

Correspondence



Interferon Gamma-1b for the Treatment of Idiopathic Pulmonary Fibrosis

To the Editor: Ziesche et al. (Oct. 21 issue)¹ report the findings of a preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis. Given that there is no successful medical therapy for idiopathic pulmonary fibrosis, with only lung transplantation holding promise for long-term survival, the authors deserve credit for performing this pilot project. Unfortunately, their findings do not justify the enthusiasm that this article has generated in the media and among people with this disease.

First, it is unclear that the patients studied had idiopathic pulmonary fibrosis.² The disease is uncommon; consequently, most centers are unable to enroll 18 patients over the course of a 22-month period. The incidence of cigarette smoking — a risk factor for idiopathic pulmonary fibrosis³ that also has an effect on survival — was not reported. An important consideration is the fact that the criteria used to define the features of idiopathic pulmonary fibrosis histopathologically and on high-resolution computed tomography are unclear and incomplete.^{2,4} Therefore, it is likely that some of the cases represent forms of idiopathic interstitial pneumonia — particularly, nonspecific interstitial pneumonia or chronic cryptogenic organizing pneumonia.

Second, the outcome and duration of survival among the patients in the study by Ziesche et al. are atypical.⁵ Standard treatment for more than six months was not effective, and seven patients required oxygen therapy (five at enrollment and two during the treatment phase). Since patients with idiopathic pulmonary fibrosis invariably have progressive disease, the absence of more severe disease in any of these patients is very unusual, especially given that there were three to seven years of follow-up.

Third, the treatment outcome was not clinically significant.² An increase of 10 percent in total lung capacity (or at least an increase of about 200 ml) is required for an improvement to be considered clinically significant. Thus, there was no clinically significant change in the total lung capacity in either the control group or the treatment group. The data on gas exchange are also problematic. Presumably, all arterial-blood gas measurements were made while the patients were breathing room air. It is difficult to compare the results of maximal exercise testing in a serial fashion, because the level of work performed must be controlled for. Since the methods used for the exercise study are not described, such a comparison is not possible. Even if we assume the outcome to be positive (stabilization in the face of previous worsening), similar short-term improvements have been reported with other agents. However, once treatment is tapered or stopped, the disease progresses, and with longer follow-up, treatment is shown to have had no effect on survival.

The promising preliminary data of Ziesche et al. should be viewed with caution. The use of interferon gamma-1b in clinical practice must await additional study. It should also be noted that in the accompanying editorial,⁶ du Bois reports that there is an ongoing study of the efficacy of interferon alfa for the treatment of idiopathic pulmonary fibrosis. I am not aware of this study; however, I am chair of the advisory committee of a multicenter study of interferon beta-1a for the treatment of idiopathic pulmonary fibrosis, sponsored by Biogen (Cambridge, Mass.). I receive a consulting fee for this role.

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1. Ziesche R, Hofbauer E, Wittmann K, Petkov V, Block L-H. A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 1999;341:1264-9.

2. Idiopathic pulmonary fibrosis: diagnosis and treatment: international consensus statement. *Am J Respir Crit Care Med* 2000;161:646-64.

3. Baumgartner KB, Samet JM, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1997;155:242-8.

4. Katzenstein ALA, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med* 1998;157:1301-15.

INSTRUCTIONS FOR LETTERS TO THE EDITOR

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5. BJORAKER JA, RYU JH, EDWIN MK, et al. Prognostic significance of histopathologic subsets of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;157:199-203.
6. du Bois RM. Interferon gamma-1b for the treatment of idiopathic pulmonary fibrosis. *N Engl J Med* 1999;341:1302-4.

The authors reply:

To the Editor: Although our study was conducted between 1996 and 1998, the survey of patients with idiopathic pulmonary fibrosis from various European countries had begun in 1994, which allowed enough time for the enrollment of our patients. All the patients were nonsmokers. We carefully considered the diagnostic criteria for idiopathic pulmonary fibrosis, taking into account the definition used by the pathology department of the Mayo Clinic.¹ In addition to established histopathological characterization of fibrotic lesions, we attempted to characterize the genes involved in the development of fibrotic lesions. Given our experience, we are convinced that, in addition to conventional procedures, the diagnosis of idiopathic pulmonary fibrosis must include molecular biologic assessment of fibrotic lesions to make sure that features compatible with the biologic changes at the cellular level are present that coincide with the clinical picture of the disease. Moreover, in addition to using the various exclusion criteria, we selected only patients whose condition did not respond to sufficient immunosuppressive therapy, which makes differential diagnoses, such as nonspecific interstitial pneumonia, rather unlikely.

The outcome, progression, and duration of idiopathic pulmonary fibrosis vary considerably. In our trial, patients with advanced fibrosis were excluded. The apparently better outcome of the patients in our study is explained by the strict enrollment criteria. Response to interferon gamma-1b decreases with greater duration of breathlessness at rest and other severe symptoms.

The treatment outcome was clinically significant in that there was a mean increase in total lung capacity of about 500 ml (or about 9 percent) per patient. Consequently, with a total lung capacity ranging from 4 to 6 liters, as was the case for the patients in our study, the improvement achieved by treatment with interferon gamma-1b is clinically important. Data on gas exchange were obtained while the patients were at rest and after maximal exertion, on the assumption that an improvement in gas exchange under both conditions would indicate a reduction of diffusion barriers. It should be noted that such an improvement was observed in all the patients who received treatment with interferon gamma-1b at rest and in seven of the nine patients after maximal exertion.

We tried to take a new approach to unravel the underlying disturbance of the cell biology in the development of fibrotic lesions in patients with idiopathic pulmonary fibrosis. We believe that the characterization of the genes involved in the inflammatory changes due to idiopathic pulmonary fibrosis is essential for understanding the pathology of idiopathic pulmonary fibrosis and provides the rationale for treatment with interferon gamma-1b.

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1. RYU JH, COLBY TV, HARTMAN TE. Idiopathic pulmonary fibrosis: current concepts. *Mayo Clin Proc* 1998;73:1085-101.

To the Editor: King addresses the issue of the selection of patients for research on idiopathic pulmonary fibrosis and the clinical significance of treatment outcomes. His observations underscore the need for further carefully targeted studies.

The final paragraph of my editorial should have referred to the ongoing study of interferon beta-1a, not interferon alfa. I look forward to the results of this study.

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Thalidomide in Multiple Myeloma

To the Editor: Singhal et al. (Nov. 18 issue)¹ report the results of a phase 2 study of thalidomide for the treatment of multiple myeloma and conclude that the drug can reduce serum and urine levels of paraprotein in some patients with refractory multiple myeloma. We are concerned that the maximal tolerated dose of thalidomide was not clarified in this study.

Thalidomide was started at a dose of 200 mg per day, and the dose was increased by 200 mg every two weeks, until a dose of 800 mg per day was reached. It is surprising that only 55 percent of the patients could tolerate receiving 800 mg per day of thalidomide. Although the authors emphasize that thalidomide had mild toxic effects and that grade 3 or 4 adverse effects were rarely observed, some adverse effects might have developed in 45 percent of the patients. These findings do not support their suggestion that thalidomide is a safe drug.

What is the minimal effective dose of thalidomide in treating multiple myeloma? Because high-dose thalidomide causes some unfavorable effects, as shown in this study, it will be important to determine whether the effect of thalidomide reported by Singhal et al. was dose-dependent.

We would also like to know whether the efficacy of this drug was influenced by the status of the multiple myeloma (i.e., the stage of the disease and the cytogenetic abnormality).

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Dr. Barlogie replies:

To the Editor: Kishi et al. correctly point out that our phase 2 study of thalidomide for the treatment of multiple myeloma was not designed to investigate dose intensity. The dose-escalation design we used permitted individual patients to receive their maximal tolerated dose, which we considered important in patients who had already received a sub-

stantial amount of chemotherapy. Patients who did not tolerate dose escalation beyond 400 mg probably would have had clinically significant toxic reactions at the 600-mg and 800-mg doses. Pharmacokinetic studies are needed to elucidate the reasons for the heterogeneity of toxic effects and responses at a given dose level that we observed. Furthermore, as suggested in the editorial accompanying our report,¹ several mechanisms may be involved in the antimyeloma activity of thalidomide, which, in turn, may be dose-related.

The minimal effective dose of thalidomide is unknown, but responses have been reported at doses as low as 50 to 100 mg in patients who had received less prior therapy than our patients had (Durie B: personal communication). We are now conducting a randomized trial to determine whether the inclusion of thalidomide at a dose of 400 mg during the induction, consolidation, and maintenance phases of a trial of high-dose chemotherapy improves results in patients with newly diagnosed multiple myeloma.² In another trial involving previously treated patients, we are evaluating two doses of thalidomide (50 mg and 200 mg) as maintenance therapy; the results should provide information on the dose-response effects of thalidomide in multiple myeloma.³

Kishi et al. also ask about prognostic factors and how they influence the response to thalidomide. We reported a high response rate among patients with a low plasma-cell-labeling index. In addition, in an analysis of all 180 patients enrolled in the trial, event-free and overall survival were significantly longer when the degree of bone marrow plasmacytosis was low and deletion of chromosome 13 was not found.⁴

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1. Raju N, Anderson K. Thalidomide — a revival story. *N Engl J Med* 1999;341:1606-8.
2. Munshi N, Desikan R, Anaissie E, et al. Peripheral blood stem cell collection (PBSC) after CAD+ G-CSF as part of total therapy II in newly diagnosed multiple myeloma (MM): influence of thalidomide (THAL) administration. *Blood* 1999;94:Suppl 1:578a. abstract.
3. Munshi N, Desikan R, Zangari M, et al. Chemoangiopathy with DT-PACE for previously treated multiple myeloma (MM). *Blood* 1999;94:Suppl 1:123a. abstract.
4. Desikan R, Munshi N, Zeldis J, et al. Activity of thalidomide (THAL) in multiple myeloma (MM) confirmed in 180 patients with advanced disease. *Blood* 1999;94:Suppl 1:603a. abstract.

Treatment of Primary Hyperparathyroidism

To the Editor: We take issue with some of the recommendations made by Utiger in his editorial on the treatment of primary hyperparathyroidism (Oct. 21 issue).¹ Measurement of serum calcium was advocated, with no mention of correction for abnormal serum albumin concentrations or measurement of serum ionized calcium. We and others have found that measurements of serum ionized calcium are superior to measurements of serum total calcium or albumin-corrected calcium in the diagnosis of primary hyperparathyroidism.^{2,3} In our study of 60 patients with pathologically confirmed primary hyperparathyroidism, 22 percent of the patients had corrected serum total calcium concentrations within the reference range, whereas all but 1 had high serum ionized calcium concentrations.² In addition, Thode et al. noted a diagnostic discordance between un-

corrected serum total calcium and ionized calcium concentrations in patients with high serum calcium concentrations and those with low serum calcium concentrations.³ We believe that in most patients with osteoporosis, especially postmenopausal women, serum ionized calcium should be measured to rule out primary hyperparathyroidism, which is a surgically correctable condition.

We do not believe that familial benign hypercalcemia can be distinguished from primary hyperparathyroidism by “careful history taking and measurements of urinary calcium.” The biochemical diagnosis of familial benign hypercalcemia is complex; measurements of serum parathyroid hormone and fasting urinary calcium excretion (corrected for the glomerular filtration rate) in combination provide the best means of discriminating between these disorders.⁴

Although preoperative imaging has improved substantially in recent years, particularly with the advent of technetium-99m sestamibi imaging, we do not believe the 1991 National Institutes of Health consensus recommendations for gland localization should be changed, as Utiger suggests. Surgical localization continues to be superior to preoperative imaging in patients who require neck exploration, particularly in those with mild hypercalcemia. Preoperative imaging should chiefly be considered if previous surgical exploration has failed.⁵

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1. Utiger RD. Treatment of primary hyperparathyroidism. *N Engl J Med* 1999;341:1301-2.
2. Glendenning P, Gutteridge DH, Retallack RW, Stuckey BGA, Kermode DG, Kent GN. High prevalence of normal total calcium and intact PTH in 60 patients with proven primary hyperparathyroidism: a challenge to current diagnostic criteria. *Aust N Z J Med* 1998;28:173-8.
3. Thode J, Juul-Jorgensen B, Bhatia HM, et al. Comparison of serum total calcium, albumin-corrected total calcium, and ionized calcium in 1213 patients with suspected calcium disorders. *Scand J Clin Lab Invest* 1989;49:217-23. [Erratum, *Scand J Clin Lab Invest* 1990;50:113.]
4. Stuckey BGA, Kent GN, Gutteridge DH, Pullan PT, Price RI, Bhagat C. Fasting calcium excretion and parathyroid hormone together distinguish familial hypocalciuric hypercalcaemia from primary hyperparathyroidism. *Clin Endocrinol (Oxf)* 1987;27:525-33.
5. Heath DA. Localization of parathyroid tumours. *Clin Endocrinol (Oxf)* 1995;43:523-4.

Dr. Utiger replies:

To the Editor: I began my editorial by considering how hypercalcemia is discovered in different patients; in ordinary practice, this discovery always means that serum total calcium has been measured. In patients with high serum total calcium concentrations, measurements of serum ionized calcium provide little additional information, because the values will be high unless a patient has severe acute volume depletion or, in very rare cases, an abnormal serum globulin with high affinity for calcium. It may be appropriate to measure serum ionized calcium, as Glendenning et al. suggest, if hyperparathyroidism is suspected in a patient who has a normal serum total calcium concentration.

With respect to familial benign hypercalcemia, I think “careful history taking” includes a family history, but I should have specified that urinary calcium must be measured in urine collected while the patient is fasting. I disagree that the diagnosis of this disorder is complex; a family history of mild hypercalcemia or hypercalciuria in a patient with fasting hypercalciuria, mild hypercalcemia with a normal or slightly high serum parathyroid hormone concentration, and normal bone density constitutes strong evidence of this disorder.^{1,2}

A parathyroid adenoma or hyperplasia is better identified by a surgeon than by a radiologist, and radiologic studies are not indicated when all parties agree that surgery is indicated. However, a positive radionuclide imaging study, particularly one showing a single region of high uptake, may encourage physicians to recommend surgery for patients who have few or no symptoms of hyperparathyroidism and who otherwise do not meet the criteria for surgery recommended by the National Institutes of Health consensus conference or may aid physicians in gaining the acceptance of surgery by patients who are reluctant to undergo a full neck exploration.

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1. Law WM Jr, Heath H III. Familial benign hypercalcemia (hypocalciuric hypocalcemia): clinical and pathogenetic studies in 21 families. *Ann Intern Med* 1985;102:511-9.

2. Segre GV, Potts JT Jr. Differential diagnosis of hypercalcemia. In: DeGroot LJ, ed. *Endocrinology*. 3rd ed. Vol. 2. Philadelphia: W.B. Saunders, 1995:1075-93.

Acute Myocardial Infarction Due to Septic Coronary Embolism

To the Editor: Lanza et al. (Sept. 30 issue)¹ described a case of acute myocardial infarction due to a coronary embolus arising from a left ventricular thrombus. We report a case of myocardial infarction that was fatal, despite fibrinolytic therapy, and that arose from the embolism of bacterial vegetation in a woman with no known coronary risk factors and incompletely treated infective endocarditis. Post-mortem examination revealed a bacteria-laden embolus in a major epicardial artery and an intraparenchymal cerebellar hemorrhage.

A 54-year-old woman, who was an intravenous drug abuser, was admitted with a four-week history of fever and interrupted treatment for bronchial pneumonia. She had no known cardiac risk factors and had no history of cardiovascular disease. A few hours after admission, she reported chest pain and shortness of breath. On physical examination, the patient was febrile and hypotensive and was in respiratory distress. Cardiac auscultation revealed a high-pitched early diastolic murmur heard best at the fourth intercostal space at the left sternal border, with moderate bibasilar crackles. An electrocardiogram showed acute ST-segment elevation in the inferolateral leads. Fibrinolytic therapy was started with “front-loaded” alteplase. Since the patient remained in cardiogenic shock, a transesophageal echocardiogram was obtained on an urgent basis; it revealed severe, diffuse left ventricular hypokinesis, severe aortic and moderate mitral-valve regurgitation, and a mobile mass on the aortic valve (Fig. 1). No left ventricular thrombus was

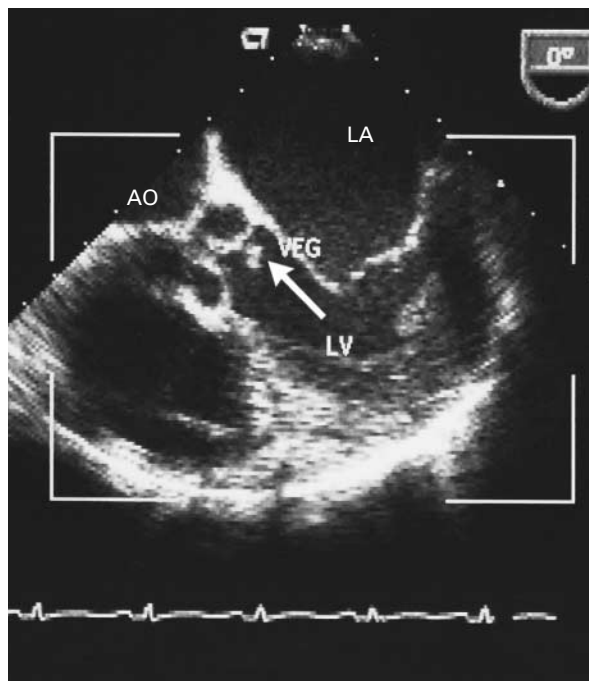


Figure 1. Transesophageal Echocardiogram Showing the Left Ventricular Outflow Tract with an Adherent Mobile Vegetation (Arrow) on the Aortic-Valve Leaflet.

AO denotes aorta, LA left atrium, LV left ventricle, and VEG vegetation.

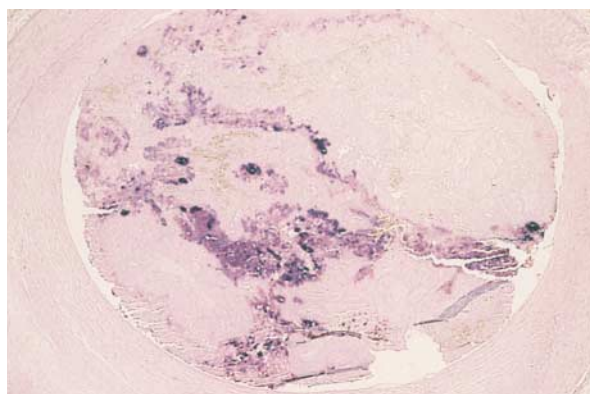


Figure 2. Septic Thromboembolism of the Left Circumflex Coronary Artery (Coincident with the Disappearance of the Aortic-Valve Vegetation Seen on Echocardiography).

Numerous gram-positive cocci are stained dark purple (Gram's stain, $\times 10$).

seen. The patient became progressively less responsive and died despite attempted cardiopulmonary resuscitation. After her death, several blood cultures that had been performed on admission showed colonies of *Staphylococcus aureus* and *Enterococcus faecalis*.

An autopsy revealed minimal vegetation on the edge of the left aortic-valve leaflet, at a distance of 3 cm from the left main ostium; the vegetation was much smaller than expected on the basis of the echocardiographic findings. The mitral and tricuspid valves appeared normal. There was a thromboembolic occlusion of the left circumflex coronary artery, which showed clusters of gram-positive cocci (Fig. 2). In the parenchyma of the right cerebellum, there was a 0.9-cm² area of hemorrhagic infarction.

Septic coronary embolism was a relatively common finding in earlier autopsy studies of infective endocarditis.² When diagnosed during life, myocardial infarction from septic embolism has usually had a poor outcome.³ There have been isolated reports of successful treatment with heparin and fibrinolytic drugs,⁴ although in patients such as ours, severe sepsis probably indicates a poor prognosis.

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1. Lanza GM, Berman BJ, Taniuchi M. Multifocal coronary thromboembolism from a left ventricular thrombus. *N Engl J Med* 1999;341:1083-4.
2. Brunson JG. Coronary embolism in bacterial endocarditis. *Am J Pathol* 1953;29:689-701.
3. Wenger NK, Bauer S. Coronary embolism: review of the literature and presentation of fifteen cases. *Am J Med* 1958;25:549-57.
4. Blum A, Sclarovsky S, Rechavia E. "Infective" myocardial infarction. *Chest* 1993;103:1084-6.

Ethics of Clinical Trials

To the Editor: We are interested in the solution proposed by Marquis (Aug. 26 issue)¹ to the ethical dilemma posed by conflicting obligations to provide patients with a treatment recommendation and to invite them to join a randomized clinical trial. The solution offered is to regard the clinical trial as yet another treatment option, one to be offered to patients within the context of the ethical process of obtaining informed consent to treatment.

Our own data support this approach. We have analyzed 26 audiotaped consultations in which informed consent to a clinical trial was sought. In consultation with ethicists, linguists, health professionals, and consumers, we identified several issues that have ethical implications. The consensus opinion was that standard treatment options (including no treatment) should be discussed, and the doctor's recommendations should be provided, before the clinical trial is introduced as another treatment option. Furthermore, doctors should routinely explain the sources of medical knowledge and the levels of evidence for the standard treatment options. This process offers the best prospect of informing patients that there are in fact treatment options and that they have a choice beyond the doctor's recommendation. Some of us have previously argued that there is currently a double standard in which standards of disclosure for a given treatment are much higher in the clinical-trial set-

ting than outside a trial, where minimal documentation is required.² . . .

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1. Marquis D. How to resolve an ethical dilemma concerning randomized clinical trials. *N Engl J Med* 1999;341:691-3.
2. Segelov E, Tattersall MHN, Coates AS. Redressing the balance — the ethics of not entering an eligible patient on a randomised clinical trial. *Ann Oncol* 1992;3:103-5.

To the Editor: In the European Carotid Surgery Trial, the rule was that if the participating surgeon and neurologist agreed that the patient should undergo carotid endarterectomy, the patient would not be randomly assigned to surgery or conventional medical therapy. Only patients for whom there was disagreement would undergo randomization.¹ This procedure was not followed in the North American Symptomatic Carotid Endarterectomy Trial.² Isn't the English approach more rational than that of the North American group?

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1. European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. *Lancet* 1991;337:1235-43.
2. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325:445-53.

To the Editor: It has not been my experience as an oncologist that patients, and especially their families, are willing to accept the option of a randomized clinical trial over the expert advice (even if not proved) of a physician. It is not uncommon for my patients to seek multiple expert opinions (from academic centers with active research protocols) on their treatment, and never has one of them returned to inform me that he or she has decided to enroll in a randomized study. Unproved is not the same as unsubstantiated.

I believe that if I would not enroll myself or a family member in a specific randomized clinical trial, then I should not enroll my patients in that trial. This approach is generally unambiguous. If I think that one treatment group is superior to another or that treatment is too toxic, that position is not necessarily a hunch but an expert opinion, one that might be based on bona fide experience, other available data, or similar studies that are finished and published. On the other hand, if I truly feel ambivalent with respect to the study groups, I would enroll myself or a family member in the trial.

I would be curious to know how often family members, friends, close associates, and employees of physician investigators as well as chief executive officers and high government officials are enrolled in randomized clinical trials and how often they are treated on an off-study basis (or in non-

randomized studies), especially for life-threatening illnesses such as those seen in oncology.

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To the Editor: Marquis's discussion of an ethical dilemma faced by clinicians is excellent. But the proposed strategy for informed consent also raises additional questions. First, the duty I have to treat my patients does not seem equivalent to my duty to serve the future, best interest of society. The former duty is one to real people and can be defined. The latter duty is to hypothetical people and is less easily defined. Should I not place a higher priority on the former duty than on the latter? Second, the line between informing and persuading is a thin one. Does Marquis suggest that I inform but not counsel my patients persuasively? How might this be done?

Third, the level of evidence supporting a particular therapy is not always clearly defined. A randomized trial may be conducted despite the availability of evidence favoring one group in the study. For instance, in the same issue of the *Journal*, Hochman et al. report on a negative clinical trial that nevertheless provided "positive" evidence in favor of the experimental intervention¹ — evidence that a clinician such as myself may find compelling. In an accompanying editorial, Ryan points out that "different levels of scientific proof are required for regulatory bodies and for clinicians in search of direction."² Suppose my institution participates in a future SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial, and I find myself caring for a patient in cardiogenic shock. Is the weight of the evidence in favor of early revascularization provided by the study by Hochman et al. sufficient to exempt me from shepherding my patient toward participation in the trial?

Although randomization is a core strategy in the design of clinical studies, it does pose ethical problems that ought not to be dismissed. Randomization may prevent both clinician and patient from exercising a freedom to choose the best therapy. I am thankful to Marquis for a thoughtful essay that keeps this important issue in full view.

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1. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *N Engl J Med* 1999;341:625-34.
2. Ryan TJ. Early revascularization in cardiogenic shock — a positive view of a negative trial. *N Engl J Med* 1999;341:687-8.

To the Editor: Marquis attempts to resolve the ethical dilemma in a physician's choice between a personal treatment preference and an obligation to offer patients the opportunity to enroll in a clinical trial. He concludes that the physician is always obligated to offer a patient the opportunity to enroll in a trial because the existence of a trial indicates that there is insufficient data to demonstrate the superiority of one treatment over another. In reality, trials are more than comparisons of treatments. They may ex-

pose patients to procedures that would not occur in routine practice. For example, timed endoscopic assessments, rather than clinically evident outcomes, form the basis of most data from trials of prophylaxis against peptic ulcers. Informed consent demands consideration of more than the treatments to be compared.

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Dr. Marquis replies:

To the Editor: I thank the correspondents for their thoughtful comments. Butow and colleagues are surely correct: because patients cannot consider the merits of entering a clinical trial without understanding the pros and cons of standard treatments, a clinical trial should be the last treatment option offered.

In the 1980s, there was strong anecdotal evidence in some cases for the benefits of carotid endarterectomy. Accordingly, Strandness's suggestion that random assignment of a patient may be ethical only when the neurologist and surgeon disagree has merit. Plainly there are situations, such as the introduction of penicillin for pneumococcal pneumonia, in which anecdotal evidence is so strong that randomization is unnecessary. Would it be surprising to discover that an informal patient-selection process similar to that endorsed by Strandness was used in the North American trial?

No doubt, Morris's remarks reflect much of the clinical reality of oncology practice. How, then, can patients honestly be encouraged to enter trials for their own sake? The best evidence we now have suggests that the thousands of patients with metastatic breast cancer who elected to receive high-dose chemotherapy with autologous bone marrow transplantation on an off-study basis were not better off than if they had enrolled in a clinical trial and been randomly assigned to conventional treatment.¹ Making patients aware of such realities may reduce their desire to undergo treatment outside a study and to follow the (qualified, I hope) recommendations of their physicians for cutting-edge treatment.

Rosenzweig is correct: the line between informing and persuading is a thin one. A physician (or philosopher) cannot draw this line without judgment and reflection. Nevertheless, being honest with patients about the uncertainties of clinical decision making can promote both patient autonomy and enrollment in studies. "Shepherding my patient" may not be the best concept to apply.

Although additional data-gathering procedures associated with a clinical trial can be unwelcome and burdensome, as Duggan notes, they may also result in better medical care because patients are being closely monitored.

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1. Stadtmauer EA, O'Neill A, Goldstein LJ, et al. Phase III randomized trial of high-dose chemotherapy (HDC) and stem cell support (SCT) shows no difference in overall survival or severe toxicity compared to maintenance chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) for women with metastatic breast cancer who are respond-

ing to conventional induction chemotherapy: the 'Philadelphia' intergroup study (PBT-1). *Prog Proc Am Soc Clin Oncol* 1999;18:1-A. abstract.

Support for Academic Medical Centers

To the Editor: In his article on support for academic medical centers, Iglehart (July 22 issue)¹ seems to describe the issue of variation in Medicare's payments for residency training as a conflict among states, with New York defending the current policy and California and Texas promoting a change. In fact, this is not an issue of New York versus California and Texas. According to an analysis conducted by the Greater New York Hospital Association's Center for Health Economics and Research, which was based on data from the Health Care Financing Administration's 1996 Minimum Data Set, high per-resident payments are received by hospitals in almost every state, including California and Texas. Furthermore, when these payments are adjusted for regional differences in the cost of living by applying the wage index for fiscal year 1999 to the entire per-resident amount (since virtually all the costs are labor costs), there are no New York hospitals among the top 10 with regard to per-resident payments. Rather, the large teaching hospitals with the highest payments for residency training are in the states of Tennessee, Wisconsin, Arkansas, Missouri, North Carolina, Louisiana, and California.

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1. Iglehart JK. Support for academic medical centers: revisiting the 1997 Balanced Budget Act. *N Engl J Med* 1999;341:299-304.

To the Editor: As a resident at one of New York City's largest teaching hospitals, I have observed firsthand the recent panic on the part of management in response to declining government support for academic medical centers and graduate medical education. The inability of the leaders of academic medicine to publicize adequately the seriousness of financial threats to the missions of their hospitals appears to stem from a combination of arrogance and resignation. These leaders initially considered academic medicine too obviously important to be gutted by even the most wayward legislator, and now this attitude has been replaced by an equally ineffective succession of pleas to Congress for increased funding.

Beneficial change might be more likely if academic medicine were more specific and rational with regard to its needs. Since legislators and administrators of entitlement programs regard with skepticism the alarmist appeals of academic medical leaders and are reluctant to increase reimbursements to hospitals in order to compensate for decreased payments by private payers, hospitals may need to ask for smaller sums that are specifically earmarked for graduate medical education. Requesting \$150,000 per resident might be reasonable. An amount of this magnitude would be sufficient not only to pay residents' salaries but also to provide generous funding for related educational activities. Administrative structures entirely distinct from those related to reimbursement for clinical care could be created to funnel funds for residency training from federal agencies directly to the di-

rectors of individual residency programs. This would ensure that the modest allocation for graduate medical education would not be lost within the cavernous operating budget of the typical academic hospital.

Planners may also wish to consider whether all current residency-training programs need to be supported by such a revamped system. Perhaps a competitive process could be established whereby only specific residency programs at specific institutions with excellent faculties and facilities for training primary care or specialist physicians would be successful in obtaining long-term federal subsidies for training. A review-driven process of grant disbursement modeled after that used by the National Institutes of Health might reassure policy makers of the integrity of the system.

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Mr. Iglehart replies:

To the Editor: The discussion about reconfiguring federal policy with regard to graduate medical education is ongoing, but Congress did enact a first increment in the Balanced Budget Refinement Act of 1999 by reducing the variation in Medicare's payments among teaching hospitals. Mr. Raske asserts that I misconstrued this variation as "an issue of New York versus California and Texas." But that is certainly how members of Congress from the latter two states viewed it. Whatever the case may be, there were winners and losers among teaching hospitals in virtually every state.

The way Congress reduced the variation was to adjust the amounts at the high and low ends of the range of payments, a policy that will redistribute many millions of Medicare dollars. Starting in fiscal year 2001, the new law establishes a payment "corridor" around a national average per-resident amount. Hospitals with per-resident amounts that fall between 70 percent and 140 percent of the national average (adjusted by a geographic factor reflecting local differences in costs) will not be affected by this provision and will continue to receive annual Medicare teaching payments with annual inflation updates as they have in the past. Hospitals with per-resident amounts below 70 percent of the national average will receive payments increased to 70 percent of their geographically adjusted value. About 250 hospitals will receive increased Medicare teaching payments. Teaching hospitals with per-resident amounts above 140 percent of the national adjusted average will not receive an inflation-adjusted payment update for two years and will then receive a lower payment update in the subsequent three years. About 90 hospitals have per-resident amounts over 140 percent of their geographically adjusted national average. Although many hospitals in this group are in New York, there are a substantial number in California and Texas as well.

Dr. Alam's call to funnel Medicare's teaching payments to program directors has a certain appeal, particularly for residents who are paid little but recognize that institutions receive substantial sums for their labor, which is designated as graduate medical education. However, such an approach would reduce the ability of teaching hospitals to cross-subsidize different residency programs and might perpetuate the fiefdoms that some departments have become, to the

detriment of the institution as a whole. Needless to say, the Association of American Medical Colleges and its Council of Teaching Hospitals strongly oppose funneling teaching payments directly to program directors.

JOHN K. IGLEHART

Shaky-Leg Syndrome and Vitamin B₁₂ Deficiency

To the Editor: A 68-year-old man presented with a three-year history of trembling of the legs. The tremor began immediately after he stood and subsided when he began walking. His medical history was irrelevant to this problem. Neurologic examination showed a fine, rapid tremor of the legs that began immediately after the patient rose to the standing position and that abated on walking. Sensation of pain and heat was impaired in a stocking distribution, and the Achilles tendon reflexes were absent. Results of the rest of the examination were normal. Results of laboratory tests were remarkable only for a serum vitamin B₁₂ level of 132 ng per liter (normal range, 222 to 753). A Schilling test demonstrated malabsorption of vitamin B₁₂. A computed tomographic scan of the brain was normal. The surface electromyogram showed a 15-Hz synchronous tremor of agonist and antagonist muscles of the legs that began when the patient stood and that was absent when he was seated or lying down. Electrophysiologic studies also showed mild sensory axonal polyneuropathy. Clonazepam (1 mg per day) and cyanocobalamin (injections of 1000 μg given daily for two weeks, then weekly for two months, and once a month thereafter) provided complete relief of the tremor. Follow-up after one year showed no abnormalities. Treatment with clonazepam was then discontinued without recurrence of the tremor.

Shaky-leg syndrome, also referred to as orthostatic tremor, is an unusual movement disorder characterized by difficulty in maintaining an orthostatic position because of a

leg tremor that subsides on walking or sitting.^{1,2} Although most cases are idiopathic, symptomatic shaky-leg syndrome has been associated with nontumoral aqueduct stenosis, relapsing polyradiculoneuropathy, head trauma, and pontine lesions.² The origin and mechanism of shaky-leg syndrome are obscure. However, positron-emission tomographic studies have demonstrated abnormal cerebellar activation, suggesting a central origin.³ The disorder has responded to treatment with clonazepam, phenobarbital, primidone, and valproic acid.⁴

The association of shaky-leg syndrome with vitamin B₁₂ deficiency in our patient might have been a coincidence. However, the fact that the tremor did not recur after discontinuation of clonazepam supports this association. We think that shaky-leg syndrome was the result of disturbances in the cerebellum or related pontine structures as a result of vitamin B₁₂ deficiency. In fact, there is evidence that these structures may be affected by vitamin B₁₂ deficiency.⁵

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