PDR Provides Latest Food and Drug Administration–Approved Dosage Guidelines

Please permit us to correct some misconceptions regarding the *Physicians' Desk Reference* (PDR) appearing in the article "Adverse Drug Effects, Compliance, and Initial Doses of Antihypertensive Drugs Recommended by the Joint National Committee vs the *Physicians' Desk Reference*," by Cohen in the March 26, 2001, issue of the ARCHIVES.[1] The *PDR* is designed as a communication vehicle to deliver Food and Drug Administration–approved prescribing information from pharmaceutical manufacturers to physicians and other health care professionals.

Cohen states that "information in the *PDR* consists mainly of the limited prerelease data that the manufacturer and the Food and Drug Administration deemed necessary for the safe and effective use of medications at the time of their approvals." That is not the case. Each year, hundreds of *PDR* entries are updated with substantial postmarketing information on newly noted dosing considerations, adverse drug reactions, drug interactions, precautions, and details of clinical pharmacology. Even the interim supplements updating the *PDR* between editions now run nearly 400 pages.

Cohen's assumption that there is "little incentive for manufacturers to update the *PDR* information regularly to reflect postrelease studies or reports" is similarly unfounded. Pharmaceutical manufacturers are under constant pressure to ensure the dissemination of new information on their products as soon as it becomes available.

Why, then, do the Joint National Committee's (JNC's) usual dose ranges often start below the levels published in the *PDR*? We cannot speak to that question, since the JNC does not cite sources for its ranges. However, it would appear that the JNC itself does not regard such variations as a significant issue, since it refers readers to the *PDR* for additional information!

Of course, like Dr Cohen, we agree that new findings on usage and dosage of existing pharmaceuticals deserve immediate and widespread dissemination. However, the Food and Drug Administration currently prohibits the pharmaceutical industry, and hence the *PDR*, from circulating such information via the package insert until the agency has approved revised product labeling.

A streamlined submission and approval process would certainly expedite the release of such information. But once approval has occurred, the mechanisms and incentives for distributing the information to physicians are ready and waiting. In addition to its annual edition and twice-yearly supplements, the *PDR* now sends out scores of printed *PDR* addenda on an as-needed basis, and publishes monthly updates on the Web (http://www.pdr.net). In fact, the *PDR* has long since provided the solution that Cohen purports to seek. In the meantime, we strongly believe that this critique is not really a *PDR* problem, even though this article and similar previous articles seem to want to make it a *PDR* problem. This same problem exists for any drug reference that carries the approved labeling including the package insert that accompanies the drug product when it is distributed to the dispensing facilities.

Mukesh Mehta, RPh
Montvale, NJ

1. Cohen JS. Adverse drug effects, compliance, and initial doses of antihypertensive drugs recommended by the Joint National Committee vs the *Physicians' Desk Reference*. *Arch Intern Med.* 2001;161:880-885.

Cohen vs *PDR*

I read with interest Dr Cohen's perfervid criticism of the *PDR*, which he assails as being neither current nor reflecting evolving standards of care, and, moreover, suggests that if it is not remedied, "perhaps the free dissemination of the *PDR* should be discouraged, and an alternative, objective source of accurate, current information should be created in its place."

Cohen's assault on the *PDR* is leveled at his perceived singular failure of the *PDR* to timely publicize the very lowest effective doses of antihypertensive drugs, observing that the Sixth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI), published 3 years earlier, recommended lower initial doses for 23 of 40 drugs (compared with the 1999 and 2000 editions of the *PDR*), and also finding 2 instances in which the American Hospital Formulary Service recommended even smaller doses for some patients than the JNC VI or the *PDR*.

In fairness to the *PDR* we ought to be cognizant that the *PDR* is a compendium of more than 4000 drugs whose product information, obtained through courtesy of the manufacturers, must be in full compliance with the Food and Drug Administration regulations and is ordinarily required to be verbatim to official package inserts. Moreover, the *PDR* publishes revised information twice annually as *PDR* supplements when new drugs, new research, and clinical findings are submitted to the database.

Many of the clinical observations made by Cohen attest to his familiarity in treatment of hypertension and skill in the art of medicine. If it is true that initiating treatment of hypertension with doses recommended by the JNC VI and/or American Hospital Formulary Service and

advocated by Cohen significantly improved compliance, then the majority of companies making antihypertensive medications have done themselves a financial disservice, and they would benefit financially by advocating the use of smaller initial doses. In my own experience I have found attending medical education courses at local hospitals, often cosponsored by drug companies, provided the best opportunity to keep abreast of current medical practice. I confess to using my *PDR* frequently, and as often as necessary, and I am pleased that it was sent to me as a gift but I also know that none of the 40 publication editors, managers, supervisors, or officers responsible for publishing the *PDR* are physicians.

Russell A. Rohde, MD
West Covina, Calif

1. Cohen JS. Adverse drug effects, compliance, and initial doses of antihypertensive drugs recommended by the Joint National Committee vs the *Physicians' Desk Reference*. *Arch Intern Med.* 2001;161:880-885.

Start Low, Go Slow, Is Not Always Best

In the article by Cohen[1] about adverse drug effects and compliance, the author appears to advocate a "start low, go slow" approach. While this approach has merit, and may minimize adverse effects, it has an important psychological flaw, which may diminish compliance. It is hard enough for patients to begin long-term treatment for a chronic disease. If they start a medication regimen, then undergo dose titrations or medication changes, they may perceive such adjustments as failures, become frustrated, and discontinue use. I agree with the author when he advocates flexible, individualized prescribing.

Daniel Reinharth, MD
New Hyde Park, NY

1. Cohen JS. Adverse drug effects, compliance, and initial doses of antihypertensive drugs recommended by the Joint National Committee vs the *Physicians' Desk Reference*. *Arch Intern Med.* 2001;161:880-885.

In reply

As Dr Reinharth suggests, no one approach works for all patients. However, in my practice, I found that compliance actually increased by using a "start low, go slow" approach if patients were informed. When the standard and low-dose approaches were explained to patients, the majority chose the latter. Many patients worry about medication side effects, and a low-dose, individually titrated approach seemed to allay many of their fears. Extra visits were minimized by written instructions and brief telephone consultations for making simple dosage adjustments. Overall, adherence was improved, and fewer visits were required for dealing with adverse effects. Some patients responded to the low initial doses and never required higher doses. In other cases, the standard approach was chosen and generally worked well. The key is patient selection.

Dr Rohde and Mr Mehta defend the integrity of the PDR. *I do not doubt the diligence and commitment of the employees of the Medical Economics Company, which publishes the* PDR. *However, the discrepancies between the recommended initial doses in the* PDR *and the JNC with so many important antihypertensive medications raises concerns about the reliability of* PDR *information in this regard.[1] These concerns are increased by similar discrepancies between the* PDR *and published studies involving other groups of medications.[2,3]*

Dr Rohde states that he obtains adequate updating of information through continuing education. However, it cannot be expected that continuing education will provide all important information in all areas to the hundreds of thousands of physicians and other health care professionals involved in treating hypertensive patients. Indeed, it has been shown that a large proportion of physicians have never heard of the JNC or of its periodic, comprehensive reviews on hypertension.[4] Continuing education is a pillar of medical training, but it is not a substitute for a drug reference that reflects the most current standards of care.

If, as Mr Mehta suggests, a major barrier to adding new information to the PDR *is the requirement for Food and Drug Administration approval for all package insert changes, then as I suggested in my article, "the ideal solution might be to establish mechanisms by which the information in the* PDR *can be kept current in order to reflect the evolving standards of care and the full range of proven effective drug doses."[1] These new mechanisms should of course include the Food and Drug Administration.*

Jay S. Cohen, MD
San Diego, Calif

1. Cohen JS. Adverse drug effects, compliance, and initial doses of antihypertensive drugs recommended by the Joint National Committee vs the *Physicians' Desk Reference*. *Arch Intern Med.* 2001;161:880-885.
2. Cohen JS. Dose discrepancies between the *Physicians' Desk Reference* and the medical literature, and their possible role in the high incidence of dose-related adverse drug events. *Arch Intern Med.* 2001;161:957-964.
3. Cohen JS. Adverse drug reactions: effective low-dose therapies for older patients. *Geriatrics.* 2000;55:54-64.
4. Lenfant C. JNC guidelines: is the message getting through? *JAMA.* 1997;278: 1778-1779.

Barriers to Communication With Dying Patients

In the article by Wenrich et al[1] about communicating with dying patients, the authors discuss reasons why physicians might find such communications difficult. An additional reason is that of physicians' fear of patient and/or family anger directed at them (whether that anger is due to actual or perceived physician failing, or due to displaced feelings such as guilt). It is also important, when interpreting patient reports of inadequate physician communication, to acknowledge that patients sometimes simply do not hear what they are told. These 2 points are not intended to be excuses—it is a physician's responsibility to attempt to overcome communication barriers—but rather to point out relevant factors not discussed in the article.

Daniel Reinharth, MD
New Hyde Park, NY

1. Wenrich MD, Curtis JR, Shannon SE, Carline JD, Ambrozy DM, Ramsey PG. Communicating with dying patients within the spectrum of medical care from terminal diagnosis to death. *Arch Intern Med.* 2001;161:868-874.

In reply

We appreciate Dr Reinharth's thoughtful comments concerning why physicians might find communicating with dying patients difficult. Dr Reinharth comments that physicians' fear of patient and/or family anger directed at them may be an additional reason that physicians find communicating with dying patients difficult. One of the investigators in this study conducted a qualitative study to identify patients' and physicians' reasons for not communicating about end-of-life care.[1,2] *Fear of anger was not identified as one of the reasons. If this is an important barrier to communication, then it may be one that patients and physicians are unwilling to discuss. Dr Reinharth also raises the issue of patients sometimes not hearing what they are told. We agree that patients may not hear what they are told. As Dr Reinharth implies in his letter, one of the goals of excellent communication is to understand what patients have heard and the reasons they do not hear what they are told. As our article points out, finding out from dying patients and their families what aspects of communication are important to them provides grounds upon which to establish the necessary dialogues that may substantially improve physician-patient communication and, as a result, quality of care.*[3]

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J. Randall Curtis, MD, MPH
Sarah E. Shannon, RN, PhD
Jan D. Carline, PhD
Donna M. Ambrozy, PhD
Paul G. Ramsey, MD
Seattle, Wash

1. Curtis JR, Patrick DLJ. Barriers to communication about end-of-life care in AIDS patients. *J Gen Intern Med.* 1997;12:736-741.
2. Curtis JR, Patrick DL, Caldwell E, Collier AC. Why don't patients with AIDS and physicians talk about end-of-life care? barriers to communication for patients with acquired immunodeficiency syndrome and their primary care clinicians. *Arch Intern Med.* 2000;160:1690-1696.
3. Wenrich MD, Curtis JR, Shannon SE, Carline JD, Ambrozy DM, Ramsey PG. Communicating with dying patients within the spectrum of medical care from terminal diagnosis to death. *Arch Intern Med.* 2001;161:868-874.

Cost-effectiveness of Electron-Beam Computed Tomography in the Diagnosis of Coronary Artery Disease

I read with interest the article on electron-beam computed tomography (EBCT) in the diagnosis of coronary artery disease (CAD) by Nallamothu et al.[1] I was particularly amused by the authors' concluding remark that "EBCT appears to be reasonably accurate at detecting obstructive CAD in patients undergoing coronary angiography, with *sensitivity and specificity comparable to those reported for traditional exercise stress testing*"[1] (italics mine). But the authors did not mention the relative costs of EBCT and traditional exercise stress testing; EBCT costs much more than the traditional exercise stress testing.

The recent American College of Cardiology/American Heart Association (ACC/AHA) expert consensus document on EBCT for the diagnosis and prognosis of CAD did not support the widespread clinical use of EBCT for the diagnosis and prognosis of CAD.[2] One reason for the lack of support for the use of EBCT has been related to a new standard for medical evidence that is increasingly applied in a cost-conscious health care environment.[3]

Despite the interest on the part of the cardiology community for new diagnositc tools to detect CAD, current data are inadequate to support the use of EBCT.[3] As a risk assessment test, EBCT is more costly than other types of testing, while currently providing less abundant evidence to justify its use.[3] As direct marketing to consumers has become a mainstay in our society, the medical community must increasingly set standards in the best interest of our patients and society, advocating clinically effective and cost-effective use of any medical procedure, including EBCT.[3]

Tsung O. Cheng, MD
Washington, DC

1. Nallamothu BK, Saint S, Bielak LF, et al. Electron-beam computed tomography in the diagnosis of coronary artery disease: a meta-analysis. *Arch Intern Med.* 2001;161:833-838.
2. O'Rourke RA, Brundage BH, Froelicher VF, et al. American College of Cardiology/American Heart Association expert consensus document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *J Am Coll Cardiol.* 2000;36:326-340.
3. Shaw LJ, O'Rourke RA. The challenge of improving risk assessment in asymptomatic individuals: the additive prognostic value of electron beam tomography? *J Am Coll Cardiol.* 2000;36:1261-1264.

Electron-Beam Computed Tomography as a Population Screening Tool

In their article, Nallamothu et al[1] conclude that, "The performance of EBCT as a diagnostic test for obstructive CAD is reasonable based on sensitivity and specificity rates." Unfortunately, the most common indication for EBCT currently in our market is the screening of asymptomatic adults, often driven by newspaper and billboard advertisements. It would have been helpful for the authors to discuss the implications of their data for such widespread screening of low-risk populations with EBCT. To be specific, if the diagnostic threshold is set to define a sensitivity of 92% and a specificity of 51%, consistent with the studies they summarize, and if the test is applied to a cohort of 1000 asymptomatic adults with a true CAD prevalence of 5% (close to the overall prevalence at age 50 years), the positive predictive power of EBCT will then be only 8.7%. If the sensitivity is reduced to 80%, and the specificity increased to 71%, a compromise that might be suggested for low-risk populations, the positive predictive power increases to only 12.7%. The true values may be lower since the specificity itself can decrease when the test is applied to other populations, eg, older patients with more incidental calcification.

Approximately 9 of 10 positive screening tests will be false-positives in the scenarios described above, requiring extensive follow-up testing, often including angiography with its attendant risks. The rare patient with a true-positive test result will present a therapeutic dilemma, since the ideal approach to asymptomatic CAD

has not been defined. The billboard advertisements for screening EBCT may serve an entrepreneurial purpose, but they are unlikely to benefit our patients. It would be unfortunate if the authors' favorable conclusions were misinterpreted to provide support for such unselected screening.

Michael Kelleher, MD
Worcester, Mass

1. Nallamothu BK, Saint S, Bielak LF, et al. Electron-beam computed tomography in the diagnosis of coronary artery disease: a meta-analysis. *Arch Intern Med.* 2001;161:833-838.

In reply

We thank Drs Cheng and Kelleher for their interest in our recent article on the use of EBCT in diagnosing CAD. We appreciate their comments and the opportunity to respond.

First, the objective of our article was "to estimate the accuracy of EBCT in diagnosing obstructive CAD."[1] Toward that objective, we believe that our concluding remarks were appropriate: EBCT is reasonably accurate at detecting obstructive CAD in patients undergoing coronary angiography with an accuracy similar to exercise stress testing. In fact, the recent ACC/AHA expert consensus document cited by Dr Cheng clearly supports our finding, stating that the "predictive accuracy of the tests is similar."[2] Dr Cheng's comments imply that our conclusion leads us to endorse the widespread clinical use of EBCT, unlike the authors of the ACC/AHA document, since we made no firm recommendations regarding its clinical use. We disagree. While we share his view that the medical community is ultimately responsible for "advocating clinically effective and cost-effective" care, the objective of our article was to better define the diagnostic accuracy of EBCT. Accordingly, we limited our discussion on cost-related issues, as these were concerns we were not directly investigating.

With regard to cost issues, however, we did make the following comments in our article and reiterate them here. First, Rumberger and colleagues[3] have shown that EBCT is potentially cost-effective as a diagnostic test in patients being evaluated for obstructive CAD compared with conventional noninvasive testing strategies. Second, we mentioned in our article that the cost of EBCT is approximately $375 to $450.

Dr Kelleher is concerned that the favorable findings of our study in symptomatic patients might be misinterpreted to provide support for EBCT screening in asymptomatic populations, potentially leading to unnecessary and dangerous follow-up testing. We share his concern. The misuse of this diagnostic test is always a possibility—even as it is with the use of exercise stress testing in asymptomatic populations.[4] In part due to these concerns, widespread screening with EBCT in asymptomatic populations is still under investigation and not currently recommended.[2] We should note, however, that the positive predictive values that Dr Kelleher calculates using our study's results refer to EBCT's ability to detect obstructive CAD. Advocates of EBCT screening point out that the rationale for its use in asymptomatic populations would be to detect subclinical atherosclerosis (in the form of coronary calcium), not obstructive CAD.[5] Ideally, EBCT results in this setting would not be used for identifying patients needing further testing such as coronary angiography, but those requiring more aggressive risk factor modification. Nevertheless, as stated in our article, while this may ultimately be the most important clinical contribution of EBCT, there is currently a lack of data on its utility in screening asymptomatic populations.

Brahmajee K. Nallamothu, MD, MPH
Sanjay Saint, MD, MPH
Melvyn Rubenfire, MD
A. Mark Fendrick, MD
Ann Arbor, Mich

1. Nallamothu BK, Saint S, Bielak LF, et al. Electron-beam computed tomography in the diagnosis of coronary artery disease: a meta-analysis. *Arch Intern Med.* 2001;161:833-838.
2. O'Rourke RA, Brundage BH, Froelicher VF, et al. American College of Cardiology/American Heart Association expert consensus document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *J Am Coll Cardiol.* 2000;36:326-340.
3. Rumberger JA, Behrenbeck T, Breen JF, Sheedy PF. Coronary calcification by electron beam computed tomography and obstructive coronary artery disease: a model for costs and effectiveness of diagnosis as compared with conventional cardiac testing methods. *J Am Coll Cardiol.* 1999;33:453-462.
4. Gibbons RJ, Balady GJ, Beasley JW, et al. American College of Cardiology/American Heart Association guidelines for exercise testing. *J Am Coll Cardiol.* 1997;30:260-315.
5. Grundy S. Coronary calcium as a risk factor: role in global risk assessment. *J Am Coll Cardiol.* 2001;37:1512-1515.

Pharmaceutical Manufacturer Sponsorship and Drug Information

The recent article "Dose Discrepancies Between the *Physicians' Desk Reference* and the Medical Literature, and Their Possible Role in the High Incidence of Dose-Related Adverse Drug Events"[1] is timely and provocative. As clinicians involved with the education of medical practitioners, we frequently discuss the limitations of the *Physicians' Desk Reference* (*PDR*). Inaccuracies in *PDR* overdose management guidelines have been described elsewhere.[2] Although some practitioners are aware of the *PDR*'s limitations, we believe that most clinicians have difficulty appreciating the consequences of these information discrepancies. This is exemplified by the persistent high utilization of the *PDR* despite the availability of alternative references, as pointed out by the authors.

The *PDR* dosing information is limited to Food and Drug Administration–approved product labeling. This creates a number of potential limitations. In the absence of periodic literature reviews and dosing reevaluation, discrepancies between *PDR* recommendations and the best available evidence are inevitable. Incentives to integrate new information are limited. The process required to constantly readdress doses or other information would be resource consuming for most manufacturers. To their credit, many companies do initiate this process. Nonetheless, even when labels are reviewed, substantial delays occur before new information is approved or disseminated.

The authors suggest several solutions, including creation of a new drug reference through collaboration of government, industry, and physician organizations. While this may be possible in the long-term, it is our belief that

private publication strategies provide a more immediate and flexible alternative. Drug information resources derived from an ongoing process of clinician authorship and review are more likely to reflect up-to-date information. With the availability of electronic publication models (Internet and downloadable handheld and personal digital assistant applications), the opportunity to provide succinct, timely drug information has been revolutionized. Information resources that link directly to MEDLINE are currently available, some of which incorporate intelligent search strategies and thus limit the need for practitioners to become familiar with MeSH (medical subject heading) terminology. These tools will facilitate unprecedented access to data that may improve patient care. Many of these resources are supported by the efforts of clinicians and are not financially tied to pharmaceutical manufacturers.

Ultimately, an appreciation for the dose-response relationship involves more than a listing of usual dosages. Therapeutic end points must be established after consideration of a patient's unique characteristics and expected benefits and risks of therapy. Systems that provide a greater breadth of information are currently available and are rapidly improving. While the efforts of pharmaceutical manufacturers and governmental agencies contribute significantly to the body of dosing data, it is our belief that private publishers are able to provide a more comprehensive and responsive presentation of this information, and will champion the development of these resources.

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Boston, Mass
Mark F. Bonfiglio, PharmD
Hudson, Ohio

As an employee of Lexi-Comp, Inc, Dr Bonfiglio participates in the preparation of drug information publications that may, in some instances, compete with the PDR *and/or other drug information publications.*

The comments in this letter are intended to differentiate between publication strategies and their ability to adapt to medical literature. No publications are identified, with the exception of the PDR, *which was the focus of the article. No Lexi-Comp publication is named in the letter nor does the original article note any Lexi-Comp publication.*

1. Cohen JS. Dose discrepancies between the *Physicians' Desk Reference* and the medical literature, and their possible role in the high incidence of dose-related adverse drug events. *Arch Intern Med.* 2001;161:957-964.
2. Mullen WH, Anderson IB, Kim SY, et al. Incorrect overdose management advice in the *Physicians' Desk Reference*. *Ann Emerg Med.* 1997;29:255-261.

In reply

Drs Basch and Bonfiglio present an elegant summary of the limitations of the PDR *and the lack of awareness of many health professionals about these limitations. As they suggest, optimal therapeutics depends on complete information about the dose-response relationship of medications as well as on individualizing this information to the needs and characteristics of specific patients.*

These doctors' faith in private publishers and electronic models is encouraging. There is no doubt that electronic resources have multiplied since Dr Paul Insel and I discussed the potential impact of these resources in our 1996 article on this topic.[1]

However, the key question still is, will any resource—whether funded by the pharmaceutical industry, government, or private publishers—undertake the responsibility and burden of presenting a complete and comprehensive source of up-to-date dosage, adverse effect, drug interaction, and other information for our vast medication arsenal? Also, will one or more resources emerge that physicians and others can quickly turn to with assurance when considering medications in a clinical setting?

Will health care professionals choose such a resource, especially if the resource requires a fee, over the PDR, *which is provided free and to which health care professionals are introduced early in their training? Contents of the* American Hospital Formulary Service Drug Information,[2] *the most comprehensive reference that is currently available, are offered at several Web sites (free at Medscape, more completely by subscription at Teton Data Systems, SilverPlatter, and Ovid), but it is unclear how many physicians presently recognize or use these resources. How can the wider utilization of such resources be facilitated?*

The advantages of a readily accessible, widely utilized, medication reference that provides up-to-date information are obvious. All participants in the health care equation—patients, physicians, pharmaceutical companies, insurers—would benefit from better therapeutics, fewer dose-related adverse events, and greater adherence to treatment by patients. Let us hope that a decade from now the issue of how to develop and implement a readily available, current, and comprehensive drug reference that becomes an everyday resource for health care professionals is moot.

Jay S. Cohen, MD
San Diego, Calif

1. Cohen JS, Insel PA. The *Physicians' Desk Reference*: problems and possible improvements. *Arch Intern Med.* 1996;156:1375-1380.
2. American Society of Hospital Pharmacists. McEvoy JK, ed. *American Hospital Formulary Service, Drug Information 2001.* Bethesda, Md: American Society of Hospital Pharmacists; 2001.

Appropriate Use of Statin Drugs

Aboorkie et al[1] are to be commended for examining an important but understudied topic: the appropriate use of statin drugs in patients with lipid disorders but no history of coronary heart disease. Their finding that 69% of patients who are taking statin drugs for primary prevention do not meet National Cholesterol Education Panel Adult Treatment Panel II (ATP II) guidelines for appropriate use suggests that overuse of pharmacologic cholesterol-lowering therapy is common.

The ATP II guidelines, however, may not be the ideal means of determining appropriateness. Previous research has shown that the ATP II guidelines perform less accurately than an explicit, quantitative risk-based strategy in predicting future coronary heart disease.[2] In par-

ticular, the ATP II guidelines tend to underemphasize the importance of age, perhaps accounting for Aboorkie and colleagues' finding that older age significantly predicted "overuse." It would be interesting to know the proportion of overuse if appropriate therapy were defined as treatment for patients with an annual risk of coronary heart disease events greater than 1.0% or 1.5% per year (a risk-based threshold).

Finally, the authors do not present data about underuse of statin drugs in primary prevention. To completely describe the appropriateness of therapy for lipid disorders, such data are essential, as failure to treat those individuals at high risk may be as or more common than it is in secondary prevention.

Michael Pignone, MD, MPH
Chapel Hill, NC

1. Abookire SA, Karson AS, Fiskio J, Bates DW. Use and monitoring of "statin" lipid-lowering drugs compared with guidelines. *Arch Intern Med.* 2001;161:53-58.
2. Grover SA, Coupal L, Hu XP. Identifying adults at increased risk of coronary disease: how well do the current cholesterol guidelines work? *JAMA.* 1995;274:801-806.

Epidemiologic Evidence Existing for Calcium Antagonists

We read with much interest the thorough review article by Kizer and Kimmel[1] on the epidemiologic evidence on calcium antagonists. In our opinion, the paragraph addressing the "major hemorrhage" issue might convey a misguided message to the reader. In particular, our study[2] on the in-hospital variations in hemoglobin levels was not focused on major hemorrhage, as the outcome variable was a decrease in the hemoglobin level of greater than 1.2 g/dL. Noticeably, that study found an independent association between use of calcium antagonists and the incident decrease in hemoglobin levels among patients with a definite diagnosis and/or treatment for peptic disease (odds ratio [OR] = 1.67; 95% confidence interval [CI] = 1.26-2.22), but not among other participants (OR = 1.02; 95% CI = 0.82-1.25). These figures correspond (as Table 7 in the article by Kizer and Kimmel should have depicted adjusted relative risks [RRs]) to RRs of 1.50 (95% CI = 1.21-1.84) and 1.01 (0.85-1.20), respectively.[3] Thus, calcium antagonists do not seem to cause bleeding; rather, their effects on hemostasis might become clinically relevant in subjects with bleeding lesions, such as surgical wounds or peptic erosions.[2,4] This finding is consistent with the inhibitory effects of calcium antagonists on in vitro and in vivo platelet aggregation and secretion, which have been documented by several studies.[5-8] In this setting, calcium antagonists should not be considered more "unsafe" than any other antiplatelet agent. Indeed, use of calcium antagonists as adjuvant antiplatelet agents has been proposed by several authors.[5-8] In a more general view, the ongoing debate for or against calcium antagonists should give way to an objective analysis of the impact of these agents in different clinical settings. The review by Kizer and Kimmel represents a substantial advancement toward this goal.

Giuseppe Zuccalà, MD
Roberto Bernabei, MD
Pierugo Carbonin, MD
Alberto Cocchi, MD
Rome, Italy

1. Kizer JR, Kimmel SE. Epidemiologic review of the calcium channel blocker drugs: an up-to-date to perspective on the proposed hazards. *Arch Intern Med.* 2001;161:1145-1158.
2. Zuccalà G, Pedone C, Cocchi A, et al. Use of calcium antagonists and haemoglobin loss in hospitalised elderly: cohort study. *Clin Pharmacol Ther.* 2000;67:314-322.
3. Zhang J, Yu KF. What's the relative risk? a method of correcting the odds ratio in cohort studies of common outcomes. *JAMA.* 1998;280:1690-1691.
4. Zuccalà G, Pahor M, Landi F, et al. Use of calcium antagonists and need for perioperative transfusion in older patients with hip fracture: observational study. *BMJ.* 1997;314:643-644.
5. Greer JA, Walker JJ, Calder AA, Forbes CD. Aspirin with an adrenergic or a calcium-channel-blocking agent as a new combination therapy for arterial thrombosis. *Lancet.* 1985;1:351-352.
6. Wallén NH, Held C, Rehnqvist N, Hjemdahl P. Platelet aggregability in vivo is attenuated by verapamil but not by metoprolol in patients with stable angina pectoris. *Am J Cardiol.* 1995; 75:1-6.
7. Akopov SE, Gabrielian ES. Effects of aspirin, dipyridamole, nifedipine and cavintoin which act on platelet aggregation induced by different aggregating agents alone and in combination. *Eur J Clin Pharmacol.* 1992;42:257-259.
8. Raymenants E, Yang B, Nicolini F, et al. Verapamil and aspirin modulate platelet-mediated vasomotion in arterial segments with intact or disrupted endothelium. *J Am Coll Cardiol.* 1993;22:684-689.

In reply

We appreciate the comments by Dr Zuccala and colleagues regarding our review of calcium channel blockers (CCBs)[1] and their further clarification of their study's findings. As Dr Zuccala et al point out, their observational study evaluated hemoglobin level decrease (≥ 12 g/dL) rather than "major hemorrhage."[2] We did try to depict this for their study in Table 7 by noting it in the "Bleeding End Point" column, but we certainly appreciate their emphasis on the study's focus. Although the section's heading of "Links to Major Hemorrhage" may not be, strictly speaking, entirely accurate, the majority of articles discussed in our review do center on clinically important bleeding.[1]

Dr Zuccala and colleagues also maintain that CCBs may predispose to bleeding only in the setting of established peptic ulcer disease or surgical wounds. While their studies[2,3] support this hypothesis, we believe that it is very difficult to distinguish "causing" bleeding from "promoting" bleeding through interference with hemostatic mechanisms. We do agree that the evidence does not suggest that CCBs are "more 'unsafe'" than other antiplatelet agents and that the overall risk-benefit ratio of treatment with CCBs must be considered in making decisions for our patients. Ultimately, the true merit of treating CCBs like antiplatelet agents in patients at high risk of bleeding can only be determined by large-scale prospective studies.

Dr Zuccala and colleagues' comments have brought to our attention an error in the footnotes to the tables. In the latter, RR indicates relative risk, not risk ratio. The footnotes should have read: "RR, relative risk (risk ratio or odds ratio)." Accordingly, we chose not to transform original study ORs to RRs in the setting of relatively frequent

end points, but instead to present the originally reported measures of effect.

Jorge R. Kizer, MD, MSc
Stephen E. Kimmel, MD, MSCE
Philadelphia, Pa

1. Kizer JR, Kimmel SE. Epidemiologic review of the calcium channel blocker drugs: an up-to-date perspective on the proposed hazards. *Arch Intern Med*. 2001;161:1145-1158.
2. Zuccala G, Pedone C, Cocchi A, et al. Use of calcium antagonists and haemoglobin loss in hospitalized elderly: cohort study. *Clin Pharmacol Ther*. 2000; 67:314-322.
3. Zuccala G, Pahor M, Landi F, et al. Use of calcium antagonists and need for perioperative transfusion in older patients with hip fracture: observational study. *BMJ*. 1997;324:643-644.

Is Hyperhomocysteinemia a Risk Factor or a Consequence of Coronary Heart Disease?

The question of whether moderately high serum or plasma levels of total homocysteine are a risk factor for coronary heart disease (CHD) and other atherothrombotic disorders has long been debated and is still unclear. The uncertainty mainly stems from the discrepant results obtained in case-control and prospective cohort studies. While case-control study results consistently showed a positive association between hyperhomocysteinemia and atherothrombotic events, prospective cohort studies gave conflicting results.[1]

In 1999, I suggested that a clear distinction should be made between prospective cohort studies of subjects who were healthy at enrollment and prospective cohort studies of patients with overt atherothrombotic disease or other at-risk conditions.[1] While studies of healthy subjects gave conflicting results, study results of patients at risk consistently showed a positive association between baseline total homocysteine levels and the risk of future atherothrombotic events. Findings from subsequent studies published from 1999 to the present strengthened the hypothesis that the plasma total homocysteine levels are predictive of future cardiovascular and cerebrovascular events only in patients at risk. This has been demonstrated not only in patients whose high risk was due to the presence of pathological conditions, such as previous cardiovascular disease, diabetes, end-stage renal disease, or systemic lupus erythematosus, but also in subjects who were at increased risk because of physiological conditions, such as advanced age and postmenopausal status.[2] Several interpretations of these findings can be given, the simplest being that hyperhomocysteinemia (a weak risk factor by itself) synergizes with other conditions to increase the risk of future events.

In agreement with previous reports, the case-control study (nested in a population-based cohort study) by Knekt et al[3] in a recent issue of the ARCHIVES showed that hyperhomocysteinemia predicts the risk of future CHD events in men with a history of CHD but not in those without previous CHD.[3] In a nested case-control study of women who had been enrolled in the same population-based cohort study, Knekt et al[4] reported similar data. Whether the data in these 2 studies by Knekt et al[3,4] are of great value to clarify further the role of homocysteine in CHD, the authors' interpretation of their data is questionable. Based on their data, they conclude that hyperhomocysteinemia is a consequence of CHD rather than a risk factor. I think that the only certain conclusion that can be drawn from the data is the opposite, ie, hyperhomocysteinemia is not a consequence of CHD. In fact, the mean serum levels of total homocysteine in subjects with a history of CHD and no incident CHD events were similar to (or, if anything, lower than) that measured in subjects without CHD and no incident CHD (0.149 mg/dL vs 0.152 mg/dL). If total homocysteine levels were a consequence of CHD, they should have been higher in the former group (with previous CHD episodes) than in the latter.

In my opinion, time is not yet ripe to draw any firm conclusions about the role of hyperhomocysteinemia in CHD. Based on the study of Knekt et al[3] and on previous ones, it is likely that hyperhomocysteinemia is associated with a heightened risk for future atherothrombotic events only in patients with previous CHD or with other at-risk conditions. Whether this association is causal is presently unknown. Only the results of ongoing clinical trials evaluating the effects of the administration of total homocysteine–lowering vitamins on the cardiovascular and cerebrovascular risk will be of some help to define this issue.

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In reply

We appreciate Dr Cattaneo's interest in our article. We found that individuals with a history of heart disease had an elevated CHD risk at higher homocysteine values during a 13-year follow-up examination. No association was, however, found in individuals free from heart disease at baseline. Because causal inference is difficult in an observational study such as ours, several interpretations for the associations are possible. Of the alternative interpretations, 2 are of special interest: (1) interaction of hyperhomocysteinemia with some other condition is a risk factor for atherothrombosis (as preferred by Dr Cattaneo) and (2) elevated homocysteine level is a marker of the pathogenesis of atherosclerosis.

The cross-sectional comparison of mean homocysteine values between controls with and without heart disease at baseline (which Dr Cattaneo interpreted as evidence for the former hypothesis) is invalid because of differences in determinants of serum homocysteine values between the groups. Such a comparison would need adjustment for confounding factors in longitudinal design. Our finding that the association between serum homocysteine value and CHD incidence was strongest in the first 2 years of follow-up sug-

gests that the elevated risk mainly concerns a newly diagnosed heart disease, the development of which has started long before the baseline measurement of homocysteine concentration. This finding is in line with the alternative interpretation that elevated homocysteine level is a marker of progressive atherosclerosis, its complication, or other comorbidity. Testing for this hypothesis should also merit attention in further research.

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Other Reports of Cerivastatin-Induced Rhabdomyolysis

Garcia-Valdecasas-Campelo et al[1] report a case of acute rhabdomyolysis associated with the administration of cerivastatin. The authors state that no previous reports of cerivastatin-induced rhabdomyolysis have been documented in the medical literature. However, a MEDLINE search conducted in April 2001 revealed multiple case reports of cerivastatin-induced rhabdomyolysis published prior to this report.[2-7] Similar to the report of Garcia-Valdecasas-Campelo and colleagues, 4 of the 6 additional reports involve patients receiving concomitant therapy with cerivastatin and gemfibrozil.[2,3,5,6] The 2 remaining reports document the development of rhabdomyolysis in patients receiving cerivastatin with cyclosporine[4] and cerivastatin with the influenza vaccine.[7]

The exact mechanism behind 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor–induced myotoxicity has not been fully elucidated.[8] Myotoxicity is considered a class effect for these drugs; however, the development of rhabdomyolysis with HMG-CoA reductase inhibitor monotherapy is rare. For some HMG-CoA reductase inhibitors (ie, simvastatin, lovastatin, and pravastatin) this effect has been shown to be dose dependent; however, cerivastatin-induced elevations of creatine kinase are not currently thought to be dose related.[8,9]

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3. Ozdemir O, Boran M, Gokce V, Uzun Y, Kocak B, Korkmaz S. A case with severe rhabdomyolysis and renal failure associated with cerivastatin-gemfibrozil combination therapy: a case report. *Angiology.* 2000;51:695-697.
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6. Pogson GW, Kindred LH, Carper BG. Rhabdomyolysis and renal failure associated with cerivastatin-gemfibrozil combination therapy. *Am J Cardiol.* 1999;83:1146.
7. Plotkin E, Bernheim J, Ben-Chetrit S, Mor A, Korzets Z. Influenza vaccine: a possible trigger of rhabdomyolysis induced acute renal failure due to the combined use of cerivastatin and bezafibrate. *Nephrol Dial Transplant.* 2000;15:740-741.
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Another Report of Acute Rhabdomyolysis Following Cerivastatin Monotherapy

Cerivastatin is the newest HMG-CoA reductase inhibitor to be introduced into clinical practice. It is metabolized via the cytochrome P450 3A4 as well as cytochrome P450 2C8 hepatic.[1] This dual metabolic elimination pathway is supposed to cause less drug-to-drug interaction. Therefore, cerivastatin is considered a safe and well-tolerated drug for the treatment of hypercholesterolemia. In clinical trials, its tolerability with regard to serum creatine kinase level and drug-induced myopathy was comparable to that of placebo.[1] However, there is a limited number of reports, including the case described by Garcia-Valdecasas-Campelo et al[2] in the March 26 issue of the ARCHIVES, which demonstrated muscle toxicity associated with cerivastatin treatment. All reports involved patients receiving cerivastatin in combination with fibrates or cyclosporine. Herein, we describe a patient who developed rhabdomyolysis after starting therapy with cerivastatin as the only lipid-lowering treatment.

Report of a Case. A 73-year-old woman was admitted to our department because of severe myalgia and colored urine. She had a 4-year history of angina and had a transient ischemic attack 2 years earlier. She had undergone subtotal thyroidectomy and right carotid endarterectomy 15 and 2 years before, respectively. She was receiving treatments with clopidogrel bisulfate (75 mg once daily), losartan potassium (50 mg once daily), and levothyroxine sodium (100 µg once daily). Twenty-four days before admission she was prescribed cerivastatin sodium (0.3 mg nocturnally) to treat hypercholesterolemia. On admission she complained of bilateral upper and lower extremity muscle pain and profound weakness culminating over the previous 3 days. Findings from laboratory studies revealed serum levels of creatinine at 0.7 mg/dL (61.9 µmol/L), creatine kinase at 72 500 U/L, aspartate aminotransferase at 1250 U/L, alanine aminotransferase at 950 U/L, lactate dehydrogenase at 7500 U/L, and aldolase at 485 U/L. A urine dipstick was positive for blood, but there were no red blood cells on urine microscopy. There was no recent history of infectious diseases or antibiotic exposure (including macrolides). Immunological (including rheumatoid factor, antinuclear, antineutrophil cytoplasmic, and anti-Jo antibodies) as well

as serological test results for active viral or bacterial infection were negative. Thyroid function test results were within normal limits. The patient was treated with aggressive hydration and alkalinization of the urine. Laboratory abnormalities and muscle tenderness gradually improved over a week. By the 12th day of hospitalization the patient was totally asymptomatic and serum muscle enzyme levels had normalized.

Comment. Most currently available statins are associated with an increased risk of myositis, including rhabdomyolysis. Risk factors include older age, female sex, renal failure, high-dose therapy, and use of other drugs, including fibrates. By using new-generation statins, such as cerivastatin, low-density lipoprotein target levels may be achieved with lower dosages than with the older ones.[1] It has been suggested that the increased efficacy of this novel agent is not accompanied by any increase in adverse events or interactions with other frequently prescribed drugs. This is important because many elderly patients at risk of coronary heart disease are often taking several other medications. Combination therapy with fibrates carries a substantial risk of muscle toxicity.[3] Cerivastatin seems to be no exception to the rule, especially in elderly patients. In agreement with Garcia-Valdecasas-Campelo et al,[2] we and others have reported cases of acute rhabdomyolysis associated with combination treatment modalities involving cerivastatin plus gemfibrozil.[2,4-7] Other fibrates, such as bezafibrate, as well as immunosuppressants (namely, cyclosporine) have also been implicated for muscle toxicity in combination with cerivastatin.[8,9]

The present case, however, clearly demonstrates that myopathy is not confined to any particular statin and may occur even with rather small doses of cerivastatin. Therefore, an individualized approach along with a risk-benefit analysis for combination lipid-lowering treatments and careful monitoring while receiving statin therapy remain strategies of paramount importance in clinical practice.

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In reply

We appreciate the meaningful comments by Drs Gabay and Lodolce and Dr Milionis and colleagues. Indeed, during the year 2000, a number of reports dealing with rhabdomyolysis associated with cerivastatin therapy appeared in the scientific literature. As with many other medical problems, something that was novel at the end of 1999 became a well-known clinical situation 1 year later. In October 1999, we treated the patient whose case we reported in our article,[1] which we sent to the ARCHIVES *for publication very early in 2000. At that time only 1 letter had been published regarding a similar case,[2] although we failed to find it in PubMed when we wrote the manuscript. As mentioned by Drs Gabay and Lodolce, many other cases have been described since then. Even in our unit we have recently treated a 67-year-old woman receiving therapy with gemfibrozil (600 mg/d) and cerivastatin sodium (0.2 mg/d) who developed severe, disabling myalgia in the upper and lower limbs. She had raised serum levels of creatine phosphokinase (>10 000 U/L), aspartate aminotransferase (1587 U/L), alanine aminotransferase (1355 U/L), and lactate dehydrogenase (5843 U/L), but a normal creatinine level (0.6 mg/dL [53 µmol/L]). This clinical picture subsided 10 days after drug treatment withdrawal and appropriate fluid therapy. The case reported by Milionis et al is especially interesting because rhabdomyolysis was related only to cerivastatin therapy. We believe that all these reports contribute to confirm the clinical importance of the life-threatening adverse effect of cerivastatin therapy.*

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1. Garcia-Valdecasas-Campelo E, Gonzalez-Reimers E, Lopez-Lirola A, Rodriguez-Rodriguez E, Santolaria-Fernandez F. Acute rhabdomyolysis associated with cerivastatin therapy. *Arch Intern Med*. 2001;161:893.
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Case Reports of Rhabdomyolysis Associated With Cerivastatin Therapy

As a medical editor who works in the area of blood lipids and coronary heart disease risk, I was called on to review literature on rhabdomyolysis related to the use of cerivastatin. As you know, cerivastatin was voluntarily withdrawn from the market by Bayer Pharmaceutical Division, West Haven, Conn, in August 2001 because of reports of sometimes fatal rhabdomyolysis.[1] In a case report published in the ARCHIVES in March of this year, Garcia-Valdecasas-Campelo et al[2] write that "no [previous] cases of rhabdomyolysis associated with cerivastatin therapy have been described." Yet even my quick PubMed search showed at least 5 reports published in 1999 or 2000 of rhabdomyolysis in cerivastatin users.[3-7] In 4 of 5 cases, cerivastatin was given in

conjunction with gemfibrozil[3,4,6,7]; in the fifth, concomitant therapy included immunosuppressant drugs for renal transplantation.[5] It strikes me that there was a serious breakdown in the peer review process of the ARCHIVES, especially given that claims of primacy should always be viewed with some skepticism. Had your peer reviewers been more careful, perhaps clinicians would have been more aware of a problem that would lead to a drug's withdrawal.

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Editor's note: This letter was submitted too late for Dr González-Reimers et al to include in the preceding reply.

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Osler on the "Positive Review of Systems" Patient

Sir William Osler noted succinctly: "A patient with a written list of symptoms-neurasthenia."[1] Jackson et al[2] have provided objective confirmation of his observation in their study of predictors of mental disorders in a primary care setting. As a physician in such a practice, I found their results helpful in providing a better understanding of those patients who are often described pejoratively (but, perhaps accurately) as "a positive review of systems" or "heartsink patients."[3] Armed with such an understanding, these patients become less an emotional and intellectual challenge and, instead, present an opportunity to provide truly beneficial care. Unfortunately, such patients, like those with somatization disorder, are often reluctant to accept that a mental disease exists.[4] Nevertheless, unneccesary testing can be avoided and a more appropriate dignostic and therapeutic approach can be followed once such patients are recognized using the clinical cues identified by Jackson and colleagues.

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In reply

We greatly appreciate the comments of Dr Sutton. In previous work, we had found that patients who are experienced by clinicians as difficult do tend to be those with somatization disorders, the so-called heartsink patient.[1] Unfortunately, treatment of somatoform disorders is largely one of reassurance and minimization, reassuring the patient that his or her symptoms are not due to a serious underlying disease and minimizing the number of tests and referrals. No treatment of somatoform disorder has yet proved to be effective. In contrast, there are very safe and effective treatments for patients who have depressive or anxiety disorders. Recognizing that a patient has a somatoform disorder may take a visit or two, but usually becomes quickly apparent. Unfortunately, many patients with depression or anxiety remain undetected, with as few as 11% recognized at any given clinical visit. Our real hope is that clinicians will use our clinical cues to improve recognition of depressive and anxiety disorders. There are numerous competing demands in the average clinician's office, and routinely screening all patients for mental disorders has not been demonstrated to be cost-effective. Our clinical cues—reporting more than 5 symptoms, reporting stress in patients' lives, reporting poor functioning in patients' daily lives, and reporting greater symptom severity—can identify a subset of patients in whom mental disorders, including depression and anxiety, are very likely to be found. While our clinical cues do identify patients with somatoform disorders, our hope is that clinicians will use our cues to help identify this latter group of underrecognized, undertreated patients, who would particularly benefit from treatment.

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Hospital Staff, Not Attending Physicians, Provide Continuity of Care

With reference to the excellent article by Kearns et al[1] in the January 22, 2001, issue of the ARCHIVES, the absence of differences in length of stay, outcome, and utilization of resources comes as a welcome reinforcement for the job done by attending physicians who supervise patient care for only a few months each year. It dampens somewhat the enthusiasm for the purported greater efficiency and quality of hospital-based physicians who attend 10 months per year.

Not mentioned in the article is the role of house staff in smoothing out the results. Duration of stay, requests for laboratory results, and adherence to guidelines for care are routinely in the hands of the ward residents in university-affiliated hospitals such as Santa Clara Valley Medical Center, San Jose, Calif, and the University of California in San Francisco. As long as there is no marked deviation from norms, there is usually very little modification of these parameters by the attending physician and therefore little likelihood for different outcomes.

These comments are not meant to belittle the role of the attending physician as teacher and overseer who contributes experience and familiarity with certain particular elements of internal medicine. Nevertheless, it is the house staff, often with input from the chief resident and subspecialty fellows, who make the minute-to-minute daily decisions and who write the orders that determine care-related outcomes. As long as this is the case and residents are allowed reasonable autonomy, I do not expect that changing attending styles will make important differences.

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1. Kearns PJ, Wang CC, Morris WJ, et al. Hospital care by hospital-based and clinic-based faculty: a prospective, controlled trial. *Arch Intern Med.* 2001; 161:235-241.

In reply

In response to Dr Perlroth, we agree with his conclusion that our findings dampen enthusiasm for populating academic programs exclusively with hospitalists attending 10 months annually.[1] Not only is there no advantage in outcome, the lifestyle is not sustainable over the long term. This feature may be of critical importance if we are to realize the full beneficial effect on outcome from the proper utilization of hospitalists.

We fondly remember Dr Perlroth as our attending. He could not object if we acknowledged his pivotal input that improved the care for several patients. We agree that the chief resident, subspecialty fellow, and his or her attending contribute meaningful suggestions, significantly influencing the length of stay, resource utilization, and clinical outcomes of hospitalized patients. This input is the reason that there is usually, as Dr Perlroth notes, "no marked deviation from norms"; and therefore "there is usually very little modification . . . by the attending physician." However, hospitalists do have an additional beneficial effect on the length of stay and hospital costs, as shown by Wachter et al[2] and Hackner et al.[3]

It is our contention that the hospitalist model shifts the paradigm of the academic model outlined by Dr Perlroth. Hospitalists preemptively direct patient care. This significantly modifies and accelerates treatment plans. As Hackner et al[3] showed, the number of consultations is significantly reduced when a patient is treated by a hospitalist. The fact that other researchers[2,3] demonstrated a difference in length of stay while we did not may reflect that the clinic-based and hospital-based attendings in our study were drawn from the same pool of physicians and started the study with similar clinical skills. As we continue our observations, differences in length of stay, pharmacy costs, and readmissions begin to materialize as hospitalists gain experience. If our findings (being prepared for publication) are substantiated, the hospitalist model, already shown to decrease length of stay and hospital costs, may prove to be increasingly superior to the traditional academic "consultation" model. We postulate that this advantage will grow with the individual hospitalist's skill. If this is true, it will be important to create a professional lifestyle that is sustainable as a career choice. Our original study may then be used to demonstrate that the 2 models can coexist, yielding the benefits of both systems.

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Is Salt So Harmful for Hypertension in Our Elderly?

We have read with great interest the article by Dr Appel, et al titled "Effects of Reduced Sodium Intake on Hypertension Control in Older Individuals" published in a recent issue of the ARCHIVES.[1] We would like to congratulate the authors and make some comments. First, they estimate as very positive the finding of an average reduction of 4 mm Hg in their population's systolic blood pressure and of 2 mm Hg in their diastolic blood pressure. These results might be statistically significant but clinically irrelevant. However, these reductions of blood pressure are not seen either in the those older than 70 years or in women of any age. Second, even if they were thought to be important, they are of lesser importance with regard to the fundamental objectives of controlling hypertension, ie, the reduction of the morbidity and mortality it causes. Other studies have also found reductions in blood pressure readings and not in morbidity or mortality.[2,3] It is surprising that none of these variables is affected in the statistical analysis conducted by Appel et al. The most significant conclusion in our opinion is that elderly patients who do not reduce salt intake do not undergo any change in morbidity and mortality. Perhaps it would be a good time to initiate a much more ambitious trial where these variables are the main objectives. The palate of our older population could be in luck.

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bidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet*. 1999;353:611-616.
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In reply

Dr Ruiz-Garcia et al raise several issues pertaining to our recently published article.[1] First, they point out that diastolic blood pressure reductions in women and blood pressure reductions in persons aged 70 and older did not reach statistical significance. The comparatively low baseline intake of sodium in women (<130 mEq/24 h) might explain the reduced effect size; still, it is noteworthy that systolic blood pressure reductions in this subgroup were statistically significant. In persons 70 and older, the most likely explanation for the nonsignificant effect size is inadequate study power. This subgroup (n=132) was the smallest of the subgroups examined in our article.

Second, Ruiz-Garcia et al question the clinical relevance of the blood pressure reductions documented in our trial. The mean systolic/diastolic blood pressure reductions of 4.3/2.0 mm Hg are actually quite impressive given the fact that participants were concurrently taking antihypertensive medication and the observation that mean baseline blood pressure was low, just 128/71.3 mm Hg. Although we did not enroll persons with poorly controlled hypertension in our trial, blood pressure reductions from nonpharmacologic interventions tend to be much greater at higher levels of blood pressure, even after accounting for regression to the mean. Also, it is important to emphasize the enormous public health impact of even an apparently small population-wide reduction in blood pressure. For instance, a 2–mm Hg reduction in diastolic blood pressure should decrease the prevalence of hypertension by 17%, the risk of coronary heart disease by 6%, and the risk of stroke and transient ischemic attacks by 15%.[2]

A third issue raised by Ruiz-Garcia et al is the lack of apparent benefit from sodium reduction on clinical cardiovascular events in our trial. Of course, our trial was not powered to assess the impact of sodium reduction on such events. However, recent methodologically rigorous, observational studies have documented that excess salt intake increases the risk of arteriosclerotic cardiovascular disease events, at least among overweight persons.[3,4] A clinical trial that directly addresses the impact of sodium reduction on arteriosclerotic cardiovascular disease events is not feasible.

Overall, data on the effects of sodium reduction on blood pressure are compelling, as are the results of the above-mentioned observational studies. In this setting, the totality of evidence strongly supports reduced sodium intake as an effective means to lower blood pressure, control hypertension, and reduce the risk of blood pressure–related clinical complications, particularly in the elderly.

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Osteoporosis Follow-up After Fracture

The article by Khan and colleagues[1] found a low rate of osteoporosis follow-up after minor trauma wrist fractures. We have recently completed a similar study in people who had a hip fracture.[2] We contacted 231 survivors of a hip fracture and found that only 9% were receiving a bisphosphonate therapy, hormone replacement therapy, or calcitriol therapy, and only 12% were taking calcium supplements alone. Only 10% had a bone density examination performed. Ironically, people younger than 65 years were more likely to be receiving treatment for osteoporosis despite the considerably greater risk of fracture for those older than 65 years.

Khan and colleagues suggest that more attention be given to case finding for people at risk of fracture. We agree. In our cohort, vitamin D concentrations were low in 22 (67%) of 33 people.

People who have already had a fracture are at very high risk of osteoporosis and another fracture. It is difficult to justify withholding effective osteoporosis treatment from such people.

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Osteoporosis Attitudes After a Colles Fracture

We read with great interest the article "Osteoporosis Follow-up After Wrist Fractures Following Minor Trauma" by Khan et al.[1] After their retrospective study, the authors conclude that recognition of the potential of osteoporosis in such patients is inadequate based on the few changes that this fracture induced in the osteoporosis follow-up strategy or in its treatment. Although the criteria used to define what could be considered osteoporosis follow-up or osteoporosis treatment after a fragility fracture were not previously validated, a 50% rate of individuals receiving advice on osteoporosis after such a fracture is a not a low result.

Khan et al state that after an unrestricted MEDLINE search "no published studies were found that determine the rate of follow-up or treatment of osteoporosis for patients who sustain a wrist fracture." We wonder if no articles were found because the MEDLINE strategy search used to identify related studies (key words: *wrist frac-*

tures, *osteoporosis*, and *follow-up studies*) was too constrained. A wider search using *Colles fracture* or *distal forearm fracture* as key words would find more related articles on this subject. For example, our group published a similar study[2] undertaken in 1 year, which included 80 postmenopausal women with a recent distal forearm fracture. The main results showed that a recent Colles fracture induced few osteoporosis diagnostic studies (4%), but the use of antiosteoporotic drugs was significantly increased (7.5% of individuals were taking antiosteoporotic drugs before a Colles fracture vs 26.3% who did so after). Our data are in concordance with those reported by Dolan[3] in response to an original article on the advice given to patients with fractures.[4] We believe that Khan et al would have found our previous work useful because the methodology and goals of our study resembled their own.

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In reply

We thank Dr Kanterewicz and Ms Yañez for their letter. While it is certainly possible that a wider search may have led to an increased number of related articles, I think the issue in question is that of timing. We carried out our search prior to April 2000 when the article[1] referred to was published, and I think it is for that reason that we missed it because indeed it would have come up with a regular search. We still believe that our study and that of Morote et al[1] show that a remarkably small proportion of patients who had a fragility fracture are receiving what is now recognized to be effective drug therapy in reducing the risk of subsequent fractures. Hopefully, with further publicity such as that provided by Dr Kanterewicz and Ms Yañez, we will all start to improve our treatment of this condition.

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Screening for Sleep-Disordered Breathing

We read with interest the article titled "Association of Hypertension and Sleep-Disordered Breathing [SDB]."[1] The authors concluded that SDB should be considered an independent risk factor for hypertension.[1] The converse may also be true, although screening for SDB on the basis of hypertension alone is not recommended.[2] A retrospective review of our 27 patients with SDB who were treated with various levels of continuous positive airway pressure while sleeping revealed that 21 had the triad of hypertension, obesity (body mass index [BMI, weight in kilograms divided by the height in meters squared] >30), and dyslipoproteinemia.

Hypertension was evidenced by blood pressure levels greater than 140/90 mm Hg on several occasions or by use of antihypertensive medication. Patients with dyslipoproteinemia were those who were on a regimen of diet and exercise or who were taking medication for lipid disorders. The active pool of adult patients (age range, 18-98 years) who were seen in the office at least once in the last 3 years in this northern Illinois solo medical practice comprised 1708 individuals. Of these active patients, only 18% had hypertension and only 10% had dyslipoproteinemia. At this time, we do not know how many patients have a BMI higher than 30, nor do we know how many patients have the triad without SDB. These evaluations are currently under way.

Prospective evaluation of this clinical setting, as well as expansion of the retrospective and prospective analyses to sleep laboratories, is also progressing. We are testing the hypothesis that the triad of hypertension, BMI higher than 30, and dyslipoproteinemia can be used in development of a clinical decision rule concerning SDB screening.[3] This preliminary evaluation suggests that there exists a distinct syndrome characterized by the quartet of SDB, hypertension, BMI higher than 30, and dyslipoproteinemia. The hypertension associated with SDB has been shown to be independent of obesity and therefore of hyperinsulinism. It is therefore likely that this association is causally and clinically different from syndrome X.[4]

Of particular interest will be the application of this triad in association with a "fifth element," depending on the clinical setting. An example would be screening for SDB in patients with the triad who present with vehicular or other trauma (unrelated to alcohol use). Another example would be "depressed" patients with the triad. This fifth element could be any historical or physical finding that could be a result of SDB but by itself would not be enough to warrant a sleep study.

We acknowledge that not all patients with SDB could be diagnosed by such a clinical decision rule, but a large subset of those affected could be identified. Such a tool would also cross practice (and specialty) barriers that currently may impede the diagnosis of SDB. We believe that this clinical constellation deserves further evaluation.

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Captopril Is an Unlikely Cause of Nephrotic Syndrome

Madaio and Harrington list captopril as a major cause of nephrotic syndrome in their review of the diagnosis of glomerular diseases.[1] Publications supporting captopril-induced nephrotic syndrome appeared in the 1980s after the introduction of the drug. Subsequent data have failed to support this concept.[2]

While it is not possible to prove the negative, captopril-induced proteinuria should be considered to be extremely rare, if it occurs at all.

The advantages of angiotensin-converting enzyme inhibition, including that achieved with captopril, have now been extensively documented. The benefits associated with its use should not be ignored because of concern about this adverse effect that has been poorly documented, if at all.

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