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### Research Article

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## Renal Mechanism of Action of Rat Atrial Natriuretic Factor

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### Abstract

There has been conflict as to whether crude extracts of atrial natriuretic factor increase renal solute excretion by a hemodynamic mechanism or by direct inhibition of tubular transport. To investigate this issue, seven rats were studied during a euvolemic control period and following continuous administration of pure, synthetic 24 amino acid atrial natriuretic factor. A 10–25-fold increase in urinary sodium and chloride excretion occurred with a brisk kaliuresis but little bicarbonaturia. Atrial natriuretic factor caused whole kidney glomerular filtration rate to increase from  $1.17 \pm 0.04$  to  $1.52 \pm 0.07$  ml/min ( $P < 0.005$ ). A parallel increase in single nephron glomerular filtration rate, from  $34 \pm 1$  to  $44 \pm 2$  nl/min ( $P < 0.001$ ), and from  $26 \pm 1$  to  $37 \pm 2$  nl/min ( $P < 0.005$ ) was measured at the end-proximal and early distal nephron sites, respectively. Appropriate for the higher flows were an increase in absolute proximal and loop reabsorptive rates for bicarbonate, chloride, and water, with a slight decrease in fractional solute and volume reabsorption in proximal and loop segments. To exclude the possibility that atrial natriuretic factor increased filtration rate only in anesthetized animals, eight unanesthetized rats were studied. Glomerular filtration rate increased by 45%, from  $2.04 \pm 0.17$  to  $2.97 \pm 0.27$  ml/min ( $P < 0.005$ ) without significant change in renal plasma flow, as reflected by  $^{14}\text{C}$ -para-aminohippurate clearance ( $5.4 \pm 0.5$ – $5.6 \pm 0.9$  ml/min). The clearance and micropuncture data did not preclude changes in relative blood flow distribution to or in transport by deep nephron segments. In conclusion, atrial natriuretic factor appears to increase renal solute excretion predominantly by a hemodynamic mechanism without directly inhibiting superficial tubular transport.

### Introduction

Within the last few years, a vasodilatory, natriuretic compound derived from granules within cardiocytes of the right atrium has been described (1–16). This substance has been very recently characterized as a closely related group of peptides of 21–26 amino acids (2–4) derived from a common precursor

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polypeptide of 152 amino acids (3, 5). The general term atrial natriuretic factor (ANF)<sup>1</sup> has been used to describe these peptides.

The mechanism of action of this factor is controversial. Studies from one laboratory have suggested that the increase in renal solute excretion is due primarily to changes in hemodynamics, specifically an increase in glomerular filtration rate (GFR) (4, 6–8). Other groups have suggested that the renal effect is not mediated by a change in GFR (1, 9–16) but rather by redistribution of blood flow (10) or by direct inhibition of proximal reabsorption (11), of loop reabsorption (10, 12), or of collecting duct reabsorption (13–16). Difficulties with these studies include: (a) use of crude, unpurified extracts of the right atrium (1, 6, 7, 9–16) that may contain contaminants with vasodilatory but not natriuretic properties (17); (b) use of volume contracted animals (10, 14, 15); (c) use of isolated renal membrane vesicles without correlation to in vivo effects (11); (d) use of an in vitro isolated perfused kidney preparation with impaired base-line hemodynamics (4, 6); and (e) unstable time controls (14). To date, there have been no micropuncture investigations examining the renal mechanism of action of ANF using a pure peptide in animals in a euvolemic state.

The principal purpose of the present study was to elucidate the mechanism of renal action of ANF using a pure, synthetic peptide in euvolemic animals. Free-flow micropuncture techniques were used to measure single nephron GFR as well as proximal and loop<sup>2</sup> reabsorption of bicarbonate, chloride, and water in response to ANF. Clearance studies were performed in awake animals to examine the hemodynamic response to ANF in the absence of anesthesia or major surgery.

### Methods

**Animals.** Sprague-Dawley rats weighing  $233 \pm 7$  g were used for micropuncture studies ( $n = 7$  males) or clearance studies ( $n = 8$  females).

**Protocol.** Animals were prepared for micropuncture (18–20) or for clearance studies (20) as previously described. In the micropuncture experiments, animals were replenished with plasma lost consequent to the preparatory surgery (18, 20). In the clearance experiments, animals were allowed at least 1 h to fully regain consciousness after the short-acting anesthesia (methohexital) used for catheter placement. Infusion of bicarbonate Ringer's solution (0.84 ml/h) with [ $^3\text{H}$ ]inulin (100  $\mu\text{Ci}$  prime and 150  $\mu\text{Ci}/\text{h}$  in the micropuncture studies and 15  $\mu\text{Ci}$  prime and 15  $\mu\text{Ci}/\text{h}$  in the clearance studies) and with  $^{14}\text{C}$ -para-aminohippurate

1. *Abbreviations used in this paper:* ANF, atrial natriuretic factor; GFR, glomerular filtration rate; PAH, para-amino-hippurate; SNGFR, single nephron GFR.

2. The superficial loop is defined for the purposes of this study to include the nephron segment between the last accessible loop of the superficial proximal convoluted tubule and the early distal tubule.

(PAH; 5  $\mu$ Ci prime and 5  $\mu$ Ci/h sustaining in the clearance studies only) was then begun. After an hour equilibration, the first control period commenced, with end-proximal and early distal samples taken in the micropuncture studies, or with four consecutive 15-min urine collections obtained in the clearance studies. All blood withdrawn for inulin, PAH, electrolyte, and blood gas measurements was replaced quantitatively with blood obtained from sibling rats on the day of study.

After the first euvoletic control period, synthetic rat 24 amino acid ANF (California Biotechnology, Inc., Palo Alto, CA) (4) was given intravenously as a prime, 12  $\mu$ g/kg, and then as a constant infusion, 1  $\mu$ g/kg  $\cdot$  min. ANF was infused in a modified Ringer's solution designed to replace urinary electrolyte losses (in meq/liter: NaCl, 100; KCl, 35; KHCO<sub>3</sub>, 5; Na<sub>2</sub>HPO<sub>4</sub>, 4; MgSO<sub>4</sub>, 1; and CaCl<sub>2</sub>, 1.8) at 30  $\mu$ l/min in the micropuncture studies and 50  $\mu$ l/min in the clearance studies, the rate designed to be less than or equal to urinary losses. After 15 min for equilibration, the second micropuncture or clearance period was performed identically to the first.

*Measurements and calculations.* Methods for measuring radioiso-

topes and electrolytes in plasma and in urine have been described previously (18–21). Tubular fluid [total CO<sub>2</sub>] was measured by micro-calorimetry and [chloride] by the microtitrimetric method. Methods for calculating filtration and reabsorption of solutes and water have been previously published (18–21). Statistical significance was assessed using the paired *t* test for results in the same animal.

## Results

The results of the micropuncture studies are shown in Table I. Arterial hematocrit, plasma electrolyte composition, and acid-base status were stable after ANF administration and there was only a slight (3 mmHg) decline in blood pressure. Urine sodium and chloride excretion rates increased 10–25-fold and remained stable throughout the study period. The >2.5-fold increase in potassium excretion was normal for the increase in sodium excretion based on previous measurements

*Table I. Micropuncture Studies on the Effect of Atrial Natriuretic Factor on Filtration and Proximal Tubule and Loop Reabsorption of Bicarbonate, Chloride, and Water*

	Control (n = 7)	ANF	P<		Control (n = 7)	ANF	P<
<b>Blood</b>				<b>Total CO<sub>2</sub> (pmol/min)</b>	86 $\pm$ 9	217 $\pm$ 28	0.005
Pressure (mmHg)	113 $\pm$ 3	110 $\pm$ 3	0.005	Cl (peq/min)	2,276 $\pm$ 91	3,320 $\pm$ 172	0.005
Hematocrit (vol%)	42.9 $\pm$ 0.5	42.6 $\pm$ 0.8	NS	<b>Absolute proximal reabsorption</b>			
[Protein] (g/dl)	4.9 $\pm$ 0.1	4.7 $\pm$ 0.1	0.025	H <sub>2</sub> O (nl/min)	17.3 $\pm$ 0.9	20.1 $\pm$ 1.3	0.005
pH	7.41 $\pm$ 0.01	7.43 $\pm$ 0.01	NS	Total CO <sub>2</sub> (pmol/min)	820 $\pm$ 28	976 $\pm$ 35	0.005
PCO <sub>2</sub> (mmHg)	37.5 $\pm$ 0.5	36.1 $\pm$ 0.7	NS	Cl (peq/min)	1,605 $\pm$ 103	1,786 $\pm$ 182	NS
[Na] (meq/liter)	145 $\pm$ 1	145 $\pm$ 1	NS	<b>Fractional proximal reabsorption</b>			
[K] (meq/liter)	3.6 $\pm$ 0.2	3.4 $\pm$ 0.1	NS	H <sub>2</sub> O	0.51 $\pm$ 0.02	0.46 $\pm$ 0.02	0.005
[Total CO <sub>2</sub> ] (mM)	24.2 $\pm$ 0.4	24.5 $\pm$ 0.5	NS	Total CO <sub>2</sub>	0.90 $\pm$ 0.01	0.82 $\pm$ 0.02	0.005
[Cl] (meq/liter)	103 $\pm$ 1	105 $\pm$ 1	0.025	Cl	0.41 $\pm$ 0.02	0.35 $\pm$ 0.03	0.025
<b>Urine (1 kidney)</b>				<b>Distal</b>			
GFR (ml/min)	1.17 $\pm$ 0.04	1.52 $\pm$ 0.07	0.005	SNGFR (nl/min)	26.3 $\pm$ 1.4	36.5 $\pm$ 2.1	0.005
<b>Excretion rate</b>				<b>Collected concentrations</b>			
Volume ( $\mu$ l/min)	2.6 $\pm$ 0.2	14.3 $\pm$ 1.9	0.005	[Total CO <sub>2</sub> ] (mM)	3.7 $\pm$ 0.9	5.2 $\pm$ 1.0	0.05
Na (neq/min)	104 $\pm$ 30	2,518 $\pm$ 478	0.005	[Cl] (meq/liter)	29.4 $\pm$ 2.7	47.9 $\pm$ 5.0	0.005
K (neq/min)	641 $\pm$ 137	1,708 $\pm$ 218	0.005	<b>Delivery from distal tubule</b>			
Total CO <sub>2</sub> (nmol/min)	19 $\pm$ 16	145 $\pm$ 57	0.05	H <sub>2</sub> O (nl/min)	4.1 $\pm$ 0.7	8.0 $\pm$ 1.1	0.025
Cl (neq/min)	324 $\pm$ 84	3,601 $\pm$ 473	0.001	Total CO <sub>2</sub> (pmol/min)	14 $\pm$ 3	37 $\pm$ 5	0.005
<b>Fractional excretion rate</b>				Cl (peq/min)	114 $\pm$ 17	377 $\pm$ 61	0.005
Volume	0.002 $\pm$ 0.0002	0.009 $\pm$ 0.001	0.001	<b>Absolute reabsorption to distal tubule (proximal + loop)</b>			
Na	0.001 $\pm$ 0.0002	0.011 $\pm$ 0.002	0.005	H <sub>2</sub> O (nl/min)	22.2 $\pm$ 1.5	28.5 $\pm$ 2.1	0.025
K	0.146 $\pm$ 0.021	0.321 $\pm$ 0.023	0.005	Total CO <sub>2</sub> (pmol/min)	684 $\pm$ 35	947 $\pm$ 60	0.01
Total CO <sub>2</sub>	0.001 $\pm$ 0.0004	0.003 $\pm$ 0.001	0.025	Cl (peq/min)	2,873 $\pm$ 35	3,836 $\pm$ 234	0.005
Cl	0.002 $\pm$ 0.0006	0.020 $\pm$ 0.002	0.001	<b>Fractional reabsorption to distal tubule (proximal + loop)</b>			
<b>Tubular fluid</b>				H <sub>2</sub> O	0.84 $\pm$ 0.03	0.78 $\pm$ 0.03	0.05
<b>Proximal</b>				Total CO <sub>2</sub>	0.98 $\pm$ 0.01	0.96 $\pm$ 0.01	0.025
SNGFR (nl/min)	34.1 $\pm$ 1.1	44.3 $\pm$ 2.2	0.001	Cl	0.96 $\pm$ 0.01	0.91 $\pm$ 0.01	0.005
<b>Filtered load</b>							
Total CO <sub>2</sub> (pmol/min)	907 $\pm$ 27	1,193 $\pm$ 61	0.001				
Cl (peq/min)	3,881 $\pm$ 108	5,106 $\pm$ 247	0.001				
<b>End-proximal</b>							
[Total CO <sub>2</sub> ] (mM)	5.1 $\pm$ 0.4	8.8 $\pm$ 0.7	0.005				
[Cl] (meq/liter)	135 $\pm$ 2	138 $\pm$ 3	NS				
<b>Delivery out of proximal tubule</b>							
H <sub>2</sub> O (nl/min)	16.9 $\pm$ 0.8	24.1 $\pm$ 1.5	0.001				

( $n = 186$ ) in euvolemic animals or in animals subjected to volume expansion or carbonic anhydrase inhibition (18–21). Bicarbonaturia was slight.

ANF caused whole kidney GFR to increase from  $1.17 \pm 0.04$  to  $1.52 \pm 0.07$  ml/min ( $P < 0.005$ ) with a parallel increase in single nephron GFR (SNGFR), from  $34 \pm 1$  to  $44 \pm 2$  nl/min ( $P < 0.001$ ) and from  $26 \pm 1$  to  $37 \pm 2$  nl/min ( $P < 0.005$ ) measured at the end-proximal and early distal nephron sites, respectively, as illustrated in Fig. 1. There was an increase in absolute proximal total  $\text{CO}_2$ , chloride, and water reabsorption, with a decline in fractional reabsorption of each (Table I). These changes in proximal solute and volume transport were appropriate for the increase in SNGFR as seen in Fig. 2. The shaded areas in Fig. 2 represent the normal reabsorptive rates for euvolemic Sprague-Dawley rats ( $n = 26$ ) with spontaneous variation of SNGFR over the range observed in the present study (20, 22). Similarly, at the early distal micropuncture site, measurements of absolute total  $\text{CO}_2$ , chloride, and volume reabsorption were increased after ANF administration. Again, the slight decline in fractional solute and volume reabsorptive rates (e.g., the decrease in fractional chloride reabsorption from  $0.96 \pm 0.01$  to  $0.91 \pm 0.01$ ,  $P < 0.005$ ) was consistent with the normal response to increased flow by loop transport processes (23, 24).

Studies in awake animals were performed to preclude the possibility that ANF increased GFR only in anesthetized animals. As shown in Table II, blood pressure and plasma electrolyte composition were relatively stable. Base-line urinary electrolyte excretion rates were higher than had been obtained in the micropuncture experiments but ANF still caused a stable, 5–7-fold increase in sodium and chloride excretion with a brisk kaliuresis and slight bicarbonaturia. GFR increased by 45%, from  $2.04 \pm 0.17$  to  $2.97 \pm 0.27$  ml/min ( $P < 0.005$ ), as shown in Fig. 1. However, the increase in GFR was not accompanied by a rise in renal plasma flow, as estimated by PAH clearance ( $5.4 \pm 0.5$ – $5.6 \pm 0.9$  ml/min, NS). PAH clearance is an accurate reflection of renal plasma flow, since extraction of PAH is unaltered by ANF and PAH clearance has correlated

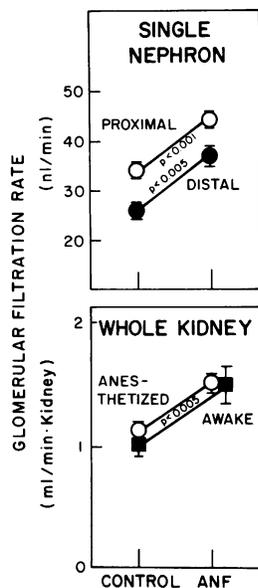


Figure 1. Change induced by ANF in single nephron glomerular filtration rate (Top) measured at the end-proximal (open circles) and early distal (closed circles) sites and in whole kidney GFR (Bottom) measured in anesthetized (open circles) and awake (closed squares) euvolemic rats.

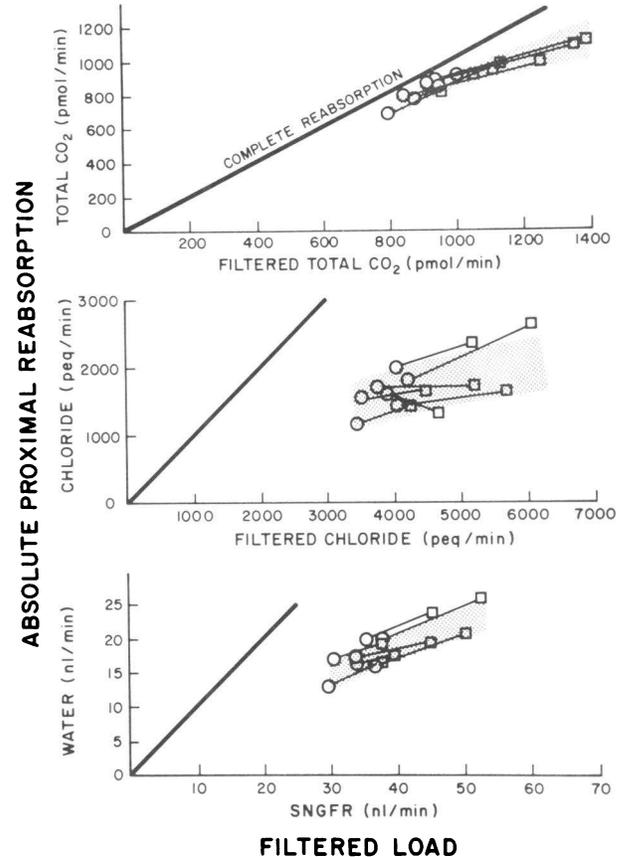


Figure 2. Effect of ANF (open squares) compared with control euvolemic values (open circles) on absolute proximal reabsorption of total  $\text{CO}_2$  (Top), chloride (Middle), and water (Bottom) as a function of filtered load. Shaded areas represent normal euvolemic reabsorptive values at comparable filtered loads from previous studies of 26 Sprague-Dawley rats (20, 22).

well with plasma flow measured by electromagnetic flowmeter during ANF administration (8). Assuming 90% extraction of PAH, the calculated filtration fraction rose from 0.35 to 0.50.

## Discussion

The present study is in agreement with those of Atlas and his colleagues (4, 6–8) in finding that ANF increases renal solute excretion principally by hemodynamic means rather than by direct tubular transport inhibition.

The increment in absolute proximal bicarbonate, chloride, and volume reabsorption in response to the increase in SNGFR induced by ANF appeared to be appropriate based on previous observations (Fig. 2).<sup>3</sup> The lack of substantial bicarbonaturia also makes the proximal tubule an unlikely site of direct generalized inhibition by ANF. Similarly, the superficial loop of Henle appeared to increase solute reabsorption normally in

3. While a depression in filtration fraction and peritubular protein concentration selectively decreases proximal  $\text{NaCl}$  reabsorption (18–20), it has yet to be demonstrated that a rise in filtration fraction, as observed in these studies, is associated with an increase in proximal  $\text{NaCl}$  reabsorption under normal free-flow conditions.

Table II. Clearance Studies in Awake Rats on the Effect of Atrial Natriuretic Factor on Whole Kidney Filtration Rate and Urinary Solute Excretion

	Control (n = 8)	ANF	P<
<b>Blood</b>			
Pressure (mmHg)	114±1	112±1	NS
Hematocrit (vol%)	42.4±0.9	45.2±0.6	0.005
[Protein] (g/dl)	5.4±0.1	5.7±0.1	0.005
[Na] (meq/liter)	141±1	139±1	NS
[K] (meq/liter)	3.7±0.1	3.5±0.1	NS
[Cl] (meq/liter)	96±1	95±1	NS
<b>Urine (2 kidneys)</b>			
GFR (ml/min)	2.04±0.17	2.97±0.27	0.005
PAH clearance (ml/min)	5.40±0.46	5.58±0.91	NS
<b>Excretion rate</b>			
Volume (μl/min)	33±3	118±10	0.001
Na (neq/min)	1,819±265	13,353±1,129	0.001
K (neq/min)	1,450±133	4,097±216	0.001
Total CO <sub>2</sub> (nmol/min)	147±68	1,024±352	0.05
Cl (neq/min)	2,637±231	13,864±1,079	0.001
<b>Fractional excretion rate</b>			
Volume	0.017±0.0016	0.042±0.004	0.005
Na	0.007±0.0010	0.034±0.003	0.001
K	0.201±0.021	0.414±0.044	0.001
Total CO <sub>2</sub>	0.003±0.0013	0.012±0.005	NS
Cl	0.014±0.0012	0.051±0.004	0.001

response to the increased load (Table I). The small decrease (−5%) in fractional sodium chloride reabsorption observed as flow increased is expected (23, 24), and is more than enough to account for the observed increase in fractional sodium and chloride excretion (1–2%). In addition to the change in delivered load, however, the present data do not preclude a small direct or indirect (i.e., by medullary washout) effect by ANF on loop transport of juxtamedullary nephrons (8, 10, 12). Finally, although a major effect by ANF on cortical collecting tubule function has been proposed (13–16), this appears to be unlikely because the large stimulation of urinary potassium excretion was appropriate for the natriuresis (18–21). This kaliuretic response to ANF stands in contrast to what is expected with diuretics that act directly on the cortical collecting tubule, such as amiloride or triamterene.

The 30–45% acute increase in GFR was associated with a 1–4% increment in fractional sodium and chloride excretion. However, a question arises as to whether this excretory response was appropriate, and not excessive, for the increased load. Put another way, it is not clear a priori that the normal renal response to an acute rise in GFR is for 6–10% of the increment in filtered sodium load to escape tubular reabsorption, as was observed in these studies. There have been only a few previous studies which have examined the load dependence of renal sodium reabsorption when GFR is acutely raised above normal values. In these studies, disruption of renal autoregulation or infusion of substances thought not to have direct tubular effects, such as glucagon or glycine, have acutely increased GFR by 17–50% above normal, and 5–19% of the increment in filtered sodium load has been excreted (25–28). Thus, the present changes in solute excretion evoked by ANF are not

inconsistent with those expected in the normal renal response to a large, acute augmentation in GFR.

In addition to the rise in GFR induced by ANF, redistribution of intrarenal blood flow may also contribute to the observed natriuresis and chloriuresis (10). This possibility is not rigorously excluded in the present studies, although the increase in superficial SNGFR was proportional to the increase in whole kidney GFR (Table I and Fig. 1).

The increase in GFR might be mediated by a substantial alteration in the hydraulic permeability-filtration area coefficient ( $K_f$ ), if filtration disequilibrium is obtained. Alternatively, if there were filtration equilibrium, then a rise in net transmembrane hydraulic filtration pressure occurred, mediated by afferent arteriolar vasodilation and efferent vasoconstriction. The changes in afferent and efferent resistances must have been reciprocal, since systemic blood pressure and renal plasma flow (as reflected by PAH clearance), and hence total renal vascular resistance, were unchanged, as has been found by others (8). The impressive increase in filtration fraction that resulted, from 0.35 to 0.50, is unprecedented when compared with other vasoactive substances (29). Thus, these results suggest either that  $K_f$  increased substantially or, more likely (given the relatively high filtration fraction in the control period), that glomerular capillary hydraulic pressure increased to  $\geq 64$  mmHg from a control value of 45 mmHg.<sup>4</sup> Direct measurement of intraglomerular pressures will be needed to confirm these predictions.

In conclusion, atrial natriuretic factor markedly increases GFR in euvoletic rats without a demonstrable direct inhibition of proximal or loop transport in superficial nephrons. The supernormal GFR appears to account for the rise in urinary solute excretion, although a change in relative blood flow distribution to or in transport by deep nephron segments cannot be excluded as contributing to the natriuresis and chloriuresis.

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4. Glomerular capillary hydraulic pressure was assumed to be greater than or equal to the sum of efferent arteriolar oncotic pressure and Bowman's space hydraulic pressure. Efferent arteriolar protein oncotic pressure was calculated by the method of Brenner et al. (30), and it was assumed that: efferent protein concentration equals afferent protein concentration/(one minus filtration fraction); filtration fraction equals GFR/(PAH clearance/0.9); and Bowman's space hydraulic pressure equals 10 mmHg.

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