

## COMMENTS AND RESPONSES

## Long-Term Outcome in Lupus Nephritis

**TO THE EDITOR:** Illei and colleagues (1) report superior long-term outcomes in patients with lupus nephritis treated with pulse cyclophosphamide with or without pulse methylprednisolone compared with those treated with pulse methylprednisolone alone. Their data also suggest that pulse methylprednisolone combined with cyclophosphamide has additional benefit. The primary outcomes defining treatment failure were need for supplemental immunosuppressive therapy, doubling of serum creatinine concentration, or death.

Illei and colleagues' mortality data, however, are intriguing. The investigators previously reported that after 5 years of follow-up, 3 of 55 cyclophosphamide-treated patients had died compared with 0 of 27 patients randomly assigned to pulse methylprednisolone alone (2). The suggestion of a true difference in mortality rates at a median of 11 years of follow-up is even more striking. In an intention-to-treat analysis combining Illei and colleagues' data on all cyclophosphamide-treated patients, we found that 10 of 55 (18%) cyclophosphamide-treated patients died versus only 1 of 27 patients (4%) treated with pulse methylprednisolone alone. This corresponds to a very large relative risk reduction of 78% in patients not exposed to cyclophosphamide. Although the authors report no significant difference among the treatment groups for the outcome of death, this difference has a *P* value of 0.09 using the conservative Fisher exact test. If the groups were compared by using a survival analysis (as was done for the composite end point used by the authors to define treatment efficacy), the *P* value would probably have been much closer to 0.05. With such small sample sizes, even *P* values between 0.05 and 0.10 should be addressed, particularly with regard to an outcome as important as death. Of interest, when an intention-to-treat analysis was used, no difference was seen in renal morbidity as an individual outcome between pulse methylprednisolone alone and cyclophosphamide-containing regimens. Only by using a composite end point that included the need for additional immunosuppressive therapy were the authors able to find an advantage to the cyclophosphamide-containing regimens. As the authors point out, a substantial percentage of patients in the methylprednisolone group ultimately received cyclophosphamide therapy. Perhaps on some level this composite analysis reflects the need for additional immunosuppressive therapy in many of the patients treated with methylprednisolone alone.

Mortality data should be a major consideration in the selection of therapy in patients with lupus nephritis. In patients with less severe disease, initial treatment with pulse methylprednisolone alone may be preferable, although salvage therapy with immunosuppressive agents may ultimately be necessary.

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2. Gourley MF, Austin HA 3rd, Scott D, Yarboro CH, Vaughan EM, Muir J, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. *Ann Intern Med.* 1996;125:549-57. [PMID: 8815753]

**IN RESPONSE:** We agree with Spiera and colleagues that the larger number of deaths in the cyclophosphamide-containing groups in our study is intriguing and that a survival analysis is the optimal statistical method to determine whether there is a true difference in mortality. However, we believe that combining the mortality data from both cyclophosphamide-containing groups and comparing them with the methylprednisolone group is flawed because this method assumes that any increased mortality in the combination group is attributable to cyclophosphamide. Comparing the methylprednisolone-only group with the cyclophosphamide-only group in a Breslow-Gehan-Wilcoxon survival analysis showed no significant difference in risk for death. We agree that borderline *P* values should be interpreted cautiously with such a small number of patients because small differences from the expected number of events (a few more or less) may cause large changes in the *P* value. To distinguish chance statistical oddities from biologically plausible trends, these results should be analyzed in the context of previous experience. To determine whether there was a biologically plausible connection to cyclophosphamide treatment, we analyzed the individual causes of deaths. Only one of five deaths in the cyclophosphamide group could reasonably be attributed to immunosuppression (*Pneumocystis carinii* pneumonia). One patient died of a clearly unrelated cause: bleeding after a kidney biopsy at another center. Removing this patient from the survival analysis changed the *P* value to 0.13. We have not seen an increased risk for death in patients treated with cyclophosphamide in previous studies, either at the end of the study or during long-term follow-up (1, 2). Spiera and colleagues also point out that in an intention-to-treat analysis, the rate of end-stage renal disease did not differ among the groups. As discussed in our paper, this apparent equality can be explained by the design of the original study and the practice at our institution to use cyclophosphamide in patients in whom pulse methylprednisolone has failed.

Our major finding was that the addition of methylprednisolone pulses to pulse cyclophosphamide leads to better long-term responses in moderate to severe lupus nephritis without conferring additional risk for adverse events. Dr. Spiera and colleagues conclude that pulse methylprednisolone alone should be the preferable option to treat mild lupus nephritis. However, this is not an appropriate extrapolation from our study because neither the original protocol nor the follow-up was designed to address this question.

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## Quality Indicators for Management and Prevention of Falls

**TO THE EDITOR:** I read with interest Rubenstein and colleagues' review on fall assessment and prevention (1). I was surprised that the authors did not comment on the fact that balance exercises, such as tai chi, were one of the best ways to reduce risk for falls. Also, although many trials showed a reduction in risk for falls, very few showed a reduction in risk for injurious falls. I think we should be concerned with fall prevention at an earlier age, when participation in such things as tai chi or yoga can be really helpful.

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1. Rubenstein LZ, Powers CM, MacLean CH. Quality indicators for the management and prevention of falls and mobility problems in vulnerable elders. *Ann Intern Med*. 2001;135(8 Pt 2):686-93. [PMID: 11601951]

**IN RESPONSE:** Exercise is one of the most potent interventions for both fall prevention and improvement of mobility dysfunction. Dr. Pierre is concerned that we omitted discussion of tai chi as being one of the best types of exercises for these purposes. We agree that tai chi is a beneficial form of exercise and discussed tai chi positively in the context of the variety of exercise regimens tested. However, although meta-analysis has confirmed the value of various types of exercises in preventing falls, tai chi has not yet been shown to be superior to other types of balance, strengthening, and endurance exercises.

The fact that fewer fall-prevention trials of all types have shown reduction in injurious falls than falls in general is mostly related to issues of sample size. Only about 10% to 15% of falls result in significant injury, and most fall-prevention trials were powered only to show reductions in total falls. Larger studies would probably have shown statistically significant reductions in injurious falls that paralleled the reduction in total falls.

Although we also agree with Dr. Pierre that exercise regimens introduced early in life will probably have lasting benefits into old age and will most likely increase the chance that older persons will remain active and fall-free, the evidence behind this assertion is thus far lacking in longitudinal or intervention trials. Nonetheless, we believe in the benefit of most forms of exercise at any age, not only for fall prevention but also for improving many other aspects of health and well-being.

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## Alternative Medicine: A Mirror Image for Scientific Medicine

**TO THE EDITOR:** Vandenbroucke and de Craen should be congratulated for writing a stimulating article on medical thinking in general (1). I fear, however, that they may have gotten some of their specifics wrong when stating that homeopathy is supported by “seemingly solid evidence” (1). Vandenbroucke and de Craen base this statement on a meta-analysis by Linde and colleagues (2). However, several subsequent attempts (3, 4) to reanalyze Linde and colleagues' data set have cast considerable doubt on their positive conclusions. Most impressive, perhaps, Linde and colleagues themselves reanalyzed their data and concluded that “there was clear evidence that studies with better methodological quality tended to yield less positive results” (5). Thus, the trial evidence of homeopathy is not “seemingly solid” but seemingly unconvincing. In other words, Vandenbroucke and de Craen may be right about how doctors think but seem to be wrong about the clinical evidence regarding homeopathy.

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**IN RESPONSE:** We are grateful that Dr. Ernst points to new literature that includes reanalyses of the original meta-analysis on homeopathy by Linde and colleagues (1). However, in our paper, we already pointed to one reanalysis (2) that casts doubt on the robustness of the original. We also acknowledged that such reanalyses have been ongoing because scientists cannot believe the results of the original and therefore try to prove that the original was “methodologically flawed.” Verdicts that a study (or a meta-analysis) is flawed are in this case based on reasoning and logic only because there is no “evidence” for “methodologic flaws.”

This reasoning fits very well with the crossword analogy that we proposed. One entry in the crossword holds that infinite solutions cannot possibly have chemical activity; this entry is very well entrenched in physics, chemistry, and biology. In line with this entry,

we prefer the entry interpreting the meta-analysis (or the original studies) as flawed, which has its own arguments embedded in reasoning and logic, as indicated by Dr. Ernst and others. Of course, this is not always immediately apparent. When the original meta-analysis on homeopathy was published, many were surprised and wondered whether there was anything in it. Gradually, however, it became clear that the findings were less robust than they originally were thought to be. In this way, all entries do now fit, and this “consilient” (3) fitting gives us an argument that endorses both methodologic and basic science reasoning.

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### Clinical Inertia

**TO THE EDITOR:** After reading the Perspective by Phillips and colleagues on clinical inertia (1), I was inclined to agree that the desire of patients and physicians to “stay the course” when treating chronic illnesses often interferes with achieving excellent care. However, on further reflection, I felt that the paper greatly oversimplified many aspects of day-to-day medical practice.

Phillips and colleagues underestimated the extent, depth, and persistence of clinicians’ discussions with patients and families about the benefits, risks, and costs of intensifying medical therapies for chronic diseases. Some patients with atrial fibrillation who are otherwise excellent candidates for anticoagulation decline it despite my best efforts at persuasion. Likewise, many diabetic patients opt to avoid the demands of more intense glycemic control, despite the attendant increased risks for hypoglycemia and weight gain. Because discussions about such decisions are ongoing and often span months and years, however, their depth may not be adequately reflected in chart notes. Over time, tolerance of the status quo may appear to an outside reviewer as “inertia.”

I also feel that target or ideal values are too frequently viewed as the ultimate marker of successful treatment. Although these goals should be something to strive for, there is frequently a subtle or even overt sense that therapy will have little benefit unless the target is achieved. In fact, most of the important studies of glycemic control, lipid lowering, and hypertension treatment show that benefits are in large part linearly or progressively associated with improvement in the measured value. Having lowered a patient’s low-density lipoprotein cholesterol level from 240 mg/dL to 140 mg/dL, we must often acknowledge that attempting to reduce it by 40 or 50 more points will greatly increase expense and risk for side effects. Is this “clinical inertia” or simply knowing when to stick with a pretty good hand?

In the end, my pendulum swung back slightly toward my orig-

inal agreement that the desire to avoid upsetting the apple cart can and does sometimes hold us back. “Inertia,” however, is a highly inaccurate characterization of the process.

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#### Reference

1. Phillips LS, Branch WT, Cook CB, Doyle JP, El-Kebbi IM, Gallina DL, et al. Clinical inertia. *Ann Intern Med*. 2001;135:825-34. [PMID: 11694107]

**TO THE EDITOR:** To be fair to the concept of inertia, best defined here as an indisposition to change, it should be acknowledged that inertia works in both directions. The attractive concept of clinical inertia proposed by Phillips and colleagues (1) should also encompass the failure of health care providers to stop or deescalate therapy. Treatment regimens too often contain medications that are continued indefinitely for little or no reason. Commonly encountered examples of lingering medications are gastric protective agents initiated long ago in the hospital for stress ulcer prophylaxis and hormone replacement therapy that no longer has clear-cut indications.

Reasons for this alternate direction of inertia parallel to that proposed by Phillips and colleagues include overestimation of the resources or adherence capacity of the patient, the use of “soft” reasons to avoid deescalating therapy, and the usual culprit: lack of adequate training or systems. This form of clinical inertia is partly responsible for the perception that physicians continue to add medicines with little consideration of cost or convenience to the patient regardless of whether there is supporting evidence. Failure to acknowledge this side of clinical inertia undermines the stewardship of resources that physicians are currently being asked to assume. For clinicians, the major point is that the patient’s medication list is dynamic, and each medication should be scrutinized along with the patient in every clinical encounter.

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1. Phillips LS, Branch WT, Cook CB, Doyle JP, El-Kebbi IM, Gallina DL, et al. Clinical inertia. *Ann Intern Med*. 2001;135:825-34. [PMID: 11694107]

**TO THE EDITOR:** In the excellent article on clinical inertia by Phillips and colleagues (1), there is a section titled “Use of ‘Soft’ Reasons To Avoid Intensification of Therapy.” I believe that the impact of such soft reasons cannot be overemphasized. As a practicing clinician, I can testify to the difficulty in getting patients to take medications for apparently asymptomatic conditions, as well as having patients continue to take such medications over the long haul. If long-term adherence to treatment is enhanced by obtaining patient “buy-in,” then strategies employing nonmedication trials may delay reaching goal levels in the short run but may convince patients that medications are necessary and increase the likelihood of long-term adherence and treatment success. A major drawback to this strategy is that patients may quietly disappear from follow-up care.

Another underappreciated “soft” reason is side effects. If a drug has a side-effect rate similar to that of placebo, we think of it as innocuous and tolerable. However, if the placebo side-effect rate is

25% to 30%, then the patient has a substantial 25% to 30% higher likelihood of side effects (at least in the short term) with the drug than without it (and, of course, most drugs have side-effect rates higher than that of placebo). Finally, better patient education through mass media would make patients more receptive to treatment and indirectly diminish clinical inertia. For example, there is now a widespread belief that statins are dangerous drugs, making patient resistance to treatment worse than ever.

All of these factors contribute to patient reluctance to accept treatment. I believe that clinicians respond to this reluctance by prescribing more slowly (clinical inertia).

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**IN RESPONSE:** Our paper was prompted by observations that although many patients have chronic disorders that confer increased morbidity and mortality (1), they are often not managed to achieve the maximum potential benefit of therapy, despite strong evidence that treatment is beneficial and cost-effective and carries little major risk. In this context, Dr. Steinberg properly emphasizes that sub-maximal intensity of management may reflect the explicit wish of the patient. However, since national standards for care *can* be met in some real-world practice settings (2, 3), failure to meet such targets in other settings must be attributed either to patient self-selection bias or to insufficient emphasis by the physician: clinical inertia. Since emphasis on overcoming clinical inertia improved diabetes outcomes in our own practice without much in the way of patient objections or complications from hypoglycemia (3, 4), we believe that clinical inertia is often the limiting problem.

We agree that if the primary goal is no hypoglycemia or orthostatic hypotension, then glucose and blood pressure targets will often not be met. However, since such a posture is usually unreasonable, the question then becomes how to improve management. We must disabuse physicians of the notion that disorders are being treated adequately if they are treated at all; the combination of “suboptimal treatment” and “no complaints” may still be much less than what could be achieved in the same setting with little further increase in cost, inconvenience, or side effects. The responsibility for recommending intensification of management is the physician’s, since only he or she can be fully informed about benefits and risks. We suspect that few physicians ask their patients specifically whether they would prefer a higher risk for stroke rather than a higher risk for orthostasis. We believe that rectifying the problem will require physician education in the details of treating to target, systems to show physicians exactly what their care consists of (since overestimation of performance is common [5]), and suggestions about ways to improve.

We agree with Dr. Wofford that periodic evaluations of medications are important. However, many patients will eventually need to be treated for combinations of diabetes *and* hypertension *and* dyslipidemia *and* heart failure *and* osteoporosis. Since management of these disorders is both evidence based and cost-effective, stopping appropriate therapy should not usually be considered until very late in life. Thus, for most patient encounters, the focus should properly be on doing more rather than doing less.

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## Guidelines for the Management of Patients with Chronic Stable Angina

**TO THE EDITOR:** The guidelines for management of patients with chronic stable angina (1) represent an update from leading cardiology associations. Overall, the publication of these types of guidelines is useful for developing uniformity of practice when there is clear consensus due to high-quality, evidence-based clinical studies. The current applicability of such evidence, however, is often questioned. In particular, in these guidelines, the recommendations for revascularization in patients with left main, three-vessel disease, or two-vessel disease with involvement of the proximal left anterior descending artery are considered class I (evidence that treatment is useful) and grade A (high-quality data based on multiple randomized clinical trials). The supporting data, however, are too old to allow these recommendations to be uncritically adopted.

Current surgical recommendations are largely derived from data from the 1970s and 1980s (1), which precede current aggressive medical therapies for ischemia management (optimizing nitrates,  $\beta$ -blockers) and for risk factor reduction (especially cholesterol). Even the most recent study of surgical versus medical management, in the mid-1990s, did not have aggressive lipid lowering as a goal (2). Yet other data clearly show that aggressive lipid management leads to clear benefit within 6 months of initiating therapy (3, 4). In a study of patients with stable coronary artery disease in whom angioplasty was recommended, Pitt and colleagues (3) found that aggressive lipid lowering with 80 mg of atorvastatin decreased ischemic events by 36% over 18 months compared with angioplasty (3). By design, Pitt and colleagues’ study excluded patients with left main or triple-vessel disease. Since no trial has compared present state-of-the-art medical management (especially aggressive lipid lowering) with surgery for these coronary lesions, which have higher mortality rates, recommen-

dations for therapy should be tempered with the caveat that no clear current data are available.

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**IN RESPONSE:** Dr. Modest makes several valid points with which we concur. First, clinical practice guidelines must be continuously updated to reflect advances in knowledge. Second, data on the efficacy of coronary bypass surgery are relatively old and may not accurately reflect current practices and outcomes. Third, data are emerging to indicate that aggressive lipid-lowering therapy is an important component of regimens to manage symptoms of ischemia as well as to prevent future complications.

With regard to updating clinical guidelines, the American Heart Association and the American College of Cardiology require that updates and revisions be performed regularly. In fact, the guideline on the management of chronic stable angina by the American Heart Association, American College of Cardiology, and American College of Physicians—American Society of Internal Medicine, on which our article was based, is currently being updated. The rules require that any new information or recommendations included in the updated guidelines be based on high-quality evidence.

As Dr. Modest points out, some of the data from which recommendations for surgery are derived were collected in trials conducted over a decade ago, when results of both surgical and medical therapy were probably poorer than they are today. In keeping with our rules of evidence, however, these trials were methodologically sound and demonstrated important differences in mortality and control of symptoms for certain specific subgroups of patients. To date, these findings have not been supplanted by newer data from randomized trials, and a recent decision analysis indicates that there have been similar improvements in mortality due to advances in medical and surgical therapy for chronic stable angina (1). In our review, we specifically stated that such studies “must be interpreted cautiously,” in part because “advances such as aggressive lipid lowering . . . were often not assessed” (2). As we also noted, similar concerns apply to comparisons of percutaneous coronary interventions because many earlier randomized trials did not incorporate the latest advances, such as intracoronary stents (with or without drug coating).

In reference to studies suggesting that aggressive lipid lowering

may alleviate anginal symptoms, we share Dr. Modest's excitement. The major trial he cites, however, enrolled patients who were at very low risk for acute coronary events, had mainly absent or mild anginal symptoms, and would probably not have been candidates for surgery under any circumstances (3). Thus, the results of that trial have little relevance to recommendations for surgical intervention. Nonetheless, we share Dr. Modest's implied optimism that future trials involving higher-risk patients with more severe symptoms will show that aggressive medical therapy can obviate the need for invasive procedures in at least some patients.

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## High-Dose Cyclophosphamide for Treatment of Aplastic Anemia

**TO THE EDITOR:** Brodsky and colleagues (1) assert that high-dose cyclophosphamide provides enduring remission from and even “cures” free from long-term complications in patients with severe aplastic anemia. However, a randomized trial by the U.S. National Institutes of Health (NIH) comparing antithymocyte globulin (ATG) with cyclophosphamide was terminated early because of unacceptable toxicity in the cyclophosphamide arm (2). This early termination, along with the subsequent observation of persistent paroxysmal nocturnal hemoglobinuria (PNH) clones, relapse, and evolution to cytogenetic abnormalities typical of myelodysplasia at similar rates in both arms (3), challenges Brodsky and colleagues' assertions.

Although Brodsky and colleagues report that PNH and myelodysplasia did not occur in their trial, they do not define these entities. Elsewhere, these authors previously reported the detection of PNH clones in most untreated patients with severe aplastic anemia and argued that clonality is an early event (4). Weren't such clones detected in the current series, and what was their fate after cyclophosphamide therapy? In addition, the determination of myelodysplasia requires frequent marrow examination and cytogenetic analysis. The

cytogenetic abnormalities observed in our trial were among patients who remain in clinical remission. We are given few details of the early deaths in Brodsky and colleagues' study. In our trial, early deaths occurred exclusively in the cyclophosphamide arm, even in younger patients with adequate neutrophil counts at presentation; other patients were saved only by aggressive neutrophil transfusions.

These excess toxicities, along with the much higher requirements for supportive care related to the myelosuppressive effects of cyclophosphamide, were highly significant and clinically indisputable. They serve to point out that properly designed, conducted, and reported randomized, controlled trials are the best way to advance clinical practice while protecting the interests of research participants. The failure of cyclophosphamide to endure the rigors of our randomized, controlled trial was famously epitomized by the late Thomas Chalmers, who said, "One only has to review the graveyard of discarded therapies to discover how many patients have benefited from being randomly assigned to a control group" (5).

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**IN RESPONSE:** Over 15 years ago, a prospective, controlled study by Speck and colleagues suggested that antilymphocyte globulin was superior to allogeneic bone marrow transplantation for aplastic anemia (1). Initially embraced by many, the conclusions of this study have not stood the test of time, and bone marrow transplantation is now the preferred treatment for patients with matched siblings.

The randomized, controlled trial can be limited by the details of study design and execution. The NIH trial reported 6-month data on just 13 patients treated with cyclophosphamide and cyclosporine and just 12 patients treated with ATG and cyclosporine. The study accrued less than 20% of its planned enrollment and was terminated although neither rules for stopping nor primary or secondary end points were ever met. In addition, in contrast to our study, the NIH started cyclosporine concomitantly with cyclophosphamide and continued it for 6 months. The concomitant use of cyclosporine with cyclophosphamide may increase toxicity (2); furthermore, cyclosporine blocks the induction of tolerance, a potential mechanism of action for cyclophosphamide (3).

We found that high-dose cyclophosphamide alone leads to durable treatment-free remissions in most patients with aplastic anemia (4). Six patients from our initial trial (4) have remained in complete remission for more than 14 years, two for more than 20 years. The reported relapse rate for patients treated with ATG and cyclosporine in an earlier NIH series (5) was 50% at 5 years and 87% at 7 years. As we detailed in our report, all three deaths in our patients occurred among the nine who had very severe aplastic anemia. Such patients had an early mortality rate of 28% while taking ATG and cyclosporine in the NIH series. The survival rate in our patients is now 88.9% with no relapses, myelodysplasia, or PNH. All of the patients in our recent study are regularly screened for PNH or myelodysplasia. It is true that most patients with aplastic anemia harbor small PNH populations before treatment. We are monitoring these minute populations with highly sensitive assays, and so far they have regressed or remained stable.

Although the jury is still out on the role of high-dose cyclophosphamide in aplastic anemia, we hope the NIH group does not believe that the results of a small trial combining cyclosporine with cyclophosphamide and having only short follow-up should halt further study on this promising treatment approach. Over 15 years ago, because of the high rate of late complications (relapse and secondary clonal disorders) in patients with aplastic anemia who received antilymphocyte globulin, Speck and colleagues recommended continued study of bone marrow transplantation.

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### Postoperative Pulmonary Complications

**TO THE EDITOR:** Arozullah and colleagues (1) describe the development of a multifactorial risk index for the prediction of postoperative pneumonia. The accompanying editorial by Lawrence (2) discusses the authors' decision to use a homogeneous outcome variable (postoperative pneumonia), in contrast to previous studies that used less clearly defined postoperative pulmonary complications as outcome

measures. I take issue with the description of hypoxemia as a postoperative complication of “little clinical significance.”

Eichhorn (3) has reviewed the importance of late desaturation and hypoxemia. There are two recognized patterns: persistent hypoxemia, which is related to preoperative respiratory function, and episodic nocturnal hypoxemia, which is closely related to episodic sleep apnea and is aggravated by postoperative physiologic disturbances. The latter form of hypoxemia has in particular been linked with possible organ dysfunction and subsequent morbidity and possibly mortality. Episodic nocturnal hypoxemia has been associated with episodes of cardiac ischemia and may contribute to the increased frequency of unexpected postoperative deaths noted at night.

A second point worthy of mention is the recent evidence showing not only that avoidance of hypoxemia is desirable but also that supplemental oxygen in the early postoperative period may improve outcome. Supplemental perioperative oxygen has been shown to reduce the incidence of surgical wound infections (4) and of postoperative nausea and vomiting (5) in patients undergoing colorectal surgery. The mechanism underlying this improvement is unknown but is thought to be related to improved tissue oxygenation and thus avoidance of subtle tissue ischemia.

Postoperative hypoxia is associated with increased morbidity and mortality, and avoidance of subtle tissue ischemia with supplemental oxygen improves outcome in terms of reduced wound infections and postoperative nausea and vomiting. To suggest that postoperative hypoxemia is of little clinical insignificance is to trivialize a potentially serious postoperative complication that is amenable to a simple and cheap preventive measure, namely the administration of supplemental oxygen in the postoperative period.

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**IN RESPONSE:** Measurement of oxygenation, purely numerically, as a surrogate, without clear linkage to clinically important outcomes, may not advance the science or art of patient care and research in perioperative pulmonary risk management. Data from a large trial of pulse oximetry in the operating room and postanesthesia care unit suggest that there is more measurable hypoxemia than there are important clinical sequelae of it (1). Mild hypoxemia, which probably has little clinical significance as a postoperative pulmonary complication, should not be considered as such in the same league as pneumonia.

There may be other reasons to care about oxygenation besides

pulmonary complications. Dr. Ramsay cites two reports from a multicenter trial of patients having colorectal surgery who were randomly assigned to receive 30% (standard care) or 80% supplemental oxygen intraoperatively and 2 hours postoperatively (2, 3). Eighty percent supplemental oxygen was associated with less postoperative nausea and vomiting and fewer wound infections (2, 3). Both reports state that oxygen saturation was maintained at greater than 92% to at least 95% in all patients.

Dr. Ramsay's mention of “subtle tissue ischemia” provides additional perspective. The definition of clinically important hypoxemia may vary among tissues. In the study of wound infection (3), mean arterial oxygen saturation was 98.7% and 99.7% in the 30% and 80% oxygen groups, respectively. The difference between these groups was statistically significant ( $P < 0.001$ ), but would anyone argue that it is clinically important? Yet clinical meaning is less clear for the similarly statistically significant differences between groups for more sophisticated measures of intraoperative tissue oxygenation: mean subcutaneous oxygen tension (59 mm Hg vs. 109 mm Hg), muscle oxygen tension (25 mm Hg vs. 40 mm Hg), and partial pressure of arterial oxygen (121 mm Hg vs. 348 mm Hg). Do the latter measures validly lower the bar for “clinical” hypoxemia, or are they irrelevant surrogate measures? It takes well-designed research that defines the link between surrogate measures and clinical outcomes to answer these questions.

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## RESEARCH LETTERS

### Permanent Paralysis of the Right Phrenic Nerve

**TO THE EDITOR:** Although right phrenic nerve paralysis is an acknowledged immediate complication of implanted venous access portals, it has only recently been recognized as a late sequela of this device. To a growing list of similar occurrences, we add this case report of a 44-year-old woman with infiltrating ductal carcinoma of the breast, treated with 5-fluorouracil, cyclophosphamide, and doxorubicin chemotherapy as a continuous 48-hour infusion through a Hickman catheter. Eighty days after successful implantation of a right subclavian venous catheter, the patient developed right shoulder pain. Plain chest radiography and venography documented a widened mediastinum, raised right hemidiaphragm, and thrombosis of the superior vena cava without dye extravasation. Despite resolu-

**Table. Permanent Paralysis of the Right Phrenic Nerve Related to Central Venous Catheters\***

Study (Reference)	Year	Central Venous Access Device	Disease	Treatment	Sample Size, n	Mean Time to Event, d	Thrombosis?	Pain?
Munzone et al. (3)	2000	Implanted port	Breast cancer	Chemotherapy infusion	15	108	NR in 15 patients	Yes (14 of 15 patients)
Aggarwal et al. (1)	2000	Double-lumen catheter	Renal failure	Hemodialysis	1	90	Yes (1 of 1 patient)	No (0 of 1 patient)
Rigg et al. (4)	1997	Hickman catheter	Colorectal cancer	Chemotherapy infusion	5	93	Yes (4 of 5 patients)	Yes (5 of 5 patients)
Leong et al. (2)	1996	Hickman double-lumen catheter	Myeloma	Chemotherapy infusion	1	60	Yes (1 of 1 patient)	Yes (1 of 1 patient)

\* NR = not reported.

tion of the thrombus with therapeutic anticoagulation, the hemidiaphragm has remained paralyzed.

The Table summarizes the 22 cases in the international literature of permanent right phrenic nerve paralysis due to late complication of indwelling central venous catheters. Various right- and left-sided catheters were used for hemodialysis (1) or systemic chemotherapy with a variety of chemotherapeutic agents (2–4). Average time to right phrenic nerve paralysis was approximately 3 months. Right shoulder pain was a prominent symptom in all but one case (1). Thrombosis was important in three reports (1, 2, 4) as well as in our case but was not mentioned in the largest series (3). Prophylactic warfarin was not preventive (4). We speculate that venous wall damage resulting from inflammation associated with thrombus formation caused phrenic nerve paralysis.

Since the use of indwelling central venous catheters has increased dramatically during the past decade, this phenomenon could be more frequent in the future. Perhaps with early detection and treatment, this event would be reversible. We therefore suggest heightened suspicion for phrenic nerve paralysis as a potential late complication of central venous catheters, usually in conjunction with right shoulder pain and thrombosis formation.

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#### Diagnosis by Death

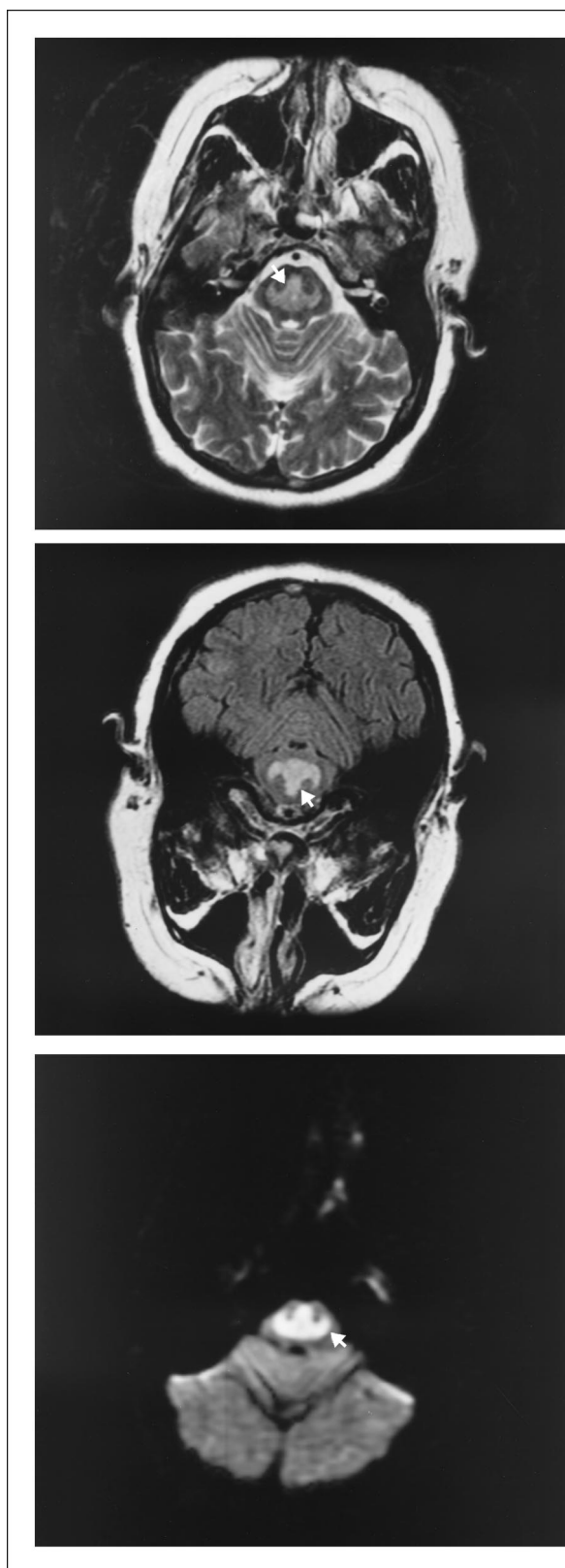
**TO THE EDITOR:** A 40-year-old previously healthy Chinese woman presented with progressive right thigh pain for 10 days. Her medical history was unremarkable except for menorrhagia since menarche, for which she irregularly took iron tablets prescribed by her family physician. Physical examination showed pallor. Passive straight-leg raising was reduced to 45 degrees on the right side, limited by pain radiating from the posterior thigh to the posterior and lateral aspect of the leg, with Lasègue sign. Blood pressure was 125/80 mm Hg, and pulse was sinus at 84 beats/min. Other physical findings were normal. Hemoglobin level was 71 g/L, mean corpuscular volume was 69 fL, leukocyte count was  $13 \times 10^9$  cells/L, and platelet count was  $35 \times 10^9$  cells/L. Serum sodium level was 140 mmol/L, potassium level was 3.9 mmol/L, creatinine concentration was 95  $\mu$ mol/L (1.1 mg/dL), alkaline phosphatase level was 2.15 nkat/L (normal range, 0.93 to 1.98 nkat/L), hepatic aminotransferase levels were just above the upper limits of normal, bilirubin level was 16  $\mu$ mol/L (0.94 mg/dL), and  $\gamma$ -glutamyltranspeptidase level was 50 IU/L (normal range, 7 to 32 IU/L). Results of radiography of the lumbosacral spine were normal. The patient received a transfusion but developed sudden hemodynamic collapse and died. Postmortem examination revealed ruptured hepatocellular carcinoma and positive results on tests for hepatitis B surface antigen.

Hepatocellular carcinoma is prevalent in southeast Asia, where hepatitis B virus infection is endemic (1). Its presentation ranges from incidental finding on surveillance detection (2) to spontaneous rupture causing acute hemoperitoneum and hypovolemic shock (3). Subclinical rupture of hepatocellular carcinoma is often difficult to diagnose. Sciatica as an initial manifestation has not been reported before to our knowledge and is certainly uncommon. Its presence in association with unexplained anemia, mild liver function derangement, and the hepatitis B carrier state should arouse suspicion of subclinical bleeding causing nerve-root irritation to the lumbosacral region. Early detection of hepatocellular carcinoma would allow lifesaving means of hemostasis, such as hepatic arterial embolization or staged hepatic resection (4).

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Figure. Findings on magnetic resonance imaging.



**Top.** Axial T2-weighted image through the brainstem. **Middle.** Fluid-attenuated inversion recovery image through the brainstem. **Bottom.** Diffusion-weighted image. Arrows indicate a process compatible with central pontine myelinolysis.

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#### Central Pontine Myelinolysis

**TO THE EDITOR:** A 42-year-old woman receiving hydrochlorothiazide for hypertension presented with nausea, vomiting, diarrhea, shock, and dehydration after binge drinking of vodka and mixed hard liquor. Serum sodium level at admission was 97 mmol/L; the patient required 4 L of intravenous normal saline infusion to achieve hemodynamic stability. Serum sodium level gradually normalized within the next 4 days (<1 L of sodium correction per hour), but the patient's course was complicated over the next 7 days by dysarthria, mutism, facial and neck weakness, and profound quadriplegia with spastic flexion of the lower limbs and Babinski signs.

On magnetic resonance imaging, an axial T2-weighted scan (Figure, top) and a fluid-attenuated inversion recovery scan (Figure, middle) through the brainstem demonstrated striking abnormal signal consistent with edema in the central tracts of white matter. Additional diffusion-weighted imaging (Figure, bottom) revealed abnormal signal consistent with restricted diffusion, implying an acute process compatible with central pontine myelinolysis.

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#### CORRECTION

##### Correction: Identification of Persons at High Risk for Type 2 Diabetes Mellitus

In an article on the identification of persons at high risk for type 2 diabetes mellitus (1), the formula in the Appendix on page 581 contained an error. The formula should read  $p = 1/(1 + e^{-x})$  rather than  $p = 1/(1 - e^{-x})$ .

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