Letters

Hypertension and Calcium

We wish to make several comments about the article "Blood pressure and nutrient intake in the United States" by David A. McCarron *et al.* (29 June, p. 1392). Using the data base of the first National Health and Nutrition Examination Survey of the National Center for Health Statistics (HANES I) (1971 through 1974) (*1*), the authors present statistical analyses suggesting associations between classification of blood pressure status and consumption of a number of nutrients in the diet of the U.S. population. There are major conceptual and statistical problems in the authors' approach which lead to inappropriate conclusions. These problems include (i) the authors' unconventional definition of hypertension, (ii) their reliance on nondiscretionary sodium intake, and (iii) their flawed statistical analyses.

One problem is the authors' definition of hypertension. Their analyses are limited to systolic blood pressure, even though medical practice considers both systolic and diastolic pressures to be clinically important. Furthermore, recent supplementation trials have suggested that diastolic pressure is more responsive to dietary treatment than is systolic pressure (*2*). Hence, the analyses would have been more rigorous and useful if the results had been systematically examined using both systolic and diastolic blood pressure measures. In addition, the authors use the nonconventional definition of hypertension as the upper 10th percentile of systolic blood pressure for their age-race-sex subgroups.

A second problem is that the sodium intake data in the HANES I estimate only the nondiscretionary sodium content of foods consumed. The data do not include estimates of intake of sodium from discretionary use of salt in food preparation or at the table, or for sodium from drinking water and medications. These sources contribute significantly to total sodium intake in variable ways for different individuals. The limitation of having a measure which estimates only one component of total sodium intake raises serious questions as to the adequacy of this measure for assessing associations between sodium intake and hypertension.

McCarron *et al.* cite four references (*3, 4*) to support their use of the single day of nondiscretionary dietary sodium data from HANES I as an adequate surrogate indicator of mean total sodium intakes of blood pressure groups. These references, however, are either irrelevant or require an assumption that type of subjects, types of diet methodology used, and number of days for which dietary information is collected will not affect the relative nature of the relationship between nondiscretionary sodium to total sodium intake or the reliability and validity of the intake estimates. There is no available information to support their assumptions.

There are also major problems with the analytic methods used by McCarron *et al.* The authors do not control appropriately and consistently for variables such as age, race, sex, and body mass index. The authors, in presenting their figures 1, 2, and 5 and parts of their table 2, purport to adjust for some relevant variables, but their methods of adjustment are inappropriate, as we will show. The remainder of their table 2, figures 3 and 4, and the "Implications" section appear not to be standardized at all. In addition, the definition of hypertension changes from analysis to analysis. A cutoff of 160 mmHg is used in their figures 1 and 4 and part of their table 2; a mean systolic blood pressure is used in their figure 3. Hypertension as defined by the upper 10th percentile for age-sex-race subgroups is used in part of their table 2 and figure 5.

We will use HANES I data throughout the rest of this letter to demonstrate the importance of the methodologic issues.

We were unable to replicate the sample sizes reported in their article. The three questions they reported using to define their sample resulted in a sample of 11,771 instead of 10,419. Therefore we assumed they deleted all people who did not respond "No" to the question "Have you ever been told by a doctor that you have high blood pressure?" in addition to those who responded positively to the three questions listed in the article. That gave us a sample of 10,404 which is the sample used for the remainder of this letter.

In some analyses, the authors attempt to control for confounding factors by direct standardization techniques. Direct standardization can be an effective method of summarizing data and controlling for confounding factors when trends in each subgroup are similar and when subgroups are sufficiently large to yield reliable results. When, however, relationships vary within subgroups or when the sizes of some constituent subgroups are very small, direct standardization may produce deceptive results. In the sample studied, some of the subgroups were extremely small or nonexistent, thus making estimates for these subgroups highly unreliable. This was particularly true when the cutoff for systolic blood pressure of ≥160 mmHg was used to classify individuals as hypertensive. Using the nonconventional approach of defining hypertension as the upper 10th percentile of systolic blood pressure for an age-sex-race subgroup resulted in a wide range of absolute cutoff values, from a low of 130 mmHg for white women 18 through 24 years old to a high of

Table 1. Linear regression models of the relationship between systolic blood pressure and 24-hour intake of calcium and sodium with different analytical approaches. Subsample of adults ages 18 through 75 in the first National Health and Nutrition Examination Survey, 1971 through 1974. The subsample consists of adults who said that they had never been told that they had high blood pressure and were not on medication for high blood pressure, on a low-salt diet, or pregnant (n = 10,404). Individuals with values for systolic or diastolic blood pressure on first reading were retained in the analysis (n = 10,358).

Age	Calcium		Sodium	
	Coefficient	P	Coefficient	P
Unweighted assuming simple random sampling				
Age not in regression	−0.0021 mmHg/mg	0.01	−0.0004 mmHg/mg	0.01
Age in regression	−0.0002 mmHg/mg	0.47	0.0003 mmHg/mg	0.02
Weighted with complex sample design				
Age in regression	0.0006 mmHg/mg	0.08	0.0006 mmHg/mg	0.01

190 mmHg for black males 65 through 74 years old. When using this definition of hypertension to compare mean nutrient intakes of the two blood pressure groups, therefore, the authors were required to average over demographic subgroups with widely disparate blood pressure cutoffs. No documentation was provided to show that there were similar trends in each subgroup.

A complex sample design was used to select the HANES I sample. The sample data were weighted to adjust for unequal sampling probabilities and nonresponse and to make national estimates. Since both the weights and the complex design can have a profound effect on results, they must be accounted for in a statistically valid analysis. The need to take the weights and sample design into account is documented on all public-use data tapes and in a National Center for Health Statistics (NCHS) monograph (*5*) and has been discussed at a number of HANES Users' Group meetings and at NCHS data users' conferences. Neither the weights nor the complex sample design were incorporated into the analyses by McCarron *et al.*

So that readers can judge the effect of incorporating confounding variables, sample weights, and the complex sample design, we are including some of the results of our reexamination of the analyses of McCarron *et al.* The data in Table 1 show that, when age is not included in a linear regression model and the weights and complex sample design are not incorporated, the results are as McCarron *et al.* report: both calcium and sodium are inversely associated with systolic blood pressure. However, when age is incorporated, the calcium association is no longer statistically significant, and the sodium association changes from a negative to a positive relationship (note that, in each model, the coefficient describing the relationships of systolic blood pressure to nutrient intake is extremely small and nutrient intakes contribute very little to the variance in systolic blood pressure). Incorporating the sample weights and design in addition to age makes little difference. In other analyses of HANES data, results and conclusions are changed by incorporating sample weights and design effects (*5*).

Our purpose in this example was not to derive conclusions concerning the associations between nutrient intake and systolic blood pressure, but rather to demonstrate that the analytical approach taken by McCarron *et al.* is incorrect and that some of their conclusions are not supported by the very data they use. An appropriate analysis of the HANES I data would involve, not only correct use of analytical techniques and sample design, but would also require a systematic and thorough evaluation of the effects of a large number of variables in addition to age. Harlan *et al.* (*6*) recently published an analysis of the HANES I data using a different subsample and incorporating the sample weights and design.

In discussing their results, McCarron *et al.* were remiss in not attempting to square their conclusions with the abundance of population-based and experimental data suggesting that dietary sodium indeed plays an important role in hypertension. In contrast, their conclusion that there is an inverse relationship between dietary calcium and blood pressure is consistent with other studies (*4, 7*). We believe that sufficient evidence has accrued to justify further experimental and clinical investigations of associations between dietary calcium and blood pressure. Hypertension is a multifactorial disease, and its relationships with nutrients are complex. Additional studies should be designed to determine precisely the role of calcium and other nutrients in the regulation of blood pressure and the pathogenesis of hypertension, as well as their potential value in prevention and therapy.

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Feinleib, Lenfant, and Miller raise several issues that are critical to understanding the relation of diet and hypertension. Our most important finding, that of decreased intake of calcium in hypertensives compared with normotensives, has now been confirmed in six other reports from five samples, some within weeks of our publication (*1, 2*). Harlan *et al.* (*2*) analyzed the HANES I sample using multiple linear regression with sample weighting and found that, of all nutrients, only calcium, phosphorus, and alcohol had a significant, consistent, and independent relation to blood pressure. No consistent association between sodium and blood pressure was reported by Harlan *et al.* Because no specific data were presented about sodium, it is unknown whether in subgroups there were significant positive or negative associations between sodium and blood pressure. However, in an earlier analysis of HANES I published by the Department of Health and Human Services (*3*), Harlan *et al.* reported two associations of sodium with blood pressure, both consistent with our findings: greater saltshaker use and greater salty snack food consumption were both associated with lower blood pressure. Although the analyses by Harlan *et al.* were commissioned by the National Center for Health Statistics, the overall results disagree with the analysis presented by Feinleib, Lenfant, and Miller.

Our emphasis on systolic hypertension was based on published data from studies that have indicated a stronger relation between cardiovascular complications and systolic, rather than diastolic, blood pressure (*4*). By choosing to define hypertension by two criteria, we could assess the relation of lifetime risk of high blood pressure in peer groups by identifying the upper 10th percentile in each age group, and also the risk of an absolute blood pressure greater than or equal to 160 mmHg.

The "unconventional definition" of hypertension we used in the upper 10th percentile analysis is well supported by the literature on tracking of the level of blood pressure within one's peer group (*5*). The use of this definition permits the identification of those individuals at greatest risk for cardiovascular complications, again within their peer group. Clearly, the greatest risk for complications would occur in a 30-year-old with single blood pressure determination of 158/90 mmHg, compared with a 70-year-old with an identical reading.

Within the HANES I data base, it has already been established that discretionary sodium consumption correlates positively with nondiscretionary sodium; that is, subjects who consume more salt from food sources more frequently use the saltshaker, which is the major source of discretionary sodium (*3*). Discretionary intake can be only qualitatively mea-

sured, because saltshaker hole size and number of shakes are required for quantification. In fact, having nondiscretionary sodium values and not total sodium values, which would have been better estimated from 24-hour urine collections, does not necessarily bias the data. Bias could only occur if discretionary sodium did not parallel nondiscretionary intake, for example, if high sodium intakes were associated with infrequent saltshaker use, and the converse. No data exist to suggest this is true. As an example of how remarkably good the data collection was in HANES I, the average sodium intake of Americans has been measured at 140 to 160 milliequivalents (meq) per day on the basis of 24-hour urinary excretion. Discretionary sodium typically may represent 25 to 40 percent of the overall intake, or an average of about 33 percent (*6*). When one uses this average, nondiscretionary sodium intake should be 100 meq. From our HANES I analysis, the average intake was 97 meq, an excellent agreement.

In regard to replication of our sample, we are under the impression, after recent contact with the National Center for Health Statistics, that our sample size was reproduced exactly.

There are a variety of issues involved in weighting that are not completely represented by Feinleib *et al.*, of which we were aware at publication. It should not be implied that there is only one correct method for dealing with these data, particularly as this is a censored subpopulation. Feinleib, Lenfant, and Miller acknowledge that using the weighted design does not change the results in their hands. More important, weighting affects only the variances and any subsequent statistical tests. As a result, the mean values we reported are not changed by weighting, and the associations we described are therefore unaffected.

We employed discriminant analysis rather than multiple regression analysis because we believe the relation between nutrients and blood pressure may not involve a continuous outcome (in terms of blood pressure), and that a threshold may exist for a nutrient beyond which point hypertension occurs. Therefore, while still a linear method, discriminant analysis may be most appropriate with a dichotomous dependent variable such as hypertension.

The contention that our analysis did not account for age, race, and sex is incorrect. In our table 2, all three confounding factors were accounted for in the first analysis, as stated on page 1393.

As with any major confounder, it is critical to adjust for these effects to demonstrate the observed relation. It may be important, however, to consider an interaction between a nutrient and aging, as nutrient intake (of, for example, calcium) and absorption frequently decrease with aging (*7*). This may be an important consideration when assessing the reasons for the increasing prevalence of hypertension in an older age group.

The intent of our article was to present an original analysis of the HANES I data base. Had we felt it was appropriate to "square" our conclusions with the abundance of population-based and experimental data suggesting that dietary sodium indeed plays an important role in hypertension, we would, of necessity, have included the now rather substantial body of newer information instead of the older information that has been the basis for the formulation of past policy. In fact, the lack of intrapopulation research indicating a positive association of sodium and blood pressure has often been noted (*8*). The most recent findings are consistent with those observed by us in HANES I. Development of high blood pressure in "salt sensitive" models of hypertension has been dissociated from the intake of sodium (*9*). In the most widely studied model of genetic hypertension, sodium restriction has resulted in growth retardation and possible acceleration of the hypertension (*10, 11*). In one of the studies (*11*), the level of sodium restriction was within the bounds currently recommended as the "safe" level of sodium reduction for the U.S. population (*12*). Finally, recently reported studies from abroad suggest no short-term benefits of moderate sodium restriction in hypertensive subjects studied under the tightest control reported to date (*13*).

We are encouraged by the acknowledgement of Feinleib *et al.* that "sufficient evidence has accrued to justify further experimental and clinical investigation of associations between dietary calcium and blood pressure." We trust that this portends a broadening from the narrow focus on sodium as the principle factor in the pathogenesis of hypertension. We hope that this new perspective will not simply encompass calcium, but will address the role of all nutrients, as well as the complicated interactions that characterize our diet. The complex issues we face in applying this information to our understanding of the pathogenesis of this common medical disorder should be a stimulus to intensify our research efforts rather than to formulate simplified and premature therapeutic recommendations to the public. Other established investigators in the research community share our perspective and have articulated it in recent public statements (*14*).

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Erratum: In the report "Cell sensitivity to gravity," by A. Cogoli *et al.* (13 July, p. 228), the legend for figure 1b should have read: "Glucose consumed by the lymphocyte cells during the experiment. The initial concentration of glucose in the medium was 1100 mg/liter; the glucose that remained in the medium after the experiment was measured by the glucose dehydrogenase method (*6*). The standard deviation of triplicate samples is shown."

Erratum: In the News and Comment article "Use of antibiotics in animal feed challenged" (12 Oct., p. 144) by Marjorie Sun, the rate of fatalities resulting from infections caused by drug-resistant *Salmonella* was incorrectly reported. The fatality rate resulting from these infections is 21 times higher than for disease caused by *Salmonella* strains that responded to conventional antibiotics. This finding was reported by Scott D. Holmberg *et al.* in *Science*, 24 Aug., p. 833.

Erratum: In two Research News articles by Arthur L. Robinson (24 Aug., p. 822; 14 Sept., p. 1137), the affiliations of three researchers were given incorrectly. Peter Smith and Thirumalai Venkatesan (24 Aug.) are with Bell Communications Research (Bellcore), not AT&T Bell Laboratories, as stated. David Hwang (14 Sept.) is also with Bellcore.