STUDIES ON ALCOHOL DIURESIS. III. THE RESPONSE TO ETHYL ALCOHOL IN CERTAIN DISEASE STATES CHARACTERIZED BY IMPAIRED WATER TOLERANCE¹

By EZRA LAMDIN,² CHARLES R. KLEEMAN, MILTON RUBINI, AND FRANKLIN H. EPSTEIN

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

(Submitted for publication November 14, 1955; accepted January 4, 1956)

Ethyl alcohol, when imbibed by normal subjects, stimulates a diuresis of water and blocks the antidiuretic effects of such stimuli as the passive erect posture, infusions of hypertonic saline, venous congestion of the lower limbs, and acetylcholine. It has been shown to inhibit transiently the release of the antidiuretic hormone (ADH) from the posterior pituitary gland, regardless of the nature of the provoking antidiuretic stimulus (1-6). Recently, Dicker (7) has demonstrated an almost complete absence of antidiuretic activity in the blood of rats given lethal amounts of ethyl alcohol. These data afford convincing argument localizing the site of action of this compound to the supraoptic-hypophyseal system.

An excessive activity of ADH has been invoked by many investigators in an attempt to explain the impaired excretion of water which is a feature of certain disease states. In view of its known action in inhibiting the release of this hormone, it was of interest to observe the effect of alcohol when administered to patients with diseases characterized by faulty metabolism of water.

MATERIALS AND METHODS

Observations were made upon 16 hospitalized patients with the following diagnoses: cirrhosis (six), arteriosclerotic, hypertensive, or valvular heart disease with congestive failure (four), cor pulmonale (one), superior vena-caval syndrome (one), nephrotic syndrome (one), Addison's disease (two), and hypoadrenocorticism secondary to panhypopituitarism (one). All but the last three had clinically evident fluid retention (edema, ascites, or both). One Addisonian (R. M.) was receiving cortisone at the time of the study, while the other, and the patient with panhypopituitarism, were

not. Impaired water tolerance is defined as failure to excrete, within three to four hours, at least fifty per cent of 1000 to 1500 milliliters of water, administered either orally or intravenously as iso- or hypotonic fructose or glucose, prior to the day of testing.

Ten patients each received a single dose of alcohol (35 to 60 grams) as either 95 per cent laboratory alcohol or 100 proof Bourbon whiskey, made up to a total volume of approximately 150 to 180 cc. with fruit juice and ice. The remaining six patients each received two to four doses of 25 to 45 grams each (total 70 to 140 grams) at intervals of one or two hours.

In an additional study, a single 45-gram dose of alcohol was ingested by two adequately hydrated patients with diabetes insipidus, who were not receiving posterior pituitary therapy at the time.

From 7:00 to 7:30 a.m. on the day of the test, the patient ate a light breakfast including 400 to 600 cc. of fluid. About one hour later, the patient emptied his bladder, and assumed the recumbent or semi-recumbent position, standing only to void. Alcohol was generally given two to three hours afterwards. Water loads of 1000 to 1500 cc. (either by mouth in 15 to 20 minutes, or as 2.5 per cent or 5 per cent glucose or fructose in one hour intravenously) were administered to five patients one and a half to three and a half hours before, and to two patients concurrently with, the ethanol. The other patients drank smaller amounts of water, as indicated in the tables. Each study lasted approximately five to seven hours.

Blood was drawn at approximately hourly intervals for the determination of sodium, creatinine and osmolarity (freezing-point depression) in the serum, and half-hourly for the determination of the concentration of alcohol. Urine, for the determination of sodium, creatinine and osmolarity, was collected in one-half- to two-hourly periods, by spontaneous voiding or indwelling catheter.

The chemical methods and calculations employed have been described in a previous publication (1).

$$C_{\text{osm}} = \text{osmolar clearance} = \frac{U_{\text{osm}} V}{P_{\text{osm}}}$$
$$C_{\text{H}_2\text{O}} = V - C_{\text{osm}}$$

where

U_{osm} = concentration of solute in the urine in mOsm./L.

V = urine flow in cc./min.

P_{osm} = concentration of solute in plasma in mOsm./L.

¹ Supported in part by the United States Public Health Service, Grant H-834.

² Work done during tenure as U.S.P.H.S. Postdoctoral fellow. Present address: Veterans Administration Hospital, Boston, Massachusetts.

RESULTS

For purposes of this study, a diuretic response is defined as the excretion of fifty per cent or more of an administered load of water within four hours after the ingestion of alcohol. For those patients who were not subjected to a provocative water load, a positive response consisted of an increase in urine flow to values significantly greater than those of the control period, a fall in urinary osmolality and a rise in free water clearance (C_{H_2O}).

I. *Patients with diabetes insipidus, Addison's disease, and panhypopituitarism (Tables I and IIa)*

Alcohol did not further augment the relatively high rates of urinary flow in two patients with diabetes insipidus (Table I).

In one patient with Addison's disease and one patient with hypopituitarism (patients 1 and 2, Table IIa), neither of whom was receiving cortisone, alcohol did not provoke a water diuresis. Patient 3, R. M., an Addisonian treated with cortisone, who had regained the normal diuretic response to water, showed a similar normal diuretic response following alcohol.

II. *Patients with clinically evident retention of fluid (Table IIb)*

In only four of thirteen patients in this category (patients 4 to 7) was ethanol successful in provoking diuresis. One of these, P. M., also responded normally to ingestion of water, during the control period, as evidenced by urine flows of 4.0 and 3.5 cc. per min in periods 2 and 3, respectively, following a water load given one hour before the beginning of period 2. Imbibing alcohol when the rate of urine flow was falling resulted in a second diuresis. Patient J. L., in whom impaired tolerance to water loading is suggested by flows of 0.4 cc. per min. during periods 1 and 2 (*i.e.*, during the second hour following ingestion of 500 cc. of water), was, however, able to diurese normally upon water loading two weeks later, following paracentesis and salt restriction. The response of patient 6, D. McC., is anomalous. From the temporal relationship between the ingestion of water, ingestion of alcohol, and onset of diuresis, the diuresis seems to be more in response to water than to alcohol. However, on two previ-

TABLE I
Response to ethyl alcohol of two patients with diabetes insipidus

Period No.	Elapsed time min.	Urinary flow cc./min.
Patient I—J. V.		
1	70	8.0
2	110	11.2
3	158	10.8
4*	213	11.0
5	332	5.6
Patient II—S. C.		
1	30	6.2
2	60	7.7
3	110	6.7
4	135	10.0
5*	198	4.21
6	240	8.8
7	270	8.3

* Alcohol was administered at the beginning of this period.

ous occasions, unequivocal impairment in excretion of a water load had been demonstrated. The least dramatic effect of ethanol is seen in patient A. D., who excreted only 53 per cent of the administered load of water. However, following each of two doses of alcohol, an increased rate of urine flow ensued, unassociated with any change in the clearance of endogenous creatinine.

The remaining nine patients did not have a diuretic response to alcohol, regardless of whether one dose (patients 8 to 13) or several doses (patients 14 to 16) were administered.

In comparing those who responded with a diuresis to alcohol with those who did not, no striking differences were apparent with respect to concentration in the serum and urine of sodium or total solutes, their rates of excretion, or the clearance of endogenous creatinine. Comparable levels of alcohol in the blood were attained in the two groups, and are consistent with values observed in normal subjects receiving equivalent amounts of ethanol (1, 2). Of those responding who received more than one dose of alcohol (patients 5 to 7), some diuretic effect was obtained from the first dose, whereas up to four doses in unresponsive patients failed to provoke an increase in the flow of urine. Patients with impaired water tolerance secondary to cirrhosis and to congestive heart failure were represented in both groups; thus the nature of the underlying disease did not, *per se*, appear to determine the response of any given patient to the diuretic stimulus of alcohol.

TABLE II
Response of patients to ethyl alcohol administration

Patient Diagnosis	Period		Dose of alc. (gm.)	Urine						Serum			Remarks	
	No.	Elapsed time (min.)		Flow cc./ min.	Na		Osm		C ₂ H ₅ O cc./ min.	Creat. cc./ min.	Na mEq./ L.	Osm mOsm./ L.		Alc mg. %
					mEq./ L.	μEq./ min.	mOsm./ L.	μOsm./ min.						
IIa Addison's Disease and Hypopituitarism														
1. T. Q. Craniopharyn- gioma with hypopitui- tarism; no hormonal R _x	1	120		1.0	158	158	618	618	2.1	-1.1	103	144	296	1,400 cc. H ₂ O P.O. with alc. 227 cc. (16%) excreted in 4 hrs.†
	2†	186	36	1.0	184	184	606	606	2.1	-1.1				16
	3	228		1.0	171	171	661	661	2.3	-1.3	102	140	294	45
	4	319		0.7	147	103	685	480	1.6	-0.9		137	291	12
	5	372		1.0	137	137	548	548	1.9	-0.9				
2. T. P. Addison's dis- ease; on DOCA; no other hor- monal R _x	1	165		0.3	158	47	649	195	0.7	-0.4	87	126	265	1,500 cc. 5% fruc- tose infusion com- pleted ½ hr. before alc. 542 cc. (36%) excreted in 4½ hrs.†
	2	255		*2.9	84	244	289	838	3.2	-0.3				
	3†	315	48	*2.3	79	182	274	630	2.5	-0.2	96			
	4	375		1.0	119	119	429	429	1.7	-0.7		120	253	127
	5	435		0.9	124	112	460	414	1.6	-0.7				
	6	495		0.6	174	104	640	384	1.5	-0.9				
3. R. M. Addison's dis- ease; on cor- tistone and DOCA	0	0		—	100	—	658	—	—	—	98			270 cc. H ₂ O P.O. 1 hr. before alc. 737 cc. (273%) ex- creted in 3½ hrs.§
	1	38		1.0	125	125	700	700	2.4	-1.4			287	
	2	90		1.5	153	153	658	987	3.5	-2.0			286	
	3†	139	48	2.8	63	176	276	773	2.7	+0.1	105			56
	4	185		4.7	27	127	122	573	2.0	+2.7			286	105
	5	217		4.1	25	103	164	672	2.4	+1.7			286	48
	6	289		2.9	31	89	208	603	2.1	+0.8			286	22
IIb Ascites and/or Edema														
4. A. D. Nephrotic syndrome; edema and hypopro- teinemia	1	97		1.0	31.3	31.3	272	272	1.0	0.0	34	125	283	1,000 cc. H ₂ O P.O. 2 hrs. before alc. 146 cc. (15%) ex- creted in those 2 hrs.; of the "re- maining" 854 cc., 384 cc. (45%) were excreted in 4 hrs.†
	2	149		1.0	31.3	31.3	312	312	1.1	-0.1				
	3†	208	45	1.8	30.6	55.1	220	396	1.4	+0.4	26		281	28
	4	269		1.1	28.8	66.2	251	276	1.0	+0.1			282	62
	5†	329	45	2.3			169	389	1.4	+0.9	25	124	283	85
	6	394		1.1			216	237	0.8	+0.3				53

* Osmotic diuresis due to infusion of fructose or glucose.

† Alcohol imbibed early in this period.

‡ Impaired diuresis to water load demonstrated previous to test day.

§ Normal diuretic response to water load demonstrated several weeks later, after paracentesis.

TABLE II—Continued

Patient Diagnosis	Period		Dose of alc. (gm.)	Urine					Serum					Remarks	
	No.	Elapsed time (min.)		Flow cc./ min.	Na		Osm mOsm./ L.	C _{Na} cc./ min.	C _{H₂O} cc./ min.	C _{creat.} cc./ min.	Na mEq./ L.	Osm mOsm./ L.	Alc mg. %		
					mEq./ L.	μEq./ min.									
IIb Ascites and/or Edema—Continued															
5. S. H. Cirrhosis, ascites, and edema	1	57		0.8	12.1	9.7					132			800 cc. H ₂ O P.O. 2 hrs. before alc.	
	2	137		1.0	9.7	9.7					135			233 cc. (29%) ex- creted in 5 hrs.†	
	3†	196	35	1.1	9.7	10.7					134			43	
	4	254		0.3	6.2	1.9					134			58	
	5	297		0.6	5.7	3.4					134			51	
6. B. G. Cirrhosis, ascites	1	30		0.5	34.7	17.4			1.4	-0.9	131	115	243	1,200 cc. 2½% glu- cose in 1 hr. i.v. completed ½ hr. be- fore alc. 129 cc. (15%) excreted in 3 hrs.†	
	2	61		0.5	1.6	0.8			1.5	-1.0		116	243		
	3	91		*0.7	1.1	0.8			2.1	-1.4		118	244		
	4	151		*0.7	1.0	0.7			2.1	-1.4	131	112	238	32	
	5†	181	60	0.3	1.7	0.5			0.9	-0.6	91	110	240	40	
	6	241		0.3	2.1	0.6			0.7	-0.4		110	235	76	
	7	333		0.2	4.0	0.8			0.6	-0.4		111	240	64	
7. M. B. Arteriosclerotic heart disease, congestive heart failure; edema	1	63		0.10	13.4	1.3			0.21	-0.11			244	150 cc. H ₂ O P.O. 1½ hrs. before alc.	
	2†	124	35	0.03					0.06	-0.03		117	245	36	
	3	225		0.05	39.7	2.0			0.07	-0.02			244	47	
8. M. A. RHD, AI, AS; no edema	0	50		0.3	1.6						143	284		1,000 cc. H ₂ O P.O. with alc. 178 cc. (18%) excreted in 4 hrs.†	
	1	132	48	0.7	0.7	0.5			1.3	-0.6			284	190	
	2†	192		0.6	0.9	0.5			1.4	-0.8					
	3	235		0.6	1.2	0.7			1.6	-1.0					
	4	257		0.9	1.3	1.2			2.5	-1.6					
	6	297		0.8	1.0	0.8			2.2	-1.4					
9. M. P. Chronic pul- monary dis- ease; cor- pulmonale; congestive failure; edema	1	35		0.7	124	87			1.0	-0.3	100	123	253	1,000 cc. 5% glu- cose i.v. in 1 hr. be- tween periods 2-4. 430 cc. (43%) ex- creted in 3½ hrs.†	
	2	115		*1.6	60	96			2.4	-0.8		118	250		
	3	145		*4.3	26	112			3.9	+0.4	65	122	251		
	4	183		*1.7	38	65			1.7	0.0		126	256		
	5†	240	45	0.6	91	55			1.0	-0.4	68				
	6	283		0.7	74	52			1.1	-0.4					

TABLE II—Continued

Patient Diagnosis	Period		Urine					Serum				Remarks		
	No.	Elapsed time (min.)	Dose of alc. (gm.)	Flow cc./ min.	Na		Osm mOsm./ L.	C _{cr} cc./ min.	C _{cr} cc./ min.	C _{cr} cc./ min.	Na mEq./ L.		Osm mOsm./ L.	Alc mg. %
					mEq./ L.	μEq./ min.								
IIb Ascites and/or Edema—Continued														
10. S. R. Superior vena-caval syndrome	1	70		1.2	24.6	29.5	526	631						1,000 cc. H ₂ O P.O. 2½ hrs. before alc. 370 cc. (37%) ex- creted in 5 hrs.†
	2	109		1.2			526	631						
	3	145		1.3			481	626						
	4	180		1.9			310	589						
	5	211		1.3			473	615						
	6†	240	45	0.7			638	446						
	7	270		0.9			704	642						
	8	340		0.6			721	433						
11. C. M. Cirrhosis with ascites and edema	1	49		0.6	3.3	2.0	329	198	0.7	-0.1	71	128	267	700 cc. H ₂ O P.O. 2½ hrs. before alc. 171 cc. (24%) ex- creted in 6½ hrs.†
	2	93		1.0	1.7	1.7	232	232	0.9	+0.1	66	124	263	70
	3†	130	35	0.5	2.7	1.4	296	148	0.6	-0.1				59
	4	165		0.4			449	180	0.7	-0.3				
	5†	228	35	0.3	11.6	3.5	459	138	0.5	-0.2		127	266	115
		258												145
		288												143
	6†	346	35	0.3	6.0	1.8	432	130	0.5	-0.2	61	128	277	142
12. P. M. Cirrhosis with ascites ± edema	7	413		0.5	2.4	1.2	284	142	0.5	0.0				
	0	0												
	1	70		1.6	4.4	2.6	348	258	0.9	0.7		139	278	600 cc. H ₂ O P.O. 2½ hrs. before alc. 435 cc. (72%) ex- creted before alc.; of the "remaining" 165 cc., 278 cc. (169%) were ex- creted in 2½ hrs. after alc.
	2	141		4.0	1.6	5.2	81	324	1.2	2.8	106			
	3	157		3.5	2.7	9.4	78	273	1.0	2.5		274		
	4†	220	35	1.3	3.3	4.3	106	138	0.5	0.8				74
	5	275		3.0	1.3	3.9	100	300	1.1	1.9	111	138	274	92
	6	336		0.7	1.2	0.8	156	109	0.4	0.3		140	277	46
13. J. L. Cirrhosis with ascites and edema	0.7													
	1	30		0.4	11.3	4.5	661	264	1.0	-0.6		133	274	500 cc. H ₂ O P.O. 2 hrs. before alc.; 25 cc. (5%) ex- creted in those 2 hrs.; of the "re- maining" 475 cc., 404 cc. (85%) were excreted in 4½ hrs. after alc.‖
	2	60		0.4	2.7	1.1	688	275	1.0	-0.6	101			
	3†	97	35	0.5	2.0	1.0	659	330	1.2	-0.7		132	273	33
	4	127		2.6	0.6	1.6	177	460	1.7	+0.9	112			
	5	159		1.1	1.7	1.9	231	254	0.9	+0.2		132	274	30
	6†	191	35	0.5	3.3	1.7	541	271	1.0	-0.5				68
	7	231		3.1	1.1	3.4	159	493	1.8	+1.3	112	135	279	78
	8	272		3.1	0.7	2.2	104	322	1.2	+1.9		132	273	96
9	317		0.2	2.5	0.5	473	95	0.3	-0.1		130	273	66	

TABLE II—Continued

Patient Diagnosis	Period		Dose of alc. (gm.)	Flow cc./ min.	Urine			Serum			Remarks		
	No.	Elapsed time (min.)			Na mEq./ L.	μEq./ min.	Osm		Na mEq./ L.	Osm mOsm./ L.		Alc mg. %	
							mOsm./ L.	μOsm./ min.					
IIb Ascites and/or Edema—Continued													
14. D. McC. Hypertensive cardiovascu- lar disease; congestive heart failure; edema	1	62		0.7	6.3	4.4	306	214	0.7	0.0	144	289	800 cc. H ₂ O P.O. 1 hr. before alc. 1,096 cc. (137%) excreted in 5½ hrs.†
	2	106		2.5			169	439	1.6	1.0			
	3†	131	35	10.0			71	721	2.6	7.4	125	280	32
	4	150		8.9			71	631	2.2	6.7			
	5	171		5.7			71	405	1.4	4.3	130	281	46
	6†	217	35	3.0			125	375	1.3	1.7	125	281	69
	7	245		2.0			155	310	1.1	0.9			
	8†	305											
	9	438	35	1.7			165	281	1.0	0.7	133	282	129
15. V. P. Cirrhosis with ascites and edema				1.0			211	211	0.7	0.3	138	283	83
	0†	0	35				500				131	268	600 cc. H ₂ O P.O. 1 hr. before alc. 400 cc. H ₂ O P.O. 10 min. before alc. 232 cc. (23%) ex- creted in 7 hrs.†
	1	57		0.4	3.6	1.4	445	178	0.7	-0.3			111
	2†	121	35	0.5			455	228	0.8	-0.3			145
	3†	180	35	0.7			337	232	0.9	-0.2		277	118
		249											134
	4†	360	35	0.7			275	193	0.7	0.0		268	173
16. L. J. RRHD, with A.S., M.I. +M.S., CHF; ascites and edema													800 cc. H ₂ O P.O. 3 hrs. before alc. 320 cc. (40%) ex- creted in 8 hrs.†
	0	0					308				136		
	1	75		1.0	0.7	0.4	221	221	0.8	0.2			
	2	120		1.1	0.5	0.6	185	204	0.8	0.3	130	264	10
	3†	167	25	0.7	0.6	0.4	224	157	0.6	0.1			
	4	212		1.6	0.3	0.5	179	286	1.1	0.5		264	28
	5†	243	45	0.2	0.6	0.1	292	58	0.2	0.0			92
		308											124
	6	390		0.5	0.7	0.4	265	133	0.5	0.0		265	110
		482										264	184
7†	501	35	0.2	0.6	0.1	289	58	0.2	0.0		266	147	

DISCUSSION

That ethanol caused no further increase in the urine flow of patients with diabetes insipidus is not surprising. If the action of alcohol is indeed inhibition of the release of ADH, then when the release of this hormone is already minimal or absent, owing to damage to the neurohypophysis, further suppression could not reasonably occur. This observation merely helps affirm earlier argument localizing the site and mechanism of alcohol diuresis.

Because of the known action of the antidiuretic hormone in inhibiting the excretion of water, attempts have been made to relate the impaired water metabolism of various clinical conditions, with and without edema, to over-production of ADH (8), diminished destruction of ADH, or increased sensitivity to this hormone (9). In support of these hypotheses are the reported findings of an elevated amount of antidiuretic substances in the urine or blood of patients with such conditions. Elevated values have been reported in cirrhosis (10-12), congestive heart failure (13, 14), hypertension (15), and Addison's disease (11). However, these substances are not the same in all instances, nor have they been shown conclusively to be identical with ADH (13). Perry and Fyles (16) found no correlation between levels of an antidiuretic substance and edema or liver damage, and no significant difference in antidiuretic activity between the sera of normals and patients with congestive failure or cirrhosis. Nelson and Welt (17) concluded that the patient with cirrhosis and ascites showed no evidence of an increased sensitivity to, or an inability to eliminate or inactivate, endogenous or exogenous posterior pituitary hormone. van Dyke, Ames, and Plough (18), and Stein, Schwartz, and Mirsky (19) report that despite increased levels of antidiuretic substance in some patients, no correlation between this and impaired water metabolism could be detected. van Dyke (20) has justly criticized much of the methodology which has been employed in the assay of antidiuretic substances.

Gaunt (21), working with animals, and Lloyd and Lobotsky (9, 11) on the basis of human studies, have postulated an antagonistic relationship between the adrenal cortex and the posterior pituitary with respect to the control of the balance of water in the body. Thus, in the adrenalectomized

rat or the adrenal-insufficient human, an increased amount of ADH may accumulate in the blood, preventing excretion of a water load in normal fashion. The administration of corticosteroids, according to this theory, by antagonizing the action of ADH (or of some factor which promotes the release of ADH), permits normal water diuresis to ensue. However, if the action of the corticosteroids is in fact the inhibition of ADH, one should expect similar results from alcohol. In the present studies, a patient with Addison's disease (T. P.) and a patient with panhypopituitarism (T. Q.), neither of whom was receiving corticoid therapy, both failed to have a diuresis after ingesting alcohol. The administration of cortisone, however, which is essential for the correction of the abnormal water tolerance in these states, to another Addisonian (R. M.) also restored the responsiveness to alcohol. One may conclude, therefore, that the action of cortisone is probably not antagonistic to ADH, but is rather "permissive" (22), allowing the organism, by mechanisms as yet undefined, to respond in normal fashion to the stimuli of both water and alcohol.

The inhibitory effect of alcohol on the neurohypophysis is transient. It appears to be related to the duration of the rise in the level of alcohol in the blood, rather than to the absolute level attained (4). Therefore, the administration of repeated doses of ethanol, when the blood level is falling, should theoretically prolong the inhibition established by the initial dose, and allow for a more leisurely dissipation of circulating ADH. A response to a second dose, in the face of minimal or absent response to the first, would suggest either that the destruction of ADH is impaired, or that an increased amount of this hormone was being secreted by the posterior pituitary into the blood. However, in patients who were unresponsive, up to four doses of alcohol failed to provoke diuresis, whereas in those who did respond to multiple doses, some increase in urine flow followed the ingestion of the initial dose.

Of the sixteen patients observed in the present study, all but three (R. M., P. M., and J. L.) had unequivocally impaired responses to water. Since ethyl alcohol, a substance known to inhibit the release of ADH from the neurohypophysis, failed to provoke diuresis in 11 of 13 patients with abnormal water tolerance, the present data do not

support the hypothesis that excessive activity of the antidiuretic hormone of the posterior pituitary is the most important causative factor in the impaired water metabolism of the diseases studied. Although some activity of ADH cannot be excluded, other factors, the nature of which remain unknown, may well play the dominant role in the pathogenesis of the impaired water tolerance that characterizes these states. Whatever these water-retaining stimuli might be, it is probable that the intensity of their action varies from individual to individual, regardless of the nature of the disease. Should this be true, the extent of water diuresis in the absence of ADH (or in response to alcohol) would be determined by the intensity of action of these extra-neurohypophyseal factors.

SUMMARY

1. Ethyl alcohol, a known inhibitor of the release of ADH from the neurohypophysis, was administered orally to 16 patients with various diseases characterized by impaired water tolerance.

2. Eleven of thirteen patients in whom impaired water tolerance was demonstrated failed to respond to ethanol with a diuresis of water.

3. Cortisone restored the ability of one patient with Addison's disease to respond normally with a diuresis both to water and to alcohol.

4. These data do not support the contention that excessive activity of ADH is chiefly responsible for the disturbed water tolerance characterizing the disease states studied.

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. Kleeman, C. R., Rubini, M. E., Lamdin, E., and Epstein, F. H., Studies on alcohol diuresis. II. The evaluation of ethyl alcohol as an inhibitor of the neurohypophysis. *J. Clin. Invest.*, 1955, **34**, 448.
3. 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.
4. Eggleton, M. G., The diuretic action of alcohol in man. *J. Physiol.*, 1942, **101**, 172.
5. van Dyke, H. B., and Ames, R. G., Alcohol diuresis. *Acta Endocrinol.*, 1951, **7**, 110.
6. Pearce, M. L., and Newman, E. V., Some postural adjustments of salt and water excretion. *J. Clin. Invest.*, 1954, **33**, 1089.
7. Dicker, S. E., A method for the assay of very small amounts of antidiuretic activity with a note on the antidiuretic titre of rats' blood. *J. Physiol.*, 1953, **122**, 149.
8. White, A. G., Rubin, G., and Leiter, L., Studies in edema. III. The effect of Pitressin on the renal excretion of water and electrolytes in patients with and without liver disease. *J. Clin. Invest.*, 1951, **30**, 1287.
9. Lloyd, C. W., Some clinical aspects of adrenal cortical and fluid metabolism in *Recent Progress in Hormone Research*, G. Pincus, Ed., New York, Academic Press, 1952, vol. 7, p. 469.
10. Ralli, E. P., Robson, J. S., Clarke, D., and Hoagland, C. L., Factors influencing ascites in patients with cirrhosis of the liver. *J. Clin. Invest.*, 1945, **24**, 316.
11. Lloyd, C. W., and Lobotsky, J., Serum antidiuretic substances and urinary corticosteroid in the human. *J. Clin. Endocrinol.*, 1950, **10**, 318.
12. Sims, J. L., A comparison of renal function with urinary antidiuretic activity in cirrhosis of the liver with ascites. *J. Lab. & Clin. Med.*, 1950, **36**, 990.
13. Bercu, B. A., Rokaw, S. N., and Massie, E., Antidiuretic action of the urine of patients in cardiac failure. *Circulation*, 1950, **2**, 409.
14. Dochios, M., and Dreifus, L. S., Antidiuretic hormone studies in patients presenting edema. *Am. J. Med. Sc.*, 1951, **222**, 538.
15. Ellis, M. E., and Grollman, A., The antidiuretic hormone in the urine in experimental and clinical hypertension. *Endocrinology*, 1949, **44**, 415.
16. Perry, W. F., and Fyles, T. W., Antidiuretic activity of the serum of normal and diseased subjects. *J. Clin. Endocrinol.*, 1953, **13**, 64.
17. Nelson, W. P., III, and Welt, L. G., The effects of Pitressin on the metabolism and excretion of water and electrolytes in normal subjects and patients with cirrhosis and ascites. *J. Clin. Invest.*, 1952, **31**, 392.
18. van Dyke, H. B., Ames, R. G., and Plough, I. C., The excretion of antidiuretic hormone in the urine of patients with cirrhosis of the liver. *Tr. A. Am. Physicians*, 1950, **63**, 35.
19. Stein, M., Schwartz, R., and Mirsky, I. A., The antidiuretic activity of plasma of patients with hepatic cirrhosis, congestive heart failure, hypertension and other clinical disorders. *J. Clin. Invest.*, 1954, **33**, 77.
20. van Dyke, H. B., The regulation of water excretion by the neurohypophysis. *Bull. New York Acad. Med.*, 1953, **29**, 24.
21. Gaunt, R., The adrenal cortex in salt and water metabolism in *Recent Progress in Hormone Research*, Pincus, G., Ed., New York, Academic Press, 1951, vol. 6, p. 247.
22. Ingle, D. J., Parameters of metabolic problems in *Recent Progress in Hormone Research*, Pincus, G., Ed., New York, Academic Press, 1951, vol. 6, p. 159.