Autonomic Nervous System and Benign Essential Hypertension in Man

I. USUAL BLOOD PRESSURE, CATECHOLAMINES, RENIN, AND THEIR INTERRELATIONSHIPS

By Jean-Louis Cuche, Otto Kuchel, André Barbeau, Yves Langlois, Roger Boucher, and Jacques Genest

ABSTRACT

The clinical entity of benign essential hypertension is often subdivided into labile essential hypertension and stable essential hypertension. To establish less arbitrary limits between normotension and labile and stable benign essential hypertension, 70 subjects (56 with benign essential hypertension) were classified according to (a) the usual blood pressure index for each subject and (b) the upper limit of variation of the usual blood pressure indexes of a normotensive population. Catecholamines, plasma renin activity, and urinary creatinine, sodium, and potassium were measured in recumbent subjects who had received a controlled-sodium diet. Our findings suggest that (1) benign essential hypertension represents a heterogeneous entity and a continuous spectrum of clinical and biochemical changes when it is related to the level of blood pressure, (2) adrenergic involvement is more evident in labile hypertension, (3) regardless of the urinary excretion of catecholamines in subjects with benign essential hypertension the urinary ratio of dopamine to norepinephrine always remains lower, and (4) a negative correlation exists between urinary sodium excretion and usual blood pressure indexes.

KEY WORDS

usual blood pressure, plasma norepinephrine, urinary dopamine, norepinephrine, epinephrine, sodium, and potassium, renal clearance of norepinephrine, heart rate, plasma renin activity

High blood pressure is considered by Pickering (1) to be a quantitative rather than a qualitative abnormality. The variability of arterial blood pressure, which is thought to be the most typical feature of this abnormality, does, however, make it difficult to distinguish between normotension and hypertension, particularly for labile (borderline) hypertension (2).

The central and autonomic nervous systems are essential to blood pressure regulation. The activity of these systems is probably mainly responsible for the extreme variations in blood pressure that often occur within seconds or minutes under the influence of common stimuli such as emotion, cold, pain, exercise, and posture (1). Other blood pressure responses mediated through the renin-angiotensin-aldosterone system occur with a more evident time delay of minutes or hours (3).

Evidence that the renin-angiotensin-aldosterone system has a regulatory role in the pathogenesis of essential hypertension has been presented previously (4). However, little new information concerning the possible role of catecholamines has appeared, even though the mode of action of catecholamines closely corresponds to the type of hypertensive reaction observed in hypertensive subjects (especially those with labile hypertension) and in spite of the fact that most of the potent hypotensive drugs exert their effects by interfering with the sympathetic regulatory system.

The difficulties encountered in investigating hypertensive subjects result from the fact that arbitrarily chosen dividing lines between normotension and hypertension place control subjects on one side and subjects with hypertension of various degrees of severity on the other. Such an approach could account for the inconsistent reports that urinary catecholamines are normal, low, or elevated in essential hypertension (5).

With these difficulties and the evidence on the relationship between the adrenergic nervous system and renin in mind (6), we recently studied a
group of subjects with benign essential hypertension. We found that those subjects with a diastolic pressure ranging from 80 mm Hg to 100 mm Hg had an increase in the excretion of total catecholamines but that the subjects with more severe diastolic hypertension had no such increase (7). This finding led us to postulate that within a limited range of blood pressure some subjects with benign essential hypertension have excessive adrenergic activity that could be involved not only in the circulatory symptoms but also in hormonal (renin) regulation.

The present study was designed to explore the whole spectrum of changes in arterial blood pressure between normotension and labile and stable benign essential hypertension, with special emphasis on blood pressure that has been corrected as much as possible for variability. Such a corrected profile of blood pressure was correlated with clinical symptomatology, catecholamines (including urinary dopamine, norepinephrine, and epinephrine concentrations, plasma norepinephrine concentration, and renal clearance of norepinephrine), plasma renin activity, and urinary sodium and potassium values.

Methods

SUBJECTS

A total of 70 subjects—a control group of 14 healthy volunteers (2 females and 12 males, 21-54 years [mean 25.5 years]) and a group of 56 subjects (27 females and 29 males, 17-61 years [mean 36 years]) with benign essential hypertension—were studied. All of the healthy subjects had blood pressures below 140/90 mm Hg and a negative family history of high blood pressure. The hypertensive subjects were chosen after a complete clinical examination which included electrocardiography (ECG), cardiopulmonary roentgenography, hypertensive intravenous pyelography, plasma sodium and potassium determinations, 24-hour clearances of creatinine, and phenolsulphophthalein tests. On an elective basis, the clinical investigation was completed by renal arteriography (41 of 56 subjects), measurement of renal blood flow by a single injection of H-orthioiodohippurate and two blood samples (8) (26 of 56 subjects), determinations of plasma T\textsubscript{3} and T\textsubscript{4} (18 of 56 subjects), and 24-hour vanilmandelic acid excretion (22 of 56 subjects). After this work-up, each subject was found to have a diagnosis compatible with benign essential hypertension.

CLASSIFICATION OF SUBJECTS WITH BENIGN ESSENTIAL HYPERTENSION

A definition of the hypertensive condition requires (a) an optimal knowledge of the actual "usual blood pressure" (2) of each subject, i.e., the role of exogenous stimuli must be reduced as much as possible and (b) as clear a distinction as possible between normotension and hypertension.

The major problem in the investigation of hypertension is the assessment of the usual blood pressure of each subject. Therefore, it was necessary to define an experimental index of the usual blood pressure for each subject. This index represented manometric blood pressure corrected for four factors. First, we attempted to "synchronize" (9) all of the subjects in the same manner. The blood pressure-increasing effect of out-patient conditions, hospitalization, or both was reduced in our subjects after at least 4 days of hospitalization at which time a decrease in blood pressure usually occurred; all control subjects were in the same hospital environment for daily meals. Second, we induced a relative dietary steady state; 3 days prior to the experiment, all subjects received a diet that was "normal" with respect to sodium (135 mEq/day) and potassium (90 mEq/day). Third, we ensured a reduction in the effects of physiological daytime variability (1) through multiple measurements. Throughout the study, blood pressure was measured each hour 8-12 times per day in hypertensive subjects and 3 times per day (before meals) in control subjects. Finally, we used values determined in recumbent subjects because upright posture can induce many quantitative and qualitative differences in blood pressure responses (10).

In summary, we considered the mean blood pressure (diastolic + \(\frac{1}{3}\) the systolic-diastolic difference) of multiple measurements in recumbent subjects on the fourth day of a controlled-sodium diet to be the usual blood pressure index of each subject.

The second major problem was to distinguish clearly between normotension and hypertension; this distinction is particularly difficult in borderline hypertension. We tried to define the limit between normotension and hypertension on the basis of blood pressure variability in a normotensive population. We plotted all the usual blood pressure indexes along the abscissa (Fig. 1), and to classify the 56 hypertensive subjects we used the mean of the usual blood pressure indexes for the 14 normotensive subjects (81.1 ± 2.73 mm Hg) as the starting point. Such a mean agrees with some recent studies (11, 12) but is slightly lower than that reported by others (13). If we assume that these 14 normotensive subjects were an acceptable sampling of the normal population, 99.73% of this population must be spread within a range including the mean ±3 SE. For this reason, we added to the mean three standard errors of this mean (or 81.1 + 3 \times 2.73 = 89.3 mm Hg) and defined this value as the upper limit of variation of the usual blood pressure indexes in 14 healthy subjects. This group of normotensive subjects was the reference group (group R). Based on the upper limit of variation of the usual blood pressure indexes for group R, we considered the 56 subjects to be hypertensive even though the term hypertension sometimes has a questionable connotation. In a further subdivision of these hypertensive subjects, the magnitude of variation of the control subjects (from mean -3 SE to mean +3 SE) was taken as a standard to determine the limits inside the hypertensive group. By adding 6 SE to 89.3 mm Hg, we obtained another upper limit of 105.7 mm Hg, which hap-
pens to be the clinical limit between labile and stable hypertension. By adding another 6 SE (105.7 + 6 x 2.73) we obtained a value of 122.1 mm Hg, which was used to split the subjects with stable hypertension into subgroups with a more or less severe form of the disease.

A useful determination for the detection of adrenergic reactivity or vagal withdrawal (12) in hypertension is the postural acceleration of the heart rate. Therefore, heart rate was repeatedly measured (usually 8-12 times daily) in all subjects in a recumbent position and then after about 2 minutes in the upright position; we also considered the mean orthostatic heart rate acceleration of each subject on the fourth day of the normal sodium diet as another criterion. The mean postural heart rate increase was 12.9 ± 1.1 beats/min in normotensive subjects, and we again added 3 SE to obtain the upper limits of variation for this parameter. Plotting this parameter against the usual blood pressure indexes (Fig. 1) indicated that the hypertensive subjects with usual blood pressure indexes between 89.3 and 105.7 mm Hg (group I) could be clearly divided into two subgroups, one with and one without an excessive accelerated postural pulse response. In most of the subjects within the other groups, the postural increase in pulse rate was roughly within the normal range.

Thus, we studied five groups of 14 subjects each. The group of normotensive subjects, mainly defined as the group with the lowest usual blood pressure index, was the reference group (group R). The hypertensive groups presented an increasing recumbent usual blood pressure index. The first of these groups was subdivided into one subgroup with low orthostatic heart rate acceleration (group IA) and another subgroup with an excessive orthostatic heart rate acceleration (group IB). Since the condition of the two last groups corresponded clinically to stable hypertension, they represented only different degrees of severity within this class and were designated groups IIA and IIB.

CLINICAL CHARACTERISTICS OF ESSENTIAL HYPERTENSIVE GROUPS

The major clinical data are reported in Table 1. A family history of high blood pressure was noted with a frequency higher than 50% in all hypertensive groups. With increasing blood pressure, an increasing frequency of dyspnea, hypertensive fundi abnormalities, and ECG signs of left ventricular hypertrophy were observed; in groups IA, IIA, and IIB, in which these signs were less frequent, a greater frequency of associated symptoms of lability of the autonomic nervous system were observed: anxiety and emotional lability, dermographism, acrohypothermia, acrohyperhidrosis, and dyspepsia or gastroduodenal ulcers.

PROTOCOL OF INVESTIGATION

For 3 days prior to and on the day of the experiment, the subjects received a diet containing 135 mEq sodium/day and 90 mEq potassium/day divided into three meals at the same time each day. The fourth day on the diet was the day of the experiment. The subjects were kept in the recumbent position after 11 PM of the preceding evening. After the subjects had first voided (micturition discharged), the urine was collected between 8:30 AM and 12:30 PM, while they were in the strictly recumbent position, for the subsequent determinations of catecholamines, creatinine, sodium, and potassium. At 12:30 PM a blood sample was drawn for determination of plasma renin activity.

In 50% of the subjects of each group (7 subjects), plasma norepinephrine values were measured in the recumbent position at the same time as plasma renin activity.

LABORATORY INVESTIGATIONS

Plasma renin activity was assayed according to the method of Boucher et al. (14), and urinary dopamine, norepinephrine, and epinephrine were determined by the method of Sourkes and Murphy (15). Urinary sodium
TABLE 1

Major Clinical Data of Subjects with Benign Essential Hypertension

<table>
<thead>
<tr>
<th>Hypertensive group</th>
<th>Ia</th>
<th>Ib</th>
<th>IIa</th>
<th>IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>31.8</td>
<td>26.8</td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.7</td>
<td>69.4</td>
<td>67.5</td>
<td>75.1</td>
</tr>
<tr>
<td>Known duration of high blood pressure (years)</td>
<td>5.7</td>
<td>3.8</td>
<td>9.2</td>
<td>5.5</td>
</tr>
<tr>
<td>Incidence of family history of high blood pressure (%)</td>
<td>65</td>
<td>57</td>
<td>71</td>
<td>57</td>
</tr>
<tr>
<td>Blood pressure on day of admission (mm Hg)</td>
<td>175/105</td>
<td>159/96</td>
<td>182/113</td>
<td>216/127</td>
</tr>
<tr>
<td>Blood pressure on test day (mm Hg)†</td>
<td>132/82</td>
<td>138/81</td>
<td>152/96</td>
<td>185/107</td>
</tr>
<tr>
<td>Incidence of hypertensive symptoms (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>21</td>
<td>28</td>
<td>50</td>
<td>28</td>
</tr>
<tr>
<td>Dyspnea (after slight exercise load)</td>
<td>14</td>
<td>28</td>
<td>28</td>
<td>64</td>
</tr>
<tr>
<td>Fundi changes</td>
<td>0</td>
<td>7</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>ECG signs of left ventricular hypertrophy</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>Incidence of associated symptoms (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermographism</td>
<td>43</td>
<td>64</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>Dyspepsia and/or gastroduodenal ulcers</td>
<td>28</td>
<td>21</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Anxiety and/or emotional lability</td>
<td>64</td>
<td>71</td>
<td>86</td>
<td>7</td>
</tr>
<tr>
<td>Acrohypothermia and acrohyperhidrosis</td>
<td>28</td>
<td>64</td>
<td>35</td>
<td>21</td>
</tr>
<tr>
<td>Renal determinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal blood flow (ml/1.73 m² min⁻¹)</td>
<td>690 ± 62</td>
<td>698 ± 43</td>
<td>632 ± 48</td>
<td>547 ± 40</td>
</tr>
<tr>
<td>N</td>
<td>7</td>
<td>10</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>24-hour clearance of creatinine (ml/1.73 m² min⁻¹)</td>
<td>112 ± 5.93</td>
<td>129 ± 5.94</td>
<td>113 ± 6.31</td>
<td>99 ± 6.31</td>
</tr>
<tr>
<td>N</td>
<td>12</td>
<td>14</td>
<td>13</td>
<td>14</td>
</tr>
</tbody>
</table>

* Age of group R: 25.5 years.
† See text for definition.

and potassium concentrations were measured with a Technicon autoanalyzer (SMA 12/60), and creatinine concentrations were measured by the method of Cooper and Biggs (16). Plasma norepinephrine was measured according to the method of Anton and Sayre (17); the recovery by this method was 81% (range 75% to 88%), and the coefficient of variation was 5.8% for seven samples (0.25 ng/ml of standard norepinephrine in plasma). Necessary corrections were made in calculations. The time that elapsed between venous puncture and beginning of plasma freezing (after centrifugation at 4°C for 10 minutes) was 16–28 minutes (mean 22.3 minutes) for 53 tested samples.

STATISTICAL ANALYSIS

A unidimensional variance analysis was used to test the effects of blood pressure variations on each parameter. When a statistical significance for the mean effect was reached, a Dunnett's test (18) was computed for results to be compared with group R; a simple comparison was made when differences between hypertensive groups were tested.

Results

AGE

A positive linear correlation was calculated between age and usual blood pressure index (r = 0.541, P < 0.01). However, we did not find any correlation between age and either plasma renin activity or urinary excretion of each catecholamine. The absence of significant correlation between these parameters and age suggests that there is no systematic bias for aging in the present study.

CARDIOVASCULAR AND RENAL DATA

The way in which the limits of blood pressure were divided implies a highly significant difference (P < 0.001) between the recumbent usual blood pressure index of each group except between groups Ia and Ib, in which the differentiation was made on the basis of postural heart rate increase (Table 2). The same pattern was observed for systolic and diastolic blood pressure. Pulse pressure (defined as the systolic-diastolic pressure difference) was significantly higher in group IIB (75.8 mm Hg) than it was in group R (47.6 mm Hg). Recumbent heart rate was significantly more accelerated in all hypertensive groups than it was in group R.

Urinary excretion of creatinine was slightly but not significantly higher in group Ib and lower in group IIb than it was in group R, with a significant difference (P < 0.05) between groups Ia and IIb. Urinary sodium excretion was significantly higher in group Ia (60.5 ± 9.44 mEq/4 hours) than it was in group R (42.7 ± 3 mEq/4 hours), with a significant difference (P < 0.05) between groups Ia and IIb.

Urinary excretion of potassium was significantly lower in group IIa and group IIb than it was in group R. The ratio of urinary sodium to potassium...
was significantly higher in groups IA and III than it was in group R.

When the correlation between urinary sodium excretion and usual blood pressure was considered in all 70 subjects, a slight, negative but significant correlation ($r = -0.323$, $P < 0.01$) was obtained (Fig. 2).

**URINARY EXCRETION OF CATECHOLAMINES**

The mean values of urinary excretion of dopamine tended to be higher in groups IA and IB and lower in groups II A and II B, but these changes were not significant (Table 3). However, the mean values of urinary excretion of norepinephrine in all four hypertensive groups were higher than those in group R, but only that of group IA ($30.44 \pm 9.66 \mu g/4$ hours) was significantly higher.

To obtain an insight into either the dopamine-norepinephrine conversion or into different urinary excretory patterns of both catecholamines (known to have different physiological action at the kidney level), a ratio of both should be used. In the recumbent position, the ratio of dopamine to norepinephrine was significantly lower (6.14 to 7.15) in all hypertensive groups compared with that in group R (12.8 $\pm$ 2.55).

**PLASMA RENIN ACTIVITY AND NOREPINEPHRINE VALUES**

Plasma renin activity was higher ($P < 0.01$) in group IB ($0.584 \pm 0.078$ ng/ml hour$^{-1}$) than it was in group R ($0.293 \pm 0.077$ ng/ml hour$^{-1}$). The values of plasma renin activity for group IA ($0.288 \pm 0.069$ ng/ml hour$^{-1}$), group II A ($0.431 \pm 0.103$ ng/ml hour$^{-1}$), and group II B ($0.353 \pm 0.098$ ng/ml hour$^{-1}$) were not significantly different from the value for group R.

Plasma norepinephrine was measured in seven subjects in each group (Table 4). It was higher ($P < 0.05$) in group II A ($0.68 \pm 0.22$ ng/ml) than it was in group R ($0.25 \pm 0.06$ ng/ml). Considering all the results together, there was a slight but significant correlation between plasma norepinephrine and urinary norepinephrine ($r = +0.343$, $P < 0.05$, $y = 11.183 + 12.371x$).

We calculated the renal clearance of norepinephrine using the formula $Cl_{NE} = UV/P$, where $Cl_{NE}$ is the renal clearance of norepinephrine (ml/min), $U$
TABLE 3

<table>
<thead>
<tr>
<th>Group</th>
<th>R</th>
<th>I_A</th>
<th>I_B</th>
<th>II_A</th>
<th>II_B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary dopamine (µg/4 hours)</td>
<td>98 ± 11.8</td>
<td>128 ± 25.3</td>
<td>125 ± 20.5</td>
<td>95.7 ± 10.8</td>
<td>85 ± 19.6</td>
</tr>
<tr>
<td>Urinary norepinephrine (µg/4 hours)</td>
<td>9.31 ± 1.07</td>
<td>30.44 ± 9.66*</td>
<td>23.41 ± 3.95</td>
<td>20.73 ± 4.30</td>
<td>15.74 ± 2.54</td>
</tr>
<tr>
<td>Urinary epinephrine (µg/4 hours)</td>
<td>2.17 ± 0.24</td>
<td>6.56 ± 2.52</td>
<td>4.80 ± 1.12</td>
<td>4.93 ± 1.37</td>
<td>3.97 ± 1.35</td>
</tr>
<tr>
<td>Ratio of dopamine to norepinephrine</td>
<td>12.8 ± 2.55</td>
<td>7.15 ± 1.31*</td>
<td>6.47 ± 1.49†</td>
<td>6.14 ± 1.13†</td>
<td>6.33 ± 1.19†</td>
</tr>
</tbody>
</table>

* P < 0.05 compared with group R.
† P < 0.01 compared with group R.

is urinary norepinephrine (ng/ml), V is urinary volume (ml/min), and P is plasma norepinephrine (ng/ml). In group I_A, four-fifths of the values for the renal clearance of norepinephrine were higher than the upper limit of group R; the mean value for group I_A was more than double that for group R although the plasma norepinephrine level for this group remained within normal limits. In group I_B, the clearance of norepinephrine decreased and mean plasma norepinephrine increased. One subject in group II_A had an extremely high renal clearance of norepinephrine (958 ml/min) for unknown reasons; when the data relating to this subject were excluded, the mean value of the group was only 158 ± 53.5 ml/min, but plasma norepinephrine was significantly higher. In group II_B, two-fifths of the values for renal clearance of norepinephrine were lower than the lower limit in group R, and the group's mean value was 117 ± 28.7 ml/min; the value of plasma norepinephrine for this group was close to that for group R.

Discussion

In the present study, 56 subjects with benign essential hypertension were classified according to blood pressure. This classification was developed using the usual blood pressure index for each subject and the upper limit of variation of the usual blood pressure indexes of the normotensive group. If the normotensive group is an acceptable group from a practical standpoint, two biases must be recognized; there was no satisfactory cross-matching between normotensive and hypertensive populations for either sex or aging. In a further subdivision of the hypertensive population, we used the magnitude of blood pressure variation of our normotensive subjects (from mean -3 SE to mean +3 SE) as a standard to determine the limits inside the hypertensive group. Even though such a choice is rather arbitrary, our first limit (105.7 mm Hg) was near the group I limit of the World Health Organization classification (107 mm Hg) (WHO Techni-

TABLE 4

<table>
<thead>
<tr>
<th>Norepinephrine Values</th>
<th>R</th>
<th>I_A</th>
<th>I_B</th>
<th>II_A</th>
<th>II_B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary (µg/4 hours)</td>
<td>6.1</td>
<td>0.29</td>
<td>87.5</td>
<td>6.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Plasma (ng/ml)</td>
<td>5.8</td>
<td>0.12</td>
<td>201.2</td>
<td>10.6</td>
<td>10.6</td>
</tr>
<tr>
<td>Clearance (ml/ min)</td>
<td>14.5</td>
<td>5.8</td>
<td>65.6</td>
<td>236.5</td>
<td>38.7</td>
</tr>
<tr>
<td></td>
<td>14.1</td>
<td>0.43</td>
<td>136.2</td>
<td>38.7</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>4.6</td>
<td>0.23</td>
<td>83.2</td>
<td>4.4</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>8.6</td>
<td>0.26</td>
<td>138</td>
<td>36.6</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>0.43</td>
<td>106.5</td>
<td>14.2</td>
<td>0.34</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>9.24</td>
<td>0.25</td>
<td>125.4</td>
<td>17.9</td>
<td>0.43</td>
</tr>
</tbody>
</table>

* No statistical calculations were performed on the clearance of norepinephrine since it is itself a product of calculation.
† P < 0.05 compared with group R.
‡ Without subject no. 6, the mean value of clearance of norepinephrine in this group was 158 ± 53.5 ml/min.

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creased activity of dopamine-β-hydroxylase; such an increase in norepinephrine could reflect an increase in the ratio of dopamine to norepinephrine, which was less evident. These different patterns are in agreement with clinical observations and with the concept of sympathetic involvement in some subjects with labile hypertension (7). When high blood pressure is more stable and severe, this adrenergic mechanism is probably less effective. The significant increase in pulse pressure in group II B suggests a decrease in arteriolar compliance. Whether such a decrease is related to the higher blood pressure in this group or to arteriolar morphological changes in this older group of subjects cannot be assessed from the present study.

Our findings about dopamine and norepinephrine are compatible with the reported (19, 20) decrease in urinary dopamine excretion in essential hypertension and the low urinary norepinephrine excretion associated with great hypertensive fundi changes and vice versa (21).

More consistent than any change in individual catecholamines were the changes in the urinary ratio of dopamine to norepinephrine, which was significantly decreased in all hypertensive groups. Although an increase in dopamine occurred in labile hypertension, relatively it lagged behind the increase in norepinephrine; thus, the ratio of both catecholamines was maintained below normal. The consistent decrease in the ratio of dopamine to norepinephrine could reflect an increase in the activity of dopamine-β-hydroxylase; such an increase has been reported in essential hypertension (22) but was not confirmed in the four subjects studied by Horwitz et al. (23). If such an increased activity exists in essential hypertension, a genetic factor should be considered, because familial factors contribute significantly to the determination of base-line circulating dopamine-β-hydroxylase activity (24). Consistent with such a possibility is the observed familial history of high blood pressure in a frequency higher than 50% in all of the hypertensive groups. However, a positive correlation has been reported between norepinephrine and dopamine-β-hydroxylase activity in essential hypertension (25), but we did not observe any correlation between the urinary ratio of dopamine to norepinephrine and plasma norepinephrine. Therefore, there is a possibility that this ratio does not reflect the dopamine-β-hydroxylase activity. The decrease in the ratio of dopamine to norepinephrine in essential hypertension could then be related at least partly to a renal defect.

In the studies of renin regulation, we observed an hyperreninemia in subjects with labile hypertension and postural tachycardia (group IA) but not in subjects without tachycardia (group IA). Both groups had comparable blood pressures, clinical pictures, and plasma and urinary catecholamine patterns. Therefore, the hyperreninemia could be attributable to an increased responsiveness of target tissues (26).

We also observed, in the range of blood pressure studied, two different types of sodium excretion. In the subjects with labile hypertension without postural tachycardia (group IA), the significant increase in sodium excretion without a change in potassium excretion suggests a natriuresis compatible with Guyton's model of renal autoregulation (3); in such a case, sodium excretion increases as a homeostatic response to an increase in blood pressure. This mechanism seems to disappear, however, when hypertension becomes more severe as shown by a negative correlation between urinary sodium excretion and the usual blood pressure. In the more severe type of stable hypertension (group II B), the urinary excretion of sodium was significantly lower than that in group IA; also it was associated with a decrease in urinary potassium and a decrease in the 24-hour clearance of creatinine.

A possible role for dopamine was also investigated. Dopamine induces a natriuretic response (27) independent of glomerular filtration rate changes (28), and a positive correlation between urinary sodium and dopamine excretion has been established (29). It is possible that the increased
significant increase in plasma norepinephrine; in subjects with labile hypertension appears to be systemic or a renal effect. (4) A buffering system for the regulation of plasma norepinephrine is represented by the urinary norepinephrine and the possible participation of clearance of norepinephrine in such interrelationships. In labile hypertension without postural tachycardia, the clearance of norepinephrine was more than twice that of group R, although plasma norepinephrine remained normal; in labile hypertension with postural tachycardia, the clearance of norepinephrine decreased but plasma norepinephrine increased, although this increase was not necessarily significant. In stable hypertension the clearance of norepinephrine was close to normal in six of seven subjects in group II A, but there was a significant increase in plasma norepinephrine; in group II A, values for plasma norepinephrine, urinary norepinephrine, and clearance of norepinephrine were close to those for group R. However, it was difficult to assess the degree to which the urinary clearance of norepinephrine was responsible for the regulation of plasma norepinephrine because there is no information as to what proportion of the metabolic clearance rate of endogenous norepinephrine is represented by the urinary norepinephrine excretion.

The present study, which covered only a segment of the hypertensive population, suggests the following four conclusions. (1) Benign essential hypertension represents a heterogeneous entity and a continuous spectrum of clinical and biochemical changes when it is related to the level of blood pressure. It is not possible to decide whether this finding reflects the natural evolutionary pattern of the essential hypertensive process, unless it is investigated on a long-term basis. (2) The adrenergic involvement in benign essential hypertension seems to be more evident in labile hypertension and less evident if present in stable hypertension. (3) Regardless of what the urinary excretion of catecholamines is in subjects with benign essential hypertension, the urinary ratio of dopamine to norepinephrine always remains lower; it is not possible to decide whether this finding reflects a systemic or a renal effect. (4) A buffering system compensating for the increase in blood pressure in subjects with labile hypertension appears to be present. It is not possible to assess to what degree the observed increases in both sodium excretion and renal clearance of norepinephrine participate in this homeostatic adjustment. The present study also underlines the necessity for a new approach to the classification of subjects with benign essential hypertension to better characterize the hypertensive process by correlating the clinical and the hormonal manifestations with blood pressure levels.

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