Elevated blood pressure is the major cause of cardiovascular disease (ie, stroke, heart failure, and coronary heart disease). A recent World Health Organization report showed that raised blood pressure is responsible for 62% of stroke and 49% of coronary heart disease worldwide. Much evidence from epidemiological, migration, intervention, genetic, and animal studies suggests that salt intake plays an important role in regulating blood pressure. Furthermore, there is increasing evidence that a high salt intake has direct harmful effects on the cardiovascular system (eg, it increases the mass of left ventricular wall, stiffens conduit arteries, and thickens and narrows resistance arteries, independent of and additive to the effect of salt on blood pressure). However, the mechanisms whereby salt raises blood pressure and induces direct cardiovascular organ damage are not clear. Much evidence suggests that in those who develop high blood pressure, there is an underlying defect in the ability of the kidney to excrete salt, and that the greater compensatory response required to restore sodium balance is responsible for the increase in blood pressure. However, the potential role of small changes in plasma sodium has rarely been considered. To look at this further, we reanalyzed 3 types of studies that we conducted on changing salt intake.

**Methods**

The methods used in the 3 types of salt studies are reported in detail previously and summarized here. All studies were approved by the local research ethics committee, and informed consent was obtained from all participants.

**Studies of an Acute and Large Reduction in Salt Intake**

Seventy-one white and 33 black patients with untreated essential hypertension (systolic \( \geq 140 \text{ mm Hg} \) or diastolic \( \geq 90 \text{ mm Hg} \)) and 39 white normotensive individuals (systolic \(< 140 \text{ mm Hg} \) and diastolic \(< 90 \text{ mm Hg} \)) were studied on a high salt intake of \( \approx 350 \text{ mmol/d for 5 days and a low salt intake of 10 to 20 mmol/d for 5 days} \). The high salt intake was achieved by supplementing the usual diet with 20 slow sodium tablets (200 mmol/d). The low salt intake provided by the metabolic unit kitchen. There were 33 male and 38 female hypertensive whites (mean age 49 years, ranging from 19 to 70), 15 male and 18 female hypertensive blacks (44 years, ranging from 29 to 62), and 25 male and 14 female normotensive whites (28 years, ranging from 19 to 62).

**Study of a Progressive Increase in Salt Intake**

Six white individuals with normal blood pressure (age range 19 to 21 years, 4 male and 2 female) were placed on a low salt intake of 10 mmol/d throughout the study. After a 4-day equilibration period on the low-salt diet, salt intake was progressively increased by a daily amount of 50 mmol by supplementing the low-salt diet with...
appropriate number of slow sodium tablets until salt intake reached 250 mmol.

Studies of a Longer-Term Modest Reduction in Salt Intake
A total of 118 patients with untreated essential hypertension were studied in randomized double-blind crossover studies of 1 month of usual salt intake and 1 month of modestly reduced salt intake. This analysis combined the data of 4 previous studies, all of which used the same protocol. In 1 of these studies, there were 3 levels of salt intakes, and for the purposes of this analysis, we have included the high and intermediate levels (ie, when urinary sodium was 190 and 108 mmol/24 h).

All participants reduced their salt intake to 50 to 80 mmol/d (3 to 5 g/d of salt) for 2 to 4 weeks, then entered an 8-week randomized double-blind crossover study of slow sodium tablets versus slow sodium placebo tablets while remaining on the low-salt diet throughout the study. This treatment regimen gave a salt intake of either 10 g/d (equivalent to the usual amount for the UK population) or 3 to 6 g/d (the currently recommended level of salt intake). There were 36 male and 27 female whites (mean age 61 years, ranging from 33 to 72), and 1 male and 1 female Asian (61 to 69 years).

Statistical Analysis
Results are reported as mean ± SEM. Changes in continuous variables were analyzed by repeated-measures ANOVA and paired t tests where appropriate. Multiple regression analysis was performed to test whether there was a significant relationship between the change in plasma sodium and other variables with adjustment for potential confounding factors. All statistical analyses were performed by Statistical Package for Social Science.

Results
Studies of an Acute and Large Reduction in Salt Intake in Normotensive and Hypertensive Individuals
Normotensive Individuals
With an acute and large reduction in salt intake, plasma sodium was reduced by 3.1 ± 0.6 mmol/L (P < 0.001), with a decrease in 24-hour urinary sodium of 293 ± 14 mmol (Figure 1). There was a large increase in plasma renin activity and aldosterone, but there was no significant change in either systolic or diastolic blood pressure. However, pulse pressure showed a significant fall (Table 1).

Hypertensive Individuals
With acute and large reductions in salt intake, there was a significant reduction in plasma sodium. In whites, plasma sodium was reduced by 3.0 ± 0.3 mmol/L (P < 0.001), with a decrease in 24-hour urinary sodium of 259 ± 14 mmol. In blacks, plasma sodium was reduced by 2.7 ± 0.4 mmol/L (P < 0.001), with a decrease in 24-hour urinary sodium of 250 ± 23 mmol (Figure 1). As expected, there was a significant rise in plasma renin activity and aldosterone and a significant fall in blood pressure (Table 1).

The reduction in plasma sodium was significantly correlated with the rise in plasma renin activity (r = 0.32; P < 0.01) and aldosterone (r = 0.24; P < 0.05) that occurred with the reduction in salt intake, indicating that the greater the reduction in plasma sodium, the larger the rise in plasma renin activity and aldosterone. There was also a significant correlation between the reduction in plasma sodium and the decrease in 24-hour urinary sodium excretion (r = 0.20; P < 0.05). However, there was no significant correlation between the reduction in plasma sodium and the fall in blood pressure.

Study of a Progressive Increase in Salt Intake in Normotensive Individuals
Plasma sodium was 138.5 ± 0.7 mmol/L when salt intake was 10 mmol/d. With the progressive increases in salt intake, there were increases in plasma sodium, so that when salt intake reached 250 mmol/d, plasma sodium was 141.5 ± 1.1 mmol/L (P < 0.001 by repeated-measures ANOVA; Figure 2). With the increase in salt intake, there was a significant increase in plasma atrial natriuretic peptide and a significant decrease in plasma renin activity and aldosterone (Table 2). Systolic blood pressure did not change significantly, but there was a significant fall in diastolic pressure. Pulse pressure showed a trend of increase, but the increase was not statistically significant (Table 2).

The average plasma sodium during the progressive increase in salt intake was significantly correlated with pulse pressure (r = 0.96; P < 0.01), atrial natriuretic peptide (r = 0.85; P < 0.05), and inversely associated with plasma renin activity (r = −0.82; P < 0.05) and aldosterone (r = −0.86; P < 0.05).

Studies of a Longer-Term Modest Reduction in Salt Intake in Hypertensive Individuals
On the equivalent of individuals’ usual salt intake (but on slow sodium tablets), plasma sodium was 140.1 ± 0.2 mmol/L, with a 24-hour urinary sodium excretion of 174 ± 6 mmol. On the reduced salt intake (ie, on placebo), plasma sodium fell to 139.7 ± 0.2 mmol/L (P < 0.05), with a 24-hour urinary sodium excretion of 96 ± 4 mmol. Therefore, the fall in plasma sodium was 0.4 ± 0.2 mmol/L, with a reduction in urinary sodium of 78 ± 6 mmol/24 h (Figure 3). With the modest reduction in salt intake, there was a small but significant
increase in plasma renin activity and aldosterone and a significant fall in blood pressure (Table 1).

The reduction in plasma sodium was weakly but significantly correlated with the fall in systolic blood pressure \((r=0.18; \ P<0.05)\), indicating that the greater the reduction in plasma sodium, the greater the fall in systolic blood pressure. This relationship was still significant after adjusting for age, sex, ethnic group, change in body weight, and plasma potassium. However, there was no significant correlation between the reduction in plasma sodium and the fall in diastolic, or pulse pressure, or the rise in plasma renin activity, aldosterone, or the decrease in 24-hour urinary sodium.

**Discussion**

Our studies demonstrate that an increase or a decrease in dietary salt intake causes changes in plasma sodium in hypertensive and normotensive individuals. This occurs even with modest and relatively long-term reductions in salt intake.

The changes in plasma sodium with the acute changes in salt intake are consistent with those reported in other experiments. In addition, our results show that in hypertensives, changes in plasma sodium are related directly to the response of the renin-angiotensin system, which suggests that changes in plasma sodium per se could be a drive that changes plasma renin activity, aldosterone, and atrial natriuretic peptide release that occur with changes in salt intake.

There are few studies looking at the effect of sustained, small reductions in salt intake on plasma sodium. Our double-blind studies of modest salt reduction for 1 month demonstrate that there is a small but significant fall in plasma sodium, and the fall in plasma sodium is weakly but significantly associated with the decrease in systolic blood pressure. In 2 other smaller trials of a modest reduction in salt intake for 1 month, there was also a small reduction in plasma sodium (a decrease of 0.5 mmol/L in 1 trial and 0.7 mmol/L in the other), but neither was statistically significant. This is likely to be attributable to the smaller number of individuals studied.

When salt intake is increased, a rise in plasma sodium is immediately buffered by the movement of fluid from the intracellular to the extracellular compartment because of the increase in osmolality in the extracellular space. At the same time, the associated small increase in osmolality stimulates the thirst center, more fluid is consumed, and the increased osmolality also stimulates arginine vasopressin secretion, and thereby more water is retained. All of these tend to reduce plasma sodium toward the previous level. Furthermore, there is an increase in sodium excretion that also helps reduce the level of plasma sodium. Some of these changes are responsible for a tendency of an increase in extracellular fluid volume, which it has been suggested is a mechanism underlying the rise in blood pressure that occurs with increasing salt intake (Figure 4). Some studies have shown that an increase in extracellular fluid volume causes a rise in blood pressure even when plasma sodium is falling.

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**TABLE 1. Changes in Plasma Sodium and Other Variables With Reductions in Salt Intake**

<table>
<thead>
<tr>
<th>Change With Salt Reduction</th>
<th>Hypertensive Whites (n=71)</th>
<th>Hypertensive Blacks (n=33)</th>
<th>Normotensive Whites (n=39)</th>
<th>Hypertensives (n=118)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>$-3.0\pm0.3;|$</td>
<td>$-2.7\pm0.4;|$</td>
<td>$-3.1\pm0.6;|$</td>
<td>$-0.42\pm0.2^{*}$</td>
</tr>
<tr>
<td>Renin activity (ng/mL per hour)</td>
<td>$2.37\pm0.28;|$</td>
<td>$1.0\pm0.3;|$</td>
<td>$5.09\pm0.46;|$</td>
<td>$0.24\pm0.07;|$</td>
</tr>
<tr>
<td>Aldosterone (pmol/L)</td>
<td>$499\pm72;|$</td>
<td>$256\pm72;|$</td>
<td>$1396\pm117;|$</td>
<td>$81.6\pm16.3;|$</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/24 h)</td>
<td>$-259\pm14;|$</td>
<td>$-250\pm23;|$</td>
<td>$-293\pm14;|$</td>
<td>$-78\pm6;|$</td>
</tr>
<tr>
<td>Volume (mL/24 h)</td>
<td>$-792\pm98;|$</td>
<td>$-1002\pm177;|$</td>
<td>$-723\pm169;|$</td>
<td>$-64\pm45;|$</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>$-17\pm2;|$</td>
<td>$-22\pm2;|$</td>
<td>$-2\pm1;|$</td>
<td>$-8\pm1;|$</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>$-6\pm1;|$</td>
<td>$-10\pm2;|$</td>
<td>$3\pm1;|$</td>
<td>$-3\pm1;|$</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>$-11\pm1;|$</td>
<td>$-12\pm2;|$</td>
<td>$-4\pm2;|$</td>
<td>$-4\pm1;|$</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>$-1.8\pm0.1;|$</td>
<td>$-1.9\pm0.2;|$</td>
<td>$-2.0\pm0.2;|$</td>
<td>$-0.14\pm0.11;|$</td>
</tr>
</tbody>
</table>

\(^*P<0.05\); \(^†P<0.01\); \(^‡P<0.001\) high salt vs low salt.
It is also possible that a rise in plasma sodium may itself directly influence blood pressure, independent of, and additive to, the effect plasma sodium has on extracellular volume. Intraperitoneal dialysis with differing physiological salt solutions in the rat has demonstrated that blood pressure rises or falls in direct relation to plasma sodium, although extracellular volume changes occur in the opposite direction. Tissue culture experiments varying the bath sodium within the physiological range have shown marked cellular changes in arterial smooth muscle and cardiac myocytes. In addition, small changes in plasma sodium may also directly affect the hypothalamus control of blood pressure through the local renin-angiotensin system.

The inherited restricted ability of patients with essential hypertension and hypertensive strain of rats to excrete sodium suggests that in such groups, a given increase in salt intake should cause a greater increase in plasma sodium. A number of cross-sectional observational studies in humans have shown an association between plasma sodium and blood pressure. Bulpitt et al reported a significant direct relationship between plasma sodium and systolic blood pressure in a study involving 3578 London civil servants, suggesting that the higher the plasma sodium, the higher the systolic blood pressure. In another study, serum sodium was measured in 3222 normotensive individuals and 741 patients with essential hypertension. The serum sodium distribution in the hypertensive patients was shifted by 2 mmol/L toward the higher values. It is possible that some of these differences could be explained by undetected primary aldosteronism in some individuals, but this is unlikely to explain all of the differences. Furthermore, in the study by Bulpitt et al., there was still a significant relationship between plasma sodium and systolic blood pressure after adjusting for potential confounding factors (eg, age, body mass index, serum potassium, calcium, proteins, blood hemoglobin, mean corpuscular volume, and alcohol intake).

**Perspectives**

Salt intake is a major regulator of blood pressure. The mechanisms whereby salt raises blood pressure are not fully

### TABLE 2. Plasma Hormone and Other Variables With Progressive Increase in Salt Intake in 6 Young Normotensive Individuals

<table>
<thead>
<tr>
<th>Variable</th>
<th>Salt Intake (mmol per day)</th>
<th>P Value (by Repeated-Measures ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial natriuretic peptide (pg/mL)</td>
<td>10.0±1.1, 11.4±1.6, 14.4±1.8, 16.9±2.1, 20.9±2.9, 20.9±3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renin activity (ng/mL per hour)</td>
<td>7.15±1.3, 7.51±1.9, 3.61±1.0, 1.99±0.4, 1.79±0.6, 1.89±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aldosterone (pmol/L)</td>
<td>2520±147, 1393±125, 786±76, 361±60, 291±43, 497±119</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine volume (L/24 h)</td>
<td>1.43±0.25, 1.40±0.32, 1.23±0.24, 1.38±0.28, 1.47±0.36, 1.96±0.41</td>
<td>0.329</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>112±2.2, 115±5.9, 107±4.2, 113±6.5, 114±3.5, 112±5.8</td>
<td>0.728</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>77±2.8, 75±3.2, 68±1.9, 70±2.9, 72±3.0, 69±3.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>35±3.1, 40±5.0, 39±3.7, 44±5.4, 42±3.7, 44±3.5</td>
<td>0.423</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.5±3.9, 64.8±4.0, 65.1±4.0, 65.2±4.0, 65.4±4.0, 65.0±4.0</td>
<td>0.123</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.01, ‡P<0.001 compared with that with a 10 mmol per day of salt intake.

### Longer-term Modest Salt Reduction

**Figure 3.** Changes in plasma sodium and urinary sodium with a longer-term modest reduction in salt intake in 118 patients with untreated essential hypertension.

**Figure 4.** Hypothesis on the possible links between salt intake, plasma sodium, and blood pressure. BP indicates blood pressure; RAS, renin-angiotensin system.
understood. The existing concepts focus on the tendency for an increase in extracellular fluid volume. Our studies demonstrate that acute and chronic changes in salt intake cause changes in plasma sodium. The changes in plasma sodium are the immediate drive to the changes in extracellular volume. However, there is now increasing evidence that small changes in plasma sodium may directly affect the hypothalamus, the local renin-angiotensin system, and the heart and vasculature, all of which may play a role in changing blood pressure independent of and additive to that which occurs with the tendency for the changes in extracellular volume. In other words, small increases in plasma sodium may be in part directly responsible for the elevated blood pressure.

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Plasma Sodium: Ignored and Underestimated
Feng J. He, Nirmala D. Markandu, Giuseppe A. Sagnella, Hugh E. de Wardener and Graham A. MacGregor

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