

## Correspondence



## Conflict-of-Interest Policies

*To the Editor:* In the November 30 issue of the *Journal*, four articles addressed financial conflicts of interest for academic investigators working with industry. The articles by Lo et al.<sup>1</sup> and McCrary et al.<sup>2</sup> provide important data and insight into the extent of the problem. The editorial by Drazen and Koski<sup>3</sup> highlights the central issue that arises when an investigator has an equity stake in a sponsoring company while conducting a clinical trial. Martin and Kasper,<sup>4</sup> representing Harvard Medical School, present their position on conflicts of interest and assert “we chose to retain our current strict standards.”

The assertion by Martin and Kasper seems peculiar in the light of the Harvard policy, which allows investigators to have an equity interest at “de minimis” levels, or up to \$20,000 in a publicly traded company. Obviously, this de minimis level is not fixed and will fluctuate with the valuation of the company. Furthermore, Martin and Kasper state that “a randomized, double-blind, multicenter trial seems less susceptible to bias than one without those features, so that investigators involved in such trials might be permitted to have a greater financial interest in the sponsoring companies.”

Having been involved with many such multicenter trials, I cannot fathom the logic of Martin and Kasper. Regardless of the rigor of any trial, the key lies in the dissemination phase and the “spin” put on the findings of the trial. For this reason, our study group has strictly prohibited any equity interest in a company whose patented therapeutic drug or device is under trial.<sup>5-7</sup> As pointed out by Lo et al., McCrary et al., and Drazen and Koski, this initial issue

needs to be addressed squarely. The current Harvard policy appears to be at variance with acceptable standards of clinical investigation.

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1. Lo B, Wolf LE, Berkeley A. Conflict-of-interest policies for investigators in clinical trials. *N Engl J Med* 2000;343:1616-20.
2. McCrary SV, Anderson CB, Jakovljevic J, et al. A national survey of policies on disclosure of conflicts of interest in biomedical research. *N Engl J Med* 2000;343:1621-6.
3. Drazen JM, Koski G. To protect those who serve. *N Engl J Med* 2000;343:1643-5.
4. Martin JB, Kasper DL. In whose best interest? Breaching the academic-industrial wall. *N Engl J Med* 2000;343:1646-9.
5. Topol EJ, Califf RM, Van de Werf F, et al. Perspectives on large-scale cardiovascular clinical trials for the new millennium. *Circulation* 1997;95:1072-82.
6. Topol EJ, Armstrong P, Van de Werf F, et al. Confronting the issues of patient safety and investigator conflict of interest in an international clinical trial of myocardial reperfusion. *J Am Coll Cardiol* 1992;19:1123-8.
7. Topol EJ, Leya F, Pinkerton CA, et al. A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. *N Engl J Med* 1993;329:221-7.

*To the Editor:* Martin and Kasper conclude by suggesting that “our ultimate aim is to find a solution that creates the most just and prudent balance among the interests of academic science, industry, and most important, the public.” However, the public to which the authors refer throughout their editorial is American.

Given that most pharmaceutical companies are transnational and that clinical trials are often conducted in countries that are subsequently unable to afford the high-priced therapy that results from such research, surely it would be an expansion of consciousness to pose the difficult question “In whose interest?” in a global context. What would our responsibilities be if research conflicted with the interest of global health?

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## INSTRUCTIONS FOR LETTERS TO THE EDITOR

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*To the Editor:* The article by Lo and colleagues is of value for its clear tabulation of conflict-of-interest policies at 10 medical schools in the United States. However, the authors' leap from the tabulated data to their conclusions seems quite unwarranted. In particular, we object to the conclusion that all coinvestigators and staff members should "be prohibited from holding stock, stock options, or decision-making positions in a company that may reasonably appear to be affected by their clinical research."

Furthermore, we find this recommendation rather draconian, probably unenforceable, and possibly illegal. In essence, it would require that all investigators and staff members (and their immediate families) refrain from holding stock in any pharmaceutical or biotechnology company. This would further exacerbate the logistic difficulties involved in recruiting and retaining qualified staff, as well as potentially limiting the participation of valuable collaborators who might be unwilling to comply with the proposed restrictions.

We suggest instead that the principal investigator avoid financial conflicts and that all coinvestigators and staff members be required to disclose potential financial conflicts to the principal investigator. The principal investigator would then behave as the "designated investigator," similar to a "designated driver," refraining from "investigating under the influence" and taking ultimate responsibility for ensuring that the entire research team engaged in unbiased behavior. Thus, under this policy the principal investigator would remain fully independent, while it would be acknowledged that some financial relations between the researchers and industry are acceptable and perhaps even beneficial.

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*Editor's note:* Dr. Ratain serves as a consultant for a number of pharmaceutical and biotechnology companies.

The authors reply:

*To the Editor:* Ratain and Sheridan contend that our recommendations are draconian and unenforceable. However, Topol's experience with large multicenter cardiology trials demonstrates that strict guidelines can be implemented without compromising the quality of the research or the willingness of respected investigators to participate in the study. Judges, government officials, and other professionals work under strict conflict-of-interest guidelines. Our recommendations do not prohibit investigators or their staff members from being compensated for their work through grants or contracts. Furthermore, there are alternatives for clinical researchers and their staff members who wish to invest in drug companies: they can invest in a stock fund that they do not control, place their assets in a blind trust, or give up their university positions and work full time for a for-profit company.

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*To the Editor:* Topol, Nurok, and Ratain and Sheridan make proposals for what conflict-of-interest policies should be. We believe that the disclosure and management of conflicts of interest is a serious ethical and public policy issue. We also believe that it would be best if policy development in this area were informed by data about the attitudes of stakeholders such as researchers, research institutions, bioethicists, funding agencies, and journals. We are in the process of collecting such data.

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*To the Editor:* The statements by Topol that the Harvard Faculty of Medicine's policy on conflicts of interest<sup>1</sup> does not contain "strict standards" and is "at variance with acceptable standards of clinical investigation" reflect a misunderstanding of the provisions of the Harvard policy and a misreading of our article.

Topol mistakenly states that the \$20,000 de minimis provision of the policy "is not fixed and will fluctuate with the value of the company." This is incorrect. Under the policy, a faculty member may have up to \$20,000 in equity in a company related to the clinical research. Contrary to Topol's assertions, the \$20,000 limit is a fixed one and does not fluctuate. Furthermore, there can only be such de minimis interest if the company is a publicly traded one and if the equity interest was acquired separately from the faculty member's involvement in the research.

Topol misreads the statement in our article in which we raise the possibility that there might be situations in which a greater financial interest might be permitted as a statement that the current policy allows for such greater financial interest. Again, his reading is incorrect. Our theorizing is meant to contribute to the national discussion of this issue and is not a reflection of the provisions of the Harvard policy.

We reaffirm our characterization of the Harvard Medical School policy as one with "strict standards." The policy is fully in accord with acceptable standards of clinical research.

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1. Faculty policies on integrity in science. Boston: Office for Research Issues, Harvard Medical School, October 2, 2000.

### To Protect Those Who Serve

*To the Editor:* Drazen and Koski (Nov. 30 issue)<sup>1</sup> argue persuasively that research institutions should adopt a uniform policy regarding financial conflicts of interest in order to protect the integrity of clinical research. In articulating their case for such a policy, however, they make unrealistic pronouncements about the ethical responsibility of investigators, including that "it is the investigator who must al-

ways act in the subject's best interests" and that "clinical investigators must be primarily interested in protecting the welfare of the brave and unselfish persons who agree to serve as the subjects of our research."

Much clinical research does not test the efficacy of diagnostic or therapeutic interventions but aims to improve the understanding of the disease. Because these studies pose risks to subjects without any compensating medical benefits, participation is not in their best interests. Moreover, even clinical trials aimed at evaluating treatments, especially those involving placebo controls, do not promote the best interests of all patients who volunteer to participate. Consequently, if the investigator always acted in the subject's best interests, much, if not most, clinical research would be impossible to conduct.

Clinical research is subject to an inherent ethical tension and a potential conflict between advancing science and protecting the well-being of research subjects.<sup>2</sup> Minimizing or even eliminating financial conflicts of interest leaves the inherent ethical tension intact. The forthright recognition of the potential of clinical research to compromise the welfare of research subjects contributes to the careful assessment of the scientific value and validity of research protocols, the determination of acceptable levels of research-related risks, scrupulous efforts to obtain informed consent, and the adequate monitoring of volunteers.<sup>3</sup>

(The opinions expressed in this letter are those of the author and do not necessarily reflect the policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.)

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1. Drazen JM, Koski G. To protect those who serve. *N Engl J Med* 2000; 343:1643-5.
2. Miller FG, Rosenstein DL, DeRenzo EG. Professional integrity in clinical research. *JAMA* 1998;280:1449-54.
3. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000;283:2701-11.

Drs. Drazen and Koski reply:

Dr. Miller points out an important issue related to the conduct of clinical research: it is critical that the benefit derived from clinical research be worth the risk to the patient who becomes a subject. We believe that clinical researchers recognize the presence of an ethical tension when neither the patient nor the treating physician knows the exact nature of the treatment being tested; this tension must be tolerated if a treatment is to pass a rigorous test of its potential benefits before it is adopted for use by practicing physicians. Our point was that to add to this ethical tension a financial tension, due to ownership by the investigator of equity in the sponsoring entity, is unacceptable.

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## Intrathecal Methylprednisolone for Postherpetic Neuralgia

*To the Editor:* Kotani and colleagues (Nov. 23 issue)<sup>1</sup> recommend intrathecal methylprednisolone acetate for treatment of intractable postherpetic neuralgia due to persistent inflammation. But the abnormalities in the cerebrospinal fluid and on magnetic resonance imaging in patients with acute herpes zoster are not persistent. The neuropathological reference that Kotani et al. cite<sup>2</sup> does not demonstrate polymorphonuclear leukocytes or "marked inflammation around the spinal cord, with massive infiltration and accumulation of lymphocytes." The usual association between neutrophil inflammation and interleukin-8 calls into question reliance on the level of interleukin-8 in acellular cerebrospinal fluid.<sup>3</sup> The authors' hypothesis that "postherpetic neuralgia provokes an intense inflammatory reaction in the spinal cord" is inverted.

The risk of complications is more important than the data on efficacy. We found that chemical meningitis accounts for half the serious complications resulting from a single intrathecal injection of 40 to 80 mg of methylprednisolone; the other complications are transverse myelitis, cauda equina syndrome, lumbar radiculitis, intractable headache, and urinary retention.<sup>4,5</sup> Chronic arachnoiditis with severe pain is most often associated with multiple injections. The neurotoxic effects of intrathecal steroid formulations have been attributed to sensitivity to the local anesthetic, the steroid, hyperbaric mixtures, or the steroid preservative (benzyl alcohol, benzalkonium chloride, or polyethylene glycol).<sup>4,5</sup> Kotani et al. misidentify polyethylene glycol as "propylene glycol."

In the accompanying editorial,<sup>6</sup> Watson describes the natural history of improvement of the illness. This supports our belief that it is neither ethical nor wise to withhold analgesic and opiate medications in favor of an invasive treatment that may cause permanent injury.

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1. Kotani N, Kushikata T, Hashimoto H, et al. Intrathecal methylprednisolone for intractable postherpetic neuralgia. *N Engl J Med* 2000;343:1514-9.
2. Watson CPN, Deck JH, Morshead C, Van der Kooy D, Evans RJ. Postherpetic neuralgia: further post-mortem studies of cases with and without pain. *Pain* 1991;44:105-17.
3. Lopez-Cortes LF, Cruz-Ruiz M, Gomez-Mateos J, Viciano-Fernandez P, Martinez-Marcos FJ, Pachon J. Interleukin-8 in cerebrospinal fluid from patients with meningitis of different etiologies: its possible role as neutrophil chemotactic factor. *J Infect Dis* 1995;172:581-4.
4. Nelson DA. Intraspinal therapy using methylprednisolone acetate: twenty-three years of clinical controversy. *Spine* 1993;18:278-86.
5. Nelson DA, Landau WM. Intraspinal steroids: history, efficacy, accidentality and controversy with review of U.S. Food and Drug Administration (FDA) reports. *J Neurol Neurosurg Psychiatry* (in press).
6. Watson CPN. A new treatment for postherpetic neuralgia. *N Engl J Med* 2000;343:1563-5.

*To the Editor:* Kotani et al. suggest that the intrathecal administration of methylprednisolone is an effective ther-

apy for postherpetic neuralgia. However, we are concerned about the potential risks of this treatment. After the acute infection, the varicella-zoster virus enters the peripheral nervous system and produces a latent infection of dorsal-root ganglia. The precise mechanisms of reactivation have not been identified.<sup>1</sup> During latency, DNA, messenger RNA, and proteins specific to the varicella-zoster virus are detectable.

Several observations support the hypothesis that in patients with postherpetic neuralgia, the varicella-zoster virus persists in ganglia at higher levels than those reached during latency.<sup>2</sup> The effects on the varicella-zoster virus of the intrathecal injection of methylprednisolone are unknown. Aseptic meningitis has been described after intrathecal injections of steroids.<sup>3</sup> Therefore, viral replication, which may have increased after therapy with intrathecal methylprednisolone, could be confused with this well-known complication.

In the study by Kotani et al., the cerebrospinal fluid was examined only by routine cytologic and biochemical tests. To rule out enhanced viral reactivation resulting from intrathecal corticosteroid therapy, we suggest screening patients for both viral DNA and antibodies to varicella-zoster virus in the cerebrospinal fluid.<sup>2</sup> Moreover, patients should be informed about the risk of increased viral replication that may follow treatment of postherpetic neuralgia with intrathecal injections of methylprednisolone.

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1. Ahmed R, Morrison LA, Knipe DM. Persistence of viruses. In: Fields BN, Knipe DM, Howley PM, eds. Fields virology. Vol. 1. Philadelphia: Lippincott-Raven, 1996:219-49.
2. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. *N Engl J Med* 2000;342:635-45. [Erratum, *N Engl J Med* 2000;342:1063.]
3. Abram SE. Intrathecal steroid injection for postherpetic neuralgia: what are the risks? *Reg Anesth Pain Med* 1999;24:283-5.

*To the Editor:* Although the results of the treatment of intractable postherpetic neuralgia with intrathecal methylprednisolone in the study by Kotani et al. are promising, I would like to sound a note of caution. The study did not include a methylprednisolone-only group. Intrathecal hyperbaric lidocaine at the dosages used by Kotani et al. has been associated with a number of neurologic side effects, including cauda equina syndrome<sup>1</sup> and transient radicular irritation<sup>2</sup> and is commonly associated with hypotension, bradycardia, and cardiac arrest even in healthy people.<sup>3</sup> Were the patients enrolled in the study by Kotani et al. informed of these adverse effects?

Intrathecal injection of methylprednisolone is not a procedure to be undertaken lightly in an office setting by personnel unfamiliar with resuscitation techniques. At a minimum, there must be appropriate monitoring, including pulse oximetry and blood-pressure monitoring; an immediately available source of oxygen and the means to administer it both passively and actively with positive-pressure ventilation; and the means to provide full resuscitative measures.

Most patients with postherpetic neuralgia are elderly and will often have associated diseases such as cardiac, cerebrovascular, and respiratory disorders. A sustained drop in blood pressure can have devastating effects on older patients.

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1. Gerancher JC. Cauda equina syndrome following a single spinal administration of 5% hyperbaric lidocaine through a 25-gauge Whitacre needle. *Anesthesiology* 1997;87:687-9.
2. Tarkkila P, Huhtala J, Tuominen M. Transient radicular irritation after spinal anaesthesia with hyperbaric 5% lignocaine. *Br J Anaesth* 1995;74:328-9.
3. Caplan RA, Ward RJ, Posner K, Cheney FW. Unexpected cardiac arrest during spinal anesthesia: a closed claims analysis of predisposing factors. *Anesthesiology* 1988;68:5-11.

*To the Editor:* The impressive results of Kotani et al. require some clarification. Although a combination of methylprednisolone and lidocaine was used, the discussion refers to methylprednisolone alone. This is unjustified, because only the combination may be effective. Why was the efficacy of methylprednisolone alone not assessed? It would be clinically important to know whether comparable results could be achieved if lidocaine were omitted. Lidocaine is neurotoxic not only when injected into the nerves but also when injected intrathecally at concentrations greater than 2 percent.<sup>1,2</sup>

Bringing a patient into a position in which the head is tilted downward immediately after intrathecal administration of 3 ml of 3 percent hyperbaric lidocaine may cause hypotension, bradycardia, and dyspnea due to blockade of the thoracic sympathetic nerves and the nerves innervating the respiratory muscles. Surprisingly, Kotani et al. provide no details regarding the hemodynamic and respiratory responses. Intrathecal methylprednisolone should be administered only by persons experienced in cardiopulmonary resuscitation.

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1. Loo CC, Irestedt L. Cauda equina syndrome after spinal anaesthesia with hyperbaric 5% lignocaine: a review of six cases of cauda equina syndrome reported to the Swedish Pharmaceutical Insurance 1993-1997. *Acta Anaesthesiol Scand* 1999;43:371-9.
2. Hodgson PS, Neal JM, Pollock JE, Liu SS. The neurotoxicity of drugs given intrathecally (spinal). *Anaesth Analg* 1999;88:797-809.

*To the Editor:* Kotani et al. propose an effective treatment for postherpetic neuralgia. However, there are several problems with their study.

An additional group is needed. Why was no group of patients given methylprednisolone alone? Is lidocaine a useful additive? This is not just a methodologic question; lidocaine administered by the intrathecal route may generate serious side effects.

Intrathecal administration of lidocaine is no longer recommended because of its neurotoxic effects.<sup>1</sup> Intrathecal

lidocaine is responsible for the transient neurologic syndrome, defined as pain in the buttocks and legs, paresthesias, and motor weakness.<sup>2</sup> These symptoms usually disappear within a few days. Nevertheless, for these reasons lidocaine is probably not a good additive to intrathecal methylprednisolone.

The authors injected patients with 90 mg of lidocaine, a dose that leads to profound spinal anesthesia with hemodynamic changes, such as hypotension and bradycardia. Placing patients in the head-down position can lead to respiratory arrest as a consequence of respiratory-muscle blockade and severe hemodynamic effects such as vasovagal syncope. The risks associated with spinal anesthesia were not clearly described in the study.

If a local anesthetic is needed, prilocaine or bupivacaine should be used instead of lidocaine because of their lower neurologic toxicity.<sup>3</sup> Such treatment should be administered only in recovery or operating rooms, and the presence of a physician skilled in the management of spinal anesthesia is essential.

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1. Gaiser RR. Should intrathecal lidocaine be used in the 21st century? *J Clin Anesth* 2000;12:476-81.
2. Hampl KF, Schneider MC, Ummenhofer W, Drewe J. Transient neurologic symptoms after spinal anesthesia. *Anesth Analg* 1995;81:1148-53.
3. Hampl KF, Heinzmann-Wiedmer S, Luginbuehl I, et al. Transient neurologic symptoms after spinal anesthesia: a lower incidence with prilocaine and bupivacaine than with lidocaine. *Anesthesiology* 1998;88:629-33.

*To the Editor:* I would like to share some of the difficulties my colleagues and I encountered in our attempt to duplicate the protocol of the study reported by Kotani et al. and to administer the intrathecal injection of methylprednisolone acetate plus lidocaine for the treatment of postherpetic neuralgia. In contrast to the findings of the authors, we were unable to obtain a homogeneous solution of methylprednisolone in the minimal amount of solute required. In response to our inquiry, the drug manufacturer (Pharmacia-Upjohn) stated that the firm did not recommend intrathecal injection because of the solubility properties of the drug.

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The authors reply:

*To the Editor:* We were fully aware that intrathecal methylprednisolone can be neurotoxic, and we therefore carefully designed our study<sup>1</sup> as well as a previous study<sup>2</sup> to minimize and fully evaluate potential complications. Complications of the use of intrathecal methylprednisolone have generally been observed after the treatment of multiple sclerosis, and multiple injections increase the risk. We therefore excluded patients with neurologic disease and gave just four

injections at weekly intervals, regardless of the intensity of neuralgia. We followed all patients for two years, and none reported treatment-related side effects or recurrent herpes zoster.

Our study population was restricted to patients with intractable postherpetic neuralgia that had lasted at least one full year and had been resistant to conventional treatments. In this population, "natural" improvement, as described by Nelson and Landau, is rare.

Our informed-consent form included detailed information about the possibility of serious adverse effects, including life-long paralysis, exacerbation of pain, recurrence of herpes zoster, and even death. We agree that the simplest and safest approaches should be used initially, as suggested in the editorial by Watson.<sup>3</sup> However, the benefit-to-risk ratio is high in patients suffering from intractable postherpetic neuralgia because conventional treatments are ineffective.

Because interleukin-8 in the cerebrospinal fluid is a well-known inflammatory mediator, and because this property was closely related to treatment efficacy, we thought that an antiinflammatory reaction was a plausible mechanism for analgesia. Although interleukin-8 is produced by neutrophils, macrophages, and monocytes, the number of leukocytes does not always correlate with the concentration of interleukin-8. In fact, Chaka and coworkers<sup>4</sup> reported that there is no leukocytosis in cerebrospinal fluid during meningitis, despite high interleukin-8 concentrations.

Srinivasan points out that methylprednisolone does not fully dissolve in lidocaine, leaving a white deposit. We measured the specific gravity of the supernatant. Lewis, Niebergall and Priebe, and Zetlaoui and Cosserat criticize our use of lidocaine. However, a local anesthetic was necessary to identify and control the cephalad spread of methylprednisolone in the 60 percent of our patients who had cervical and upper thoracic neuralgia. Lewis, Niebergall and Priebe, and Zetlaoui and Cosserat argue that our results do not eliminate an interaction between lidocaine and methylprednisolone. However, we compared the outcomes for a control group that received lidocaine only with those for the lidocaine-plus-methylprednisolone group, and our results indicate that the benefits of intrathecal methylprednisolone in patients with postherpetic neuralgia are not due to lidocaine.

Spinal anesthesia is a routine procedure that is used millions of times each year. It is safe and rarely associated with neurologic complications.<sup>5</sup> Spinal anesthesia is, of course, often accompanied by transient hemodynamic and respiratory depression. Our procedure should thus be performed only by anesthesiologists, with appropriate monitoring and equipment.

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1. Kotani N, Kushikata T, Hashimoto H, et al. Intrathecal methylprednisolone for intractable postherpetic neuralgia. *N Engl J Med* 2000;343:1514-9.
2. Kikuchi A, Kotani N, Sato T, Takamura K, Sakai I, Matsuki A. Comparative therapeutic evaluation of intrathecal versus epidural methylprednisolone for long-term analgesia in patients with intractable postherpetic neuralgia. *Reg Anesth Pain Med* 1999;24:287-93.
3. Watson CPN. A new treatment for postherpetic neuralgia. *N Engl J Med* 2000;343:1563-5.

4. Chaka W, Heyderman R, Gangaidzo I, et al. Cytokine profiles in cerebrospinal fluid of human immunodeficiency virus-infected patients with cryptococcal meningitis: no leukocytosis despite high interleukin-8 levels. *J Infect Dis* 1997;176:1633-6.
5. Horlocker TT, McGregor DG, Matsushige DK, Schroeder DR, Besse JA. A retrospective review of 4767 consecutive spinal anesthetics: central nervous system complications. *Anesth Analg* 1997;84:578-84.

The editorialist replies:

*To the Editor:* There has been a great deal of interest from all over the world with regard to the use of methylprednisolone acetate for the treatment of postherpetic neuralgia, as evidenced by the requests I have had for further information. These letters raise the important issue of the safety of this therapy.

Nelson and Landau are quite correct in stating, as pointed out in my editorial, that there is little pathological evidence of inflammation in chronic cases of postherpetic neuralgia. In fact, only one patient in the study they quote<sup>1</sup> had evidence of persistent inflammation several months after the onset of herpes zoster.

An important issue, raised by Nelson and Landau and in my editorial, is the possibility of complications from intrathecal methylprednisolone. The preparations in the United States and Canada consist of a multidose vial of methylprednisolone acetate for intramuscular use that contains, among other ingredients, benzyl alcohol and polyethylene glycol (both of which may be neurotoxic), or a single-dose vial that contains myristyl gamma picolinium chloride. A mixture of methylprednisolone acetate and lidocaine is also available and contains benzyl alcohol, polyethylene glycol, and myristyl gamma picolinium chloride. Methylprednisolone succinate is available for intravenous use. None of these products are recommended for use intrathecally or epidurally by the manufacturer (Pharmacia-Upjohn). I am informed by Pharmacia-Upjohn that it is theoretically possible to manufacture a preservative-free formulation of methylprednisolone, but this would need to be tested for safety and would require a considerable delay before it could be marketed, a situation that creates a barrier to the implementation of this treatment.

Finally, as Nelson and Landau mention and as I concluded in my editorial, patients with postherpetic neuralgia should have an adequate trial of standard therapies before an invasive procedure is considered.

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1. Watson CPN, Deck JH, Morshead C, Van der Kooy D, Evans RJ. Postherpetic neuralgia: further post-mortem studies of cases with and without pain. *Pain* 1991;44:105-17.

### The Effect of Fecal Occult-Blood Screening on the Incidence of Colorectal Cancer

*To the Editor:* Mandel and associates (Nov. 30 issue)<sup>1</sup> show that either annual or biennial fecal occult-blood testing significantly reduces the incidence of colorectal cancer. Their findings were primarily the result of using the equivalent of the rehydrated Hemoccult II card, a fecal occult-blood test that has good sensitivity but poor specificity and

that is not currently recommended for use by its manufacturer (Beckman Coulter, Fullerton, Calif.). Thus, the results with the rehydrated Hemoccult II card cannot be used to support its use in routine clinical practice.

The nonrehydrated Hemoccult II is the most widely used fecal occult-blood test in the United States. It has low sensitivity for detecting colorectal neoplasms in patients at average risk who do not have symptoms.<sup>2,3</sup> There are immunochemical fecal occult-blood tests, such as FlexSure OBT (Beckman Coulter) and Immudia-HemSP (formerly Heme-Select, Fujirebio America, Fairfield, N.J.), that are more sensitive and specific, and more such tests will probably soon be available.<sup>4</sup> As Fletcher<sup>5</sup> has pointed out, if new screening tests are truly more accurate than Hemoccult II, their effectiveness need not be confirmed by randomized, controlled trials, since the ability of Hemoccult II to save lives that might have been lost to colorectal cancer has already been shown. Now may be the time to start using these new and better tests.

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*Editor's note:* Dr. Allison has conducted research that has been supported in part by SmithKline Diagnostics (now Beckman Coulter) and has served in the past as a consultant to Beckman Coulter and Enterix (Falmouth, Me.).

1. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 2000;343:1603-7.
2. Allison JE, Feldman R, Tekawa IS. Hemoccult screening in detecting colorectal neoplasm: sensitivity, specificity, and predictive value: long-term follow-up in a large group practice setting. *Ann Intern Med* 1990;112:328-33.
3. Ahlquist DA, Wieand HS, Moertel CG, et al. Accuracy of fecal occult blood screening for colorectal neoplasia: a prospective study using Hemoccult and HemoQuant tests. *JAMA* 1993;269:1262-7.
4. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. *N Engl J Med* 1996;334:155-9.
5. Fletcher RH. Commentary. *ACP J Club* 1996;124:74.

*To the Editor:* The "statistically significant association between the positive predictive value of a test and the number of positive slides" does not demonstrate that "the fecal occult-blood test was sensitive for larger polyps," as suggested by Mandel et al. in their report on participants in the Minnesota Colon Cancer Control Study. The positive predictive value of a test depends, in general, much more on specificity than on sensitivity. In this case, as the number of positive slides required for a positive test is increased, the test becomes more specific; positive tests are much more likely to be associated with colorectal cancer, and the positive predictive value rises accordingly. Sensitivity actually decreases in this trade-off.

Although it is clear that screening with the fecal occult-blood test can reduce mortality from colorectal cancer, the magnitude of the reduction remains unclear. The potential reduction is limited by the sensitivity of an individual fecal occult-blood test and of a program of screening for both colorectal cancer and large polyps. Clinical trials have shown that programs of fecal occult-blood screening lead to a reduction in mortality from colorectal cancer of about 16 to 33 percent over periods of 8 to 13 years.<sup>1-3</sup> If compliance were increased, however, this rate might be even higher. It would be interesting to know the findings in the Minne-

sota study among persons who were compliant with screening. They would presumably represent the upper limit of the reduction in mortality with the use of fecal occult-blood testing.

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1. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. *N Engl J Med* 1993; 328:1365-71. [Erratum, *N Engl J Med* 1993;329:672.]
2. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996;348:1467-71.
3. Hardcastle JD, Chamberlain JO, Robinson MHE, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996;348:1472-7.

The authors reply:

*To the Editor:* We agree with Allison that we should continue to seek screening tests with greater accuracy. Although both rehydrated and nonrehydrated Hemoccult tests have been shown to be effective in significantly reducing mortality from colorectal cancer, there are tests that could result in even greater benefit because of their increased accuracy. Sufficiently establishing the performance of these tests may be possible without randomized, controlled trials.

Ransohoff and Pignone misinterpret what we stated. They imply that we suggested that sensitivity increases with increasing numbers of positive slides. In fact, we stated that the increase in positive predictive value with an increasing number of positive slides meant that the sensitivity of the test for polyps was greater than chance; that is, fecal occult-blood testing did not select cases randomly. They recognize this when they say that "as the number of positive slides required for a positive test is increased, . . . positive tests are much more likely to be associated with colorectal cancer." By chance alone, a positive test would detect colorectal cancer in a proportion equal to the prevalence in the population, regardless of how many slides were positive. If the rate increases with an increasing number of positive slides, then the sensitivity is greater than it would be if cases were randomly selected. The specificity would also be greater than that expected by chance.

Ransohoff and Pignone also state that the reduction in mortality observed in the Minnesota study would have been greater if compliance were increased. We made this point in our article. It is likely that the reductions in both mortality and incidence would have been greater if all the people in the screening groups had complied with all the tests and if none in the control group had been screened.

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## Increased Incidence of Perforated Appendixes in Hmong Children in California

*To the Editor:* Health care for Hmong immigrants from Southeast Asia to the United States has been associated with major social, cultural, and communication problems.<sup>1</sup> To determine whether the health care received by Hmong patients differs from that received by other patients, I studied the incidence of appendiceal perforation among 118 Hmong children and an equal number of randomly selected white children who underwent primary appendectomy between January 1989 and December 1997. The research was conducted at Valley Children's Hospital in Fresno, California. The hospital serves central California, where many of the 120,000 Hmong immigrants in the United States live. The research was part of fieldwork conducted in central California between September 1996 and August 1998; it was supported by grants from the Agency for Health Care Policy and Research, the National Science Foundation, and Valley Children's Hospital.<sup>2</sup>

The two groups of children were similar with respect to age and sex (Table 1). The incidence of appendiceal perforation was significantly higher among the Hmong children (66 percent, as compared with 37 percent among the white children;  $P < 0.001$ ). The mean time from the onset of symptoms to the child's arrival at the emergency room was 3.3 days for the Hmong children, as compared with 2.2 days for the white children ( $P = 0.008$ ). The interval between arrival at the hospital and arrival at the operating room for surgery was 8.6 hours for the Hmong children and 6.3 hours for the white children ( $P = 0.003$ ). The longer interval for the Hmong children was related to the wait for an interpreter and the longer time required for the Hmong parents to provide consent for surgery.

The Hmong children had a significantly longer mean

**TABLE 1.** CHARACTERISTICS OF HMONG AND WHITE CHILDREN WHO UNDERWENT PRIMARY APPENDECTOMY BETWEEN JANUARY 1989 AND DECEMBER 1997.\*

VARIABLE	HMONG PATIENTS (N=118)	WHITE PATIENTS (N=118)	P VALUE†
Age — yr	9.5±4.0	9.8±4.1	NS
Male sex — no. (%)	74 (63)	85 (72)	NS
Appendiceal perforation — no. (%)	78 (66)	44 (37)	<0.001
Duration of symptoms — days	3.3±4.3	2.2±2.0	0.008
Interval between arrival at hospital and arrival at OR — hr	8.6±7.0	6.3±4.2	0.003
Hospital stay — days	6.7±3.4	4.8±3.3	<0.001
Perforation	7.4±2.6	7.4±3.8	NS
No perforation	4.9±4.2	3.2±1.2	0.002
Type of appendectomy — no. (%)‡			
Laparoscopic	42 (61)	60 (87)	<0.001
Open abdominal	27 (39)	9 (13)	<0.001

\*Plus-minus values are means ±SD. NS denotes not significant, and OR operating room.

†P values were calculated with a two-sided Student's t-test.

‡Laparoscopic appendectomy was not performed at Valley Children's Hospital until 1994. Data were available for 69 Hmong children, who were matched with 69 white children, for the period from 1994 through 1997.

hospital stay (6.7 days, as compared with 4.8 days for the white children;  $P < 0.001$ ). In the group with appendiceal perforation, the length of the hospital stay was the same for the Hmong children (7.4 days). In the group without perforation, however, the hospital stay was significantly longer for the Hmong children (4.9 days, as compared with 3.2 days for the white children;  $P = 0.002$ ). This difference was associated with the surgical methods used. A larger proportion of Hmong children underwent open abdominal appendectomies (39 percent, as compared with 13 percent of the white children;  $P < 0.001$ ). The surgeon who participated in two thirds of the operations explained that open abdominal appendectomies were more likely to be performed in the Hmong children because it was easier to explain the procedure to their parents and to obtain consent. The laparoscopic appendectomy was harder to explain because it involved four incisions and removal of the appendix under video guidance. The surgeon stated that perforation was not a factor in the choice of surgery, since the laparoscopic technique is effective in patients with perforation and the surgical approach can be converted to an open procedure if necessary.

My findings are consistent with previous reports that delayed treatment is the most important risk factor for ap-

pendiceal perforation<sup>3,4</sup> and that laparoscopic appendectomy reduces the length of the hospital stay.<sup>5,6</sup> The results of this study suggest that social and cultural barriers and communication difficulties substantially compromised the health care received by the Hmong children.

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1. Fadiman A. *The spirit catches you and you fall down: a Hmong child, her American doctors, and the collision of two cultures*. New York: Farrar, Straus, and Giroux, 1997.
2. Hu J. *Under the knife: medical "noncompliance" in Hmong immigrants*. (Ph.D. dissertation. Atlanta: Emory University, 2000.)
3. Temple CL, Huchcroft SA, Temple WJ. The natural history of appendicitis in adults: a prospective study. *Ann Surg* 1995;221:278-81.
4. Brender JD, Marcuse EK, Koepsell TD, Hatch EI. Childhood appendicitis: factors associated with perforation. *Pediatrics* 1985;76:301-6.
5. Ortega AE, Hunter JG, Peters JH, Swanstrom LL, Schirmer B. A prospective, randomized comparison of laparoscopic appendectomy with open appendectomy. *Am J Surg* 1995;169:208-13.
6. Frazee RC, Roberts JW, Symmonds RE, et al. A prospective randomized trial comparing open versus laparoscopic appendectomy. *Ann Surg* 1994;219:725-31.

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