Nineteen patients with normal renin idiopathic hypertension were arbitrarily classified as salt-sensitive or salt-resistant depending on whether their mean arterial pressure did or did not increase by 8% or more when sodium intake was increased. The responses of the two subsets and of five normal subjects to sodium intakes of 9, 109, and 249 mEq/day given for 7 days were as follows: The salt-sensitive subjects retained more sodium than normal and plasma or urinary norepinephrine did not decrease when they were given a high sodium intake; urinary dopamine was normal but did not increase normally when sodium intake was increased. The salt-resistant subjects excreted sodium normally and plasma and urinary norepinephrine was decreased by 30 and 37%, respectively, when they were given a high sodium intake; urinary dopamine was supernormal and did not increase further when sodium intake was increased. Cumulative sodium retention during the high sodium intake was directly related to the percentage of change in plasma norepinephrine in the hypertensive subjects, suggesting that renal adrenergic activity was a factor in the impaired sodium excretion in the salt-sensitive patients. Cumulative sodium retention and the percentage of change in plasma norepinephrine were inversely related to urinary dopamine in the hypertensive subjects, suggesting that increased formation of dopamine in renal and neural tissue in the salt-resistant subjects may have been responsible for the differences between the subsets in renal and adrenergic responses to a high sodium intake. Supernormal sodium retention and a failure to suppress adrenergic activity may explain, in part, the phenomenon of salt sensitivity of blood pressure in salt-sensitive patients and may also be factors in the pathogenesis of hypertension in this subset. (Hypertension 11: 312–319, 1988)
(PRA) was suppressed to an equal extent by a high sodium intake in both SS and SR patients and responded normally to a low sodium intake in SR patients, it responded subnormally to a low sodium intake in the SS patients.1-3,5 These findings suggest that SS patients, in contrast to SR, may show sodium retention and a blunted suppression of plasma NE that, alone or in concert with other factors, may mediate the altered responses of the cardiovascular system to ingestion of sodium chloride. If these features prove to be characteristic of SS patients, they may be responsible for the phenomenon of salt sensitivity of blood pressure and factors in the pathogenesis of hypertension in this subset.

The present studies were performed to examine sodium metabolism and adrenergic function in SS and SR patients with normal renin idiopathic hypertension in more detail to determine how these two subsets differ from each other and from normal. Urinary dopamine (DA) was also measured to assess the possibility that DA, which appears to play a role in normal sodium metabolism and adrenergic function,12,13 may also be a determinant of the physiological responses of SS and SR patients.

Subjects and Methods
Protocol
Twenty-four patients previously diagnosed in this clinic as having uncomplicated idiopathic hypertension, 14 women and 10 men aged 20 to 75 years, discontinued antihypertensive medications and 2 weeks later were admitted to the Clinical Center of the National Institutes of Health. Five normotensive subjects without a family history of hypertension, three women and two men, aged 20 to 62 years, were also admitted for study as normal controls. All participants gave their written informed consent before entering the protocol, which had been approved by the Clinical Research Committee of the National Heart, Lung, and Blood Institute. The subjects were housed on an air-conditioned metabolic unit and fed a constant isocaloric diet containing 9 mEq of sodium. Supplements of sodium as sodium chloride were given as follows: 100 mEq/day for 7 days (normal sodium intake); no supplement for 7 days (low sodium intake); 240 mEq/day for 8 days (high sodium intake). Fluid intake was constant throughout. Blood pressure was measured by Sentron sphygmomanometer (Bard, Lombard, IL, USA) every 4 hours after 5 minutes or more of bed rest, and the results expressed as mean arterial pressure (MAP), which was calculated by adding one third of the pulse pressure to the diastolic pressure. Blood was drawn in the fasting state every 2 or 3 days for sodium, potassium, chloride, carbon dioxide content, and creatinine. Blood for determination of PRA, aldosterone, and NE was drawn on Day 7 of normal sodium intake, on Day 7 of low sodium intake, and on Days 4 and 8 of high sodium intake. On these days, the subjects remained at bed rest and a heparin lock was placed in an antecubital vein; 20 minutes later when pulse was stable a blood sample was drawn (basal values). The subjects then stood for 5 minutes, and a second sample was taken for plasma NE (standing values). The subjects then stood or walked for 2 hours, and a blood sample for PRA and aldosterone was taken (upright values). The heparinized blood sample was collected on ice, separated in a refrigerated centrifuge, and stored frozen at -80°C until assayed. Urine was collected daily throughout the study in 24-hour aliquots; each voiding was equally divided between two containers, one containing 20 ml 6 N HCl and the other containing no preservative. Urine was kept cold during the period of collection, then aliquots were frozen and stored at -80°C until assayed. Acidified aliquots were used for determination of NE and DA. The aliquots without preservative were used for the determination of sodium, potassium, creatinine, and aldosterone.

Assays
PRA and plasma aldosterone were determined by radioimmunoassay at Hazelton Laboratories (Vienna, VA, USA). Plasma NE was measured in duplicate by the radioenzymatic method of Durrett and Ziegler.14 In this assay the enzyme catechol-O-methyltransferase is used to catalyze the transfer of a $^3$H-labeled S-adenosylmethionine to the n-hydroxyl group of norepinephrine in the plasma forming $^3$H]normetanephrine. The sensitivity of the assay was 20 to 30 pg/ml. Intra-assay and interassay coefficients of variation were 4.67 and 7.54%, respectively. Urinary NE and DA were measured by high performance, reverse-phase liquid chromatography with electrochemical detection.15 The sensitivity of the assay was 10 μg/L for NE and DA. Intra-assay coefficients of variation were 4.1 and 4.5% for NE and DA, respectively; interassay coefficients of variation were 7.1 and 6.5% for NE and DA, respectively. For each patient, all samples for a particular hormone were measured in the same assay. Serum and urinary creatinine and serum sodium, potassium, chloride, and carbon dioxide content were determined by autoanalyzer. Urinary sodium and potassium were determined by flame photometry.

Statistical Analysis
The data are presented as means ± SEM. Two sample comparisons were analyzed by t tests, and changes of repeated measurements were analyzed by paired t tests. The correlations of variables were evaluated by determination of Pearson product-moment correlation coefficients.16 Where appropriate, Hotelling's $T^2$ test for comparison of two multivariate sample mean vectors was performed.17 Because of the small sample size of the study, we did not consider the problem caused by multiple comparisons. All the p values quoted are nominal and are considered significant at the 0.05 level.

Results
Five of the 24 hypertensive patients had PRA levels ranging from 0.1 to 2.2 ng of angiotensin I (Ang I)/ml/hr in response to ambulation on the 7th day of
low sodium intake; these patients were considered to have low renin essential hypertension and were omitted from the study. The remaining 19 patients, who fulfilled the criteria for normal renin essential hypertension, were then further classified as SS or SR depending on the difference between MAP at the end of the low sodium intake and that at the end of the high sodium intake: Eight patients had increases in their blood pressure 8 to 14% (mean change, 10%; \( p<0.05 \)), and they were arbitrarily classified as SS; the other 11 patients, who had blood pressure changes of -7 to 7% (mean change, 1%), were classified as SR (Table 1). Blood pressure in the normal subjects changed by -3 to +7% (mean change, 5%).

The SS subset had a mean age of 61 ± 2.8 years (range, 53–75 years), a female to male ratio of 6:2, and a white to black ratio of 5:6, and a white to black ratio of 9:2. The older age of the SS subjects is a characteristic that has been observed in other studies. Mean creatinine clearance (CCT) was 84 ± 2.6 ml/min in the SS and 112 ± 3.7 ml/min in the SR subjects. This difference in glomerular filtration rate is probably attributable to the preponderance of women with a smaller body surface area in the SS subset and to the difference in mean age between the two subsets, since there was no evidence of parenchymal disease in the SS subjects and the duration and severity of hypertension was not different between SS and SR subjects.

In comparison to the SR and normal subjects, the SS subjects tended to have a blunted response of PRA, determined during bed rest and after ambulation, at the end of the low sodium intake, but the differences were not significant (SS, 1.35/4.4 ± 0.68/0.91 ng Ang I/ml/hr; SR, 2.5/7.3 ± 0.44/0.68 ng Ang I/ml/hr; normal, 2.4/9.5 ± 0.60/2.38 ng Ang I/ml/hr). The responses of plasma aldosterone paralleled those of PRA, tending to be lower in SS than in SR and normal subjects (SS, 10/49 ± 2.1/8.6 ng/dl; SR, 20/112 ± 5.4/18 ng/dl; normal, 38/95 ± 7/21 ng/dl). During the high sodium intake PRA and plasma aldosterone were suppressed to values that were low and similar for all three groups.

Mean urine sodium during the last 2 days of the low sodium intake was similar for SS and SR subjects, but the mean value for the SR still exceeded that for the normal subjects (92 ± 3.7 mEq/day). During the low sodium intake mean cumulative sodium loss for the 7 days, calculated as the sum of daily urinary sodium minus sodium intake, was similar for SS and SR subjects, 83 ± 10 and 103 ± 18 mEq, respectively, but significantly (\( p<0.01 \)) less than the 170 ± 20 mEq lost by the normal subjects (Figure 1). During the high sodium intake mean cumulative sodium retention for the 7 days, the sum of sodium intake minus daily urinary sodium, was greater for the SS than for the normal subjects (427 ± 33 vs 256 ± 44 mEq, \( p<0.01 \)) whereas that for the SR (329 ± 46 mEq) was not significantly different from that for either SS or normal subjects (see Figure 1).

Mean urine DA during the last 2 days of the low sodium intake was higher (\( p<0.01 \)) in the SR subjects (301 ± 32 \( \mu \)g/day) than in either the SS or normal subjects (173 ± 21 and 137 ± 18 \( \mu \)g/day, respectively) (Figure 2). When sodium intake was increased, urinary DA, which increased (\( p<0.05 \)) in the normal subjects, did not change in either the SS or SR subjects, but the mean value for the SR still exceeded (\( p<0.01 \)) that for the normal subjects (see Figure 2). In the hypertensive subjects as a group cumulative sodium retention correlated inversely with mean urinary DA (\( r=-0.65,\ p<0.01 \)) those subjects with the higher urinary DA had less sodium retention (Figure 3). Since CCT was different in the two subsets and may have been a factor in the difference in sodium retention, five SR subjects with the lowest CCT were compared with five SS subjects with the highest CCT during the last 4 days of the high sodium intake when blood pressure for the two subsets showed the least difference. When differences in CCT and MAP were thus minimized, SS subjects still tended to show greater cumulative sodium retention and the relationship of sodium retention to urinary DA was even more apparent (\( r=-0.90,\ p<0.001 \); Figure 4).

Mean plasma NE was similar in all three groups on Day 7 of the low sodium intake; in response to the high sodium intake it decreased (\( p<0.01 \)) in the SR subjects but did not change in the SS or normal subjects.

### Table 1. Effect of Sodium Intake on Blood Pressure

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Na&lt;sup&gt;+&lt;/sup&gt;</th>
<th>Na&lt;sup&gt;+&lt;/sup&gt;</th>
<th>Na&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS (n = 8)</td>
<td>113 ± 3.3 *</td>
<td>104 ± 9.8</td>
<td>114 ± 1.3 *</td>
</tr>
<tr>
<td>SR (n = 11)</td>
<td>114 ± 2.2</td>
<td>114 ± 2.3</td>
<td>114 ± 4.2</td>
</tr>
<tr>
<td>Normal (n = 5)</td>
<td>81 ± 3.3</td>
<td>79 ± 4.3</td>
<td>83 ± 3.4</td>
</tr>
</tbody>
</table>

*Values are means ± SEM. SS = salt-sensitive; SR = salt-resistant.

*\( p<0.05 \) when compared with the blood pressure measured during sodium intake of 9 mEq/day.
No-Intake mEq/d

Urinary Dopamine µg/d

Normal

SS

SR

P<0.05

P>0.1

FIGURE 2. Mean urinary dopamine during the last 2 days of the low sodium intake (9 mEq/day) and the first 2 days of the high sodium intake (249 mEq/day) for normal, salt-sensitive (SS), and salt-resistant (SR) subjects. Note that urinary dopamine was high in the SR subjects and did not show a normal increase in either SS or SR subjects.

(normal, 184 ± 31 vs 173 ± 20 pg/ml; SS, 209 ± 25 vs 190 ± 13 pg/ml; SR, 190 ± 19 vs 119 ± 9 pg/ml; Figure 5). Urinary NE showed a pattern of response similar to that of plasma: On Day 7 of the low sodium intake mean urinary NE was similar in all three groups, and in response to the high sodium intake it decreased (p<0.05) in the SR subjects but did not change in the SS or normal subjects (normal, 21 ± 3.6 vs 15 ± 3.8 µg/day; SS, 35 ± 4.7 vs 42 ± 12 µg/day; SR, 35 ± 4.7 vs 22 ± 3.7 µg/day). Plasma NE during rest (basal) and after standing for the SR and SS subjects during each of the three sodium intakes are shown in Table 2. Values for the SS subjects showed an increase in response to low sodium and a fall in response to a high sodium intake, whereas those for the SS subjects showed an increase in response to low sodium that was sustained throughout the high sodium intake. Thus, during the high sodium intake plasma NE was significantly (p<0.02) higher in the SS than in the SR subjects. The differences in plasma NE may also have contributed to the differences in sodium retention observed in the two hypertensive subsets, since cumulative sodium retention during the high sodium intake correlated directly with the percent change in plasma NE that occurred when sodium intake was increased (r = 0.62, p<0.01; Figure 6). Those hypertensive subjects with an increase or only a small decrease in plasma norepinephrine had the greatest cumulative sodium retention (see Figure 6). The differences in response of plasma NE to a high sodium intake in the two hypertensive subsets may be related to differences in the amount of DA formed or released centrally or peripherally at sympathetic nerves since the percent change in plasma NE was inversely related to mean urinary DA (r = -0.67, p<0.01; Figure 7).

The differences in urinary DA and NE between SS and SR subjects during a high sodium intake may be useful in the characterization of patients with idiopathic hypertension and normal renin. In the present study, the subjects characterized as SS or SR on the basis of the response of blood pressure to a change from a low to a high sodium intake, with one exception, would have been similarly grouped on the basis...
Patients with idiopathic hypertension and normal renin responded to a change from a low to a high sodium intake with changes in blood pressure that ranged from -7 to 14%. Those patients who increased their blood pressure by 8 to 14% were arbitrarily classified as SS, and the remainder were classified as SR. When sodium metabolism, plasma and urinary NE, and urinary DA during normal, low, and high sodium intakes were compared in these two subsets and in a group of normal subjects, additional differences between the two subsets as well as differences from normal were found. The SS patients retained more sodium than normal and plasma or urinary NE did not decrease when they were given a high sodium intake; mean urinary DA was normal but did not increase, as it does in normal subjects, when sodium intake was increased (see Figures 1, 2, and 5). The SR patients excreted sodium normally and plasma and urinary NE decreased by 30 and 37%, respectively, when they were given a high sodium intake; mean urinary DA increased (see Figures 1, 2, and 5). The SS hypertensive patients may also explain why some patients with idiopathic hypertension have high levels of circulating atrial natriuretic peptide.19

The cause of the impaired sodium excretion observed in the SS hypertensive patients in this and other studies is unknown, but it may be attributable, in part, to an increase in reabsorption of sodium by the proximal tubule. The clearance of lithium, an index of proximal tubular reabsorption of sodium, was lower in a group of patients who had idiopathic hypertension (but who had not been characterized for salt sensitivity) than it was in normal subjects.20 Although the investigators did not identify the cause of the abnormality in proximal tubular function in the hypertensive patients, they concluded that it was genetically determined because the normal subjects who had a family history of hypertension had a significantly lower clearance of lithium than those who did not.20 Such a "genetic determinant" could be an intrinsic abnormality in the proximal tubule, a stimulus to proximal tubular reabsorption, or both. In the present studies, the direct correlation between the percentage of change in plasma NE and cumulative sodium retention (see Figure 6), together with the sustained plasma NE in the SS subjects during the high sodium intake (see Figure 5, Table 2), suggests that renal adrenergic activity may have been a determinant of the enhanced renal sodium reabsorption. The notion that renal adrenergic activity may have stimulated tubular function is supported by considerable experimental evidence indicating that renal nerves may alter reabsorption of tubular fluid by the proximal tubule.21 22 A role for renal nerves need not necessarily exclude an intrinsic abnormality enhancing the tubular reabsorption of sodium. Indeed, two observations in the SR subjects are consistent with the existence of such an abnormality. First, during the low sodium intake SR subjects, like the SS subjects, showed less sodium loss than normal despite supernormal mean urinary DA (see Figure 1). Second, during the high sodium intake, the SR subjects showed a normal cumulative sodium retention associated with a supernormal mean urinary DA (see Figures 1 and 2). These findings of a normal or enhanced renal reabsorption of sodium rather than a
decreased reabsorption that one might expect to be associated with a supernormal renal generation of DA suggest the possibility that the SR subjects, in contrast to the SS subset, may have compensated for an intrinsic tubular abnormality by increasing renal DA formation. If the values for mean urinary DA in both the SR and SS subjects represented maximal achievable compensatory responses to enhanced tubular sodium reabsorption, this may explain why urinary DA was not increased above normal in SS subjects and why it showed only a slight increase or none at all in the two subsets when sodium intake was increased. The notion that DA may be an important determinant of sodium excretion in the hypertensive subjects, as it appears to be in normal subjects, and that differences in renal formation of DA by the two subsets may be responsible for differences in sodium excretion is supported by the finding that cumulative sodium retention was inversely correlated with mean urinary DA in SR and SS subjects (see Figure 3).

When sodium intake was increased, plasma NE decreased in the SR but not in the SS subjects, confirming reports of others that plasma NE was higher in SS than in SR subjects during a high sodium intake. In the SS subjects both resting and ambulatory plasma NE on Days 4 and 8 of the high sodium intake were similar to the values on the low sodium intake and were significantly higher than those in the SR subjects (see Table 2). Since cumulative sodium retention for the initial 3 days of the high sodium intake was not different (294 ± 20 mEq in SS vs 311 ± 43 mEq in SR), it cannot account for the difference in plasma NE between the two subsets on Day 4. Subsequently, as the difference in cumulative sodium retention became greater, it may have been a factor contributing to the greater release of NE in the SS subjects. Mean plasma and urinary NE also did not decrease in the normal subjects when sodium intake was increased (see Figure 5). This finding contrasts with the findings in other studies with larger numbers of normal subjects that mean plasma or urinary NE decreased when sodium intake was increased. The present study did not confirm the earlier results because two of five normal subjects did not show a decrease in plasma NE. Although some normal subjects in each of two other studies also did not show a decrease in plasma or urinary NE when sodium intake was increased, they were not sufficient in number to prevent the group as a whole from showing a significant decrease.

Recently published studies indicate that normal subjects, like hypertensive patients, exhibit the phenomenon of salt sensitivity of blood pressure. The
SS normal subjects, like the SS hypertensive patients, have an attenuated response of PRA and aldosterone to a low sodium intake and tend to have a higher plasma NE.\textsuperscript{5, 21} These observations suggest that the SS segment of the normal population may represent those at risk for the development of SS idiopathic hypertension.

Estimates of NE release in SS and SR hypertensive patients during a high sodium intake indicated that the higher plasma NE in the SS patients was associated with a greater release of NE, presumably reflecting a greater outflow of adrenergic activity.\textsuperscript{9} Although the basis for the postulated increase in adrenergic outflow is unknown, several observations suggest that it may be a function of peripheral or central formation or release of DA, which has been shown to modulate it. Measurements of catecholamines in the spinal fluid of patients with idiopathic hypertension have shown that when the content of DA was low that of NE was increased.\textsuperscript{24} The DA agonist bromocriptine, which has been found to inhibit release of NE from peripheral nerves and to decrease its content in spinal fluid,\textsuperscript{25} decreased both resting and stimulated plasma NE in normal\textsuperscript{13} and hypertensive subjects.\textsuperscript{26} Administration of bromocriptine to patients with idiopathic hypertension for a longer period decreased plasma NE, all but abolished its circadian rhythm, and lessened its relationship to MAP.\textsuperscript{27} In the present study the percentage of change in plasma NE in response to the high sodium intake was inversely correlated with urinary DA (see Figure 7). This correlation is consistent with the notion that the lower rate of renal DA production in SS subjects may be accompanied by lower formation or release of DA centrally or at peripheral adrenergic neurons.

The greater than normal cumulative sodium retention and the lack of suppression of adrenergic activity despite supernormal sodium retention may explain, at least in part, the phenomenon of salt sensitivity of blood pressure in SS subjects. Excessive sodium retention and sustained adrenergic outflow may lead, in turn, to the increases in cardiac output\textsuperscript{2} and in the resistance of vascular beds such as that observed in the forearm of SS patients and thought to be responsible for the increase in blood pressure when sodium intake was increased.\textsuperscript{9, 11} Indeed, mean urinary DA, which was inversely correlated with cumulative sodium retention and the change in plasma NE during the high sodium intake, also tended to be inversely correlated with the change in MAP ($r = -0.41$).

It is likely that the abnormalities in sodium metabolism and adrenergic function also play a role in the pathogenesis of hypertension in SS patients. Other factors such as decreased baroreceptor reflex–cardiac sensitivity, enhanced pressor responsiveness,\textsuperscript{28} and defective α-adrenergic receptors that may mediate it\textsuperscript{29} are probably also involved. Thus, while it is possible to deduce from the present studies a number of potential etiological factors in SS subjects, the pathogenesis of the hypertensive process in SR subjects is more obscure. Since sodium metabolism and adrenergic function appear to be relatively normal in this subset, other potential causes for the increase in peripheral resistance must be sought.

The differences between SS and SR hypertensive patients observed in previous studies\textsuperscript{1–6, 9, 11} and confirmed and extended in the present study are considerable. As other variables that participate in the regulation of blood pressure and cardiovascular function are examined in these two subsets, the list of differences between SS and SR subjects may become even longer. The characterization of patients with idiopathic hypertension into SS and SR subsets has, to date, depended on manipulation of sodium intake and treatment with diuretics.\textsuperscript{1–6} The urinary DA/NE ratio determined during a high sodium intake in the present study has proven to be a reliable index of salt sensitivity and salt resistance of blood pressure in a small series of patients. The urinary dihydroxyphenylacetic acid (DOPAC)/NE ratio, a variation of the urinary DA/NE that depends on the DOPAC metabolite of DA, has been found to be a good index of the state of sodium balance in normal subjects.\textsuperscript{30} The quite different values for the DA/NE ratio in the two hypertensive subsets on a similar high sodium intake may explain why the DOPAC/NE ratio was not a good index of sodium balance in unselected hypertensive subjects.\textsuperscript{30} It is possible, however, that urinary DOPAC/NE ratio, like the urinary DA/NE ratio, may be a good predictor of salt sensitivity and salt resistance. If this proves to be the case as larger numbers of patients are evaluated, then such a ratio may provide an additional, somewhat simpler tool with which to categorize patients for study.

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