

STUDIES ON ALCOHOL DIURESIS. II. THE EVALUATION OF ETHYL ALCOHOL AS AN INHIBITOR OF THE NEUROHYPOPHYSIS^{1, 2}

By CHARLES R. KLEEMAN, MILTON E. RUBINI,³ EZRA LAMDIN,⁴ AND FRANKLIN H. EPSTEIN

(From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn.)

(Submitted for publication September 7, 1954; accepted November 24, 1954)

In the normally hydrated semi-recumbent individual, alcohol causes a rise in urine flow that is characterized by an increase of free water clearance (C_{H_2O}) and a decreased excretion of sodium, potassium and chloride (1). The evidence to date strongly suggests that the rise of C_{H_2O} is caused by inhibition of the release of antidiuretic hormone.

The present study was undertaken to evaluate the effect of alcohol on the excretion of water and solutes in physiologic states in which alterations in the activity of antidiuretic hormone have been demonstrated or suggested. The following states were studied: 1) Minimal antidiuretic hormones (ADH) activity produced by sustained positive loads of water; 2) Increased ADH activity produced by infusions of hypertonic sodium chloride solutions, a) during water diuresis with high urine flows (10 to 15 cc. per min.), and b) in subjects with low urine flows (1 to 2 cc. per min.); 3) Increased antidiuretic activity produced by venous congestion of the limbs.

MATERIALS, METHODS AND RESULTS

Subjects were normal males, aged 25 to 32. No control of diet prior to the day of study was attempted. One to one and a half hours after a light breakfast the subjects voided and reclined in a semi-recumbent position. All studies were begun at 8:30 to 9:00 A.M.; diurnal variations in urinary flow and composition (2) were therefore presumably similar in all experiments. Alcohol was given as 120 cc. of 100 proof bourbon whisky imbibed over a 10-minute period. Techniques for collection of blood and urine and chemical methods have been described in the previous paper (1). In all studies insensible water loss was assumed to be approximately 50 cc. per hour. Changes in extracellular

space were calculated approximately from changes in the chloride space (3), assuming an initial extracellular volume of 20 per cent of body weight. Changes in plasma volume were calculated from changes in hemoglobin and hematocrit (1). Urine flow was divided into two fractions:

Osmolar clearance (C_{osm})

$$= \frac{\text{milliosmols per kilo of urine}}{\text{milliosmols per kilo of plasma}} \times \text{urine flow (cc. per min.)}$$

$$\text{Free water clearance } (C_{H_2O}) = \text{urine flow} - C_{osm}$$

Group I. Effect of alcohol during water diuresis (Table I, Figure 1C)

A positive water balance was induced in two semi-recumbent subjects by drinking one liter of water, and was maintained by infusing 4 per cent fructose solution intravenously and administering supplemental water by mouth. The accuracy of this technique was checked by weighing the subject at the beginning and the end of each experiment. Fructose solution was chosen because of its minimal effect on the total hexose in the blood. By limiting the rate of infusion to 8 cc. per minute or less, no reducing substances could be detected in the urine by qualitative test with Benedict's solution. After a maximal steady urine flow had been maintained for at least two 30-minute periods, alcohol was imbibed. Urine was collected at 15 to 30-minute intervals during the next three hours.

Under these circumstances, alcohol did *not* induce a further increase in urine flow or C_{H_2O} (Figure 1C). If large positive loads of water (1000 cc.) completely inhibit ADH release ("physiologic diabetes insipidus"), this result would be expected.⁵ The rates of excretion

⁵ The statement that maximum water diuresis is associated with complete inhibition of ADH release or so-called "physiologic diabetes insipidus" probably is true for the recumbent and semi-recumbent positions only. In unpublished experiments the authors have demonstrated that when a positive water load of 1000 cc. is maintained, the maximum urinary flow and free water clearance (C_{H_2O}) attained in the standing or 45° position were further increased by lying down. This suggests a continual "tonic" release of ADH in the upright positions in spite of the sustained water load or non-hormonal factors blocking the maximum rise in urinary flow.

¹ Supported in part by a Grant from the U. S. Public Health Service.

² Presented in abstract form at the meeting of the American Society for Clinical Investigation, Atlantic City, May 2-5, 1954.

³ Major, MC, USA.

⁴ Postdoctorate Research Fellow of the U. S. Public Health Service.

TABLE I
Group I—1000 cc. positive H₂O load with and without alcohol

Subject	Time	pH	Urine												Blood						PV† PV _v
			Excretion rates/min.						Clearances/min.						pH	Osmolarity		% Δ			
			Min.	Units	μEq.	μEq.	μEq.	μOsm.	cc.	Free	Creat.	Na	K	Cl		Alc.	Obs.		Corr.*		
			μEq.	μEq.	μEq.	μEq.	cc.	cc.	cc.	mEq./L.	mEq./L.	mEq./L.	mg. %	mOsm./L.	mOsm./L.	%					
K.	73	6.5	113	79	121	19	4	650	1.6	2.2	-0.6	126	146.7	4.64	105.0	303	303	0			
Exp. 1	32	6.1	98	50	110	40	9	945	9.8	3.2	6.6	130									
	30	6.1	88	41	111	36	7	820	10.0	2.8	7.2	121									
	32	6.2	93	41	107	38	7	865	10.3	2.9	7.4	127									
	27	6.3	114	38	107	35	9	880	10.5	3.0	7.5	132									
	31†	6.2	127	33	129	39	10	890	10.9	3.1	7.8	148	140.6	4.78	99.5	290	290	+5			
	31	5.9	120	23	123	37	7	840	10.3	2.9	7.4	145	142.1	3.50	101.2	303	288	+17			
	28	5.8	122	19	122	36	7	840	10.2	2.9	7.3	139	142.1	3.30	102.5	313	287	+18			
	32	5.8	105	16	98	37	9	785	9.5	2.7	6.9	145	142.2	3.07	100.7	314	285	+16			
H.	31	6.2	101	14	93	34	8	795	9.7	2.7	7.0	140	142.0	3.49	103.0	312	290	+16			
	57	6.0	149	49	157	33	11	860	0.6	3.0	-2.4		140.5	4.00	105.5	288	288				
Exp. 2	38	6.9	162	87	180	28	4	900	2.0	3.1	-1.2										
	18	6.6	100	104	133	27	10	1,030	7.8	3.6	4.2	132									
	24	6.6	113	94	117	25	16	1,020	11.3	3.5	7.8	138									
	27	6.3	96	71	94	28	8	930	12.2	3.2	9.0	130									
	42	6.3	72	43	64	28	7	770	9.9	2.7	7.2	121									
	37	6.3	79	38	66	30	8	760	9.7	2.7	7.0	128	137.0	3.90	101.5	284	284				
	51†	6.2	79	32	60	30	16	670	8.8	2.4	6.4	125	138.0	4.12	101.5	306	280				
	43	5.9	87	20	64	31	20	720	9.4	2.6	6.8	136									
40	6.1	89	21	62	31	21	710	9.1	2.5	6.6	136										
41	6.0	78	21	48	27	19	650	8.2	2.3	5.9	122	137.0	3.92	101.7	301	280					

* Observed osmolarity—osmolar contribution of alcohol. † PV = Plasma volume. ‡ Alcohol imbibed during first 10 minutes of this period.

of Na and Cl did not decrease after alcohol ingestion and although the urine became more acid, excretion of ammonium was not enhanced. These results contrast sharply with the findings when alcohol is administered to subjects with low or moderate urinary flows (1).

Group IIa. Effect of the simultaneous administration of alcohol and hypertonic saline to water-loaded subjects (Table IIA, Figure 1A and 1B)

Positive water balances were achieved in four experiments in a manner similar to that described for Group I. In two control tests (No. 1 and No. 2 Table IIA) 500 cc. of hypertonic saline (5 to 6 per cent) was infused without alcohol. In two further experiments (No. 3 and No. 4, Table IIA), alcohol was imbibed simultaneously with the beginning of the hypertonic infusion.

The administration of hypertonic saline without alcohol, at the height of a water diuresis, was followed by a prompt decrease in urine flow and free water clearance (Figure 1A). In contrast, the subjects receiving alcohol not only failed to show an antidiuresis, but actually increased their flow of urine above the levels reached during maximal water diuresis (Figure 1B). Free water clearance (CH₂O) increased in spite of a 4 to 5 per cent rise in the osmolarity of the serum. It is apparent that alcohol effectively blocked the antidiuretic response to hypertonic saline.

Group IIb. Effect of alcohol on the antidiuresis following hypertonic saline in subjects with low urine flows (Table IIB, Figure 2)

In two subjects, 300 cc. of 5 to 6 per cent saline were infused intravenously after a suitable control period. Approximately 30 minutes after starting the infusion alcohol was imbibed.

In neither subject did a water diuresis occur after alcohol. Prior administration of hypertonic saline, with a consequent increase in the effective osmotic pressure of extracellular fluid, presumably induced the release of increased amounts of ADH from the posterior pituitary (4). Since alcohol affects neither exogenous ADH nor the ability of the tubules to respond to this hormone (5) an excess of circulation ADH probably masked the inhibitory effect of alcohol upon the supraopticohypophysial system in these experiments.

Group III. Effect of alcohol on the antidiuresis of venous congestion (Table III, Figure 3)

The effect of alcohol on the antidiuresis produced by venous congestion of the limbs was tested in three subjects in whom sphygmomanometer cuffs were inflated about the thighs to a pressure of 70 to 80 mm. Hg. (In all, a positive water load of 500 cc. was established and maintained throughout the experiment.) In two studies (No. 1 and No. 2, Table III) a control period of venous congestion for 30 minutes, instituted after maximal urine flow had been attained, produced a prompt fall in urine flow, CH₂O, and C_{osm}, as well as in the rates of excretion of sodium, potassium, chloride, and creatinine. These

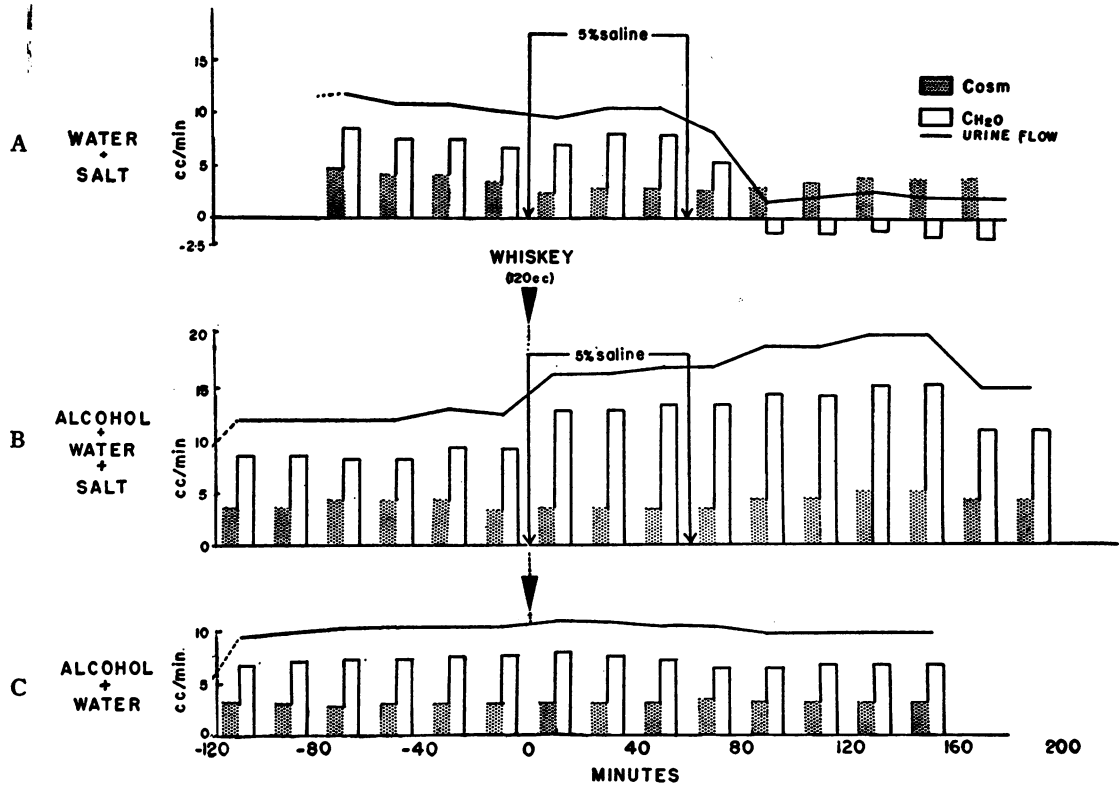


FIGURE 1

Alcohol produced no increase in an established water diuresis (Figure 1C). In contrast, when alcohol was given with an intravenous load of hypertonic saline, urine flow and CH_2O increased (Figure 1B), and the characteristic antidiuretic effect of hypertonic saline (Figure 1A) was blocked.

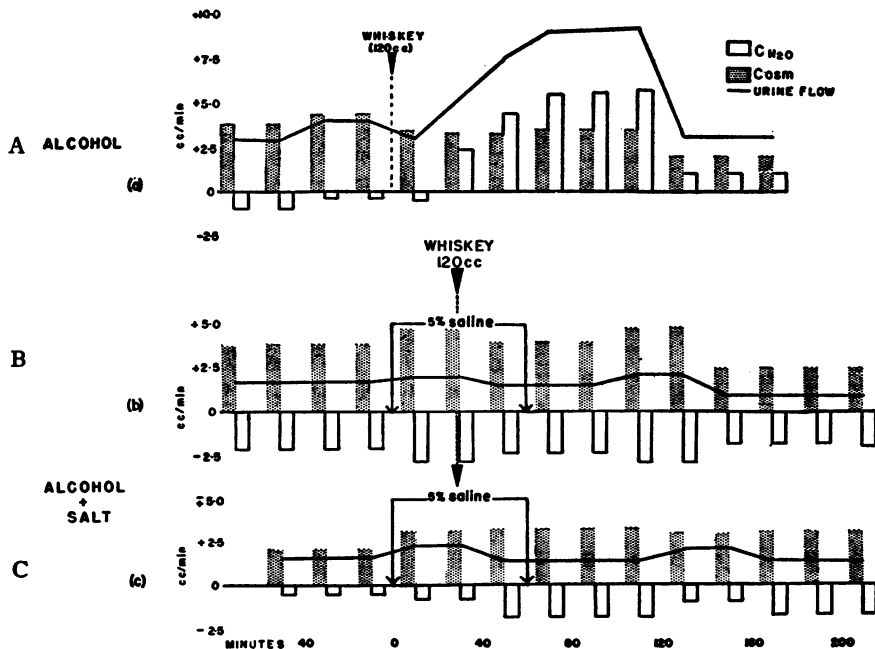


FIGURE 2

Prior administration of hypertonic saline (Figures 2B and 2C) blocked the characteristic diuresis following alcohol (Figure 2A).

II. ETHANOL INHIBITION OF THE NEUROHYPOPHYSIS

TABLE IIA
Group Ila—Hypertonic salt administration with and without alcohol in subjects with maximum water diuresis

Subject	Time	Urine											Blood												
		Excretion rates/min.							Clearances/min.				pH	Na	K	Cl	CO ₂	Alc.	pH	Osmolarity		PV [†] PV _i	Cl space		
		μEq. μEq. μEq.	μEq. μEq. μEq.	μEq. μEq. μEq.	cc. cc. cc.	cc. cc. cc.	Obs. mOsm./L.	Corr.* mOsm./L.	% Δ																
Mins.	Units	μEq.	μEq.	μEq.	μEq.	μEq.	cc.	cc.	cc.	cc.	cc.	cc.	cc.	cc.	mEq./L.	mEq./L.	mEq./L.	mEq./L.	Units	Units	Units	Units			
Kl.	117	188	78	169	17	2.3	1,640	7.3	9.2	126	144.7	4.08	108.5	290	290	0	14.1								
	19	414	147	242	42	16.5	1,640	7.3	9.2	141															
	6.3	457	146	272	34	18.3	1,580	6.8	10.6	118															
	15	415	104	160	45	11.0	1,990	4.7	8.5	123															
	17	5.6	261	78	45	13.2	1,090	6.7	7.5	119															
	38	5.5	215	82	40	11.0	1,030	4.1	7.5	121	138.9	4.50	104.2	277											
	30	5.9	160	61	62	46	855	3.5	6.6	125															
	20	5.8	132	48	68	57	685	2.5	7.0	121															
	36	5.9	181	44	94	42	810	2.9	8.1	121															
	33		277	31	194	32	800	2.7	5.4	110	142.0	4.30	111.4	289											
20		295	38	269	35	875	3.0	3.5	123	146.0	4.30	114.8	289												
24		306	70	371	39	1,005	1.6	1.4	128																
25		354	106	372	38	1,005	2.7	3.8	127																
21		328	120	385	38	1,085	2.1	3.8	127																
31		324	123	371	37	1,110	2.1	3.9	123																
57		257	163	328	52	1,335	6.8	4.6	2.2	156	143.8	4.15	112.7	288											
34		271	201	361	43	1,325	12.9	5.0	7.9	152	143.0	4.59	105.0	290											
40		198	127	147	47	1,420	17.1	3.9	13.2	140															
47		138	82	124	46	1,145	16.8	3.6	13.2	144	139.3	4.38	101.0	273											
68		197	90	182	39	1,320	15.2	3.3	11.9	140															
46		288	86	304	42	1,220	11.1	3.4	7.7	138	147.2	4.26	110.4	332											
37		304	122	304	49	1,335	11.0	4.2	6.8	142															
31		347	122	416	40	1,340	9.4	4.6	4.8	139	143.5	4.61	107.6	297											
31		332	120	385	38	1,355	11.0	5.2	5.8	145															
109		346	125	390	33	1,560	4.4	3.2	1.2																
R.	111	435	205	477	24	1,685	7.1	6.0	1.1	161	133.0	4.20	101.5	283											
	56	358	163	379	22	1,470	6.9	5.2	1.7	155															
	35	165	89	151	25	4	970	12.0	3.6	8.4	142														
	40	6.3	195	55	84	36	1,100	12.0	3.9	8.1	132														
	30	6.3	196	31	64	42	1,050	13.0	3.8	9.2	140														
	24	6.6	160	20	68	37	885	12.3	3.2	9.1	140	133.0	3.68	100.0	276										
	41	6.6	295	36	194	35	6,990	16.2	3.5	12.7	150	133.9	3.18	108.0	302										
	33	6.6	231	11	165	39	970	16.7	3.3	13.4	166	144.8	3.43	113.0	311										
	36	6.5	304	23	188	35	1,250	18.7	4.3	14.4	135														
	37	6.7	332	180	26	6	1,420	20.0	4.9	15.1	135	135.3	4.20	107.5	296										
43	6.2	279	15	138	35	1,195	14.9	4.1	10.8	138															
R.	65	174	90	167	22	0	960	3.7	3.1	0.6	117	139.1	4.30	98.5	307										
	27	6.6	171	59	126	24	0	1,055	11.1	3.5	7.6	121													
	23	5.5	166	71	75	43	27	1,245	11.5	4.1	7.4	128													
	17	5.3	237	47	61	54	19	1,530	13.8	5.1	8.7	111													
	19	5.3	275	28	85	51	18	1,660	14.5	5.0	9.5	108													
	20	5.2	234	26	73	50	8	1,285	13.3	4.3	9.0	115													
	19	5.5	203	21	93	43	11	1,130	13.7	3.9	9.8	111	139.8	4.32	95.0	302									
	25	5.4	280	28	148	31	7	1,130	14.3	3.7	10.6	109													
	31	5.5	239	21	177	26	6	1,125	14.8	3.6	11.2	123	145.5	4.10	103.0	312									
	25	6.0	309	20	257	23	6	1,335	16.7	4.2	12.5	110													
20	6.0	332	28	294	25	8	1,375	17.0	4.2	12.8	121	145.3	4.31	103.5	322										
18	5.8	513	21	402	16	25	1,625	16.6	5.0	11.6	122														
17	5.8	616	25	493	37	37	1,740	17.2	5.4	11.8	117	143.3	4.23	105.2	318										
21	5.5	452	20	399	35	22	1,405	15.5	4.4	11.1	117	143.3	4.23	105.2	318										
20	5.5	526	26	401	36	22	1,555	15.8	4.9	10.9	118	143.3	4.08	105.0	332										
21	5.5	535	15	368	45	28	1,570	16.2	5.0	11.2	116	143.3	4.08	105.0	332										
30		317	11	263	36	18	1,065	6.7	3.4	3.3															

* Observed osmolarity—osmolar contribution of alcohol.
 † PV = Plasma volume.
 ‡ Alcohol imbibed during first 10 minutes of this period.
 § Period of infusion of hypertonic salt.

TABLE IIB
Group IIB—Hypertonic salt and alcohol administration in subjects with low urine flow

Subject	Time	Urine											Blood											
		Excretion rates/min.							Clearances/min.				Na	K	Cl	CO ₂	Alc.	pH	Osmolarity		PV _f †	Cl space		
		μEq. Na	μEq. K	μEq. Cl	NH ₄	TA	Osm.*	Vol.	cc.	Osm.	Free	Creat.							cc.	cc.			mEq./L.	mEq./L.
K.	65	142	90	178	13	4	640	1.6	2.1	-0.5	149	cc.	136.7	4.18	102.6	27.6	0	7.49	292	292	5	14.4		
	40	222	104	260	18	4	915	2.3	3.1	-0.8	132	cc.	137.4	4.18	104.9	25.5	0	7.47	298	298	+5	15.1		
	75	295	90	358	23	21	1,010	1.4	3.3	-1.9	140	cc.	143.5	3.90	109.7	23.9	106	7.27	309	309	+15	15.3		
Exp. 1	32	234	83	296	28	24	960	2.1	3.0	-0.9	133	cc.	141.0	4.46	109.5	26.0	128	7.33	325	314	+10	15.2		
	77	280	90	329	24	27	1,000	1.4	3.3	-1.9	148	cc.	141.5	4.49	109.1	25.9	62	7.42	322	310	+16	15.1		
L.	81	7.4	249	142	298	20	0	1,025	3.8	-2.1	122	cc.	137.6	3.98	101.5	25.7	7.41	268	268	+6	17.0			
	38	341	168	438	22	0	1,310	2.0	4.7	-2.7	121	cc.	141.6	4.04	105.2	25.0	7.45	278	278	+14	17.3			
	52	408	117	510	24	2	1,210	1.5	4.1	-2.6	127	cc.	144.1	3.98	105.5	22.5	7.34	311	311	+14	18.2			
Exp. 2	40	6.8	402	118	500	33	15	1,430	2.1	3.0	132	cc.	143.0	4.16	105.0	23.0	96	7.43	299	274	+12	18.1		
	50	5.0	203	92	281	26	29	795	2.8	-1.9	126	cc.	141.6	4.30	104.2	22.8	7.4	265	275	+12	18.1			
	63	223	62	241	25	31	820	0.9	2.9	-2.0	128	cc.	140.5	4.30	103.0	24.7	7.43	288	274	+12	18.2			

* Observed osmolarity—osmolar contribution of alcohol.

† PV = plasma volume.

‡ Alcohol infused during first 10 minutes of this period.

] Period of infusion of hypertonic salt.

functions returned to or toward control levels after the congestion was released. After a suitable period of recovery, during which the urine flow stabilized, alcohol was administered 30 minutes prior to the application of congesting cuffs for the second time, this time for 60 minutes. Despite a more prolonged period of venous congestion, only slight falls in urine flow and free water clearance were produced, although the decrease in solute excretion and C_{osm} was comparable to that during the control period of cuffing. Under these circumstances, therefore, prior ingestion of alcohol minimized the anti-diuretic effect of venous congestion (Figure 3A).

In a third subject (No. 3, Table III), alcohol was imbibed 100 minutes after the cuffs had been inflated. Urine flow and CH_2O , which had diminished after the cuffs had been applied, did not increase after alcohol was administered, and started to rise only after the cuffs were released (Figure 3B).

DISCUSSION

In the present study, alcohol prevented or minimized the fall of urine flow and free water clearance (CH_2O) that characteristically follows the administration of hypertonic solutions of sodium chloride or venous congestion of the extremities. Alcohol will also prevent the antidiuresis of dehydration (6) or the administration of acetylcholine (7) and nicotine (6), and it has no effect on urine flow when it is given at the height of water diuresis or to dogs with diabetes insipidus (7). These observations constitute overwhelming evidence that it has an inhibitory action on the supra-opticohypophyseal system.

The antidiuresis that regularly follows venous congestion of the lower extremities or stationary standing has been ascribed in part to increased activity of the neurohypophysis as a result of diminished effective blood volume (8, 9). Facts in favor of this interpretation are: 1) a diminished or absent response in subjects with diabetes insipidus or in hydropenic subjects with maximal ADH activity who are undergoing a mannitol diuresis (10); 2) a fall in urine flow out of proportion to the changes in electrolyte excretion and glomerular filtration (8, 9); 3) the appearance of an antidiuretic substance in the blood of normal subjects after circulatory collapse induced by motionless standing (11). The ability of alcohol to inhibit the antidiuresis of venous congestion lends added weight to the concept that changes in urine flow following alterations in the volume and distribution of body fluids are to an important degree

II. ETHANOL INHIBITION OF THE NEUROHYPOPHYSIS

TABLE III
Group III—Venous congestion of the lower extremities with and without alcohol

Subject	Time	Urisis	Urine						Blood										PV ₁ † PV ₁	% Δ			
			Excretion rates/min.						Clearances/min.				pH	Na	K	Cl	CO ₂	Alc.			pH	Osmolarity	
			μEq. μEq. μEq. μEq. μEq. μEq.	μEq. μEq. μEq. μEq. μEq. μEq.	cc. cc. cc. cc. cc. cc.	mEq./L. mEq./L. mEq./L. mEq./L. mEq./L. mEq./L.	Obs. mOsm./L.	Corr.* mOsm./L.															
N. Exp. 1	76	6.8	241	148	226	20	20	984	1.4	3.5	-2.1	166	140.0	4.10	105.3	0	280	280	0				
	37	7.0	39	168	32	23	880	12.4	3.2	6.2	164	140.6	4.21	104.0	0	275	275	+5					
	26	6.8	196	62	170	23	955	16.0	3.5	12.5	160	138.0	4.05	103.3	0	272	272						
	21	6.9	210	57	173	31	1,000	20.0	3.0	16.3	159												
	36	6.9	167	42	153	23	820	8.0	3.0	5.0	159												
	46	6.7	145	30	88	24	675	9.6	2.5	7.1	130												
	22	6.7	211	45	141	31	1,010	20.7	3.7	17.0	184												
	17	6.7	219	41	146	29	1,000	19.4	3.7	15.7	179												
	20	6.8	228	39	152	28	1,060	20.8	3.9	16.9	173												
	25†	6.9	236	37	160	27	915	19.0	3.4	15.6	145												
	25	7.0	248	31	174	20	932	19.4	3.5	15.9	147												
	28	6.3	161	22	111	51	720	15.0	2.7	12.3	146												
36	6.4	168	24	120	61	845	17.6	3.2	14.4	133													
26	6.5	115	18	114	65	810	16.9	3.1	13.8	130													
20	6.6	107	19	88	18	730	15.2	2.8	12.4	134													
20	6.6	122	20	91	22	825	17.2	3.1	14.1	137													
W. Exp. 2	65	6.8	245	219	314	31	1,230	6.6	4.4	2.2	160	139.4	3.70	103.7	0	280	280	0					
	47	6.8	268	123	298	26	1,190	13.2	5.3	7.9	168												
	26	342	152	392	33	1,480	16.8	5.4	11.4	166													
	35	350	171	399	22	1,650	17.5	6.1	11.4	162													
	32	221	108	274	33	1,060	10.9	3.9	7.0	151													
	42	6.3	178	75	204	35	870	9.6	3.2	6.4	131												
	64	6.5	189	63	204	30	816	8.9	3.0	5.9	148												
	23†	6.7	273	89	288	31	1,015	11.3	4.1	7.2	155												
	21	6.6	274	63	271	33	940	11.0	4.0	7.0	151												
	32	6.9	222	44	222	37	750	8.9	2.9	6.0	122												
	31	6.2	222	32	225	40	770	8.9	3.0	5.9	145												
	32	6.0	191	19	184	46	700	8.1	2.7	5.4	140												
38	6.1	194	25	186	33	845	9.4	3.2	6.2	158													
31	6.2	171	16	156	34	825	9.8	3.1	6.7	166													
S. Exp. 3	65	6.6	175	79	179	20	6	905	1.2	3.1	-1.9	145	145.6	3.96	105.8	26.9	0	7.38	292	292	0		
	34	6.9	267	146	278	26	8	1,300	8.1	4.5	3.6	124											
	21	6.9	287	164	290	25	12	1,430	14.8	5.0	9.8	124											
	19	6.8	332	174	333	22	16	1,575	17.9	5.5	12.4	129											
	20	6.7	345	185	354	25	21	1,615	19.7	5.6	14.1	133											
	18	6.7	356	181	365	24	21	1,615	20.3	5.6	14.7	134											
	24	6.6	289	154	290	30	27	1,395	18.1	4.9	13.2	122											
	17	6.5	256	141	262	31	30	1,305	17.6	4.6	12.0	131											
	18	6.3	199	113	204	33	26	1,115	15.9	3.9	12.0	134											
	22	6.3	185	106	185	35	28	1,065	15.4	3.7	11.7	141											
	18	6.3	173	88	162	33	31	1,035	15.0	3.5	11.5	145											
	21	6.2	168	78	139	38	31	1,028	14.2	2.9	11.3	143											
21	5.4	162	50	97	28	33	815	10.5	2.6	7.9	127												
20	5.5	152	44	94	27	33	745	10.5	2.8	7.7	134												
20	5.6	110	28	66	28	34	800	10.8	2.6	8.2	139												
20	5.6	106	21	65	27	33	740	10.9	2.5	8.4	131												
17	5.6	88	24	45	28	33	720	10.6	2.5	8.1	139												
21	5.6	94	21	48	30	29	740	11.2	2.6	8.6	143												
20	5.8	92	20	48	28	31	720	11.3	2.5	8.8	134												
20	5.9	112	20	54	26	32	750	12.5	2.6	9.9	139												
20	6.0	122	21	62	24	29	755	13.0	2.6	10.4	136												
20	6.9	133	22	75	28	32	755	14.0	2.6	11.4	141												

* Observed osmolarity—osmolar contribution of alcohol.

† PV = Plasma volume.

‡ Alcohol imbibed during first 10 minutes of this period.

§ Period venous congestion.

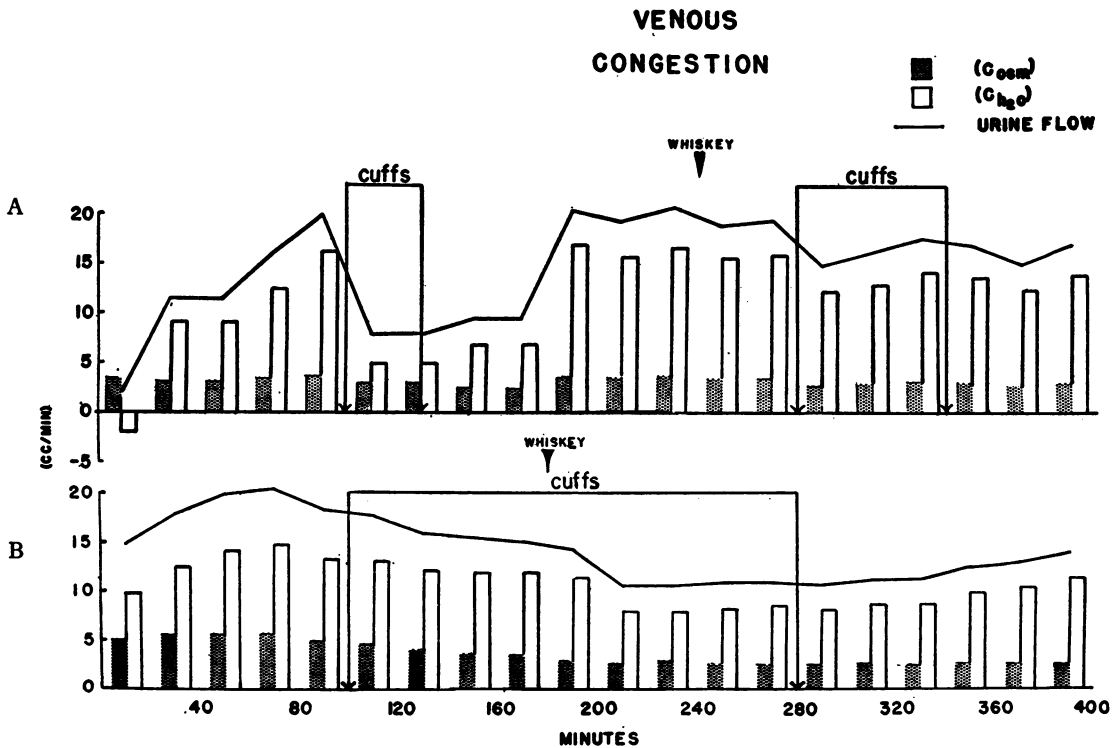


FIGURE 3

Alcohol minimized the antidiuretic effect of venous congestion when given *prior* to the latter (Figure 3A). In contrast, alcohol had little effect when given *during* the period of venous congestion (Figure 3B).

secondary to variations in the activity of the neurohypophysis.⁶

Alcohol had little effect on urine flow and free water clearance in those experiments in which it was given *after* an infusion of hypertonic saline or venous congestion had been initiated. Once the neurohypophysis has been stimulated the resultant excess of circulating antidiuretic hormones might, until it is inactivated or destroyed, mask the temporary inhibition of the posterior pituitary by alcohol. These experiments suggest that alcohol diuresis may be blocked by a prior rise in circulating endogenous ADH as well as by the administration of exogenous Pitressin® (5, 6).

In the experiments of Group I, when the release of ADH was presumably completely inhibited by a positive water load in the semi-recumbent position, administration of alcohol caused no further rise in urine flow and free water clearance.

⁶In a study published since completion of this paper Newman (12) demonstrated that alcohol could effectively block the antidiuresis of quiet standing.

The increase in CH₂O which occurred in the water-loaded subjects of Group IIb, to whom alcohol was given simultaneously with an infusion of hypertonic saline, was therefore unexpected. The situation in these experiments is probably comparable to the rapid administration of large solute loads to patients with diabetes insipidus, in whom an increased volume of isosmotic fluid is suddenly delivered to a distal tubular segment in which water reabsorption is blocked but where further reabsorption of solute does occur. In this case an increase in the calculated value of free water clearance (CH₂O) might be produced, not by diminished reabsorption of water in the distal tubule (Smith, 13), but by an increased distal reabsorption of solute. An increase in CH₂O during mannitol or solute diuresis in subjects with diabetes insipidus can in fact be demonstrated by recalculating the data of Brodsky and Rapoport (14). Similar increases in CH₂O, C_{osm}, and urine flow were shown by Welt, Young, Thorup, and Burnett (15) to follow the adminis-

tration of a carbonic anhydrase inhibitor to water-loaded subjects who were in a state of "physiological diabetes insipidus." Although tubular secretion of water (14) could explain such changes, there seems little reason to invoke such a concept.

A relative or absolute increase in antidiuretic hormone has been implicated in the abnormal water metabolism of such clinical states as hyponatremia, cirrhosis of the liver, congestive heart failure, adrenal insufficiency, and panhypopituitarism. The results of the present and previous studies (1, 5) suggest that the effects of alcohol in states of abnormal water metabolism might be of value in interpreting their pathophysiology. Such investigations are now in progress.

SUMMARY

1. Alcohol had no effect upon urine flow or solute excretion when given at the height of a water diuresis.

2. Alcohol blocked the antidiuretic response to hypertonic saline when both were simultaneously administered to water-loaded subjects.

3. Alcohol minimized the antidiuretic effect of venous congestion of the legs in water-loaded subjects, when imbibed before the legs were congested.

4. The characteristic diuretic response to alcohol was blocked by prior infusion of hypertonic saline or cuff congestion of the limbs.

5. When administered prior to the stimulus, alcohol will effectively block stimulation of the release of ADH.

ACKNOWLEDGMENT

The authors wish to thank Dr. John P. Peters for his advice and criticism and Drs. D. Lester and L. J. Greenberg of the Department of Applied Physiology, Yale University for their suggestions and assistance in setting up the technique for alcohol determination in the blood. The technical assistance of Mrs. M. Browning and Mrs. M. Kompare is gratefully acknowledged.

REFERENCES

1. Rubini, M. E., Kleeman, C. R., and Lamdin, E., Studies on alcohol diuresis. I. The effect of ethyl

- alcohol ingestion on water, electrolyte and acid-base metabolism. *J. Clin. Invest.*, 1955, **34**, 439.
2. Stanbury, S. W., and Thomson, A. E., Diurnal variation in electrolyte excretion. *Clin. Sc.*, 1951, **10**, 267.
3. Elkinton, J. R., and Taffel, M., Prolonged water deprivation in the dog. *J. Clin. Invest.*, 1942, **21**, 787.
4. Verney, E. B., The antidiuretic hormone and the factors which determine its release. *Proc. Roy. Soc., London, s. B.*, 1947, **135**, 25.
5. Strauss, M. B., Rosenbaum, J. D., and Nelson, W. P., III, The effect of alcohol on the renal excretion of water and electrolyte. *J. Clin. Invest.*, 1950, **29**, 1053.
6. Eggleton, M. G., The diuretic action of alcohol in man. *J. Physiol.*, 1942, **101**, 172.
7. van Dyke, H. B., and Ames, R. G., Alcohol diuresis. *Acta Endocrinol.*, 1951, **7**, 110.
8. Wilkins, R. W., Tinsley, C. M., Culbertson, J. W., Burrows, B. A., Judson, W. E., and Burnett, C. H., The effects of venous congestion of the limbs upon renal clearances and the excretion of water and salt. I. Studies in normal subjects and in hypertensive patients before and after splanchnicectomy. *J. Clin. Invest.*, 1953, **32**, 1101.
9. Fitzhugh, F. W., Jr., McWhorter, R. L., Jr., Estes, E. H., Jr., Warren, J. V., and Merrill, A. J., The effect of application of tourniquets to the legs on cardiac output and renal function in normal human subjects. *J. Clin. Invest.*, 1953, **32**, 1163.
10. Judson, W. E., Epstein, F. H., Tinsley, C. M., Burrows, B. A., and Wilkins, R. W., The hemodynamics and renal functional effects of venous congestion of the limbs in patients with diabetes insipidus. *J. Clin. Invest.*, 1950, **29**, 826.
11. Brun, C., Knudsen, E. O. E., and Raaschou, F., On the cause of post-syncopal oliguria. *Acta med. Scandinav.*, 1945, **122**, 486.
12. Newman, E. V., Metabolic adjustments to normal and disturbed circulation in man. *New England J. Med.*, 1954, **250**, 347.
13. Smith, H. W., *The Kidney, Structure and Function in Health and Disease*. New York, Oxford University Press, 1951.
14. Brodsky, W. A., and Rapoport, S., The mechanism of polyuria of diabetes insipidus in man. The effect of osmotic loading. *J. Clin. Invest.*, 1951, **30**, 282.
15. Welt, L. G., Young, D. T., Thorup, O. A., Jr., and Burnett, C. H., Renal tubular phenomena under the influence of a carbonic anhydrase inhibitor. *Am. J. Med.*, 1954, **16**, 612.