A Clinical Study of the Role of Catecholamine in Blood Pressure Regulation

Urinary Excretion of Catecholamines during Salt Restriction and Thiazide Medication in Hypertensive Subjects

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In 1894, when Oliver and Schaefer first demonstrated the hypertensogenic property of adrenal extracts, the question arose as to the role of this gland in the genesis of hypertension. By the late 1940's both epinephrine and norepinephrine were extracted from biological materials, and norepinephrine was recognized as a neurohormonal transmitter of the sympathetic nervous system. Since it was known that the hemodynamics prevailing in essential hypertension can be closely simulated by the infusion of norepinephrine in the normotensives, and that adrenal medullary tumors, which contain varying increased amounts of catecholamines, cause hypertension which is relieved when the tumors are removed surgically, many investigators have contributed towards the elucidation of the role of these pressor amines, catecholamines, in essential hypertension. If norepinephrine plays a role in the genesis of essential hypertension, the question then is whether an increased amount of catecholamines is present in the blood and urine of hypertensives. A slight increase in urinary catecholamines was shown by Holz et al. in essential hypertension. Ishihara and Ishigaki found a correlation between blood pressure and plasma catecholamine levels. These facts suggested that increased catecholamines played some role in the genesis of hypertension. But von Euler et al. noted, in studying 500 unselected patients with hypertension, that an increased urinary excretion of catecholamines occurred in only 16 per cent of the cases. Birke et al. observed that during night hours there was no difference in urinary excretion of catecholamines between patients with essential hypertension and the normotensives, and that during daytime the excretion decreased in the former group of subjects. Between these two groups, i.e., the hypertensives and the normotensives, no such differences were found by Goldenberg, Burn as to urinary catecholamines, by Gitlow et al. as to urinary VMA, by Croft et al. as to catecholamines, metanephrine and VMA, and by Manger as to plasma catecholamines. Maekawa et al. also found no statistically significant correlation between urinary catecholamines and blood pressure among the hypertensives. Further, Möller and Yoshinaga reported that the catecholamine excretion was decreased in hypertensive subjects. From these observations it would appear that an excessive production of norepinephrine by the sympathetic nervous system and adrenal medulla is not the usual feature of hypertensive patients.

In addition, in 1934 Goldblatt and his colleagues produced an experimental, persistent
hypertension by inducing renal ischemia in dogs. Closely following this discovery, the renin-hypertensin (angiotensin) system was thought to be responsible for this type of experimental hypertension\textsuperscript{15,20}. Maekawa\textsuperscript{21} concluded from his experimental and clinical studies that the true cause of the hypertension, namely of essential hypertension, is a disturbance of ATP–ATPase systems in cardiovascular tissues, and that neurogenic, endocrine or renal factors, heredity, constitution and other factors are only the particular constituents of the condition that bring the "true cause" into operation. Thus, in the genesis of essential hypertension factors other than catecholamine have been called into attention.

On the other hand, there is a large body of evidences indicating that a psychic stress may raise the blood pressure\textsuperscript{22–25} and may modify the secretion of catecholamines\textsuperscript{26–29}. Furthermore, Swan\textsuperscript{30} and Mendelowitz et al.\textsuperscript{31} have reported that blood vessels of the skeletal muscle are more "sensitive" to circulating norepinephrine in patients with essential hypertension than in normal subjects.

Thus, it is suggested that catecholamine must play some role in the genesis of hypertension.

In order to investigate the role of catecholamine in hypertension, changes in blood pressure and urinary excretion of catecholamines were studied in patients with hypertension of various origins and degrees, before and during salt restriction with or without thiazide medication. Parenthetically, salt restriction and thiazide, per se, are known to have no direct effect on the catecholamine metabolism.

Materials and Methods

The subjects studied were ten non-edematous patients with hypertension of various origins and degrees, 5 males and 5 females, ranging in age from 15 to 61. These included: 4 cases with essential hypertension and 6 other cases of hypertension associated with pyelonephritis, Cushing's disease, acromegaly, occlusive thromboaortopathy, coarctation of aorta; the last case had rheumatic carditis with iatrogenic steroid hypertension. Important clinical data found in these patients are summarized in Table I.

During the control period of one to three weeks, the patients took bed rest and were usually placed on a diet containing 170 mEq of sodium daily. After the control period, the dietary intake of sodium was restricted in various manners, e. g., to 85, 51 or 17 mEq per day. After the effect of salt restriction was evaluated thiazide therapy was started. Thiazides used in this study were: diazoxide (7-chloro-3-methyl-1, 2, 4-benzothiadiazine-1, 1-di-oxide) in dose of 150 to 300 mg and trichlormethiazide in dose of 4 to 6 mg. The amount of sodium intake was changed when necessary. Throughout all experimental periods, daily potassium intake was kept at 60 mEq as a rule, and the use of other drugs likely to affect the autonomic nervous function and blood pressure was avoided. Blood pressure and urinary catecholamines were determined serially and paying a close attention to the electrolyte balance of the patients.

Blood pressure was the same measured at almost hour of the day everyday.

Urinary catecholamines, i. e., epinephrine and norepinephrine, were measured in the hydrolyzed form\textsuperscript{35} by the trihydroxyindole method of von Euler and Lishajko\textsuperscript{36,37} with some modifications\textsuperscript{38}. The values of catecholamines will be given in this paper as corrected for the recovery rate of this method.

The 24 hour-urine sample was usually diluted to 2 liters. Fifty milliliters of diluted urine were hydrolyzed at 100°C, for 15 min. and were added with 0.5 g of EDTA–Na\textsubscript{2}. This sample was adsorbed to alumina column at pH 8.2 and then eluted by 20 m/ of 0.3 N-acetic acid. This eluate, added with 2 m/ of 4 per cent EDTA–Na\textsubscript{2} solution, was readorsed to Amberlite CG–50 column (10 × 40 mm) at pH 6.5 which was followed by elution with 20 m/ of N-hydrochloric acid. This second eluate was adjusted to pH 6.2, and one m/ of this eluate was used for the fluorometric measurement and another one m/ for blank measurement. The oxidation of sample with potassium ferricyanide was carried out at 0°C for 45 min. At the end of the oxidation time, two m/ of combined reagent which consisted of 1.8 m/ of 20 per cent sodium hydroxide and 0.2 m/ of 2 per cent ascorbic acid was added to the sample. Blank used was made up in the following manner: the second eluate of urine was oxidized and after complete fading of fluorescence with sodium hydroxide, ascorbic acid was added. Fluorescence was measured with two filter sets, set A and set B, using "Yagi microfluorometer". The interference filters gave maximum transmission at 405 and 490 m/Î for set A, and 435 and 540 m/Î for set B. Epinephrine and norepinephrine were calculated differentially and corrected for the recovery rate of this method. Using this method, mean values found in normal subjects were 9.0 mcg/day for epinephrine (standard error 1.3) and 50.9 mcg/day for norepinephrine (standard error 3.9).

*Japanese Circulation Journal* Vol. 29 May 1965
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注: 本文献中所列数据仅供参考，具体数据请参阅原始文献。
ROLE OF CATECHOLAMINE IN BLOOD PRESSURE REGULATION

RESULTS

A) Restriction of Salt Intake.
After a drastic restriction of salt intake, moderate changes in blood pressure and urinary catecholamine (CA) were observed in most cases, either abruptly or gradually. The manner in which these changes occurred differed in indi-

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Remarks: D, diazoxide; T, trichlormethiazide; PD, prednisolone; PM, paramethazone. Blood pressure values were given on an average of the values during a period.

Japanese Circulation Journal Vol. 29 May 1965
individual cases (Table II). The observed patterns of the changes in blood pressure and urinary CA could be classified into three groups. Namely, (1) a group of subjects who showed a fall of blood pressure and an increase in urinary CAs, especially in norepinephrine (NE), (2) a group of subjects who showed an increase in urinary CAs, especially in NE but without any marked change in blood pressures, and (3) a group who showed no changes in blood pressure and urinary CA (Fig. 1). These patterns of the change are tentatively called Type I, II and III.

1) The group in which blood pressure declined and urinary CA increased (Group I).

![Fig. 1. Changes in Blood Pressure and Urinary Catecholamines after Dietary Sodium Restriction. A: Control Period. B: After Dietary Sodium Restriction. In blood pressure, solid line shows systolic blood pressure and dotted line diastolic blood pressure. In urinary catecholamines, solid line shows norepinephrine and dotted line epinephrine.]

Case 2: After the sodium intake was restricted to 17 mEq/day, the blood pressure decreased (from 169/100 to 150/94) and urinary CAs markedly increased (E, from 16.2 to 26.3; NE, from 50.8 to 129.4). After 33 days, when placebo of diazoxide was administered, the blood pressure began to decrease further slightly from 150/94 to 141/86 and urinary CAs decreased also moderately (E, from 26.3 to 17.7; NE, from 129.4 to 93.9). And after the sodium supply was increased from 17 to 85 mEq, a slight rise in blood pressure (from 141/86 to 149/98) and a slight decrease in urinary NE (from 93.9 to 71.6) were observed.

Case 6: After the daily sodium intake was re-
duced from 85 to 17mEq, blood pressure declined from 214/122 to 173/105 and urinary CAs increased markedly (E, from 13.0 to 30.3; NE, from 32.0 to 112.8).

Case 9: When the sodium intake was reduced from 170 to 85mEq, a slight decline in blood pressure (from 185/98 to 173/94) and an increase in urinary NE (from 45.2 to 64.5) were observed. After a more drastic sodium restriction, i.e., down to 17mEq, blood pressure declined further to 158/96, but urinary CAs showed no further change.

In this group of subjects, a moderate fall of blood pressure was observed after the salt restriction. And in all cases the urinary CAs, especially NE, increased markedly (Type I).

2) The group in which no marked change in blood pressure but a marked increase in urinary CAs were observed after salt restriction (Group II).

Case 3: After the restriction of daily sodium intake from 170 to 17mEq, systolic blood pressure remained at the control level and diastolic blood pressure was elevated rather slightly (from 135 to 143), but urinary CAs increased markedly (E, from 7.2 to 17.3; NE, from 32.6 to 226.1) (Fig. 3).

Case 4: After the daily sodium intake was restricted from 170 to 17 mEq, blood pressure did not lower but rather rose slightly (from 182/111 to 195/115). And urinary NE was moderately increased (from 24.7 to 91.3). After 10 days, when placebo of diazoxide was administered, blood pressure began to lower (from 195/115 to 177/100) and urinary NE decreased (from 91.3 to 74.4).

Case 8: After the sodium restriction (17mEq), systolic blood pressure did not change, while diastolic blood pressure rather rose slightly (from 70 to 76). Urinary CAs increased markedly (E, from 15.3 to 43.9; NE, from 30.0 to 118.3).

When the salt intake was restricted in this group, there was no change or rather slight elevation of blood pressure level and urinary CAs (especially NE) increased moderately or markedly (Type II).

3) The group in which neither blood pressure nor urinary CAs changed after salt restriction (Group III).

Case 5: After the daily sodium intake was restricted from 170 to 17 mEq, no change in systolic blood pressure occurred, but diastolic blood pressure rose slightly from 106 to 112. No changes in urinary CAs were observed (Fig. 4).

Fig. 3. A Representative Case In Group II.

In this case, when the sodium intake was restricted from 170 to 17 mEq/day, blood pressure did not decrease but increased slightly, and a marked increase in urinary norepinephrine was observed simultaneously. Twenty days later, when diazoxide in dose of 150mg was added to salt restriction, blood pressure began to decline gradually, but urinary excretion of norepinephrine remained at an elevated level. When dosis of diazoxide was increased to 300mg, blood pressure declined further and the level of urinary norepinephrine decreased slightly.

Fig. 4. A Representative Case In Group III.

When the sodium intake was restricted from 170 to 17 mEq, no changes were observed in systolic blood pressure and also in urinary catecholamines, and only diastolic blood pressure rose slightly. Thirteen days later, when diazoxide in dose of 150 mg was added to salt restriction systolic blood pressure did not change, but a slight decrease in diastolic blood pressure and a marked increase in urinary norepinephrine occurred simultaneously. After additional medication of trichlormethiazide in dose of 4 mg a slight decrease in diastolic blood pressure and a further increase in urinary norepinephrine were observed, while systolic blood pressure did not change.
Case 7: After the sodium intake was restricted from 170 to 17 mEq, there were no changes in both blood pressure and urinary CA excretion.

Case 10: After the daily sodium intake was restricted to 85 mEq, no changes occurred in both blood pressure and urinary CAs. Diastolic blood pressure rose slightly from 107 to 115.

In this group, no marked changes occurred in blood pressure and urinary CAs (Type III).

B) The Administration of Thiazide in Addition to Salt Restriction.

Thiazide was administered following the sodium restriction, and changes in both blood pressure and urinary CAs were studied (Fig. 5 and Table II).

Fig. 5. Changes in Blood Pressure and Urinary Catecholamines after Thiazide Medication in Addition to Sodium Restriction.
B: After Sodium Restriction.
C: During Thiazide Medication added to Sodium Restriction.
D: During Additional Administration of Thiazide.

In blood pressure, solid line shows systolic pressure and dotted line diastolic pressure. In urinary catecholamine, solid line shows norepinephrine and dotted line epinephrine.

1) Group I in which changes in blood pressure and urinary CAs after sodium restriction were of Type I.

<table>
<thead>
<tr>
<th>Table III Changes of the Reaction Type in Blood Pressure and Catecholamine After Salt Restriction with or Without Thiazide Medication</th>
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</thead>
<tbody>
<tr>
<td>Low Salt Diet</td>
</tr>
<tr>
<td>BP CA</td>
</tr>
<tr>
<td>Group I</td>
</tr>
<tr>
<td>Group II</td>
</tr>
<tr>
<td>Group III</td>
</tr>
</tbody>
</table>

Remarks: ↑ increased, ↓ decreased, → no change.

Case 1: After the administration of diazoxide in daily dose of 150 mg in addition to sodium restriction (17 mEq), no marked change in blood pressure was observed. But the already increased urinary excretion of NE showed further increase (from 153.3 to 236.6) (Fig. 2).

Case 2: With 150 mg daily of diazoxide given atop of sodium restriction (85 mEq), the blood pressure, lowered by the salt restriction, was further lowered in a slight degree (from 149/98 to 135/78) associated with a slight increase in urinary NE (from 71.6 to 83.3).

Case 6: After the administration of diazoxide in daily dose of 150 mg in addition to sodium restriction (17 mEq), blood pressure declined in a slight degree (from 177/109 to 160/95), and urinary NE increased slightly (from 33.0 to 46.5). After the additional administration of trichlormethiazide in daily dose of 4 mg, blood pressure level was somewhat elevated (from 160/95 to 169/104), while urinary NE increased markedly (from 46.5 to 165.7).

Case 9: After the administration of trichlormethiazide in daily dose of 4 mg in addition to sodium restriction (17 mEq), the blood pressure, lowered by the salt restriction, was further lowered (from 158/96 to 136/84) and the already increased excretion of NE showed further increase (from 67.0 to 103.2).

In this group, even with thiazide given in addition to the salt restriction, blood pressure remained at the same level as that found after the sodium restriction only, or it declined somewhat further. Urinary E remained at elevated levels and urinary NE, which was already increased by sodium restriction, increased further.
more or less. Thus, the pattern of the changes in blood pressure and urinary CAs was that of Type I.

2) **Group II, in which urinary CA increased whereas there was no change in blood pressure after sodium restriction.**

**Case 3:** With 150 mg daily of diazoxide given in addition to sodium restriction (17 mEq), blood pressure declined slightly (from 212/143 to 191/130) and urinary E increased moderately (from 17.3 to 33.1) while urinary NE remained elevated. When the dose of diazoxide was increased up to 300 mg daily, blood pressure was lowered markedly (from 191/130 to 162/107) associated with a decrease in urinary NE (from 230.8 to 153.2) (Fig. 3).

**Case 4:** Following the administration of diazoxide in daily dose of 150 mg in addition to sodium restriction, blood pressure declined markedly (from 195/115 to 165/91) whereas there was no marked change in urinary CAs.

**Case 8:** After the administration of trichlormethiazide in daily dose of 4 mg, there were no marked changes in both blood pressure and urinary NE, though urinary E decreased slightly (from 45.9 to 24.5). Even with additional administration of diazoxide in daily dose of 150 mg, there was no marked change in systolic blood pressure and urinary CAs, and diastolic blood pressure lowered slightly (from 77 to 59).

In this group, with thiazide administered in addition to salt restriction, reduction of blood pressure was observed except in Case 8, in which reduction was limited to the diastolic blood pressure. Urinary CAs remained increased or further increased. Thus, the pattern of changes in blood pressure and urinary CA transformed itself from Type II into Type I. In Case 8, the observed change seems to belong to an intermediate pattern, between Type II and I.

3) **Group III, in which there was no change in either blood pressure or urinary CAs.**

**Case 5:** After the administration of diazoxide in daily dose of 150 mg in addition to sodium restriction (17 mEq), diastolic blood pressure declined slightly (from 112 to 102), and there was a marked increase in urinary NE and a slight increase in urinary E (E, from 5.5 to 11.8; NE, from 37.1 to 95.5). And after additional administration of trichlormethiazide in daily dose of 4 mg, further but slight reduction in diastolic blood pressure (from 102 to 97) and marked increase in urinary NE (from 95.5 to 156.8) were observed. Throughout this experimental period systolic blood pressure showed no change (Fig. 4).

**Case 7:** With diazoxide administered in dose of 150 mg in addition to sodium restriction (17 mEq), blood pressure declined moderately (from 164/54 to 148/44) and urinary CAs increased slightly (E, from 11.5 to 21.4; NE, from 16.6 to 37.3). After the additional administration of trichlormethiazide in daily dose of 4 mg, diastolic blood pressure somewhat declined (from 44 to 33), and urinary NE increased moderately (from 37.3 to 85.8).

**Case 10:** With 4 mg daily of trichlormethiazide administered in addition to sodium restriction (85 mEq), there was no marked change in blood pressure, while urinary CAs increased markedly (E, from 15.1 to 30.2; NE, from 85.1 to 174.9). About 20 days later, blood pressure began to lower gradually (from 177/119 to 149/112) and, simultaneously with this, urinary NE decreased (from 174.9 to 133.8).

In this group, when thiazide was added atop of salt restriction, urinary CAs increased in all cases, and blood pressure declined moderately in Cases 7 and 10, but only diastolic blood pressure declined in Case 5. Thus, the pattern of the response became that of Type I for Case 7. For Case 10 the pattern became that of Type I through that of Type II. And the pattern of response became that of an intermediate form between Type I and II for Case 5.

C) Thiazide Medication Without Salt Restriction.

**Case 4:** After the start of diazoxide therapy in daily dose of 150 mg without salt restriction (daily sodium intake, 170 mEq), blood pressure did not change, whereas urinary NE increased in a slight degree (from 17.1 to 27.4). After the additional trichlormethiazide in daily dose of 4 mg, blood pressure declined moderately (from 180/95 to 155/90) and urinary CAs increased moderately (E, from 5.1 to 14.6; NE, from 27.4 to 51.6).
The changes that were obtained after the administration of thiazide alone and without salt restriction were analogous, with regard to the blood pressure change and urinary CA change, to the changes obtained with the salt restriction with or without the concomitant use of thiazides. However, with thiazide alone, changes with the urinary CA excretion were relatively mild.

Discussion

It has been well known that the dietary intake of salt has certain effects on the blood pressure in hypertension, that is, excess intake of salt raising the blood pressure and restriction declining it. Attention was called to this problem when it became known that the low blood pressure, usually prevailing among tuberculous patients, was elevated upon the administration of salts. Grollman and his associates\(^\text{41}\) and Selve et al.\(^\text{43}\) and Knowlton et al.\(^\text{49}\) demonstrated that various steroids were hypertensogenic only when additional salt was provided. Furthermore, Meneely and his associates\(^\text{46-48}\) reported that the chronic ingestion of excess sodium chloride to rats produced hypertension which mimicked human hypertension morphologically. Dahl\(^\text{47}\) observed that the incidence of hypertension and atherosclerosis can be correlated very well with the level of salt intake in different geographic areas and even in different races.

On the other hand, convincing evidences that the salt restriction is effective in hypertension were presented by Allen and Sherrill\(^\text{49}\) in 1917, and by Martin\(^\text{50}\) in 1938. Grollman and Harrison\(^\text{41}\) demonstrated that with drastic sodium restriction the blood pressure of hypertensive rats could be lowered. Grollman and his associates\(^\text{50}\) clearly demonstrated that it was the sodium rather than the chloride ion which was responsible for the hypotensive effects of salt restriction. Nevertheless, the manner in which the variation in sodium intake modifies the level of blood pressure still remains obscure. It is suggested that the fall of blood pressure following sodium restriction is partly due to the reduction of the plasma volume which is found to be expanded in the hypertensive patient\(^\text{53-56}\). It is also suggested that a decrease in sodium contents in the vascular wall, consequent on the sodium deprivation, causes vascular hyporeactivity to pressor substances and this tends to make the blood pressure to decline\(^\text{57,58}\). Although the exact mechanism whereby the thiazides depress the blood pressure remains yet obscure, the drugs seem to exert their main pharmacological action through electrolytes metabolism\(^\text{59-62}\); in other words, thiazides seem to induce sodium depletion, so that they produce the same effects as does the salt restriction, and when thiazides are used in conjunction with salt restriction, they enhance the effect of the salt restriction\(^\text{65,66}\). Diazoixide acts to retain sodium and water in contrast with other thiazides\(^\text{67,68}\). The depressor action of diazoxide, then, cannot be explained by the consideration mentioned above, but this drug may bring about a redistribution of sodium and water between intracellular and extracellular compartments and subsequently affect the blood pressure\(^\text{69}\). Tobian\(^\text{69}\), Griebel\(^\text{70}\) and Leonard\(^\text{71}\) demonstrated separately that blood pressure levels paralleled the potassium content of the arterial wall in the hypertensives. Freed\(^\text{72}\) and Freed and Friedman\(^\text{73}\) reported similar variations of potassium content of the arterial wall with blood pressures in rats during a period of diazoxide administration and a fall in blood pressure during dietary potassium restriction. Other actions of thiazides not involving the electrolytes metabolism were also invoked\(^\text{69,74}\). It may be safely stated that catecholamine does not play a primary role in the causation of hypotensive action due to salt restriction and thiazide medication.

In the present study the author has classified the patients into three groups on the basis of the pattern of changes in blood pressure and urinary catecholamines that occur following the salt restriction (Table III). Urinary catecholamines, particularly norepinephrine increased markedly in all cases in which blood pressure fell markedly (Group I). In cases in which blood pressure did not decline, urinary catecholamines were increased in some cases (Group II), while no changes in others (Group III). When thiazides were used in conjunction with salt restriction, blood pressure decreased in cases of group II,

*Japanese Circulation Journal Vol. 29 May 1965*
which means that the type of reaction changed from II into I; in Group III where increase in the blood pressure occurred, excretion of catecholamines increased, which means that the type of reaction changed from Type III into Type II. It seems therefore that the thiazide medication promotes the effect of salt restriction. Similar changes in urinary catecholamine and blood pressure were obtained following the thiazide medication without the use of salt restriction (Case 4). Therefore, thiazide medication and salt restriction seem to have analogous effects. Thus, with the use of thiazides in conjunction with salt restriction the type of reaction in individual cases changed with definite trends, that is, from Type III (Group III) into Type II or I, or from Type II (Group II) into Type I; Type I (Group I) did not change.

How the increased urinary excretion of catecholamines is brought about is not known. Release of stored catecholamine from cardiovascular tissues, hypersecretion from chromaffin cell or from sympathetic nerve ending, and change in the mode of metabolic pathway of catecholamine may be the possible sources. Question arises at first as to whether such a fall in blood pressure was caused by the excretion of larger than normal doses of catecholamines from cardiovascular tissues following the thiazide medication. The marked increase in catecholamines is sustained, however, as long as the condition, which causes hyperexcretion of catecholamines in urine — salt restriction and/or thiazide medication — continues. For example, increased urinary excretion of catecholamines continued for more than one month in case 3. Such a long-term increase in the excretion of catecholamines is not seen after the reserpine administration, a drug which causes the release of stored catecholamines as well as their hypoproduction. It is not likely, therefore, that the increased urinary output of catecholamines is derived only from stored catecholamines. Catecholamines, infused intravenously, are excreted as catecholamines (about 4 per cent), VMA (about 30 to 35 per cent) and metanephrine (about 50 per cent) (or normetanephrine in amounts equivalent to about 20 to 30 per cent of the amount given). It seems that this percentage proportion holds also for naturally occurring catecholamines. In hypertensive patients, this percentage proportion may change after the start of salt restriction and/or thiazide medication, indicating a change in the metabolism during the course of its action and degradation. Under similar conditions of sodium depletion, Mita found a hyperexcretion of urinary VMA, though the change of urinary VMA is not always in parallelism to catecholamines. These observations suggest a hypersecretion of catecholamines, especially of noradrenaline, and some changes in the mode of catecholamine metabolism; and they also suggest an increase in plasma catecholamine concentration that is consequent to these changes.

Nevertheless, the blood pressure declines under such conditions as salt restriction or thiazide medication. Decreased vascular reactivity to catecholamine caused by sodium depletion explains this inverse phenomenon. Thus, it seems that the pressor action of the secreted catecholamine antagonizes the depressor effect of sodium depletion; blood pressure is determined by the total sum of these two counter-actions.

The mechanism whereby hypersecretion of catecholamine occurs is not yet known, but there is some evidence suggesting the mechanism. It is suggested that an increased excretion of catecholamine is caused by reflex activation of the sympathetic nerve when blood pressure falls. Sandin and Hickler et al. noted that when body was tilted the blood pressure was maintained by hypersecreted catecholamines, especially noradrenaline, and when the secretion of noradrenaline did not increase hypotension occurred. Goodall et al. demonstrated increased plasma catecholamine under the state of high gravitational stress. Acute reduction of circulating blood volume also increased catecholamine secretion. These depressor maneuvers seem to activate baroreceptors which lie in the arterial wall and in other organs, causing catecholamines to be secreted reflexly in excess amounts. As salt restriction and the thiazide medication tend to lower the blood pressure of the hypertensives, it may be safely presumed that under this circumstance cate-
Cholamines are secreted reflexly in excess amounts in order to maintain the blood pressure. In Cases 2 and 4, where dietary sodium restriction caused a marked increase in urinary catecholamine output, blood pressures declined in parallel with decreases in urinary catecholamines after administration of placebo. And in Case 3, where urinary catecholamines had been markedly increased by diazoxide medication in addition to the dietary sodium restriction, blood pressures declined in parallel with decreases in urinary catecholamines after the daily dose of diazoxide was increased from 150 to 300 mg. These data suggest that catecholamines secreted in excess amount after the sodium depletion play some role in maintaining the given level of blood pressure. In most of the cases of Group II, salt restriction was followed by a slight rise in blood pressure, probably owing to an overshoot of catecholamine secretion that was called into action to maintain the blood pressure; and in most of the cases of Group III, salt restriction was followed by no marked change of blood pressure, probably as a consequence of the fact that there was no increase in catecholamine secretion. But in some cases of this group, the diastolic blood pressure rose slightly. It is suggested that the rise of diastolic pressure was caused by the factors other than the catecholamine, called into action by depressor maneuvers such as dietary salt restriction and thiazide medication, or the rise of the diastolic pressure is presumably effected by the release of a minimal dose of catecholamine, too small to be detected by the assay of the urinary catecholamine output.

Why didn't the blood pressure in these subjects react uniformly to the same depressor stimuliutons such as salt restriction and thiazide medication? If the changes of hemodynamics of these subjects are caused by sodium depletion due to dietary salt restriction, it is likely that the patterns of the changes in blood pressure and urinary catecholamine during sodium depletion depend on the stability of hemodynamics to these depressor stimulations and also depend on the intensity of the stimulations. Page postulated a mosaic theory to explain the pathogenesis of essential hypertension. Peterson suggested a control mechanism of blood pressure regulation. Maekawa postulated that the blood pressure level was set by the myosin-ATPase-ATP system in the cardiovascular system, and that the blood pressure was controlled by regulation systems which involved hypophysoadrenocortical and sympatho-adrenomedullary system. The observation that, in Cases 6 and 9, after the administration of steroids the excretion of catecholamines decreased with or without change in blood pressures, suggests that there is a subtle interrelation among the factors affecting blood pressures. Furthermore, Tobian suggested the existence of "the extracellular volume regulating center". Thus, it is certain that various systems take part in setting and regulating blood pressure, and that the conditions of all these systems affect the stability of hemodynamics. As blood pressure is regulated not only by catecholamine but also by other factors, it is only natural that the blood pressure is not parallel to plasma catecholamine level. Where catecholamine is the predominant factor over other factors, blood pressure changes approximately parallel to plasma catecholamine concentration, but such a condition obtains rather rarely. When a case is not treated by any procedures affecting blood pressure, blood pressure of the case lies on its set level and catecholamine excretion is within normal range independently of the absolute value of the blood pressure. When the blood pressure is apt to be depressed from its set level, then excessive amount of catecholamine is secreted as well as mineralo-corticoiids, glucocorticoiids and so on, so that the blood pressure is controlled to maintain as its set level. After the sodium depletion, the pattern of the change in blood pressure and urinary excretion of catecholamine was thus determined by the interrelation between the intensity of the depressor action and the stability of setting mechanism of blood pressure. When the blood pressure is set stably and does not surrender to the effect of salt depletion, no change in blood pressure occurs and there is, therefore, no change in the catecholamine secretion. This is apparently the case with Type III response. When the depressor effect of salt depletion overwhelms the stability of the
blood pressure setting mechanism, blood pressure tends to fall and this activates the hypersecretion of catecholamine, with the result that the blood pressure is maintained at the original level. This is apparently the case with Type II response. When the depressor effect of salt depletion is strong disproportionately to the stability of blood pressure setting mechanism, or when the blood pressure setting mechanism is too labile to square with the depressor effect of salt depletion, the catecholamine secretion increases markedly. But even with this greatly increased secretion of catecholamine the depressor effect of salt depletion cannot be overcome and a reduction of blood pressure results. Intermediate forms between these reaction types is well explainable on the basis of this dynamic concept.

Since the blood pressure is regulated by many interrelated systems, it is straightforward and rational to attempt to treat the hypertensives by the blocking strategic points of these regulating systems. For example, when a patient stays in the state of Type II response to sodium depletion, this patient may be successfully treated by blocking the production of catecholamine. Of course, this is only effective on the functional part of blood pressure elevation, but are ineffective on the part of blood pressure elevation originating in established morphological changes in the cardiovascular system. By a long-term antihypertensive therapy, however, the set level of the blood pressure may go down gradually, when the blood pressure is kept at a lowered level for a sufficiently long time. But when the set level of blood pressure is yet higher than the real blood pressure even after effective antihypertensive therapy, regulation to maintain blood pressure occurs more or less. And when the set level of blood pressure goes down to the real blood pressure level, regulation to maintain blood pressure is no longer necessary and urinary catecholamine decreases to normal range. This point is suggested by the fact that urinary excretion of catecholamine is normal in the well treated patient, and his blood pressure no longer rises even after the therapy is discontinued.

It is interesting to note that such changes of catecholamine and blood pressure during sodium depletion are observed independently in the kinds of hypertension studied. Owing to the lack of such a study in the normotensives, it may remain a matter of controversy whether the regulating mechanism of blood pressure is specific to the hypertensives. Since hypersecretion of catecholamine can be activated by various maneuvers, such as acute postural change[80,81], high gravitational stress[82] and acute bleeding in the normotensives[83], variations in urinary catecholamine excretion associated with, or dissociated from, blood pressure changes may constitute an expression of commonplace reflex mechanism of homeostasis, that are in operation in the normotensives as well as the hypertensives, although the stability of the blood pressure setting mechanism may be different between normotensives and hypertensives.

**SUMMARY AND CONCLUSION**

In order to investigate the role of catecholamine in hypertension, changes in blood pressure and urinary catecholamines were studied in ten cases of non-edematous patients with hypertension of various origins and degrees, before and during the salt restriction with or without thiazide medication. Parenthetically, the salt restriction and the thiazide therapy, per se, have no direct effects on the catecholamine metabolism. The observed patients were classified into three groups according to the pattern of responses caused in these patients by salt restriction:

- **Group I**: Blood pressure fell, but urinary catecholamines increased (Type I response).
- **Group II**: No change in blood pressure, but urinary catecholamines increased (Type II response).
- **Group III**: Changes occurred in neither blood pressure nor urinary catecholamines (Type III response).

With the addition of thiazide therapy atop of salt restriction, the type of response changed with definite trends, that is, in Group III from Type III into Type II or I, or in Group II from Type II into Type I, while Type I did not change in Group I. Furthermore, these changes in type occurred independently of the kind of
hypertension studied.

These results were interpreted to mean that when blood pressure fell, or tended to fall, catecholamines were secreted in excess amounts as a homeostatic response so as to adjust the hemodynamic change and to keep the homeostasis. This hemodynamic adjustment by catecholamine seemed to constitute the regulation mechanism of blood pressure associated with other regulating systems, and also seemed to exist even in the normotensive subjects.

Acknowledgement

The author wishes to express his sincere gratitude to Prof. Magojirō Maekawa, M.D. for precious advice and valuable suggestions in guiding this study. The author is greatly indebted to Dr. Koichi Ogino for his practical direction and helpful criticism throughout this study. Thanks are also due to Dr. S. Motomura, Dr. M. Matsunaga, Dr. A. Wakahayashi, Dr. Y. Mitamura and Dr. H. Yasui for their valuable cooperation and consultation.

Thanks are also tendered to Miss M. Osumi, Miss H. Takagi and Miss H. Asada for their technical assistance.

(An outline of this study was reported at the XXVI General Assembly of the Japanese Circulation Society, 1962 (Tokyo), and was reported by Prof. M. Maekawa at the VII International Congress of Internal Medicine, 1962 (München.).

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