Metabolic Studies on Hypertensive Patients with Suppressed Plasma Renin Activity Not Due to Hyperaldosteronism

By OSCAR M. HELMER, PH.D., AND WALTER E. JUDSON, M.D.

SUMMARY

Metabolic data obtained during sodium depletion (10-mEq Na, 90-mEq K diet plus thiazide) from 13 hypertensive patients (HT) with low plasma renin activity (PRA) were compared with data from 15 normotensive subjects and three patients with renovascular hypertension (RHT). With Na depletion plasma renin activity and urinary aldosterone excretion increased promptly in NT and RHT. In contrast, PRA in HT after 5 days of Na depletion was only one third that of the NT after 2 days of depletion, and aldosterone excretion did not change significantly. This depressed renin and aldosterone response in HT can be overcome by extending the depletion period and administering spironolactone. In HT, Na and loss of weight was significantly lower than in NT. HT Negroes retained more potassium than HT whites and four out of seven NT Negroes and none of eight NT white subjects had a positive K balance. The hypertension of patients with low PRA appears to be due to genetic or environmental factors or to both.

Additional Indexing Words:
Alcohol excretion  Sodium depletion  Spironolactone

THE DEVELOPMENT of methods for the assay of renin activity in human plasma has made it possible to separate from the hypertensive population an interesting group of patients with suppression of renin secretion. In 174 of our original group of 600 patients with hypertension,1 renin could not be detected in the peripheral plasma. Although a great deal of interest was aroused by reports that suppression of renin activity occurs in hypertensive patients with primary aldosteronism,2 the prevalence of primary aldosteronism among hypertensive patients with renin suppression has not yet been ascertained.3-7 In 1954, Helmer and associates8 reported studies on sodium exchange in the gastrointestinal tract of patients with essential hypertension in whom they found a greater amount of sodium available for exchange with a cationic resin than in normotensive subjects. Since it is now known that aldosterone causes an increased absorption of sodium from the colon those patients could not be classified as having hyperaldosteronism.9

In this study, metabolic data obtained during severe sodium depletion in a group of hypertensive patients with low renin activity in peripheral plasma were compared with data from normotensive subjects and patients with renovascular hypertension. Since McDonough and his colleagues10 have postulated that the higher incidence of hypertension in the Negro might be due to the frequency of a hypertensive gene, approximately equal numbers of Negro and white subjects were included in both the control and hypertensive...
groups. The data to be presented indicate that renin suppression in the patients with essential hypertension cannot be attributed to primary aldosteronism. It appears more likely that suppressed renin activity reflects a more subtle alteration of electrolyte metabolism due to genetic factors.

Methods

Diuretic drugs were withdrawn for at least 2 weeks before patients were admitted to the Clinical Research Ward. The 13 hypertensive patients (seven white and six Negro) with low renin activity in plasma were placed on regular house diet for the initial 3 days. During the following 5-day sodium depletion period, the subjects received a 10-mEq sodium, 90-mEq potassium diet, analyzed daily for variations in components. Cyclothiazide (Anhydron K), 2 mg, was given orally every morning during the experimental period.

The 15 normotensive control subjects (eight white and seven Negro) were admitted to the ward on Friday afternoon and discharged Monday morning. Their sodium depletion regimen was the same as that of the hypertensive patients except that the depletion period was shortened to 2 days.

To obtain metabolic data on hypertensive patients who respond to sodium depletion with an increase in renin secretion, three patients with renovascular hypertension were also placed on the 5-day sodium depletion regimen. Diagnosis was established in these patients by arteriography, Stamey test, and assay of renin in renal venous blood.11 In addition, three of the 13 hypertensive patients were placed on the sodium depletion regimen for 10 days with the administration of the aldosterone antagonist, spironolactone (Aldactone A), during the last 5 days to determine the degree to which renin suppression could be overcome.

Plasma-renin activity (PRA) was assayed by the method of Helmer and Judson.12 Values were expressed in nanograms (ng) of angiotensin/ml/hr. Normal values in recumbency range from 0 to 1.9 ng (mean, 0.75 ng); ambulatory values range from 0.35 to 2.8 ng (mean, 1.6 ng). Twelve plasma samples ranging in renin activity from 0.49 to 9.10 ng/ml/hr were assayed in duplicate; so of the mean = 0.057. At 8 a.m. blood was obtained after the patients had been in a recumbent position for at least 30 min. Between 11:00 and 11:30 a.m. blood samples were collected after 2 or 3 hr of ambulation.

Urinary aldosterone excretion was determined by Bio-Science Laboratories, the normal range being 3 to 32 μg/24 hr.

The urinary and serum electrolytes were analyzed with the Technicon Auto Analyzer, as were serum uric acid, blood sugar, and urinary creatinine.

Blood volume was determined by the RISA technique by the staff of the radioisotope laboratory. Five microcuries of 131I human serum albumin were injected. Total blood radioactivity was measured with the use of a 10-min equilibrium sample and plasma volume calculated from the diluent volume and venous hematocrit.13 Results were expressed as a percentage of the normal expected value by means of Hidalgo and associates,14 modification of Allen's height-body mass prediction formula.15

In addition, the following analyses were performed: Urinary catecholamines, 17-ketosteroids, and 17-hydroxycorticosteroids, urinary pH, total serum proteins, albumin-globulin ratio, blood urea nitrogen, 15-min PSP excretion, and creatinine clearance. Complete blood counts, concentrations of hemoglobin hematocrit values, and x-ray films of the chest were obtained.

The patients were weighed daily, and blood pressure was recorded four times daily with the patients lying and standing.

Results

Control data on the hypertensive patients obtained on the third day of house diet are presented in table 1. Most of these subjects had low renin activity values in peripheral plasma when examined as outpatients on two or more occasions before being admitted to the Research Ward. Not shown in the table are the urinary-free catecholamine values which were in the normal range for all of these patients.

In table 2, control data on the normotensive subjects are presented. The only significant differences between the normotensive and hypertensive groups at the <0.05 mEq/L level are those for serum sodium (tables 1 and 2). The mean value for serum sodium for the hypertensive patients was 141.3 mEq/L compared to 138.2 for the normotensive subjects.

Figure 1 illustrates the degree of renin response to sodium depletion in the hypertensive patients as compared with normotensive control subjects. After 2 days of sodium depletion, the mean value for renin activity in the plasma of the normotensive subjects
### Table 1

**Control Data on 13 Hypertensive Subjects**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age, sex</th>
<th>B.P. (mm Hg)</th>
<th>Duration of hypertension (yr)</th>
<th>Serum electrolytes (mEq/L)</th>
<th>Fasting blood glucose (mg%)</th>
<th>BUN (mg%)</th>
<th>Blood vol.% of normal</th>
<th>Aldosterone excreted (µg/24 hr)</th>
<th>Plasma renin activity (ng/ml/hr)</th>
<th>Ambulatory</th>
<th>Reclining</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 MN</td>
<td>L170/130</td>
<td>8</td>
<td>140 4.8 103 29.0</td>
<td>110 17</td>
<td></td>
<td></td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>54 MN</td>
<td>L170/130</td>
<td>3</td>
<td>139 5.0 104 26.0</td>
<td>91 9</td>
<td></td>
<td></td>
<td>32</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>53 FN</td>
<td>L190/110</td>
<td>20</td>
<td>141 4.4 105 25.5</td>
<td>89 16</td>
<td>+11.2</td>
<td></td>
<td>28</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>47 FW</td>
<td>L190/98</td>
<td>12</td>
<td>144 5.3 105 27.5</td>
<td>90 26</td>
<td>+25.0</td>
<td></td>
<td>23</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5*</td>
<td>60 MW</td>
<td>L228/120</td>
<td>2</td>
<td>142 4.7 105 26.5</td>
<td>102 16</td>
<td></td>
<td></td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6*</td>
<td>48 FW</td>
<td>L190/110</td>
<td>16</td>
<td>141 4.4 108 25.0</td>
<td>105 15</td>
<td>+5.0</td>
<td></td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>55 MW</td>
<td>L228/138</td>
<td>11</td>
<td>142 4.6 101 32.0</td>
<td>102 16</td>
<td></td>
<td></td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>48 MN</td>
<td>L150/110</td>
<td>9</td>
<td>143 3.7 104 26.0</td>
<td>104 12</td>
<td>+16.1</td>
<td></td>
<td>24</td>
<td>0</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>9*</td>
<td>47 MW</td>
<td>L167/108</td>
<td>0.5</td>
<td>140 4.2 98 28.0</td>
<td>85 12</td>
<td>+12.1</td>
<td></td>
<td>10</td>
<td>0.26</td>
<td>1.33</td>
<td></td>
</tr>
<tr>
<td>10*</td>
<td>57 FW</td>
<td>L192/98</td>
<td>10</td>
<td>143 4.0 102 28.5</td>
<td>120 18</td>
<td></td>
<td></td>
<td>17.2</td>
<td>0.63</td>
<td>1.14</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>34 FW</td>
<td>L144/100</td>
<td>4</td>
<td>138 4.6 102 25.0</td>
<td>76 23</td>
<td>+42.1</td>
<td></td>
<td>12</td>
<td>0.49</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>54 MN</td>
<td>L208/124</td>
<td>9</td>
<td>140 5.1 104 28.0</td>
<td>103 18</td>
<td>+11.0</td>
<td></td>
<td>23</td>
<td>0.90</td>
<td>1.02</td>
<td></td>
</tr>
<tr>
<td>13*</td>
<td>50 FN</td>
<td>L223/138</td>
<td>10</td>
<td>142 4.0 103 28.0</td>
<td>128 12</td>
<td>+10.4</td>
<td></td>
<td>4</td>
<td>1.40</td>
<td>1.93</td>
<td></td>
</tr>
</tbody>
</table>

*Positive glucose tolerance test. Abbreviations: BUN = blood urea nitrogen; L = lying; S = supine.
### Table 2

**Control Data on 15 Normotensive Subjects**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, race, sex</th>
<th>B.P. (mm Hg)</th>
<th>Serum electrolytes (mEq/L)</th>
<th>Fasting blood glucose (mg%)</th>
<th>BUN (mg%)</th>
<th>Blood vol.% of normal</th>
<th>Aldosterone excreted (ug/24 hr)</th>
<th>Plasma renin activity (ng/ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29 FN</td>
<td>L134/87</td>
<td>137 Na, 4.3 K, 108 Cl, 26.5 CO₂</td>
<td>100</td>
<td>15</td>
<td>-5.1</td>
<td>17</td>
<td>0.61</td>
</tr>
<tr>
<td>2</td>
<td>22 MW</td>
<td>L116/66</td>
<td>131 Na, 4.3 K, 104 Cl, 27.2 CO₂</td>
<td>106</td>
<td>9</td>
<td></td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>28 MW</td>
<td>L123/77</td>
<td>133 Na, 4.3 K, 104 Cl, 29.5 CO₂</td>
<td>99</td>
<td>17</td>
<td>-2.9</td>
<td>28</td>
<td>0.39</td>
</tr>
<tr>
<td>4</td>
<td>28 MW</td>
<td>L132/93</td>
<td>132 Na, 4.1 K, 102 Cl, 28.5 CO₂</td>
<td>102</td>
<td>14</td>
<td></td>
<td>6</td>
<td>0.53</td>
</tr>
<tr>
<td>5</td>
<td>23 MN</td>
<td>L125/75</td>
<td>138 Na, 4.3 K, 102 Cl, 29.0 CO₂</td>
<td>110</td>
<td>18</td>
<td>-6.4</td>
<td>0.98</td>
<td>1.19</td>
</tr>
<tr>
<td>6</td>
<td>27 MN</td>
<td>L137/83</td>
<td>144 Na, 4.4 K, 101 Cl, 30.5 CO₂</td>
<td>81</td>
<td>11</td>
<td>+16.2</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>23 MW</td>
<td>L117/82</td>
<td>141 Na, 5.1 K, 100 Cl, 29.5 CO₂</td>
<td>82</td>
<td>16</td>
<td>-12.5</td>
<td>8</td>
<td>0.35</td>
</tr>
<tr>
<td>8</td>
<td>24 MW</td>
<td>L105/76</td>
<td>141 Na, 4.0 K, 104 Cl, 27.5 CO₂</td>
<td>98</td>
<td>15</td>
<td>+14.0</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>24 FN</td>
<td>L104/66</td>
<td>142 Na, 4.9 K, 100 Cl, 28.0 CO₂</td>
<td>82</td>
<td>10</td>
<td></td>
<td>19</td>
<td>0.63</td>
</tr>
<tr>
<td>10</td>
<td>47 MN</td>
<td>L121/84</td>
<td>139 Na, 4.6 K, 106 Cl, 27.0 CO₂</td>
<td>85</td>
<td>16</td>
<td>-15.5</td>
<td>0</td>
<td>1.12</td>
</tr>
<tr>
<td>11</td>
<td>19 FN</td>
<td>L108/74</td>
<td>133 Na, 4.1 K, 109 Cl, 23.5 CO₂</td>
<td>106</td>
<td>11</td>
<td>+18.9</td>
<td>20</td>
<td>0.74</td>
</tr>
<tr>
<td>12</td>
<td>24 FW</td>
<td>L107/63</td>
<td>141 Na, 4.5 K, 104 Cl, 28.5 CO₂</td>
<td>90</td>
<td>12</td>
<td>+19.7</td>
<td>29</td>
<td>1.58</td>
</tr>
<tr>
<td>13</td>
<td>19 FW</td>
<td>L104/76</td>
<td>143 Na, 4.6 K, 107 Cl, 28.0 CO₂</td>
<td>96</td>
<td>14</td>
<td>+6.4</td>
<td>29</td>
<td>0.67</td>
</tr>
<tr>
<td>14</td>
<td>20 FW</td>
<td>L119/58</td>
<td>141 Na, 4.5 K, 107 Cl, 29.0 CO₂</td>
<td>95</td>
<td>15</td>
<td>+23.1</td>
<td>14</td>
<td>0.35</td>
</tr>
<tr>
<td>15</td>
<td>21 FN</td>
<td>L118/80</td>
<td>138 Na, 4.4 K, 103 Cl, 25.5 CO₂</td>
<td>94</td>
<td>12</td>
<td>-13.9</td>
<td>7</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Same abbreviations as table 1.
in the recumbent position was 2.8 times higher than that of the hypertensives following 5 days of sodium depletion. After ambulation, the difference increased to 3.6 fold.

The lower panel of figure 2 shows that urinary aldosterone excretion mirrors renin activity. In the normotensive group, the sharp increase in renin secretion, as previously shown in figure 1, stimulated a prompt elevation of aldosterone excretion \( P < 0.02 \). In the hypertensive patients, the statistically insignificant \( P < 0.2 \) increase in aldosterone excretion was in keeping with the small elevation of renin activity from the stress of 5-day sodium depletion. Only two of the patients had aldosterone excretion values above the normal range on the fifth day. Patient 2, table 1, had a 32 \( \mu \)g urinary aldosterone excretion value during the control period which fell to 9 \( \mu \)g on the second day and 16 \( \mu \)g on the fifth day of Na depletion.

In the upper panel of figure 2 the data on changes in blood volume with sodium depletion are shown. The normotensives fell from a +3.5 to -10.5% after 2 days while the hypertensives dropped from a mean value of +16.6% in the control period to +5.0% after 5 days of sodium depletion. Although the control values for the hypertensive patients are higher than for the normotensive subjects, the difference is not statistically significant \( P < 0.1 \).

Control data from patients with renovascular hypertension are presented in table 3. The significant increases in values for PRA and urinary aldosterone excretion after 5 days of sodium depletion are also shown.

**Cumulative Sodium and Potassium Balances**

Figure 3 demonstrates the effect of the sodium depletion regimen on cumulative sodium and potassium balances in the hypertensive and normotensive subjects. On the second day of depletion, the mean sodium loss was 159 mEq/m² of body surface area (BSA) for the normotensives compared to 87.6 mEq for the hypertensive group \( P < 0.001 \). Even after 5 days of sodium depletion, the loss of sodium by the hypertensive

---

**Figure 1**

Effect of Na depletion on renin activity in plasma expressed in ng angiotensin formed on incubation. Horizontal open bars mark depletion period. Dots joined by solid lines represent recumbent renin activity. Those joined by broken lines are ambulatory values. The vertical bracketed lines show range.

**Figure 2**

Effect of Na depletion on blood volume and urinary aldosterone excretion. Horizontal open bars mark depletion periods.

**Figure 3**

Effect of Na depletion on cumulative sodium and potassium balances in the hypertensive and normotensive subjects. On the second day of depletion, the mean sodium loss was 159 mEq/m² of body surface area (BSA) for the normotensives compared to 87.6 mEq for the hypertensive group \( P < 0.001 \). Even after 5 days of sodium depletion, the loss of sodium by the hypertensive
Data on Three Patients with Renovascular Hypertension

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age, race, sex</th>
<th>Control B.P. (mm Hg)</th>
<th>Duration of hypertension</th>
<th>Control serum electrolytes (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45 MW*</td>
<td>L156/107 S148/114</td>
<td>4 wks.</td>
<td>Na 140 K 4.4 Cl 104 CO2 26.0</td>
</tr>
<tr>
<td>2</td>
<td>42 FW</td>
<td>L106/106 S154/115</td>
<td>3 yr.†</td>
<td>Na 142 K 4.2 Cl 104 CO2 29.5</td>
</tr>
<tr>
<td>3</td>
<td>58 MW</td>
<td>L223/130 S199/131</td>
<td>3 mo.</td>
<td>Na 142 K 4.2 Cl 105 CO2 26.0</td>
</tr>
</tbody>
</table>

*Positive glucose tolerance test.
†Hypertension 10 years ago with pregnancy.

depression the mean weight loss in hypertensives in the same units was 1.20, which is not statistically different from the 2-day weight loss in normotensives.

As shown in figure 4, the Negro hypertensive patients had a greater positive potassium balance and a greater negative sodium balance than the white hypertensives. The three white patients with renovascular hypertension had not only a greater negative sodium balance but also a greater negative potassium balance, which did not differ significantly from
that of the normotensives. There was also no statistical difference in sodium balance between white and Negro normotensive control subjects. Although the 2-day cumulative potassium balance for the Negro controls was +2.1 compared to −12.9 mEq/m² BSA for the white normotensives, the difference was not significant (P < 0.11).

In figure 5 the 2-day potassium balances of individual normotensive and hypertensive subjects are plotted against renin activity in plasma. It was interesting to note that four of the seven Negro controls had positive potassium balances which fell into the range of the hypertensive patients with renin suppression. One of these normotensive subjects (no. 1, table 2) also had values for PRA after 2 days of sodium depletion that did not exceed the upper range of the hypertensive group. In contrast, none of the eight white normotensives had a positive potassium balance.

**Effect of Sodium Depletion on Serum Electrolytes**

As shown in table 4, there was a prompt fall in serum chloride and an equally prompt rise in bicarbonate concentration in the three groups. In only the patients with renovascular occlusive disease was there a significant fall in potassium values. There was a significant fall in serum sodium in both hypertensive groups.

**Effect of Renin Activity in Plasma on Blood Pressure**

The mean blood pressure of the patients with essential hypertension, as a group fell

<table>
<thead>
<tr>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect of Na Depletion on Serum Electrolytes (Mean Values with Standard Error)</strong></td>
</tr>
<tr>
<td><strong>Hypertensives with low renin activity</strong></td>
</tr>
<tr>
<td>Na</td>
</tr>
<tr>
<td>K</td>
</tr>
<tr>
<td>Cl</td>
</tr>
<tr>
<td>CO₂</td>
</tr>
<tr>
<td><strong>Normotensives</strong></td>
</tr>
<tr>
<td>Na</td>
</tr>
<tr>
<td>K</td>
</tr>
<tr>
<td>Cl</td>
</tr>
<tr>
<td>CO₂</td>
</tr>
<tr>
<td><strong>Renovascular hypertensives</strong></td>
</tr>
<tr>
<td>Na</td>
</tr>
<tr>
<td>K</td>
</tr>
<tr>
<td>Cl</td>
</tr>
<tr>
<td>CO₂</td>
</tr>
</tbody>
</table>

*mEq/L.*
10.6% in the lying and 22.2% in the standing position following Na depletion. Individually, the patients showed an interesting relationship between renin activity in response to sodium loss and the height of blood pressure at the end of the depletion period. Figure 6 shows that patients with higher PRA/100 mEq of Na loss/m² BSA had higher values for mean blood pressure. The correlation coefficient with lying mean pressure is 0.78335 ($P < 0.01$), with standing mean pressure, 0.75899 ($P < 0.01$).

With the exception of one control subject (no. 1), who had the least increase in renin activity in the plasma as a result of Na depletion, there was no change in mean blood pressure in the normotensive group. This subject had a fall in mean blood pressure of 8 mm in the lying and 17 mm in the upright position.

**Effect of Addition of Spironolactone to Sodium Depletion Regimen of Hypertensive Patients**

As shown in figures 3 and 4, the cumulative Na loss plateaued at about 5 days of Na

**Figure 5**

Relationship of plasma renin activity after 2 days of Na depletion to cumulative K balance in hypertensive and normotensive subjects.

**Figure 6**

Relation of plasma renin activity to mean blood pressure on fifth day of Na depletion in patients with essential hypertension.

**Figure 7**

Stimulation of renin secretion in a hypertensive patient with renin suppression by a second course of Na depletion with the addition of Aldactone. Left side of figure, first admission; right side of figure, second admission after an interval of 8 months. Abscissa: open bars, days of thiazide administration; solid bars, Aldactone. Lower panel: open circles, recumbent PRA; solid circles, ambulatory PRA. Middle panel: solid circles, urinary aldosterone excretion with broken line marking upper limit of normal value (32 µg/24 hr); open circles, cumulative Na balance. Upper panel: solid line, lying blood pressure; broken line, standing blood pressure.
depletion. It was thought that it would be of interest to find out to what degree the administration of spironolactone could stimulate the release of renin by the kidney and consequently the synthesis of aldosterone by the adrenal cortex. To three patients with different degrees of suppressed PRA and whose aldosterone excretion did not rise above normal after the 5-day Na depletion regimen, spironolactone (Aldactone A, 150 mg daily in divided doses) was added on the sixth day of a 10-day Na depletion period.

Patient 8, table 1, had an increase in PRA of only 0.11 ng on his first admission. After an interval of 8 months this patient was readmitted to Research Ward. As an outpatient he was treated with cyclothiazide, reserpine, and guanethidine which were discontinued 16 days before readmission. As shown in figure 7, PRA began to rise the day before the administration of the Aldactone and subsequently rose to higher levels with the sharp increase in cumulative Na loss. Coincidently with the rise in PRA, aldosterone excretion increased to 45 µg/24 hr. In the 5-day depletion period of the first admission, endogenous creatinine clearance (corrected for surface area) fell from 89 to 79 ml (−13%) while in the 10 days of the second study it changed from 97 to 57 ml (−41%). In both balance studies there was a fall in blood pressure to near normal range. Over a period of 8 years this patient has responded well to antihypertensive therapy.

Patient 6, table 1, had no detectable PRA 8 years ago as an outpatient nor on her first

---

**Figure 8**

Stimulation of renin secretion in a hypertensive patient with renin suppression by a second course of Na depletion with the addition of Aldactone. Left side of figure, first admission; right side of figure, second admission after an interval of 5 months. Abscissa: open bars, days of thiazide administration; solid bars, Aldactone. Lower panel: open circles, recumbent PRA; solid circles, ambulatory PRA. Middle panel: solid circles, urinary aldosterone excretion with broken line marking upper limit of normal value (32 µg/24 hr); open circles, cumulative Na balance. Upper panel: solid line, lying blood pressure; broken line, standing blood pressure.

**Figure 9**

Effect of addition of spironolactone to Na depletion regimen of patient with highest renin response in control period. Abscissa: open bars, days of thiazide administration; solid bars, Aldactone. Lower panel: open circles, recumbent PRA; solid circles, ambulatory PRA. Middle panel: solid circles, urinary aldosterone excretion with broken line marking upper limit of normal value (32 µg/24 hr); open circles, cumulative Na balance. Upper panel: solid line, lying blood pressure; broken line, standing blood pressure.
admission to the Research Ward. She responded to Na depletion with the greatest increase of PRA of any patient with essential hypertension. The data on this patient are shown in figure 8. During the interval of 5 months before her second admission she was treated with one tablet daily of Eutron (pargyline hydrochloride and methyclothiazide). During the interval the urinary aldosterone excretion fell from 20 to 6 μg/24 hr. The serum K, which also fell to 3.4 mEq/L, promptly rose to 4.3 in the first 5 days of the second balance study. There was also a greater cumulative Na loss than in the same period of the first balance study. The administration of Aldactone caused only a minimal additional loss of Na. However, there was a three-fold increase in ambulatory PRA with an increase in urinary aldosterone excretion to 133 μg/24 hr. No fall in blood pressure occurred.

Patient no. 13, table 1, had been on metyldopa (Aldomet) and thiazide therapy until 2 weeks before admission for a 10-day balance study. The patient was obese but did not have congestive heart failure or impairment of kidney function. PRA values in the control period were the highest in the group but were still in normal range. Figure 9 shows that on the low Na diet plus thiazide, a significant increase in PRA did not occur. Even though the addition of Aldactone caused a further Na loss of 95 mEq/m² BSA the increase in PRA was modest and urinary aldosterone excretion increased to only 16 μg/24 hr from a value of 11 μg.

It is interesting to note that in patients 8 and 13 (figs. 7 and 9), in whom there was little difference in the lying and standing blood pressures, the values for recumbent and ambulatory PRA were less than for patient 6 (fig. 8) whose readings for standing blood pressure were generally much lower than those found in recumbency. This patient also had the lowest value for blood volume after aldosterone administration. Endogenous creatinine clearance fell from 97 to 57 ml/min (−41%) during the second admission of patient 8 who had a cumulative Na loss of 300 mEq/m² BSA, whereas patient 6, who lost 180 mEq of Na under the same regimen, had only a 5% decrease in creatinine clearance. The fall in creatinine clearance of patient 13, who had a Na loss of 190 mEq, was 21.5%. In all three patients there was a tendency for blood pressure to rise with the attainment of Na equilibrium. In patients 8 and 13 with the natriuresis produced by Aldactone, the blood pressure began to fall again. In patient 6, in whom Aldactone did not cause a natriuresis, no fall in blood pressure occurred. In this patient the dose of Aldactone may not have been sufficient to counteract the effect of the marked increase of aldosterone secretion on sodium reabsorption.

**Discussion**

The hypertension of the patients with suppression of renin activity in plasma presented in this paper cannot be due to primary aldosteronism because of the following findings: (1) Their urinary aldosterone excretion was not elevated in the control period. (2) Thiazide administration caused a positive potassium balance with no fall in serum potassium. (3) Judged by the response to severe sodium depletion, the adrenals of these hypertensive patients appear to have a reduced capacity to synthesize aldosterone. (4) The reduced ability to secrete aldosterone is most likely due to the reduction of the formation of angiotensin as the result of a prolonged suppression of renin secretion. In this respect the response of the adrenals in these patients is similar to that observed by Conn, and Biglieri and his colleagues after unilateral adrenalectomy for an aldosterone-producing tumor. Biglieri found that during the first month after the removal of such a tumor the excretion of aldosterone did not increase normally as a result of sodium restriction or angiotensin administration.

The findings in this paper on aldosterone excretion agree with those made earlier when cationic resins were administered to patients with essential hypertension. After 12 to 15 days of sodium depletion the resins took up 0.7 to 1.5 mEq of Na/g compared to 0.5
mEq for normotensive subjects and 5.0 mEq of Na/g of resins in adrenalectomized patients as reported by Emmerson and co-workers.\textsuperscript{17} After 30 to 60 days of Na depletion, sodium uptake per gram of resin fell to normal values. As shown in this report if sodium depletion is continued long enough, renin secretion can be overcome.

The finding that four out of seven normotensive Negro subjects responded to sodium depletion with potassium retention as did hypertensive patients with low PRA was interesting in view of our previous report demonstrating a 52\% incidence of suppressed PRA in hypertensive Negroes compared to 3\% in white hypertensives.\textsuperscript{18} Whether or not this finding proves to be an early manifestation of a genetic mechanism, it does point out the importance of studying normotensive members of families with a history of hypertension before adaptive changes occur.

Fasola and Helmer\textsuperscript{19} found that some children of hypertensive parents failed to respond to the stress of strenuous exercise with an increase in PRA as did their hypertensive parents. In preliminary work quoted by Helmer\textsuperscript{20} these authors found a marked increase in PRA as a result of exercise or tilting in the younger age group (7 to 15 yr) of 15 normotensive Negro children from six families with a history of hypertension. As age increased, there was a decrease in renin response until complete suppression occurred without an elevation of blood pressure. It is interesting to compare these findings with those of Dahl and associates\textsuperscript{21, 22} who has developed, by the use of a technique of selective inbreeding, two strains of rats: one very prone, the other very resistant to the development of hypertension after chronic excess salt feeding. He found that the earlier salt feeding was started, the more frequently hypertension developed. Dahl and associates have suggested that similar genetic factors operate in man.\textsuperscript{23}

As Tobian states, it is no wonder that a certain portion of the human population reacts to the biologically abnormal load of salt by becoming hypertensive.\textsuperscript{24} In the evolution of the vertebrates, survival depended on development of mechanisms which maintained a normal body content of sodium, and thus a normal circulation of blood and tissue fluids.\textsuperscript{25} With this biological background, the hypertension of the patients presented in the paper may be due to their adaptation to the high sodium content and not always adequate potassium intake of refined modern diets.\textsuperscript{26} These patients have normal urinary aldosterone excretion values, and with sodium depletion lose less sodium and retain more potassium than normal subjects or patients with renovascular hypertension. Their low plasma renin activity on control diets and decreased renin release from the kidney with sodium loss may indicate a disturbance of vascular tissue electrolyte distribution. Such abnormalities might be difficult to demonstrate by exchangeable sodium and potassium studies because of large differences in the distribution of Na, K, and water in intracellular and extracellular phases of vascular and skeletal muscle.\textsuperscript{27}

Our patients are obviously not similar to those described by Biglieri and associates\textsuperscript{28} with a deficiency of 17-hydroxylase in the adren gland nor to the father and son with low PRA reported by Sutherland and co-workers.\textsuperscript{29}

\textbf{Acknowledgment}

We wish to thank the staff of the Research Ward for their cooperation.

\section*{References}


Metabolic Studies on Hypertensive Patients with Suppressed Plasma Renin Activity Not Due to Hyperaldosteronism
OSCAR M. HELMER and WALTER E. JUDSON

_Circulation._ 1968;38:965-976
doi: 10.1161/01.CIR.38.5.965

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1968 American Heart Association, Inc. All rights reserved.
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:
http://circ.ahajournals.org/content/38/5/965

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/