

## COMMENTS AND RESPONSES

## Smallpox Vaccination Risks and Public Policy

**TO THE EDITOR:** The review of smallpox vaccination risks and public policy by Lane and Goldstein (1) was timely and informative. However, their recommendation for smallpox-infected patients to wear the N95 respirator in isolation rooms is not necessary and is potentially harmful.

The N95 respirator was designed to filter air before being inhaled by the person wearing the respirator, not to filter the expulsion of secretions when breathing, coughing, or sneezing. The N95 and other high-efficiency particulate air-filtered masks subject the wearer to discomfort and increased resistance to breathing as well as increased dead space. This discomfort would probably be intolerable for a patient ill with smallpox.

The primary defense against transmission of small droplet and airborne spread of pathogens is an isolation room with proper ventilation and directional airflow. When patients with communicable diseases are cared for in such rooms, there is no need to mask the patient. Guidelines for respiratory isolation specifically state that N95 masks are not for use by patients (2). In situations when additional respiratory secretion barriers are appropriate, a simple surgical mask or tissue held to the mouth while coughing and sneezing is sufficient to limit spread of varicella, measles, and tuberculosis (3). In my opinion, this would suffice for smallpox.

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1. Lane JM, Goldstein J. Evaluation of 21st-century risks of smallpox vaccination and policy options. *Ann Intern Med.* 2003;138:488-93. [PMID: 12639083]
2. Garner JS. Guideline for isolation precautions in hospitals. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol.* 1996;17:53-80. [PMID: 8789689]
3. Guidelines for preventing the transmission of tuberculosis in healthcare facilities. *MMWR* 1994;43:1-132.

**IN RESPONSE:** We appreciate Dr. Cooper's letter and agree with him completely. Exhalation of variola virus is reduced by wearing a simple surgical mask (1). We erroneously extrapolated that datum into use of an N95 respirator. In addition to Dr. Cooper's points, the edema and facial distortion of patients with smallpox make N95 respirators impractical.

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## Reference

1. Downie AW, Meiklejohn M, St Vincent L, Rao AR, Sundara Babu BV, Kempe CH. The recovery of smallpox virus from patients and their environment in a smallpox hospital. *Bull World Health Organ.* 1965;33:615-22. [PMID: 4285461]

## Complementary and Alternative Medical Education

**TO THE EDITOR:** I disagreed with the first sentence of the abstract of "Complementary and Alternative Medical Therapies: Implications for Medical Education" (1) and with most of the rest of the article as well. Although we try to limit ourselves to evidence-based approaches for medical treatment, the authors would have medical education become a scientific "free-fire zone" for every unvalidated whim, notion, and economic and political agenda in our diverse society. Instead of making an eloquent argument that we should drop our standards for the medical curriculum to below those for medical practice (and publication), the authors would have made a more convincing case for inclusion if they had presented more than a handful of examples (perhaps even a table or list) of known important interactions between unproven and conventional therapies. Although we try to strictly adhere to scientific standards ourselves, we must remember that the vast bulk of the business of "alternative medicine" actually consists of entrepreneurs promoting and selling (for profit) substances with no proven benefit. These entrepreneurs have no responsibility to the patient and work in a world (business) where exaggerated claims and misleading advertising are considered ethical. The fact that a credulous public finds their promotions efficacious (they do test their advertising scientifically) is not itself a justification for altering the medical curriculum. Rather, we must face them on their own ground and ours, and demand the same level of scientific proof of efficacy (and safety) for everything our patients use. This will not necessarily be easy, but the alternative to leadership is a gradual "dumbing down" of medical education to the point where the promoters of every fad and trend will demand a place in the curriculum.

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## Reference

1. Wetzel MS, Kaptchuk TJ, Haramati A, Eisenberg DM. Complementary and alternative medical therapies: implications for medical education. *Ann Intern Med.* 2003; 138:191-6. [PMID: 12558358]

**TO THE EDITOR:** Dr. Wetzel and her colleagues (1) have pleaded forcefully for the inclusion of complementary and alternative medicine (CAM) topics in medical education and have advocated a teaching partnership with schools preparing chiropractors, acupuncturists, mind-body therapists, massage therapists, and naturopaths. The goal of this effort is to make practicing physicians aware of the benefits of these interventions and familiar with the local alternative practitioners and offerings.

The proposal did not discuss the central dimension of the issue, however, which is that CAM practitioners divert a substantial portion of patients' health care dollars away from the evidence-based, comprehensive, and continuous primary care available in the United States. If alternative medicine interventions are scientifically sound, we should learn them, use them, and be reasonably reimbursed for the service.

Primary care physicians may want to compete aggressively for patients with the CAM providers and need to be supported in this endeavor by the American College of Physicians and the American

Board of Internal Medicine. Postgraduate medical education should provide an avenue for training and certification in CAM similar to the models provided by geriatric medicine, palliative care, and pain management.

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#### Reference

1. Wetzel MS, Kaptchuk TJ, Haramati A, Eisenberg DM. Complementary and alternative medical therapies: implications for medical education. *Ann Intern Med.* 2003;138:191-6. [PMID: 12558358]

**TO THE EDITOR:** Wetzel and colleagues (1) make a strong case for integrating CAM into medical education. Their deliberations are very much centered on the situation in the United States, but it might be interesting to look further and include perspectives from elsewhere. The 3 countries in which I have detailed experience differ considerably in terms of CAM education of (future) medical doctors. In Germany, an element of CAM has long been a compulsory part of the official medical education. Austria seems to be gradually following this model, while in the United Kingdom, CAM is still largely confined to electives. All 3 countries have 1 major problem, which as far as I can see also exists in the United States: Educators are either “uncritical enthusiasts” or “uninformed skeptics” (2). Neither attitude seems appropriate if we want to spare our future doctors an element of “brainwashing.” The adequate teaching of CAM may first require adequate education of the educators themselves. Familiarization with CAM should cover the “potential benefits and [the] . . . main weaknesses and dangers” of the procedures involved (3).

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1. Wetzel MS, Kaptchuk TJ, Haramati A, Eisenberg DM. Complementary and alternative medical therapies: implications for medical education. *Ann Intern Med.* 2003;138:191-6. [PMID: 12558358]  
2. WHO global strategy on traditional and alternative medicine. *Public Health Rep.* 2002;117:300-1. [PMID: 12452183]  
3. House of Lords Science and Technology Committee. House of Lords Report: Science and Technology, 6th report. London: The Stationery Office; 2000.

**TO THE EDITOR:** I read with great interest the *Academia and Clinic* article “Complementary and Alternative Medical Therapies: Implications for Medical Education” (1) and applaud the authors for succinctly summarizing the key issues of this very important topic. As we have embarked upon such curricular developments at our home institution, fellow colleagues and I who are interested in CAM education concur with the advice and guidelines that were presented. I wish to share with your readership an additional, excellent resource for those pursuing curricular developments in CAM. The Educational Development for Complementary and Alternative Medicine (EDCAM) Project, sponsored by the American Medical Student Association Foundation and funded through the National Institutes of Health National Center for Complementary and Alternative Medi-

cine, offers an extensive array of evidence-based resources on its free Web site (2). Information includes proposed goals and objectives for various CAM topics, as well as background reviews and well-referenced bibliographies. The EDCAM Project staff intends to update the site regularly and thus offers a valuable resource to all educators interested in developing a CAM curriculum.

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1. Wetzel MS, Kaptchuk TJ, Haramati A, Eisenberg D. Complementary and alternative medical therapies: implications for medical education. *Ann Intern Med.* 2003;138:191-6. [PMID: 12558358]  
2. Educational Development for Complementary and Alternative Medicine Project. Accessed at [www.amsa.org/humed/cam/resources.cfm](http://www.amsa.org/humed/cam/resources.cfm) on 24 November 2003.

**IN RESPONSE:** In his criticism, Dr. Neff raises a few points we can agree with. It is precisely because there are so many entrepreneurs promoting treatments and products under the rubric of CAM that doctors and other legitimate health care providers need to be knowledgeable about CAM. As we point out, the average person needs help to sort out the unproven and possibly harmful treatments and products from those that are supported by evidence. Who better to supply this help and advice than a well-educated, knowledgeable physician? We also agree that CAM therapies should be tested for safety and efficacy and applaud the increasing efforts in that direction through funding for rigorous research by such agencies as the National Center for Complementary and Alternative Medicine and other institutes of the National Institutes of Health (1). To ignore the existence of CAM and omit it entirely from medical school curricula, as Dr. Neff suggests, would be to ignore medical practices and therapies used by more than half of the U.S. population (2). This would be a disservice to future doctors and to the patients who will rely on them for guidance about the use or avoidance of these therapies.

Dr. Manu has correctly interpreted our goal of educating physicians and other health care providers to be informed about the range of therapies and practitioners of CAM. As for the economic implications for primary care physicians, the reality is that most patients consult a primary care provider first and do not see alternative practitioners exclusively (3). It is a matter of sharing the health care dollar rather than competing for it. Predictably, primary care physicians who are knowledgeable about CAM practices and can coordinate care for their patients will be increasingly in demand.

Dr. Ernst makes a valid point by suggesting that U.S. medical educators look to countries, such as Germany, that have long incorporated familiarization of CAM into their required medical curricula. He is also correct that the medical school curriculum should present a balanced view of the proven benefits and potential dangers of CAM therapies. In our article, we point out the need to teach students to be skilled readers of the research literature and to critically evaluate all therapeutic options. Certainly the tendency to be “uncritical enthusiasts” or “uninformed skeptics” benefits no one and should be countered by appropriately trained faculty and a curriculum that includes all rigorous evidence concerning the potential of CAM for benefit or harm.

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1. Stokstad E. Alternative medicine. Stephen Straus's impossible job. *Science*. 2000; 288:1568-70. [PMID: 10858130]
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3. Eisenberg DM, Davis RB, Etnner SL, Appel S, Wilkey S, Van Rompay M, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA*. 1998;280:1569-75. [PMID: 9820257]

### The Future of Primary Care

**TO THE EDITOR:** The supplement on The Future of Primary Care would have been strengthened by more participation from general internists who practice daily in the trenches. I do not know if we can endure until the laudable recommendations of the writers can be effected. We survive only by being able to see more and more patients in our workday. These patients are amazing in their complexity. I doubt that their care could be relegated to nonphysicians.

I recommend the following near-future strategies for helping general internists: 1) All subspecialty societies of medicine should pledge their active support for improved pay for their primary care colleagues; 2) the American College of Physicians should seek a signed pledge from chairs of internal medicine that they will aggressively promote careers in internal medicine; 3) the College should establish and support an ongoing task force that includes practicing general internists to address the crisis in primary care; and 4) medical schools and training programs need to raise the visibility of primary care physicians by formally recognizing their achievements.

At stake here is the future quality of health care in our nation.

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**TO THE EDITOR:** Thank you for your excellent series on primary care, which was summed up nicely by the editorial by Dr. Sox (1). However, I would summarize things even more concisely. I think that, above all, we are asking for respect. We want our health care executives to respect our profession enough to see us as the foundation of health care delivery. We want our academic leaders to respect us enough to recommend primary care practice to residents and students. We want our government to respect us enough to direct payment our way. We want our patients to respect us enough to trust us even when we disagree with their requests.

How do we gain that respect? Only by earning it. For those of us already in practice, this means that a lifelong commitment to balancing the art of medicine with the hard work of an evidence-based practice needs to be more than just a cliché.

For future generations of general internists, we need to recog-

nize that 4 years of residency was barely adequate during my training in the 1980s and is clearly inadequate now. I propose that training as a general internist be expanded to at least 4 postgraduate years. After the third year of combined residency, those wishing to become medical specialists could branch off but would not be "board eligible" in general medicine. Residents wishing to practice primary care would finish the full 4 years of general medicine and become eligible to take a boards test separate from the medical specialists. Perhaps the academic deans would then see general medicine as a valid specialty, not a haven for those not "good enough" for a fellowship. Perhaps we would gain enough confidence to see ourselves as a valid specialty.

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#### Reference

1. Sox HC. The future of primary care [Editorial]. *Ann Intern Med*. 2003;138:230-2. [PMID: 12558363]

**TO THE EDITOR:** The *Annals* supplement on the many challenges confronting the future of primary care was a timely and insightful review by many of the nation's opinion leaders in medicine. However, references to "primary care" in the collective risk overgeneralizing the constituent specialties, namely general internal medicine, family practice, and general pediatrics. While these specialties do share a set of core principles and are influenced by a similar set of political and social factors, their fates may not be fully intertwined. In his editorial (1), Dr. Sox mentioned the declining workforce of primary care physicians, as well as a "shortage" of primary care physicians. Our recent work calls this assertion into question (2). However, unlike their counterparts in internal medicine, pediatric residents have historically chosen primary care careers over subspecialties by a factor of 3 to 1, resulting in substantial growth in the workforce of general pediatricians. With relatively flat projections for child population growth, the general pediatrician workforce is expanding significantly more rapidly than its target population. Our research reveals that population-to-physician ratios (that is, the number of potential patients per physician) for general pediatricians will expand 1.5 times more than those for general internists and family practitioners over the next 20 years. Future research and policy discussions targeting "primary care" should carefully consider the degree to which the topics in question can be accurately generalized across the 3 primary care specialties.

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1. Sox HC. The future of primary care [Editorial]. *Ann Intern Med*. 2003;138:230-2. [PMID: 12558363]
2. Shipman SA, Lurie JD, Goodman DC. The general pediatrician: projecting future supply and requirements. *Pediatrics* [In press].

## Payment and the Future of Primary Care

**TO THE EDITOR:** I applaud the editorial by Ginsburg (1) on payment and primary care. He has highlighted a major financial issue in primary care—the increasing expectations from patients, insurers, and others for management outside of office visits and thus not reimbursed. I present the following figures from an academic general internal medicine practice in support of Ginsburg's position and to demonstrate the magnitude of this issue.

During a recent 6-month period, I provided 698 office visits in a 30% clinical practice. In that period, I personally provided 2513 services outside of office visits, or 3.6 per visit. These consisted of 613 patient phone calls and/or e-mails, 316 results letters sent, 156 forms completed, 246 refills written or phoned in, 382 nursing actions reviewed, and 800 test results and consultations reviewed. Subtracting tests and consultations reviewed, which are theoretically included in visit reimbursement, yields a ratio of 2.45 nonreimbursed services for each reimbursed visit.

Granted, some of the services described are not time-consuming. However, businesses can't survive offering 2.45 free services for each 1 reimbursed. Patients rightfully want advice or new prescriptions when they are ill, but these are services and should be reimbursed. Solutions such as either billing directly for or not providing phone visits, refills, and paperwork are being tried gingerly (2). I agree with Ginsburg, however, that a better approach is that an annual management fee should be provided for each primary care patient. This could be paid either by insurance or by the patient. It could be affordable (for example, \$25 to \$50 annually per person) since, as with traditional insurance, sicker patients who use services more would be subsidized by relatively healthy patients. The feasibility and acceptance for this idea should be explored. This simple idea may be imperative to the future support of primary care.

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- Maguire P. Taking a tough stand on non-billable care. *ACP-ASIM Observer.* 2003; 23:1,16-17.

## Hospice Benefits and Phase I Cancer Trials

**TO THE EDITOR:** The article by Byock and Miles (1) is an excellent brief review of some of the problems in hospice care. I do not agree, however, with the authors' opinion that phase I clinical trials should be made available to hospice patients. For cancer patients in hospice, there are no effective chemotherapies. Through the dying process, patients will eventually come to accept death as inevitable. This acceptance is important for a peaceful death. A fight to the bitter end can only produce anxiety. Chemotherapy provides hope that the end can be prolonged. This is counterintuitive to the idea of hospice. In addition, it will delay the patient's final acceptance of death and will adversely affect the dying process.

The purposes of phase I drug trials are to evaluate adverse reac-

tions, identify the maximum tolerated dose, and identify the dose for use in a phase II trial. The goal of hospice care is to provide physical, emotional, and spiritual comfort to the patient. Therapies that do not provide comfort, such as phase I chemotherapy, are not part of hospice care.

Finally, dying patients are extremely vulnerable. They will grasp for any therapy that may help them live longer. It is our duty as physicians not to offer therapies that will not benefit these patients. The altruistic notion that patients can assist future generations by their participation is not sufficient justification to offer potentially harmful medications to patients who are going to die anyway.

I believe that continued research for improved palliative therapies is important, but we must not forget that the ultimate objective of hospice care is helping patients to die well. Patients should trust their physicians to provide only care that will help them reach this goal.

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### Reference

- Byock I, Miles SH. Hospice benefits and phase I cancer trials. *Ann Intern Med.* 2003;138:335-7. [PMID: 1255832]

**TO THE EDITOR:** I heartily endorse the concepts advanced by Byock and Miles (1). I would add 2 additional points, however. First, the concerns expressed by the authors should not be restricted to phase I cancer trials. In fact, phase I trials might be considered less important than phase II clinical trials. It is well recognized that patients are referred far too late to hospice care. Among the hurdles, as Byock and Miles pointed out, are the limitations in care that are imposed by most hospice benefits programs. There are certainly patients who would be candidates for hospice as well as suitable candidates for phase II trials of new agents. I would suggest that the prohibition of active therapy in hospice programs runs counter to the merits and potential benefits of both phase I and phase II clinical investigations.

Second, while it is common wisdom that phase I trials are "not designed, or intended, to have therapeutic effects," I, and I suspect most of my colleagues who perform phase I trials, do not approach these studies in this manner. I have actively participated in and designed phase I trials throughout my medical career. I have entered hundreds of patients in phase I trials and have never done so without the conviction that these trials embody therapeutic intent. Therapeutic effects are measured in phase I trials. Therapeutic benefits are seen as frequently among patients participating in phase I trials as in patients receiving "standard" second- and third-line chemotherapy for many advanced diseases. Finally, I believe that it is morally and ethically deficient, at the very least, to discuss with patients entry in a phase I trial whose sole motivation is altruism. As Byock and Miles pointed out in their discussion, there is certainly literature to support the concept of therapeutic intent in phase I trials. I wholeheartedly support the concepts advanced by Drs. Byock and Miles and suggest that they extend these concepts somewhat further.

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**Reference**

1. Byock I, Miles SH. Hospice benefits and phase I cancer trials. *Ann Intern Med.* 2003;138:335-7. [PMID: 12585832]

**IN RESPONSE:** We asserted that people who qualify for hospice care under Medicare must not be rendered ineligible for hospice services if they choose to enter a phase I trial. We do not share Dr. Avery's view that people who enroll in hospice should not be allowed to participate in phase I trials. Hospice is a service delivery model for providing palliative care. Neither research nor patient care is served by denying patients with incurable cancer the opportunity to contribute to determining safe doses for therapies that may help others. Many terminally ill patients value a sense of contributing to others (1). People with advanced, incurable cancer may well benefit from receiving hospice services as they participate in clinical research. The Promoting Excellence in End-of-Life Care program sponsored 4 cancer programs of concurrent oncology care, including participation in phase I and phase II clinical trials, and palliative care. These projects were well received by patients, families, and clinicians (2).

We agree with Dr. Trump that hospice care should be available to eligible patients who enter phase II trials to test new treatment regimens against a placebo. Such patients are misled if they believe the experimental protocols represent effective treatments and are diserved if their willingness to participate in research precludes receiving funded hospice services. Institutional review boards must examine research protocols to ensure compliance with standards for providing palliative care. They must scrutinize the informed consent process to ensure that terminally ill persons are not denied the opportunity to receive services that may benefit them and their families.

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1. Steinhauer KE, Clipp EC, McNeilly M, Christakis NA, McIntyre LM, Tulsky JA. In search of a good death: observations of patients, families, and providers. *Ann Intern Med.* 2000;132:825-32. [PMID: 10819707]
2. Promoting Excellence in End-of-Life Care. [www.promotingexcellence.org](http://www.promotingexcellence.org). Accessed 18 May 2003.

## Alzheimer Disease: Current Concepts and Emerging Diagnostic and Therapeutic Strategies

**TO THE EDITOR:** Clark and Karlawish misstated an important fact in their Update on Alzheimer disease (1). The practice parameter of the American Academy of Neurology that they referenced in the section on cognitive treatment does not state that "the use of cholinesterase inhibitors constitutes a standard of care for patients with Alzheimer disease." What the guideline says is, "Cholinesterase inhibitors should be considered in patients with Alzheimer disease (Standard), although studies suggest a small average degree of benefit" (2).

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**References**

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2. Doody RS, Stevens JC, Beck C, Dubinsky RM, Kaye JA, Gwyther L, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2001; 56:1154-66. [PMID: 11342679]

## Diagnostic Evaluation of Elderly Patients with Mild Memory Problems

**TO THE EDITOR:** In their review of the diagnostic evaluation of elderly patients with mild memory problems (1), Drs. Karlawish and Clark presented the case of a 70-year-old man who lived alone. The case presentation was used to highlight the elements of a thorough evaluation of a patient with suspected dementia. Realizing the potential risks of driving with impaired memory, the authors recommended a driving test at a facility with expertise in evaluating elderly people with impairments. The authors, however, neglected to advise an evaluation of the safety of the home environment. While it is common to evaluate the home environment in a patient with gait or balance problems, such as after a hip fracture, rarely do we consider the risks of dementia for a person living alone.

In this case, the patient and his son should develop a system to ensure that the patient takes the correct medication each day, such as using a pill box that the son fills each week. The son should evaluate the safety and operability of the home's heating system and water heater. Adjusting the hot water temperature in the water heater to a safe level should also be considered. Smoke alarms and carbon monoxide detectors should also be checked.

The nutritional aspects of living alone should also be evaluated, with the son ensuring that his father is eating a balanced diet. In that regard, and possibly of greatest importance, the son should ensure that his father can safely operate the appliances in the kitchen. As the patient's short-term memory worsens, the patient may forget that food is cooking in the oven or on the stove, presenting a fire risk. Observing the father heat water for a cup of tea is often an easy test of this risk.

Including these elements in the evaluation will help ensure that all of the patient's needs are addressed.

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**Reference**

1. Karlawish JH, Clark CM. Diagnostic evaluation of elderly patients with mild memory problems. *Ann Intern Med.* 2003;138:411-9. [PMID: 12614094]

**TO THE EDITOR:** Drs. Karlawish and Clark (1) stated that the Mini-Mental Status Examination (MMSE) measures executive function. This conflicts with many publications that have shown otherwise. Valid bedside executive instruments, such as the Executive Interview

(EXIT25) and an executive clock-drawing task (CLOX), continuously outperform the MMSE in detecting executive impairment (2, 3). Our unpublished data showed that 53% of general medicine patients did not pass either CLOX1 or the EXIT25, compared with 9% who did not pass the MMSE (using a cut-point of 24). Our published data showed that 72% of medicine and surgery patients seen by a psychiatry consult service did not pass either CLOX1 or the EXIT25 compared with 30% who did not pass the MMSE (4). Dr. Folstein (5) even stated that the MMSE is an inadequate executive measure and recommends the addition of a clock-drawing task to specifically detect executive impairments.

The authors proposed a list of cognitive tests, including a clock-drawing task, to better assess a patient's cognition. However, their suggested scoring system for the clock-drawing task is subjective and vague. Furthermore, not all clock-drawing tasks are equivalent. The CLOX1 is more sensitive to executive impairment, as measured by the EXIT25, than similar clock-drawing tasks (6).

Because executive function is associated with medication adherence, capacity to consent, level of medical care required, and rehabilitation potential, we feel it is important for readers to know that practical, valid measures of executive function exist. However, the MMSE is not one of them, and clinicians who depend on it are likely to miss a substantial number of impaired patients. The CLOX1 and the EXIT25 are efficient executive measures that can be easily administered and scored by any clinician.

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1. Karlawish JH, Clark CM. Diagnostic evaluation of elderly patients with mild memory problems. *Ann Intern Med.* 2003;138:411-9. [PMID: 12614094]
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5. Folstein M. Mini-mental and son. *Int J Geriatr Psychiatry.* 1998;13:290-4. [PMID: 9658261]
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**IN RESPONSE:** To apply the label of “neurodegenerative dementia” to a patient, a clinician needs to show declines in a person's cognition that explain changes in the person's ability to perform usual and everyday activities, such as managing a checkbook or preparing a cup of tea (1). The point of showing deficits in at least 2 domains of cognition is to reduce the chance that the problem could be due to a single brain lesion rather than diffuse neurodegenerative pathology. As elegant as these criteria are in linking disease with a set of signs and symptoms, several challenges hinder clinicians putting them into clinical practice. Chief among these challenges is the lack of a coherent language to measure the presence and severity of both functional

and cognitive deficits (2). Unlike diseases such as hypertension or diabetes, no set of measures exist that have the same power as measurement of systolic and diastolic blood pressure or glycosylated hemoglobin. Such measures are powerful because they appear objective, are critical in making the diagnosis, and establish efficacy of an intervention both in clinical trials and clinical practice. In this context, the letters from Drs. Hirsch, Horton, and Schillerstrom are a welcome addition to the dialogue over what measures will best comprise a clinically useful language to talk about dementia. Hirsch refines the set of functional measures presented in our case report, reinforces the role of the physician to partner with a family member to assess them, and illustrates the interrelated goals of an assessment. These goals are to document that there is clinically significant cognitive decline and to identify the patient's functional needs. Functional assessment and advance planning are perhaps the most important reasons to pursue early diagnosis of dementia. The longer unappreciated cognitive losses progress, the more the person suffers from unmet needs. We fully agree with Horton and Schillerstrom that unlike CLOX1 and EXIT25, the MMSE is not a test of executive function. It tests a smattering of cognitive functions. Nonetheless, it is one of the few cognitive tests that is widely used in clinical practice. Whether the scoring, administration, and norms of CLOX1 and EXIT25 can become part of usual and everyday clinical practice is a challenge to the expert medical community and clinician-educators.

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#### CLINICAL OBSERVATIONS

##### Optimized Virologic Response in Hepatitis C Virus Genotype 4 with Peginterferon- $\alpha$ 2a and Ribavirin

**TO THE EDITOR:** *Background:* Infection with hepatitis C virus (HCV) genotype 4 has been termed “difficult to treat” because of poor sustained virologic response to conventional interferon (1). Monotherapy with peginterferon- $\alpha$ 2a (40 kilodalton) (PEGASYS, Hoffmann-La Roche Ltd., Basel, Switzerland) improves sustained virologic responses (45% vs. 0% for interferon- $\alpha$ 2a) (2).

*Objective:* To study effects of treatment with peginterferon- $\alpha$ 2a (40 kilodalton) and ribavirin (COPEGUS, Hoffmann-La Roche Ltd.) in patients infected with HCV genotype 4.

*Methods and Findings:* We conducted 2 studies; both were approved by institutional review boards, and all patients gave informed consent. Patients in the first study ( $n = 13$ ) were treated with peginterferon- $\alpha$ 2a (40 kilodalton), 180  $\mu$ g once weekly, and 1000 or 1200 mg of ribavirin daily for 48 weeks (3). Patients in the second

study ( $n = 36$ ) were treated with peginterferon- $\alpha 2a$  (40 kilodalton), 180  $\mu\text{g}$  once weekly, and 800 mg or 1000 or 1200 mg of ribavirin daily for 24 or 48 weeks (4). Patients received 1000 or 1200 mg of ribavirin on the basis of body weight ( $<75$  kg or  $\geq 75$  kg). Sustained virologic response was defined as undetectable HCV RNA level at the end of the follow-up period (AMPLICOR HCV MONITOR, v.2.0, Roche Diagnostics, Basel, Switzerland; detection limit  $<50$  IU/mL).

Patients treated with peginterferon- $\alpha 2a$  (40 kilodalton) and 1000 or 1200 mg of ribavirin for 48 weeks ( $n = 24$ ) achieved a sustained virologic response of 79%. Patients treated with 800 mg of ribavirin for 48 weeks ( $n = 8$ ) or with 1000 or 1200 mg ribavirin for 24 weeks ( $n = 12$ ) achieved lower sustained virologic responses (63% and 67%, respectively). No patient treated with 800 mg of ribavirin for 24 weeks ( $n = 5$ ) achieved a sustained virologic response. Treatment regimens were well tolerated; 4 patients discontinued therapy because of adverse events, laboratory abnormalities, or both.

**Conclusion:** As with HCV genotype 1 (4, 5), treatment duration and ribavirin dose affect treatment outcome in patients infected with HCV genotype 4. Maximal efficacy is probably achieved with the most intensive regimen, but it may no longer be appropriate to categorize infection with HCV genotype 4 as "difficult to treat."

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### Gatifloxacin-Induced Hepatotoxicity and Acute Pancreatitis

**TO THE EDITOR:** *Background:* Quinolones may induce transient abnormalities in serum aminotransferase levels. Severe hepatotoxicity and acute pancreatitis are rare. Gatifloxacin (Tequin, Bristol-Myers Squibb, New York, New York) is one of the newest members of the group (1). Increased serum bilirubin, aminotransferase, or amylase levels occur in less than 1% of patients exposed; 1 case of acute hepatitis has been reported (2).

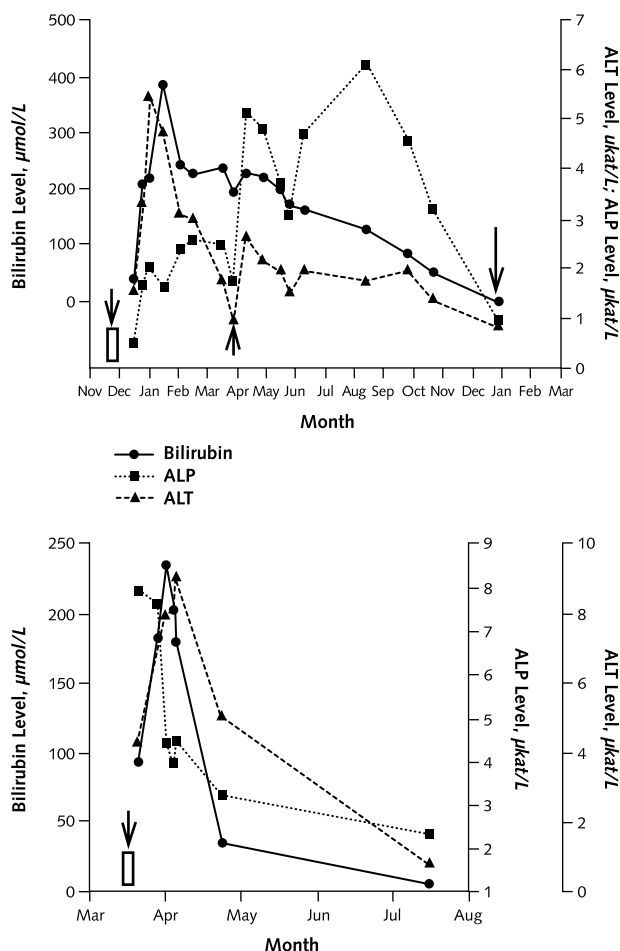
*Objective:* We describe 2 patients who developed acute cholestatic liver injury and acute pancreatitis while being treated with gatifloxacin.

*Case Reports:* Patient 1, a 41-year-old woman, was treated for an upper respiratory tract infection with oral ciprofloxacin. After 2 doses, the drug was withdrawn because of nausea and vomiting. Gatifloxacin was initiated orally at 400 mg/d. Two days later, skin rash appeared on the patient's upper trunk, followed by dark urine, pale stools, and abdominal pain in the right upper quadrant. The patient was not taking other medications.

Laboratory studies revealed a total bilirubin level of 87.2  $\mu\text{mol/L}$  (5.1 mg/dL) with conjugated fraction of 61.6  $\mu\text{mol/L}$  (3.6 mg/dL), an aspartate aminotransferase level of 139 U/L, an alanine aminotransferase level of 145 U/L, an albumin level of 30 g/L, an alkaline phosphatase level of 8.03  $\mu\text{kat/L}$ , a  $\gamma$ -glutamyl transpeptidase level of 8.62  $\mu\text{kat/L}$ , an amylase level of 1.38  $\mu\text{kat/L}$ , a lipase level of 6.5  $\mu\text{kat/L}$ , and a prothrombin time of 6.1 seconds. Serologic studies excluded viral and autoimmune hepatitis. Abdominal imaging (ultrasonography and computed tomography scan) revealed no evidence of biliary obstruction. Liver biopsy showed portal edema and cholestasis with moderate macrovesicular steatosis. Two weeks after withdrawal of gatifloxacin, the patient's abdominal pain resolved and prothrombin time returned to normal. The patient began taking and continues to take ursodeoxycholic acid. Over the next 3 months, the results of her liver tests remained abnormal (Figure). Results of endoscopic retrograde cholangiopancreatography were normal. Prednisone was started at 30 mg/d. A follow-up liver biopsy 8 months after her initial presentation showed increased portal fibrosis, early bridging fibrosis, and bile duct loss. A repeated serum anti-mitochondrial antibody measurement 10 months later was negative. The patient's jaundice completely resolved 1 year later. However, she continues to have persistent elevation of alkaline phosphatase and aminotransferase levels.

Patient 2, a 49-year-old man, presented with jaundice and abdominal pain. He had received oral gatifloxacin, 400 mg/d, for an upper respiratory tract infection. Three days later, he developed severe malaise, jaundice, pale stools, and abdominal discomfort. Laboratory studies revealed a bilirubin level of 94.05  $\mu\text{mol/L}$  (5.5 mg/dL), an aspartate aminotransferase level of 216 U/L, an alanine aminotransferase level of 520 U/L, an alkaline phosphatase level of 4.47  $\mu\text{kat/L}$ , a  $\gamma$ -glutamyl transpeptidase level of 9.9  $\mu\text{kat/L}$ , an amylase level of 5.12  $\mu\text{kat/L}$ , and a lipase level of 60.01  $\mu\text{kat/L}$ . Results of abdominal ultrasonography and computed tomography scan and endoscopic retrograde cholangiopancreatography were nor-

**Figure. Serum liver enzyme values associated with gatifloxacin administration.**



To convert  $\mu\text{kat/L}$  to U/L, divide by 0.01667; to convert  $\mu\text{mol/L}$  to mg/L, divide by 17.104. The arrows in the top panel represent the following, from right to left: gatifloxacin therapy started, prednisone therapy started, prednisone withdrawn. The arrow in the bottom panel represents the following: gatifloxacin therapy started. ALP = alkaline phosphatase; ALT = alanine aminotransferase.

mal. Results of serologic studies for viral and autoimmune hepatitis were negative. Liver biopsy showed portal edema, bile ductular proliferation, and portal inflammatory infiltrate that included eosinophils with lobular cholestasis. At 3 months after initial presentation, serum bilirubin level had normalized but serum aminotransferase and alkaline phosphatase levels remained mildly elevated.

**Discussion:** Several characteristics in these 2 patients support gatifloxacin as the cause of liver injury, including the temporal relationship between the administration of gatifloxacin and injury onset. Liver biopsies in both patients showed cholestasis with portal edema, bile duct injury, and eosinophilic infiltration. These changes are consistent with drug-induced hepatotoxicity, although it can be argued that underlying steatohepatitis contributed to the disease process in patient 1. Following discontinuation of gatifloxacin, patient 2 improved but patient 1 developed progressive liver disease and ductopenia. Both patients also had concurrent acute pancreatitis, a complication that has not been described with gatifloxacin before to our knowledge. Of interest, only 3 cases of acute pancreatitis have been

reported with other quinolones (3–5). Acute pancreatitis therefore appears to be a rare complication of quinolone-induced toxicity.

**Conclusions:** Gatifloxacin is a possible cause of severe hepatic and pancreatic injury. Although these complications appear to be infrequent, a heightened awareness is needed because gatifloxacin and other quinolones are used extensively.

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#### Arm Position and Blood Pressure Measurement

**TO THE EDITOR:** *Background:* Blood pressure is assessed as a part of the routine physical examination. Blood pressure values stratify patients into epidemiologic groupings and direct selection of therapy. Studies dating back to 1906 suggest that arm position affects blood pressure measurement; however, little attention is given to this fact (1–5).

*Objective:* To determine whether arm position affects arm blood pressure measurement.

*Methods:* We conducted a prospective study using a convenience sample in an emergency department. The inclusion criteria were age older than 17 years and a chief symptom unlikely to be associated with cardiovascular instability. The exclusion criteria were any injury or symptom that would preclude repeated measurement of brachial blood pressure in different arm and body positions.

An institutional review board approved the study, and all patients provided written consent. Investigators measured blood pressure using an automated noninvasive device (Medical Data Electronics, Model E100, Orlando, Florida). Patients' brachial blood pressure was measured in the left arm with a cuff of 22 × 12 cm or 32 × 15 cm in each of 3 body positions: standing, sitting, and supine. In each body position, the investigators used 2 arm positions: perpendicular and parallel to the torso. We obtained 6 measurements on each patient. Perpendicular position was defined as the arm in front of the patient creating a 90-degree angle with the torso, and parallel posi-

tion was defined as the arm fixed at the patient's side. We obtained blood pressure measurements at 2-minute intervals and calculated mean systolic and diastolic blood pressure and 95% CIs.

**Findings:** The study included 100 patients, 45 of whom were women. The patients' ages ranged from 18 to 88 years (mean age, 44 years). Participants' weight ranged from 45.5 kg to 141 kg (mean weight, 75 kg). We recorded mean systolic and diastolic measurements for each body and arm position (Table). Using the Joint National Committee's definition of hypertension (6), we found that the proportion of seated patients classified with hypertension was 0.22 (95% CI, 0.15 to 0.31) with the arm perpendicular and 0.41 (CI, 0.32 to 0.51) with the arm parallel. In every body position, the systolic and diastolic blood pressure measured with the arm perpendicular to the body was significantly lower than with the arm in a parallel position.

A standard technique of blood pressure measurement is rarely mentioned in medical literature or used in practice. A review of 116 papers on blood pressure from major medical journals found that only 6 mentioned the arm position used during blood pressure measurement (7). The American Heart Association (8) formally recommends that blood pressure should be measured with the patient's elbow flexed at heart level. Villegas and colleagues' recent study on blood pressure measurement reported that 73% of the health care workers who participated in the study failed to use proper arm and cuff positions (9).

The range of blood pressure differences in our study (8.8 to 14.4 mm Hg) is greater than the traditional blood pressure range of 5 to 10 mm Hg used to modify antihypertensive therapy (6). If standard values for classification of hypertension were used, a significantly different proportion of patients would have been classified as hypertensive depending on arm position during blood pressure measurement.

From these results, several perplexing issues arise: What arm position should be used to determine a patient's actual blood pressure? Is it possible that a significant change in measured blood pressure is secondary to the arm position rather than therapeutic intervention? The failure to stipulate arm position during blood pressure measurement in trials of antihypertensive medications raises the possibility that the observed decline was secondary to arm position rather than medication effect.

**Conclusions:** Measured blood pressure values are higher when the arm is parallel to the torso and will decrease by 8.8 to 14.4 mm Hg with the arm raised to a perpendicular position, an effect independent of body position. A designated and consistent arm position should be adhered to when measuring blood pressure. Future studies of blood pressure should describe arm position in their Methods sections.

**Table. Mean Blood Pressure Measurements\***

Body Position	Arm Position	Mean Systolic Blood Pressure (95% CI), mm Hg	Mean Diastolic Blood Pressure (95% CI), mm Hg
1	A	125.1 (121.6–128.6)	72.9 (70.7–75.2)
	B	134.6 (131.1–138.1)	83.1 (80.8–85.3)
	B – A	9.5 (7.1–11.9)	10.2 (8.1–12.2)
2	A	124.9 (121.4–128.4)	71.5 (69.2–73.7)
	B	133.7 (130.4–137.0)	81.6 (79.5–83.7)
	B – A	8.8 (6.7–10.9)	10.1 (8.5–11.7)
3	A	120.0 (116.4–123.7)	63.6 (61.1–66.0)
	B	133.3 (129.3–137.3)	77.9 (75.5–80.3)
	B – A	13.2 (11.2–15.3)	14.4 (12.3–16.4)

\* 1 = standing; 2 = sitting; 3 = supine; A = arm perpendicular to the torso; B = arm parallel to the torso.

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## Risk Stratification for Noncardiac Surgery

**TO THE EDITOR:** Grayburn and Hillis (1) present a timely perspective on the role of noninvasive testing for cardiac risk stratification among patients undergoing noncardiac surgery. However, we believe it is premature to conclude that “the era of routine noninvasive testing has ended.” We agree that many patients with a score of 2 or less on the revised cardiac risk index (RCI) (2) receiving perioperative  $\beta$ -blockade represent a low-risk population among whom noninvasive cardiac testing probably adds no information. However, we disagree that all patients with an RCI of 3 receiving  $\beta$ -blockade are uniformly at acceptable risk and believe that noninvasive cardiac testing may contribute additional information in this select population. This is suggested by Boersma and colleagues (3). In this report, an incidence of perioperative death and myocardial infarction of 6.5%, 10%, and 16% was found in patients with respective scores on a modified RCI of 3, 4, and 5 who were treated with perioperative  $\beta$ -blockade but had findings of ischemia on preoperative dobutamine stress echocardiography (DSE). These complication rates are unacceptably high and would not have been recognized if preoperative DSE had not been done. Future investigation should examine strategies to further modify this risk beyond the provision of  $\beta$ -blockade alone. We also believe that noninvasive testing may provide incremental information about cardiac risk among patients with compromised functional capacity. Grayburn and Hillis comment on the difficulty of evaluating such patients by stating that among those who cannot “ambulate effectively . . . their histories may not provide an accurate assessment of symptoms.” We therefore advocate a strategy that considers noninvasive cardiac testing according to perioperative  $\beta$ -blockade for patients with limited functional capacity (4). Existing evidence supports a more restrictive use of preoperative noninvasive cardiac testing reserved for populations at high risk or limited functional capacity. However, further research is needed before preoperative noninvasive cardiac testing is deemed useless in every situation.

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**TO THE EDITOR:** I was disturbed by the algorithm proposed by Drs. Grayburn and Hillis (1), which essentially said that if cardiac catheterization were not indicated independent of the need for surgery,

virtually *all* patients could undergo surgery without further testing (using  $\beta$ -blockers). I currently favor a combination of the American College of Cardiology– and Lee-revised cardiac index modified with the use of  $\beta$ -blockers (2), and I am a strong proponent of minimizing preoperative tests that are unlikely to change management. I agree with the proposed algorithm for patients with low and intermediate clinical risk; however, at this time, I disagree with that approach for clinically high-risk patients.

The text does indicate that if  $\beta$ -blockers are contraindicated or surgical risk is considered excessive, surgery should be deferred and DSE may be helpful. However, the algorithm states that only “if  $\beta$ -blockers are contraindicated” should one of these alternatives be considered. The Boersma study (3) clearly showed that DSE could further define lower- and higher-risk subgroups, the latter of which did not benefit from  $\beta$ -blockers and warranted revascularization. Subsequently, several other papers have demonstrated that certain patients were at higher risk on the basis of ischemic threshold (4) or abnormal left ventricular ejection fraction (5) and had postoperative complications despite the use of  $\beta$ -blockers.

Until a larger-scale, double-blind, randomized, controlled trial demonstrates improved outcomes in clinically high-risk patients in various surgical settings, I think it is premature to eliminate or even minimize use of noninvasive testing in this group. One may need to adapt an algorithm on the basis of individual circumstances, but the average physician might get the idea from this proposed algorithm that no one needs noninvasive testing, even in the high-risk group. I would suggest that the authors modify the algorithm for patients with 3 or more clinical risk factors to indicate that noninvasive testing may be beneficial, with  $\beta$ -blockers as a potential option that still requires additional evidence.

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**IN RESPONSE:** As stated in our paper, the ultimate goal of “risk stratification” is to reduce risk. Accordingly, diagnostic tests that are used to define risk should first have likelihood ratios that accurately define risk and second should sort patients into clearly defined risk groups. Unfortunately, the diagnostic tests that are currently used in

preoperative risk stratification for noncardiac surgery do not accomplish these goals, and under most circumstances, fail to add to the known clinical risk profile. Moreover, decision analytic models indicate that a strategy of routine preoperative testing followed by cardiac catheterization and revascularization in patients with abnormal test results does more harm than good (1, 2). In contrast,  $\beta$ -blockers reduce the risk for perioperative complications, even in so-called high-risk patients (3). For these reasons, we believe strongly that the focus of perioperative management should be on therapy and prevention, not costly diagnostic testing with an unproven effect on outcomes. In short, we stand by our conclusion that “the era of routine noninvasive testing has ended.”

Precisely which patients might benefit from preoperative noninvasive testing is unclear. Frost and Michota propose that such noninvasive testing should be reserved for those at high risk or limited functional capacity. On the basis of the data of Boersma and colleagues (4), we support the use of preoperative dobutamine echocardiography in patients with 3 or more clinical risk factors, unless they have a clear indication for coronary angiography independent of the need for noncardiac surgery. We agree with Dr. Cohn that this recommendation may not have been as clear in the algorithm as it was in the text. We also with Frost and Michota that “additional research is needed” in this field.

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