Urinary Concentration in the Papillary Collecting Duct of the Rat

ROLE OF THE URETER

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ABSTRACT Urine was observed to flow intermittently in the collecting ducts of the extrarenal papilla of antidiuretic rats. The purpose of this investigation was to test Reinking and Schmidt-Nielsen's hypothesis that intermittent flow plays an important role in the production of maximally concentrated urine. Samples of collecting duct fluid were obtained from the base and tip of the papilla by micropuncture through the intact ureter. Fluid osmolality rose sharply from base, 894±120 mosmol/kg H_2O^{-1} (mean±SE), to tip, 1,667±114 ($P<0.001$), a distance of only 2 mm, and was due exclusively to reabsorption of water. After excision of the ureter, which abolished intermittent flow, osmolality fell modestly at the base to 723±82 mosmol/kg H_2O^{-1} ($P < 0.02$), but strikingly at the tip to 1,012±103 ($P < 0.001$). The pelvic ureter was paralyzed by topical verapamil and dimethylsulfoxide, which abolished intermittent flow. Osmolality of urine at the tip was not changed (1,959±184 mosmol/kg H_2O^{-1} before, vs. 1,957±126 after paralysis). The ureter was severed just beyond the papillary tip, a maneuver which preserved intermittent flow but abolished urinary reflux over the papilla. Urinary osmolality fell from 1,876±134 mosmol/kg H_2O^{-1} to 1,284±115 ($P < 0.005$). These findings demonstrate that when the ureter is intact, over half of the increase in urinary osmolality above isotonicity occurs in the terminal one-fourth of the medullary collecting duct and is due exclusively to water reabsorption (no net solute addition). It is the continuity of the ureter, rather than intermittent flow due to ureteral peristalsis, which is essential for the formation of a maximally concentrated urine.

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INTRODUCTION

The medullary collecting duct plays a key role in urinary concentration. The specific contribution of the terminal collecting duct to urinary concentration has been assessed by micropuncture of the exposed renal papilla of rodents (1–5). Unfortunately, excision of the overlying ureter results in a substantial reduction (one-third or more) in urinary osmolality, a phenomenon attributed to interruption of the bathing of the papilla by urine (specifically, interruption of pelvic urea recycling) (6–8) or increased medullary blood flow with "washout" of medullary solute (3). Recently, Reinking and Schmidt-Nielsen (9) have redirected attention to Steinhausen's observation (10) of bolus, or intermittent flow, in the terminal collecting duct associated with ureteral peristalsis. They suggested that intermittent flow plays a key role in urinary concentration (9). If that were the case, even the technique of microcatheterization of the collecting duct (11, 12), which requires incision of the ureter, might introduce an artifact.

The purpose of this study was to evaluate the contribution of the undisturbed terminal collecting duct to urinary concentration, and to determine the importance of intermittent flow to urinary concentrating ability. For these purposes we employed a new technique, micropuncture of the papillary collecting duct through the intact ureter, and abolished intermittent flow by paralysing the ureter with the calcium-blocking agent, verapamil.

METHODS

Young Munich-Wistar rats (Timco Breeding Laboratories, Houston, Tex.) of either sex weighing 70–100 g were allowed free access to water until the day of experiment. The animals were anesthetized with Inactin (Andrew Lockwood Assoc.,

East Lansing, Mich.), 100 mg/kg body wt, and prepared for micropuncture of the left renal papilla as previously described (1). After exposure of the left kidney, a small catheter (PE-50, Clay Adams, Div. of Becton, Dickinson & Co., Parsippany, N. J.) was inserted into the lower one-third of the left ureter. The animal was placed on its right side and the left kidney gently inserted into a glass cup so that the dorsal aspect of the left kidney was exposed. The kidney and pelvic ureter were bathed continuously with mineral oil warmed to 38°C, which helped preserve the initial transparency of the ureter. The papilla was illuminated through the intact ureter with a fiber optic light guide and Fiber-Lite lamp (model 150, Scientific Instruments Co., McBain Instruments, Chatsworth, Calif.). Micropuncture was performed using sharpened glass pipettes with an inner tip diameter of 9–10 μm. Throughout the experiment animals received an intravenous infusion of 0.9% sodium chloride at 0.025 cm^3/min^{-1}. During surgery inulin was added to the infusate at a concentration sufficient to maintain plasma inulin concentrations between 80–100 mg/dl^{-1}.

Group I (n = 9). The experimental protocol consisted of two periods. During the first period samples were taken through the ureter with peristalsis present from the highest accessible portion of collecting duct at the papillary base and subsequently from the ducts of Bellini at the papillary tip (Fig. 1). In some animals lissamine green dye was injected intravenously before micropuncture to confirm the presence of intermittent flow in the collecting ducts. Only collecting ducts which were visible through the ureter were selected for micropuncture. A small column of colored oil (Kel F, 3M Co. 3M Center, St. Paul, Minn.) was injected through the micropipette into the collecting duct lumen to confirm location before collection of fluid samples. Care was taken to collect fluid samples at less than the flow rate of tubule fluid.

During the second period, the ureter was completely excised (1) and collecting duct fluid samples were again taken from the highest accessible portion of collecting duct at the papillary base and subsequently from the ducts of Bellini at the papillary tip (Fig. 2). From 5 to 40 min elapsed between excision of ureter and collection of the first sample (average 16±4.5 min). Intermittent fluid flow in the collecting ducts, as judged by the transit of lissamine green dye, was abolished following ureteral excision.

Group II (n = 5). To assure that the procedure of puncturing the papillary collecting ducts through the ureter did not adversely affect papillary collecting duct function, a separate group of animals were prepared in an identical way and subjected to "sham" micropuncture. During the first period several collecting ducts were punctured at the base of the papilla and their identity confirmed by injecting a small column of oil. No fluid samples, however, were collected. In the second period, the papilla was displaced from the pelvic ureter upward into the renal pelvis, but the ureter was not excised. Fluid samples were then collected from the papillary tip through the intact ureter. The time-course of fluid sampling corresponded to periods 1 and 2 in group I.

Group III (n = 8). To assess the role of intermittent fluid flow in the collecting ducts on urinary concentration, samples of fluid were taken from the papillary tip through the intact ureter during the first period. Intermittent flow was verified following the intravenous injection of lissamine green. Subsequently, the ureter was paralyzed (period 2) by the topical application of an aqueous cream containing verapamil (Isoptin, Knoll Pharmaceutical Company, Whippany, N. J.) 10% by weight, and 1–2 μl of a 95% solution of dimethyl sulfoxide (Domoso Inc., Diamond Laboratories, Modesto, Calif.) applied to the pelvic ureter. After 5–10 min, paralysis of the ureter was complete and intermittent flow was entirely abolished as judged by the passage of lissamine green. Neither drug applied separately paralyzed the ureter or altered urinary osmolality or flow. Samples of fluid were taken from the papillary tip through the paralyzed ureter. The timing of the latter collection approximated the average time lapse between periods 1 and 2 in group I. The ureter was subse-

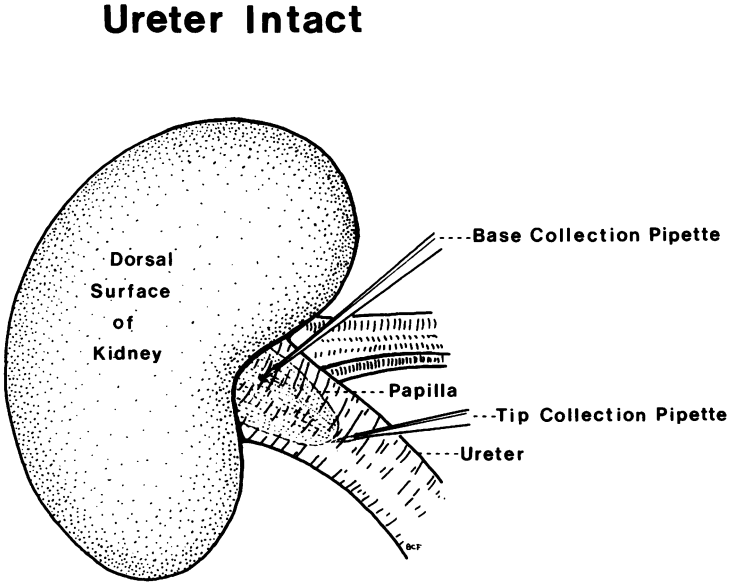

FIGURE 1 Dorsal surface of kidney as seen during the first period. In group I base collections were taken through the intact ureter from the highest accessible portion of papillary collecting duct.

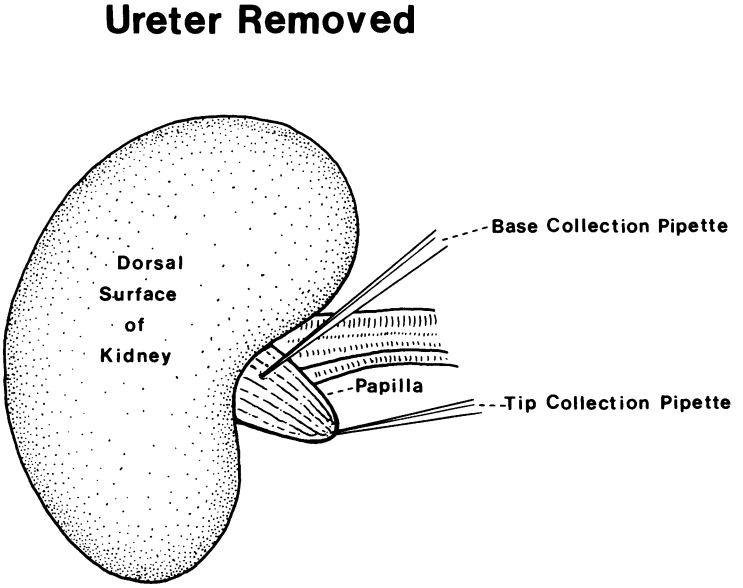

FIGURE 2 Dorsal surface of kidney during the second period of group I, after ureteral excision. Collecting ducts at the papillary base were sampled at the highest accessible point.

quently removed and further fluid samples were taken from the ducts of Bellini.

Group IV (n = 6). To determine renal function, glomerular filtration rate was measured before and after ureteral paralysis by collection of urine through the left ureteral catheter. The ureter was subseqently removed and further fluid samples taken from the ducts of Bellini.

Group V (n = 10). To evaluate the importance of urinary reflux over the papilla (13) to urinary concentration, fluid samples were taken at the papillary tip through the intact ureter. The ureter was then excised just beyond the papillary tip. Intermittent flow was preserved, but urine no longer appeared to reflux over the papilla. A PE-100 catheter, with a 2-mm segment further tapered by pulling, was inserted into the remnant ureter and threaded to a point below the papillary tip. After a period of time corresponding to period 2 in Groups I, II, and III, fluid samples were taken from the left ureteral catheter. Animals were discarded if the samples contained blood.

The osmolality and inulin concentrations of plasma, urine, and tubule fluid samples were determined by methods previously described (1, 14, 15). Sodium and potassium in the plasma ultrafiltrate and tubule fluid were determined by electron microprobe in the Center for Materials Research, Stanford University (Materials Analysis Corporation, MAC-5, Palo Alto, Calif.) by methods previously described (4). Data were analyzed using Student's *t* test for paired and unpaired comparisons as appropriate, and expressed as the mean±SE.

RESULTS

Group I. Ureteral excision. The osmolality of tubule fluid rose dramatically along the medullary collecting duct when the ureter was intact (Fig. 3 and Table 1). The length of accessible terminal collecting duct averaged 2 mm, which is ~25% of the length of the medullary collecting duct. With the ureter intact, the osmolality of fluid in the terminal collecting duct increased strikingly from 894±120 mosmol/kg H_2O^{-1} at the papillary base to 1,667±114 at the tip ($P < 0.001$). Of the total rise in tubule fluid osmolality along the medullary collecting duct, therefore, approximately one-half occurred in the terminal collecting duct (Table I). After ureteral excision urinary osmolality declined to 1,012±103 mosmol/kg H_2O^{-1} (a decline of 39%). Most of the decline was confined to the terminal collecting duct (Fig. 3). That this decline is specifically due to ureteral removal is indicated by the fact that urinary osmolality in the untouched right kidney remained the same (Table I).

Fig. 4 depicts the tubule fluid-to-plasma (TF/P)[1] inulin values in the collecting duct at the base and tip of the papilla in group I. The (TF/P) inulin at the papillary tip dropped twofold from 302±51 before ureteral removal to 172±22 after removal ($P < 0.02$) while the decline in (TF/P) inulin at the base was not significant. The rise in (TF/P) inulin between base and tip was significantly less after ureteral excision than before ($P < 0.025$).

Fractional delivery of total solute to the tip of the papilla was slightly but not significantly less than that to the base in the first period as shown in Fig. 5, and did not change after ureteral excision. Thus the decline

[1] *Abbreviation used in this paper:* TF/P, tubule fluid-to-plasma.

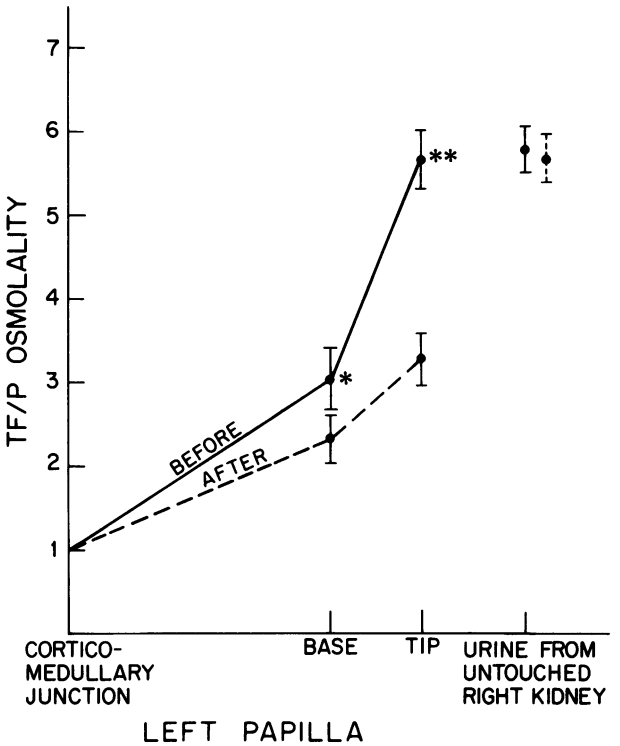

FIGURE 3 The TF/P osmolality of collecting duct fluid at the base and tip of the papilla before (solid line) and after (dashed line) excision of the ureter. The TF/P osmolality is assumed to be unity at the corticomedullary junction. TF/P osmolality in the right kidney is shown on the right for comparison. The vertical bar represents ±1 SE. The difference in TF/P osmolality at the base before and after excision is significant ($P < 0.05$)*, as is the difference in TF/P osmolality at the tip ($P < 0.001$)**. The rise in TF/P osmolality from base to tip was significantly less after ureteral excision than before ($P < 0.05$).

in urinary osmolality following ureteral removal (Fig. 3) is due exclusively to decreased water reabsorption from the terminal collecting duct.

The fraction of filtered sodium remaining declined significantly ($P < 0.05$) from papillary base to tip before and after ureteral excision, is shown in Fig. 6. Sodium reabsorption by the terminal collecting duct thus continued unchanged after ureteral removal. The function of the right kidney for group I is shown in Table II.

Group II. Sham micropuncture control. The effect on final urine osmolality of puncturing the collecting ducts at the papillary base through the intact ureter is shown in Table I. No significant changes in osmolality occurred.

Group III. Ureteral paralysis. Following paralysis of the ureter, intermittent flow was abolished. The absence of intermittent flow, however, had no effect on final urinary osmolality as shown in Table I. Right kidney osmolality did not change significantly. Following period 2, the paralyzed ureter was excised. Urinary osmolality fell by 566±183 mosmol/kg H_2O^{-1} ($n = 8$, $P < 0.025$) after excision (not shown in table), a value similar to the fall after ureteral excision in group 1.

Group IV. Renal function in the left kidney, ureteral paralysis. Renal function (Table III) did not change following ureteral paralysis.

Group V. Remnant ureter. After the ureter was severed below the tip of the papilla, urinary osmolality fell significantly ($P < 0.005$) (Table I). Urinary osmolality from the right control kidney remained unchanged. The collecting ducts exhibited intermittent flow, which persisted unchanged after severing the ureter.

DISCUSSION

The principal findings of these experiments are the following: the terminal one-fourth (last 2 mm) of the medullary collecting duct plays a critical role in elaborating a maximally concentrated urine, contributing

TABLE I
Urinary Osmolality

	Group I Ureteral excision ($n = 9$)			Group II Sham control ($n = 5$)			Group III Ureteral paralysis ($n = 8$)			Group V Remnant ureter ($n = 10$)		
Period	1	P*	2	1	P	2	1	P	2	1	P	2
Left kidney	1,667±114‡	<0.001	1,012±103	1,682±118	NS	1,710±110	1,959±184	NS	1,952±126	1,876±134	<0.005	1,284±115
P§	NS		<0.001	NS		NS	NS		NS	NS		<0.001
Right kidney	1,701±89	NS	1,736±88	1,724±86	NS	1,785±91	2,068±243	NS	1,880±124	1,883±138	NS	1,946±130

Data are means±SE.

* Significance of the difference between first and second period.

‡ mosmol/kg of water.

§ Significance of the difference between right kidney and left kidney during the same period.

half of the total increase in urinary osmolality along the medullary collecting duct; intermittent flow of urine normally occurs in the collecting duct secondary to ureteral peristalsis and plays no important role in the urinary concentrating process, but the continuity of the ureter is somehow essential to maximum urinary concentrating ability.

Role of the terminal papillary collecting duct. Several techniques have been used to study the function of the terminal collecting duct, including micropuncture of the papilla exposed by excision of the ureter (1–5); microcatheterization of the collecting duct through an opening in the ureter at the papillary tip (11, 12); and perfusion of excised segments of the papillary collecting duct in vitro (16). Each technique necessitates disruption of the overlying ureter; maximum urinary concentration is invariably compromised.

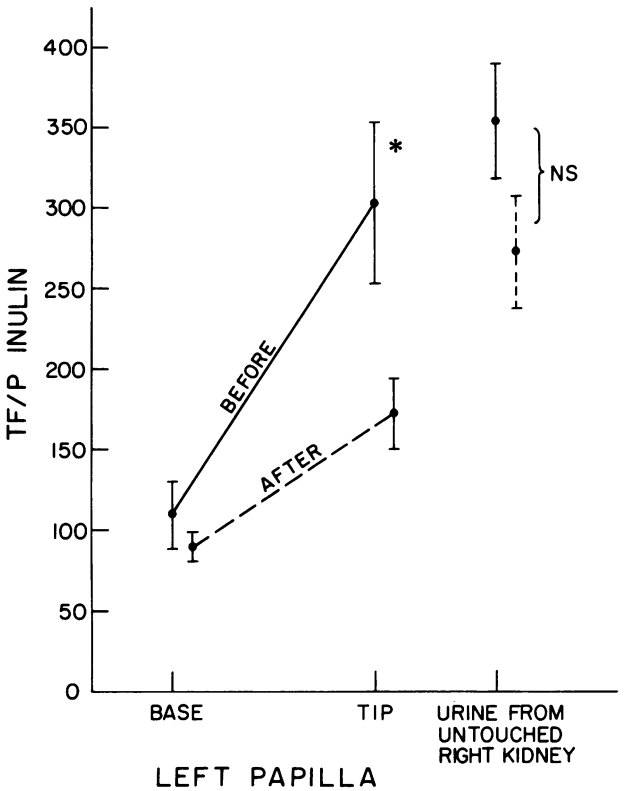

FIGURE 4 TF/P inulin of collecting duct fluid at the papillary base and tip before (solid line) and after (dashed line) excision of the ureter. The value for urine from the right kidney is shown on the right. The vertical bars denote±1 SE. The difference in TF/P inulin at the tip before and after is significant ($P<0.02$)* but the difference at the base between the two periods is not significant. The rise in TF/P inulin between base and tip was significantly less after excision ($P < 0.025$). The difference in TF/P inulin in the right kidney between the two periods is not significant (NS).

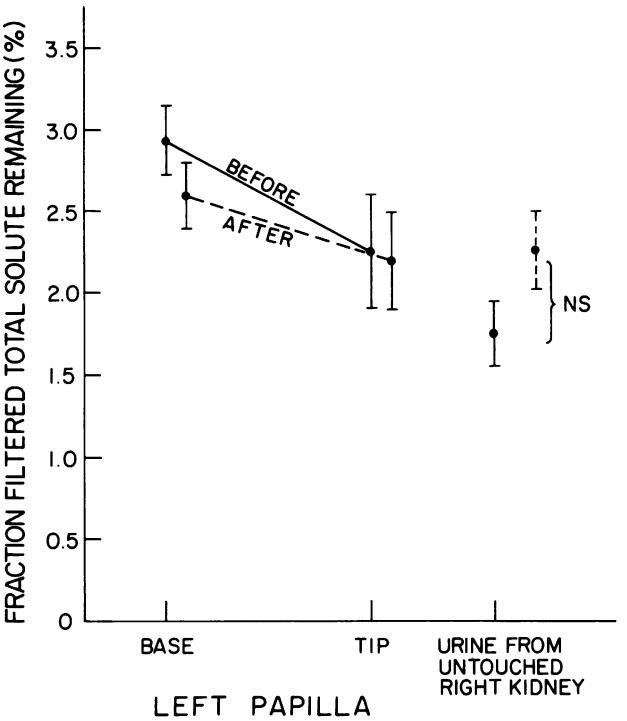

FIGURE 5 Fractional delivery of total solute to collecting duct at papillary base and tip expressed as percentage of filtered load. See legend to Fig. 4.

The technique of micropuncture through the intact ureter permits for the first time an assessment of the concentrating process in the terminal collecting duct in its normal environment and has yielded several important observations. First, the rise in urinary osmolality in the terminal 2 mm of the collecting duct accounts for more than half of the total rise in urinary osmolality along the entire medullary collecting duct, assuming that in antidiuresis fluid entering the medullary collecting tubule is isoosmotic with the cortical interstitium (2). Secondly, the rise in osmolality is due exclusively to water reabsorption; solute secretion does not contribute. Concomitantly, sodium reabsorption in the terminal collecting duct occurs, amounting to 0.5% of the filtered load of sodium.

Third, removal of the ureter impairs urinary osmolality by reducing water reabsorption along the terminal collecting duct. Assuming that osmotic equilibration occurred between collecting duct, urine, and the papilla after ureteral excision (as has been demonstrated previously [1, 2]), the reduction in papillary osmolality was clearly not caused by increased water reabsorption diluting the interstitium as prob-

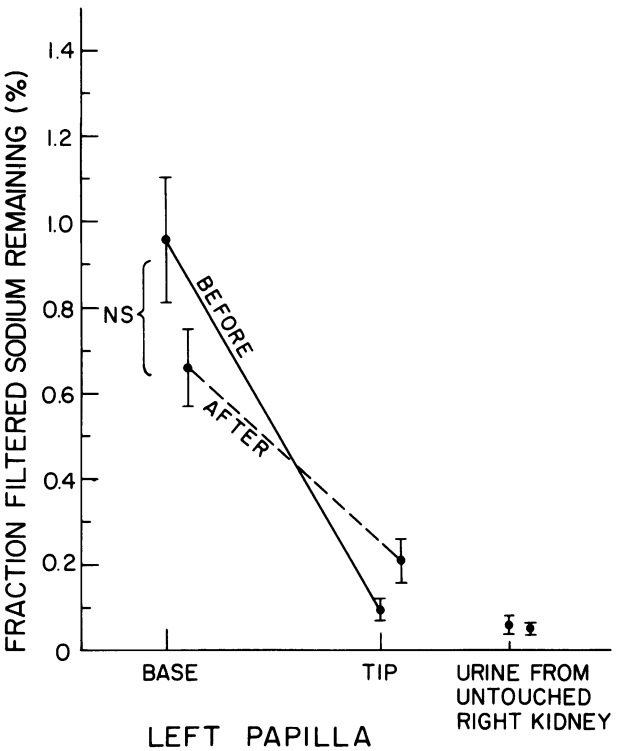

FIGURE 6 Fractional delivery of filtered sodium to collecting duct at base and tip of papilla. The fall from base to tip was significant before and after excision of the ureter ($P < 0.001$). Fractional reabsorption of sodium in the papillary collecting duct is unaffected by uretral excision. See legend to Fig. 4.

ably occurs in the absence of antidiuretic hormone (2). Rather there must have been a primary reduction in papillary solute concentration due to solute washout secondary to increased papillary blood flow (3), solute loss through the papillary epithelium into the pelvis (6), or failure of normal solute replenishment (8) (see below).

That impairment of water reabsorption is a selective effect of ureteral excision is implied by the persistence of normal sodium reabsorption by the terminal collecting duct after ureteral removal (Fig. 6).

Role of intermittent flow. Normally in antidiuresis there is intermittent or "bolus" flow of urine in the terminal collecting duct due to periodic closure of the collecting duct, as originally described in 1964 (10) and thoroughly investigated recently (9). The fact that the periodicity coincides with ureteral peristaltic contractions and is abolished when the ureter is paralyzed, strongly suggests that the periodic closure of the terminal collecting duct is due to peristalsis of the pelvic ureter. Moreover, it is likely a widespread phenomenon occurring in man and other species (9, 17). Reinking and Schmidt-Nielsen (9) proposed that ureteral peristalsis enhances processes that increase urinary osmolality by exerting a milking action on the papilla, thereby interrupting, among other things, urinary flow in the collecting ducts and blood flow in the vasa recta. They suggested that peristalsis might enhance water reabsorption from collecting ducts (Fig. 4) or decrease solute washout by ascending vasa recta (9). Either effect would increase urinary osmolality (18). Our results, however, indicate that ureteral peristalsis and intermittent flow do not enhance urinary osmolality.

Role of the ureter. Our results confirm previous findings that the continuity of the ureter is essential to concentrate urine maximally. Schutz and Schnermann (6) suggested that the final urine bathing the papilla enhances papillary osmolality perhaps by removing water; their findings were extended recently by Bonventre et al. (8), who showed that the presence of urea in the urine is key to the preservation of urinary

TABLE II
Right Kidney Function

	Group I (n = 9)		
	First period	Second period	P*
Urine flow, $\mu l\ min^{-1}$	1.97±0.29	2.57±0.30	NS
GFR, $\mu l\ min^{-1}$	673±98	689±88	NS
U/P inulin	354±35	272±34	NS
FE total solute, %	1.76±0.18	2.26±0.24	NS
FE sodium, %	0.06±0.02	0.05±0.01	NS

Data are means±SE. The average kidney weight was 0.37 ±0.01 g.

* Significance of the difference between first and second period, using paired comparison.

FE, fractional excretion as percent of load; GFR, glomerular filtration rate; U/P inulin, urine-to-plasma inulin; NS, P > 0.05.

TABLE III
Left Kidney Function following Paralysis

	Group IV (n = 6)		
	Before paralysis	After paralysis	P*
Urine flow, $\mu l/min$	1.92±0.17	2.10±0.28	NS
GFR, $\mu l/min$	437±96	538±66	NS
U/P inulin	242±63	280±47	NS

Data are means±SE.

* Significance of the difference before paralysis and after paralysis.

GFR, glomerular filtration rate; NS, P > 0.05; U/P inulin, urine-to-plasma inulin.

osmolality. The latter authors postulated that urinary urea recycles into the papillary interstitium enriching it exactly like urea reabsorption from the medullary collecting duct. A conceptual problem, however, is apparent. It is well established that a hyperosmotic papilla is necessary to establish a concentrated urine (18); the new proposal implies that a concentrated urine is necessary to establish a concentrated papilla. These would appear to be mutually exclusive views. Furthermore, if urea without water reenters the papilla, urinary osmolality would be reduced between the tip of Bellini's duct and further down in the ureter, since mass flow of urea would decrease. Marsh and Martin (5), however, compared the mass flows of urea and total solute between the collecting duct at the papillary tip and in the ureter well below the papillary tip and found no difference in either mass flow. Thus, if urea does recycle between urine and pelvic tip, the amount of urea by which the papilla is thereby enriched is very small.

Chuang and her co-workers (3), using ^{125}I-albumin accumulation as a marker of papillary plasma flow, found that ureteral removal simultaneously decreased urinary osmolality and increased papillary plasma flow. Prostaglandin synthetase inhibitors, administered shortly before exposure of the papilla, prevented both the decline in urinary osmolality and the rise in papillary plasma flow. Chuang et al. postulated that papillary exposure leads to an increased papillary plasma flow by a prostaglandin-mediated pathway (3). Using video-microscopic techniques to determine erythrocyte velocity in individual vasa recta, Gussis and his co-workers (19) detected a progressive rise in vasa recta erythrocytes velocity after exposure of the papilla while concomitantly urinary osmolality decreased. Moreover, Jamison et al. (20) demonstrated that prostaglandin inhibitors administered after exposure of the papilla prevented the rise in erythrocytes velocity. Although these findings and those of Chuang et al. are in good agreement and imply that exposure of the papilla may stimulate prostaglandin synthesis that leads to increased papillary blood flow, vascular washout of papillary solute, and impaired urinary concentrating ability, in neither study was urinary excretion of prostaglandins determined. Furthermore, even if exposure of the papilla causes increased papillary blood flow and vascular washout, that does not explain the fall in urinary osmolality observed in group V (remnant ureter), which occurred even though the papilla was not exposed.

Whatever the true explanation for the role of the ureter in the concentrating mechanism, our results affirm that the continuity of the ureter is essential (1, 3, 6, 8). It may be that rather than supplying solute to or removing water from the papilla, the intact ureter prevents the loss of solute from the hyperosmotic papilla. The role of reflux in this regard is unclear.

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