COMMENTS AND RESPONSES

Prognostic Disclosure

TO THE EDITOR: The study by Lamont and Christakis (1) on how physicians give prognoses to preterminal patients with cancer confirms what many have observed anecdotally for some time. I would suggest yet another possible reason for the lack of "explicit, frank verbal communication about prognosis to dying patients." Physicians too often consider the death of a patient a virtual defeat. We are by psychology, education, training, and societal expectations encouraged to believe that we can rescue all patients and fix anything. Until we accept that there is a death rate of one per person; that comfort, mental, spiritual, and physical, is the appropriate response when cure is impossible; and that there are limits (2), behaviors and the results of future studies such as this one are not likely to have different outcomes.

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TO THE EDITOR: In response to the article by Lamont and Christakis (1), I would like to add another confounding problem. Their study was designed to determine whether physician behavior could contribute to the disparity between patients' and physicians' expectations about outcomes of treatment. I cannot agree enough that incorrect information transmitted from physician to patient will have a negative impact on the concordance between physicians' expectations of outcome, patients' expectations of outcome, and the reality of data-based outcome. However, even honest and accurate information delivered by physicians is filtered through the emotional screens of patients and their families as they grapple with their illnesses.

I have found, as a practicing oncologist, that I frequently tell patients that there are no good treatments and that further treatments would be fraught with risk that outweighs any chance of a meaningful outcome. It is not rare for me to then have a patient request more treatment with little chance for meaningful success despite my recommendation to stop therapy. In my collaboration with patients, I am reluctant to deny them a treatment if they want it, as long as I don't think I will hurt them. I generally comply with their wishes as I continue to try to bring them to the place where they are ready to accept the end of their lives. It is also not rare for me to strongly recommend a palliative treatment with a good chance of success and have patients refuse because of their biases about chemotherapy, their biases about the prognosis of their cancer, or their family's biases.

The filter we must pierce in patients is not always penetrable, even with completely accurate information. They bring their own hopes, fears, and experiences to our examination rooms when we must talk to them about these devastating issues. The first place to start is with accurate prognoses and information, but from there, all bets are off as to where some people will go.

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Reference

1. Lamont EB, Christakis NA. Prognostic disclosure to patients with cancer near the end of life. Ann Intern Med. 2001;134:1096-105. [PMID: 11412049]

TO THE EDITOR: The poignancy of the article by Lamont and Christakis (1) is that it reaches to the boundaries of where science can take us. Physicians sometimes prefer to misrepresent the truth, and no prognostic algorithm will be able to tell us why. I believe the problem cannot be approached without coming to terms with the dissociative process physicians undergo in their selection and training as scientists. We are taught neither to nurture our humanity nor to call on it as a recourse for approaching our patients. We are encouraged to rely on scientific methods, statistical verification, and "evidence-based" approaches to care. I grant that we owe the great advances in medicine to the scientific method, but eventually there will be artificial intelligence sophisticated enough to diagnose, treat, and prognosticate without the worries of waning knowledge or human error. What will it mean to be a physician *then*, if not to be human? And if it means to be human, what does *that* mean, if not to be empathetic, integrated, and, among other things, faithful? These are lights that guide us when knowledge fails.

Patients may ask "How long?", and some really want to know, but at the root of the query is often the dismayed cry, "What now?" It is self-serving to refuse engagement under the guises of science's limits ("Nobody knows" or "There's nothing we can do"), job description ("I think someone else should handle this"), or artificial hopefulness ("There's always a chance. . ."). However, that is what commonly happens in today's harried, circumscribed, and fragmented health care systems. For me, the concern isn't so much that physicians may give false information to patients; it's that medicine may become so calculated and impersonal that it loses the qualities most needed for the care of the dying.

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Reference

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IN RESPONSE: Drs. Webster, Grossman, and GuntherMaher each help to explain the results of our study by placing them within the social context of U.S. medicine. They suggest that constraints related to the societal concepts of "the physician," "the patient," and "the health care system" itself may lead physicians away from frank disclosure of prognoses to patients with cancer at the end of life. Regarding the physician, Dr. Webster suggests that until physicians stop viewing death as preventable and thus a professional failure, their efforts to cultivate good deaths for their patients will be scant (1). Regarding the patient, Dr. Grossman suggests that patients too view death as preventable and a failure and develop cognitive and

emotional filters that help them to deny poor prognoses from physicians and to yearn for further futile anticancer therapy (2). Finally, Dr. GuntherMaher suggests that the "harried" and "fractionated" health care system favors nondisclosure and optimistic disclosure over frank disclosure because these styles simply take less time. In sum, nonfrank disclosure of prognoses at the end of life is easier, quicker, and cheaper for physicians, patients, and the health care system.

In the current context of U.S. medicine, undue optimism regarding prognosis at the end of life may be a Pareto optimal solution. This suggests that with respect to physicians' prognostic behavior at the end of life, change will occur only as the societal constraints related to U.S. medicine are relaxed. We suspect that as Americans—patients, physicians, and health care administrations—come to understand that death is inevitable and that palliation is both kinder and perhaps less expensive than futile anticancer therapy, the prognoses physicians give their dying patients will more often be frank and efforts to cultivate a good death will be more common.

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Continuous Positive Airway Pressure in Patients without Daytime Sleepiness

TO THE EDITOR: Barbé and colleagues (1) described 55 patients with sleep apnea (apnea–hypopnea index > 30) without subjective sleepiness (score ≤ 10 on the Epworth sleepiness questionnaire) who did not benefit from continuous positive airway pressure. The patients were divided into "optimally treated" and "sham treated" groups. Neither group showed any significant improvement in sleep latency time (according to scores on the Multiple Sleep Latency Test [MSLT]) or in measures of quality of life and cognitive function.

Inspection of Barbé and colleagues' Figure 2 shows that 21 of the 55 patients had an abnormally short MSLT score of less than 10 minutes and that in 9 patients the score was less than 5 minutes (indicating pathologic daytime sleepiness). These numbers are incompatible with the authors' description of their patients as having "no daytime sleepiness." What would the findings have been if the objectively sleepy patients had been analyzed separately from those who truly were not sleepy? Engleman and coworkers examined a group of sleepy patients and found that scores on the MSLT, as well as depression scores, improved after continuous positive airway pressure if patients adhered to therapy (2). Since Barbé and colleagues did not analyze the objectively sleepy patients separately, the patient mix in the sham and treatment groups could have skewed the results.

Table. **Quality of Life, Daytime Sleepiness, and Results on Psychological Tests before and after 6 Weeks of Treatment in Patients with a Baseline MSLT Score of Less than 5 Minutes***

Measure	CPAP Group (n = 5)			Sham CPAP Group (n = 7)			*P* Value†
	Before Treatment	After Treatment	Difference	Before Treatment	After Treatment	Difference	
SF-36							
PCS score	53 ± 2	54 ± 3	1 ± 2	50 ± 3	53 ± 1	3 ± 3	>0.2
MCS score	52 ± 2	51 ± 2	−2 ± 6	50 ± 4	52 ± 2	6 ± 3	>0.2
FOSQ score	103 ± 6	102 ± 7	−1 ± 1	110 ± 5	115 ± 2	6 ± 3	0.1
Epworth Sleepiness Scale score	8 ± 0.6	10 ± 1	2 ± 1	7 ± 1	6 ± 1	−1 ± 2	>0.2
MSLT score, *min*	3.3 ± 0.4	8.1 ± 1	4.7 ± 1	3.8 ± 0.4	6.4 ± 2	2.6 ± 2	>0.2
Hits on Steer-Clear test, %	5 ± 2	3 ± 2	−1 ± 1	5 ± 2	5 ± 1	−0.6 ± 1	>0.2
Wechsler Adult Intelligence Scale							
Digit symbols	45 ± 5	46 ± 7	1 ± 3	49 ± 7	53 ± 8	4 ± 3	>0.2
Block design	33 ± 2	33 ± 3	−0.4 ± 1	33 ± 4	35 ± 4	2 ± 2	>0.2
Digits span	9 ± 1	10 ± 1	1 ± 0.4	10 ± 0.5	10 ± 1	0 ± 1	>0.2
PASAT 1	16 ± 1	14 ± 2	−2 ± 2	15 ± 1	17 ± 1	2 ± 1	0.1
PASAT 2	14 ± 2	16 ± 1	2 ± 2	15 ± 1	16 ± 1	0.5 ± 1	>0.2
PASAT 3	10 ± 2	14 ± 1	5 ± 1	10 ± 2	12 ± 1	2 ± 1	0.1
PASAT 4	4 ± 1	5 ± 1	1 ± 1	3 ± 1	5 ± 1	2 ± 1	>0.2
Trail making test, *s*							
Part A	49 ± 4	52 ± 5	3 ± 6	45 ± 4	39 ± 4	−5 ± 5	>0.2
Part B	201 ± 74	109 ± 10	−92 ± 66	119 ± 30	118 ± 26	1 ± 29	>0.2
Wechsler Memory Scale							
Mental control	5 ± 1	6 ± 1	1 ± 1	6 ± 1	6 ± 1	1 ± 1	>0.2
Verbal paired associated	13 ± 1	17 ± 1	4 ± 2	15 ± 1	14 ± 1	−1 ± 1	0.04

* Data are shown as the mean ± SE. CPAP = continuous positive airway pressure; FOSQ = Functional Outcomes of Sleep Questionnaire; MCS = mental component summary; MSLT = Multiple Sleep Latency Test; PASAT = Paced Auditory Serial Addition Test; PCS = physical component summary; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey.
† By *t*-test comparing the change over time (difference) observed in each group (CPAP vs. sham CPAP).

It would be helpful if the authors could provide this information so we could better apply the suggested conclusion.

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IN RESPONSE: We thank Dr. Kline and colleagues for their interest in our paper, and we are happy to respond to their comments. First, based on the MSLT results shown in our Figure 2, Kline and colleagues suggest that some of our patients had pathologic daytime sleepiness. In our study, we did not use the MSLT to define pathologic daytime sleepiness. Instead, we used the Epworth Sleepiness Scale because it is the tool most widely used to evaluate daytime sleepiness in clinical practice (the MSLT is time-consuming and is not routinely used). Furthermore, there are some concerns regarding the accuracy of the MSLT for the quantitative assessment of sleepiness (1, 2). Kline and colleagues also suggest that a separate analysis of the patients with pathologic MSLT scores might be useful. As reported in our manuscript, we performed such analysis in patients with an MSLT score of less than 10 minutes. The **Table** on page 369 shows the results obtained in the subgroup of patients with an MSLT score less than 5 minutes. In these patients, as in those originally analyzed in our study, continuous positive airway pressure did not improve sleep latency time, quality of life, or cognitive function. We therefore believe that available evidence does not support treatment with continuous positive airway pressure in patients without subjective daytime sleepiness.

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Colloid Use in the Critically Ill

TO THE EDITOR: In their editorial, Cook and Guyatt (1) contend that the results of our meta-analysis on albumin administration in acutely ill persons (2) are similar to those of an earlier meta-analysis by the Cochrane Injuries Group Albumin Reviewers (3). Cook and Guyatt feel that the apparent differences between this study and ours arise from the "spin" imparted to the findings by the authors of each study. This interpretation does not square with the data. We reported a pooled relative mortality risk of 1.11 (95% CI, 0.95 to 1.28), compared with 1.68 (CI, 1.26 to 2.23) in the earlier meta-analysis. Thus, there was minimal overlap in the confidence intervals. Furthermore, the point estimate of relative risk in the earlier meta-analysis was 51% higher than ours. In addition, the absolute difference in point estimates of relative risk between the two meta-analyses was 0.57 (CI, 0.17 to 1.09), as calculated by using bootstrapping with bias correction (4). Because zero is absent from this confidence interval, the difference in pooled relative risk was statistically significant, clearly indicating that the two meta-analyses did not yield similar results.

The editorial asserts that our data are "reassuring only insofar as they fail to show a statistically significant increase in mortality" (1). This is not the case. We also showed that relative risk was substantially and consistently lower among trials of higher methodologic quality (for example, 0.73 [CI, 0.48 to 1.12] in blinded trials and 0.94 [CI, 0.77 to 1.14] in larger trials). A relative risk below 1 signifies lower mortality rates in albumin recipients. Therefore, these observations suggest that albumin may reduce mortality.

Although Cook and Guyatt assert otherwise, we did evaluate the effects of study objectives. Relative risk was 1.00 (CI, 0.84 to 1.18) among trials with mortality as a study end point versus 1.49 (CI, 1.11 to 2.00) for trials designed to address only other end points, such as acute physiologic or biochemical variables.

Cook and Guyatt propose that our funding source might have influenced our conclusions. However, as we disclosed, the funding source played no part at all in our study. The earlier meta-analysis was funded by Britain's National Health Service, an organization that defrays the costs of health care, including albumin, and pursues the objective of "minimizing its budget" (5). Its role was undisclosed.

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3. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. Cochrane Injuries Group Albumin Reviewers. BMJ. 1998;317:235-40. [PMID: 9677209]

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IN RESPONSE: Drs. Wilkes and Navickis raise both ethical and scientific issues. The topic of publication ethics has been featured recently in a partial revision of the document "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Scientific Publication" (1), which was developed by the International Committee of Medical Journal Editors. Financial rela-

tionships such as employment, stock ownership, and honoraria are still considered the most easily recognized potential conflicts of interest and are often not apparent unless they are specifically declared (1). Disclosure of these relationships is crucial for review articles and editorials because bias can be more difficult to detect in these publications than in reports of original research (2). These guidelines also acknowledge that research sponsored by government and other agencies is subject to influence. Contemporary standards of transparent reporting include reporting both consultant relationships and receipt of project funding.

The meta-analysis by Wilkes and Navickis (3) remains unable to "allay concerns regarding the safety of albumin" for many reasons (4). The 95% CI around the pooled relative risk for death associated with albumin includes a substantial increased risk for death, which is both comparable with the Cochrane meta-analysis (4) and a cause for concern. The data underscore ongoing questions about the risk–benefit and cost–benefit ratios of albumin administration. This uncertainty is directly illustrated by the worldwide launch of further randomized trials reevaluating the effect of albumin and other colloids on morbidity and mortality.

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Clinical Assessment and D-Dimer Testing in Deep Venous Thrombosis

TO THE EDITOR: I would like to congratulate Kearon and colleagues for their well-designed study (1) and for increasing our understanding of the role of D-dimer testing in suspected deep venous thrombosis. However, a major limitation not discussed in the paper is that the applicability of the findings may be poor. The design of the study is such that it does not allow the findings to be confidently applied outside the restricted setting of the evaluation, for two reasons. First, whole-blood D-dimer testing, although quick and simple to perform, is limited because the interpretation is subjective. Although the test is relatively accurate in experienced hands, there is a learning curve in performing and interpreting the results. Second, the whole-blood D-dimer test in the study was performed by a technologist. Many emergency departments do not have such expertise readily available.

A more clinically relevant study would be one in which clinicians are trained to perform the bedside assay. This will allow the findings to be more confidently translated into everyday clinical practice. In addition, a less subjective D-dimer test (for example, a turbidimetric assay) would allow a more scientifically valid study. New turbidimetric immunoassays may be equal in sensitivity and may even have slightly better specificity than enzyme-linked immunosorbent assays, the gold standard of D-dimer assay methods (2). Moreover, the turbidimetric assays are faster and require less complex laboratory equipment than the cumbersome enzyme-linked immunosorbent assay, which is not suitable for emergency use.

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IN RESPONSE: Dr. Wakai is concerned that other clinical centers, and particularly emergency departments, may have difficulty replicating the results of our study. We believe that the two limitations he discusses, which are common to most diagnostic tests, are interrelated and can be readily overcome. In contrast to other D-dimer assays, the assay we used in our study, SimpliRED (AGEN Biomedical, Ltd., Brisbane, Australia), can be performed at the bedside on a fingerstick sample and yields a result within minutes. At our institution, a nurse or a technician with previous training performs the test; we estimate that it takes about 2 hours of training to learn how to perform and interpret it. Alternatively, the SimpliRED assay can be performed in the laboratory on an anticoagulated venous blood sample (1). Regardless of where and on what type of sample the test is performed, the interpretation of presence (positive result) or absence (negative result) of red cell agglutination is subjective. Although interobserver agreement has been reported to be excellent (2), this may not always be the case; subjective errors of interpretation are probably responsible for the high false-negative rate of this test for venous thromboembolism reported by some investigators (3).

Provided that diagnostic accuracy is not sacrificed and that there is a short "turnaround time," we agree with Dr. Wakai about the advantage of an objective D-dimer test. Rapid enzyme-linked immunosorbent assays (4) and novel microparticle latex-based tests (5) seem to satisfy these requirements. However, compared with SimpliRED, the equipment required to perform these assays is substantial. Regardless of the type of D-dimer assay used, staff training and ongoing quality control of test performance will be required.

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Physicians and Patient Spirituality

TO THE EDITOR: Dr. Graner's comments in his letter to the editor reflect a misunderstanding of the concept of separation of church and state (not "politics") (1). The U.S. Constitution requires that the government not sanction a particular religion. It makes no statements about what I may have in my personal, nongovernmental office. My office is my personal space, which contains personal photographs, mementos of travels, gifts from patients, and other reflections of my personality that include symbols of my personal faith. I may choose to wear a cross and thereby proclaim to all my personal beliefs. This in no way suggests that I "impose [my] particular belief structure on others." I agree with Dr. Bodey (2) that if one is a Christian it is a way of living 24/7, not a Sunday activity. As a palliative medicine physician, I routinely deal with the spirituality of my patients. I must be sensitive to the belief systems of all of my patients. This does not require that I deny an essential part of who I am.

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IN RESPONSE: In my previous letter, I was not referring to constitutional legalities, so I did mean to use the word "politics." I did not address the issue of whether it is constitutionally legal to display a religious icon in a medical office. Rather, I am primarily concerned with the meaning of such display. This meaning varies according to the nature of the activities taking place within that office. Similarly, it does not matter whether Dr. LeGrand's office is a "governmental" one or not. As a matter of fact, very little true political activity takes place in most governmental offices! I use the term "political" in the traditional sense of public interaction, and the public–secular realm is indeed the "political sphere, properly speaking" (1). Patient care, because all citizens are entitled (and hopefully welcome) to such care, is indeed a public, secular activity.

The significance of the display of "personal photographs, mementos of travels," and other such items is distinct from the display of religious icons. This seems obvious to me. The opposite of the political sphere is the private one. And if Dr. LeGrand does not use her office for patient care, it is indeed her uniquely "personal" (that is, private) space. Needless to say, I have nothing against the adorning of one's private rooms with religious icons—I do so myself in my own home.

I notice that Dr. LeGrand insinuates a subtle but distinctly different topic for discussion into her argument. My previous letters have addressed the display of religious icons on examining room walls. She, instead, seems to be discussing her choice of jewelry: "I may choose to wear a cross and thereby proclaim . . . my personal beliefs." She is therefore not really talking about the public display of a religious symbol on the wall of her clinic, but rather her own apparel. Jewelry is appropriately personal and makes no institutional reference, even if by her jewelry Dr. LeGrand is attempting to "proclaim to all (her) personal beliefs."

I could say a great deal about the many dangers inherent in the practice of a physician "routinely deal(ing) with the spirituality" of her or his patients. I realize this is a hot topic these days. But such a presentation would entail a philosophical and historical discussion far exceeding the 400 words allotted to me here!

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Sprout-Associated Outbreaks

TO THE EDITOR: In their analysis of six separate outbreaks, Mohle-Boetani and colleagues (1) note that sprouts have been a source of foodborne illness. They suggest that sprout seeds can be contaminated by unpasteurized fertilizers, nonpotable water, or grazing livestock. They then give suggestions to remedy the situation before concluding that "production of pathogen-free sprout seeds is not currently feasible." I found the article very interesting but have two issues of concern.

First, while foodborne illness from *Salmonella* species and *Escherichia coli* O157 occasionally involves produce, the numbers are dwarfed by those associated with animal products. The authors note that during the 2 years covered by their six outbreaks, an estimated 22 800 cases of either *Salmonella* or *E. coli* O157 infection associated with sprouts. Compare that with 4 million cases of *Salmonella* infection, mostly associated with poultry and eggs (2), then add at least 98 400 cases of *E. coli* O157 infection, mostly from hamburger, that would also occur over this 2-year period (3). Thus, the authors' suggestion that people should avoid sprouts if they want to avoid foodborne illness seems unbalanced. To avoid being misleading, the authors should include poultry, eggs, and beef in their warnings.

Second, the authors recommend that seed growers use synthetic fertilizers and potable water to decrease the risk for contamination. They also recommend that seed mills keep seeds for sprouting separate from other seeds and that the mills disinfect equipment between seed runs. In addition, the U.S. Food and Drug Administration now recommends the testing of sprouts before marketing. I suggest that, as opposed to the authors' conclusion, the combination of the authors' and the Food and Drug Administration's recommendations

would probably result in a pathogen-free product. Following these recommendations would obviate the need for irradiation or other potentially harmful treatment and would prevent continued use of septic farming methods.

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IN RESPONSE: Dr. Lodato's comments provide us a chance to clarify a few points. The estimated number of cases in our outbreaks is, indeed, small compared with the estimated number of cases in the United States. However, the estimated national cases are mostly sporadic rather than associated with an outbreak. They could have had many sources of exposure, including contact with infected animals and humans; when they do have foodborne sources, these are rarely identified. But investigations of outbreak-associated cases allow us an opportunity to identify foodborne sources and to then intervene to prevent additional cases. While human salmonellosis has had a long history of association with animals and their products (for example, raw milk), investigations by public health agencies have identified a growing number of foodborne outbreaks due to fresh produce items (1–3).

Although we cannot identify the proportion of all cases of foodborne disease that are due to sprouts, we believe it is important that both clinicians and the public know about the risk of eating raw sprouts. Many people know that meat and poultry are commonly contaminated and that these should be handled cautiously and cooked thoroughly before consumption. But many think of sprouts as healthful foods and thus consume these raw. Our caution about eating sprouts should not detract from our continuing recommendation that animal products be handled properly and thoroughly cooked to decrease the risk for foodborne illness.

We agree with Dr. Lodato's statement about the need for a combination of prevention and control steps. This need is addressed in our Discussion section, where we categorized the recommendations into those that should be implemented by the seed growers/seed mills and those that should be implemented by the sprout growers. From sprout harvesting to consumption, proper refrigeration is also critical. We believe that full implementation of these recommendations by all seed growers and sprout growers will significantly reduce foodborne disease due to sprouts. However, we do not believe that even strict adherence to these recommendations will result in pathogen-free products 100% of the time because seeds and sprouts are grown in nonsterile environments that cannot be completely controlled.

We do not concur with Dr. Lodato's suggestion that irradiated foods would be harmful. Irradiation has been shown by numerous scientific studies to be a safe and effective option for controlling pathogens in food products (4, 5). Irradiation has been used successfully for many years in numerous countries, even by our own military forces, with no adverse effects.

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Newspaper Reporting of Screening Mammography

TO THE EDITOR: The paper by Wells and colleagues on newspaper reporting of screening mammography (1) was clearly biased and thus bad science. The authors criticize the sources the newspapers used, but are we to assume that the National Cancer Institute, the American Cancer Society, radiologists, the National Institutes of Health, and data presented at medical conferences are all unreliable and biased? Are they duping the U.S. public into performing mammography on women 40 to 49 years of age for some purpose other than to protect their welfare? If that were the case, would these people and institutions perhaps not go further and advise women in their 30s to get mammography, given that some cases do present in this age range?

The authors point out that newspapers go for sensationalism. However, this very journal and several other reputable ones (for example, *The Lancet* and the *Journal of the American Medical Association*) use press releases to promote their stories. Such media coverage serves to raise the values of their own journals. By submitting to *Annals*, Wells and colleagues are participating in the very problem (as they see it) that they are criticizing.

While there may be a public policy issue over the cost-effectiveness of mammograms in younger women, for individuals mammograms are noninvasive and inexpensive, and have been shown in well-controlled studies to be beneficial to women 40 to 49 years of age. Wells and colleagues do not shed light on the issue with which they are concerned: that mammography may not benefit women in

this age range. If they believe this is true, they should make it the hypothesis to prove, stop studying U.S. newspaper articles on the topic, and instead set up a prospective multicenter study to assess the question. At any rate, they should quit shooting the messenger when the message is unfavorable to their viewpoint.

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TO THE EDITOR: Wells and colleagues (1) recommend that "some basic criteria for medical journalism could be identified," such as "disclosing sources' possible conflicts of interest [and] the type of evidence on which assertions and recommendations are based" and "fram[ing] benefit in absolute as well as relative terms" (1). In 1997, three academic internists from McMaster University in Hamilton, Ontario, Canada; five Canadian health reporters; and the dean of one of Canada's schools of journalism met to generate these very critreia, which were published in the *American Medical Writers Association Journal* (2). These guidelines were based on several meetings held in Toronto and were designed specifically for health reporters without much training in critical appraisal or the health sciences.

Wells and colleagues state that journalists and medical researchers should take a more active role to ensure that the public receives "objective, relevant, and comprehensible [health] information" (1). In theory, I agree, but there clearly exist practical limitations to this assertion. Medical journalists are not motivated by the need to objectively report scientific information as "facts." Instead, they are faced with rapidly approaching deadlines, the need to be brief, and pressure to make the health story as interesting as possible. Ultimately, health reporters are controlled by editors (and publishers or broadcasters) who define what is newsworthy to maximize the sale of newspapers and advertising slots, while each attempt to maintain the practice of "fair" journalism. It is naive to believe that educating the public about health (3) or practicing "evidence-based journalism" will overtake these other themes.

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Research Letters

Clozapine-Associated Neuroleptic Malignant Syndrome

Clozapine has been associated with atypical presentation of neuroleptic malignant syndrome (1). We observed a patient who had atypical neuroleptic malignant syndrome related to an increased clozapine dose.

A 35-year-old man with bipolar disorder and schizophrenia presented to a community hospital with a 3-day history of diarrhea, fever (temperature, 38.9 °C), tachycardia (heart rate, 150 beats/min), and hallucinations. Medications included valproate sodium and oral clozapine, 100 mg/d. The latter had been started 3 weeks before admission and the dose had been increased to 150 mg/d 2 days before presentation. Upon admission, therapy with all medications was discontinued. The patient was given acetaminophen and ibuprofen for fever and intravenous metoprolol, 5 mg, for sinus tachycardia. After receiving metoprolol, the patient became hypotensive (blood pressure, 50/30 mm Hg) and had seizures, which resolved with intravenous fluids and diazepam. For further management, the patient was transferred to our hospital.

The patient's clinical presentation included diaphoresis and visual and auditory hallucinations. Examination was remarkable for tachycardia (heart rate, 125 beats/min) with no rigidity or signs of meningism. Pertinent laboratory values were leukocytosis with a left shift, elevated aminotransferase levels, normal creatine kinase levels, and a negative toxicology screen. Five days after discontinuation of clozapine therapy, symptoms resolved. Discharge medications were valproate sodium and trazodone.

The literature contains reports of atypical presentation of clozapine-associated neuroleptic malignant syndrome characterized by fever, diaphoresis, no muscle rigidity, and mild or no elevation in creatine kinase level (1–3). Typically, neuroleptic malignant syndrome is characterized by fever, muscle rigidity, autonomic dysfunction, elevated creatine kinase levels, and myoglobinuria (4, 5). The atypical picture seen with clozapine is postulated to include imbalances among norepinephrine, serotonin, acetylcholine, and γ-aminobutyric acid; disordered calcium regulation; and state-dependent changes in receptor sensitivity. In our case, we ruled out infection, heat stroke, and other neurologic disorders. Previous medications included trazodone, risperidone, ziprasidone, and benzotropine; the patient had no history of neuroleptic malignant syndrome. We caution other practitioners to remain alert for this atypical clozapine presentation.

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Superior Sagittal Sinus Thrombosis and HIV

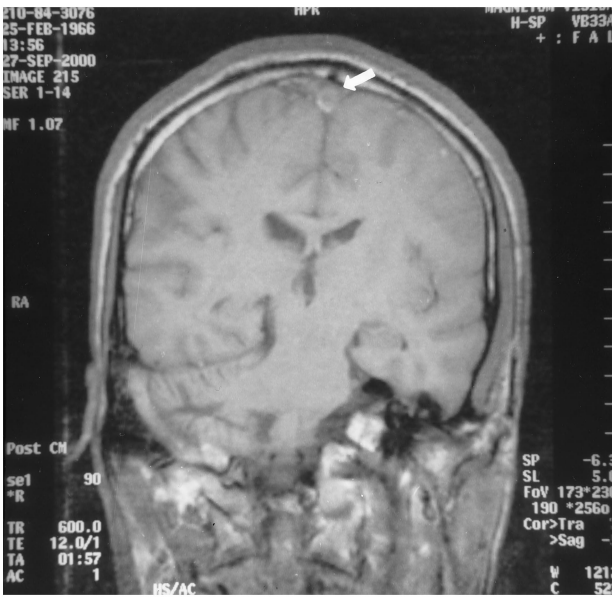
TO THE EDITOR: Although myriad neurologic complications have been reported in patients with HIV infection, thromboembolic phenomena have been limited to scattered reports. Most of these reports have been anecdotal and have implicated lupus anticoagulant, anticardiolipin antibody, and protein S deficiency (1–3). To our knowledge, cerebral venous sinuses thrombosis, a rare disease described as early as 1825, has not been described as an initial presentation of HIV.

A 34-year-old man presented with right-sided weakness. The patient had no family history of premature cardiac or cerebrovascular events. He had no history of recent falls or head trauma. He did not have fever, visual symptoms, or neck pain. Other than an oral temperature of 37.7 °C, his vital signs were normal. Neurologic examination revealed right-sided hemiparesis and an upper motor neuron weakness of his right seventh cranial nerve. The rest of his physical examination was unremarkable. The following laboratory findings were either normal or negative: complete blood count, serum chemistry, calcium level, liver function tests, thyroid function test results, coagulation profile, blood alcohol level, and urine toxicologic screen.

Magnetic resonance imaging revealed subarachnoid hemorrhage and superior sagittal sinus thrombosis (**Figure**). A four-vessel angiogram confirmed the previous findings and revealed a congenital absence of the right posterior cerebral artery with no aneurysms or arteriovenous malformations.

Levels of proteins C and S, antithrombin III, and factor V Leiden were normal. Findings on blood cultures, viral serology, Lyme titer, and cerebrospinal fluid examination were all negative. The patient tested positive for HIV and had a CD4 cell count of 445 cells/mm^3.

Figure. **Magnetic resonance imaging coronal section of head, with magnetic resonance venography showing a thrombosed superior sagittal sinus (*arrow*).**



Cerebral venous sinus thrombosis has been infrequently described as a complication of HIV; one report implicated a postmortem diagnosis of central nervous system lymphoma (4), and another involved the diagnosis of other simultaneous central nervous system infections (5).

Likely explanations for the association we observed include the local release of a procoagulant factor emanating from a lymphomatous process, a direct HIV necrotic injury on the endothelium, as-yet unrecognized opportunistic infection, or an alteration of an unknown thrombogenic factor triggered by the virus (1, 2, 4).

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Rapidly Progressive Glomerulonephritis

TO THE EDITOR: *Background:* Rapidly progressive glomerulonephritis is a clinicopathologic syndrome defined by the development of renal failure over days to months and the appearance of crescentic glomerulonephritis (1). Two major causes of rapidly progressive glomerulonephritis are anti–glomerular basement membrane (GBM) disease and vasculitis associated with antineutrophil cytoplasmic antibodies (ANCAs). These conditions have distinct clinical, serologic, and pathologic features. Nevertheless, a proportion of patients with rapidly progressive glomerulonephritis possess both anti–GBM antibodies and ANCAs. The clinical and serologic characteristics of such patients have not been well defined, in part because of the small numbers of patients seen at any single center.

Objectives: Our laboratory has provided a nationwide service for measurement of anti–GBM antibodies and ANCAs over the past 20 and 10 years, respectively. We retrospectively reviewed the clinical and serologic characteristics of patients who had positive results on tests for both antibodies (dual positive).

Methods and Findings: Anti-GBM antibodies were detected by using Western blot analysis and were quantified by using enzyme-linked immunosorbent assay. Antineutrophil cytoplasmic antibodies were detected by using immunofluorescence; antigen specificity was confirmed by immunoassays for proteinase-3 and myeloperoxidase. Frozen serum from patients with anti-GBM antibodies, detected before the introduction of the ANCA test, were analyzed retrospec-

tively for ANCA. A standard clinical questionnaire was sent to referring institutions.

We have detected 136 patients with anti–GBM antibodies. Of these, 58 (42.6%) also had ANCAs: 42 (72.4%) on myeloperoxidase immunoassay, 14 (24.1%) on proteinase-3 immunoassay, and 2 (3.4%) on both assays. The mean age (±SD) of dual-positive patients was 56.9 ± 19 years versus 46 ± 19 years in patients with anti–GBM antibodies alone. Detailed clinical information was returned on 38 of 58 dual-positive patients. Presenting clinical features in these 38 cases included fever (39%), arthralgia (45%), symptoms of upper respiratory tract infection (37%), and rash (23%).

The mean duration of symptoms before presentation (±SD) was 3.0 ± 0.9 months. Pulmonary hemorrhage was documented in 39% of patients. Forty-two of 58 patients (72%) underwent renal biopsy. Mean percentage of crescents (±SD) were 60% ± 8%. Linear IgG staining along the GBM was observed in all cases. Mean creatinine concentration (±SE) at presentation was 495 ± 62 μmol/L (5.6 ± 0.7 mg/dL), and acute dialysis (defined as the need for hemodialysis during the first hospital admission) was required in 24 patients. Of these, 22 remained dialysis dependent. Treatment consisted of corticosteroids (89%), cyclophosphamide (61%), and plasma exchange (50%).

Discussion: Our study confirms that many patients with anti–GBM antibodies also have ANCAs, a proportion higher than previously described (typically 21% to 32%) (2, 3). The reason for such coexistence is unknown. These antibodies are not cross-reactive, and there is no difference in the antigen specificity of anti-GBM antibodies in the presence or absence of ANCAs (4). Perhaps glomerular damage, mediated by ANCA-associated disease, uncovers hidden epitopes that promote anti-GBM autoantibody formation.

Patients with dual positivity shared clinical characteristics of both ANCA-associated vasculitis and anti-GBM disease. Thus, dual-positive patients tended to be older and to have a high incidence of prodromal systemic symptoms, consistent with systemic vasculitis. However, most dual-positive patients presented with severe renal dysfunction and a high proportion required acute dialysis. More important, dual-positive patients responded poorly to treatment and 90% of patients initially requiring dialysis remained dialysis dependent. This poor renal outcome is typical of anti-GBM disease but not ANCA-associated vasculitis (5). These findings contrast those of a smaller report (5), which suggested that dual positivity portended an improved prognosis compared with anti-GBM antibodies alone. The prognostic information obtained from this study may be useful for the management of this patient population.

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