Letters

The Editors welcome submissions for possible publication in the Letters section. Authors of letters should: • Include no more than 300 words of text, three authors, and five references • Type with double-spacing • Send three copies of the letter, an authors' form (see Table of Contents for location) signed by all authors, a diskette containing the letter, and a cover letter describing any conflicts of interest related to the contents of the letter.

Letters commenting on an *Annals* article will be considered if they are received within 6 weeks of the time the article was published. Only some of the letters received can be published. Published letters are edited and may be shortened; tables and figures are included only selectively. Authors will be notified that the letter has been received. If the letter is selected for publication, the author will be notified about 3 weeks before the publication date. Unpublished letters cannot be returned.

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Sponsorship, Authorship, and Accountability

TO THE EDITOR: Academic researchers must have complete freedom to participate in and approve all aspects of industry-sponsored clinical trials, including any publication resulting from such a trial. The Pharmaceutical Research and Manufacturers of America encourages all authors to abide by the new rules outlined in the editorial by the International Committee of Medical Journal Editors (1).

That having been said, the editorial has serious defects. Its biased tone slights the vital contributions of our industry to the clinical trial process. Throughout the editorial, the integrity of academic investigators is assumed, while the industry's integrity is constantly questioned. The editorial ignores the fact that the trial sponsors usually do most of the actual work in clinical trials. There are many well-respected, highly ethical, and experienced clinicians working for the industry who are not subject to pressures that affect most academicians, such as the need to obtain grants and secure tenure.

Thus, while our industry supports the need to ensure the independence of researchers, the editorial is unnecessarily antagonistic, which weakens its impact. A more balanced approach would have recognized the essential roles that both industry and investigators play in developing safe and effective medicines for patients.

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Reference

1. Davidoff F, DeAngelis CD, Drazen JM, Hoey J, Hojgaard L, Horton R, et al. Sponsorship, authorship, and accountability [Editorial]. Ann Intern Med. 2001;135: 463-6. [PMID: 11560460]

TO THE EDITOR: We represent seven of the largest global contract research organizations (CROs). We agree with the International Committee of Medical Journal Editors (ICMJE) (1) that all research must be conducted and reported objectively, dispassionately, and with the highest levels of scientific accuracy and integrity.

Rather than as stated in the ICMJE editorial, however, the perception of "head-to-head" competition between CROs and academic sites is erroneous and does not accurately portray the roles, objectives, and operations of CROs in the clinical research process. Contact research organizations work on a sponsor's behalf in a highly regulated environment (2) to implement and manage a clinical trial according to the study protocol. They provide research services that include consultation in study design; facilitation of the recruitment of investigators and study patients; assurance of patient protection, data integrity, and data analysis to maximize the quality of research; and, in particular, guidance through the complex regulatory environment. Contract research organizations do not sponsor clinical trials, do not own trial data, do not provide routine patient care, and do not participate in agreements concerning publication rights and responsibilities, which are negotiated between sponsors and investigators. The CRO's contractual obligation is to ensure the integrity of data and compliance with U.S. Food and Drug Administration and international regulations, not specific results. This enhances, not erodes, the quality and standards of clinical trials.

Today, most clinical research in the United States is conducted by physicians in group practice settings, who are directly involved in office-based patient care. The research environment is strengthened, not jeopardized, by the increased numbers of clinical researchers and the expansion of research settings. The increased participation of private-practice physicians broadens the populations from which study participants are drawn, creating a vital population of primary care patients to complement the tertiary care populations typical of academic medical centers. At the same time, according to the survey referenced in the editorial, major medical centers are consistently reporting double-digit growth in both National Institutes of Health– and industry-sponsored clinical grant revenue.

Both academic and community-based investigators participate in CRO-managed clinical investigations, and many participate in the development of study protocols. In CRO-managed studies, the investigator is neither our employee nor our customer but an integral partner in the research process. The breadth of our research spectrum encourages us to seek the best and brightest physician-scientists across all clinical disciplines.

We maintain that CROs contribute to high-standard clinical research by working in collaboration with—not competing against—clinical investigators at both academic medical centers and community-based clinics.

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Reference

1. Davidoff F, DeAngelis CD, Drazen JM, Hoey J, Hojgaard L, Horton R, et al. Sponsorship, authorship, and accountability [Editorial]. Ann Intern Med. 2001;135: 463-6. [PMID: 11560460]

2. Henderson L. More AMCs finding growth from reform. CenterWatch. 2000;7: 1,10-3.

IN RESPONSE: Mr. Holmer (for the Pharmaceutical Research and Manufacturers of America) presents one pole in the debate over studies funded by industry and performed by academics. Academic investigators and industrial sponsors both contribute to the accrual of new medical knowledge. An appropriate balance is struck when a novel treatment can be tested in an environment in which all data are freely available to all investigators. When a report is prepared for publication, the primary goal must be the fair, honest, accurate, and complete dissemination of the accrued information. The system is best served when there is no attempt to present the study results in a more favorable light by selectively reporting the data.

The CRO Consortium argues that CROs have an auxiliary function in the performance of clinical trials and that CROs do not compete with academic investigators. We did not wish to diminish the role of CROs; these organizations provide substantial benefit with respect to the orderly accrual of complex clinical research data sets. However, CROs act as agents for the sponsor, not the investigator. When a sponsor does not want to deal with an investigator, the CRO may provide just enough separation to make such discrimination easy.

International Committee of Medical Journal Editors

Note: Part or all of this response may be published in other ICMJE journals.

Low-Dose Thiazide and Bone Density

TO THE EDITOR: LaCroix and colleagues (1), in a 3-year randomized, controlled trial, demonstrated that low-dose hydrochlorothiazide increased bone density in elderly normotensive men and women. They subsequently recommended considering hydrochlorothiazide in osteoporosis prevention programs. I believe this recommendation is too general and deserves further clarification.

The beneficial effect of hydrochlorothiazide on bone is probably related to its action on kidney tubules to promote calcium reabsorption. Urinary calcium excretion increases in postmenopausal women. This physiologic phenomenon, also known as postmenopausal renal calcium leak, has been attributed to reduced tubular reabsorption of calcium secondary to decreased estrogen effect on kidney tubules in the postmenopausal period (2). In the trial by LaCroix and colleagues, the greater effect of hydrochlorothiazide on bone density in women than in men is probably linked to postmenopausal calcium leak. The relationship between urinary calcium excretion and effect on bone density was not assessed in this study.

Calcium leak can be estimated by 24-hour urinary calcium excretion, and a normal reference range in postmenopausal women has been established (3). Estrogen therapy has been shown to decrease urinary calcium excretion in postmenopausal women (4). In addition, calcium supplementation may help restore serum calcium levels and prevent the development of secondary hyperparathyroidism and osteoporosis. The trial by LaCroix and colleagues excluded women taking estrogen, and mean total calcium intakes for both men and women were less than current recommendations (5).

Considering these facts, the clinical implications of this study may be summarized as follows. First, clinicians should consider the beneficial effect of hydrochlorothiazide on bone while deciding on a treatment plan for older adults with hypertension. Second, hydrochlorothiazide may be indicated in postmenopausal women with excessive degrees of renal calcium leak. Last, there is currently not enough evidence to recommend hydrochlorothiazide to normotensive elderly men or to women who have an adequate calcium intake and do not have significant calcium leak.

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References

1. LaCroix AZ, Ott SM, Ichikawa L, Scholes D, Barlow WE. Low-dose hydrochlorothiazide and preservation of bone mineral density in older adults. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2000;133:516-26. [PMID: 11015164]

2. Nordin BE, Horowitz M, Need A, Morris HA. Renal leak of calcium in postmenopausal osteoporosis. Clin Endocrinol (Oxf). 1994;41:41-5. [PMID: 8050130]

3. Heaney RP, Recker RR, Ryan RA. Urinary calcium in perimenopausal women: normative values. Osteoporos Int. 1999;9:13-8. [PMID: 10367024]

4. McKane WR, Khosla S, Burritt MF, Kao PC, Wilson DM, Ory SJ, et al. Mechanism of renal calcium conservation with estrogen replacement therapy in women in early postmenopause—a clinical research center study. J Clin Endocrinol Metab. 1995; 80:3458-64. [PMID: 8530583]

5. NIH Consensus conference. Optimal calcium intake. NIH Consensus Development Panel on Optimal Calcium Intake. JAMA. 1994;272:1942-8. [PMID: 7990248]

IN RESPONSE: We agree with Dr. Kamel that reversal of renal calcium leak may be one mechanism whereby hydrochlorothiazide preserves bone density in older adults, a possibility noted in our discussion. We also noted that evidence supports other mechanisms as well.

In our trial, calcium deficiency did not explain the observed beneficial effects of thiazide. Although we did not provide calcium supplements, we did inform participants of their baseline calcium intake. Subsequently, at every visit, we assessed calcium intake and actively encouraged participants to maintain intakes of at least 1000

mg/d. As shown in the **Figure**, the mean total daily calcium intake during the study was 1600 mg/d among women in the placebo group compared with 1400 mg/d among women in the two hydrochlorothiazide groups. In men, the mean calcium intake was about 1200 mg/d in all three study groups during the 3-year follow-up. Therefore, the significant treatment effect seen with hydrochlorothiazide is over and above any effect of adequate calcium intake. On the basis of data from Dawson-Hughes and colleagues (1), the relatively stable levels of bone density in our placebo group might be attributed to adequate calcium intake. We are currently investigating the renal physiologic effects of thiazide in these participants. This analysis is complex, involving such factors as calcium, sodium, and protein intakes; urine sodium, phosphate, and creatinine levels; and serum levels of calcium, creatinine, and parathyroid hormone.

We agree that evidence from a fracture outcome trial is lacking as a basis for recommending hydrochlorothiazide for fracture prevention in healthy older adults. On the basis of available experimental and epidemiologic evidence, we continue to believe that low-dose thiazide could play a role in prevention of bone loss.

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Reference

1. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997;337:670-6. [PMID: 9278463]

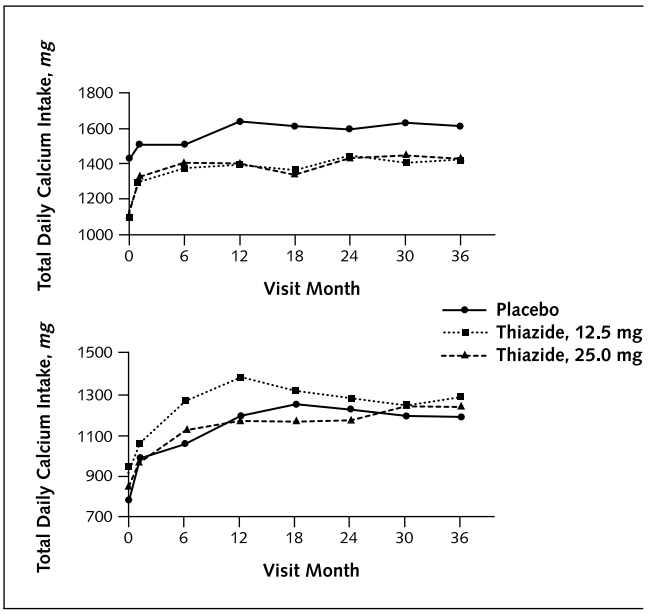
Correction: Adherence to Protease Inhibitor Therapy and Outcomes in Patients with HIV Infection

In an article on adherence to protease inhibitor therapy and outcomes in HIV infection (1), the General Health Questionnaire score in Table 4 should be 6.8 ± 0.8 for patients with less than 95% adherence, and the *P* value for this variable should be 0.0014.

Reference

1. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med. 2000;133:21-30. [PMID: 10877736]

Figure. **Total calcium intake from diet plus supplements during 3 years of follow-up among 205 women (*top*) and 115 men (*bottom*), according to study group.**



Correction: Blood Flow to the Heart during the Menstrual Cycle

In a recent summary for patients (1) that accompanied the paper by Kawano and colleagues (2), the last sentence in the section "What did the researchers find?" should read "Ischemia was least frequent in the middle of the menstrual cycle (around the time of ovulation), when estrogen levels were *lowest* and the blood vessels were most likely to dilate."

References

1. Blood flow to the heart varies during the menstrual cycle in premenopausal women with heart disease. Ann Intern Med. 2001;135:I-40.

2. Kawano H, Moroyama T, Ohgushi M, Kugiyama K, Ogawa H, Yasue H. Menstrual cyclic variation of myocardial ischemia in premenopausal women with variant angina. Ann Intern Med. 2001;135:977-81. [PMID: 11730398]