the relation of our findings to magnesium balance, energy metabolism, sodium and potassium handling by vascular and renal tissue, and the contribution of essential vitamins to cardiovascular physiology. It is also possible that the condition of hypertension predisposes individuals to decrease their calcium intake.

There is evidence that humans with essential hypertension, as well as laboratory animals used as models of hypertension, have associated abnormalities of calcium metabolism (*7–9, 18*). Data from a number of epidemiologic studies indicate an inverse correlation between the calcium content of drinking water and the mean arterial blood pressure or prevalence of hypertension in humans living in specified geographical regions (*19*). In laboratory animals, increased calcium intake lowers blood pressure in normotensive animals and attenuates the development of hypertension in hypertensive models (*8, 11, 12*); the earlier a calcium supplement is introduced, the greater the long-term reduction in blood pressure (*11*).

Our results are interesting for several reasons. First, the HTN patients and NL volunteers reported typical values for the other nutritional components of their diet. Second, although the calcium intake of the HTN's was significantly lower than that of the NL's, the HTN's intake was still within the lower limits recommended for Americans. If, as the data suggest, HTN subjects require a normal or even increased amount of dietary calcium, the calcium intakes reported by the HTN's in our survey may be inadequate. Third, in contrast to the values for sodium or potassium intake, we found a significant difference in calcium intake when the study population was segregated on the basis of the presence or absence of high blood pressure. Overall these data suggest a link between decreased calcium intake and excessive dietary sodium in the pathogenesis of human hypertension. For example, increased sodium intake is associated with enhanced sodium excretion by the kidney and consequent calciuresis (*20*). At the cellular level, modification of calcium homeostasis in vascular tissue may alter intracellular concentrations of $Na^+$ and $K^+$ as well as transmembrane fluxes (*21*).

Calcium intake is decreasing in the United States (*22*), and dietary calcium is already well below acceptable levels among some segments [black and elderly subjects (*23*)] of the society who are at greater risk of developing high blood pressure. The results of our survey should also sound a note of caution as several of the dietary restrictions (for example, low cholesterol, low sodium) now recommended to persons with hypertension could potentially result in concurrent, inadvertent, additional reduction in calcium intake.

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13. The HANES was undertaken by the National Center for Health Statistics to collect measures of nutritional status for a scientifically designed representative sample of the U.S. population between ages 1 and 74 years. The survey sampled 28,043 persons at 65 locations between April 1971 and June 1974. The data are available from Vital and Health Statistics, Series 11:202, National Center for Health Statistics, Division of Health Examinations Statistics, Rockville, Md.
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17. There was no correlation between age and reported calcium or sodium intake in either the NL's or the HTN's when all subjects were considered; however, within the female subset (NL and HTN), calcium intake declined with age ($P < .05$).
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23. The HANES documented insufficient levels of calcium intake (< 650 mg/day) in blacks and in individuals over 65 years of age.
24. Supported in part by grant RR00334 from the General Clinical Research Branch of the Divison of Research Resources, National Institutes of Health, and by a grant-in-aid from the Oregon Heart Association. We thank J. Paquet for preparation of the manuscript.

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## Intrathecal Interferon for Multiple Sclerosis

Jacobs *et al.* (*1*) reported a clinical trial in which intrathecal interferon reduced exacerbations in patients with multiple sclerosis. However, the methods these authors used and certain errors in their report raise questions about their findings.

Although Jacobs *et al.* described their study as "a randomized controlled study," the number of years on study was longer for every patient in the treated group than for any patient in the control group (*2*). The reason for this was not explained.

The authors reported a statistically significant difference ($P < .05$) in the rates of exacerbation in the treated and control groups during the study, but, according to the data in their table 1, the probability was .104 (two-tailed *t*-test). A further difficulty is that the non-normality of the rates makes the *t*-test inappropriate; with the more appropriate Mann-Whitney *U* test (*3*), $P = .12$.

Jacobs *et al.* did not describe the procedure for retrospectively determining the number of exacerbations before the study or the duration of disease. The treated patients reported a significantly higher prestudy rate of exacerbations than controls (which is unlikely in a truly randomized study). Since a spuriously high rate in the treated group would overstate the efficacy of the treatment,


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the prestudy exacerbation rate should have been measured before the patients were assigned to the treatment or control groups to avoid the possibility of the measurement being biased by knowledge of whether interferon was to be given. If such an evaluation procedure was not used, the difference in the prestudy and on-study rates of exacerbation in the treated group would give no evidence of an effect of interferon.

The decision to exclude from the data an interferon recipient who died received little discussion. If this patient's death was caused by an exacerbation of multiple sclerosis and if this result was included in the comparison of clinical assessments of recipients and controls, the difference between the two groups would not have been significant; likewise, the difference in the prestudy and on-study rates of exacerbation for recipients would probably not have attained statistical significance.

Several of the derived numbers in table 1 are inconsistent. For example, recipient 8 had five exacerbations before the study over a period of 7.0 years, which leads to a rate of 0.71 exacerbations per year and not 0.9 as reported. There are similar difficulties with controls 3 and 4. Rounding of the numbers reported in table 1 cannot account for the discrepancies.

In view of these criticisms I cannot agree with the authors' statement that "These findings warrant cautious optimism about the efficacy of intrathecal IFN-B [human fibroblast interferon] in altering the course of multiple sclerosis and support concepts of a viral or dysimmune etiology of the disease."

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4. I thank C. Jablecki, R. Olshen, and T. Patterson for their comments.

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Our patients (*1*) were randomized to recipient or control groups at the same time but, because of manpower limitations, the controls were not formally entered onto the study until a mean of 0.3 years after the recipients. That is why the recipients have been on the study longer than the controls. One of us (J.O'M.) randomly assigned patients to recipients and controls stratified according to prestudy durations and types of illness but not according to prestudy exacerbation rates; J.O'M. never saw the patients nor participated in their care. The prestudy exacerbations and disease durations were determined by histories obtained from the patients, their families, and the records of their neurologists. Fifteen patients had been followed on a long-term basis in our multiple sclerosis clinic (13 had been followed since the first diagnosis of their disease). Five patients were referred to us by two well-qualified outside neurologists with whom we have a long-standing association and whose abilities to diagnose and document prestudy exacerbations and clinical conditions were assured. The random allocation of the patients to recipient and control groups resulted in a recipient group with a higher prestudy exacerbation rate than the controls. Although the high prestudy exacerbation rates of the recipients might be expected to regress to the mean rate of the total population during the study, the dramatic decrease in their rates from significantly greater than controls before study to significantly less than controls during the study would not be expected as a natural phenomenon. The Mann-Whitney test showed the exacerbation rates of the recipients to be higher than the controls before ($P < .013$) and lower than the controls during the study ($P < .056$). The idea that the decrease in the recipients' exacerbations reflected a "burn out" during the normal course of the disease is not supported by observations on annual relapse rates in 393 cases of multiple sclerosis. These observations (*2*) show that, at the time our recipients entered the study (mean duration of illness, 8 years), a maximum decrease in relapse rate of 16 percent during the study might be attributed to the disease's natural course, but we observed a mean decrease in the recipients' relapse rate of 86 percent during the study. In addition, a multiple linear regression analysis was performed in which patient change in exacerbation rate was regressed on the various patient characteristics (*3*). This analysis indicates that the only significant determinants of change in exacerbation rate are the prestudy rate and the interferon treatment. The regression coefficients indicate that, even when the influence of the prestudy exacerbation rates is adjusted for, the interferon treatment alone resulted in a reduction in the recipients' exacerbation rates of 0.7 exacerbation per year. The minor inconsistencies in table 1 were due to transpositional errors that do not influence the results in any way [see erratum (*4*)]. The deceased recipient, a male, became ill during the third week of the study and was then removed from it. He died 5 months later. As stated in our report (*1*), his death was not related to interferon administration; he did not experience an exacerbation of multiple sclerosis while he was on the study or after his removal from it. We believe that the two parameters analyzed in our report (exacerbation frequency, serial neurologic assessment) are logical for assessing therapeutic response and that our findings do warrant a cautious optimism for a beneficial effect of intrathecal interferon in multiple sclerosis. The ultimate tests of our findings will be continued observation of our recipients over time, crossover of the controls to the recipient group, and repeated studies expanded to include larger numbers of patients. Such a study is now under design.

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