FACTORS INFLUENCING THE COURSE OF MERCURIAL DIURESIS DURING PITRESSIN® INFUSION IN NORMAL SUBJECTS [1, 2]

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(Submitted for publication March 29, 1955; accepted July 11, 1955)

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, Goodyer, Darragh, Abele, and Meroney (6) who studied three men receiving Pitressin® infusions, drew similar conclusions. More recently, Capps, Wiggins, Axelrod, and Pitts (7) and Dale and Sanderson (8) suggested that because Mersalyl increased 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® 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 post-absorptive 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.[4] 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-

[1] Presented in part at the Annual Meeting of the American Physiological Society, New York City, April 16, 1952.

[2] This work was supported in part by grants from the National Heart Institute, U. S. Public Health Service, Martha Hall Foundation, Montefiore Hospital, Eli Lilly & Co., Wyeth, Inc., Campbell Pharmaceutical Co., G. D. Searle & Co., and the New York Heart Association.

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[4] One patient, L. G., received 6 mu. per Kg. with consequent excessive Pitressin® effect.

TABLE I

Procedure (1)	Time (2)	Urine									"Tubular" rejectate (post-mercurial)						Serum			
			Sodium		Chloride		Potassium		Osmolarity*			Sodium		Chloride		Osmolarity				
		Flow (3)	Conc. (4)	Exc. (5)	Conc. (6)	Exc. (7)	Conc. (8)	Exc. (9)	Conc. (10)	Exc. (11)	Water (12)	Exc. (13)	Conc. (14)	Exc. (15)	Conc. (16)	Exc. (17)	Conc. (18)	Osmol. (19)	Na (20)	Cl (21)	K (22)
	min.	*ml./min.*	*mEq./L.*	*μEq./min.*	*mEq./L.*	*μEq./min.*	*mEq./L.*	*μEq./min.*	*mOs./L.*	*μOs./min.*	*ml./min.*	*μEq./min.*	*mEq./L.*	*μEq./min.*	*mEq./L.*	*μOs./min.*	*mOs./L.*	*mOs./L.*	*mEq./L.*	*mEq./L.*	*mEq./L.*
J. L., Age 50; 65 Kg., Hepatitis, Conv. 1/6/51																				
Begin inf.†	14	10.5	7	76	10	110	5.6	59	26	270								135	96.8	4.53
	12½	11.0	7	81	11	123	5.9	65	27	293										
	17	11.7	8	91	9	105	5.7	67	27	316										
	13½	11.9	9	103	10	117	5.1	61	28	329								136	98.0	4.73
Pit. 1 mu./Kg.‡	13	3.1	25	78	31	98	18.2	58	86	271										
	20	1.0	115	120	130	137	75.5	79	381	400										
	20	1.0	124	124	125	125	51.3	51	350	350								135	97.5	4.48
	25	1.1	155	167	134	145	47.1	51	404	437										
Hg§	25	1.0	172	166	148	142	42.6	41	429	412										
	30	1.3	195	260	168	223	22.0	29	434	578	0.3	93	300	78	252	141	455	136	97.7	4.67
	20	4.6	158	725	159	731	6.0	28	327	1,500	3.6	558	156	586	164	1,060	296			
	20	6.6	151	1,000	151	1,000	4.1	27	311	2,070	5.6	833	148	858	152	1,630	289			
	20	7.2	150	1,080	150	1,080	3.0	21	306	2,200	6.2	841	136	937	151	1,760	285			
	14	8.2	149	1,230	152	1,250	2.5	21	304	2,500	7.2	1,060	148	1,100	153	2,060	286	134	96.4	4.66
	15	7.2	155	1,110	156	1,120	3.4	25	317	2,280	6.2	948	153	975	158	1,840	288			
	15½	5.8	166	966	166	964	3.3	19	340	1,970	4.8	799	167	819	171	1,530	320			
	20	5.8	163	948	161	932	2.9	17	333	1,930	4.8	781	163	787	165	1,490	312	133	95.9	4.66
T. S., Age 50, 70.4 Kg., Pulmonary fibrosis, Bronchiectasis 3/20/51																				
Begin inf.	17½	1.0	141	145	180	185	74.0	76	430	443										
	23½	1.9	69	131	91	174	38.1	73	214	409										
	15	4.2	31	132	39	165	16.9	71	96	408										
	15	5.9	24	141	28	167	12.1	71	72	426										
	25	7.5	22	167	26	195	10.0	75	65	486										
Pit. 2 mu./Kg.	18	2.6	122	323	124	327	36.3	96	317	837										
	20	1.5	225	344	223	342	54.2	83	558	854										
	45½	1.2	227	280	228	280	43.1	53	540	664										
	27½	1.0	220	224	219	223	57.4	58	555	566										
Hg	22½	1.1	202	220	208	227	45.5	50	495	540	0.1			4	572					
	19	4.3	180	779	185	797	10.9	47	382	1,650	3.3	555	168	574	174	796	241			
	14½	8.5	159	1,360	164	1,400	7.1	61	332	2,840	7.5	1,130	151	1,180	157	1,990	264			
	15	11.0	154	1,690	157	1,720	6.2	68	320	3,520	10.0	1,460	147	1,500	150	2,670	267			
	19	8.2	163	1,340	165	1,360	6.7	55	339	2,790	7.2	1,110	155	1,140	158	1,940	269			
	12½	7.8	171	1,340	174	1,370	7.0	55	356	2,790	6.8	1,110	164	1,150	168	1,940	284			
	17½	7.3	175	1,270	179	1,300	6.8	49	364	2,640	6.2	1,040	168	1,070	172	1,790	286			

* Osmolarity calculated, except in patients P. F., P. G., and C. W.
† Begin constant (3.4 or 3.0 ml. per min.) intravenous infusion of NaCl (in patients J. L., T. S., E. M.) or Lactated Ringers' (in patients P. F., P. G., C. W.) solution.
‡ Dose given stat., and equivalent dose per 60 minutes placed into infusion.
§ Thiomerin®—2 ml., I.V.

TABLE I—*Continued*

Procedure (1)	Time (2)	Urine									"Tubular" rejectate (post-mercurial)							Serum			
			Sodium		Chloride		Potassium		Osmolarity*			Sodium		Chloride		Osmolarity					
		Flow (3)	Conc. (4)	Exc. (5)	Conc. (6)	Exc. (7)	Conc. (8)	Exc. (9)	Conc. (10)	Exc. (11)	Water (12)	Exc. (13)	Conc. (14)	Exc. (15)	Conc. (16)	Exc. (17)	Conc. (18)	Osmol. (19)	Na (20)	Cl (21)	K (22)
	min.	*ml./min.*	*mEq./L.*	*μEq./min.*	*mEq./L.*	*μEq./min.*	*mEq./L.*	*μEq./min.*	*mOs./L.*	*μOs./min.*	*ml./min.*	*μEq./min.*	*mEq./L.*	*μEq./min.*	*mEq./L.*	*μOs./min.*	*mOs./L.*	*mOs./L.*	*mEq./L.*	*mEq./L.*	*mEq./L.*
E. M., Age 39, 59.1 Kg., Hyperthyroidism 3/27/51																					
Begin inf.	12½	12.5	20	248	20	250	8.3	104	56	703									142	104	4.67
	13½	10.3	25	263	26	272	8.3	86	68	696											
	15½	12.6	21	271	22	276	6.2	78	55	698											
	18	14.3	18	262	20	281	5.7	82	48	687									141	104	4.63
Pit. 3 mu./Kg.	16	3.9	58	224	54	209	17.9	69	151	586											
	39½	1.2	203	239	215	254	41.5	49	489	578									140	104	4.25
	32	1.1	226	258	231	264	27.4	31	507	578											
	39½	1.0	246	254	242	249	30.2	31	552	569									138	103	4.07
	22	1.0	255	255	256	256	29.0	29	568	568											
Hg	17	1.1	240	255	240	255	26.7	28	533	565									138	103	4.07
	18	2.4	196	467	204	489	13.4	32	419	1,000	1.4	212	152	233	168	432	311				
	10	11.7	156	1,820	160	1,870	3.6	42	319	3,730	10.7	1,570	147	1,610	151	3,160	295				
	11½	15.4	155	2,390	153	2,360	2.8	44	316	4,870	14.4	2,130	148	2,100	146	4,300	299				
	11	15.2	155	2,350	154	2,340	2.6	39	315	4,790	14.2	2,090	148	2,080	147	4,220	297		136	99	4.17
	12	14.2	155	2,190	154	2,190	2.5	35	315	4,490	13.2	1,930	146	1,930	146	3,920	296				
	13	12.7	162	2,060	162	2,060	2.6	33	329	4,180	11.7	1,800	154	1,800	154	3,610	309				
	16	10.4	165	1,720	164	1,710	2.8	29	336	3,500	9.4	1,460	156	1,450	155	2,930	312		135	100	4.11
P. F., Age 19, 70 Kg., Acute rheumatic fever—Healed 5/19/53																					
Begin inf.	49	1.3	270	340	289	364	96.4	122	873	1,100											
	10	4.7	32	152	42	198	4.75	175	210	998								290	140	105	1.82
	9	8.1	23	191	28	227	22.9	186	144	1,170								292	141	104	3.87
	8	5.7	33	187	38	216	26.8	154	174	1,000											
	10	4.4	50	222	55	245	21.3	95	235	1,050											
Pit. 3 mu./Kg.	24	1.4	122	168	136	188	32.8	45	516	712								292	141	105	3.80
	36	1.1	174	197	177	200	69.2	78	714	807											
	37	1.1	217	232	233	249	56.0	60	761	814											
	26	1.2	223	274	201	247	57.9	71	772	949								294	142	105	3.80
	23	1.1	254	277	227	247	51.3	56	818	892											
	19	1.3	246	310	207	261	44.0	55	735	926											
	22	1.0	268	273	220	224	39.4	40	832	849								296	143	103	3.60
Hg	15	0.9	265	240	220	200	40.0	36	804	729											
	17	0.9	275	252	217	199	41.2	38	819	752											
	18	1.4	225	315	218	305	36.0	50	687	962	0.4	42	111	81	213	113	297				
	10	7.9	160	1,260	162	1,280	7.3	58	385	3,040	6.9	992	144	1,050	154	2,190	319	296	143	104	3.58
	7	13.1	153	2,000	147	1,930	3.8	50	350	4,590	12.0	1,720	143	1,700	141	3,740	310				
	8	17.4	152	2,650	170	2,960	2.7	46	340	5,920	16.3	2,370	145	2,730	167	5,070	310				
	8	18.5	151	2,790	149	2,760	2.1	39	330	6,100	17.4	2,510	144	2,530	145	5,250	300				
	8	17.6	155	2,730	152	2,680	2.1	37	334	5,880	16.5	2,450	148	2,450	148	5,030	303	292	141	103	3.75
	8	15.5	157	2,430	155	2,400	2.2	34	346	5,360	14.4	2,150	149	2,170	150	4,510	312				
	8	16.2	158	2,570	159	2,580	2.0	32	348	5,660	15.2	2,290	151	2,350	155	4,810	316				
	12	13.5	159	2,150	158	2,130	2.3	31	358	4,830	12.4	1,870	150	1,900	153	3,980	319				
	11	11.8	165	1,950	166	1,960	3.1	37	363	4,290	10.7	1,670	156	1,730	161	3,440	319				
	22	11.2	165	1,850	167	1,870	3.0	34	364	4,080	10.1	1,570	155	1,640	162	3,230	318	292	141	101	3.78
	22	11.5	164	1,890	160	1,840	3.6	41	367	4,220	10.4	1,610	154	1,610	154	3,370	321				
	21	10.3	165	1,700	166	1,710	4.7	48	369	3,800	9.3	1,420	154	1,480	160	2,950	318	286	138	100	3.82

TABLE I—*Continued*

Procedure (1)	Time (2)	Urine								"Tubular" rejectate (post-mercurial)						Serum			
			Sodium		Chloride		Potassium		Osmolarity*		Sodium		Chloride		Osmolarity					
		Flow (3)	Conc. (4)	Exc. (5)	Conc. (6)	Exc. (7)	Conc. (8)	Exc. (9)	Conc. (10)	Exc. (11)	Water (12)	Exc. (13)	Conc. (14)	Exc. (15)	Conc. (16)	Exc. (17)	Conc. (18)	Osmol. (19)	Na (20)	Cl (21)	K (22)
	min.	*ml./ min.*	*mEq./ L.*	*μEq./ min.*	*mEq./ L.*	*μEq./ min.*	*mEq./ L.*	*μEq./ min.*	*mOs./ L.*	*μOs./ min.*	*ml./ min.*	*μEq./ min.*	*mEq./ L.*	*μEq./ min.*	*mEq./ L.*	*μOs./ min.*	*mOs./ L.*	*mOs./ L.*	*mEq./ L.*	*mEq./ L.*	*mEq./ L.*
P. G., Age 23, 56 Kg., Disseminated sclerosis 6/23/53																				
Begin inf.	13	6.8	14	95	13	92	9.2	63	83											
	9½	10.9	17	187	9	102	8.0	88	75								284	142	105	4.13
	10	10.6	17	180	9	94	7.6	80	72											
	12½	6.6	23	150	17	114	10.3	68	102											
Pit. 3 mu./Kg.	30	0.7	151	113	116	87	72.3	54	615	461							284	142	104	4.04
	20	0.7	189	134	133	94	64.4	46	744	528										
	20	0.7	224	150	144	96	57.2	38	795	533										
	20	0.7	246	182	155	115	58.8	43	830	614										
Hg	20	0.8	260	203	153	119	55.4	43	820	640							278	140	103	4.13
	21	0.8	278	236	177	150	46.0	39	821	696	0.1	54	391	33	239	56 405				
	19	1.1	254	275	202	219	30.6	33	755	816	.4	93	249	102	276	176 470				
	10½	2.4	236	586	206	511	16.0	40	582	1,440	1.8	404	228	394	213	803 453	277	139	102	4.27
	9½	3.4	226	762	210	708	10.4	35	553	1,860	2.7	580	218	591	222	1,220 459				
	10	4.2	233	978	213	894	8.7	37	516	2,170	3.5	796	228	777	223	1,530 438				
	10	3.6	248	905	222	810	8.7	32	544	1,980	2.9	723	246	693	236	1,350 459	281	140	101	4.07
	10	3.5	259	906	232	812	10.4	36	561	1,960	2.8	721	260	695	249	1,320 473				
	10	3.4	260	892	237	812	10.1	35	575	1,970	2.7	710	261	695	255	1,330 489				
	20	3.1	274	849	244	756	12.6	39	603	1,870	2.4	662	279	639	267	1,230 514				
	20	2.7	280	750	250	670	16.3	44	640	1,710	2.0	568	288	553	281	1,080 548	270	138	103	4.12
	21½	2.3	282	640	256		19.0	43	675	1,530	1.6	458	294			892 572				
	20	2.0	294	588	257		23.2	46			1.3	406	298				270	139	100	3.96
C. W., Age 32, 76.3 Kg., Rheumatoid arthritis 12/16/54																				
Begin inf.	13	0.8	246		250												285	140	105	4.80
	24	0.9	200	192	145	139	68.0	65	783	750										
	22	1.0	207	216	155	162	45.2	47	720	752										
	23	1.1	214	228	165	176	42.0	45	720	767										
	24	1.2	216	270	172	215	39.8	50	709	886										
	18	1.2	233	284	191	233	39.3	48	739	902										
	17	1.3	240	314	194	254	37.6	49	727	952							283	143	106	4.75
Hg	20	1.2	238	295	190	236	31.6	39	716	888										
	10	1.6	220	352	187	299	16.0	26	617	987	0.3	54	159	55	162	60 176				
	9	4.3	181	774	169	723	6.1	26	426	1,820	3.0	476	157	479	158	896 297				
	9	7.8	169	1,310	159	1,240	4.0	31	367	2,860	6.5	1,010	156	996	153	1,930 297				
	8	10.8	160	1,730	157	1,700	2.8	30	345	3,730	9.5	1,430	150	1,450	152	2,800 294				
	8	12.9	160	2,060	156	2,010	2.1	28	332	4,280	11.6	1,760	151	1,760	152	3,350 289				
	8	14.2	158	2,310	156	2,220	1.6	23	331	4,720	12.9	2,010	155	1,970	152	3,790 292				
	8	14.0	164	2,310	159	2,240	2.0	28	333	4,680	12.8	2,010	157	1,990	156	3,750 293				
	8	13.2	167	2,210	161	2,130	1.8	24	340	4,510	11.9	1,910	159	1,880	157	3,580 299	278	137	104	4.56
	10	13.2	169	2,240	162	2,150	1.8	24	339	4,490	11.9	1,940	162	1,900	159	3,560 297				
	12	11.9	169	2,010	163	1,940	2.1	25	343	4,090	10.6	1,710	160	1,690	159	3,160 297				
	15	9.8	166	1,630	165	1,620	4.0	39	356	3,490	8.5	1,330	156	1,370	161	2,560 300				

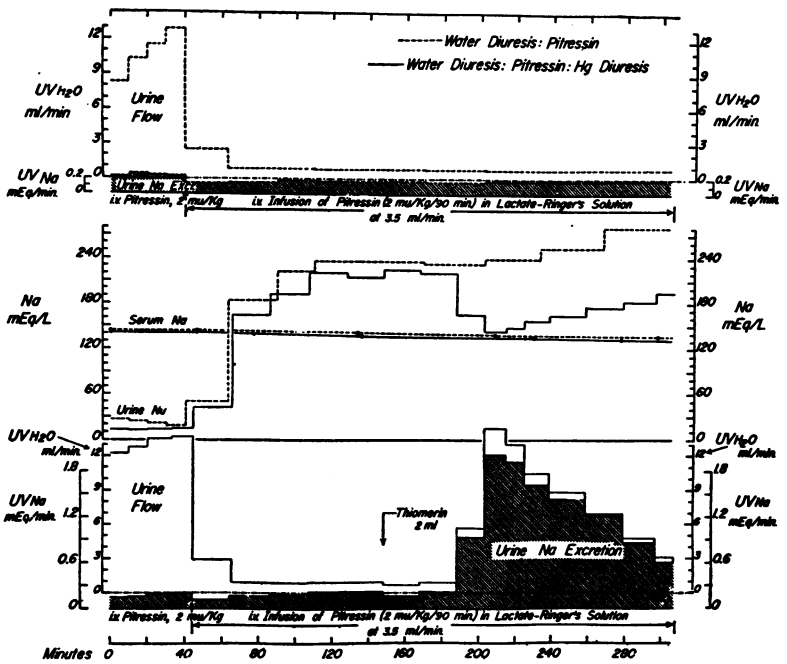


FIG. 1. COMPARISON OF A CONTROL (PITRESSIN® ALONE) AND EXPERIMENTAL (PITRESSIN® PLUS MERCURIAL) PROCEDURE IN THE SAME SUBJECT (M. S.)

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.[5]

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.

[5] Manufactured by Fiske Associates, Inc., Boston, Mass.

Effects of Pitressin® infusion on electrolyte and water excretion

Administration of Pitressin® 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® 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® 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

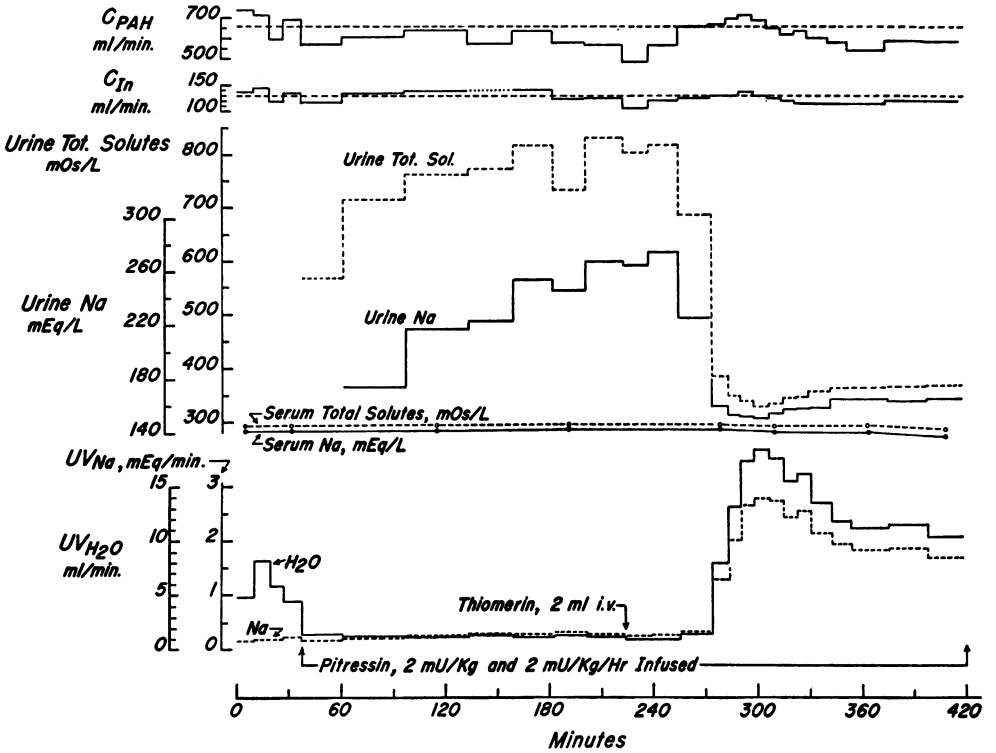


FIG. 2. RESPONSE OF SUBJECT P. F. TO ADMINISTRATION OF MERCURIAL DIURETIC DURING PITRESSIN® ADMINISTRATION

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 diuresis on urinary electrolytes during Pitressin® infusion

On the doses of Pitressin® 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.[6] 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

[6] The procedures had to be discontinued before return to the original control levels was reached.

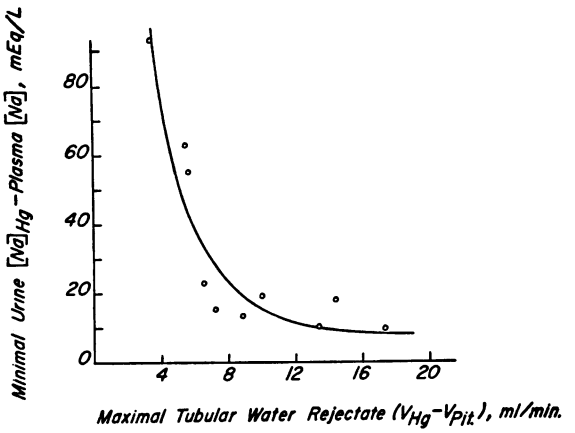


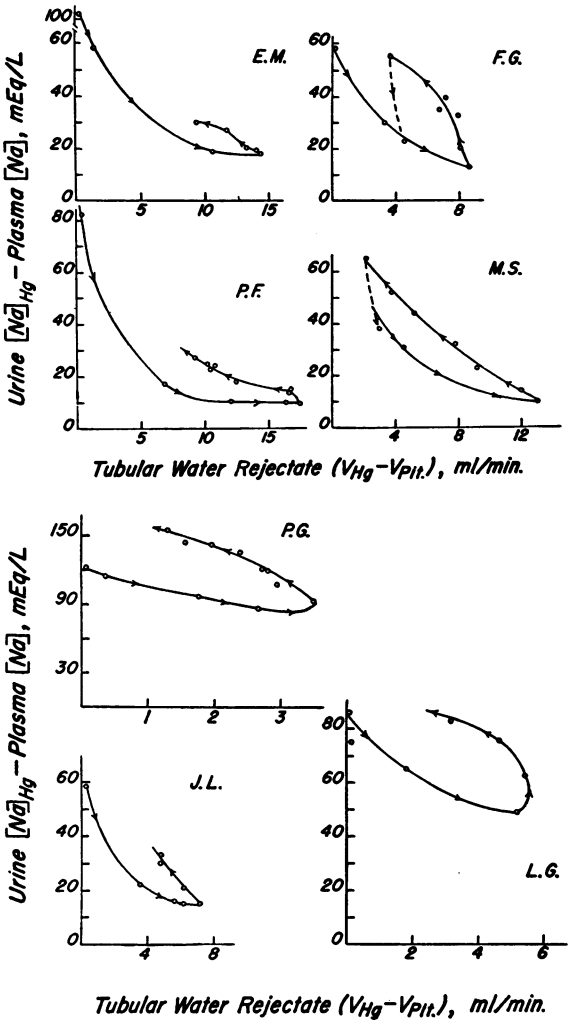
FIG. 3. RELATIONSHIP BETWEEN THE URINE-PLASMA CONCENTRATION DIFFERENCE (URINE $[Na]_{Hg}$ − PLASMA [Na]) AND TUBULAR WATER REJECTATE AT MAXIMAL DIURESIS ($V_{Hg} - V_{Plt}$) IN ALL SUBJECTS

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® alone is diluted by an approximately isotonic fluid.

support the hypothesis that the very small volume of highly concentrated urine resulting from Pitressin® 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 solutes (osmolarity) or chloride in the tubular fluid rejected under the influence of the mercurial may be determined (Table I, Columns 16 and 18).

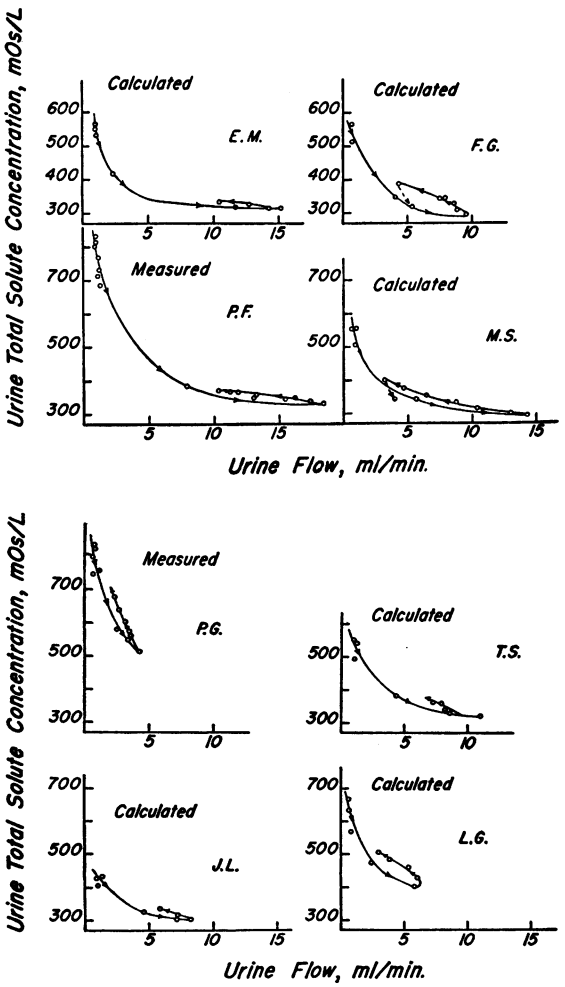
[7] The tubular rejectate concentrations are calculated as follows: If the constant flow under Pitressin® alone is subtracted from the total urine flow during mercurial diuresis, the difference represents the additional water passing down, and unresorbed by, the distal tubules, working almost maximally. 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



FIGS. 4a AND 4b. RELATIONSHIP BETWEEN THE URINE-PLASMA SODIUM CONCENTRATION DIFFERENCE (URINE $[Na]_{Hg}$ − PLASMA [Na]) AND THE TUBULAR WATER REJECTATE ($V_{Hg} - V_{Plt}$) DURING THE COURSE OF DIURESIS 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®.

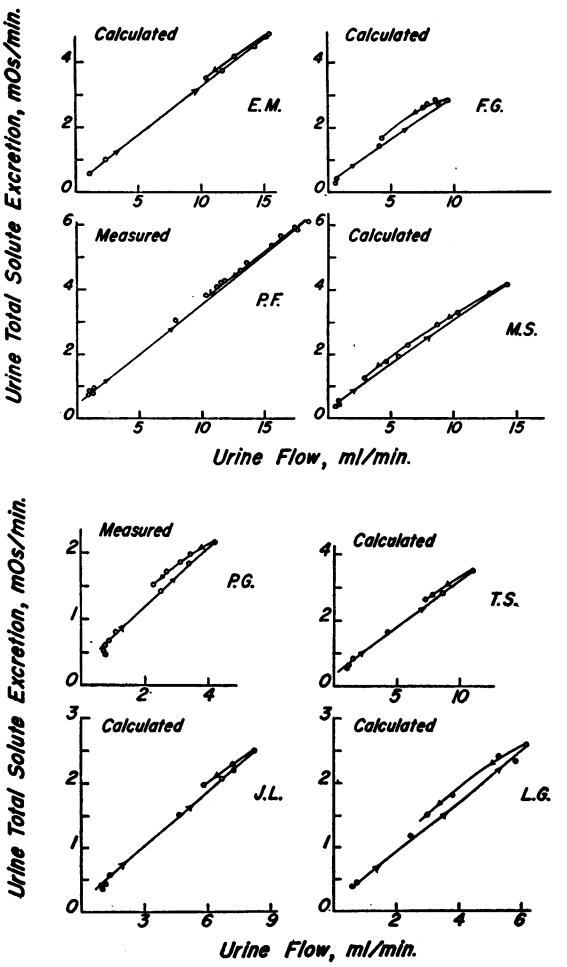


FIGS. 5a AND 5b. RELATIONSHIP BETWEEN URINE TOTAL SOLUTE CONCENTRATION AND URINE FLOW DURING THE COURSE OF DIURESIS IN INDIVIDUAL SUBJECTS

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® 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.

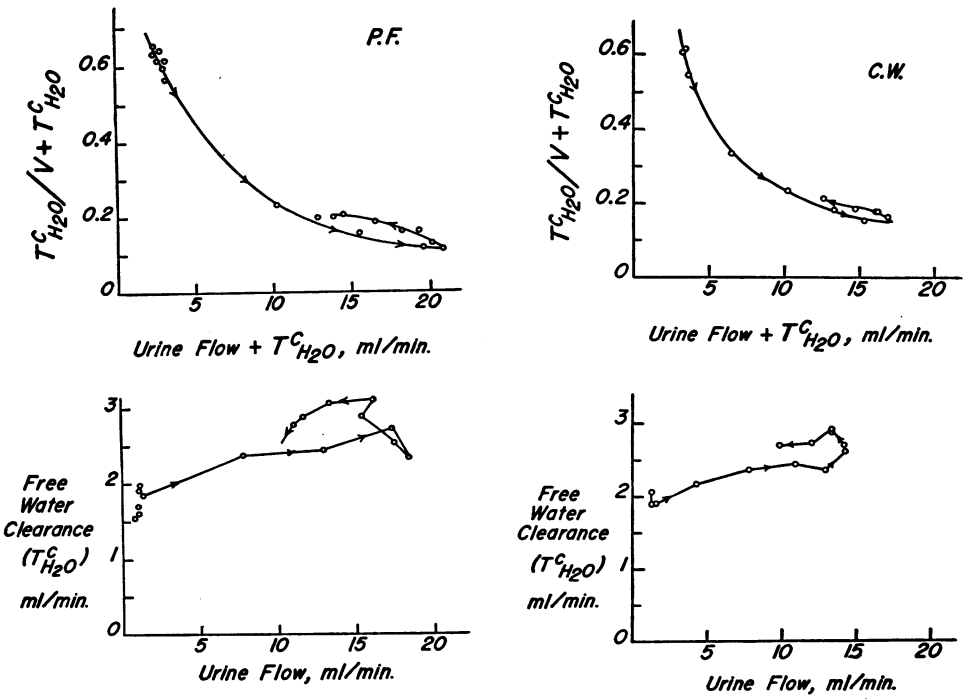


FIG. 7. CHANGES IN NEGATIVE FREE WATER CLEARANCE DURING THE COURSE OF DIURESIS

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) + $T^e_{H_2O}$) increases during diuresis, the fraction of water resorbed $T^e_{H_2O}/(T^e_{H_2O}+V)$ anisosmotically falls. As diuresis subsides, this reabsorbed fraction at any given urine flow is increased.

tressin® 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.[8] 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

[8] 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.

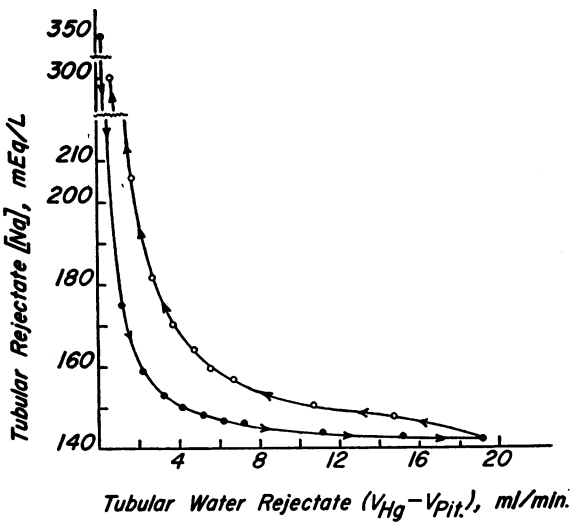


FIG. 8. RELATIONSHIP BETWEEN TUBULAR REJECTATE SODIUM CONCENTRATION AND TUBULAR REJECTATE VOLUME

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® 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® accumulation, the (negative) free water clearance [9] would rise throughout the procedure. However, examination of Figure 7 reveals that the negative free water clearance re-

[9] The free water clearance ($T^c_{H_2O}$) 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. $T^c_{H_2O} = [1 - (U_{osm}/P_{osm})]V$, where U_{osm} and P_{osm} are the osmolarities of the urine and plasma, respectively, and V is the urine flow. $T^c_{H_2O}$ 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 ($T^d_{H_2O}$), leaving the urine isotonic; and 2) hyper-osmotic, which concentrates the urine lower in the distal tubules or in the collecting ducts ($T^c_{H_2O}$). 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 $T^c_{H_2O}$. 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® 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 ¼ to ⅓ 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 ($T^c_{H_2O}$) (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 ($T^c_{H_2O}$) to the total fluid leaving the proximal or isosmotic segment (urine volume + $T^c_{H_2O}$), 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 iso-

tonic mixture during the waning phase of diuresis. Because the rise in $T^c_{H_2O}$ is stepwise rather than continuous, these data do not simply reflect accumulation of Pitressin® 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 re-

taining 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® 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.

ACKNOWLEDGMENT

The authors wish to thank Mr. Morris Wolfman, laboratory supervisor, for his valuable assistance.

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