

# The INTERSALT Study: background, methods, findings, and implications<sup>1-3</sup>

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**ABSTRACT** The INTERSALT Study is a standardized, worldwide epidemiologic study of large sample size ( $n = 10\,079$  men and women aged 20–59 y from 32 countries) that tested both within- and cross-population prior hypotheses on 24-h sodium excretion and blood pressure. For individuals, a significant, positive, independent linear relation between 24-h sodium excretion and systolic blood pressure (SBP) was found. With multivariate adjustment for underestimation, the estimated effect of a sodium intake higher by 100 mmol/d was higher SBP/DBP (diastolic blood pressure) by  $\approx 3.6/0.3$  mm Hg. This relation prevailed for both men and women, for younger and older people, and for 8344 people without hypertension. In tests of prior cross-population hypotheses ( $n = 52$ ), significant, independent relations were found between sample 24-h median urinary sodium excretion and sample median SBP and DBP, prevalence rate of hypertension, and slope of SBP and DBP from age 20 to 59 y (median sodium intake greater by 100 mmol/d was associated with a 30-y increase in SBP/DBP, ie, at the age of 55 y compared with 25 y, of 10–11/6 mm Hg). The INTERSALT results, which agree with findings from other diverse studies, including data from clinical observations, therapeutic interventions, randomized controlled trials, animal experiments, physiologic investigations, evolutionary biology research, anthropologic research, and epidemiologic studies, support the judgment that habitual high salt intake is one of the quantitatively important, preventable mass exposures causing the unfavorable population-wide blood pressure pattern that is a major risk factor for epidemic cardiovascular disease. *Am J Clin Nutr* 1997;65(suppl):626S–42S.

**KEY WORDS** Sodium, salt intake, blood pressure, INTERSALT Study, cardiovascular diseases

## BACKGROUND FINDINGS RELATED TO THE INTERSALT STUDY AND TO ASSESSMENT OF ITS RESULTS AND IMPLICATIONS

This report focuses on facts related to disease origins, not mechanisms (1), that is, the many facts showing that habitual high salt intake is one of several key mass exposures producing adverse blood pressure in a majority of adults aged  $\geq 35$  y (2), and particularly data from the international cooperative INTERSALT Study. Because sound judgment on the role of dietary salt in high blood pressure requires consideration of all the evidence from all research methods, INTERSALT findings are presented here in the context of key results from clinical,

animal-experimental, epidemiologic, evolutionary biological, and anthropologic investigations.

### The population-wide blood pressure problem

To grasp the importance of the relation of dietary salt to blood pressure, one must first appreciate that the blood pressure problem is virtually population-wide and not limited to the minority of adults (43 000 000 Americans) with frank hypertension [ie, systolic blood pressure (SBP)  $\geq 140$  mm Hg, diastolic blood pressure (DBP)  $\geq 90$  mm Hg, or receiving antihypertensive drug treatment] (2–6). This is documented in data from many large-scale, prospective epidemiologic studies (6), as illustrated in **Table 1** for data from a cohort of  $\approx 350\,000$  men aged 35–57 y in 1973–1975 when screened in 18 US cities in the recruitment effort of the Multiple Risk Factor Intervention Trial (MRFIT). Only 18% had optimal blood pressure at baseline. For every other blood pressure stratum, risks of death from ischemic heart disease, stroke, and all causes were progressively and significantly increased. These relations of SBP/DBP to risk were manifest for both nonsmokers and smokers, for men at all levels of serum cholesterol concentrations, and for African American, Asian, Hispanic, and non-Hispanic white men (*see* references 5 and 6 for similar findings on women). All these risk estimates are underestimates quantitatively because they are based on blood pressure measured at a single visit for each man, without correction for regression-dilution bias (4). For less-educated Americans the situation is even worse because they have even higher SBP/DBP values (7–10). These findings indicate that for research the primary problem requiring clarification is not

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<sup>2</sup> The INTERSALT Study was supported by the National Heart, Lung and Blood Institute (United States); the Wellcome Trust (United Kingdom); the International Society of Hypertension; the World Health Organization; the Heart Foundations of Canada, Great Britain, Japan, and Netherlands; the Chicago Health Research Foundation; the FWGO-FMRS (Belgian National Research Foundation); and the ASLK-CGER (Parastatal Insurance Company, Brussels). Other research by the author and his colleagues reported here was supported by the American Heart Association and its Chicago and Illinois Affiliates; the Illinois Regional Medical Program; the National Heart, Lung and Blood Institute; and many private donors.

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TABLE 1

Baseline blood pressure, JNC-V strata, and mortality by cause for men screened for the Multiple Risk Factor Intervention Trial<sup>1</sup>

Blood pressure stratum	Ischemic heart disease mortality		Stroke mortality		All mortality	
	Percentage <sup>2</sup>	Relative risk <sup>3</sup>	Percentage <sup>2</sup>	Relative risk <sup>3</sup>	Percentage <sup>2</sup>	Relative risk <sup>3</sup>
	%		%		%	
Optimal ( <i>n</i> = 63 371; 18.2%)	1.4	1.00	0.10	1.00	6.1	1.00
Normal, not optimal ( <i>n</i> = 85 273; 24.5%)	1.9	1.31 <sup>4</sup>	0.19	1.73 <sup>4</sup>	7.2	1.11 <sup>4</sup>
High normal ( <i>n</i> = 77 248; 22.2%)	2.6	1.61 <sup>4</sup>	0.24	2.14 <sup>4</sup>	8.4	1.23 <sup>4</sup>
High blood pressure						
Stage 1 ( <i>n</i> = 90 015; 25.9%)	4.1	2.33 <sup>4</sup>	0.45	3.58 <sup>4</sup>	11.4	1.65 <sup>4</sup>
Stage 2 ( <i>n</i> = 24 744; 7.1%)	6.3	3.20 <sup>4</sup>	0.83	6.90 <sup>4</sup>	16.2	2.04 <sup>4</sup>
Stage 3 ( <i>n</i> = 5783; 1.7%)	9.3	4.64 <sup>4</sup>	1.57	9.66 <sup>4</sup>	22.8	2.77 <sup>4</sup>
Stage 4 ( <i>n</i> = 1544; 0.4%)	12.6	6.88 <sup>4</sup>	3.05	19.19 <sup>4</sup>	29.5	3.83 <sup>4</sup>

<sup>1</sup> *n* = 347 978 men free of myocardial infarction history at baseline. Blood pressure strata are as follows (SBP, systolic blood pressure; DBP, diastolic blood pressure): optimal, SBP <120 and DBP <80; normal, not optimal, SBP 120–129/DBP <85 or SBP <130/DBP 80–84; high normal, SBP 130–139/DBP <90 or SBP <140/DBP 85–89; HBP stage 1, SBP 140–159/DBP <100 or SBP <160/DBP 90–99; HBP stage 2, SBP 160–179/DBP <110 or SBP <180/DBP 100–109; HBP stage 3, SBP 180–209/DBP <120 or SBP <210/DBP 110–119; HBP stage 4, SBP ≥210 or DBP ≥120 mm Hg. JNC-V, Fifth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure. From reference 7.

<sup>2</sup> Cumulative percentage dying in 15 y; data from reference 6.

<sup>3</sup> Relative risk adjusted by proportional-hazards regression model stratified by clinic and adjusted for baseline age, race, income, serum cholesterol, cigarettes smoked/d, and use of medication for diabetes.

<sup>4</sup> *P* < 0.001.

origins of hypertension, but rather origins of the generally adverse SBP/DBP values throughout the population and causes of the rarity of optimal SBP/DBP values in persons aged ≥ 35 y (11, 12).

Adverse SBP/DBP values in persons aged ≥ 35 y result from sizable upward slopes of SBP and DBP with age, from youth through young adulthood and middle age (3, 13–17). For example, for 48 of 52 population samples from around the world in the INTERSALT Study (ie, for all samples except 4 remote ones with habitual low salt intake), slopes of both SBP and DBP from the age of 20 y to 59 y were positive and significant (14, 15). On average, for persons aged 55 y compared with those aged 25 y, SBP/DBP was higher by 15/11 mm Hg.

Data from long-term studies of cohorts followed prospectively from youth into late middle age confirm that SBP/DBP rises with age during adulthood (13). These data also show that, although degree of change in blood pressure with age varies among individuals, blood pressure does rise with age in most persons, and < 20% do not register increases. Thus, an increase in SBP/DBP with age is likely, but not inevitable.

### Findings on salt and blood pressure from other studies

#### *Clinical observations, clinical interventions, and randomized controlled trials*

About 4500 y ago, the following was noted in the Chinese Yellow Emperor's classic of internal medicine *Nei Ching*: "Hence if too much salt is used for food, the pulse hardens. . ." (18). A hard pulse is, of course, a sign of possible high blood pressure. This was only a few millennia after mankind made the transition from food gathering to food producing, and, as a consequence, began adding salt to preserve food, thus shifting from habitual low salt intake toward high salt intake.

Blood pressure measurement came only after Riva-Rocci's (19) invention of the indirect method, reported in 1896. Not long after, in 1904, Ambard and Beaujard (20) in France

reported that treatment of hypertensive patients with a low-salt diet reduced blood pressure. In the United States, Allen and Sherrill (21) verified this finding in the early 1920s, followed by Kempner (22) in the 1940s, then by many others. This research culminated with the demonstration in the 1950s of the antihypertensive efficacy of oral thiazide, a natriuretic.

Dietary therapy initially involved very low salt intakes for patients with severe high blood pressure (20–22). Beginning in the 1970s, trials were undertaken on the effects of moderate dietary salt reduction in adults with less severe high blood pressure or blood pressure in the nonhypertensive range. In the 1990s five overviews (meta-analyses) have been published on results of salt reduction trials (23–27). Critical review of the individual trials and of the overviews is beyond the scope of this paper. Briefly, as to the individual trials, there are multiple problems with many of them regarding design and methods (23), eg, sample sizes (generally small), duration (generally short), approaches to blinding (limited), information on possible confounding variables (limited), and assessment of degree of sodium reduction achieved (limited). In many trials, estimates of net decreases in sodium intake, based on urine collection, may have been biased overestimates, reflecting the difficulties of validly assessing adherence in free-living participants.

As to the trial overviews, meta-analyses—like other research tools—have limitations and problems. A primary one is the selection of trials to include in the analyses (28). Thus, one overview dealt with 24 studies (23), another with 78 (25), and the most recent with 56 (27). A second problem is the approach taken to possible heterogeneity of findings across trials. If present, why? And is it scientifically sound to pool data in a single meta-analysis? Further, conclusions of questionable validity can result not only because of method flaws in meta-analysis, but also because of unsound generalization unwarranted by the findings (28–31). In this regard, sound judgments on the pivotal issue, the etiologic significance of a relation such as that between dietary salt and blood pressure, must be based

on the totality of research findings from all investigative methods. Meta-analysis of trials is not a method that generates results and conclusions that override or replace judgment on the totality of the data.

As to results, several overviews consistently found significant reductions in SBP in both nonhypertensive and hypertensive (younger and older) adults because of a reduction in salt intake by trial intervention groups (23–27, 29). Thus, these findings are concordant with and not contrary to (27) findings from several other studies leading to the conclusions that 1) habitual high salt intake adversely influences blood pressure of adult populations and 2) recommendations for reduced salt ingestion by the population, from postweaning on, are sound public health policy.

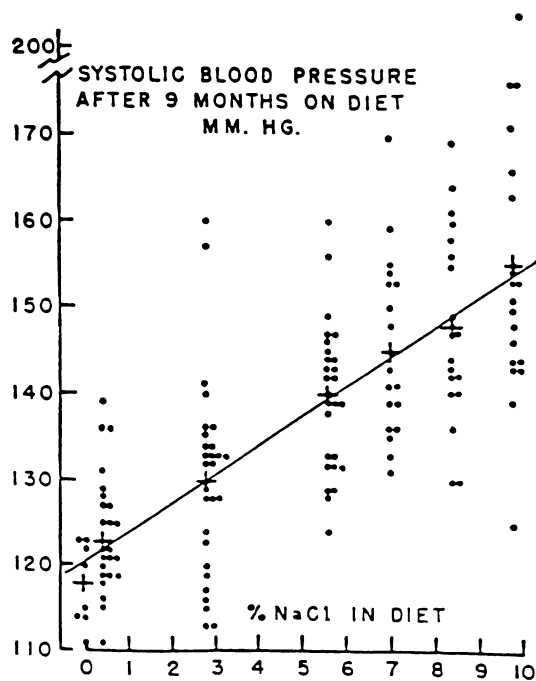
In this regard, trial data on infants merit attention (32, 33). In the Rotterdam trial of salt intake and blood pressure during the first 6 mo of life, the group randomly assigned to higher salt intake had significantly higher SBP by 2.1 mm Hg at 6 mo compared with the group randomly assigned to lower salt intake (32). Fifteen years later, the group fed more salt during the first 6 mo of life had significantly higher SBP (adjusted for confounders) by 3.6 mm Hg, even though there had been no known intervention since infancy (33). These data indicate the possibility of pathophysiologic conditioning by high salt intake in infancy, with adverse effects on blood pressure for years. They lend further support to the concept of the primary prevention of blood pressure rise with age, and of adult adverse blood pressure levels, by means of improved lifestyles, including lower salt intake, from postweaning on (2).

The cited overviews (23–27) all dealt only with trials involving individual volunteers; they did not include results from the few intervention studies involving whole communities. Findings from the intervention studies in communities are summarized and interpreted in the report by Staessen et al (34); critical review of the separate community studies and of this overview is beyond the scope of this paper. In this writer's judgment, reported results of one of the community trials particularly merit attention because this trial recorded substantial reductions in salt intake in the intervention community (35). This trial was done in Portugal, a country with high intakes of salt, high blood pressure, and high stroke mortality. At years 1 and 2, SBP/DBP values were lower for both men and women in the intervention group than for those in the control community: net reductions were 10.2/7.2 (year 1) and 13.3/6.1 (year 2) mm Hg.

#### *Animal-experimental and pathophysiologic research*

**Figure 1** gives results of an experiment in the 1950s on feeding graded amounts of salt to rats (36, 37). As noted later (37), "The experience with experimental forms of hypertension is in keeping with the data from studies in humans. In an early experiment, Meneely and colleagues fed rats different amounts of salt in their diet for 12 months and found a linear variation between sodium consumption and systolic blood pressure over the entire range of intake." These findings agree with those for humans (38), as shown by the INTERSALT Study.

Rats are not the only species in which blood pressure rises in response to increased dietary salt (39–41); in 1948 this result was reported in chickens, and subsequently in other species. Findings in chickens included aggravation of cholesterol-induced coronary and aortic atherosclerosis when blood pressure was raised by increased salt feeding (39), ie, the combined



**FIGURE 1.** Relation of dietary salt to systolic blood pressure in rats. From references 36 and 37. Reproduced with permission from WB Saunders Company (36).

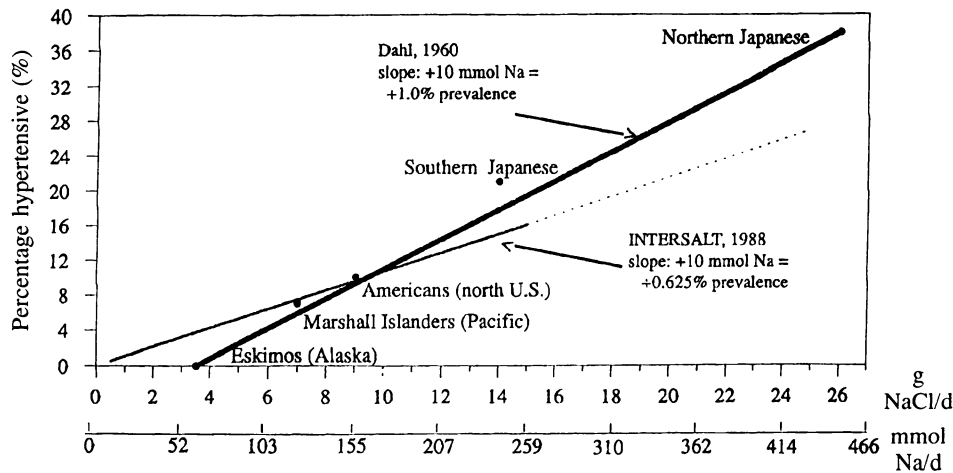
effect of major nutritional and metabolic risk factors, as recorded later in prospective human population studies.

In the intervening decades, investigators worldwide have done thousands of experiments involving salt feeding to raise blood pressure in animal models, including strains genetically inbred to be sensitive or resistant to the blood pressure influence of salt. In learning from such studies, researchers need to remember that humans as a species are like rats were before inbreeding segregated the disparate strains (Figure 1), not like the polarized strains, ie, blood pressure of most people is salt sensitive in various degrees.

Much experimentation involving salt feeding and blood pressure is concerned with mechanisms, the complex pathophysiologic pathways leading to blood pressure rise with salt feeding. Whatever the intricacies of mechanisms, regarding the origin of the experimentally induced upward shifts in blood pressure distribution (1), dietary salt is the primary causative factor. The importance of this concept is underscored by results of an experiment in chimpanzees reported in 1995 (41). When salt was added to the usual low-sodium diet of chimpanzees (the closest genetic relative of humans), the quantitative effect on average blood pressure was substantial: with 5 g NaCl/d (86 mmol Na), SBP rose 12 mm Hg; with 15 g NaCl/d (259 mmol Na), SBP rose 26 mm Hg; with cessation of added dietary salt, the original low-normal blood pressure was restored.

#### *Cross-population (ecologic) research and findings from anthropology and evolutionary biology*

In addition to his important animal experiments on salt and blood pressure, Dahl (14, 42) made a key contribution to epidemiologic research on relations between group mean salt intake and prevalence of clinical hypertension in contrasting populations around the world (**Figure 2**). In so doing > 30 y



**FIGURE 2.** Average daily salt intake of population samples and prevalence of high blood pressure in studies by Dahl (42) and in the INTERSALT Study (14). INTERSALT criteria for high blood pressure were systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg, or use of antihypertensive medication.  $n = 52$  in the INTERSALT Study; values are adjusted for age and sex. A portion of this figure is reproduced with permission from Springer-Verlag (42).

ago, Dahl enhanced awareness among Western investigators of the high salt intake in Japan, particularly in northern Japan, in early post-World War II decades and the associated high rates of hypertension and stroke (43). Subsequently, both Gleibermann (44) and Froment et al (45) reported a linear relation across populations between average salt intake and blood pressure and high blood pressure. These analyses were limited because they were based largely on published data from diverse studies not standardized for methods of measurement of either salt intake or blood pressure, and not controlled for possible confounding variables. These limitations were important considerations for the INTERSALT Study.

The analyses by Dahl, Gleibermann, and Froment included data on remote populations that into the 20th century had not adopted the practice of adding salt to food, and hence consumed a diet habitually low in salt. Over decades, data were amassed on several such populations. On average these populations experienced little or no blood pressure rise, even a modest decline, from youth through middle age and maintained optimal low-normal average SBP/DBP throughout adult life (46). Such populations had several lifestyle characteristics in addition to low salt intake: a low ratio of dietary sodium to potassium (Na:K), leanness throughout life, daily or almost daily physical activity, and little or no use of alcohol. It has therefore been difficult to assess definitively the role of low salt intake as distinct from other factors in the origin of the favorable blood pressure values in these populations. A few data sets on remote populations shed light on these matters. For example, findings on six Solomon Islands population samples showed that only one of these, the Lau, had prevalent high blood pressure (47). In contrast with the other five samples, all of whom consumed low-salt diets, the Lau cooked their food in brackish water from a Pacific inlet and hence had high salt intake. Otherwise, lifestyles tended to be similar for these six peoples. These and related data (48) support the inference that low salt intake is a key factor in the origin of optimal blood pressures of isolated populations.

Other studies of such peoples showed that their favorable blood pressure patterns were not consequences of unusual

population genetics because with acculturation and lifestyle changes blood pressure distributions shifted upward (46, 49–52). For blood pressure, as for many other physiologic traits essential for life and hence under multigene influence, the classic concept on the interplay between nature and nurture applies: “Heredity [ie, genetics] loads the cannon but obesity and other stresses [ie, environmental exposures] pull the trigger” (53). This basic thesis needs to be remembered when assessing the meaning of findings on genetic polymorphisms influencing blood pressure of individuals (54). Susceptibility loci (55) or predisposition loci (56) (along with lifestyles) influence the place of individuals in the distribution of blood pressure around population means; those means and their patterns with age are determined overwhelmingly by environmental, particularly nutritional, factors.

The root reason for this lies in evolution; during 70 million years of mammalian and primate evolution and 4–15 million years of hominoid and hominid evolution leading to *Homo sapiens* (40, 41, 56, 57–63), our predecessors had no exposures to the several components of contemporary lifestyles now known to be related to present-day population blood pressure patterns: habitual high salt intake from daily addition of salt to foods, a fare with a high Na:K, alcohol intake, or energy intake commonly exceeding expenditure, leading to obesity. On the contrary, having evolved in the warm climate of Africa, a salt-poor continent, on a fare low in salt, the human species became exquisitely adapted for the physiologic conservation of the limited salt naturally present in foods, ie, for salt retention, not for excretion of a chronically excessive intake,  $\geq 10$ –20 times physiologic need (8–10 mmol/d) (57). Regular addition of salt to food came late in human evolution,  $\approx 6000$ –8000 y ago or less, in connection with the development of agriculture and animal husbandry and their multiple consequences, including a need for the first time to have a substantial reserve of food and hence to preserve food (ie, to salt meat, fish, vegetables, and dairy products). This new exposure came too late for genetic adaptation by natural selection, particularly because

its pathophysiologic consequences almost always take their toll in cardiovascular disease (CVD) morbidity, disability, and death after sexual reproduction.

*Within-population epidemiologic studies on the relation between salt intake and blood pressure of individuals: method problems*

When INTERSALT was undertaken in 1982–1985, data available from within-population studies were limited (64); such research was held back by method problems, particularly the difficulty of validly characterizing salt intake of individuals to order them correctly from relatively low to high. In most populations everyone is exposed to added dietary salt as part of daily eating. Contrast this with research on smoking and disease: at the height of the smoking epidemic there remained a substantial minority of adults who had never smoked. The exposed and those who were never exposed could be sharply delineated and their comparative risks—of ischemic heart disease, CVD, lung cancer, etc—determined.

This problem for within-population studies of validly ranking individuals by their level of exposure to dietary variables (given that everyone is exposed) is particularly troublesome for studies of salt because of several special difficulties: how validly to measure salt added in commercial manufacture of processed foods, salt added in kitchens of restaurants and canteens, salt added in cooking by the homemaker, and salt added at the table by the consumer. Although these last two sources supply a good deal less than one-quarter of the total salt consumed daily by individuals nowadays ( $\approx 75\%$  comes from processed and manufactured foods) (57, 65–68), this proportion varies from person to person and from day to day. Therefore, assessing only salt present in foods as purchased reduces validity in classification of individuals. These difficulties place special limitations on dietary assessment methods, and drive researchers to the alternative procedure of 24-h urine collection, also a method fraught with complexities (64).

Furthermore, individuals vary their intake of foods and nutrients daily. Intraindividual variation is generally much greater than interindividual variation. In this circumstance, with use of a 1-d diet record, attempts to correlate individual nutrients with some other characteristic of an individual are likely to fail, even though a highly important relation between the dietary pattern and the characteristic in question may really exist (69). This problem is illustrated in **Table 2** (67, 70–76). Note the contrasts in reliability between nutritional variables and other variables, especially weight. For all nutrients, including salt intake as estimated by either 24-h sodium excretion or 24-h dietary recall, ratios of intra- to interindividual variability exceed 1.0. The consequence is that with only a single 1-d measurement of salt intake per individual, misclassification is considerable; regression coefficients for the sodium–blood pressure relation are driven toward zero. Observed coefficients are  $< 50\%$ , even  $< 25\%$ , of true coefficients; hence, significant findings are detectable only with large sample sizes.

Most within-population studies on sodium and blood pressure have had inadequate sample sizes (64). With measurement of 4 d of salt intake per person, this problem is blunted; observed regression coefficients are  $> 50\%$  of true coefficients (but still with considerable regression-dilution bias). However, high-quality collection and analysis of four 24-h urine specimens per person or four 24-h diet recalls on large population

**TABLE 2**

Ratio of intra- to interindividual variances and effects on observed coefficient as a percentage of the true coefficient with one and four measurements<sup>1</sup>

Study and variables	Ratio, intra- to interindividual variances	Observed coefficient as percentage of true coefficient <sup>2</sup>	
		One measurement	Four measurements
%			
Peoples Gas			
Weight	0.04	96.2	99.0
Serum cholesterol	0.38	72.5	91.3
Serum uric acid	0.38	72.5	91.3
1-h Post-load plasma glucose	0.94	51.5	81.0
Systolic blood pressure	0.34	74.6	92.2
Diastolic blood pressure	0.47	68.0	89.5
Heart rate	0.47	68.0	89.5
International Harvester			
24-h Urinary Na excretion	3.20	23.8	55.6
INTERSALT			
24-h Urinary Na excretion	1.17	46.0	77.3
MRFIT <sup>3</sup>			
Protein (% of energy)	3.8	21.0	51.5
Carbohydrate (% of energy)	1.9	34.7	68.0
Fat (% of energy)	3.5	22.2	53.3
Cholesterol (mg/4184 kJ)	4.1	19.6	49.4
Alcohol (% of energy)	0.9	53.0	81.9
Na (mg/d)	3.4	22.7	54.0
K (mg/d)	1.8	35.7	68.9
Ca (mg/d)	1.9	34.1	67.4
Mg (mg/d)	1.6	37.8	70.8
Fiber (g/d)	2.6	27.9	60.7
Vitamin A (IU/d)	15.4	6.1	26.3
Vitamin C (mg/d)	3.4	22.7	54.3

<sup>1</sup> From references 14, 67, 73, and 75.

<sup>2</sup> Observed regression coefficient as percentage of true regression coefficient =  $[1/1 + (\text{ratio}/n)] \times 100$ , where ratio is the ratio of intra- to interindividual variance and  $n$  is the number of measurements; time intervals between measurements were  $\geq 1$  y.

<sup>3</sup> Multiple Risk Factor Intervention Trial.

samples is a major undertaking. Understandably, therefore, studies in this area with adequate methods—large sample sizes and valid approaches for measuring salt intake of individuals—have been few. The INTERSALT Study was deliberately undertaken with a design and methods to address these challenges.

## THE INTERSALT STUDY

### Aims, design, and methods

The origins, aims, design, and methods of the INTERSALT Study have been reported in detail (10, 14, 15, 67, 75–92). The aim was to test two sets of prior hypotheses in a sample of  $> 10\,000$  men and women aged 20–59 y from 52 diverse sites in 32 countries worldwide.

*Within-population prior hypotheses*

The hypotheses tested were that for the > 10 000 participants, SBP and DBP would be directly and independently related to 24-h urinary sodium excretion, Na:K excreted, body mass index (BMI), and alcohol use and inversely related to 24-h potassium excretion. One carefully collected 24-h urine sample would be used to assess dietary sodium and potassium. It was recognized that with only one urine sample collection per person, observed coefficients would be considerably less than true coefficients (regression-dilution bias). To assess this and correct for it, the protocol provided for repeat 24-h urine collection in a random sample of participants.

*Cross-population (ecologic) prior hypotheses*

The hypotheses tested were that for the 52 samples worldwide, five blood pressure endpoints would be directly related to sample median 24-h sodium and Na:K excretion, sample median BMI, and sample alcohol intake, and inversely related to sample median 24-h potassium excretion; the five blood pressure-dependent variables would be sample median SBP, sample median DBP, sample slope of SBP with age (20–59 y), sample slope of DBP with age, and sample prevalence of high blood pressure (SBP  $\geq$  140 mm Hg, DBP  $\geq$  90 mm Hg, or both, or receiving antihypertensive drugs). (Data were computed with use of means as well as medians; results were virtually identical.)

For tests of both sets of hypotheses, data would be collected on several other variables to control for possible confounders, including 24-h urinary magnesium and calcium, pulse, ethnicity, education, physical activity, smoking, and medication use, and for women, parity and menopausal status. Despite its serious limitations, 24-h urinary creatinine could be used as a crude guideline to completeness of collection, along with urine volume and a careful interview with each participant. The beginning and end of each urine collection would take place at the local clinical research center to achieve maximal accuracy in timing of the 24-h specimen. Prior criteria were stipulated for rejection of a specimen as incomplete before any data analyses and for recruitment of a randomly selected substitute participant. At the first clinic visit, two standardized blood pressure measurements would be made per person, with average SBP and DBP to be used in analyses.

To maximize data quality, the study would follow a single protocol and manual of operations (77), with uniform standardized supplies, equipment, and procedures for data collection and processing, with key field staff trained and certified at international regional training sessions. Biochemical analyses of 24-h urine samples would be done in one central laboratory (Leuven, Belgium) with standardized procedures for shipment of properly preserved specimens serially from local centers to this laboratory, deep-freezing of specimens before analysis, and automated biochemical analytic methods, with ongoing internal and external monitoring and control of laboratory quality. All work would be jointly led and supervised by two coordinating centers, in Chicago and London, the latter serving as the statistical center. At each of the 52 centers, the effort would be to collect data on population-based samples made up of 200 men and women aged 20–59 y, with 25 persons in each of eight sex-decade strata.

*Statistical methods*

To test prior within-population hypotheses ( $n = \geq 10,000$ ), linear regression of SBP and DBP of individuals at each center would be done on their 24-h urinary sodium excretion, controlled first for age and sex and then for age, sex, BMI, alcohol use, and 24-h urinary potassium. This analysis would be done for each of the 52 samples of  $\approx 200$  people to yield two sets of 52 regression coefficients; the 52 coefficients for SBP (and then for DBP) would be pooled, with weighting by inverse of their variance, to obtain the two overall regression coefficients of SBP and of DBP on sodium for all 10 079 individual participants. Each pooled regression coefficient would be adjusted for reliability (originally based on a univariate model, subsequently based on multivariate modeling) (14, 15, 75, 76). To test cross-population (ecologic) prior hypotheses ( $n = 52$ ), linear regression would be done across the 52 population samples of each of the 5 sample blood pressure variables on sample median (or mean) 24-h sodium excretion, first controlled for age and sex, then controlled for age, sex, BMI, and alcohol use.

**INTERSALT results***Findings on INTERSALT prior within-population hypotheses*

The univariate estimate for the reliability of sodium measurement based on repeat measurement of 24-h sodium excretion for the random subsample (8%) of participants was 0.460 (14); the multivariate estimate was 0.375 (75). As others have reported (65), BMI and 24-h sodium excretion of individuals were significantly correlated for both male and female INTERSALT participants ( $r = 0.209$  for 5045 men and  $r = 0.225$  for 5034 women). Therefore, inclusion of BMI in multiple-linear-regression analyses on the sodium–blood pressure relation can lead to overadjustment because some of the BMI–blood pressure relation can be due to greater salt intake by persons with greater BMIs (14, 15, 80, 85, 86). Also, inclusion in the same multiple-linear-regression analysis of correlated variables measured with low and high reliability (ie, sodium and BMI) can cause the relation of the trait with lower reliability to blood pressure to be underestimated (75, 76, 83, 85, 86, 93). In addition to regression-dilution bias, these are two other (among

**TABLE 3**

Twenty-four-hour urinary sodium excretion and blood pressure in the INTERSALT Study: relation in persons with 100-mmol/d lower excretion<sup>1</sup>

	SBP	DBP
Unadjusted for reliability (mm Hg)	-1.0 <sup>2</sup>	-0.10
Initial univariate adjustment for reliability (mm Hg)	-2.2 <sup>2</sup>	-0.06
Multivariate adjustment for reliability (mm Hg)	-3.1 <sup>2</sup>	-0.10
Multivariate adjustment for reliability, without BMI in model (mm Hg)	-6.0 <sup>3</sup>	-2.5 <sup>3</sup>

<sup>1</sup>  $n = 10\,074$ ; of the total (10 079 persons), five were not included because of missing data on alcohol intake. All four analyses controlled for age, sex, 24-h potassium excretion, and alcohol intake, and the first three also controlled for BMI. SBP, systolic blood pressure; DBP, diastolic blood pressure. From references 14, 76, 83, and 85.

<sup>2</sup>  $P < 0.001$ .

<sup>3</sup>  $P < 0.01$ .

seven) probable sources of biased underestimation of the strength of the sodium–blood pressure relation for individuals.

INTERSALT results for the sodium-SBP and sodium-DBP relations for individuals are summarized in **Table 3**. A significant independent relation was found between 24-h urinary sodium excretion and SBP. On the basis of multivariate correction for reliability, with and without BMI in the analysis, estimates of the size of the sodium-SBP/DBP relation were 3.1–6.0/0.1–2.5 mm Hg lower on average with 100-mmol/d lower sodium intake (85). Analyses of sodium–blood pressure relations also including 24-h urinary magnesium and calcium in the model yielded similar results.

Further data for the INTERSALT tests of prior within-population hypotheses are given in **Table 4**. BMI and heavy use of alcohol ( $\geq 300$  mL/wk) were directly and independently related to SBP and DBP, as was 24-h Na:K excreted, and 24-h potassium excretion was inversely related (14). The combination of more favorable sodium and potassium intakes is estimated to be associated with average SBP/DBP values lower by 6.5/2.0 to 9.3/4.1 mm Hg. This estimate is quantitatively concordant with results of the Rotterdam mineral salt trial of combined lower dietary sodium and higher dietary potassium for older hypertensive persons (94).

The INTERSALT estimates in Tables 3 and 4 (in four-factor analyses with correction for three sources of bias) are probably still underestimates of electrolyte–blood pressure relations because there are at least seven sources of bias leading to probable underestimation (15, 64, 67, 85, 86): 1) use of a single 24-h urine collection to quantify habitual sodium intake, a weak method because of large individual day-to-day variability that results in misclassification of individuals and thus biasing of true associations toward zero, ie, the regression-dilution bias

problem; 2) in multiple-regression analyses of blood pressure on sodium, a variable measured imprecisely in INTERSALT, the effect of inclusion of confounders measured with high reliability, eg, BMI; 3) in multiple-regression analyses of blood pressure on sodium controlled for BMI, the possibility of over-adjustment because part of the blood pressure–body mass association may be due to the positive correlation of body mass with sodium; 4) possible incompleteness of urine collection by some participants, varying in degree; 5) prior reduction in salt intake by some participants, varying in degree, biased toward occurrence in people with higher blood pressures; 6) effects of antihypertensive drugs on blood pressure; 7) lack of prospective data on long-term influences of salt on blood pressure, ie, the cross-sectional nature of the study. Underestimates are reported in other studies as well, for example, underestimation of the sodium–blood pressure relation because of variable incompleteness of 24-h urine collection was objectively shown in the North London Study with use of oral  $p$ -aminobenzoic acid to detect unreported incomplete collections (95).

Results on sodium and blood pressure in INTERSALT prevailed for both younger (aged 20–39 y) and older (aged 40–59 y) participants, with coefficients about two to three times larger for older than younger persons; results also prevailed for both men and women, with coefficients larger for women (15, 85). Analyses were also done of the best fit for the sodium-SBP relation, ie, linear, exponential (log SBP), or asymptotic (log Na or  $\sqrt{\text{Na}}$ ). Linear and exponential fits were virtually identical in their multivariate adjusted Z score, which is used to assess goodness of fit. In contrast, log Na and  $\sqrt{\text{Na}}$  were consistently smaller, indicating that these models were not the best fits. These findings indicate that reported conjectures (96) are incorrect that sodium intake  $> 100$  or  $> 150$  mmol/d has little further influence in raising blood pressure. INTERSALT data indicated that the sodium–blood pressure relation did not differ significantly for individuals with lower ( $< 24.1$ , in kg/m<sup>2</sup>) and higher ( $\geq 24.1$ ) median BMIs (83).

Results similar to those for all INTERSALT participants (Table 4) were also recorded in within-population analyses for 9343 individuals, not including those from four remote samples with low sodium intake (14) (Table 5). These findings are

**TABLE 4**  
Coefficients for lifestyle traits and blood pressure in the INTERSALT Study: analyses with five or four variables<sup>1</sup>

	SBP		DBP	
	Five-factor analyses	Four-factor analyses	Five-factor analyses	Four-factor analyses
24-h Urinary Na excretion 100 mmol lower (mm Hg)	-3.1 <sup>2</sup>	-6.0 <sup>2</sup>	-0.1	-2.5 <sup>2</sup>
24-h Urinary K excretion 50 mmol higher (mm Hg)	-3.4 <sup>2</sup>	-3.3 <sup>2</sup>	-1.9	-1.6 <sup>3</sup>
Alcohol intake 0 or 1–299 mL/wk (mm Hg)	-0.5	-0.6	-0.1	-0.2
Alcohol intake 0 or $\geq 300$ mL/wk (mm Hg)	-3.5 <sup>2</sup>	-3.2 <sup>2</sup>	-2.1 <sup>2</sup>	-1.8 <sup>2</sup>
BMI 3 units lower (mm Hg)	-2.2 <sup>2</sup>	—	-1.8 <sup>2</sup>	—

<sup>1</sup>  $n = 10\,074$ ; of the total (10 079 persons), 5 were not included because of missing data on alcohol intake. Multivariate coefficients were adjusted for regression-dilution bias. SBP, systolic blood pressure; DBP, diastolic blood pressure. From references 76, 83, and 85.

<sup>2</sup>  $P < 0.001$ .

<sup>3</sup>  $Z = -1.933$ .

**TABLE 5**  
Coefficients for lifestyle traits and systolic blood pressure in the INTERSALT Study: analyses with five or four variables<sup>1</sup>

	Five-factor analyses	Four-factor analyses
24-h Urinary Na excretion 100 mmol lower (mm Hg)	-3.2 <sup>2</sup>	-6.2 <sup>2</sup>
24-h Urinary K excretion 50 mmol higher (mm Hg)	-4.3 <sup>2</sup>	-4.3 <sup>3</sup>
Alcohol intake 0 or 1–299 mL/wk (mm Hg)	-0.5	-0.01
Alcohol intake 0 or $\geq 300$ mL/wk (mm Hg)	-3.6 <sup>2</sup>	-3.3 <sup>2</sup>
BMI 3 units lower (mm Hg)	-2.2 <sup>2</sup>	—

<sup>1</sup>  $n = 9343$ ; of all participants (10 079 persons), 731 were not included from the four populations with low sodium intake (Kenya, Papua, Xingu, and Yanomamo); 5 others were not included because of missing data on alcohol intake. Multivariate coefficients were adjusted for regression-dilution bias on the basis of reliability data for all 10 079 participants.

<sup>2</sup>  $P < 0.001$ .

<sup>3</sup>  $P < 0.01$ .

displayed here because of controversy surrounding them (97, 98).

INTERSALT within-population analyses also showed that the inverse relation between educational attainment and blood pressure (8, 9) prevails in many population samples worldwide (10). INTERSALT was able to elucidate for the first time reasons for this finding: the less the educational attainment of individuals, the greater their 24-h sodium excretion, alcohol intake, and BMI and the lower their 24-h potassium excretion. These four lifestyle-related variables accounted for a significant proportion of the inverse association between education and blood pressure (10).

To explore whether the sodium–blood pressure relation in INTERSALT was due largely to salt sensitivity among hypertensive participants, analyses were repeated involving only nonhypertensive persons (SBP < 140 mm Hg, DBP < 90 mm Hg, and not receiving antihypertensive drugs) (Table 6) (89). Coefficients for the Na-SBP and Na-DBP relations were similar for the 8344 nonhypertensive individuals and all 10 079 participants. These findings indicate that salt sensitivity is common throughout the population.

#### *Findings on INTERSALT prior cross-population (ecologic) hypotheses on sodium and blood pressure*

Data for tests of the five prior hypotheses on relations of sample median 24-h sodium excretion to five blood pressure endpoints are given in Table 7 (14). With standardization for age and sex, all coefficients were significant ( $P < 0.01$  or  $< 0.001$ ) and strong. Thus, with sample median sodium intake lower by 100 mmol/d, the upward slope in sample SBP/DBP from the age of 25 y to 55 y was estimated to be less by 9.0/6.3 mm Hg; the sample median SBP/DBP was estimated to be less by 7.1/3.8 mm Hg; and the sample prevalence of hypertension was estimated to be less by 6.2 percentage points (14, 43). With further adjustment in ecologic analyses for BMI and alcohol intake, four of five coefficients were significant ( $P < 0.05$ , <

0.01, or  $< 0.001$ ) (Table 8) (14). All relations continued to be strong.

In response to criticism of the linear-regression method used to estimate slope of blood pressure with age, the INTERSALT research group recently reported further analyses applying three additional methods to assess blood pressure differences of persons aged 55 compared with 25 y for each of the 52 samples, and relating sample median (and mean) 24-h sodium excretion to these differences (Table 8) (85). All methods gave similar highly significant estimates ( $P < 0.001$ ): an increase of 10–11/6 mm Hg in SBP/DBP over 30 y with sodium excretion higher by 100 mmol/d. These results were found with cross-sample adjustment for BMI and alcohol use, and also in further analyses with adjustment for blood pressure at age 20–29 y (85). These INTERSALT findings indicate that much of the total overall upward slope of SBP/DBP with age, eg, from the age of 25 y to 55 y (averaging  $\approx 15/11$  mm Hg for the 52 samples), could be attributable to high salt intake.

#### *Findings in INTERSALT original post hoc ecologic analyses*

On the basis of scattergrams from the original analyses (14), three other sets of ecologic analyses were undertaken in the INTERSALT Study before its first report. One used Spearman rank-order correlation rather than linear regression to assess consistency of results with the two methods (14). For all samples, rank-order correlations were significant for sample 24-h median sodium and sample SBP slope with age ( $r = 0.451$ ,  $P < 0.001$ ), and for sample 24-h median sodium and sample DBP slope with age ( $r = 0.537$ ,  $P < 0.001$ ). Other  $r$  values were not significant.

A second set of post hoc ecologic analyses involved truncation of the data, by exclusion of findings for four remote samples with low 24-h sodium excretion (14, 79) to evaluate the influence on the overall results of data from these four centers. With standardization by age, sex, BMI, and alcohol intake, relations of 24-h median sodium excretion to slopes of SBP and DBP with age were significant ( $P < 0.01$ ), with coefficients of 9.0 and 4.5 per 30 y per 100 mmol Na, respectively. Other coefficients were not significant. For 48 samples, analyses by four methods consistently gave significant results for the relation of sample average sodium excretion to difference in blood pressure at the age of 55 y compared with 25 y (85). Estimates were of an increase in SBP/DBP by 9–12/4–5 mm Hg with sodium excretion higher by 100 mmol/d; with adjustment also for blood pressure at age 20–29 y, SBP/DBP was greater by 9–11/3–4 mm Hg. In a third set of post hoc ecologic analyses, INTERSALT researchers confirmed from data for the four isolated samples observations that had been repeatedly noted in previous reports that habitual low salt intake is associated with low-normal SBP/DBP, little or no rise in SBP/DBP with age, and little or no hypertension (14, 67, 79).

#### **Controversial statements about INTERSALT findings**

Repeated controversy may have tended to obscure INTERSALT findings. One example was referenced above (97, 98). Others have emanated from the Salt Institute, a trade organization of commercial companies producing salt, eg, in a letter from the institute to the Dietary Guidelines Advisory Committee of the US Department of Agriculture and the US Depart-

**TABLE 6**  
Coefficients for 24-h urinary sodium excretion and systolic blood pressure in the INTERSALT Study: relation in nonhypertensive persons with 100-mmol/d lower excretion compared with that for all participants<sup>1</sup>

	Nonhypertensive participants ( $n = 8344$ ) <sup>2</sup>	All participants ( $n = 10\,074$ ) <sup>3</sup>
Unadjusted for reliability (mm Hg)	–1.0 <sup>4</sup>	–1.0 <sup>4</sup>
Multivariate adjusted for reliability (mm Hg)	–3.0 <sup>5</sup>	–3.1 <sup>4</sup>
Multivariate adjusted for reliability, without BMI in model (mm Hg)	–4.9 <sup>5</sup>	–6.0 <sup>4</sup>

<sup>1</sup> All three analyses were controlled for age, sex, 24-h potassium excretion, and alcohol intake; the first two were also controlled for BMI. From reference 89 and INTERSALT analyses.

<sup>2</sup> Persons with systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg and not taking antihypertensive drugs.

<sup>3</sup> Of the total (10 079 persons), 5 were not included because of missing data on alcohol intake.

<sup>4</sup>  $P < 0.001$ .

<sup>5</sup>  $P < 0.01$ .



ment of Health and Human Services (RL Hanneman, written communication, 1995), to which I responded in detail (J Stamler, written communication, 1995). Contrary to proposals from the Salt Institute, the report of the Dietary Guidelines Advisory Committee reaffirmed for the new (4th) edition of the guidelines (99) the recommendation present in earlier editions of lower salt intake for the general population. Further, the committee advised that the guideline on salt be made more explicit by citing the Nutrition Facts label listing of 2400 mg/d ( $\approx 100$  mmol/d) for sodium as an upper limit (100).

A further recent example is a commentary by the Salt Institute in the *British Medical Journal* (101). The INTERSALT Steering and Editorial Committee comprehensively refuted the multiple statements made in this piece (102, 103), and other colleagues also responded (104–106). In another journal, a UK academic physician said that INTERSALT cross-population findings on the relation of sample median 24-h sodium excretion to slopes of SBP and DBP with age may be “an artifact of retrospective sub-group analysis” (107). This statement should be corrected because 1) these analyses were not retrospective, they were part and parcel of testing INTERSALT prior ecologic hypotheses, formulated early by INTERSALT at the initiative of London INTERSALT colleagues (Paul Elliott and Michael Marmot) before field data were available for analysis, and 2) they were not subgroup analyses, they involved all 52 INTERSALT samples.

In a review on salt and blood pressure, two European medical researchers summarized the INTERSALT within-population findings by giving only separate results for individuals at each of the 52 centers (96). They stated, “The relation between sodium excretion and blood pressure was greatly diminished when body mass index, alcohol consumption, and potassium excretion were factored out. Positive correlations decreased to eight centers for systolic blood pressure and no centers for diastolic blood pressure” (96). This statement is

**TABLE 7**  
Multiple-linear-regression coefficients for 24-h median sodium excretion and blood pressure: tests of the INTERSALT prior ecologic hypotheses<sup>1</sup>

Dependent variable	Adjusted for age and sex	Adjusted for age, sex, BMI, and alcohol
SBP slope with age (mm Hg over 30 y with 100-mmol/d greater Na intake)	9.0 <sup>2</sup>	10.2 <sup>2</sup>
DBP slope with age (mm Hg over 30 y with 100-mmol/d greater Na intake)	6.3 <sup>2</sup>	6.3 <sup>2</sup>
Median SBP (mm Hg with 100-mmol/d greater Na intake)	7.1 <sup>2</sup>	4.5 <sup>2</sup>
Median DBP (mm Hg with 100-mmol/d greater Na intake)	3.8 <sup>3</sup>	2.3 <sup>4</sup>
Hypertension prevalence with 100-mmol/d greater Na intake <sup>5</sup>	6.2 <sup>3</sup>	4.8 <sup>6</sup>

<sup>1</sup>  $n$  = all 52 INTERSALT population samples. SBP, systolic blood pressure; DBP, diastolic blood pressure. From reference 14.

<sup>2</sup>  $P < 0.001$ .

<sup>3</sup>  $P < 0.01$ .

<sup>4</sup>  $P = 0.08$ .

<sup>5</sup> Hypertension is defined as SBP  $\geq 140$  mm Hg, DBP  $\geq 90$  mm Hg, or receiving antihypertensive drugs. Units of prevalence are percentage points.

<sup>6</sup>  $P < 0.05$ .

incorrect in detail, in essence, and by omission. As to detail, data in Table 1 of the 1988 INTERSALT paper show that the multivariate-adjusted sodium-SBP coefficient had a positive sign for 33 of 52 samples, not 8 (14). As to essence, these sample-specific data were descriptive statistics, not tests of any INTERSALT prior hypothesis. With sample sizes of  $\leq 200$  at each of the 52 INTERSALT field centers, statistical power was completely lacking to test the sodium–blood pressure relation sample by sample. From the beginning, the INTERSALT statistic for testing the within-population sodium–blood pressure relation was the pooled coefficient for all 10 079 individuals from all 52 samples (14). The cited review omits mention of this pooled coefficient; its  $P$  value is  $< 0.001$  (Tables 3 and 4). Note that the first page of the cited review (96) states, “Publication costs were defrayed by educational grants from the European Committee for the Study of Salt, Vienna and Paris; and the Salt Institute, Washington, DC.”

### Implications of INTERSALT and related findings

#### *Significance of the sodium–blood pressure relation*

The independent, significant positive relations found by INTERSALT, in both its within-population analyses on  $\geq 10\ 000$

**TABLE 8**  
Estimated greater average difference in blood pressure (mm Hg) over 30 y (age 55 y minus age 25 y) with daily median urinary sodium excretion higher by 100 mmol in INTERSALT cross-population analyses<sup>1</sup>

Model	SBP		DBP	
	Difference greater by	$t$	Difference greater by	$t$
Linear	10.2	5.7 <sup>2</sup>	6.3	6.6 <sup>2</sup>
Linear adjusted	10.1	5.5 <sup>2</sup>	6.2	6.3 <sup>2</sup>
Difference	10.7	5.1 <sup>2</sup>	5.7	5.0 <sup>2</sup>
“Best fit”	11.3	6.1 <sup>2</sup>	6.4	6.7 <sup>2</sup>

<sup>1</sup> SBP, systolic blood pressure; DBP, diastolic blood pressure. The four models used to estimate average blood pressure at age 55 y and at age 25 y, and to estimate difference (age 55 y minus age 25 y) for each of the 52 samples, were as follows: linear, univariate linear regression of SBP and DBP on age for each sample, as in reference 19; linear adjusted, linear regression of SBP and DBP on age for each sample, with adjustment for sex, 24-h urinary potassium excretion, BMI, and alcohol intake entered as two 0–1 variables, 1–299 mL/wk and  $\geq 300$  mL/wk; difference, difference in population sample median SBP (and DBP) at ages 50–59 and 20–29, computed separately for men and for women, then average of these two values; “best fit,” polynomial curve fitting of blood pressure on age, up to the fifth order term, with use of root-mean-square error (the estimated residual SD of blood pressure unexplained by the model) to determine whether higher order terms of age improved the “fit” of regression of SBP and DBP on age. Each blood pressure difference, obtained with each of the four models, was entered as the dependent variable in a cross-population (ecologic) analysis with the independent variable sample 24-h median or mean sodium excretion, adjusted across the 52 population samples for sample median BMI and alcohol intake (sample median alcohol intake/wk of drinkers, and sample prevalence of alcohol drinking). The resultant regression coefficients (data columns two and four of the table) estimate the greater difference in SBP and in DBP over a 30-y period (age 25 y to age 55 y) attributable to sample average sodium excretion higher by 100 mmol/d. Results were similar with use of median and mean 24-h sodium excretion; those in the table are for the median as independent variable. From reference 85.

<sup>2</sup>  $P < 0.001$ .

people and its cross-population analyses on 52 samples, between 24-h sodium excretion and blood pressure agree with extensive findings by all research methods. Thus, they strongly support the judgments that habitual population-wide excess high salt intake is a mass exposure playing an important causative role in the rise in blood pressure with age during adulthood, the consequent population-wide adverse blood pressure values from the age of 35 y on, the high incidence and prevalence rates of frank hypertension, and the high incidence and mortality rates from major CVDs that are due to adverse blood pressure values (2, 7, 23–26, 36, 38, 41, 43, 57, 99, 100, 104–106, 108–115). It is these judgments that underlie national and international public policy statements, developed by expert groups, recommending moderation in salt intake by the whole population: < 6 g/d (< 100 mmol Na/d) or preferably < 4.5 g/d (< 75 mmol/d) (2, 7, 57, 99, 100, 110–115). INTERSALT within-population findings are based on data for an overall sample of  $\geq 10\,000$  men and women aged 20–59 y, from 52 population samples in 32 countries worldwide. This broad base lends weight to the judgment that the foregoing assessments are robust and widely generalizable.

INTERSALT findings on the shape of the curve relating 24-h sodium excretion of individuals to their blood pressure also have important implications. Linear and exponential curves tested similarly as best fits, ie, the higher the sodium intake of individuals, the greater their blood pressure on average. The asymptotic curve was a poorer fit, a result lending no support to the hypothesis that in the range of sodium intake of 125–250 mmol/d, blood pressure on average levels off, with little or no further rise with greater sodium intake. Therefore, for many populations, with salt intake averaging  $\approx 10$  g/d (172 mmol Na/d) and with sizable numbers of people consuming  $\geq 12$  g/d ( $\geq 207$  mmol Na/d), a significant reduction in salt intake to < 6 g/d (< 103 mmol Na/d) as recommended can be expected to produce substantial reductions in blood pressure.

This inference is also supported by INTERSALT findings for 8344 nonhypertensive participants. The similar significant coefficients for the sodium-SBP relation for nonhypertensive and all participants indicate that salt sensitivity of various degrees is widespread. This inference is supported by data in overviews of population-based observational studies and trials (23–28, 64) but seems contrary to results from clinical studies of salt sensitivity (116). However, there are problems with the data from clinical studies, eg, they have not been population-based, hence their generalizability is unclear; sample sizes have been small; and arbitrary cutoff points have been used to define acute blood pressure responsiveness to salt (ie, yes or no), which is in fact continuously distributed (117). Furthermore, only limited data are available on the meaning of results from such salt-sensitivity studies (eg, relation of findings to risks of blood pressure rise with age). Also, only limited findings have been reported on reproducibility in individuals of acute blood pressure response to salt loading or unloading. These indicate that results of acute tests of salt sensitivity are of limited reproducibility, eg, with the conservative criterion of a fall of  $\geq 10$  mm Hg in mean arterial blood pressure with acute salt depletion after intravenous salt loading, 17 of 28 participants (60.7%) were positive at the first or second testing within 12 mo; only 7 (25.0%) were positive at both (agreement on positive response:  $7/17 = 41.2\%$ ) (117). This was a small clinical study, however, and the generalizability of its findings is not clear.

It seems likely that the considerable intraindividual variability in response to salt-sensitivity testing is similar to that for serum cholesterol response to dietary lipid loads (118) and for glycemic response to oral glucose load (73, 119). Today's nonresponder is next month's or next year's responder. Therefore, currently available estimates on prevalence of salt sensitivity that are based on one-time studies are underestimates. If the criterion is a decrease in mean arterial blood pressure of  $\geq 10$  mm Hg on one or both of two tests, most people, for example, 61% of those in the cited study, are salt sensitive (117). The proportion is even higher if the criterion is shifted downward, for example, to a decrease of 6 or 8 mm Hg. Thus, these clinical data agree with those from INTERSALT and other population-based studies in indicating that salt sensitivity in varying degrees is common throughout the population.

#### *Size of the sodium–blood pressure relation*

Best estimates from INTERSALT data on the size of its significant sodium–blood relations are the following:

- 1) From within-population analyses, SBP/DBP is 3–6/0–3 mm Hg lower on average per 100-mmol/d lower 24-h sodium excretion with and without BMI in the analyses, with multivariate adjustment for reliability, and with control for age, sex, alcohol intake, and potassium (85); for subgroups, SBP/DBP is 5/2 mm Hg lower for nonhypertensive persons, 8/4 mm Hg lower for those aged 40–59 y, 4/1 mm Hg lower for those aged 20–39 y, 5/2 mm Hg lower for men, and 8/3 mm Hg lower for women, without BMI in the analyses. All these values for individuals are almost certainly underestimates.
- 2) From estimates from cross-population analyses controlled for age, sex, BMI, and alcohol intake, with population median sodium lower by 100 mmol/d, median SBP/DBP is lower by 5/2 mm Hg; for persons aged 40–59 y, SBP/DBP is lower by 7/4 mm Hg; for those aged 20–39 y, it is lower by 2/0.4 mm Hg. With sodium lower by 100 mmol/d, the average difference in the population sample SBP/DBP, age 55 y compared with 25 y, is a decrease of 10–12/6–7 mm Hg (85).

These within-population and cross-population estimates generally agree with each other and with those from other analyses (25, 64, 104).

The emphasis here on the etiologic significance of the salt–blood pressure relation and on its strength, hence its importance, is in no way meant to underplay the known role of other environmental exposures that also adversely influence blood pressure, including inadequate dietary potassium, energy imbalance with consequent obesity, heavy alcohol use, and physical inactivity (2, 7, 10, 14, 15, 57, 67, 70, 74, 76, 83–92, 99, 100, 102, 110–115). All the foregoing dietary variables plus sodium were shown by INTERSALT to relate significantly, sizably, and independently to blood pressure. Hence, improvements in nutrition related to all of them, as components of broad improvements in eating and drinking patterns to combat chronic diseases (57), have great potential to prevent and control adverse blood pressure. These appropriate multifactorial emphases have nothing in common with the contention that obesity and excess alcohol intake are more important risk factors for adverse blood pressure than dietary salt, an assertion contrary to the available data (82). It can be anticipated that research advances over the next years will produce extended nutritional recommen-

dations for improving population blood pressure values, possibly regarding dietary magnesium, calcium, fiber, cholesterol, saturated fat, and protein (74, 120, 121).

*Effect of lower blood pressure on risks of major CVD and all-cause mortality*

Even small differences in population average blood pressure relate importantly to CVD and all-cause mortality risks (4–6, 11, 12, 85, 86, 88, 89, 111, 122–127). Representative data derived from multivariate analyses of 16-y prospective findings for the MRFIT cohort are given in **Table 9** (5, 6). The focus is on estimated favorable effects of lower SBP because from about the age of 40 y on, SBP is more strongly related to risks than is DBP. Given the large size of this cohort, the large numbers of deaths, and control for other risk factors, these are highly precise estimates, albeit underestimates because they are not corrected for regression-dilution bias. As is evident, even SBP lower by 2 mm Hg is associated with significant and meaningful benefit: lower ischemic heart disease and CVD death rates by 4–5% and lower all-cause mortality by 3%. A population average SBP lower by 2 mm Hg is consequential, not inconsequential, assertions to the contrary notwithstanding (128). Estimated effects of greater improvements in population average SBP are considerably greater. For example, for the above-cited INTERSALT estimates of SBP (lower overall by 6 mm Hg) with daily sodium intake lower by 100 mmol, ischemic heart disease and CVD death rates are lower by  $\approx$ 13% and the all-cause death rate is lower by  $\approx$ 9% (Table 9). For 10-mm Hg lower SBP, estimated from INTERSALT ecologic data on sodium and SBP slope with age, ischemic heart disease and CVD mortality rates were lower by  $\approx$ 20–21% and the all-cause death rate was lower by 14%. With SBP lower by 20 mm Hg on average, as observed in low-risk cohorts of men and women with optimal status for all ischemic major ischemic heart disease and CVD risk factors (122, 129, 130), even more favorable effects can be anticipated.

**TABLE 9**

Relation of lower systolic blood pressure (SBP) to risks of mortality in the Multiple Risk Factor Intervention Trial<sup>1</sup>

SBP lower by:	16-Year mortality lower by:		
	Ischemic heart disease	All cardiovascular diseases	All causes
		%	
2 mm Hg	4.4	4.6	3.0
3 mm Hg	6.5	6.8	4.4
4 mm Hg	8.6	9.0	5.8
6 mm Hg	12.6	13.2	8.6
8 mm Hg	16.5	17.2	11.3
10 mm Hg	20.1	21.0	13.9
20 mm Hg	36.2	37.6	25.9

<sup>1</sup> Cohort of 342 815 men free at baseline of history of hospitalization for heart attack and drug-treated diabetes; data are based on coefficients for the relation of baseline SBP to 16-y risk of ischemic heart disease, cardiovascular diseases, and all causes of death, from multivariate proportional-hazard regression analyses with baseline serum cholesterol, cigarettes smoked/d, age, sex, income, and race also in the model. Coefficients were as follows: for SBP–ischemic heart disease, 0.0225; for SBP–cardiovascular diseases, 0.0236; and for SBP–all causes mortality, 0.0150. From reference 6.

**Possible increases in risk of other diseases with high habitual salt intake**

The foregoing estimates need to be weighed also in the context of mounting research evidence that excess dietary salt has possible adverse effects on population risks of several other major threats to health. These include gastric cancer, asthma, renal lithiasis, osteoporosis, cardiac left ventricular hypertrophy, left ventricular dysfunction during exercise by hypertensive patients, and stroke (independent of blood pressure effects on risks of these last three) (67, 131–141).

**Safety of moderate reduction in salt intake**

It was noted in the monograph *Diet and Health* that the recommended salt intake ( $\leq$  6 g/d) will have no detrimental effect on the general population (57). This judgment is disputed by some who allege that such moderate reduction in salt intake may have unfavorable effects, for example, increase in blood pressure, serum cholesterol, and glucose, and risk of heart attack (27). Some of these alleged effects, for example, those on plasma biochemical variables, are suggested on the basis of extrapolations from reports of acute studies in subjects with very low salt intakes (27, 142). Other suggested effects, for example, that blood pressure increases in some people in response to moderate salt intake, are from studies without parallel control groups, and hence cannot validly account for random blood pressure fluctuations in individuals (96). Controlled data, available from the Australian trial of salt reduction and the US Trial of Hypertension Prevention, show not only lower average blood pressure values for the group with lower salt intake, but also a smaller percentage of individuals in the intervention than in the control group with an apparent rise above baseline in blood pressure (24, 26, 143). These data indicate that such apparent blood pressure increases are not attributable to dietary salt reduction.

In MRFIT, for men randomly assigned into the two trial groups, 24-h dietary recalls were done at baseline and repeatedly at subsequent annual visits (74). These data permit exploration of questions about the safety of salt intake at the moderate amounts recommended in public policy statements. With four or five recalls per person, estimates of sodium intake are reasonably reliable (Table 2). Mean values for plasma cholesterol, glucose, and uric acid were similar across the quintiles of sodium intake for both SI and UC groups (data available from author on request). Also, changes from baseline in plasma cholesterol, glucose, and uric acid were similar for all quintiles of change in sodium intake for both groups (**Table 10**). Substantial lowering of sodium intake to moderate amounts ( $\approx$ 70 mmol/d) did not induce increases in plasma cholesterol, glucose, or uric acid. These findings do not support the hypothesis that long-term, moderate reduction in salt intake is harmful for the general population. Rather, they support the conclusion of the National Academy of Science monograph that this level of salt intake is associated with no detrimental effects. Nor is this conclusion undermined by a recent report from a study on treated hypertensive men suggesting that lower salt intake may be associated with a greater rate of myocardial infarction in such persons (144). A critique of this report is beyond the scope of this paper; see the concurrent editorial on it, dealing with its limitations (145). Given the extensive data on adverse effects of habitual high salt intake on population blood pressure

TABLE 10

Quintiles of mean change in dietary sodium, trial years 1–6 minus baseline, and mean change in plasma cholesterol, glucose, and uric acid for men in the Multiple Risk Factor Intervention Trial<sup>1</sup>

Quintile (Q) of mean change in Na (mmol/d)	Mean plasma cholesterol change	Mean plasma glucose change	Mean plasma uric acid change
	<i>mmol/L</i> ( <i>mg/dL</i> )	<i>mmol/L</i> ( <i>mg/dL</i> )	<i>μmol/L</i> ( <i>mg/dL</i> )
Usual care group ( <i>n</i> = 6159)			
Q1: -112.5 ( <i>n</i> = 1227)	-0.18 (-6.9)	0.17 (3.0)	0.0 (0.0)
Q2: -32.0 ( <i>n</i> = 1233)	-0.17 (-6.4)	0.11 (2.0)	0.0 (0.0)
Q3: 1.6 ( <i>n</i> = 1230)	-0.15 (-5.7)	0.14 (2.5)	0.0 (0.0)
Q4: 32.3 ( <i>n</i> = 1240)	-0.15 (-5.8)	0.12 (2.1)	0.0 (0.0)
Q5: 87.1 ( <i>n</i> = 1229)	-0.16 (-6.0)	0.19 (3.4)	-5.9 (-0.1)
Special intervention group ( <i>n</i> = 6196)			
Q1: -131.4 ( <i>n</i> = 1238)	-0.32 (-12.3)	0.06 (1.1)	11.9 (0.2)
Q2: -48.0 ( <i>n</i> = 1234)	-0.37 (-13.0)	0.07 (1.2)	5.9 (0.1)
Q3: -12.7 ( <i>n</i> = 1246)	-0.29 (-11.3)	0.09 (1.6)	5.9 (0.1)
Q4: 17.8 ( <i>n</i> = 1240)	-0.30 (-11.7)	0.16 (2.8)	5.9 (0.1)
Q5: 68.0 ( <i>n</i> = 1238)	-0.31 (-12.1)	0.16 (2.9)	5.9 (0.1)

<sup>1</sup> Change data are based on one measurement per man at baseline and the mean of six annual plasma measurements per man during the trial; four and five 24-h dietary recalls were collected at annual visits for men in the usual care and special intervention groups, respectively. Means are adjusted for age, race, baseline diastolic blood pressure and cigarettes smoked/d, change in weight, change in energy consumed/d, change in percent of energy from dietary saturated and polyunsaturated fatty acids and alcohol, change in dietary cholesterol (mg/4184 kJ), and year-6 antihypertensive medication status.

values and the lack of well-controlled confirmed evidence on hypothesized adverse effects, expected benefits from a moderate reduction in salt intake far outweigh putative risks.

It was stated here that the foregoing assessment is not well founded because trials of salt reduction have had only blood pressure (an intermediate variable) as the endpoint, not incidence of major CVD or mortality. Without data from such trials, it was averred, public policy recommending that the general population reduce their salt intake to moderate levels is inappropriate. This argument ignores the fact that there are data showing adverse influences of high salt intake on cardiovascular endpoints, as cited above (138–141). Moreover, this assertion needs scrutiny for another reason: recent experience with proposals for definitive large-scale, long-term, randomized controlled trials on the diet-heart issue casts light on the realities and implications of this approach to the salt-health issue. The diet-heart trial issue concerned the use of randomized controlled trials to assess primary preventive effects of dietary lipid modification on ischemic heart disease and CVD incidence and mortality and (possibly) on all-cause mortality in people free of clinical ischemic heart disease and CVD. Developments on this issue from the late 1950s to its resolution in the early 1970s are well documented (146–148). For multiple reasons, scientific and administrative, the policy decision was made to not undertake such trials (148).

Any effort to mount a salt-health trial in nonhypertensive people from the general population, with ischemic heart disease and CVD incidence and mortality or all-cause mortality as the primary endpoint, faces the formidable problems that confronted proposed diet-heart trials. No investigative groups or funding agencies are considering undertaking such salt-health trials. Therefore, it is unrealistic to speak of data from such trials as prerequisites for recommendations to the general population on moderating salt intake to improve health. As with dietary lipids and health, advice to the general population can and must go forward on the basis of

extensive evidence from several research disciplines short of definitive, hard-endpoint trials.

Particularly in the mid-1990s, after celebration of the 30th anniversary of the landmark report to the Surgeon General on smoking and health (149), the lesson of this report merits attention. The expert group set up by the Surgeon General had the explicit charge to set down its judgments on the etiologic significance of several sets of observational data, mainly epidemiologic, showing associations between smoking and lung cancer, chronic obstructive pulmonary disease, ischemic heart disease, etc, as a basis for recommendations for population-wide public policy. No data were available or pending from randomized controlled trials with hard disease endpoints. The expert group systematically addressed this assignment, disease by disease, aided by a set of guidelines for evaluating the etiologic significance of epidemiologic associations (149). The result is history: productive recommendations to the general population on improving lifestyles to enhance health and longevity with health.

Those who reject present recommendations on salt intake, for example, a salt intake < 6 g/d by Americans, are implicitly endorsing the status quo as the best of all possible worlds nutritionally, that is, endorsing the large amounts of salt added to thousands of food products in food manufacturing and processing (a source of  $\geq 75\%$  of all ingested salt), including many products that are generally recognized as undesirable for multiple nutritional reasons. Silence means consent. It is also argued that reducing population salt intake is controversial and that experts disagree. In brief reply, national and international recommendations, eg, to lower population mean salt intake to 4.5–6.0 g/d, have been made repeatedly on the basis of detailed consideration of the evidence by responsible expert groups (2, 7, 57, 99, 100, 110–115, 150, 151). There is consensus, and there has been for years.

Unanimity, the absence of controversy, has never been a criterion for public policy and public action. Major advances in

knowledge, of significance for medical care and public health, have always been associated with controversy, eg, Harvey and circulation of the blood, Darwin and evolution of species, Pasteur and causation of disease by bacteria, Semmelweis and puerperal fever, Lister and antiseptics, Goldberger and pellagra, and in the present era dietary lipids and atherosclerotic disease, and smoking and ischemic heart disease, chronic obstructive pulmonary disease, lung cancer, etc. Such controversy is inherent in the social process of development of knowledge and in the fact that knowledge never is, and by its very nature cannot be, complete or final. Moreover, as the record documents, controversy also has its roots in special interests, including entrenched academicians and commercial organizations. Application of knowledge for the safe improvement of lifestyles, to prevent and control epidemic diseases afflicting the population, cannot, and need not, wait on cessation of controversy. Witness the important advances made in recent decades in prevention and control of major CVDs through reduction of saturated fat and cholesterol in the diet and in percentage of smokers in the population (both still controversial efforts according to some sectors of the food and tobacco industries).

#### PERSPECTIVE: SOURCES OF THE HIGH INTAKE OF SALT BY THE POPULATION


Contrary to some assertions, excess salt intake by populations can be moderated. The above-cited outcome of the Portuguese community trial is one research-based experience. There are also positive national public policy experiences. Japan is one example: note the points for northern and southern Japan on the Dahl curve (Figure 2): 448 mmol per person per day for men and women in Akita (north) in 1954 and 241 mmol in Hiroshima (south) for men in 1958. By the latter 1980s, when INTERSALT studied three population samples in Japan, median 24-h sodium excretion was 169–214 mmol for men, still high but substantially reduced. This reflects a national undertaking in Japan, to improve nutrition and treat high blood pressure. It is a reasonable inference that the remarkable decline of  $\approx 80\%$  in stroke death rates for both men and women, from rates that were the highest for any industrialized country, has resulted from this effort (67, 123). Concomitantly, ischemic heart disease death rates, the lowest among industrialized countries for decades, have declined so that life expectancies in Japan are now the longest of any nation.

Belgium is a second example. Between October 1976 and July 1978, by royal decree of the Ministry of Health, the high salt content of bread was gradually reduced by 23%, from 15.6 to 12 g/kg (152). In the United States there was evidence of a downturn of  $\approx 36\%$  in purchase of table salt by the general population from 1972 to 1985, from 2.2 to 1.4 lb per person per year (67), evidently in response to repeated recommendations by responsible public health agencies.

Regarding achieving an end to excess salt intake by the population, one must first understand where most of the salt in modern fare comes from: it is not from salt added in the kitchen by the homemaker or at the table by the consumer, it is a result of salting by food processors. Salt is a major food additive. In 1987,  $\approx 83\%$  of ingested salt in British food came from processed foods,  $\approx 7\%$  from salt added in the kitchen, and  $\approx 10\%$

from salt added at the table (57, 65). Similar data are available for Americans (66–68, 153).

The concluding paragraph in the third of three British papers on salt and blood pressure deals with the essence of this matter (25): “Advising the public to reduce consumption of salt is important, but the widespread use of salt in food processing limits what individual people can readily achieve. Labelling of the salt content of foods and, above all, reduction in the amount of salt added by manufacturers to processed food is a vital public health objective. Such action by food manufacturers, as well as people not adding salt to food. . . could reduce sodium intake by 100 mmol/24 h. . . Few measures in preventive medicine are as simple and economical and yet can achieve so much.”

For the United States, the strategic essentials, including the possibilities for population-wide health progress, and the challenges, among them to the food industry, were set down in the 1993 National Heart, Lung and Blood Institute report on primary prevention of hypertension (2). The recommendations of this landmark document, developed and approved after months of deliberation by experts, merit comprehensive implementation. 

It is a pleasure to express appreciation to Alan Dyer and Rose Stamler for thoughtful advice on this paper and to the many colleagues worldwide who participated in the INTERSALT Study, including those at the Chicago Coordinating Center (Alan R Dyer, Kiang Liu, and Rose Stamler), at the London Coordinating Center (Paul Elliott, Michael Marmot, Robert Nichols, the late Geoffrey Rose, and Martin Shipley), and at the Central Laboratory in Leuven, Belgium (particularly Hugo Kesteloot); to acknowledge the many colleagues nationwide who collected the MRFIT data, and the staff of the MRFIT Coordinating Center, particularly James D Neaton, Deborah Wentworth, and Greg Grandits; to express appreciation to the many colleagues who contributed to the collection and analyses of the Chicago population study data cited here; to express appreciation to colleagues in these studies at Northwestern University Medical School (Alan R Dyer, Dan Garside, Philip Greenland, Kiang Liu, Karen Ruth, Rose Stamler, Linda Van Horn, and Molly Walsh); and to acknowledge publishers who kindly gave permission to reproduce data here, specifically the American Heart Association (*Hypertension*); the publishers of *American Journal of Cardiology*, *American Journal of Epidemiology*, *Annals Internal Medicine*, *Annals of the New York Academy of Sciences*, *British Medical Journal*, *Journal of Chronic Diseases* (*Journal of Clinical Epidemiology*); Raven Press; and Springer-Verlag.

#### REFERENCES

1. McKeown T. The direction of medical research. *Lancet* 1979; 2:1281–4.
2. National High Blood Pressure Education Program Working Group. National High Blood Pressure Education Program Working Group report on primary prevention of hypertension. *Arch Intern Med* 1993;153:186–208.
3. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the adult US population: results from the third National Health and Nutrition Examination Survey, 1988–91. *Hypertension* 1995;25: 305–13.
4. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765–74.
5. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. *Arch Intern Med* 1993;153:598–615.

6. Neaton JD, Kuller L, Stamler J, Wentworth DN. Impact of systolic and diastolic blood pressure on cardiovascular mortality. In: Laragh JH, Brenner BM, eds. *Hypertension: physiology, diagnosis, and management*. 2nd ed. New York: Raven Press, 1995:127-44.
7. National High Blood Pressure Education Program. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med* 1993;153:154-83.
8. Hypertension Detection and Follow-up Program Cooperative Group. Race, education and prevalence of hypertension. *Am J Epidemiol* 1977;106:351-61.
9. Liu K, Cedres L, Stamler J, et al. Relationship of education to major risk factors and death from coronary heart disease, cardiovascular diseases and all causes: findings of three Chicago epidemiologic studies. *Circulation* 1982;66:1308-14.
10. Stamler R, Shipley M, Elliott P, et al. Higher blood pressure in adults with less education: some likely explanatory factors. Findings of the INTERSALT Study. *Hypertension* 1992;19:237-41.
11. Stamler J. Blood pressure and high blood pressure: aspects of risk. *Hypertension* 1991;18(suppl 1):I-97-107.
12. Stamler J. Research opportunities and directions on the blood pressure problem: combining predictors. *Am J Hypertens* 1991;4:646S-60S.
13. Stamler J. *Lectures on preventive cardiology*. New York: Grune and Stratton, 1967.
14. Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *Br Med J* 1988;297:319-28.
15. INTERSALT Co-operative Research Group. Elliott P, ed. *The INTERSALT Study—an international co-operative study of electrolyte excretion and blood pressure: further results*. *J Hum Hypertens* 1989;3:279-407.
16. Baba S, Pan W, Ueshima H, et al. Blood pressure levels, related factors, and hypertension control status of Japanese and Americans. *J Hum Hypertens* 1991;5:317-32.
17. Huang Z, Wu X, Stamler J, et al. A north-south comparison of blood pressure and factors related to blood pressure in the People's Republic of China: a report from the PRC-USA Collaborative Study of Cardiovascular Epidemiology. *J Hypertens* 1994;12:1103-12.
18. Ruskin A. *Classics in arterial hypertension*. Springfield, IL: Charles C Thomas, 1956.
19. Riva-Rocci S. A new sphygmomanometer. *Gazz Med Torino* 1896;47:981-1001 (in Italian).
20. Ambard L, Beaujard E. Causes of arterial hypertension. *Arch Gen Med* 1904;1:520-33 (in French).
21. Allen FM, Sherrill JW. The treatment of arterial hypertension. *J Metab Res* 1922;2:429-545.
22. Kempner W. Treatment of hypertensive vascular disease with a rice diet. *Am J Med* 1948;4:545-77.
23. Cutler JA, Follmann D, Elliott P, Suh I. An overview of randomized trials of sodium reduction and blood pressure. *Hypertension* 1991;17(suppl 1):I-27-33.
24. Cutler JA, Follman D, Allender PS. Randomized trials of sodium reduction: an overview. *Am J Clin Nutr* 1997;65(suppl):643S-51S.
25. Law MR, Frost CD, Wald NJ. By how much does salt restriction lower blood pressure? I. Analysis of observational data among populations. II. Analysis of observational data within populations. III. Analysis of data from trials of salt reduction. *Br Med J* 1991;302:811-24.
26. Whelton PK, Kumanyika SK, Cook NR, et al. Efficacy of nonpharmacologic interventions in adults with high-normal blood pressure: results from phase I of the Trials of Hypertension Prevention. *Am J Clin Nutr* 1997;65(suppl):652S-60S.
27. 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.
28. Lenfant C. High blood pressure: some answers, new questions, continuing challenges. *JAMA* 1996;275:1604-6.
29. Stamler J. Letter to the editor (on Midgley JP, et al. *JAMA* 1996;275:1590-7). *JAMA* 1996;276:1467.
30. Stamler J, Stamler R, Brown WV, et al. Serum cholesterol: doing the right thing. *Circulation* 1993;88:1954-60.
31. Stamler J, Stamler R, Brown WV. Reply to letters to the editor on editorial, "Doing the right thing." *Circulation* 1994;90:2573-7.
32. Hofman A, Hazebroek A, Valkenburg HA. A randomized trial of sodium intake and blood pressure in newborn infants. *JAMA* 1983;250:370-3.
33. Geleijnse JM. Sodium, potassium, and blood pressure. Studies in the young and the old. PhD dissertation. Rotterdam, Netherlands: Erasmus University, 1996.
34. Staessen JA, Lijnen P, Thijs L, Fagard R. Salt and blood pressure in community-based intervention trials. *Am J Clin Nutr* 1997;65(suppl):661S-70S.
35. Forte JG, Miguel JM, Miguel MJ, De Padua F, Rose G. Salt and blood pressure: a community trial. *J Hum Hypertens* 1989;3:179-84.
36. Meneely GR. The experimental epidemiology of sodium chloride toxicity in the rat. In: Stamler J, Stamler R, Pullman TN, eds. *The epidemiology of hypertension*. New York: Grune and Stratton, 1967:240-6.
37. Laragh JH, Pecker MS. Dietary sodium and essential hypertension: some myths, hopes, and truths. *Ann Intern Med* 1983;98(pt 2):735-43.
38. Tobian L. Salt and hypertension: lessons from animal models that relate to human hypertension. *Hypertension* 1991;17(suppl 1):I-52-8.
39. Stamler J, Katz LN, Pick R, Rodbard S. Dietary and hormonal factors in experimental atherogenesis and blood pressure regulation. In: Pincus G, ed. *Recent progress in hormone research*. New York: Academic Press, 1955:401-52.
40. Denton D. *The hunger for salt: an anthropological, physiological and medical analysis*. Berlin: Springer-Verlag, 1982.
41. Denton D, Weisinger R, Mundy NI, et al. The effect of increased salt intake on blood pressure of chimpanzees. *Nature Med* 1995;1:1009-16.
42. Dahl L. Possible role of salt intake in the development of hypertension. In: Cottier P, Bock KD, eds. *Essential hypertension: an international symposium*. Berlin: Springer-Verlag, 1960:53-65.
43. Sasaki N. High blood pressure and the salt intake of the Japanese. *Jpn Heart J* 1962;3:313-24.
44. Gleibermann L. Blood pressure and dietary salt in human populations. *Ecol Food Nutr* 1973;2:143-56.
45. Froment A, Milon H, Gravier C. Relationship of sodium intake and arterial hypertension. Contribution of geographical epidemiology. *Rev Epidemiol Sante Publique* 1979;27:437-54.
46. Shaper AG. Communities without hypertension. In: Shaper AG, Hutt MSR, Fejfar Z, eds. *Cardiovascular disease in the tropics*. London: British Medical Association, 1974:77-83.
47. Page LB, Damon A, Moellering RC. Antecedents of cardiovascular disease in six Solomon Islands societies. *Circulation* 1974;49:1132-46.
48. Page LB, Vandevent DE, Nader K, Lubin NK, Page JR. Blood pressure of Qash'qai pastoral nomads in Iran in relation to culture, diet, and body form. *Am J Clin Nutr* 1981;34:527-38.
49. Stamler J, Stamler R, Pullman T, eds. *The epidemiology of hypertension*. New York: Grune and Stratton, 1967.
50. Paul O, ed. *Epidemiology and control of hypertension*. New York: Symposia Specialists, 1975.
51. He J, Thell G, Tang YC, Mo PS, He GQ. Effect of migration on blood pressure: the Yi People Study. *Epidemiology* 1991;2:88-97.
52. Poulter N, Khaw KT, Hopwood BE, et al. Blood pressure and its correlates in an African tribe in urban and rural environments. *J Epidemiol Community Health* 1984;38:181-5.
53. Joslin EP, as quoted in: Walker A. Diabetes in Europe and beyond. *Br Med J* 1991;302:1231.

54. Shimkets RA, Warnock DG, Bositis CM, et al. Liddle's syndrome: heritable human hypertension caused by mutations in the B subunit of the epithelial sodium channel. *Cell* 1994;79:407-14.
55. Caulfield M, Lavender P, Farrall M, et al. Linkage of the angiotensinogen gene to essential hypertension. *N Engl J Med* 1994;330:1629-33.
56. Harrap SB. Hypertension: genes versus environment. *Lancet* 1994;334:169-71.
57. National Research Council, Committee on Diet and Health, Food and Nutrition Board, Commission on Life Sciences. Diet and health: implications for reducing chronic disease risk. Washington, DC: National Academy Press, 1989.
58. Clagg JB. Travels with DNA in the Pacific. *Lancet* 1994;344:1070-2.
59. Blyth WB. Salt and water in culture and medicine. *N Engl J Med* 1994;330:1909-10 (book review).
60. Dawkins R. The blind watchmaker. London: Penguin Books, 1988.
61. Eldredge N. Reinventing Darwin. New York: John Wiley and Sons, 1995.
62. Gould SJ. Bully for brontosaurus. New York: WW Norton, 1991.
63. Leakey RE. The origin of humankind. New York: BasicBooks, 1994.
64. Elliott P. Observational studies of salt and blood pressure. *Hypertension* 1991;17(suppl 1):1-3-8.
65. Sanchez-Castello CP, Warrender S, Whitehead TP, James WPT. An assessment of the sources of dietary salt in a British population. *Clin Sci* 1987;72:95-102.
66. Mattes RD, Donnelly D. Relative contributions of dietary sodium sources. *J Am Coll Nutr* 1991;10:383-93.
67. Stamler J. Dietary salt and blood pressure. *Ann N Y Acad Sci* 1993;676:122-56.
68. Dennis BH. Public health policy and salt: doing the right thing. *Perspect Appl Nutr* 1995;3:121-23.
69. Keys A. Dietary survey methods in studies on cardiovascular epidemiology. *Voeding* 1965;26:464-83.
70. Stamler J. Assessing diets to improve world health: nutritional research on disease causation in populations. *Am J Clin Nutr* 1994;59(suppl):146S-56S.
71. Liu K, Stamler J, Dyer A, McKeever J, McKeever P. Statistical methods to assess and minimize the role of intra-individual variability in obscuring the relationship between dietary lipids and serum cholesterol. *J Chronic Dis* 1978;31:399-418.
72. Liu K, Cooper R, McKeever J, et al. Assessment of the association between habitual salt intake and high blood pressure: methodological problems. *Am J Epidemiol* 1979;110:219-25.
73. Liu K, Stamler J, Stamler R, et al. Methodological problems in characterizing an individual's plasma glucose level. *J Chronic Dis* 1982;35:475-85.
74. Stamler J, Caggiula A, Cutler J, et al, eds. Dietary and nutritional methods and findings: the Multiple Risk Factor Intervention Trial (MRFIT). *Am J Clin Nutr* 1997;65(suppl):183S-402S.
75. Dyer AR, Shipley M, Elliott P, for the INTERSALT Cooperative Research Group. Urinary electrolyte excretion in 24 hours and blood pressure in the INTERSALT Study. I. Estimates of reliability. *Am J Epidemiol* 1994;139:927-39.
76. Dyer AR, Shipley M, Elliott P, for the INTERSALT Cooperative Research Group. Urinary electrolyte excretion in 24 hours and blood pressure in the INTERSALT Study. II. Estimates of electrolyte-blood pressure associations corrected for regression dilution bias. *Am J Epidemiol* 1994;139:940-51.
77. Elliott P, Stamler R, in consultation with other investigators of INTERSALT. Manual of operations for "INTER-SALT": an international cooperative study on the relation of sodium and potassium to blood pressure. *Control Clin Trials* 1988;9:1S-118S.
78. INTERSALT Cooperative Research Group. Sodium, potassium, body mass, alcohol and blood pressure: the INTERSALT Study. *J Hypertens* 1988;6(suppl. 4):S584-6.
79. Mancilha-Carvalho JJ, Baruzzi RG, Howard PF, et al. Blood pressure in four remote populations in the INTERSALT Study. *Hypertension* 1989;14:238-46.
80. Dyer AR, Elliott P, Shipley M, for the INTERSALT Cooperative Research Group. Body mass index versus height and weight in relation to blood pressure: findings for the 10,079 persons in the INTERSALT Study. *Am J Epidemiol* 1990;131:589-96.
81. Stamler J, Rose G, Elliott P, et al, for the INTERSALT Cooperative Research Group. Findings of the international cooperative INTERSALT Study. *Hypertension* 1991;17(suppl 1):1-9-15.
82. Marmot MG, Elliott P, Dyer AR, et al. Alcohol and blood pressure: the INTERSALT Study. *Br Med J* 1994;308:1263-7.
83. Dyer AR, Elliott P, Shipley M, Stamler R, Stamler J, on behalf of the INTERSALT Cooperative Research Group. Body mass index and associations of sodium and potassium with blood pressure in INTERSALT. *Hypertension* 1994;23:729-36.
84. Stamler J, Dyer AR, Elliott P, Kesteloot H, Marmot M, Stamler R. Salt sensitivity in general populations: majority or minority phenomenon? INTERSALT findings. *Circulation* 1995;91:931 (abstr).
85. Elliott P, Stamler J, Nichols R, et al. INTERSALT revisited: further analysis of the 24 hour sodium excretion and blood pressure within and across populations. *Br Med J* 1996;312:1249-53.
86. Dyer AR, Elliott P, Marmot M, et al. Commentary: strength and importance of the relationship of dietary salt to blood pressure. *Br Med J* 1996;312:1661-4.
87. Elliott P, Marmot M, Dyer A, et al. The INTERSALT Study: main results, conclusions and some implications. *Clin Exp Hypertens A* 1989;11:1025-34.
88. Stamler J, Rose G, Stamler R, Elliott P, Dyer A, Marmot M. INTERSALT study findings—public health and medical care implications. *Hypertension* 1989;14:570-7.
89. Stamler R. Implications of the INTERSALT Study. *Hypertension* 1991;17(suppl 1):1-16-20.
90. Elliott P, Dyer A, Stamler R, Stamler J. Correcting for regression dilution in INTERSALT. *Lancet* 1993;342:1123 (letter).
91. Elliott P, Stamler J, Stamler R, Dyer A. Dietary salt and blood pressure. *Lancet* 1994;343:546 (letter).
92. Elliott P, Stamler J, Stamler R, Dyer AR, Kesteloot H, Marmot M. Excess alcohol intake and other risk factors for adverse blood pressure patterns in populations: a commentary. *Cardiovasc Risk Factors* 1994;4:162-4.
93. Liu K. Measurement error and its impact on partial correlation and multiple linear regression analyses. *Am J Epidemiol* 1988;127:864-74.
94. Geleijnse JM, Witteman JCM, Bak AAA, den Breeijen JH, Grobbee DE. Reduction in blood pressure with a low sodium, high potassium, high magnesium salt in older subjects with mild to moderate hypertension. *Br Med J* 1994;309:436-40.
95. Elliott P, Forrest RD, Jackson CA, Yudkin JS. Sodium and blood pressure: positive associations in north London population with consideration of the methodological problems of within-population surveys. *J Hum Hypertens* 1988;2:89-95.
96. Muntzel M, Druke T. A comprehensive review of the salt and blood pressure relationship. *Am J Hypertens* 1992;5(4 pt 1):1S-42S.
97. Alderman M. Non-pharmacological treatment of hypertension. *Lancet* 1994;344:307-11.
98. Stamler J, Elliott P, Stamler R, Dyer A, Marmot M, Kesteloot H. Non-pharmacological treatment of hypertension. *Lancet* 1994;344:884-5 (letter).
99. US Department of Agriculture, US Department of Health and Human Services. Dietary guidelines for Americans. 4th ed. Washington, DC: US Government Printing Office, 1995.
100. Dietary Guidelines Advisory Committee. Report of the Dietary Guidelines Advisory Committee on the dietary guidelines for Americans. Washington, DC: US Government Printing Office, 1995.
101. Hanneman RL. Hypertension rise with age revisited. *Br Med J* 1996;312:1283-4.
102. Stamler J, Elliott P, Dyer AR, et al. Commentary: sodium and blood

- pressure in the INTERSALT Study and other studies—in reply to the Salt Institute. *Br Med J* 1996;312:1285–7.
103. Stamler J, Elliott P, Dyer AR, et al. Sodium and blood pressure in the Intersalt study and other studies—in reply to the Salt Institute, extended commentary. *British Medical Journal Online*. Version current 18 May 1996. World Wide Web: <http://www.tecc.co.uk/bmj/archive/7041ed3.htm>
  104. Law M. Commentary: evidence on salt is consistent. *Br Med J* 1996;312:1284–5.
  105. Godlee F. The food industry fights for salt. But delaying salt reductions has public health and commercial costs. *Br Med J* 1996;312:1239–40 (editorial).
  106. Thelle D. Salt and blood pressure revisited. *Br Med J* 1996;312:1240–1 (editorial).
  107. Swales JD. Studies of salt intake in hypertension: what can epidemiology teach us? *Am J Hypertens* 1990;3:645–9.
  108. Freis ED. Salt, volume and the prevention of hypertension. *Circulation* 1976;53:589–95.
  109. Cutler JA, Kotchen TA, Obarzanek E, eds. *The National Heart, Lung, and Blood Institute Workshop on Salt and Blood Pressure*. Hypertension 1991;17(suppl 1):I-1-221.
  110. Ernst ND. Health promotion roles of the federal government and food industry in nutrition and blood pressure. *Hypertension* 1991;17(suppl 1):1-196-200.
  111. WHO Expert Committee on the Prevention of Coronary Heart Disease. Prevention of coronary heart disease. *World Health Organ Tech Rep Ser* 1982;678.
  112. WHO Expert Committee On Prevention in Childhood and Youth of Adult Cardiovascular Disease. Prevention in childhood and youth of adult cardiovascular diseases—time for action: report of a WHO expert committee. *World Health Organ Tech Rep Ser* 1990;792.
  113. WHO Study Group. Diet, nutrition, and the prevention of chronic diseases. *World Health Organ Tech Rep Ser* 1990;797.
  114. Task Force on Research in Epidemiology and Prevention of Cardiovascular Diseases. National Heart, Lung, and Blood Institute report of the Task Force on Research in Epidemiology and Prevention of Cardiovascular Diseases. Bethesda, MD: National Institutes of Health, 1994.
  115. Department of Health. Nutritional aspects of cardiovascular disease. Report of the Cardiovascular Review Group, Committee on Medical Aspects of Food Policy. London: Her Majesty's Stationery Office, 1994. (Report of Health and Social Subjects #46.)
  116. Luft FC, Weinberger MH. Heterogeneous responses to changes in salt intake: the salt-sensitivity paradigm. *Am J Clin Nutr* 1997;65(suppl):612S–7S.
  117. Weinberger MH, Fineberg NS. Sodium and volume sensitivity of blood pressure: age and pressure change over time. *Hypertension* 1991;18:67–71.
  118. Beynen AC, Katan MB. Reproducibility of the variations between humans in the response of serum cholesterol to cessation of egg consumption. *Atherosclerosis* 1985;57:19–31.
  119. Vaccaro O, Ruth KJ, Stamler J. Relationship of postload plasma glucose to mortality with 19-yr follow-up: comparison of one versus two plasma glucose measurements in the Chicago Peoples Gas Company Study. *Diabetes Care* 1992;15:1328–34.
  120. Stamler J, Caggiula A, Grandits GA, Kjelsberg M, Cutler JA. Relationship to blood pressure of combinations of dietary macronutrients: findings of the Multiple Risk Factor Intervention Trial (MRFIT). *Circulation* 1996;94:2417–23.
  121. Stamler J, Elliott P, Kesteloot H, et al. Inverse relationship of dietary protein markers with blood pressure of individuals: findings for 10,020 men and women. The INTERSALT Study. *Circulation* 1996;94:1629–34.
  122. Stamler J. Established major coronary risk factors. In: Marmot M, Elliott P, eds. *Coronary heart disease epidemiology: from aetiology to public health*. New York: Oxford UP, 1992:35–66.
  123. Stamler J. Potential for prevention of major adult cardiovascular disease. In: Toshima H, Koga Y, Blackburn HJ, eds. *Lessons for science from the Seven Countries Study*. Tokyo: Springer-Verlag, 1995:195–235.
  124. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. *J Chronic Dis* 1978;31:201–306.
  125. McGee T, Gordon T, eds. *The Framingham Study—an epidemiological investigation of cardiovascular disease*. Section 31. The results of the Framingham Study applied to four other U.S.-based epidemiologic studies of cardiovascular disease. Washington, DC: Public Health Service, 1976.
  126. Stamler R, Stamler J, eds. *Asymptomatic hyperglycemia and coronary heart disease: a series of papers by the International Collaborative Group, based on studies in fifteen populations*. *J Chronic Dis* 1979;32:683–837.
  127. Stamler J, Dyer AR, Shekelle RB, Neaton J, Stamler R. Relationship of baseline major risk factors to coronary and all-cause mortality, and to longevity: findings from long-term follow-up of Chicago cohorts. *Cardiology* 1993;82:191–222.
  128. Swales JD. Salt saga continued. *Br Med J* 1988;297:307–8.
  129. Stamler J, Neaton JD, Wentworth D, for the MRFIT Research Group. Mortality of low risk and other men: 16-year follow-up of 353,340 men screened for the Multiple Risk Factor Intervention Trial (MRFIT). *Circulation* 1994;89:938 (abstr).
  130. Stamler J, Garside K, Stamler R, et al. Low risk women and men: 19-year mortality data, Chicago Heart Association Detection Project in Industry (CHA). *Circulation* 1994;89:938 (abstr).
  131. Montes G, Cuello C, Correa P, et al. Sodium intake and gastric cancer. *J Cancer Res Clin Oncol* 1985;109:42–5.
  132. Joossens JV, Hill MJ, Elliott P, et al. Dietary salt, nitrate and stomach cancer mortality in 24 countries. *Int J Epidemiol* 1996;25:494–504.
  133. Burney PG, Britton JR, Chinn S, et al. Response to inhaled histamine and 24-hour sodium excretion. *Br Med J* 1986;292:1483–6.
  134. Knox AJ. Salt and asthma. *Br Med J* 1993;307:1159–60.
  135. Pless TB, ed. *The epidemiology of childhood disorders*. New York: Oxford University Press, 1994.
  136. Cirillo M, Laurenzi M, Panarelli W, Stamler J, on behalf of the Gubbio Population Study Research Group. Urinary sodium to potassium ratio and urinary stone disease. *Kidney Int* 1994;46:1133–9.
  137. MacGregor GA, Cappuccio FP. The kidney and essential hypertension: a link to osteoporosis? *J Hypertens* 1993;11:781–5.
  138. Liebson PR, Grandits GA, Dianzumba S, et al. Comparison of five antihypertensive monotherapies and placebo for change in left ventricular mass in patients receiving nutritional-hygienic therapy in the Treatment of Mild Hypertension Study (TOMHS). *Circulation* 1995;91:698–706.
  139. Ferrara LA, De Simone G, Pasanisi F, Mancini M, Mancini M. Left ventricular mass reduction during salt depletion in arterial hypertension. *Hypertension* 1984;6:755–9.
  140. Blake J, Devereux RB, Borer JS, Szulc M, Pappas TW, Laragh JH. Relation of obesity, high sodium intake, and eccentric left ventricular hypertrophy to left ventricular exercise dysfunction in essential hypertension. *Am J Med* 1990;88:477–85.
  141. Antonios TFT, MacGregor GA. Salt—more adverse effects. *Lancet* 1996;348:250–1.
  142. Egan BM, Stepniakowski KT. Adverse effects of short-term very low salt diets in subjects with risk-factor clustering. *Am J Clin Nutr* 1997;65(suppl):671S–7S.
  143. Australian National Health and Medical Research Council Dietary Salt Study Management Committee. Fall in blood pressure with modest reduction in dietary salt intake in mild hypertension. *Lancet* 1989;1:399–402.
  144. Alderman MH, Madhavan S, Cohen H, Sealey JE, Laragh JH. Low urinary sodium is associated with greater risk of myocardial infar-



- tion among treated hypertensive men. *Hypertension* 1995; 25:1144–52.
145. Cook NR, Cutler JA, Hennekens CH. An unexpected result for sodium—causal or casual? *Hypertension* 1995;25:1153–4 (editorial).
  146. National Diet-Heart Study Research Group. The National Diet-Heart Study final report. *Circulation* 1968;37(suppl 1):I-1-428.
  147. Diet-Heart Review Panel of the National Heart Institute. Mass field trials of the diet-heart question: their significance, timeliness, feasibility, and applicability. New York: American Heart Association, 1969. (American Heart Association Monograph no. 28.)
  148. Zukel WJ, Paul O, Schnaper HW, for the MRFIT. The Multiple Risk Factor Intervention Trial (MRFIT). I. Historical perspectives. *Prev Med* 1981;10:387–401.
  149. Advisory Committee to the Surgeon General. Smoking and health. Washington, DC: US Department of Health, Education and Welfare, 1964.
  150. US Department of Health and Human Services. The Surgeon General's report on nutrition and health. Washington, DC: US Government Printing Office, 1988.
  151. US Department of Health and Human Services. Healthy people 2000: national health promotion and disease prevention objectives (summary report). Washington, DC: US Government Printing Office, 1991. [DHHS publication no.(PHS) 91–50213.]
  152. Joossens JV, Sasaki S, Kesteloot H. Bread as a source of salt: an international comparison. *J Am Coll Nutr* 1994;13:179–83.
  153. Hegsted DM. A perspective on reducing salt intake. *Hypertension* 1991;17(suppl 1):I-201-4.