

Correspondence



Activated Protein C for Severe Sepsis

To the Editor: In this issue of the *Journal*, Warren et al.¹ and Siegel² offer their views on the approval of drotrecogin alfa (activated), or recombinant human activated protein C, for the treatment of severe sepsis. We concur with Dr. Siegel's comments regarding the extensive testing to ensure the potency and consistency of drotrecogin alfa (activated) used in the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial.³ It is fortunate that the master cell bank used to produce the drug administered in the latter portion of the trial will be sufficient to meet clinical needs for several decades.

The PROWESS protocol amendment, which was developed in a blinded fashion very early in the trial and approved by the Food and Drug Administration, clarified the entry criteria as outlined in Table 1. Our intent was to enroll patients with a high likelihood of dying from severe sepsis and a low likelihood of dying from other causes. In addition, we wished to exclude patients in whom life support might be curtailed during the 28-day study period.

The observed absolute reduction in the risk of death was greatest among the most seriously ill patients, including those with coexisting conditions and advanced age. This is an expected finding with effective treatment of any condition for which the risk of death varies widely. Data from PROWESS on the quartile of the Acute Physiology and Chronic Health Evaluation (APACHE II) score suggest this effect, but as Warren et al. indicate, use of this score in clin-

ical practice is problematic for many reasons. The common technique of predicting the prognosis according to the number of dysfunctional organs showed that the absolute risk reduction for mortality was 1.7 percent (relative risk reduction, 7.8 percent) among patients with a single dysfunctional organ and 7.4 percent (relative risk reduction, 21.8 percent) among those with two or more dysfunctional organs. A large number of subgroups were examined, and only one did not meet the trial definition of subgroup consistency. This was the subgroup containing patients in the lowest interleukin-6 quartile; the treatment benefit for these patients was larger than that for the entire population.

Drotrecogin alfa (activated) has now been administered to more than 2786 patients with severe sepsis in controlled and open-label trials, and overall mortality has been between 25.1 percent and 26.1 percent. We conducted an independent review of all suspected intracranial hemorrhages. The current rate is 0.5 percent (hemorrhages in 13 of the 2786 patients) during the infusion period; 9 of the 13 occurred in patients with a platelet count of less than 30,000 per cubic millimeter, meningitis, or both. Patients with a platelet count of less than 30,000 per cubic millimeter were excluded from the PROWESS trial. The intracranial-hemorrhage rate of 2.5 percent cited by Warren et al. was based on unvalidated data in fewer than 600 patients. Clinicians should not treat patients with contraindications and should avoid treating patients with profound thrombocytopenia, markedly prolonged prothrombin times, or both. The mortality rates reported in the PROWESS trial include any deaths due to bleeding, so that the 6.1 percent absolute benefit with respect to mortality (13 percent for patients with an APACHE II score of more than 25) takes bleeding into account.

Although clinicians can already incorporate level I evidence from PROWESS into their practice to obtain life-saving benefit for their patients, our understanding of the role of activated protein C in severe sepsis will be enhanced by additional studies, including long-term follow-up studies and studies of children, patients with neutropenia and trans-

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TABLE 1. AMENDMENTS TO THE ENTRY CRITERIA FOR THE PROWESS TRIAL.*

ORIGINAL PROTOCOL	AMENDED PROTOCOL
Inclusion criteria	
PaO ₂ :FiO ₂ based on arterial blood gas results or conversion of cutaneous oxygen saturation to calculate PaO ₂ ; use of cutaneous oxygen saturation to calculate PaO ₂ :FiO ₂ ratio required approval from coordinating center	PaO ₂ :FiO ₂ must be based on arterial blood gas results
Metabolic acidosis defined as either arterial blood pH <7.3 or elevated venous blood lactic acid concentration	Metabolic acidosis defined as arterial blood pH <7.3 and elevated lactic venous blood acid concentration
Exclusion criteria	
Known or suspected portal hypertension	End-stage liver disease as evidenced by esophageal varices, chronic jaundice, cirrhosis, or chronic ascites
Survival not expected, given preexisting medical conditions	Survival not expected, given preexisting uncorrectable medical conditions, or death imminent; approval from coordinating center required for enrollment of patients with cancer
Advance directive prohibiting life support other than cardiopulmonary resuscitation	Advance directive prohibiting life support other than cardiopulmonary resuscitation, or absence of family commitment to aggressive management
No organ-transplant exclusions	Bone marrow, lung, liver, pancreas, or small-bowel transplantation (patients with renal or heart transplants still eligible)
Inclusion criteria present for more than 24 hours; drug administration to begin within 24 hours after randomization, such that a maximum of 48 hours allowed from time of meeting criteria for severe sepsis to treatment	First sepsis-induced organ failure present for more than 24 hours (clarifying which specific event actually started the clock); drug administration to begin within 24 hours after randomization, such that a maximum of 48 hours allowed from development of first sepsis-induced organ failure to treatment

*PaO₂ denotes the partial pressure of arterial oxygen, and FiO₂ the fraction of inspired oxygen.

plant recipients, and patients at low risk for death as determined in the PROWESS trial.

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Low-Dose Heparin for Severe Sepsis

To the Editor: In their report on the efficacy of activated protein C in reducing mortality from sepsis at 28 days (March 8, 2001, issue),¹ Bernard et al. presented the results of a retrospective subgroup analysis, which showed that the administration of low-dose heparin, in addition to activated

protein C, had no effect on safety.¹ Heparin and low-molecular-weight heparin are anticoagulants with antiinflammatory properties.² Heparin is recommended for prophylaxis against thromboembolism in patients with sepsis.³ We conducted a study to determine whether the administration of heparin affected efficacy, hypothesizing that the use of low-dose (or low-molecular-weight) heparin would improve survival in patients with sepsis.

We searched Medline for reports published between 1991 and 2001 in order to identify trials of treatment for sepsis that were of high methodologic quality, in which the use of heparin was allowed, and in which mortality rates could be determined for patients who received heparin and those who did not. We found two trials, one evaluating activated protein C^{1,4} and one evaluating antithrombin III.⁵ Seventy-five percent of the patients in one study¹ and 70 percent of the patients in the other study⁵ received heparin or low-molecular-weight heparin. Among 1995 pooled placebo recipients from the two trials, the odds of survival for the patients who received heparin, as compared with those who did not, was 1.45 (95 percent confidence interval, 1.18 to 1.78; P<0.001) (Table 1). In each trial, heparin use was associated with improved survival among placebo recipients. Heparin is relatively inexpensive (in contrast, a 96-hour infusion of activated protein C costs \$6,700).

Our findings are hypothesis-generating only, and caution is warranted in their interpretation. The primary limitation is that the administration of heparin was not randomly as-

TABLE 1. SURVIVAL AT 28 DAYS AMONG PATIENTS WITH SEPSIS WHO RECEIVED LOW-DOSE (OR LOW-MOLECULAR-WEIGHT) HEPARIN AS COMPARED WITH THOSE WHO DID NOT.*

TRIAL AND TREATMENT GROUP	SURVIVAL AT 28 DAYS		ODDS OF SURVIVAL (95% CI)	P VALUE
	YES	NO		
APC trial				
Placebo recipients			1.66 (1.19–2.31)	0.002
Heparin	458	179		
No heparin	123	80		
APC recipients			0.96 (0.67–1.38)	0.80
Heparin	476	158		
No heparin	164	52		
ATIII trial				
Placebo recipients			1.34 (1.04–1.73)	0.03
Heparin	514	296		
No heparin	195	150		
ATIII recipients			0.94 (0.72–1.21)	0.62
Heparin	489	318		
No heparin	220	134		
All placebo recipients			1.45 (1.18–1.78)	<0.001
Heparin	972	475		
No heparin	318	230		

*CI denotes confidence interval, APC activated protein C, and ATIII antithrombin III.

signed, and selection bias is therefore possible (i.e., heparin might have been withheld from patients at higher risk for bleeding and also for death). However, we consider this explanation unlikely, since both trials administered experimental anticoagulants and excluded patients at high risk for bleeding. We estimate that the number needed to treat with heparin to prevent one death is 11, but this effect size is also uncertain, because the heparin dosage was not controlled.

Treatment with activated protein C represents an important advance in the care of selected patients with sepsis. Further study of low-dose heparin and related agents in such patients is warranted.

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Oophorectomy in Carriers of *BRCA* Mutations

To the Editor: Kauff et al. (May 23 issue)¹ present data suggesting that salpingo-oophorectomy provides protection against breast or gynecologic cancer in women with a *BRCA1* or *BRCA2* mutation. Although the follow-up period was relatively short and overall survival data are not yet available, the authors should be applauded for undertaking the only known prospective study of its kind. Since there are other options for reducing the risk of breast cancer,^{2,3} we believe that the benefit of salpingo-oophorectomy should be evaluated separately in women with breast cancer and in those with gynecologic cancer. In a separate analysis shown in Table 3 of the article by Kauff et al., the 95 percent confidence intervals for the hazard ratios for breast and gynecologic cancer both include 1 and hence fail to show statistical significance.

In Table 2 of the article, a Kaplan–Meier estimate shows a significant benefit in reducing the risk of gynecologic cancer but not of breast cancer. This analysis is limited by a potential bias introduced as a result of the fact that the authors excluded from the analysis the three cases of ovarian cancer found at surgery but included any potential early-stage cancers in the surveillance group. Figure 1 of the article shows that 5 of the 12 cancers in the surveillance group were

detected during the first eight months, whereas no cancers were detected in the surgery group. This observation is consistent with a bias due to the delayed detection of tumors in the surveillance group.

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To the Editor: Rebbeck et al. (May 23 issue)¹ and Kauff et al. demonstrate that prophylactic oophorectomy in women with a *BRCA1* or *BRCA2* mutation significantly decreases the risk of ovarian and breast cancer. Clarification of these data is important for clinical practice. Although the two studies showed that the risks of both cancers are significantly reduced after prophylactic oophorectomy, the data reported by Rebbeck et al. showed that the residual risk of ovarian cancer is very low (4 percent), whereas the residual risk of breast cancer remains high (47 percent). The residual risk of breast cancer among women with *BRCA* mutations certainly remains high enough to warrant additional management strategies (e.g., surveillance, chemoprophylaxis, and in some cases, prophylactic mastectomy). Also, most of the benefit of oophorectomy in terms of the reduction in the risk of breast cancer was found in premenopausal carriers of *BRCA* mutations who did not have a history of breast cancer. Rebbeck et al. did not report the effects of prophylactic oophorectomy according to menopausal status, but among women who were 50 years of age or older, the hazard ratio for breast cancer was 0.52. However, the 95 percent confidence interval was quite wide and included 1.0. In addition, for women with unilateral breast cancer diagnosed before the age of 50 years, prophylactic oophorectomy may substantially reduce the risk of cancer in the contralateral breast.² Thus, postmenopausal women should not be advised that prophylactic oophorectomy is effective in reducing their risk of breast cancer. Our approach to counseling high-risk women is to explain that prophylactic oophorectomy is mainly a means of reducing the risk of ovarian cancer, with the added potential benefit, for some women, of reducing the risk of breast cancer.

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To the Editor: Kauff et al. and Rebbeck et al. report that prophylactic oophorectomy reduced the risks of *BRCA1*- or *BRCA2*-related gynecologic cancer and hereditary breast cancer. As Haber notes in the accompanying editorial,¹ a mean age for the entire data set of 50.8 years at the time of the diagnosis of ovarian cancer supported the recommendation of delaying risk-reducing oophorectomy until the completion of childbearing, but such a delay may be problematic in the case of hereditary breast cancer. Notably, in the study by Kauff et al., hereditary breast cancer had developed in 70 percent of the women with a *BRCA* mutation when prophylactic surgical menopause was deferred until 47.5 years of age.

Moreover, the effect of surgical menopause on hereditary breast cancer in women with a *BRCA* mutation may vary according to the type of mutation,² and age-specific incidence rates vary dramatically according to the genotype.^{2,3} Analogous to rates of sporadic breast cancer stratified according to estrogen-receptor status,^{4,5} rates of *BRCA1*-related hereditary breast cancer rise initially then flatten after menopause, as do rates of sporadic estrogen-receptor-negative breast cancer, whereas rates of *BRCA2*-related hereditary breast cancer increase regardless of menopausal status, as do rates of sporadic estrogen-receptor-positive breast cancer.^{2,3,6} A pattern of age-specific rates that rise and then stabilize after 50 years of age suggests that early endogenous hormonal interactions have a greater effect on carcinogenesis for estrogen-receptor-negative and *BRCA1*-related breast cancers than for estrogen-receptor-positive and *BRCA2*-related breast cancers.^{2,4,5} Therefore, early prophylactic oophorectomy may be very important for the prevention of *BRCA1*- and *BRCA2*-related breast cancer, especially *BRCA1*-related hereditary breast cancer, but this should be tested in studies stratified according to whether women have *BRCA1* or *BRCA2* mutations. Combining carriers of *BRCA1* mutations and carriers of *BRCA2* mutations may blur the etiologic differences, typified by two fundamentally different patterns of the age-specific risk of breast cancer.

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To the Editor: Kauff et al. excluded three patients found to have early gynecologic cancer at the time of prophylactic salpingo-oophorectomy, whereas the comparison (surveillance) group included five women who had gynecologic cancer after a mean of only 17 months. Some of these five cancers were almost certainly present at the beginning of the follow-up period. The exclusion of patients with preexisting cancers in one study group only, in a study designed to determine the incidence of cancer, biases the results substantially, particularly given the short mean follow-up of two years.

The correct approach is to include the women in whom gynecologic cancers were detected at the time of prophylactic salpingo-oophorectomy. The authors mention in their discussion that with this approach, the hazard ratio for the development of breast or gynecologic cancer would be 0.37 (0.12 to 0.90), which is still statistically significant. However, they fail to point out that the correct analysis would very much weaken their conclusions about, for example, the estimated proportion of women who would be free from gynecologic cancer at five years (given in Table 2 of their article as 98 percent in the oophorectomy group vs. 83 percent in the surveillance group) or free from breast or gynecologic cancer at five years (given as 94 percent, vs. 69 percent).

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The authors reply:

To the Editor: Anderson et al. raise the possibility that estrogen deprivation may have distinct effects on early breast carcinogenesis in carriers of *BRCA1* mutations as compared with carriers of *BRCA2* mutations. We agree that, for this reason, it is important to perform mutation-specific analyses in future studies. The results of studies that have examined the preventive effects of tamoxifen on *BRCA1*-associated breast cancer as compared with *BRCA2*-associated breast cancer have been inconsistent.^{1,2} However, because of the significantly elevated risk of postmenopausal ovarian cancer in carriers of some *BRCA2* mutations,³ there is a rationale apart from breast-cancer prevention for considering risk-reducing salpingo-oophorectomy in such women.

Since the reduction in the risk of breast cancer that is associated with salpingo-oophorectomy presumably results from estrogen deprivation, we agree with Peshkin et al. that the greatest preventive effect with respect to breast cancer

is likely to occur in women who are premenopausal at the time of surgery; 66 percent of the women opting for surgery in our series were 50 years of age or younger, and 83 percent were 55 or younger.

Both Zhuang et al. and Whitfield suggest that the optimal statistical analysis of our data would include the three clinically occult gynecologic cancers detected at the time of surgery as events in the surgical group. When this analysis was performed, the reduction in the risk of breast or ovarian cancer remained significant, as Whitfield notes. In our study and that of Rebbeck et al., cancers detected at the time of preventive surgery were not included in the primary comparison of surgery and surveillance, since the incidence of cancer after surgery is the clinical end point of greatest concern to women who are deciding whether to undergo the procedure. Furthermore, in considering the effect on survival of occult cancers identified at the time of planned preventive surgery, it is important to recall the limitations of screening for ovarian cancer. Nine occult gynecologic cancers, all stage I, were found among a total of 360 women undergoing risk-reducing oophorectomy in our series and that of Rebbeck et al.; it remains unclear whether a similar proportion of ovarian cancers detected by screening will be early stage cancers.

We agree with the comments of Zhuang et al. regarding the importance of separately evaluating the effect of salpingo-oophorectomy on the incidence of breast cancer and gynecologic cancer. Rebbeck et al. provide retrospective data indicating that prophylactic oophorectomy was effective in reducing the risk of each of these end points separately. Continued follow-up of our cohort will provide prospective data for a better definition of the magnitude of this effect.

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To the Editor: Zhuang et al. state that Kauff and colleagues performed the only known prospective study of bilateral prophylactic oophorectomy in women with *BRCA* mutations. Although we included women ascertained to have undergone bilateral prophylactic oophorectomy before their ascertainment for participation in the study or genetic testing (i.e., a "retrospective" sample), we also included women for whom ascertainment, testing, or both occurred before bilateral prophylactic oophorectomy was performed. This portion of our sample (55 percent) represents a "prospective"

sample. We reported similar hazard ratios for both the total study sample (i.e., prospective and retrospective participants) and the subgroup of prospective participants. For example, the hazard ratio for ovarian cancer was 0.04 in the total sample and 0.02 in the prospective subgroup. This suggests that our primary results were not severely biased by the inclusion of the retrospective participants. More important, our data and those reported by Kauff et al. provide compelling evidence that oophorectomy is strongly associated with a reduction in the risk of cancer. On the basis of the compelling evidence now available that bilateral prophylactic oophorectomy almost eliminates the risk of ovarian cancer in carriers of *BRCA1* or *BRCA2* mutations, we believe this intervention should be the standard of care after childbearing in such women and that additional prospective studies would be unethical.

Anderson et al. suggest that combining women with *BRCA1* mutations and women with *BRCA2* mutations may be misleading if the patterns of risk (and therefore risk reduction) differ between genes. A limitation of our data is the small number of cancers that developed after bilateral prophylactic oophorectomy and the small number of *BRCA2*-mutation carriers and, thus, the limited power of the study to evaluate the *BRCA2* group separately. We continue to accumulate data and will address this issue as our sample expands.

Peshkin et al. argue that postmenopausal bilateral prophylactic oophorectomy would not be predicted to reduce the risk of breast cancer and that management of breast-cancer risk in women who undergo bilateral prophylactic oophorectomy after menopause may therefore require additional intervention. Similarly, Anderson et al. address the difficulty in determining the optimal timing of oophorectomy, which may have a significant benefit in terms of reducing the risk of ovarian cancer, even if the procedure is delayed until after childbearing, but may have more limited value for reducing the risk of breast cancer. Although both points are valid, we believe that since the reduction in the risk of ovarian cancer that is associated with bilateral prophylactic oophorectomy is almost complete and the age at diagnosis is unpredictable, bilateral prophylactic oophorectomy should be performed once childbearing is finished, regardless of the woman's age at that time. The risk of breast cancer in women who use postoperative estrogen-replacement therapy until the age of 50 years (the approximate time of natural menopause) should be lower than the risk in women who defer surgery until menopause.

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Mast Cells in Airway Smooth Muscle

To the Editor: Brightling et al. (May 30 issue)¹ report that, in patients with asthma, there is mast-cell infiltration of airway smooth muscle associated with hyperresponsiveness. As pointed out by the authors and by Black in an accompany-

ing editorial,² it is not known whether such infiltration is a specific feature of asthma or a general characteristic of obstructive airway diseases.

In our study of a method of inflammation analysis,³ we found high concentrations of mast cells (63 per square millimeter) in the smooth muscle of bronchial specimens obtained from smokers. To confirm that mast cells also infiltrate smooth muscle in obstructive airway diseases other than asthma, we performed an immunohistochemical analysis of bronchi obtained from 13 smokers with chronic obstructive pulmonary disease (COPD) who were undergoing lung resection. Proximal bronchi were dissected from a normal part of the lung specimen and processed in glycol methacrylate, as described by Brightling et al. Within the smooth muscle, we found 61.4 tryptase-positive cells per square millimeter (range, 26 to 74) and 42 chymase-positive cells per square millimeter (range, 16 to 82) — levels even higher than those reported in asthma. In a study of the peripheral bronchi of smokers,⁴ we also found infiltration of smooth muscle by both subtypes of mast cells. Interestingly, the number of chymase-positive cells within smooth muscle was correlated with the degree of air trapping, which reflects peripheral obstruction.

Taken together, these observations provide some evidence that mast cells also interact with smooth muscle in COPD. In addition, they raise the question of the smoking status of patients included in the study by Brightling et al., since cigarette smoking may account for differences observed among the groups.

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The authors reply:

To the Editor: The data of Dr. Tunon-de-Lara and colleagues on mast-cell density in the smooth muscle of the proximal airways of subjects with COPD raise the possibility that mast-cell infiltration into airway smooth muscle is a feature of COPD as well as of asthma. However, conclusions cannot be drawn, since they do not report data from well-characterized normal controls or from subjects with asthma. We would be cautious about directly comparing mast-cell density between our study and theirs because of methodologic differences between the studies, particularly in the measurement of the area of airway smooth muscle and in the depth of the airway smooth muscle sampled.

We are puzzled by the suggestion of Tunon-de-Lara and

colleagues that, in our study, the increased density of mast cells in airway smooth muscle in subjects with asthma may be due to smoking, since they previously reported no difference between smoking and nonsmoking subjects in mast-cell numbers in airway smooth muscle.¹ Even if smoking had such an effect, it probably would not account for the differences observed in our study, since all of our subjects were current nonsmokers with a smoking history of less than 10 pack-years.

The findings of Tunon-de-Lara and colleagues highlight the need for detailed, carefully controlled, immunopathologic study of larger airway specimens in a wider range of obstructive lung disease than those we studied. Interestingly, one such study² has reported that mast-cell numbers and mast-cell degranulation were greater in the small airways of subjects who had asthma but who died of other causes, than in the airways of normal controls.

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Physician-Assisted Death

To the Editor: According to Ganzini and Block (May 23 issue),¹ “experts assert that with excellent palliative care, most requests for hastened death would not be made.” They consider rates of physician-assisted death of 10 to 20 percent, as reported for patients with cancer and amyotrophic lateral sclerosis (ALS) in the Netherlands, unacceptably high. Expert opinions offer no proof or strong evidence in this regard. The rate may also depend, for example, on “moral questions surrounding life, suffering, and death.”² Population polls in the Netherlands have repeatedly shown that a majority is in favor of physician-assisted death in well-defined circumstances, including those in which there is no hope for the future, unbearable suffering, and repeated and consistent requests for such assistance. For many Dutch people, this mode of death is not taboo and there is no moral objection to it. The best that patients with ALS may hope for in the terminal stage of their disease is to go on living for a limited period under a blanket of morphine. Is it so surprising that 17 percent of Dutch patients with ALS are not looking forward to this prospect and that they prefer an almost certainly gentle and quick death?

Ganzini and Block indicate that excellent palliative care is available for, at most, 50 percent of patients in the United States who die at home. What happens to patients with ALS who are not fortunate enough to receive excellent care in the terminal stage of their disease and who ask for a has-

tened death? Is it acceptable that the law forbids physicians to help them?

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To the Editor: The report by Veldink et al.¹ and the accompanying editorial by Ganzini and Block mention that loss of autonomy and control contributes to the high frequency of requests for physician-assisted death in patients with ALS. If patients know that assistance in dying is available, it may relieve their anxiety and restore their sense of control. After the legalization of physician-assisted suicide in Oregon, more than a third of the persons who received a lethal prescription did not ingest the medication.^{2,3}

I worked with an anxious patient with ALS who feared loss of control. She threatened to jump out the window so that “it would be over,” but when assured that her primary clinicians would provide terminal sedation when she wanted it, her anxiety melted, her threats ceased, and she later died peacefully in her sleep without any death-hastening interventions. Terminal sedation, which is legal throughout the United States, has in common with physician-assisted suicide the hastening of death and the relief of suffering. In terminal sedation, however, hastened death is regarded as an unwanted but unavoidable side effect, rather than an intended outcome.⁴

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To the Editor: The data presented by Veldink et al. add to a growing body of evidence that suggests that despite our best efforts at cure and palliation, there will continue to be patients for whom suicide is preferable to continued suffering. Although the focus of our attention and resources should be on improving treatment, the rights and needs of patients who wish to commit suicide but who require assistance in doing so cannot be overlooked. The erroneous assumption that this assistance must be provided by the

treating physician hopelessly complicates the ethical dilemma of assisted suicide with legitimate concern about potential conflicts of interest or inappropriate selective application. This complication can be circumvented by limiting the activities of physicians to the provision of treatment, palliation, and prognostic information to patients with incurable diseases. Patients who still seek assistance with suicide should be able to turn to licensed nonphysicians who can provide such assistance in a carefully prescribed and scrutinized way. If society's consensus is that assisted suicide is acceptable, it need not and should not be physicians who provide it.

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The authors reply:

To the Editor: Leeman addresses the important issues of reasons why patients request physician-assisted death. Few researchers have asked patients why they want physician-assisted suicide or euthanasia.¹ Anxiety and pain correlate with an interest in physician-assisted death but clearly do not fully explain this interest. We agree that the knowledge that assistance in dying is available may be reassuring to patients and may restore part of their autonomy. Many patients who request assistance in dying or who receive lethal prescriptions do not die with a physician's assistance.^{2,3} Nevertheless, it cannot be inferred that the availability of assistance in dying leads to increased feelings of control. As Leeman notes, such an inference is based on anecdotal evidence and not on the results of carefully designed studies.

Leeman's second point relates to the option of terminal sedation in terminally ill patients. We do not know of any study on terminal sedation in patients with ALS; in contrast, there have been many such studies in patients with cancer. In the latter patients it is unlikely that deep sedation hastens death, unless hydration and nutrition are also foregone. There are essential differences between patients with cancer and patients with ALS, including the fact that terminally ill patients with ALS have respiratory insufficiency. As a consequence, the use of benzodiazepines for terminal sedation in patients with ALS will have the added effect of hastening death in a manner analogous to the use of opiates. Although terminal sedation can be an adequate palliative treatment for terminally ill patients, we do not see the need for it among patients who are terminally ill with ALS.

Druck sees the practice of physician-assisted suicide as immoral and contrary to a physician's oath, and he therefore proposes that licensed nonphysicians carry out this practice. However, we think that it should be physicians who provide assistance with dying, for several reasons. Physicians are medically and technically qualified to perform this task, given the possible complications.⁴ End-of-life decisions, including those involving terminal sedation, euthanasia, and physician-assisted suicide, can be seen as last options in programs of palliative care. Discussing these issues with patients and their relatives and making a final decision require the knowledge, experience, and compassion of a physician and should be part of the physician-patient relationship. Of course, there

is a conflict of duties, but this conflict is not resolved by bringing in a nonmedical person.

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The editorialists reply:

To the Editor: We contend that the rate of physician-assisted death in the Netherlands is unacceptably high. Nevertheless, we agree with Jennekens and Kater that this contention does not have strong empirical support. We remain troubled by the absence of evidence that Dutch patients receive adequate palliative care as an alternative to euthanasia. We hope that our Dutch colleagues proceed with studies to address these concerns.

In the United States, one's fortune is an important determinant of access to excellent palliative care. A system in which patients may choose euthanasia primarily because they cannot get basic treatment for their symptoms is unacceptable. If a patient requests euthanasia and the physician anticipates that treatment of his or her symptoms could result in a change of preference, the physician's obligation is to use all available means to help in palliation.

Some patients take comfort in knowing about the option of refusing life-sustaining treatment, including food and fluids. A discussion of terminal sedation may be valuable for patients who fear that their physical suffering at the end of life will go untreated. In our clinical experience with patients who persistently request assisted suicide, these alternatives may not be accepted by those who have a strong desire to control the timing and manner of their death or those who find the idea that they will be dependent on others before death intolerable.

Not all health care professionals agree that existential suffering warrants acts that hasten death, although these acts may be legal. Not all physicians are comfortable in caring for a patient whose request for terminal sedation represents a deliberate attempt to hasten death.¹

(The views expressed are those of the authors and do

not necessarily represent those of the Department of Veterans Affairs.)

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Financial Associations of Authors

To the Editor: In 1990, I proposed the *Journal's* stringent policy for authors of review articles and editorials¹ because I thought it was the best way to preserve our readers' confidence in the objectivity of those articles. The recent extraordinary expansion of academic-industrial ties arguably may necessitate some revision of that policy, as Drs. Drazen and Curfman suggest in their editorial (June 13 issue),² but I do not think the new guidelines are sufficiently strict or explicit. A limit on honorariums of \$10,000 per annum per company still allows total payments large enough to influence authors' attitudes. And prohibition of "major" research support might reasonably be construed by authors who are also researchers as still allowing industrial support of 10 or 20 percent of their research program — an amount that could well bias the author in favor of the sponsor's products. Mere disclosure of these ties will not be a sufficient remedy, although it certainly is necessary.

Editors are on safer ground when they prohibit such conflicts of interest altogether rather than attempt to manage them by establishing flexible guidelines and negotiating with authors. That is why, despite the changing environment, I am not fully persuaded of the need to modify the *Journal's* policy.

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To the Editor: Your policy of allowing authors with financial ties to the pharmaceutical industry to write related reviews and editorials will have two serious consequences: bad science and a betrayal of the public trust.

Bodenheimer cites several instances in which industrial funding may have influenced the conclusions of published articles.¹ Angell and Kassirer² decried the publication of an editorial in the *Journal* that presented a favorable risk-ben-

efit analysis of antiobesity drugs after it was revealed that the authors were paid consultants for the companies marketing dexfenfluramine. Gerard Piel, editor of *Scientific American* from 1948 until 1986, reviewed the chief scientific advances of the 20th century in the book *The Age of Science* but consciously omitted the topic of health care. He wrote, "The intrusion of market forces compromises work in the life sciences especially. Whole university medical-school departments now operate as subsidiaries of pharmaceutical companies."³

Nowadays, corporate affiliations are more common than academic titles. Academic physicians may not be willing to criticize their sponsors, whose final responsibility is to shareholders, not to patients or physicians.⁴

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To the Editor: Your editorial is a step forward in addressing conflicts of interest of authors of editorials and review articles. It presupposes that such conflicts — whether real or apparent — can be managed instead of serving as a reason for precluding authorship entirely. This position is realistic. It is consistent with the policies adopted by most academic institutions and governmental funding agencies — policies that, in turn, reflected the increase in industry-sponsored biotechnology relationships stimulated by federal legislation such as the Bayh-Dole Act and the Stevenson-Wydler Technology Innovations Act.

A residual issue is whether this approach ought to be applied to all submissions. Currently, medical journals have a liberal policy with respect to authors of other types of articles. Journals publish good-faith disclosures of conflicts of interest supplied by the authors but do not determine whether a conflict is important enough to result in the rejection of an original-research article. Yet, subtle biases can distort the design, analysis, and reporting of original research. Why not extend the policy of managed conflicts of interest to all submissions, while applying clear rules for determining whether a conflict is a disqualifying one? The threshold for disqualification would doubtless be lower for editorials and review articles, but the same processes could nonetheless be applied to all submissions.

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To the Editor: When will we finally be rid of paternalism? Your editorial represents, by and large, a meaningful advance

in selecting authors for review articles. However, the policy remains both ambiguous and unsettling. The ambiguity lies in the fact that it is not completely clear whether the annual income limits pertain to each relationship or to the sum of relationships. If the limits pertain to each one, authors could have a mighty incentive to support wide rather than narrow use of the class of agents reviewed.

With respect to the question of whether “acceptable” payments will be disclosed to readers, it is unsettling that the *Journal* editors seek to maintain control over whether financial associations are disclosed. It is rather for the readers ultimately to decide the extent to which a report is biased by conflicts of interest. To do that there must be complete disclosure, and such disclosure should be automatic rather than discretionary on the part of editors. Otherwise, editorial bias may influence our perceptions of the objective validity of a paper.

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The editors reply:

To the Editor: Dr. Relman acknowledges that some revision of the *Journal's* policy was necessary but is concerned that our new guidelines are neither strict nor explicit. Our revised guidelines are strict and explicit; they are in agreement with the well-accepted community standard set by the National Institutes of Health and the Association of American Medical Colleges. These organizations represent the physician-scientists whose original research we publish. Our policy sets a strict ceiling on financial interests. We do not negotiate with authors. In each case, we make an independent assessment and may choose not to consider an article by an author whose financial associations are within the limits of the policy if we believe that the associations could preclude objectivity on the part of the author or give that appearance. This is a time-consuming task that we take very seriously.

We would prefer that therapeutic research not be funded directly by commercial entities, but we are not the decision makers in this matter. We encourage the initiation of an informed national debate on this subject. However, as long as companies serve directly as research sponsors, medical journals will need to have policies to safeguard against conflicts of interest. There is no perfect policy. We have a “zero-tolerance” approach in that our guidelines are clear and we have no leniency for authors who fail to disclose their financial associations fully. However, the solution favored by Drs. Relman and Bittl would exclude from the *Journal* the views of some of our top researchers and would instead favor authors who are not actively working in the field. For editorials and review articles, we prefer a policy that sets a clear de minimis for financial interests but allows editors to exercise judgment within that explicit boundary. We disagree with Dr. Ferris, however; we believe that editorial decisions on original-research reports should be based on the quality of the research, not on the type of sponsorship.

In response to Dr. Korenman, our policy is explicit and

sets the de minimis level at \$10,000 per commercial entity per year. To ensure transparency, we disclose all relevant financial interests of authors, regardless of the amount.

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Health Care Workers and Addiction

To the Editor: The report by Ostrowsky et al. (May 16 issue)¹ and the Perspective by Verghese² highlight the importance of impairment due to alcohol and drug dependence among physicians and other health care workers. Addiction spares no race or class in our society, and the economic, social, and personal costs make its treatment a priority.

We are troubled, however, by Verghese's strong emphasis on highly confrontational interventions in the treatment of addiction. Such interventions are not among the treatments with the most persuasive evidence of effectiveness. The outbreak described by Ostrowsky et al. involved the abuse of an opioid, fentanyl; addiction to opioids is treated most effectively with methadone, not with confrontation or drug-free or detoxification treatment. A number of behavioral interventions have also been shown in randomized trials to be effective in treating addiction. These include client-centered, nonconfrontational approaches such as motivational enhancement therapy,³ cognitive-behavioral therapy, and 12-step facilitation.⁴

Although observational studies of programs that use confrontational interventions with physicians who have addiction problems have shown positive results, no trials have compared such interventions with other approaches to treatment. Indeed, in one trial, confrontational interventions were associated with increased resistance and denial on the part of patients.⁵ Perhaps such resistance is not fundamental to addiction as traditionally understood but, instead, is shaped by the relationship between the provider and the patient. Reliance on confrontational interventions may keep physicians or others with addiction problems from seeking help at earlier stages of their addiction, knowing that coercive treatments might be mandated. This may fulfill the prophecy of denial rather than the promise of effective therapy.

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Dr. Vergheze replies:

To the Editor: Merrill and Marlatt point out that client-centered, nonconfrontational approaches such as motivational enhancement therapy are useful in treating addiction. The study they cite suggests that confrontational approaches increase patients' resistance and denial.¹ However, the subjects in that study were volunteers recruited by advertisements for a "free drinkers' check-up." It is difficult to extrapolate these results to physicians who surreptitiously abuse a drug while practicing medicine. Even a 50 percent reduction in the kinds of end points normally measured (mean drinking days per week or weekly peak blood alcohol levels) would be of little comfort to society if the subjects were practicing physicians. The goal of treatment for an impaired physician who wishes to practice medicine has to be complete abstinence and sobriety.

Many impaired physicians do voluntarily seek help, and they find a system in America that I think is not punitive but supportive and caring. For physicians who will not seek help and whose impairment is obvious to others, an inter-

vention is inevitable. I disagree with Merrill and Marlatt's characterization of the kind of intervention I described as "highly confrontational." One meaning of the word "confrontation" is simply a face-to-face meeting; confrontation does not in any way preclude empathy. It can be excruciatingly painful, sorrowful, and nerve-racking for spouses, children, friends, peers, and supervisors to bring about this face-to-face intervention. Their willingness to do so should stem from their concern for the life and livelihood of the physician.

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