**Abstract.** Salt and BP have been linked for more than a century. Recent data indicate that, given free access to sodium, in most populations, intake is between 100 and 200 mmol/d, although individual variation is wide. There is good evidence that individual differences are influenced by genetics, environment, and behavior. There is also solid clinical trial data suggesting that substantial reduction in sodium intake (75 to 100 mmol/d) will, on average, lower diastolic pressure by approximately 1 mmHg and systolic by approximately 3 to 5 mmHg. In addition, there is good evidence that sodium restriction is accompanied by other hemodynamic and nonhemodynamic effects. The health effect of sodium restriction can be assessed only by outcome study in humans. The best available evidence in this regard derives from observational study. The several available studies in the general population are inconsistent and demonstrate heterogeneity across subgroups in the relation of sodium intake to cardiovascular morbidity and mortality. Only a single study has been reported in hypertensive patients that links baseline sodium, measured by 24-h urinary excretion, and subsequent cardiovascular outcomes. In that study, controlling for other risk factors, there was a significant, independent, inverse association of urinary sodium excretion and coronary morbidity and mortality. Indeed, an increase of 66 mmol/24 h was associated with a 36% reduction in events. Taken together, these data provide no support for the notion that either normotensive or hypertensive individuals should routinely decrease (or increase) dietary sodium intake.

Sodium intake, for individuals with unfettered access to salt, is remarkably consistent across a wide range of peoples, cultures, and environments. The Intersalt study, which used similar collection measures in 52 sites around the globe, demonstrated that, except for four remote and unacculturated societies, 10,000 people on average, in 48 sites in 3 dozen countries, ranging from high to low income, market versus managed economies, and temperate versus tropical climates, consumed diets that contained between 100 and 200 mmol/24 h of sodium (1). At the same time, these studies demonstrate dramatic differences in individual sodium consumption within those populations.

Not surprising, there is good evidence that environmental factors influence salt intake (2). For example, early exposure to sodium intake may have a lasting impact. People who exercise vigorously or who are exposed to high ambient temperatures seem to maintain the normal hemodynamic balance by automatically replacing large, insensible sodium losses. Because most salt is consumed in food, it is not surprising that there is a high correlation between caloric intake and (like most other nutrients) salt intake. Thus, among people with high-energy consumption, salt intake is also higher. Moreover, it seems likely that because energy intake (and therefore sodium intake) probably reflects energy expenditure, people who are physically active (athletes, people who follow advice to maintain good cardiovascular fitness, etc.) probably eat more salt and calories than do their sedentary conferees. A reasonable hypothesis, then, might be that those with the most favorable cardiovascular profile might be those who exercise vigorously and therefore eat (and drink) enthusiastically and, in the process, consume lots of salt!

At the same time, there is solid evidence that genetic endowment also helps to determine salt intake. Most inherited influences on BP involve alterations in the renal handling of sodium. Of particular interest is Gitelman’s syndrome (3). People who have this particular genetic variant have a deficit in the ability to conserve sodium. These individuals, whether heterozygotes or homozygotes, naturally consume larger-than-normal amounts of salt (without awareness of their heightened salt appetite) and by this means are able to maintain a low normal BP. Altogether, genetic variants account for only a very small fraction of the normal variation of sodium intake within populations. What they do tell us, however, is that the hope of identifying a single universally appropriate sodium intake is unrealizable. Instead, inheritance, behavior, and environment conspire to ensure that normal individuals will be heterogeneous in regard to their optimal intake of sodium.

**Impact of Restricted Salt Intake on BP**

Modern interest in the salt-to-health relationship began a century ago with the observation that salt intake could effect BP. Subsequent ecological study, both between societies and among migrants, led to the belief that a habitually low sodium intake produced low BP, which, in contrast to the experience of societies with access to plentiful salt, did not rise with age. The
possibility that confounding variables may have explained this apparent association was provided by the experience of the Kuna Indians of the San Blas Islands near Panama (4). When first studied in 1948, they had low BP and minimal sodium intake. When restudied 50 yr later, sodium had become available, and, not surprisingly, the Kuna had adopted a salt intake similar to that in the developed world. Unexpected, however, was the finding that BP were still low and showed no increase with age. Clearly, factors other than dietary sodium accounted for the sustained normotension of these adherents to a non-Western traditional social structure.

In fact, of course, the salt-to-BP hypothesis does not rest on either ecological or cross-sectional linkage study. Instead, >100 high-quality, randomized, controlled studies have tested the notion that a reduced sodium intake could lower BP. Careful meta-analyses of these trials consistently show that, in aggregate, a reduction in sodium intake by approximately half (75 to 100 mmol/24 h) will lower diastolic BP by approximately 1 mmHg and systolic BP by 3 to 5 mmHg (5). These modest numbers are slightly increased for older subjects and those with elevated pressure and reduced for younger and normotensive subjects.

In addition to the general salt–BP effect, it is clear that the effect of salt varies widely between individuals. This heterogeneity has led to the concept of “salt sensitivity,” defined as the ability to alter BP by >5 mmHg in response to altering sodium intake. It seems that something less than half of studied subjects are classified as “salt sensitive.” Moreover, it is also clear now that “salt sensitivity” is a mutable phenomenon. For example, Morris et al. (6) found that the proclivity of blacks to be salt sensitive can be eliminated by a high-potassium diet.

Unfortunately, little is known of the relative cost and benefit of this technique for the reduction in BP. One abstract reported that the cost of a nutritional intervention substantially exceeded that of conventional care (7). Another abstract found that initiating antihypertensive therapy with a diuretic produces far more satisfactory BP reduction than a low-salt diet (8). Neither of these two reports is surprising, but the absence of serious inquiry into the costs and benefits of this form of antihypertensive intervention is surprising.

In short, a relation of salt to BP is well established and varies among individuals, and its influence can be modified by other factors. Because most salt intake derives from foods and is not added by the consumer, it has proved difficult to achieve and sustain the kind of sodium restriction required to lower pressure meaningfully.

Non-BP Effects of Sodium Restriction

Interventions designed to alter one aspect of the milieu interior tend to have additional effects. Reduction in sodium intake is no exception. It should come as no surprise that a change in diet designed to cut sodium intake by half would have multiple consequences—some of which have been documented. BP fall is not even the only hemodynamic effect of sodium restriction. Vascular compliance, a measure of the health of vessels, is better on a high- than low-sodium diet (9). This is consistent with the fact that reduced blood volume also impairs compliance (10).

An additional hemodynamic effect is mediated by the renin-angiotensin system (RAS). Under usual circumstances, the RAS modulates volume and vasoconstriction to maintain pressure. As part of this physiologic process, there is an inverse relation of sodium intake and activity of the RAS. Thus, a 100 mmol/24 h reduction in sodium intake generates a threefold increase in plasma renin activity—a measure of the activity of the RAS (5). Although this mechanism is appropriate to sustain BP, an elevated RAS also has adverse effects on the vascular endothelium and smooth muscle cells and stimulates inflammatory agents. The net result is atherogenic (11). In fact, among hypertensive subjects, all other things being equal, an increased renin predicts increased myocardial infarction. Other untoward cardiovascular effects of sodium restriction, linked to the RAS, include generation of aldosterone and sustained stimulation of the sympathetic nervous system. The latter is perhaps responsible for the increased insulin resistance known to accompany low-sodium diets (12).

There has been some evidence that a low-sodium diet interferes with glucose metabolism and may be associated with increased cholesterol; it is also possible that the latter may reflect modest vasoconstriction generated by sustained sodium restriction. A low-sodium diet has also been implicated in chronic fatigue syndrome. Evidence of a positive effect on bone mineral metabolism to prevent osteoporosis has also appeared, and there is some ecological data to support the contention that a low-sodium diet may reduce the incidence of gastric cancer.

The point is that all medical interventions have multiple effects and one should avoid the pitfall of focusing only on a single effect—no matter how attractive. Multiple examples of misadventures with drugs provide a cautionary tale about the hazards of not assessing all of the effects of our interventions. If more warning were necessary, then experience with weight reduction during pregnancy provides it, by showing that tampering with diet can have unintended and unwanted consequences (13). Indeed, the only satisfactory way to assess all of the effects of any medical or health intervention is to determine its impact on the quality and duration of life.

Overall Health Effects of Sodium Restriction

In fact, there is virtually no evidence regarding the impact of reducing sodium intake by 75 to 100 mmol/24 h. This would optimally require a randomized clinical trial, and none has been performed. Indeed, the recent Cochrane Collaboration report noted the absence of such data and suggested that a clinical trial is justified if sodium restriction is to remain a standard public health recommendation (14).

What is available are bits of ecological and observational evidence. For what it is worth, for people bereft of salt, growth and development are poor and life expectancy is short. By contrast, throughout the highest income countries, sodium intake is, as we have seen, in the 100 to 200 mmol/d range, and life expectancy is long and extending. Indeed, in Japan, a country characterized by a very high sodium intake, life ex-
pectancy is among the highest of any nation. Clearly, however, this says nothing about the actual relation of sodium intake to longevity. For this purpose, epidemiologic data provide a better source of information.

Unfortunately, the available data are scanty. There is one prospective study of the relation of sodium intake to cardiovascular morbidity and mortality in treated hypertensive subjects. In roughly 3000 employed, systematically treated mild and moderate, well-controlled hypertensive patients, 24-h urine was collected before initiation of therapy and then related to events over an average of 4 yr (Figure 1). There was a significant inverse association of sodium intake to mortality, so an increase in sodium intake of 66 mmol/24 h was associated with a 36% reduction in coronary events (15). That result was independent of plasma renin activity. There has been no other published epidemiologic study in hypertensive patients since this 1995 report. These data are consistent with the finding in the same population of significant association of increased plasma renin activity with increased coronary events (16).

There have, however, been several reports in the general population. The first linked baseline sodium intake as assessed by 24-h dietary recall to 22-yr mortality in the National Health and Nutrition Examination Survey Epidemiological Follow-Up (17). In 11,348 subjects from this representative national sample, there were nearly 4000 deaths, almost half of which were cardiovascular. Here, too, an inverse, albeit modest, relation of salt intake to cardiovascular mortality was observed. When analysis was restricted to subjects without prevalent cardiovascular disease at entry, results were similar. Subsequently, He et al. (18) reported on a subgroup of the full National Health and Nutrition Examination Survey cohort. They limited the analysis to those without prevalent cardiovascular disease or hypertension at entry and restricted cardiovascular end points. In this constricted subgroup, they found that in the 28% classified as obese, there was a direct, positive, and significant association of sodium intake to morbidity and mortality. There was no relation of sodium to outcome in the remaining 72% of subjects. A Finnish study, in a very different population, again demonstrated the differing effect of a low-sodium diet on obese individuals as compared with individuals of normal body mass (19). Two other reports of the salt-to-health outcome showed no consistent pattern (20,21).

Taken together, these data provide convincing evidence of heterogeneity in the relation of sodium intake to health outcome. This can hardly be surprising in view of the multiple and sometimes undesirable effects of sodium restriction, as well as the genetic and environmental heterogeneity of the human species. The implication of this heterogeneity is clear. No single sodium intake that will be suitable for either the hypertensive subgroup or the entire population can be identified.

Conclusion
Salt has been prized as a critical component of human diets forever. More recently, by virtue of its proven relation to BP, its appropriate dietary role has been questioned. Many health-related organizations and agencies have urged that diets be modified to achieve a sharp reduction to <100 mmol/d sodium. Other equally respected agencies have concluded that
such a universal recommendation is unjustified. Because the first recommendations to restrict salt intake largely preceded the availability of any data linking salt to health, it seems reasonable to reconsider those recommendations in light of available evidence.

What is now known is considerable. Sodium intake is approximately 150 mmol/d throughout the world, but individual variation based on genetics, behavior, and environment is substantial. The relation of salt restriction to BP varies but in some people results in a significant negative and positive BP effect and, in whole populations, a modest reduction. At the same time, salt restriction produces multiple, often conflicting, physiologic changes. It is the sum total of these effects, which can be assessed only by outcome studies, that determines its clinical or health effect. In the absence of a clinical trial, the meager observational data available are inconsistent and indicate, not surprising, heterogeneity in the effect of a low-sodium diet on morbidity and mortality. In sum, available evidence.

References

20. MRFT. Presented at the National Institutes of Health Conference; January 29, 1999; Bethesda, MD