Chronic Hydronephrosis: Observations on the Mechanism of the Defect in Urine Concentration[1] (34850)

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(Introduced by H. Brown)

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Chronic hydronephrosis results in an impairment in urine concentration (1, 2). The function of the ascending limb in chronic hydronephrosis has been examined by Suki *et al.* (3). In studies during water diuresis it was concluded that the ascending limb is intact, since solute-free water clearance (C_{H_2O}) corrected to the glomerular filtration rate (GFR) was actually greater on the hydronephrotic as compared to the control side. This difference was attributed to overperfusion of the residual nephrons of the hydronephrotic kideny although other possibilities were not eliminated.

The present experiments were designed in an attempt to elucidate further the defect in urine concentration in chronic hydronephrosis.

Methods. Mongrel dogs of either sex weighing 15–20 kg were used. Chronic urinary tract obstruction was produced by placing a 2-cm cellophane band around the left ureter about 5–6 cm above its entry into the bladder. A catgut suture was placed snugly at each end of the cellophane band, and the free end of the cellophane sutured to the posterior abdominal wall. To ascertain the presence and degree of hydronephrosis, an intravenous pyelogram was performed 1 week later while the animals were under light sedation, and repeated at weekly intervals thereafter, until a satisfactory degree of hydronephrosis was judged to have developed. In most animals this required approximately 2 weeks, although the interval varied between 1 and 6 weeks.

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On the day of study the animals were anesthetized by the intravenous administration of pentobarbital, 30 mg/kg body weight, and the level of anesthesia maintained throughout the study by the periodic administration of 5–10 mg of pentobarbital as needed. The femoral vein and artery were then exposed on one side and a polyethylene catheter introduced into each. Through a small midline suprapubic incision the ureters were cannulated near the point of their entry into the bladder. The ureteral catheter on the left side was advanced to just below the point of partial obstruction. The one on the right was advanced into the renal pelvis.

Hydropenia and solute diuresis studies. Eight dogs were deprived of food and water for 24–36 hr prior to study. One hour prior to the study, each animal received 5 U Pitressin Tannate in oil intramuscularly. In addition, a maintenance solution calculated to deliver 50 mU/kg/hr of aqueous Pitressin was infused throughout the study. Thirty minutes after the start of maintenance Pitressin, a urine sample was collected for the determination of maximal urine osmolality. A 4% sodium chloride solution was then infused at 1 ml/min and the rate gradually increased. Urine was collected for periods of 10–30 min from each ureter as flow rate increased. At the mid-point of each collection, blood samples were taken.

Water diuresis studies. Each of nine dogs received 30 ml of water per kg body weight via a nasogastric tube on the day before study and again 1 hr before beginning the experiment. Water diuresis was maintained by the intravenous infusion of hypotonic saline (0.22%). When water diuresis was well

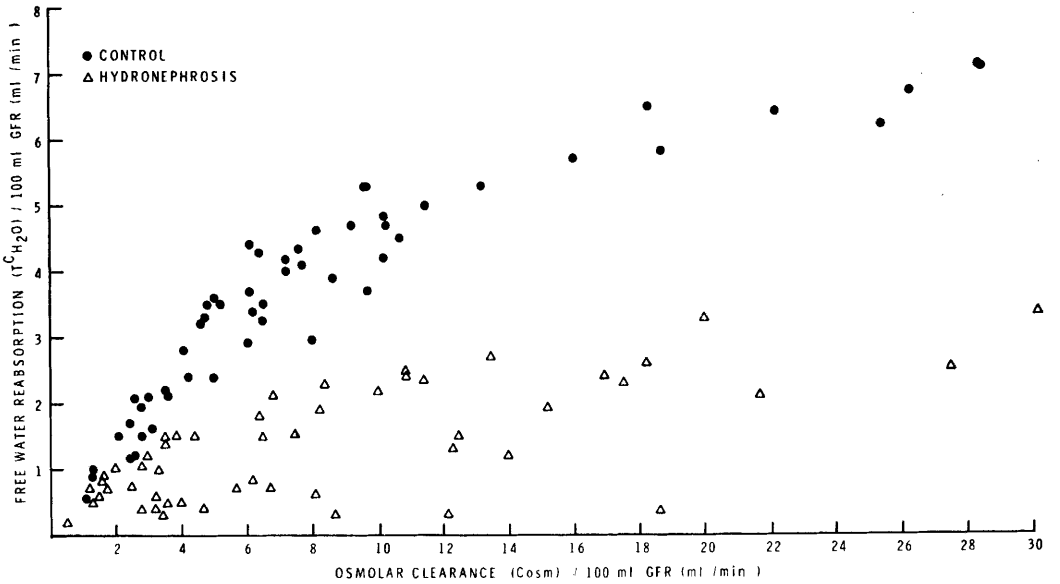

FIG. 1. The effect of chronic hydronephrosis on renal concentrating capacity. Free water reabsorption ($T^C_{H_2O}$) is plotted against osmolar clearance (C_{osm}), both values corrected to 100 ml GFR.

established, two urine and blood collections were made. Hypotonic saline (0.45%) was then started at gradually increasing rates and collections continued as the rate of urine flow rose.

Tissue Analysis. Both kidneys were removed immediately after the last collection period in six of the dogs undergoing water diuresis and in six hydropenic dogs undergoing hypertonic saline diuresis. Sections of cortex, outer medulla, and papillary tip were removed for analysis of sodium and potassium by methods previously described (4).

The glomerular filtration rate was measured by the clearance of sodium iothalamate ^{125}I as described previously from this laboratory (5). Sodium and potassium in urine and plasma were determined by flame photometry. Osmolality was measured in an Advanced osmometer. Osmolar clearance (C_{osm}), free water clearance and free water reabsorption ($T^C_{H_2O}$) were calculated by standard formulae.

Results. Maximum urine osmolality (U_{max}). The maximum urine osmolality was consistently and significantly lower on the hydronephrotic side as compared to the normal control kidney ($p<.01$). The mean value of U_{max} on the normal side was 1409 ± 364 mOsm/kg H_2O, whereas, on the hydronephrotic side it was 714 ± 215 mOsm/kg H_2O. U_{max} on the diseased kidney was never lower than the plasma osmolality, indicating the persistence of some concentrating ability.

Free water reabsorption. The results of two representative experiments, one with moderate and the other with severe reduction in GFR in the experimental kidney, are presented in Table I. With infusion of hypertonic saline, urine flow (V), C_{osm}, and $T^C_{H_2O}$ rose progressively on both sides. Except in one animal (Dog 18-69), these values were lower on the hydronephrotic side. In Dog 18-69, V and C_{osm} were higher on the hydronephrotic side.

In all animals GFR was reduced below control on the hydronephrotic side. The degree of reduction, however, varied from one experiment to another and ranged from 12–89%.

Since both C_{osm} and $T^C_{H_2O}$ were reduced on the hydronephrotic side, it was important to determine whether the reduction in $T^C_{H_2O}$ was proportional to that of C_{osm}. To permit comparison of the two sides, all values of C_{osm}

TABLE I. Effect of Chronic Hydronephrosis on Water and Solute Excretion.[a]

Time	V (ml/min) C	V (ml/min) H	GFR (ml/min) C	GFR (ml/min) H	$U_{Na}V$ (μEq/min) C	$U_{Na}V$ (μEq/min) H	U_KV (μEq/min) C	U_KV (μEq/min) H	U_{osm} (mOsm/kg) C	U_{osm} (mOsm/kg) H	C_{osm} (ml/min) C	C_{osm} (ml/min) H	$T^c_{H_2O}$ (ml/min) C	$T^c_{H_2O}$ (ml/min) H	C_{osm}/100 ml (GFR) C	C_{osm}/100 ml (GFR) H	$T^c_{H_2O}$/100 ml (GFR) C	$T^c_{H_2O}$/100 ml (GFR) H	Plasma Na^+ (mEq/liter)	Plasma K^+ (mEq/liter)	Plasma Osm (mOsm/kg)
−115	5 U Pitressin Tannate in oil im																				
− 50	Maintenance solution of iothalamate ^{125}I in 0.9% NaCl with aqueous Pitressin (50 mU/kg/hr) at 0.15 ml/min																				
0	Begin 4% NaCl at 1 ml/min and increase gradually																				
Dog 18-69																					
50– 65	0.1	0.7	35	22	35	93	24	23	1328	370	0.5	0.8	0.35	0.1	1.3	3.6	1.0	0.5	152	3.9	316
65– 80	0.3	1.2	33	23	89	175	22	32	981	374	0.9	1.4	0.6	0.2	2.7	6.2	1.8	0.9	153	3.7	322
80–100	0.5	1.0	35	22	137	154	22	24	776	374	1.2	1.2	0.7	0.16	3.4	5.4	2.0	0.7	155	3.8	322
120–130	1.3	2.9	29	24	351	484	38	44	596	342	2.4	3.0	1.1	0.14	8.3	12.2	3.8	0.6	159	3.6	326
Dog 401-69																					
40– 70	0.4	0.1	23	4	114	13	18	4	1150	573	1.1	0.1	0.8	0.03	4.8	2.5	3.5	0.75	162	3.2	344
85–110	1.8	0.5	22	4	454	131	40	6	560	425	2.9	0.7	1.1	0.1	13.2	18.2	5.2	2.5	166	3.2	350
130–150	4.2	1.0	22	4	940	191	43	10	483	409	5.6	1.1	1.4	0.1	25.4	27.5	6.4	2.5	177	3.1	365

[a] Abbreviations: V = urine flow rate; GFR = glomerular filtration rate; $U_{Na}V$ and U_KV = urine sodium and potassium excretion; U_{osm} = urine osmolality; C_{osm} = osmolar clearance; $T^c_{H_2O}$ = free water reabsorption; C = control side; H = hydronephrotic side; Osm = osmolality.

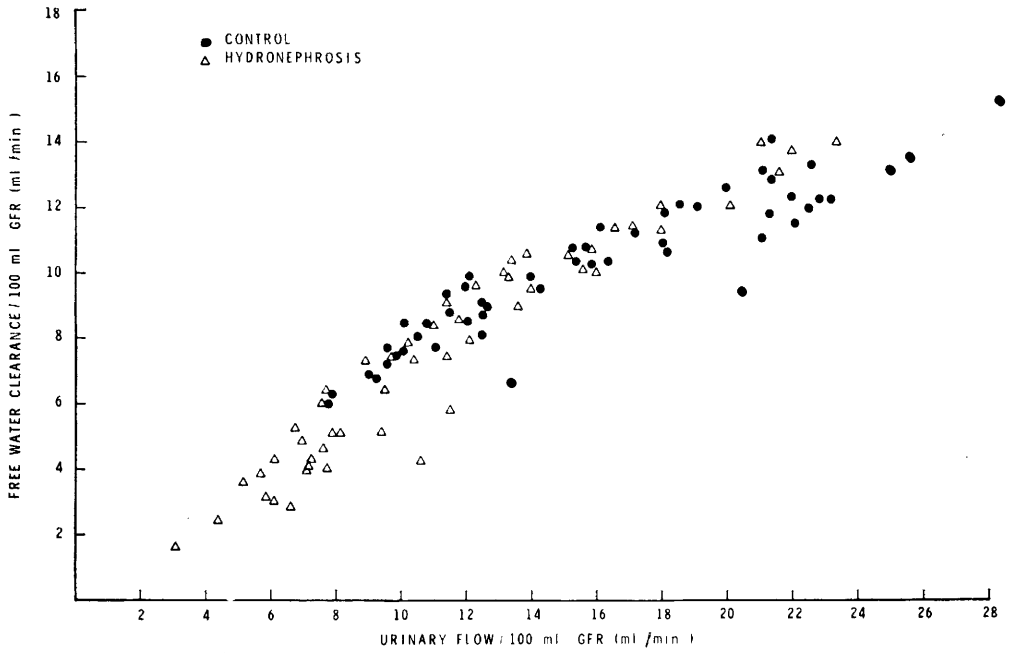

FIG. 2. The effect of chronic hydronephrosis on renal diluting capacity. Free water clearance (C_{H_2O}) is plotted against urine flow rate (V), both values corrected to 100 ml GFR.

and $T^C_{H_2O}$ were corrected to 100 ml GFR and plotted against each other (Fig. 1). With increasing C_{osm}, from 1.2 to 28.4 ml/min/100 ml GFR, there was a progressive rise in $T^C_{H_2O}$ from 0.6 to 6.7 ml/min/100 ml GFR on the control side. On the obstructed side, as C_{osm} rose from 0.5 to 30.4 ml/min/100 ml GFR, $T^C_{H_2O}$ rose from 0.2 to 3.3 ml/min/100 ml GFR. Throughout this range there is a clear-cut reduction in $T^C_{H_2O}$ on the hydronephrotic as compared to the control side, at every level of C_{osm}.

Free water clearance. The results of these studies are shown in Fig. 2. C_{H_2O}/100 ml GFR is plotted as a function of V/100 ml GFR. No difference in C_{H_2O} is present between the hydronephrotic and the control side throughout the range of distal delivery examined.

Tissue analysis. The results of tissue analysis in hydropenic and hydrated animals are shown in Table II. Papillary and medullary sodium and nonurea solute concentration were consistently lower on the hydronephrotic as compared to the control side in all dogs during hydropenia. This was also the case during water diuresis except in one dog (H-7). Paired analysis of the differences in nonurea solute concentration between control and experimental kidneys revealed them to be significant in the papilla ($p < .01$ in hydropenic group; $p < .05$ in the hydrated group) and medulla ($p < .01$ in hydropenic and hydrated groups).

Discussion. The results demonstrate that there is a marked impairment in the ability to maximally concentrate the urine (U_{max}) and in the capacity to reabsorb solute free water ($T^C_{H_2O}$) in the chronically hydronephrotic kidney of the dog. In contrast, as has been previously shown, the renal diluting capacity is preserved (3).

Impairment in concentrating capacity may result from: (1) a reduction in sodium delivery to the ascending limb of Henle's loop; (2) diminished sodium transport in this segment of the nephron; (3) diminished permeability of the collecting duct to water; or (4) altered medullary hemodynamics (6, 7). Reduction in sodium delivery to the distal

TABLE II. The Effect of Chronic Hydronephrosis on the Electrolyte and Water Content of the Renal Medulla and Papilla.

	Medulla								Papilla							
	Water (% wet wt)		Sodium[a]		Potassium[a]		NUS[a]		Water (% wet wt)		Sodium[a]		Potassium[a]		NUS[a]	
Dog no.	C	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H
Hydropenic dogs																
H-2	85	88	199	140	77	70	552	420	96	96	292	138	65	54	714	384
H-4	84	85	237	193	59	59	592	504	86	87	218	199	70	50	576	498
H-5	80	82	160	141	83	79	486	440	84	85	296	215	91	75	774	580
H-6	82	86	174	148	65	59	478	414	87	87	237	183	58	57	590	480
H-12	84	81	220	142	80	71	600	426	89	86	315	181	79	53	788	468
401-69	84	87	200	193	59	51	518	488	87	88	225	193	55	45	560	476
							$p < .01$								$p < .01$	
Hydrated dogs																
H-7	84	87	198	131	102	74	600	410	89	90	207	219	75	66	564	570
H-11	85	87	146	134	59	52	410	372	88	90	183	124	56	41	478	330
H-18	83	84	163	122	58	52	442	348	87	88	205	172	45	43	500	430
308-69	86	85	173	112	49	59	444	342	93	94	204	179	88	102	584	562
364-69	87	86	198	184	66	64	528	496	94	96	196	179	49	49	490	456
394-69	87	87	162	143	67	58	458	402	90	90	212	216	79	57	582	546
							$p < .01$								$p < .05$	

[a] Expressed per kilogram tissue water. C = control kidney; H = hydronephrotic kidney.

nephron may be the result of either reduced GFR per nephron or enhanced proximal tubular reabsorption. In studies during water diuresis it was shown that the relationship between GFR and functioning renal mass, measured as Tm PAH, was increased in chronic hydronephrosis (3). This indicates that GFR per nephron is increased in the chronically hydronephrotic kidney, rather than decreased. Moreover, fractional C_{H_2O} in those studies was increased. indicating that delivery of sodium to the distal diluting segment of the nephron must have been increased also. These findings, therefore, mitigate against decreased delivery of sodium to the ascending limb of Henle's loop as an explanation for the impaired urinary concentration.

Diminished sodium transport in the ascending limb of Henle's loop may also lead to reduced $T^{C}_{H_2O}$, and U_{max} (6). In the present experiments, however, C_{H_2O}, a measurement of sodium reabsorption in this segment of the nephron (8), was intact. This finding is inconsistent with an impairment in sodium transport in the ascending limb. The normal relationship of C_{H_2O} to V observed in the present studies is also evidence against diminution in water permeability of the collecting duct. Impairment in water permeability of the collecting duct would be expected to reduce obligatory water back diffusion during water diuresis and alter the slope of the regression of C_{H_2O} on V (4). This was obviously not the case (Fig. 2). The possibility exists that a small defect in sodium transport in the ascending limb may be exactly counterbalanced by a defect in water permeability of the collecting duct, resulting in a fortuitously normal relation of C_{H_2O} to V. This is considered unlikely. Even if present, decreased water back diffusion will not explain the observed decrease in nonurea solute concentrations in the medulla and papilla of the diseased kidney during both hydropenia and water diuresis.

Increased medullary blood flow may dissipate medullary hypertonicity (9) and lead to the concentrating defect. Data on this point were not obtained in this study. An alterna-

tive explanation may be a decrease in the number of functioning loops of Henle in the medulla, a possibility strongly suggested by other studies (1, 3, 10). It is possible, therefore, that the reduction in the functioning nephrons results in a decrease in the amount of sodium transported into the interstitium and, therefore, in reduced medullary tonicity. This would result in a decrease in free water back diffusion out of the collecting duct and lead to the impaired urinary concentrating ability and capacity.

Summary. The renal concentrating and diluting mechanism was examined in dogs with unilateral chronic hydronephrosis and compared to the contralateral normal side. Urine concentrating ability and concentrating capacity were markedly impaired in the chronically hydronephrotic kidney. However, as previously reported, fractional free water clearance over a large range of distal delivery was identical in both kidneys. Significant reductions in papillary and medullary nonurea solute concentration were present in the hydronephrotic kidneys as compared to controls during both hydropenia and hydration.

It is postulated that reduction in the number of functioning nephrons in the medulla results in a decrease in sodium transport into the interstitium and, therefore, in reduced medullary hypertonicity. This, by decreasing free water back diffusion out of the collecting duct, would result in the impaired urinary concentrating ability and capacity observed in chronic hydronephrosis.

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