Effects of Five Per Cent Dextrose-Water Infusions in Normal and Hypertensive Man

Evidence for Increased Proximal and Distal Tubular Sodium Rejection by Hypertensive Patients and Its Relation to Renal Hemodynamics

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SUMMARY
During infusions of 5% dextrose in water urinary sodium excretion and the renal tubular rejection of filtered sodium (E/F Na %) were significantly higher in hypertensive than in normotensive subjects. Increased E/F Na % did not result from alterations in plasma sodium, in filtered sodium, or from an osmotic diuresis.

Fractional sodium reabsorption in proximal (isosmotic) portions of the nephron was diminished in the hypertensive patients. Free water formation (CH2O) rose with increased "distal" sodium delivery (V) in both groups; however, fractional sodium reabsorption in the "distal" nephron was significantly impaired in the hypertensive patients and urinary osmolality was increased.

Mean arterial blood pressure and E/F Na % were related in curvilinear fashion in the 31 studies, and there was a direct relation between E/F Na % and the magnitude of renal vascular resistance. The data suggested that alterations of renal arterial pressure and vascular resistance in hypertensive disease modify sodium transport in proximal and diluting segments of the nephron and determine to a major extent the increased natriuresis exhibited by hypertensive subjects during infusions that expand extracellular fluid volume.

Additional Indexing Words:
Sodium excretion Extracellular fluid volume expansion Hypertension Natriuresis

Factors that influence the rate of renal tubular sodium reabsorption under normal circumstances have not been completely clarified. Studies from many laboratories have indicated that the diminished renal tubular sodium reabsorption developing in response to infusions of saline or Ringer's solution in normal animals does not result from changes in glomerular filtration rate, the filtered load of sodium, or aldosterone secretion.1–6 To explain this phenomenon of "saline diuresis" attention has recently been directed toward the presence of a "third factor,"7 which may either be a "natriuretic" hormone8–10 or an intrarenal hemodynamic adjustment to extracellular fluid (ECF) volume expansion5, 11, 12 or a combination of both.13

Patients with arterial hypertension exhibit an exaggerated natriuresis in response to infusions of saline or mannitol14–27. The mechanism limiting tubular sodium reabsorption in hypertensive more than in normal subjects during the infusions remains unexplained. It is probably a functional abnormality rather
than the result of structural damage to the renal tubules since (1) increased natriuresis by hypertensive subjects is manifest only during the infusions of saline or mannitol, and (2) renal salt wasting is not apparent in hypertensive subjects not receiving infusions when they are maintained on a normal or low sodium intake.23, 28

The present studies were designed to investigate hemodynamic factors that might be involved in the phenomenon of salt rejection in normal and hypertensive man during a mild degree of expansion of the extracellular fluid volume. To this end renal hemodynamics and the natriuretic responses of hypertensive patients were examined during rapid infusions of 5% dextrose in water and were compared to those of normal and salt-depleted control subjects. The studies confirm observations of Ek29 that an exaggerated natriuresis does occur in hypertensive patients in response to infusion of 5% dextrose and water. In addition they demonstrate (1) that in hypertensive patients during the infusions, sodium reabsorption is impaired not only in the proximal tubules but also in distal "diluting" segments of the nephron, and (2) that the degree of sodium rejection is correlated with the mean arterial blood pressure and the renal vascular resistance.

**Methods**

Thirty-one renal clearance studies were performed in nine normal volunteers and 18 patients with essential hypertension and one patient with hypertension caused by an aldosterone-secreting adenoma. Each of the hypertensive subjects and six control subjects prior to study received a diet containing 4 to 6 g of sodium; five studies were performed after the control subjects had received a low-sodium diet (less than 0.875 g of NaCl per day) for 4 to 7 days. None of the patients received medication other than occasional bedtime sedation with barbiturates. None had papilledema or congestive heart failure or a blood area nitrogen level above 26 mg/100 ml.

All experiments were performed at the same early morning hour with the subjects fasting, resting quietly in bed. Water diuresis was induced by oral administration of 500 ml of water during the hour prior to the infusion and was maintained by intravenous administration of a 5% dextrose solution at a rate of 15 ml/min in 26 studies and 9 ml/min in nine studies, held constant by a motor-driven pump. Urine collections were made and discarded until a steady state of maximal urine flow was achieved. Three or four 10-minute clearance periods were then obtained.

Venous blood samples were collected at appropriate intervals through an indwelling needle. Urine was collected continuously via an indwelling catheter. Blood pressure was measured from the arm during the clearance periods by a standard cuff mercury sphygmomanometer.

The rates of glomerular filtration (GFR) and of effective renal plasma flow (ERPF) were measured by the administration of inulin or 14C-inulin and para-aminohippuric acid (PAH). Adequate priming doses were given intravenously; then these substances were added to the 5% dextrose infusion in amounts to maintain constant plasma concentrations. PAH was added to the sustaining infusion immediately before use to avoid the depression in PAH extraction that can occur when PAH and dextrose are incubated together for several hours.30 Plasma and urine samples were analyzed for inulin by the anthrone method,31 for 14C-inulin by the method of Cotlove,32 and for PAH by the method of Smith.33 Sodium and potassium concentrations in plasma and urine were measured by an Instrumentation Associates flame photometer. Chloride concentrations were measured by potentiometric titration with the Cotlove chloridometer. Urine and plasma total-solute concentrations were measured with an Advanced Instruments osmometer.

Calculations: Mean arterial blood pressure was calculated as the average of systolic and diastolic pressures in millimeters of mercury. Effective renal blood flow was calculated as the clearance of PAH divided by 1 – hct and was expressed in milliliters per minute. Renal vascular resistance was calculated by dividing effective renal blood flow by the mean arterial blood pressure and was reported in arbitrary resistance units (RU). The glomerular filtration rate was estimated from the clearance of inulin (CIN) and expressed in milliliters per minute. Osmolar and free water clearances were calculated in the manner described by Smith:33

\[ C_{\text{osm}} = U_{\text{osm}} \times V/P_{\text{osm}}; \quad C_{\text{H}_2\text{O}} = V - U_{\text{osm}} \times V/P_{\text{osm}}, \]

where \( V \) is the urine flow in milliliters per minute and \( U_{\text{osm}} \) and \( P_{\text{osm}} \) are the solute concentrations of urine and plasma in milliosmoles per kilogram of water. Filtered solute load was calculated as the osmolality of plasma in micro-osmoles per milligram: \( \text{H}_2\text{O} \times C_{\text{osm}}, \) in milliliters per minute was expressed as micro-osmoles per minute. The percentage of the urinary solute concentration due to salt was calculated by the formula:

\[ U_{\text{Na}} \text{mEq}/L + U_{\text{Cl}} \text{mEq}/L + U_{\text{osm}} \text{mOsm}/\text{kg H}_2\text{O} \times 100. \]
The excretion of "non-salt" solutes was calculated by subtracting the urinary sodium and chloride excretion rates in microequivalents per minute from the total solute excretion in micro-osmoles per minute.

In studies performed during maximal water diuresis, fractional reabsorption of sodium in the proximal tubules and in distal "diluting" segments of the nephron (ascending limb of Henle's loop, distal tubules) was assessed indirectly. The "distal sodium load" was calculated as \( \frac{U_{Na}V \mu Eq/min + (P_{Na} \mu Eq/ml \times C_{H_2O} \mu Eq/ml)}{C_{IN} \times P_{Na}} \) × 100. Fractional rejection of sodium in distal "diluting" segments of the nephron was estimated by computing the percentage of the "distal sodium load" excreted in the urine, that is, \( \frac{U_{Na}V}{U_{Na}V + (P_{Na} \times C_{H_2O})} \) × 100. Results are reported in the text as mean and standard deviation (SD). Differences between the means found in groups of studies were
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Compared with the Student t test for unpaired variables. Regression lines and correlation coefficients were calculated according to standard statistical techniques.34

Results

The results are presented in tables 1 to 3 and figures 1 to 7. Each number in the tables and each point on the graphs represent the mean of values obtained in one study during three or four 10-minute clearance periods at a steady state of water diuresis.

Electrolyte Excretion

The patterns of electrolyte excretion exhibited by hypertensive patients during the dextrose and water (D/W) infusions appear in tables 1 to 3 and figure 1. Also shown for comparison are the patterns exhibited by normal and sodium-depleted control subjects.

An exaggerated natriuretic response to 5% D/W infusion was observed in all but two of the hypertensive subjects (fig. 1). Urinary sodium excretion in the patients with elevated blood pressure averaged 458 ± 210 μEq/min, a value significantly higher than the mean sodium excretion of normal subjects on similar diets who received similar amounts of fluid (15 ml/min), 133 ± 29 μEq/min (P < 0.01). The urinary sodium excretion of hypertensive patients who received the infusion
Electrolyte Excretion During Five Per Cent Dextrose-Water Infusions in Normal Subjects

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<th>CPAR (ml/min)</th>
<th>RBF (ml/min)</th>
<th>Filtration fraction (%)</th>
<th>Renal resistance (RU)</th>
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Table 3

Sodium excretion of hypertensive patients and normal subjects during 5% D/W infusions is plotted against the simultaneous urinary volume in each study. An exaggerated natriuresis was apparent in the hypertensive patients. In studies performed with a D/W infusion rate of 15 ml/min, the sodium excretion rate (UNaV) was higher in the hypertensive (●) than in the normal (○) subjects, even when the urinary flow rates (V) were comparable. Values from studies of hypertensive patients receiving D/W at 9 ml/min are indicated by ■ and from studies of salt-depleted normal subjects are indicated by ●.

Figure 1

d of D/W at the slower rate of 9 ml/min was also above normal and averaged 317 ± 178 μEq/min (P < 0.02).

Mean serum sodium concentration was not significantly different in the hypertensive and normal subjects (130 ± 6 mEq/L and 140 ± 4 mEq/L, respectively), and the mean filtered load of sodium was somewhat lower in the hypertensive group as a consequence of a lower mean glomerular filtration rate (vide infra). Despite this, the fraction of filtered sodium excreted in the urine (E/FNa) (averaged 4.51 ± 2.84% in the hypertensive subjects and was significantly higher than the E/FNa of 0.74 ± 0.17% noted in the control subjects (P < 0.001). Mean E/FNa in hypertensive subjects who received the slower infusion was also increased to 3.60 ± 3.40%.

Dietary sodium depletion diminished the sodium excretion observed in the control subjects during a D/W infusion; in these studies urinary sodium output averaged 39 ± 18 μEq/min, and there was a corresponding decline in the tubular rejection fraction for sodium to 0.21 ± 0.08%.

Urinary potassium output was 80 ± 41 μEq/min and 50 ± 11 μEq/min in the two sets of studies of hypertensive patients, not significantly increased above the values observed in normal persons on regular sodium diets, 52 ±
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23 μEq/min, or after sodium deprivation 63 ± 47 μEq/min.

Renal Hemodynamics

Mean arterial blood pressure of the hypertensive patients was significantly elevated and averaged 158 ± 19 mm Hg during the 11 studies with 5% D/W at 15 ml/min and 185 ± mm Hg during the nine studies at 9 ml/min (tables 1 and 2). Mean blood pressure during studies of the control subjects who received normal sodium diets averaged 92 ± 5 mm Hg (table 3). During studies of control subjects after sodium depletion mean arterial blood pressure was reduced to 84 ± 4 mm Hg.

Glomerular filtration rate of the hypertensive patients was reduced; the inulin clearance ($C_{IN}$) was 82 ± 28 ml/min in those who received the more rapid D/W infusions and 80 ± 20 ml in the other group. In the

**Figure 2**

*The level of mean arterial blood pressure during each study is plotted against the renal blood flow (ERBF) in left column, the glomerular filtration rate ($C_{IN}$) in center column, and against the filtration fraction (%) in right column.*

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control subjects the $C_{IN}$ was $129 \pm 21$ ml/min in those on regular sodium diets and $138 \pm 27$ ml/min in those who were deprived of sodium. Effective renal blood flow (ERBF) was also decreased in the two hypertensive groups, averaging $735 \pm 182$ ml/min in the former and $628 \pm 148$ ml/min in the latter. In the control subjects ERBF was $1334 \pm 249$ ml/min and $1090 \pm 121$ ml/min after sodium depletion.

Among the entire group of studies of normal and hypertensive patients there was an inverse relationship between the height of mean blood pressure and the effective renal blood flow (fig. 2 left). No directly inverse relationships between the level of blood pressure and the glomerular filtration rate or filtration fraction were apparent however (fig. 2 left, center, and right).

**Relationships Between Salt Excretion and Solute Load**

In order to examine the possibility that the increased tubular salt rejection by hypertensive subjects might have resulted from an osmotic diuresis in these patients, various relationships between sodium excretion and solute load were calculated. In the studies of hypertensive patients and normotensive control subjects there was a poor correlation between the filtered solute load and the rate of urinary sodium excretion ($r = 0.493$). Similarly, the correlation between the urinary excretion of solutes exclusive of sodium and chloride and the rate of urinary sodium excretion was also poor ($r = 0.083$). The "non-salt" solute excretion was calculated per 100 ml of glomerular filtration in both normal and hypertensive patients to correct for possible differences in renal mass; this value also did not correlate well with the $E/F_{Na\%}$ ($r = 0.6468$).

**Increased Sodium and Osmolar Concentrations in Hypertensives (Table 1)**

During a steady state of water diuresis urinary osmolality averaged $92 \pm 12$ mOsm/L in the hypertensive patients, a value significantly higher than the mean osmolality of $69 \pm 7$ mOsm/L observed in the normal subjects who received the same amounts of fluid (15 ml/min) ($P < 0.01$). Urinary osmolality was $152 \pm 70$ mOsm/L in the hypertensive subjects who received the D/W infusion at a slower rate, and was $58 \pm 15$ mOsm/L during studies of salt-depleted normal subjects.

The increased urinary osmolality of the hypertensive subject was largely due to increased urinary sodium and chloride concentrations. During peak water diuresis the urinary sodium concentration ($U_{Na}$) of the hypertensive patients averaged $38 \pm 4$ mEq/L, a value significantly higher than the ($U_{Na}$) of $19 \pm 4$ mEq/L observed in control subjects receiving the same diet and similar D/W infusions (15 ml/min) ($P < 0.01$). The data plotted in figure 1 indicate that hypertensive patients excreted more sodium per unit volume of urine even when urinary flow rates were in the same range as those of the normal controls. The percentage of the urinary osmolality due to salt

$$\left(\frac{U_{Na} + U_{Cl}}{U_{osm}} \times \%ight)$$

averaged $43 \pm 14\%$ and $52 \pm 11\%$, respectively, in the two groups of hypertensive patients but only $22 \pm 8\%$ in control subjects receiving regular diets and $7 \pm 3\%$ in control subjects after sodium depletion. Thus the increased contribution of sodium and chloride to urinary osmolality in the hypertensive patient was highly significant ($P < 0.01$).

**Patterns of Solute and Free Water Clearance During Water Diuresis (Table 1)**

The urinary flow rate during the rapid dextrose-water infusion averaged $19.6 \pm 7.8$ ml/min in the hypertensive patients and $17.0 \pm 2.6$ ml/min in the control subjects. In the hypertensive group the osmolar clearance ($C_{osm}$) of $6.2 \pm 2.0$ ml/min was significantly increased above that of normal subjects, $3.7 \pm 0.6$ ml/min ($P < 0.02$). However, there was no significant difference in the free water clearance ($C_{H_{2}O}$) of the two groups; $C_{H_{2}O}$ averaged $13.4 \pm 6.0$ ml/min in the patients with hypertension and $13.4 \pm 2.2$ ml/min in the control subjects. In both normal and hypertensive subjects $C_{H_{2}O}$ and the urinary flow rate ($V$) were directly related (fig. 3); however, less free water was
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Sodium Rejection

Fractional not extensive free water values in the hypertensive patients in each level of V in the hypertensive group.

excreted per unit of urine flow in the hypertensive than in the normal subjects (fig. 3). Although not shown, the relationship between CH2O and V remained unchanged when the values in both groups were calculated per 100 ml of glomerular filtrate.

Fractional Sodium Rejection in the Proximal (Isosmotic) and Distal (Diluting) Portions of the Nephron

The fraction of filtered sodium rejected from portions of the nephron, where reabsorption is isosmotic (proximal tubules), has been calculated for each study during peak water diuresis (see Methods). The mean “proximal” sodium rejection observed during the rapid D/W infusions in the hypertensive patients averaged 17.9 ± 5.4% of the filtered sodium load, a value that was higher than the 11.4 ± 2.6% observed in the normal group (P < 0.05). Mean “proximal” rejection was not significantly reduced in the control subjects after sodium depletion, 9.5 ± 1.8% (P < 0.2).

The fraction of the “distal” sodium load excreted during the infusions was also calculated for each study (see Methods). The percentage of the “distal sodium load” that escaped reabsorption in the diluting segments of the nephron averaged 19.3 ± 7.4% in the hypertensive patients, a value significantly above the 6.8 ± 1.7% found in the normal subjects (P < 0.001). Distal sodium reabsorption was increased by salt depletion in the control subjects; the fraction of the distal sodium load that escaped reabsorption in the diluting segments was only 2.0 ± 0.8% in these studies.

In figure 4 the amount of sodium delivered beyond the sites of isosmotic (proximal) reabsorption in studies of hypertensive and normal subjects is plotted against the percentage of this “distal sodium load” that escaped reabsorption in the diluting segments. In the hypertensive patients the amounts of sodium presented to the diluting segments of the nephron were as large as or larger than those in normal subjects. Nevertheless, despite comparable or increased sodium delivery to the distal nephron, the percentage of the “distal sodium load” that escaped the urinary flow rate (V) is plotted against the simultaneous free water clearance (CH2O). In both hypertensive and normal subjects, CH2O increased as the urinary flow rate V rose. Less free water (CH2O) was formed at each level of V in the hypertensive group.

The amount of sodium that was delivered beyond sites of isosmotic (proximal) reabsorption was calculated for each study during peak water diuresis (UNa = UNa/100). This “distal sodium load” is plotted against the percentage of the distal sodium load excreted in the urine—“distal rejection fraction %.” At comparable levels of delivery of sodium to diluting segments of the nephron, the distal rejection fraction was significantly elevated in the hypertensive patients (P < 0.001).

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tubular reabsorption in the diluting segments was increased in the hypertensive patients.

Relation of Renal Tubular Rejection of Sodium to Mean Arterial Blood Pressure and to Renal Vascular Resistance

In the 31 studies of normal and hypertensive subjects there was a curvilinear positive correlation between the mean arterial blood pressure and the fraction of filtered sodium excreted in the urine (fig. 5). Renal vascular resistance (BP/ERBF) was elevated in the hypertensive patients and averaged 23.01 ± 7.75 RU in those who received the rapid infusions and 31.92 ± 12.78 in those receiving D/W at 9 ml/min; renal vascular resistance averaged 7.13 ± 1.37 RU in control subjects on regular diets and 7.76 ± 0.84 RU in those who had been deprived of sodium. The magnitude of the renal vascular resistance bore a direct linear relationship to the E/FNa\% observed during the D/W infusions (r = 0.8226, fig. 6). Lesser degrees of correlation were found when glomerular filtrate rate and renal blood flow were related to E/FNa\% (r = 0.6938, r = 0.7298).

Relation of Renal Tubular Rejection of Sodium to Renal Tubular Rejection of Solute and of Water

The fraction of filtered sodium that appeared in the urine during the dextrose-water infusions is plotted against the fraction of filtered solute that simultaneously appeared in the urine in figure 7 left; a linear relationship with a correlation coefficient of 0.9486 was obtained. In figure 7 right, data from 22 studies during peak water diuresis (D/W infusion at 15 ml/min) are plotted; the rejection of filtered sodium by the renal tubules (E/FNa\%) in these studies was directly related to the fraction of filtered water simultaneously rejected by the tubules (V/GFR\%), with a correlation coefficient of 0.9057.

Discussion

The present study indicates that hypertensive patients exhibit an exaggerated natriuresis in response to an intravenous infusion of 5%
dextrose and water. This finding confirms a report by Ek, who in 1955 reported increased sodium excretion by hypertensive patients in response to infusions of 5% D/W, but differs from observations of Hollander and Steinmetz and associates, who did not observe increased natriuresis in hypertensive patients during infusions of 3.5% and 2.5% glucose in water. As will be discussed subsequently, differences in the degree of extracellular fluid expansion produced by the infusions* and in the renal hemodynamics of the patients studied may account for the discrepancy between the various reports.

The increased urinary sodium excretion exhibited by the hypertensive patients in the present studies did not result from larger increases in the filtered load of sodium in response to 5% D/W because (1) mean serum sodium concentration of the hypertensive patients during diuresis was not significantly elevated above that of the control subjects, and (2) mean glomerular filtration rate was lower in patients with increased blood pressure. Since the fraction of filtered sodium excreted by the hypertensive subjects was significantly increased above that of the control subjects, the data indicate that renal tubular sodium reabsorption was reduced in the patients with arterial hypertension during the D/W infusions.

In the study of Ek, the possibility that increased natriuresis in patients with hypertension resulted from a concomitant glucose

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*Undoubtedly both intracellular and extracellular fluid compartments increased as glucose present in the 5% D/W was metabolized by the body. However, since the infusions were rapid, the rate of glucose intake probably exceeded the rate of its metabolism as suggested by an occasional trace of glycosuria. Hence a greater expansion of the extracellular fluid compartment was probably present throughout the studies.
osmotic diuresis was not rigidly excluded. It seems most unlikely that an osmotic diuresis accounted for the impaired renal tubular sodium reabsorption observed in hypertensive patients in the present studies for several reasons: (1) there was a poor correlation between the filtered osmotic load and the rejection fraction of sodium, (2) increased tubular rejection of filtered sodium was apparent in individual hypertensive subjects who exhibited rates of glomerular filtration that equaled or exceeded those of individual control subjects (table 1), (3) the percentage of the urinary osmolality due to sodium and chloride was increased more than twofold above normal in the hypertensive patients, and (4) there was a poor correlation between the excretion rate of solutes other than sodium and chloride and the urinary sodium output.

It also seems unlikely that an osmotic diuresis of functioning residual nephrons accounts for the increased E/F_{Na}% of hypertensive patients during D/W loading, even though such a mechanism may explain in part the increased sodium rejection observed in uremic patients: First, none of the hypertensive patients subjected to D/W infusion had a blood urea nitrogen greater than 25 mg%; with only a few exceptions they exhibited only moderate reductions of glomerular filtration. Second, during an osmotic diuresis of residual nephrons, a linear correlation would be anticipated between the excretion of solutes other than sodium and chloride calculated per 100 ml of glomerular filtration and the fraction of filtered sodium that escaped reabsorption; the absence of such a correlation in the present study tends to make this mechanism an unlikely cause for increased salt rejection by the hypertensive patients.

From an analysis of the patterns of solute and free water clearance that accompany tubular salt rejection during water diuresis, one may ascertain whether impaired tubular sodium transport occurred in portions of the nephron where reabsorption is isosmotic (proximal tubules) or in more distal portions of the nephron where osmotically free water is generated by the selective reabsorption of sodium (loops of Henle, distal tubules).

The finding that the "proximal" sodium rejection fraction was increased in hypertensive patients (P<0.05) suggests that some of the increased sodium rejection induced by a D/W infusion in the hypertensive group may have occurred in the proximal tubules. This interpretation is consistent with the report of Metzger and associates, who found that C_{H_{2}O}/GFR per unit C_{osm}/GFR was increased in hypertensive patients during oral water loads. In animal studies extracellular volume expansion by infusion of saline or Ringer's solution has been demonstrated to depress proximal tubular reabsorption in rats and dogs by a mechanism independent of glomerular filtration rate, plasma protein concentration, aldosterone activity, or antidiuretic hormone. That extracellular fluid (ECF) expansion with dilute dextrose solutions can produce a similar effect on proximal salt reabsorption in animals is supported by observations of Martino and Earley; these investigators noted depressed fractional reabsorption of sodium in the proximal tubules of dogs with diuretic-induced blockade of distal tubular sodium reabsorption during rapid infusions of distilled water or dilute solutions of glucose.

To assess accurately sodium reabsorption in "distal" segments of the nephron it is necessary to consider both the delivery of sodium to the diluting sites and also the intrinsic characteristics of sodium reabsorption in these areas. Since little water escapes from the distal segments at high rates of water diuresis, the urinary flow rate, V, was taken as an approximation of the amount of sodium-containing fluid reaching the diluting segments, and C_{H_{2}O} was taken as an approximation of selective sodium reabsorption in these areas. As delivery of sodium-containing

* Although C_{H_{2}O} actually represents the amount of free water generated in the ascending limb and distal tubules minus any back diffusion of water that occurs in the distal tubule and collecting duct, it is
fluid to the diluting segments increased in both the normals and hypertensives, $C_{H_2O}$ also increased (fig. 3). Thus during the D/W load a complete inhibition of distal sodium reabsorption was not apparent in either group of subjects, nor was a transfer maximum for distal sodium transport demonstrated over the range of distal delivery achieved in these studies.

However, fractional sodium reabsorption in diluting segments of the nephron was depressed in the hypertensives during the D/W infusions. Nineteen per cent of the “distal sodium load” of the hypertensive patients was excreted in the urine whereas only 7% of the “distal sodium load” escaped reabsorption in the normal subjects on regular diets, and only 2% in normals after sodium depletion. The difference between hypertensive and normal subjects in fractional rejection of the sodium delivered to the distal nephron was highly significant ($P < 0.001$) and was proportionally greater than the increase in “proximal” rejection found in hypertensive patients during the same infusions.

Micropuncture studies in normal rats and dogs have indicated that the marked depression of fractional sodium reabsorption that occurs in the proximal tubules during ECF volume expansion with saline is accompanied by a much smaller change in sodium excretion, because there occurs simultaneously an increased reabsorption of sodium in the distal nephron, particularly in the loops of Henle. The present finding that the fractional “distal” sodium reabsorption was reduced 12% below normal in hypertensive patients during 5% D/W infusion suggests that reduced distal tubular sodium transport may explain to a major extent why hypertensive patients excrete more sodium than normal subjects in response to infusions that expand extracellular fluid volume.

Other data also indicate that urinary dilution was altered in the hypertensive patients during the (15 ml/min) D/W infusions: (1) mean $U_{osm}$ and $U_{Na}$ were higher in the hypertensive than in the normal subjects; (2) mean $C_{H_2O}/GFR$ per $C_{osm}/GFR$ was lower in the hypertensive patients; (3) slightly less $C_{H_2O}$ was formed by hypertensive patients at any given urinary flow rate (fig. 3); and (4) at comparable levels of “distal sodium load,” the hypertensive patients exhibited greater “distal” tubular sodium rejection (fig. 4) and were unable to lower $U_{osm}$ and $U_{Na}$ to the levels attained by normal subjects.

Whether the altered urinary dilution and the reduced fractional “distal” sodium reabsorption demonstrated in hypertensive patients during the D/W infusions occurred in the loop of Henle or in the “cortical” diluting segment or in both sites cannot be ascertained from the present studies. However, reductions in urinary concentrating ability in dehydrated hypertensive patients have been reported by other investigators. Moreover, Buckalew, Ramirez, and Goldberg have recently found a reduced $Tc_{H_2O}$ per unit $C_{osm}$ during the natriuresis induced by hypertonic saline in antidiuretic hypertensive patients. Together with the present findings the accumulated observations suggest that at least some of the impaired urinary dilution and “distal” sodium rejection observed in hypertensive patients during ECF volume expansion results from a defect in sodium reabsorption in the ascending limb of the loop of Henle.

The curvilinear positive correlation between the level of mean arterial blood pressure and tubular sodium rejection observed in the normal and hypertensive subjects during the D/W infusions (fig. 5) suggests that renal arterial pressure is in some way involved in the mechanism for increased sodium rejection by the latter group. Rough correlations between the magnitude of natriuresis and the height of blood pressure have been reported in several studies of hypertensive patients receiving saline loads. In
addition, a variety of renal perfusion studies have indicated that increases of renal arterial blood pressure may increase urinary salt and water excretion without affecting glomerular filtration rate. In stop-flow studies of Tobian and associates the “distal” nephron was the site of impaired sodium reabsorption in rat kidneys that were perfused with blood at elevated pressures.

Although depressed glomerular filtration rate and renal blood flow were to some extent correlated with increased \( E/F_{\text{Na}} \% \) in the present studies, these correlations were less significant than the linear positive relationship between the degree of tubular sodium rejection and the calculated renal vascular resistance (fig. 6). This finding is similar to the direct correlation between salt rejection and renal vascular resistance noted by Cottier, Weller, and Hoobler in a group of hypertensive patients given saline infusions. Renal vascular resistance is a numerical expression of the intensity of hypertensive renovascular disease; these observations therefore suggest that alterations of renal pressure and vascular resistance in the kidneys of hypertensive patients may determine the increased salt rejection exhibited by these patients during saline, mannitol, or 5% D/W infusions.

It has been suggested that proximal tubular sodium reabsorption is regulated by a natriuretic hormone of extrarenal or intrarenal origin. Whether greater amounts of a postulated natriuretic hormone are elicited by volume expansion in patients with increased blood pressure and increased vascular resistance, or whether normal amounts of this substance elicit greater natriuresis in hypertensive patients because of abnormalities of renal hemodynamics are questions that await further study.

Alternatively, physical factors may influence tubular sodium transport. Earley and associates have provided evidence to support the hypothesis that transmission of arterial blood pressure along the renal vasculature may act to inhibit tubular sodium transport, possibly by altering renal interstitial volume. In the present studies during water diuresis the rejection fraction of sodium was directly related not only to the rejection fraction of total solute (\( E/F_{\text{om}} \% \)) but also to that of filtered water (\( V/GFR \% \)). Such a balance between the fractional excretion of sodium and water is not characteristic of the action of any known hormone and suggests that the changes in sodium and water output were mediated by physical factors. Mechanisms whereby the combination of increased blood pressure and increased renal vascular resistance could produce proportionate changes in the tubular rejection of filtered sodium, solute, and water during ECF expansion in hypertensive man remain speculative at this time. It is conceivable however that (1) medullary washout secondary to a pressure induced increase in medullary blood flow; (2) increased passive back diffusion of reabsorbed sodium and water due to altered pressure and resistance in peritubular capillaries, or (3) a pressure-induced distortion of the normal relationship between the quantity of glomerular filtrate and tubular volume, with a consequent increased linear velocity of tubular flow, could contribute to a hemodynamically mediated natriuresis in these patients.

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