Electrolyte and Water Excretion in Arterial Hypertension
II. Studies in Subjects with Essential Hypertension after
Antihypertensive Drug Treatment

By William Hollander, M.D., and Walter E. Judson, M.D.

The increased capacity of hypertensive subjects to excrete sodium is frequently reduced by effective antihypertensive drug treatment. This reduction in sodium excretion is not necessarily associated with changes in renal hemodynamic function or resting sodium excretion. It appears to result from an alteration in renal tubular activity. The findings suggest that the arterial pressure per se may operate to control sodium excretion. They also are consistent with the hypothesis that certain disturbances in sodium excretion in arterial hypertension may be the result and not necessarily the cause of an elevated blood pressure.

The renal excretory responses to hypertonic saline infusions have been shown by several workers to be different in hypertensive than in normotensive subjects. Although both groups show increases in sodium excretion following an infusion of concentrated saline solution, the increases are significantly greater in the hypertensive than in the normotensive group. These differences in the renal capacity to excrete sodium appear to be due to differences in the renal tubular handling of sodium. In a recent study on normotensive subjects and patients with essential hypertension not treated with drugs, sodium excretory capacity was observed to correlate significantly with arterial blood pressure but not with renal plasma flow, glomerular filtration rate or control sodium excretion. In view of these findings the present study was undertaken mainly in the same group of hypertensive subjects to determine whether a chronic lowering of the blood pressure produced by antihypertensive drug therapy might be accompanied by a reduction in sodium excretory capacity.

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Supported in part by a grant from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service.

Material and Methods

Eleven subjects with essential hypertension were studied who were compensated and had no history of congestive heart failure. All had grade 1 to 2 hypertensive retinopathy but a normal blood urea nitrogen. The routine urine analysis was normal except in 4 subjects, F. P., R. O., C. F., and J. W. who had 1+ albuminuria. One of the subjects, V. V., had a bilateral lumbodorsal sympathectomy 4 years prior to the study.

During the control period, which was at least 3 months in duration, the subjects were given placebos. After this period, the group was treated continuously with oral antihypertensive drugs for 3 to 13 months. Five subjects received hydralazine, 3 others were given reserpine, and the remaining 3 received hexamethonium. The daily dosages and duration of treatment for each subject are listed in Table I. Throughout the study clinical observations of blood pressure were obtained in the supine position at 2 to 3 week intervals. At no time was the dietary intake of salt restricted.

Renal studies identical to those previously described were carried out in the same individual before and after the antihypertensive drug treatment. On the day of the test no medication was given. The subjects were studied in the morning in the postabsorptive state while lying supine. Urine was collected through an indwelling bladder catheter. Following the "control" period which consisted of 3 to 4 urine-collection periods of 10 to 15 minutes each, 300 ml. of 5 per cent sodium chloride was administered intravenously at the rate of 10 to 12 ml./min. At the end of the infusion a urine collection designated as "5 per cent NaCl" was made. Thereafter at least 3 additional urine collections were obtained in the
“recovery” period at intervals of 15 minutes. The brachial artery pressure was measured with an electromanometer and recorded by direct-writing oscillograph.

The measurements of para-aminohippuric acid and inulin clearances, hematocrit, and concentrations of sodium and potassium in the urine and serum were made by methods previously reported.

### Table 1.—Effect of Antihypertensive Drug Treatment on Renal Function

<table>
<thead>
<tr>
<th>Patient, age, sex</th>
<th>Treatment and duration</th>
<th>Procedure</th>
<th>$\text{C}_{\text{PAH}}$ ml./min./1.73 M.$^2$</th>
<th>$\text{C}_{\text{IN}}$ ml./min./1.73 M.$^2$</th>
<th>UV ml/min.</th>
<th>$\text{U}_{\text{Na}}, \text{V}$ (microEq./min.)</th>
<th>$\text{U}_{\text{K}}, \text{V}$ (microEq./min.)</th>
<th>Arterial pressure mm. Hg</th>
<th>S</th>
<th>D</th>
<th>M</th>
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<tr>
<td>C.C. 48 F</td>
<td>Control 6 mos.</td>
<td>Control</td>
<td>458</td>
<td>106</td>
<td>8.0</td>
<td>250</td>
<td>78</td>
<td>185/100/135</td>
<td>210/110/145</td>
<td>200/110/140</td>
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<td>5% NaCl</td>
<td>643</td>
<td>128</td>
<td>8.2</td>
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<td>9.3</td>
<td>1726</td>
<td>128</td>
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<td></td>
<td>Hydralazine 75 mg./day</td>
<td>Control</td>
<td>447</td>
<td>93</td>
<td>9.3</td>
<td>234</td>
<td>50</td>
<td>170/95/120</td>
<td>160/85/105</td>
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<td>601</td>
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<td>Recovery</td>
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<td>5.9</td>
<td>1131</td>
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<td>Hydralazine 75 mg./day</td>
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<td>84</td>
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<td>654</td>
<td>62</td>
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<td>5.1</td>
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<td>Reserpine 0.5 mg./day</td>
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RESULTS

The renal responses to intravenous 5 per cent sodium chloride before and after antihypertensive drug treatment are summarized in Table 1. The statistical analyses of the responses are given in Table 2.

\textbf{PAH Clearance (Renal Plasma Flow).} The renal plasma flow at rest and during and following the saline infusion was not significantly altered by treatment. The increases in renal plasma flow that followed the saline infusion were likewise not significantly different after treatment.

\textbf{Inulin Clearance (Glomerular Filtration Rate).} The glomerular filtration rates before and after the intravenous saline load were not significantly different from the values obtained before treatment (figs. 1 and 2). Although significant increases in glomerular filtration rate occurred before but not after...
ELECTROLYTE AND WATER EXCRETION IN HYPERTENSION

Fig. 1 Left. The effect of oral hydralazine therapy on the renal responses to intravenous hypertonic saline in a subject with essential hypertension.

Fig. 2 Right. The effect of oral reserpine therapy on the renal responses to intravenous hypertonic saline in a subject with essential hypertension.

treatment, statistically they were not significantly greater than those after treatment.

Urine Volume (UV). The control urine flow after treatment was not significantly different from the flow prior to treatment. However, during and following the saline infusion, urine excretion was significantly less after than before treatment. As opposed to an insignificant change in urine flow during the recovery period before treatment, urine flow after treatment decreased significantly in this period (fig. 1).

Sodium Excretion (UsV). The control sodium excretion, which was elevated in the group, was not significantly altered by treatment. However, the excretion of sodium following the saline infusion was significantly less after than before treatment by a mean of 556 microEq./min. This marked reduction in sodium excretion toward normal after treatment was due to significantly smaller increases in sodium excretion in the recovery period after than before treatment (figs. 1 and 2).

In the 3 subjects (R.D., C.P., and J.W.) who had not received an infusion of PAH and inulin either before or after treatment, sodium excretion at rest and in response to intravenous hypertonic saline was not noticeably different from the values of sodium excretion obtained in the remaining subjects who had received such an infusion.

Ratio of Excreted Sodium to Filtered Sodium (E/F Sodium). The calculated ratio of excreted sodium to filtered sodium (E/F Na) in the control period after treatment was not significantly different from the ratio before treatment. Both before and after treatment the E/F Na significantly increased after the saline infusion. The increase in the ratio, however, was significantly less after than before treatment.

Potassium Excretion. Potassium excretion before and after the infusion of saline was not significantly altered by treatment. Although significant increases in potassium excretion occurred during the saline infusion before but not after treatment, statistically they were not significantly greater than those after treatment.

Arterial Hematocrit. After treatment the arterial hematocrit at rest and following the saline infusion was not significantly different from the hematocrit obtained before treat-
## Table 2.—Mean Data and Statistical Analysis

<table>
<thead>
<tr>
<th></th>
<th>PAH clearance (ml./min./1.73 M²)</th>
<th>Inulin clearance (ml./min./1.73 M²)</th>
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</thead>
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<tr>
<td></td>
<td>Control 5% NaCl 5% NaCl control p</td>
<td>Recovery Recovery control p</td>
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<td></td>
<td>425 ± 34 557 ± 61 ±30 12 &lt;0.01</td>
<td>550 ± 52 ±29 &lt;0.01</td>
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<tr>
<td>Therapy</td>
<td>468 ± 45 553 ± 53 ±22 &lt;0.01</td>
<td>546 ± 41 ±24 0.02</td>
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<tr>
<td>Mean</td>
<td>43 ± 20 -4 ± 41 ±22 &lt;0.01</td>
<td>-5 ± -5 ±36 0.02</td>
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<td>Diff.</td>
<td>0.08 &gt;0.9 0.2 0.2</td>
<td>0.9 ± 0.2</td>
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<tr>
<td>UV (ml./min.)</td>
<td>Control 6.0 ± 1.1 0.01 7.3 ± 1.2 0.4</td>
<td>0.01 1349 ± 167 ±161 0.01</td>
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<td>Therapy 6.7 ± 1.0 0.8 6.4 ± 1.1 0.8</td>
<td>4.1 ± 0.7 ±9 0.02</td>
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<td>Mean</td>
<td>+0.6 ± 1.3 6.3 ± 1.3 +0.8 ± 1.3 0.01</td>
<td>+5 ± -43 ±7 0.01</td>
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<td>Diff.</td>
<td>0.7 ± 0.02 &lt;0.01 ±0.01 0.01</td>
<td>&gt;0.9 0.08 ±0.02 &lt;0.01</td>
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<td>E/F Na (%)</td>
<td>Control 3.1 ± 0.7 8.2 ± 0.9 5.1 ± 1.0 0.01</td>
<td>8.8 ± 0.8 ±5.7 ±0.5</td>
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<td>Therapy 3.2 ± 0.8 6.1 ± 1.4 2.9 ± 0.8 0.01</td>
<td>5.7 ± 0.8 ±2.4 ±0.5</td>
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<td>Mean</td>
<td>+0.1 ± 0.9 ±1.4 ±1.3 ±0.8 ±0.7 0.01</td>
<td>+19 ± -9 ±28 ±3 ±18 ±37 0.01</td>
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<td>Diff.</td>
<td>&gt;0.9 ± 0.2 ±0.08 &lt;0.01 ±0.01 &lt;0.01</td>
<td>0.5 ± 0.6 ±0.3 0.2 0.2</td>
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</table>

<table>
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<tr>
<th>Hematocrit (%)</th>
<th>Mean arterial pressure (mm. Hg)</th>
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<td>Control 41.5 ± 1.0 38.2 ± 1.0 37.3 ± 0.4 0.01</td>
<td>144 ± 6 143 ± 6 ±0 0.9 143 ± ±6 ±2 0.7</td>
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<tr>
<td>Therapy 43.6 ± 0.9 38.8 ± 1.2 ±0.9 ±0.9 0.01</td>
<td>121 ± 6 ±6 ±18 ±3 ±12 0.3 120 ± ±5 ±2 ±0.5</td>
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<td>Mean +2.1 ±0.2 ±0.4 ±1.0 ±0.7 ±2.3 0.01</td>
<td>±23 ± ±25 ±2 ±23 ±0.01 0.5 ± ±4 ±4 ±0.2</td>
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<td>Diff. +0.07 ±0.5 ±0.9 ±0.1 ±0.1 ±0.1 0.01</td>
<td>&lt;0.01 &lt;0.01 ±0.6 ±0.01 &lt;0.01 ±0.1 0.9</td>
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Hematocrit. Both before and after treatment the hematocrit was significantly reduced by the hypertonic infusion.  

Arterial Pressure. Following treatment the average mean brachial arterial pressure at rest remained elevated but was significantly re-
duced by 22 mm. Hg. The insignificant changes in blood pressure caused by the saline infusion were not significantly different before and after treatment. In general, before and during treatment the averages of the clinically measured arterial pressures were the same as those obtained by direct intra-arterial measurements.

**Discussion**

The increased capacity of subjects with essential hypertension to excrete sodium was significantly reduced toward normal by antihypertensive drug therapy. The reduction in sodium excretory capacity appeared to result from an alteration in renal tubular activity, since the calculated load of filtered sodium was not significantly different after than before treatment. Although sodium excretion following an infusion of hypertonic saline was significantly decreased by drug treatment, the control sodium excretion remained elevated. The latter finding is in contrast to the significant reduction in control sodium excretion reported by Green and associates in a larger group of treated hypertensive subjects. The present observations nevertheless suggest that sodium excretory capacity does not necessarily depend upon the control sodium excretion. The changes in sodium excretion following treatment likewise do not appear to be due to alterations in body fluid and electrolyte composition, since it has been found in collateral studies that exchangeable body sodium, potassium, and extracellular fluid volume are not significantly altered by hypotensive treatment. These findings also argue against a direct blocking action by hypotensive drugs on the renal excretion of sodium.

A reduction in blood pressure produced by surgical as well as medical treatment in subjects with essential or renal hypertension has likewise been found to be accompanied by a reduction in sodium excretory capacity. These findings are consistent with the hypothesis that the renal capacity to excrete sodium is in part regulated by the arterial pressure. Studies by Selkurt and by Epstein and co-workers on the renal responses to acute alterations in blood pressure suggest that the effect of arterial pressure on sodium excretion might be a direct one on renal tubular function.

Other factors that have been shown to be capable of altering sodium excretory capacity are the dietary intake of salt and the level of adrenal cortical activity. It is therefore conceivable that a reduction in salt intake or adrenal cortical activity might operate after antihypertensive treatment to reduce sodium excretory capacity. However, such changes in diet and in adrenal function following treatment were not apparent from the clinical findings, the control sodium excretion, or the measurements of exchangeable body sodium, potassium, and extracellular fluid volume.

**Summary**

The increased capacity of hypertensive subjects to excrete sodium is significantly reduced toward normal by antihypertensive drug treatment. The reduction in sodium excretory capacity appears to result from an alteration in renal tubular function. The findings suggest that the arterial pressure per se may play an important role in the control of sodium excretion. It therefore is conceivable that certain disturbances in electrolyte and water metabolism in essential hypertension may be the result and not necessarily the cause of an elevated blood pressure.

**Summario in Interlingua**

Le augmentate capacitate de subjectos hypertensive a excerner natrium es reduceit significativemente in le direction de valores normal per un therapia a drogas antihypertensive. Le reduction del capacitate excretoiri por natrium resulta apparentemente ab un alteration del function del tubulos renal. Le constatation suggere que le pression arterial per se ha possibilemente un rolo importante in le regulation del excretion de natrium. Per consequence il es conceipibile que certe disturbationes del metabolismo del electrolitatos e de agua in casos de hypertension essential es le effecto e non necessarimente le causa de un elevate pression del sanguine.
REFERENCES


In a clinical and pathologic study of the cardiovascular and renal lesions of 17 autopsied patients with Cushing's syndrome, hypertension was found in all patients even though only 2 were more than 40 years of age. In 15 patients the heart was enlarged. Three patients died in congestive heart failure with pulmonary edema. In 8 patients changes in the arterioles of the kidneys, liver, pancreas, and skeletal muscles were demonstrated that could not be differentiated from the arteriolar lesions frequently associated with essential hypertension. In 11 patients renal calculi or nephrocalcinosis or both were found, and in 8 per cent these osteoporosis was also present. The results of this study emphasize the seriousness of Cushing's syndrome from the standpoint of changes in the cardiovascular system and kidneys of a relatively young group of patients.

Sagall
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Circulation. 1958;17:576-582
doi: 10.1161/01.CIR.17.4.576
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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