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### Research Article

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In separate studies, subjects were progressively infused with saline to 57 ( $E_1$ ) and to 80 ( $E_2$ ) ml/kg body wt, and appeared to divide into "excreters" (maximum  $U_{Na}V > 1000 \mu\text{Eq}/\text{min}$ ) and "nonexcreters" (maximum  $U_{Na}V < 550 \mu\text{Eq}/\text{min}$ ). In the excreters, GFR rose, proximal FSR decreased by 7.1% after  $E_1$  and only 0.9% further after  $E_2$ . Distal FSR fell by 14.8% after  $E_1$  and by an additional 4.9% after  $E_2$ . In the nonexcreters, GFR was stable and proximal FSR did not fall significantly after  $E_1$  or  $E_2$ . Distal FSR decreased 4.5% after  $E_1$  and 1.3% further after  $E_2$ . It is concluded that both acute and chronic extracellular expansion decrease proximal FSR in man, but only acute loading depresses distal FSR. Ability of some men to excrete sodium rapidly after acute infusion is related to larger increases [...]

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# Tubular Reabsorption of Sodium during Acute and Chronic Volume Expansion in Man

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**ABSTRACT** Renal hemodynamics and tubular fractional sodium reabsorption (FSR) were evaluated by clearance techniques during acute and chronic extracellular volume expansion in man.  $(1 - V/GFR) \times 100$  was used as an index of proximal and  $(C_{H_2O}/V) \times 100$  as an estimate of distal fractional reabsorption. After acute loading with isotonic saline 37 ml/kg body wt, proximal FSR decreased by 4.8% and distal FSR decreased by 4.4%. After comparable chronic expansion by mineralocorticoids ("escape"), proximal FSR also decreased by 3.9%, but distal reabsorption was not altered.

In separate studies, subjects were progressively infused with saline to 57 ( $E_1$ ) and to 80 ( $E_2$ ) ml/kg body wt, and appeared to divide into "excreters" (maximum  $U_{Na}V > 1000 \mu\text{Eq}/\text{min}$ ) and "nonexcreters" (maximum  $U_{Na}V < 550 \mu\text{Eq}/\text{min}$ ). In the excreters, GFR rose, proximal FSR decreased by 7.1% after  $E_1$  and only 0.9% further after  $E_2$ . Distal FSR fell by 14.8% after  $E_1$  and by an additional 4.9% after  $E_2$ . In the nonexcreters, GFR was stable and proximal FSR did not fall significantly after  $E_1$  or  $E_2$ . Distal FSR decreased 4.5% after  $E_1$  and 1.3% further after  $E_2$ . It is concluded that both acute and chronic extracellular expansion decrease proximal FSR in man, but only acute loading depresses distal FSR. Ability of some men to excrete sodium rapidly after acute infusion is related to larger increases in GFR and greater decreases in both proximal and distal FSR than occur in men in whom natriuresis is more limited.

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## INTRODUCTION

Numerous clearance studies have established that overall tubular reabsorption of sodium is inhibited by acute saline infusion in the dog (1, 2). The same phenomenon probably occurs during chronic expansion of extracellular volume by mineralocorticoids and dietary salt (3, 4). Micropuncture experiments have demonstrated convincingly that the proximal tubule is one site at which fractional sodium reabsorption (FSR)<sup>1</sup> is inhibited by saline loading (5). The evidence is conflicting as to whether the magnitude of proximal inhibition is correlated with the volume of saline infused (6-9). One study (10) suggested that chronic extracellular expansion also inhibits proximal FSR but subsequently (11) proximal FSR was found to be unchanged. Both clearance and micropuncture experiments have suggested that distal FSR is inhibited during saline infusion<sup>2</sup> (11) but conclusive evidence for distal inhibition is lacking (12). There are no data on distal FSR during chronic expansion.

There is little information about any of these points during volume expansion in man. We have used clearance techniques to characterize proximal and distal FSR during acute and chronic volume expansion in normal

<sup>1</sup> Abbreviations used in this paper:  $C_{H_2O}$ , free-water excretion;  $C_{H_2O}/V$ , ratio of free-water clearance to urinary volume;  $C_{In}$  and  $C_{PAH}$ , clearance of inulin and PAH;  $C_{Osm}$ , osmolar excretion; ECF, extracellular fluid;  $F_{Na}$ , filtered load of sodium;  $FE_{Na}$ , fraction of filtered sodium excreted; FSR, fractional sodium reabsorption;  $P_{Na}$ , plasma sodium concentration; PAH, *p*-aminohippurate;  $U_{Na}V$ , urinary sodium excretion;  $U_{Osm}$ , urinary osmolality;  $V$ , urine flow;  $V/GFR$ , ratio of urinary volume to inulin clearance.

<sup>2</sup> Davidman, M., E. Alexander, R. Lalone, and N. G. Levinsky. 1972. Nephron function during volume expansion in the rat. *Am. J. Physiol.* 223: 188.

subjects. The results indicate that both proximal and distal FSR can be inhibited by volume loading in man. However, the tubular responses to acute and chronic expansion differ. Moreover, there were striking differences among subjects in the magnitude of the tubular response to acute, progressive saline loading.

## METHODS

All subjects were studied as inpatients of a metabolic research unit. They had no evidence of renal, cardiovascular, or endocrine disorders and were males between 21 and 45 yr of age. Urine was obtained by voluntary voiding or indwelling bladder catheter. An i.v. infusion of inulin and *p*-aminohippurate (PAH) in isotonic saline was maintained at a rate of approximately 0.5 ml/min throughout each study. Plasma samples for measurement of osmolality, sodium, inulin, and PAH were obtained approximately every 30 min throughout each experiment. All studies were begun early in the morning with the subject in bed.

**Protocol I.** Nine subjects ate a constant diet containing 200–250 mEq of Na daily for 2–5 days before the initial clearance study. After an overnight fast, 10 mg desoxycorticosterone acetate was injected and 20 ml/kg body wt of water were ingested. Throughout the remainder of the experiment, subjects drank water equal to total urine output in the preceding clearance period plus about 10% additional at 10–15 min intervals. After  $U_{O_{sm}}$  had stabilized at less than 75 mOsm/kg, three to five collections were obtained. 0.85% saline was then infused at 35 ml/min for 1 hr, then decreased to 6–8 ml/min for the remainder of the study. Water drinking continued throughout the infusion, so that the net effect was to produce hypotonic expansion. Approximately 90 min after the start of the saline infusion, three to five additional periods were collected. Total saline infusion averaged  $37 \pm 3$  ml/kg body wt. Immediately after the initial study, six subjects were given 20 mg/day of desoxycorticosterone acetate and maintained on the same diet. After establishment of “mineralocorticoid escape” (constant body weight with sodium intake and excretion approximately equal) over a period of 6–9 days, the clearance studies were repeated in an identical manner.

**Protocol II.** Subjects ate a constant diet of 100–150 mEq of sodium daily before study. After an overnight fast, they ingested 20 ml/kg of water and thereafter water intake equalled or exceeded urinary output. Urine collections were obtained with the subject briefly standing at the bedside. After  $U_{O_{sm}}$  had stabilized at less than 75 mOsm/liter, four to five control collections were begun. Upon completion of the control periods, 3–3.5 liters of 0.85% saline was infused over the next 60 min. The rate was then decreased to approximately 10 ml/min and after 30 min the first set of experimental periods ( $E_1$ ) was obtained. Total saline infused averaged 57 ml/kg (range 43–71). The saline infusion was then increased to 20–30 ml/min for 30 min and then slowed to 10 ml/min. After 15 min, the second set of experimental periods was obtained ( $E_2$ ). Total saline infusion averaged 80 ml/kg (range 69–97).

Analytical methods in this laboratory have been described previously (2). Each individual value in the tables and figures is the mean of at least three periods during which the clearance of inulin ( $C_{In}$  or GFR) was stable.

In this paper, proximal and distal are defined on a functional basis, proximal meaning that portion of the nephron between the glomerulus and the diluting site; distal meaning

that portion at or beyond the diluting site.  $(V/GFR) \times 100$ , the ratio of urine flow (V) to GFR during water diuresis, is used as an approximate index of the per cent of filtered sodium and water delivered to the diluting site, and  $[1 - (V/GFR)] \times 100$ , the per cent reabsorbed before the diluting site.  $(C_{H_2O}/V) \times 100$  the ratio of free-water clearance  $(V - C_{O_{sm}})$  to V, is used as an estimate of fractional reabsorption of sodium by the diluting segments. The fraction of filtered sodium ( $C_{In} \times P_{Na}$ ) excreted ( $FE_{Na}$ ), equals the ratio of excreted to filtered sodium multiplied by 100. Statistical significance was determined by Student's *t* test.

## RESULTS

*Effect of saline infusion on sodium reabsorption during water diuresis before and after “mineralocorticoid escape.”* The effect of saline infusion and “mineralocorticoid escape” on several parameters of renal function in a representative subject studied according to protocol I is shown in Table I. The mean values for six subjects so studied are recorded in Table II and Fig. 1.

After escape, the subjects had gained  $2.8 \pm 0.7$  kg in weight.  $C_{In}$  increased in each subject after escape (mean 18%) while  $C_{PAH}$  rose in all but one. Filtration fraction was  $0.25 \pm 0.01$  before and  $0.23 \pm 0.01$  after escape.  $1 - (V/GFR) \times 100$  decreased in every subject, mean 89–85% ( $P < 0.01$ );  $C_{H_2O}/V$  was unchanged at 81%. Sodium excretion and the  $FE_{Na}$  increased after escape in five of the six subjects studied and the changes were both significant ( $P < 0.01$ ).

The changes in  $1 - (V/GFR)$  and  $(C_{H_2O}/V)$  in response to infusion of  $37 \pm 3$  ml/kg saline were determined in these six subjects before and after escape. After saline

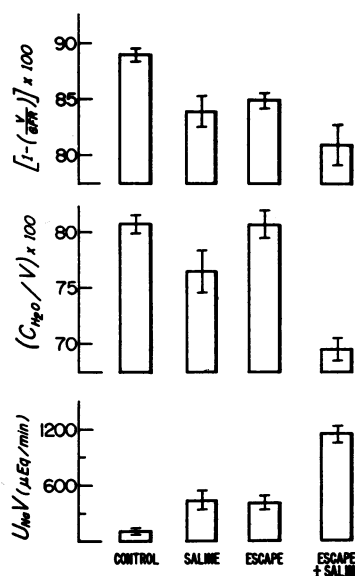


FIGURE 1 The effect of acute (saline) and chronic (escape) expansion on proximal  $[(1 - V/GFR) \times 100]$  and distal  $[(C_{H_2O}/V) \times 100]$  fractional sodium reabsorption and on sodium excretion.

TABLE I  
Representative Experiment—Protocol I

Time	C <sub>IN</sub>	C <sub>PAH</sub>	P <sub>Na</sub>	F <sub>Na</sub>	V	U <sub>Osm</sub>	[1 - (V/ GFR)] × 100	C <sub>H<sub>2</sub>O</sub>	(C <sub>H<sub>2</sub>O</sub> /V) × 100	C <sub>Osm</sub>	U <sub>Na</sub> V	FE <sub>Na</sub> × 100
min	ml/min	ml/min	mEq/liter	mEq/min	ml/min	mOsm/kg	%	ml/min	%	ml/min	μEq/min	%
Day 1-3, sodium intake = 250 mEq/day.												
-150	Day 4, desoxycorticosterone acetate (DOCA), 10 mg, i.m., 20 ml/kg body wt of tap water ingested and then water ingestion q 15 min equal to urine volume plus 10%, continued throughout the study. Inulin and PAH prime given and infusion I, containing inulin and PAH begun at 0.5 ml/min.											
0-10	143	561	126	18.0	16.5	62	88.5	12.7	77.0	3.8	165	0.92
10-20	132	548	126	16.6	16.3	59	87.7	12.7	77.9	3.6	151	0.91
20-30	129	551	126	16.3	17.5	55	86.4	13.9	79.4	3.6	158	0.97
30-40	141	560	126	17.8	19.0	53	86.5	15.1	79.5	3.9	176	0.99
42	Infusion II started: 0.85% NaCl at 35 ml/min.											
102	Infusion II slowed to 8 ml/min.											
125-135	156	630	126	19.7	31.4	78	79.9	22.1	70.3	9.3	809	4.1
135-145	146	627	126	18.4	31.8	80	78.2	22.0	69.2	9.8	875	4.8
145-155	132	519	125	16.7	30.7	81	76.7	21.2	69.1	9.5	791	4.7
155-165	139	611	125	17.4	28.3	70	79.6	20.7	73.1	7.6	594	3.4
Day 5-10, sodium intake 250 mEq/day, DOCA 20 mg, i.m. daily.												
-150	Day 11, as on Day 4.											
0-10	156	612	133	20.7	29.0	53	85.8	23.5	81.0	5.5	210	1.01
10-20	131	480	129	16.9	21.2	47	83.8	16.6	78.3	3.6	70	0.41
20-30	147	554	132	19.3	21.5	52	85.4	17.5	81.4	4.0	91	0.47
30-40	142	666	129	18.2	20.2	59	85.8	15.9	78.7	4.3	167	0.92
40-50	146	866	128	18.5	24.5	52	83.2	19.9	81.2	4.6	135	0.73
52	Infusion II as above, at 35 ml/min.											
112	Infusion II slowed to 8 ml/min.											
130-140	183	1258	129	23.6	45.3	86	75.2	31.3	69.1	14.0	1121	4.8
140-150	160	974	128	20.4	34.4	83	78.5	23.9	70.0	10.2	955	4.7
150-160	164	955	131	21.5	34.8	82	78.8	24.4	70.1	10.4	966	4.5
160-170	168	1007	128	21.5	37.9	81	77.4	26.9	71.0	11.0	758	3.5
170-180	176	1055	126	22.2	38.8	79	78.0	27.8	71.7	11.0	766	3.5

infusion, C<sub>IN</sub> rose in three studies, fell in one and was virtually unchanged in two. C<sub>PAH</sub> varied similarly so that the mean filtration fraction was unchanged. Sodium excretion increased in all subjects, the increments ranging from 76 to 606 μEq/min. 1 - (V/GFR) and C<sub>H<sub>2</sub>O</sub>/V also decreased in every subject (P < 0.01). After escape, acute saline loading produced a natriuresis in only four of the six subjects. In these four, the decrement in 1 - (V/GFR) was from 85 to 69% (P < 0.01) and (C<sub>H<sub>2</sub>O</sub>/V) fell from 81 to 69% (P < 0.01). U<sub>Na</sub>V increased reaching levels of 535-824 μEq/min. In subjects 5 and 6, U<sub>Na</sub>V fell after saline. In subjects 5, 1 - (V/GFR) and (C<sub>H<sub>2</sub>O</sub>/V) rose, while in subject 6, 1 - (V/GFR) fell slightly and (C<sub>H<sub>2</sub>O</sub>/V) was unchanged. The data from these two subjects are not included in the "escape and saline" column in Fig. 1.

*Effect of progressive saline expansion in hydrated man.* 11 men undergoing maximal water diuresis were studied during progressive saline expansion. A typical study according to protocol II is shown in Table III. Mean data for all subjects are in Table IV and Fig. 2. Clearance collections were obtained during a control period, during saline infusion averaging 57 ml/kg (E<sub>1</sub>) and 80 ml/kg (E<sub>2</sub>). The subjects were divided into two groups: those in whom maximum sodium excretion was < 550 μEq/min, nonexcreters; and those excreting > 1000 μEq/min of sodium, excreters. One subject excreted 790 μEq/min and was arbitrarily assigned to the nonexcreters. In the excretor group, 1 - (V/GFR) decreased from 87 to 80% during E<sub>1</sub> (P < 0.01) but did not fall significantly further during E<sub>2</sub>. C<sub>H<sub>2</sub>O</sub>/V fell significantly from 78 to 63% during E<sub>1</sub> and was even further depressed to 58.5%

TABLE II  
The Effect of Acute Saline Loads and "Mineralocorticoid Escape"

Subject No.	C <sub>in</sub> ml/min	CPAH ml/min	PNa mEq/liter	FN <sub>a</sub> mEq/min	V ml/min	U <sub>om</sub> mOsm/kg	[1 - (V/GFR)] % X 100	CR <sub>50</sub> ml/min	(CR <sub>50</sub> /V) % X 100	Comm ml/min	UN <sub>a</sub> V μEq/min	FE <sub>Na</sub> % X 100	Weight kg
1 Control	152	814	130	19.8	18.7	46	87.7	15.5	83.4	3.2	74	0.4	81.0
Saline	144	754	128	18.4	26.0	50	82.0	21.3	82.0	4.8	234	1.3	82.5
Escape	186	875	139	25.9	31.8	56	82.9	25.5	80.7	6.2	491	1.8	82.5
Escape & Saline	180	925	141	25.4	40.0	93	77.9	27.1	68.6	12.9	1362	5.4	71.5
2 C	136	555	126	17.1	17.3	77	87.3	13.6	79.1	3.7	161	0.9	71.5
S	143	597	126	18.0	30.6	77	78.2	21.5	70.4	9.1	767	4.3	73.0
E	145	636	131	19.0	23.3	53	83.9	18.7	80.4	4.4	135	0.7	73.0
E & S	170	1050	128	21.8	38.2	82	77.6	26.9	70.7	11.3	913	4.2	57.5
3 C	129	492	133	17.2	12.7	57	90.2	10.1	80.2	2.6	42	0.2	57.5
S	148	689	129	19.1	22.9	72	84.6	16.9	74.5	6.1	509	2.7	59.0
E	173	640	139	24.0	22.2	50	86.9	18.6	84.5	4.1	362	1.5	59.0
E & S	209	807	139	29.1	32.9	93	84.2	21.9	67.1	11.1	1186	4.1	83.0
4 C	166	676	132	21.9	17.4	54	89.5	13.8	79.3	3.6	139	0.6	83.0
S	213	813	136	29.0	30.1	73	85.9	21.7	72.3	8.3	743	2.6	86.5
E	202	754	143	28.9	28.3	60	85.9	22.0	78.8	6.2	592	2.0	86.5
E & S	222	769	143	31.8	35.4	80	83.8	25.2	71.2	10.2	1127	3.5	67.0
5 C	176	634	127	22.4	19.7	55	88.8	15.7	80.6	4.0	134	0.6	67.0
S	175	710	128	22.4	22.0	56	87.5	17.3	79.3	4.7	210	0.9	72.5
E	194	765	129	25.1	30.8	65	84.3	23.3	76.3	7.2	580	2.3	72.5
E & S	181	758	127	23.0	23.7	58	86.8	18.6	79.4	5.0	254	1.1	65.5
6 C	128	506	133	17.0	14.1	45	90.0	11.6	82.3	2.4	61	0.4	65.5
S	128	545	132	17.0	17.1	55	86.5	13.6	80.1	3.6	170	1.0	68.5
E	148	492	141	20.9	20.6	45	86.0	17.3	84.3	3.3	231	1.1	68.5
E & S	142	453	139	19.7	21.4	47	84.9	17.8	84.5	3.6	225	1.1	70.9±4.0
Means	148±8	613±50	130±1.2	19.2±1.0	16.7±1.1	52±2.2	88.9±0.49	13.4±0.9	80.8±0.7	3.3±0.26	102±20	0.5±0.12	70.9±4.0
C (n = 6)	159±12	685±40	130±1.5	20.7±1.8	24.8±2.1	64±4.7	84.1±1.4	18.7±1.4	76.4±1.9	6.1±0.89	439±111	2.1±0.53	73.7±4.0
S (n = 6)	175±10	694±56	137±2.3	24.0±1.5	26.2±1.9	55±2.9	85.0±0.61	20.9±1.3	80.8±1.3	5.2±0.62	399±77	1.6±0.24	73.7±4.0
E (n = 6)	177±12	726±57	138±2.5	24.5±2.1	26.4±2.2	55±2.1	84.9±0.9	21.2±1.6	81.1±1.2	5.2±0.57	395±99	1.5±0.29	73.7±4.0
E & S (n = 4)	195±12	888±63	138±3.4	27.0±2.2	36.6±1.6	87±3.5	80.9±1.8	25.3±1.2	69.4±1.0	11.4±0.56	1147±93	4.3±0.38	73.7±4.0
P values													
C vs. S	NS	NS	NS	NS	<0.01	<0.05	<0.05	<0.01	<0.05	<0.05	<0.05	<0.05	
(n = 6)													
C vs. E	<0.01	<0.05	<0.05	<0.01	<0.01	NS	<0.01	<0.01	<0.05	<0.05	<0.05	<0.05	
(n = 6)													
E vs. S	<0.05	NS	<0.05	<0.01	NS	NS	NS	NS	NS	NS	NS	NS	
(n = 6)													
E vs. E & S	NS	NS	NS	NS	<0.01	<0.01	<0.05	<0.05	<0.05	<0.01	<0.01	<0.05	
(n = 4)													

TABLE III  
Representative Experiment—Protocol II

Time	C <sub>in</sub>	C <sub>PAH</sub>	P <sub>Na</sub>	F <sub>Na</sub>	V	U <sub>osm</sub>	$\left[ \frac{1 - (V/GFR)}{\times 100} \right]$	C <sub>H<sub>2</sub>O</sub>	$\left( \frac{C_{H_2O}}{V} \right) \times 100$	C <sub>osm</sub>	U <sub>Na</sub> V	F <sub>ENa</sub> × 100
min	ml/min	ml/min	mEq/liter	mEq/min	ml/min	mOsm/kg	%	ml/min	%	ml/min	μEq/min	%
	Day 1, sodium intake 150 mEq/day.											
-150	Day 3, 20 ml/kg body wt of tap water ingested and then water ingestion q 15 min equal to urine volume plus 10% continued throughout the study. Prime and Infusion I as in Table I.											
0-15	159	846	141	22.1	22.3	41	86.0	19.1	86.0	3.1	185	0.84
15-30	153	808	143	21.3	19.1	41	87.5	16.5	86.2	2.6	162	0.76
30-40	159	809	143	22.6	19.1	41	88.0	16.5	86.3	2.6	153	0.68
42	Infusion II started: 0.85% NaCl at 50 ml/min.											
102	Infusion II slowed to 10 ml/min.											
135-145	155	682	146	22.6	38.8	93	74.9	26.7	68.8	12.1	1591	7.0
145-155	155	664	146	22.8	35.3	87	77.3	24.9	70.6	10.4	1270	5.6
155-165	162	706	146	23.9	34.2	87	78.9	24.1	70.6	10.1	1231	5.2
165-175	167	790	146	24.6	37.2	91	77.7	25.8	69.2	11.5	1396	5.7
175-185	168	912	147	24.9	36.4	95	78.2	24.6	67.7	11.8	1394	6.0
186	Infusion II increased to 25 ml/min.											
216	Infusion II slowed to 12 ml/min.											
235-245	146	789	145	21.2	34.4	111	76.5	21.5	62.2	13.0	1641	7.7
245-255	151	703	147	22.3	39.9	111	73.6	25.2	63.2	14.7	1935	8.7
255-265	146	615	147	21.6	38.6	110	73.7	24.3	63.2	14.2	1850	8.6

with continued expansion ( $P < 0.02$ ). The mean increase in sodium excretion was 1012 μEq/min during E<sub>1</sub> and 1267 μEq/min during E<sub>2</sub>. The increment from E<sub>1</sub> to E<sub>2</sub> was also significantly different ( $P < 0.05$ ). The fraction of filtered sodium excreted ranged between 5.1 and 9.1% (mean 7.3±0.6) during E<sub>2</sub>. In the nonexcreter group 1 - (V/GFR) fell only from 87 to 84% ( $P > 0.1$ ) during E<sub>1</sub> with little further change during E<sub>2</sub>. (C<sub>H<sub>2</sub>O</sub>/V) declined 4.5% during E<sub>1</sub> ( $P < 0.02$ ) with little additional change ( $P > 0.1$ ) during E<sub>2</sub>. Sodium excretion increased only 266 μEq/min during E<sub>1</sub> ( $P < 0.01$ ) and negligibly during E<sub>2</sub>. The fraction of filtered sodium excreted increased from 1.1 to 3.0% during E<sub>1</sub> ( $P < 0.05$ ) and to 3.1% during E<sub>2</sub>. Control GFR was greater in absolute terms in the excreter group ( $P < 0.02$ ) but when factored by body weight, there was no difference; C<sub>in</sub>/kg body wt was 1.64±0.12 in nonexcreters and 1.74±0.14 in excreters. In the excreters, GFR increased in all six subjects after saline. In the nonexcreter group, GFR rose in three and decreased in two subjects. There was no significant change in filtration fraction in either group. Hematocrit fell from 39±1.2 to 35±1.7% and 38±1.5 to 34±1.4% during E<sub>1</sub> and was unchanged during E<sub>2</sub>; plasma protein decreased from 6.3±0.1 to 5.3±0.1 g/100 ml and from 6.1±0.3 to 5.2±0.2 g/100 ml in the nonexcreters and excreters, respectively.

Also shown in Table IV and Fig. 2 for comparison are data from nine other subjects infused with 37±3 ml/kg saline. These include the six subjects shown in Table II and three additional subjects studied with an identical acute saline protocol, but who did not participate in the escape part of the studies summarized in Table II.

## DISCUSSION

The validity of free-water measurements as indices of tubular FSR has been evaluated by a number of workers (13-15) and no extended discussion will be attempted here. The most important limitations on the accuracy of the method are, first, the required assumption that no water is reabsorbed distally, and, second, the necessity to induce water diuresis. With respect to the first point, there is little doubt that some water is reabsorbed beyond the diluting site (16). With regard to the second point, water loading itself may depress tubular sodium reabsorption (17), while the dilutional hyponatremia necessarily induced may enhance reabsorption (18, 19). While it is unlikely, therefore, that the values for FSR obtained are quantitatively exact, changes in FSR derived from free-water calculations appear to be qualitatively valid when compared in animals with more direct evidence from micropuncture (5, 11, 15). In any case, more direct methods are inapplicable in men. In our experi-

TABLE IV  
The Effect of Large Saline Loads

Saline load	C <sub>In</sub> ml/min	C <sub>PAH</sub> ml/min	P <sub>Na</sub> mEq/liter	F <sub>Na</sub> mEq/min	V ml/min	U <sub>osm</sub> mOsm/kg	[1 - (V/GFR)] X 100		C <sub>H<sub>2</sub>O</sub> ml/min	(C <sub>H<sub>2</sub>O/V</sub> ) X 100		C <sub>osm</sub> ml/min	U <sub>NaV</sub> μEq/min	FENa X 100
							%	%		%	%			
Infusion of isotonic saline 37 ml/kg (n = 9)														
Control	148 ± 7	621 ± 33	132 ± 1.5	19.1 ± 0.8	16.8 ± 1.1	59 ± 5	88.8 ± 0.4	13.3 ± 0.8	79.2 ± 0.9	3.6 ± 0.3	139 ± 25	0.71 ± 0.12		
Saline	37 ± 3	155 ± 10*	667 ± 31*	132 ± 1.7*	20.3 ± 1.3*	73 ± 6 †	85.3 ± 1.1 †	16.5 ± 1.6 †	73.4 ± 2.0 †	6.0 ± 0.6 †	443 ± 79 †	2.2 ± 0.37 †		
Infusion of isotonic saline, 53-63 ml/kg followed by 76-86 ml/kg (n = 11)														
Control	123 ± 6	591 ± 49	138 ± 1.1	16.9 ± 0.9	15.5 ± 0.9	62 ± 4	87.3 ± 0.5	12.2 ± 0.8	78.4 ± 1.3	3.3 ± 2.1	199 ± 18	1.1 ± 0.1		
E <sub>1</sub>	57 ± 2	129 ± 8*	610 ± 43*	139 ± 1.1 †	17.9 ± 1.0*	90 ± 5 †	82.0 ± 1.1 †	15.9 ± 1.4 †	68.2 ± 2.0 †	7.8 ± 1.1 †	872 ± 142 †	4.7 ± 0.6 †		
E <sub>2</sub>	80 ± 3	130 ± 8*	592 ± 47*	141 ± 1.3 †	18.4 ± 1.1 †	101 ± 6 †	81.1 ± 1.2 †	15.4 ± 1.1 †	65.0 ± 2.4 †	8.9 ± 1.2 †	1032 ± 171 †	5.4 ± 0.8 †		
Nonexcretors (n = 5)														
Control	110 ± 9	497 ± 41	138 ± 1.7	15.1 ± 1.3	14.3 ± 0.8	62 ± 6	87.2 ± 0.4	11.2 ± 0.6	78.5 ± 2.1	3.1 ± 0.4	182 ± 26	1.1 ± 0.2		
E <sub>1</sub>	63 ± 3	111 ± 8*	546 ± 18*	139 ± 1.4*	15.5 ± 1.2*	75 ± 5 †	84.1 ± 1.6*	13.0 ± 1.1*	74.0 ± 2.1 †	4.8 ± 0.7 †	448 ± 98 †	3.0 ± 0.7 †		
E <sub>2</sub>	86 ± 4	112 ± 9*	500 ± 32*	141 ± 2.4*	15.9 ± 1.5*	81 ± 4 †	83.2 ± 1.6*	13.4 ± 0.8*	72.7 ± 1.4 †	5.1 ± 0.5 †	496 ± 55 †	3.1 ± 0.5 †		
Excretors (n = 6)														
Control	134 ± 6	669 ± 71	137 ± 1.8	18.4 ± 0.7	16.6 ± 1.4	62 ± 5	87.4 ± 0.9	13.0 ± 1.4	78.2 ± 1.9	3.5 ± 2.1	213 ± 26	1.1 ± 0.1		
E <sub>1</sub>	53 ± 2	144 ± 9*	664 ± 72*	140 ± 1.2*	19.9 ± 1.2*	103 ± 4 †	80.3 ± 1.0 †	18.4 ± 1.9 †	63.4 ± 1.0 †	10.3 ± 0.9 †	1225 ± 115 †	6.1 ± 0.4 †		
E <sub>2</sub>	76 ± 3	145 ± 9*	669 ± 69*	140 ± 1.8*	20.5 ± 1.0 †	119 ± 3 †	79.4 ± 1.6 †	17.1 ± 1.6 †	58.5 ± 1.2 †	12.0 ± 0.8 †	1480 ± 133 †	7.3 ± 0.6 †		

In each case, control value was compared with saline loading value.

\* Not significant.

† P < 0.01.

‡ P < 0.05.

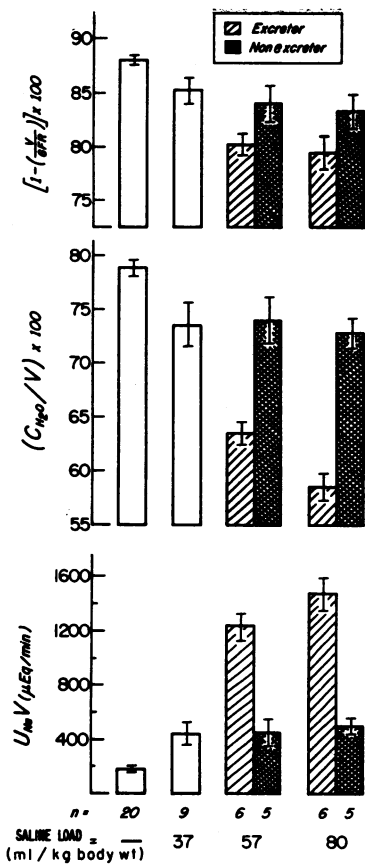


FIGURE 2 A comparison of the effect of small and large saline loads on proximal  $[(1 - V/GFR) \times 100]$  and distal  $[(C_{H_2O}/V) \times 100]$  fractional sodium reabsorption and on sodium excretion.  $n$  = number of subjects studied: 9 who received the smaller saline load and 11 different subjects who received the two larger saline loads.

ments, subjects drank 20 ml/kg of water at the start of the study and control periods were not obtained until  $U_{Osm}$  was less than 75 mOsm/kg (Tables II and IV). Subjects drank large amounts of water throughout the remainder of each experiment, while saline was being infused. In effect, hypotonic expansion of extracellular volume occurred during saline loading. Plasma Na changed  $\leq 4$  mEq/liter and  $U_{Osm}$  was less than 125 mOsm/kg throughout the saline collections. Thus, it is legitimate to assume that antidiuretic hormone was suppressed throughout each study and that changes in  $1 - (V/GFR)$  and  $C_{H_2O}/V$  reflect altered tubular reabsorption of sodium. With respect to the use of  $C_{H_2O}/V$  as an index of distal FSR, it is recognized that it does not measure sodium reabsorbed distally in "exchange" for other cations, such as potassium or hydrogen (ammonium or titrable acidity). Thus,  $C_{H_2O}/V$  may more precisely be characterized as an index of "sodium, reabsorbed distally in the diluting process" than as an index

of overall "distal" FSR. However, under usual circumstances, as in protocol II, cation secretion is negligible in comparison to Na reabsorption in the diluting process. Distal cation secretion during mineralocorticoid stimulation in protocol I may have been somewhat greater; no measurements of potassium and hydrogen secretion were made. For convenience, in the absence of specific data on this component of distal Na reabsorption,  $C_{H_2O}/V$  is described as an index of distal FSR, according to the usual convention.

Acute expansion with 35 ml/kg body wt of saline increased  $(V/GFR) \times 100$  significantly from 11 to 15%, indicating that proximal FSR was inhibited. The increase of about 4% in  $V/GFR$  is comparable to those found by Buckalew, Puschet, Kintzel, and Goldberg (20) in normal man and by Lindheimer and Weston (21) in pregnant women given similar hypotonic saline loads. Larger increases in  $V/GFR$  apparently occurred after hypertonic saline infusions in patients with diabetes insipidus (14). The difference may be due to the somewhat larger volumes of saline infused. However, hypernatremia inhibits (22-24) and hyponatremia enhances (18, 19) over-all tubular reabsorption of sodium in dogs. The apparently greater increase in  $V/GFR$  during hypertonic (14) than hypotonic (20, 21, present data) expansion suggests that the proximal tubule is probably a site at which plasma Na concentration alters FSR.

Our studies demonstrate consistent depression of proximal FSR during chronic extracellular fluid (ECF) expansion by dietary sodium and mineralocorticoids. By calculation from weight changes (Table II), chronic expansion of ECF volume during escape was about equal to acute expansion by saline in the same subjects, i.e., about 3-4% body wt or perhaps 15-20% of initial ECF volume. Inhibition of proximal FSR in the same group of subjects was virtually identical after acute saline loading or chronic expansion (Table II). No comparable studies in man are available. In dogs, micropuncture studies of proximal FSR have been inconclusive; evidence for (9) and against (10) inhibition of proximal reabsorption has been published. These micropuncture experiments require comparison of FSR in different groups of dogs; variability among dogs may well account for the disparate results. In our studies in man, each subject served as his own control. The data are quite consistent:  $1 - (V/GFR)$  was less after escape in each of the six subjects studied (Table II).

During acute infusion of large volumes of saline, there appeared to be a limit on the degree to which proximal FSR was inhibited. Taking all subjects together (Table IV),  $1 - (V/GFR)$  decreased by 5.3% after 57 ml/kg and by 6.2% after 80 ml/kg, not a significant difference. Indeed, neither increase differs statistically from the de-



crease of 3.5% in  $1 - (V/GFR)$  after 37 ml saline/kg. However, this latter comparison is of different groups of subjects. Quantitative interpretation of FSR from changes in  $1 - V/GFR$  is hazardous, as already noted above. Nevertheless, the data suggest that inhibition of proximal FSR by acute saline infusion does not increase when loading increases from 6 to 8% of body weight. It may well not be substantially greater at either degree of expansion than at 3%. However, it should be noted that proximal reabsorption was inhibited further by an infusion of 3.5% body wt saline into subjects already chronically expanded by about 3-4% (Table II). When subjects were divided into excreters and nonexcreters according to their maximum rates of Na excretion (Table IV), there was no significant further proximal inhibition in either group, when the saline load was increased from 6 to 8% body wt. The conclusion that inhibition of proximal FSR in man is relatively stable after moderate ECF expansion has been achieved is in agreement with several clearance and micropuncture studies in dogs and rats (7, 8),<sup>2</sup> although the contrary conclusion has been reached from micropuncture experiments in rats (6). No other observations in man have been published.

Distal FSR, estimated from changes in  $C_{H_2O}/V$ , decreased significantly after infusion of 35 ml saline/kg; decreases were noted in each subject studied (Tables II and IV). Although aldosterone enhances distal Na reabsorption and  $C_{H_2O}$  formation (24), this effect cannot be attributed to decreased endogenous aldosterone secretion after saline infusion, since each subject had received a large dose of a mineralocorticoid at least 2 hr before the clearance periods were collected. Evidence for inhibition of distal FSR during infusion of somewhat larger volumes of hypertonic saline in patients with diabetes insipidus was found by Buckalew and associates (14). However, changes in  $C_{H_2O}/V$  in pregnant women infused with saline were inconsistent in the studies of Lindheimer and Weston (21). Inhibition of distal FSR appeared to increase progressively with greater loads of saline.  $C_{H_2O}/V$  fell by 5.8% after saline equal to 3.5% body wt, by 10.2% after 6% body wt, and by 13.4% after 8% body wt saline (Table IV). Only the difference between 3.5 and 8% loading was statistically significant ( $P < 0.02$ ), but it should be noted that different subjects received 3 and 6% saline loads. When the subjects who received the larger loads were divided according to maximum sodium excretion (Table IV), progressive changes in  $C_{H_2O}/V$  were noted in excreters when saline loading increased from 6 to 8% body wt. In the nonexcreters,  $C_{H_2O}/V$  remained stable over this range of loading. The further distal inhibition in excreters correlated with a significant increment in Na excretion from 6 to 8% loading; sodium excretion did not increase significantly in the nonexcreters. The decrease in distal FSR noted in our studies in

man is in agreement with substantial evidence that similar changes occur during saline infusion in dogs and rats<sup>3</sup> (11). It is uncertain whether the decrease in the fraction of the delivered load of sodium reabsorbed distally is simply a response to the increase in distal delivery or whether distal reabsorption is directly inhibited by saline loading. Studies in man (14) and animals (25) have suggested specific distal inhibition. However, this phenomenon could not be demonstrated by micropuncture in the loop of Henle or distal convoluted tubule (12). It is of interest that there was no evidence for distal inhibition after chronic expansion by mineralocorticoids, despite a greater increment in distal delivery from control than occurred after acute saline loading. This suggests that the decrease in  $C_{H_2O}/V$  after 3.5% body wt saline is not due simply to the increment in distal delivery.

Some comparisons between the responses of man and dog to acute saline loads are instructive. In general, man has been described as having a relatively smaller natriuretic and renal hemodynamic response to saline loads than the dog (26, 27). In part, the difference is undoubtedly methodological, since previous studies in man have used relatively small infusion volumes, roughly comparable to our 3.5% body wt load, while saline infusions equal to 10% body wt are commonly employed in dogs (26). Our data show that increased loads of saline induce substantial increases in sodium excretion in man, as would be expected. However, even at comparable infusion volumes, sodium excretion in man is less both absolutely and, even more strikingly, as a fraction of filtered sodium. We found that human subjects can be separated into two rather sharply differentiated groups, in terms of the renal response to saline. The excreters, whose peak natriuresis exceeded 1000  $\mu\text{Eq}/\text{min}$ , demonstrated an increase in GFR and relatively larger decreases in both proximal and distal FSR after 8% body wt saline. The changes approached in magnitude those found in dogs (26). On the other hand, the nonexcreters demonstrated no change in GFR and much smaller decrements in proximal and distal FSR. The differences between the two human groups in each of these renal responses was statistically significant. We cannot explain these differences from obvious characteristics of the subjects. The small size of the two groups precludes any firm categorization of renal response to saline in man into two definitive subgroups. However, the data do show that differences in sodium excretion in man correlate well with differences both in proximal and distal inhibition of FSR, as calculated by clearance techniques. In dogs, proximal inhibition has been reported to be the same in dogs which respond to saline with minimal natriuresis as in dogs which excrete sodium rapidly (28). According to that study, differences in distal reabsorption alone appear to determine the natriuretic response of dogs.

In conclusion, our data indicate that both proximal and distal FSR are inhibited by acute saline infusions in man. Proximal inhibition appears to be relatively stable as the volume of infusate is increased from 3 to 8% body wt; the increase in Na excretion during progressive expansion may be related to increasing distal inhibition. Chronic ECF expansion also depresses proximal FSR, but distal FSR is not inhibited. Na excretion is increased comparably above control by acute or chronic ECF expansion equal to 3% body wt. The increase in excretion appears to be due to a modest increase in distal delivery and a decrease in distal FSR after acute loading. In chronic expansion, a larger increment in distal delivery, due to increased GFR as well as decreased proximal FSR, apparently is sufficient to increase excretion comparably despite the lack of change in distal FSR. Finally, the "exaggerated" natriuresis in response to acute saline loads described as characteristic of chronically expanded subjects (29, 30) seems to be due to inhibition of distal FSR and further proximal inhibition by the acute load. Comparable total expansion by acute infusions alone or by a combination of chronic expansion and acute saline loading produce similar tubular adjustments.

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