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Increased Renal Biosynthesis of Prostaglandin E_2 and Thromboxane B_2 in Human Congenital Obstructive Uropathy[1]

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ABSTRACT. Animal experiments have shown that after ureter obstruction hydronephrotic kidneys release increased amounts of prostaglandin E_2 (PGE_2) and thromboxane A_2 (TxA_2), suggesting that these prostanoids modify renal blood flow and excretory function in this model. To test the hypothesis that these mechanisms are also operative in congenital obstructive uropathy, we measured prostanoid excretion rates in 12 neonates and infants with congenital unilateral or bilateral hydronephrosis. Prostanoid determinations were performed by gas chromatography mass spectrometry. PGE_2 and thromboxane B_2 (TxB_2) (non-enzymatic metabolite of TxA_2) excretion exceeded the normal range in eight and 11 of 12 patients, respectively. Median PGE_2 excretion was 22, range 4–572 ng/h/1.73 m^2 (normal 3–16). Median TxB_2 excretion was 22, range 3–188 ng/h/1.73 m^2 (normal 3–7). No other renal prostanoids (prostaglandin $F_{2\alpha}$, 6-keto-prostaglandin $F_{1\alpha}$) or systemic prostanoid metabolites (PGE-M, 2,3-dinor-thromboxane B_2, 11-dehydro-thromboxane B_2, 2,3-dinor-6-keto-prostaglandin $F_{1\alpha}$) were consistently elevated. A second group of 12 neonates with congenital obstructive uropathy was followed sequentially. PGE_2 and thromboxane B_2 excretion rates increased even further after surgical decompression and gradually normalized during follow-up. There was a significant relationship between elevated FeNa and enhanced PGE_2 and TxB_2 excretion. These data suggest that endogenous renal formation of PGE_2 and TxA_2 is selectively stimulated in hydronephrotic kidneys in neonates and infants. PGE_2 and TxA_2 may be involved in modulating renal function in these infants. (*Pediatr Res* 27: 103–107, 1990)

Abbreviations

GFR, glomerular filtration rate
Fe_{Na}, fractional excretion of sodium
PGE_2, prostaglandin E_2
PGE-M, 7α-hydroxy-5,11-diketo-tetranor-prostane-1,16-dioic acid
TxA_2, thromboxane A_2
TxB_2, thromboxane B_2
Dinor-TxB_2, 2,3-dinor-thromboxane B_2
11-dehydro-TxB_2, 11-dehydro-thromboxane B_2
6-keto-$PGF_{1\alpha}$, 6-keto-prostaglandin $F_{1\alpha}$
Dinor-6-keto-$PGF_{1\alpha}$, 2,3-dinor-6-keto-prostaglandin $F_{1\alpha}$
$PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$

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Obstructive uropathies rank among the most frequent congenital malformations. There is abundant evidence from animal studies that eicosanoids modulate the perfusion and function of hydronephrotic kidneys (1–8). Using the model of unilateral ureter ligation, these studies have demonstrated that hydronephrotic kidneys elaborate increased amounts of vasodilatory PGE_2. Indomethacin, an inhibitor of prostaglandin synthesis, raised renal perfusion pressure of the hydronephrotic kidneys, suggesting that PGE_2 caused vasodilation of cortical resistance vessels under these conditions (1, 9). Formation of the potent vasoconstrictor prostanoid TxA_2 was also increased, and suppression of TxA_2 biosynthesis by specific synthase inhibitors augmented renal blood flow and excretory function, implicating TxA_2 as an important mediator of reduced kidney function in this model (5, 6). Renal macrophages have been identified as the cellular source of prostanoids in hydronephrotic kidneys (10, 11).

No studies of renal prostaglandin biosynthesis in patients with hydronephrosis have been published. We therefore selected neonates and young infants with congenital uni- and bilateral hydronephrosis, assuming that these patients closely resembled the experimental model in that secondary influences, *e.g.* recurrent infections, had not yet modified the pathophysiologic situation. We wanted to assess renal and systemic prostanoid formation noninvasively in these patients by measuring urinary excretion of primary prostanoids, their hydration products, and enzymatic metabolites (12). Although a tissue of origin cannot be ascribed definitively to a compound measured in urine, corroborative evidence has been obtained to indicate the predominant tissue source of most prostanoids. Thus, the primary prostaglandins, PGE_2 and $PGF_{2\alpha}$, are considered of renal origin (13). Whereas TxB_2 and 6-keto-$PGF_{1\alpha}$, the hydration products of TxA_2 and prostacyclin, respectively, are mainly derived from the kidney, they may partly reflect extrarenal formation of the parent compound in stimulated systems (12, 14, 15). The enzymatic prostanoid metabolites PGE-M, dinor-6-keto-$PGF_{1\alpha}$, dinor-TxB_2, and 11-dehydro-TxB_2 have been demonstrated to reflect essentially extrarenal, systemic biosynthesis (12, 13, 16, 17).

MATERIALS AND METHODS

Patients. We determined the urinary prostanoid profile in our first study group consisting of 12 neonates, infants, and children, 10 males and two females, ranging in age from 2 d to 4½ y (median 8 d). The levels and types of urinary obstruction were defined by the combined results of ultrasonography, intravenous urography, and voiding cystourethrography. Three patients suffered from unilateral obstruction, and one suffered from bilateral ureteropelvic junction obstruction. Three infants had ureteroves-

ical obstructions, two were unilateral and one was associated with complete bilateral duplication of the urinary collecting system. In five patients, a subvesical obstruction was demonstrated. None of the patients was consistently hypertensive. Urine was collected over a 12- to 24-h period, urine output was determined, and an aliquot was stored at -80°C until analysis for the primary prostanoids PGE_2, $PGF_{1\alpha}$, 6-keto-$PGF_{1\alpha}$, TxB_2, and the enzymatic metabolites PGE-M, dinor-6-keto-$PGF_{1\alpha}$, dinor-TxB_2, and 11-dehydro-TxB_2.

In a second study group, we serially determined the urinary excretion of PGE_2 and TxB_2 in relation to surgical intervention and indices of renal function. This group consisted of 12 neonates, 10 males and two females, with whom the diagnosis of obstructive uropathy had been suspected antenatally. The definite diagnosis was established by the procedures outlined above: ureteropelvic junction obstruction ($n = 7$, six unilateral and one bilateral), unilateral ureterovesical junction obstruction ($n = 1$), subvesical obstruction ($n = 4$). Depending on the site of obstruction, various surgical interventions were performed: uni- or bilateral nephrostomy, suprapubic catheter, pyeloplasty, and transurethral resection. In these patients, urine was collected serially from the 1st wk of life. Depending on the clinical situation, urine was collected by self-adhesive bags, suprapubic catheters, or nephrostomy tubes over a 12- to 24-h period. In cases of supravesical obstruction, separate collections of bladder urine by bags or suprapubic catheters and by nephrostomy tube could be performed. Urine output was determined and aliquots were stored for analysis of urinary prostanoids, sodium, and creatinine. As part of routine clinical care, blood was drawn during the collection periods for determination of serum sodium and creatinine. From these data, creatinine clearances and Fe_{Na} were calculated by standard formulas. The study protocol was approved by the Ethics Committee of University Children's Hospital, Heidelberg.

Methods. For the analysis of urinary prostanoids, only gas chromatographic mass spectrometric methods were used, which have previously been described. Following the principle of stable isotope dilution assays, endogenous prostanoids were quantitated against their respective tetradeuterated analogues that were added as internal standards at the beginning of the procedure. The determination of PGE_2, $PGF_{2\alpha}$, PGE-M, and 6-keto $PGF_1\alpha$ involved extraction by octadecyl silica and normal phase silica cartridges, purification by HPLC, derivatization to the methylester-methoxime-trimethylsilylethers, and quantitation by capillary gas chromatography mass spectrometry in the electron impact mode (14, 18). Dinor-6-keto-$PGF_{1\alpha}$ was purified by extraction and back extraction under alkaline and acidic conditions and thin-layer chromatography. The pentafluorobenzylester-methoxime-trimethylsilylether derivative was analyzed by gas chromatography mass spectrometry in the negative ion chemical ionization mode (19). Dinor-TxB_2 and TxB_2 were extracted chemoselectively by phenylboronic acid columns, purified by thin-layer chromatography and derivatized, and quantitated in analogy to dinor-6-keto-$PGF_{1\alpha}$ (20). 11-dehydro-TxB_2 was extracted from urine by octadecyl silica cartridges, purified by thin-layer chromatography, and analyzed as the pentafluorobenzylester-trimethylsilylether by gas chromatography-tandem mass spectrometry as described previously (21). Prostanoid excretion rates were expressed as ng/h/1,73 m^2 using Haycock's ht-wt formula for determination of body surface area (22). The normal range (10_{th}-90_{th} percentile) of prostanoid excretion was defined in 25 healthy neonates and infants using the methods previously described. Analyses of sodium and creatinine in serum and urine were performed by routine laboratory methods.

To avoid assumptions regarding distribution of data, groups were compared by Wilcoxon's rank sum test. The relationship between prostanoid excretion and renal function was examined by linear regression analysis. $p < 0.05$ was accepted as statistically significant.

RESULTS

The urinary prostanoid profile in 12 neonates and infants (first study group) with congenital unilateral and bilateral obstructive uropathy is illustrated in Figure 1. PGE_2 excretion exceeded the normal range in eight patients and TxB_2 excretion exceeded the normal range in 11 of 12 patients in this study group. Excretion rates tended to be higher in bilateral disease, although this difference did not reach statistical significance. The other two renal prostanoids $PGF_{2\alpha}$ and 6-keto-$PGF_{1\alpha}$ and the systemic prostanoid metabolites PGE-M, dinor-TxB_2, 11-dehydro-TxB_2, and dinor-6-keto-$PGF_{1\alpha}$, were excreted in similar amounts in patients and in controls. Although individual values were outside the normal range, the medians of the whole study group were not.

Urinary excretion of PGE_2 and TxB_2 and renal function was sequentially monitored in 12 patients (second study group) in relation to surgical decompression of the obstructed urinary tract. Figure 2 illustrates the course of a neonate with bilateral ureteropelvic junction obstruction in whom bilateral nephrostomies were performed on the 6th postnatal d allowing collection of urine from the nephrostomy tubes in addition to bladder urine. Excretion of PGE_2 was initially increased, rose dramatically after decompression, and gradually declined toward normal values.

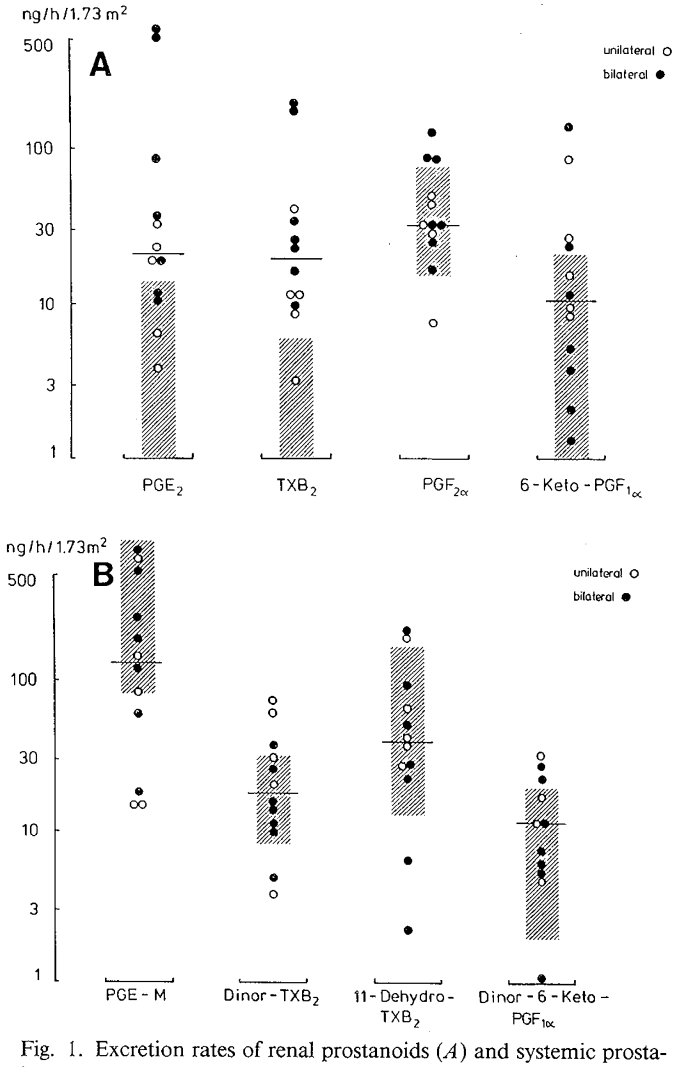

Fig. 1. Excretion rates of renal prostanoids (*A*) and systemic prostanoid metabolites (*B*) in 12 neonates and infants with congenital obstructive uropathy. Individual patients are represented by *open* (unilateral disease) and *closed circles* (bilateral obstruction), and the medians for the whole study group are represented by *horizontal lines*. The *hatched bars* indicate the normal excretion rates (10th to 90th percentile).

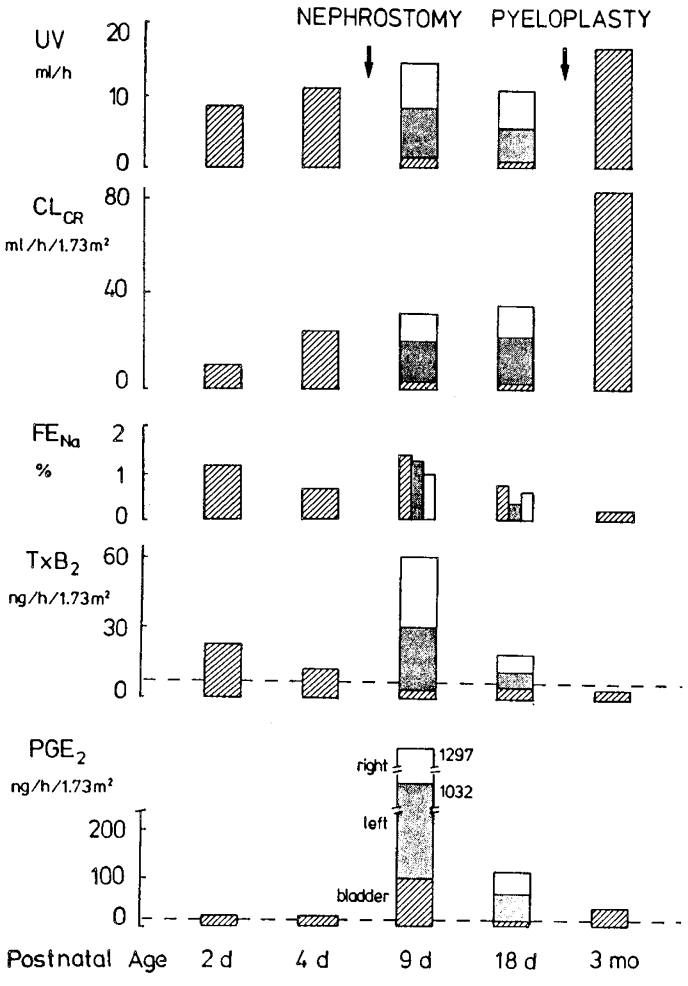

Fig. 2. Time course of urine output (*UV*), creatinine clearance (Cl_{Cr}), Fe_{Na}, and excretion rates of PGE_2 and TxB_2 in a patient with bilateral ureteropelvic junction obstruction. After bilateral nephrostomy, urine could be collected separately from the bladder (*hatched bars*), the left (*shaded bars*) and right (*open bars*) nephrostomy tubes. The *broken lines* indicate the upper limits of normal prostanoid excretion.

The same pattern, albeit quantitatively less, was evident for TxB_2 excretion. Fe_{Na}, initially elevated, normalized after decompression and corrective surgery. Creatinine clearances and urine output increased in the usual postnatal fashion.

The course of PGE_2 and TxB_2 excretion after surgical decompression is summarized in Figure 3 for study group 2. PGE_2 excretion rose in all patients after surgery and returned toward normal values at the last follow-up study. The duration of follow-up ranged from 2 to 99 d (median 42 d). With few exceptions, TxB_2 excretion rates exhibited the same postoperative rise and persistent elevation at a minor level for up to several weeks or months.

To address the potential functional relevance of altered prostanoid excretion in obstructed kidneys, the relationship between PGE_2 and TxB_2 excretion and urine output, creatinine clearances, and Fe_{Na} were examined by linear regression analysis for the whole study group. However, none of these indices of renal function showed any significant relationship to PGE_2 and TxB_2, respectively. Large interindividual variations of prostanoid excretion and the normal postnatal changes of renal function, however, might have obscured such a relationship that, for example, was evident for PGE_2 and Fe_{Na} in the individual patients.

To eliminate these confounding factors, individual urine samples were categorized as to whether Fe_{Na} and creatinine clearances were or were not in the age-specific normal ranges derived from the literature (23, 24). Then PGE_2 and TxB_2 excretion rates were compared in urine samples with normal and abnormal indices of renal function (Table 1) PGE_2 and, to a lesser degree, TxB_2 excretion, was higher in samples of pathologically elevated Fe_{Na}. However, prostanoid excretion rates did not discriminate between normal and abnormally reduced creatinine clearances.

DISCUSSION

This study was designed to evaluate the prostanoid system in neonates and infants with congenital obstructive uropathy. Excretion rates of PGE_2 and TxB_2 were selectively elevated in these patients. Normal excretion of the systemic metabolites of PGE_2 and TxA_2 (PGE-M, dinor-TxB_2 ,and 11-dehydro-TxB_2, respectively) and the rise of prostanoid excretion after surgical decompression, support the assumption that increased urinary PGE_2 and TxB_2 were derived from the obstructed kidneys. In addition, two arguments suggest that enhanced excretion of these prostanoids represents increased renal production of PGE_2 and TxA_2, the active precursor of TxB_2. First, excretion rates of PGE_2 and TxB_2 did not correlate with urine outputs excluding alterations in urine flow as a source of the increment. Second, augmented urinary prostanoids persisted for several weeks after surgical decompression. The cause of the elevation of PGE_2 and $Tx8_2$ excretion after surgical relief of obstruction remains speculative. Whereas a mere wash-out phenomenon seems unlikely (17), postobstructive diuresis may have unmasked increased prostanoid biosynthesis that was not reflected in the urine during obstruction. Improved perfusion of the kidney, and the medulla in particular, might be another explanation. Enhanced biosynthesis of PGE_2 and TxA_2 was selective in that excretion of the other prostanoids ($PGF_{2\alpha}$, 6-keto-$PGF_{1\alpha}$, PGE-M, dinor-TxB_2, 11-dehydro-TxB_2, and dinor-6-keto-$PGF_{1\alpha}$) did not differ from the normal range.

Enhanced biosynthesis of PGE_2 and TxB_2 in congenital obstructive uropathy agrees well with the results obtained in animal studies. Using the model of isolated perfused rabbit kidneys with ureteral obstruction, several authors have demonstrated increased PGE_2 basal production of PGE_2 that was further accentuated upon stimulation with bradykinin, angiotensin II, norepinephrin, and N-formyl-methionyl-leucyl-phenylalanine (1, 2, 6, 7). Increased production has also been shown in isolated medullary collecting ducts after ureteral ligation in rats (8). Moreover, experimental hydronephrosis in rabbits and rats causes increased TxA_2 biosynthesis that has been demonstrated by isolated perfusion (2, 5–7) and by increased urinary TxB_2 (11). Presumably, TxA_2 is synthesized by macrophages invading the kidney after ureteral ligation (10, 11). Notwithstanding the different experimental approach, identical alteration of PGE_2 and TxA_2 biosynthesis appear to be present in neonates and infants with hydronephrosis as evidenced by the data obtained in our study.

The pathophysiologic relevance of increased PGE_2 and TxA_2 production in hydronephrotic kidneys has been investigated in experimental animals by non-steroidal antiinflammatory drugs, such as indomethacin and aspirin, that inhibit biosynthesis of all prostanoids, and by selective inhibitors of thromboxane production, such as imidazole and its derivatives (4–7). Both the vasodilator PGE_2 and the vasoconstrictor TxA_2 seem to be involved in the modulation of renal blood flow and glomerular filtration rate (1, 4, 5, 6, 9). TxA_2, in particular, appears to diminish renal perfusion and glomerular filtration in hydronephrotic kidneys (4–7, 11, 25). At the tubular level, PGE_2 increases excretion of sodium and water (26–28). Indomethacin, an inhibitor of PGE_2 production, has been shown to reduce elevated fractional water and sodium excretion in hydronephrotic kidneys (8).

In our patients, no pharmacologic intervention was performed and no definitive conclusion regarding the relevance of enhanced

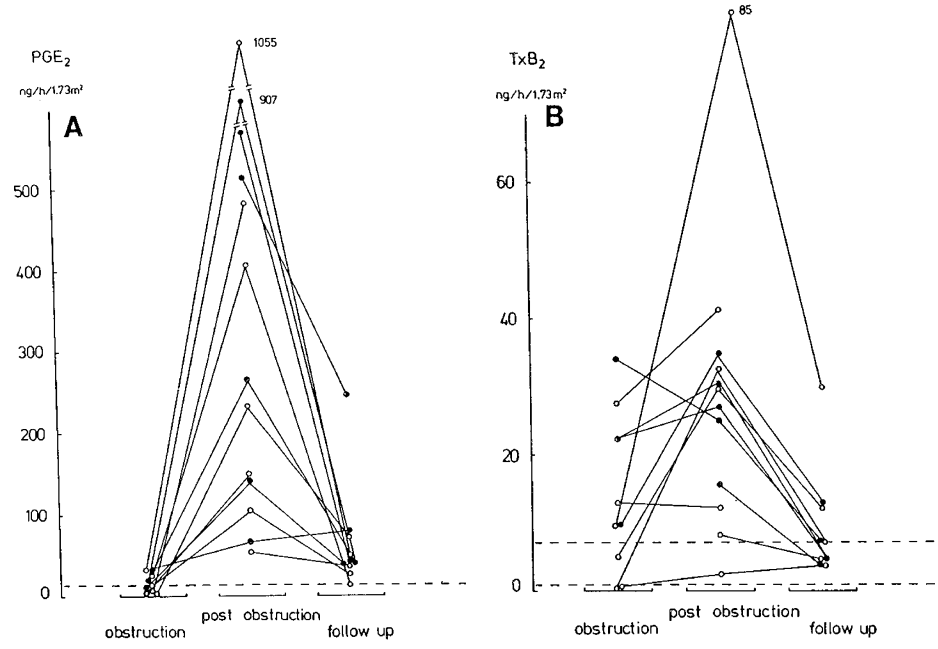

Fig. 3. Excretion rates of PGE_2 (*A*) and TxB_2 (*B*) in relation to surgical decompression in 12 neonates with unilateral (*open circles*) and bilateral (*closed circles*) congenital obstructive uropathy.

Table 1. *Relationship between PGE_2 and TxB_2 excretion rates (ng/h/1.73 m^2; median and range) and indices of renal function in sequential urine samples of 12 patients with congenital obstructive uropathy*

		PGE_2	TxB_2
Fe_{Na}	Normal	12.9 (0.9–72.2)	5.4 (0.1–29.7)
Fe_{Na}	↑	59.0 (1.3–1054.5)*	9.8 (0.8–188.4)*
Cl_{Cr}†	Normal	35.5 (1.4–572.3)	9.7 (2.5–188.4)
Cl_{Cr}	↓	63.4 (14.6–907.7)	8.5 (4.4–42.4)

* $p < 0.05$ compared to normal Fe_{Na}.
† Creatinine clearance.

PGE_2 and TxA_2 biosynthesis can be drawn. However, the association of increased PGE_2 production and elevated Fe_{Na} suggests that PGE_2 may be the mediator of natriuresis in congenital obstructive uropathy. From animal studies, one would have hypothesized a correlation between reduced GFR and TxB_2 excretion. We have used endogenous creatinine clearances as an estimate of GFR and were unable to detect such a relationship. However, several explanations are available. Determination of creatinine clearance in the neonatal period is fraught with potential sources of error, *e.g.* absence of steady state conditions that may have obscured an existing relationship. In addition, TxA_2 released in the glomeruli might be metabolized and/or reabsorbed during the tubular passage. However, a negative influence of increased TxA_2 production on GFR may have been offset by simultaneously enhanced PGE_2 biosynthesis. Furthermore, our patients differ from the animal model in that they may have sustained some degree of nephron loss. Thus, their changes of GFR and Fe_{Na} are not predominantly regulatory phenomena as in experimental animals, but may also reflect nephron loss. In view of experimental data in animals, increased production of PGE_2 and TxA_2 in neonates and infants with congenital obstructive uropathy may represent an important pathophysiologic factor rather than a mere epiphenomenon.

What is the potential clinical significance of these findings? Increased excretion of PGE_2 and TxB_2 might be an indicator of relevant hydronephrosis and help in the differential diagnosis of obstructive *versus* nonobstructive dilatation (29). Further studies would have to be initiated to test the hypothesis that might also solve the problem of individual values overlapping with the normal range. In terms of treatment, surgical correction of obstructive lesions is the most direct approach in congenital hydronephrosis. However, prospective studies would be needed to investigate the possibility that thromboxane synthesis inhibitors or receptor antagonist might improve perfusion and glomerular filtration and facilitate recovery of kidney function after corrective surgery of congenital obstructive uropathy.

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