# FACTORS INFLUENCING THE COURSE OF MERCURIAL DIU-RESIS DURING PITRESSIN® INFUSION IN NORMAL SUBJECTS <sup>1</sup>, <sup>2</sup>

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Studies on the mechanism and site of mercurial action have led to conflicting conclusions, because of differences in experimental design. Thus, since sodium excretion during heavy sodium loading did not exceed about 20 per cent of that filtered, Duggan and Pitts (1) deduced that the action of mercurials is exerted upon the distal segment, although additional effects on the proximal tubules could not be excluded. On the other hand, Farah, Cobbey, and Mook (2) obtained sodium excretions under mercurials approximating 35 to 40 per cent of that filtered, a significantly greater fraction than that generally attributed to the distal tubule.

In an earlier study (3), the hypertonic urine resulting from continuous infusion of concentrated sodium chloride solution was found to be diluted almost to isotonicity during mercurial diuresis. Since facultative water reabsorption, under control of the anti-diuretic hormone, occurs low in the nephron and is probably unaffected by mercurials (4), it was suggested that this decrease in concentration may reflect inhibition of more proximal isosmotic reabsorption. From the changes in urine osmolarity, Brodsky and Graubarth (5), who studied hydropenic animals, and Welt, Goodver, Darragh, Abele, and Meronev (6) who studied three men receiving Pitressin<sup>®</sup> infusions, drew similar conclusions. More recently, Capps, Wiggins, Axelrod, and Pitts (7) and Dale and Sanderson (8) suggested that because Mersalyl in-

<sup>8</sup> Present address : Department of Medicine, U.C.L.A., School of Medicine, Los Angeles, California. creased sodium and chloride excretion without augmenting urine volume during maximal water diuresis, mercury and post-pituitary ADH must act on the same (distal) segment. Subsequently, however, the latter investigators (9) indicated uncertainty as to the renal site of mercurial diuretic effect. Studies on renal excretion of substances other than sodium and chloride have demonstrated that mercurials inhibit certain proximal (10, 11), but not other, presumably distal, tubular functions (3).

The present report is concerned with an extension of our earlier observations (3) on the dilution of hypertonic urines following administration of mercurials during infusion of a concentrated salt solution. Because the resulting increasing electrolyte excretion complicates analysis of the data, constant and virtually maximal distal reabsorption of water was maintained by the continuous infusion of Pitressin<sup>®</sup> throughout the procedure.

## MATERIAL AND METHODS

The eleven subjects, all of whom were free of clinically evident cardiovascular and renal disease, were previously maintained on regular diets. Each study was begun between 8 and 9 A.M., with the patient in the postabsorptive state. Hydration was maintained by means of a measured oral water intake and an intravenous infusion of physiological saline or lactated Ringer's solution given at 3 to 4 ml. per minute by means of a constant infusion pump. Following several control collection periods, Pitressin® (1 to 3 mu. per Kg.) was injected intravenously, and a quantity calculated to provide an equivalent dose each 60 or 90 minutes was added to the infusion mixture.<sup>4</sup> Fairly constant anti-diuresis was thereby achieved although, at times, slowly increasing concentration of urine occurred.

When constant minimal urine flow was achieved, 2 ml. (80 mg. Hg) of mercaptomerin, a xanthine-free mercurial diuretic, were injected intravenously, and fre-

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<sup>&</sup>lt;sup>4</sup> One patient, L. G., received 6 mu. per Kg. with consequent excessive Pitressin<sup>®</sup> effect.

						Urine						nqn.,,	lar" reje	ctate (po	st-mercu	urial)					
			Sod	lium	6 B	loride	Potas	sium	Osmo	larity*		Sodi	H	Chlo	ride	Osmol	arity		Ser	m	
Procedure (1)	Time (2) min.	Flow (3) mil./ min.	Conc. #Eq./	Exc. (5) min.		: Exc. (7) min.	Conc. (8) L.	Exc. (9) min.	Conc. 10) L.C./	Exc. LOS./ min.	Water (12) ml./ min.	Exc. [13) #Eq./	Conc. (14) <i>mEq.</i> /	Exc. [15] #Eq./	Conc. (16) <i>m</i> Eq./	Exc. 117) min.	Conc. (18) <i>m</i> 0s./ L.	Osmol. (19) mOs./ L.	Na (20) L.	CI 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1.	1. 1. 1. 1.
J. L., Age 50; 6	5 Kg., He	patitis, Con	<b>7/0/</b>	13																	
Begin inf.†	14	10.5	~~	76 81	11	110	5.6	82 SO	26 27	270 293									135	96.8	4.53
Dit 1 mm /K +	13 <b>1</b> 2	11.9		16 16 16 16 16 16 16 17	103ž	117	5.1	555	582	316 329 271									136	98.0	4.73
1 10 1 mm·/ 22	188		115	120	125	137	75.5 51.3	82 5 5	330	350									135	97.5	4.48
H <b>2</b> }	1188 1188	<b>4</b> 0110	172 158 158	220 200 200 200 200 200 200 200 200 200	148 158 158 158	142 223 731	42.6 22.0 6.0	53 <del>6</del> 1	434 327	412 578 1,500	0.3 3.6	93 558	300 156	78 586	252 164	141 1,060	455 296		136	7.79	4.67
	884:	9000 9000	151 150 149	1,080	151 152 152	1,000	4.1 2.5 4	2122	311 30 <b>6</b> 30 <b>6</b>	2,200 2,500 2,500	88 8 8 9 9 7 9 7 9 8 8 8 8 8 8 8 8 8 8 8	833 1,060 1,060	148 136 153	858 937 1,100	152 153 153	1,630 2,060 1,760 1,760 1,760	286 286 286 286		134	96.4	4.66
	50 <b>1</b> 2	5.85	<u> </u>	966 948	819 19 19	964 932	3.3	195	333	1,970	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	799	167	819	171 165	1,490	320		133	95.9	4.66
T. S., Age 50, 7	0.4 Kg., F	ulmonary f	Ebrosis.	Bronchi	ectastis 3,	120/21															
Begin inf.	23 15 23	1.0 5.5 7.5	141 88 24 28	1 <b>45</b> 131 132 141 167	180 39 28 39 28 39 28 39 28 30 28 30 28 30 28 30 28 30 28 30 28 30 28 30 28 30 28 30 28 30 28 30 28 30 28 30 29 20 20 20 20 20 20 20 20 20 20 20 20 20	185 174 167 167	74.0 38.1 16.9 12.1 10.0	221132	430 214 55 55 55	443 409 408 408 408 408											
Pit. 2 mu./Kg.	82 54 12	2.6 1.2 1.2	122 225 227	323 344 280	124 223 228 210	327 342 280	36.3 54.2 57.4	8888	317 558 540	837 854 664											
Hg	22	1	202 202	220	208	227	45.5	88	495	540	0.1			4	572						
	119 119 1124 1124	4.3 8.5 11.0 7.3 7.3 7.3	159 154 171 171	779 1,360 1,340 1,340 1,270	185 157 157 174	797 1,400 1,720 1,300 1,300	10.9 7.1 6.7 6.8 6.8	49 55 55 61 47	382 332 339 356 356 356	1,650 3,520 2,790 2,640	3.3 7.5 6.8 6.8 7 7 7 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8	555 1,130 1,110 1,110 1,040	168 151 151 155 164 168	574 1,180 1,500 1,140 1,150 1,070	174 157 150 158 158 172	796 1,990 1,940 1,940 1,790	241 264 284 286				
* Osmolari † Begin cor	ty calcula stant (3.4	ted, except t or 3.0 ml.	in patie per mi	ents P. F n.) intra	T., P. G.	, and C. 1	W. Maci	in patie	nts J. L	T.S., E	l, M.) or Le	totated R	tingers'	(in patie	ats P. F.	P. G. 0	C. W.) sol	ution.			

TABLE I

1612

F Begin constant: (3.4 or 3.0 ml. per min.) intravenous intuston of Nacl. (in pa 2.00ee given stat., and cquivalent dose per 60 minutes placed into infusion. 7 Those ziven stat. I.V. for the stat. and set in the state of the state of

						Urine						"Tubula	ır" reject	ate (pos	t-mercuri	al)					
			Sod	lium	CF	loride	Potass	ium	Osmol	arity*		Sodiu	E	Chlori	ide	Osmolai	rity		Serut	e	
Procedure (1)	Time (2) <i>min.</i>	Flow (3) ml./ min.	Conc. (4) <i>m</i> Eq./	Exc. (5) min.	Conc. (6) L.	. Exc. (7) min.	Conc. (8) L.	Exc. (9) nin.	Conc. 10):/	Exc. (11) min.	Water (12) ml./ min.	Exc. (13) µEq./ 7 min.	Conc. (14) L.	Exc. ( (15) µEq./ 1 min.	Conc. [16] L.	Exc. C (17) min.	L. 30 00 00 00 00 00 00 00 00 00 00 00 00	L. 19	1.20 1.20 1.20 1.20 1.20 1.20 1.20 1.20		N(2)2
E. M., Age 39,	59.1 Kg.,	Hyperthyro	idism 3,	127/51																	
Begin inf.	12	12.5	52 52	248 263	50 20	250 272	80 80 E : E : E : E : E : E : E : E : E : E :	104 86	28 88	703 696								-	42 1	2	<b>4</b> .67
	12	12.6 14.3	1281	271 262	282	276 281	5.7	828	48 78	698 687								1	41 1(	2	<b>1</b> .63
FIL. 3 mu./Kg.	39 <b>4</b>	5.9 1.2	203	224	54 215	254	41.5	6 <del>0</del>	151 489	580 578								1	40 1	4	<b>1.</b> 25
	32 39	1.1	226 246	258 254	231 242	264 249	27.4 30.2	31 31	507 552	578 569								1	38 1	3	4.07
Не	22	1.1	255 240	255 255	256 240	256 255	29.0 26.7	28 28	568 533	568 565								-	38 11	33	1.07
ŗ	10	2.4	156	467 1,820	20 <del>4</del> 160	489 1,870	13.4 3.6	33 42	319	1,000 3,730	1.4 10.7	212 1,570	152 147	233 1,610	168 151	432 3,160	311 295	I			
	ta:	15.4 15.2 14.2	155 155	2,390 2,350 2,190	153 154 154	2,360 2,340 2,100	2.6 2.6	44 39	315	4,870 4,790 4,400	14.4 14.2	2,130 2,090	148 148 146	2,100 2,080	146 147 146	4,300 4,220 1,220	299 297 206	1	99 99	8	4.17
	1212	12.7	162	2,060	162	2,060	2.8	888	336	4,180	11.7 9.4	1,800	154 156	1,800	154	3,610	312	-	35 1(	8	11.4
P. F., Age 19,	70 Kg., Ac	ute rheuma	tic fever-	Healed	5/19/5	3															
Begin inf.	0400 x	4.7 8.1 5.7	270 32 33 33	340 152 191	289 42 38 38	364 198 227 216	96.4 4.75 22.9 26.8	122 175 186 154	873 210 144 174	1,100 998 1,170 1,000								292 1	40 11 11	54	1.82
Pit. 3 mu./Kg.	10 24	4.4 4.1	50 122	222 168	55 136	245 188	21.3 32.8	95 45	235 516	1,050								292 1	41 1(	35	3.80
	1538338 1538338	312211	174 217 223 254 254	197 232 274 310	177 233 201 227 207	200 249 247 261	69.2 56.0 51.3 44.0	78 56 55 55	714 761 772 818 735	807 814 892 926								294 1	42 10	35	3.80
Hg	22 15	1.0 0.9	268 265	273 240	220 220	22 <del>4</del> 200	39.4 40.0	40 36	832 804	849 729								296 1	43 1	33	3.60
	11 10 10	0.9 1.4 7.9	275 225 160	252 315 1,260	217 218 162	199 305 1,280	41.2 36.0 7.3	82 23 28 23	819 687 385	752 962 <b>3,04</b> 0	0.4 6.9	42 992	111 144	81 1,050	213 154	113 2,190	297 319 2	296	43 10	<b>1</b>	3.58
	►∞∞∞	13.1 17.4 18.5 17.6	153 152 151 155	2,000 2,650 2,730 2,730	147 170 152	1,930 2,960 2,760 2,680	3.8 2.1 2.1	33882	350 340 334 334 334 334	4,590 5,920 6,100 5,880	12.0 16.3 16.5	1,720 2,370 2,510 2,450	143 145 144 148	$ \begin{array}{c} 1,700\\ 2,730\\ 2,530\\ 2,450\end{array} $	141 167 145 148	3,740 5,070 5,250 5,030	310 300 303 303 303 303 303 303 303 303	292 1	41 10	33	3.75
	8 8 2 : 1 2 8 8	15.5 16.2 13.5	157 159 159	2,430 2,570 2,150	155	2,400 2,580 2,130	2.3	31 32 34	346 358 358	5,360 5,660 4,830	14.4 15.2 12.4	2,150 2,290 1,870	151	2,170	150 153	4,510 4,810 3,980	315				
	122	112	331	1,850	801 167 167	1,870	3.0	5 <b>7</b>	2 <b>4</b> 5	4,290 4,080 4 220	10.1	1,570	155	1,640	162	3,230	318	292 1	41 1(	10	3.78
	21	10.3	165	1,700	160	1.710	4.7	48	369	3,800	9.3	1,420	154	1,480	160	2,950	318	286 1	38 1	8	3.82

FACTORS INFLUENCING MERCURIAL DIURESIS

TABLE I-Continued

1613

												-			
		K (22) <i>mEq.</i> / L.		4.13	4.04	4.13	4.27	4.07	4.12	3.96	4.80		4.75		4.56
	um	CI 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1.		105	104	103	102	101	103	<b>1</b> 00	105		<u>1</u> 0		104
	፠	L. 1. (20) L. 1. (20) L. 1. (20)		142	142	140	139	140	138	139	140		143		137
		Osmol. (19) <i>m0s./ 1</i>		284	284	278	277	281	270	270	285		283		278
	arity	Conc. (18) <i>m</i> 0s./				405 470	453 459	438 459 473	489 514 548 572	5			176	297 294 292	293 297 300
rial)	Osmol	Exc. 17): 17: 17: 17:				56 176	803 1.220	1,530	1,330 1,230 1,080 892	5			8	896 1,930 3,790 3,790	3,750 3,580 3,560 3,160 2,560
st-mercu	ide	Conc. (16) <i>mEq./</i> L.				239 276	213 222	522	255 267 281				162	153 153 152 152 152	156 159 161
tate (no	Chlor	Exc. [15] #Eq./				33 102	39 <b>4</b> 591	693 693	695 639 553			•	55	479 996 1,450 1,760	1,990 1,880 1,900 1,370
ar'' reiec	Ę	Conc. (14) <i>mEq./</i> L.				391 249	228 218	540 540 540	261 279 288 288	298			159	150 150 151 151	157 159 160 156
luduT"	Sodi	Exc. [13] min.				54	404 580	223	710 568 458	<b>Q</b>			54	470 1,010 1,760 2,010	2,010 1,910 1,940 1,710 1,330
		Water (12) mi./ min.			·	0.1 .4	1.8 2.7	2.0 2.8 2.8	2.7 7.9 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	13			0.3	3.0 6.5 11.6 12.9	12.8 11.9 10.6 8.5
	larity*	Exc. 11):			461 528	533 614 640 816 816	1,440 1.860	2,170 1,980 1,960	1,970 1,870 1,710 1,530		750	752 767 886 902	952 888 987	1,820 2,860 4,280 4,720	4,680 4,510 4,090 3,490
	Osmo	L.:/		82 102 102	615 744	795 830 821 755	582 553	516 544 561	575 603 640 675		783	2000 2000 2000 2000 2000 2000 2000 200	727 716 617	420 367 332 331	333 340 343 356 356
	ssium	Exc. Bro. (9):		28888	<b>3</b> 4	33 <b>4</b> 4 38	<b>4</b> 0 32	32 36 32	X844	4	65	4388	<b>\$</b> 88	82883	30254428 30254428
	Pota	Conc. 1.68) L.		9.2 8.0 10.3	72.3	57.2 58.8 55.4 30.6	16.0 10.4	8.7 8.7 10.4	10.1 12.6 19.0	23.2	68.0	45.2 39.8 39.3	37.6 31.6		2.0 2.1 2.1 2.1
Urine	oride	Exc. Exc. min.		26124 11222	87 94	96 115 119 219 219	511 708	894 810 812	812 756 670		139	162 176 215 233	288 S	1,240 1,700 2,010 2,220	2,240 2,130 2,150 1,940 1,620
	CFI	L'EG Trigi	3	17 <sub>99</sub> 13	116	144 155 177 202	200 210	213 222 232	237 244 250 250	257 /54	250 145	155 165 191	<b>2</b> 6161	120 120 120	159 162 165 165
	lium	Exc. Eg./ SSr.	s 6/23/5.	95 187 180	113	150 182 203 275 275	586 762	978 905 905	892 849 640 640	588 is 12/16	192	216 270 284 284	314 352 352	1,310 1,730 2,060 2,310	2,310 2,210 2,210 2,010 1,630
	Š	Conc. Trail	l sclerosi	4772	151 189	224 246 278 278 278	236 226	233 248 259	260 274 282 282	294 id arthréi	288 288	207 214 233 233	538 538 538 538 538 538 540	12001 120000000 120000 1200000000	499999 499999
		Flow (3) ml:/ min.	Disseminated	6.8 10.9 6.6 6.6	0.7	0.7 0.8 1.1	2.4 3.4	4.2 3.5 3.5	3.4 3.1 2.3	2.0 Rheumato	8.0 8.0	9333	100	7.8 10.8 12.9	14.0 13.2 11.9 9.8
		Time (2) <i>min.</i>	56 Kg., 1	13 10 12	ິຂຸຊ	122828	<u>0</u>	222	2885	20 76.3 Ke	13	18733	283	~~~~~~	880223
		Procedure (1)	P. G., Age 23,	Begin inf.	Pit. 3 mu./Kg.	Hg				C. W A ee 32.	Begin inf.		Hg		

TABLE I-Continued

1614 JACOB GROSSMAN, RAYMOND E. WESTON, E. RAYMOND BORUN, AND LOUIS LEITER



FIG. 1. COMPARISON OF A CONTROL (PITRESSIN® ALONE) AND EX-PERIMENTAL (PITRESSIN® PLUS MERCURIAL) PROCEDURE IN THE SAME SUBJECT (M. S.)

The urine flow and sodium excretion during the control study are depicted in the upper third of the graph (broken line). In the middle third, the control serum and urinary sodium concentrations (broken lines) are plotted together with those of the experimental study (solid lines). Note the decline in urinary sodium concentration toward isotonicity associated with the increasing urine volume and sodium excretion (solid lines below) during mercurial diuresis.

quent urine collections were continued until the resulting diuresis had ebbed significantly.

Blood was removed periodically from an indwelling arterial needle. Urine specimens were collected by washing the bladder with 10 or 15 ml. of sterile distilled water and 100 to 200 ml. of air through an indwelling, multi-holed, rubber catheter. When osmolarity was measured, air alone was used for emptying the bladder.

The determinations of inulin, para-aminohippurate, sodium, chloride, and potassium, in plasma and urine, were performed by the standard methods employed in this laboratory (3). Total solute concentration was measured in some patients with a thermistor-osmometer.<sup>5</sup>

### **RESULTS AND DISCUSSION**

The results are summarized in Table I and Figures 1-7. In those patients studied prior to the availability of the osmometer, the urinary electrolyte osmolarity was calculated as: 2([Na] + [K]), ignoring the contribution of urea and other substances of low molecular weight.

# Effects of Pitressin<sup>®</sup> infusion on electrolyte and water excretion

Administration of Pitressin<sup>®</sup> produced a rapid fall in urine flow and a corresponding rise in urinary solute concentrations. In two control studies (Figure 1) in which the Pitressin<sup>®</sup> infusion was continued for several hours and the mercurial withheld, the urine flow and concentration of sodium and chloride remained constant, independent of the usual diurnal variation.

In all but one subject (T. S.), Pitressin<sup>®</sup> produced an initial decrease in electrolyte output. This fall is probably factitious in that the decreased urine flow results in a greater relative quantity of solute in the anatomical "dead space." This explanation is supported by the fact that renal hemodynamics similarly fell, and together with urinary electrolyte excretion, invariably rose again during the very next period. Following this transient fall, the urinary sodium and chloride

<sup>&</sup>lt;sup>5</sup> Manufactured by Fiske Associates, Inc., Boston, Mass.



FIG. 2. RESPONSE OF SUBJECT P. F. TO ADMINISTRATION OF MERCURIAL DIURETIC DURING PITRESSIN® ADMINISTRATION

Note that with maximal diuresis, the urinary sodium and total solute concentrations most closely approach isotonicity. Renal hemodynamics do not change significantly during the procedure.

excretion usually rose, reaching or slightly exceeding the control levels. Whereas initial chloride concentration generally exceeded that of sodium, following Pitressin® administration, the sodium concentration tended to equal or slightly exceed that of chloride in three patients (J. L., R. C., T. S.), none of whom received excessive sodium as PAH. The natriuretic action of Pitressin®, postulated by some (12) may explain this increased urinary Na/Cl ratio. The fall in urinary excretion of potassium, despite apparently insignificant changes in its serum level may reflect, in part, the post-absorptive state.

Throughout the procedure, serum electrolyte concentration usually fell slightly, probably secondary to dilution, and tended to rise again during diuresis.

# Effect of mercurial divresis on urinary electrolytes during Pitressin<sup>®</sup> infusion

On the doses of Pitressin<sup>®</sup> and mercurial administered, a clear-cut diuretic response to the mercurial was obtained in each case. Following the usual latent period, urine flow increased to maximal values of 4.2 to 18.5 ml. per min., and gradually subsided.<sup>6</sup> This increase in urine flow and salt excretion was invariably accompanied by a fall in urinary sodium and chloride concentrations which, following maximal diuresis, rose toward the previous, more hypertonic levels. The potassium excretion continued to fall in these normal individuals in striking contrast to the increase in potassium excretion following mercurials observed in cardiac patients or other subjects exhibiting increased sodium conservation.

Examination of Table I and Figures 1 and 2 reveals that the lowest urinary concentration of sodium and chloride attained during diuresis always exceeded the patient's plasma sodium level. Moreover, the greater the increase in urine flow, the more closely did the urinary sodium concentration approach isotonicity (Figure 3). These data

<sup>&</sup>lt;sup>6</sup> The procedures had to be discontinued before return to the original control levels was reached.

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Maximal Tubular Water Rejectate (V<sub>Ha</sub>-V<sub>Pit</sub>), ml/min.

FIG. 3. RELATIONSHIP BETWEEN THE URINE-PLASMA CONCENTRATION DIFFERENCE (URINE [Na]He - PLASMA [Na]) AND TUBULAR WATER REJECTATE AT MAXIMAL DIURESIS  $(V_{Hg} - V_{Pit})$  IN ALL SUBJECTS

It is apparent that the greater the diuresis, especially beyond 4 to 6 ml. per min., the more closely does the urinary sodium concentration approach isotonicity. This strongly suggests that the hypertonic urine excreted under Pitressin<sup>®</sup> alone is diluted by an approximately isotonic fluid.

support the hypothesis that the very small volume of highly concentrated urine resulting from Pitressin<sup>®</sup> administration is diluted by an increasingly larger volume of isotonic fluid, rejected by the tubule due to the mercurial's action. In such case, no matter how great the diuresis, the final concentration must, however slightly, exceed isotonicity.

The data in Columns 14, 16, and 18 reveal that, following administration of the mercurial, the calculated tubular rejectate concentrations 7 of so-



Tubular Water Rejectate (VHa-VPIL), ml/min.

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J.L.

FIGS. 4a AND 4b. RELATIONSHIP BETWEEN THE URINE-PLASMA SODIUM CONCENTRATION DIFFERENCE (URINE [Na]<sub>Hg</sub> - Plasma [Na]) and the Tubular Water REJECTATE  $(V_{Hg} - V_{Pit})$  during the Course of Diu-RESIS IN INDIVIDUAL SUBJECTS

During the phase of increasing urine flow, urinary sodium concentration falls toward that of plasma.

During falling urine flow, each curve returns at a somewhat higher level, indicating a greater concentration of electrolyte at any given flow. Moreover, the smaller the diuresis, the greater is this deviation. These curves suggest that additional resorption of a relatively constant volume of water occurs during waning flows. The arrows indicate course of diuresis. The broken line portions of the curves for subjects F. G. and M. S. were obtained following discontinuance of Pitressin®.

L.G.

<sup>&</sup>lt;sup>7</sup> The tubular rejectate concentrations are calculated as follows: If the constant flow under Pitressin<sup>®</sup> alone is subtracted from the total urine flow during mercurial diuresis, the difference represents the additional water passing down, and unresorbed by, the distal tubules, working almost maximally. This quantity has been designated the tubular water rejectate (Table I, Column 12, Figures 3 and 4). Similarly, if the sodium excreted under Pitressin® alone, just prior to the administration of the mercurial, is subtracted from that during mercurial diuresis, the difference represents the additional sodium now reaching, and unresorbed by, the distal segment (i.e., the tubular sodium rejectate, Table I, Column 13). By dividing this tubular sodium rejectate by the tubular water rejectate, the concentration of sodium in the additional urine resulting from the mercurial's effect may be calculated (Table I, Column 14). Similarly, the

concentrations of total solute (osmolarity) or chloride in the tubular fluid rejected under the influence of the mercurial may be determined (Table I, Columns 16 and 18).



FIGS. 5a AND 5b. RELATIONSHIP BETWEEN URINE TOTAL SOLUTE CONCENTRATION AND URINE FLOW DURING THE COURSE OF DIURESIS IN INDIVIDUAL SUBJECTS

The deviations in the curves during waning diuresis are similar to those observed in Figures 4a and 4b. Total solute concentrations were calculated as 2([Na] + [K])in most subjects and measured in two (P. F., P. G.).

dium, chloride, and total solutes are not isotonic, but approach a limiting value somewhat above the plasma level. One explanation for this might lie in the fact that a steady state of anti-diuresis may not have been achieved prior to the administration of the mercurial. Thus, in two subjects (R. F., T. S.), the urine flow was still falling slightly at the time the mercurial was given. Moreover, in the two control studies, the urine solute concentrations continued to rise slowly as the Pitressin<sup>®</sup> infusions were maintained. It is apparent that subtraction from the total urine excretion of a "Pitressin®" figure of slightly smaller volume and higher sodium concentration, due to Pitressin® accumulation, would result in a rejectate sodium concentration which is lower and, therefore, closer to isotonicity. However, correcting for such accumulation of Pitressin® in the two subjects who were given the same dose of Pitressin® without a mercurial in a second control study failed to eliminate this hypertonicity of the tubular rejectate. Moreover, continued Pi-



FIGS. 6a AND 6b. RELATIONSHIP BETWEEN URINE TOTAL SOLUTE EXCRETION AND URINE FLOW DURING THE COURSE OF DIURESIS IN INDIVIDUAL SUBJECTS

The linear relationship and the general similarity of slope are consistent with the postulated dilution of the originally hypertonic urine by an approximately isotonic fluid. Note the smaller urine flow per mOs. excreted during waning diuresis.



FIG. 7. CHANGES IN NEGATIVE FREE WATER CLEARANCE DURING THE COURSE OF DIURESIS In the lower portion, the negative free water clearance is plotted against urine flow. With the onset of diuresis, there is an increase in tubular water resorption, which remains fairly constant until maximal flow. Subsequently, a further increase in water resorption occurs. The upper portion demonstrates that as the volume of fluid passing down the tubule (urine flow  $(V) + T^{e}_{H_{2}0}$ ) increases during diuresis, the fraction of water resorbed  $T^{e}_{H_{2}0}/(T^{e}_{H_{2}0} + V)$ anisosmotically falls. As diuresis subsides, this reabsorbed fraction at any given urine flow is increased.

tressin<sup>®</sup> accumulation would lead to rising rejectate sodium concentrations during increasing diuresis. Actually the converse occurs, the tubular rejectate sodium concentration being maximal at the onset of diuresis, and falling as the urine flow increases.

Other factors may contribute to the hypertonicity of the tubular rejectate with regard to sodium. These include the fall in potassium excretion during most experiments and the isosmotic reabsorption of other constituents of the glomerular filtrate, such as glucose. It is of interest that during osmotic (urea or mannitol) diuresis, complete reabsorption of glucose (13) contributes 5 mM per L. to the isosmotic resorbate concentration.<sup>8</sup> However, a real increase in rejectate tonicity is indicated by the fact that this increase was observed not only when total solute concentrations were calculated, but also when measured directly by osmometry.

The persistence of a slightly hypertonic tubular rejectate suggests that during mercurial diuresis a small additional volume of water is resorbed from an isotonic tubular fluid, presumably distal to the site of mercurial action. At the onset of diuresis, when the volume of fluid passing down from the proximal segment has increased only slightly, this will result in a significant increase in the calculated rejectate sodium concentration. However, as the tubular flow increases, the distal

<sup>&</sup>lt;sup>8</sup>During forced osmotic diuresis, relatively small amounts of the diuretic agent are reabsorbed. Therefore, the sodium concentration of the isosmotic reabsorbate is greater, and that of the rejectate less, than that of the

glomerular filtrate. Conversely, mercurial diuretics which exert a primary effect on sodium reabsorption, would, assuming the resorbate to be isosmotic, produce a tubular rejectate hypertonic with respect to sodium, the degree of hypertonicity reflecting the contribution of other substances to the isotonicity of the resorbate.



Tubular Water Rejectate (V<sub>Ha</sub>-V<sub>Pit</sub>), ml/min.

FIG. 8. RELATIONSHIP BETWEEN TUBULAR REJECTATE Sodium Concentration and Tubular Rejectate Volume

This hypothetical diuresis curve is based upon the following assumptions: At the onset (Pitressin® alone), the urine flow is 1.0 ml. per min., and urinary sodium concentration is 288 mEq. per L. During increasing diuresis, a constant increment of 0.3 ml. per min. of water without solute is absorbed; following maximal flow, an additional 0.5 ml. per min. of water is reabsorbed. It is apparent that at smaller urine flows, additional reabsorption of a given amount of water without solute will produce a considerably greater increase in tubular rejectate sodium concentration than at higher flows.

tubular capacity to reabsorb water at this Pitressin<sup>®</sup> dose is soon exceeded, and the small increment of water resorption assumes progressively less importance. Subsequently, the additional rejectate remains isotonic and continues to dilute the concentration of both the urine (Figure 5) and the tubular rejectate (Figure 8).

This explanation is compatible with the findings of an initially high tubular rejectate sodium or solute concentration which asymptotically approaches isotonic levels, as urine flow increases, and rises again, as urine flow falls. The theoretical additional distal water resorption required to produce the observed rejectate sodium concentrations is very small in comparison with the total distal water resorption of 15 to 20 ml. per min. probably occurring under the conditions of our experiments (Figure 8). It appears, then, that the distal tubules, already absorbing water at a near-maximal rate can reabsorb some additional water when presented with a larger flow from the proximal segment. Once the capacity to reabsorb water is exceeded, however, the urine volume increases and the solute concentration of both rejectate and urine falls toward that of plasma.

The fact that this additional moiety of water resorption remains small and fairly constant despite a falling urine concentration suggests that under these experimental conditions, the elaboration of a more concentrated urine is prevented by the inability of the distal tubules to resorb water beyond a given rate. Thus, the capacity for distal water resorption is evidently limited by either of two factors: 1) The maximal concentration gradient which the tubule can establish by doing osmotic work; and 2) the maximal rate at which the tubule can transport water, per se. Normally, the osmotic ceiling is the chief determinant of distal water reabsorption, but under special conditions like osmotic (13) or mercurial diuresis, the maximal water resorptive capacity may be exceeded long before the predicted concentration gradient for a given level of anti-diuretic activity is reached.

If this additional distal water absorption were due to Pitressin<sup>®</sup> accumulation, the (negative) free water clearance <sup>9</sup> would rise throughout the procedure. However, examination of Figure 7 reveals that the negative free water clearance re-

<sup>9</sup> The free water clearance (T<sup>e</sup><sub>H20</sub>) as defined by Wesson and Anslow (14), is that amount of water which must be added to or removed from urine to render it isosmotic with the plasma.  $T^{e}_{H_{2}O} = [1 - (U_{osm}/P_{osm})]V$ , where U<sub>0sm</sub> and P<sub>osm</sub> are the osmolarities of the urine and plasma, respectively, and V is the urine flow. T<sup>e</sup><sub>H20</sub> is negative when the urine is hyper-osmotic, and positive when hypo-osmotic. It should be noted that the Pitressin@-induced formation of a hypertonic urine from an isotonic filtrate is not necessarily equated with the entire distal tubule, either in an anatomical or in the usual physiological sense. These investigators subdivided distal tubular reabsorption of water into at least two components: 1) Facultative, which is associated with active distal sodium reabsorption  $(T^{d}_{H_{20}})$ , leaving the urine isotonic; and 2) hyper-osmotic, which concentrates the urine lower in the distal tubules or in the collecting ducts  $(T^{e}_{H_{2}O})$ . Of these, only the latter represents the free water clearance. Ladd (15) and Zak, Brun, and Smith (16) have demonstrated that mercurials do not affect the T<sup>e</sup><sub>H20</sub>. Whatever water diuresis occurs following a mercurial must therefore be due to the osmotic effect of the increased solutes claiming excretion or to a direct effect upon water reabsorption proximal to the segment where concentration occurs.

mains fairly constant prior to the mercurial and rises only as diuresis begins. In accord with the above hypothesis, once the distal tubular capacity for reabsorbing water at this level of anti-diuretic activity is exceeded, the negative free water clearance remains at this new value throughout the period of rising urine flow.

Following maximal diuresis, the negative free water clearance increases again. The significance of this second rise becomes apparent from examination of Figures 4 to 6, which reveals that during falling urine flows, the curves invariably fail to trace the path followed during the diuretic phase. If mercurial diuresis represents a relatively simple process which rises to maximal intensity and subsides as the pharmacologic effect is dissipated, then the curves would be expected to rise and fall symmetrically; that is, along the same path. Instead, in each instance, during the falling phase, the urine, at any given flow, is more concentrated than during increasing diuresis.

When the rise and fall in urine flow during diuresis are plotted against sodium or total solute excretion (Figure 6), in some patients an almost linear relationship appears to exist. However, the return to low urinary flows during the falling phase occurs at a slightly higher rate of sodium or total solute excretion per volume of urine. It would appear that following maximal diuresis, the kidney reabsorbs more water than previously, for less water is excreted per mOsm. of solute as diuresis subsides.

Since it is unlikely that the mercurial directly caused this increased tubular water reabsorption. and since significant Pitressin<sup>®</sup> accumulation did not occur during these studies, the possibility that mercurial diuresis may have evoked other mechanisms affecting water excretion must be considered. Previous studies from this laboratory (17) have shown that a large fraction of intravenously administered mercury appears in the urine before diuresis has begun. More significantly, as much as  $\frac{1}{4}$  to  $\frac{1}{3}$  of the injected mercury is excreted after diuresis has subsided. Therefore, although little is known of the relationship between the chemical form and diuretic activity of mercury, the fall in urine flow cannot be ascribed simply to the absence of mercury as such. Rather, it may reflect secondary activation of compensatory mechanisms which combat the mercurial effect by increasing tubular reabsorption of salt and water.

The relationship of solute excretion to urine flow under the influence of a mercurial has been studied by Brodsky and Graubarth (5) in hydropenic dogs, presumably under conditions of continued release of ADH. From the linear relationship between osmotic load (excretion) and urine flow, they concluded that mercurial diuresis is essentially an osmotic diuresis, the amount of distal water resorption being determined by the number rather than the chemical nature of the particles claiming excretion. While the present data support this concept, the altered level of the waning phase of diuresis suggests that other factors or mechanisms may modify this relationship. Thus, the amount of distal water reabsorption, and therefore of osmotic work performed, is a function not only of the number of particles involved, as suggested by Rapoport, Brodsky, West, and Mackler (18), but of the degree of anti-diuretic activity at the time. Only during maximal antidiuresis does the simpler relationship apply.

That the increased sodium and calculated total solute concentrations during the falling urine flows do not merely reflect decreased concentration of other solute particles, for example, urea, is established by the finding of similar changes in measured urinary osmolarity. Further evidence that increased reabsorption of water occurred following maximal mercurial action is provided by the calculated free water clearances  $(T^{c}_{H_{2}0})$  (Figure 7). Because the concentration of urine tends to approximate that of plasma during mercurial diuresis, mercurials produce no marked effects on the free water clearance, after the initial increase discussed above. However, as diuresis subsides, the (negative) free water clearance at any given urine flow is higher than during the periods of increasing flow (Figure 7), indicating that, following maximal diuresis, more water in excess of solute is being reabsorbed. Similarly, the ratio of free water clearance  $(T^{e}_{H_{2}0})$  to the total fluid leaving the proximal or isosmotic segment (urine volume  $+ T^{c}_{H_{2}0}$ ), or the fraction of water of the isotonic mixture absorbed distally, falls, as expected, during increasing diuresis, and returns at a higher level as flow subsides. Thus, a greater fraction of water per unit urine flow down the distal tubules is removed from the isotonic mixture during the waning phase of diuresis. Because the rise in  $T^{\circ}_{H_{2}O}$  is stepwise rather than continuous, these data do not simply reflect accumulation of Pitressin<sup>®</sup> during the procedure, but suggest instead that some other, presumably endogenous, mechanism is activated.

Of interest is the finding of a tubular rejectate chloride concentration approximating that of sodium. While it has been contended, on the basis of the potentiating action of chloruretic agents, that mercurials act primarily to inhibit chloride resorption (19), our data neither support nor refute this hypothesis. The tubular rejectate chloride concentration of about 140 mEq. per L., confirming the results of the micropuncture experiments of Walker, Bott, Oliver, and MacDowell (20), reflects rather the combined influences of the Donnan effect, as a result of which the glomerular filtrate chloride concentration may reach 112 to 115 mEq. per L., and the virtually complete, isotonic reabsorption of bicarbonate, phosphate, and glucose (13, 14). The high chloride concentration in the tubular rejectate and urine is simply the result of the normal plasma ion partition, and does not help localize the site of mercurial action.

The decreased urinary potassium excretion during mercurial diuresis in these normal subjects is in direct contrast to the increased potassium excretion observed in individuals in whom sodium conserving mechanisms have been activated by low sodium intake, specific cardiac, hepatic, or renal diseases, adrenal cortical steroid administration, or ammonium chloride acidosis. Potassium excretion involves filtration at the glomerulus, proximal reabsorption, and distal secretion of this cation. A purely proximal tubular inhibition by mercurials should result in increased potassium excretion in both normal and cardiac subjects. An effect limited to the distal segment, if it inhibited potassium secretion, would account for the decreased excretion encountered in normal subjects, but not for the increased excretion of potassium in cardiacs and other sodium retainers.

The explanation for this particular effect of the mercurial may depend upon the balance of factors adjusting potassium excretion at a given time to the body's previous conditioning. Thus, in normal, post-absorptive subjects, any potassium escaping reabsorption more proximally ordinarily would be largely reabsorbed lower in the tubule. In subjects exhibiting marked sodium conservation, the increased sodium delivered to the distal tubule as a result of mercurial inhibition of proximal reabsorption, is exchanged for potassium, ammonia, and hydrogen ion, by distal tubular base-conserving mechanisms, which are unaffected by therapeutic doses of mercurial (3). This leads to both an increased excretion of potassium and the relatively greater excretion of chloride than sodium (21, 22).

On the basis of available evidence, certain tentative conclusions as to the site and mode of action of mercurial diuretics in man may be drawn. The failure of mercurials to increase urine flow during maximal water diuresis suggests a primary effect on the distal tubule salt reabsorption (7, 8). However, the following observations strongly suggest a predominant diuretic effect on the proximal segments: 1) Minimal toxic doses of mercury produce histologic damage and histochemical evidence of enzyme inhibition only in cells of proximal tubules; 2) mercurials depress renal transport of substances other than sodium and chloride, presumably handled by the proximal segments (10, 11) but not those secreted by the distal tubule (3); and 3) the changes in hydrogen ion and potassium excretion following mercurials in man (3, 21). The present data and analogous studies from other laboratories support such an interpretation.

The degree and duration of mercurial diuresis ultimately depend upon the balance between factors increasing or decreasing water and electrolyte reabsorption by the tubules. The present data suggest that, with the reduction in extracellular fluid volume resulting from diuresis, mechanisms normally preserving body fluid volume are activated, leading to increased reabsorption of electrolyte and water. In addition to explaining the described alterations in rejectate solute concentration, this hypothesis is consistent with other facts regarding mercurial diuresis. For example, despite their normal renal hemodynamics, normal serum electrolytes, and high urinary sodium and chloride excretion rates, normal subjects on regular diets exhibit a shorter, and smaller, diuretic response to mercurials than do edematous patients on low sodium diets, who are actively retaining sodium. The normal subject achieves a peak diuretic response greater than that of the cardiac, but, with the consequent decrease in extracellular fluid and plasma volume (23), sooner invokes secondary mechanisms for maintaining body fluid volume and the circulation. Further studies on these mechanisms which result in increased tubular reabsorption of sodium and water are now in progress.

### SUMMARY AND CONCLUSIONS

1. Mercurial administration, in hydrated patients receiving 1 to 3 mu. per Kg. per hr. of Pitressin<sup>®</sup> intravenously and excreting a hypertonic urine of low volume (0.6 to 1.0 ml. per min.), results in a diuresis of urine slightly exceeding isotonicity. This implies that the effect of the mercurial is to add a relatively large volume of isotonic urine to the previously small, hypertonic flow. Support for this explanation is found in the fact that the greater the diuresis the more closely is plasma tonicity approached.

2. The fact that mercurial diuresis is isotonic implies that the principal site of action is proximal to the segment of the nephron at which anisosmotic or free water resorption occurs.

3. The calculated concentration of sodium in the fluid unresorbed (rejected) by the tubules as a result of mercurial action is hypertonic to that of plasma. The probable reasons for this phenomenon have been discussed.

4. The relationship between urinary total solute concentration, or excretion, and urine flow during the rising and subsiding phases of mercurial diuresis strongly suggests that an altered bodily or renal response results in somewhat greater reabsorption of water per unit load of solutes excreted after maximal diuresis has been attained. Calculation of the free water clearance corroborates this finding.

5. It is suggested that the subsidence of mercurial diuresis represents not simply the dissipation of a drug effect, but, in part, reflects the activation of compensatory counter-mechanisms promoting fluid retention.

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