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R H Harris, W E Yarger

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Research Article

To investigate the pathogenesis of post-obstructive diuresis, a state of functional "anuria" during ureteral obstruction was created in awake rats by (a) bilateral obstruction (BO); (b) unilateral obstruction and contralateral nephrectomy (UO-Nx); or (c) unilateral obstruction and continuous i.v. reinfusion of urine from the intact contralateral kidney (UO-reinf). These groups were compared with unilaterally obstructed (UO) and sham-operated control (sham) rats. After release of obstruction of 24 h duration, mean urine flows (V) and sodium excretion rates (UNaV) were significantly elevated above those of sham rats in BO, UO-Nx, and UO-reinf animals, but slightly decreased in UO rats. Glomerular filtration rates were comparably depressed in UO, BO, UO-Nx, and UO-reinf rats. These results suggest that post-obstructive diuresis is due to one or more circulating diuretic factors that are normally excreted in the urine, and which, when retained)as in BO or UO-Nx rats) or returned to the circulation (as in UO-reinf rats), exert a diuretic affect. In additional experiments, UO rats infused with urea exhibited post-obstructive diuresis, if extracellular volume contraction was prevented. This result suggests that urea may be an important diuretic factor in post-obstructive diuresis, but does not exclude possible roles for other humoral factors. The intact kidney of UO-reinf rats displayed a massive unilateral diuresis and natriuresis, further suggesting the presence of potent diuretic factors in the […]

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The Pathogenesis of Post-Obstructive Diuresis

THE ROLE OF CIRCULATING NATRIURETIC AND DIURETIC FACTORS, INCLUDING UREA

ROBERT H. HARRIS and WILLIAM E. YARGER

From the Division of Nephrology, Department of Medicine, Duke University Medical Center, and Durham Veterans Administration Hospital, Durham, North Carolina 27710

ABSTRACT To investigate the pathogenesis of post-obstructive diuresis, a state of functional "anuria" during ureteral obstruction was created in awake rats by (*a*) bilateral obstruction (BO); (*b*) unilateral obstruction and contralateral nephrectomy (UO-Nx); or (*c*) unilateral obstruction and continuous i.v. reinfusion of urine from the intact contralateral kidney (UO-reinf). These groups were compared with unilaterally obstructed (UO) and sham-operated control (sham) rats. After release of obstruction of 24 h duration, mean urine flows ($\dot{V}$) and sodium excretion rates ($U_{Na}V$) were significantly elevated above those of sham rats in BO, UO-Nx, and UO-reinf animals, but slightly decreased in UO rats. Glomerular filtration rates were comparably depressed in UO, BO, UO-Nx, and UO-reinf rats. These results suggest that post-obstructive diuresis is due to one or more circulating diuretic factors that are normally excreted in the urine, and which, when retained (as in BO or UO-Nx rats) or returned to the circulation (as in UO-reinf rats), exert a diuretic effect. In additional experiments, UO rats infused with urea exhibited post-obstructive diuresis, if extracellular volume contraction was prevented. This result suggests that urea may be an important diuretic factor in post-obstructive diuresis, but does not exclude possible roles for other humoral factors.

The intact kidney of UO-reinf rats displayed a massive unilateral diuresis and natriuresis, further suggesting the presence of potent diuretic factors in the urine. A marked increase in the fractional excretion of glomerular filtrate ($\dot{V}$/GFR) by the intact kidney suggests that this diuresis may be attributable, in part, to impaired proximal reabsorption.

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INTRODUCTION

The pathogenesis of post-obstructive diuresis, a syndrome in which an exaggerated and inappropriate excretion of water and electrolytes follows release of urinary tract obstruction, is not completely clear. In rats, post-obstructive diuresis occurs after the release of bilateral ureteral obstruction of 24 h duration (1–3), but not after release of unilateral obstruction in the presence of an intact contralateral kidney (1, 4, 5). Glomerular filtration rate (GFR)[1] has been shown to be comparably depressed in both models (1, 4). Hence, the appearance of a diuresis after the release of bilateral obstruction is probably not the result of hyperfiltration, but rather of impaired tubular reabsorption (1, 2).

The present study was undertaken to examine the possibility that diuresis after release of bilateral obstruction is a consequence of the complete lack of excretory function during obstruction, i.e., the retention of normally excreted urinary substances. The results indicate that post-obstructive diuresis may occur after release of unilateral obstruction, when renal excretory

[1] *Abbreviations used in this paper:* BO, bilateral ureteral obstruction; C_{Na}/GFR, excreted fraction of filtered sodium; C_{PAH}, clearance of PAH; GFR, glomerular filtration rate (inulin clearance); P_u, plasma urea concentration; PAH, para-aminohippuric acid; UO, unilateral ureteral obstruction; UO-Nx, UO with contralateral nephrectomy; UO-reinf, UO with i.v. reinfusion of urine from the contralateral kidney; UO-urea-anesth, UO with urea loading in anesthetized rats; UO-urea-deplete, UO with urea loading and no replacement of urinary losses; UO-urea-replete, UO with urea loading and replacement of urinary losses; U_KV, $U_{Na}V$, urinary potassium and sodium excretion rates; $\dot{V}$, urine flow rate; $\dot{V}$/GFR, fractional excretion of filtered water.

function during antecedent obstruction has been totally interrupted by either (*a*) removal of the contralateral kidney or (*b*) continuous intravenous reinfusion of urine from the intact contralateral kidney. The appearance of post-obstructive diuresis after functional anuria in these latter models suggests that the diuresis is the result of retention of one or more diuretic factors that are normally excreted. The results of additional experiments suggest that more than one factor is involved, and that urea is one of these factors.

In the unilaterally obstructed rats in which urine from the intact contralateral kidney was reinfused, the intact kidney displayed a massive unilateral diuresis and natriuresis, further suggesting the presence of diuretic and natriuretic factors in the urine.

METHODS

Experiments were performed in 37 male Sprague-Dawley rats weighing 250–350 g. 34 of the 37 animals, studied while awake and partially restrained, were prepared as follows. On the day before study, during brief anesthesia with ether or i.p. pentobarbital, polyethylene PE-50 catheters were implanted in a femoral artery and vein. In addition, in 26 of the 34 awake rats, a PE-50 catheter was implanted in the left ureter. The free ends of the catheters were brought externally. All rats received vasopressin in oil (Pitressin; Parke, Davis & Company, Detroit, Mich.), 0.5 U i.m. at the time of surgery. Each awake animal was then placed in a restraining cage consisting of cylindrically arranged metal bars that permitted limited mobility. An insulated electric heating coil, regulated by a rectal thermistor probe and temperature controller (Yellow Springs Instrument Co., Yellow Springs, Ohio) encircled the cage and prevented body temperature from falling below 37°C. In the 26 rats with left ureteral catheters, unilateral ureteral obstruction for 24 h was then produced by occluding the exposed ureteral catheter. Food and drinking water were withheld during the 24 h of obstruction. A continuous i.v. infusion of 5% dextrose in water, 2% of body wt/24 h, containing 5 mg/ml chloramphenicol was given throughout the period of obstruction. On the day of the study, obstruction of the left ureteral catheter was released, and renal function was examined by clearance techniques, Priming doses of [*carboxyl*-^{14}C]inulin and [*glycyl*-^{3}H]para-aminohippuric acid (PAH) were given i.v., followed by continuous infusion in Ringer's lactate at a rate of 0.021 ml/min. All rats received aqueous vasopressin 50 mU/kg per h in the infusion. Urine collections were begun 20–60 min after release of obstruction and continued for 2–3 h thereafter. Urine was collected in weighed containers for clearance periods lasting 15–40 min. Arterial blood was sampled at the midpoint of each urine collection, and arterial blood pressure was measured frequently throughout the experiment via the arterial catheter. At the end of the experiment, the rat was exsanguinated, and this blood was used to measure plasma urea concentration by an Autoanalyzer (Technicon Instruments Corp., Tarrytown, N. Y.). Urine volumes were determined by weighing. [^{14}C]Inulin and [^{3}H]PAH were measured by liquid scintillation techniques as previously described (4). Plasma and urine sodium and potassium concentrations were determined by flame photometry.

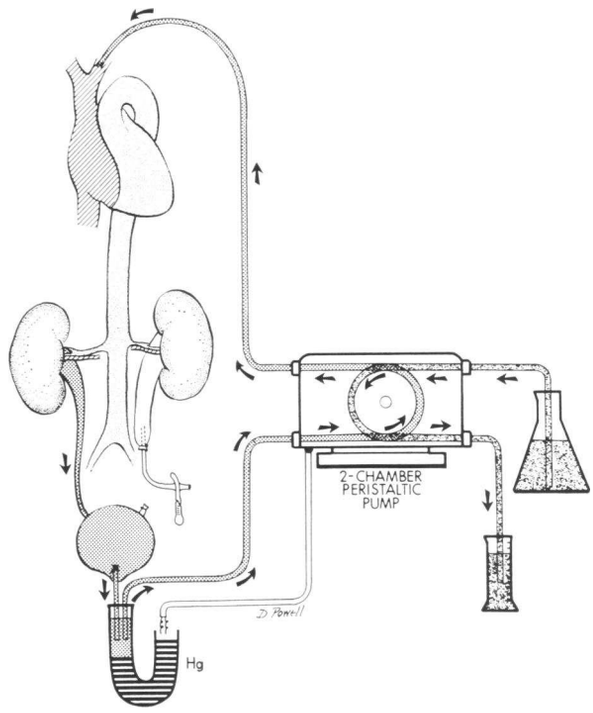


FIGURE 1 Schematic depiction of mechanism for continuously reinfusing urine from the unobstructed kidney i.v. in group V (UO-reinf) rats. See text for explanation.

The following experimental protocols were carried out:

Group I. Sham-operated controls (sham). 8 of the 34 awake rats were studied without ureteral cannulation or obstruction; instead, during antecedent anesthesia, a PE-60 catheter was implanted in the bladder and brought externally. Except for the absence of obstruction, these animals were studied as described above. Clearance values were divided by 2, and results for this group are expressed as the values per kidney.

Group II. Unilateral obstruction (UO). Eight rats were subjected to left UO as described above. In addition, a PE-60 catheter was implanted in the bladder and brought externally. During the 24 h of UO, the bladder catheter was allowed to drain freely. 1 h after the release of obstruction, clearance studies were performed on both kidneys for an additional 60–90 min. Immediately after these studies, these same eight animals were studied by an additional protocol (See UO-urea, below).

Group III. Bilateral obstruction (BO). Four rats had left UO. Simultaneously, the right ureter was ligated near the bladder and remained ligated throughout the entire study.

Group IV. UO with contralateral nephrectomy (UO-Nx). Four rats had left UO and simultaneous excision of the right kidney via a small flank incision.

Group V. UO with continuous i.v. reinfusion of urine from the contralateral kidney (UO-reinf). Six rats underwent left UO. Additionally, a PE-90 catheter was implanted in the bladder, brought externally, and connected to a servo-activated pump apparatus, as illustrated in Fig. 1. This apparatus continuously reinfused the urine from the unobstructed contralateral kidney into the rat i.v. throughout the 24 h of UO. The operation of this

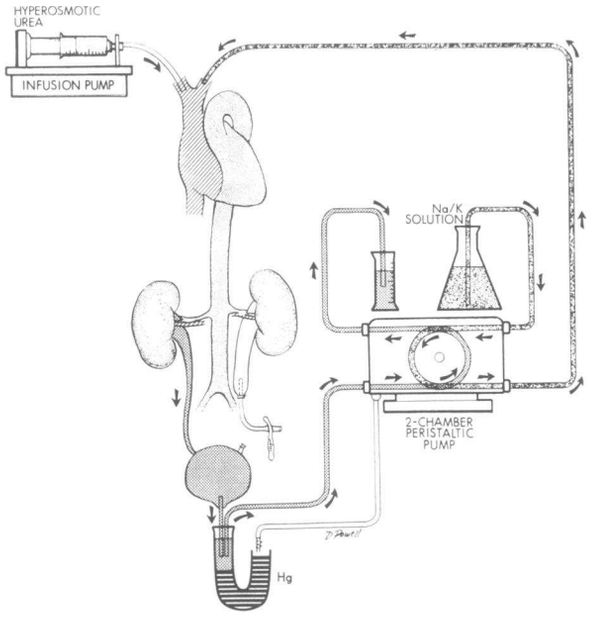


FIGURE 2 Schematic depiction of method for urea-loading and simultaneously replacing urinary losses of water, sodium and potassium from the unobstructed kidney i.v. in group VI (UO-urea-replete) rats. See text for explanation.

pump apparatus was as follows: urine from the bladder catheter was directed into a U-shaped glass tube (ID 5 mm) containing mercury, positioned below the rat so as to maintain a hydrostatic pressure of approximately -30 cm H_2O within the bladder. As the urine level rose in one side of the tube, the mercury level rose in the opposite side, closing an electric contact to activate, via an electrical relay (not depicted in Fig. 1), a peristaltic pump (Holter, Extracorporeal Medical Specialties, Inc., King of Prussia, Pa.) with two matched pumping chambers. Urine was withdrawn from the U-tube by one chamber and infused into the venous catheter. Thus, as urine was excreted by the unobstructed kidney, the pump was intermittently activated to immediately reinfuse the urine into the animal. While one pump chamber reinfused the urine, the other chamber was used to pump water into a measuring container. Since the two chambers delivered equal flow rates, the volume of water collected permitted continuous determination of urine flow rate (V) by the unobstructed kidney.

After 24 h, the obstruction was released, while reinfusion of urine from the unobstructed kidney was continued. Function of the previously obstructed kidney was studied as in the protocols described above. Simultaneously, function of the unobstructed kidney was studied by periodically interrupting the urine reinfusion for brief periods to permit collection of 0.1–0.2-ml urine samples. These withdrawals of urine were replaced by equivalent volumes of 0.9% saline.

UO with urea-loading (UO-urea)

Group VI. UO-urea with replacement of urinary losses (UO-urea-"replete"). Eight rats (four of which belonged to group II, above) had left ureteral obstruction and implantation of a PE-60 bladder catheter. These animals were given an i.v. infusion of hyperosmotic (30%) urea in 0.9% saline as a loading dose (volume infused 0.7% of body wt), followed by a sustaining infusion. This urea infusion was given approximately 3 h after release of obstruction in five rats, and before release in three rats. Simultaneously with urea infusion, urine from the unobstructed kidney was directed, via the bladder catheter, into a servoactivated pump apparatus, illustrated in Fig. 2. As in the urine reinfusion apparatus, the flow of urine into the U-tube activated a peristaltic pump with two matching chambers. As one chamber withdrew urine from the U-tube, the opposite chamber infused i.v. an equal volume of a NaCl and KCl solution into the rat. Sodium and potassium concentrations of bladder urine were measured at frequent intervals, and the concentrations of the infusion solution quickly adjusted to match those of the urine. Thus, as the unobstructed kidney excreted urine, the pump was intermittently activated to exactly replace urinary losses of water, sodium, and potassium. This apparatus, it should be noted, only replaced urine losses and should not be expected to produce extracellular fluid (ECF) volume expansion.

Group VII. UO-urea, urinary losses not replaced (UO-urea-"deplete"). Four rats (all of which belonged to group II, above) were given an i.v. infusion of hyperosmotic urea in saline, after release of obstruction. The urea solution was given as described above for group VI. However, urinary losses of fluid and electrolytes from the unobstructed kidney were not replaced.

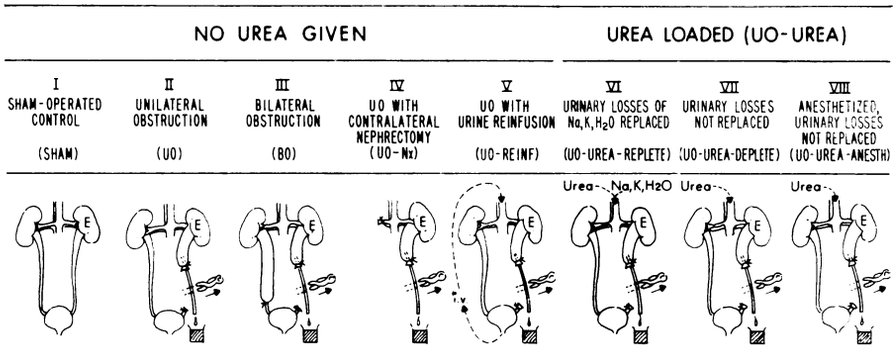
Group VIII. UO with urea-loading in anesthetized rats (UO-urea-anesth). In addition to the 31 rats described above, three rats were prepared as follows: On the day before study a small midline suprapublic incision was made during ether anesthesia. The left ureter was ligated near the bladder. All rats received 0.5 U vasopressin in oil i.m. After surgery, food was withheld, but drinking water was given ad libitum for 24 h. On the day of the study, the animals were anesthetized with Inactin (ethyl-[1-methyl-propyl]-malonyl-thio urea, sodium salt; Promonta, Hamburg, W. Germany) 100 mg/kg i.p., placed on a heated table, and tracheostomized. A femoral artery and vein were cannulated with PE-50. The abdomen was reopened, and a PE-50 catheter was inserted in the left ureter, above the ligature. Clearance studies were performed as described above. Hyperosmotic urea was given i.v. as described above for groups VI and VII, and urinary losses of fluid and electrolytes from the unobstructed kidney were not replaced.

Calculations. Statistics were calculated according to methods described by Steel and Torrie (6). Analysis of variance, with Duncan's multiple range test as modified by Kramer, and the Student t test were used as appropriate to compare group means. A probability value less than 0.05 was regarded as significant. Values are presented as means±1 SEM.

RESULTS

Experimental (obstructed) kidney

Urine flow (V). During 24 h of obstruction of the experimental (left) kidney, a state of fuctional anuria was produced in three groups, as shown in Fig. 3: group III, rats with BO; group IV, UO-Nx; and group V, UO-reinf. In these three groups, release of obstruc-



	I	II	III	IV	V	VI	VII	VIII
n	8	8	4	4	6	8	4	3
URINE FLOW ($\dot{V}$) $\mu l/min/kg$	22 ±4	16 ±3	199 ±17	272 ±44	130 ±20	208 ±19	76 ±15	13 ±2
GFR ml/min/kg	5.84 ±0.42	0.79 ±0.30	1.21 ±0.17	1.10 ±0.22	0.76 ±0.11	2.12 ±0.30	1.31 ±0.30	0.18 ±0.01
C_{PAH} ml/min/kg	15.2 ±1.5	3.6 ±1.2	4.9 ±1.0	4.8 ±1.3	3.4 ±0.8	11.2 ±1.5	7.5 ±1.5	0.8 ±0.1
$U_{Na}V$ $\mu eq/min/kg$	4.9 ±1.6	2.0 ±0.5	19.0 ±2.2	26.9 ±2.8	12.9 ±2.6	19.0 ±2.5	5.6 ±1.7	1.2 ±0.2
C_{Na}/GFR %	0.6 ±0.1	6.2 ±3.5	11.6 ±1.6	19.2 ±3.7	12.8 ±2.7	7.8 ±2.0	3.3 ±1.1	4.7 ±0.8
U_KV $\mu eq/min/kg$	4.31 ±0.58	0.56 ±0.12	8.26 ±1.34	6.94 ±1.47	4.48 ±0.86	4.60 ±0.48	1.63 ±0.31	0.22 ±0.04
PLASMA UREA mM	6.0 ±0.9	—	56.9 ±2.0	50.7 ±4.7	58.7 ±5.1	52.1 ±3.6	57.6 ±5.8	71.3 ±2.3

FIGURE 3 Post-obstructive renal function of experimental kidney (E) and plasma urea concentrations. Values are means±SEM.

tion of the left ureter was followed by a marked post-obstructive diuresis. Mean values for $\dot{V}$ of BO, UO-Nx, and UO-reinf rats were approximately 9, 12, and 6 times, respectively, that of sham rats. All these elevations were significant.

In contrast to the above three groups, which exhibited post-obstructive diuresis, a diuresis did not appear in group II (UO rats), which had uninterrupted excretory function of one kidney throughout. Mean $\dot{V}$ for the UO animals was not significantly different from the value for sham rats, but was significantly less than those for BO, UO-Nx, and UO-reinf rats.

To examine the possible role of an elevation of plasma urea (consequent to the occurrence of azotemia during functional anuria) in the post-obstructive diuresis of the BO, UO-Nx, and UO-reinf animals, three additional groups of rats, group VI (UO-urea-replete), group VII (UO-urea-deplete), and group VIII (UO-urea-anesth), were given an i.v. urea infusion. A marked diuresis was observed in the UO-urea-replete rats, in which acute ECF volume contraction was prevented by the continuous i.v. replacement of urinary losses of water, sodium, and potassium by the intact kidney. $\dot{V}$ in the UO-urea-replete rats was significantly greater than the values of either UO or sham rats, but not significantly different from that of BO rats. In the UO-urea-deplete rats, in which fluid and electrolyte losses were not replaced, $\dot{V}$ was significantly less than BO, UO-Nx, UO-reinf, or UO-urea-replete values.

In the UO-urea-anesth rats, $\dot{V}$ was the lowest of any group (60% of the value of sham rats). This result is in accord with previous studies by Yarger et al. (1) and Jaenike (3), in which urea infusion in anesthetized UO rats was not followed by post-obstructive diuresis.

Sodium excretion. The rate of sodium excretion generally paralleled urine flow in the previously obstructed kidneys of all eight groups. A marked natriuresis was observed in the BO, UO-Nx, and UO-reinf rats, in which both absolute ($U_{Na}V$) and fractional (C_{Na}/GFR) sodium excretion were significantly greater than the values in the sham rats.

In contrast with these three groups, $U_{Na}V$ in UO rats was lower than the value for sham animals, although the difference was not significant.

Among the urea-loaded groups, the UO-urea-replete rats exhibited a marked post-obstructive natriuresis, with a mean $U_{Na}V$ identical to that of the BO animals. C_{Na}/GFR in UO-urea-replete rats was less than that of the BO rats (7.8 vs. 11.6%), although this difference was not significant. In the UO-urea-deplete animals, $U_{Na}V$ was significantly less than either UO-urea-replete or BO values, although not significantly different from the mean for sham rats. As with urine

TABLE I

Summary of Measurements on Arterial Blood and Blood Pressure (BP)

	[Na]	[K]	Hct	BP
	meq/liter	*meq/liter*	%	*mm Hg*
No urea given				
I Sham	137±5	4.2±0.1	44±1	125±3
II UO	139±1	4.3±0.1	43±1	126±7
III BO	139±2	6.3±0.4*	44±1	146±10*
IV UO-Nx	140±2	6.3±0.5*	42±1	148±9*
V UO-reinf	142±1	6.7±0.3*	42±2	152±18*
Urea-loaded				
VI UO-urea-replete	141±1	4.7±0.2	40±1*	131±11
VII UO-urea-deplete	141±1	3.9±0.1	43±2	126±13
VIII UO-urea-anesth	140±3	4.8±0.3	52±2*	120±7

Values are expressed as the means±1 SEM.
* $P < 0.05$ compared with group I (sham rats).

flow, the lowest mean $U_{Na}V$ (25% of the value of sham rats) was seen in the UO-urea-anesth rats.

Potassium excretion (U_KV). A rather wide range of potassium excretion rates (2.0–6.7 μeq/min per kg) was observed among the individual sham rats. Among the rats exhibiting post-obstructive diuresis (BO, UO-Nx, UO-reinf, and UO-urea-replete), there was a general tendency toward an increase in U_KV; however, only in the BO rats was the value significantly greater than the mean of sham animals.

In the UO animals, a marked and significant depression in U_KV was observed (13% of the value of sham rats), consistent with previously reported observations (4). Potassium excretion was also significantly decreased compared with that of the sham rats in the UO-urea-deplete and UO-urea-anesth rats.

Inulin clearance or GFR. GFR was significantly decreased in the previously obstructed kidney of all seven groups with ureteral obstruction, compared with the mean of sham rats. In the four obstructed groups not given urea (UO, BO, UO-Nx, UO-reinf), mean GFR was greatly decreased, as has been reported previously in rats after release of ureteral obstruction (1–5). Among these four groups, there were no significant differences in GFR. In particular, the GFR of the UO rats, which did not exhibit diuresis, did not differ significantly from the GFR of the BO, UO-Nx or UO-reinf animals, in which diuresis did occur.

GFR in the UO-urea-replete rats, although significantly less than that of sham rats, was significantly greater than the value observed in any of the other previously obstructed groups. In particular, the GFR of the four obstructed groups not given urea (UO, BO, UO-Nx, UO-reinf) ranged from approximately one-third to one-half that of the UO-urea-replete animals. GFR in the UO-urea-deplete rats was greater, though not significantly, than the values of UO, BO, or UO-Nx rats. The lowest mean GFR (3% of the value of sham rats) was seen in the UO-urea-anesth animals.

PAH clearance (C_{PAH}). C_{PAH} was significantly depressed, compared with the value for sham rats in all seven obstructed groups. Mean C_{PAH} ranged from 22 to 33% of the value of sham rats in the four obstructed groups not given urea. As with GFR, there were no significant differences in C_{PAH} among these four groups.

C_{PAH} in the UO-urea-replete rats was the highest of all the obstructed groups, and was significantly greater than any of the four obstructed groups not given urea. Among these four groups, C_{PAH} ranged from 30 to 44% of the mean of the UO-urea-replete animals. C_{PAH} in the UO-urea-anesth rats, as with GFR, was the lowest observed in any group (5% of the value for sham rats).

Plasma urea concentration (P_u). P_u was measured in arterial blood at the end of each experiment except in the UO rats. This model has previously been shown to have P_u levels not significantly different from sham-operated hydropenic rats (4). In the present study, the collection of a blood sample large enough to permit urea analysis by the Autoanalyzer technique used was avoided in order to minimize interference with subsequent use of the UO rats in the UO-urea protocols. In the obstructed groups in which P_u was measured, P_u ranged from 8 to 12 times the value for sham rats.

Other measurements on arterial blood and blood pressure. Mean values for plasma sodium and potassium concentrations, arterial hematocrit, and mean blood pressure are given in Table I. There were no differences in plasma sodium concentration among the eight groups. Plasma potassium concentration was significantly elevated compared with the value of sham rats in the BO, UO-Nx, and UO-reinf rats, in which functional anuria existed during obstruction, but in the remaining four groups was not significantly different from that of sham rats. The hematocrit did not differ significantly from that of sham rats except in two urea-loaded groups. There was a slight but significant fall in hematocrit in the UO-urea-replete rats, while the hematocrit rose significantly in the UO-urea-anesth animals. Arterial blood pressure was significantly increased in the BO, UO-Nx, and UO-reinf rats, but not significantly altered in the other groups.

Contralateral (unobstructed) kidney

The function of the unobstructed kidney was studied in the six UO-reinf and in seven UO-urea-replete rats. In both of these models, it should be noted, urinary losses of water, sodium, potassium, and urea by the unobstructed kidney were replaced continuously. Of the two groups, P_u was slightly but not significantly higher in the UO-reinf rats. The unobstructed kidney in both the UO-reinf and the UO-urea-replete animals displayed a

TABLE II

Function of the Unobstructed Kidney in UO-Reinf and UO-Urea-Replete Rats

Rat no.	$\dot{V}$	GFR	C_{PAH}	$U_{Na}V$	C_{Na}/GFR	U_KV
	μl/min/kg	*ml/min/kg*	*ml/min/kg*	*μeq/min/kg*	%	*μeq/min/kg*
			UO-reinf			
1	1,180	4.91	14.0	134	19.3	42.5
2	1,660	4.52	9.3	208	30.8	40.8
3	1,690	3.96	6.6	192	35.7	24.6
4	1,000	6.23	19.3	111	12.7	40.1
5	1,380	6.69	14.8	175	18.0	40.7
6	4,080	10.10	19.8	495	35.3	71.3
Mean	1,830	6.07	14.0	219	25.3	43.3
SEM	±460	±0.91	±2.2	±57	±4.0	±6.2
			UO-urea-replete			
7	440	7.97	31.9	49	4.3	18.3
8	850	10.00	45.6	110	7.7	36.4
9	420	6.25	19.4	30	3.4	15.4
10	520	6.27	25.5	35	4.2	8.3
11	930	4.41	12.3	74	12.6	16.8
12	880	4.64	11.3	90	13.9	24.5
13	1,860	7.90	18.5	198	18.1	27.3
Mean	843	6.78	23.5	84	9.2	21.0
SEM	±188	±0.75	±4.6	±22	±2.2	±3.5
*P**	NS‡	NS	NS	<0.05	<0.01	<0.01

* *P* value compared with the UO-reinf group. NS, not significant.

‡ $P < 0.05$ if value for rat 6 is omitted (see text).

pronounced diuresis and natriuresis. These data are shown in Table II.

The diuresis by the unobstructed kidney of the UO-reinf rats was massive. Generally within several hours of the simultaneous obstruction of the left ureter and reinfusion of urine from the unobstructed kidney, urine excretion by the latter began to increase markedly, and attained profound proportions by the end of 24 h. Clearance data from the unobstructed kidney were obtained after release of the UO of the opposite kidney. Urine flow rates of five of the six animals of this group were elevated to comparable degrees. One of the six (rat 6) demonstrated an astonishing diuresis, 4,080 μl/min per kg, a flow rate equivalent to the excretion of almost six times the animal's body wt/24 h. The fractional excretion of glomerular filtrate ($\dot{V}$/GFR) ranged from 16.2 to 40.5%. GFR, although quite variable among individual rats, did not differ from the value of sham rats. GFR was substantially increased in the animal with the highest urine flow. Sodium excretion, both in absolute and fractional terms, was massively elevated, generally paralleling urine flow. C_{Na}/GFR exceeded 30% in three of the six rats, and was significantly elevated in all six animals. Potassium excretion was also remarkably increased, the highest U_KV being observed in rat 6, the animal with the greatest urine flow.

In the UO-urea-replete rats, mean $\dot{V}$ from the unobstructed kidney was less than half of the value observed in the UO-reinf animals. This difference in $\dot{V}$ barely misses statistical significance. However, if the extremely high value for rat 6 is removed, the difference is significant (1,380±130 μl/min per kg for the UO-reinf vs. 843±188 for UO-urea-replete, $P < 0.05$). Mean GFR values for the two groups did not differ significantly. C_{PAH} varied widely among individual UO-urea-replete rats, striking elevations being recorded in two animals (rats 7 and 8). However, mean C_{PAH} was not significantly different from that of UO-reinf rats. A variable but pronounced natriuresis occurred in all UO-urea-replete animals; however, mean $U_{Na}V$ was less than half the value of the UO-reinf rats, a significant difference. Likewise, C_{Na}/GFR, although markedly elevated, was significantly less than the UO-reinf value. Potassium excretion rate was also significantly below that of the UO-reinf rats.

DISCUSSION

The pathogenesis of post-obstructive diuresis has not been fully defined by previous investigations. In the present study, particular attention has been directed toward the previously reported observations that post-

obstructive diuresis in rats follows release of 24 h of BO (1–3), but does not follow UO in the presence of an intact kidney (1, 4, 5). The initial object of this study was to examine the possibility that post-obstructive diuresis in the BO model was mediated by diuretic (and/or natriuretic) factors in the systemic circulation. Bourgoignie et al., have previously demonstrated the presence of a natriuretic factor(s) in the serum of patients with chronic uremia (7). Such natriuretic factors might normally be largely eliminated by urinary excretion. Were this the case, elevated levels of such factors might result from (*a*) retention in (BO and UO-Nx models) or (*b*) return to (UO-reinf model) the circulation. Post-obstructive diuresis appeared in all these models in which functional anuria existed during the obstruction of the experimental kidney (BO, UO-Nx, and UO-reinf) but did not occur in UO rats. Thus, these data support the concept that diuretic factors, normally excreted in the urine, may accumulate when urine excretion is interrupted, and may lead to a diuresis upon release of ureteral obstruction. These findings do not identify the number, chemical nature, or source of these factors.

It is possible that urea might be one of the factors responsible for the appearance of post-obstructive diuresis (8–10). Plasma urea concentrations were elevated in all diuretic animals (BO, UO-Nx, and UO-reinf). The importance of urea in post-obstructive diuresis, however, has been questioned. Yarger et al. (1) and Jaenike (3) reported that post-obstructive diuresis did not occur when the plasma urea concentration of anesthetized UO rats was increased by intravenous urea infusion. We confirmed this observation (UO-urea-anesth), but noted that urea infusion also produced a substantial diuresis from the opposite intact kidney (Table II). Thus, acute ECF volume contraction resulting from urea diuresis by the intact kidney may override any diuretic effect of urea on the previously obstructed kidney.

To examine more fully the extent to which urea might contribute to post-obstructive diuresis, we studied three models of urea-loaded UO rats. The UO-urea-replete model was designed to simulate certain features of the BO, UO-Nx, and UO-reinf animals; namely, an elevated plasma urea and the prevention of acute alterations in ECF volume and electrolyte balance. Although a definite post-obstructive diuresis appeared in these UO-urea-replete rats, their GFR and C_{PAH} values were over twice those seen in the BO, UO-Nx, or UO-reinf rats. These findings suggest that urea infusion somehow partially reverses the renal vasoconstriction that follows obstructive uropathies (1, 4, 5). The mechanism of this apparent vasodilatation is not clear. It seems unlikely that this was due to ECF volume expansion (5)[2] or to a direct effect of urea per se, since plasma urea elevations in this group were comparable to those of the BO, UO-Nx, and UO-reinf rats. Regardless of the mechanism, it appears that the vasodilatation that follows urea infusion contributed, in part, to the post-obstructive diuresis observed in the UO-urea-replete rats. Thus, although these data suggest that elevation of the plasma urea may play an important role in the pathogenesis of post-obstructive diuresis, they do not exclude the presence of other factors.

The other two groups of UO rats infused with urea were used to assess the effects of ECF volume contraction and barbiturate anesthesia as factors capable of attenuating post-obstructive diuresis. The UO-urea-deplete rats were studied while awake, but a urea osmotic diuresis by the opposite kidney led to acute ECF volume contraction. This acute volume contraction also occurred in the UO-urea-anesth rats, studied under barbiturate anesthesia. The diuresis and natriuresis displayed by both groups of rats were considerably less than that displayed by the UO-urea-replete rats. In particular, in the UO-urea-anesth rats, $\dot{V}$ and $U_{Na}\dot{V}$ were the lowest of any group, and GFR and C_{PAH} were markedly depressed. These data demonstrate that acute ECF volume contraction and anesthesia are both capable of reducing or abolishing the post-obstructive diuresis that follows urea infusion in awake UO rats. The vasoconstrictor effects of anesthesia may explain why the post-obstructive diuresis observed in our BO rats was greater than that reported previously in anesthetized animals (1–3).

The present findings in our three groups of urea-loaded rats suggest that (*a*) urea, which accumulates in animals during anuria, may exert a considerable diuretic action upon release of obstruction; however, other factors may be of comparable importance; (*b*) acute ECF volume contraction exerts a pronounced blunting influence on post-obstructive salt and water excretion; and (*c*) barbiturate anesthesia markedly increases the existing vasoconstriction of the previously obstructed kidney, thereby exerting an antidiuretic and antinatriuretic effect.

The function of the unobstructed contralateral kidney in the UO-reinf rats provides additional strong evidence for the presence of diuretic factors in the urine. The massive diuresis and natriuresis of the unobstructed kidney in this model equal or exceed those reported with massive saline infusion (11–13) or with large doses of diuretic drugs, i.e., 25 mg/kg furosemide (14). Furthermore, since water and electrolyte balance remained

[2] The total volume of urea infusate was approximately 1.2% of body wt, of a 30% urea solution. Such a solution contains 78% fluid (measured in our laboratory). Hence, the rats received in the urea infusion a total fluid load less than 1% of body wt, usually over a period of 2 h.

essentially unchanged throughout the period of left ureteral obstruction, the diuretic and natriuretic responses of the intact kidney are not due to overload of salt or water. Rather, the data suggest that potent diuretic factors (other than electrolytes or water) are excreted by the kidney, and that they exert their effects on salt and water excretion when returned to or retained in the circulation. In the UO-reinf model, although both kidneys are probably under the influence of the same circulating diuretic factors, the far more intense diuretic response in the unobstructed kidney suggests that post-obstructive diuresis is not dependent upon direct effects of ureteral obstruction on the kidney itself. On the contrary, the lower C_{Na}/GFR values for the previously obstructed kidneys compared with unobstructed kidneys (12.8±2.7% vs. 25.3±4.0%, $P < 0.05$) suggest that the net morphological and functional consequences of obstruction per se are probably antinatriuretic.

To assess the degree to which the diuresis by the intact kidney can be attributed to urea, the function of these kidneys in UO-reinf and UO-urea-replete rats were compared (See Table II). Urine flow rates and both absolute and fractional sodium excretion were substantially higher in the UO-reinf rats, despite somewhat higher GFR and C_{PAH} values in the UO-urea-replete animals. Again, it should be noted that plasma urea concentrations are similar in these two models and urinary losses of water and electrolytes were continuously replaced in both. These findings suggest that the massive diuresis and natriuresis by the intact kidney of the UO-reinf rats are only partially attributable to urea, and that other potent diuretic factors are excreted in the urine. The chemical nature and anatomical source of these nonurea diuretic factors remain to be identified.

The present data indicate that tubular sodium reabsorption is markedly inhibited during post-obstructive diuresis, since absolute sodium excretion by the previously obstructed kidneys of the BO, UO-Nx, and UO-reinf rats was substantially increased while GFR was decreased. These findings agree with previous micropuncture demonstrations of defective tubular reabsorption (1, 2) after release of BO in rats. Similar conclusions may be drawn regarding tubular sodium reabsorption by the intact kidney of the UO-reinf rats. Although the mean GFR of these unobstructed kidneys was not altered, absolute and fractional sodium excretion were markedly increased. These findings suggest that the retained (or reinfused) diuretic factors markedly inhibit sodium transport in both the intact and previously obstructed kidneys.

In summary, our findings support the following conclusions: (*a*) the post-obstructive diuresis that follows release of anuric forms of ureteral obstruction in the rat results, to a large extent, from the retention of potent diuretic and natriuretic factors normally excreted in the urine; and (*b*) urea appears to be one of these factors.

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