

Evidence-Based Reduction of Heart Failure Events With the Involvement of Pharmacists

The recent report by Gattis et al¹ describing how the role of pharmacists on a multidisciplinary heart failure team can improve the outcomes of heart failure provides an excellent example of the multidisciplinary approach to chronic diseases. Studies involving the participation of pharmacists in the treatment of hypertension have revealed that 55% of patients with uncontrolled hypertension at baseline achieved their goal blood pressure (<140/90 mm Hg) after 6 months in the intervention arm compared with 20% in the control arm.² The *number needed to treat* (NNT) is a term that has gathered prominence in recent years, and the NNT has been used to determine clinical significance in many studies. The NNT is defined as the number of patients needed to achieve one favorable outcome.³ The NNT is calculated as 1 divided by absolute risk reduction.

The following important question still needs to be answered: does the addition of a pharmacist to a multidisciplinary heart failure team improve the outcome of these patients? Using the data presented in Table 2 and Table 3 of the article by Gattis et al,¹ I came up with the data for the NNT (**Table**). My data indicate that to justify adding a pharmacist to a multidisciplinary heart failure team, 9 patients need to be treated to prevent episode of 1 nonfatal heart failure. My analysis of the data of Gattis et al also indicated that there was a clinically significant reduction of all-cause mortality (NNT, 8). In other words, if 100 patients were treated for heart failure, the addition of a pharmacist to the team would result in 13 fewer deaths. How-

ever, the use of alternative therapy, although statistically significant in the report of Gattis et al, produced an NNT of 20.

The findings of Gattis et al are of increased relevance given the current trend of increasing prevalence of congestive heart failure.⁴ The involvement of pharmacists on multidisciplinary teams could improve the outcome of other chronic diseases because tighter control and increased follow-up can result in earlier therapeutic interventions.

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1. Gattis WA, Hasselblad V, Whellan DJ, O'Connor CM. Reduction in heart failure events by the addition of a clinical pharmacist to the heart failure management team: results of the Pharmacist in Heart Failure Assessment Recommendation and Monitoring (PHARM) Study. *Arch Intern Med.* 1999;159:1939-1945.
2. Bogden PE, Abbott RD, Williamson P, Onopa JK, Koontz LM. Comparing standard care with a physician and pharmacist team approach for uncontrolled hypertension. *J Gen Intern Med.* 1998;13:740-745.
3. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ.* 1995;310:452-454.
4. The sixth report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure [published correction appears in *Arch Intern Med.* 1998;158:573]. *Arch Intern Med.* 1997;157:2413-2444.

Pneumococcal Vaccination of the Elderly: Do We Need Another Trial?

The prevention of pneumococcal infections deserves more attention because of aging populations and antimicrobial resistance.¹ In this light, Nichol and colleagues² reported important positive findings from a community-based, nonexperimental study on influenza and pneumonia immunization among those at highest risk: elderly patients with chronic pulmonary disease. In spite of this report, however, the issue of the incremental health and economic benefit of combined pneumococcal and influenza vaccination compared with influenza vaccination alone among a wider target group of high-risk patients remains unsolved.

So far, the Dutch Health Council has only recommended the latter vaccination for all elderly patients and those with high-risk disease. To further enhance physician adoption of the influenza immunization guideline, a nationwide collaborative program among general practitioners was initiated in 1995.³ As vaccine uptake remained persistently low among patients with chronic lung disease, we conducted a general practitioner-based cost-effectiveness study.⁴ In accordance with data of Nichol et al, we observed cost savings resulting from this vaccine alone in elderly patients with lung disease and a considerable reduction in the occurrence of any influenza-related complication (50%; 95% confidence interval,

Frequency of Adverse Effects and Use of Alternative Therapy Among Patients Receiving Additional Care by a Pharmacist (Intervention Group) vs Control Group*

	Intervention Group Experimental Event Rate	Control Group Control Event Rate	NNT
Nonfatal heart failure	0.011	0.121	9
Nonfatal cardiovascular events	0.089	0.253	6
All-cause mortality	0.033	0.055	45
All-cause mortality and nonfatal heart failure	0.044	0.176	8
Alternative therapy			
Baseline	0.1	0.05	20
Follow-up	0.1	0.05	20

*Created from data presented in Tables 2 and 3 of Gattis et al.¹ The absolute risk reduction for a pharmacist's intervention is the control event rate minus the experimental event rate. NNT indicates number needed to treat and is calculated as 1 divided by absolute risk reduction.

17%-70%). This clearly supports the need to make such vaccination a priority in primary care prevention policy.

The additive benefit of pneumococcal and influenza vaccination compared with influenza vaccination alone has long been a matter of debate in the Netherlands. Honkanen et al⁵ observed no such benefit among 26925 elderly persons in Finland. Although point estimates of hospitalization and mortality rates in the comparison groups as observed by Nichol et al suggest potential incremental benefits of the combined vaccination, the study lacks adequate power to estimate statistically significant differences. Since uncertainty remains regarding this issue, we are convinced that a larger cost-effectiveness study designed as a pragmatic randomized controlled trial enrolling various high-risk patient groups is now warranted.

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- Örtqvist Å, Hedlund J, Burman LA, et al, for the Swedish Pneumococcal Vaccination Study Group. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. *Lancet*. 1998;351:399-403.
- Nichol KL, Baken L, Wuorenma J, Nelson A. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. *Arch Intern Med*. 1999;159:2437-2442.
- Hak E, Hermens RPMG, van Essen GA, Kuijvenhoven MM, de Melker RA. Population-based prevention of influenza in Dutch general practice. *Br J Gen Pract*. 1997;47:363-366.
- Hak E, van Essen GA, Buskens E, Stalman W, de Melker RA. Is immunising all patients with chronic lung disease against influenza cost-effective? evidence from a prospective general practice based clinical cohort study in Utrecht, the Netherlands. *J Epidemiol Community Health*. 1998;52:120-125.
- Honkanen PO, Keistinen T, Miettinen L, et al. Incremental effectiveness of pneumococcal vaccine on simultaneously administered influenza vaccine in preventing pneumonia and pneumococcal pneumonia among persons aged 65 years or older. *Vaccine*. 1999;17:2493-2500.

In reply

Hak and colleagues raise important questions regarding the incremental benefits of pneumococcal vaccination over influenza vaccination alone among community-dwelling elderly persons.

In our 2-year cohort study of 1898 persons with chronic lung disease, we found that pneumococcal vaccination was associated with significant reductions in hospitalizations for pneumonia and deaths from all causes.¹ In our multivariate analyses, we controlled for influenza vaccination status for each of the two influenza seasons included in the 2-year

follow-up period. Thus, our findings present the statistically significant independent contribution of pneumococcal vaccination status. There was no evidence of interaction between the two vaccinations, suggesting that their benefits were additive.

Analyses of the effectiveness of these vaccinations in reducing hospitalizations for pneumonia by season (influenza vs interim) for the 2 years included in our study provide additional evidence of the independent contributions of pneumococcal vaccinations in this high-risk cohort (Table).

Whereas influenza vaccination was clearly effective only during the influenza seasons, pneumococcal vaccination effectiveness was similar during both the influenza seasons and interim periods. These findings provide strong evidence that pneumococcal vaccinations are associated with reductions in the risk of hospitalization for pneumonia that are independent of and in addition to those observed with influenza vaccinations—at least among elderly persons with preexisting chronic lung disease. How these findings might apply to other risk groups is, however, unclear.

In the meantime, the data from other studies demonstrating that pneumococcal vaccinations are associated with a reduced risk for acquiring pneumococcal bacteremia remain sufficient justification to recommend the use of pneumococcal vaccine for high-risk groups, including the elderly.^{2,3} The finding of the study by Honkanen et al⁴ that pneumococcal vaccination in addition to influenza vaccination was associated with a 60% reduction in pneumococcal bacteremias, while not statistically significant, provides evidence in support of current recommendations for pneumococcal vaccination.

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- Nichol KL, Baken L, Wuorenma J, Nelson A. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. *Arch Intern Med*. 1999;159:2437-2442.
- Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practice (ACIP). *MMWR Morb Mortal Wkly Rep*. 1997;46(RR-8):1-24.
- Sisk JE, Moskowitz AJ, Whang W, et al. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. *JAMA*. 1997;278:1333-1339.
- Honkanen PO, Keistinen T, Miettinen L, et al. Incremental effectiveness of pneumococcal vaccine on simultaneously administered influenza vaccine in preventing pneumonia and pneumococcal pneumonia among persons aged 65 year or older. *Vaccine*. 1999;17:2493-2500.

Effectiveness of Pneumococcal and Influenza Vaccinations in Reducing Hospitalizations for Pneumonia by Season (Influenza Season vs Interim)*

	Adjusted Risk Ratio (95% CI)		
	Overall	Influenza Seasons Only	Interim Periods Only
Pneumococcal vaccination	0.57 (0.38-0.84)	0.61 (0.37-1.02)	0.55 (0.33-0.95)
Influenza vaccination	0.47 (0.26-0.87)	0.46 (0.25-0.88)	0.93 (0.52-1.65)

*CI indicates confidence interval.

Adverse Drug Reactions in the Elderly: Need for Dedicated Databases

We read with much interest the article by Bates and coworkers¹ in the November 1999 issue of the ARCHIVES. The authors searched for patient risk factors for adverse drug events in a series of hospitalized patients with a mean age of less than 60 years. They concluded that patient characteristics, chiefly advanced age and polypharmacy, should not be used for risk stratification. In addition, they stated that impaired renal function is a relatively infrequent problem. Adverse drug reactions (ADRs) currently represent a major threat to older patients, since these patients are the major drug consumers in Western countries, and the consequences of ADRs might be most severe in the frailest subjects. Thus, caution is mandatory when denying the necessity of focusing on older patients for preventing ADRs.

Indeed, while we cannot disagree about the authors' attempt to develop a "practical" method to study ADRs, we feel that this issue is too relevant and complex to be addressed by retrospective analyses of "limited" sets of administrative data; rather, specific, prospective studies on elderly populations based on dedicated tools for data collection are required. This type of research has been conducted by the Gruppo Italiano di Farmacovigilanza nell'Anziano (GIFA), which has undertaken a collaborative study of ADRs in hospitalized patients. In this ongoing study, all patients who were admitted to 81 academic centers in Italy from May 1, 1988, to June 30, 1988; from November 1, 1988, to December 31, 1988; and from May 1 to June 30 and September 1 to October 31, 1993, 1995, and 1997, were enrolled and observed until discharge.

For each patient a form was completed on admission and updated daily by a trained physician. Data were recorded at clinical centers using dedicated software that controls for suitability and internal consistency of data. This software automatically codes diagnoses (with *International Classification of Diseases, Ninth Revision [ICD-9]*, codes), ADRs, and drugs (with Anatomical, Therapeutic, and Chemical [ATC] codes) simply by entering the description of the disease, ADR, or commercial drug name.² The program contains 1560 descriptions of ADRs, according to World Health Organization coding, and all drugs available in Italy. The data recorded include demographic characteristics; objective tests results and measures (including those for thorough blood chemistry analysis); drugs taken before admission, during hospital stay, and at discharge; and admission and discharge diagnoses. Whenever an ADR is suspected, a dedicated form is completed and updated. The probability of a causal relationship between drugs and ADRs is assessed by the Naranjo algorithm.³

The GIFA database currently includes data on 28411 patients with a mean \pm SD age of 70 ± 16 years, in whom 4886 possible ADRs (ie, a rate of 17 per every 100 ad-

missions) have been detected. When only probable to definite ADRs (total score ≥ 5) are considered, the incidence is reduced to 9.7%, which is still greater than the 5.8% incidence reported by Bates et al.¹ In addition, serum creatinine levels greater than 106 $\mu\text{mol/L}$ (1.2 mg/dL) were detected in 24% of participants in the GIFA database. This figure is probably underestimated, since assessment of serum creatinine levels generally under-values creatinine clearance in older subjects. Thus, renal failure cannot be disregarded when attempting to prevent ADRs in elderly populations.

The effects of advanced age on the risk of ADRs might become relevant only for the most advanced age groups, which were poorly represented in the Adverse Drug Events (ADE) Prevention Study Group population sample. For instance, an independent effect of age on the risk of ADRs to calcium antagonists and loop diuretics was observed in the GIFA database only for subjects older than 75 years,^{4,5} whereas 80 years and older was the age cutoff for increased risk of digoxin toxic effects, after adjusting for potential confounders.⁶ In addition, advanced age can lead to reduced risk of some ADRs. For instance, age was independently and inversely associated with headache caused by nitrates.⁷ In the same database, polypharmacy has also been proven to be a powerful predictor of ADRs. In fact, taking more than 4 drugs and having more than 4 active medical conditions were independently associated with the in-hospital occurrence of ADRs.⁸

We believe that the dispute surrounding the impact of age and polypharmacy on the risk of ADRs is still far from being settled. At present, age 75 years or older and polypharmacy should not be ignored in programs aiming at reducing the incidence of ADRs in hospitalized patients.

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1. Bates DW, Miller EB, Cullen DJ, et al, for the Adverse Drug Events (ADE) Prevention Study Group. Patient risk factors for adverse drug events in hospitalized patients. *Arch Intern Med.* 1999;159:2553-2560.
2. Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin PU. Drug data coding and analysis in epidemiologic studies. *Eur J Clin Epidemiol.* 1994;10:405-411.
3. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30:239-245.
4. Pahor M, Manto A, Pedone C, Carosella L, Guralnik JM, Carbonin PU, for the Gruppo Italiano di Farmacovigilanza nell'Anziano (GIFA). Age and severe adverse drug reactions caused by nifedipine and verapamil. *J Clin Epidemiol.* 1996;49:921-928.
5. Zuccalà G, Pedone C, Cocchi A, et al. Older age and in-hospital development of hypokalemia from loop diuretics: results from a multicenter survey. *J Gerontol Med Sci.* In press.
6. Pahor M, Guralnik JM, Gambassi G, Bernabei R, Carosella L, Carbonin PU, for the Gruppo Italiano di Farmacovigilanza nell'Anziano (GIFA). The impact of age on risk of adverse drug reactions to digoxin. *J Clin Epidemiol.* 1993;46:1305-1314.
7. Pahor M, Cecchi E, Fumagalli S, et al, for the Gruppo Italiano di Farmacovigilanza nell'Anziano (GIFA). Association of serum creatinine and age with headache caused by nitrates. *Clin Pharmacol Ther.* 1995;58:470-481.
8. Carbonin PU, Pahor M, Bernabei R, Sgadari A. Is age an independent risk factor of adverse drug reactions in hospitalized medical patients? *J Am Geriatr Soc.* 1991;39:1093-1099.

In response to the letter of Zuccala et al about our study of the risk of adverse drug events (ADEs) in hospitalized patients,¹ we came to this area with the same prior hypotheses of Zuccala's group—namely, that old age, polypharmacy, and renal failure would be associated with the presence of ADEs. However, we were surprised to find that despite an abundance of commentary on these topics, comparatively few published empiric data are available to support the strength of these associations, especially for hospitalized patients. It is important to note that the primary goal of our study was to identify a high-risk subset of patients who could be targeted for extra scrutiny to decrease their risk of ADEs.

Regarding age, when the patients we studied were stratified into the age groups (≤ 50 , 51-60, 61-70, and >70 years), there was no significant relationship either in the case-control analysis ($P = .89$) or when patients were compared with the entire cohort ($P = .97$). We did have relatively few patients who were older than 75 years. It is ironic that the authors' primary conclusion in one of the articles inquiring whether age and adverse drug reactions are associated was that "age is not an independent risk factor of adverse drug reactions."² For ADEs caused by individual drugs, ADEs may constitute an independent risk factor as the authors note, but in our study we were attempting to develop an index that worked across medications. As patients get older, they tend to have more comorbid conditions and less renal reserve, and these factors may be more important than chronological age.

Regarding polypharmacy, we found only weak, non-significant associations between the number of drugs patients received and the presence of an ADE or preventable ADE. We agree that many patients receive more drugs than necessary and that good pharmacology practice demands the careful initial choice of medications followed by regular reassessment of the need for each individual medication.

We agree that renal failure is an important issue³ and that medications are often incorrectly dosed in patients with renal insufficiency, but in our data set, while this was a univariate predictor, it was not an independent predictor.

Zuccala et al also suggest that our data were "retrospective" and "administrative"; neither is correct. Our data were gathered prospectively. While we did an analysis using only administrative data to determine how well such data would work for risk stratification, an important operational question, our comparison was with data collected from detailed chart reviews.

Databases such as the Gruppo Italiano di Farmacovigilanza nell'Anziano (GIFA) database do represent a rich source of information on this topic and should receive support.

The lack of association between these and other factors with the presence of ADEs and preventable ADEs supports the primary conclusion of our article: that systems changes that promote better use of medications for all hospitalized patients will be most effective in reducing ADE frequency.^{4,5} These will eventually include suggestions regarding dosing that consider a patient's age, other medications, and renal function. Such changes are more likely to

improve medication safety than programs that identify high-risk individuals.

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1. Bates DW, Miller EB, Cullen DJ, et al, for the Adverse Drug Events (ADE) Prevention Study Group. Patient risk factors for adverse drug events in hospitalized patients. *Arch Intern Med.* 1999;159:2553-2560.
2. Carbonin PU, Pahor M, Bernabei R, Sgadari A. Is age an independent risk factor of adverse drug reactions in hospitalized medical patients? *J Am Geriatr Soc.* 1991;39:1093-1099.
3. Lee J, Chertow GM, Kuperman GJ, et al. Benefits of computerized guided dosing in in-patients with renal dysfunction [abstract]. *J Gen Intern Med.* 1999;14(suppl 2):47.
4. Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *JAMA.* 1998;280:1311-1316.
5. Bates DW, Teich J, Lee J, et al. The impact of computerized physician order entry on medication error prevention. *J Am Med Inform Assoc.* 1999;6:313-321.

We Must Save the Art of Medicine

The article by Woywodt and colleagues¹ addresses a very important issue. It highlights the clinical value of cardiac auscultation. The authors showed their enthusiasm to establish the diagnosis of an anomalous chordae in the right ventricle based on careful physical examination. Their suspicion was not substantiated until they requested a second echocardiogram.

Physical examination is an integral part of evaluating the patient. The more thorough the history and clinical examination, the more focused and cost-effective will be the subsequent laboratory evaluation.² However, it is disappointing that many physicians have lost their faith in clinical skills, relying too heavily on laboratory and diagnostic investigations for solving clinical problems. As an example, it has become common practice to refer patients for echocardiogram to "evaluate a murmur."

Studies that showed low performance in clinical examination of physicians in training³ should not be surprising, as there is less emphasis on physical examination in medical schools and during the training of physicians.⁴ More emphasis is needed to stimulate and improve the clinical skills of physicians and physicians in training, using different educational tools, such as computer-based programs.⁵

I strongly agree with Marcus⁶ that incorporating the physical examination as part of the board certification examination will have a positive impact.

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1. Woywodt A, Hofer M, Pilz B, Schneider W, Dietz R, Luft FC. Cardiopulmonary auscultation: duo for strings—Opus 99. *Arch Intern Med.* 1999;159:2477-2479.
2. Tavel ME. Cardiac auscultation: a glorious past—but does it have a future? *Circulation.* 1996;93:1250-1253.
3. Mangione S, Nieman LZ. Cardiac auscultatory skills of internal medicine and family practice trainees: a comparison of diagnostic proficiency. *JAMA.* 1997;278:717-722.

4. Mangione S, Neiman LZ, Gracely E, Kaye D. The teaching and practice of cardiac auscultation during internal medicine and cardiology training. *Ann Intern Med.* 1993;119:47-54.
5. Waugh RA, Mayer JW, Ewy GA, et al. Multimedia computer-assisted instruction in cardiology. *Arch Intern Med.* 1995;155:197-203.
6. Marcus FI. The lost art of the auscultation [commentary]. *Arch Intern Med.* 1999; 159:2396.

In reply

I appreciate Eledrisi's thoughtful comments. I agree completely that a careful history and physical examination are clinically valuable and highly cost-effective in terms of avoiding unnecessary procedures and testing. The physical examination, especially of the heart, has never been more fun, since current imaging procedures now permit verification of the findings, as was the case in our patient. Furthermore, excellent computer-based teaching programs are available that show the heart with various imaging techniques and provide hemodynamic information, heart sounds, and murmurs, all in stereophonic sound and vivid living color. I understand that the American Board of Internal Medicine is preparing a section that incorporates the clinical examination as part of the board certification examination. Finally, and ultimately most important, skilled teachers are required to instruct physicians in the art of the physical examination. While a resident at Indiana University in the late 1960s, I was fortunate to have such teachers as Pat Genovese, Charles Fisch, Suzanne Knoebel, and Morton Tavel. Thanks to them, the duo for strings was not difficult.

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Alendronate and Nonsteroidal Anti-inflammatory Drug Interaction Safety Is Not Established

The suggestion by Bauer et al¹ that there is no increased alendronate-related risk of upper gastrointestinal (GI) tract events "even in high-risk subgroups" must be questioned. The recent report by Graham and Malaty² focused attention on the additional risk posed by concomitant use of alendronate with cyclooxygenase 1 (COX-1) nonsteroidal anti-inflammatory agents (NSAIDs), compounds with their own gastropathy risk. In addition to demonstrating a statistically significant gastric ulcer risk for alendronate therapy, Graham and Malaty² documented quadrupled risk with concomitant NSAID ingestion. As these studies^{1,2} are disparate in their conclusions, it seems reasonable to examine the methods of the study by Bauer et al.¹

The study by Bauer et al,¹ also known as the Fracture Intervention Trial (FIT), was not designed to assess the risk of concomitant NSAID usage. While statisticians might argue the validity of such subsequent analysis, other issues seem more problematic.

The definition of the NSAID group must be challenged. The inclusion of individuals who received as little as one NSAID dose must be questioned. It is quite sur-

prising that patient-year NSAID exposure is not presented, which would perhaps allow for true comparison of the actual relative risk that alendronate usage adds to NSAID usage. It would also be of great interest to separately evaluate aspirin and NSAID use, and of course, to assure that the gastropathy-sparing COX-2 agents (which probably entered general clinical practice during the course of the study) were segregated from COX-1 NSAIDs in the analysis.

Another factor compromises the applicability of the Bauer et al study findings to clinical practice: alendronate dosage. Bauer et al administered alendronate at 5 mg in a fasting state for the first 2 years. That is half the clinically recommended/used dosage. The clinically applicable comparison might more reasonably be for GI events with or without concomitant NSAID usage, but only in that third year. However, there is another consideration: the package insert recommends only a half-hour predose avoidance of food, as opposed to a fasting state. Thus, it is unclear that the study dosing regimen used by Bauer et al can be applied to clinical practice.

Bauer et al incidentally reported events in patients treated with half the dosage and more stringent precautionary measures than those suggested (by the package insert) for clinical practice. Their patients were not prospectively or even concurrently evaluated for the occurrence of "upper GI tract events." It was also surprising that only recognized events were reported without comment on analysis of hemoglobin reductions (possible surrogates for blood loss and GI events).

It therefore seems appropriate to suggest that a prospective GI event occurrence study is indicated before we can feel comfortable prescribing alendronate to patients receiving COX-1 NSAIDs.

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1. Bauer DC, Black D, Ensrud E, et al. Upper gastrointestinal tract safety profile of alendronate: the Fracture Intervention Trial. *Arch Intern Med.* 2000;160: 517-525.
2. Graham DY, Malaty M. The combination of alendronate and naproxen is synergistic regarding the production of gastric ulcers [abstract]. *Arthritis Rheum.* 1999;42:S291.

Faculty and Agora

As a physician who has served in all areas of internal medicine for 55 years, I certainly agree with Eisenberg's assessment of the academic hospital problem.¹ Years ago the Macy Report showed that the cost of postgraduate education in academic medical centers was increased by the rush to have large subspecialty programs with full-time staff members and increasingly costly technology. This does equate with the need to cover educational costs with a nationwide universal health insurance system. Medical schools tend to keep the faculty with the largest research budgets and the "golden wands" that bring financial benefit to the university and are of the least direct benefit to patient care. It is difficult to get some faculty members to participate

in clinical chores, and, with the exception of the annual outstanding teacher award, the clinician is less rewarded than the investigator and publisher. This parallels the clinical practice problem of rewarding procedures over cognitive skills.

Dr Clyde Kluckhohn (Harvard University) and Dr Dennis (University of Oklahoma and University of Arkansas) point out the cultural role of the priest/medicine man in society. We have not seen clearly in the rearview mirror of the past (culture) in which the "Hero Physicians" of our time were raised the extent of the shift in society's paradigm of the "health care provider" until the person becomes dis-eased. Many of our current physicians are from societal backgrounds that, as Kissinger says, "don't think like we do" and whose desires and motives to serve vary considerably. However, cultural anthropology will win out; as Dr Reinhardt says, "we will muddle through."

The "one-size-fits-all" application of national health insurance will further complicate the muddle of Medicare and Medicaid and is no substitute for the reward of charity (Latin, *caritas*; Greek, *agape*). Thus far, it has been a disaster to have mandated equal, "usual, customary, and cost-based" fee schedules for the well-to-do and the indigent; no society can bear this cost, as was proven by the failed "Great Society" of Dingell, Anderson, and Johnson.

I have practiced in multispecialty teaching clinics and hospitals, university medical center hospitals, charity hospitals, Veterans Affairs teaching hospitals, specialty groups with independent offices in medical centers, health maintenance organizations, and, to my delight, a country clinic in Arkansas that was far more sophisticated than my great grandfather Dr William Anderson Beasley (University of Georgia, 1847) and grandfather Dr Joshua Beasley (Memphis Medical College) ever dreamed. All of these organizations have individual problems, which Harvard University and the University of New Mexico are in the process of addressing. One financial size will not fit all and should not. There is a "Divine Diversity" in medicine as there is in the church, and to have all directed from Rome or Washington, DC, will lead to obvious problems.

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1. Eisenberg L. Whatever happened to the faculty on the way to the agora? *Arch Intern Med.* 1999;159:2251-2256.

A Medical Emancipation Proclamation

The recent commentary by Eisenberg¹ goes right to the heart (literally) of the matter and hits every nail on the head in detailing and deploring the increasingly sorry state our profession, our health care system, and our academic medical centers have fallen into. It could well serve as the manifesto for a movement to regain what was good and bury what is bad about medicine before the advent of managed care organizations. If

"the answer lies with us," what exactly does Eisenberg suggest we do as a profession to regain control of the process so that we may practice as free rather than as slave doctors?

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Faculty Should Remain Agoraphobic

I am no great fan of managed care,¹ but the alternative of universal health insurance that Eisenberg² exhorts us to embrace is the worse of two evils.

Can physicians be trusted to do the right thing if resources are made available ad lib by third parties? The answer is a resounding no. Since Medicare began in 1965, health care costs have gone up from 6% to 14% of the gross domestic product. How this oversupply of money has helped and harmed medicine has been discussed in detail elsewhere,¹ but one thing is certain, extension of Medicare-style universal health coverage will escalate costs further.

As for quality of care, if we take as an example Eisenberg's specialty before managed care shook the industry, the average length of stay for mental patients in the Northville State Hospital of Michigan was 5 years. Strongly supported by the science of the 1980s, the administration of stupefying dosages of psychotropic medications was the norm. Today the average length of stay has dropped from 5 years to 28 days. Neuroleptic malignant syndrome, sudden cardiac death, seclusion, restraints, physical violence, and electroconvulsive therapy have virtually disappeared.

It is difficult to buy Eisenberg's argument that when faculty members have low clinical responsibility they teach better. As a rule, the more nonclinical time faculty members have, the more unnecessary medical consultations, complexities, and conundrums they create to act out their hostilities, rivalries, and power plays at the expense of patient health.¹ In fact, the culture of imparting medical knowledge to one's charge through continuous onepersonship is so strong that I would not hesitate to describe it as the sine qua non of the academy. The arrogance of the profession will only go away if medical teaching changes from its current format of a bunch of sparring doctors walking from one bed to another in bizarre hierarchies to medical trainees observing the faculty directly taking care of patients.

Managed care has brought a lot of fiscal sanity to the practice of medicine; in the long run, however, it is an incorrect option because its primary interest is in saving money for the employers. The answer lies in eliminating all laws that require employers to buy health insurance for their workers. Medicine is not an exception to the magic of the marketplace, provided it is a real agora and not a hodgepodge of free enterprise and government-

tal rules. If people will pay directly from their pockets, medical cost and care will dramatically improve.

For those who cannot afford private medical care, there should be sliding-scale clinics and hospitals run by medical schools. Such medical centers for the less well-off should receive most of the governmental clinical, teaching, and research grants,¹ and that is where the bulk of the medical faculty should go, instead of trying to cling to the agora, where, so far, they have done a lousy job.

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1. Kelwala S. *Blood Money: Modern Medicine's Abuse of Power*. Ann Arbor, Mich: Proctor Publications; 1996.

2. Eisenberg L. Whatever happened to the faculty on the way to the agora? *Arch Intern Med*. 1999;159:2251-2256.

HM-no!

Thanks, Dr Eisenberg! I happened to be reading the ARCHIVES last Thanksgiving Eve after hospital rounds and saw his fabulous editorial.¹ I congratulate him for the clear insight and honest overview of the present managed care system vs the old, virtually extinct system.

I thank Eisenberg because it takes courage as a Harvard academician to confront reality and state things as they are. I believe, following his text, that as Socrates said, most of us are treating patients the way slave doctors once treated slave patients: rushing, careless, and looking for the best way to profit in a hypocritical way. I still try to deliver care as I was taught to do in medical school and later during my residency. Capitation should disappear from the face of this world, and we should stand together for what we were taught: to care for the patient, not for the paycheck. It is a shameful state of affairs when physicians no longer want to see certain patients because it will mean less reimbursement or when nurse practitioners are asked to see certain patients because physicians love the uncomplicated sore throat more than the challenging patient in the intensive care unit who belongs to an HMO.

Hopefully, many other brave physicians will join Eisenberg and help to deliver excellent care to our patients, the same standard of care that we would like to receive if we were the patients. We should open our eyes and the eyes of the world before all of the teaching hospitals are destroyed or gobbled up by managed-care mergers!

Finally, I strongly agree with Eisenberg's views on health care delivery to minorities. It is worse than ever. We should stop government intervention in health care at once. The current system is failing, and new alternatives must be presented, particularly in this election year.

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1. Eisenberg L. Whatever happened to the faculty on the way to the agora? *Arch Intern Med*. 1999;159:2251-2256.

Managed Care vs Universal Health Insurance: Whose Whips Are Gentler?

As a solo practitioner of internal medicine who has refused health maintenance organization affiliation for 17 years, I was stirred by Eisenberg's descriptions of the free doctor, as opposed to the enslaved provider, in his commentary.¹ True, his self-pity does get in the way of his message, such as his bemoaning the erosion of his professorial prestige when his university chose to grant faculty status to any old *hoi polloi* doc whose practice it bought. But hey, we freedom-loving physicians can use all the friends we can get, right?

Eisenberg, however, betrays the cause of the very freedom he claims to champion when he discloses his solution to managed care: universal health insurance. As practiced from Canada to Mexico to England, such systems result in precisely the "minimally adequate care on the cheap"¹ that he professes to deplore. Patients in these nations have increasingly fled from government-controlled 7-minute physician visits; they have fled southward across the US-Canadian border, into private English insurance schemes, and even into Mexican versions of managed care. It would seem that Eisenberg, far from fighting for freedom, is begging for a kinder, gentler master, one that perhaps will be more respectful of his academic prerogatives, come what may for patients and community physicians.

The most damning indictment of managed care may be that its abuses of bureaucratic power make even the federal government (the folks who bring you the US Post Office and the Internal Revenue Service) seem patient- and physician-friendly by comparison. But before you change masters, Eisenberg, consider the following: in Boston, you may leave managed care with 90 days' contractual notice, then compete for patients in the very agora that fills you with such phobia. In Toronto, your choices would be to endure the government system, emigrate, or leave medical practice. Kindly spare your fellow physicians those alternatives.

If you are serious about reforming the health care delivery system disaster you have so eloquently described, you might find better solutions in many areas: empowerment of physicians and patients against the insurance and pharmaceutical cartels, reduction of crippling government overregulation of medical practice, and—oh, yes—recommitment of academic medicine to the values of individual and institutional liberty. We freedom fighters are counting on you!

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1. Eisenberg L. Whatever happened to the faculty on the way to the agora? *Arch Intern Med*. 1999;159:2251-2256.

plasma exchanges, his neurologic status, platelet count, and hemoglobin level were improved. Methylprednisone therapy was slowly tapered. On day 45, the patient was discharged, and steroid therapy was discontinued. His hemoglobin level was 110 g/L, his platelet count was $146 \times 10^9/L$, and his lactate dehydrogenase level was normal. The creatinine level was 77 $\mu\text{mol/L}$ (0.87 mg/dL). The left hemiplegia improved. One year later, no relapse of TTP had occurred.

Comment. This patient was diagnosed as having TTP, with fever, neurologic changes, renal dysfunction, thrombocytopenia, and microangiopathic hemolytic anemia with normal coagulation test results. In a cytomegalovirus prophylaxis trial evaluating treatment with high-dose valacyclovir hydrochloride (8 g/d) vs acyclovir, a high frequency of cases of TTP was reported (18 among 1227 HIV-infected patients).³ Our patient showed the same characteristics that were observed among these HIV-infected patients with TTP related to treatment with valacyclovir: no associated infection, a gradual onset of TTP in contrast to the usual sudden onset, and a better prognosis among patients with neurologic manifestations. The link between our patient's TTP and valacyclovir therapy may be circumstantial; HIV may have been the causal agent.² Moreover, Chulay and Bell⁵ reported that no cases of TTP were observed among more than 700 HIV-infected patients who were treated with valacyclovir (1 g/d).

Nevertheless, this report highlights the importance of the postmarketing surveillance of newly marketed drugs, especially those used to treat HIV-infected patients who receive numerous drugs.

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1. Leaf AN, Laubenstein LJ, Raphael B, Hochster H, Baez L, Karpatkin S. Thrombotic thrombocytopenic purpura associated with human immunodeficiency virus type 1 (HIV-1) infection. *Ann Intern Med.* 1988;109:194-197.
2. Thompson CE, Damon LE, Ries CA, Linker CA. Thrombotic microangiopathies in the 1980s: clinical features, response to treatment, and the impact of the human immunodeficiency virus epidemic. *Blood.* 1992;80:1890-1895.
3. Bell WR, Chulay JD, Feinberg JE. Manifestations resembling thrombotic microangiopathy in patients with advanced human immunodeficiency virus (HIV) disease in a cytomegalovirus prophylaxis trial (ACTG 204). *Medicine (Baltimore).* 1997;76:369-380.
4. Bell WR, Braine HG, Ness PM, Kickler TS. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: clinical experience in 108 patients. *N Engl J Med.* 1991;325:398-403.
5. Chulay JD, Bell AR. Long-term safety of valacyclovir for suppression of herpes simplex virus infections [letter]. *Clin Infect Dis.* 1996;23:879.

From a Darwinian perspective, suicide at first glance seems an aberration, since the goal of the evolutionary game is to live in order to pass on one's genes. If one reflects further, however, it may be that suicide has evolved as a way for a damaged organism to cease being a drain on resources that could otherwise be used by its offspring or kin, which share its genes in varying degrees. The desire to die arising from the perception of being severely damaged physically or mentally may have made sense in times past from an evolutionary perspective. Arguably, it does not make sense in today's society, with its social safety nets and medical advances.

The desire to end one's life, whether by suicide or euthanasia, is generally prompted by protracted physical pain¹ or by delirium, psychosis,² or depression.³ Depression in particular is often underrecognized and undertreated,⁴ and it can have a variety of biological, psychological, and social precipitants. With modern pharmacological and non-pharmacological interventions, all of the above are treatable. If adequately treated, we postulate that the triggering of the suicide switch in the brain would not occur, and people would likely not choose to die.⁵

This model is testable. If it is true, then the goals of medicine should be to treat pain and suffering completely and to delay death for as long as possible, certainly as long as meaningful cognitive ability remains. It should not encourage and provide euthanasia. These goals are quite attainable nowadays with aggressive and sophisticated treatment and will be even more so in the future.⁶ A few more months or years would give patients more time to spend with loved ones and to impart experience and wisdom, a nonnegligible benefit to individuals and to society as a whole.

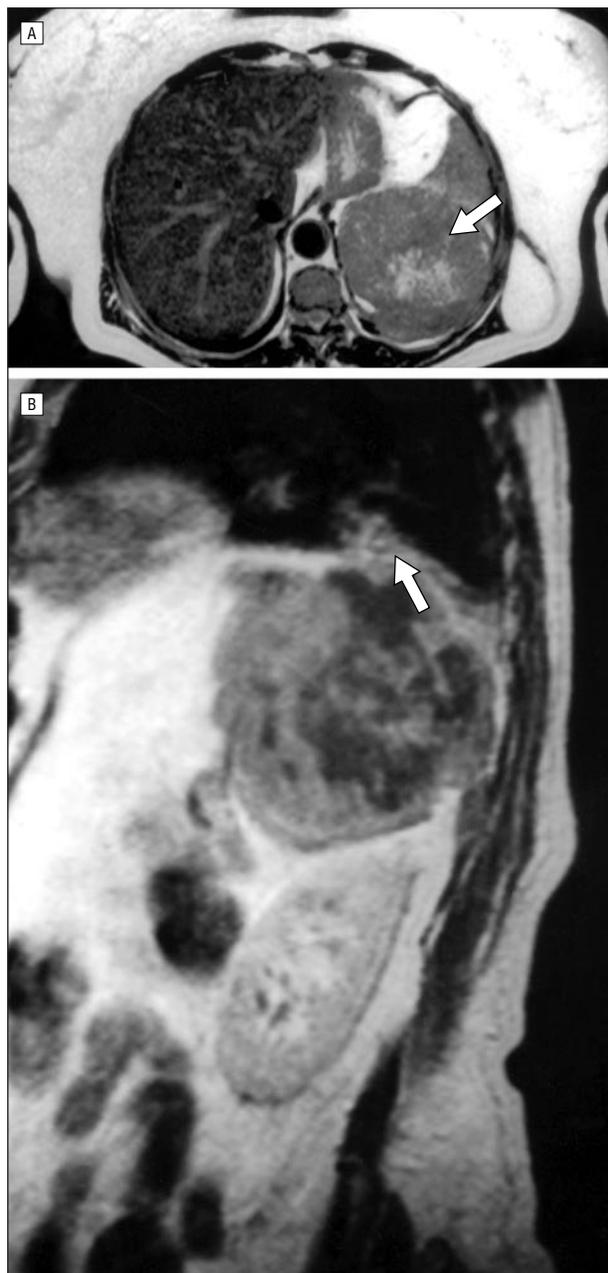
1. Fishbain DA. The association of chronic pain and suicide. *Semin Clin Neuropsychiatry.* 1999;4:221-227.
2. Radomsky ED, Haas GL, Mann JJ, Sweeney JA. Suicidal behavior in patients with schizophrenia and other psychotic disorders. *Am J Psychiatry.* 1999;156:1590-1595.
3. Chochinov HM, Tataryn D, Clinch JJ, Dudgeon D. Will to live in the terminally ill. *Lancet.* 1999;354:816-819.
4. Niculescu AB. Prophylactic antidepressant treatment before patients are admitted. *Lancet.* 2000;355:406-407.
5. Kugaya A, Akechi T, Nakano T, Okamura H, Shima Y, Uchitomi Y. Successful antidepressant treatment for five terminally ill cancer patients with major depression, suicidal ideation and a desire for death. *Support Care Cancer.* 1999;7:432-436.
6. Niculescu AB. Brainology: understanding of the brain is within our grasp, and it will change everything. *Medscape General Medicine* [serial online]. August 4, 1999. Available at: <http://oncology.medscape.com/Medscape/GeneralMedicine/journal/1999/v01.n08/mgm0804.nicu/mgm0804.nicu.html>. Accessibility verified March 14, 2000.

The Will to Live, Suicide, and Euthanasia

We would like to propose a model that may confer simplicity, consistency, and moral clarity to end-of-life issues facing physicians and their patients.

Magnetic Resonance Imaging in Primary Lymphoma of the Spleen

Report of a Case. A 74-year-old woman presented with a 3-month history of progressive weakness, 5-kg weight loss, and pain in the right upper abdominal quadrant. On physical examination, there was splenomegaly without lymphadenopathy and no other remarkable findings.



A, Magnetic resonance imaging shows a splenic mass 12 cm in diameter (arrow) with isointensity relative to normal splenic parenchyma in T2-weighted sequences, with heterogeneous enhancement after injection of gadolinium. B, Magnetic resonance imaging also shows local invasion of diaphragmatic and pleural surfaces (arrow), which was not demonstrated on ultrasonograms or computed tomographic scans.

Laboratory tests revealed a hematocrit of 0.38, a white blood cell count of $5.5 \times 10^9/L$, a platelet count of $226 \times 10^9/L$, a lactate dehydrogenase level of 1468 U/L,

an erythrocyte sedimentation rate of 71 mm/h, and a β_2 -microglobulin level of 4.6 mg/L (normal range, 0.8-2.1 mg/L). Ultrasonography and computed tomography (CT) of the abdomen demonstrated a solid, large splenic mass with lobulated margins without other abnormalities. Magnetic resonance imaging (MRI) showed a splenic mass 12 cm in diameter with isointensity relative to normal splenic parenchyma in T2-weighted sequences, with heterogeneous enhancement after injection of gadolinium (**Figure**). Magnetic resonance imaging also disclosed local invasion of diaphragmatic and pleural surfaces (**Figure, B, arrow**), which was not demonstrated on ultrasonograms or CT scans. The histopathologic diagnosis was diffuse large B cell lymphoma. The result of bone marrow biopsy was normal.

Comment. Magnetic resonance imaging is important in the diagnosis of the focal lesions of the spleen.¹ For example, MRI has been shown to be reliable in differentiating hamartomas from hemangiomas of the spleen.² On T1-weighted MRI scans, the normal signal intensity of the spleen is less than that of hepatic tissue and slightly greater than that of muscle. On T2-weighted MRI scans, the spleen shows higher signal intensity, appearing brighter than the liver.³ Irregular or poorly defined border contours, which provide evidence of invasion and cystic or necrotic areas, are characteristic but not pathognomonic of malignant splenic lesions.^{1,4,5} Additional imaging features of malignant lesions are transgression of the splenic capsule with involvement of adjacent organs and the lack of delayed contrast enhancement.^{1,4,5} In our case, MRI showed invasion of diaphragmatic and pleural surfaces, which ultrasonograms and CT scans did not reveal. In conclusion, CT is currently the diagnostic test of choice for evaluation of the spleen; however, MRI is being used increasingly. Enhancement-contrast MRI is capable of contributing useful information in the study of the focal lesions of the spleen.

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1. Gualdi GF, Volpe A, Poletti E, Melone A, Ceroni AM, Ferriano MG. Focal lesions of the spleen: contribution of magnetic resonance imaging [in Italian]. *Clin Ter.* 1994;145:49-52.
2. Ramani M, Reinhold C, Semelka RC, et al. Splenic hemangiomas and hamartomas: MR imaging characteristics of 28 lesions. *Radiology.* 1997;202:166-172.
3. Rabushka LS, Kawashima A, Fishman EK. Imaging of the spleen: CT and supplemental MR examination. *Radiographics.* 1994;14:307-332.
4. Weissleder R, Elizondo G, Stark DD, et al. The diagnosis of splenic lymphoma by MR imaging: value of superparamagnetic iron oxide. *AJR Am J Roentgenol.* 1989;152:175-180.
5. Irie H, Honda H, Kaneko K, et al. Inflammatory pseudotumors of the spleen: CT and MR findings. *J Comput Assist Tomogr.* 1996;20:244-248.

17. Geerlings SE, Stolk RP, Camps MJ, Netten PM, Collet TJ, Hoepelman AI, for the Diabetes Mellitus Women Asymptomatic Bacteriuria Utrecht Study Group. Risk factors for symptomatic urinary tract infection in women with diabetes mellitus. *Diabetes Care*. 2000;23:1737-1741.
18. Semetkowska E, Horoszek-Maziarz S, Galinski J, Manitius A, Krupa-Wojciechowska B. The clinical course of untreated asymptomatic bacteriuria in diabetic patients: 14-year follow-up [in Polish]. *Pol J Med Pharm*. 1969;27:91-95.
19. Hooton TM, Scholes D, Hughes JP, et al. A prospective study of risk factors for symptomatic urinary tract infection in young women. *N Engl J Med*. 1996;335:468-474.
20. Stamm WE, McKeivitt M, Roberts PL, White NJ. Natural history of recurrent urinary tract infections in women. *Rev Infect Dis*. 1991;13:77-84.
21. Ikaheimo R, Siitonen A, Heiskanen T, et al. Recurrence of urinary tract infection in a primary care setting: analysis of a 1-year follow-up of 179 women. *Clin Infect Dis*. 1996;22:91-99.
22. Batalla MA, Balodimos MC, Bradley RF. Bacteriuria in diabetes mellitus. *Diabetologia*. 1971;7:297-301.
23. Freedman LR. Natural history of urinary tract infection in adults. *Kidney Int Suppl*. 1975;8(suppl 4):S96-S100.
24. Geerlings SE, Brouwer EC, van Kessel KC, Gaastra W, Stolk RP, Hoepelman AI. Cytokine secretion is impaired in women with diabetes mellitus. *Eur J Clin Invest*. 2000;30:955-1001.
25. Hebanowski M, Galinski J, Semetkowska-Jurkiewicz E, Horoszek-Maziarz S, Manitius A. Proba oceny klinicznego znaczenia bakterii bezobjawowej u kobiet chorych na cukrzyce [Clinical significance of asymptomatic bacteriuria in women with diabetes mellitus]. *Pol Tyg Lek*. 1981;36:1413-1416.
26. van den Broek PJ, van Everdingen JJ, for the Dutch Institute for Quality Assurance. Herziene CBO-richtlijn "Urineweginfecties" ['Urinary tract infections'—revised CBO guideline]. *Ned Tijdschr Geneesk*. 1999;143:2461-2465.
27. Nelson RG, Knowler WC, Pettitt DJ, Bennett PH. Kidney disease in diabetes. In: National Diabetes Data Group, eds. *Diabetes in America*. 2nd ed. Bethesda, Md: National Institute of Health; 1995:349-401.
28. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. *N Engl J Med*. 1999;341:1127-1133.

Correction

Clarification. A letter to the editor by Jose A. Quiros, MD, published in the June 12, 2000, issue (2000;160:1704) and commenting on the "clear insight and honest overview of the present managed care system vs the old, virtually extinct system" in a commentary by Dr Eisenberg (1999;159:2251-2256), was titled "HM-no!" Neither the author nor the editorial staff at the journal were aware that "HMNo" is a federally registered service mark and is the property of Jonathan Sheldon, MD, and Heather Sowell, MD. The journal apologizes for its unwitting use of a phrase so close to this service mark as the title of this letter.