

Importance of Sodium Intake and Mineralocorticoid Hormone in the Impaired Water Excretion in Adrenal Insufficiency

R. C. UFFERMAN and R. W. SCHRIER

From the Department of Medicine and Cardiovascular Research Institute, University of California San Francisco, San Francisco, California 94122

ABSTRACT The response of trained, conscious dogs to an acute water load was studied before adrenalectomy and under five conditions of hormonal replacement and sodium intake after adrenalectomy. Before adrenalectomy, with the dogs drinking isotonic saline, the minimal urinary osmolality (U_{osm}) was 47 ± 7 (SEM) mOsm and free-water clearance (C_{H_2O}) was 8.6 ± 1 ml/min. These values were not different after adrenalectomy with or without deoxycorticosterone (DOCA) if the animals continued to drink saline and receive dexamethasone. Moreover, after adrenalectomy in the presence of saline drinking both dexamethasone and DOCA could be withdrawn for up to 4 days without impairment of diluting ability (U_{osm} , 54 ± 7 mOsm and C_{H_2O} , 7.3 ± 1 ml/min). In contrast, when the dogs drank tap water (Na intake 30 mEq/day), water loading in the absence of dexamethasone and DOCA was associated with a significantly higher U_{osm} (127 ± 28 mOsm) and lower C_{H_2O} (2.7 ± 0.3 ml/min). Replacing DOCA alone in the presence of this limited Na intake returned diluting ability to normal (U_{osm} 31 ± 7 mOsm, C_{H_2O} 7.7 ± 0.5 ml/min). Glomerular filtration rate for each animal was the same under each condition except for a significant diminution which occurred when dexamethasone and DOCA were withdrawn while the animals were on a 30 mEq sodium intake. In contrast to previous conclusions, the present results indicate that in the absence of adrenal hormones normal renal diluting ability may occur, indicating both maximal suppression of vasopressin release and maximal distal tubular impermeability to water. In the present study the diluting defect observed after adrenalectomy related to

negative sodium balance and could be overcome by either replacement with DOCA or a high intake of sodium alone.

INTRODUCTION

There is considerable evidence that adrenal insufficiency is associated with an impaired ability to attain a normal water diuresis (1-13). The mechanisms involved in this impairment of water excretion have not been clearly elucidated, however, two possible mechanisms have been proposed. One (3-8) is that, although the release of antidiuretic hormone (ADH)¹ from the hypothalamus in adrenal insufficiency is normally suppressed during water loading, the water impermeability of the distal nephron is incomplete in the absence of glucocorticoid hormone. In contrast, other authors (9-11) have suggested that the release of ADH is not suppressed normally during water loading in the presence of adrenal insufficiency and increased circulating levels of ADH account for the inability to excrete water normally. Utilization of the bioassay of ADH in adrenal insufficiency has not distinguished between these possible mechanisms, since evidence has been presented that ADH levels are both increased (9) and undetectable (8) in adrenal insufficiency. Green, Harrington, and Valtin (13) recently examined this problem in adrenalectomized rats with hereditary hypothalamic diabetes insipidus which thereby avoids the necessity for assaying ADH. These investigators found a persistent defect in water excretion in these adrenalectomized rats with a congenital absence of ADH and this defect could be completely reversed only by the simultaneous administration of both glucocorticoid and

Dr. Schrier is an Established Investigator of the American Heart Association. Dr. Ufferman was a postdoctoral fellow supported by Training Grant AM 05670 from the National Institutes of Health.

Received for publication 22 October 1971 and in revised form 27 December 1971.

¹*Abbreviations used in this paper:* ADH, antidiuretic hormone; C_{H_2O} , free-water clearance; C_{osm} , osmolar clearance; DOCA, deoxycorticosterone acetate; GFR, glomerular filtration rate; U_{osm} , urinary osmolality.

mineralocorticoid hormones. Although renal hemodynamics were not measured, the authors suggested that the effect of glucocorticoid hormone on water excretion could be due to a combination of an effect on renal hemodynamics and a direct effect of the hormone on permeability to water of the renal tubular epithelium.

The present study was undertaken to elucidate further the mechanisms involved in the impaired water excretion in adrenal insufficiency. The studies were performed in conscious, trained dogs and the same animals served as their own control both before and after adrenalectomy. The results demonstrate that the adrenalectomized conscious dog drinking isotonic saline retains a normal renal diluting capacity, as judged by minimal urinary osmolality and free-water clearance, in the absence of both glucocorticoid and mineralocorticoid hormones for periods up to 4 days. A defect in renal diluting capacity did occur, however, if both hormones were withdrawn and the animal's sodium intake was restricted. This defect in renal diluting capacity could be corrected within days by mineralocorticoid replacement alone. On the basis of these findings, we conclude therefore that glucocorticoid is not necessary for either maximal suppression of ADH or maximal water impermeability of the renal tubular epithelium during acute water loading. In the circumstances of the present study, the defect in water excretion in the adrenalectomized dog was related primarily to sodium balance and could be overcome by either mineralocorticoid or a high intake of sodium.

METHODS

29 studies were performed during water loading in five trained, conscious, female, mongrel dogs weighing 18.6–25.4 kg. 1–2 wk before the water-loading studies the dogs ingested a potassium-free diet containing 30 or 70 mEq of sodium (Hartroft Formulation, General Biochemicals, Chagrin Falls, Ohio). 3 g of potassium chloride (KCl) was added to their daily diet except on the two days before each study. The composition of the diet was otherwise the same for all of the studies. The animals were maintained on this diet and offered either isotonic saline or tap water to drink for at least 1 wk before each acute water-loading study. After the animal's weight stabilized a preadrenalectomy water-loading study was performed in the following manner. A urethral catheter was inserted to allow collection of urine. Polyethylene catheters were placed in two leg veins. Into one of these catheters an isotonic saline infusion (0.5 ml/min) containing sufficient inulin for clearance measurements was started at least 1 hr before beginning urine and blood collections. A water load of 2.5% glucose in water was infused through the same catheter at 20 ml/min for 60 min. 20 min after completion of this water load, infusion of 2.5% glucose in water was restarted and continued at 10 ml/min throughout the remainder of the experiment. Collections were started 100 min after beginning the infusion of 2.5% glucose in water. Urine was collected every 10 min and blood specimens were withdrawn through an indwelling venous catheter at the

midpoint of alternate periods. The experiments consisted of 7 or 14 10-min urine collections. This same protocol was used in all of the experiments, both pre- and postadrenalectomy. After the first study in each animal a bilateral adrenalectomy was performed through a midline abdominal incision under pentobarbital anesthesia. On the morning of surgery and daily thereafter the animals were given 0.8 mg of dexamethasone intramuscularly (i.m.). For the first three postoperative days the animals also received 50 mg of hydrocortisone i.m. daily. The animals were allowed to recover from the effects of surgery for at least 2–3 wk before study. Completeness of adrenalectomy was assessed by measuring plasma cortisol levels at a time when the dogs had not received replacement steroid hormones for 72 hr and again after 3 consecutive days of 40 U of adrenocorticotropin hormone gel i.m.

The experiments were divided into six groups as follows. Each animal served as its own control.

Group I. Water loading before adrenalectomy with the animals on a 70 mEq sodium diet and drinking isotonic saline.

Group II. Water loading after adrenalectomy with the animals on 70 mEq sodium diet and drinking isotonic saline. The only steroid replacement given was 0.8 mg of dexamethasone i.m. daily.

Group III. Water loading after adrenalectomy with the animals on a 70 mEq sodium diet and drinking isotonic saline. Daily replacement with dexamethasone (0.8 mg i.m.) was given as well as 2–5 mg of deoxycorticosterone acetate (DOCA) i.m. on the morning of the water-loading experiment.

Group IV. Water loading after adrenalectomy with the animals on a 70 mEq sodium diet and drinking isotonic saline. All steroid replacement was withdrawn for a period of 50–100 hr before the study.

Group V. Water loading after adrenalectomy with the animals on a 30 mEq sodium diet and drinking tap water. All steroid replacement was withdrawn for a period of 50–100 hr before the study.

Group VI. Water loading after adrenalectomy with the animals on a 30 mEq sodium intake and drinking tap water. Dexamethasone therapy was withdrawn for 50–100 hr before the study. DOCA (2 mg i.m.) was administered for at least 7 days before and including the day of the acute water load.

The methods of analysis for inulin, osmolality, sodium, and potassium have been referred to elsewhere (14). The clearance of inulin and rates of electrolyte excretion were calculated in the conventional manner. The plasma cortisol levels were measured by the fluorometric technique (15).

RESULTS

The results of acute water loading before and after adrenalectomy in an animal drinking isotonic saline are shown in Fig. 1. In the preadrenalectomy study and in the three postadrenalectomy studies the urinary osmolalities (U_{osm}) achieved during the acute water load were very similar. The mean U_{osm} achieved was 69 mOsm before adrenalectomy (group I), 75 mOsm after adrenalectomy with chronic dexamethasone replacement (group II), 63 mOsm after adrenalectomy with chronic dexamethasone replacement and DOCA on the day of study (group III), and 74 mOsm after adrenalectomy with no

steroid replacement for 4 days (group IV). Thus, in the presence of a liberal sodium intake the U_{osm} achieved during the acute water load in this animal was not altered by adrenalectomy, independent of adrenal steroid replacement. The rate of free-water clearance (C_{H_2O}) was also comparable in all of these same circumstances (Fig. 1). The mean C_{H_2O} in this animal was 6.6 ml/min in the preadrenalectomy study (group I), 7.6 ml/min in the group II study, 7.3 ml/min in the group III study, and 7.1 ml/min in the group IV study. The comparable U_{osm} and C_{H_2O} during these acute water-loading studies was also associated with a similar GFR. Before adrenalectomy the mean GFR was 64 ml/min (group I), while in the three postadrenalectomy studies (groups II-IV) the mean GFR was 64, 66, and 65 ml/min, respectively.

The results in this animal are representative of the results in the other animals. The U_{osm} in the preadrenalectomy and three postadrenalectomy studies for all animals while drinking saline are shown in Fig. 2. The U_{osm} attained during the water-loading studies after adrenalectomy (groups II-IV) was similar in all

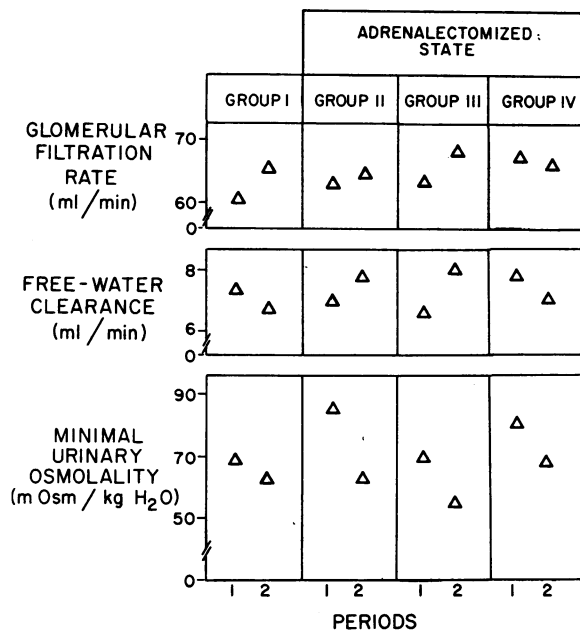


FIGURE 1 Responses to an acute water load before and after adrenalectomy in a dog drinking isotonic saline. Each value is the mean of seven consecutive 10-min urine collections. The GFR, free-water clearance, and urinary osmolality were comparable in this animal in the preadrenalectomy and three postadrenalectomy studies. Steroid replacement with daily dexamethasone alone (group II), daily dexamethasone plus DOCA on the day of study (group III), or complete withdrawal of steroid replacement (group IV) did not alter this animal's response to the acute water load as compared to the preadrenalectomy study (group I).

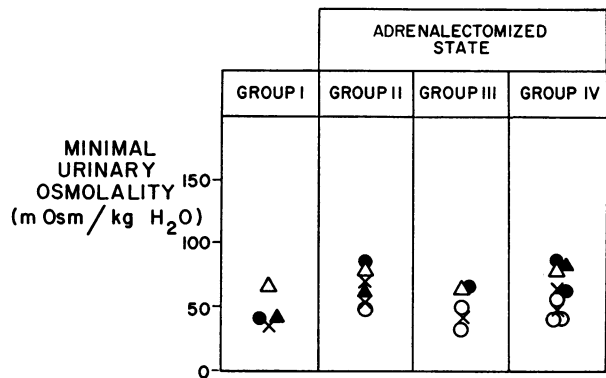


FIGURE 2 Response of urinary osmolality to an acute water load before and after adrenalectomy. Each value is the mean of 14 consecutive 10-min urine collections. In an occasional dog only 7 rather than 14 10-min urine collections were made because of hyperexcitability of the animal. Dogs 7698, 7720, 8511, 7772, and 7840 are denoted by the following respective symbols: Δ , \times , \circ , \blacktriangle , and \bullet . In some animals more than one study was performed in each group. In dog 8511 no preadrenalectomy study was performed. In dog 7772 no group III, V, or VI studies were performed because the animal escaped from the vivarium and died of nontraumatic causes. In none of these animals drinking isotonic saline was the urinary osmolality altered either by adrenalectomy or by adrenal steroid replacement in the adrenalectomized state.

five animals to the U_{osm} observed during the preadrenalectomy study (group I). Values for C_{H_2O} for all of the animals are shown in Fig. 3. As with U_{osm} , C_{H_2O} was not different for any of the animals in the postadrenal-

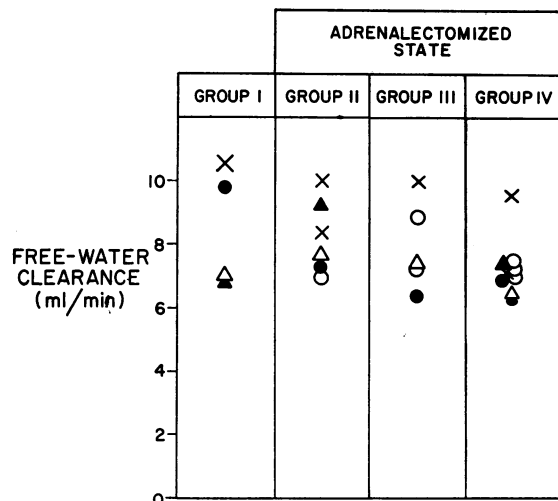


FIGURE 3 Response of the free-water clearance to an acute water load before and after adrenalectomy. The symbols are the same as those used in Fig. 2. C_{H_2O} was not altered in these animals drinking isotonic saline by adrenalectomy or adrenal steroid replacement or withdrawal after adrenalectomy.

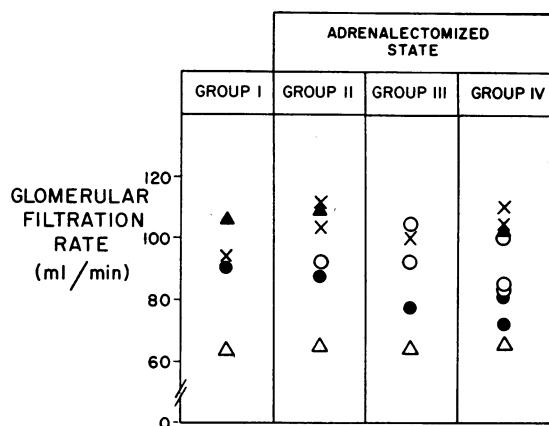


FIGURE 4 Response of GFR to an acute water load before and after adrenalectomy. The symbols are the same as those used in Fig. 2. In none of these animals drinking isotonic saline did adrenalectomy or adrenal steroid replacement or withdrawal in the adrenalectomized state alter GFR.

ectomy studies (groups II-IV) as compared to the preadrenalectomy study (group I) when the animals were drinking isotonic saline. GFR for each animal was also comparable for all four groups of studies (Fig. 4). The mean rate of fractional sodium reabsorption during the water-loading studies performed before adrenalectomy (group I) was 99.7%. The same mean fractional sodium reabsorption of 99.7% was present after adrenalectomy with replacement of both dexamethasone and DOCA (group III). In the studies in the adrenalectomized animals not receiving DOCA the mean fractional sodium reabsorption diminished to 98.7% in group II and 99.0% in group III experiments. In parallel with these changes in fractional sodium reabsorption the mean osmolar clearance (C_{osm}) was 1.7 and 1.8 ml/min in groups I and III, respectively and was 2.5 and 2.2 ml/min in groups II and IV, respectively. The body weight of the animals

during the postadrenalectomy studies was either equal to or less than their weight during the preadrenalectomy study except in one dog (7720) in which a 2% increase in body weight from the preadrenalectomy state was observed.

In contrast to the results without steroid hormone replacement while the animals drank saline (group IV), withdrawal of adrenal steroids for up to 4 days when the animals were on a 30 mEq sodium intake and drinking tap water (group V) was associated with definite impairment in water excretion in each animal. However, when these same animals were maintained on the same 30 mEq sodium intake and given only mineralocorticoid hormone for 7 days (group VI) the U_{osm} , C_{H_2O} , and GFR were comparable to those values observed in all of the studies with the animals drinking isotonic saline (groups I-IV). A comparison of the results obtained in the Groups IV-VI studies is shown in Fig. 5. The results which are illustrated in Fig. 5 demonstrate that the 30 mEq sodium intake (group V) was associated with an increase in U_{osm} and a decrease in C_{H_2O} as compared to the values obtained when the same animals were drinking isotonic saline (group IV). No adrenal steroids were administered to the animals in either the group IV or V studies. In each instance the GFR was lower when the animal was on a 30 mEq sodium intake rather than drinking isotonic saline. When the animals were maintained on the 30 mEq sodium intake and treated with DOCA (group VI) for 7 days the U_{osm} and C_{H_2O} were comparable to those values obtained with the animals drinking isotonic saline. In three of the four animals the GFR also increased in association with the chronic DOCA administration. The mean fractional sodium reabsorption and C_{osm} were 98.7% and 2.2 ml/min in group V and 99.7% and 1.0 ml/min in the group VI studies.

The importance of sodium balance in the capacity of the adrenalectomized dog to excrete water was not only indicated by the acute water-loading studies but also by

TABLE I
Effect of Sodium Intake and Chronic DOCA Therapy on Plasma Sodium Concentration and Weight in Adrenalectomized Dogs

Dog No.	Group IV High sodium intake with no steroid replacement		Group V 30 mEq Sodium intake with no steroid replacement		Group VI 30 mEq Sodium intake with chronic DOCA replacement	
	Plasma sodium concentration	Body weight	Plasma sodium concentration	Δ Body weight	Plasma sodium concentration	Δ Body weight
	mEq/liter	lb.	mEq/liter	lb.	mEq/liter	lb.
7698	141	46.0	124	-2.0	154	+0.5
8511	139	50.0	127	-2.0	156	+1.0
7840	142	50.0	122	-1.5	152	+1.0
7720	140	56.5	130	-2.0	151	+2.0

the more chronic effect on plasma sodium concentration and body weight (Table I).³ The restricted sodium intake in the group V studies was associated with weight loss and hyponatremia in each animal, effects which were reversible with the administration of DOCA. Evidence for the completeness of the adrenalectomy is shown in Table II. There were no detectable levels of plasma cortisol either under basal conditions or after stimulation with adrenocorticotropin hormone.

DISCUSSION

The present investigation was undertaken to explore further the mechanism(s) involved in the abnormality of water excretion associated with adrenal insufficiency. Several aspects of the experimental design of the present study are different from many previous studies of this problem. In all of the present experiments each animal served as its own control, both before and after adrenalectomy. In addition, a further control observation was obtained during replacement of both glucocorticoid and mineralocorticoid hormone in the adrenalectomized state. Another aspect of the experimental design involved the use of physiological amounts of glucocorticoid hormone replacement rather than the larger doses of glucocorticoid hormone replacement which have been used previously to reverse the defect in water excretion in adrenal insufficiency (1-13).³ In an effort to avoid any secondary effects related to negative sodium balance and depletion of extracellular fluid volume, the initial group of studies were performed while the animals were offered a high sodium intake as saline drinking water. Also, in the present studies the withdrawal of glucocorticoids was for a period of time (50-100 hr) of sufficient duration to insure absence of glucocorticoid activity,⁴ but of short enough duration to avoid any profound effects of chronic glucocorticoid deficiency on systemic hemodynamics. In addition to evaluating the effect of glucocorticoid replacement on the renal excretion of water during the state of adrenal insufficiency, the role of mineralocorticoid was also examined. In all of these circumstances, the effect of adrenal insufficiency and hormone replacement on glomerular filtration rate was evaluated.

³The modest hypernatremia (151-156 mEq/liter) observed during the DOCA treatment (group VI) may be similar to the hypernatremia which occurs in primary hyperaldosteronism, the etiology of which is not well understood.

⁴Although Green et al. (13) treated some of their rats with 0.1 mg of prednisone, a smaller dose by body weight than most previous studies, this amount would approximate 28 mg of prednisone for a 70 kg man and thus probably deliver more glucocorticoid activity than normally produced by these rats.

⁴The half-life of dexamethasone is 200 min (16).

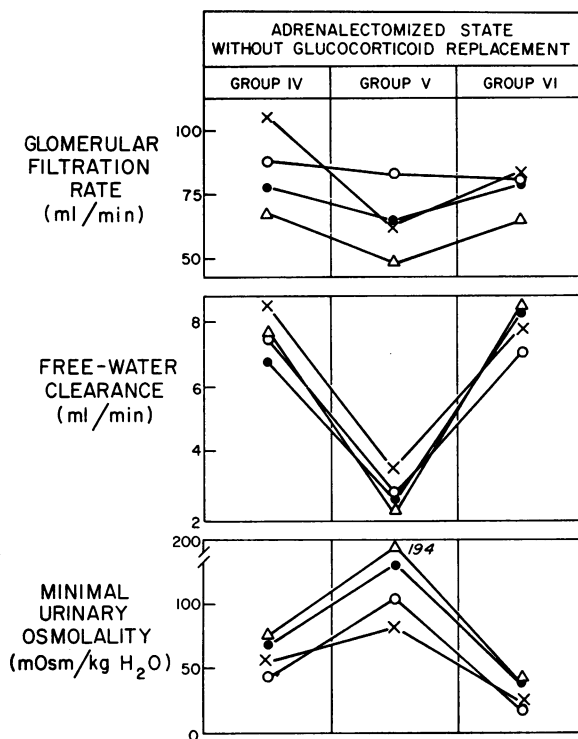


FIGURE 5 Effect of sodium intake and chronic DOCA treatment on GFR, free-water clearance, and urinary osmolality in the adrenalectomized dogs not receiving glucocorticoid replacement. The symbols are the same as those used in Fig. 2. A lower GFR and free-water clearance and a higher urinary osmolality was observed when the animal's sodium intake was 30 mEq/day (group V, middle panel) as compared to the same animals drinking isotonic saline (group IV, left panel). Administration of DOCA for 7 days with continued 30 mEq sodium intake was associated with correction of these abnormalities (group VI, right panel).

Under these experimental conditions the results of the present investigation demonstrate that on a high sodium intake the renal diluting capacity is comparable when the same dog is studied before adrenalectomy and after

TABLE II
Plasma Cortisol Levels in Adrenalectomized Dogs
without Steroid Replacement

Dog. No.	Plasma cortisol 72 hr after no steroid replace- ment	Plasma cortisol after daily stimu- lation with 40 U of ACTH gel for 3 days
	$\mu\text{g}/100\text{ ml}$	$\mu\text{g}/100\text{ ml}$
7698	<2	<2
7720	<2	<2
8511	<2	<2
7772	<2	No determination
7840	<2	<2

adrenalectomy with glucocorticoid replacement. In addition, the administration of mineralocorticoid hormone (DOCA) on the morning of study did not alter the renal diluting capacity of these adrenalectomized dogs offered a high sodium intake. The most important finding, however, was that after adrenalectomy when the animals were drinking isotonic saline, renal diluting capacity was not impaired even when both mineralocorticoid and glucocorticoid hormone replacement were withheld for up to 4 days (Figs. 1-3). This finding is of particular importance in view of the two main proposed mechanisms for the impaired water excretion in adrenal insufficiency. Many investigators (1-13) have suggested that the presence of glucocorticoid hormone is necessary for normal renal diluting capacity. This importance of glucocorticoid hormone has been proposed by some authors to be related to a direct action of the hormone on the water permeability of the tubular epithelium of the collecting duct (3-8), while other authors have suggested that the presence of glucocorticoid hormone is necessary for the maximal suppression of vasopressin release (9-11). The present results do not support either of these hypotheses, since in the presence of a high intake of sodium, glucocorticoid hormone was not necessary for a normal response to the water load. The mean osmolality (57 mOsm) achieved in the present adrenalectomized animals drinking isotonic saline and not receiving adrenal hormones for 2-4 days was sufficiently low to indicate suppression of vasopressin release and water impermeability of the collecting duct epithelium. Moreover, this level of urinary osmolality was similar to the level achieved in the same animals before adrenalectomy and after adrenalectomy with glucocorticoid replacement. In addition, withdrawal of glucocorticoid hormone replacement in these adrenalectomized animals drinking isotonic saline was also associated with rates of free-water clearance and glomerular filtration which were not different from those obtained in the same animals before adrenalectomy and after adrenalectomy with adrenal steroid replacement.

In contrast to the normal diluting capacity observed with the animals drinking isotonic saline, when these same adrenalectomized animals were on a 30 mEq sodium intake and receiving no adrenal steroid replacement a definite impairment of renal water excretion occurred. In this circumstance, urinary osmolality was higher and free-water clearance was lower when compared to the values observed under the various conditions with the animals drinking isotonic saline (groups I-IV). In addition to the impaired excretion of an acute water load, weight loss and the development of hyponatremia were also observed when these adrenalectomized animals received a 30 mEq sodium intake and no adrenal steroid replacement. These findings suggest that the level of so-

dium intake was of crucial importance in the pathogenesis of the defect in water excretion after adrenalectomy. Also, it seemed likely that the effect of mineralocorticoid deficiency on sodium balance was of primary importance in this impairment in the renal excretion of water. Studies therefore were performed in which the animals were continued on the same 30 mEq sodium diet but replaced for 7 days with exogenous mineralocorticoid (DOCA) but not glucocorticoid therapy. This mineralocorticoid therapy was associated with correction of the impaired response to the acute water load, as well as a reversal of the weight loss and hyponatremia.

Since during the group V studies the animals were able to dilute their urine during the acute water load, albeit not maximally, this degree of impairment of diluting mechanism would not explain the chronic hyponatremia which developed during this group of studies. Urinary dilution, however, may be more pronounced when the same water load is administered acutely over 1 hr period as compared to chronic ingestion over several hours. Thus, any defect in urinary dilution observed during an acute water load may not be directly applicable to explain the development of chronic hyponatremia. Even more important, since the chronic hyponatremia in these group V studies was associated with weight loss and was prevented by a high sodium intake or treatment with DOCA, negative sodium balance rather than retention of water appeared to be the initiating factor in the development of the hyponatremia.

Taken together, the present results provide evidence that the defect of urinary dilution in adrenal insufficiency is related, at least in part, to a deficit of sodium balance. In this regard, Gill, Gann, and Bartter (17) have previously demonstrated that either acute or chronic volume expansion with isotonic saline improves renal diluting capacity in patients with adrenal insufficiency. Other authors (7, 18), however, have disputed the possibility that significant hypovolemia is involved in the impaired renal excretion of water with adrenal insufficiency. The present results support the suggestion of Gill et al. (17) that depletion of extracellular fluid volume is an important factor in the impaired renal excretion of water in adrenal insufficiency. In contrast to these previous results (17), however, in the present study significant expansion of the extracellular fluid volume was not a prerequisite for the demonstration of normal diluting capacity in the adrenal insufficient state. Although daily sodium balances were not performed, the rates of fractional sodium reabsorption, osmolar clearances, and body weight measurements were such as to exclude excessive expansion of extracellular fluid volume. Thus, the objection that excessive expansion of the extracellular fluid volume may have overcome a defect in diluting capacity which was unrelated to mineralocorticoid de-

iciency and sodium balance, although relevant to the interpretation of the results of Gill et al. (17), does not seem to be applicable to the present results.

The concomitant decrease in glomerular filtration rate which occurred during the period of restricted sodium intake could have accounted, at least partially, for the impaired excretion of water in these adrenalectomized animals. Such a conclusion is reasonable since a similar impairment of diluting capacity has been demonstrated when glomerular filtration rate is diminished by constriction of the aorta (19) or renal artery (20). This interpretation is compatible with the findings of Green et al. (13) which indicated that factors other than ADH are involved in the impaired water excretion associated with adrenal insufficiency. In the present study, however, some increase in circulating levels of ADH cannot be excluded as a contributing factor in mediating the effect of sodium balance on water excretion. Support that an increased level of ADH may indeed be responsible, at least in part, for the effect of sodium balance on water excretion in adrenal insufficiency is provided by the recent results of Share and Travis (21). In this regard, the recent findings of Schrier, Lieberman, and Ufferman (22) raise the possibility that changes in autonomic neural tone may be the primary pathway whereby alterations in sodium balance and body fluid volume influence ADH release. Somewhat against the possibility for a role of ADH in the present study, however, was the finding that the urine achieved a significant degree of hypotonicity, even in the studies in which an impairment in water excretion was demonstrable (group V). Hypotonic urine, however, may occur in the dog in the presence of submaximal levels of ADH (23). Although this effect is most frequently observed at high rates of solute excretion, it may occur at solute excretion rates comparable to those observed in the present dogs (23).

The results of the present investigation must be considered on the background of the previous suggestions that the impaired renal diluting capacity characteristic of adrenal insufficiency is due to glucocorticoid deficiency and is mediated either by sustained release of ADH (9, 10) or by a failure to achieve maximal impermeability to water of the distal nephron (3-8). Of primary importance is the fact that the duration of glucocorticoid withdrawal in most previous studies has been in excess of the period of glucocorticoid deficiency in the present studies. Since more prolonged glucocorticoid deficiency may be associated with substantial cardiovascular effects (24-26), any observed impairment in water excretion under these conditions could be related either to a direct effect of glucocorticoid deficiency on ADH release or renal tubular water impermeability, or alternatively to any secondary effects of glucocorticoid deficiency on sys-

temic hemodynamics. Such an effect on systemic hemodynamics could affect water excretion by diminishing renal hemodynamics and/or stimulating the release of ADH. Although the defect in water excretion in adrenal insufficiency previously has been shown to be improved by replacement of glucocorticoid hormone, supraphysiological doses of the hormone have been used in these previous studies (1-13). In this regard, Oleesky (27) did not observe improvement in diluting capacity in humans with adrenal insufficiency who were treated with physiological doses of glucocorticoid hormone and improvement required the administration of amounts of the hormone in excess of that normally produced by the adrenal gland. Moreover, the administration of large doses of glucocorticoid hormone to normal subjects with intact adrenal glands has been shown to enhance renal diluting capacity (28). More recently, however, Agus and Goldberg (29) have reported that the impaired water excretion associated with anterior hypopituitarism may in some instances be, at least partially, correctable by the administration of physiological amounts (5-20 mg) of hydrocortisone. On the basis of the effect of ethanol to improve diluting ability in these patients, these investigators suggest that this effect of hydrocortisone may be related to a suppression of release of ADH (29). It should be emphasized, however, that in this study (29), as well as previous studies (1-13), the effect on chronic glucocorticoid deficiency was examined while glucocorticoid deficiency of a shorter duration was investigated in the present study. In any event, and independent of the mechanisms whereby more chronic glucocorticoid deficiency (1-13, 29) may impair diluting ability or the mechanisms whereby large amounts of glucocorticoids may reverse this defect (1-13), the present results demonstrate that glucocorticoid hormone is not necessary for achieving normal urinary dilution in the adrenalectomized dog. These results thus suggest that glucocorticoid hormone is not necessary for either maximal suppression of ADH release or water impermeability of the renal tubular epithelium. Although this conclusion is in contrast to previous proposals, it is compatible with *in vitro* studies in the toad bladder which have demonstrated that glucocorticoid hormone enhances, rather than impedes, the vasopressin-induced osmotic movement of water (30).

ACKNOWLEDGMENTS

A preliminary report of this work was presented at the American Society of Nephrology Meeting in Washington, D. C., 21 November 1971.

The authors would like to express their appreciation to Dr. Peter Forsham for the plasma cortisol determinations and Lisbeth Streiff and Judith A. Harbottle for their excellent technical assistance. These studies were supported in part by grants AM 12753, Training Grant AM 05670, and

HE 13310-01A1 from the National Institutes of Health; Grant NGR 05025007 from the National Aeronautics and Space Administration; and grants from the Bay Area Heart Association, Academic Senate, and Harris Robert Benjamin Grants from the University of California, San Francisco.

REFERENCES

- Kottke, F. J., C. F. Code, and E. H. Wood. 1942. Urine dilution and concentration tests in adrenalectomized dogs. *Amer. J. Physiol.* **136**: 229.
- Roemmelt, J. D., O. W. Sartorius, and R. F. Pitts. 1949. Excretion and reabsorption of sodium and water in the adrenalectomized dog. *Amer. J. Physiol.* **159**: 124.
- Garrod, O., and R. A. Burston. 1952. The diuretic response to ingested water in Addison's disease and panhypopituitarism and the effect of cortisone thereon. *Clin. Sci.* **2**: 113.
- Garrod, O., S. A. Davies, and G. Cahill, Jr. 1955. The action of cortisone and desoxycorticosterone acetate on glomerular filtration rate and sodium and water exchange in the adrenalectomized dog. *J. Clin. Invest.* **34**: 761.
- Kleeman, C. R., M. H. Maxwell, and R. E. Rochney. 1958. Mechanisms of impaired water excretion in adrenal and pituitary insufficiency. I. The role of altered glomerular filtration rate and solute excretion. *J. Clin. Invest.* **37**: 1799.
- Kleeman, C. R., J. Koplowitz, M. H. Maxwell, R. Cutler, and J. T. Dowling. 1960. Mechanisms of impaired water excretion in adrenal and pituitary insufficiency. II. Interrelationships of adrenal cortical steroids and antidiuretic hormone in normal subjects and in diabetes insipidus. *J. Clin. Invest.* **39**: 1472.
- Cutler, R. E., C. R. Kleeman, J. Koplowitz, M. H. Maxwell, and J. T. Dowling. 1962. Mechanisms of impaired water excretion in adrenal and pituitary insufficiency. III. The effect of extracellular or plasma volume expansion or both, on the impaired diuresis. *J. Clin. Invest.* **41**: 1524.
- Kleeman, C. R., J. W. Czaczkes, and R. Cutler. 1964. Mechanisms of impaired water excretion in adrenal and pituitary insufficiency. IV. Antidiuretic hormone in primary and secondary adrenal insufficiency. *J. Clin. Invest.* **43**: 1641.
- Ahmed, A. B., B. C. George, C. Gonzalez-auvert, and J. F. Dingman. 1967. Increased plasma arginine vasopressin in clinical adrenocortical insufficiency and its inhibition by glucosteroids. *J. Clin. Invest.* **46**: 111.
- Dingman, J. F., and R. H. Despointes. 1960. Adrenal steroid inhibition of vasopressin release from the neurohypophysis of normal subjects and patients with Addison's disease. *J. Clin. Invest.* **39**: 1851.
- Gaunt, R., J. H. Birnie, and W. J. Eversole. 1949. Adrenal cortex and water metabolism. *Physiol. Rev.* **29**: 281.
- Stolte, H., J. P. Brecht, M. Wiederholt, and K. Hierholzer. 1968. Einfluss von adrenalectomie und glucocorticoiden auf die wasserpermeabilitat corticaler nephroabschnitte der ratteniere. *Pflugers Arch. Gesamte Physiol. Menschen Tiere.* **200**: 99.
- Green, H. H., A. R. Harrington, and H. Valtin. 1970. On the role of antidiuretic hormone in the inhibition of acute water diuresis in adrenal insufficiency and the effects of gluco- and mineralocorticoids in reversing the inhibition. *J. Clin. Invest.* **49**: 1724.
- Schrier, R. W., and L. E. Earley. 1970. Effects of hematocrit on renal hemodynamics and sodium excretion in hypotonic and volume expanded dogs. *J. Clin. Invest.* **49**: 1656.
- Mattingly, D. 1962. A simple fluorometric method for the estimation of free 11 hydroxycorticoids in human plasma. *J. Clin. Pathol. (London).* **15**: 374.
- Bunin, J. J., R. L. Black, L. Lutwak, R. E. Peterson, and G. D. Whedon. 1958. Studies on dexamethasone, a new steroid, in rheumatoid arthritis—a preliminary report. *Arthritis Rheum.* **1**: 313.
- Gill, J. R., D. S. Gann, and F. C. Bartter. 1962. Restoration of water diuresis in Addisonian patients by expansion of the volume of extracellular fluid. *J. Clin. Invest.* **41**: 1078.
- Ackerman, G. L., and C. Lindsey Miller. 1970. Role of hypovolemia in the impaired water diuresis of adrenal insufficiency. *J. Clin. Endocrinol. Metab.* **30**: 252.
- del Greco, F., and H. E. de Wardener. 1956. The effect on urine osmolarity of a transient reduction in glomerular filtration rate and solute output during a "water" diuresis. *J. Physiol.* **131**: 307.
- Berliner, R. W., and D. G. Davidson. 1957. Production of hypertonic urine in the absence of pituitary antidiuretic hormone. *J. Clin. Invest.* **36**: 1416.
- Share, L., and R. H. Travis. 1970. Plasma vasopressin concentration in the adrenally insufficient dog. *Endocrinology.* **86**: 196.
- Schrier, R. W., R. Lieberman, and R. C. Ufferman. 1972. Mechanism of antidiuretic effect of beta adrenergic stimulation. *J. Clin. Invest.* **51**: 97.
- Orloff, J., H. N. Wagner, Jr., and D. G. Davidson. 1958. The effect of variations in solute excretion and vasopressin dosage on the excretion of water in the dog. *J. Clin. Invest.* **37**: 458.
- Clarke, A. P. W., R. A. Cleghorn, J. K. W. Ferguson, and J. L. A. Fowler. 1947. Factors concerned in the circulatory failure of adrenal insufficiency. *J. Clin. Invest.* **26**: 359.
- Reidenberg, M. M., E. A. Ohler, R. W. Seuy, and C. Harakal. 1963. Hemodynamic changes in adrenalectomized dogs. *Endocrinology.* **72**: 918.
- Lefler, A. M., R. L. Verrier, and W. W. Carson. 1968. Cardiac performance in experimental adrenal insufficiency in cats. *Circ. Res.* **22**: 817.
- Oleesky, S. 1953. A specific water diuresis test for adrenocortical insufficiency. *Lancet.* **1**: 769.
- Lindeman, R. D., H. C. Van Buren, and L. G. Raisz. 1961. Effect of steroids on water diuresis and vasopressin sensitivity. *J. Clin. Invest.* **40**: 152.
- Agus, Z. S., and M. Goldberg. 1971. Role of antidiuretic hormone in the abnormal water diuresis of anterior hypopituitarism in man. *J. Clin. Invest.* **50**: 1478.
- Handler, J. S., A. S. Preston, and J. Orloff. 1969. Effect of adrenal steroid hormones on the response of the toad's urinary bladder to vasopressin. *J. Clin. Invest.* **48**: 823.