A relationship between dietary sodium intake and the development of hypertension has been proposed since antiquity; however, the very notion and its implications continue to engender controversy. Recently the matter has been brought to national public attention by various communications media.1 Lobbying groups have been formed dedicated to the task of influencing the legislative branch of the federal government to enact laws affecting the sodium content of foods and the labeling of food products.2 The implications of these activities are considerable. In addition to presenting a major public health issue, the socioeconomic impact of such legislation is great. Thus, it is particularly important that available evidence regarding dietary sodium intake and the development of hypertension be critically examined. Areas in which adequate information is wanting must be identified. Additional research to address specific issues should receive the necessary support. The feasibility of modifying human dietary behavior, and monitoring that behavior, must be addressed. Additional dietary intervention studies examining the sodium-hypertension hypothesis are necessary. Fortunately, the National Institutes of Health recognizes these problems. A task force has identified deficits in the currently available body of knowledge,3 and support has been earmarked for specific projects; however, current levels of funding will not be enough. Additional support from other sources will be necessary.

Mechanisms Relating Sodium and Hypertension

Evidence relating dietary sodium intake to the development of hypertension is compelling, but largely circumstantial.4 Comparisons of populations suggest that in unacculturated persons, who ingest a diet very low in sodium and relatively high in potassium, hypertension is much less likely to occur, and blood pressure does not increase with age, as it does in acculturated societies where sodium is ingested in large amounts. Considerable evidence suggests that humans ingest much more sodium than the minimal requirement, although the amount providing maximum well-being is not defined. The homeostatic mechanisms in healthy persons probably require an intake of less than 10 mEq/day.5 However, attempts to relate blood pressure to sodium intake within given populations have met with little success. Failure to show such a relationship may stem from the fact that the range of sodium intake...
within the population is relatively narrow, or that only a minority of individuals within that population are sensitive to the blood-pressure-raising effects of sodium. 6

The available epidemiological studies have been properly criticized. 7 The blood pressure measurements were not always standardized. 7 The societies often differed vastly in ways other than dietary sodium intake. 8 The documentation of dietary sodium intake was often obtained in only a subset of the population examined, or depended on poorly established methodology such as dietary recall, or "spot" urine collections. 9

Recently it has been proposed that the blood cells of individuals with essential hypertension, or their normotensive relatives, transport sodium abnormally. 10'14 This abnormal transport may promote an intracellular excess of sodium because of net pump underactivity. 15 However, current studies reporting both erythrocyte sodium concentration and content have yielded conflicting results. Some investigators have found normal sodium and potassium concentrations , 13, 16~18 while others have reported elevated sodium concentrations , 10, 19~21 Certain pumps have been identified that are overactive, perhaps in an attempt to compensate for the underactivity of other pumps. 16 These abnormalities, which presumably occur in other cells as well, may result in constriction of vascular smooth muscle and hypertension. Such a notion would explain the increased amounts of sodium found within some smooth muscle cells. 12~22 It has been suggested that an inhibitor of sodium transport circulates to facilitate renal sodium excretion at high sodium intake. 13, 25 Such an inhibitor may be elaborated in response to an as yet unclear renal defect in sodium excretion in patients with essential hypertension. 29 In other subjects, a genetically determined deficiency of such a factor may predispose them to increased sodium sensitivity and a greater risk for the development of hypertension. 26, 27

Thus, an elevated blood pressure would occur in individuals who are genetically susceptible and who indulge in a high sodium intake.

A conceptual framework, which has received considerable attention, maintains that a reduction in the ability of the kidneys to excrete sodium at a given arterial pressure leads to sodium retention. This retention raises blood pressure to the point where sodium balance is restored. 26 Increased arterial pressure results in increased urinary sodium excretion. 27 In the intact organism, the relationship between arterial pressure and urinary sodium excretion is modulated by numerous homeostatic mechanisms, including the autonomic nervous system, the renin-angiotensin-aldosterone system, the kallikrein-kinin system, and the renal prostaglandins. 28 The pressure-natriuresis relationship may be modified, or displaced, by changes in these control mechanisms, as well as by changes in renal function. 30 An example of the pressure-natriuresis relationship generated in a study of normotensive men is shown in figure 1. 31 Alterations in the normal pressure-natriuresis relationship would serve to modify blood pressure in response to changes in sodium intake. Modification of the curve, such as increasing the slope, would indicate an increased dependency of blood pressure on changes in sodium intake. Displacing the entire curve upward, without altering its configuration, would depict a greater arterial pressure for a given sodium intake; however, only modest decreases in blood pressure would occur in response to sodium restriction unless sodium restriction were severe. In this way the entire relationship would be "reset."

Figure 1. The relationship between mean arterial blood pressure (MABP) and urinary sodium excretion (\( U_{NaV} \)) as defined in 14 normal men (see ref. 31).
These three mechanisms relating sodium and hypertension — namely, dietary sodium, cellular sodium transport, and renal sodium homeostasis — are by no means mutually exclusive, but rather are likely to be interrelated in a complex fashion. Initial mechanisms elevating blood pressure are probably numerous and heterogeneous. However, initiating mechanisms may result in secondary lesions, such as renal disease, which then serve to further elevate blood pressure and augment sensitivity to dietary sodium intake or hamper the ability of the kidney to respond to a sodium load by increasing its excretion.

**Sodium Intake and Sodium Sensitivity**

It is unlikely that a high sodium intake raises the blood pressure of most people. If that were to be the case, blood pressure of persons within a given population should be correlated with their sodium intake, and hypertensive subjects should eat and excrete more sodium than normal subjects. Neither appears to be the case. Alternatively, it is possible that only a susceptible minority within a population will experience an increased blood pressure when exposed to a high sodium intake. Thus, if the range of sodium intake within that population is relatively small, even though the sodium intake itself is large, no correlation between arterial pressure and sodium intake would be found.

Considerable evidence from studies in both hypertensive and normotensive humans supports heterogeneity in sensitivity to sodium intake. In hypertensive patients sodium restriction does not invariably lower blood pressure. The dietary approach advocated by Kempner decreased sodium intake to less than 10 mEq/day. Although Kempner reported dramatic reductions in blood pressure, there were patients whose blood pressures did not decrease. When Kawasaki et al. gave patients with essential hypertension sodium at either 9 or 249 mEq/day, they were able to divide their patients into two distinct groups, a “salt-sensitive” and a “salt-resistant” group. The former group retained more sodium on the high sodium diet than the latter. Similar responses have been observed in hypertensive patients following more modest dietary sodium restriction. While some patients exhibit a decrease in blood pressure others may actually be adversely affected. Adverse effects may be related to stimulation of the renin-angiotensin and sympathetic nervous systems. Potential explanations for these diverse responses are outlined elsewhere.

If dietary sodium intake is responsible for blood pressure elevations in at least some hypertensives, certain changes in body electrolyte composition would be expected. The dietary, cellular, and renal-sodium hypotheses would all predict a correlation between total body sodium and arterial blood pressure, at least in subjects with hypertension. Total body sodium in hypertensives may not necessarily be increased, since the increased arterial pressure may establish a new equilibrium in the presence of a normal total body sodium.

Lever et al. have recently reviewed their elegant and extensive studies of electrolyte composition in normal and hypertensive subjects of different ages. In their hands, total body and exchangeable sodium and potassium were highly correlated (r = 0.91 and r = 0.96 respectively). They found that total body and exchangeable sodium were positively correlated with blood pressure in hypertensives but not in normal subjects. These correlations were greater for older than for younger patients. Younger patients had exchangeable sodium values less than those of normal subjects. Plasma, exchangeable, and total body potassium were inversely correlated with blood pressure in hypertensives. These correlations were greater in the young patients. Their findings led Lever and associates to conclude that young hypertensives differ from older hypertensives in several important respects. In young hypertensives, blood pressure seems more closely related to potassium than to sodium. A secondary abnormality, such as a renal lesion, develops later, possibly as a consequence of hypertension. This secondary abnormality displaces the pressure-natriuresis relationship, so that the susceptibility to a high dietary sodium intake is increased.

The data of Lever et al. support the notion of a variable sensitivity to high sodium intake. The correlation of exchangeable sodium and blood pressure in hypertensives, coupled with the correlation of exchangeable sodium and age in hypertensives, suggests a progressively steeper pressure-natriuresis relationship with age. Moreover, it is possible that more sodium is retained by hypertensives during sodium-loading and is accompanied by arterial pressure changes greater than those that would occur in normotensive individuals. In the sodium-loading experiments illustrated in figure 1, we noted a considerable heterogeneity in response. While some individuals developed an obvious increase in blood pressure at 800 mEq/day sodium intake, others demonstrated no increase in blood pressure, even at 1500 mEq/day sodium intake (fig. 2). When demographic factors such as race were considered, black subjects were noted to exhibit a greater increase in blood pressure than whites. Sodium loading also augmented urinary potassium excretion causing potassium loss by exceeding the dietary intake. When negative potassium balance was avoided (fig. 3), the increases in blood pressure were significantly attenuated. Thus an interaction between potassium and sodium in influencing the blood pressure response to high dietary sodium intake was apparent.

In other experiments we examined the excretory capacity for sodium in three groups of normotensive individuals who exhibit a greater propensity for the development of arterial hypertension than the general population. Blacks, subjects greater than 40 years of age, and first-degree relatives of essential hypertensives were each given a standardized 150 mEq/day sodium diet, and then also received 2 liters of normal saline intravenously over 4 hours. Short-term sodium excretion, during the 4 hours of saline infusion, was not different among the groups. Thus, we did not iden-
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FIGURE 2. The heterogeneity of blood pressure responses in 14 normal men exposed to extremes of sodium intake (see ref. 37).

FIGURE 3. Blood pressure responses at extremes of sodium intake in eight men. In the second experiment potassium depletion was avoided (see ref. 37).

FIGURE 4. Natriuretic responses after brief sodium loading in three groups of normal subjects at risk for hypertension compared to controls (see ref. 38).

Sodium Restriction in Prevention and Treatment

Dietary intervention in the prevention and treatment of hypertension has considerable appeal. The risks and side effects of drug therapy may be reduced. Sodium restriction may provide a cost advantage, particularly when considering that the size of the population in-

subjects. Moreover, blacks and older subjects excreted proportionately more of their sodium loads at night. Blacks and the older subjects also had lower renin values, as well as an alteration in the normal diurnal variation of creatinine clearance. The first-degree relatives of essential hypertensives, who were relatively young individuals, had higher renin values than controls. We concluded that in blacks and older individuals a renal lesion may develop capable of resetting or modifying the pressure-natriuresis relationship. Such a change would increase the susceptibility to a high dietary sodium intake. In the relatives of hypertensives a different mechanism, perhaps related to the renin-angiotensin system, appeared to be initially operative. However, the data suggest that each of these groups at risk for the development of hypertension excretes sodium in a fashion that may contribute to increased susceptibility to hypertension following a generous dietary intake. Finally, the sodium excretory capacity and its regulatory mechanisms have been shown to be under genetic influences. Since essential hypertension is heritable, it is highly likely that sensitivity to dietary sodium intake is heritable as well.
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Table 1. Randomized Controlled Studies of Sodium Restriction in Hypertensives (mean ± SEM)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention duration</th>
<th>No restriction</th>
<th>Restriction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parijs et al.</td>
<td>Cross-over</td>
<td>1 mo</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Morgan et al.</td>
<td>Parallel</td>
<td>24 mos</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>MacGregor et al.</td>
<td>Cross-over</td>
<td>1 mo</td>
<td>19</td>
<td>19</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Study</th>
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<th>Restriction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parijs et al.</td>
<td>Cross-over</td>
<td>1 mo</td>
<td>191 ± 13</td>
<td>191 ± 13</td>
</tr>
<tr>
<td>Morgan et al.</td>
<td>Parallel</td>
<td>24 mos</td>
<td>191 ± 13</td>
<td>191 ± 13</td>
</tr>
<tr>
<td>MacGregor et al.</td>
<td>Cross-over</td>
<td>1 mo</td>
<td>167 ± 9</td>
<td>167 ± 9</td>
</tr>
</tbody>
</table>

Critical studies examining the value of sodium restriction are very difficult to perform. The first major obstacle is developing a dietary program that not only achieves the desired sodium restriction, but also gains the cooperation of the patient. The second is developing the means of documenting patient compliance. The latter obstacle requires solution in order to examine the progress of the former. Problems inherent in establishing sodium restriction are detailed elsewhere. Currently, no investigation has convincingly and simultaneously solved both problems.

Proponents of lowering sodium intake in the entire population are hopeful that the development of hypertension will be slowed. In short-term studies, it has not been shown that lowering sodium intake of normal individuals to low levels lowers their blood pressure. However, even potent antihypertensive drugs may have little or no effect on the blood pressure of normal subjects. Whitten and Stewart fed two groups of black infants either 1.93 or 9.25 meq Na/100 Kcal for 5 months starting at 3 months of age. They found no difference in blood pressure at 8 months of age. Long-term follow-up showed no difference in blood pressure at 8 years of age. The authors noted a 6% increase in extracellular fluid volume in salt-fed infants, but no correlation with blood pressure. They concluded that a sodium intake representing the 99th percentile of U.S. infants had no hypertensive effect in infancy, or at 8 years. Nor was there an indication of salt preference imprinting.

Gillum et al. modified the dietary sodium intake of 80 school children with blood pressures above the 95th percentile. Sodium intake was lowered from 130 to 87 meq/day according to periodic dietary records and urine values. No change in blood pressure was found. These results do not necessarily mitigate against the value of sodium restriction, since mechanisms independent of sodium may serve to initiate hypertension.

The study of sodium restriction in the treatment of essential hypertension presents the same problems outlined above. Table 1 summarizes the results of three clinical trials. These trials were specifically selected because each was prospective and the subjects were randomly assigned to sodium restriction or control regimens. Two of the studies were of cross-over design. Two included drug treatment periods or drug-treated groups, the results of which are not included in the table. One of the studies was long-term. In each study the sodium restriction attained was modest. The degree to which compliance was documented was variable and not altogether convincing in any of the studies. In the study by Morgan et al., UNaV after intervention exceeded that observed in free-living citizens. Nevertheless, each study demonstrated that relatively modest sodium restriction in mild hypertensives reduced blood pressure significantly by about 8 mm Hg. This degree of decrease was not different from that evoked by thiazides alone in the trial of Morgan et al. Parijis et al. noted a greater blood pressure decrease with combined diuretic therapy. Utilizing both strategies decreased blood pressure still further. In these three controlled trials, no attempt was made to select individuals who might be particularly sensitive to sodium restriction. Accordingly the responses within individuals were variable.

Although the decreases in arterial pressure produced in these trials appear modest, the results are not to be belittled. According to the Framingham Study data, a difference of 8 mm Hg diastolic blood pressure would produce a change in death rate in the order of 10% to 15%. To attain such a decrease without any defined risk is a worthy achievement indeed.

Conclusions

Dietary sodium intake is an important issue with socioeconomic as well as medical ramifications. The evidence that a high sodium diet increases blood pressure, or aggravates increases in blood pressure of other causes, is substantial. Current thinking emphasizes the importance of cellular transmembrane sodium transport, the influence of circulating mediators of sodium transport, and the role of the kidney and its control mechanisms. Human studies indicate that not all people are at risk from a high sodium intake, and that not all hypertensives will respond to sodium restriction. Although sodium-sensitive hypertensives have not been clearly identified, older individuals and hypertensive black Americans may be in his category. Three prospective, randomized, and controlled trials indicate that sodium restriction of a practical degree will decrease blood pressure by 8 mm Hg. Such a decrease could influence cardiovascular morbidity substantially. Additional controlled trials are needed to identify sodium-sensitive hypertensive individuals.
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