POINT-COUNTERPOINT

Salt, blood pressure and health: a cautionary tale

Michael H Alderman

By virtue of its central role in maintaining intravascular and extracellular volume, sodium is essential to human survival. Taste, habit, environment, genes, and behaviour probably all influence sodium intake. In view of the heterogeneity that characterizes humankind, it is remarkable that the vast majority of the world’s citizens, everywhere, given free access to salt, consume between 100 and 200 mmol of sodium per 24 hours. Despite this uniformity of sodium intake across all dietary, cultural, environmental, and hereditary circumstances, and the fact that life spans that are steadily increasing worldwide, many authorities now contend that current salt intake is too high by half. Advocates of universal restriction of sodium intake to <100 mmol/24-h base their case on the belief that this will produce a population-wide reduction of blood pressure which, in turn, will reduce cardiovascular morbidity and mortality. There is even stronger enthusiasm for strict control of sodium intake for hypertensive people. Indeed, these dogma are often preached with a fervour usually associated with religious zealotry. I will argue here that the available data provides insufficient evidence to justify any universal target for sodium intake for either the whole population or for its hypertensive subset.

The Link of Salt to Blood Pressure

Recognition of the strong, continuous, independent, and significant relationship of blood pressure to the occurrence of cerebral, cardiac, and renal disease, provided the reasonable stimulus for seeking safe, simple, and effective means for reducing blood pressure on a population-wide basis. Dietary intake of sodium, or salt, both because of its ubiquity in the human diet, and its centrality in determining blood volume, presented an obvious opportunity to intervene on blood pressure. The first indication that differences in dietary sodium might explain variation in blood pressure came from cross-cultural studies. In unacculturated societies, blood pressures tended to be lower, and did not appear to rise with age. This contrasted sharply with the age-related rise in pressure and high levels of ‘hypertension’ common in most industrialized nations. Sodium intake, among many other factors, was found to differ between ‘developed’ and ‘undeveloped’ communities. In fact, people confined to an economy of hunting and gathering, with little access to salt, had daily intakes of sodium often limited to 20–40 mmol sodium.

This ecological association of salt intake to blood pressure led to the suspicion that changes in sodium intake could alter pressure. Investigation of migrant experience produced the first test of that hypothesis. As it turned out, those who exchanged an acculturated environment for an urban setting generally increased their blood pressure. Among the multiple changes inherent in such an environmental transformation, sodium intake generally rose to the intake of the host cosmopolitan population, thus supporting the view that an increase in sodium intake produced a rise in blood pressure.

Recent findings among the Kuna Indians, initially residents of the San Blas Islands off the coast of Panama, cast doubt upon the notion that salt is responsible for the change in blood pressure associated with migration. As long as the San Blas island people had minimal access to sodium, both sodium intake and pressures were low throughout life. Over the past 50 years, as the Kuna established trade relations with the mainland, sodium availability increased to the level consumed by mainland Panamanians. Remarkably, however, these island people, still maintaining their traditional cultural patterns, except for a dietary sodium intake which now is about 140 mmol/24-h, still have low blood pressures, without any age-related rise. In short, salt is only one of many factors that change with migration. There is no shortage of other possible explanations for the observed change in blood pressure.

For example, in a 30-year observational study comparing 144 nuns living in seclusion to 138 lay women in the same region of Italy, although sodium intake was similar, an age-related increase in blood pressure was limited to the community group. The community group also experienced a significant increase in blood pressure. Investigation of migrant experience produced the first test of that hypothesis. As it turned out, those who exchanged an unacculturated environment for an urban setting generally increased their blood pressure. Among the multiple changes inherent in such an environmental transformation, sodium intake generally rose to the intake of the host cosmopolitan population, thus supporting the view that an increase in sodium intake produced a rise in blood pressure.

The community group also experienced a significant increase in cardiovascular mortality and morbidity. The point, of course, is that factors other than sodium intake may be more powerful environmental and behavioural determinants of blood pressure. This study highlights the potential effect of difficult to measure sociocultural circumstances and reinforces the view that ecological analysis is simply too blunt an instrument through which to link a single factor, like dietary sodium, to the blood pressure of individuals.

Observational Studies of Sodium and Blood Pressure

More precise exploration of the relationship between sodium intake and blood pressure has been possible in epidemiological studies. The most ambitious of these has been the Intersalt Study, a cross-sectional assessment of more than 10 000 subjects in 52 locations around the world. Its most important finding was that, in those 48 of 52 sites where salt was freely accessible,
iniates were invariably between 100 and 200 mmol sodium/24-h. Analysis limited to those 48 cosmopolitan centres revealed no association between sodium intake and blood pressure. However, after age stratification, in societies with greater sodium excretion as opposed to those consuming less, blood pressure rose with increasing age. Because Intersalt was cross-sectional, and not a prospective longitudinal study, the notion that pressure rises with age represents one possible extrapolation from the available data. Overall, the results of cross-sectional studies have been inconsistent and inconclusive.

Experimental Studies of Sodium and Blood Pressure

Because association does not prove causality, the salt to blood pressure relationship needed experimental validation. Animal studies have shown that sodium reduction can lower pressure, and, conversely, that sodium addition, as was the case in a study involving a dozen chimpanzees, could elevate arterial pressure. In humans, the issue has been more complicated. There is enormous variation between individuals on the effect of salt on pressure (Figure 1). This has given rise to the notion that the population includes salt 'sensitive' and 'insensitive' individuals. This may be associated with genetic variation. The fraction of people classified as sodium sensitive is unknown. A recent study of 269 male medical students revealed that roughly half had no response to changing sodium intake from 20 to 270 mmol/24-h, while 1/4 had a rise in response to moving from low to high salt intake, and an almost exactly (66 versus 67) equal fraction had a similar fall in blood pressure in response to this 12-fold increase in sodium intake. It is this inter-individual variation that may explain the inconsistency of human experimental results.

Perhaps the best estimate of the effect of sodium intake on blood pressure can be gained from meta-analyses of randomized trials. Meta-analyses can only reflect the studies included. Unfortunately, well-designed and conducted studies involved considerable variation in sodium consumption, and many were of short duration. Nevertheless, the most rigorous meta-analyses are in general agreement. They indicate that, among hypertensive and older subjects, a 75–100 mmol/day reduction in salt intake generates a change of 3–5 mmHg systolic, and about 1–2 mmHg difference in diastolic pressure. The effect on younger and normotensive subjects is less—about 2–3 mmHg for systolic, and <1 mmHg diastolic. It would appear that the largest decline is achieved when small groups of subjects were studied for short periods of time. It has been difficult to sustain, beyond a year, either the blood pressure reduction, or the sodium restriction in free-living subjects. It should be noted, however, that a sustained decrease of even a few mmHg could, assuming the method in its achievement produced no harm, reduce morbidity and mortality more than is currently achieved by restricting treatment to patients with high blood pressure. It is that possibility that energizes advocates of sodium restriction.

In sum, these data indicate that a large (50–75%) reduction in sodium intake by a population can produce, on average, but with wide individual variation, at least for periods of months, a modest, but detectable decline in mean blood pressure. The multiple studies supporting these conclusions are sufficiently robust to make it unlikely that further study will alter their essential findings.

Other Effects of Sodium Reduction

Attempts to alter one aspect of the interior milieu may produce other effects. It is not surprising that so profound and pervasive an intervention as dietary manipulation designed to alter sodium intake by half would also produce non-blood pressure effects. Moreover, just as individuals vary in the way that sodium modulation effects blood pressure, it is to be expected that other physiological responses may also vary.

Blood pressure is not even the only haemodynamic effect of variation in dietary sodium. Increasing attention is being paid to arterial compliance as a measure of vascular health. New, non-invasive techniques now make it possible to assess compliance in the clinical setting. It has been shown that in hypertensive and normal subjects, arterial compliance is positively related to urinary sodium excretion. This finding is, of course, consistent with the positive relation of blood volume to compliance previously reported.

The renin/angiotensin/aldosterone/sodium mechanism for the regulation of haemodynamic integrity is well understood. An inverse relation of sodium/volume to renin release is part of the normal mechanism for control of blood pressure and flow. But, in addition, an activated renin/angiotensin system, particularly in the face of elevated blood pressure, adversely affects the vascular endothelium, smooth muscle cells, and inflammation associated with atherosclerotic lesions. Reduction of sodium intake by 100 mmol/24-h increases plasma renin activity by threefold, and the relation of sodium intake to plasma renin is
continuous across the usual range of dietary sodium. Increased aldosterone activity, also stimulated by reduced sodium intake, has similar unwanted cardiovascular effects.\textsuperscript{9,14} It has also been shown that sodium restriction stimulates the sympathetic nervous system and increases insulin resistance.\textsuperscript{15}

The complexity of the effects of changes in sodium intake has recently been demonstrated in an exploration of the relation of salt to heart rate.\textsuperscript{16} Folkow had previously demonstrated the importance of increases in heart rate on cardiac work and cardiovascular morbidity. It has now been shown that, in people whose blood pressure increases with sodium restriction, a higher sodium intake actually decreased left ventricular workload, and this was in contrast to the salt sensitive subjects. In this regard, the recent report by Weinberger,\textsuperscript{17} revealing greater cardiovascular mortality in salt sensitive than insensitive subjects, suggests that these phylogenetic characteristics may have real clinical relevance. Since the Weinberger observational study included no data on actual sodium intake, it is not possible to draw any inferences about whether sodium intake might have influenced outcomes of either group.

The point of these examples is, of course, that intervention on sodium, like virtually all other medical interventions, will have multiple effects. The only way to determine the total or health effects of these interventions is to determine their effect on the multiple effects. The only way to determine the total or health effects of these interventions is to determine their effect on the quality and duration of life. We commonly recognize this need in regard to pharmacological interventions, but have been less vigilant in assessment of so-called ‘natural’ interventions.\textsuperscript{18} This has not always been wise. For example, pregnant women were once advised to contain weight gain during pregnancy to <20 lbs to reduce the risk of rising blood pressure and eclampsia. In fact, limiting weight gain did produce those desired outcomes. Unfortunately, at the same time, this intervention unexpectedly increased fetal morbidity and mortality. Women are no longer advised to avoid weight gain in pregnancy.\textsuperscript{19–21}

The Overall Health Effects of Sodium Restriction

Unfortunately, very little data currently exist linking salt intake to the duration or quality of life. It has been shown in rodents that a restricted sodium intake, while reducing blood pressure, also stunts growth and shortens life.\textsuperscript{22} Members of non-aculturated societies with minimal sodium intake also have short life spans. By contrast, in developed societies, with strikingly uniform sodium intakes between 100–200 mmol/24-h, life expectancy is nearly twice as long. In Japan, where sodium intakes tend to be high, life expectancy is among the highest in the world. Thus, ecological data, albeit weak evidence, provides no suggestion that a reduced sodium intake will extend life, nor that a high sodium intake is inconsistent with a prolonged life expectancy.

Epidemiological data, in which individual sodium intake and health outcomes are linked, is the next level of evidence through which to determine whether dietary sodium might influence the length or quality of life. Unfortunately, despite intense interest in this issue, regrettably little solid data are available. The Scottish Heart Study, a population-based longitudinal study of 10 000 people designed to assess the association of a variety of individual characteristics, measured at baseline, to subsequent morbidity and mortality, did include an estimate of sodium intake obtained by measuring 24-h urinary sodium excretion.\textsuperscript{23} In this study there was no consistent association between sodium intake and cardiovascular or all-cause mortality.

A subsequent study of 3000 treated hypertensive patients, in whom pretreatment 24-h sodium intake (measured after advice to refrain from excess salt intake for 5 days) and baseline plasma renin activity (PRA) were measured, showed there was a step-wise, significant, and independent inverse relationship between level of sodium measured in a 24-h urine, and subsequent strokes and heart attacks.\textsuperscript{24} Although this relationship held for the group as a whole, after stratification, it was significant only for men—who accounted for 75% of events. Among men, this relationship persisted after stratification by age, ventricular mass, and race (Figure 2). Not unexpectedly, in view of the inverse association of sodium intake and PRA, a good deal of the association of sodium to events was accounted for by level of PRA. Nevertheless, even after accounting for PRA in multivariable analysis, sodium intake retained an independent and inverse association with cardiovascular disease (CVD) events.

Our group also analysed the NHANES I epidemiological follow-up data to further explore the relationship of sodium intake to CVD and all-cause mortality.\textsuperscript{25} In this study of 14 000 adults selected randomly to represent the entire US population, sodium intake was estimated on the basis of a 24-h dietary recall. Again, sodium intake proved to be inversely related to CVD mortality. Those in the lowest quartile of sodium intake were 20% more likely to die of a cardiovascular cause than were those in the highest quartile of sodium consumers.

He and colleagues re-analysed the same NHANES I epidemiological follow-up data.\textsuperscript{26} Presumably, although not stated, conclusions drawn from their analysis of the entire data set did not differ from that already published. Consistent with the expected heterogeneity of response to sodium restriction, and the possibility that effects in the obese might be greater, the focus of this analysis was on the salt to CVD relationship in the normal sized majority and those 28% who were classified as obese. After eliminating participants with prior evidence of CVD, and removing a large fraction of cardiovascular end points from consideration, they found that the obese subjects in the remaining subgroup, expressed a direct and positive relation of sodium intake to morbidity and mortality outcomes. For the 72% of this subset who were not obese, no association of sodium intake to the restricted definition of CVD morbidity and mortality was found. These data are consistent with the expectation that there would be heterogeneity in the relation of sodium intake to health outcomes.

An analysis of the available MRfit data, widely quoted, although still available only in abstract, found no relationship between sodium intake, estimated by an overnight urine collection, and subsequent CVD events or mortality.\textsuperscript{27} Visual examination of this data in graphic form suggests a tendency for those consuming the least sodium to have the highest coronary heart disease event rates. Full analysis must await publication of the data.

Most recently published have been the results of an observational study of more than 2300 Finnish men and women in whom baseline cardiovascular risk data included measurement of 24-h urinary sodium excretion.\textsuperscript{28} This group is of particular interest because median sodium intake was 205 (25–552 mmol/24-h) in men, and 154 (12–512 mmol/24-h) in women—an
average of 216 and 162 mmol/24-h, respectively. Over up to 13 years of follow-up, it was found that increasing sodium excretion bore an independent and significant association with acute coronary events, but not stroke, and only in obese men. Thus, among the 47% of the male participants who were not obese, consuming up to 500 mmol of sodium per day was not associated with any apparent adverse effect. This relationship was not found in women, nor in non-obese men. Interestingly, the Conclusions and Abstract failed to note that the association applied to a minority of the study subjects. Instead, they concluded that ‘These results provide direct evidence of the harmful effects of high salt intake in the adult population’.

The fact, of course, is that these data, somewhat concordant with the findings in the subgroup analysis of NHANES, suggest, not surprisingly, that the impact of sodium intake probably depends upon subject characteristics. No doubt this heterogeneity reflects the varied influence of genetics, environment, and behaviour on the interaction of sodium intake and human health.

Each of these epidemiological studies share the weakness associated with non-experimental techniques. Unrecognized confounders, if they influence both the exposure variable and the outcome, can distort results. All studies attempt to control for recognized confounders. No matter how diligent, however, this may be imperfect. Moreover, all these studies are based upon a single determination of sodium intake. The inevitable intra-individual variation in such measures would tend to diminish any association between an exposure and outcomes.

The fact that in four of the six available studies, a significant independent association between salt intake and outcome was found, suggests that the available data may underestimate the true strength of the association of sodium intake to morbidity and mortality—both to the advantage and disadvantage of lower sodium intake depending upon the group studied. In sum, the available data suggests that the association of sodium intake to health outcomes reflected in morbidity and mortality are modest and inconsistent. Therefore, existing evidence provides no support for the highly unlikely proposition that a single dietary sodium intake is an appropriate or desirable goal for the entire population. This is not surprising in view of the genetic, behavioural, and environmental heterogeneity that characterizes human beings.

What Further Data are Needed

The gold standard for assessing the value of any medical or health intervention is the randomized clinical trial. The goal is to have similar subjects, selected without bias, exposed to regimens that differ only in terms of the intervention in question. Somewhat surprisingly, in view of the professed potential value of this approach, no such study has been powered to assess the effect of sodium intake on cardiovascular morbidity and mortality. Several randomized studies have, however, reported some health outcomes. Whelton and others have reported no difference in headaches, hospitalizations, etc, between low sodium/weight loss and control subjects within a

Figure 2 Urinary sodium excretion levels shown for age, race, and left ventricular hypertrophy (LVH). Alderman MH: 'Salt, Blood Pressure, and Human Health'. Hypertension 2000;36:890–93
mildly hypertensive population. Although eight deaths occurred in this study, their distribution was not reported.

Conclusions
Little controversy surrounds much of what is known about the effects of dietary sodium. Substantial variation in intake (75–100 mmol/24-h) can produce measurable, but modest changes in aggregate blood pressure. However, that effect is variable, and subjects have been arbitrarily described as salt sensitive and resistant. The effect seems to be more substantial in older subjects and in those with higher pressures. Any decision to adopt a low sodium diet should be made with awareness that there is no evidence that this reduction is either safe, in terms of ultimate health impact, or that it will produce cardioprotection. Clearly, there is no justification for a population-wide, public health recommendation for radical reduction (30–50%) in sodium intake.

For hypertensive subjects, sodium restriction can be viewed as another technique to lower blood pressure. Neither its efficacy, nor its safety, nor its contribution to cardioprotection has been compared to other antihypertensive therapies—for drugs which, for example, have been shown to be safe, efficacious, and cardioprotective. Adherence to an evidence-based approach to medical care suggests that sodium restriction should be reserved for patients in whom these proven drug therapies are ineffective, unacceptable, or inadequate. Its use should be carefully monitored to assess both efficacy and safety.

Any sound general dietary salt recommendation must await knowledge of the sum of its multiple consequences on the quality and duration of human life. Until then, no universal dietary recommendation can be scientifically justified.

References
27 MRRIT. Presented 29 January 1999, NIH Conference, Bethesda, MD.
Commentary: Evidence on salt and blood pressure is consistent and persuasive

Paul Elliotta and Jeremiah Stamlerb

Alderman’s paper gives a selected and unbalanced account on salt and blood pressure, and reaches unsound conclusions. Time and again when the totality of evidence has been scrutinized by independent expert committees, they have concluded that the average sodium consumption at the population level is too high, that reductions to no more than 100 mmol sodium/day (6 g salt/day) is desirable, and that public health benefits would accrue. Alderman obliquely notes these recommendations, but quickly dismisses them as ‘… dogma …’ without any attempt at specific refutation. These recommendations have received wide acceptance among professional organizations and government departments responsible for protecting the health of the public, but they have been opposed by powerful commercial interests among the salt manufacturers (represented by the Salt Institute in the US) and some food companies. Alderman’s results of the DASH-Na trial which crucially illuminate this issue. The DASH-Na trial differed from most in two key respects. During 70 million years of mammalian and primate evolution, and 4–15 million years of hominoid and hominid evolution leading to human sapiens sapiens genes in common, these data highlight the findings on dietary salt was removed. Particularly since chimpanzees and humans have 95+% genes in common, these data highlight the findings on dietary salt from anthropology and evolutionary biology—findings bypassed by Alderman. During 70 million years of mammalian and primate evolution, and 4–15 million years of hominoid and hominid evolution leading to Homo sapiens, and—for Homo sapiens—tens of thousands of years of evolution as a nomadic food gatherer and hunter, until 6000–8000 years ago when agriculture and animal husbandry were invented, our predecessors knew nothing about salt as a food additive. Evolving on a low salt diet of no more than 20–40 mmol sodium/day, generally in warm climates (e.g. Africa), our species became—and remains usual American fare, lower compared to higher sodium produced an 8 mmHg fall in systolic blood pressure (SBP), considerably greater than the estimates (4 and 6 mmHg) in the two cited meta-analyses. Crucially, in terms of salt and population-wide adverse blood pressure levels, for non-hypertensive DASH-Na participants (SBP/diastolic blood pressure [DBP] 120–139/80–89 mmHg, i.e. normal but not optimal, and high-normal blood pressures), lower versus higher sodium (again, 77 mmol/day lower) produced a 5.5 mmHg fall in SBP (7 mmHg in African-Americans, 4 mmHg in other groups), versus 1.6 and 1.2 mmHg in the two meta-analyses. For all DASH-Na participants, lower versus higher sodium reduced SBP/DBP 6.7/3.5 mmHg, versus about 3/2 from the meta-analyses. Further, the effect on blood pressure of salt reduction in the DASH-Na trial was greater for lower versus intermediate sodium than for intermediate versus higher sodium: –4.6 versus –2.1 mmHg SBP, for sodium lower by 42 and 35 mmol/day, respectively. This is a finding seminal for public policy recommendations.

Randomized Clinical Trials and Evidence from Clinical Practice and Anthropology

The evidence on salt and blood pressure comes from animal and clinical studies, clinical trials, epidemiological and anthropological findings. In discussing randomized controlled trials, Alderman focuses on findings from two meta-analyses, and ignores a third and concludes that ‘… a large (50–75%) reduction in sodium intake …’ produces on average a ‘… modest …’ fall in blood pressure, ‘… with wide individual variation…’. In so doing, he is silent on the crucial matter of varying quality among the many trials in these meta-analyses, including varying adherence of participants to counselling for salt intake reduction, leading to underestimation of true effects on blood pressure. Correspondingly, he is silent on the recently published results of the DASH-Na trial which crucially illuminate this issue. The DASH-Na trial differed from most in two key respects. It was a feeding study with all food supplied to participants to achieve very high adherence, and its design provided for three 24-hour urine samples. For hypertensive participants eating

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Correspondingly, Alderman’s discussion of INTERSALT findings is critically flawed, repeating his previously published incorrect assertions despite our written communications setting the record straight. Thus, he continues to claim that INTERSALT found no association between sodium and blood pressure when analyses were restricted to 48 population samples (excluding four low sodium population samples). In fact, the highly significant within-population association between urinary sodium excretion and SBP across all 52 population samples was virtually unchanged when the four low-sodium populations were excluded (N = 9343 instead of 10 074), and the association between sodium excretion and upward slope of blood pressure with age found across 52 population samples persisted across 48 samples. Alderman also states that ‘the notion that pressure rises with age … is in no way a genuine observation.’ Though the INTERSALT data were cross-sectional, there is repeated evidence from many longitudinal population studies of a genuine rise of blood pressure with age.

Adjusted INTERSALT estimates are quantitatively similar to the DASH-Na feeding trial results for influences of sodium on the blood pressure of individuals. Particularly in view of the much larger effects in the chimpanzee experiments and in the ecological analyses of INTERSALT estimating effects of 100 mmol less sodium/day on upward slope of blood pressure from age 25 to age 55, it is reasonable to infer that there is also a large decades-long influence operating from early in life—a concept supported by the findings of the Rotterdam study of infants.

Alderman cites two of his own studies to imply that reduced sodium intakes may be harmful, but fails to cite subsequent letters to the editor and articles that have been highly critical of both studies. The first of his studies followed up treated hypertensive patients who had been instructed to refrain from excess salt intake for 5 days prior to plasma rennin activity measurement. Their urinary sodium excretion was then used—in a way that was obviously flawed methodologically—as an index of their usual salt intake. Sodium excretion in the lowest quartile was unusually low (reflecting likely under-collection), and results could have been further biased by the fact that those with the highest risk may have reduced their sodium intake more extensively (i.e. reverse causality). The second of Alderman’s studies gave follow-up data from the NHANES-I study, but was fatally flawed because of inadequacies of measurement of sodium consumption at baseline. Alderman, citing a further analysis of the MRFIT data, which (unlike his study) reported no association between sodium intake and subsequent mortality, claims (with no supportive data) that the study showed a ‘tendency for those consuming the least sodium to have the highest coronary heart disease event rates’. Alderman then cites a recent Finnish study that found significant direct—not inverse—associations between urinary sodium excretion and subsequent coronary heart disease, cardiovascular and all-cause mortality, with adjusted hazard ratios (men and women combined) of 1.56 (95% CI : 1.15–2.12), 1.36 (95% CI : 1.05–1.76) and 1.22 (95% CI : 1.02–1.47), respectively per 100 mmol sodium. The paper included a sub-group analysis that stratified the population by gender and weight, thus reducing statistical power: for normal-weight men, hazard ratio for cardiovascular disease mortality was 1.23 (95% CI : 0.76–1.98) per 100 mmol sodium, while for overweight men it was 1.44 (95% CI : 1.02–2.04). Alderman claims that these findings—exquisitely adapted for the physiological conservation of the limited salt naturally present in foods, i.e. for salt retention, not for excretion of a chronically excessive intake 10–20+ times physiological need (8–10 mmol/day). Thus, when Alderman talks about current intake ‘… between 100 and 200 …’ mmol sodium/day and its ‘… uniformity across all dietary, cultural, environmental and hereditary circumstances …’, he one-sidedly ignores human prehistory, unscientifically equates levels of current sodium intake (100 and 200 mmol/day) that are not uniform in their effects on blood pressure and, by implying that present-day usual = normal = optimal, infers that current intake relates positively to worldwide increasing life spans, without specifying whether he means 100 or 200 mmol (or what level) sodium per day. For example, in Japan (erroneously cited by Alderman in support of this concept), public health efforts have led to decreasing salt intake from levels as high as 400 mmol/day, a change associated with declines in stroke mortality (from Alderman’s studies of a genuine rise of blood pressure that accompanied migration. Counter examples are not mentioned, including findings on the Qash’qai nomads of Iran and six Solomon Islands population samples, where only one, the Lau, had prevalent high blood pressures. In contrast with the other five population samples that consumed low salt diets, the Lau cooked their food in brackish water from a Pacific inlet, hence had higher salt intake. Neither of Alderman’s examples directly involved migration, in contrast to data from China, Africa, and elsewhere. For example, when the Luo in Kenya moved from their rural villages to Nairobi, the move was accompanied by a rapid rise in blood pressure associated with higher urinary sodium:potassium ratio and higher body weight.

The senior of us (JS) has déjà vu in reading Alderman’s arguments, since all of them are repeats 30–40 years later of assertions put out, with support from special commercial interests, to undermine the conclusion that dietary cholesterol-saturated fat plays a key aetiological role in producing epidemic atherosclerotic disease through its major adverse influences on serum lipids, etc. The immediate argument about ‘exceptional’ populations was a favourite then too—there were Eskimos in the Arctic, Masai in Africa and others. These ‘exceptions’ died on the vine as the aetiological issue became fully resolved. Particularly against this background, it is relevant to note that an exception tests the rule; it does not refute it. An exception may have many roots. It may reflect the fact that the exposure (e.g. high lipid intake) may be necessary to produce the effect (e.g. high serum cholesterol on average), but it may in certain circumstances not be sufficient, given that multiple factors are at work causatively. Or, an exception may be due to flawed data, or to lack of statistical power due to small sample size, i.e. it really is not an exception at all. Again, Alderman does not come to grips with such basic issues.

Observational Studies of Salt and Blood Pressure

The same problems prevail in Alderman’s account of the observational data from epidemiology. Thus, he cites studies on the Kuna Indians and Italian nunsidthers to support this concept), public health efforts have led to decreasing salt intake from levels as high as 400 mmol/day, a change associated with declines in stroke mortality (from levels originally highest in the world) of 80–90%, which have made an important contribution to Japan’s recent emergence as the country with highest population life spans.

Alderman’s studies gave follow-up data from the NHANES-I study, but was fatally flawed because of inadequacies of measurement of sodium consumption at baseline. Alderman, citing a further analysis of the MRFIT data, which (unlike his study) reported no association between sodium intake and subsequent mortality, claims (with no supportive data) that the study showed a ‘tendency for those consuming the least sodium to have the highest coronary heart disease event rates’. Alderman then cites a recent Finnish study that found significant direct—not inverse—associations between urinary sodium excretion and subsequent coronary heart disease, cardiovascular and all-cause mortality, with adjusted hazard ratios (men and women combined) of 1.56 (95% CI : 1.15–2.12), 1.36 (95% CI : 1.05–1.76) and 1.22 (95% CI : 1.02–1.47), respectively per 100 mmol sodium. The paper included a sub-group analysis that stratified the population by gender and weight, thus reducing statistical power: for normal-weight men, hazard ratio for cardiovascular disease mortality was 1.23 (95% CI : 0.76–1.98) per 100 mmol sodium, while for overweight men it was 1.44 (95% CI : 1.02–2.04). Alderman claims that these findings
imply that only obese people are at risk from high sodium intake, a claim refuted by the author in answer to a letter to the editor by Alderman on this very point. As Alderman then notes, the associations between sodium intake and mortality are likely to have been diluted because sodium estimates were based on only a single 24-hour measurement of urinary excretion. In the light of this point, Alderman’s argument—against a significant positive overall relation of sodium intake to mortality in this population—is further flawed.

Finally, Alderman raises issues about the safety of sodium reduction, based on results of small short-term studies with very large manipulations in sodium intake. However, he fails to cite articles highly critical of this position, indicating that the metabolic changes are not seen with longer-term, moderate sodium reduction.

Conclusions

By ignoring the overwhelming scientific consensus on this issue, Alderman appears to condone the ‘do nothing’ approach favoured by some elements of the food industry (who have much to gain commercially from the status quo). Alderman calls for a long-term randomized trial of sodium reduction with a focus on cardiovascular morbidity and mortality. But for reasons of costs and practicality (including sample size, problems of blinding and confounding) such a trial is not being seriously considered by any responsible agency, governmental or non-governmental, national or international. It will never be done. Instead, as with many matters in public health (e.g. on dietary lipid and atherosclerotic disease) and in other walks of life, reasoned decisions need to be taken based on the weight of evidence to hand.

For sodium and blood pressure, as attested by many independent scientific reviews, the evidence from animal studies, clinical trials and epidemiological observation is strong, consistent and persuasive. Recent analysis demonstrates both the potential health and economic benefits of adopting a population approach to sodium reduction. The proponents of the ‘do nothing’ approach have no case for the status quo as the preferred public health option. In fact, the body of scientific knowledge affords no basis for valid debate; efforts to promote the idea that there is a scientifically grounded ‘controversy’ in this area—as in the area of tobacco and disease—are scientifically unsound and detrimental to health. With his faulty methodological thrust involving a heterogeneous mix of errors and omissions, Alderman has no trouble coming to conclusions about salt and blood pressure which are contrary to repeated expert group reviews, and supportive of the position adopted by special commercial interests.

References

Commentary: Salt, blood pressure and public policy

David A Freedmana and Diana B Petittib

The ‘salt hypothesis’ is that higher levels of salt in the diet lead to higher levels of blood pressure, increasing the risk of cardiovascular disease. The corollary is a public health recommendation to higher levels of blood pressure, increasing the risk of cardiovascular disease. The 'salt hypothesis' is that higher levels of salt in the diet lead to increased blood pressure.

Alderman1 provides an incisive review of the evidence from epidemiological studies, as well as experiments on humans and animals. He concludes that existing data do not support the dramatic restrictions on salt intake. He even cites some studies showing that a marked reduction in salt levels will do more harm than good, while properly noting the limitations in such data. Results depend on making the proper adjustments, but statistical science offers only the most general guidelines as to which adjustments should be made and which should not.

Alderman also mentions two remarkable and little-known natural experiments—the San Blas Indians and the Italian nuns—which demonstrate that the link between dietary salt and blood pressure is weak at best. The San Blas study is cross-sectional rather than longitudinal, which perhaps weakens the force of the data.

What would be the health effects of cutting salt intake in half? To settle the question, Alderman points out that long-term clinical trials would be needed, measuring primary endpoints of mortality and morbidity rather than intermediate endpoints like blood pressure. Others have reached similar conclusions about the state of the evidence and its policy implications.2,3 as does our own review.4

We examined4 the summary data published by INTERSALT,5 if anything, these data contradict the salt hypothesis. The data cover 52 centres scattered around the world—ranging from two Indian tribes in Brazil, through Chicago and Warsaw to Kenya and Beijing. As Alderman notes, however, such ecologic comparisons are especially prone to confounding.
Alderman does not address the recent DASH-sodium trial that measured the effects of diet and salt on blood pressure.6 This trial randomized subjects to two diets—a control diet like a typical American diet, and a modified ‘Mediterranean’ diet. Subjects were rotated through three levels of salt.

The protocol for this trial7—published two years after the trial was underway—states that one of the two primary research questions was the effect of the DASH diet at various levels of salt intake. Additivity and linearity of effects of diet and salt were protocol-specified secondary questions. Such questions are given short shrift in the final report, which stresses the impact of reducing salt intake.6 The accompanying news release is even more one-sided.8

Published data summaries, sketchy as they are, indicate that adopting the DASH diet will lead to a marked reduction in systolic blood pressure, at ordinary levels of salt intake; but there are striking non-linear interactions between salt and diet.6 Indeed, one way to read the data is this: with a good diet, salt has almost no impact on systolic pressure.

Practically no attention is given to the effect of salt on diastolic pressure, which is independently associated with cardiovascular mortality, and is the benchmark for estimating public health benefits from blood-pressure reduction.11 The response of the DASH investigators to these points is unconvincing.9 The INTERSALT investigators refuse to make additivity and linearity of effects of diet and salt were protocol-specified secondary questions. Such questions are given short shrift in the final report, which stresses the impact of reducing salt intake.6 The accompanying news release is even more one-sided.8

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Moreover, the study population substantially over-represents salt-sensitive demographic groups; extrapolating to the general population is therefore unwarranted,4,9 despite sweeping claims.6

The response of the DASH investigators to these points is unconvincing.9 The INTERSALT investigators refuse to make their data public.8 So do the DASH investigators, who even decline requests for data on diastolic pressure.9 The take-home message from the DASH trials,6,10 despite the NHLBI spinmeisters, is that diet matters more than salt. The effect of diet has been confirmed by a clinical trial on secondary prevention, with endpoints defined in terms of mortality and morbidity.11

Funding agencies and medical journals have taken a stronger position favouring the salt hypothesis than is warranted, raising questions about the interaction between the policy process and science. Dietary advice on salt is presented to the public with rhetorical force that is not in any reasonable balance with the evidence. How did this come about?

As we see it, public policy programmes, once in place, rapidly develop a life of their own. The possibility of benefits becomes probability, and probability becomes certainty. Ambiguity must be suppressed—just as data must be hidden—because the public is too easily confused. Only professionals can be trusted to weigh the evidence, and not all professionals at that. Besides, where is the harm in salt reduction?

The harm is to rational discourse. The appearance of scientific unanimity is a powerful political tool, especially when the evidence is weak. Dissent becomes a threat, which must be marginalized. There soon comes about the pretence of public policy based on science, without the substance. Salt is only one example of this phenomenon.

References
overweight, do not smoke and are very fit. Their blood pressure
does not rise with age although they spend much of their time
fighting and are under great stress. This tribe does not develop
vascular disease, although many die of infection. However,
when they migrate to a Venezuelan or Brazilian town and adopt
a western lifestyle, they, like native Americans, become over-
weight and develop diabetes and premature vascular disease.
They appear therefore, to be a group which, though predisposed
to vascular disease, is protected by the way they live. There
are other similar examples which clearly indicate that cardio-
vascular disease (strokes, heart attacks and heart failure) could
be entirely prevented if we changed our diet and lifestyle.

Approximately half of the population in the UK dies of
cardiovascular disease yet very little is done to prevent this
by changing lifestyle or diet. Clearly, much greater efforts are
needed to try to understand what simple changes could have
beneficial effects. To relate dietary variables such as salt, saturated
fat, fruit and vegetable consumption to outcome is not easy
because at present the intake of salt, fat, fruit and vegetables
varies considerably from day to day, as does the blood pressure.
Unfortunately it is not possible to set up dietary outcome experi-
ments in which babies are randomized at birth, or ideally at
conception, into one group that eats less salt or less fat and more
fruit and vegetables, while another group continues on a normal diet for life. Such experiments are never going to be done, we thereforere have to rely on evidence from epidemiology, migration,
intervention, treatment, animal and genetic studies. In spite of
the difficulties of quantifying salt intake in an individual because
of the variability of western diets and the variability of the blood
pressure, the evidence that dietary salt is related to blood pres-
sure, both in the rise that occurs with age and the number of
people whose blood pressure is raised, is stronger than all other
dietary variables.

Alderman has been one of the main proponents of the
dangers of reducing salt intake. He encouraged the National
Heart, Lung and Blood Institute (NHLBI) in the USA to set up a
large workshop on sodium and blood pressure in January 1999
in order to critically review all of the current scientific evidence
on salt. For reasons that are unclear Alderman did not attend
the meeting which concluded that ‘a high sodium intake is
associated with higher blood pressure levels, and other cardio-
vascular and non-vascular conditions continue to increase’, and
that ‘a population wide strategy of reducing salt in the food
supply is an important public health strategy that can lower blood pressure among populations’. Alderman’s current
overview of the subject is highly selective. He ignores over
40 careful studies in unacculturated human populations who at
one time consumed, or continue to consume, less than 3 grams
of salt per day. In these populations blood pressure did not
and does not rise with age. Furthermore, there are other unac-
culturated populations which demonstrate that it is the low salt
intake which is responsible for the lack of rise in blood pressure,
not some other aspect of unaculturation. Alderman points
out that Kuna Indians appear to be an exception to the general
experience that a high salt intake is associated with a rise in
blood pressure with age but he does not mention that in this
study 24-h urinary sodium excretion was not measured. The
estimation of salt intake relied in part on the recollection of how
many teaspoons of salt each person had added to their food.

One of the reasons the large InterSalt study was set up with
careful attention to methodology, including 24-h urine collec-
tions, was precisely because of the difficulty of estimating salt
intake from dietary history. Alderman also refers to an observa-
tional study in Italian nuns where the blood pressure did not
rise with age but he does not quote the investigators’ own
conclusions. It appeared to them that in order to avoid the cus-
tomary rise in blood pressure with age it is necessary to live in
a stress free environment, characterized by total silence, con-
tinuous meditation and isolation from society. It is noticeable
that although the first account of these nuns appeared 10 years ago the findings have never been confirmed elsewhere.

The InterSalt study was set up to study a wide range of
salt intakes across the world and measure blood pressure and
other variables under well controlled conditions. By the time
the study was completed there were only four communities
who ate less than 3 grams of salt a day. The others were in a
very narrow range of salt intake, approximately 7–12 grams
of salt a day. The majority of these communities were eating
a western diet in which salt intake varies so much from day to
day that individual variations in sodium excretion may be
considerable, e.g. more than five-fold. It follows that in many
of these communities salt intake in any one individual might
vary from day to day by the same amount as the variability
between individuals. It is not surprising therefore that, in the
InterSalt study, if one excludes the few communities who eat
less than 3 grams of salt, and only considers those communities
which consume between 7 and 12 grams of salt a day, there is
no clear relationship with blood pressure. Alderman fails to
point out that if all the communities are considered, there is
a clear relationship between salt intake and blood pressure
and the rise in blood pressure with age (Figure 1).

The only intervention study that has successfully managed to
reduce salt intake remains the Portuguese study where two
villages were studied. One village was given information on
how to reduce salt intake, particularly in relation to processed
foods, and it was given processed foods with less salt. Salt intake
was reduced by approximately 50%, as judged by 24-h urinary
sodium. Over two years this resulted in substantial differences

Figure 1. The relation of salt excretion to the slope of the rise in
systolic blood pressure with age in 52 centres in the INTERSALT study.
(Adapted from Ref. 9.)
in blood pressure, compared to the control village where no reduction in salt intake was made (Figure 2).

Perhaps it is understandable that Alderman all but ignores all the animal work that relates salt intake to blood pressure. He reduces it to one dismissive sentence. There are now numerous studies in the rat, dog, chicken, rabbit, baboon and chimpanzee, all of which have shown that when there is a prolonged increase in salt intake there is an increase in blood pressure. Furthermore in all forms of experimental hypertension, whatever the animal model, a high salt intake is essential for the blood pressure to rise. A recent study was carried out in chimpanzees, the nearest relative to humans (98.8% genetic-homology). The normal salt intake of a chimpanzee, which weighs up to 50 kg, is less than 0.5 gram a day. When it was increased to 15 grams a day the blood pressure rose slowly and the rise became significant after one year when it was still rising. Blood pressure returned to normal when the salt intake was reduced (Figure 3). These results show that if the animal species most closely related to humans, which normally consumes a diet as low in salt as the one it (and the human race) is genetically programmed to eat, increases its salt intake into the same range as that of present day humans, they, like humans, develop hypertension.

Alderman now concedes that when salt intake is reduced there is a fall in blood pressure in both normotensive and hypertensive humans. He even concedes that a fall of ‘a few millimetres of mercury if sustained, assuming the method of its achievement induces no harm, could produce more reductions in morbidity and mortality than is currently achieved by treating high blood pressure’. His ensuing comment that this ‘possibility energises advocates of sodium restriction’ presumably indicates that nevertheless Alderman wishes to distance himself from these findings. It could be put forward that this is a reasonable uncritical reaction to meta-analyses which have included studies of extremely large changes in salt intake over periods of less than one week. Such manoeuvres have been known to stimulate the sympathetic nervous system. The inclusion of such short term studies, particularly in normotensives, is inappropriate when the recommendations for public health are for a modest reduction in salt intake from 10 grams to 5 grams a day over a lifetime, not a few days. A more recent meta-analysis that only included studies of modest and longer term reductions in salt intake, showed that the fall in blood pressure in normotensives was greater than in the previous meta-analyses. In the most rigorous trial (DASH Sodium Study) in which there were several hundred participants, and the daily sodium intake was well controlled, the fall in pressure was even greater (Figure 4). There is evidence that the full effect of salt restriction may not be seen within a month so that with longer term reductions in salt intake there may well be greater falls in blood pressure. In other words, there is every indication that the recommendations of a modest reduction of salt intake from 10 grams to 5 grams a day over a prolonged period of time has a pronounced effect on blood pressure, not only in the hypertensives but also in the normotensive population.

When discussing the other effects of ‘sodium restriction’, Alderman forgets to mention that in addition to, and independent of, raising blood pressure, a high salt intake increases the mass of the left ventricular wall, stiffens conduit arteries and thickens and narrows resistance arteries, including the coronary and renal arteries. A high salt intake is also directly related to the number of strokes, severity of cardiac failure, adhesiveness of platelets, carcinoma of the stomach and, to bone demineralization. Alderman misunderstands the relationship of sodium intake to vascular compliance; he conveniently reverses it—what has been found is that a reduction in sodium intake increases vascular compliance. He rightly but ominously points out that salt intake is well documented to relate closely to the renin angiotensin system. It is true that the renin angiotensin aldosterone system is one of the major compensatory mechanisms that maintains blood pressure and reduces the excretion of sodium, and thus when extracellular volume is reduced with diarrhoea or diuretics there is a rise in plasma renin. This is an entirely normal physiological response, and to try to intimate that it is abnormal, and harmful, for plasma renin to rise in response to a reduction in extracellular volume, is extraordinary. The Yanomamo Indians, who still live an evolutionary form of life and have a very low salt intake

**Figure 2** Blood pressure changes with time in two Portuguese villages, one of which was advised on how to reduce salt intake and given processed foods with a reduced salt content, the other had similar measurements of blood pressure but no advice on diet. Note the significant differences in blood pressure at 1 year and continuing differences at 2 years. (Adapted from Ref. 13.)

**Figure 3** Blood pressure in chimpanzees who either continued on their usual diet (10 mmol sodium per day) or were given an increased salt intake (200 mmol sodium per day). At the end of the 20-month study, the salt supplements were stopped and blood pressure declined to that of the control group. (Adapted from Ref. 15.)
Ref. 19.)

American diet (i.e. control diet) and on DASH diet. (Redrawn from activity angiotensin II or aldosterone.32,33 There may cause damage, not the absolute level of plasma renin and aldosterone to the blood volume or extracellular volume that disease at an early age. Animal experiments, however, have shown that it is the appropriateness of the level of renin and aldosterone should precipitate an acceleration of vascular disease, i.e. strokes, heart failure and coronary artery disease, particularly in the elderly, but they cause increases in plasma renin activity and aldosterone which, according to Alderman, should be harmful. A modest reduction in salt intake lowers blood pressure in an identical way to diuretics and increases both renin and aldosterone to the same levels. Alderman needs to explain why he considers diuretics to be so beneficial, and yet according to him salt restriction is not.

Whilst it is true that non-acculturated societies have shorter life spans, this is not due to an increase in the incidence of cardiovascular disease, which they almost totally avoid, but to the greater risk of infection, particularly when exposed to western populations. It is true that the Japanese are an example of a society that has a longer life expectancy than many of those in the west. As the Japanese have a high salt intake, Alderman suggests that this illustrates that salt intake is not related to life expectancy. But the Japanese did not, and to a large extent still do not, eat much fat and they have a low plasma cholesterol57 which protects them from the development of vascular disease and atherosclerosis. Alderman fails to point out that the major causes of death in Japan are cerebral haemorrhage38 and cancer of the stomach,29 both of which are due to the high salt intake. Indeed, he appears to be unaware that in the 1960s there was a government campaign in Japan to reduce salt intake. It was successful in lowering blood pressure and causing large reductions in stroke mortality.39 It is very likely that if the Japanese were to reduce their salt intake further, whilst continuing to eat a minimum amount of saturated fat, they would live even longer than they do now.

Alderman fails to mention the North Karelia project in northern Finland where the incidence of cardiovascular disease was very high. In co-ordination with the food industry, a government-backed campaign has been successful in reducing salt and fat intake, increasing fruit and vegetable consumption and cutting cigarette smoking. This has resulted in a reduction in blood pressure and fat intake and significant falls in stroke and coronary heart disease mortality.40,41 Three-quarters of the fall in coronary heart disease and two-thirds of the fall in stroke mortality were due to the change in risk factors. This study clearly indicates that if we were prepared to change our lifestyle, particularly our diet, major reductions in cardiovascular mortality could ensue.

In a final attempt to obfuscate, Alderman once more revives the myth42 that a moderate reduction in salt intake is harmful. He again quotes completely inappropriate experiments in which the sodium intake of rats was so low that it stunted growth.43 The intake of sodium was lower than occurs naturally in mammals eating only fruit and vegetables. Therefore when discussing the possible effects of reducing salt intake from approximately 10 grams to 5 grams a day such experiments are irrelevant. For instance, in comparative terms, a reduction in salt intake to 5 grams a day, which has been suggested for humans at present, is about a thousand times less of a reduction than that used in the animal studies he is quoting.

Alderman’s other attempts to suggest that a low salt intake is dangerous in humans are based on two of his own publications in which a claim is made that there is a relationship between habitual salt intake and myocardial infarction.44,45 The data on sodium excretion in the first paper and of sodium intake in the second are so seriously flawed however, that the claim is unacceptable. In the first study, 24-h urine collections were made in

![Figure 4](Image) Changes in blood pressure and 24-hour urinary sodium excretion with the reduction in salt intake in all participants (hypertensives: n = 169; normotensives: n = 243) on the normal American diet (i.e. control diet) and on DASH diet. (Redrawn from Ref. 19.)

(<0.5 g per day), have the highest renin and aldosterone levels measured. But they do not develop vascular disease. According to Alderman’s hypothesis, such high levels of angiotensin and aldosterone should precipitate an acceleration of vascular disease at an early age. Animal experiments, however, have shown that it is the appropriateness of the level of renin and aldosterone to the blood volume or extracellular volume that may cause damage, not the absolute level of plasma renin activity angiotensin II or aldosterone.32,33 There are experiments in animals that demonstrate that salt loading per se has identical effects to that of giving aldosterone or angiotensin II.22,34,35 In other words, the deleterious effect of aldosterone on cardiac fibrosis, etc, appears to be due to the associated retention of an excess amount of salt and water.

In view of Alderman’s belief in the dangers of an increase in renin and aldosterone, it is surprising that he supports the use of diuretics for the treatment of hypertension.36 Diuretics have been shown to be very effective in reducing cardiovascular disease, i.e. strokes, heart failure and coronary artery disease,
been problems with urine collections. But as creatinine excretion was noticed that the sodium excretion paralleled the nature of the diet the patients were supposed to be eating. Alderman and his colleagues’ estimate of the dietary sodium that the patients were consuming, which was based on a 24-h urine collection, was also inaccurate. The 3000 patients were divided into four groups depending on the 24-h urinary sodium excretion. It was noticeable that the sodium excretion paralleled creatinine clearance which strongly suggested that there had been problems with urine collections. But as creatinine excretion had not been given it was not possible to be certain. Subsequently, however, Dr Alderman released the data on creatinine excretion. This should be relatively constant and unaffected by glomerular filtration but it rose with the creatinine clearance which confirmed that there had been serious problems with urine collections. This conclusion was re-enforced by the urine volume and potassium excretion which also followed creatinine excretion. In other words, because of inaccurate urine collections, many patients and their results had been classified into spurious sodium excretion quartiles and not into true sodium intake quartiles. One can conclude therefore that the claim that an habitual low salt intake in hypertensive patients is inversely related to myocardial infarction cannot be sustained.

In Alderman’s second paper, a 24-h dietary recall on nutrient intake was used to gauge the habitual salt intake of sodium and calories in more than 10,000 subjects between 1971 and 1975. The subjects were then re-examined 20 years later. The calculation of sodium intake, which was based on dietary recall, took no account of discretionary salt intake, i.e. salt added by an individual at the table or in his own cooking which, around 1980, would have accounted for approximately half of salt intake. The measurement of salt intake in this study is therefore inaccurate. A simple inspection of the overall results of the paper also reveals that these are insecure. For instance, Engleman pointed out that in the lowest quartile of daily salt intake in both men and women (approximately 1 and 2 grams respectively) calorie intake was 50% lower than the national recommended daily dietary allowance. Karppanen and Mervaala commented that they thought it remarkable that on such a near starvation diet there were so many survivors. They thought it should have surprised, even Alderman, that women on this extraordinary low calorie intake were on average 4 kilograms heavier than those in the higher sodium quartile, who were apparently eating twice as many calories. The misrepresentation of habitual salt intake which resulted from faulty urine collections in the first paper and the defective questionnaire data on sodium and calorie intake in the second paper invalidate any claim that a low sodium intake is related to myocardial infarction. Recent evidence from Finland shows that there is a clear relationship between mortality and salt intake (Figure 5). Unfortunately for Alderman’s argument it shows that the higher the salt intake the greater the mortality.

Salt was only discovered by humans about 5000 years ago when it was found to have the magical property of preserving food. It therefore became of great importance in the development of settled communities and civilizations. Now, however, with the development of the deep freeze and refrigerator, salt is no longer required for preservation. Unfortunately, with the development of processed foods, salt has once again become of great commercial importance, not only to the salt manufacturers and extractors, but also to the food and soft drinks industries. Many of the cheap processed foods are only palatable with the addition of large amounts of salt, the cheapest ingredient. When people are exposed to foods which contain high concentrations of salt the salt taste receptors are suppressed. The individual therefore becomes habituated to this type of food, which increases the demand for highly salted processed foods. Salt is also very important to the processed meat industry, for a higher salt concentration increases the water binding capacity. In this way the weight of the product can be raised by 10 to 20% at no cost to the producer. Total salt intake is an important stimulus to thirst and therefore fluid consumption. Any reduction in the population’s salt intake will have a large effect on soft drinks, mineral water and beer consumption.

It is not surprising, therefore, that commercial interests which represent the salt manufacturers and extractors, e.g. the Salt Institute in the US and the soft drinks industry, together with many sections of the food processing industry, have co-operated in perpetuating the idea that salt is not involved in hypertension. They have also suggested that dietary salt only affects a small number of people and that therefore it is not worthwhile for the normotensive population to reduce its salt intake. They also perpetuate the myth that reducing salt intake can be dangerous.

Alderman has acted as a member of the Medical Advisory Board for the Salt Institute in the US, which represents the salt manufacturers and extractors not only in the US but worldwide. The Institute kindly distributed his paper in which the claim was made that salt intake was related to myocardial infarction as a ‘professional courtesy’. At the same time the Institute put out a news release which claimed that this study unequivocally ‘showed that hypertensives consuming low
Sodium diets had dramatically increased rates of having heart attacks. This so-called evidence formed the main plank of the Salt Institute’s aborted petition to the FDA to try to change the regulations concerning commercial claims for low salt foods. Alderman was one of the co-signatories of this petition.

When all of the evidence is considered from epidemiological, migration, intervention, treatment trials, genetic studies in humans and animal studies that relates salt intake to blood pressure and other harmful effects, the evidence is very strong. It is stronger than evidence for other dietary variables that are also important in cardiovascular disease, e.g. saturated fat intake and fruit and vegetable consumption. Nearly all government appointed bodies and nutrition experts who have considered the evidence have recommended a reduction in salt intake from around an average consumption of 10–12 grams to 5–6 grams per day. This recommendation was made in the US in 1970 and in the UK in 1994. Nevertheless salt intake is increasing due to the much greater consumption of processed and ready prepared foods which are very high in salt, often equivalent to that of seawater. In the UK there is a strategy to make small, i.e. 10 to 25%, reductions in the salt concentration of all processed foods. These reductions will not be detected by the consumer and as the salt taste receptors get used to the lower concentration, further reductions can be made in four or five years time. In this way salt intake could be reduced throughout the population without the consumer having to reduce their salt intake consciously. However, the reduction would be greater if consumers themselves added less salt to the food both in cooking and at the table. In this way it should be possible to reduce salt intake in the Western world by half over the next decade. Of all the dietary strategies to reduce the intake of salt, this is probably the easiest to achieve, provided the food industry is prepared to co-operate. In the UK, by manoeuvres which resemble those employed by the tobacco industry, such steps are being vigorously opposed by the Salt Manufacturers’ Association and the Food and Drink Federation, an umbrella organization representing the soft drinks, the snack producers (many of which are owned by the soft drinks producers) and other food processors.

References
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Hence if too much salt is used for food, the pulse hardens ...

Huang Ti Nei Ching Su Wen, 2698–2598 BC (the Yellow Emperor’s classic on internal medicine).

Although ancient Chinese medical literature—the Yellow Emperor’s classic on internal medicine—reported that a high intake of dietary salt (sodium chloride) might produce a hardened pulse nearly 5000 years ago, the first meaningful scientific evidence for a positive association between salt consumption and level of blood pressure was published by Dahl in 1960.1 Dahl described a remarkable linear relationship between average sodium intake and prevalence of hypertension across five population groups.1 Since then, abundant evidence of a causal association between dietary sodium intake and high blood pressure has emerged from animal experiments and from observational epidemiological studies and randomized controlled clinical trials.2,3

Animal Experiments

Studies in a variety of laboratory animals have demonstrated that a high dietary intake of salt results in hypertension.4 Recently, Denton et al. reported the findings of a 3-year experiment conducted in 26 chimpanzees with a baseline diet which was very low in sodium and high in potassium content.5 Following a year of baseline observations, salt was added to the diet of 13 animals in increasing amounts (5 g/day for 19 weeks, 10 g/day for 3 weeks, and then 15 g/day for 67 weeks) during an 89-week period of active intervention. Dietary intake of salt remained unaltered in the other 13 control animals. The average level of blood pressure did not change significantly during the intervention phase in the control group. However, in the 13 animals assigned to the active intervention mean systolic blood pressure (SBP) increased by 12 mmHg compared to the corresponding baseline level (P = 0.05) after the first 19 weeks of supplementary salt intake (5 g/day). Following the 39 weeks of supplementation with 10 g/day salt (3 weeks) and 15 g/day salt (36 weeks), mean SBP was increased by 26 mmHg (P < 0.001) and mean diastolic blood pressure (DBP) was increased by 5 mmHg (P = 0.05). Following a further 26 weeks of supplementation with 15 g of salt/day (a total of 84 weeks of supplementation with dietary salt), mean SBP was increased by 33 mmHg (P < 0.001) and DBP was increased by 10 mmHg (P < 0.01). Twenty weeks after the end of the period of salt addition, the animals’ average level of blood pressure returned its baseline level. This experiment, conducted in the species that is phylogenetically closest to humans, provides direct evidence in favour of a causal relationship between high salt intake and hypertension.5

Observational Epidemiological Studies

Studies in low blood pressure populations and in migrants from these societies to more westernized environments provide strong evidence for a causal relationship between high salt intake and hypertension. More than 30 populations with an average blood
pressure that is lower than in westernized societies and in whom blood pressure does not rise or rises very little with age, and hypertension is virtually absent, have been reported in the scientific literature.\textsuperscript{6,7} Typically, these populations live in fairly isolated settings, eat unprocessed foods, are lean, physical active, and consume less dietary sodium than their counterparts in westernized societies.\textsuperscript{6,7} Migration from relatively isolated societies to more westernized environments has been associated with an increase in the average level of blood pressure, a steeper slope of blood pressure with increasing age and a higher prevalence of hypertension.\textsuperscript{6,7} We examined the effect of lifestyle change including dietary sodium intake on blood pressure in the Yi people, an ethnic minority group in Southwestern China.\textsuperscript{7,8} Blood pressure rose very little with increasing age after puberty in the Yi farmers who lived in their natural environment in remote mountainous areas and consumed a diet low in sodium content. In contrast, Yi migrants and Han people who lived in urban areas consumed a diet which was higher in sodium content and experienced a much greater increase in blood pressure with progressive ageing.\textsuperscript{7,8} In a sample of 417 men, we documented a positive relationship between sodium intake and higher blood pressure and also demonstrated the importance of other factors, such as increasing body mass index, in the higher prevalence of hypertension. These findings suggest that changes in lifestyle, including a higher intake of dietary sodium, contribute to the higher blood pressure among Yi migrants.\textsuperscript{8}

INTERSALT, a cross-sectional study of 10,074 participants from 52 populations in 32 countries reported a strong, positive association between urinary sodium excretion and blood pressure.\textsuperscript{9} In within-population analyses, after adjustment for age and sex and correction for regression dilution bias, a 100 mmol higher 24-hour urinary sodium was associated with a 4.3 mmHg higher SBP and a 1.8 mmHg higher DBP. After additional adjustment for 24-hour urinary potassium and alcohol intake, the corresponding differences in SBP and DBP were 6.0 and 2.5 mmHg, respectively. After further adjustment for body mass index, the differences in blood pressure were 3.1 mmHg for SBP and 0.1 mmHg for DBP. Estimates of the association were larger for older compared to younger participants. In cross-population analyses, a 100 mmol 24-hour urinary sodium was associated with a 4.5 mmHg higher SBP and 2.3 mmHg higher DBP after adjustment for several important potential confounding variables.\textsuperscript{9} These estimates of the association between sodium intake and blood pressure are similar to those for the same age groups published in a meta-analysis of data from studies other than INTERSALT.\textsuperscript{10,11}

Randomized Controlled Trials

Randomized controlled clinical trials provide unbiased evidence for a causal relationship between dietary sodium intake and blood pressure. During the past 30 years, more than 80 randomized controlled trials have been conducted to explore the efficacy and effectiveness of changes in sodium consumption on blood pressure in hypertensive and normotensive participants.\textsuperscript{12-14} The findings from these trials have been summarized in three recent meta-analyses.\textsuperscript{12-14} There were differences in the eligibility criteria and statistical methods employed in the three meta-analyses but in each case a reduced intake of dietary sodium was associated with a significant diminution in blood pressure. As expected, the effect was smaller in normotensive people compared to hypertensive patients. For example, compared to the control group, the reported mean reduction in blood pressure was –3.9 to –5.9 mmHg for SBP and –1.9 to –3.8 mmHg for DBP in hypertensives; –1.2 to –1.9 mmHg for SBP and –0.3 to –1.1 mmHg for DBP in normotensives.\textsuperscript{12-14} Despite differences in study design, sample size, participant characteristics, initial level of blood pressure, and baseline dietary sodium intake among the trials, a significant dose-response relationship between net change in urinary sodium and net change in blood pressure was detected in both the hypertensive and normotensive trials.\textsuperscript{12,13}

Several recently published trials which were not included in these meta-analyses deserve mention.\textsuperscript{15-17} The Trial of Nonpharmacologic Interventions in the Elderly (TONE) was a randomized controlled trial designed to determine whether weight loss and/or a reduction in dietary sodium intake enhance blood pressure control and reduce the need for antihypertensive drug therapy in older people with hypertension. The trial was conducted in 975 hypertensives, aged 60–80 years, with baseline SBP <145 mmHg and DBP <85 mmHg on one antihypertensive medication.\textsuperscript{15} Using a factorial design, those meeting the National Center for Health Statistics criteria for overweight were randomly assigned to either counselling aimed at a reduction in sodium consumption, weight loss, combined sodium reduction and weight loss, or usual care. Those who were in the normal weight category were randomly assigned to either counselling aimed at sodium reduction or usual care. Those assigned to usual care received counselling in health-related topics remote to the goals of the trial but had the same investigator contact schedule as their counterparts who were assigned to the sodium reduction and/or weight loss counselling intervention arms. Mean 24-hour urinary sodium excretion was reduced by 40 mmol in those assigned to counselling in sodium reduction (alone) and by 24 mmol for those assigned to counselling in the combination of sodium reduction and weight loss. Prior to attempting tapering or withdrawal of antihypertensive medication a significant reduction in blood pressure was noted in those assigned to the active intervention groups compared to their counterparts in the usual care group. For example, average SBP in those assigned to counselling in sodium reduction alone was further reduced by 3.4 mmHg compared to the corresponding value in the usual care group. After 30 months, the per cent of participants who were free of an endpoint (blood pressure >150/90 mmHg, resumption of antihypertensive medication, or a blood pressure-related clinical complication) was 38% in those assigned to counselling in sodium reduction versus 24% in those assigned to usual care (\(P < 0.001\)). Cappuccio and colleagues conducted a double-blind crossover trial, in which 47 untreated elderly people (age range: 60–78 years, blood pressure range: 123–205/64–112 mmHg) were randomly assigned to a ‘usual’ salt intake (10 g/day) or modestly reduced dietary salt intake (5 g/day) group for a 2-month period.\textsuperscript{16} In this trial, a reduction in sodium intake of 83 mmol/day was significantly associated with a reduction of 7.2 mmHg in SBP and 3.2 mmHg in DBP. In the DASH-Sodium trial conducted in 412 people with average SBP of 120–159 mmHg and average DBP of 80–95 mmHg, reduction in sodium intake from a high (142 mmol/day) to an intermediate (107 mmol/day) level reduced SBP by 2.1 mmHg (\(P < 0.001\)) during consumption of a usual American control diet and by 1.3 mmHg (\(P = 0.03\)) during consumption of a
SALT, BLOOD PRESSURE AND HEALTH

Salt Intake and the Risk of Cardiovascular Disease

Two studies published by the same investigative team have been cited as providing evidence for an adverse effect of low sodium diet on human health. In the first of these studies, Alderman and colleagues reported the presence of a significant inverse association between urinary sodium excretion and incidence of myocardial infarction in a prospective cohort study conducted in 2937 treated hypertensive patients. As indicated in an accompanying editorial and in subsequent letters to the editor, however, unmeasured variables and imprecision in the measurement of potentially confounding variables might have contributed to the occurrence of this unexpected finding. In addition, urinary sodium excretion was measured after 5 days of reduced dietary sodium intake. This is likely to have resulted in an invalid assessment of an individual's habitual intake of dietary sodium. Finally, the study was conducted in hypertensive patients who were enrolled in a work-site treatment programme making it difficult to know whether the findings have general application. Given these and other considerations, we agree with others that the findings in this study are difficult, if not impossible to interpret. In a second study, Alderman and colleagues examined the relationship between dietary sodium intake and mortality from cardiovascular disease and all causes in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. They identified an inverse relationship between sodium intake and mortality from cardiovascular disease (P < 0.05) and all causes (P < 0.007) and a positive relationship between sodium/calorie ratio and mortality from cardiovascular diseases (P = 0.006) and all causes (P < 0.001). Again, however, methodological concerns make it difficult to interpret the findings in this study. For instance, the authors did not exclude participants with a baseline history of cardiovascular diseases in their main analysis, albeit such participants might be expected to have changed their dietary intake of sodium. In addition, they did not exclude participants who were already on a low sodium diet due to their health concerns at baseline. Acute rheumatic fever, chronic rheumatic heart disease and diseases of the pulmonary circulation were included as cardiovascular disease mortality outcomes although there is no obvious biological basis for a relationship between sodium intake and these outcomes. Perhaps of greatest concern is the fact that they included sodium intake, caloric intake, and sodium/calorie ratio as continuous variables in the same multivariate model. Given that an interaction term was included in their analysis model, it is not possible to interpret the main effect of sodium intake alone on the outcomes of interest. The inconsistency of the association between the two indicators of sodium intake (sodium alone and sodium/calorie ratio) and the corresponding outcomes of interest in Alderman’s study might reflect the heterogeneity of this relationship in a study population with different body weights.

In an independent examination of data from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study, we found a consistent and positive relationship between dietary sodium intake and risk of cardiovascular diseases and total mortality in overweight people. For an average caloric intake, a 100 mmol higher intake of dietary sodium was associated with a 32% increase in all-cause mortality (RR = 1.32; 95% CI: 1.07–1.64) in stroke incidence, an 89% increase in stroke mortality, a 44% increase in coronary heart disease mortality, and a 39% increase in mortality from all causes in the overweight. Dietary sodium intake was not significantly associated with risk of cardiovascular disease in participants with a normal weight. In a recently published prospective cohort study conducted in 1173 Finnish men and 1263 women aged 25–64 years, the hazard ratios for coronary heart disease, cardiovascular disease, and all-cause mortality, associated with a 100 mmol higher level of 24-hour urinary sodium excretion, were 1.51 (95% CI: 1.14–2.00), 1.45

Salt Intensity

The magnitude of the blood pressure reduction resulting from a lowering of dietary sodium varies among different population subgroups. The proportion of salt-sensitive and salt-resistant individuals has varied from one study to another based on the definition of salt-sensitivity and the methods used to assess its presence or absence. Both genetic and environmental factors may play an important role in determining salt-sensitivity. Results from several prospective cohort studies have suggested that salt-sensitivity increases the risk of cardiovascular disease and all-cause mortality. Morimoto and colleagues followed 62 salt sensitive hypertensive patients and 94 non-salt sensitive patients for an average of 7.3 years. Salt-sensitivity was defined as a difference of more than 10% in mean blood pressure between a lower-salt (1–3 g sodium chloride per day) and higher-salt diet (12–15 g sodium chloride per day) diet. Salt-sensitivity was associated with a 3-fold increase in SBP (RR = 3.05; 95% CI: 1.34–6.89) in the risk of cardiovascular disease. Weinberger et al. followed a cohort of 278 hypertensive and 430 normotensive participants for up to 27 years. Salt-sensitivity, determined at baseline by an individual's blood pressure response to sodium loading and depletion, was associated with a 73% increase in mortality (RR = 1.73; 95% CI: 1.02–2.94) in all-cause mortality. Due to the technical difficulties of performing such studies, population-based investigations to assess the frequency of salt-sensitivity in the general population have not been conducted. Based on the available data, however, a majority of hypertensive and normotensive people respond to sodium reduction. Therefore, one could expect that salt-sensitivity is a common phenomenon in human populations.

Salt-sensitivity is a common phenomenon in human populations.
(95% CI: 1.14–1.84), and 1.26 (95% CI: 1.06–1.50), respectively.28 There was a significant interaction between sodium excretion and body mass index for cardiovascular and total mortality, with sodium intake being a significant predictor of mortality in men who were overweight. These data support the premise that a lower intake of dietary sodium reduces the risk of subsequent cardiovascular disease, especially in those who are also concurrently overweight.

Public Health Implications of Reducing Dietary Salt

An intervention to lower blood pressure in the general population should not only result in a substantial reduction in the prevalence of hypertension but also a large decrease in cardiovascular risk. Cook and colleagues examined the potential impact of a population-wide reduction in blood pressure using data from the Framingham Heart Study and the National Health and Nutrition Examination Survey II.29 According to their estimates, a population-wide reduction in DBP of as little as 2 mmHg should result in a 17% reduction in the prevalence of hypertension, a 15% reduction in the risk of stroke and transient ischaemic attack and a 6% reduction in the risk of coronary heart disease.29 Further, they estimated that this blood pressure reduction would prevent 93% of the strokes and transient ischaemic attacks, as well as 100% of the incident coronary heart disease events that could be prevented by treatment of all hypertensive patients with antihypertensive drug therapy.29 The results underscore the potential value of complementing traditional hypertension detection and treatment approaches with public health interventions aimed at achieving a slight downward shift in the blood pressure of the general population.30

Conclusion

Evidence from animal experiments, observational studies, and randomized controlled trials provide overwhelming support for a causal relationship between dietary sodium intake and elevated blood pressure. Three large meta-analyses have provided consistent evidence of blood pressure lowering following a reduction in dietary sodium intake.12–14 In addition, results from the large TONE and DASH community-based trials and a recent trial by Cappuccio et al., provide additional confirmation that sodium reduction significantly lowers blood pressure in both hypertensive and normotensive populations.15–17 Recent prospective cohort studies indicate that a higher dietary intake of salt increases the risk of cardiovascular disease.28,29 The increasingly strong body of scientific evidence related to the relationship between dietary sodium and cardiovascular disease should lay to rest the long-standing controversy over whether sodium reduction lowers blood pressure and improves cardiovascular health in general population.

References


Response

Michael H Alderman

I appreciate the opportunity to review and comment on the four responses to my review of sodium and human health. The fair-minded assessment by Drs Freedman and Petitti is most valued, but I must admit to some disappointment at the less supportive reviews registered by Drs MacGregor, and Stamler and Elliott. I will try to briefly clarify the points I tried to make in the original piece.

First of all, I want to emphasize the wide areas of agreement. Sodium intake is related to blood pressure. Meta-analyses of more than 100 randomized clinical trials provide the best estimate of the aggregate effect produced by roughly halving dietary sodium intake, which is in the middle single-digit range for systolic, and the low single digits for diastolic blood pressure —more for hypertensive and less for normotensive subjects. But it is also well established that the aggregate changes in blood pressure associated with sodium restriction mask great individual variation. Moreover, reduction in sodium intake activates the renin angiotensin and sympathetic nervous systems, and increases insulin resistance. The human health effect of sodium variation is thus the sum of perturbations of these, and probably other unrecognized surrogate physiological endpoints. This net health impact cannot be determined by extrapolating from effects on selected surrogate, but requires a direct examination of the relation of sodium intake to the quality and duration of human life.

That leads to my second point. For the general population, there are no experimental studies to determine the impact of salt intake on morbidity and mortality. There are four published observational studies, and a fifth unpublished but widely presented observational study, linking a baseline measure of sodium intake with subsequent morbidity and mortality. Two of these show no association of sodium intake to outcome, two show a positive relation of dietary sodium to outcome among the obese minority and no relationship in the normal weight majority. The final study shows increased salt intake to be associated with longer survival. As I see it, this heterogeneity in health associations is the logical consequence of the genetic, behavioural, and environmental variety of humankind, and the well-demonstrated heterogeneity in physiological responses to reduced sodium intake. No doubt, it is this lack of compelling support from available observational studies that has kept any salt hypothesis from submission to an empirical test.

Finally, I tried to assess the role that sodium restriction might play in the management of hypertensive patients. Sodium restriction does lower the pressure of some, but not all hypertensive patients, and like other interventions, sodium restriction affects many non-blood pressure surrogate endpoints. To the disappointment of adherents to evidence-based medicine, there are no randomized studies to assess the net health effect suggested by changes in these surrogate endpoints among hypertensive patients. Indeed, only one observational study addresses the relationship of sodium intake to outcome. In that study of 3000 patients, a strong inverse relation of 24-hour urinary sodium to cardiovascular outcome was found. Because of the potential for confounding, physician scientists are wisely reluctant to draw therapeutic conclusions from that single observational study. Much ink has been spilled debating whether the one existing observed association is what it seems to be. Of course, were we to discount the one available study, data linking salt intake to health outcome would fall to zero! Perhaps it is time to repeat the study, avoiding its weaknesses. In the meantime, my own position is that sodium restriction is one of many interventions that can lower blood pressure. It is a relatively weak and costly intervention but, like others, it does lower the blood pressure of some patients. Based upon my understanding of evidence-based medicine, this approach should be reserved for higher risk patients in whom proven therapies are either inadequate or unacceptable. For this group, it seems likely that if salt restriction lowered pressure, benefit is more likely to result than harm.

Many respected and thoughtful scholars and policy makers would extrapolate from the positive segments in these data, and dismiss those which are at variance with their views. Others feel

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that it is generally safer to pay attention to all the data, particularly when they are inconsistent with preconceived beliefs. They would argue that change in the diets of millions of healthy people or hypertensive patients should be based on empirical evidence that the net result of such a change would be positive.

Where should we go from here? We could continue to dissect the few shards of data available to support or refute particular views, but I think opinion, no matter how passionately or widely espoused, is a poor substitute for solid scientific evidence when making medical or public health recommendations.
The photographs featured on the following pages are taken from *Southampton’s Women*, a collection of photographs of the daily lives of young women in the city of Southampton in the south of England taken by Magda Segal. The images, of women, their daily lives and the intimacy of their fridges, were taken to complement the Southampton Women’s Survey, a study of the diet, health and lifestyles of women aged 20–34 years. The study is assessing the influence of factors before and during pregnancy on the growth of the fetus. It forms part of the wider programme of work investigating the effects of the fetal environment on health outcomes in later life, known to epidemiologists as the ‘Fetal Origins Hypothesis’. Thanks to Magda Segal for permission to reproduce the images.

*Southampton’s Women* is published by the Medical Research Council Environmental Epidemiology Unit in 2000 (University of Southampton) ISBN 0 901723 25 8.
One of Southampton's women ...
... and the inside of her fridge