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Research Article

STUDIES ON ALCOHOL DIURESIS. III. THE RESPONSE TO ETHYL ALCOHOL IN CERTAIN DISEASE STATES CHARACTERIZED BY IMPAIRED WATER TOLERANCE [1]

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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 supraoptico-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).

$$C_{osm} = \text{osmolar clearance} = \frac{U_{osm} V}{P_{osm}}$$

$$C_{H_2O} = V - C_{osm}$$

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.

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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 osmolarity 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).

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.

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 previous 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 No.	Period Elapsed time (min.)	Dose of alc. (gm.)	Urine Flow cc./min.	Urine Na mEq./L.	Urine Na μEq./min.	Urine Osm mOsm./L.	Urine Osm μOsm./min.	C_{osm} cc./min.	C_{H_2O} cc./min.	$C_{creat.}$ cc./min.	Serum Na mEq./L.	Serum Osm mOsm./L.	Serum Alc mg. %	Remarks
IIa Addison's Disease and Hypopituitarism															
1. T. Q.															
Craniopharyngioma with	1	120		1.0	158	158	618	618	2.1	−1.1	103	144	296		1,400 cc. H_2O P.O.
hypopituitarism; no	2†	186	36	1.0	184	184	606	606	2.1	−1.1				16	with alc. 227 cc.
hormonal R_x	3	228		1.0	171	171	661	661	2.3	−1.3	102	140	294	45	(16%) excreted in
	4	319		0.7	147	103	685	480	1.6	−0.9		137	291	12	4 hrs.‡
	5	372		1.0	137	137	548	548	1.9	−0.9					
2. T. P.															
Addison's disease; on	1	165		0.3	158	47	649	195	0.7	−0.4	87	126	265		1,500 cc. 5% fructose infusion completed ½ hr. before alc. 542 cc. (36%) excreted in 4½ hrs.‡
DOCA; no	2	255		*2.9	84	244	289	838	3.2	−0.3					
other hormonal R_x	3†	315	48	*2.3	79	182	274	630	2.5	−0.2					
	4	375		1.0	119	119	429	429	1.7	−0.7	96				
	5	435		0.9	124	112	460	414	1.6	−0.7		120	253	127	
	6	495		0.6	174	104	640	384	1.5	−0.9					
3. R. M.															
Addison's disease; on cortisone and	0	0		—	100	—	658	—	—	—					270 cc. H_2O P.O.
	1	38		1.0	125	125	700	700	2.4	−1.4	98		287		1 hr. before alc.
	2	90		1.5	153	153	658	987	3.5	−2.0			286		737 cc. (273%) excreted in 3¾ hrs.§
DOCA	3†	139	48	2.8	63	176	276	773	2.7	+0.1				56	
	4	185		4.7	27	127	122	573	2.0	+2.7	105		286	105	
	5	217		4.1	25	103	164	672	2.4	+1.7			286	48	
		242													
	6	289		2.9	31	89	208	603	2.1	+0.8			286	22	
IIb Ascites and/or Edema															
4. A. D.															
Nephrotic syndrome;	1	97		1.0	31.3	31.3	272	272	1.0	0.0	34	125	283		1,000 cc. H_2O P.O.
	2	149		1.0			312	312	1.1	−0.1					2 hrs. before alc.
edema and	3†	208	45	1.8	30.6	55.1	220	396	1.4	+0.4			281	28	146 cc. (15%) excreted in those 2 hrs.; of the "remaining" 854 cc., 384 cc. (45%) were excreted in 4 hrs.‡
hypoproteinemia	4	269		1.1			251	276	1.0	+0.1	26		282	62	
	5†	329	45	2.3	28.8	66.2	169	389	1.4	+0.9			282	85	
	6	394		1.1			216	237	0.8	+0.3	25	124	283	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 previous to test day.
‖ Normal diuretic response to water load demonstrated several weeks later, after paracentesis.

TABLE II—*Continued*

Patient Diagnosis	Period No.	Period Elapsed time (min.)	Dose of alc. (gm.)	Urine Flow cc./min.	Urine Na mEq./L.	Urine Na μEq./min.	Urine Osm mOsm./L.	Urine Osm μOsm./min.	C_{osm} cc./min.	C_{H_2O} cc./min.	$C_{creat.}$ cc./min.	Serum Na mEq./L.	Serum Osm mOsm./L.	Serum Alc mg. %	Remarks
							IIb Ascites and/or Edema—*Continued*								
5. S. H.															
Cirrhosis,	1	57		0.8	12.1	9.7						132			800 cc. H_2O P.O.
ascites, and	2	137		1.0	9.7	9.7					146	135			2 hrs. before alc.
edema	3†	196	35	1.1	9.7	10.7					144			43	233 cc. (29%) ex-
	4	254		0.3	6.2	1.9						134		58	creted in 5 hrs.‡
	5	297		0.6	5.7	3.4						134		51	
6. B. G.															
Cirrhosis,	1	30		0.5	34.7	17.4	678	339	1.4	−0.9	131	115	243		1,200 cc. 2½% glu-
ascites	2	61		0.5	1.6	0.8	726	363	1.5	−1.0		116	243		cose in 1 hr. i.v.
	3	91		*0.7	1.1	0.8	722	505	2.1	−1.4		118	244		completed ½ hr. be-
	4	151		*0.7	1.0	0.7	731	512	2.1	−1.4	131				fore alc. 129 cc.
	5†	181	60	0.3	1.7	0.5	721	216	0.9	−0.6		112	238	32	(15%) excreted in
	6	241		0.3	2.1	0.6	574	172	0.7	−0.4	91	110	240	40	3 hrs.‡
		271										110	235	76	
	7	333		0.2	4.0	0.8	667	133	0.6	−0.4		111	240	64	
7. M. B.															
Arteriosclerotic	1	63		0.10	13.4	1.3	549	55	0.21	−0.11			244		150 cc. H_2O P.O.
heart disease,	2†	124	35	0.03			488	15	0.06	−0.03			245	36	1½ hrs. before alc.
congestive	3	225		0.05	39.7	2.0	340	17	0.07	−0.02		117	244	47	12 cc. (9%) ex-
heart failure;															creted in 3½ hrs.
edema															
8. M. A.															
RHD, AI,	0				1.6							143	284		1,000 cc. H_2O P.O.
AS; no	1	50		0.3											with alc. 178 cc.
edema	2†	132	48	0.7	0.7	0.5	535	374	1.3	−0.6			284	190	(18%) excreted in
	3	192		0.6	0.9	0.5	642	385	1.4	−0.8					4 hrs.‡
	4	235		0.6	1.2	0.7	776	466	1.6	−1.0					
	5	257		0.9	1.3	1.2	792	713	2.5	−1.6					
	6	297		0.8	1.0	0.8	797	637	2.2	−1.4					
9. M. P.															
Chronic pul-	1	35		0.7	124	87	374	262	1.0	−0.3	100				1,000 cc. 5% glu-
monary dis-	2	115		*1.6	60	96	378	604	2.4	−0.8		123	253		cose i.v. in 1 hr. be-
ease; cor	3	145		*4.3	26	112	229	985	3.9	+0.4		118	250		tween periods 2–4.
pulmonale;	4	183		*1.7	38	65	246	418	1.7	0.0	65	122	251		430 cc. (43%) ex-
congestive	5†	240	45	0.6	91	55	410	246	1.0	−0.4			256		creted in 3¼ hrs.‡
failure;	6	283		0.7	74	52	418	293	1.1	−0.4	68	126			
edema															

TABLE II—*Continued*

Patient Diagnosis	Period No.	Period Elapsed time (min.)	Dose of alc. (gm.)	Urine Flow cc./min.	Urine Na mEq./L.	Urine Na μEq./min.	Urine Osm mOsm./L.	Urine Osm μOsm./min.	C_{osm} cc./min.	C_{H_2O} cc./min.	$C_{creat.}$ cc./min.	Serum Na mEq./L.	Serum Osm mOsm./L.	Serum Alc mg. %	Remarks
							IIb Ascites and/or Edema—*Continued*								
10. S. R.															
Superior	1	70		1.2	24.6	29.5	526	631							1,000 cc. H_2O P.O.
vena-caval	2	109		1.2			526	631							2½ hrs. before alc.
syndrome	3	145		1.3			481	626							370 cc. (37%) excreted in 5 hrs.‡
	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	1	49		0.6	3.3	2.0	329	198	0.7	−0.1	71	128	267		700 cc. H_2O P.O.
with ascites	2	93		1.0	1.7	1.7	232	232	0.9	+0.1		124	263		2½ hrs. before alc.
and edema	3†	130	35	0.5	2.7	1.4	296	148	0.6	−0.1	66			70	171 cc. (24%) excreted in 6½ hrs.‡
	4	165		0.4			449	180	0.7	−0.3				59	
	5†	228	35	0.3	11.6	3.5	459	138	0.5	−0.2		127	266		
		258												115	
		288												145	
	6†	346	35	0.3	6.0	1.8	432	130	0.5	−0.2	61			143	
	7	413		0.5	2.4	1.2	284	142	0.5	0.0		128	277	142	
12. P. M.															
Cirrhosis	0	0			4.4		348					139	278		600 cc. H_2O P.O.
with ascites	1	70		1.6	1.6	2.6	161	258	0.9	0.7					2½ hrs. before alc.
±edema	2	141		4.0	1.3	5.2	81	324	1.2	2.8	106				435 cc. (72%) excreted before alc.;
	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	of the "remaining"
	5	275		3.0	1.3	3.9	100	300	1.1	1.9	111	138	274	92	165 cc., 278 cc.
	6	336		0.7	1.2	0.8	156	109	0.4	0.3		140	277	46	(169%) were excreted in 2¾ hrs.
				0.7											after alc.
13. J. L.															
Cirrhosis	1	30		0.4	11.3	4.5	661	264	1.0	−0.6		133	274		500 cc. H_2O P.O.
with ascites	2	60		0.4	2.7	1.1	688	275	1.0	−0.6	101				2 hrs. before alc.;
and edema	3†	97	35	0.5	2.0	1.0	659	330	1.2	−0.7		132	273		25 cc. (5%) excreted in those 2
	4	127		2.6	0.6	1.6	177	460	1.7	+0.9	112			33	
	5	159		1.1	1.7	1.9	231	254	0.9	+0.2		132	274	30	hrs.; of the "remaining" 475 cc.,
	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	404 cc. (85%) were excreted in 4½ hrs.
	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	after alc.‖

TABLE II—*Continued*

Patient Diagnosis	Period No.	Period Elapsed time (*min.*)	Dose of alc. (*gm.*)	Urine Flow *cc./min.*	Urine Na *mEq./L.*	Urine Na *μEq./min.*	Urine Osm *mOsm./L.*	Urine Osm *μOsm./min.*	C_{osm} *cc./min.*	C_{H_2O} *cc./min.*	$C_{creat.}$ *cc./min.*	Serum Na *mEq./L.*	Serum Osm *mOsm./L.*	Serum Alc *mg. %*	Remarks
							IIb Ascites and/or Edema—*Continued*								
14. D. McC.															
Hypertensive	1	62		0.7	6.3	4.4	306	214	0.7	0.0		144	289		800 cc. H_2O P.O.
cardiovascu-	2	106		2.5			169	439	1.6	1.0	60				1 hr. before alc.
lar disease;	3†	131	35	10.0			71	721	2.6	7.4		125	280	32	1,096 cc. (137%)
congestive	4	150		8.9			71	631	2.2	6.7	71				excreted in 5¼ hrs.‡
heart failure;	5	171		5.7			71	405	1.4	4.3		130	281	46	
edema	6†	217	35	3.0			125	375	1.3	1.7				69	
	7	245		2.0			155	310	1.1	0.9	58	125	281	83	
	8†	305												113	
		401	35	1.7			165	281	1.0	0.7		133	282	129	
	9	438		1.0			211	211	0.7	0.3	51	138	283	83	
15. V. P.															
Cirrhosis	0†	0	35				500					131	268		600 cc. H_2O P.O.
with ascites	1	57		0.4	3.6	1.4	445	178	0.7	−0.3	36				1 hr. before alc.
and edema	2†	121	35	0.5			455	228	0.8	−0.3	58			111	400 cc. H_2O P.O.
	3†	180	35	0.7			337	232	0.9	−0.2	51		277	145	10 min. before alc.
		249												118	232 cc. (23%) ex-
		329												134	creted in 7 hrs.‡
	4†	360	35	0.7			275	193	0.7	0.0	48		268	173	
16. L. J.															
RHD, with	0	0			0.7		308					136			800 cc. H_2O P.O.
A.S., M.I.	1	75		1.0	0.4	0.4	221	221	0.8	0.2	61				3 hrs. before alc.
+M.S.,	2	120		1.1	0.5	0.6	185	204	0.8	0.3		130	264	10	320 cc. (40%) ex-
CHF; ascites	3†	167	25	0.7	0.6	0.4	224	157	0.6	0.1					creted in 8 hrs.‡
and edema	4	212		1.6	0.3	0.5	179	286	1.1	0.5	77		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	60		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.

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