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*J Clin Invest.* 1959;**38**(3):545-550. <https://doi.org/10.1172/JCI103832>.

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# THE EFFECT OF CHANGING SERUM OSMOLALITY ON THE RELEASE OF ANTIDIURETIC HORMONE IN CERTAIN PATIENTS WITH DECOMPENSATED CIRRHOSIS OF THE LIVER AND LOW SERUM OSMOLALITY

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(Submitted for publication October 15, 1958; accepted November 13, 1958)

Hyponatremia and lowered total solute concentration of the serum are commonly observed in patients with cirrhosis of the liver with ascites and edema (1-4). The mechanisms responsible for this chronic depression of the osmolality of the body fluid are not clear. The normal person maintains the tonicity of his body fluid within narrow limits, and lowering this by the addition of sufficient water to the body promptly results in diminished secretion of antidiuretic hormone (ADH) and the excretion of increased volumes of hypotonic urine until the osmolality of the serum returns to normal (5-7). In contrast, the patient with decompensated cirrhosis may excrete small volumes of hypertonic urine despite a much lower than normal serum osmolality (1-4). However, further lowering of the osmotic pressure in such a patient by the ingestion or infusion of water often leads to a diuretic response similar to that of the normal subject (1, 4).

It would thus appear that the patient with cirrhosis and with a hypotonic milieu who is able to vary urinary concentrations through wide ranges is either releasing ADH in response to a stimulus other than tonicity [such as changes in effective extracellular fluid volume (2, 3)], or that the responses to changes in osmotic pressure are regulated about a lower than normal tonicity. This study is concerned with patients with decompensated cirrhosis who maintain a low serum osmolality, and only those who are able to achieve a diuresis in response to hydration. It was the purpose to determine if, while such pa-

tients were undergoing a water diuresis, returning the serum osmolality to its original low level would result in the release of ADH, as reflected by alterations in the flow and concentration of the urine.

## METHODS

Subjects selected for study were patients with decompensated cirrhosis associated with the prolonged and excessive intake of alcoholic beverage. All had tense ascites with or without peripheral edema, mild to moderate elevations of serum bilirubin, and a persistently depressed serum osmolality.<sup>1</sup> All were free of cardiovascular and renal disease, and all had previously demonstrated the ability to produce a concentrated as well as a dilute urine. Only subjects able to achieve a flow of urine greater than 6 ml. per minute during the water load were studied. The group consisted of five male and two female patients.

Each study was begun in the morning at least one hour after a light breakfast, and where possible the study was carried out in a private room. Smoking was prohibited after the preceding evening, and the subjects remained recumbent throughout the procedure. All samples of urine were collected through an indwelling urethral catheter which was inserted on the morning of the study. Infusions were delivered through a needle inserted into a forearm vein or through a polyethylene catheter inserted into an antecubital vein. Samples of blood were collected through an indwelling Cournand needle inserted into a forearm vein of the opposite arm. To minimize the influence of emotional reactions on the results of the study the catheterization and venipunctures were performed at least 45 minutes prior to beginning the study. After an initial collection of urine and blood, each subject received a water load as an infusion of 4 per cent hexose (either invert sugar or fructose) solution alone, or in combination with tap water by mouth. The total gain of water was individualized in each subject so that high rates of urinary flow were achieved and

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<sup>1</sup> Determinations of the osmolality of the serum of 16 healthy adults ranged from 281 to 294 mOsm. The range of osmolalities of the sera of subjects chosen for study was 266 to 272 mOsm.

maintained. Fifteen hundred ml. was given during the first hour, and thereafter the infusion was regulated to deliver water in amounts equal to the flow of urine plus an additional 50 ml. per hour for insensible losses. When rates of urinary flow greater than 6 ml. per minute had been reached and maintained for a period of 45 to 60 minutes the infusion was changed to either 3 per cent or 5 per cent sodium chloride. The total amount of sodium chloride given was calculated to correct but not exceed the dilution effect of the water load. This was given rapidly over a period of 15 to 30 minutes. The infusion was then continued as 4 per cent hexose solution at a rate equal to the rates of urinary flow and estimated insensible losses. The positive balance of water was not allowed to fall below that which existed at the time of the maximal water diuresis.

Samples of blood were collected during the period of dilution and maximal urinary flow, midway through the infusion of hypertonic sodium chloride, and during the

periods of diminishing urinary flow. The total volume of blood withdrawn prior to the infusion of saline was not in excess of 60 ml. in any subject. Samples of urine were collected at intervals of 10 to 20 minutes, the shorter intervals being necessary to avoid distention of the bladder during high rates of urinary flow. Bladder rinsing was not employed. All samples of serum and urine were frozen immediately.

Total solute concentrations in serum and urine were determined by freezing point depression using a Fiske osmometer. Concentrations of sodium were determined with an internal standard flame photometer. Creatinine concentrations in serum and urine were determined by the method of Hare (8). Calculations of the endogenous clearance of creatinine and the rate of sodium excretion were determined from periods when the flow of urine and the excretion of total solutes were stable in order to minimize the effect of urinary tract dead space and delay time.

TABLE I  
*Data pertaining to three subjects who experienced discomfort during the infusion of hypertonic NaCl*

Subject	Elapsed time	Urine flow	Urine conc.	Serum conc.	Infusion
	<i>min.</i>	<i>ml./min.</i>	<i>mOsm./L.</i>	<i>mOsm./L.</i>	
A	-30-0	0.7	259	269	800 ml. water P.O. and 1,250 ml. 4% invert sugar I.V.
	0-15	5.9	126		
	15-30	7.3	84	272	
	30-45	14.0	57		
	45-60	12.5	55	261	
	60-75	11.5	58	268	230 ml. 5% NaCl
	75-90	7.1	52		
	90-105	0.6	262	274	75 ml. 4% invert sugar
	105-120	0.8	323	272	
B	-30-0	0.7	347	270	760 ml. water P.O. and 1,450 ml. 4% invert sugar I.V.
	0-30	4.3	82		
	30-45	5.3	78	258	
	45-60	5.8	69		
	60-75	5.8	50	255	
	75-90	6.3	44		370 ml. 5% NaCl
	90-105	6.4	40	253	
	105-120	8.7	30	271	
	120-135	3.0	53	274	
C*	135-150	0.5	320	271	50 ml. 4% invert sugar
	150-165	0.5	453	268	
	0-15	2.7	305	266	600 ml. water P.O. and 1,500 ml. 4% fructose I.V.
	15-30	3.6	294		
	30-45	5.4	238		
	45-60	7.5	168	253	
	60-75	6.3	157		380 ml. 5% NaCl
	75-90	2.0	332		150 ml. 4% fructose
	90-105	2.5	360	262	

\* Subject C received the water load as an infusion of 4 per cent fructose solution, and the samples of urine during the period of dilution gave a 4-plus reaction with Clinitest. The presence of fructose in these samples probably would have prevented minimal dilution even in the absence of ADH. All other subjects received 4 per cent invert sugar solution, and reducing substance was not detected in other urine samples.

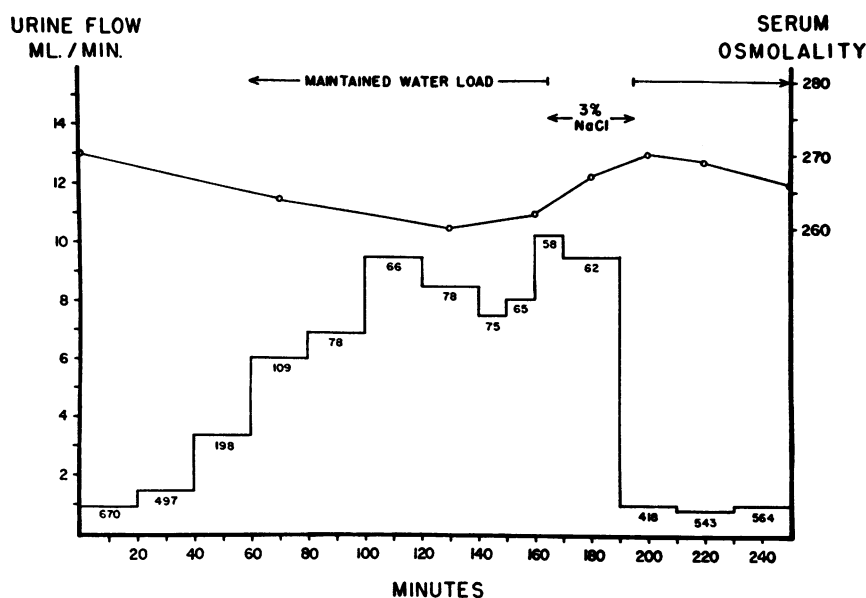


FIG. 1. WATER DIURESIS FOLLOWED BY ANTIDIURESIS WHEN SERUM OSMOLALITY IS RETURNED TO THE INITIAL LOW LEVEL (SUBJECT F)

The line graph at the top represents osmolality of the serum. The bars below represent rates of urine flow. Figures superimposed on the bars denote osmolalities of the respective urine samples. The positive balance of water was maintained constant after the first hour as shown, and the period of infusion of hypertonic saline is indicated.

## RESULTS

One subject was eliminated from the results of the study because of a spontaneous antidiuresis which occurred in association with observed emotional stress. Of the remaining six subjects, three experienced mild discomfort at the site of the infusion of hypertonic sodium chloride, and it cannot be concluded with certainty that the observed response was due to a change in tonicity and not to the distress associated with the infusion (9). Data pertaining to these subjects are summarized in Table I. The subjects who received the infusions through venous catheters did not perceive the change from 4 per cent invert sugar solution to hypertonic sodium chloride, and no stimulus other than the changing tonicity was apparent. The data pertaining to these subjects are given in detail in Table II. Figure 1 graphically represents a typical subject from this latter group. The results are qualitatively the same in each of the six studies.

Lowering the osmolality of the serum 7 to 17 mOsm. as a result of dilution by the water load

was associated with a rise in the rate of urinary flow and a fall in the osmolality of the urine in all six subjects. The peak rates of urinary flow ranged from 6.4 to 14.0 ml. per minute, and the minimal total solute concentrations ranged from 30 to 58 mOsm. (except Subject C who had hexosuria during the diluting phase and who had a minimal urinary concentration of 168 mOsm). Restoration of the osmolality of the serum to the pre-experimental levels by the hypertonic infusion was followed by a prompt decrease in the rate of urinary flow and rise in urinary concentration. In each subject small volumes of concentrated urine were produced during the first collection period following the infusion of sodium chloride. Maximal urinary total solute concentrations during the antidiuresis ranged from 323 to 544 mOsm. In each instance the hypertonic NaCl returned the total solute concentration of the serum to within 3 mOsm. of the initial level. During the study of Subject B the osmolality of the serum exceeded the initial level by 4 mOsm. during the infusion of hypertonic saline, but in no subject did the con-

TABLE II  
Data pertaining to three subjects who attained water diuresis followed by antidiuresis without discomfort

Subject	Elapsed time	Urine flow	Urine conc.	Serum conc.	Serum sodium	Renal excretion rate of		Clearance of creatinine	Infusion
						Total solute	Sodium		
	min.	ml./min.	mOsm./L.	mOsm./L.	mEq./L.	$\mu\text{Osm./min.}$	$\mu\text{Eq./min.}$	ml./min.	
D	-30-0	0.6	543	272	128	326	16.8		950 ml. water P.O. and 1,450 ml. 4% invert sugar I.V.
	0-15	0.7	599			419		104	
	15-30	0.6	576			346			
	30-45	1.0	368			368			
	45-60	3.8	130			494			
	60-75	11.5	66	262		759			
	75-90	13.2	52			689			
	90-105	11.7	57	261	123	667	30.4	128	
	105-120	8.3	72	260		598			360 ml. 5% NaCl
	120-135	1.5	384	270		576			
	135-150	1.3	544	271	129	707			75 ml. 4% invert sugar
	150-165	0.7	511	273		358	14.7	125	
E	-35-0	0.9	437	270	131	393	24.5	200	2,600 ml. 4% invert sugar I.V.
	0-20	0.8	439			351			
	20-40	1.5	335			503			
	40-60	3.4	135			459			
	60-80	5.4	86			465			
	80-100	7.1	65			462			
	100-125	9.0	49	264		441			
	125-145	7.3	58	265	128	448	34.7	221	
	145-165	3.0	98	263		294			250 ml. 5% NaCl
	165-185	1.8	207	268	128	373			
	185-205	1.1	318			350			200 ml. 4% invert sugar
	205-225	1.3	314			408	79.3	201	
	225-245	1.2		268					
	245-270	1.6	354	271	131	566			
F	-35-0	0.7	692	270	131	488			2,400 ml. 4% invert sugar I.V.
	0-20	0.9	670			570	1.6	161	
	20-40	1.4	497			662			
	40-60	3.3	198			644			
	60-80	6.0	109	264		654			
	80-100	6.9	78			538			
	100-120	9.5	66			624			
	120-140	8.5	78	260		643			
	140-150	7.5	75			563			
	150-160	8.2	65	262	128	533			
	160-170	10.2	58			592	7.1	145	520 ml. 3% NaCl
	170-190	9.6	62	267	132	595			
	190-210	1.0	418	270		418			150 ml. 4% invert sugar
	210-230	0.8	543	269		415			
	230-250	1.0	564			564			
	250-270	1.0	552	266	131	552	13.2	159	

centration reach the normal range of serum osmolality.

The endogenous clearance of creatinine was determined in three subjects. In one subject there was a small rise which persisted after hydration, in one there was a small rise during hydration and a return to the initial level during the antidiuresis, and in the third subject there was no

significant change throughout the procedure. These values were all within normal limits.

#### DISCUSSION

The ability of the decompensated cirrhotic to excrete a standard intake of water has been quantitatively studied and reported elsewhere (1, 4). Many may achieve varying degrees of diuresis,

but occasionally the decompensated cirrhotic may be unable to produce a urine more dilute than plasma (2, 3). The water loads given here were intended primarily to produce, where possible, an obvious water diuresis, and no conclusions can be made regarding the variation in diuretic responses. Only subjects who underwent a water diuresis were studied, and thus conclusions are applicable to *this group only*.

In normal subjects changes in effective osmotic pressure of the body fluids result in changes in the release of ADH. Lowering the osmotic pressure by the gain of water results in an inhibition of the release of ADH and a loss of body water through the excretion of urine of lowered total solute concentration. Elevation of the osmotic pressure above normal by the loss of water or by the gain of effective solute (such as NaCl and other substances which do not readily cross the cell membrane) results in the release of ADH and the conservation of body water by the excretion of a concentrated urine. In this fashion the osmoreceptor-ADH system maintains the tonicity of the body fluids within narrow limits (5-7). Besides pharmacologic and psychic stimuli (10), another apparent mechanism concerned in the release of ADH appears to be related to changes in the extracellular fluid volume or some function thereof (9, 11-14).

The subjects reported here produced large volumes of dilute urine in association with lowering the osmotic pressure of the serum. Restoration of the original osmotic pressure, without a fall in total body volume, resulted in prompt anti-diuresis. That these changes in urinary flow and concentration were probably due to changes in the release of ADH seems clear from the character of the urine. There were no marked variations in the rates of solute excretion, and it is unlikely that abrupt changes in the rates of glomerular filtration occurred. In the absence of such changes the observed differences in the flow and concentration of urine may be interpreted as the result of variations in the release of ADH (15, 16). Without pharmacologic and psychic stimuli and with total body volume constant, these changes in the release of ADH seem clearly related to the changes in tonicity and its consequent effects. It may be concluded that at the time these subjects were studied they were sensitive to changes in osmotic

pressure, and that the balance of water was regulated to maintain a fixed, although lower than normal, tonicity of the body fluids.

These studies shed no light on the mechanisms responsible in such subjects for a lowered tonicity of the body fluids. In other situations it has been observed that excessive ADH activity may result in the retention of water in excess of solute and thereby lead to hypotonicity (17, 18). It has been suggested that in cirrhosis of the liver decreased hepatic inactivation of the hormone may be a source of excessive antidiuretic activity (19-21), and likewise a decrease in effective extracellular fluid volume could be a stimulus for inappropriate release of the hormone. However, it would not appear that a constant high level of antidiuretic activity exists in subjects who are able to alter abruptly the rates of excretion of water such as those reported here and those of other reports where prompt responses to water loads were observed (1, 4). This subject has been critically reviewed recently by Papper (3).

Such a lowered setting of the osmoreceptor-ADH system as demonstrated by the subjects reported here may possibly be related to a diminished amount of intracellular osmotic activity as has been suggested in other types of chronic hyponatremia (22). The results observed in this study are consistent with such a concept, but confirmation must await accurate volume determinations of the various fluid compartments in these and other states associated with altered osmotic pressure of the serum.

#### SUMMARY

The antidiuretic effect of hypertonic sodium chloride given during water diuresis was studied in six subjects with decompensated Laennec's cirrhosis and chronically depressed osmolality of the serum. It was found that marked antidiuresis ensued when the osmolality of the serum was restored to the initial low level without a change in the total volume of water in the body. It is concluded that these subjects with low serum sodium and total solute concentration were sensitive to further changes in tonicity, and that the release of antidiuretic hormone was regulated in a qualitatively normal fashion about a lower than normal level of osmolality.

## ACKNOWLEDGMENTS

The authors are gratefully indebted to Drs. Maurice B. Strauss and Solomon Papper for encouragement and suggestions during the course of these studies and preparation of this manuscript, and to Drs. Thomas C. Chalmers and C. Gardner Child, III, for the use of their laboratories.

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