exhibiting it was excluded from the series.

*Experimental model.* To produce a unilateral partial obstruction the psoas-implanting technique described in 1962 by Ulm and Miller [17] was adapted [14–15]. The rats were operated on at 5 days of age under light ether anesthesia. A left paramedian incision was made. The kidney was not touched and the dissection was reduced to a minimum. The ureter was freed from the peritoneum, placed in a prepared trough in the psoas muscle, and secured by an 8-0 nonabsorbable suture. By varying the tightness of the latter suture we were able to control the degree of hydronephrosis. The grouping into moderate hydronephrosis HN (m) and severe hydronephrosis Hn (s) was based on the degree of pelvic dilatation; it was made blindly after the completion of the study. The two types of hydronephrosis are illustrated in Figure 1.

Immediately after the 5-min operation, the infant rats were placed in a heated baby incubator with extra oxygen until they awakened. Then, each rat was returned to its mother. A few of the pups were not accepted by the mother. Apart from this instance, there was no immediate postoperative mortality. The total mortality in the series was less than 5%.

*Clearance studies.* The animals were anesthesized with Inactin (Byk, West Germany), 80 mg/kg i.p., and then tracheotomized. Polyethylene catheters (PE 50) were placed in one of the carotid arteries and in one of the femoral veins. A 5% polyfructosan (Loevosan Gesellschaft, West Germany) solution in isotonic saline was used as an indicator of the GFR. It was given in a prime dose of 10 $\mu$l/g of rat body weight and then as a continuous infusion at a rate of 10 $\mu$l/g of rat body weight per hour. After 45 to 90 min of continuous infusion the urine was collected for determination of total GFR during two 20-min periods by means of a polyethylene catheter with its tip placed in the renal pelvis proximal to the obstruction. The total GFR was thus determined in a postobstructive kidney. The longest periods of continuous infusion were used for the severely hydronephrotic rats. Only those rats were used where the values from periods 1 and 2 did not differ more than ± 20%. All control rats and approximately 80% of the hydronephrotic rats fulfilled this criterion. The GFR for each rat was calculated as the mean of two clearance determinations.

The clearance studies were performed in seven Hn (m) rats, seven Hn (s) rats, and five untouched rats, and five sham-operated rats.

*Micropuncture studies.* Because we wanted to study the intrarenal pressure in the kidney with intact obstruction, we did not catheterize the ureter and measure the GFR in those animals. The animals were prepared for micropuncture as described earlier in reports from this laboratory [18]. Polyfructosan was administered in the same manner as for the clearance studies. Random proximal convoluted tubules were punctured with a sharpened glass capillary having a tip diameter of 5 to 7 $\mu$m. The glass capillary was filled with sudan-stained mineral oil. Following the puncture, an oil drop 3 to 4 tubular diameters was injected into the tubule and allowed to pass the tip. Collection of tubular fluid was initiated by slight suction. The tubular fluid was then collected spontaneously for 60 to 100 sec. Several collections were made in each rat. The SNGFR was calculated as the mean of values obtained. The size of the collected tubular fluid sample was determined by transferring it to a microcap with a known and constant inner diameter. The length of the drop was measured under a stereomicroscope.

The hydrostatic pressure in the surface proximal convolutions was determined by the servocontrolled counterpressure measuring device, described by Widerhielm in 1964 [19] and modified by Inglietta, Pawula, and Tamphions [20] in 1970. This was connected to a sharpened glass capillary having a diameter of about 4 $\mu$m.

Following the measurement of the free-flow pressure in an early segment of the proximal tubule, a more distal segment was punctured by another glass capillary filled with mineral oil. The oil was injected until a new pressure level was established, which was considered to be the stop-flow pressure. In each study SNGFR as well as free- and stop-flow pressures were measured in at least three nephrons. The arterial blood pressure was monitored throughout the study. Toward the end of the study an arterial blood sample was withdrawn.

The concentration of polyfructosan in tubular fluid, blood, and urine samples was analyzed using the anthron method described by Hilger, Klümper, and Ullrich [21].

The micropuncture studies were performed in ten Hn (m) rats, seven Hn (s) rats, and six untouched rats.

*Glomerular counting.* To facilitate the determination of the number of functioning glomeruli, they were marked in vivo by injecting 1 to 2 ml of India ink in the descending aorta just above the renal arteries. A good marking was only obtained if the circulation was intact. We did therefore not use the rats that had been studied with regard to renal function, since those studies were terminated with a 1-ml blood sample. Immediately after the injection the kidneys were removed, freed from perirenal tissue and capsule and then weighed. The cortex was separated from the medulla and weighed. A large slice was then cut from the central part of the cortex. This cortical slice was weighed and digested with 70% HCl for 2 hr at room temperature. The digested material was then diluted 1:10 in isotonic saline and ten 50-$\mu$l samples were examined under a light microscope. Only those experiments were used where fragmented glomeruli were not found. The India ink-stained glomeruli in each sample were counted and the total number of glomeruli per milligrams of cortex was calculated from the mean values of the ten samples. This method is a modification of the method described by Damadian, Shwayri, and Bricker [22].

The number of glomeruli was measured in seven Hn (m) rats, seven Hn (s) rats, four untouched rats, and four sham-operated rats.

*Calculations.* Analyses of variance was used for statistical comparisons between the groups. Data are expressed as mean ± SEM. $P$ values less than 0.05 were considered significant.

## Results

Figure 2 depicts the total number of glomeruli in the right and left kidney in control rats and hydronephrotic rats. The values for the untouched control rats and the sham-operated rats did not differ. The total numbers of glomeruli/cortex in the contralateral kidney in Hn (m) and Hn (s) rats were not significantly different from control values. The total number of glomeruli/cortex was significantly depressed in both Hn (m)

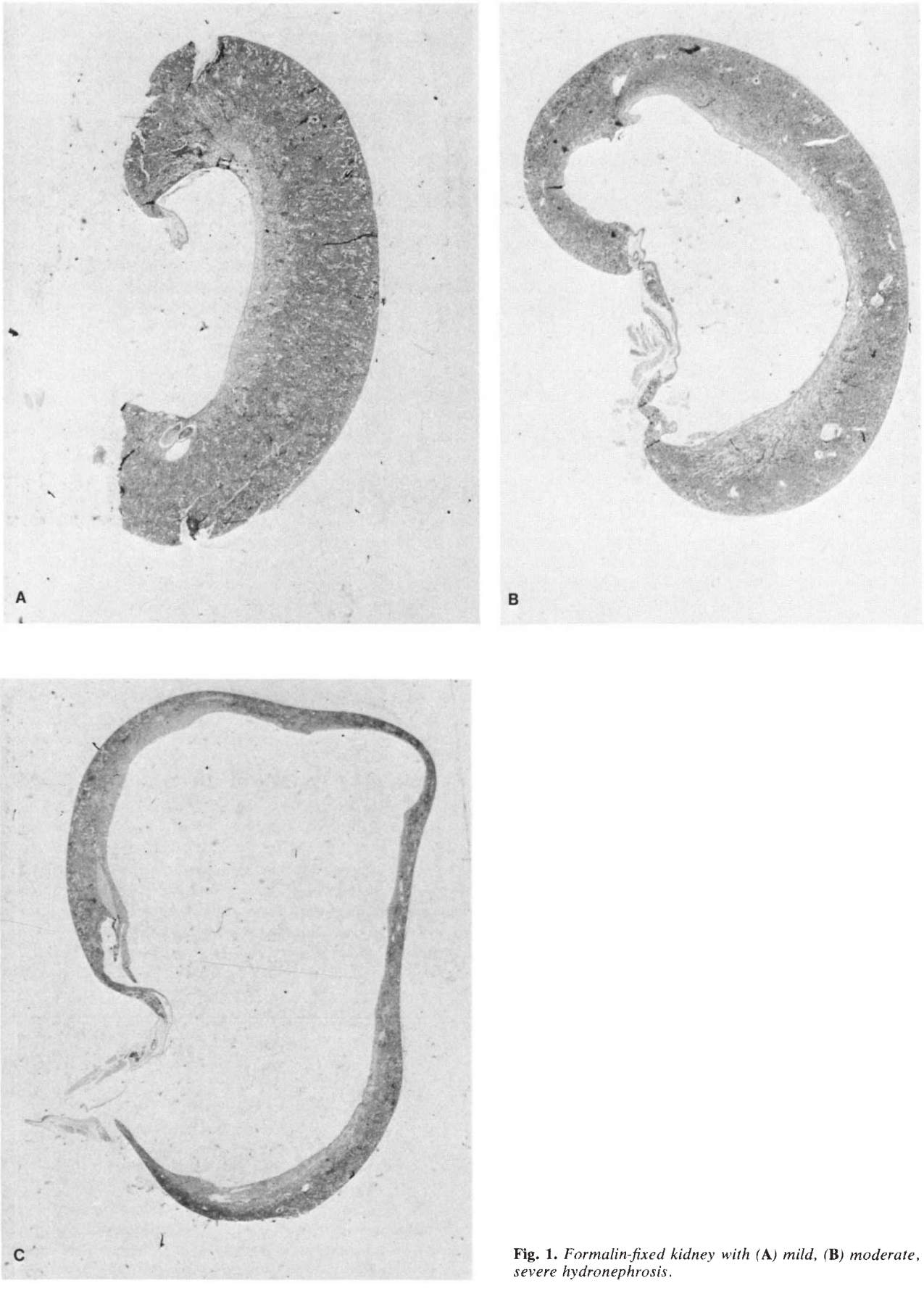


**Fig. 1.** *Formalin-fixed kidney with* (**A**) *mild,* (**B**) *moderate, and* (**C**) *severe hydronephrosis.*

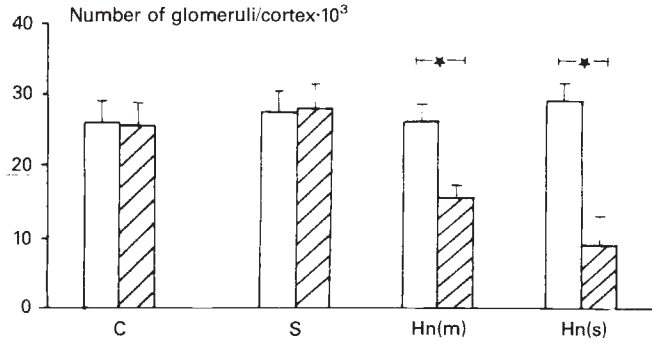


**Fig. 2.** *Number of glomeruli in right* (open columns) *and left* (hatched columns) *kidneys in untouched control rats, sham-operated rats, and rats with mild-to-moderate and severe hydronephrosis.* The *bars* indicate SEM. The *star* (*) denotes a significant difference between the right and left kidney. The number of rats in each study varied between 4 and 7.

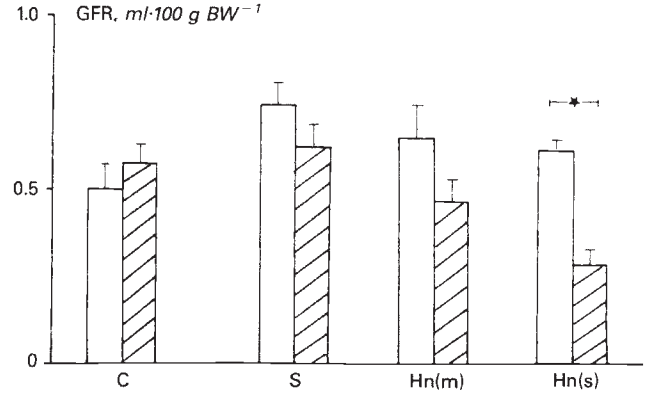


**Fig. 3.** *Total GFR in right* (open columns) *and left* (hatched columns) *kidneys in untouched control rats, sham-operated rats, and rats with mild-to-moderate and severe hydronephrosis.* The *bars* indicate SEM. The *star* (*) denotes a significant difference between the right and left kidney. The number of rats in each study varied between 4 and 7. Total GFR was recorded in the immediate postobstructive stage in the hydronephrotic kidneys.

**Table 1.** Cortical weight and glomerular density in hydronephrotic (Hn) and control rats

| Group | *N* | Cortical weight *g · 100 g body weight*$^{-1}$ | Glomerular density *g · mg cortex*$^{-1}$ |
|---|---|---|---|
| Hn (s) rats | 7 | | |
| Hn kidney | | 0.250 ± 0.056[a] | 11.3 ± 2.3[a] |
| Contralateral kidney | | 0.513 ± 0.042 | 25.6 ± 2.1 |
| Hn (m) rats | 7 | | |
| Hn kidney | | 0.409 ± 0.020 | 16.5 ± 0.6[a] |
| Contralateral kidney | | 0.460 ± 0.054 | 24.8 ± 1.3 |
| Sham-operated rats | 4 | | |
| Left kidney | | 0.434 ± 0.022 | 30.3 ± 2.0 |
| Untouched rats | 4 | | |
| Left kidney | | 0.397 ± 0.017 | 28.9 ± 2.1 |

[a] The values are significantly lower than those found in the contralateral kidney.

**Table 2.** Results from micropuncture studies[a]

| | Hn (s) | Hn (m) | Control kidney[b] |
|---|---|---|---|
| SNGFR, *nl · min*$^{-1}$ · *100 g body weight*$^{-1}$ | 11.2 ± 1.0 *N* = 7 | 17.3 ± 1.5[c] *N* = 10 | 11.4 ± 0.7 *N* = 6 |
| PT, *mm Hg* | 20.0 ± 2.9[c] *N* = 6 | 20.2 ± 5.5[c] *N* = 6 | 12.4 ± 1.5 *N* = 6 |
| SFP, *mm Hg* | 40.4 ± 5.0[c] *N* = 6 | 45.0 ± 10.8[c] *N* = 6 | 33.3 ± 3.9 *N* = 6 |
| MAP, *mm Hg* | 175 ± 8[c] *N* = 7 | 148 ± 6 *N* = 10 | 137 ± 6 *N* = 6 |

Abbreviations: Hn (s), severe hydronephrosis; Hn (m), mild hydronephrosis.

[a] Values are mean ± SEM.

[b] The values refer to the left kidney in untouched control rats.

[c] The values were significantly different from the control kidney; Hn (s) and Hn (n) kidneys did not differ significantly with regard to any of the parameters studied.

and Hn (s) kidneys in comparison to the contralateral kidneys (38 and 73% reduction, respectively).

Total GFR in the right and left kidney in control rats and hydronephrotic rats is illustrated in Figure 3. The values for untouched control rats and sham-operated rats did not differ. The GFR of the hydronephrotic kidney was recorded proximal to the obstruction. Total GFR was not significantly lower in the postobstructive Hn (m) kidney than in the contralateral kidney but was significantly depressed (54%) in the postobstructive Hn (s) kidney as compared to its contralateral kidney.

The density of the glomeruli in the cortical tissue was significantly lower in the hydronephrotic than in its contralateral kidney (Table 1) in both the Hn (s) and Hn (m) groups. Although the average values for glomerular density were lower in the contralateral kidneys of the Hn rats than in the kidneys of control rats, the differences were not significant. The weight of the cortex was significantly lower in the severely hydronephrotic kidney than in the contralateral kidney.

The results of the micropuncture studies are summarized in Table 2. These studies were performed with the obstruction intact to obtain representative pressure recordings. A few rats in each group were subjected only to SNGFR determinations. In Hn (m) the SNGFR was signficantly higher than in the control kidney. The SNGFR in the severely hydronephrotic kidney was not significantly different from the SNGFR in the control kidney. The variation coefficient for several SNGFR recordings in individual rats was in the same range, 10 to 25%, in control and Hn kidneys. All tubules that were inspected on the surface of both hydronephrotic and control kidneys were patent. The free-flow tubular pressure was significantly higher than in the control kidney in both Hn (m) and Hn (s). The stop-flow pressure was significantly higher in the Hn (s) kidney than in the control kidney. The mean arterial blood pressure (MAP) was significantly increased in Hn (s) rats.

## Discussion

A chronic unilateral partial ureteral obstruction is created by our experimental model. By creating this obstruction in infant

rats at 5 days of age, one can study the influence of obstruction on the developing renal parenchyma. This obstruction leads to a variable degree of hydronephrosis and renal damage. If the hydronephrosis is severe, it will also result in hypertension. A similar experimental model has been reported by Josephson et al [15] and Josephson [16], who created partial ureteral obstruction in infant rats that lead to mild hydronephrosis and found a reduction of the number of nephrons (19%) which was somewhat more pronounced than the reduction in GFR (10%). They did not record hypertension in those mildly hydronephrotic rats.

We found that obstructive hydronephrosis resulted in a decrease in the number of functioning nephrons and that the decrease was proportionate to the degree of hydronephrosis. If unilateral obstruction is created in adult animals, there will also be a decrease in the number of functioning nephrons [22, 23]. The loss of nephrons appears to be more pronounced when the obstruction dates from infancy. Damadian, Shwayri, and Bricker [22] studied the effects of 3 to 25 days total unilateral ureteral obstruction in five adult dogs and found that the number of glomeruli varied from almost normal to 50% fewer than normal, with an average decrease of 22%. We found a 38% reduction in the moderately hydronephrotic kidney and a 73% reduction in the severely hydronephrotic kidney.

In the severely hydronephrotic kidney the nephron density in the cortex was decreased significantly. This finding implies compensatory growth of primarily the tubular segments in the remaining nephrons in the hydronephrotic kidney.

Clearance determinations in kidneys with obstructive hydronephrosis are generally considered unreliable, because urine occupies a large dead space in the pelvis [24]. To minimize this error, we studied the rats under stable physiological conditions and took urine samples from a point above the obstruction. Our primary goal with this determination was to obtain an index of the reduction in the total GFR in kidneys with partial ureteral obstruction rather than to establish the effect to the obstruction as such on the total GFR. The reduction which we found in the total GFR in the hydroncphrotic kidneys can be attributed almost completely to the loss of nephrons. The filtration rate in the remaining functioning nephrons was either normal or increased. In Hn (m) the number of glomeruli was reduced, but there was a compensatory increase of the filtration rate in the remaining nephrons. The total GFR was almost preserved. To optimize the experimental conditions, three protocols were used. Total GFR was studied in postobstructive kidneys while SNGFR was determined in obstructed kidneys. There was evidence that total GFR will increase significantly after the obstruction is relieved [25]. For this reason we have refrained from comparing the absolute values measured for total GFR with the values for total GFR derived from the product of SNGFR and number of glomeruli. We can therefore not evaluate whether the average value for SNGFR in the superficial nephrons that we studied might be lower than the average value for SNGFR in the deeper nephrons. Studies in adult rats, however, have not shown any evidence for a redistribution of the filtering capacity from superficial to deep nephrons in moderately to severely hydronephrotic kidneys [26].

Our results suggest that when partial ureteral obstruction is present from infancy, the nephrons will either be destroyed or continue to function at a normal or a supernormal level. However, it is likely that the dynamics of glomerular filtration in the remaining functioning nephrons in the hydronephrotic kidney are different from those in a normal kidney. The tubular free-flow pressure which counteracts the driving force for filtration was significantly increased in Hn (m) as well as in Hn (s), suggesting that partial ureteral obstruction elicits adaptive changes of the determinants of the filtration rate. MAP is one determinant of GFR and was increased in Hn (s) but not in Hn (m). The recorded increase in stop-flow pressure in Hn implies that the hydrostatic pressure in the glomerular capillaries might be increased in this type of obstructive hydronephrosis. Ichikawa and Brenner [13] studied the dynamics of glomerular ultrafiltration in rats with mild partial ureteral obstruction. The obstruction was created in adult rats 30 days before the study. Using direct measurements, they found a significant increase in the hydrostatic pressure in glomerular capillaries.

In contrast to our finding of a normal or a supernormal SNGFR, Wilson [11] found a significant decrease in the SNGFR in rats with chronic partial ureteral obstruction. Dal Canton et al [3, 4] found a decrease in the SNGFR in rats with total unilateral ureteral obstruction. Ichikawa and Brenner [13] found that rats with mild partial ureteral obstruction had a normal SNGFR but a markedly increased hydrostatic pressure in the glomerular capillaries, which suggested a markedly reduced glomerular capillary ultrafiltration coefficient. All these studies were performed in rats in which the obstruction had been created in adulthood. Rats we used were operated on at the age of 5 days. In 5-day-old SD rats, s-shaped bodies are still found in the superficial cortex [27]. Complete structural maturation of the nephrons is reached between postnatal days 30 and 40 [28]. The fact that we found an increase in the SNGFR may therefore be explained by a greater capacity of the glomerular capillaries in the developing than in the adult kidney to adapt to an increased tubular pressure due to partial ureteral obstruction. It is well established that the response to nephron loss differs at least quantitatively in the developing and the adult kidney. Unilateral nephrectomy carried out in 5-day-old rats elicits a higher degree of compensatory hypertrophy and hyperfunction than unilateral nephrectomy in 40-day-old rats [27]. Although it has been suggested that a compensatory increase in the SNGFR will result in premature sclerosis of the glomerular capillaries [29], we did not evaluate this aspect because we examined the rats in early adulthood.

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