Renin Release in Patients with
Benign Essential Hypertension

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Gosuke Inoue, M.D., Hitoshi Tagawa, M.D., and Hideo Ueda, M.D.

SUMMARY
In 16 of 28 patients with benign essential hypertension, reduction of mean arterial pressure to 75 to 120 mm Hg by infusion of sodium nitroprusside caused significant increase in renin release estimated by the renal-systemic difference of renin activity and renal plasma flow (RPF). The threshold at which renin release increased was shifted to a range that was intermediate between that previously reported for normotensive subjects and that for patients with renovascular hypertension, but the average magnitude of renin release was almost comparable to that in normotensive subjects. In the other 12 patients, no significant renin release occurred during reduction in pressure of comparable degree.

The difference in renin release was difficult to explain by the difference in severity of hypertensive disease or in sodium excretion, but increased renin release was usually associated with a decrease in RBF and a rise in renal vascular resistance, while insignificant release was usually associated with an insignificant change in RBF and a decrease in resistance. The average known duration of hypertension was significantly greater in the unresponsive patients. It is suggested that renal sympathetic nerve activity may be a factor in the variations in renin release in patients with essential hypertension.

Additional Indexing Words:
Pathogenesis of essential hypertension Renal blood flow Renal autoregulation
Sympathetic nerve activity Renal nerves Primary aldosteronism
Renovascular hypertension Sodium excretion Sodium nitroprusside

The role of the renin-angiotensin system in the pathogenesis of human essential hypertension is still unknown. Although circulating renin levels are usually within or near the normal range,1-18 the possibility still exists that the renal pressor system might be involved in the pathogenesis of this disease.14,15 Skinner and associates16,17 suggested that, if the renal pressor system be concerned in the genesis of hypertension, the working range of the renal mechanism controlling renin secretion must be changed. In a previous paper,18 we have shown that acute reduction of mean arterial pressure to below a level of 70 to 75 mm Hg causes significant increase in renin release in normotensive subjects and that, in the involved kidney of renovascular hypertensive patients, the threshold for renin release is shifted to much higher systemic arterial pressure levels and the magnitude of renin release is significantly greater than that in normotensive subjects. It is not yet known, however, whether there is any change in this renal mechanism releasing renin in essential hypertension. The present study is designed to examine the effect of acute reduction of arterial pressure on renin release in patients with benign essential hypertension.

Methods
Studies were performed on 28 hospitalized patients with benign essential hypertension (17

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Table 1

Effect of Reduction of Arterial Blood Pressure on Renin Activity of Renal and Systemic Venous Plasma and Renal Plasma Flow in Twenty-eight Patients with Essential Hypertension

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Admission BP (mm Hg)</th>
<th>Known duration of hypertension (yr)</th>
<th>Ocular findings (grade+)</th>
<th>Rate of infusion of SN (ag/10 min)</th>
<th>BP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
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</thead>
<tbody>
<tr>
<td>M.Y.</td>
<td>27</td>
<td>M</td>
<td>186/104</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>128/60</td>
<td>108/63</td>
<td>96</td>
</tr>
<tr>
<td>K.S.</td>
<td>18</td>
<td>M</td>
<td>178/98</td>
<td>3</td>
<td>1</td>
<td>86</td>
<td>146/84</td>
<td>128/64</td>
<td>105</td>
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<td>196/104</td>
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<td>1</td>
<td>87</td>
<td>134/82</td>
<td>100/70</td>
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<td>102/68</td>
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<td>160/110</td>
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<td>1</td>
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<td>67</td>
<td>172/104</td>
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<td>1</td>
<td>53</td>
<td>155/78</td>
<td>111/63</td>
<td>104</td>
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<tr>
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<td>40</td>
<td>M</td>
<td>220/110</td>
<td>5</td>
<td>2</td>
<td>36</td>
<td>204/130</td>
<td>144/108</td>
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<td>H.I.</td>
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<td>M</td>
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<td>119/71</td>
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<td>F</td>
<td>230/120</td>
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<td>2</td>
<td>85</td>
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<td>116/78</td>
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<td>180/130</td>
<td>11</td>
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<td>2</td>
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<td>2</td>
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<tr>
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<td>118</td>
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<td>129/83</td>
<td>134</td>
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<td>53</td>
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<td>135/84</td>
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<tr>
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<td>230/150</td>
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<td>163/83</td>
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<td>K.G.</td>
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<td>106/76</td>
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<td>95.3</td>
<td>166/100</td>
<td>116/74</td>
<td>122</td>
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</table>

| se       | ±4.0     | ±2.0   | ±2.3    | ±3.7    |

Abbreviations: BP = blood pressure; SN = sodium nitroprusside; MAP = mean arterial pressure; HR = heart rate; RRA = renin plasma flow; C = control period; Exp. = during administration in pressure; se = standard error of the mean.

*Keith-Wagener classification.

males and 11 females, ranging in age from 18 to 66 years). Their arterial blood pressure ranged from 160/90 to 230/136 mm Hg on admission. The diagnosis of essential hypertension was made after thorough examinations, including excretory pyelography, angiography, and tests for pheochromocytoma, and patients known or suspected of having primary renal disease, renal artery stenosis, primary aldosteronism, or pheochromocytoma were excluded. Patients having malignant hypertension were not included either, and none of the patients included showed clinical evidence of heart or renal failure. Their clinical findings are shown in tables 1 and 2. Known duration of hypertension was calculated from the time when 160/90 mm Hg or higher blood pressure was first noticed. Na and K were measured by flame photometry, and renal plasma (blood) flow by the Fick principle using para-aminophippurate (PAH).

The purpose and the procedure of the study were explained to all subjects and their free consent was obtained. The patients had been on a normal diet containing from 130 to 200 mEq of sodium daily for at least 1 week, and were fasting for about 5 hours at the time of measurements performed in the supine position, usually between 2 and 5 o'clock in the afternoon. All medication, except for small amounts of sedatives, had been discontinued at least 10 days prior to the study. To collect renal venous blood, we introduced a polyethylene catheter (KIFA red-1) into a femoral vein with the patient under local anesthesia and advanced it into a renal vein. Position of the catheter was confirmed by observing extraction of PAH in each case. In some patients, two catheters were introduced into both femoral veins and passed into the bilateral renal veins at the same time. Systemic venous blood was collected through another catheter introduced into a femoral vein or from a vein of one arm or leg. Approximately 10-min urine samples were col-

Circulation, Volume XXXVIII, August 1968
lected through a catheter from the bladder using sterile water as rinsing fluid, and the total measured. Samplings of renal and systemic venous plasma; SRA = renin activity of systemic venous plasma; \( \Delta \text{RA} \) = renal-systemic difference of renin activity; ntral pressure, the rate of infusion was decreased until the symptoms disappeared; there were no serious reactions in any subjects tested. In some cases, samplings were repeated when arterial pressure had returned almost to the pre-infusion level after termination of the infusion.

The details of the procedure used for determination of renin activity of plasma were described previously. In brief, plasma of renal and systemic venous blood was incubated, in the presence of disodium ethylenediamine tetraacetic acid (EDTA) and di-isopropyl fluorophosphate (DFP), for 24 hr at 37 °C at pH 5.5, and the pressor activity generated in plasma as a result of 24-hour incubation was determined by bioassay in rats treated with sodium pentobarbital and

\[
\begin{array}{ccccccccccc}
\text{C} & \text{Exp. Change} & \text{SRA (ng/ml)} & \Delta \text{RA (ng/ml)} & \text{RFF (ml/min)} & \Delta \text{RA} \times \text{RFF (ng/ml)} \\
\hline
8 & 12 & 4 & 7 & 8 & 1 & 1 & 4 & 3 & 717 & 746 & +29 & 0.72 & 2.98 & 2.26 \\
1 & 2 & 1 & 1 & 0 & 0 & 1 & 1 & 471 & 432 & 39 & 0 & 0.43 & 0.43 \\
4 & 4 & 0 & 3 & 3 & 0 & 1 & 1 & 650 & 472 & 178 & 0.65 & 0.47 & -0.18 \\
2 & 11 & 9 & 2 & 3 & 1 & 0 & 8 & 8 & 672 & 533 & 139 & 0 & 4.26 & 4.26 \\
8 & 11 & 3 & 7 & 9 & 2 & 1 & 2 & 692 & 594 & 98 & 0.69 & 1.19 & 0.50 \\
16 & 70 & 54 & 13 & 27 & 14 & 3 & 43 & 40 & 760 & 248 & 512 & 2.28 & 10.66 & 8.38 \\
12 & 106 & 94 & 9 & 44 & 35 & 3 & 62 & 59 & 660 & 498 & 162 & 1.98 & 30.88 & 28.90 \\
16 & 17 & 7 & 8 & 14 & 6 & 1 & 2 & 1 & 387 & 344 & 43 & 0.39 & 0.69 & 0.30 \\
1 & 1 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 444 & 337 & 107 & 0 & 0 & 0 \\
24 & 47 & 23 & 16 & 33 & 17 & 8 & 14 & 6 & 462 & 352 & 110 & 3.70 & 4.93 & 1.23 \\
5 & 8 & 3 & 5 & 7 & 2 & 0 & 1 & 1 & 424 & 396 & 28 & 0 & 0.40 & 0.40 \\
3 & 17 & 14 & 3 & 4 & 1 & 0 & 13 & 13 & 350 & 152 & 198 & 0 & 1.98 & 1.98 \\
9 & 54 & 45 & 7 & 16 & 9 & 2 & 38 & 36 & 539 & 480 & 59 & 1.08 & 18.24 & 17.16 \\
14 & 21 & 7 & 10 & 14 & 4 & 4 & 7 & 3 & 382 & 256 & 128 & 1.53 & 1.79 & 0.28 \\
3 & 5 & 2 & 2 & 4 & 2 & 1 & 1 & 0 & 627 & 559 & 68 & 0.63 & 0.56 & -0.07 \\
16 & 35 & 19 & 14 & 31 & 17 & 2 & 4 & 2 & 653 & 423 & 230 & 1.31 & 1.69 & 0.38 \\
1 & 1 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 563 & 616 & +53 & 0 & 0 & 0 \\
5 & 7 & 2 & 5 & 6 & 1 & 0 & 1 & 1 & 496 & 655 & +159 & 0 & 0.66 & 0.66 \\
9 & 32 & 23 & 6 & 17 & 11 & 3 & 15 & 12 & 620 & 475 & 145 & 1.86 & 7.13 & 5.27 \\
4 & 8 & 4 & 3 & 5 & 2 & 1 & 3 & 2 & 645 & 530 & 115 & 0.65 & 2.12 & 1.47 \\
7 & 46 & 39 & 5 & 12 & 7 & 2 & 34 & 32 & 673 & 332 & 341 & 1.35 & 11.29 & 9.94 \\
13 & 35 & 22 & 12 & 23 & 11 & 1 & 12 & 11 & 582 & 600 & +18 & 0.58 & 7.20 & 6.62 \\
3 & 6 & 3 & 3 & 4 & 1 & 0 & 2 & 2 & 384 & 238 & 126 & 0 & 0.52 & 0.52 \\
6 & 44 & 38 & 6 & 10 & 4 & 0 & 34 & 34 & 446 & 352 & 94 & 0 & 11.97 & 11.97 \\
5 & 6 & 1 & 5 & 5 & 0 & 0 & 1 & 1 & 372 & 292 & 80 & 0 & 0.39 & 0.29 \\
9.0 & 30.5 & 21.5 & 6.9 & 14.9 & 8.0 & 2.1 & 15.6 & 13.5 & 554 & 431 & 123 & 1.22 & 5.95 & 4.74 \\
\pm 1.4 & \pm 5.9 & \pm 5.0 & \pm 0.8 & \pm 2.7 & \pm 1.9 & \pm 0.6 & \pm 3.9 & \pm 3.6 & \pm 24 & \pm 27 & \pm 24 & \pm 0.32 & \pm 1.46 & \pm 1.30 \\
<0.001 & <0.001 & <0.001 & <0.001 & <0.001 & <0.001 & <0.001 & <0.001
\end{array}
\]
pentolinium tartrate, expressed in terms of nanograms (ng) of angiotensin equivalent per milliliter of plasma, and designated as plasma renin activity. Evidence that the substances assayed are renin and angiotensin was given in the previous paper.18 Renin activity of renal and systemic venous plasma of 13 normotensive subjects on a normal diet, measured by this method in the supine position, was $8.1 \pm 0.8$ (SE) ng/ml and $6.4 \pm 0.6$ ng/ml, respectively.18 A difference in renin activity between individual plasma samples was considered significant when it exceeded both 36% and 5 ng/ml.18 In all experiments, the differences in the means were tested by Student's $t$ test.

### Results

#### Effect of Reduction of Arterial Pressure on Plasma Renin Activity and on the Products of Renal-Systemic Difference of Renin Activity and Renal Plasma Flow

The effects of reduction of arterial pressure by infusion of sodium nitroprusside in 28 patients with essential hypertension were shown in Table 1. Reduction of average mean arterial pressure from 122 to 88 mm Hg caused significant increase of renin activity in renal venous plasma in 16, and no significant change in 12 of the 28 patients; the mean renin activity increased from 9.0 to 30.5 ng/ml ($P < 0.001$). The increase in renin activity of renal venous plasma was usually accompanied by one in systemic venous plasma, which was significant but less in magnitude. The renal-systemic difference in renin activity ($\Delta RA$) increased or was unchanged; the mean difference increased from 2.1 to 15.6 ng/ml ($P < 0.001$). The increase in renin activity persisted for the hypotensive period and then returned almost to the control value 15 to 20 min after arterial pressure returned to near the preinfusion level, following termination of the infusion. In four patients, renal venous blood was collected from both kidneys simultaneously. There was no significant difference in renin activity, either in the control or the hypotensive period.

During reduction in arterial pressure, total renal plasma flow (RPF), measured simultaneously by the Fick principle, decreased or was not significantly changed; the mean RPF decreased from 554 to 431 ml/min ($P < 0.001$). $\Delta RA \times$ RPF, calculated as an index of the amount of renin released from the kidney, increased or was not significantly changed; the mean value increased from 1.22 to 5.95 $\mu$g/min ($P < 0.005$; table 1).

In six patients, renin substrate activity of systemic venous plasma was measured at the same time by the method described previously.18 There was no significant change in plasma substrate activity during reduction in pressure; the average activity was $647 \pm 50$ (SE) ng/ml in the control period and $631 \pm 51$ ng/ml during the hypotensive period.

### Table 2

**Comparison of Clinical Findings Between Group A and Group B**

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>37.9 ± 2.9</td>
<td>42.6 ± 4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (males : females)</td>
<td>10 : 6</td>
<td>7 : 5</td>
<td></td>
</tr>
<tr>
<td>BP on admission (mm Hg)</td>
<td>192 ± 8/112 ± 3</td>
<td>192 ± 7/113 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>BP at time of study (mm Hg)</td>
<td>168 ± 8/101 ± 4</td>
<td>163 ± 9/99 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Known duration of hypertension (yr)</td>
<td>3.1 ± 0.6</td>
<td>5.7 ± 1.0</td>
<td>$P &lt; 0.025$</td>
</tr>
<tr>
<td>Ocular fundi (grade)</td>
<td>I : 4; II : 9; III : 3</td>
<td>I : 4; II : 6; III : 2</td>
<td></td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>0.46 ± 0.02</td>
<td>0.48 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Serum Na (mEq/L)</td>
<td>140 ± 0.7</td>
<td>141 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Serum K (mEq/L)</td>
<td>4.1 ± 0.1</td>
<td>4.1 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>BUN (mg/100 ml)</td>
<td>15.7 ± 0.6</td>
<td>15.9 ± 1.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Abbreviations:** BUN = blood urea nitrogen. Values given refer to means ± standard error. NS = not significant.
Renal Responsiveness to Reduction in Pressure: Renal Blood Flow, Renal Vascular Resistance, and Rate of Sodium Excretion

Since there were marked variations in the renal response to reduction in arterial pressure among the patients tested, the patients were classified, for comparison, into two groups on the basis of renal responsiveness: 16 patients who showed a significant increase of renin activity in renal venous plasma exceeding 36% and 5 ng/ml following reduction in pressure, group A, and 12 patients who showed no significant change in renin activity, group B.

As shown in table 3, in patients in group A, there was also a significant increase in ΔRA and in ΔRA × RFP during reduction in pressure. Renin activity of renal venous plasma measured during the hypotensive period, expressed on the logarithmic scale, showed a significant correlation with the degree of reduction in pressure, expressed in terms of ΔMAP/MAP (r = 0.53, P < 0.001). The correlation was similar to that previously found in normotensive subjects.14 In patients in group B, the average renin activity in the

### Table 3

<table>
<thead>
<tr>
<th>Comparison of Effects of Reduction in Arterial Pressure Between Sixteen Patients in Group A and Twelve Patients in Group B</th>
<th>Significance of Difference</th>
<th>p Value</th>
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</thead>
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<tr>
<td>Control</td>
<td>Group A*</td>
<td>Change</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>120 ± 6.0</td>
<td>103 ± 5.4</td>
</tr>
<tr>
<td>ΔMAP/MAP (g)</td>
<td>79 ± 3.6</td>
<td>123 ± 5.4</td>
</tr>
<tr>
<td>RRA (ng/ml)</td>
<td>94 ± 0.9</td>
<td>128 ± 1.8</td>
</tr>
<tr>
<td>ΔRRA × RFP (ng/ml)</td>
<td>1.92 ± 0.49</td>
<td>2.02 ± 0.54</td>
</tr>
<tr>
<td>RBF (ml/min)</td>
<td>1015 ± 68</td>
<td>1015 ± 68</td>
</tr>
<tr>
<td>UNaV (µg/kg/min)</td>
<td>2.27 ± 0.27</td>
<td>2.27 ± 0.27</td>
</tr>
<tr>
<td>RVR (mm Hg/ml/min)</td>
<td>0.129 ± 0.013</td>
<td>0.129 ± 0.013</td>
</tr>
</tbody>
</table>

*Values given refer to means ± standard error. Rate of infusion of sodium nitroprusside: group A: 90 ± 10 µg/min; group B: 102 ± 17 µg/min.

*Change during reduction in pressure. Abbreviations: NS = not significant; RVR = renal vascular resistance.

**Figure 1**

Relationship between renin activity of renal venous plasma and renal blood flow measured simultaneously during 47 hypotensive periods in 28 patients with essential hypertension. Renin activity is plotted on the logarithmic scale and renal blood flow in per cent of the control value on the arithmetic scale.

Circulation, Volume XXXVIII, August 1968
control period was significantly lower than that in patients in group A, both with renal and systemic venous plasma \( (P<0.001) \), and reduction in arterial pressure to the extent comparable to group A caused little increase in ΔRA and in ΔRA × RPF (table 3); there was no significant correlation between renin activity and the degree of reduction in pressure.

When total renal blood flow (RBF) was compared in the two groups, there was no significant difference in the control period, but there was during the hypotensive period (table 3); in group A, reduction in arterial pressure was accompanied by a significant \( (P<0.001) \) decrease of RBF, while in group B, no significant change was observed in RBF during the hypotensive period. When renin activity of renal venous plasma was compared with RBF through both groups, there was a reciprocal correlation between renin activity expressed in logarithms and RBF expressed in per cent of the control value. The correlation measured during 47 hypotensive periods in 28 patients was significant \( (r = -0.69, P<0.001, \text{fig. 1}) \). Total renal vascular resistance was then calculated from the formula: renal vascular resistance = mean arterial pressure ÷ RBF. Between the two groups, renal resistance was not significantly different in the control period, but there was a significant difference in the change in resistance during the hypotensive period \( (P<0.025, \text{table 3}) \), as expected; in group B, it decreased significantly \( (P<0.01) \) during reduction in pressure, while it usually increased in group A. The average sodium excretion rate in the control period was not significantly different between the two groups, and reduction of arterial pressure caused a significant decrease in group B \( (P<0.025) \) as well as in group A \( (P<0.001) \); the degree of the decrease was not significantly different in the two groups (table 3).

**Renal Responsiveness and Clinical Findings**

Table 2 compares the clinical data between groups A and B. No significant differences were found between the two groups in levels of arterial blood pressure on admission and at time of the study, in ocular fundi, heart size, serum Na and K, and blood urea nitrogen. However, the average known duration of hypertension in group B was significantly \( (P<0.025) \) longer than that in group A.

**Comparison with Normotensive Subjects and Patients with Renovascular Hypertension**

The effect of reduction in arterial pressure was compared among patients with essential hypertension (groups A and B), and normotensive subjects and patients with renovascular hypertension studied previously. The average magnitude of increase in renin activity of renal venous plasma following reduction in pressure in patients in group A \( (36.3\pm6.6 \text{ ng/ml, table 3}) \) was not significantly different from that for normotensive subjects \( (45.6\pm11.1 \text{ ng/ml}) \) and was significantly \( (P<0.001) \) smaller than that for renovascular hypertensive patients \( (131\pm30.5 \text{ ng/ml}) \). In patients in group B, the average renin activity of renal \( (P<0.001) \) and systemic \( (P<0.005) \) venous plasma in the control period (table 3) was significantly lower, and the magnitude of increase in renal venous renin

**Table 4**

**Comparison of Threshold for Renin Release among Essential Hypertensive Patients (Group A), Normotensive Subjects, and Renovascular Hypertensive Patients**

<table>
<thead>
<tr>
<th></th>
<th>Levels of mean arterial pressure at which renin activity increased</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
</tr>
<tr>
<td>(1) Essential hypertension (group A)</td>
<td>16</td>
</tr>
<tr>
<td>(2) Normotensive</td>
<td>8</td>
</tr>
<tr>
<td>(3) Renovascular hypertension (involved kidney)</td>
<td>10</td>
</tr>
</tbody>
</table>
activity during reduction in pressure (1.9 ± 0.4 ng/ml, table 3) was significantly ($P < 0.01$) less, as compared to those for normotensive subjects. The average degree of reduction in arterial pressure in terms of $\Delta$MAP/MAP was not significantly different in these four groups.

When the level of threshold of mean arterial pressure at which there was an increase in renin activity of renal venous plasma was compared for group A and the normotensive and the renovascular hypertensive groups, the mean threshold level in group A was significantly ($P < 0.001$) higher than that in the normotensive group but was significantly ($P < 0.05$) lower than that in the renovascular hypertensive group (table 4).

**Discussion**

The present results indicate that a majority of patients with benign essential hypertension release renin in response to acute reduction of arterial pressure by sodium nitroprusside while a large minority of patients do not. The results are in accord with those recently reported by Küchel and associates who showed that reduction of arterial pressure by diazoxide causes similar increase in renin activity of systemic venous plasma in a majority of patients with essential hypertension while little affecting renin activity in other patients.

In the responsive group of 16 patients (group A), reduction of mean arterial pressure to a range from 75 to 120 mm Hg caused significant increase in renin activity of renal venous plasma. At the same time, the products of the renal-systemic difference of renin activity and RPF increased significantly, whereas renin substrate activity of plasma was unchanged, indicating that there was an increase in renin release during reduction in pressure. Renin activity of renal venous plasma showed a significant correlation with the degree of reduction in pressure. The average magnitude of renin release during the hypertensive period was almost comparable to that previously found for normotensive subjects and was significantly less than that for renovascular hypertensive patients. The average threshold of mean arterial pressure at which renin release increased was significantly higher than that in normotensive subjects, but significantly lower than that in patients with renovascular hypertension. The findings suggest that, in most patients in this group, the working range of the mechanism releasing renin is shifted to higher systemic arterial pressure levels than that in normotensive subjects, but the renal mechanism retains normal responsiveness. However, there were three patients (T.E., I.M., and F.H., table 1) who showed evidently greater increase in $\Delta$RA × RPF compared to that of normotensive subjects. The upward shift of the renal mechanism may imply possible participation of the renin-angiotensin system in maintenance of hypertension in patients in this group, although the role of the renal pressor system seems minor when compared with that of patients with renovascular hypertension.

In the unresponsive group of 12 patients (group B), renin activity of renal and systemic venous plasma was usually low in the control period, and reduction of arterial pressure to the extent comparable to group A caused no significant release of renin; the magnitude of increase in renin activity during the hypotensive period was markedly less than that of normotensive subjects. The findings indicate that there was a suppression of the renal mechanism releasing renin in patients in this group. For comparison, the effect of similar reduction of arterial pressure was observed in one patient with primary aldosteronism, the diagnosis of which was later confirmed by a fall in blood pressure to normotensive levels following the surgical removal of a left adrenal cortical tumor. Renin activity of both renal and systemic venous plasma was undetectably low (0 ng/ml) in the control period and was unaffected by reduction of mean arterial pressure from 129 to 90 mm Hg; the pattern of renal response was similar to that found in patients in group B. It is not known whether the patients in group B might have included indistinguishable cases with primary aldosteronism, but the possibil-

*References*

Circulation, Volume XXXVIII, August 1968
ity appeared less likely from the findings that none of them had hypokalemia or symptoms suspecting this disease. Besides, Küchel and associates showed that most patients with essential hypertension who were unresponsive to diazoxide hypotension did not have an increased rate of aldosterone secretion.

The difference in renin release observed during reduction in pressure was difficult to explain by the difference in severity of hypertensive disease judged from clinical findings, or by the difference in sodium balance evaluated from serum Na levels (table 2) and sodium excretion rate in the control period (table 3). However, it seems possible that the state of sodium balance is associated, in part, with the variations in renal responsiveness, since it has been shown in dogs that sodium balance affects the sensitivity of the renin releasing mechanism. It was also difficult to attribute the difference in renin release to the one in the degree of reduction in mean arterial pressure or in sodium excretion during the hypertensive period; the results suggest that it was largely initiated by an extra-renal renin stimulating mechanism. The additional finding that the difference in renin release was associated with the one in changes in RBF and in renal vascular resistance during reduction in pressure, then, suggests that it was a manifestation of different effects of the sympathetic stimulation on the kidney caused reflexly by reduction in pressure. It has been well established in animals that increased sympathetic discharge to the kidney, caused directly or reflexly, is capable of increasing renin release, and accumulating evidence indicates that renin release greatly diminishes when the kidney is denervated, or the sympathetic supply is chemically blocked, or is insufficient.

On the other hand, Korner and associates have shown in rabbits that the sympatho-adrenal system is essential in the renal vasoconstrictor response to hypotension due to hemorrhage. Although the magnitude of compensatory tachycardia during the hypertensive period was not different between the groups A and B (table 3), the finding does not exclude a possibility of a difference in sympathetic nerve activity, since the tachycardia caused reflexly in supine men has been shown to be mediated predominantly by a decrease in parasympathetic activity. Thus, it is probable that the increase in renin release and the decrease in RBF observed in patients in group A were associated with renal sympathetic activity activated by reduction in pressure; the present study does not clarify to what extent the change in renal hemodynamics and the increased renin release were causally related to each other. It is also likely that the suppression of the renal mechanism releasing renin observed in patients in group B was associated with reduced sympathetic activity in the kidney caused either by a decrease in the sympathetic discharge or by one in responsiveness to the discharge. It should be noted, however, that it is unknown whether the difference in renal sympathetic activity is parallel to the difference in overall sympathetic activity since the sympathetic supply to the kidney is unique in that it may not be tonic and may be activated without correspondingly severe participation of other regions.

The present results also indicate that, during reduction in pressure due to sodium nitroprusside infusion, the kidney usually did not increase renin release when autoregulation of blood flow was maintained and it increased renin release only when the autoregulatory mechanism failed. It remains to be elucidated whether renin plays any role in the renal autoregulatory mechanism.

The significance of the finding that the average known duration of hypertension in group B was significantly longer than that in group A is not known. It might imply that duration of hypertension may exert an inhibitory effect on the sympathetic nerve activity in the kidney, resulting in a suppression of the renal mechanism controlling renin release. The observations of Frohlich and associates that neural activity is highest in patients with mild hypertension and is least in patients with more severe hypertension might
favor this speculative hypothesis. The possibility would appear to exist, then, that enhanced sympathetic nerve activity in the kidney in response to various stimuli might be involved, in part, in the initiating mechanism of essential hypertension. Kottke and associates\textsuperscript{33} early attempted to produce hypertension in dogs by stimulating the renal nerves, but the work was not extended subsequently. On the other hand, McCubbin and associates\textsuperscript{14} showed in dogs that the infusion of subpressor amounts of angiotensin results in sustained hypertension which resembles the early stage of essential hypertension.

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75 Years Ago
Discovery of Epinephrine

Oliver says: “During the winter of 1893-4, while prosecuting an inquiry as to the agents that vary the calibre of the arteries as determined by an instrument (the arteriometer) which I have elsewhere described, I found that the administration by the mouth of a glycerine extract of the adrenals of the sheep and calf produced a marked constrictive action on the arteries. . . . This position has since been confirmed by a research undertaken by Professor Schäfer and myself in the Physiological Laboratory of University College. . . .”

Schäfer says: “In the autumn of 1893 there called upon me in my laboratory at University College a gentleman who was personally unknown to me, but with whom I had a common bond of interest—seeing that we had both been pupils of Sharpey. . . . whilst many of the extracts which had been dealt with clinically by Oliver were inert or at any rate not specific in their action, the suprarenal capsules, and to a lesser extent the pituitary body, yielded to glycerine and to water and to saline solutions principles which have an extraordinary effect upon the tone of the heart and arteries, transcending that of any known drug. . . .”

Renin Release in Patients with Benign Essential Hypertension
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