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J Clin Invest. 1952;31(1):60-71. <https://doi.org/10.1172/JCI102578>.

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AN ANTIDIURETIC MECHANISM NOT REGULATED BY EXTRACELLULAR FLUID TONICITY^{1, 2}

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(Submitted for publication August 9, 1951; accepted October 15, 1951)

In the preceding paper (1) we have described the antidiuretic mechanism in normal man and dogs which preserves within narrow limits the total effective solute concentration of the extracellular fluid. The increase in serum solute concentration that occurs with water deprivation stimulates outpouring of antidiuretic hormone which leads to a concentrated urine and renal conservation of body water. The dilution of the extracellular fluid that follows water administration suppresses activity of the supraopticohypophyseal system permitting water diuresis and renal excretion of the administered water load. This sequence of events was first recognized and demonstrated by Verney (2, 3).

If the above is accepted as the normal physiology, then the common clinical observation of sustained low serum sodium concentrations in patients who have no apparent intrinsic renal disease needs explanation. As sodium is the major osmotically active constituent of the extracellular fluid it might be expected that total solute concentration would be low if sodium were markedly reduced. But a dilute extracellular fluid would cause inhibition of antidiuretic hormone production with resultant water diuresis and return of serum sodium and total solute concentration to the normal level. Why does this not occur?

METHODS

Sodium determinations in serum and total solute concentrations of serum and urine were obtained as described (1). Urine sodiums were done with an internal standard flame photometer (4). The assays for serum antidiuretic activity were carried out as described (1).

¹ Supported in part by a Grant-in-Aid from the American Heart Association.

² Presented in part at the Forty-third Annual Meeting of the American Society for Clinical Investigation, Atlantic City, N. J., April 30, 1951.

³ National Research Council Fellow in the Medical Sciences, 1949-1951.

The "p" value following each assay gives the probability of its significance (1).

The subjects for this study were: (1) patients on the medical wards of the Massachusetts General Hospital including four patients with Addison's disease on whom 19 tests of water excretion were conducted and eight patients with congestive heart failure on whom 13 studies were performed; (2) three mongrel female dogs. The dogs were first depleted of extracellular fluid electrolyte by the intraperitoneal dialysis technique of Darrow and Yannet (5) and tested 24 hours later for their ability to excrete a water load. Urine collections were obtained from the dogs by catheterization. These same animals were then tested for their ability to excrete water following repeated small injections of Pitressin Tannate in Oil (Parke, Davis and Co.) 1.0 to 2.0 units twice daily.

RESULTS

A. In Addison's disease

Table I and Figure 1 show data obtained from a female patient whose Addison's disease was inadequately treated with 5 mgs. of desoxycorticosterone glucoside intramuscularly daily. It is clear that the low serum total solute concentration

TABLE I
(6/2/50) E. S. Female. Addison's disease receiving 5 mgs. DOCG daily

Time (hours)	Serum		Urine		Assay
	Na (mEq/L)	Total solutes (mOsm/L)	Flow (ml./min.)	Total solutes (mOsm/L)	
0				510	
1.5	125	281	0.5	456	
1.5-2.0		500 ml. water orally			
3.0	123	277	1.8	444	
4.0	124	262	0.8	552	+167 (p < 0.03)
5.0	121	260	0.6	660	
6.0	118	270	1.0	486	
7.5			0.9	564	
10.0	120	262	1.0	417	
12.5			1.6	369	
14.5			0.8	435	
19.0			1.3	288	
22.0			0.7	495	
24	125	279			

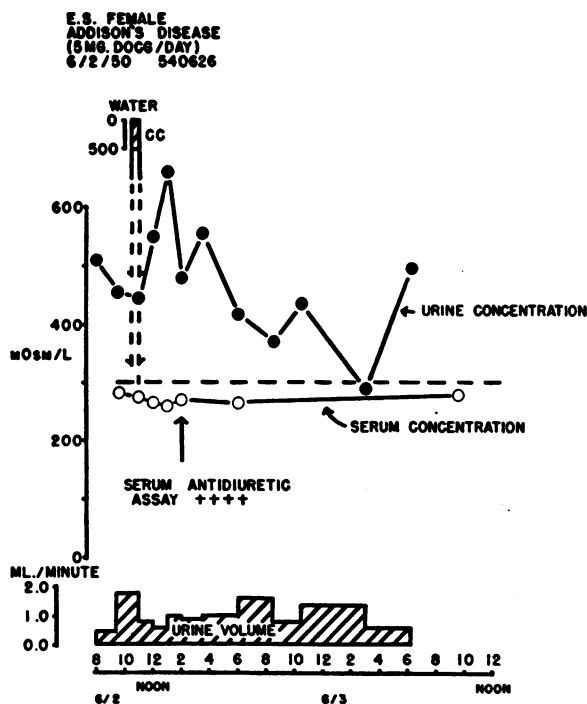


FIG. 1. THE ABNORMAL ANTIURETIC PATTERN IN A PATIENT WITH INADEQUATELY TREATED ADDISON'S DISEASE

Urine and serum total solute concentrations are plotted on the ordinate with time on the abscissa. Note that the serum total solute concentration is well below the normal level for man, indicated by the broken line. In spite of this the urine is concentrated and there is failure of prompt dilution of the urine following water administration. Antidiuretic activity was demonstrated in the serum at a time following water ingestion when the normal would show no antidiuretic activity in the serum.

does, in fact, reflect the low concentrations of serum sodium commonly associated with this condition. In spite of this the urine is found to be hypertonic to the serum. This finding is clearly not in accord with the normal physiology previously described (1).

It was first thought that this patient's osmotic regulating mechanism might be set to preserve some level of concentration lower than the normal—275 mOsm/L, say, instead of the normal 314 mOsm/L. If this were the case the patient should promptly excrete a water load with preservation of serum total solute concentration as does the normal (1). As seen in Figure 1, the expected dilution of the serum occurred following water

administration but there was no diuresis or prompt dilution of the urine.

Furthermore, two hours following the water ingestion when the normal subject would have a polyuria with a dilute urine and would show no antidiuretic activity in his serum, this patient's urine was concentrated and her serum gave a strongly positive assay for antidiuretic activity. Though nothing can be said from this experiment regarding the source of the antidiuretic activity, it is apparent that this patient's osmotic regulating mechanism was not showing the normal response to a dilution of the serum. As a diuresis of dilute urine would obviously abolish this hypotonicity of the extracellular fluid, it is clear that this abnormal antidiuresis is responsible for the hypotonic state of the extracellular fluid.

That the ingested water load was sufficient to produce a normal diuretic pattern is shown in Figure 2. At this time the patient was receiving 100 mgs. of cortisone acetate intramuscularly daily. Her serum total solute concentration had returned to normal and the same dose of water resulted on two occasions in a prompt diuresis of dilute urine.

B. In congestive heart failure

Very low concentrations of sodium in the serum are seen in occasional patients with congestive heart failure who have been vigorously treated by measures to remove sodium from the body in the attempt to reduce edema. Unfortunately, all too commonly sodium is removed but extracellular fluid volume is not reduced proportionately and serum sodium concentrations fall.

Table II and Figure 3 show data from two such cases. Again we encounter low serum solute concentrations together with low concentrations of serum sodium. The urine, in spite of this, is found to be concentrated and there is no diuresis or dilution of the urine following water ingestion although the serum showed slight further dilution.

Assay of the serum of patient N.A.B. indicated the presence of antidiuretic activity at a time following water ingestion when the serum of a normal subject would have been free of antidiuretic activity. Thus the pattern of water excretion in this group of patients is found not to differ from

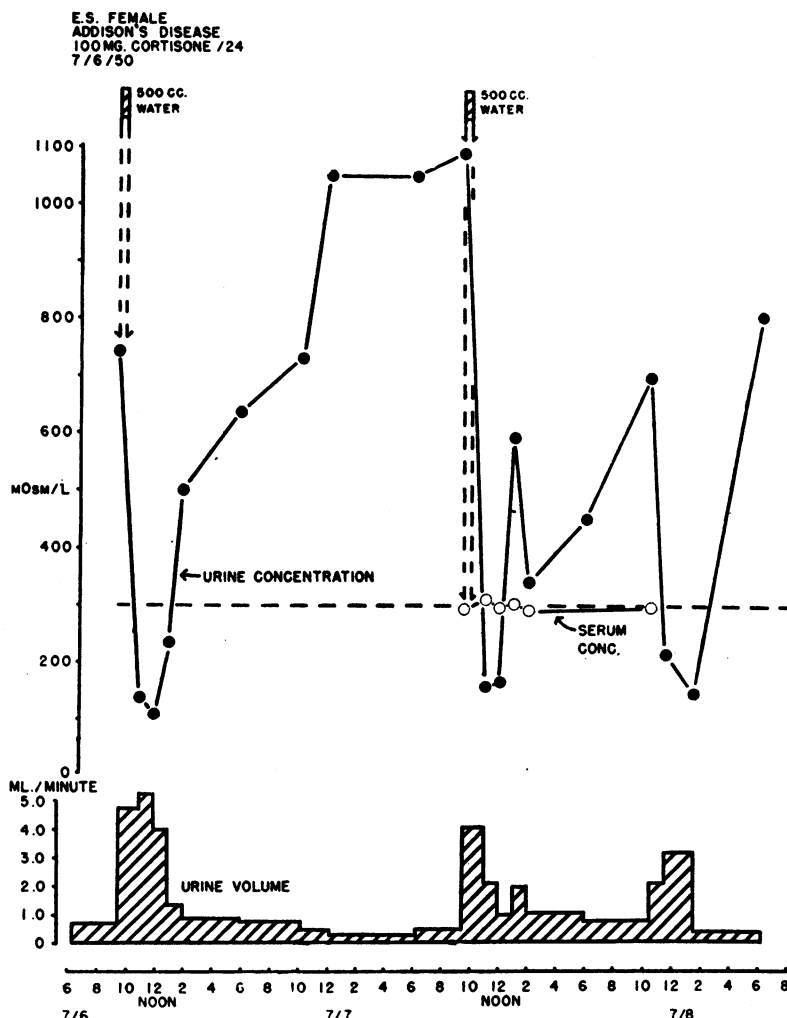


FIG. 2. THE NORMAL DIURETIC PATTERN ON TWO OCCASIONS IN THE SAME PATIENT WITH ADDISON'S DISEASE FROM WHOM THE DATA FOR FIGURE 1 WERE OBTAINED

In this instance the patient had been receiving 25 mgs. of cortisone acetate intramuscularly four times daily for seven days. Note that now serum total solute concentration is normal and the same dose of water that previously failed to cause a diuresis now is effective in causing prompt diuresis and dilution of the urine. Aside from a six-hour period following the two test water loads the patient was on an *ad lib* water intake. Thus the third episode of polyuria with dilution of the urine resulted from fluids spontaneously ingested.

that of the patient with uncontrolled Addison's disease. That adrenal insufficiency is not a factor in this group of patients is indicated by the very low concentrations of sodium in the urine shown in Table II and the low circulating eosinophile counts in this group—10 and 16 per cubic millimeter of fasting venous blood in subject N.A.B. on the day of study.

C. In dogs depleted of extracellular fluid electrolyte

It seemed that the factor common to both the above clinical groups might be a depletion of extracellular fluid electrolyte. If this were correct one should perhaps be able to convert a normal animal from the normal diuretic pattern to this abnormal pattern by depleting it of extracellular fluid electrolyte. Table III records the protocol

TABLE II
(3/26/51) N. A. B. Coronary heart disease and congestive failure

Hour	Serum		Urine		Na (mEq/L)	Assay
	Na (mEq/L)	Total solutes (mOsm/L)	Flow (ml./min.)	Total solutes (mOsm/L)		
0				576	2.0	
0-1	600 ml. water orally					
1	117	282	0.6	585	3.0	+67 (p=0.03)
2			0.8	576		
3	118	272	0.6	576		
4			0.6	600		
5			0.8	570		
6	119	288	0.5	591	5.0	
8			0.6	576		
9			0.9	570		
10			0.4	594		
12			0.5	585		
14			0.4	591		
19			specimen lost			
21			1.0	585		
22			1.0	655		
25	119	279				

of a depletion study on Dog B presented in Figure 4. Parts A and C are the control hydration observations before and after the depletion (Part B) and are in every respect the normal response to a water load (1).

TABLE III

Part A. Hydration control, 12/4/50, Dog B (10.4 kilo)

Hour	Serum		Urine		Na (mEq/L)	Assay
	Na (mEq/L)	Total solutes (mOsm/L)	Flow (ml./min.)	Total solutes (mOsm/L)		
0	147	338		1562	74	
0-0.1	300 ml. water by stomach tube					
1			1.0	150	6.5	+58 (p=0.43)
2	143	318	2.2	82		
3			0.5	375		
4	147	330	0.3	655		
5			0.1	1413		

Part B. Dog B depleted of 130 mEq Na by peritoneal dialysis, 12/8/50 (9.9 kilo)

Hour	Serum		Urine		Na (mEq/L)	Assay
	Na (mEq/L)	Total solutes (mOsm/L)	Flow (ml./min.)	Total solutes (mOsm/L)		
0	122	295		600	1.9	
0-0.1	300 ml. water by stomach tube					
1			0.2	595	0.8	+184 (p=0.03)
2	121	280	0.3	585		
3			0.3	680		
4			0.2	620		
5	119	273	0.4	600		

Part C. Hydration control after return to diet and salt, 12/11/50, Dog B (9.8 kilo)

Hour	Serum		Urine		Na (mEq/L)	Assay
	Na (mEq/L)	Total solutes (mOsm/L)	Flow (ml./min.)	Total solutes (mOsm/L)		
0	147	327		1617	2.0	
0-0.1	300 ml. water by stomach tube					
1			0.2	640	1.4	+22 (p=0.43)
2	140	300	2.2	72		
3			0.7	150		
4			0.1	720		
5	142	307	0.1	994		

D E D. 706278
CONGESTIVE FAILURE
MALE

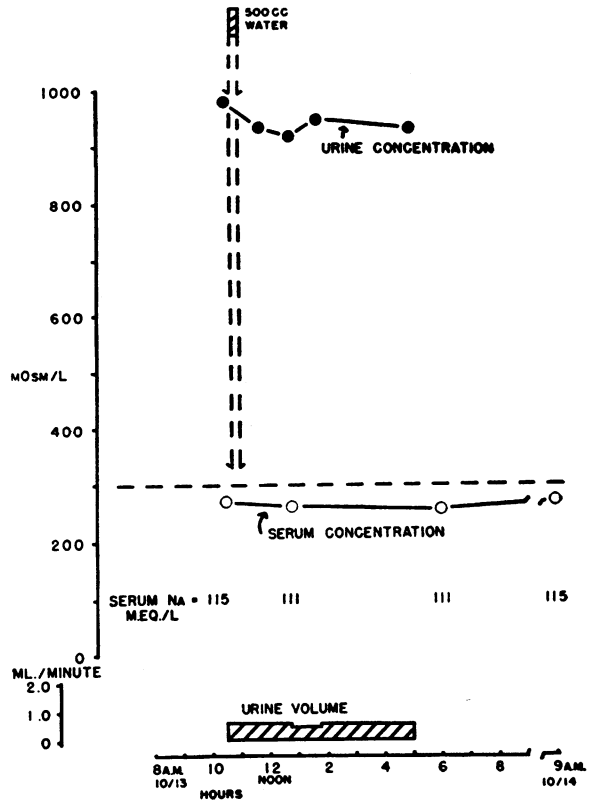


FIG. 3. THE ABNORMAL ANTIDIURETIC PATTERN IN A PATIENT WITH CONGESTIVE HEART FAILURE WHO DEVELOPED A VERY LOW CONCENTRATION OF SERUM SODIUM DURING TREATMENT OF HIS EDEMA

Note the dilute serum (271, 262, 256, and 272 mOsm/L, respectively) but the concentrated urine with complete absence of diuresis or dilution of the urine following water ingestion. The urine concentration remains not much below the maximum concentration for man. The urine sodium concentrations were 1.6, 1.8, 1.2, 1.5, and 1.5 mEq/L, respectively. These minimal urine sodium concentrations, in spite of the high urine total solute concentrations, indicate that the subject was conserving sodium as well as water.

Following the peritoneal dialysis with removal of nearly half the estimated normal sodium content of the extracellular fluid, this animal became listless, anorexic and oliguric showing loss of skin turgor and severe dehydration as described by Darrow and Yannet in their classic studies (5). The serum sodium was found to be low in association with a low total solute concentration. However, the urine was concentrated and there was

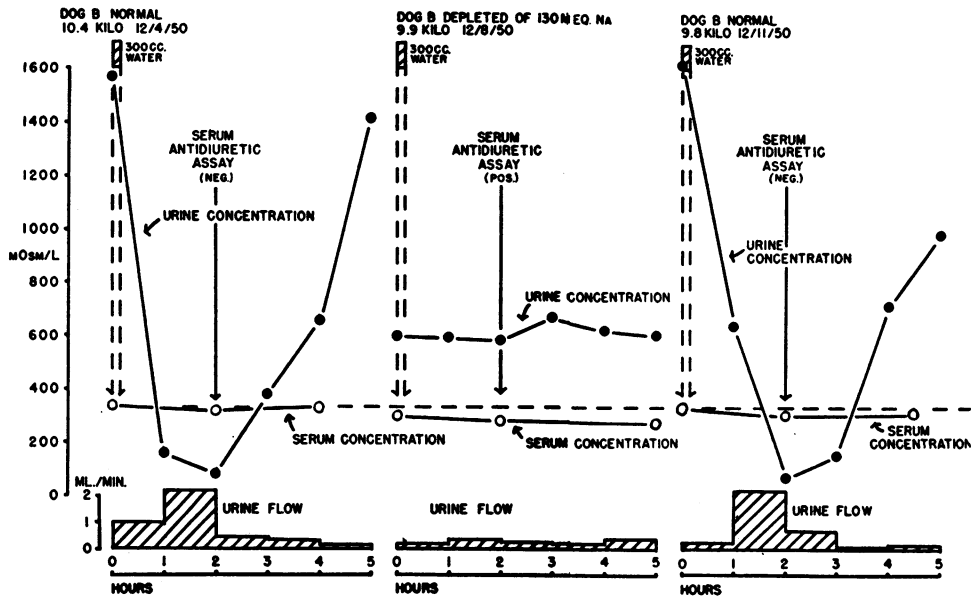


FIG. 4. THE EFFECT OF DEPLETION OF EXTRACELLULAR ELECTROLYTE ON THE DIURETIC PATTERN IN THE DOG

The right and left hand portions show the diuretic pattern before and following depletion. These are entirely normal diuretic patterns. The middle section shows conversion to the abnormal antidiuretic pattern following removal of 130 mEq of sodium by peritoneal dialysis. In this section we see again a dilute serum but a hypertonic urine and failure of dilution of the urine or diuresis following water administration. Antidiuretic activity was demonstrated in the serum during depletion but not in the controls.

failure of diuresis and dilution of the urine following the same water load which prior to and following depletion resulted in a satisfactory diuresis. Also antidiuretic activity was demonstrable in the serum of the depleted animal whereas no significant evidence of antidiuretic activity could be obtained in the two control periods. One animal, whose state of depletion was maintained by a sodium-free intake for eight days, excreted a persistently concentrated urine and exhibited this abnormal antidiuresis when tested on the second, fifth, and eighth days. Thus the normal dog depleted of extracellular fluid electrolyte mimics the abnormal antidiuretic mechanism described above in patients with inadequately treated Addison's disease and certain cases of congestive heart failure that develop low concentrations of serum sodium.

D. In dogs during administration of small amounts of posterior pituitary extract

The finding of antidiuretic activity in the serum of patients and dogs exhibiting this abnormal antidiuretic phenomenon obviously suggested an over-

activity of the supraopticohypophyseal antidiuretic mechanism in spite of the dilution of extracellular fluid which normally inhibits its activity. If such were the case one should be able again to reduplicate this abnormal pattern by the continuous administration of posterior pituitary antidiuretic hormone.

Figure 5 shows the results on water excretion on the third day of administration of 2.0 units of Pitressin Tannate in Oil (Lot K888G) twice daily intramuscularly to Dog C together with 1 liter of water daily by stomach tube. A control hydration study is shown in the same figure. A similar study in Dog B is shown in Figure 6 in which half the dose of Pitressin was used. Again we see the abnormal antidiuretic pattern repeated in all details studied.

The same results have been obtained in humans on five occasions using the smaller dose of Pitressin Tannate in Oil. Undoubtedly similar results could be obtained with considerably smaller amounts of Pitressin Tannate in Oil but the difficulty in measuring smaller volumes of this prepa-

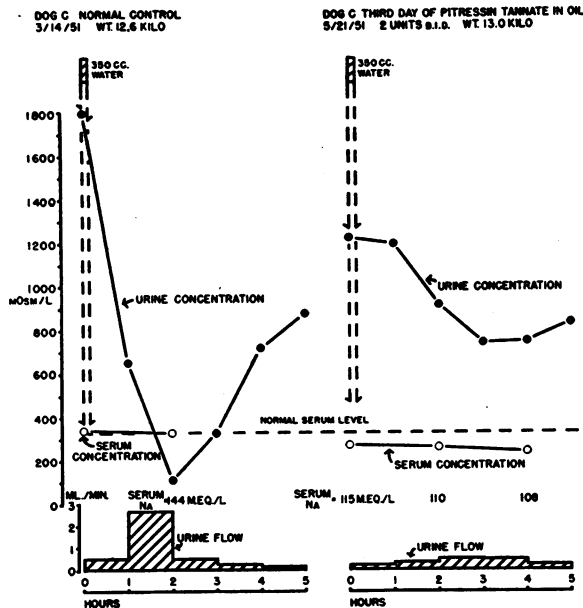


FIG. 5. THE EFFECT OF POSTERIOR PITUITARY EXTRACT ON WATER DIURESIS IN THE DOG

On the left is shown a normal control diuretic pattern. On the right is shown the abnormal antidiuretic pattern produced by 2.0 units of Pitressin Tannate in Oil administered twice daily for two days together with 1,000 ml. of water by stomach tube daily. Again we see a dilute serum but a concentrated urine and failure of diuresis following water administration. This animal gained little weight during Pitressin administration and in appearance simulated the signs of salt depletion shown at the time of peritoneal dialysis (see text). It is interesting that under these circumstances, in spite of large exogenous antidiuretic hormone administration, the urine concentration was not nearly so great as that achieved by spontaneous endogenous antidiuretic hormone activity during water restriction.

ration prevented further reductions in dosage. The dosage used in man approximates the estimated physiological endogenous output of the posterior pituitary (6, 7).

As can be seen in the figures the gain in body weight observed with Pitressin administration was insufficient to explain the dilution on the basis solely of water retention. A large diuresis of sodium and chloride probably occurred during the period of Pitressin administration such as may occur in man (8). This possibility is supported by the ensuing loss of weight to over 1 kilo below the control weight following the post-Pitressin diuresis when the serum sodium and total solute concentrations had returned to normal.

DISCUSSION

The finding of low concentrations of serum sodium in patients who were elaborating distinctly hypertonic urines was not sufficient evidence for concluding that the normal regulation of diuresis and antidiuresis was not operating. Retention of other substances in the extracellular fluid could theoretically have compensated for low sodium and chloride concentrations. When the total solute concentration of the serum, as well as its sodium and chloride concentrations, was found to be low this theoretical possibility was excluded. It was at once evident that the normal physiology did not pertain in these cases.

Baldes and Smirk (9) emphasized that it was the acute drop in serum total solute concentration following water ingestion which acts as the stimulus for water diuresis rather than the absolute concentration. They found that the gradual decrease in serum total solute concentration produced in normal subjects by low salt diets plus sweating did not give rise to a state of diuresis.

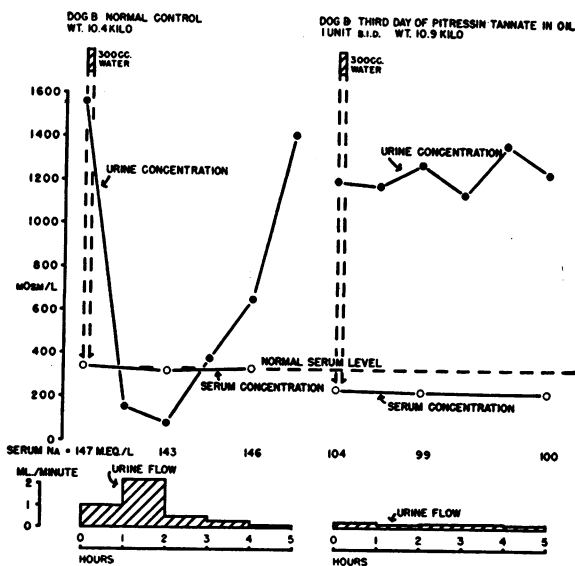


FIG. 6. THE EFFECT OF POSTERIOR PITUITARY EXTRACT ON WATER DIURESIS IN THE DOG

On the left is shown a normal control diuretic pattern. On the right is shown the abnormal antidiuretic pattern produced by 1.0 unit of Pitressin Tannate in Oil administered twice daily for two days with 1,000 ml. of water by stomach tube daily. The serum was found to be very dilute but the urine concentrated following Pitressin administration and water ingestion produced no diuretic response.

Furthermore, a dose of water given to such a depleted subject was noted to produce a prompt diuresis. Thus their subjects still responded, as does the normal, to protect the existing level of serum solute concentration. However, the drop in serum total solute concentration they produced was only some 9 and 13 mOsm/L in two instances.

Our data clearly indicate that in some cases exhibiting depression of serum total solute concentration of 40 to 50 mOsm/L below the normal a diuresis or dilution of urine may not occur in response to water administration. Serum solute concentration in these patients is thus not promptly protected from further dilution. In cardiac patients showing more moderate reductions of serum sodium and solute concentration (serum sodium concentration circa 130–135 mEq/L and total solute concentrations of 290–300 mOsm/L) an intermediate diuretic response was frequently observed. Such patients had a delayed diuresis with hypotonic urine occurring only five or more hours following the water ingestion. This intermediate response was also seen in patients with Addison's disease who were receiving inadequate therapy with cortisone or desoxycorticosterone and in our dogs when the depletion by intraperitoneal dialysis was less severe.

Obviously a delay in the rate of water absorption from the gastrointestinal tract could account for absence of diuresis and dilution of the urine. The observed dilution of serum total solute concentration is proof of absorption of the ingested water. Early in this study 3 liters of water were given as the test water load to a patient with untreated Addison's disease. The severe water intoxication with coma that ensued was convincing evidence that absorption of water from the gut did in fact occur. With administration of the major portion of the water load intravenously to one case of Addison's disease and one of the cardiac subjects, the abnormal antidiuretic pattern was not altered.

Because of the preeminence of sodium in determining serum total solute concentration, excretion of urine which is hypertonic but low in sodium concentration could correct the extracellular fluid hypotonicity. The concentrated urine of the edematous subjects and salt depleted dogs was in fact very low in sodium concentration but was of in-

sufficient volume to restore serum tonicity to the normal level.

It was difficult to distinguish in the normal but depleted dog and in the untreated patient with Addison's disease what effects were solely the result of altered renal hemodynamics secondary to insufficiency of extracellular fluid volume. Thus the profound dehydration in the dogs, though not associated with shock, may be expected to reduce renal blood flow and glomerular filtration rate. How much of the failure of diuresis and the persistence of hypertonic urines can be attributed to the decreased glomerular filtration rate which must of necessity accompany depletion of extracellular fluid volume is obviously of importance to this problem.

A direct answer to this question is not currently available. However, the patients with congestive failure demonstrating this abnormal antidiuretic pattern still had excessive extracellular fluid volumes as evidenced by the clinical presence of edema. They frequently had normal concentrations of blood urea nitrogen suggesting that glomerular filtration rates were not markedly reduced. Furthermore, in one 31 year old female with severe rheumatic heart disease and intractable congestive failure the inulin clearance was found to be 106 ml./min./1.73 m² (10) or some 88% of normal mean. This clearance value was obtained two hours following the ingestion of 1,000 ml. of water when the serum sodium concentration was 120 mEq/L, the rate of urine flow less than 1.0 ml./min. and the urine concentrated (956, 910, and 904 mOsm/L for the three 30-minute periods, respectively). On the other hand, one patient with posterior and anterior pituitary insufficiency, to be reported (8), who was never observed spontaneously to produce a hypertonic urine even with severe dehydration (with serum sodium concentrations as high as 173 mEq/L), was found to have an inulin clearance of 63 ml./min./1.73 m² (10) or some 53% of normal mean. This clearance was obtained with no preceding hydration at a time when her serum sodium was 151 mEq/L, her urine flow 6.2, 5.7, and 6.2 ml./min. with urine concentrations of 141, 148, and 148 mOsm/L for the three clearance periods, respectively. These observations of a nearly normal glomerular filtration rate in one patient exhibiting the abnormal antidiuretic pattern and a distinctly reduced fil-

tration rate in another patient, who characteristically had a very dilute urine, make it seem improbable at the present time that reduction in glomerular filtration rate is alone responsible for the abnormal antidiuretic pattern described. Somewhat in support of this is the recent report by Holmes and Cizek (11) that some of their dogs, depleted of extracellular fluid electrolyte by osmotic diuresis with sucrose, failed to have a prompt water diuresis following water administration, but showed no reduction in glomerular filtration rate. The osmotic diuretic used by these workers, however, admittedly may produce renal damage. Clearly, more data will be necessary to settle this crucial point.

This abnormal pattern of antidiuresis, characterized by a dilute extracellular fluid but a concentrated urine with failure of diuresis or dilution of the urine following water administration, suggested abnormal activity of the neurohypophyseal antidiuretic mechanism. This pattern was reproduced readily by injections of posterior pituitary extract into normal dogs and man. It is the antithesis of what one sees in posterior pituitary insufficiency during water deprivation (1), namely, a concentrated extracellular fluid but a dilute urine. In the present situation body water is unduly conserved while with posterior pituitary insufficiency it is wasted. The demonstration of antidiuretic activity in the serum perhaps also supports this view although nothing can be said regarding the specificity of the assay for antidiuretic material of posterior pituitary origin. At the present time we are attempting to repeat the salt depletion experiment on a post-hypophysectomized dog to test whether loss of neurohypophyseal function will abolish the abnormal pattern described.

In 1939, Winter, Ingram and Gross (12) showed that adrenalectomized cats had a drop in serum sodium and chloride concentrations while diabetes insipidus cats when adrenalectomized did not develop a reduction in these concentrations. Treatment of the latter group with sufficient Pitressin to control the polyuria caused a return of low serum sodium and chloride concentrations. Their work seems to show conclusively that the abnormal antidiuretic pattern, at least in the subject with adrenal insufficiency, is dependent upon an intact posterior pituitary gland. As the pattern is so similar in other conditions associated with a dilute

extracellular fluid (excluding the anuric subject over-loaded with water), it is strongly suspected that over-activity of the posterior pituitary antidiuretic mechanism is common to them all.

It is common clinical practice to consider a low serum sodium concentration as evidence of sodium depletion. As indicated in the introduction to this paper, however, present physiological concept that posterior pituitary activity is regulated by changes in tonicity of extracellular fluid makes the very occurrence of a low serum sodium concentration difficult to explain. As sodium is the major osmotically active constituent of the extracellular fluid its loss could be masked, so far as concentration change is concerned, by rejection of a proportional amount of water by the kidney. In view of the large volume of glomerular filtrate, even in the sodium depleted subject, the occurrence of dilution of extracellular fluid sodium can only mean that something has influenced the renal tubules to reabsorb not 145 mEq of sodium with each liter of water, as normally from the glomerular filtrate, but rather 120 or so mEq per liter of water reabsorbed. Is this influence, which causes a relatively greater than normal reabsorption of water than of sodium by the renal tubules of the sodium depleted subject, antidiuretic hormone?

The water content of the body is the balance between the intake of water and its precursors in the diet, on the one hand, and the continuous sensible and insensible loss of water from the body on the other. A cessation or a reduction of water intake below the minimal obligatory volume of urine and insensible loss of water would soon correct a dilution of the extracellular fluid. The desire for water, which caused some of these patients with dilute extracellular fluids to complain bitterly when attempts were made clinically to correct their state of dilution by water restriction, attested to the fact that the "thirst center," as well as the kidney, was cooperating to maintain the hypotonic state of the extracellular fluid. This observation suggests that there are other stimuli for thirst than an increase in tonicity of the extracellular or intracellular fluid (13).

Our findings are in accord with those of Darrow and Yannet in dogs (5) and McCance and Widdowson in man (14), who noted that experimental salt deficiency in both species produced an impaired water diuresis. We do not find ex-

planation in our more acute salt depletion studies for the polyuria and polydipsia reported by Cizek and his colleagues (15) for chronic salt depletion studies in dogs. Our results are in general confirmatory of those of Martin, Herrlich and Fazeikas (16) who reported finding antidiuretic activity in the urine of adrenalectomized cats and salt depleted cats. In the latter group the urinary antidiuretic activity was said to be inversely proportional to the serum sodium level.

The question arises as to whether one type of stimulus could be sufficient to activate supraoptico-hypophyseal function and liberation of antidiuretic hormone both in the normal and the salt depleted animal. Verney's work is convincing that tonicity change of the serum constitutes the effective stimulus in the normal animal. The results presented here seem to exclude tonicity change as a possible stimulus to antidiuretic activity in the salt depleted animal, and some function of change in extracellular fluid volume has been considered the effective stimulus under these circumstances.⁴ Thus "volume-receptors" are postulated much as Verney has postulated "osmoreceptors." Physiologically these two receptors might conceivably

⁴ There has been recent work showing that in the adrenalectomized animal the rate at which the liver destroys the antidiuretic activity of posterior pituitary extracts is considerably slower than in the normal (17, 18). This finding is cited as the explanation for the inability of the adrenalectomized animal to have a water diuresis (19). It would seem that one encounters logical difficulties in attempting to explain the entire defect in water excretion on this basis. Regardless how slow inactivation of antidiuretic hormone might be, the dilution of extracellular fluid in the subject with Addison's disease should prevent further release of antidiuretic hormone. When all circulating antidiuretic hormone finally would be inactivated a water diuresis should then occur and continue until serum total solute concentration returns to normal. This is not what happens as serum total solute concentration persists at low levels. Hence it seems that there is required an over-production of antidiuretic hormone as well as the demonstrated delayed inactivation to explain the entire disturbance in water excretion. Admittedly a delayed inactivation of antidiuretic hormone in combination with a setting of the "osmoreceptors" to preserve some level of total solute concentration lower than normal could also explain the results observed in the patients with Addison's disease. Until more data on this point are available which will permit a physiological basis for subdividing the conditions associated with hypotonicity, the authors include them in one group.

have been identical. In the normal animal loss of water without salt from the extracellular fluid would result in a decrease in volume of that compartment as well as an increase in its concentration. In the salt depleted animal loss of salt and of water would likewise reduce extracellular fluid volume. A decrease in volume then might be the effective stimulus in both instances. However, the clear-cut experiments of Verney in which he infused hypertonic solutions into the internal carotid arteries of hydrated dogs causing prompt antidiuresis definitely excludes such a unitary stimulus. It is most difficult to see how a further intravascular infusion in a hydrated animal can in any way be considered to cause a reduction of any part of the extracellular fluid compartment. Thus it seems that at the present we are left with two distinct but effective stimuli for prolonged supraoptico-hypophyseal activity,⁵ tonicity change and possibly volume change of some portion of the extracellular fluid compartment.⁶

Normally the total effective solute concentration of the extracellular fluid is jealously guarded. It is apparent, however, that a mechanism exists which effects conservation of water irrespective of serum solute levels. Teleologically, it seems that with depletion of extracellular fluid electrolyte and the resulting threat of death from vascular insufficiency, the tonicity of extracellular fluids is sacrificed and water is retained in an attempt to ex-

⁵ Other stimuli have been shown effectively to cause release of antidiuretic hormone and inhibition of water diuresis. Emotion (20, 21), pain (22, 3), exercise (23, 20), quiet standing (24, 25) and syncope (26) all inhibit water diuresis presumably by causing release of antidiuretic hormone. The short duration of the antidiuresis produced by these stimuli place them into quite a different category than the protracted antidiuresis we are discussing. The antidiuresis of quiet standing and syncope, however, may operate through the same volume-receptor mechanism postulated here (or presso-receptor of Brun, Knudsen and Raaschou [24]).

⁶ It is quite possible that the sequence of events leading from extracellular fluid volume insufficiency to the presumed increased activity of the neurohypophysis is not nearly as direct as here indicated. The volume insufficiency may impair circulation in certain organs so as to alter metabolism causing local formation of substances that exhibit antidiuretic activity through release of posterior pituitary hormone. The demonstration by Shorr and his associates (27) of the antidiuretic action of the hepatic vasodepressor ferritin (VDM) constitutes an example of one such possibility.

pand volume. This disparity between salt and water retention which produces a hypotonic serum can probably only arise under the artificial conditions of a low salt intake but an *ad lib* water intake. If salt is made available, the expansion or reexpansion of extracellular fluid volume will be accomplished with preservation of isotonicity. The artificial conditions have been utilized simply to separate out this different mechanism for water retention which is thus shown to operate irrespective of extracellular fluid solute concentration.

That the edematous cardiac subject apparently utilizes the same mechanism grossly to over-expand extracellular fluid volume that the normal uses to correct a deficit, adds perhaps further interest to this phenomenon. It indicates clearly that it is not change in total extracellular fluid volume, but more likely insufficiency of some critical portion, probably intravascular,⁷ which sets off this volume-expanding antidiuretic mechanism. Something about the failing myocardium produces perhaps a volume insufficiency in this critical zone which is met by a retention of water and of salt (if the latter is available in the intake) with a generalized expansion of extracellular fluid volume. Such a generalized expansion of extracellular fluid volume in a salt depleted but otherwise normal animal might sufficiently replenish vascular volume so as to correct the insufficiency in this critical zone. With a severely damaged myocardium the retention of fluid and electrolyte may not accomplish this end and the stimulus for further expansion would then persist with massive edema formation as the end result. The low serum oncotic pressures associated with edema of nephrotic syndrome and cirrhosis may in some way act to set off this same trigger mechanism.

In congestive heart failure venous pressures are increased while in the animal depleted of extracellular fluid electrolyte with resultant reduced vascular volume, venous pressures seem to be reduced. If each is utilizing the same pathways for expanding extracellular fluid volume, then it appears unlikely that a high venous pressure is in

⁷ From studies of the effect of plasma volume increase in normal subjects produced by infusions of albumin solutions Welt and Orloff (28) have recently hypothesized that uncomplicated expansion of the plasma volume initiates a diuresis of water by suppressing the activity of the posterior pituitary gland.

itself the effective stimulus for edema formation and attention should perhaps be concentrated on looking for local insufficiencies on the arterial side.

Borst has stated (29) that acute hemorrhage (which by definition is loss of isotonic fluid) results in a concentrated urine low in chloride concentration. This would seem to be another instance of a volume conserving antidiuretic mechanism.

As shown in the tables of results the sodium depleted animal and the edematous cardiac subjects were maximally conserving sodium as indicated by its very low concentrations in the urines. Expansion of extracellular fluid volume would occur with sodium as well as water retention if the former were available in the intake. Thus the response is to expand volume by retention of its two major constituents, salt and water. This study has dealt with only one phase of the process of water retention, but it seems that in edema formation both are occurring and the salt retention is the more important of the two, as the usual edematous subject with essentially normal concentrations of serum sodium can handle large water loads with little, if any, difficulty (30). Does the same "volume" stimulus which apparently activates posterior pituitary activity similarly influence adrenal cortical activity with resultant salt retention (31)? The low circulating eosinophile counts in our cardiac subjects is perhaps evidence for this.

SUMMARY AND CONCLUSIONS

It is shown that patients with inadequately treated Addison's disease, certain cases of congestive heart failure who develop low serum sodium concentrations during treatment of their edema, and normal dogs depleted of extracellular fluid electrolyte show an abnormality of water excretion. This consists of a dilution of the serum but, in spite of this, a concentrated urine and a failure to have a prompt water diuresis or dilution of the urine following administration of water. This antidiuretic pattern is reduplicated by continuous action of small amounts of posterior pituitary extract in normal dogs and man. It is considered at present that this abnormal antidiuretic pattern does represent a continued activity of the supraopticohypophyseal antidiuretic system in the

presence of a dilute extracellular fluid which normally would inhibit its activity. It is suggested that the stimulus for posterior pituitary activity in the subject depleted of extracellular fluid electrolyte is an insufficiency of some function of volume in a crucial portion of the extracellular fluid volume, possibly intravascular. The significance of finding this phenomenon in the edematous subject is discussed.

ACKNOWLEDGMENTS

The authors wish to acknowledge their gratitude to Dr. James Howard Means whose interest and support made possible this study and to thank Dr. J. D. Crawford who generously made available the use of his freezing point depression apparatus.

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