See corresponding Perspective on page 1020.

The dietary guideline for sodium: should we shake it up? Yes![1,2]

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ABSTRACT The dietary guidelines established under the auspices of public health policy are intended to promote healthy diets in the general public. The current recommendations for sodium intake stem from studies and publications that are older than much of the public they are designed to benefit. The past 2 decades have seen a dramatic increase in our knowledge of nutritional science, particularly our understanding of the role of sodium in blood pressure regulation. With a myriad of data from observational studies and randomized, controlled trials, we have the information to finally put sodium into its correct context in terms of its role in the regulation of blood pressure and hypertension. Not the sole and pervasive dietary villain it was once believed to be, sodium is but one factor in the complex interplay of multiple, inextricably related regulatory systems of which hypertension is the end result. With the data now available concerning dietary sodium, including the minimal and specific blood pressure effects of sodium in normotensive adults and both the benefits and risks of sodium reduction, future public health recommendations can be based on carefully acquired, consistent, and rational science. *Am J Clin Nutr* 2000;71:1013–9.

KEY WORDS Sodium, blood pressure, hypertension, nutrition policy, salt, dietary guidelines

INTRODUCTION

The long-held premise that salt is the dietary villain in the pathogenesis of hypertension has governed nonpharmacologic treatment of high blood pressure for decades. Despite its entrenchment in medical philosophy, this hypothesis has never been fully supported by either the researchers or the data in this area of investigation (1–8). The early 1980s brought an initial wave of published challenges to the purported sodium–blood pressure connection (3–7) that raised questions that, at the time, could not be answered fully. In recent years, however, the hold of the salt–blood pressure hypothesis has been severely weakened by a large volume of new information that has shown, with increasing clarity, that although dietary salt does play a role, it is certainly not the archenemy of normal blood pressure regulation.

The current dietary guideline for salt intake is based on a document that was published 20 y ago (9). The conclusions in that report were based on data acquired as many as 40 y before that. Considering the dramatic progress that has been made in nutrition research and science in just the past 5–10 y—including advancements in methodology and a broad expansion of knowledge regarding specific nutrients and their effects on disease states—it is obvious that any dietary guideline should be based on the most current and comprehensive information available. Here, we examine the historical justification for the current guideline, review the abundant contemporary data that disprove the commonly held salt–blood pressure hypothesis, and elucidate the need to incorporate verity into public health policy.

HISTORICAL PERSPECTIVE

Although sodium was alleged to be a possible factor in the pathogenesis of cardiovascular disease > 100 y ago (2), it was in the 1930s and 1940s that observations suggesting a pathogenetic and therapeutic rationale for such a role were reported. Publications from investigators at the Cleveland Clinic (10) and at Duke University (11) indicating an effect of sodium on blood pressure were predicated on experiments in impaired renal function. The work of Grollman et al (10) showed that if renal mass and blood flow were reduced in experimental animals, blood pressure increased predictably. Kempner (11) at Duke University reported that the malignant hypertension associated with renal insufficiency or failure could be greatly attenuated by an extremely-low-sodium diet.

This work prompted laboratory investigations such as those of Tobian and Binion (12) in the early 1950s, in which it was observed that the sodium content of blood vessels correlated with arterial pressure. Laboratories worldwide attempted to reproduce hypertension related to salt intake, but found that only an extreme manipulation of vertebrate physiology and nutrition would predictably produce elevated arterial pressure. In all of these investigative efforts, sodium chloride intakes were increased to amounts 10–20 times greater than those recommended for rodents, renal (excretory) mass was reduced to less than half, and mineralocorticoid hormones were administered in pharmacologic doses (13). Although these laboratory conditions do not reflect the circumstances extant in the human population, the reported effect of sodium on blood pressure in animal studies accomplished by dramatic physiologic manipulations was generally accepted and presumed to carry over to human blood pressure.

Dahl et al's (14) description of a genetically salt-sensitive rat in the early 1960s provided an acceptable alternative model that did not require surgical reduction in renal mass or administration of mineral-

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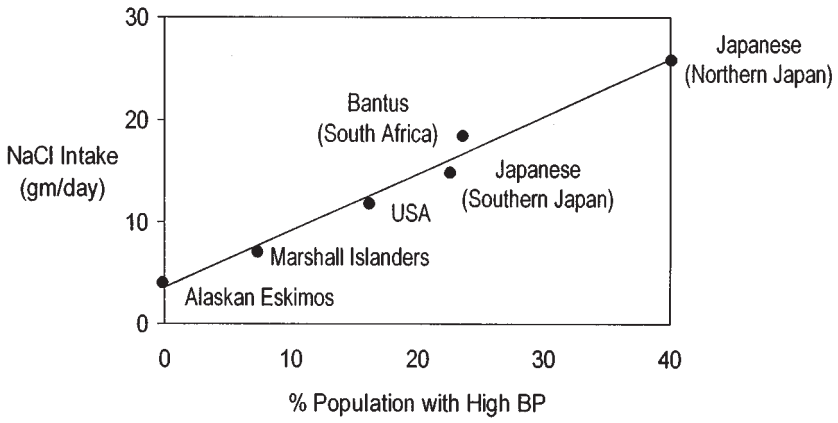

FIGURE 1. Published by Dahl to "prove" the linear relation between sodium intake and blood pressure across populations (15). Despite the lack of any published data to support the depiction, this graph has long been the cornerstone of the sodium–blood pressure myth. Reprinted with permission from Springer-Verlag.

ocorticoid hormones to produce salt-induced elevations in blood pressure. Often overlooked was the fact that the model still required the ingestion of sodium chloride in amounts 10–20 times higher than those recommended for rats. Again, this should have raised the question of the model's relevance to the human condition, but that did not occur. Dahl (15), however, recognized the importance of showing the existence of a dose-dependent effect of dietary sodium on blood pressure. He set out to show this effect over the assumed wide range of sodium chloride intakes worldwide in his now famous graph (**Figure 1**), which has been reproduced in numerous review articles and textbooks. However, there is no published information regarding the method used to acquire the data underlying its construction. It was not until more than 2 decades later that actual patterns of worldwide dietary sodium consumption were determined by carefully executed studies, such as Intersalt (16). The results from these studies do not agree with those in Dahl's graph.

In the late 1960s and early 1970s, investigators executed the first human studies of the effect of sodium restriction on blood pressure (17). Unfortunately, virtually all the results of these initial attempts to characterize the effect on blood pressure of reduced salt intakes were seriously flawed by design errors; most were uncontrolled, were not randomized, or used subjects who were taking blood pressure medication, and none studied individuals with normal blood pressures (18–20). It was not until the late 1970s that Luft et al (21, 22) initiated their landmark metabolic studies of the hemodynamic and hormonal effect of short-term manipulations of sodium chloride intake over the physiologic range in both normotensive and hypertensive subjects. However, publication of these findings followed the release of the 1979 Surgeon General's report (9), which, on the basis of earlier presumptions, labeled salt as a clear cause of high blood pressure; national health policy regarding salt intake was therefore set.

RUSH TO JUDGMENT

At the time of this rush to judgment, the only information regarding the role of salt in blood pressure control that was supported by valid scientific data was as follows:

1) Excessive sodium intake produced blood pressure increases under extreme conditions.
2) In patients with renal disease, blood pressure decreased with severe sodium restriction.
3) Animal studies suggested a possible genetic link.

Because these few facts fit the expected association between sodium and blood pressure based on presumed relations between sodium, fluid volume, and blood pressure, they were summarily accepted—without critical assessment—as the foundation of public health policy regarding dietary management of hypertension.

The critical information that was not known about the influence of sodium intake on blood pressure, when government guidelines regarding it were being established, included a vast number of issues that bear far more heavily on the relevance and rationality of national dietary recommendations for hypertension management than do the few pieces of information noted above. The missing data included *1*) carefully executed observational studies of the relation of salt intake to arterial pressure in humans and the prevalence of hypertension across populations; *2*) well-designed, randomized, controlled trials of the effects of sodium reduction on blood pressure in nonhypertensive and hypertensive humans; *3*) prospective assessments of the relation between salt intake and cardiovascular mortality; and *4*) information about nutrient interactions and the effects of dietary patterns, rather than of single nutrients, on blood pressure.

Lacking this information, numerous myths have grown up around the sodium–blood pressure hypothesis. Among these are the assumptions that sodium intake has increased dramatically over the past century, that humans consume far more sodium than they require, that the benefits of salt reduction observed under extreme conditions in early studies can be extrapolated to normal populations, that the results of animal studies can be applied directly to humans, and that effects of reduced dietary sodium would be uniform across populations. It was presumed that the high prevalence of hypertension in African Americans was attributable to high sodium intakes and that the blood pressure–lowering effect of diuretics in hypertensive persons was due to medication-induced increases in sodium excretion. At an individual level, it was assumed that modifying sodium intake would not affect the intakes of other nutrients, that nutrient interactions were not related to blood pressure regulation, that lower salt consumption would benefit every person, and that

TABLE 1
Summary of blood pressure changes observed in meta-analyses of randomized, controlled trials of sodium restriction

	Number of participants		Blood pressure changes			
			Hypertensive participants		Normotensive participants	
	Hypertensive	Normotensive	Systolic	Diastolic	Systolic	Diastolic
			mm Hg			
Cutler et al (28)	873	760	−4.9 (±1.3)[1]	−2.6 (±0.8)	−1.7 (±1.0)	−1.0 (±0.7)
Midgley et al (29)	1131	2374	−3.7 (2.35, 5.05)	−0.9 (−0.13, 1.85)	−1.0 (0.51, 1.56)	−0.1 (−0.32, 0.51)
Cutler et al (30)	1043	1689	−4.8 (±1.04)	−2.5 (±0.68)	−1.9 (±0.72)	−1.1 (±0.48)
Graudal et al (31)	2161	2581	−3.9 (3.0, 4.8)	−1.9 (1.3, 2.5)	−1.2 (0.6, 1.8)	−0.26 (−0.3, 0.9)

[1] $\bar{x}$; 95% CI in parentheses.

reduction of sodium intake could be easily accomplished and maintained.

Without evidence to support or refute these broad assumptions, they became commonly accepted beliefs for many people and "frantic orthodoxy" for others. The dynamic surrounding the propagation of these myths might be explained by the phrase attributed to Reinhold Niebuhr that frantic orthodoxy is never rooted in faith but in doubt; those who are not sure are doubly sure. Considering the battle that has long raged around this hypothesis, despite the deluge of data it has spawned over the past 50 y, it would seem that it is not science that is motivating the controversy but rather the entrenched opinions of the scientists who are involved in it (1).

DISMANTLING THE MYTHS

A thorough review of the medical literature since the early 1980s indicates several important aspects of the dietary salt–hypertension paradigm that challenge many of the myths that had become dogma for the medical community and the public alike. The essence of the transition in the science on this topic in the past 20 y is the acquisition of extensive data in humans, which has elucidated several aspects of the relation between sodium chloride intake and hypertension that had not been addressed at the time public policy was first set.

Sodium sensitivity

The disparate results of sodium trials have contributed greatly to the lack of consensus within the scientific community regarding the effect of sodium intake on blood pressure regulation. One consistent feature of the results of these studies has been their heterogeneity, with individual blood pressures varying widely in response to the dietary intervention. With higher or lower sodium intakes, blood pressures were reported to decrease, increase, and remain stable in participants within the same studies (13, 23, 24). This is clearly shown in the results of a study by Overlack et al (25), who investigated this heterogeneity. They found that ≈18% of 163 participants with a high salt intake had blood pressure increases >5 mm Hg, whereas ≈15% had blood pressure decreases >5 mm Hg, with changes of <5 mm Hg in 66% of participants.

An individual's blood pressure response to changes in sodium intake is determined by whether or not she or he is salt sensitive. Those whose blood pressure changes in response to altered sodium intake are considered salt sensitive, whereas those in whom changes in sodium intake do not elicit a blood pressure response are considered salt resistant. The concept of salt-sensitivity was initially put forth in the late 1970s (26) and has become the subject of widespread investigation in recent years (23, 27). Salt-sensitivity has now been shown to be a reproducible phenomenon (24), but as yet there is not a specific definition of what constitutes a salt-sensitive response or an accepted means of predetermining this condition.

Population studies

The National Heart, Lung, and Blood Institute (NHLBI)-funded Intersalt trial (16), initiated in 1984, was designed to finally answer the questions surrounding Dahl's unproved postulates of 20 y earlier (14, 15) and to provide reliable data regarding sodium intakes and blood pressures between and within cultures. Intersalt used standardized methods for collection and analysis of 24-h urine samples and random-zero blood pressure measurements. More than 10 000 subjects participated in the study, recruited at 52 centers in 32 countries worldwide. Sodium excretion ranged from 0.2 to 242 mmol/d; however, in 48 of the centers, the range was only 100–242 mmol/d. Sodium excretion was related to blood pressure in individuals, but the relation was not robust. When data from the 4 centers with the lowest intakes were deleted, no relation could be identified. Assessment of the slope of blood pressure with age within the centers identified a relation between that variable and median sodium excretion. As stated by the authors of the original Intersalt publication: "Across the other 48 centres sodium was… not [significantly related] to median blood pressure or prevalence of high blood pressure" (16). Thus, the alleged close relation between salt intake and blood pressure, as hypothesized by Dahl, could not be shown.

Meta-analyses

In the past decade, several investigative groups, using the advanced tools of summary statistical analysis, reported meta-analyses of sufficient numbers of randomized, controlled trials of sodium restriction in both hypertensive and normotensive subjects to precisely establish the blood pressure effect of moderate sodium restriction (28–31). Although the interpretation of the meta-analysis findings by the 3 investigative groups differed, as shown in **Table 1**, the numbers (ie, magnitude of blood pressure reduction) did not. On average, systolic blood pressure in normotensive populations was lowered by ≈1 mm Hg when salt intake was reduced from 30% to 50%, depending on the trial. These results do not come even close to the perceived effect that has long been postulated by the advocates of sodium restriction and are an inadequate defense of the extensive efforts of government

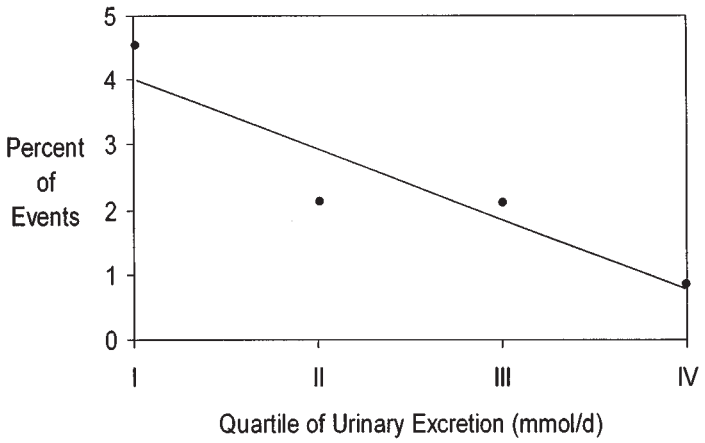

FIGURE 2. Fitting a linear regression between quartiles of urinary sodium and proportions of myocardial events, Alderman et al (36) showed a significant linear trend in these data from a prospective cohort study of men with hypertension. Reprinted with permission from Lippincott Williams & Wilkins.

health organizations to influence public health policy recommendations for population-wide sodium restriction.

Cardiovascular disease outcomes

Accepting the results of well-designed and -executed epidemiologic and clinical studies is critical to determining the appropriateness of a public health initiative; of at least equal importance, with regard to setting policy, is definitive proof of the benefit of sodium reduction for reduced cardiovascular disease mortality. It is this evidence that is most essential to the decision to establish dietary recommendations for the general population regarding dietary salt intake—it is obviously not in society's best interest to expend resources on a public health initiative that is not going to reduce premature morbidity and mortality. In recent years, an increasing number of reports of adverse effects of restricted sodium intake have been published (31–37). Notably, drawing on 2 federally funded databases, Alderman et al (36, 37) reported that in stark contrast with perceived wisdom, reduced sodium intake is associated with increased fatal and nonfatal cardiovascular events (**Figure 2**).

These 2 reports prompted immediate and harsh criticism from the supporters of sodium restriction, who turned to other databases to discredit the findings (38). At the 1997 annual meeting of the American Society of Hypertension, Cutler presented an analysis of the Multiple Risk Factor Intervention Trial (MRFIT) follow-up data (Cutler JA, unpublished observations, May 1997). Before adjustment for confounders, these data showed the same disturbing trends as those identified by Alderman et al; with adjustment, no adverse cardiovascular effects were observed. Of equal or perhaps greater importance to public policy, Cutler could identify no benefit of sodium restriction in terms of reduced cardiovascular morbidity or mortality. Since then, the Scottish Heart Health Study (39), a Finnish report presented at the 1998 American Heart Association (AHA) annual meeting (40), and an analysis of the second National Health and Nutrition Examination Survey (NHANES) follow-up data presented in January 1999 at the NHLBI Workshop on Sodium and Blood Pressure (Cohen J, unpublished observations, January 1999) have all reported no identifiable benefit of lower-sodium diets on cardiovascular mortality. Thus, although questions of the safety of low-sodium diets may be unresolved, there are now ≥6 studies, involving tens of thousands of high-risk individuals followed for many years, that failed to show any long-term cardiovascular benefit of a lower-sodium diet. Given these consistent findings from well-designed observational studies, the likelihood seems bleak that a policy of population-wide reduction in sodium chloride intake will have any meaningful benefit in terms of reducing cardiovascular endpoints for healthy individuals.

Nutrient interactions

Another area of data that has emerged in the past 2 decades is information on nutrient interactions and the effect on blood pressure of the overall diet rather than single nutrients. Had these data been available previously, they would likely have shaped a very different federal policy on diet and hypertension. We now have evidence of the major role of nutrient interactions in the prevention and treatment of high blood pressure. Kotchen et al (41) first reported that the hypertensive effect of sodium chloride in Dahl salt-sensitive rats is preceded by the emergence of disturbances in calcium homeostasis. In humans, Kurtz and Morris (42) postulated that the induction of calciuresis may indicate a mechanism by which sodium chloride raises blood pressure. A protective effect of potassium on blood pressure elevation is suggested by the clinical data of Krishna et al (43), who observed that severe, short-term potassium restriction induces salt sensitivity in normotensive humans, and by the epidemiologic findings of Khaw and Barrett-Connor (44), which indicate that adequate potassium intake protects against adverse effects of sodium chloride on blood pressure regulation.

In the index report that characterized the calciuresis of essential hypertension, this metabolic defect was reported to be more evident at higher rates of urinary sodium excretion (45). Similar observations have now been noted in both experimental (41, 46) and human studies (47, 48). Hamet et al (49) reported that individuals consuming high amounts of sodium chloride could fall into the highest or lowest blood pressure group depending on whether they were consuming deficient or adequate amounts of calcium. On the basis of their analysis of the NHANES I database, McCarron et al (50) reported a weak inverse relation between sodium intake and blood pressure that was later sup-

ported by Gruchow et al (51), using the same database, who reported that higher sodium chloride intake with adequate calcium and potassium intakes was indeed related to lower blood pressure. Collectively, these data concerning effects of physiologic interactions among electrolytes on blood pressure show that these electrolytes do not function independently. Thus, it is adequate consumption of all essential nutrients rather than modification of any single nutrient that should be the focus of population-wide dietary recommendations for blood pressure reduction.

Dietary patterns

Although clues existed before 1980 that other nutrients or dietary factors might be more important than the isolated nutrient sodium, 2 articles published in *Science* in the early 1980s (50, 52) raised the specific possibility that multiple dietary components—such as dairy products and fruit and vegetables—had much greater influence on an individual's blood pressure than did any single dietary component. Since then, numerous epidemiologic studies (53–55); randomized, controlled trials (56, 57); and laboratory studies (58) have verified the critical blood pressure benefit of the calcium, potassium, magnesium, phosphorus, and fiber that would be included in a diet containing adequate amounts of dairy products and fruit and vegetables.

The definitive clinical trial in this area is the Dietary Approaches to Stop Hypertension (DASH) study, the results of which were published in the *New England Journal of Medicine* in 1997 (59). This NHLBI-sponsored intervention trial assessed the effects of dietary patterns rather than of single nutrients on blood pressure in at-risk subjects. The DASH study tested the typical American diet—high fat, low fiber, and low mineral—against *1*) a diet rich in fruit and vegetables, and *2*) the fruit-and-vegetables diet combined with low-fat dairy products (the DASH diet). Sodium intake and weight were kept stable throughout the intervention.

With the DASH diet, systolic blood pressure was reduced by 5 mm Hg more and diastolic pressure by 3.0 mm Hg more than with the control diet. Blood pressure reductions with the fruit-and-vegetables diet compared with the control diet were also highly significant, but were only about half (2.8 mm Hg systolic and 1.1 mm Hg diastolic) of those achieved with the DASH diet. In persons with mild hypertension, the DASH diet reduced systolic blood pressure by 11.4 mm Hg and diastolic blood pressure by 5.5 mm Hg. The effect of this diet is 3–5 times greater than the best results reported from any salt restriction study in mild-to-borderline hypertension.

With the results of the DASH study, we finally have clear and strong evidence of where the emphasis of our nutrition policy should be placed to improve the nation's blood pressure profile—on correcting the mineral deficiencies extant and worsening in the adult population. Encouraging increased consumption of low-fat dairy products and fruit and vegetables holds far greater potential for improving society's cardiovascular risk profile through improved blood pressure control than does focusing on altering the intake of any single nutrient. Of equal or perhaps greater importance is the fact that such a strategy is consistent with other aspects of national nutrition policy for reducing the risk of osteoporosis and cancer (60, 61).

SEEKING CONSENSUS

In January 1999, the NHLBI of the National Institutes of Health (NIH) convened the NHLBI Workshop on Sodium and Blood Pressure to discuss the most current data available in this area of scientific research for the purpose of assessing the current criteria by which public health recommendations regarding sodium intake are established. The outcomes of these proceedings have not yet been published, but several points gained general agreement among many of the investigators in attendance. These individuals included nationally and internationally recognized scientists and physicians in the field of sodium and blood pressure and officials representing the NIH, NHLBI, Food and Drug Administration, US Department of Agriculture, and AHA.

The data presented at this symposium led the participants to conclude that the following previously debated issues were now resolved. It was agreed that sodium restriction is likely to be most beneficial for older persons with established hypertension; that the results of the randomized, controlled trials of sodium reduction show only a minimal effect on blood pressure in the general population; and that only a minority of the US population is sensitive to the hypertensive effects of sodium. Independent statistics experts reported that the Intersalt analyses are inappropriate for arguing that a reduction in salt intake would reduce the rate of increase in blood pressure with age—the argument consistently used by the advocates of sodium chloride restriction. Furthermore, it was pointed out that mineral deficiency likely accounts for much of the sensitivity to sodium, and that a nutrient-complete diet, ie, the DASH diet, can produce far greater blood pressure improvements than can be achieved with sodium restriction. Finally, it was acknowledged that there may be adverse effects associated with reduced sodium intake and that there is little evidence that lowering sodium intake will improve cardiovascular outcomes.

PUBLIC HEALTH POLICY

By definition, public health policy is intended to promote the health of the public. If such policy is to accomplish this goal, the policy must meet criteria established to promote public health. A public health policy recommendation can be justified only if the answers to the following questions are all "yes":

1) Will its implementation benefit most of the population?
2) Will the benefit be significant across the general population?
3) Is it the most effective means of achieving the stated goal?
4) Is it safe?
5) Will it reduce the incidence of cardiovascular disease endpoints?

When recommending specific sodium intakes to reduce blood pressure or reduce the risk of developing hypertension, not one of these questions can be answered with an unequivocal "yes." Therefore, we have the answer to the question posed by the title of this paper: "should we shake up the dietary guideline for sodium?" Unequivocally yes.

REFERENCES

1. Taubes G. The (political) science of salt. Science 1998;281:898–907.
2. Porter GA. Chronology of the sodium hypothesis and hypertension. Ann Intern Med 1983;93:720–3.
3. Kolata G. Value of a low-sodium diet questioned. Science 1982; 216:38–9.
4. Laragh JH, Pecker MS. Dietary sodium and essential hypertension: some myths, hopes, and truths. Ann Intern Med 1983;98:735–43.
5. Brown JJ, Lever AF, Robertson JIS, et al. Salt and hypertension. Lancet 1984;2:456 (letter).
6. McCarron DA. Is calcium more important than sodium in the pathogenesis of essential hypertension? Hypertension 1985;7:607–27.

7. Swales JD. Salt saga continued: salt has only small importance in hypertension. BMJ 1988;297:307–8.
8. McCarron DA. Diet and blood pressure—the paradigm shift. Science 1998;281:933–4.
9. US Department of Health, Education, and Welfare. Healthy people: Surgeon General's report on health promotion and disease prevention. Washington, DC: US Government Printing Office, 1979.
10. Grollman A, Shapiro AP, Gafford G. The volume of the extracellular fluid in experimental and human hypertension. J Clin Invest 1953;32:312–6.
11. Kempner W. Treatment of hypertensive vascular disease with rice diet. Am J Med 1948;4:545–77.
12. Tobian L Jr, Binion JT. Tissue cations and water in arterial hypertension. Circulation 1952;5:754–8.
13. Muntzel M, Drüeke T. A comprehensive review of the salt and blood pressure relationship. Am J Hypertens 1992;5:1S–42S.
14. Dahl LK, Heine M, Tassinari L. Effects of chronic excess salt ingestion: evidence that genetic factors play an important role in susceptibility to experimental hypertension. J Exp Med 1962;115:1173–90.
15. Dahl LK. Possible role of salt intake in the development of essential hypertension. In: Bock KD, Cottier PT, eds. Essential hypertension. Berlin: Springer-Verlag, 1960:53.
16. Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24-hour urinary sodium and potassium excretion. BMJ 1988;297:319–28.
17. Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? III. Analysis of data from trials of salt reduction. BMJ 1991;302:819–24.
18. Parijs J, Joosens JB, Linden LV, Verstreken G, Amery AKPC. Moderate sodium restriction and diuretics in the treatment of hypertension. Am Heart J 1973;85:22–34.
19. Morgan T, Gillies A, Morgan G, Adam W, Wilson M, Carney S. Hypertension treated by salt restriction. Lancet 1978;1:227–30.
20. Longworth DK, Drayer JIM, Weber MA, Laragh JH. Divergent blood pressure responses during short-term sodium restriction in hypertension. Clin Pharmacol Ther 1980;27:544–6.
21. Luft FC, Grim CE, Willis LR, et al. Natriuretic response to saline infusion in normotensive and hypertensive man. The role of renin suppression in exaggerated natriuresis. Circulation 1977;55:779–84.
22. Luft FC, Grim CE, Fineberg N, Weinberger MC. Effects of volume expansion and contraction in normotensive whites, blacks, and subjects of different ages. Circulation 1979;59:643–50.
23. Luft FC. Salt and hypertension at the close of the millennium. Klin Wochenschr 1998;110:459–66.
24. Luft FC, Weinberger MH. Heterogeneous responses to changes in dietary salt intake: the salt-sensitivity paradigm. Am J Clin Nutr 1997;65(suppl):612S–7S.
25. Overlack A, Ruppert M, Kolloch R, et al. Divergent hemodynamic and hormonal responses to varying salt intake in normotensive subjects. Hypertension 1993;22:331–8.
26. Kawasaki T, Delea CS, Bartter FC, Smith H. The effect of high-sodium and low-sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. Am J Med 1978;64:193–8.
27. Weinberger MH, Miller JZ, Luft FC, Grim CE, Fineberg NS. Definitions and characteristics of sodium sensitivity and blood pressure resistance. Hypertension 1986;8(suppl):II–127–34.
28. Cutler JA, Follmann D, Elliott P, Suh IL. An overview of randomized trials of sodium reduction and blood pressure. Hypertension 1991;17(suppl):I–27–33.
29. Midgley JP, Matthew AG, Greenwood CM, Logan AG. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. JAMA 1996;275:1590–7.
30. Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: an overview. Am J Clin Nutr 1997;65(suppl):643S–51S.
31. Graudal NA, Galløe AM, Garred P. Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride. A meta-analysis. JAMA 1998;279:1383–91.
32. Masugi F, Ogihara T, Hashizume K, Hasegawa T, Sakaguchi K, Kumahara Y. Changes in plasma lipids and uric acid with sodium loading and sodium depletion in patients with essential hypertension. J Hum Hypertens 1988;1:293–8.
33. Weder AB, Egan BM. Potential deleterious impact of dietary salt restriction on cardiovascular risk factors. Klin Wochenschr 1991; 69(suppl):45–50.
34. Iwaoka T, Umeda T, Ohno M, Inoue J, Sato T, Kawakami I. The effect of low and high NaCl diets on oral glucose tolerance. Klin Wochenschr 1988;66:724–8.
35. Lind L, Lithell H, Gustafsson IB, Pollare T, Ljunghall S. Metabolic cardiovascular risk factors and sodium sensitivity in hypertensive patients. Am J Hypertens 1992;5:502–5.
36. Alderman MH, Madhavan S, Cohen H. Low urinary sodium associated with greater risk of myocardial infarction among treated hypertensive men. Hypertension 1995;25:1144–52.
37. Alderman MH, Cohen H, Madhavan S. Dietary sodium intake and mortality: the National Health and Nutrition Examination Survey (NHANES I). Lancet 1998;351:781–5.
38. Cook NR, Cutler JA, Hennekens CH. An unexpected result for sodium—causal or casual? Hypertension 1995;25:1153–4.
39. Tunstall-Pedoe H, Woodward M, Tavendale, et al. Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish Heart Health Study: cohort study. BMJ 1997;315:722–9.
40. Valkonen V-P, Voutilainen S, Myyssonen, et al. Sodium and potassium excretion and the risk of acute myocardial infarction. Circulation 1998;98(suppl):I–374 (no. 1962). [Erratum: per the authors, the final sentence is incorrect; no relationship was observed.]
41. Kotchen TA, Ott CE, Whitescarver SA, et al. Calcium and calcium regulating hormones in the "prehypertensive" Dahl salt sensitive rat (calcium and salt sensitive hypertension). Am J Hypertens 1989; 2:747–53.
42. Kurtz TW, Morris RC. Dietary chloride as a determinant of "sodium-dependent" hypertension in men. N Engl J Med 1987;317: 1043–8.
43. Krishna GG, Miller E, Kapoor S. Increased blood pressure during potassium depletion in normotensive men. N Engl J Med 1989; 320:1177–82.
44. Khaw K-T, Barrett-Connor E. Dietary potassium and stroke-associated mortality. A 12-year prospective population study. N Engl J Med 1987;316:235–40.
45. McCarron DA, Pingree PA, Rubin RJ, et al. Enhanced parathyroid function in essential hypertension: a homeostatic response to a urinary calcium leak. Hypertension 1980;2:162–8.
46. Kurtz TW, Morris RC Jr. Dietary chloride as a determinant of disordered calcium metabolism in salt-dependent hypertension. Life Sci 1985;36:921–9.
47. Luft FC, Zemel MB, Sowers JR, et al. Sodium carbonate and sodium chloride: effects on blood pressure and electrolyte homeostasis in normal and hypertensive men. J Hypertens 1990;8: 663–6.
48. Strazzullo P, Nunziata V, Cirillo M, et al. Abnormalities of calcium metabolism in essential hypertension. Clin Sci 1983;65:37–41.
49. Hamet P, Daignault-Gelinas M, Lambert J, et al. Epidemiological evidence of an interaction between calcium and sodium intake impacting on blood pressure. Am J Hypertens 1992;5:378–85.
50. McCarron DA, Morris CD, Henry HJ, Stanton JL. Blood pressure and nutrient intake in the United States. Science 1984;24: 1392–8.
51. Gruchow HW, Sobocinski KA, Barboriak JJ. Calcium intake and the relationship of dietary sodium and potassium to blood pressure. Am J Clin Nutr 1988;48:1463–70.
52. McCarron DA, Morris C, Cole C. Dietary calcium in human hypertension. Science 1982;217:267–9.
53. Witteman JCM, Willett WC, Stampfer MJ, et al. A prospective study of nutritional factors and hypertension among US women. Circulation 1989;80:1320–7.

54. Ascherio A, Rimm EB, Giovannucci EL, et al. A prospective study of nutritional factors and hypertension among US men. Circulation 1992;86:1475–84.
55. Birkett NJ. Comments on a meta-analysis on the relationship between dietary calcium intake and blood pressure. Am J Epidemiol 1998;148:223–8.
56. Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. JAMA 1997;277:1624–32.
57. Bucher HC, Cook RJ, Guyatt GH, et al. Effects of dietary calcium supplementation on blood pressure: a meta-analysis of randomized controlled trials. JAMA 1996;275:1016–22.
58. Hatton DC, McCarron DA. Dietary calcium and blood pressure in experimental models of hypertension: a review. Hypertension 1994; 23:513–30.
59. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. N Engl J Med 1997; 336:1117–24.
60. NIH Consensus Development Panel on Optimal Calcium Intake. Optimal calcium intake. JAMA 1994;272:1942–8.
61. Dietary Guidelines Advisory Committee, US Department of Agriculture and US Department of Health and Human Services. Nutrition and your health: dietary guidelines for Americans. Washington, DC: US Government Printing Office, 1995.