The Regulation of Antidiuretic Hormone Release in Man

I. EFFECTS OF CHANGE IN POSITION AND AMBIENT TEMPERATURE ON BLOOD ADH LEVELS

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ABSTRACT It has been postulated that alterations in the intravascular distribution of blood affect antidiuretic hormone (ADH) secretion in man. The studies reported here were designed to alter blood distribution by thermal and by positional change to test this thesis.

Human blood ADH levels have been shown to vary with position: a mean value of 0.4 ± 0.6 (SD) $\mu U/ml$ was obtained while the subject was supine, a value of 1.4 ± 0.7 $\mu U/ml$ while sitting, and 3.1 ± 1.5 $\mu U/ml$ while standing. In 79 control subjects, sitting comfortably for 30 min in a normal environment, a blood ADH level of 1.65 ± 0.63 $\mu U/ml$ was found. It is suggested that subjects assume this position during experiments in which blood is drawn for measurement of ADH levels.

In eight seated subjects the ADH level rose from 1.6 ± 0.4 to 5.2 ± 0.8 $\mu U/ml$ after a 2 hr exposure at 50°C and fell to 1.0 ± 0.26 $\mu U/ml$ within 15 min at 26°C.

Six subjects with a mean ADH level of 2.2 ± 0.58 $\mu U/ml$ sat quietly in the cold (13°C) for 1 hr, and the ADH level fell to 1.2 ± 0.36 $\mu U/ml$. After 15 min at 26°C, the level rose to 3.1 ± 0.78 $\mu U/ml$. The serum sodium and osmolal concentrations remained constant during all studies.

Water, sodium, and total solute excretion decreased during exposure to the heat, whereas the urine to plasma (U/P) osmolal ratio increased. During cold exposure, water, sodium, and total solute excretion increased, and there was a decrease in the U/P osmolal ratio.

These data are interpreted as indicating that changes in activity of intrathoracic stretch receptors, in response to redistribution of blood, alter ADH secretion independently of changes in serum osmolality. The rapidity of change of blood ADH concentration indicates a great sensitivity and a prime functional role for the "volume receptors" in the regulation of ADH secretion.

INTRODUCTION

There is evidence that at least two mechanisms regulate the release of antidiuretic hormone (ADH) and thereby control the tonicity and volume of the body fluids. The first of these has been elucidated by the investigations of Verney (1) and many subsequent workers (2–4) who have demonstrated the existence of receptors, probably located in the hypothalamus (5), which are sensitive to changes in the effective solute concentration of the extracellular fluid. These receptors stimulate the release of ADH in response to increased extracellular solute concentration and

inhibit ADH secretion when the extracellular fluid becomes dilute.

The second mechanism was originally predicted by Peters (6). His suggestion that the fullness of the intravascular compartment could be "sensed" by the organism directed attention toward a search for receptors sensitive to changes in intravascular volume which, in turn, might influence the release of ADH. Henry, Gauer, and Reeves (7, 8) have demonstrated the presence of such receptors in the thoracic vessels of dogs. They observed that distention of the left atrium was associated with an increase in urine flow, whereas diuresis was not observed during distention of other segments of the intrathoracic vascular system. Subsequent studies have demonstrated that this response can be blocked by vagotomy (9). Thus, although this mechanism is well established in the experimental animal, its presence has not been demonstrated convincingly in man.

The studies to be reported support the concept that intravascular stretch receptors, presumably intrathoracic, in response to alteration in left atrial filling, alter ADH release independently of changes in serum osmolality in man. Furthermore, the rapidity of change of blood ADH concentration indicates a great sensitivity and a prime functional role for the "volume receptors" in the regulation of ADH secretion.

METHODS

Vasopressin assay. The procedure of extraction, absorption, concentration, and bioassay of ADH were modified from methods described by Weinstein, Berne, and Sachs (10), Share (11), Yoshida, Motohashi, and Okinaka (12), and Moran, Miltenberger, Shu'Ayb, and Zimmerman (13). These modifications and the dose-response relationship are described by Rogge, Moore, Segar, and Fasola (14). The method involves extraction of ADH from blood with trichloroacetic acid (TCA), removal of the TCA with ether, absorption on a column of resin, Amberlite CG-50 (Rohm & Haas, Philadelphia, Pa.), and elution with 50% acetic acid. The eluent is lyophilized and taken up in 1.0 ml of a solution containing 0.85% NaCl and 0.03% acetic acid. Weinstein et al. (10) have demonstrated, and we have confirmed in isolated experiments, that the material contained in the eluent has the biological and chemical properties of vasopressin. It is soluble in 10% TCA, insoluble in ether, stable to the action of pepsin, and rapidly inactivated by trypsin and by 0.01 M thioglycollic acid. It is present in the blood of hydropenic subjects and disappears with hydration (15). Share (16) has performed studies on the

gradient elution of the eluate from carboxymethyl cellulose and demonstrated that the antidiuretic activity emerged as a single peak in a position similar to that found with highly purified arginine vasopressin.

The material is assayed by injection of 0.1–0.5 ml of the acidified saline solution containing the vasopressin originally present in 1.0–5.0 ml of blood into water-loaded (5 ml/100 g) ethanol-anesthetized Holtzman rats weighing 150–200 g. During the assay the rats are maintained at a constant ambient temperature (35°C) in an Armstrong incubator. The high ambient temperature is used to prevent a fall in the rectal temperature of the ethanol-anesthetized bioassay animal, to maintain a constant central blood volume and constant renal hemodynamics, to insure that all solutions are administered at a temperature of 35°C, and to maintain a constant temperature on the conductivity cell. The assay animals are maintained on a constant fluid load by the continuous intravenous replacement of urine losses with an equal volume of a solution containing 0.3% NaCl, 1.6% glucose, and 2% ethanol. All samples and solutions are administered intravenously. Urine conductivity is recorded continuously via a conductivity cell and recording device described by Rothe, Johnson, and Moore (17). The area under the conductivity curve is taken as an index of response and is measured by planimetry beginning with the initial upward deflection of the recording pen above a stable base line and continuing for 10 min. A 2×2 factorial design is used to estimate the potency of the unknown solutions, and a complete assay consists of at least two injections of standard synthetic arginine vasopressin (Sandoz, Inc., Hanover, N. J.) and at least two injections of unknown, each at two dose levels. The procedure detects 1 μU/ml (95% confidence limits) of arginine vasopressin (14). When kept in a frozen state until use, the synthetic arginine vasopressin has seemed to be a reliable reference standard as indicated by the linearity and reproducibility of the dose response curve (14). Since this standard was not checked against USP Reference Standard a significant error in absolute values may have been introduced. Since the aliquot of the acidified saline solution injected into the assay animal may contain the amount of vasopressin present in as much as 5 ml of blood, the assay will detect concentrations of blood ADH as low as 0.20 μU/ml. Recovery of arginine vasopressin (2.5–5.0 μU/ml) added to whole blood in 18 trials is $92 \pm 5\%$ (SEM). The specificity and limitations of such bioassay procedures for ADH have been reviewed recently by Share (18).

10 ml of whole blood was withdrawn from the antecubital vein and transferred directly to 4 volumes of cold 12.5% TCA and carried through the extraction and purification procedure. No precautions against pain were taken; the blood was drawn rapidly to minimize stasis, and glass syringes were used. The extracts were frozen immediately and stored in the frozen state until the time of assay.

Sodium, potassium, chloride, creatinine, and osmolality analyses of blood and urine were conducted by conventional methods.

TABLE I

Effect of Body Position on Blood ADH Concentration in Man

	Blood ADH		
Subject	Reclining; 60 min	Sitting; 60 min	Upright; 20 min
		$\mu U/ml$	
1*	0.0‡	1.5	3.1
2*	1.2	1.7	1.9
3	0.0‡	1.9	4.0
4	0.0‡	1.0	1.6
5	0.0‡	1.5	3.2
6	1.3	2.3	5.9
7	0.0‡	1.0	1.9
8	0.4	1.5	3.1
Mean	0.4	1.4	3.1
SD	0.6	0.7	1.5

ADH, antidiuretic hormone.
* Samples taken during upright, then sitting and reclining position. All others taken in reversed order.
‡ No ADH detected. Maximal concentration of blood ADH is therefore less than 0.20 $\mu U/ml$.

RESULTS

Volunteer male human subjects were used throughout. In the first experiment the effect of alteration of position on blood ADH level was determined in eight subjects. In six instances the initial sample was obtained after the subject had been lying supine for 60 min, a second specimen was drawn after sitting quietly for 60 min, and a final sample was obtained after 20 min of quiet standing. In the latter position the subject was resting against a high stool. The subjects' legs were held motionless in a dependent position and

bore little weight. In two subjects the sequence of positions was reversed with no difference in results. Each blood sample was analyzed for sodium, chloride, and solute concentration, as well as for ADH. The results are summarized in Table I. The mean ADH level in the recumbent position was 0.4 ± 0.6 $\mu U/ml$. The mean value in the sitting position was 1.4 ± 0.7 $\mu U/ml$, and this value increased to 3.1 ± 1.5 $\mu U/ml$ after 20 min of quiet standing. The serum Na, Cl, and solute concentrations remained unchanged during these studies. The lowest ADH level was obtained in each subject after reclining, the highest after standing 20 min.

In the course of these and subsequent experiments, blood ADH determinations have been conducted on samples taken at the end of control periods from subjects on 79 separate occasions. In each instance the subject was an adult male who emptied his bladder and sat quietly for at least 30 min before the blood and urine samples were obtained. Each sample for ADH assay was drawn during the midmorning, and each subject had eaten his usual breakfast but had consumed no fluid since that time. In each the urine to plasma osmolal ratio (U_{osmol}/P_{osmol}) was between 1.95 and 3.75. The mean blood ADH concentration for this group was 1.65 $\mu U/ml$ with a standard deviation of 0.63 $\mu U/ml$. The distribution of these values is illustrated in Fig. 1.

The blood ADH level was measured before, during, and after an abrupt increase in environmental temperature in a second study. Eight comfortably seated subjects had a blood sample
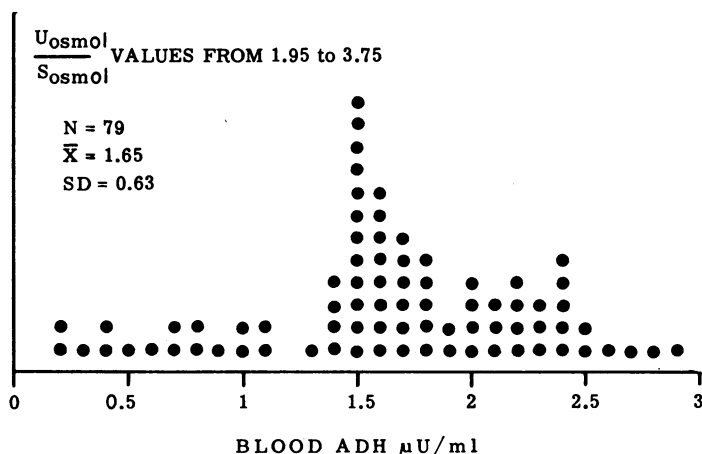

FIGURE 1 Distribution of blood antidiuretic hormone (ADH) concentration (X) in adult male subjects (clothed, seated, room temperature 26°C) studied on 79 separate occasions (N).

drawn after a control period of 60 min at normal room temperature (26°C). They were then exposed to an environmental temperature of 50°C in a constant temperature room. After a 2 hr exposure to the hot environment a second blood sample was obtained. The subjects were returned to a comfortable environment (26°C), and a third blood specimen was obtained 15 min later. Each subject voided before and at the termination of the control period, the 2 hr period of exposure to heat, and the 15 min period after removal from the heat.

The blood specimens were analyzed for ADH concentration, and the serum concentration of total solute, sodium, potassium, and chloride were obtained. Urine was analyzed for sodium, potassium, chloride, creatinine, and total solute.

The mean blood ADH level during the control period was 1.6 ± 0.4 μU/ml of blood. After exposure to heat the mean value rose to 5.2 ± 0.7 μU/ml and then fell 15 min later to 1.0 ± 0.3 μU/ml. These results and other data are summarized in Table II. In each case the highest blood ADH concentration occurred after 2 hr exposure to the heat, and in each case the ADH concentration fell below control values after the subject was returned to a normal environment. The subjects lost an average of 1.13 kg of weight during the experiment, but changes in the serum concentration of sodium and chloride and in serum osmolality were not detectable.

Changes in urine-to-serum (U/S) solute concentration ratio and in urine flow are also summarized in Table II. Adequate urine collections were obtained from six of the eight subjects. Although each individual was moderately hydropenic initially, the U/S osmolal ratio rose from 2.66 ± 0.46 to 3.27 ± 0.51. This increase in U/S osmolal ratio is significant ($P < 0.001$). During the final period there was a further slight increase in U/S osmolal ratio to 3.42 ± 0.31, a value significantly above control, but not different from the value obtained after heat exposure.

Urine flow decreased significantly in each subject during exposure to the heat. Minute volume was 1.1 ± 0.3 ml/min during the control period and fell to a mean value of 0.6 ± 0.2 during heat exposure ($P < 0.001$). In each instance minute volume increased during the period after heat exposure, although in only one subject did it return to control values. During the 15 min recovery period the mean minute volume was 0.8 ± 0.2 ml/min.

There was also a significant decrease in sodium excretion per minute during heat exposure (Table II). Initially the mean sodium excretion was 201 ± 97 μEq/min. During the experimental period this value fell to 97 ± 43 μEq/min ($P < 0.01$) and then rose to 122 ± 34 μEq/min during recovery. This latter value also differs significantly from the initial control value ($P < 0.05$). A

TABLE II
Effect of Increase in Ambient Temperature on Blood ADH Concentration and on Serum and Urine Composition in Man

	Period 1	Period 2	Period 3	P*		
				1–2	2–3	1–3
Ambient temperature	26°C	50°C	26°C			
Blood ADH ($\mu U/ml$)	1.6 ± 0.4‡	5.2 ± 0.7	1.0 ± 0.3	<0.001	<0.001	<0.01
S_{Na} ($mEq/liter$)	142 ± 1	142 ± 1	142 ± 1	NS	NS	NS
S_{osmol} ($mOsm/kg$)	296 ± 3	296 ± 3	295 ± 3	NS	NS	NS
V (ml/min)	1.1 ± 0.3	0.6 ± 0.2	0.8 ± 0.2	<0.01	NS	<0.05
U_{osmol}/S_{osmol}	2.66 ± 0.46	3.27 ± 0.51	3.42 ± 0.31	<0.001	NS	<0.001
$U_{Na}V$ ($\mu Eq/min$)	201 ± 97	97 ± 43	122 ± 34	<0.01	NS	<0.05
$U_K V$ ($\mu Eq/min$)	78 ± 43	72 ± 31	102 ± 34	NS	<0.01	<0.05
$U_{osmol}V$ ($\mu Osm/min$)	832 ± 304	546 ± 175	759 ± 93	<0.01	<0.01	NS
$U_{CR}V$ (mg/min)	1.43 ± 0.15	1.31 ± 0.26	1.48 ± 0.22	<0.01	NS	NS

ADH, antidiuretic hormone; S_{Na}, serum sodium concentration; U_{osmol}/S_{osmol}, urine-to-serum solute concentration ratio; V, minute volume; $U_{Na}V$, sodium excretion; $U_K V$, potassium excretion; $U_{osmol}V$, total solute excretion; $U_{CR}V$, creatinine excretion.

* The probability of differences between experimental periods is tested by applying Student's t test on paired observations for each subject.

‡ Mean $\pm$ standard deviation.

TABLE III

Effect of Decrease in Ambient Temperature on Blood ADH Concentration and on Serum and Urine Composition in Man

	Period 1	Period 2	Period 3	P*		
				1–2	2–3	1–3
Ambient temperature	26°C	13°C	26°C			
Blood ADH ($\mu U/ml$)	2.2 ± 0.6‡	1.3 ± 0.4	3.1 ± 0.8	<0.005	<0.001	<0.02
S_{Na} (*mEq/liter*)	142 ± 1	143 ± 1	142 ± 1	NS	NS	NS
S_{osmol} (*mOsm/kg*)	293 ± 3	293 ± 3	293 ± 3	NS	NS	NS
V (*ml/min*)	0.8 ± 0.2	1.1 ± 0.2	1.0 ± 0.2	<0.01	NS	<0.01
U_{osmol}/S_{osmol}	3.37 ± 0.25	3.08 ± 0.26	3.03 ± 0.38	<0.05	NS	<0.05
$U_{Na}V$ ($\mu Eq/ml$)	166 ± 41	243 ± 36	222 ± 41	<0.005	<0.05	<0.05
$U_K V$ ($\mu Eq/min$)	68 ± 27	84 ± 28	77 ± 25	<0.05	NS	NS
$U_{osmol}V$($\mu Osm/min$)	756 ± 162	964 ± 137	842 ± 23	<0.01	<0.05	<0.05
$U_{CR}V$(*mg/min*)	1.18 ± 0.29	1.21 ± 0.22	1.09 ± 0.19	NS	<0.05	NS

See Table II for explanation of abbreviations.

* The probability of difference between experimental periods is tested by applying Student's t test on paired observations for each subject.

‡ Mean ± standard deviation.

significant increase in potassium excretion occurred during the final 15 min period, but potassium excretion did not change during the period of heat exposure. Alterations in total solute excretion reflected changes in the excretion of sodium. Total solute excretion fell from 832 ± 304 to 546 ± 175 μOsm/min during heat exposure ($P < 0.01$) and rose to the control value during recovery. Creatinine excretion decreased by a small (8.5%) but statistically significant amount during heat exposure.

In the last of this series of experiments six slightly hydropenic volunteers clothed only in shorts and undershirts were exposed to a cold environment. Again the subjects were seated during a 60 min control period at 26°C, a 60 min period of exposure in a constant temperature room to an ambient temperature of 13°C, and a 15 min recovery period at room temperature (26°C). Blood for ADH determinations and serum for sodium, potassium, chloride, and osmolal determinations were obtained at the end of each period. Urine was collected at the conclusion of each period and was analyzed for sodium, potassium, chloride, total solute, and creatinine. Gross shivering did not occur during the period of cold exposure.

Changes in blood ADH concentration are illustrated in Table III. The initial ADH level was 2.2 ± 0.6 μU/ml. This value fell to 1.3 ± 0.4 during the period in the cold and then rose to 3.1 ±

0.8 μU/ml after 15 min in comfortable environment. These changes were consistent; in each subject the lowest ADH was obtained after cold exposure, and in each the highest value was found after recovery. Changes in the serum concentrations of sodium, potassium, chloride, and solute could not be detected.

A mild diuresis occurred in each subject during the experimental period. Mean minute volume increased significantly ($P < 0.01$) from 0.8 ± 0.2 ml/min to 1.1 ± 0.2 ml/min, and remained elevated during the recovery period (1.0 ± 0.2 ml/min, $P < 0.01$). The U/S osmolal ratio fell significantly ($P < 0.05$) from 3.37 ± 0.25 to 3.08 ± 0.26 and 3.03 ± 0.38 during the periods of cold exposure and during recovery, respectively.

Sodium excretion increased from a mean of 166 ± 41 μEq/min during control to 243 ± 36 μEq/min ($P < 0.005$) during the experimental period and to 222 ± 41 μEq/min ($P < 0.05$) during the recovery period. The decrease in sodium excretion during recovery differs ($P < 0.05$) from that observed during exposure to cold. Total solute excretion paralleled sodium excretion. During the period of cold exposure solute excretion rose from 756 ± 162 μOsm/min to 964 ± 137 μOsm/min ($P < 0.01$) and then fell to 842 ± 23 μOsm/min during recovery, a value still significantly above control ($P < 0.05$), and significantly less than the value for mean solute ex-

cretion during cold exposure ($P < 0.05$). These data are summarized in Table III.

DISCUSSION

Each of the experiments described above was designed to alter the intravascular distribution of blood by thermal and positional change without concurrent changes in plasma osmolality. As such, they test the thesis that, in man, alterations in filling of certain portions of the intravascular compartment influence the release of ADH.

Hemorrhage is known to cause an increase in blood ADH levels in the rat and dog. Share (11), in a series of experiments designed to produce small gradual changes in blood volume, demonstrated that progressive reduction in extracellular fluid volume led to a progressive rise in blood vasopressin titer. Reexpansion of blood volume to a level slightly greater than control restored blood ADH concentration to approximately control values.

Although the evidence that relatively small changes in blood volume alter blood ADH concentrations is impressive, the location of the "volume" or "stretch" receptors which initiate this response is uncertain. Henry, Gauer, and their associates (7, 8) have amassed a large body of data which suggests that a volume receptor concerned with ADH release has an intrathoracic site. Positive pressure breathing, which would decrease filling of the intrathoracic vessels, has been shown in dogs to induce antidiuresis (19), whereas negative pressure breathing, which would facilitate filling of intrathoracic vessels, results in diuresis (20). These same investigators have subsequently shown that when a balloon is inflated in the left atrial appendage of an anesthetized dog, urine volume is increased (8). More direct evidence that a left atrial stretch receptor is involved in the regulation of ADH release has been provided by Baisset and Montastruc (21), Share (22), and Shu'ayb, Moran, and Zimmerman (23), and Johnson, Moore, and Segar (24) have shown that when a balloon in the left atrial appendage is inflated progressively so that small increments in transmural pressure are produced, blood ADH concentration falls progressively and proportionately as the transmural pressure is increased. The variations in transmural pressure produced in the experiments

of Johnson et al. are within a physiologic range as opposed to the far greater pressure changes produced in similar experiments of other investigators who obtained comparable results (21–23).

There is also evidence that receptors elsewhere in the cardiovascular system may play a role in the control of vasopressin release. Carotid occlusion has been shown to increase ADH release, and Share and Levy (25) have demonstrated that the decreased activity of the carotid sinus baroreceptors after carotid artery occlusion induces an increase in ADH release. These receptors would be of functional significance, however, only when marked changes in mean arterial blood pressure occur. The activity of a left atrial volume receptor would not be altered by change in mean arterial pressure, but it would be altered by any circumstance, physiological or pathological, that might alter the filling of that chamber.

Each of the procedures described in this study would be expected to alter filling of the left atrium as well as the filling of other intrathoracic capacitance vessels. The effect of alterations in position on filling of the low pressure intrathoracic vessels seems apparent. It has been estimated that 80% of the blood pooled in the extremities during orthostasis comes from the thoracic vascular bed (26). Presumably left atrial filling would be least during standing and greatest when the subject is supine. As a result of the stretch induced by left atrial filling in the supine position afferent impulses arising in the wall of the left atrium are transmitted by vagal fibers to centers in the central nervous system which, in turn, inhibit ADH release. With standing, and the resultant decrease in stretch, the stretch or baroreceptor becomes inactive, and the absence of inhibitory stimuli allows ADH release. The well known antidiuresis of quiet standing results (27).

It seems likely that alterations in blood ADH which result from changes in environmental temperature are also mediated by the intrathoracic stretch receptors. If this is the case, peripheral vascular beds open in a hot environment and fill with blood whereas the central blood volume, including the intrathoracic volume, decreases. In a cold environment the converse occurs. Peripheral vascular resistance increases, peripheral blood volume is diminished, and that volume of blood that

has been in the peripheral beds increases filling of the capacitance vessels, including those in the thorax (28). The phenomenon of cold diuresis provides suggestive evidence for relationship between intrathoracic blood volume and alterations in blood ADH. Gauer and Henry (8) report that they have observed an increase in central venous pressure upon taking a subject from a hot into a cold environment, and they as well as Bader, Eliot, and Bass (29) have postulated that cold diuresis results from a decrease in ADH secretion.

In hot room experiments reported here, the marked increase in blood ADH level could result from either a redistribution of blood due to an increased flow to peripheral beds or to the loss of extracellular fluid from sweating or both. Since no measurable changes in serum sodium or total solute concentrations occurred, it is not likely that an "osmoreceptor" could have mediated the ADH release. The abrupt drop in blood vasopressin concentration that occurred within 15 min after return to a normal ambient temperature provides evidence that the changes in ADH concentration were the result of redistribution of blood. Had either the loss of extracellular fluid due to sweating or an undetectable increase in body solute concentration been the prime stimulus for ADH release, the blood ADH concentration should have remained elevated during the recovery period. Lauson (30) has reviewed available half-life data for blood ADH in man and has noted the variability of published values (3.9–46 min). From our own studies in patients with untreated diabetes insipidus, we have estimated that ADH half-life is approximately 7 min,[1] a finding which indicates that ADH release was markedly inhibited immediately after removal of the subjects from the hot environment; otherwise the precipitous drop in ADH concentration noted over a 15 min period could not have occurred.

During exposure to a cold environment the sequence of events is presumably reversed. With increased resistance to flow in peripheral vascular beds, central filling is increased, and ADH release is inhibited. When the subject is returned to a normal environment flow to the peripheral beds is increased, filling of intrathoracic capacitance ves-

sels is decreased, inhibition of ADH release is diminished, and blood ADH levels become elevated. In this situation there is no significant change in weight, the total extracellular volume remains constant, and total solute concentration is not altered.

It is possible that heating and cooling the subject influence ADH release directly via unknown pathways. The changes in cutaneous blood vessels caused by the alterations in ambient temperature are mediated by the autonomic nervous system governed, presumably, by controls located in the hypothalamus. Afferent information from the skin thermal receptors reaching the hypothalamus may, conceivably, affect centers regulating ADH release. It is true, also, that stress of any sort may result in ADH release (18). However, the fall in blood ADH during cooling, which was the less comfortable of the two procedures, and the observation that the ADH level increases after recovery from cooling, indicate that the results cannot be attributed to a nonspecific stress effect.

The alterations observed in urine volume and in urine solute concentration, as measured by the U/S osmolal ratio, in the course of these experiments are reasonably consistent with the changes in blood ADH concentration. A marked antidiuresis occurred during warming and was associated with a significant increase in U/S osmolal ratio. During the brief recovery period urine flow and U/S ratio did not change significantly. Similarly, a mild diuresis occurred with cooling, and the urine became slightly more dilute. During recovery neither urine flow nor urine solute concentration changed. Of interest, also, are the changes in sodium and total solute excretion that occurred in the course of these experiments. Both sodium excretion and total solute excretion decreased significantly while the subjects were in a hot environment, and the urine solute concentration rose to control values, whereas urine sodium excretion increased but remained below control values during recovery. The converse occurred while the subjects were in a cold environment. Both urine sodium and total urine solute excretion increased significantly and remained elevated, although less so, during recovery. The mechanisms responsible for these alterations in sodium and solute excretion are not clearly established. These changes could

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[1] Segar, W. E., and W. W. Moore. Unpublished observation.

TABLE IV

Effect of Head-Down Tilting on Blood ADH Level and Serum Na Concentration in Comatose Patients

Diagnosis	Initial values		After 48 hr tilt	
	Blood ADH	S_{Na}	Blood ADH	S_{Na}
	$\mu U/ml$	$mEq/liter$	$\mu U/ml$	$mEq/liter$
Myxedema coma	3.4	128	1.2	142
Posthypoxic coma	4.2	117	0.9	155
Hemophilus influenzae Meningitis with coma	11.7	114	1.7	138

See Table II for explanation of abbreviations.

be a direct result of alterations in blood ADH per se, although our own studies,[2] as well as those of others (31), indicate that ADH has little effect on mineral excretion, of alterations in blood aldosterone secretion, a thesis which cannot be supported or disproven by these data, or a result of changes in the production of release of a "third factor" (32–35). The release of such a "natriuretic hormone" with increased filling of the capacitance vessels could account for the natriuresis noted during cold exposure, and the inhibition of release resulting from decreased filling of the intrathoracic vessels could explain the antinatriuresis noted after warming. Finally, since precise clearance data are not available, small changes in glomerular filtration rate may be responsible for the observed alterations in sodium and solute excretion.

The work herein reported is, we believe, of clinical significance. First, a "normal" blood ADH level in the slightly hydropenic, clothed subject seated in a comfortable environment has been established. Because of the wide variation in blood ADH concentration that results from alteration in position, it is necessary that control data be collected under prescribed conditions. A sitting position seems most appropriate.

The supine position is less satisfactory. Although low levels of ADH are found in the conscious volunteer who has been supine for 60 min, the levels will remain low only if blood return to the thorax is optimal. During sleep and particularly during coma, blood may pool in the vessels of the extremities or abdomen, and ADH levels

[2] Balsley, J., P. Moseley, W. E. Segar, and W. W. Moore. Unpublished observation.

should then increase. The antidiuresis of sleep may be on this basis, although we have not tested this thesis. We have, however, some preliminary data on ADH levels during coma (Table IV). Such individuals have high blood ADH levels. However, in each of the three cases studied after slight head-down tilting (5°), the blood ADH levels returned in 48 hr to values within the normal range. Each of these three subjects had marked hyponatremia initially, and in each the serum sodium concentration became normal, although each remained on a constant water and electrolyte intake. Each had a brisk diuresis with tilting. These observations, although far from conclusive, suggest that the hyponatremia observed in association with severe central nervous system (CNS) disease may be explained on the basis of inadequate filling of thoracic capacitance vessels. The large amount of ADH produced probably represents a physiological response to inadequate atrial filling and is not due to the release of "inappropriate" amounts of vasopressin as a result of CNS disease per se (36).

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